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THE RELATIVE CONFIGURATION OF FLAVIPUCINE

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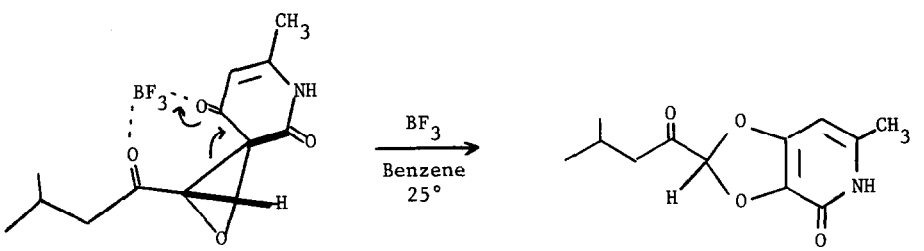
Summary. The relative configuration of the antibiotic flavipucine as inferred from a differential rearrangement reaction was confirmed by ozonolysis to a crystalline oxidoester amide identical with a specimen of this same compound prepared by synthesis.

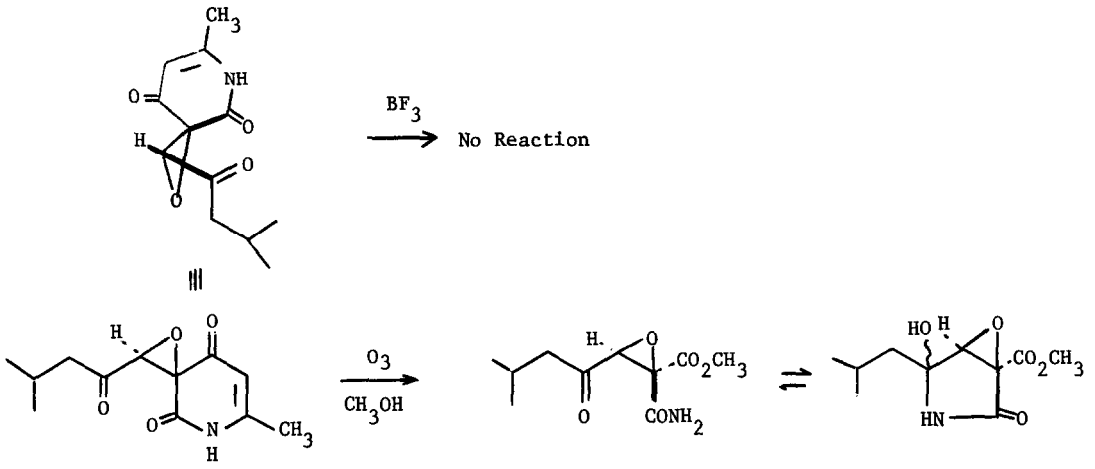
A recent disclosure[1] concerned with the X-ray crystallographic analysis of (±)-flavipucine, prompts us to report our work on the relative configuration of this uniquely labile antibiotic, determined by the chemical route.

We had reported[2] earlier on the rearrangement of (±)-flavipucine and its diastereoisomer (±)-epi-flavipucine under a wide variety of conditions including the Lewis acid, boron trifluoride[3]. A close scrutiny of the BF_3-reaction subsequently revealed that this catalyst singularly evokes rearrangement of epi-flavipucine (1) while leaving flavipucine (3) itself essentially unchanged[4]. This finding signaled the role of configurational differences between the two isomers as the causative factor. The flavipucine-iso-flavipucine rearrangement, (1 or 3 → 2), entails bond reorganization involving the annular C_4-carbonyl function and the C-C bond of the epoxide grouping. In the present instance this rearrangement would seem rationally to follow from complexation of BF_3 with the annular C_4-carbonyl group of that isomer (1) in which stabilization of the intermediate complex is possible by virtue of the cis-disposition of the side-chain keto function. On the basis of these considerations, configuration 1 was provisionally assigned to epi-flavipucine; structure 3 would follow for flavipucine itself.



1 epi-flavipucine

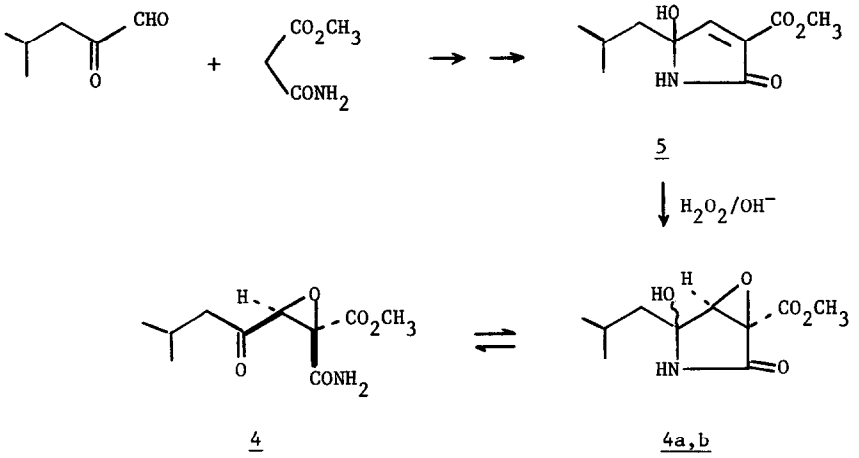
2 iso-flavipucine



3 flavipucine 4 4a,b

Recently we have secured confirmatory evidence for the above configurational assignments. Ozonolysis of (±)-flavipucine (O_3-CH_3OH/$(CH_3)_2S$/-78°)[10] provided a crystalline oxidoester amide[5], mp 126-129°, identified as 4: Calcd for $C_{10}H_{15}O_5N$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.47; H, 6.70; N, 6.20, M^+ 229; $\lambda_{max}^{CHCl_3}$ 2.83, 2.92, 5.69, 5.78, 5.85 and 6.31μ; nmr ($CDCl_3$) δ4.13 (s, -CO-CH<epoxide>), 3.87 (s, $-CO_2CH_3$), 2.53 (broad d, $-CH_2-C(=O)$) and 0.94 (d, J = ca 6HZ, $-HC(CH_3)_2$). The cis orientation of the isovaleroyl and amide functions with respect to each other was established by contacting 4 with silica gel in chloroform solution whereupon ring-closure to the carbinol amide 4a,b occurred. This transformation 4 → 4a,b was accompanied by major disappearance of the isovaleroyl C=O at 5.78μ as well as the primary amide II band at 6.31μ. The nmr spectrum correspondingly exhibited a significant decrease in the signal at δ2.53 ($-CH_2-C(H)=O$) and the appearance of a major signal at 1.76 ($-CH_2-C(O-)(NH-)-$) plus the development of multiple patterns for the epoxide hydrogen (δ4.13, 4.18 and 4.21) as well as the ester CH_3O group (δ3.87 and 3.71)[6].

Independent synthesis of the oxidoester amide 4 was achieved by condensation of isobutylglyoxal[7] with methyl malonamidic ester[8] in tetrahydrofuran with 1,5-diazabicyclo[4.3.0]-non-5-ene as catalyst (25°), to afford after treatment with Ac_2O/py the unstable carbinol amide 5[9], mp 118 dec; mass spec. 214 (M^++1), 213 (M^+, wk), 195 (M^+-H_2O), 182 (M^+-OCH_3) and 170 ($M^+-(CH_3)_2-CH$). Epoxidation of 5 with alkaline hydrogen peroxide in aqueous methanol yielded 4 + 4a,b which in ether solution deposited crystalline 4, mp 126-127° identical in all respects with the ozonolysis product obtained from (±)-flavipucine.



REFERENCES

1. P. S. White, J. A. Findlay and W. H. J. Tam, Can. J. Chem., 1904 (1978).
2. N. N. Girotra, A. A. Patchett and N. L. Wendler, Heterocycles, 6, 1299 (1977).
3. In most of the instances rearrangement studies were effected with mixtures of the two isomers.
4. The rearrangement was effected in benzene solution containing an equimolar amount of boron trifluoride etherate at 25° for 16-18 hours. At the end of this time the epi-flavipucine 1 had disappeared completely and only flavipucine 3 together with the rearrangement product, iso-flavipucine 2 were present.
   This differential rearrangement of epi versus nat isomers is general as exemplified by the parallel behavior of octyl side chain analog (1, $CH_3(CH_2)_7$ instead of $(CH_3)_2CHCH_2$) of (±)-flavipucine. In this connection, the flavipucine analogs with the natural configuration are more mobile on silica gel than the corresponding epi-isomers. The nat-isomers also exhibit a higher field epoxide proton and a lower field pyridone proton than their epi counterparts. (see N. N. Girotra, A. A. Patchett, S. B. Zimmerman, D. L. Achimov and N. L. Wendler, J. Med. Chem., in press).
5. Compare, for example, L. N. Nysted and R. Pappo, U.S. 3,109,016 (1963) for a similar ozonolytic reaction course in the steroid series.
6. The ring-chain tautomeric mixture consisting of 4, 4a and 4b was formed in two ways: 1) stirring a chloroform solution of the epoxidation product with Brinkmann silica gel H (type 60) or 2) by tlc on Analtech silica gel GF plates (chloroform-acetone 65:35). The

mixture of 4, 4a and 4b thus produced, consisted of essentially equal amounts of the three components as measured by the relative heights of the respective epoxide proton peaks. The acyclic amide 4 preponderated (~75%) when the mixture was heated neat at ~120° (mp) for several minutes. Subsequent crystallization from ether provided pure 4.

7. The isobutylglyoxal was prepared by the method employed in the synthesis of flavipucine. Cf. N. N. Girotra, Z. S. Zelawski and N. L. Wendler (JCS) Chem. Comm. 566 (1976).
8. Prepared by method of A. Pinner, Ber., 28, 473 (1895); mp 38-39°.
9. This compound exists exclusively in the cyclized form (5).
10. Propylene oxide was also present with the methanol (1:1) to neutralize the formic acid generated.

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