STUDY OF THE HYDROXYLATION OF N-SUBSTITUTED 1,2,5,6-TETRAHYDROPYRIDINES

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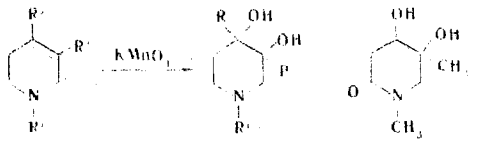
N-Substituted 1,2,5,6-tetrahydropyridines are readily converted to the corresponding 1,2-diols by treatment with an aqueous solution of potassium permanganate in a neutral medium. The yields of the desired products depend on the character of the substituent attached to the nitrogen atom and decrease in the case of N-methyl-1,2,5,6-tetrahydropyridines as a consequence of the formation of side products formed as a result of more profound oxidation. The acylation of the synthesized diols was studied. The three-dimensional structures of the synthesized cis-diols were established by IR spectroscopy.

It is known that the oxidation of complex ethylene compounds with an aqueous solution of potassium permanganate very often proceeds ambiguously and, depending on the conditions (the solvent, pH of the medium, and temperature), leads to the formation of α-ketols, α-diketones, aldehydes, and carboxylic acids in addition to 1,2-diols [1-4]. Relatively little study has been devoted to the cis hydroxylation of unsaturated heterocyclic compounds, although in a number of cases the high efficiency of this method for the preparation of racemic sugars by oxidation of dihydropyran compounds has been noted [5].

We have investigated the possibility of the synthesis of 1,2-diols of the piperidine series by cis hydroxylation of a number of substituted 1,2,5,6-tetrahydropyridines (Ia-j) with an aqueous solution of potassium permanganate in a neutral medium. The properties and yields of the synthesized N-substituted 3,4-dihydroxypiperidines (IIa-i) are presented in Table 1.



Ia-j IIa-i IIj

We have established that the oxidation of N-alkoxycarbonyl-1,2,5,6-tetrahydropyridines (Ia-e) leads to the formation of the corresponding 2,4-dihydroxypiperidines (IIa-e) in high yields. However, all attempts to oxidize 4-phenyltetrahydropyridines If, g under the conditions of the Wagner reaction were unsuccessful, and only the starting tetrahydropyridines If, g were isolated from the reaction mixtures. This inertness of the double bond in If, g, as well as the dependence of the yields of diols IIa-e on the structures of the starting tetrahydropyridines, can be explained by the fact that electron-acceptor substituents attached to the double bond of olefins increase the rate of their oxidation [6] by facilitating the formation of an intermediate cyclic ether. However, an increase in the number of methyl groups in the molecule (Ia-e) hinders the formation of an ether of this sort, and this leads to a decrease in the yields of diols. Steric factors also probably have a significant effect on the course of the process.

In contrast to N-alkoxycarbonyltetrahydropyridines Ia-e, the oxidation of N-methyltetrahydropyridines Ih, i proceeds ambiguously and leads to diols IIh, in only 30% yields as a consequence of the formation of products of more profound oxidation with unestablished compositions.

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TABLE 1. N-Substituted 3,4-Dihydroxypiperidines

Compound	R^1	R^2	R^3	mp, °C	bp, °C (mm)	n_D^{20}	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N	Yield, %
IIa	$COOCH_3$	H	H		135—136 (2)	1.4915	48.2	7.4	8.1	$C_7H_{13}NO_4$	48.0	7.5	8.0	87
IIb	$COOC_2H_5$	H	H		140—141 (2)	1.4943	50.8	7.5	7.3	$C_8H_{15}NO_4$	50.8	8.0	7.4	86
IIc	$COOCH_3$	H	CH_3		152—153 (2)	1.4848	50.7	8.0	7.4	$C_8H_{15}NO_4$	50.8	8.0	7.4	82
IId	$COOC_2H_5$	H	CH_3		155—158 (2)	1.4845	53.2	8.1	6.9	$C_9H_{17}NO_4$	53.2	8.5	6.9	82
IIe	$COOCH_3$	CH_3	CH_3		110—112 (0.1)	1.4818	53.1	8.2	7.0	$C_9H_{17}NO_4$	53.2	8.4	6.9	40
IIf	$COOCH_3$	H	C_6H_5											0
IIg	$COOC_2H_5$	H	C_6H_5											0
IIh	CH_3	H	H	70—71			54.9	9.5	10.5	$C_6H_{13}NO_2$	54.9	10.0	10.7	30
IIi	CH_3	H	CH_3	115—116			57.9	10.0	9.9	$C_7H_{15}NO_2$	57.9	10.4	9.6	32

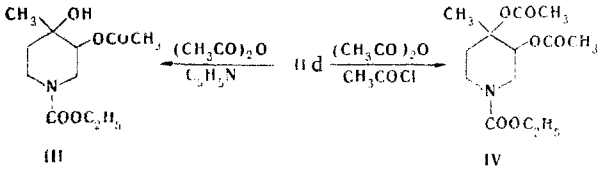
TABLE 2. Spectral Characteristics of Dihydroxypiperidines IIa-d

Compound	Stretching vibrations of the hydroxy group, ν_{OH}, cm^{-1}				
	ν_{OH} free	$\nu_{OH\ldots OH}$	$\Delta\nu_1=\nu_{OH}$ free $-\nu_{OH\ldots OH}$	$\nu_{OH\ldots COOR}$	$\Delta\nu_2=\nu_{OH}$ free $-\nu_{OH\ldots COOR}$
IIa	3650	3610	40	3480	170
IIb	3650	3610	40	3480	170
IIc	3645	3600	45	3480	165
IId	3630	3590	40	3470	160

In the case of the oxidation of 1,3-dimethyltetrahydropyridine Ij, in addition to cis hydroxylation of the double bond, the methylene grouping in the α-position relative to the nitrogen atom undergoes oxidation to give 1,5-dimethyl-4,5-dihydroxypiperidin-2-one (IIj) as the principal product. In addition to bands of stretching vibrations of free and associated hydroxy groups (3620, 3585, 3510, and 3470 cm^{-1}), the IR spectrum of a dilute solution of IIj contains an absorption band of stretching vibrations of an $\geq NCH_3$ group (2800 cm^{-1}), as well as bands of associated and free carbonyl groups of an amide grouping at 1710 and 1670 cm^{-1}. Signals at 1.02 (5-H), 2.13 (NCH_3), and 2.94 ppm (6-H), as well as multiplet signals of 3-H and 4-H protons centered at 1.68 and 3.6 ppm, respectively, are observed in the PMR spectrum of IIj.

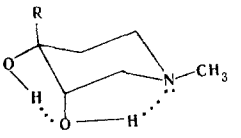
This anomalous course of the reaction is probably associated with the oxidizing action of the manganese dioxide that is formed in the reaction on amines [7].

In the case of acetylation of diol IId we showed that the secondary hydroxy group is selectively acylated to give 1-ethoxycarbonyl-4-hydroxy-3-acetoxy-4-methylpiperidine (III) when acetic anhydride in pyridine is used as the acylating agent under mild conditions, whereas acylation with a mixture of acetic anhydride and acetyl chloride with heating leads to the production of diacetate IV.



III IV

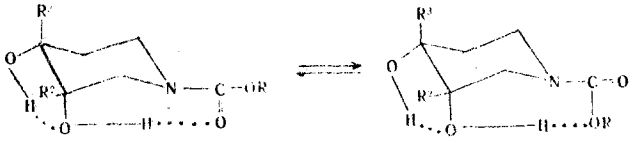
The IR spectra of dilute solutions of IIh, i contain an absorption band of a free hydroxy group at 3654 cm^{-1} and of an associated hydroxy group included in an intramolecular hydrogen bond of the OH...O (3585 cm^{-1}) and OH...N (3530 cm^{-1}) types; this makes it possible to assign a conformation in which the 3-OH group is axially oriented and the 4-OH group is equatorially oriented to 1-methyl-3,4-dihydroxypiperidines (IIh, i).



IIh,i

A similar three-dimensional structure was previously established for cis-1-methyl-6-phenyl-3,4-dihydroxypiperidine [8].

The IR spectra of dilute solutions of IIa-e contains, in addition to an absorption band of a free hydroxy group (Table 2), two absorption bands of hydroxy groups tied up in a hydrogen bond. One of them belongs to a hydroxy group included in an intramolecular hydrogen bond of the OH...OH type, as indicated by the shifts of the absorption band of the associated hydroxy group [9] relative to the band of a free hydroxy group, which are equal to 40-45 cm^{-1}, while the other belongs to a hydroxy group included in an intramolecular hydrogen bond with an alkoxycarbonyl group [10], which is confirmed by the shifts of the absorption bands of an associated hydroxy group, which are equal to 160-170 cm^{-1}. The development of hydrogen bonds of this type in the IIa-e molecules is possible when an axial 3-OH group and an equatorial 4-OH are present, which, in principle, is possible for rotamers A and B.



A B

EXPERIMENTAL

The IR spectra of solutions ($5 \cdot 10^{-3}$ M) of the compounds in carbon tetrachloride were recorded with a UR-10 spectrometer with an LiF prism. Thin-layer chromatography (TLC) was carried out on Silufol in a hexane–chloroform–methanol system (8:15:2). The PMR spectra of solutions of the compounds in CCl_4 were recorded with Varian HA-100 and RS-60 spectrometers with tetramethylsilane as the internal standard.

General Method for the Preparation of N-Substituted 3,4-Dihydroxypiperidines. A solution of 0.1 mole of potassium permanganate and 0.1 mole of magnesium sulfate in 200 ml of water was added with stirring to a cooled (to 0°C) solution of 0.1 mole of tetrahydropyridine I in a mixture of 20 ml of water and 20 ml of ethanol at such a rate that the temperature did not exceed 2°C, after which the mixture was stirred at this temperature for another hour. The precipitated manganese dioxide was removed by filtration and washed on the filter with ethanol. The filtrate was evaporated to dryness in vacuo, and the solid residue was extracted with refluxing methanol (three 100-ml portions). The methanol was removed by distillation, and the residue was extracted with boiling chloroform (five 100-ml portions). The chloroform extract was dried with magnesium sulfate, the chloroform was removed by distillation, and the oily residue was vacuum distilled.

1,5-Dimethyl-4,5-dihydroxypiperidin-2-one (IIj). The reaction of 4 g of tetrahydropyridine Ij as in the preceding experiment gave 2.4 g (42%) of IIj with bp 107-108°C (14 mm) and n_D^{20} 1.4894. Found %: C 52.7; H 8.1; N 8.7. $C_7H_{13}NO_3$. Calculated %: C 52.8; H 8.2; N 8.6.

1-Ethoxycarbonyl-3-acetoxy-4-methyl-4-hydroxypiperidine (III). A 3.7-g sample of acetic anhydride was added to a cooled (to 0°C) solution of 2.03 g (0.01 mole) of 1-ethoxycarbonyl-4-methyl-3,4-dihydroxypiperidine (IIg) in 4.5 ml of anhydrous pyridine, after which the mixture was allowed to stand at room temperature for 48 h. It was then poured over ice, and the aqueous mixture was extracted with chloroform. The chloroform extracts were dried with magnesium sulfate and worked up to give 2.1 g (87%) of III with bp 142-145°C (1.5 mm), n_D^{20} 1.4742, and R_f 0.46. The IR spectrum of a thin layer of the compound contained bands at 3300-3600 (OH included in an intermolecular hydrogen bond), 1740 (ester C=O), and 1705 cm^{-1} (amide C=O). PMR spectrum : 1.13 (t, CH_3CH_2O), 1.26 (s, 4-CH_3), 1.44 (m, 5-H_a), 1.60 (m,

5-H_e), 2.00 (s, $CH_3C(=O)-$), 3.24 (m, 6-H_a), 3.62 (m, 6-H_e), 4.20 (q, CH_3CH_2O), 4.30 (s, 2H), and 4.48 ppm (q, 3H). Found %: C 53.8; H 7.6; N 5.7. $C_{11}H_{19}NO_5$. Calculated %: C 53.8; H 7.8; N 5.7.

1-Ethoxycarbonyl-3,4-diacetoxy-4-methylpiperidine (IV). A 1.08-g sample of acetyl chloride and 1.41 g of acetic anhydride were added to a solution of 1.4 g (6.9 mmole) of IId in 50 ml of benzene, and the mixture was refluxed for 4 h. It was then cooled to room temperature, and the solvent was removed by distillation. The residue was vacuum distilled to give 1.64 g (82%) of IV with bp 112-125°C (0.4 mm), n_D^{20} 1.4632, and R_f 0.68. IR spectrum (thin layer): 1740 (ester C=O) and 1710 cm^{-1} (amide C=O). Found %: C 54.2; H 7.5; N 4.9. $C_{13}H_{21}NO_6$. Calculated %: C 54.3; H 7.4; N 4.9.

LITERATURE CITED

1. J. Strogl, M. Janda, J. Stibor, and J. Kucera, Collect. Czech. Chem. Commun., 38, 455 (1973).
2. L. G. Efremenko and A. M. Korolev, Izv. Akad. Nauk SSSR, No. 1, 147 (1970).
3. K. B. Wiberg and K. A. Saegebarth, J. Am. Chem. Soc., 79, 2822 (1957).
4. J. E. Coleman, C. Ricciuti, and D. Swern, J. Am. Chem. Soc., 78, 5344 (1956).
5. V. B. Mochalin and A. N. Kornilov, Zh. Obshch. Khim., 44, 2334 (1974).
6. K. B. Sharpless and D. R. William, Tetrahedron Lett., No. 35, 3045 (1975).
7. O. Meth-Cohn and H. Suschitzky, Chem. Ind., No. 5, 433 (1969).
8. L. S. Stanishevskii, I. G. Tishchenko, A. S. Puzikov, A. M. Zvonkov, and A. A. Zil'manovich, Zh. Org. Khim., 11, 643 (1975).
9. P. L. Kuhn, J. Am. Chem. Soc., 74, 2492 (1952).
10. A. R. U. Cole and G. T. A. Muller, J. Chem. Soc., No. 3, 1224 (1959).

INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES. 38.* REACTIONS OF 2-MERCAPTO-3-UREIDOPYRIDINES WITH HALO β-DIKETONES

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The reaction of 2-mercapto-3-ureido-6-chloropyridine with chlorodibenzoylmethane in the presence of alkali leads to 2-(benzoylmethylthio)-3-benzamido-6-chloropyridine, whereas the reaction in the absence of alkali leads to 2-chloro-6-phenyl-7-benzoylpyrido[2,3-b][1,4]thiazine. Under similar conditions 2-(diacetylmethylthio)-3-ureido-6-chloropyridine, 2-(acetylmethylthio)-3-ureido-6-chloropyridine, and 2-chloro-6-methyl-7-acetylpyrido[2,3-b][1,4]thiazine were obtained from 2-mercapto-3-ureido-6-chloropyridine and chloroacetylacetone. Treatment of 2-(diacetylmethylthio)-3-ureido-6-chloropyridine with alcoholic alkali leads to 2-(acetylmethylthio)-3-ureido-6-chloropyridine. 2-Chloro-6-phenyl-7-acetylpyrido-[2,3-b][1,4]thiazine and 2-(benzoylmethylthio)-3-ureido-6-chloropyridine are formed in the reaction of 2-mercapto-3-ureido-6-chloropyridine with chlorobenzoylacetone in the presence of an equimolar amount of alkali, while 2-(benzoylmethylthio)-3-acetamido-6-chloropyridine is formed when excess alkali is used.

*See [1] for communication 37.

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