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OXIDATIVE REACTIONS OF AZINES. 9.* CASCADE AND STAGE OXIDATION OF 1,4-DISUBSTITUTED 1,2,3,6-TETRA-HYDROPYRIDINES BY POTASSIUM PERMANGANATE

A. T. Soldatenkov, A. V. Temesgen, and I. A. Bekro

A general scheme was developed for the cascade and stage oxidation of 1,4-disubstituted 1,2,3,6-tetrahydropyridines by potassium permanganate, based on the successive oxidation of the allylic triad of carbon atoms in the piperideine ring. In the case of 4-aryltetrahydropyridines 2-oxotetrahydropyridines are formed initially. 3,4-Dihydroxypiperidin-2-ones and finally 1-aminoalkan-3-ones are then formed. The oxidation of 4-methyl-substituted tetrahydropyridines to the analogous 1-aminoalkanones begins differently – with 3,4-dihydroxylation followed by lactamization of the piperidinediols.

Keywords: 1-aminoalkan-3-one, 1,2,3,6-tetrahydropyridines, oxidative reactions.

Systematic study of the transformations of 1,2,3,6-tetrahydropyridines under the influence of potassium permanganate shows that their reactivity and degree of oxidation depend to a significant degree on the structure of the substrate and the reaction conditions [1-10]. Thus, N-substituted 4-methyltetrahydropyridines are successfully dihydroxylated under the conditions of the classical Wagner reaction (cooling, alcohol), whereas 4-phenyltetrahydropyridines of type **1** are inert substrates [2]. However, the reactivity of the latter is greatly increased, it would appear, by a slight modification of the Wagner method, i.e., by oxidation without cooling (at room temperature) in acetonitrile, which led to the introduction of three functional groups into the piperidine ring at once [3]. The discovery of this oxodihydroxylation of 3-piperideines made it possible to develop a one-pot preparative method for the synthesis (path c) of a new important group of compounds, i.e., 4-aryl-substituted 3,4-dihydroxypiperidin-2-ones **3** [3-5]. More recently it was shown experimentally that such lactamdiols are formed in steps (by paths a and b) through the intermediate unsaturated lactams **2**, which can be isolated (with reduction of the time for oxidation of the initial tetrahydropyridines **1** [6-8]), and are then dihydroxylated smoothly in separate experiments both by the Wagner method and under the modified conditions [8, 9]. The cascade oxidation of 4-aryltetrahydropyridines **1** (path d) to 1-(formylamino)alkan-3-ones **4** was also realized [1, 6, 9].

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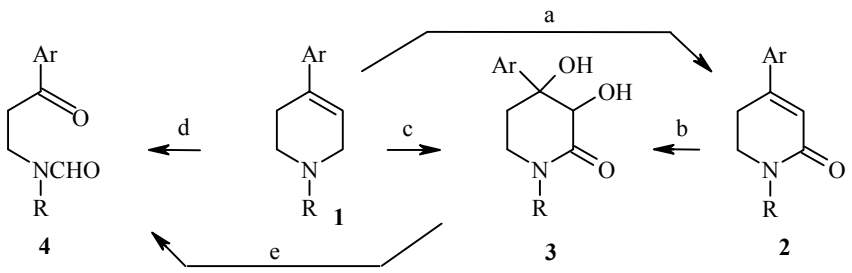
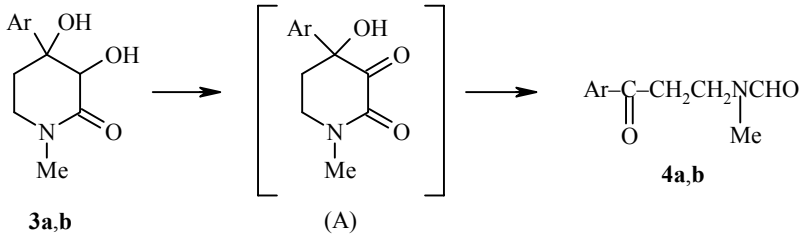


Ar = Ph, C_6H_4Me-*p*, C_6H_4OMe-*p*, 4-Py; R = Me, Et, Bn, $CH_2C_6H_4Cl$-*p*

The present work describes a further study of the transformations of 1,2,3,6-tetrahydropyridines under the influence of potassium permanganate with the aim of developing a general scheme for their cascade and stage oxidation. First of all the problem of experimental investigation of a possible third step in the studied reaction sequence – the oxidative decyclization of the lactamdiols **3** (path e) – was resolved. For this purpose the dihydroxy-substituted 4-phenyl- and 4-pyridylpiperidones **3a** and **3b** were oxidized by potassium permanganate with moderate heating of their acetonitrile solutions. Here the corresponding amides were isolated from the reaction mixture by chromatography with yields of 34-58%, and their spectral characteristics were identical with those of authentic samples of the amides **4a**,**b** obtained earlier by the cascade method [1, 6].

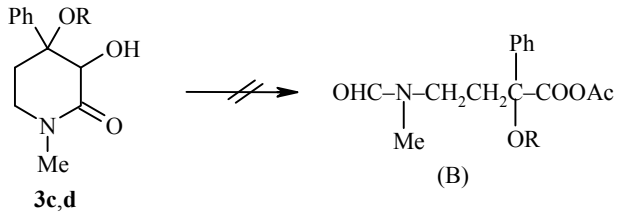


3a, **4a** Ar = Ph; **3b**, **4b** Ar = 4-Py

It was logical to suppose that the decyclization stages must be preceded by the formation of 2,3-dioxopiperidols of type (A), which could then be cleaved at the $C_{(2)}$–$C_{(3)}$ or $C_{(3)}$–$C_{(4)}$ bonds followed by the elimination of one carbon atom. However, we were unable to isolate such diketones A during either cascade or stepwise oxidation of the substrates. This was probably due to their low stability and their rapid transformation to the noncyclic amido ketones **4** stable under the reaction conditions.

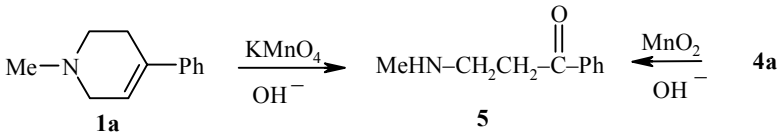
It seemed that the oxidative decyclization of the monoester **3c** and the diester **3d** (obtained earlier by ourselves [3]) would give the possibility of establishing the preferred point of cleavage of the heterocycle and, moreover, of synthesizing derivatives of the natural neuromediator 4-aminobutyric acid (a compound of type B). However, the oxidation of the monoester **3c** (acetone, 20-50°C, 2-3 h; or boiling in acetonitrile, 5 h) did not lead to its decyclization – it was recovered unreacted (yield 67-90%). In the case of the diester **3d** more prolonged heating (boiling in acetonitrile, acetone, or ethanol for 15 h) also did not make it possible to obtain the noncyclic amide. Nevertheless, here it gave 55-75% yields of a substance which, although it had ^{1}H NMR and mass spectra identical with the spectra of the initial substance, differed greatly in its melting point (190-192°C) from the initial *cis*-diester (mp 165-167°C), the structure of which had previously been established unequivocally by

X-ray crystallographic analysis [3]. The repeated production of this high-melting substance using various solvents during oxidation rules out the formation of the polymorphous structure of the diester **3d**. The authors suppose that during oxidation of the *cis*-diester **3d** inversion of the stereochemistry occurs at one of the two asymmetric centers on account of oxidative decyclization–recyclization with the formation of the *trans*-diester **3d**, which has a higher melting point.



3c,**d**

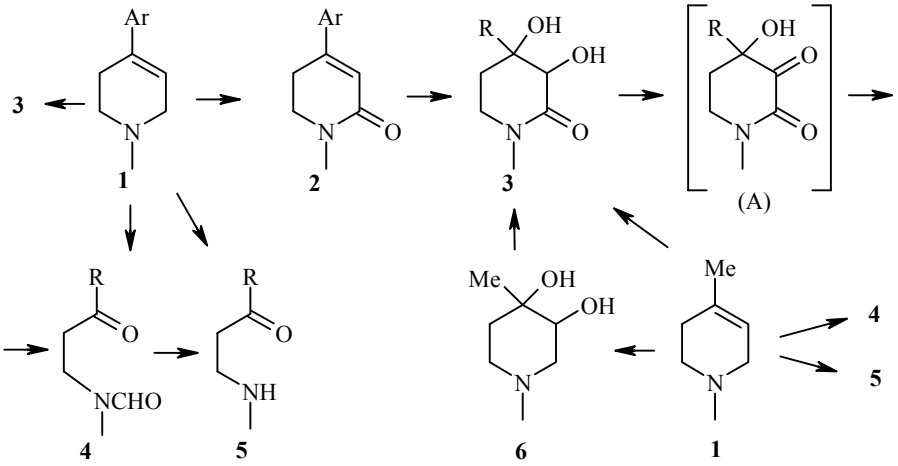
It is known that N-formyl-substituted tertiary amines can be transformed into secondary amines by eliminating a formyl group in the presence of manganese dioxide [11] or under the conditions of alkaline hydrolysis [12]. In connection with the fact that oxidation with potassium permanganate takes place with the release of manganese dioxide and an increase in the pH of the medium to alkaline values an attempt was made at the cascade oxidation of 4-phenylpiperideine **1a** to the secondary amine **5**. In fact, with more prolonged heating of the reaction mixture (to 8 h instead of the 2 h required in the synthesis of the amides **4**) after treatment it was possible to isolate the expected secondary amine **5** with a yield of 12-20%.



1a **5**

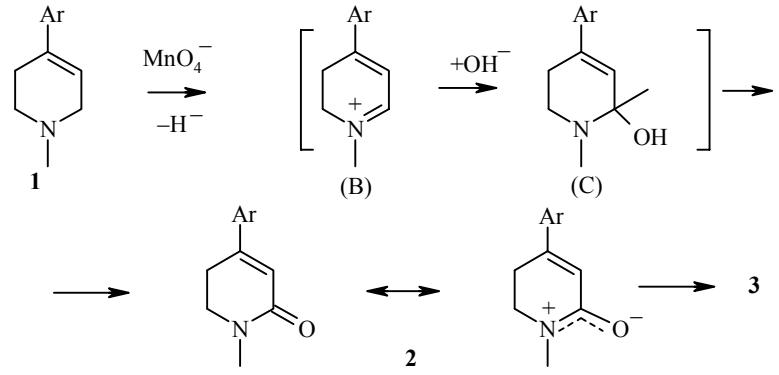
In the ^{1}H NMR spectrum of compound **5** there is no signal for the formyl proton, and splitting of the signals for the protons of the aliphatic groups, typical of the amides **4**, is not observed [1]. At the same time the signals for the protons of the N-methyl and N-methylene groups are shifted upfield by Δδ 0.4 and 1.0 ppm respectively compared with the analogous spectrum of the initial amide. In the IR spectrum of the amine **5** there are absorption bands for the ketone (at 1678 cm^{-1}) and NH (3345 and 3450 cm^{-1}) groups. Its mass spectrum contains a peak for the molecular ion M^+ with *m*/*z* 163 with low intensity and strong peaks for the fragment ions $[PhCO]^{+\cdot}$ and $[CHNHMe]^{+\cdot}$, which also confirm the structure of the secondary amine **5**. The direct formylation of the amide **4a** was also realized. This step in the series of oxidative reactions was realized by keeping a water–alcohol solution of the amide **4a** in the presence of alkali and manganese dioxide (8 h at 20°C). The secondary amine **5** was isolated here with a yield of 60.6%.

In order to establish the generality and the differences in the sequence of transformations of 4-substituted tetrahydropyridines in the presence of potassium permanganate the 4-methyltetrahydropyridines **1e**,**f** were also oxidized. During the oxidation of N-benzyltetrahydropyridine **1f** in the cold (1 h by the Wagner method [2]) the dihydroxylation product 1-benzyl-4-methylpiperidine-3,4-diol (**6**) was isolated with a 29% yield. The N-ethyltetrahydropyridine **1e** was subjected to the brief action of an oxidizing agent at room temperature (0.5 h), and this made it possible to realize its oxodihydroxylation, i.e., to synthesize 2-ethyl-3,4-dihydroxy-4-methylpiperidin-2-one (**3e**) (yield 40%). In both cases it was not possible to isolate unsaturated lactams of type **2** or intermediate diketols of type (A) from the reaction mixtures.



Thus, together the data obtained in the present work and published previously [1-9] make it possible to propose a general scheme of cascade and stage transformations of two groups of substrates – 4-aryl- and 4-alkyl-substituted tetrahydropyridines – in the presence of potassium permanganate. The general principle of the scheme involves a gradual increase in the degree of oxidation of the triad of carbon atoms contained in the allylamine fragment of the hydropyridine ring. Both groups of substrates are oxidized to the lactamdiols **3**, which then undergo decyclization (probably through the intermediate diketols A) with the elimination of one or two carbon atoms. At the same time a substantial difference was established in the sequence of the first two stages of their transformations, due to the nature of the substituents at $C_{(4)}$ in the initial compounds. Thus, the oxidative cascade of reactions of 4-methyltetrahydropyridine begins with a normal (for the Wagner reaction) electrophilic addition of the permanganate ion to the double bond of the heterocycle, which is favored by the electron-donating methyl substituent. In the presence of an additional equivalent of the oxidant and with increase in the temperature to room temperature (modified conditions) the 1,2-diol of type **6** formed at the first stage is readily transformed by brief treatment into the lactamdiol **3** and then (with more prolonged oxidation) into the decyclization products **4**, **5**.

Dihydroxylation does not occur under the conditions of the Wagner reaction in the case of 4-aryltetrahydropyridines, and this is probably explained by the decrease in the electron density at the double bond of piperideine on account of π-conjugation with the aromatic ring. With modification of the Wagner method (with increase in temperature) the position of initial attack on the substrate **1** by permanganate ion changes completely, and in this case it begins with the removal of a hydride ion from the methylene group of the allylamine fragment. The hydroxide ion adds nucleophilically to the obtained carbocation, which is stabilized in the form of the iminium cation (B), leading to the unstable vicinal aminols (C), which are quickly oxidized to the unsaturated lactams **2**.



The participation of the two electronegative heteroatoms of the amide function in the lengthened chain of π-conjugation proved so effective that the reactivity of the aryl-substituted lactams **2** to electrophilic dihydroxylation becomes comparable with that of 4-alkyltetrahydropyridines.

The developed scheme for the oxidation of tetrahydropyridines may prove useful in the refinement of the mechanisms of oxidation of various groups of heterocyclic compounds. It is also capable of providing an effective laboratory method for the synthesis of several important types of compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250 MHz) with TMS as standard in $CDCl_3$. The IR spectra were recorded in KBr tablets on a UR-20 instrument. The mass spectra were obtained on an MX-1303 instrument with direct injection of the sample into the ion source (70 eV electrons). The reaction and the individuality of the products were monitored by TLC on Silufol UV-254 plates. Separation and purification were realized by column chromatography on silica gel L-60 (40/100).

Oxidation of Lactamdiols 3a,b to 3-Aryl-1-(N-formylamino)-3-propanones 4a,b. To a solution of the phenyl-substituted lactamdiol **3a** (0.74 g, 3 mmol) in acetone (30 ml) over 15 min at room temperature we added potassium permanganate (0.71 g, 4.5 mmol). The mixture was stirred for 1 h and was then heated at 50°C for 30 min. The precipitated manganese dioxide was separated and washed with acetone (60 ml). The combined filtrates were evaporated under vacuum, and the residue was separated on a chromatographic column. We obtained 0.22 g (34%) of the amide **4a**, the ^{1}H NMR spectrum of which was identical with the spectrum of the amide obtained previously by the cascade oxidation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1a**) [1, 6]. Similarly, by oxidation of a solution of the diol **3b** (0.1 g, 0.45 mmol) in acetonitrile (50 ml) 50 mg (58%) of a substance was obtained the spectral characteristics of which were identical with those of the amide **4b** obtained previously by the cascade oxidation of 1-methyl-4-(4-pyridyl)-1,2,3,6-tetrahydropyridine (**1b**) [1].

An Attempt at the Oxidative Cleavage of 3-Acetoxy-4-hydroxy-1-methyl-4-phenyl-2-piperidone (3c). A. Potassium permanganate (0.22 g, 1.4 mmol) was added to a solution of the monoester **3c** (0.3 g, 1.14 mmol) in a mixture of acetone (30 ml) and acetic acid (1 ml). The mixture was kept at room temperature for 2 h. After analogous treatment of the reaction mixture (see above) 0.21 g (72%) of a substance identical with the initial ester **3c** in its ^{1}H NMR spectrum and melting point (136-137°C) was isolated by chromatography [3].

B. A similar mixture of the initial reagents was heated at 50°C for 3 h. After treatment the initial unreacted monoester **3c** was isolated with a 67% yield.

C. To a solution of the monoester **3c** (0.2 g, 0.76 mmol) in acetonitrile (50 ml) at 70°C we added potassium permanganate (0.18 g, 1.14 mmol). The mixture was boiled for 5 h, and after analogous treatment 0.18 g (90%) of the initial substance **3c** was obtained.

Oxidation of 3,3-(*cis*-Diacetoxy)-1-methyl-4-phenyl-2-piperidone (3d). A. To a solution of the *cis*-diester **3d** (0.5 g, 1.6 mmol) in acetonitrile (30 ml) over 15 min we added potassium permanganate (0.4 g, 2.4 mmol). The mixture was kept at room temperature for 3 h. After the analogous treatment (see above) of the reaction mixture 0.42 g (84%) of a substance was obtained; the chromatographic mobility R_f 0.72 (acetone), melting point (165-167°C), and ^{1}H NMR spectrum of which were identical with those of the initial diester **3d** [3].

B. To a solution of the *cis*-diester **3d** (0.3 g, 0.98 mmol) in acetone (30 ml) we added potassium permanganate (0.23 g, 1.47 mmol). The mixture was kept at room temperature for 2 h and then at 50°C for 1.5 h. After treatment we isolated 0.22 g (73%) of the initial *cis*-diester.

C. A mixture of the *cis*-diester **3d** (0.4 g, 1.3 mmol) with potassium permanganate (0.2 g, 1.3 mmol) in acetone (50 ml) was boiled for 3 h. After the usual treatment we obtained 0.32 g (70%) of a colorless crystalline substance (probably the *trans*-diester **3d**), having a ^{1}H NMR spectrum, mass spectrum, and chromatographic mobility identical with those of the initial *cis*-diester. However, its melting point (190-192°C) was 25°C higher than that of the *cis*-diester **3d**.

D. A mixture of the *cis*-diester **3d** (0.2 g, 0.65 mmol) with potassium permanganate (0.15 g, 0.98 mmol) in acetonitrile (50 ml) was boiled for 12 h and was then kept at room temperature for 12 h. After the usual treatment we isolated 0.11 g (55%) of a compound melting at 190-192°C and identical with the compound obtained by method C.

E. A mixture of the *cis*-diester **3d** (0.12 g, 0.39 mmol) with potassium permanganate (0.13 g, 0.78 mmol) in ethanol (50 ml) was boiled for 15 h and was then kept at room temperature for 48 h. We obtained 0.09 g (75%) of a compound melting at 190-192°C and identical with the compound obtained in experiments C and D.

1-N-Methylamino-3-phenyl-3-propanone (5). A. To a solution of 4-phenyltetrahydropyridine **1a** (1 g, 5.8 mmol) in aqueous acetonitrile (15 ml) over 15 min we added potassium permanganate (1.8 g, 11.6 mmol). The mixture was stirred at 50-60°C for 8 h. The manganese dioxide was filtered off and washed with acetonitrile (30 ml). The combined extracts were evaporated under vacuum, and the residue was separated by chromatography. Yield 0.11 g (12%) of the secondary amine **5** in the form of a yellow oil (darkening with time); R_f 0.5 (acetone). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.15 (1H, br. s, NH); 2.20 (2H, t, *J* = 11.5, 2-H); 2.40 (3H, s, Me); 3.83 (2H, t, *J* = 11.5, 1-H); 7.45-7.6 (3H, m, Ph); 7.79 (2H, d, *J* = 7.4, Ph). IR spectrum, ν, cm^{-1}: 3450, 3345 (NH), 2805 (NMe), 1678 (PhC=O). Mass spectrum, *m/z* (%):163 (3) [M^+], 131 (8), 120 (30), 105 (100) [$PhCO]^{+\cdot}$, 77 (83), 58 (45) [$M–PhCO]^{+\cdot}$, 44 (42) [$CH_2NHMe]^{+\cdot}$, 43 (90). Found, %: N 8.37. $C_{10}H_{13}NO$. Calculated, %: N 8.59.

B. The experiment was carried out similarly by heating at 50-60°C for 2 h and then holding the mixture at room temperature for 24 h. Yield 0.18 g (20%) of the amine **5**.

C. To a solution of the noncyclic amide **4a** (0.78 g, 3.66 mmol) in ethanol (30 ml) we added manganese dioxide (0.2 g, 5.5 mmol) and a 10% aqueous solution of sodium hydroxide (2 ml). The mixture was stirred at room temperature for 8 h, the alcohol was distilled under vacuum, and the residue was extracted with chloroform (3×20 ml). From the extract after removal of the solvent we isolated by chromatography 0.4 g (60.6%) of an oily substance which was identical in its chromatographic mobility and spectral characteristics with the secondary amine **5**, obtained by the cascade oxidation of the tetrahydropyridine **1a** by methods A and B.

1-Benzyl-4-methyl-3,4-piperidinediol (1f). A solution of potassium permanganate (1 g, 6.4 mmol) and magnesium sulfate (0.77 g, 6.4 mmol) in water (100 ml) was added to a solution of 1-benzyl-4-methyltetrahydropyridine **1f** (1.2 g, 6.4 mmol) in ethanol (40 ml) at such a rate that the temperature of the mixture did not exceed 1°C. The mixture was stirred at this temperature for a further hour, and the manganese dioxide was then separated and washed with ethanol (30 ml). The extracts were evaporated, and the residue was extracted with hot chloroform (3×15 ml). The extract was purified on a column of silica gel, and 0.42 g (29%) of the diol **6** was obtained in the form of a thick oil; R_f 0.8 (4:8:1 hexane–chloroform–ethanol). ^{1}H NMR spectrum, δ, ppm: 1.82-2.2 (2H, m, 5-H); 2.0 and 2.1 (1.5H each, both s, Me); 2.3-2.65 (4H, m, 2- and 6-H); 2.73 (1H, m, 3-H); 2.8 and 3.9 (1H each, br. s, OH); 3.5 and 3.6 (1H each, both s, CH_2Ar); 7.2-7.5 (5H, m, Ph). Mass spectrum, *m/z* (%): 221 (10) [M^+], 204 (5), 203 (4), 130 (7), 112 (4), 91 (100). IR spectrum: broad band centered at 3330 cm^{-1}. Found, %: C 70.8; H 8.89; N 6.57. $C_{13}H_{19}NO_2$. Calculated, %: C 70.59; H 8.6; N 6.34.

1-Ethyl-4-methyl-3,4-piperidinediol-2-one (3e). An aqueous solution of potassium permanganate (1.9 g, 12 mmol) was added to a solution of 4-methyl-1-ethyltetrahydropyridine **1e** (1 g, 8 mmol) in acetone (40 ml) over 20 min at 10°C. The mixture was stirred at room temperature for 30 min, and the manganese dioxide was then separated and washed with acetone (40 ml). The filtrates were evaporated, and the residue was extracted with chloroform (3×20 ml). From the extract after chromatographic separation 0.55 g (40%) of the lactamdiol **3e** was obtained in the form of a thick colorless oil. IR spectrum, ν, cm^{-1}: 3350 (broad band); 1640 (NC=O). Mass spectrum, *m/z* (%): 173 (42) [$M]^+$; 156 (17) [$M–OH]^{+\cdot}$; 155 (15); 144 (35) [$M–Et]^{+\cdot}$; 126 (25) [$M–Et–H_2O]^{+\cdot}$; 114 (25); 102 (30) [$M–EtNCO]^{+\cdot}$; 100 (58); 86 (100); 72 (58); 71 (55) [$EtNCO]^{+\cdot}$. Found, %: C 55.12; H 9.03; N 7.81. $C_8H_{15}NO_3$. Calculated, %: C 55.49; H 8.67; N 8.09.

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