REARRANGEMENT OF (±)-FLAVIPUCINE AND ITS DIASTEREOISOMER. CHEMISTRY OF THE TRANSFORMATION PRODUCT

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Flavipucine rearranges under a variety of conditions *via* bond reorganization involving C-C bond cleavage of the epoxide function to yield the isobutylglyoxal acetal of 3,4-dihydroxy-6-methyl-2-pyridone. Transformations of this product are presented in support of its structure.

In view of a recent article by Findlay *et al.*[1] concerned with the rearrangement of (-)-flavipucine, we are prompted to report our findings which differ from those of the aforementioned authors in significant respects.

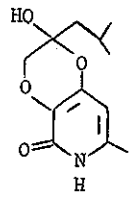
Recently we published the total synthesis of (±)-flavipucine and its diastereoisomer.[2] It had been observed at that time that both of these substances on silica gel produce a minor amount of the same entity, more polar than flavipucine. The substance in question may be prepared by a variety of techniques including warming in benzene at 50° with DABCO, treatment in benzene with BF_3 etherate at ambient temperatures, by melting,[1a] or best by refluxing in xylene. By the latter technique an 80% yield of rearrangement product can be realized after 10 hr. M.p. 163-64°;[1b] ir ($CHCl_3$) 2.20-4.40, 5.78, 5.98 and 6.17μ; λ_{max}^{MeOH} 304 (ε, 6290), 250 (2100) and 216 nm (20550); nmr ($CDCl_3$) δ6.02 (s, 7-H), 5.95 (broad s, 5-H), 2.37 (s, 6-CH_3 and 0.93 (d, J 6 Hz $CHMe_2$); M^+ 237; Calcd

for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.90. Found: C, 61.01; H, 6.07; N, 5.82.

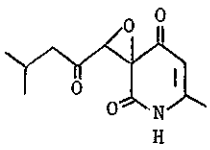
In this regard Findlay et al. (loc. cit.) state that they were unable to effect rearrangement in xylene. As a result of their observation, moreover, they were led to mechanistic conclusions which no longer appear tenable. We must assume that these authors effected the xylene procedure for too short an interval. In a similar vein these same authors report effecting the rearrangement (2% yield) in sodium carbonate solution (followed by silica gel separation). This conclusion would appear to be questionable since we have demonstrated that rearrangement occurs on silica gel alone.

Our early observation that ozonolysis of the rearrangement product produces isobutylglyoxal had given rise to the misleading deduction that this substance possesses the $(CH_3)_2CHCOCH=$ side-chain. The subsequent finding that hot hydrolysis with 2.5N hydrochloric acid produced isobutylglyoxal 4[3] together with 3,4-dihydroxy-6-methyl-2-pyridone 5[4] provided compelling evidence that the rearrangement product was, in fact, an acetal of these two components. The uv spectrum, moreover, exhibits two principle maxima at 304 (ε, 6290) and 216 (ε, 20550) nm compatible with 2-pyridone [293 (ε, 5900) and 224 (ε, 7230) nm] but incompatible with 4-pyridone [single max 253 (ε, 14800) nm] thus making 3 clearly the most probable structure for this substance.[5] Subsequent chemical and physical observations were in complete accord with this assignment.[6] In this connection Findlay et al. (loc. cit.) do not state how their data differentiate 3 from its equally probable alternative 2.

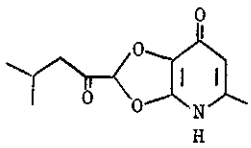
Reduction of 3 with zinc in acetic acid (75°, 3.5 hr) yielded 6 resulting from cleavage of the C_4-oxygen attachment, the latter being a good leaving-group by virtue of the delocalization pathway 1 → 6.[7] M.p. 131-34°; $\lambda_{max}^{CH_3OH}$ 289 nm (ε, 7510), 244 nm (ε, 2370); $\lambda_{max}^{CH_3OH+OH^-}$ 276 nm (ε, 7920); ir ($CHCl_3$) 2.70-4.60, 5.83 and 6.10μ; ir (Nujol) 2.70-4.40, 6.13μ and no band at 5.83; nmr (C_5D_5N) δ5.97 (broad s, 5-H), 4.77 (broad s, 7-Hs), 2.20 (s, 6-CH_3) and 0.92 (d, J 6 Hz $CHMe_2$); M^+ 239; Calcd for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16;



6a



1



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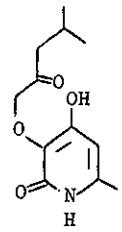
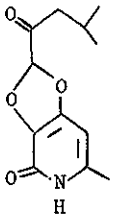


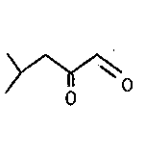
6

Zn
HOAc



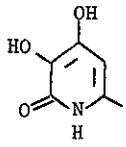
3

H_3O^+



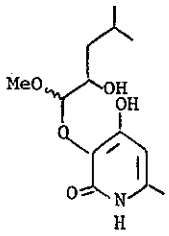
4

+



5

CH_3O^-



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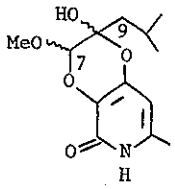

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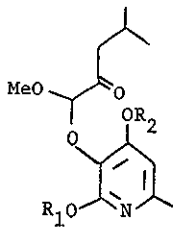
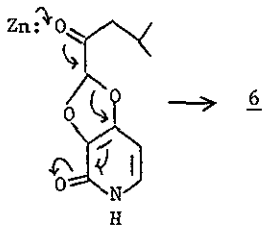


8a R_1=H; R_2=Na

8b R_1=R_2=Ac

N, 5.85. Found: C, 60.03; H, 7.29; N, 5.80. The hypsochromic shift in the



1

uv of 6 in alkaline solution is characteristic of 4-hydroxy-2-pyridones in contrast to 3-hydroxy-2-pyridones which exhibit a marked bathochromic shift under the same conditions.[8] In the solid state 6 exists as the hemiacetal 6a as adjudged from the absence in its ir spectrum in Nujol of the side-chain carbonyl band at 5.83μ which is present in chloroform solution. The 2,4-diacetate of 6 (m.p. 48-49°; Calcd for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.22; H, 6.70; N, 4.08) exhibited a ^{13}Cnmr spectrum (δ_{C_2} 151.1; δ_{C_3} 136.4, $^3J_{C_3..H_5}$ = 6.4, $^3J_{C_3OCH}$ = 1.8; δ_{C_4} 151.6, $^2J_{C_4..H_5}$ = 3.7) in complete accord with this structure based on long range coupling constants paralleling those of 8b (see below).

Treatment of the rearrangement product 3 with sodium methoxide in methanol at 25°, resulted in methoxyl group incorporation with concomitant rupture of the C_4-oxygen attachment to give 7 as a crystalline isomeric mixture. M.p. 165-67°; $\lambda_{max}^{CH_3OH}$ 290 nm (ε, 7510), 242 nm (ε, 2830); $\lambda_{max}^{CH_3OH+OH^-}$ 278 nm (ε, 7700); nmr (CD_3OD) δ5.83 (broad s, 5-H), 4.95, 4.90 (each s, due to isomeric 7-H), 3.52, 3.45 (each s, due to isomeric 7-OCH_3), 2.19 (s, 6-CH_3) and ca 1.83 (broad signal, 9-Hs); ir (Nujol) 2.70-4.70, 6.13 and 6.20μ; M^+ 269; Calcd for $C_{13}H_{19}O_5N$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.74; H, 7.36; N, 5.13. The hypsochromic shift in the uv in alkaline solution again demonstrated that

this system (7 ⇌ 8) is a 4-hydroxy-2-pyridone as in the case of 6 (see above).

Acid hydrolysis of 7, as in the case of 3, likewise yielded isobutylglyoxal and 3,4-dihydroxy-6-methyl-2-pyridone. In the solid state and neutral solution 7 exists as the hemiacetal. Conversion to the acyclic form occurs on forming the sodium salt 8a (1 eq. NaOH in methanol) as demonstrated by the appearance of the side-chain carbonyl group at 5.80μ (Nujol) in the ir. The nmr of this salt in water further exhibited a downfield shift of the pertinent α-protons to δ5.20 (s, 7-H) and 2.60 (d, J 6.5 Hz, 9-Hs), respectively. The nmr in CD_3OD-NaOD resulted in rapid exchange of the pertinent α-protons by deuterium in the developing carbonyl side-chain. The mass spectrum of the exchanged product exhibited M^+ 272 representing an increase of 3 mass units.

Acetylation of 7 (Ac_2O-py/25°) generated the acyclic diacetate 8b; ir ($CDCl_3$) 5.62, 5.80 and 6.23μ; nmr ($CDCl_3$) δ6.93 (broad s, 5-H), 4.83 (s, 7-H), 3.40 (s, 7-OCH_3), 2.47 (s, 2-OAc), 2.30 (s, 6-CH_3 and 4-OAc) and 0.95 (d, J 6 Hz $CHMe_2$); M^+ 353. Confirmation of structure 8b as deduced from the uv (see above) was afforded by the ^{13}Cnmr based on the long range ^{13}C-H coupling constants (δ_{C_2} 151.2, δ_{C_3} 134.6, $^3J_{C_3..H_5}$ = 6.6, $^3J_{C_3OCH}$ = 2.5, δ_{C_4} 151.6, $^2J_{C_4..H_5}$ = 3.7). In the alternative structure (side-chain at C_4), C_4 would have exhibited two couplings both significantly smaller than 6.5 Hz still residing at low field while C_3 would only have been a doublet with $J \gtrsim 6$ Hz residing at high field.

Reduction of 7 in alkaline solution with sodium borohydride afforded the stable acyclic carbinol 9 as a mixture of isomers at C_7 from which one isomer separated in pure form from methanol [m.p. 185-87°; ir ($CHCl_3$) 2.60-4.60 and 6.10μ; nmr (C_5D_5N) δ6.08 (broad s, 5-H), 5.43 (d, J 2.5 Hz, 8-H), 4.17 (m, 9-H), 3.83 (s, 8-OCH_3) and 2.20 (s, 6-CH_3); Calcd for $C_{13}H_{21}O_5N$. C, 57.55; H, 7.80; N, 5.16. Found: C, 57.40; H, 7.83; N, 4.91] yielding a triacetate [M^+ 397; ir ($CDCl_3$) 5.61 and 5.74μ].

Finally, the side-chain carbinol[1] derived from 3 by reduction ($Li[CH_3)_3$-$CO]_3AlH$-tetrahydrofuran) was found to be stable to the conditions of the methoxide catalyzed conversion of 3 → 7, thereby demonstrating the functional role of the carbonyl group in mediating this unusual transformation.[9]

ACKNOWLEDGEMENT

The authors are indebted to Dr. A. Douglas and Mr. R. Reamer for the determination and interpretation of the ^{13}Cnmr.

REFERENCES AND NOTES

1. J. A. Findlay, J. Krepinsky, A. Shum, C. G. Casinovi and L. Radics, Can. J. Chem., 1977, 55, 600. (a) These authors achieved rearrangement by melting only and (b) reported m.p. 166-71°, uv (95% ethanol) 307 (ε, 10260) and 221 (ε, 26090) nm for the rearrangement product.

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

3. Isolated as the bis-semicarbazone m.p. 247-249° Fd: C, 41.90; H, 7.15; N, 36.71. Bis-DNPH m.p. 234-236° Fd: C, 45.30; H, 3.87; N, 23.47. Cf. H. D. Dakin and H. W. Dudley, J. Biol. Chem., 1914, 18, 29. These authors were in fact dealing with the bis-semicarbazone, their data notwithstanding. Despite all efforts we were unable to prepare the mono-semicarbazone.

4. Identical with material prepared according to A. Lapworth and J. N. Collie, J. Chem. Soc., 1897, 828. M.p. 262-265° (dec) same as that reported by A. Hess, Ber., 1899, 32, 1985.

5. A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The MacMillan Co., New York, 1964, p. 178, 182.

6. This rare rearrangement type was first observed recently in a simpler system by H. Wittmann, E. Ehrlich, H. Siegel and H. Sterk, Z. Naturforschung (Sect. B), 1976, 31, 1716.

7. Under forcing conditions (HOAc-Ac_2O/125°) the reaction could be made to proceed further to yield the 2,4-diacetate of 5 (m.p. 155-158°, M^+ 225).

8. Cf. e.g. 4-Hydroxy-2-pyridone: $\lambda_{max}^{CH_3OH}$ 277 nm (ε, 4000); $\lambda_{max}^{CH_3OH+OH^-}$ 258 nm (ε, 5700). 3-Hydroxy-2-pyridone: $\lambda_{max}^{CH_3OH}$ 296 nm (ε, 7400), 237 nm (ε, 4300); $\lambda_{max}^{CH_3OH+OH^-}$ 309 nm (ε, 9000), 259 nm (ε, 6700).

9. Although an oxido ether is a likely intermediate based on precedent, (cf. C. L. Stevens, W. Malik and R. Pratt, J. Am. Chem. Soc., 1950, 72, 4758), it would appear to be excluded by the observed stability of the carbinol derived from 3 to the action of base.

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