

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

OXIDATION OF TETRAHYDROPAPAVEROLINE

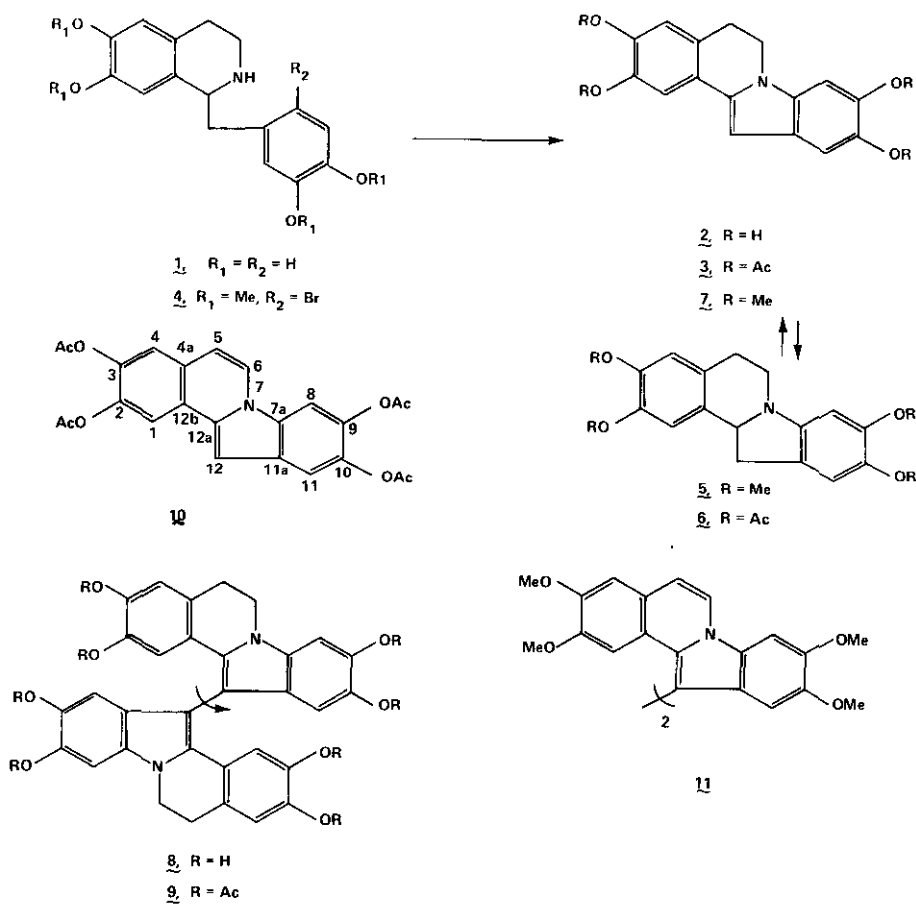
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Abstract - THP was oxidized in aqueous alkaline milieu into a mixture of compounds. Two of them were dihydrodibenzoindolizines, isolated as their O-acetates. One was identical with a known monomer, the second proved to be a dimer.

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 (CHCl₃) 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) 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(CHCl₃) 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) see Table I; anal. calcd for C₄₈H₄₀N₂O₁₆: 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°); ¹³C NMR (CDCl₃) see Table I; 7: mp 209-210° (lit.⁴ 202-4°); ¹³C



NMR ($CDCl_3$) see Table I. The general spectroscopic characteristics of $\underline{5}$ are in good agreement with those of the tetrahydrotetraacetate $\underline{6}$, obtained from $\underline{3}$ by reduction with diborane in THF, in the presence of trifluoroacetic acid⁶ (r.t.; 18 h; 77%): foam; IR ($CHCl_3$) 1775, 1495, 1375 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, $J = 14, 9$ Hz), 3.73 (d of d, 1, $J = 14, 7$ Hz), 4.91 (d of d, 1, $J = 9, 4$ Hz), 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

¹³C NMR Chemical Shifts and Multiplicities

	<u>3</u>	<u>9</u>	<u>6</u>	<u>5</u>	<u>7</u>
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 ¹³C 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.

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