HETEROCYCLES, Vol 12, No.11, 1979

BIS-(TETRAHYDROXY-DIBENZ[b,g]INDOLIZINE)[1] BY AIR OXIDATION OF TETRAHYDROPAPAVEROLINE

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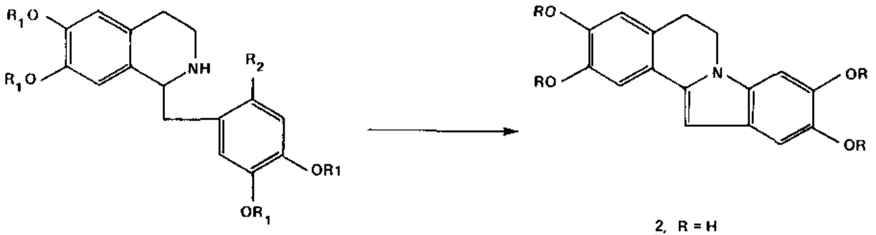
Abstract - THP was oxidized in aqueous alkaline milieu into a mixture of compounds. Two of them were dihydrodibenzoindolizines, isolated as their O-acetates. One was identical with a known monomer, the second proved to be a dimer.

Tetrahydropapaveroline (**1**, THP), a mammalian alkaloid,[2] is very sensitive to oxidation. One of the oxidation products is the dihydrodibenz[b,g]indolizine **2**, obtained many years ago by oxidation of THP with potassium ferricyanide and isolated as its tetraacetate **3**.[3] Repetition of this procedure afforded **3**, in variable yield (5-30%) identical with reported material: mp 216° (lit.[3] 214-5); IR ($CHCl_3$) 1765, 1465, 1370, 1165, 1095 cm^{-1}; MS (70eV) 451 (M^+); UV (EtOH) 331 (ε28,260), 258(18,590), 255(27,430) nm; ^1H NMR ($CDCl_3$) δ 2.27-2.39 (m, 12), 3.09 (t, 2, J = 7Hz), 4.11 (t, 2, J = 7Hz) 6.73 (s, 1), 7.09 (s, 1), 7.14 (s, 1), 7.36 (s, 1), 7.49 (s, 1); ^{13}C NMR ($CDCl_3$) see Table I.

Further oxidation of the tetrol **2** gave a deep violet compound which, upon acetylation, afforded a polyacetate of mp 297° (dec) (lit.[3] 269-270°) in 70% yield (a thin film of tetrol **2** was exposed to air for 2 days, followed by treatment with excess pyridine-acetic anhydride). The following evidence suggests that this compound is not the proposed dibenz[b,g]indolizine **10**,[3] but the dimer **9**: IR($CHCl_3$) 1770, 1460, 1370, 1160, 1110 cm^{-1}; MS (70eV) 900 (M^+), fragmentation pattern confirms the presence of eight acetyl groups; UV (EtOH) 332 (ε43,290) 257 (ε30,300), 228 (ε47,200) nm; ^1H NMR ($CDCl_3$) δ 2.11 (s, 6), 2.19 (s, 6), 2.20 (s, 6), 2.34 (s, 6), 3.02-3.27 (m, 4), 4.07-4.55 (m, 4), 7.00-7.34 (m, 8); ^{13}C NMR ($CDCl_3$) see Table I; anal. calcd for $C_{48}H_{40}N_2O_{16}$: C 64.10, H 4.25, N 3.10; found: C 64.50, H 4.66, N 3.09.

In order to support our structural assignment and to get further information about the physical characteristics of hydrogenated dibenz[b,g]indolizines, the tetramethoxy-tetrahydro derivative **5** was prepared from 6'-bromonorlaudanosine (**4**) via the benzyne procedure.[4,5] This afforded a mixture of the tetrahydro product **5** and its dihydro analog **7** (64% yield). The mixture could easily be analyzed by tlc and converted to **7** by air oxidation in benzene solution: **5**: mp 105-7° (lit.[4] 105-7°); ^{13}C NMR ($CDCl_3$) see Table I; **7**: mp 209-210° (lit.[4] 202-4°); ^{13}C



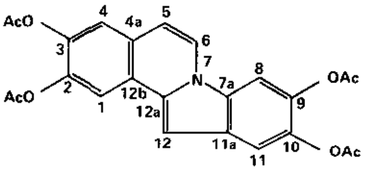
1, $R_1 = R_2 = H$

4, $R_1 = Me$, $R_2 = Br$

2, R = H

3, R = Ac

7, R = Me



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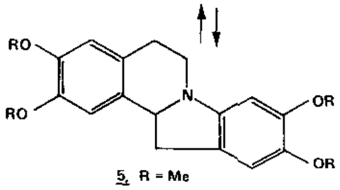
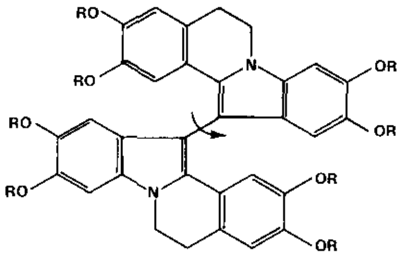


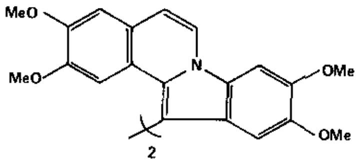
5, R = Me

6, R = Ac



8, R = H

9, R = Ac



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NMR ($CDCl_3$) see Table I. The general spectroscopic characteristics of 5 are in good agreement with those of the tetrahydrotetraacetate 6, obtained from 3 by reduction with diborane in THF, in the presence of trifluoroacetic acid[6] (r.t.; 18 h; 77%): foam; IR ($CHCl_3$) 1775, 1495, 1375 910 cm^{-1}; MS (70eV) 453 (M^+); ^1H NMR ($CDCl_3$) 2.23 (s, 3), 2.27 (s, 9), 2.55 (d, 1, J = 14 Hz), 2.96-3.18 (m, 2), 3.31 (t of d, 1, J = 14, 4 Hz), 3.50 (d of d, 1, J = 14, 9Hz), 3.73 (d of d, 1, J = 14, 7Hz), 4.91 (d of d, 1, J = 9, 4Hz), 6.36 (s, 1), 6.85 (s, 1), 6.86 (s, 1), 6.99 (s, 1), ^{13}C NMR ($CDCl_3$) see Table I.

Table I

^{13}C NMR Chemical Shifts and Multiplicities

	3	9	6	5	7
C-1	118.9(d)	119.2(d)	120.1(d)	110.7(d)	107.2(d)
C-2*	137.8(s)	140.4(s)	141.4(s)	148.8(s)	148.4(s)
C-3*	136.1(s)	138.3(s)	140.4(s)	147.5(s)	148.3(s)
C-4	123.0(d)	122.4(d)	123.2(d)	111.2(d)	111.6(d)
C-4a	127.0(s)	130.9(s)	128.7(s)	126.8(s)	124.0(s)
C-5	28.4(t)	29.1(t)	25.6(t)	24.4(t)	28.8(t)
C-6	40.0(t)	40.3(t)	42.0(t)	42.8(t)	40.5(t)
C-7a	141.0(s)	140.6(s)	148.5(s)	141.8(s)	134.4(s)
C-8	103.2(d)	103.2(d)	101.8(d)	94.2(d)	92.9(d)
C-9	135.3(s)	136.1(s)	137.3(s)	147.2(s)	146.8(s)
C-10	133.8(s)	133.1(s)	133.3(s)	144.3(s)	145.2(s)
C-11	113.8(d)	113.6(d)	119.5(d)	108.8(d)	102.8(d)
C-11a	122.1(s)	126.0(s)	127.0(s)	119.9(s)	121.7(s)
C-12	97.3(d)	104.5(s)	36.4(t)	37.1(t)	94.8(d)
C-12a	130.2(s)	131.4(s)	62.8(d)	62.9(d)	131.2(s)
C-12b	125.9(s)	126.8(s)	130.8(s)	130.7(s)	122.0(s)
OCH_3	--	--	--	55.8-56.9(q)	56.1,56.5(q)
OC=O	168.0-168.8(s)	167.1-168.6(s)	168.1-168.8(s)	--	--
$OCOCH_3$	20.6(q)	20.3-20.6(q)	20.7(q)	--	--

*C-2 and C-3 may be interchanged.

Detailed ^{13}C NMR analysis of these heterocyclic compounds listed in Table I allows the assignment of all the carbon atoms, and supports the postulated structure of the dihydro-dimer 9. A closely related C-12/C-12' dimer 11 was recently obtained by electrochemical oxidation of papaverine.[7] It can be concluded that formation of C-12/C-12' dimer 8 from the monomer 2 is the preferred route of oxidation, rather than aromatization to the postulated fully aromatic dibenz[b,g]indolizine corresponding to 10.[8] This is further supported by the finding that air oxidation of an aqueous solution of THP (1) at pH 7.5 gave, besides other products, 2 and 8, isolated as acetates 3 and 9 in low yield. Molecular model analyses show that free rotation around the C-12/C-12' axis of dimer 8 and 9 is restricted and compound 9 may well constitute one of the theoretically distinct rotomers.

Acknowledgement

We would like to thank Dr. W. Toome of the Research Division of Hoffmann-La Roche Inc., Nutley, New Jersey for obtaining the mass spectrum of the dimer 9 and Dr. H. Yeh of this Laboratory for running the ^{13}C NMR spectra.

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Received, 28th July, 1979