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SYNTHESIS AND STRUCTURE OF 1-BENZOYL-2,5-DIMETHYL- AND 1,2,5-TRIMETHYL-4-ARYLPIPERIDEINS

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Isomeric 1-benzoyl-2,5-dimethyl-Δ^3-piperidein and 1-benzoyl-2,5-dimethyl-Δ^4-piperidein were prepared from disubstituted γ-piperidols and were hydroxylated with osmium tetroxide. The isomeric 1,2,5-trimethyl-4-(p-nitrophenyl)-Δ^3- and -Δ^4-piperideins were obtained from trisubstituted γ-piperidols.

Some piperideins are known to exhibit physiological activity; a related compound, the alkaloid phecolin, for example, is used in medicine. In our laboratory, piperideins, prepared by the dehydration of disubstituted and trisubstituted γ-piperidols, are intermediates in the synthesis of pyridine bases [1, 2]. However, very little is known about the structure (position of the double bond) of these piperideins.

We have synthesized a number of piperideins in order to determine their structure and to study their biological action. A mixture of isomeric substituted γ-piperidols, obtained by benzoylation of a mixture of the isomers of 2,5-dimethylpiperidin-4-ol, was used for the synthesis. At this stage in the synthesis of 1-benzoyl-2,5-dimethylpiperidin-4-ol (I), we obtained information on the spacial structure of one of its isomers, isolated as a crystalline material with mp 131-133°C. Its configuration and conformation were determined by ^{1}H and ^{13}C NMR, and also by x-ray structural analysis.

The ^{1}H NMR spectrum showed a quadruplet with coupling constant 3.5 Hz ($H_{3a,4} \approx J_{3e,4} \approx J_{4,5}$) for the proton at the 4-position. This, together with the absence of large (>3 Hz) coupling constants for the 6a and 6e protons allows the substituents at $C_{(4)}$ and $C_{(5)}$ to be assigned axial positions. The coupling constants for the $C_{(2)}$ proton ($J_{3a,2}$ = 6.4 Hz and $J_{3e,2}$ = 2.7 Hz) are considerably lower than typical values, such as those for 2,6-diphenyl- and dimethyl-derivatives of piperidol-4 with equatorially disposed substituents [3]. This agrees with the report [4] that in 1-benzoyl-2-methyl- and 1-benzoyl-cis-2,6-dimethylpiperidines, the methyl groups occupy axial positions due to spatial overlap of the 2e-methyl and phenyl groups on rotation around the N–C amide bond. Thus, all three substituents have the axial orientation and compound I has the configuration 4r-OH, 2c-CH_3, 5t-CH_3.

The ^{13}C NMR spectra of compound I confirm this conclusion. The difference between experimentally obtained δ_e and the theoretically expected δ_t values for the piperidine ring carbon atoms are as follows:

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	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$
δ_e	41.3	32.2	69.9	35.9	40.2
δ_t	37.8	30.5	64.8	32.3	37.8

(calculated using increments for 2a- and 5a-CH_3 [5] and 4a-OH [6]).

$\delta_e-\delta_t$	3.5	1.7	5.1	3.6	2.4

The differences are within acceptable limits, since the calculation of δ_t did not take into account interaction between pairs of substituents [7].

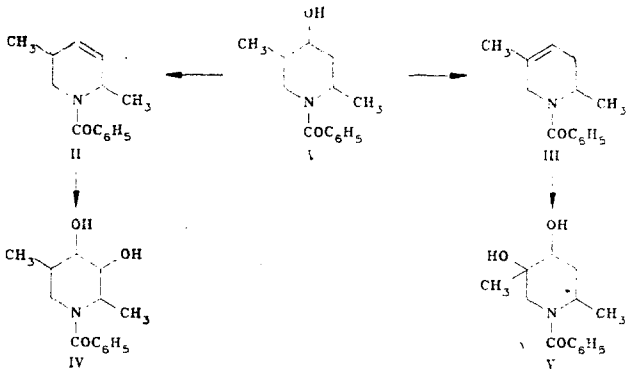
The spatial structure of this isomer of I (Fig. 1) was determined by x-ray structural analysis; the piperidine ring has a distorted chair conformation.

The nitrogen and carbon atoms deviated from the $C_{(2)}C_{(3)}C_{(5)}C_{(6)}$ plane by 0.621(3) Å and 0.622(4) Å (probable error 0.028(4) Å). The dihedral angles between the $C_{(2)}C_{(3)}C_{(5)}C_{(6)}$ plane and the $C_{(2)}NC_{(6)}$ and $C_{(3)}C_{(4)}C_{(5)}$ planes are 52.1 and 46.7°. The hydroxyl group and the $C_{(2)}$ methyl group are in the trans position relative to the $C_{(5)}$ methyl group.

The amide fragment $C_{(9)}C_{(1)}O_{(1)}N$ is planar to within 0.003(3) Å. The phenyl substituent is tilted from its plane by 58.4°. The nitrogen atom has virtually plane trigonal coordination (sum of the bond angles is 359.1°). The length of the $N-2-C_{sp}$ bond is 1.357(4) Å and indicates conjugation between the unshared electron pair on the nitrogen atom and the carbonyl group oxygen atom (in the absence of conjugation, the length of the $N-2-C_{sp}$ bond is 1.425(5) Å [8]). The $C_{(1)}=O_{(1)}$ bond length is 1.240(4) Å, greater than both the reported value (1.215(5) Å [9]), and the corresponding value for N-benzoyl-1-2-methyldecahydroquinoline-4-one (1.230 Å [10]) and N-benzoyl-2,6-dimethylpiperidine (1.219 Å [11]); apparently this is due both to its participation in conjugation with the unshared electron pair on the nitrogen atom and to the formation of a stable intermolecular hydrogen bond $O_{(2)}H...O_{(1)}=C_{(1)}$. Because of such bonds, in the crystalline form, molecules of compound I are linked to form an endless chain along the axis $O_{(2)}-H$ 0.80(4), $O_{(2)}...O_{(1)}$(x, 1/2 − y, −1/2 + z) 2.72(4), $H...O_{(1)}$ 1.94(4) Å, angles $O_{(2)}HO_{(1)}$ 164.2(4), $C_{(1)}O_{(1)}H$ 133.3(4)°.

Apparently, the isomer of piperidol I which we isolated was formed from the isomer of 2,5-dimethylpiperidin-4-ol with substituents in the equatorial position, and, by analogy with the corresponding piperidone [12], an axial unshared electron pair on the nitrogen atom. Benzoylation of this piperidol should take place in the axial region. Subsequent compression of the amide nitrogen atom as a result of conjugation of its unshared electron pair with the carbonyl oxygen atom causes an inversion of the piperidone ring.

Isomers of piperidol I were converted to piperideins by treating them with thionyl chloride or phosphorous tribromide in benzene and the reaction products were separated by chromatography on aluminum oxide, to give the isomeric piperideins II and III. The structures of 1-benzoyl-2,5-dimethyl-Δ^3-piperidein II and 1-benzoyl-2,5-dimethyl-Δ^4-piperidein III were studied by PMR. The position of the double bond in the piperidein II was shown by the presence of doublets corresponding to the $C_{(2)}$ and $C_{(5)}$ methyl groups at 1.24 ppm (J = 7 Hz), and at 1.0 ppm (J = 7 Hz), respectively, and multiplets at 5.6 ppm due to the olefinic protons at $C_{(3)}$ and $C_{(4)}$. The spectrum of piperidein III contained a singlet due to the methyl group at the double bond (1.65 ppm) and a doublet from the methyl group at the $C_{(2)}$ atom (1.24 ppm, J = 6.5 Hz).



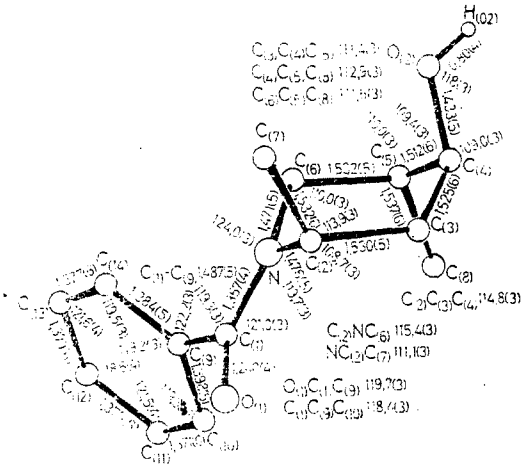
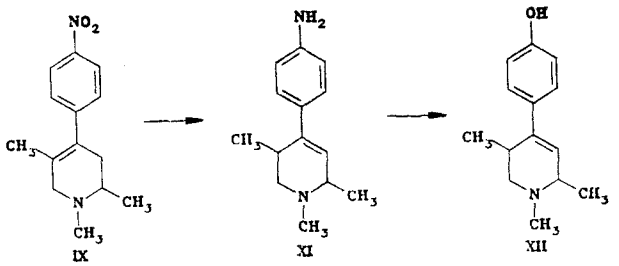


Fig. 1. Molecular geometry of compound I.

Additional information on the structure of piperideins II and III was obtained from their hydroxylation with osmium tetroxide. The piperidein α-glycols obtained are themselves of considerable interest. Oxidation of the mixture of piperideins containing an excess of the Δ^4-isomer III gave 1-benzoyl-2,5-dimethyl-4,5-dihydroxypiperidein V, and oxidation of the piperidein II gave 1-benzoyl-2,5-dimethyl-3,4-dihydroxypiperidein (IV). The coupling constants (J = 11.2 and 5.4 Hz) of the 4-H proton in the NMR spectrum of the piperidol V indicates that it is in the axial position. Thus, since hydroxylation using osmium tetroxide gives the cis-glycol, it can be assumed that in the diol V, the OH group at $O_{(5)}$ is axial, and the methyl group equatorial.

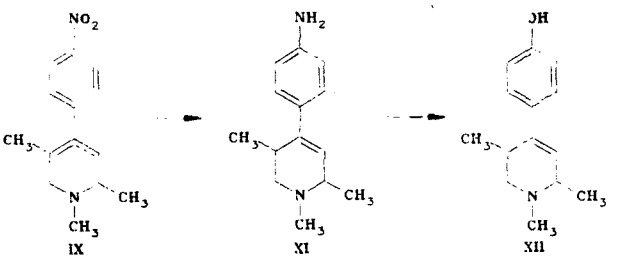
It has been reported that some of the γ-nitrophenylsubstituted piperidines are effective narcotic antagonists [13]. As we had available γ-phenylsubstituted piperidines, we used them to synthesize the nitro compounds. As starting materials we used a mixture of the isomers of 1,2,5-trimethyl-4-phenylpiperidol-4 (VI) and its propionate VII, and also the γ-isomer of 2,5-dimethyl-4-phenylpiperidin-4-ol (VIII). Nitration was carried out with a nitrating agent in methylene chloride at −5°C. In all cases, nitration of the phenyl ring occurred only in the p-position and was accompanied by the formation of a piperidein.*



IX XI XII

VI, VII $R^1=CH_3$; VIII $R^1=H$; VI, VIII $R^2=OH$; VII $R^2=OCOC_2H_5$

From the mixture of isomers of piperidol VI and its ester VII was obtained a mixture of 1,2,5-trimethyl-4-(p-nitrophenyl)-Δ^3- and Δ^4-piperideins (IXa, b). The position of the double bond in the piperidein IXa was shown by the presence of an olefinic proton signal (narrow multiplet centered at 5.76 ppm), and two doublets from the methyl group at positions $C_{(2)}$ and $C_{(5)}$ (1.22 ppm, J = 6.3 Hz and 0.90 ppm, J = 7 Hz, respectively). In the spectrum of the isomer IXb, the methyl group at the double bond gives rise to a broad singlet at 1.58 ppm and the $C_{(2)}$ methyl group a doublet at 1.14 ppm (J = 6 Hz). The position and multiplicity of the remaining signals in the spectrum correspond with the structure IX.



IX XI XII

*As in Russian original. The schemes shown here and below appear to be identical — Publisher.

Using analogous conditions, the piperidol VIII gave 2,5-dimethyl-4-(p-nitrophenyl)piperidein-Δ^4 (X). The position of the double bond is confirmed by NMR spectral data; a broad singlet from the methyl group at the double bond at 1.55 ppm and a doublet (1.2 ppm, J = 6.5 Hz) from the methyl group at the $C_{(2)}$ position. With the γ-isomer of piperidol VIII, the hydroxyl group and the methyl group at the $C_{(5)}$ position are in the cis-position. Therefore, trans-dehydration of this alcohol should lead to the piperidein X.

To prepare samples for a study of physiological activity, the nitro derivative IX was converted first to 1,2,5-trimethyl-4-(p-aminophenyl)piperidein (XI), and then to 1,2,5-trimethyl-4-(p-hydroxyphenyl)piperidein (XII). From the mixture of isomeric piperideins XI and XII, the corresponding Δ^3-piperideins were separated chromatographically; the structures of these compounds were confirmed by NMR.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were taken on a Bruker WP-80 instrument, using $CDCl_3$ as solvent and TMS as internal standard. IR spectra of the compounds in KBr pellets were taken on a UR-20.

Crystals of piperidol I were monoclinic: a = 7.3303(4), b = 11.0425(3), c = 16.193(1) Å. β = 90.156(5)°, Y = 1310.7(1) Å^3, Z = 4, d_{calc} = 1.18 g/cm^3, space group $P2_1/c$. Cell parameters and intensities of 1688 independent reflections with $F^2 \geq 2\sigma$ were measured on a Hilger-Watts four-circle diffractometer ($\lambda_{Cu\ K_\alpha}$ graphite monochromator, $\theta - 2\theta$ scanning, $\theta \leq 66°$). The structure was obtained by the direct method using MULTAN and was refined by the full-matrix least squares method, at first in isotropic and then in anisotropic approximation. All the hydrogen atoms which were located with difference synthesis were included in refinement with fixed isotropic temperature factors (B_{iso} = 6 Å). The final R-factor was 0.063 (R_w = 0.076). Calculations were carried out on an EVM Eclipse S/200 with INEXTL [12]. Column and thin-layer chromatography were carried out on aluminum oxide (Brockman activity 2).

1-Benzoyl-2,5-dimethylpiperidin-1-ol (I). To a solution of 19 g (150 mmole) of 2,5-dimethylpiperidin-4-ol and 7.8 g (200 mmoles) of sodium hydroxide in 60 ml of water was slowly added 21 g (150 mmole) of freshly prepared benzoyl chloride; after 4 h, the reaction product was extracted with ether, and dried with sodium sulfate. The ether extract was concentrated to a volume of 100 ml. On cooling, 6.4 g of crystals with mp 118-130° were isolated and were refluxed for 4 h in 50 ml of absolute ether. The insoluble material (1.3 g) was one of the isomers of piperidol, mp 131-133°C. IR-spectrum 3600 (free OH), 3400 (assoc. OH), 1610 cm^{-1} (CO). NMR spectrum: 7.35 (s, 5H, COC_6H_5); 4.42 (a, d, 1H, J = 6.4 and 2.7 Hz, 2-H); 3.77 (a, 1H, J = 3.5 Hz, 4-H); 3.60 (m, 2H, 6-H); 2.4 (s, 1H, OH); 1.4-2.1 (m, 3H, 3-H, 5-H); 1.39 (d, 3H, J = 6.5 Hz, 2-CH_3); 0.96 ppm (d, 3H, J = 6.5 Hz, 5-CH_3). Found, %: C 72.2, H 8.3, N 5.8; M^+ 223. $C_{14}H_{19}NO_2$. Calculated, %: C 72.1, H 8.2, N 6.6; M 233. Total yield of mixture of isomeric piperidols I was 180 g (53%).

1-Benzoyl-2,5-dimethylpiperidein-Δ^3 (II) and -Δ^4 (III). A. With mixing and cooling, a solution of 7 g (60 mmole) of thionyl chloride in 5 ml of benzene was added to a solution of 5 g (20 mmole) of piperidol I (mixture of isomers) in 20 ml of benzene. The reaction mixture was maintained at 20°C for 1 h and at 80°C for a further hour. The excess thionyl chloride and benzene were distilled off. The residue was treated with 5% sodium carbonate, the reaction products were extracted with ether, and the extract dried over magnesium sulfate. The residue (2.7 g) from the ether extract was chromatographed on a column (h = 30 cm, d = 2.3 cm, eluant — 5:1 hexane and ethyl acetate) to afford 2.5 g (47%) of piperidein II, a yellow oil with R_f 0.42 (1:3 ethyl acetate-hexane). IR spectrum: 1650 (N—COC_6H_5), 1600 cm^{-1} (C=C). NMR spectrum: 5.4-5.9 (m, 2H, 3-H, 4-H); 4.8 (br. s, 1H, 2-H); 3.7 (br. s, 1H, 6e-H); 3.22 (d, d, 1H, J = −13.0, 3.5 Hz, 6a-H); 2.20 (m, 1H, 5-H); 1.24 (d, 3H, J = 7 Hz, 2-CH_3); 1.0 ppm (d, 3H, J = 7 Hz, 5-CH_3). Found, %: C 78.4, H 7.6, N 6.3; M^+ 215. $C_{14}H_{17}NO$. Calculated, %: C 78.1, H 7.9, N 6.5; M 215.

B. A mixture of 2.7 g (12 mmole) of alcohol I, 3.3 g (12 mmole) of phosphorus tribromide and 130 ml of benzene was refluxed for 3 h, and then poured into 50 ml of water. The benzene layer was separated, and the product was extracted from the aqueous layer with benzene. The combined extracts were dried with magnesium sulfate. The residue, after evaporation of the benzene, was chromatographed on a column (h = 20 cm, d = 2.3 cm, eluant — 5:1 hexane and ethyl acetate). The first fraction contained 0.4 g (16%) of piperidein II, an oil with R_f 0.42 (1:3 ethyl acetate—hexane) and the next fraction gave 0.6 g (2.4%) of piperidein III, an oil with R_f 0.5 (1:3 ethyl acetate—hexane). IR spectrum: 1650 (N—COC_6H_5),

TABLE 1. Coordinates of the Atoms ($\times 10^4$, for H atoms $\times 10^3$)

Atom	x	y	z	Atom H	x	y	z
$O_{(1)}$	1001(4)	2206(3)	7683(2)	$H_{(02)}$	101(5)	330(3)	383(3)
$O_{(2)}$	1086(4)	3323(3)	4325(2)	$H_{(2)}$	282(5)	241(4)	662(2)
N	314(4)	3113(3)	6469(2)	$H_{(3,1)}$	158(5)	106(3)	573(3)
$C_{(1)}$	−99(5)	2786(3)	7255(2)	$H_{(3,2)}$	316(5)	186(3)	515(3)
$C_{(2)}$	2134(5)	2834(4)	6132(2)	$H_{(4)}$	45(5)	152(3)	435(3)
$C_{(3)}$	1912(6)	1942(4)	5415(2)	$H_{(5)}$	−222(5)	302(3)	480(3)
$C_{(4)}$	462(6)	2292(4)	4781(2)	$H_{(6,1)}$	−43(5)	444(4)	557(2)
$C_{(5)}$	−1333(5)	2591(4)	5192(2)	$H_{(6,2)}$	−222(5)	372(3)	613(3)
$C_{(6)}$	−1037(5)	3547(3)	5865(2)	$H_{(7,1)}$	443(5)	387(3)	568(3)
$C_{(7)}$	3158(5)	3995(4)	5901(3)	$H_{(7,2)}$	253(5)	453(4)	565(2)
$C_{(8)}$	−2315(6)	1467(4)	5531(3)	$H_{(7,3)}$	344(5)	440(4)	632(2)
$C_{(9)}$	−1892(5)	3142(3)	7607(2)	$H_{(8,1)}$	−256(5)	84(4)	508(3)
$C_{(10)}$	−3020(5)	2234(4)	7924(2)	$H_{(8,2)}$	−180(5)	109(3)	596(2)
$C_{(11)}$	−4647(5)	2544(5)	8283(3)	$H_{(8,3)}$	−359(5)	163(3)	575(3)
$C_{(12)}$	−5179(5)	3728(4)	8356(3)	$H_{(10)}$	−267(5)	128(3)	846(3)
$C_{(13)}$	−4039(6)	4615(4)	8069(3)	$H_{(11)}$	−535(5)	193(3)	846(3)
$C_{(14)}$	−2418(5)	4339(3)	7684(2)	$H_{(12)}$	−632(5)	397(3)	855(2)
				$H_{(13)}$	−438(5)	531(4)	810(2)
				$H_{(14)}$	−166(5)	486(3)	751(2)

TABLE 2. Torsion Angles τ (deg) in I

Angle	τ, degrees	Angle	τ, degrees
$C_{(1)}—N—C_{(2)}—C_{(3)}$	115,7(5)	$C_{(4)}—C_{(5)}—C_{(6)}—N$	−57,0(4)
$C_{(1)}—N—C_{(2)}—C_{(7)}$	−118,2(5)	$C_{(8)}—C_{(5)}—C_{(6)}—N$	69,1(4)
$C_{(6)}—N—C_{(2)}—C_{(3)}$	−54,0(4)	$C_{(5)}—C_{(6)}—N—C_{(2)}$	59,7(4)
$C_{(6)}—N—C_{(2)}—C_{(7)}$	72,1(5)	$C_{(5)}—C_{(6)}—N—C_{(1)}$	−109,5(5)
$N—C_{(2)}—C_{(3)}—C_{(4)}$	48,7(4)	$C_{(6)}—N—C_{(1)}—O_{(1)}$	165,5(5)
$C_{(7)}—C_{(2)}—C_{(3)}—C_{(4)}$	−75,7(5)	$C_{(6)}—N—C_{(1)}—C_{(9)}$	−15,1(4)
$C_{(2)}—C_{(3)}—C_{(4)}—O_{(2)}$	70,3(4)	$C_{(2)}—N—C_{(1)}—O_{(1)}$	−3,3(4)
$C_{(2)}—C_{(3)}—C_{(4)}—C_{(5)}$	−50,6(4)	$C_{(2)}—N—C_{(1)}—C_{(9)}$	176,1(5)
$O_{(2)}—C_{(4)}—C_{(5)}—C_{(6)}$	−67,5(4)	$O_{(1)}—C_{(1)}—C_{(9)}—C_{(10)}$	−56,0(4)
$C_{(3)}—C_{(4)}—C_{(5)}—C_{(6)}$	53,1(4)	$N—C_{(1)}—C_{(9)}—C_{(10)}$	124,6(5)
$O_{(2)}—C_{(4)}—C_{(5)}—C_{(8)}$	167,1(6)	$O_{(1)}—C_{(1)}—C_{(9)}—C_{(14)}$	119,4(5)
$C_{(3)}—C_{(4)}—C_{(5)}—C_{(8)}$	−72,3(5)	$N—C_{(1)}—C_{(9)}—C_{(14)}$	−60,1(4)

1600 cm^{-1} (C=C). NMR spectrum: 5.45 (n, M, 1H, 4-H); 2.3-1.7 (m, 2H, 3a-H, 3e-H); 1.65 (br. s, 3H, 5-CH_3); 1.24 ppm (d, 3H, J = 6.5 Hz, 2-CH_3). Found, %: C 77.8, H 7.9, N 6.3; M^+ 215. $C_{14}H_{17}NO$. Calculated, %: C 78.1, H 7.9, N 6.5; M 215.

1-Benzoyl-2,5-dimethyl-3,4-dihydroxypiperidine (IV). A solution of 1 g (4.6 mmole) of piperidein II and 1.17 g (4.7 mmole) of osmium tetroxide in 25 ml of freshly prepared pyridine was kept at 20° for 2 h and a solution of 15 g of sodium bisulfite in 20 ml of pyridine added. After 1 h, the reaction products were extracted with chloroform, and the extract dried with sodium sulfate. The chloroform was removed, leaving a tarry residue from which the diol was extracted with ether to give 0.25 g (21%) of colorless crystals mp 110-113°C (from ethyl acetate). IR spectrum: 3600 (free OH), 3400 and 3200 cm^{-1} (assoc. OH). NMR spectrum: 7.36 (s, 5H, COC_6H_5); 4.5 (br. q, 1H, J = 7 Hz, 2-H); 4.0 (br. d, 1H, J = −13.5 Hz, 6e-H); 3.70 and 3.95 (m, 2H, 3-H, 4-H); 3.13 (d, d, 1H, J = −13.5 Hz, 3.3 Hz, 6a-H); 2.95 (br. s, 2H, 3-OH, 4-OH); 1.17 (d, 3H, J = 7.0 Hz, 2-CH_3); 1.05 ppm (d, 3H, J = 7.0 Hz, 5-CH_3). Found, %: C 67.7, H 7.4, N 5.9; M^+ 249. $C_{14}H_{20}NO_3$. Calculated, %: C 67.5, H 7.6, N 5.6; M 249.

1-Benzoyl-2,5-dimethyl-4,5-dihydroxypiperidine (V). Using the same conditions as in the previous synthesis, 0.86 g (4 mmole) of a mixture of piperideins II and III, containing a larger amount of isomer III, 1.04 g (4.1 mmoles) of osmium tetroxide and 15 ml of pyridine. Yielded 0.22 g (22%) of the glycol V, mp 141-143°C (from ethyl acetate). IR spectrum: 3630 (free OH), 3400 and 3200 cm^{-1} (assoc. OH). NMR spectrum: 7.35 (s, 5H, COC_6H_5); 4.8-3.8 (br. m, 2H, 2e-H, 6e-H); 3.65 (d, d, d, 1H, J = 11.2, 8.5, 5.4 Hz, 4-H); 2.90 (1H, d, J = −14.4 Hz, 6a-H); 2.8 (s, 1H, 5-OH); 2.37 (d, 1H, J = 8.5 Hz, 4-OH); 1.25 (d, 3H, J = 7 Hz, 2-CH_3); 1.27 (s, 3H, 5-CH_3); 1.45-2.1 ppm (m, 2H, 3-H). Found, %: C 67.3, H 7.4, N 5.4; M^+ 249. $C_{14}H_{20}NO_3$. Calculated, %: C 67.5, H 7.6, N 5.6; M 249.

1,2,5-Trimethyl-4-(p-nitrophenyl)piperidein (IX). A. To a solution of 7.5 g (34 mmole) of piperidol VI in 50 ml of methylene chloride at −5°, with vigorous stirring was added 32.13 g (330 mmole) of sulfuric acid (d 1.7), followed by 2.14 g (34 mmole) of nitric acid (d 1.5). The reaction mixture was held at this temperature for 1 h, poured onto ice and neutralized with sodium hydroxide solution. The reaction products were extracted with chloroform and dried with sodium sulfate. Evaporation of the chloroform afforded 7.76 g (84%) of the nitro derivative IX (mixture of isomeric piperideins) as a yellow oily substance; 1 g of the piperidein mixture was separated chromatographically (h = 20 cm, d = 2.0 cm, eluant — 1:6 ethyl acetate and heptane). The first fraction yielded 0.3 g (30%) of piperidein-Δ^3 (IXa), R_f 0.43 (1:4 ethyl acetate—heptane), the second fraction gave 0.7 g (70%) of the piperidein-Δ^4 (IXb), R_f 0.24 (1:4 ethyl acetate—heptane). IR spectrum: 1520 and 1350 cm^{-1} (NO_2). NMR spectrum: isomer IXa: 8.18 (d, 2H, J = 8.5 Hz, aryl o-proton); 7.44 (d, 2H, J = 8.5 Hz, aryl m-proton); 5.76 (m, 1H, 3-H); 3.3-1.8 (m, 4H, 2-H, 5-H, 6-H); 2.46 (s, 3H, N-CH_3); 0.9 (d, 3H, 5-CH_3); 1.22 ppm (d, 3H, 2-CH_3); isomer IXb: 3.26-3.08 (m, 2-H, 6-H); 2.3-2.6 (m, 3H, 2-H, 3-H); 1.58 (s, 3H, 5-CH_3); 1.11 ppm (d, 3H, J = 6 Hz, 2-CH_3). Picrate of mixed piperideins — mp 178-180° (from alcohol). Found, %: N 14.8; M^+ 246. $C_{14}H_{17}N_2O_2 \cdot C_6H_3N_3O_7$. Calculated, %: N 14.7; M 246.

B. Using the same method as in A, 2.6 g (10 mmole) of the hydrochloride VII, 25 ml of methylene chloride, 8.55 g (87 mmole) of sulfuric acid and 0.54 g (8.7 mmole) of nitric acid gave 1.5 g (61%) of a mixture of isomers of compound IX. There was no depression of melting point on admixture with a sample prepared in A.

2,5-Dimethyl-4-(p-nitrophenyl)piperidein-Δ^4 (X). Using the same method, 0.75 g (3.7 mmole) of piperidol VIII gave 0.45 g (58%) of compound X as a yellow oil. IR spectrum: 1510, 1356 (NO_2) and 3350-3310 cm^{-1} (NH). NMR spectrum: 8.27 (d, 2H, J = 8.5 Hz, aryl o-proton); 7.28 (d, 2H, J = 8.5 Hz, aryl m-proton); 1.55 (s, 3H, 5-CH_3); 1.20 (d, 3H, 2-CH_3); 3.42 (m, 2H, 6-H); 2.15 (m, 2H, 3-H); 3.0 (m, 1H, 2-H); 2.75 ppm (s, 1H, N-H). Fumarate of compound X — mp 191-192°C (from alcohol). Found, %: C 58.4, H 6.0, N. 8.4; M^+ 232. $C_{17}H_{20}N_2O$. Calculated, %: C 58.7, H 5.7, N 8.0; M 232.

1,2,5-Trimethyl-4-(p-aminophenyl)piperidein-Δ^3 (XI). A mixture of 1.2 g (43 mmole) of the hydrochloride of IX, 22 ml of concentrated H_2SO_4 and 1.22 g (130 mmole) of metallic tin was heated at 65°C until the tin had completely dissolved. The reaction mixture was cooled, and treated with sodium carbonate until strongly alkaline. Evaporation of the chloroform afforded 0.2 g (16%) of compound XI, as an oil with Rf 0.12 (1:1 ethyl acetate—heptane). IR spectrum: 3450 and 3350 cm^{-1} (N-H). NMR spectrum: 7.03 (d, 2H, J = 8 Hz, aryl m-proton); 6.57 (d, 2H, J = 8 Hz, aryl o-proton); 3.65 (m, 2H, NH_2); 3.3-1.8 (m, 4H, 6-H, 5-H, 2-H); 5.50 (m, 1H, 3-H); 1.15 (d, 3H, J = 6.5 Hz, 2-CH_3); 0.85 (d, 3H, J = 6.5 Hz, 5-CH_3); 2.33 ppm (s, 3H, N-CH_3). Found, %: C 77.6, H 9.0, N. 11.7; M^+ 216. $C_{14}H_{20}N_2$. Calculated, %: C 77.8, H 9.3, N 12.1; M 216.

1,2,5-Trimethyl-4-(p-hydroxyphenyl)piperidein-Δ^3 (XII). To a solution of 1.8 g (8 mmole of piperidein XI in 4.6 ml (24 mmole) of 18% HCl at 5°C was added 3.3 ml of 2 M sodium nitrate. The excess nitric acid was neutralized with urea (negative reaction to congo). The reaction mixture was heated on a boiling water bath until no more nitrogen was evolved, saturated with sodium carbonate, and extracted with ether. The ether extract was dried over magnesium sulfate. The ether was removed and the residue chromatographed on a column (h = 25 cm, d = 2 cm, eluant — 2:1 hexane and ether) to give 0.4 g (22%) of compound XII, an oil with Rf 0.05 (1:2 ethyl acetate—hexane). IR spectrum: 3600 cm^{-1} (free OH). NMR spectrum: 8.2 (s, 1H, OH); 5.6 (m, 1H, 3-H); 2.48 (s, 3H, N-CH_3); 1.8-3.3 (m, 5H, 6-H, 2-H, 3-H, 5-H); 1.30 (d, 3H, J = 7.0 Hz, 2-CH_3); 0.92 ppm (d, 3H, J = 6.5 Hz, 5-CH_3). Found, %: C 77.0, H 8.5, N 6.2; M^+ 217. $C_{14}H_{19}NO$. Calculated, %: C 77.4, H 8.8, N 6.5; M 217.

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SYNTHESIS OF STEREOISOMERIC ALKYL- AND PHENYL-SUBSTITUTED 5-CYANOPIPERIDINE-3,4-DIOLS

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α-Hydroxy-β-[N-(2-cyanoethyl)amino]ketones were obtained by the reaction of methyl- and phenyl-substituted 2-acyloxiranes with 3-alkylaminopropionitriles. Treatment of the products with sodium tert-butoxide gave stereoisomeric 5e-cyanopiperidine-3,4-diols, the three-dimensional structures of which were established by means of spectral data, as well as by means of isomerization and oxidation with periodic acid.

The development of new methods for the synthesis of functionally substituted piperidine-3,4-diols is of considerable interest, since some natural compounds such as the alkaloid fagomine [1], as well as substances that have antihypoxia and surface-anesthetic activity [2], belong to this group of piperidine derivatives. Alkyl- and aryl-substituted piperidine-3,4-diols are generally obtained by hydroxylation of the corresponding tetrahydropyridines [3-6], by reduction of 3-hydroxy-4-piperidones [2, 7-9], or by reaction of the latter with organometallic compounds [10]. We have previously demonstrated [11] the possibility of the synthesis of isomeric 1,3,4-trimethyl-5-cyanopiperidine-3,4-diols via intramolecular cyclization of hydroxy derivatives of β-aminoethyl ketones containing a β-cyanoethyl group attached to the nitrogen atom [12].

In the present research, we studied the reaction of a number of methyl- and phenyl-substituted 2-acyloxiranes with 3-alkylaminopropionitriles, as a result of which we obtained the corresponding α-hydroxy-β-[N-(2-cyanoethyl)amino]ketones Ia-d in 76-96% yields. We found that acyloxiranes that contain substituents in the methylene link do not undergo this transformation, in conformity with the established regioselectivity of the process. Because of their tendency to undergo isomerization in the presence of bases, unsubstituted acyloxiranes (R^1 = H) also form virtually no adducts with alkylaminopropionitriles (see scheme on following page).

The IR spectra of Ia-d contain an absorption band at 3400-3470 cm^{-1} due to a hydroxy group involved in an intramolecular hydrogen bond with the nitrogen atom of the amino group, as well as an absorption band of a nitrile group at 2240 cm^{-1}. A band of carbonyl absorption of the acetyl group of Ia, b is observed at 1710 cm^{-1}, and a band of the benzoyl group of amino ketones Ic, d is observed at 1680-1690 cm^{-1}. The PMR spectra also confirm the structure of Ia-d; in particular, a quartet of diastereotopic protons of an N–CH_2 group with

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