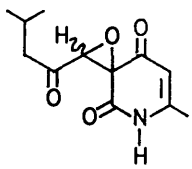
Synthesis of a Flavipucine Reduction Product

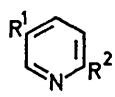
By J. A. Findlay and D. Kwan, Chemistry Department, University of New Brunswick, Fredericton, New Brunswick, Canada

Flavipucine has been reduced by a two-step sequence to 4-hydroxy-6-methyl-3-(4-methylpentyl)-2-pyridone (3b), which has been synthesised independently. The result corroborates the structure (1) proposed earlier for the antibiotic.

In a recent paper [1] on the metabolites of a strain of *Aspergillus flavipes* we presented chemical and spectroscopic evidence in support of structure (1) for the antibiotic factor [2] flavipucine. The assignment of the positions of the alkyl side-chains with respect to the ring nitrogen atom was based on the structure (2a) of a 2,5-disubstituted pyridine alcohol obtained by reduction of flavipucine with lithium aluminium hydride. The alternative structure (2b) was excluded solely on the basis of n.m.r. chemical shift data for the allylic protons.

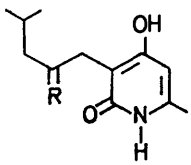


(1)



(2)a; $R^1 = Me_2CH \cdot CH_2 \cdot CH(OH) \cdot CH_2$, $R^2 = Me$

b; $R^1 = Me$, $R^2 = Me_2CH \cdot CH_2 \cdot CH(OH) \cdot CH_2$



(3)a; R = O

b; R = H_2

We considered it desirable to corroborate our conclusions with synthetic studies.

The pyridine alcohol (2b) was prepared by condensation of the lithium salt of 2,5-dimethylpyridine with isovaleraldehyde in ethereal solution and proved to be non-identical with the pyridine alcohol obtained by hydride reduction of flavipucine. In particular the n.m.r. spectrum of ($CDCl_3$) of the synthetic product (2b) displayed signals at δ 2·3 (3H, s, MeC=) and 2·85 (2H, m, allylic CH_2) p.p.m.; the corresponding signals of (2a) appeared at 2·5 and 2·7 p.p.m. Differences in other spectral parameters and t.l.c. behaviour were also noted. Thus the alternative structure (2b) for the metabolite reduction product is excluded.

By catalytic hydrogenation of flavipucine with platinum in ethanol under pressure we have now prepared a crystalline dihydrodeoxy-derivative (3a). This product displays the typical 4-hydroxy-2-pyridone chromophore [3] [$\lambda_{max.}$ (EtOH) 287 nm (ε 10,500)] and its mass spectrum shows major ions (*m/e* 223, *M* − 15, *M* − 57, and *M* − 85) in accord with the indicated side-chain sequence. The n.m.r. spectrum [$(CD_3)_2SO$] is consistent with the formulation and shows signals at δ 5·7 (1H, s, −CH=), 3·35 (2H, s, allylic CH_2), 2·2 (2H, m, $Pr^i CH_2 \cdot CO$), 2·1 (3H, s, allylic Me), 1·8 (1H, m, Me_2CH), and 0·82 (6H, d, *J* 6·5 Hz, Me_2CH) p.p.m. The i.r. spectrum (KBr) shows a strong band at 1718 cm^{-1} (side-chain carbonyl group).

The dihydrodeoxyflavipucine (3a) was converted into 4-hydroxy-6-methyl-3-(4-methylpentyl-2-pyridone (3b) in 59% yield by Wolff–Kishner reduction. This product displayed spectral characteristics in complete accord with its formulation, and was identical with material synthesised by condensation of diethyl 4-methylpentylmalonate with ethyl β-aminocrotonate in boiling ethanol

[1] J. A. Findlay and L. Radics, *J.C.S. Perkin I*, 1972, 2071.
[2] C. G. Casinovi, G. Grandolini, R. Mercantini, N. Oddo, R. Olivieri, and A. Tonolo, *Tetrahedron Letters*, 1968, 3175.
[3] C. R. Kolder and H. J. Den Hertog, *Rec. Trav. chim.*, 1960, **79**, 474.

in the presence of sodium ethoxide, a known procedure [4] for the preparation of 3,6-dialkyl-4-hydroxy-2-pyridones.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer model 457 grating spectrophotometer and u.v. spectra with a Perkin-Elmer model 402 instrument. Mass spectra were determined with an Hitachi–Perkin-Elmer RMU-6D spectrometer. Varian spectrometers HA-100 and T-60 were used for the n.m.r. spectra with tetramethylsilane as internal standard. M.p.s were measured with a Kofler hot-stage apparatus.

4-Methyl-1-(5-methyl-2-pyridyl)pentan-2-ol (2b).—To a stirred suspension of finely cut lithium (0·69 g) in anhydrous ether (50 ml), bromobenzene (5·3 ml) was added dropwise at such a rate that the mixture refluxed gently. The mixture was then stirred overnight at room temperature. 2,5-Dimethylpyridine (5·35 g) was added and stirring was continued for 1 h. The solution was cooled in ice and isovaleraldehyde (*ca.* 10 ml) was slowly distilled in until the solution became yellow. Stirring was continued for another 15 min and water (10 ml) was added, followed by conc. hydrochloric acid (10 ml). The acid layer was poured into a stirred aqueous suspension of sodium carbonate (7·5 g in 15 ml). The lithium carbonate was filtered off and washed once with chloroform (25 ml), and the filtrate was extracted with chloroform (3 × 25 ml). The washing and extracts were combined and evaporated to leave an orange-red liquid (5·91 g). Steam-distillation removed unchanged dimethylpyridine and the residue (1·68 g) was purified by preparative t.l.c., yielding the alcohol (2b) (0·65 g) as a yellow oil homogeneous on t.l.c., $\nu_{max.}$ (CCl_4) 3400 (OH) cm^{-1}, $\lambda_{max.}$ (EtOH) 214, 269, and 276 nm (ε 11,670, 5600, and 4500), *m/e* 193 (M^+), 178 ($M - CH_3$), 175 ($M - H_2O$), 160 [$M - (H_2O + CH_3)$], 136 (M − Me_2CH), 107 (100%, $M - Me_2CH{\cdot}CH_2{\cdot}CHO$), and 106 (M−$Me_2CH{\cdot}CH_2{\cdot}CH{\cdot}OH$), δ (100 MHz; $CDCl_3$) 0·92 (6H, d, *J* 6·5 Hz, Me_2CH), 1·2—2·0 (3H, m), 2·3 (3H, s, MeC=C), 2·85 (2H, m, allylic CH_2), 4·1 (1H, m, C*H*·OH), 5·0br (1H, s, OH), 7·0 (1H, d, *J* 8 Hz, aromatic γ), 7·4 (1H, d, *J* 8 Hz, aromatic β), and 8·3br (1H, s, aromatic α) p.p.m.

Dihydrodeoxyflavipucine (3a).—Flavipucine (0·256 g) in absolute ethanol (50 ml) was hydrogenated (15 lb in^{-2}) for 22 h over platinum oxide (0·05 g). After filtration and evaporation the crude product was recrystallized from ethyl acetate and dioxan yielding dihydrodeoxyflavipucine (3a) (0·125 g, 52%) as white crystals, m.p. 188—192°, $\nu_{max.}$ (KBr) 3300—3000 and 2300—2800 (bonded NH/OH), 1718 (C=O), and 1640 and 1620 (pyridone) cm^{-1}, $\lambda_{max.}$ 287 nm (ε 10,500), *m/e* 223 (M^+), 166 ($M - Me_2CH{\cdot}CH_2$), 138 ($M - Me_2CH{\cdot}CH_2{\cdot}CO$), and 139 (100%, $M - Me_2CH{\cdot}CH_2{\cdot}CO + H$); for n.m.r. data see Discussion section.

4-Hydroxy-6-methyl-3-(4-methylpentyl)-2-pyridone (3b).—(a) *From dihydrodeoxyflavipucine* (3a). Dihydrodeoxyflavipucine (0·206 g), potassium hydroxide (0·175 g), hydrazine hydrate (0·125 ml), and triethylene glycol (1·25 ml) were mixed and refluxed. The temperature of the mixture was kept between 140 and 160° for 1·5 h by occasional addition of hydrazine hydrate. The condenser was removed and the temperature allowed to increase to 200°. The condenser was then replaced and heating was continued for 4 h. The cooled mixture was diluted with an equal volume of water and acidified with hydrochloric acid (3N), and the precipitate was filtered off and washed with water (yield 0·112 g, 59%). The product showed m.p. 240—245° (from dioxan) $\nu_{max.}$ (KBr) 3500—3000 and 2600 (broad, bonded OH/NH), and 1635 and 1610 (pyridone) cm^{-1}, $\lambda_{max.}$ (EtOH) 288 nm (ε 6890), δ [60 MHz; $(CD_3)_2SO$] 0·85 (6H, d, Me_2C), 1·2—1·6 (5H, m, methylenic and methine), 2·1 (3H, s, allylic Me), 2·25 (2H, m, allylic CH_2), and 5·8 (1H, s, aromatic) p.p.m., *m/e* 209 (M^+), 166 ($M - Me_2CH$), 152 ($M - Me_2CH{\cdot}CH_2$), 138 (100%, $M - Me_2CH{\cdot}CH_2{\cdot}CH_2$), and 139 ($M - Me_2CH{\cdot}CH_2{\cdot}CH_2 + H$) (Found: C, 68·35; H, 9·0; N, 6·95; O, 15·55. Calc. for $C_{12}H_{19}NO_2$: C, 68·95; H, 9·1; N, 6·95; O, 15·55%).

(b) *By synthesis.* To a solution of sodium (0·1 g) in absolute ethanol (2 ml) diethyl 4-methylpentylmalonate (0·856 g) and ethyl β-aminocrotonate (0·51 g) were added; the solution was refluxed under nitrogen for 24 h. The ethanol was evaporated off, water was added to the residual paste, and the resulting solution was washed with two portions of ether. On acidification with 3N-hydrochloric acid a white precipitate was formed, which was filtered off and washed with ether. The product (3b) (0·093 g, 17%) was recrystallized three times from dioxan to furnish a sample of analytical purity which was identical (i.r., u.v., n.m.r., and mass spectra and mixed m.p.) with the compound obtained by procedure (a).

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[4] K. Schreiber and G. Adam, *Chem. Ber.*, 1960, **93**, 1848.