Chemistry of Heterocyclic Compounds, Vol. 36, No. 12, 2000

OXIDATIVE REACTIONS OF AZINES. 6*. LACTAMIZATION OF 4-ARYL- AND 4-PHENETHENYL-SUBSTITUTED 1,2,3,6-TETRAHYDROPYRIDINES AND DIHYDROXYLATION OF 4-ARYL-1,2,5,6-TETRAHYDROPYRID-2-ONES USING POTASSIUM PERMANGANATE

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Oxidation of 4-phenyl-, 4-(4-pyridyl)-, and 4-phenethenyl-1,2,3,6-tetrahydropyridines with potassium permanganate can stop at the stage of the introduction of an oxo group into the allyl $C_{(2)}$ position of the piperideine fragment. In contrast to their precursors, 4-aryltetrahydropyridin-2-ones obtained in this way can be converted to 3,4-dihydroxy-2-oxopiperidines under Wagner reaction conditions.

Keywords: tetrahydropyridines, tetrahydropyridin-2-ones, dihydroxylation, lactamization, potassium permanganate oxidation.

The presence of a bulky paracyclophane substituent at $C_{(4)}$ of 3-piperideine provides an efficient steric hindrance to the oxidation of the heterocycle to the corresponding diol lactam [2]. The reaction stops under ketodihydroxylation conditions [3] at the stage of the unsaturated lactam. On the one hand this experimental observation indirectly confirms the proposed sequence of one-pot polyfunctionalization of 4-arylpiperideines [3, 4] but on the other hand it stimulates a search for oxidative conditions which might serve as a general method for the introduction of an oxo group at position 2 of 3-piperideines, i.e. their lactamization.

In this work we used 4-phenyl-, 4-(γ-pyridyl), and 4-(2-phenethenyl)-1,2,3,6-tetrahydropyridines **1-3** and **7, 8** respectively as substrates for this oxidative lactamization. Their oxidation to the unsaturated lactams was carried out using potassium permanganate in acetonitrile over 0.5-1 h, i.e. for a shorter interval of time than in the case of the one-pot synthesis of lactam diols (2 h) [1, 3, 4]. The reaction mixture from the oxidation of the indicated compounds was separated using column chromatography on silica gel to give a 42-70% yield of tetrahydropyridin-2-ones **4-6, 9, 10** (Scheme 1) (the synthesis of lactam **4** was reported in [5]).

The IR spectra of these unsaturated lactams contain strong absorption peaks at 1640-1657 cm^{-1} which are assigned to the amide carbonyl conjugated to the double bond. In their ^{13}C NMR spectra they show signals for the amide group carbon at 164.1-165.5 ppm. Evidence that, of the two allyl positions, only the methylene group found in the allylamine fragment is regioselectively oxidized comes from their NMR spectra in which the 3-H vinyl

* For Communication 5 see [1].

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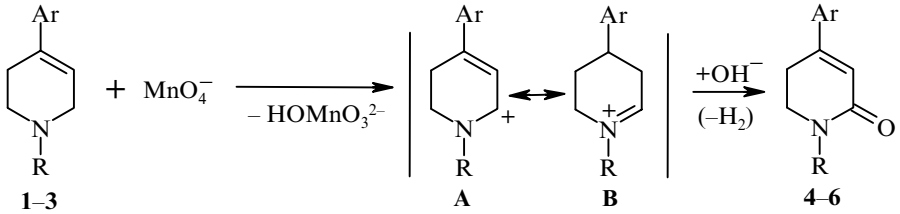
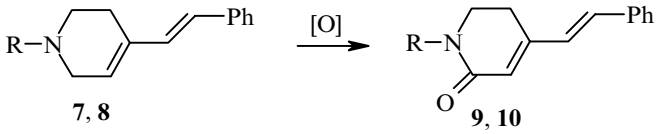
 0009-3122/00/3612-1426$25.00

Scheme 1



1, 4 R = Me, Ar = Ph; **2, 5** R = Me, Ar = 4-Py; **3, 6** R = $CH_2C_6H_4Cl$-*p*, Ar = 4-Py



7, **9** R = Me; **8**, **10** R = CH_2Ph

proton signal of the tetrahydropyridine ring is observed as a singlet (in the starting compounds it resonates as a broadened triplet). This is also indicated by the shift in the methylene proton signals (compounds **4**, **5** and **9**) or the exomethylene group (compounds **6** and **10**) and also the 3-H proton signal to low field (by $\Delta\delta$ = 0.1-1.0 ppm).

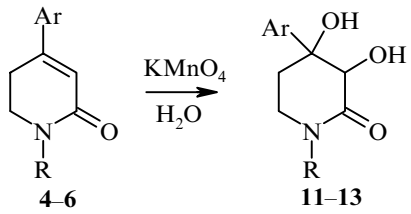
The key step in the formation of lactams is evidently the removal of a hydride ion from one of the allyl methylene groups by a permanganate anion. A similar mechanism is thought to be most likely in the oxidation of toluene by potassium permanganate in the presence of water [6]. The tertiary amino group of the tetrahydropyridine ring, as an internal nucleophile, stabilises the adjacent carbocation (A) in the iminium ion form (B). Similar intermediates dictate the regioselectivity of the intermolecular attack by the OH^- nucleophile from solution at position 6 of the starting tetrahydropyridine.

Dienes **7-10** are single compounds (as indicated by the presence in their ^{1}H NMR spectra of three vinyl proton signals with an integrated intensity of one proton in each unit) and so it was of interest to examine the type of isomer formed. For determination of the configuration of the diene fragment we have carried out calculations of their ^{1}H NMR spectra and an investigation of the nuclear Overhauser effect (NOE) in compounds **8** and **10**. Comparison of the calculated and experimental chemical shifts has shown them to be in good agreement (see Experimental) and allowed us to assign the low field components in the AB system of the exocyclic olefinic group ($C_{(1')}$=$C_{(2')}$) to the 1'-H proton signal. However, the calculated values for the parameters in the model spectra for the s-*cis* and s-*trans* isomers are just the same and this does not allow a choice between them. Investigation of the NOE permitted an unambiguous assignment of the configuration of the indicated diene fragment in both compounds. Upon saturation of the 3-H proton signal there is observed a response at the 1'-H proton and when irradiating the 5-CH_2 proton signal it is seen at the 2'-H proton. These experimental data in combination with that calculated for geometry and steric energy (derived by the molecular mechanics method) indicate that the starting diene **8** has the s-*trans* configuration and that this is retained upon its oxidative conversion to amide **10**. The generally good yield of lactams points to the fact that oxidation by potassium permanganate under mild conditions is a convenient method for the lactamization of tetrahydropyridines and similar azines.

With the aim of a direct confirmation of the hypothesis concerning the course of the ketodihydroxylation of 4-arylpiperid-3-eines *via* the intermediate 2-oxopiperideine [3] we have carried out the oxidation of lactams **4-6** using aqueous $KMnO_4$ in acetonitrile both in the cold (0-5°C, using the Wagner method conditions) and at 20-35°C (Scheme 2).

In the first case (0°C) lactam **4** gave a 54% yield of the diol lactam **11** (characterized previously [3]) and in the second (30°C) its yield was increased to 74%. Lactams **5, 6** were hydroxylated to the diol lactams **12, 13** at 0-30°C in 45 and 61% yield respectively (compound **12** had been obtained before [4]). The lactam diol **13** was prepared for the first time (see Experimental section). Hence the obtained experimental results confirm the proposal that piperidein-2-ones are intermediate products in the one-pot oxidation of 4-arylpiperide-3-ines to

Scheme 2



11 R = Me, Ar = Ph, **12** R = Me, Ar = 4-Py;
13 R = $CH_2C_6H_4Cl$-*p*, Ar = 4-Py

3,4-dihydroxypiperidin-2-ones at increased temperature. Since 4-arylpiperideines are not hydroxylated under Wagner method conditions [7], the ease of hydroxylation of piperideines **4-6** is evidently connected with the high degree of polarization of the endocyclic vinyl group due to the influence of the electron acceptor amide group. This still does not preclude the possibility of a decreased steric hindrance of the phenyl substitutent towards attack on the olefinic bond by permanganate anion (due to a decrease in its coplanarity with the piperideine ring).

EXPERIMENTAL

^{13}C and ^{1}H NMR spectra were recorded in the pulsed regime on Bruker AM-300 and AC-200 spectrometers for $CDCl_3$ solutions. The difference between the CH_3, CH and CH_2, and C_{quat} signals in the ^{13}C NMR spectra were obtained using the standard JMODXH program for editing the spectrum. Calculations of the NMR spectra were carried out using the ACDLABS program. IR spectra were obtained on a UR-20 instrument for KBr tablets and mass spectra on a MX-1303. Monitoring of the course of the reaction and the purity of the compound was carried out by TLC on Silufol UV-254 plates. Separation and purification of the substances was performed by column chromatography on L-60 grade (40/100) silica gel.

1-(4-Chlorobenzyl)-4-(4-pyridyl)-1,2,3,6-tetrahydropyridine (3). A solution of 1-(4-chlorobenzyl)-4-(4-pyridyl)pyridinium chloride (1 g, 3.16 mmol) in water (15 ml) was added to a suspension of sodium borohydride (0.18 g, 4.73 mmol) in a 10% aqueous solution of sodium carbonate (30 ml) at 0°C. The mixture was held at 0°C for 15 min, then for 2 h at 20°C, and then diluted with water (40 ml) and extracted with chloroform. The extract was dried with magnesium sulfate and the solvent was evaporated to give tetrahydropyridine **3** (0.62 g, 69%) as beige crystals; mp 64-66°C, R_f 0.7 (acetone–heptane, 5 : 4). IR spectrum: 1653 cm^{-1} (C=C). Mass spectrum: 284 (M^+). ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 2.5 (2H, br. s, 3-H); 2.70 (2H, t, *J* = 5.3, 2-H); 3.18 (2H, br. s, 6-H); 3.6 (2H, s, NCH_2Ar); 6.3 (1H, br. s, 5-H); 7.3 (4H, s, Ar); 7.25 and 8.5 (4H, AA'XX' type spectrum, Py). ^{13}C NMR spectrum: 27.2, 49.6, 53.1 and 61.8 (4 × CH_2); 119.3 and 149.9 (CH-pyridyl); 125.5 (3-CH); 128.5 and 130.4 (CH-phenyl); 132.9, 136.7, 144.3 and 147.6 (C_{quat}). Found, %: C 71.9; H 6.01; N 9.9. $C_{17}H_{17}ClN_2$. Calculated, %: C 71.7; H 5.98; N 9.84.

1-Methyl- (7) and 1-Benzyl-4-(2-phenethen-1-yl)-1,2,3,6-tetrahydropyridines (8). Sodium borohydride (0.34 g, 8.95 mmol) was added with stirring to a solution of 4-(2-phenethen-1-yl)pyridinium iodomethylate (2.6 g, 8 mmol) in ethanol (50 ml) which had been cooled to 0°C and the mixture was held for 12 h at room temperature. The solvent was evaporated in vacuo and the residue was extracted with chloroform. The extract was purified by column chromatography on silica gel (eluent hexane, then ether) to give piperideine **7** (0.7 g, 44%) as yellowish crystals; mp 84°C, R_f 0.7 (ether–alcohol, 1 : 1). IR spectrum: 1640 cm^{-1}. Mass spectrum: 199 (M^+). ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 2.45 (3H, s, Me); 2.5 (2H, m, 3-H); 2.7 (2H, t, *J* = 5.9, 2-H); 3.15 (2H, br. s, 6-H); 5.8 (1H, br. s, 5-H); 6.5 and 6.8 (2H, AB-system, *J* = 16.2, CH=CHPh); 7.2-7.45 (5H, m, Ph). Found, %: C 85.1; H 8.6; N 7.1. $C_{17}H_{17}N$. Calculated, %: C 84.82; H 8.54; N 7.03.

4-(2-phenethen-1-yl)pyridinium chlorobenzylate (2 g, 6.5 mmol) similarly gave tetrahydropyridine **8** (1.25 g, 70%) as a yellowish, viscous oil; R_f 0.4 (benzene). IR spectrum: 1640 cm^{-1}. Mass spectrum: 275 (M^+). ^1H NMR spectrum, δ, ppm, *J*, Hz (the calculated data given in round brackets is virtually the same for the s-*cis*- and s-*trans*- isomers): 2.43 (2.32) [2H, br. s (*J* = 5.1), 3-H]; 2.7 (2.64) [2H, t, *J* = 5.8 (^3J = 5.1), 2-H]; 3.18 (3.17) [2H, br. s, (*J* = 3.6), 6-H]; 3.64 (3.59) [2H, s, NCH$_2$Ph]; 5.82 (5.46) [1H, br. s (^3J = 3.6, $^4J_{5,1}$ = 0.3, $^5J_{5,2}$ = 0.8), 5-H]; 6.47 (6.67) and 6.80 (6.88) [each 1 H, AB system, *J* = 16.1 (16.1), CH=CHPh and CH=CHPh respectively]; 7.2-7.45 (7.19-7.37) [10H, m, Ph]. ^{13}C NMR spectrum: 25.6 (30.3) [3-CH_2]; 49.7 (53.7) [2-CH_2]; 53.4 (56.8) [6-CH_2]; 62.8 (59.9) [NCH$_2$Ph]; 126.0 (121.8) [CH=CHPh]; 126.3 (125.7) [5CH=]; 126.3, 127.1, 127.3, 128.3, 128.6 and 129.2 (127.1, 127.4, 128.5, 128.7, 128.9 and 129.1) [CH arom.]; 131.0 (130.1) [CH=CHPh]; 134.3, 137.8 and 138.4 (135.7, 137.4 and 139.3) [C_{quat}]. Found, %: C 87.42; H 7.80; N 5.10. $C_{20}H_{21}N$. Calculated, %: C 87.27; H 7.64; N 5.09.

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridin-2-one (4). Potassium permanganate (0.57 g, 3.64 mmol) was added at room temperature over 10 min to a solution of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine **1** (0.63 g, 3.64 mmol) in aqueous acetonitrile (15 ml). The reaction mixture was stirred for 30-50 min (at the end of the reaction pH was 10) and the precipitate of manganese dioxide was separated and washed with hot acetonitrile (3 × 20 ml). The filtrates were combined, the solvent was evaporated, and the residue was chromatographed on a column, eluting with hexane and then ether, to give piperidein-2-one **4** (0.44 g, 65%) as yellow crystals; mp 78-80°C, R_f 0.81 (ether). IR spectrum: 1600 (C=C), 1657 cm^{-1} (C=O). Mass spectrum: 187 (M^+). ^1H NMR spectrum, δ, ppm, *J*, Hz: 3.03 (3H, s, Me); 2.79 and 3.53 (each 2H, both t, *J* = 7.13 and 7.0, 5-CH_2 and 6-CH_2); 6.29 (1H, s, 3-H); 7.3-7.5 (5H, m, Ph). ^{13}C NMR spectrum: 26.3 and 47.4 (CH_2); 34.0 (Me); 119.7 (3-CH); 125.6, 128.6 and 129.3 (CH arom.); 137.5 and 148.9 (C_{quat}); 165.5 (C=O). Found, %: C 77.2; H 7.52; N 7.4. $C_{12}H_{13}NO$. Calculated, %: C 77.0; H 6.95; N 7.49.

1-Methyl-4-(4-pyridyl)-1,2,5,6-tetrahydropyridin-2-one (5). Obtained similarly to compound **4** from piperideine **2** (0.55 g, 2.9 mmol) and potassium permanganate (0.69 g, 4.4 mmol). Yield 0.17 g (27%); mp 84-85°C, R_f 0.18 (ether). IR spectrum: 1600 (C=C), 1650 cm^{-1} (NC=O). Mass spectrum: 188 (M^+). ^1H NMR spectrum, δ, ppm, *J*, Hz: 2.78 and 3.58 (each 2H, both t, *J* = 7.0, 5-CH_2 and 6-CH_2); 3.03 (3H, s, Me); 6.43 (1H, s, 3-H); 7.37 and 8.64 (each 2H, AA'BB' spectrum, ^2J = 5.0, ^3J = 1.5, Py). Found, %: C 69.86; H 6.83; N 14.82. $C_{11}H_{12}N_2O$. Calculated, %: C 70.21; H 6.38; N 14.89.

1-(4-Chlorobenzyl)-4-(4-pyridyl)-1,2,5,6-tetrahydropyridin-2-one (6). Obtained similarly to compound **4** from tetrahydropyridine **3** (1.38 g, 4.85 mmol) and potassium permanganate (0.76 g, 4.81 mmol). Tetrahydropyridone **6** (0.74 g, 54.5%) was separated as yellowish crystals; mp 74-76°C. IR spectrum: 1595 (C=C), 1642 cm^{-1} (NC=O). Mass spectrum: 298.5 (M^+). ^1H NMR spectrum, δ, ppm, *J*, Hz: 2.66 and 3.40 (each 2H, both t, *J* = 7.1, 5-CH_2 and 6-CH_2); 4.54 (2H, s, N-CH$_2$Ar); 6.39 (1H, s, 3-H); 7.1-7.25 (4H, m, ArH); 7.28 and 8.53 (each 2H, AA'XX' type spectrum, ^2J = 4.6, ^3J = 1.8, Py). ^{13}C NMR spectrum: 25.6, 44.3, 48.9 (3 × CH_2); 119.8 (3-C); 122.3, 128.2-130.2 and 150.1 (CH Ar and Py); 132.2, 135.5, 144.6 and 146.7 (4 × C_{quat}); 164.1 (C=O). Found, %: N 9.11. $C_{17}H_{15}ClN_2O$. Calculated, %: N 9.38.

1-Methyl-4-(2-phenethen-1-yl)-1,2,5,6-tetrahydropyridin-2-one (9). Potassium permanganate (0.63 g, 4 mmol) was added with stirring to a solution of tetrahydropyridine **7** (0.7 g, 3.5 mmol) in acetonitrile (30 ml) cooled to 0°C at such a rate that the temperature did not exceed +5°C. The mixture was then held for 40 min at room temperature. After work up of the reaction mixture (similarly to that described above) tetrahydropyridone **9** (0.37 g, 49%) was obtained as a yellowish, viscous oil; R_f 0.24 (acetone–alcohol, 2 : 1). IR spectrum: 1650, 1640, 1608 cm^{-1}. Mass spectrum, *m/z*, (I_{rel}, %): 213 (M^+, 70), 212 (10), 103 (50), 77 (100). ^1H NMR spectrum, δ, ppm, *J*, Hz: 2.65 and 3.50 (each 2H, both t, *J* = 7.1, 5-CH_2 and 6-CH_2); 3.0 (3H, s, Me); 5.95 (1H, s, 3-H); 6.8 (2H, br. s, –CH=CHPh); 7.2-7.6 (5H, m, Ph). Found, %: C 78.83; H 7.14; N 6.52. $C_{14}H_{15}NO$. Calculated, %: C 78.87; H 7.04; N 6.57.

Tetrahydropyridine **8** (1.0 g, 3.64 mmol) similarly gave 1-benzyl-4-(phenethen-1-yl)-1,2,5,6-tetrahydropyridin-2-one **10** (0.74 g, 70%) as yellow crystals; mp 101-103°C, R_f 0.44 (benzene). IR spectrum: 1650, 1640, 1600 cm^{-1}. Mass spectrum, *m/z* (I_{rel}, %): 289 (M^+, 70), 275 (100). ^1H NMR spectrum, δ, ppm, *J*, Hz: 2.6 and 3.4 (each 2H, both t, *J* = 7.0, 5-CH_2 and 6-CH_2); 4.7 (2H, s, NCH$_2$Ph); 6.07 (1H, s, 3-H); 6.80 and 6.88 (each 1H,

AB system, J = 16, CH=CHPh); 7.2-7.5 (10H, m, 2 × Ph). ^{13}C NMR spectrum: 24.0, 44.4, 49,6 (3 × CH_2); 122.8-133.6 (CH=CH)); 136.1, 137.5, 147.5 (3 × C_{quat}); 165.6 (C=O). found, %: C 83.0; H 6.62; N 4.92. $C_{20}H_{19}NO$. Calculated, %: C 83.04; H 6.57; N 4.84.

Hydroxylation of Tetrahydropyridin-2-ones (4-6). A. Potassium permanganate (0.42 g, 2.7 mmol) was added with stirring to a solution of tetrahydropyridinone **4** (0.35 g, 1.87 mmol) in a mixture of water (10 ml) and acetonitrile (15 ml) which had been cooled to 0°C at such a rate that the temperature of the reaction mass did not exceed 1°C and then stirred for 1 h. The residue of manganese dioxide was separated and washed with hot acetonitrile (5 × 5 ml). The filtrates were combined, the solvent removed in vacuo, and the product crystallized from ether to give 3,4-dihydroxy-1-methyl-2-oxo-4-phenylpiperidine **11** (0.22 g, 54%) as colorless crystals which were identical in melting point (117°C) and NMR spectrum to a known sample [3].

B. The oxidation was carried out similarly but at +30°C over 2 h. Tetrahydropyridinone **4** (1.87 mmol) gave lactam diol **11** (0.34 g, 76%).

C. Dihydroxylation of tetrahydropyridinone **5** (0.15 g, 0.8 mmol) was carried out by the addition of potassium permanganate (0.19 g, 1.2 mmol) at 0°C over 15 min and the reaction mixture was then stirred for 2 h at room temperature. After a similar work up, the reaction mixture gave 3,4-dihydroxy-1-methyl-2-oxo-4-(4-pyridyl)piperidine **12** (0.08 g, 45%) which was identical in melting point (220-222°C), R_f (0.19, acetone) and NMR spectrum to a known sample [4].

According to method B, 1-(*p*-chlorobenzyl)tetrahydropyridinone **6** (0.6 g, 2 mmol) gave 1-(*p*-chlorobenzyl)-3,4-dihydroxy-2-oxo-4-(4-pyridyl)piperidine **13** (0.41 g, 61%) as a colorless powder; mp > 200°C (decomp.). IR spectrum: 3410 and 3250 (OH), 1630 cm^{-1}(C=O). Mass spectrum: 332 (M^+). ^{1}H NMR spectrum, δ, ppm, J, Hz: 2.95 and 4.55 (each 1H, br. signals, 2 × OH); 3.08 and 3.25 (each 1H, both m, 5-CH_2); 3.62 (2H, m, 6-CH_2); 4.5 (2H, s, N–CH_2Ar); 4.53 (1H, s, 3-H); 7.2-7.4 (4H, m, Ar); 7.55 and 8.8 (each 2H, AA'BB' type spectrum, Py). Found, %: C 61.5; H 5.32; N 8.6. $C_{17}H_{17}ClN_2O_3$. Calculated, %: C 61.35; H 5.11; N 8.45.

This work was carried out with the financial support of the Russian fund for basic research (grant No. 99-03-32940a).

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