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OXIDATIVE REACTIONS OF AZINES.

2*. SYNTHESIS AND MOLECULAR STRUCTURE OF 3,4-DIHYDROXY-1-METHYL-2-OXO-4-(γ-PYRIDYL)PIPERIDINE

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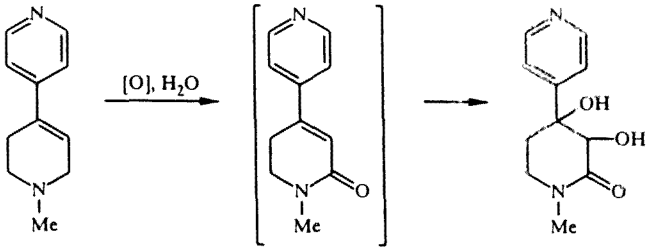
The oxidative ketodihydroxylation of a 1,2,3,6-tetrahydropyridine is reported. Using PMR and x-ray structural analysis, the product was shown to be 3,4-dihydroxy-1-methyl-2-oxo-4-(γ-pyridyl)piperidine.

A previous report [1] has identified a novel regioselective oxidation of 1,2,3,6-tetrahydropyridines having a phenyl group in the 4 position. In this work we have studied the oxidation of the tetrahydropyridine I which has a γ-pyridyl substituent at C_4. Through its conjugation with the allylamine part of the piperidine ring, this heteroaromatic π-deficient substituent can affect the reactivity in two ways. Firstly, it can activate oxidation of the C_2 methylene group to a ketone and secondly (to a greater extent than the phenyl substituent [2]) it may inhibit dihydroxylation of the ethylenic bond. Thus, even under our modified oxidation conditions (potassium permanganate, water–acetonitrile, ~ +25°C [1]) it was expected that piperidine I would form the unsaturated lactam II, and would be quite stable towards subsequent hydroxylation. Its preparation would prove an important step in identifying the primary stage in the overall mechanism of oxidative conversion to lactamdiols.



I II III

However, in the case of this modification, it was only possible to separate the final oxidation product (3,4-dihydroxy-1-methyl-2-oxo-4-(γ-pyridyl)piperidine, III) in 65% yield, which exceeds the yield of the phenyl analog by 11% [1]. The IR spectrum of III shows two absorption bands for the hydroxyl groups at 3450 (broad) and 3070 (broad) cm^{-1} and one strong band at 1640 cm^{-1} assigned to the amide carbonyl. The PMR spectrum of this lactamidiol, taken in DMSO-D_6 at 25°C, shows signals for the C_4 and C_3 hydroxyl groups as two doublets with chemical shifts of 5.58 ($^4J_{5a,4\text{-}OH}$ = 1.2 Hz) and 4.84 ppm ($^3J_{3,3\text{-}OH}$ = 4.0 Hz) respectively. On heating to 60°C they are shifted to high field by 0.27 (4-OH) and 0.3 ppm (3-OH). The doublet at 4.3 ppm ($^3J_{3,3\text{-}OH}$ = 4.0 Hz) is assigned to 3-H. The axial and equatorial protons on C_5 and C_6 appear as complex multiplets reflecting their geminal (^2J) and vicinal (^3J) spin–spin interactions (see Experimental section). The C_6 proton signals appear at lower field than those for C_5. The multiplets for the axial protons 5_a-H (δ 2.37 ppm) and 6_a-H (δ 3.48 ppm) are found at lower field than those of the equatorial protons on the same carbons (5_e-H at 1.78 and 6_e-H at 3.24 ppm). The value of the

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*For communication 1, see [1].

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TABLE 1. Atomic Coordinates (× 10^4) in the III Molecule

Atom	*x*	*y*	*z*
$O_{(1)}$	-61(4)	5000	4363(2)
$O_{(2)}$	681(4)	5577(4)	7206(2)
$O_{(3)}$	5519(3)	5687(3)	6821(2)
$N_{(1)}$	2800(4)	6367(4)	3744(2)
$N_{(2)}$	4793(4)	9019(3)	10815(2)
$C_{(1)}$	1415(4)	5853(4)	4698(3)
$C_{(2)}$	1581(4)	6458(4)	6213(3)
$C_{(3)}$	4080(4)	6838(4)	6765(3)
$C_{(4)}$	4931(5)	7776(4)	5631(3)
$C_{(5)}$	4939(5)	7108(4)	4169(3)
$C_{(6)}$	4259(5)	7553(4)	8224(3)
$C_{(7)}$	6300(5)	7497(4)	9149(3)
$C_{(8)}$	6504(5)	8238(4)	10416(3)
$C_{(9)}$	2852(6)	9057(4)	9931(3)
$C_{(10)}$	2504(5)	8369(4)	8637(3)
$C_{(11)}$	2533(8)	5889(5)	2253(3)
$H_{(20)}$	-666(97)	5333(64)	6852(54)
$H_{(30)}$	5275(57)	5212(35)	7544(36)
$H_{(3)}$	692(48)	7278(33)	6155(29)
$H_{(41)}$	6438(51)	8053(29)	5928(27)
$H_{(42)}$	3982(67)	8526(38)	5570(38)
$H_{(51)}$	6261(58)	6406(36)	4203(32)
$H_{(52)}$	5204(49)	7784(30)	3418(30)
$H_{(7)}$	7598(55)	6908(33)	8889(32)
$H_{(8)}$	7891(55)	8220(33)	11102(33)
$H_{(9)}$	1660(67)	9637(42)	10225(39)
$H_{(10)}$	1107(63)	8363(40)	8101(38)
$H_{(111)}$	2807(82)	6524(55)	1637(51)
$H_{(112)}$	1046(100)	5503(78)	2058(59)
$H_{(113)}$	3634(117)	5150(84)	2044(68)

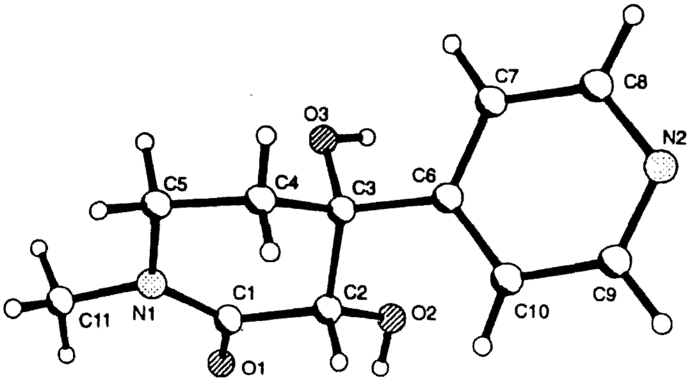

Fig. 1. Overall view and numbering of the atoms in III.

vicinal constant ${}^3J_{5a,6a}$ = 11.9 Hz points to a large contribution of a chairlike conformation for the piperidine ring in solutions of III.

The structure of the lactamdiol III was proved using x-ray structural analysis. The piperidine ring has a half chair conformation, the deviations of C_3 and N_1 being −0.72 and +0.24 Å respectively from the mean plane through atoms $C_1-C_2-C_4-C_5$ (mean deviation from the plane −0.03 Å). The pyridine substituent is located equatorially and is twisted out of the piperidine plane by 59.2°. Intramolecular hydrogen bonds are absent. In the crystalline structure the lactamdiol III is linked through a three-dimensional network of intermolecular hydrogen bonds $O_2-H\cdots O'_3$ (relative to M the molecule M′ has

TABLE 2. Bond Lengths in the III Molecule

Bond	λ, Å	Bond	λ, Å
$O_{(1)}-C_{(1)}$	1,226(4)	$C_{(2)}-C_{(3)}$	1,526(3)
$O_{(2)}-C_{(2)}$	1,411(3)	$C_{(3)}-C_{(6)}$	1,525(3)
$O_{(3)}-C_{(3)}$	1,422(3)	$C_{(3)}-C_{(4)}$	1,528(4)
$N_{(1)}-C_{(1)}$	1,350(3)	$C_{(4)}-C_{(5)}$	1,512(4)
$N_{(1)}-C_{(11)}$	1,455(4)	$C_{(6)}-C_{(10)}$	1,384(4)
$N_{(1)}-C_{(5)}$	1,460(4)	$C_{(6)}-C_{(7)}$	1,385(4)
$N_{(2)}-C_{(9)}$	1,319(4)	$C_{(7)}-C_{(8)}$	1,386(4)
$N_{(2)}-C_{(8)}$	1,340(4)	$C_{(9)}-C_{(10)}$	1,382(4)
$C_{(1)}-C_{(2)}$	1,524(4)		

TABLE 3. Valence Angles in the III Molecule

Angle	ω (deg.)	Angle	ω (deg.)
$C_{(1)}-N_{(1)}-C_{(11)}$	118,7(3)	$O_{(3)}-C_{(3)}-C_{(4)}$	107,7(2)
$C_{(1)}-N_{(1)}-C_{(5)}$	123,7(2)	$C_{(6)}-C_{(3)}-C_{(4)}$	108,6(2)
$C_{(11)}-N_{(1)}-C_{(5)}$	115,6(2)	$C_{(2)}-C_{(3)}-C_{(4)}$	106,3(2)
$C_{(9)}-N_{(2)}-C_{(8)}$	116,5(3)	$C_{(5)}-C_{(4)}-C_{(3)}$	111,7(2)
$O_{(1)}-C_{(1)}-N_{(1)}$	122,8(2)	$N_{(1)}-C_{(5)}-C_{(4)}$	113,1(2)
$O_{(1)}-C_{(1)}-C_{(2)}$	119,5(2)	$C_{(10)}-C_{(6)}-C_{(7)}$	116,8(2)
$N_{(1)}-C_{(1)}-C_{(2)}$	117,5(2)	$C_{(10)}-C_{(6)}-C_{(3)}$	122,5(2)
$O_{(2)}-C_{(2)}-C_{(1)}$	110,8(2)	$C_{(7)}-C_{(6)}-C_{(3)}$	120,5(2)
$O_{(2)}-C_{(2)}-C_{(3)}$	109,5(2)	$C_{(6)}-C_{(7)}-C_{(8)}$	119,9(3)
$C_{(1)}-C_{(2)}-C_{(3)}$	112,3(2)	$N_{(2)}-C_{(8)}-C_{(7)}$	123,1(3)
$O_{(3)}-C_{(3)}-C_{(6)}$	111,3(2)	$N_{(2)}-C_{(8)}-C_{(10)}$	124,4(3)
$O_{(3)}-C_{(3)}-C_{(2)}$	109,5(2)	$C_{(8)}-C_{(10)}-C_{(6)}$	119,3(3)
$C_{(6)}-C_{(3)}-C_{(2)}$	113,2(2)		

the coordinates x − 1, y, z) and $O_3-H\cdots N''_2$ (coordinates of M″ are 1 − x, y − 0.5, 2 − z). The distances $O_2\cdots O'_3$ and $O_3\cdots N''_2$ are 2.958 and 2.779 Å. The angles at the hydrogen atoms taking part in hydrogen bonding are 145.4° and 171.0° and the $H\cdots O'_3$ and $H\cdots N''_2$ bond lengths are 2.22 and 1.94 Å respectively.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WP-200 instrument at 200 MHz for DMSO-D_6 solutions with TMS internal standard. IR spectra were taken on a UR-20 instrument for KBr tablets. Mass spectra were obtained on an MX-1303 instrument with direct introduction of the sample into the ionization source and an ionization energy of 70 eV.

X-Ray Structural Investigation of III. Crystals of III were grown from acetone and were monoclinic with space group $P2_1$ and unit cell parameters a = 5.753(1), b = 10.064(1), c = 9.261(1) Å, β = 95.640(10)°, V = 533.60(12) Å^3, d_{calc} = 1.383 g/cm^3. The analysis was carried out on a CAD-4 automatic diffractometer (λMoKα irradiation, $\theta/2\theta$ scanning to sin θ/λ = 0.6 A^{-1}). In all 824 measured reflections, 742 were independent (R_{int} = 0.013). Absorption was not taken into account (μ = 1.02 cm^{-1}). The structure was solved by a direct method and refined in a full matrix least squares analysis in the anisotropic approximation for nonhydrogen atoms and isotropic for hydrogen atoms to R = 0.022, ωR^2 = 0.057. All calculations were performed using the SHELXL-93 program [3]. Atomic coordinates are given in Table 1 and bond lengths and valence angles in Tables 2 and 3.

3,4-Dihydroxy-1-methyl-2-oxo-4-(γ-pyridyl)piperidine III was prepared by [1] in 65% yield from 1,2,3,6-tetrahydro-1-methyl-4-(γ-pyridyl)piperidine I (17 mmole) as colorless crystals with mp 220-222°C (from acetone) and R_f 0.3 (Silufol UV-254 plates, ether − alcohol eluant, 2:1). IR spectrum: 3450 br, 3400 sh, 3070 br, 1640 cm^{-1}. PMR spectrum: 1.78 (1H, ddd, $J_{5a,5e}$ = 14, $J_{5e,6a}$ = 5, $J_{5e,6e}$ = 1.5, 5_e-H); 2.37 (1H, dddd, $J_{5a,5e}$ = 14, $J_{5a,6a}$ = 11.9, $J_{5a,6e}$ = 6.4, $J_{OH,5a}$ = 1.2 Hz, 5a-H); 2.86 (3H, s, CH_3); 3.24 (1H, ddd, $J_{6e,6a}$ = 11.9, $J_{6e,5a}$ = 6.4, $J_{6e,5e}$ = 1.5, 6e-H); 3.48 (1H, ddd, $J_{6a,6e}$ = $J_{6a,5a}$ = 11.9, $J_{6a,5e}$ = 5, 6_a-H); 4.3 (1H, d, $J_{OH,3a}$ = 4 Hz, 3_a-H); 4.84 (1H, d, $J_{OH,3}$ = 4.0 Hz, 3-OH); 5.58 (1H, d, $J_{OH,5a}$ = 1.2

Hz, 4-OH); 7.5 and 8.51 ppm (each 2H, AA'BB' system, J = 6.1 Hz, H_{Py}). Mass spectrum, m/z (I, %): M^+ 222 (45), $[M-C_5H_5]^{+\cdot}$ 156(100). Found, %: C 59.7, H 6.54, N 12.9. $C_{11}H_{14}N_2O_3$. Calculated, %: C 59.46, H 6.31, N 12.61%.

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