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OXIDIZING REACTIONS OF AZINES. 8*. ONE-REACTOR OXIDATION OF 4-ARYL AND 4-METHYL-1,2,3,6-TETRAHYDROPYRIDINES TO 1-FORMYLAMINO-SUBSTITUTED ALKAN-3-ONES

A. T. Soldatenkov, A. W. Temesgen, K. B. Polyanskii, I. A. Bekro, S. A. Soldatova, A. A. Pupov, and N. D. Sergeeva

One-reactor oxidation by potassium permanganate has been carried out for a series of 4-aryl- and 4-methyl-1,2,3,6-tetrahydropyridines to give 1-formylamino-substituted 3-arylpropan-3-ones and butan-3-ones. The effect has been studied of the nature of the substrate, the temperature, and interphase transfer catalysts on the yield of amino alkanone. It is proposed that the reaction proceeds through the intermediate formation of 3,4-dihydroxypiperidin-2-ones which then undergo oxidative decyclization with elimination of one carbon atom.

Keywords: 1-aminobutan-3-one, oxidation of 1,2,3,6-tetrahydropyridines.

Carrying out the classical Wagner reaction at slightly elevated temperatures (20-30°C) enables activation of 4-aryltetrahydropyridines and the introduction of three functional groups into the piperidine ring at one stroke [2,3]. Under these conditions 3,4-dihydroxypiperidin-2-ones proved to be stable products. It was later established by us (see preliminary communication [4]) that, if 1-methyl-4-phenyltetrahydropyridine hydrochloride (**1a**) is used as the substrate being oxidized, under the same mild conditions the reaction stops at the stage of forming 1-(N-formyl-N-methyl)amino-3-phenylpropan-2-one (**2a**), the product of a more profound oxidation process. In the present work the effect has been studied of substrate structure, temperature, interphase transfer catalysts, and solvent on the extent of oxidation of tetrahydropyridines by potassium permanganate.

First of all it seemed important to establish the possibility and extent of the further oxidation of various 4-aryltetrahydropyridines **1a-e** as free bases at temperatures higher than those used in [2,3]. It turned out that in the first place substrates **1a-c** were oxidized by potassium permanganate in acetonitrile at 50-60°C to 1-(N-formyl-N-methyl)amino-3-arylalkan-3-ones **2a-c**, and secondly the yield of the latter (48-56%) depended less on the replacement of the phenyl group at $C_{(4)}$ in the initial substances by the electron-withdrawing γ-pyridyl (substrates **1a,c**) or the N-methyl group by N-(*p*-chlorobenzyl) (substrates **1a,b**). Introduction of such electron-donating substituents as a methyl or a methoxy group (i.e. transition from the initial **1a** to substrates

* For part 7 see [1].

Russian People's Friendship University, Moscow 117198; e-mail: NVENSKOVSKI@mx.pfu.edu.ru.
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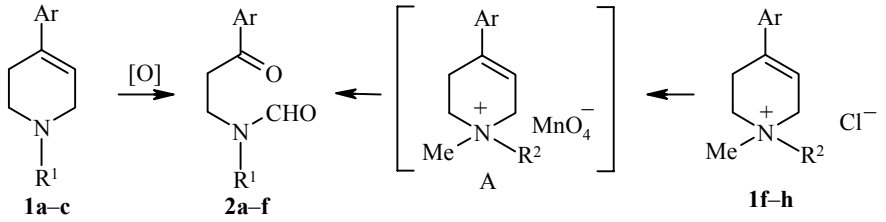
1d,e) into the *para* position of the phenyl substituent at $C_{(4)}$ of the hydropyridine ring shows up sharply in the process of oxidation. In the temperature range 50-60°C substrates **1d,e** were oxidized (reaction time 0.5-1 h) with the formation of a complex mixture of products. From this mixture amino ketones **2d,e** were successfully isolated in low yield and only carrying out the reaction with cooling to -15 to -20°C (reaction time 2 h) enabled them to be obtained in satisfactory yield (47-63%). The substrate with a methoxy group is the more reactive and its oxidation must be carried out only at temperatures below zero.



1a,**b**,**f**,**g**, **2a**,**b**,**f** Ar = Ph; **1c**,**h**, **2c** Ar = 4-Py; **1d**, **2d** Ar = C_6H_4Me-*p*; **1e**, **2e** Ar = C_6H_4OMe-*p*; **1a**,**c-e**, **2a**,**c-e** R^1 = Me; **1b**, **2b** R^1=$CH_2C_6H_4Cl$-*p*; **1f**, **2f** $R^1 = R^2 = CH_2Ph$; **1g**,**h** R^2 = H

Since oxidation under phase-transfer catalysis conditions enables more efficient use of the oxidizing agent and reduction of the temperature of oxidation [5], we studied the oxidation of tetrahydropyridines **1a,b** by potassium permanganate (ratio 1 : 1) in the presence of certain quaternary ammonium salts as phase-transfer catalysts (see Experimental). It was established that oxidation also occurs with the formation of amino ketones **2a,b** and it was observed even at room temperature, the yield (40-48%) is determined to an insignificant extent by the structures of the substrate and catalyst used. On cooling to 0°C this reaction, as also oxodihydroxylation, does not take place (according to TLC). The oxidation of substrate **1a** to amino ketone **2a** also occurs in the absence of potassium permanganate, if air is used as the oxidizing agent and is bubbled through the reaction mixture containing tetrabenzylammonium iodide at a temperature of 80°C.

The need to purify the reaction mixture from the catalyst and the products of its oxidation reduces the efficiency of the process. Consequently the possibility of oxidizing substrates **1a,c** (as the hydrochlorides **1g,h**) without adding an extraneous catalyst was studied. It was expected that the quaternary salts **1g,h** may serve as phase-transfer catalysts due to the formation of intermediate products in which chloride anion is substituted by permanganate anion. Similar products (A), being carriers of permanganate anion as counterion, may probably be subject to self-oxidation (by a type of autocatalysis). In the present case the formation of products of more profound oxidation was observed at room temperature in place of diol-lactams [2,3]. The quaternary salts **1g,h** were readily converted into amino ketones **2a,c** (43-85% yield).

In the analogous oxidation of N-benzyl-N-methyltetrahydropyridinium chloride **1f,** the expected opening of the heterocycle must be accompanied not only by the elimination of one ring carbon atom $C_{(3)}$, but also by the fission of the N-methyl or the N-benzyl group. Only the N-benzyl derivative of the amino alkanone **2f** was successfully isolated and characterized (7% yield) from the complex mixture of products obtained in this way.

Oxidation of the 4-aryltetrahydropyridine **1a** as the free base may be sharply accelerated by the addition of acetic acid to the reaction mixture. In this case the initial substrate **1a** reacts completely (check by TLC) at room temperature in 15 min, probably due to the more efficient decomposition of the oxidizing agent in the acidic medium and to the protonation of substrate **1a**.

When studying the oxidation of a series of 4-methyl-substituted tetrahydropyridines **3a-e** it was established that even at room temperature all the initial compounds, irrespective of the nature of the substituent at the nitrogen atom, were readily converted by potassium permanganate into N-formylaminobutan-3-ones **4a-e**. These were obtained, like the aminoalkanones **2a-f,** as viscous colorless liquids (60-69% yield). The use of an phase-transfer catalyst when oxidizing substrate **3e** led to a fall in the yield of aminobutanone **4e** almost to a half.

TABLE 1. Characteristics of Aminoalkanones **2** and **4**

Compound being oxidized/method of synthesis	Compound synthesized	Empirical formula	Found, % / Calculated, %			IR spectrum, ν, cm^{-1}	M^+	Yield, % (method of synthesis)
			C	H	N			
1a/A/B/D	**2a**	$C_{11}H_{13}NO_2$	68.93 / 69.11	7.22 / 6.81	7.10 / 7.33	1675, 1545	91	53 (A), 48 (B), 30 (D)
1g/C	**2a**							85 (C)
1b/A/B	**2b**	$C_{17}H_{16}ClNO_2$	67.02 / 67.66	5.75 / 5.31	4.66 / 4.64	1680, 1640	301	56 (A), 40 (B)
1c/A	**2c**	$C_{10}H_{12}N_2O_2$	61.96 / 62.50	6.47 / 6.25	14.21 / 14.58	1676, 1646	192	48 (A)
1h/C	**2c**							43 (C)
1d/A	**2d**	$C_{12}H_{15}NO_2$	70.13 / 70.24	7.45 / 7.32	6.72 / 6.83	1700, 1640	205	63 (A)
1e/A	**2e**	$C_{12}H_{15}NO_3$	65.32 / 65.16	6.96 / 6.79	6.21 / 6.34	1700, 1640	221	47 (A)
1f/C	**2f**	$C_{17}H_{17}NO_2$	76.33 / 76.41	6.61 / 6.37	5.11 / 5.24	1705, 1660	267	7 (C)
3a/A	**4a**	$C_6H_{11}NO_2$	55.78 / 55.81	8.50 / 8.53	10.13 / 10.85	1680, 1635	129	65 (A)
3b/A	**4b**	$C_7H_{13}NO_2$	58.57 / 58.74	9.29 / 9.09	9.29 / 9.79	1678, 1636	143	60 (A)
3c/A	**4c**	$C_{12}H_{15}NO_2$	70.75 / 70.24	6.83 / 7.32	6.49 / 6.83	1707, 1660	205	69 (A)
3d/A	**4d**	$C_{12}H_{14}ClNO_2$	60.40 / 60.13	5.98 / 5.85	5.93 / 5.85	1713, 1649	239	65 (A)
3e/A/B	**4e**	$C_{16}H_{17}NO_2$	75.59 / 75.29	6.83 / 6.67	5.69 / 5.49	1685, 1640	255	60 (A), 30 (B)

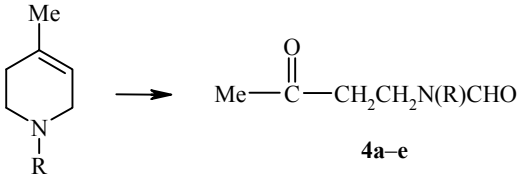
TABLE 2. ^{1}H NMR Spectra of Aminoalkanones **2a-f** and **4a-e** (δ, ppm, *J* (Hz))

Com-pound	1-CH_2 (2 t, about 1H)	2-CH_2 (2 t, about 1H, *J* = 6.0-6.7)	1-NCHO (2 s, about 0.5H)	3-R^2	1-NR^1
2a*	3.74 and 3.72	3.23 and 3.30	8.02 and 8.18	7.48-7.94 (5H, m, Ph)	2.88 and 3.03 (about 1.5 H, two s, Me)
2b	3.65 and 3.70	3.12 and 3.28	8.28 and 8.37	7.15-7.9 (5H, m, Ph)	4.51 and 4.53 (about 1H, two s, CH_2Ar); 7.15-7.9 (4H, m, H_{arom})
2c	3.80 and 3.76	3.25 and 3.30	8.01 and 8.2	7.75 and 8.85 (about 2H, dd, *J* = 4.5 and 1.5)	2.92 and 3.12 (about 1.5 H, s, Me)
2d	3.75 and 3.73	3.25 and 3.28	8.05 and 8.13	2.38 (3H, s, 4-ArMe); 7.25 and 7.83 (about 2H, dd, *J* = 8.0 and 2.0, H_{arom})	2.81 and 3.12 (about 1.5 H, two s, Me)
2e*[2]	3.67 and 3.70	3.13 and 3.2	8.0 and 8.13	3.85 (3H, s, OMe); 6.91 and 7.9 (about 2H, dd, *J* = 8.7 and 3.3 and t, *J* = 8.1, H_{arom})	2.84 and 2.99 (about 1.5 H, two s, Me)
2f	3.9-4.2 (m)	3.4-3.6(m)	8.02 and 8.11	7.1-7.7 (5H, m, Ph)	4.45 (2H, br. s, CH_2Ar); 7.1-7.7 (5H, m, Ph)
4a*[3]	3.23 and 3.21	2.43 and 2.45	7.65 and 7.77	1.85 (1H, s, Me)	2.5 and 2.66 (about 1.5 H, two s, Me)
4b	3.38 and 3.36	2.58 and 2.61	7.87 and 7.91	2.0 and 2.05 (about 1.5 H, 2s, Me)	0.96 and 1.03 (about 1.5H, t, *J* = 8.0, Et); 3.16 (2H, q, Et)
4c	3.30 and 3.28	2.42 and 2.5	8.05 and 8.1	1.8 and 1.9 (about 1.5 H, 2s, Me)	4.25 and 4.33 (about 1H, two s,CH_2); 7.05-7.2 (5H, m, Ph)
4d	3.48 and 3.43	2.58 and 2.71	8.2 and 8.26	2.03 and 2.1 (about 1.5 H, 2s, Me)	4.4 and 4.45 (about 1H, two s, CH_2); 7.16 and 7.33 (about 2H, two d, *J* = 8.5, H_{arom})
4e	3.56 and 3.41	2.4 and 2.72	8.3 and 8.35	1.9 and 2.05 (about 1.5 H, 2s, Me)	4.93 and 5.05 (about 1H, two d, *J* = 14.0, CH_2); 7.4-8.1 (7H, m, H_{arom})

* Calculated ^{1}H NMR spectrum for the *Z′*-isomer of **2a**: 3.02 (NMe); 3.06 (2-CH_2); 3.55 (1-CH_2); 7.39 (3CH, Ph); 7.97 (2CH, Ph); 8.57 (CHO). ^{13}C NMR spectrum of 2a, experimental: 29.43 and 35.39 (Me); 36.05 and 36.58 (2-C); 40.38 and 44.36 (1-C); 127.8, 128.5, 133.4 and 136.45 (6S, Ph); 162.7 and 163.0 (NCHO); 197.2 and 198.3 (C=O). Calculated for *Z′*-isomer (for *E′*-isomer in square brackets): 34.9 (Me) [29.8]; 37.6 (2-C) [37.6]; 42.2 (1-C) [52.6]; 127.48 and 127.54 (4S, Ph) [127.4 and 127.54]; 132.7 (S, Ph) [132.7]; 135.3 (C_{quat}, Ph) [135.3]; 166.9 (NCHO) [166.9]; 194.7 (C=O) [194.7].

*[2] ^{13}C NMR spectrum of **2e**: 29.6 (NMe); 35.6-44.65 (2- and 1-CH_2); 55.5 (OMe); 113.8, 113.9, 129.6, 113.02 and 113.33 (Ph); 162.7 and 163.8 (NCO); 195.6 and 196.75 (C-C=O).

*[3] In the ^{13}C NMR spectrum of compounds **2a-e** the carbonyl carbon of the NCHO group gives a signal at 162-163 ppm, and the carbonyl of the COMe group at 205-207 ppm.



3a–e **4a–e**

a R = Me; **b** R = Et; **c** R = CH_2Ph; **d** R = $CH_2C_6H_4Cl$-*p*; **e** R = CH_2-1-naphthyl

These results indicate that replacement of the aryl substituent at $C_{(4)}$ by a methyl group reduces the stability of the intermediate oxidation products of the piperidinediol and lactamdiol type, and leads to a more efficient flow of the subsequent processes of decyclization-elimination with the formation of N-formylaminobutanones stable under mild temperature conditions.

The structures of all the aminoalkanones were confirmed by elemental analysis and spectral data (Tables 1 and 2). Two absorption bands were present in their IR spectra for the carbonyl groups (ketone at 1660-1716 and amide at 1635-1660 cm^{-1}). For the ^1H NMR spectra of the aminoalkanones, typical triplet signals were present for the protons of the two methylene groups located between the amide nitrogen and the carbonyl group (2.4-3.8 ppm, J = 6.0-6.7) and a singlet signal for the formyl proton (at 8.01-8.37 ppm). The signals for the groups indicated were doubled which indicates the existence of Z', E' conformational isomers due to hindered rotation about the amide bond. The integrated intensity of these signals indicates that the rotational isomers are formed in a ratio of 1 : 1 for all the aminoalkanones synthesized.

In the ^{13}C NMR spectra the amide carbonyl carbon of all the compounds resonates at 162-163.8, the ketone carbon for aryl ketones **2a-e** at 195-198 ppm, and for butanones **4a-e** at 205-207 ppm. Comparison of the chemical shifts in the calculated and experimental ^1H and ^{13}C NMR spectra, obtained for the **2a** molecule, shows a good convergence (see Table 2).

The results of the investigations carried out enable a conclusion to be drawn on the possibility of more profound one-reactor oxidation of 4-aryl- and 4-methyl-substituted 1,2,3,6-tetrahydropyridines by potassium permanganate to 1-(formyl)aminoalkan-3-ones. The presence of electron-donating substituents at $C_{(4)}$ of the tetrahydropyridines, the application of phase-transfer catalysts, the oxidation of substrates as quaternary salts, or in the presence of acetic acid, lead to an acceleration of the oxidation reaction of tetrahydropyridines to N-formylaminoalkanones and enables the preparative synthesis of the latter at room temperature or below. Variation of the structure of the alkyl and aralkyl substituents on the nitrogen atom of the hydropyridine ring showed no significant effect on the direction of the oxidation or on the yield of alkanone.

EXPERIMENTAL

The ^{13}C and ^1H NMR spectra were recorded on Bruker AM 300 (300 MHz) and AC 200 (200 MHz) spectrometers in impulse mode in deuterochloroform solution. The difference between the signals for CH_3, CH and CH_2, C_{quat} in the ^{13}C NMR spectra was obtained using the standard JMODXH program for editing spectra. Calculations of the NMR spectra were carried out using the ACDlabs program. The IR spectra were recorded on a UR-20 instrument in KBr disks. The mass spectra were obtained on a MX-1303 instrument. A check on the progress of reactions and the homogeneity of compounds was effected by TLC on Silufol UV 254 plates. Separation and purification was effected by column chromatography on silica gel type L-60 (40/100). The physicochemical characteristics and data of NMR spectra are given in Tables 1 and 2.

1-(N-Formylamino)-3-arylpropan-3-ones (2a-e). General Procedure. A. Potassium permanganate (0.57 g, 3.6 mmol) was added during 10 min to a solution of 4-aryltetrahydropyridine (**1a-c**) (2.4 mmol) in a mixture of acetonitrile (50 ml) and water (5 ml) at room temperature. The mixture was stirred for 1 h at 50°C (TLC check). The precipitate of manganese dioxide was removed and washed with hot acetonitrile (3 × 20 ml).

The filtrate was evaporated under vacuum, and the residue purified on a column of silica gel (eluent hexane, then ether). Compounds **2a-c** were thick colorless oils. For the synthesis of compounds **2d,e** the oxidation of the substrate **1d** was carried out analogously with the reaction mixture cooled to -15 to 0°C, and for substrate **1e** at 0 to 20°C.

B. An phase-transfer catalyst (tetrabutylammonium iodide (TBAI), triethylbenzylammonium chloride (TEBAC), or cetyltrimethylammonium bromide (CTMAB)) (1.5 mmol) was added to a solution of 4-phenyltetrahydropyridine (**1a,b**) (3 mmol) in dichloromethane (30 ml). Then a solution of potassium permanganate (3 mmol) in water (30 ml) was added during 10 min. The mixture was stirred for 1 h (TLC check). The precipitate of manganese dioxide was removed and washed with dichloromethane (5 × 10 ml). The filtrates were combined and, after extracting the catalyst with water, were evaporated under vacuum. The residue was separated by column chromatography. According to TLC the oxidation reaction does not proceed at 0°C. An analogous oxidation of substrate **1a** with air in benzene leads to the formation of amino ketone **2a** in 10% yield.

C. Potassium permanganate (0.76 g, 4.81 mmol) was added during 10 min to a suspension of 1-methyl-4-phenyltetrahydropyridine hydrochloride **1g** (0.5 g, 2.4 mmol) in a mixture of acetone (25 ml) and water (10 ml), and the mixture was stirred for 2 h at room temperature. It was then processed as in method A and amino ketone **2a** (0.4 g, 85%) was obtained. R_f 0.73 (acetone) and 0.49 (ether). Analogously amino ketone **2c** (0.78 g, 43%) was obtained from 1-methyl-4-(4-pyridyl)tetrahydropyridine hydrochloride **1h** (2 g, 7.7 mmol). R_f 0.4 (acetone). Amino ketone **2f** (7%) was synthesized similarly by the oxidation of 1-benzyl-1-methyl-4-phenyltetrahydropyridinium chloride **1f** (0.5 g, 1.67 mmol). R_f 0.73 (acetone).

D. A solution of potassium permanganate (2 g, 12.5 mmol) in a mixture of acetone (35 ml) and water (8 ml) was added at room temperature during 5 min to a solution of piperidine **1a** (1.6 g, 9 mmol) in a mixture of acetone (56 ml), water (12 ml), and acetic acid (1.2 ml). The mixture was stirred for 15 min (check by TLC), then cooled to 0°C, and sodium nitrate (1 g) and dilute (1:8) sulfuric acid (20 ml) were added, and the mixture stirred until complete solution of the manganese dioxide. The resulting solution was saturated with sodium chloride and extracted with ether (3 × 20 ml). The ether extract was washed with aqueous 5% sodium hydroxide solution, then with saturated sodium chloride solution, and dried over sodium sulfate. Amino ketone **2a** (0.53 g, 30%) was obtained after distilling off the solvent.

N-Substituted 1-(formylamino)butan-3-ones (4a-e) were obtained by method A adding the oxidizing agent on cooling and then stirring the mixture for 1.5-2 h at room temperature. Compound **4e** was also obtained by method B.

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