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OXIDATIVE REACTIONS OF AZINES. 1. KETOHYDROXYLATION OF 4-PHENYL-1,2,5,6-TETRAHYDROPYRIDINES. SYNTHESIS AND STRUCTURE OF 3,4-DIHYDROXY-4-PHENYLPIPERIDIN-2-ONES AND THEIR ACETOXY DERIVATIVES

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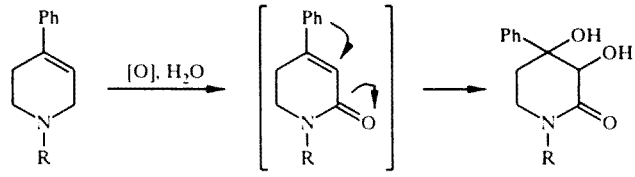
N-Alkyl substituted 4-phenyl-1,2,5,6-tetrahydropyridines which do not undergo Wagner hydroxylation are converted in good yields to the corresponding 3,4-dihydroxy-2-oxo-piperidines under modified conditions for this reaction. The molecular structures of a 3,4-dihydroxy-4-phenyl-piperidin-2-one and its diacetatate have been studied by x-ray crystalographic analysis.

Under Wagner reaction conditions, 4-aryl substituted 1,2,5,6-tetrahydropyridines remain inert to the action of aqueous solutions of potassium permanganate [1]. We have studied the possible hydroxylation of N-alkyl-4-phenyl-1,2,5,6-tetrahydropyridines I and II under modified reaction conditions. We have found that successful hydroxylation of the olefinic bond can be achieved using an aqueous acetonitrile medium at increased temperature (20-30°C) but that this is accompanied by oxidation of the α-methylene group to a ketone. 3,4-Dihydroxy-4-phenylpiperidine-2-ones (III, IV) are obtained in high yields.



I, II III, IV

I, III R = Me; II, IV R = Et

Evidently an increase in the reaction temperature initiates a radical oxidation of the methylene group of the allylamino function to a ketone. Thanks to its electron acceptor properties, the amide group formed weakens the conjugation of the olefin bond with the benzene ring thus assisting its reaction with the permanganate anion.

The IR spectrum of lactamdiol III shows two overlapping, broad bands for OH absorption at 3400 and 3320 cm^{-1} together with a broad, intense band for the amide C=O group absorption centered at 1610 cm^{-1} and two inflections at 1645 and 1655 cm^{-1}. The mass spectrum of III shows a maximum intensity peak assigned to the molecular ion M^+ at m/e 221, confirming its empirical formula. The presence of a hydroxyl group at C_4 is confirmed by an intense peak for the fragment ion $[PhCO]^+$ with m/e 105 (69%). The substitution in the piperidine ring is confirmed from ^1H and ^{13}C NMR data. In the PMR spectrum taken in $CDCl_3$ the two hydroxyls give two very broad signals centered at about 4.0 and 3.3 ppm which change

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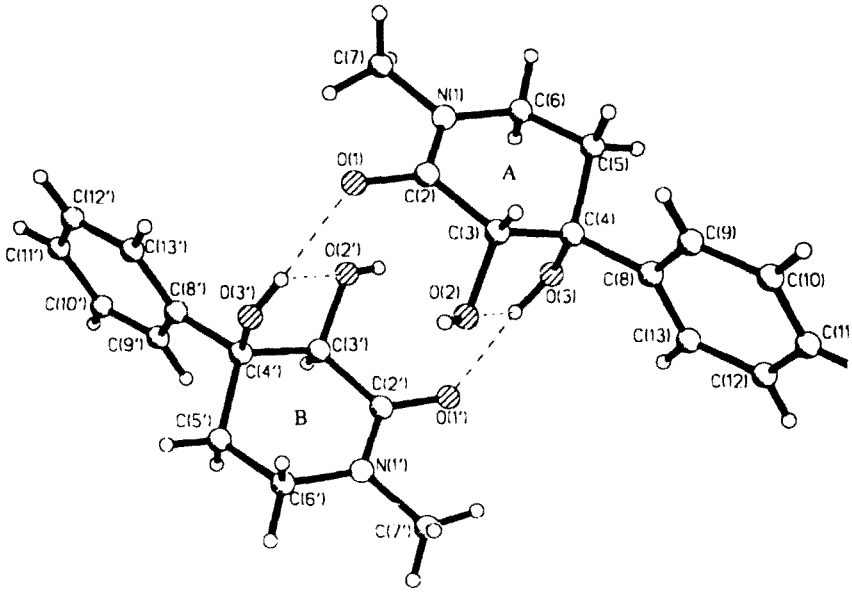
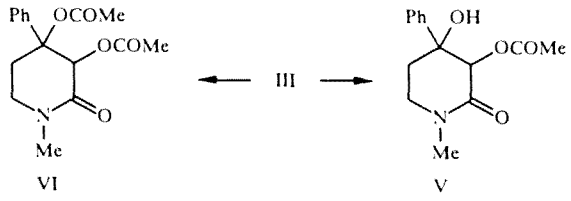


Fig. 1. Overall view of the crystallographically independent molecules of lactamdiol III.

in dimethylsulfoxide solution to broad singlets at 4.55 and 5.20 ppm. The C_3 methine proton gives a singlet signal at 4.44 ppm (shifted by about 1.6 ppm to high field of its position in the starting piperidine I) as a result of the change in configuration at this carbon atom from sp^2 to sp^3. The four protons at C_5 and C_6 form an ABMX type spin system shows that only one of the three CH_2 groups in I is oxidized to a ketone, specifically that it is the methylene alpha to the nitrogen atom in the allyl fragment. The N-CH_3 proton signal is shifted by about 0.6 ppm to low field of its position in I (at 2.33 ppm) which also supports the formation of the amide fragment.

X-ray analysis confirms the molecular structure of lactamdiol III (Fig. 1).* This compound exists in the crystalline state as a dimer with independent molecules IIIA and IIIB joined by the hydrogen bonds $O_3-H...O_{1'}$ and $O_{3'}-H...O_1$. The hydrogen atoms of these hydroxyl groups take part simultaneously in the formation of two hydrogen bonds, both intra- and intermolecular, giving a "forked" or three centered bond. The hydroxyl group O_2-H of one dimer forms a hydrogen bond with $O_{1'}$ of the other dimer thus combining these pairs of molecules in an infinite chain. Atoms N_1 and C_2 in both molecules have a planar trigonal configuration (overall valence angles 359.3-360°). The deviations of atoms C_4 and C_5 from the mean square plane taken through the four atoms $C_6-N_1-C_2-C_3$ are -0.299 Å and $+0.456$ Å. There data show that the piperidine ring has an unsymmetrical half chair conformation. The phenyl substituent occupies an equatorial position and is twisted out of the piperidine plane by 101.7°. The 3-OH group has a pseudoequatorial orientation. In molecule IIIA the torsional angles typifying the orientation of the peripheral substituents have the following values: $C_2-C_3-C_4-C_8$ $+164.4°$, $C_2-C_3-C_4-O_3$ $-70.6°$, $O_2-C_3-C_4-O_3$ $+52.0°$, $O_2-C_3-C_4-C_8$ $-73.0°$.



In molecule B the analogous angles have the same numerical values but opposite signs thus indicating that the independent molecules IIIA and IIIB in the dimer are a pair of enantiomers.

*Detailed quantitative data for the x-ray analysis of compounds I and VI will be reported separately.

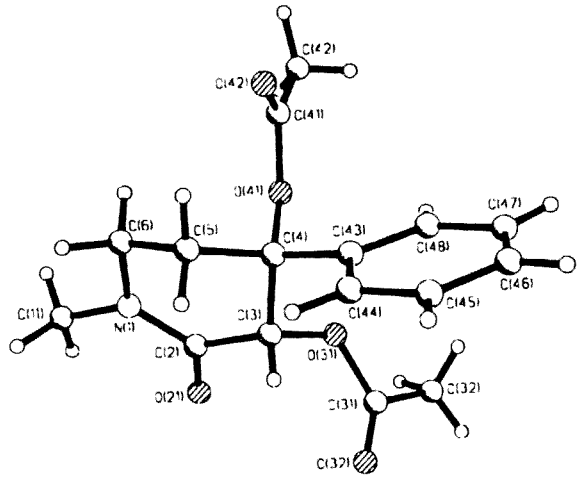


Fig. 2. Geometry of crystalline diester VI and atom numbering.

With the aim of synthesizing biologically active compounds (in particular potential analgesics and anesthetics) lactamdiol III was converted to a monoester (V) using acetic anhydride and to the diacetate (VI) using acetyl chloride. The IR spectrum of monoester V shows three absorption bands at 3380, 1720, and 1640 cm^{-1}, confirming the esterification of only one of the hydroxyl groups. Its mass spectrum has an intense (67%) M^+ peak and peaks for $[M-COMe]^+$ and $[M-COMe-OH]^+$ ions which also confirm monesterification of the starting lactamdiol. The PMR spectrum shows doubling of the signals for the protons of 3-H (5.85 and 5.27 ppm, singlets in the ratio 4:3, overall one proton), $N-CH_3$ (2.96 and 2.98 ppm), and $COCH_3$ (2.0 and 2.03 ppm) confirming the presence of two diastereomers. The relative positioning of the substituents at C_4 and C_3 in these diastereomers was studied using ^{13}C NMR spectroscopy in which a double set of signals was seen for all carbon atoms except $N-CH_3$. Signal assignment was made using the edited ^{13}C spectral method with broad band decompling. The marked γ-effect seen for the C_5 atoms (31.1 ppm in the major isomer and 27.9 ppm in the minor) permits assignment of the major isomer as that with retention of the equatorial orientation of the acetoxy group, corresponding to an equatorial hydroxyl at C_3 in the starting diol but with inversion of the configuration at C_3 in the minor isomer. The structure of diester VI was confirmed spectrally (see Experimental) and also be x-ray analysis. Figure 2 shows the geometry of the diester VI. A special feature of the piperidine ring in this molecule is the position in one plane of not only the four atoms C_6, N_1, C_2, C_3 (as a result of the planar trigonal configuration of N_1 and C_2) but also C_4, not usually found in this plane. Hence, the piperidine ring has a sofa conformation in contrast to lactamdiol III which is a nonsymmetrical half chair. The probable reason for this change in conformation is distortion of the tetrahedral configuration of atom C_4 due to mutual repulsion of the bulky phenyl and acetoxy substituents. The tetrahedral angle $C_5-C_4-C_3$, being an intracyclic angle of the piperidine ring, is decreased to 104.1°, the $O_{41}-C_4-C_5$ decreased to 103.1°, and $C_{43}-C_4-C_5$ is increased to 115.4° when compared with the standard value of 109.28° for a tetrahedral angle.

The orientation of the peripheral substituents of the piperidine ring are retained in the same way as in the starting dihydroxy derivative III with the phenyl ring at C_4 and the ester group at C_3 occupying pseudoequatorial positions and the acyloxy group at C_4 a pseudoaxial one. The torsional angles $C_2-C_3-C_4-C_{43}$, $O_{41}-C_4-C_3-O_{31}$, and $C_2-C_3-C_4-C_{41}$ are 171.7, 52.7, and −69.7° respectively. The plane of the phenyl ring is twisted by 106.0° which exceeds the value in the 3,4-dihydroxy derivative III by 5°. The torsional angles $C_4-O_{41}-C_{41}-C_{42}$ and $C_3-O_{31}-C_{31}-C_{32}$ are 171.9 and 175.4° pointing to a trans orientation of the methyl groups relative to the C_4-O_{41} and C_3-O_{31} bonds.

EXPERIMENTAL

PMR spectra were taken on Bruker WM-250 (250 MHz) and WM-400 (400 MHz) instruments using $CDCl_3$ solvent and TMS internal standard. IR Spectra were recorded on a UR-20 instrument for KBr tablets. Mass spectra were obtained on

an LKB-2091 instrument with direct introduction of the sample into the ionization source and an electron ionization energy of 70 eV. Monitoring of the course of the reaction and the purity of the compounds obtained was carried out using TLC on Silufol-254 plates with ether (compounds III and IV), benzene-acetone (3:5, compound IV), or ether-alcohol (1:1, compound V) with iodine vapor visualization.

Elemental analytical data for C, H, and N agreed with those calculated for all compounds.

X-Ray Analysis of III and VI. Crystals of lactamdiol III were grown from diethyl ether. $C_{12}H_{15}NO_3$, M = 221.25. Rhombic, d_{calc} = 1.296 g/cm^3. Crystals of ester VI. $C_{16}H_{19}NO_5$, M = 305.32. Monoclinic, d_{calc} = 1.281 g/cm^3. Unit cell parameters and intensities of 2702 reflections (compound III) or 3261 reflections (diester VI) were measured on a Siemens P3/PC7 four circle automatic diffractometer. The structure was solved by a direct method and refined in a full matrix, least squares method in the anisotropic approximation for nonhydrogen atoms. Hydroxyl group hydrogen atoms were localized directly by Fourier difference synthesis and refined in the isotropic approximation.

3,4-Dihydroxy-1-methyl-4-phenyl-2-oxopiperidine (III). Potassium permanganate (2 g, 11.6 mmole) was added with stirring over 45 min to a solution of compound I [2] (1 g, 5.8 mmole) in a mixture of acetonitrile (30 ml) and water (5 ml) cooled to 0°C. The mixture was held at 20-30°C for 1.5 h and the precipitate of manganese dioxide formed was filtered off and washed with hot acetonitrile. The filtrates were combined, the solvent distilled off, and the residue extracted with chloroform. The extract was purified on a silica gel column (eluent hexane–ether, 1:9) to give diol III (0.96 g, 76%) as colorless crystals with mp 117°C (from ether) and R_f 0.17. IR spectrum: 3400, 3320, 1610 (br), 1655 (sh), 1645 (sh) cm^{-1}. PMR spectrum: 2.97 (3H, br.s, Me), 4.44 (1H, m, J_{36a} = 0.73 Hz, 3-H), 3.3 and 4.4 (two br.s, each 1H, 3-OH and 4-OH), 2.0 and 2.2 (2H, two ddd in first order approximation, J_{5a5e} = 14.6, J_{5a6a} = 11.4, J_{5a6e} = 6.1, J_{5e6a} = 5.5, J_{5e6e} = 1.9 Hz, 5-H_e, 5-H_a), 3.22 and 3.65 (2H, two ddd, J_{6a6e} = 11.96 Hz, 6-H_e, 6-H_a), 7.25-7.5 ppm (Ph). ^{13}C NMR spectrum: 33.7 (C_5), 34.5 (Me), 46.2 (C_6), 72.1 (C_3), 73.2 (C_4), 124.7-144 (Ph), 171 ppm (C=O). Mass spectrum, m/z (I, %): M^+ 221 (100), 169 (17), 149 (18), $[M\text{-}Ph]^{+\cdot}$, 144 (31), 115 (30), $[PhCO]^{+\cdot}$, 105 (69). Found, %: C 65.1, H 6.7, N 6.3. $C_{12}H_{15}NO_3$. Calculated, %: C 65.2, H 6.8, N 6.3. M 221.

3,4-Dihydroxy-1-ethyl-4-phenyl-2-oxopiperidine (IV) was obtained similarly from N-ethylpiperidine II (0.9 g, 4.8 mmole) to give lactamdiol IV (0.5 g, 60%) as a viscous oil with R_f 0.58. IR spectrum: 3450, 3340, 1670 br, cm^{-1}. PMR spectrum: 1.0 (4H, two br, Me + OH), 1.8 (1H, br, OH), 2.9-3.55 (6H, m, $CH_2NCH_2CH_2$), 7.0-8.0 ppm (6H, two m, Ph, 3-H). ^{13}C NMR spectrum: 14.2 (Me), 36.0-42 (3 CH_2), 76-77 (C_4, C_3), 127.3-135 (Ph), 162 ppm (C=O). Mass spectrum: 217 (2) $[M\text{-}H_2O]^{+\cdot}$, 205 (34), $[M\text{-}H\text{-}Et]^{+\cdot}$, Φ_1, 188 (7), $[\Phi_1\text{-}OH]^{+\cdot}$, 187 (6), 105 (100), $[PhCO]^{+\cdot}$, 100 (65), 77 (90). Found, %: C 66.3, H 7.0, N 5.9. $C_{13}H_{17}NO_3$. Calculated, %: C 66.4, H 7.2, N 6.0. M 235.

3-Acetoxy-4-hydroxy-1-methyl-2-oxo-4-phenylpiperidine (V). Acetic anhydride (3.7 g, 36 mmole) was added to a solution of lactamdiol III (2.03 g, 10 mmole) in dry pyridine (4.5 ml) cooled to 20°C. The mixture was held at 20°C for 48 h and poured onto ice (20 g), extracted with chloroform, and the extract dried (magnesium sulfate) to give the monoester V (1.83 g, 76%) as colorless crystals with mp 138-140°C (from ether) and R_f 0.69. IR spectrum: 3380, 1720, 1640 cm^{-1}. PMR spectrum (mixture of two isomers): 2.0 and 2.03 (3H, two s, C-Me), 2.0 (1H, br, OH), 2.1 (1H, m, 5-H_e), 2.75 (1H, m, 5-H_a), 2.96 and 2.98 (3H, two s, N-Me), 3.3 (2H, 6-H_e, OH), 3.65 (1H, m, 6-H_a), 5.27 and 5.85 (1H, two br.s, integrated ratios 3:4, 3-H), 7.2-7.5 ppm (5H, m, Ph). ^{13}C NMR spectrum: (chemical shifts given for the minor and major isomers respectively): 20.5 and 21.7 (C-Me), 28.0 and 35.1 (C_5), 34.5 (N-Me), 45.4 and 49.9 (C_6), 72.9 and 74.2 (C_3), 74.5 and 81.7 (C_4), 124.6-128.7 (Ph), 138.4 and 143.3 ($C_{quat,\ arom}$), 165.2 and 166.5 (O–C=O), 169.6 and 169.9 ppm (N–C=O). Mass spectrum, %: M^+ 263 (87), $[M\text{-}CH_2CO]_+$, 221 (53), $[M\text{-}MeCO]^+$ 220 (29), $[M\text{-}CH_2CO\text{-}H_2O]^{+\cdot}$, 203 (25), $[M\text{-}Ph]^{+\cdot}$, 186 (9), 133 (82), 101 (100), 88 (28), 76 (25). Found, %: C 64.0, H 6.2, N 5.4. $C_{14}H_{17}NO_4$. Calculated, %: C 63.9, H 6.5, N 5.3. M 263.

3,4-Diacetoxy-1-methyl-2-oxo-4-phenylpiperidine (VI). Acetyl chloride (0.17 g, 2.2 mmole), and acetic anhydride (0.45 g, 4.4 mmole) were added to a solution of lactamdiol III (0.5 g, 2.2 mmole) in dry benzene (20 ml) and the mixture was reflexed for 4 h. The solvent was evaporated under vacuum and the residue crystallized from ether to give the diester VI (0.55 g, 85%) as colorless crystals of mp 165-167°C and R_f 0.34. IR spectrum: 1660 cm^{-1}. PMR Spectrum: 2.06 and 2.16 (6H, two s, C-Me), 3.03 (3H, s, N-Me), 2.75 (1H, m, 5-H_e), 3.32 (3H, m, 5-H_a, 6-CH_2), 5.32 (1H, s, 3-H), 7.27-7.38 (5H, m, Ph). Found, %: C 62.8, H 6.2, N 4.6. $C_{16}H_{19}NO_5$. Calculated, %: C 63.0, H 6.4, N 5.0. M 305.

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