9.8 mg (61%) of the porphyrin with mp > 200° (dec.). Spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$), in methanol: 398 (140), 498 (9.2), 530 (6.18), 565 (4.6), 617 (2.76). In chloroform containing 10% methanol: 415 (162), 531 (5.7), 555 (9.4), 598 (3.22). In chloroform containing 0.1% HCl: 416 (176), 553 (11.0), 594 (4.6). Mass spectrum, m/e (%): $(M - H_2SO_4)^+$ 462 (100), 447 (20), 435 (8), 417 (4.7).

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SYNTHESIS AND THREE-DIMENSIONAL STRUCTURE OF THE BENZOATES AND p-NITROBENZOATES OF THE GEOMETRICAL ISOMERS OF SUBSTITUTED 4-HYDROXYPIPERIDINES

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The corresponding stereoisomeric p-nitrobenzoates were obtained by reaction of the geometrical isomers of 1,3-dimethyl-, 1,2,5-trimethyl-, and 1-tert-butyl-3-methyl-4-hydroxypiperidines with p-nitrobenzoyl chloride. The stereoisomers of the corresponding benzoates were also synthesized from the geometrical isomers of 1,3-dimethyl-4-hydroxypiperidines. The primary conformations of the investigated compounds in solution were established by means of their PMR spectra.

In the development of our research on the interrelationship between the structure and the physicochemical characteristics of substituted piperidines [1, 2] we found it necessary to ascertain the primary conformations of the p-nitrobenzoates of the geometrical isomers of substituted 4-hydroxypiperidines. With this end in mind, we synthesized the p-nitrobenzoates of 1-methyl- (I), 1-tert-butyl-3-methyl- (IIβ, γ), 1,3-dimethyl- (IIIβ, γ), and 1,2,5-trimethyl-4-hydroxypiperidines (IVβ, γ) and established their primary conformations in solution.

We used the previously described geometrical isomers of the corresponding 4-hydroxypiperidines [3-6] as the starting compounds for the synthesis of p-nitrobenzoates I-IV.

In conformity with the configuration of the geometrical isomers of the starting 4-hydroxypiperidines [4-6], II-IV were subdivided into two configurational series (the β and γ isomers) as a function of the mutual orientation and spatial orientation of the substituents attached to C_3 and C_4. The acyloxy group attached to C_4 in geometrical isomers IIγ-IVγ is in the cis position with respect to the adjacent methyl group attached to C_3 in IIγ

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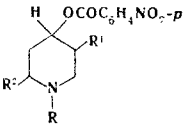
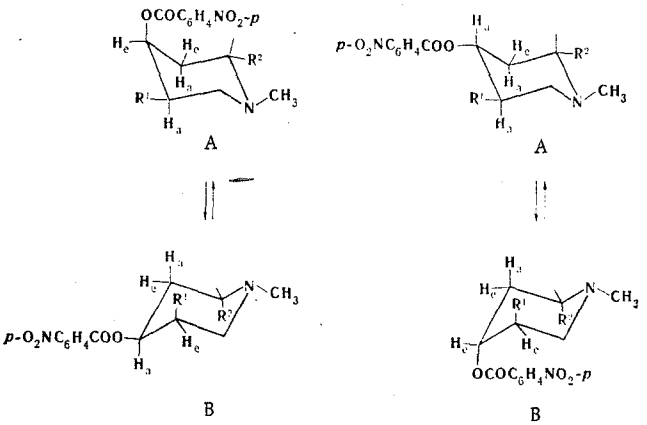
TABLE 1



Compound	R	R¹	R²	mp, °C	Base: empirical formula	Base: found, % C	Base: found, % H	Base: found, % N	Base: calc., % C	Base: calc., % H	Base: calc., % N	Yield, %	Hydrochloride, mp, °C	*Methiodide, mp, °C
I	CH_3	H	H	83—84	$C_{13}H_{16}N_2O_4$	59,7	6,2	10,6	59,5	6,1	10,6	85	210—211	277—278
IIβ	$-C_4H_9$	CH_3	H	104—105	$C_{17}H_{24}N_2O_4$	63,7	7,8	8,5	63,7	7,6	8,7	69	245—245,2	207—208
IIγ	C_4H_9	CH_3	H	94—95	$C_{17}H_{24}N_2O_4$	63,5	7,7	8,7	63,7	7,6	8,7	88	250—250,4	232—233
IIIβ	CH_3	CH_3	H	59—60	$C_{14}H_{18}N_2O_4$	60,7	6,5	9,8	60,4	6,5	10,1	75	242—243	250—251
IIIγ	CH_3	CH_3	H	72—73	$C_{14}H_{18}N_2O_4$	60,4	6,4	9,9	60,4	6,5	10,1	82	230—231	267—268
IVβ	CH_3	CH_3	CH_3	—	$C_{15}H_{20}N_2O_4$	—	—	—	—	—	—	73	193—194	—
IVγ	CH_3	CH_3	CH_3	—	$C_{15}H_{20}N_2O_4$	—	—	—	—	—	—	79	187—188	—

*Satisfactory analytical results for halogen were obtained for the hydrochlorides and methiodides.

and IIIγ and to C_5 in IVγ; in isomers IIβ-IVβ the acyloxy group is in the trans position relative to the same substituent [4-6].



γ isomers of III, IV β isomers of III, IV

III $R^1=CH_3$, $R^2=H$; IV $R^1=R^2=CH_3$

The orientation of the substituents is as yet unknown because of the lack of data on the primary conformation of the investigated compounds in solution.

The corresponding geometrical isomers of the p-nitrobenzoates of alcohols I and IIβ, γ-IVβ, γ were obtained by reaction of the individual stereoisomers of the substituted 4-hydroxypiperidines with p-nitrobenzoyl chloride (Table 1).

To establish the primary conformations of the stereoisomeric p-nitrobenzoates I and IIβ, γ-IVβ, γ we used PMR spectral data. The signal of the 4-H proton in the PMR spectra of I and IIβ-IVβ is found at δ 4.59-5.06 ppm with a width (with respect to the outer peaks) of 24.0-28.0 Hz, which reflects the sum of the constants of spin–spin coupling (SSCC) of this proton with the vicinal 3-H and 5-H protons (Table 2), and this constitutes evidence for its axial orientation. It is precisely in this case that the sum of the SSCC of the 4-H protons and the 3-H and 5-H vicinal protons ($\Sigma J = 2J_{aa} + J_{ae}$) is 25-30 Hz (assuming J_{aa} = 10-12 and J_{ae} = 3-5 Hz) [7]. This constitutes evidence that I and geometrical isomers IIβ-IVβ, under the conditions used to record the PMR spectra, have primarily a conformation with equatorial 4-acyloxy groups and adjacent methyl groups attached to C_3 of the ring in the case of IIβ and IIIβ and attached to C_5 in the case of IVβ. On the other hand, the signal of the 4-H proton appears as a multiplet with a width of 6-10 Hz in the spectra of stereoisomers IIγ-IVγ (Table 2), and this confirms its equatorial orientation (inasmuch as in this case $\Sigma J = 2J_{ae} + J_{ee}$ = 8 Hz) [7]. The signal of

TABLE 2. Chemical Shifts and Widths of the Signal of the 4-H Proton in the PMR Spectra of the Benzoates and p-Nitrobenzoates of the Geometrical Isomers of Substituted 4-Hydroxypiperidines I, IIβ, γ-VIβ, γ

Compound	Chemical shift, δ, ppm		Signal width (with respect to the outer peaks), Hz		Solvent	
	base	hydrochloride	base	hydrochloride	base	hydrochloride
I	5,06	—	24,0	—	$CDCl_3$	—
IIβ	4,59	4,80	24,5	25,0	$CDCl_3$	CD_3COOD
IIγ	5,16	5,17	9,5	6,0*	$CDCl_3$	CD_3COOD
IIIβ	4,59	4,82	24,0	24,0	$CDCl_3$	CD_3COOD
IIIγ	5,18	5,22	8,5*	8,0*	$CDCl_3$	CD_3COOD
IVβ	—	4,94	—	28,0	—	$CDCl_3$
IVγ	—	5,35	—	6,0	—	$CDCl_3$
Vβ	4,60[2]	4,98	25,5[2]	24,0	$CDCl_3$	$CDCl_3$
Vγ	—	5,28	—	15,5	—	$CDCl_3$
	—	5,32	—	15,0	—	CD_3OD
VIβ	4,62	4,86	24,0	23,0	$CDCl_3$	$CDCl_3$
VIγ	5,30	5,18	10,0	7,0	CCl_4	$CDCl_3$

*This is the peak width at half the height of the peak.

the 4-H proton in the spectra of IIγ-IVγ is shifted to weak field as compared with the signal of the same proton in the spectra of I and IIβ-IVβ; this is also characteristic for the equatorial proton [8]. Consequently, both the bases and the hydrochlorides of p-nitrobenzoates IIγ-IVγ do not undergo a conversion of the A ⇌ B type in solution and have primarily a conformation with an axial acyloxy group attached to C_4 and an equatorial methyl group attached to C_3 in IIγ and IIIγ and to C_5 in IVγ.

We studied the PMR spectra of the previously synthesized hydrochlorides of the benzoates of the geometrical isomers of 1,2,5-trimethyl-4-hydroxypiperidines Vβ, γ. The width of the signal of the 4-H proton in the spectra of the hydrochloride of the γ isomer (Vγ) of 1,2,5-trimethyl-4-benzoxypiperidine in various solvents is 15 Hz (Table 2). On the basis of this value of the sum of the constants of spin–spin coupling of the 4-H proton with the vicinal protons one may assume the presence of conformational equilibrium A ⇌ B in the case of the geometrical isomer Vγ, as we have previously observed in solutions of the base of Vγ, for which the ΣJ value of the SSCC of the 4-H proton was 19.5-20.5 Hz rather than 8 Hz [2].

In this connection, it seemed of interest to compare these results with the data from the PMR spectra of the geometrical isomers of 1,3-dimethyl-4-benzoxypiperidine (VIβ, γ). With this end in mind, we synthesized the corresponding stereoisomeric benzoates VIβ, γ by reaction of the geometrical isomers of 1,3-dimethyl-4-hydroxypiperidines with benzoyl chloride. All of the regularities characteristic for the analogs of VIβ (I, IIβ-IVβ) are retained in the PMR spectrum of isomer VIβ (Table 2), i.e., the width of the signal of the 4-H proton of VIβ at δ 4.86 ppm (for the hydrochloride) and at 4.62 ppm (for the base) is 23.0 and 24.0 Hz, respectively; this indicates its axial orientation [7, 8] and, consequently, a primary conformation with an equatorial acyloxy group. All of the regularities characteristic for compounds with an equatorial orientation of the 4-H proton are also retained for geometrical isomer VIγ (widths of 7.0 and 10.0 Hz at δ 5.18 and 5.30 ppm, respectively, for the hydrochloride and base).

Thus we observed a conversion of the A ⇌ B type only in the case of solutions of the base and the hydrochloride of the geometrical isomer of 1,2,5-trimethyl-4-benzoxypiperidine (Vγ) [2]; this conversion does not take place in the case of their analogs (IIγ-IVγ and VIγ). These results have not yet been explained and require additional investigation.

EXPERIMENTAL

The PMR spectra of the compounds were obtained with a ZKR-60 spectrometer with tetramethylsilane as the internal standard.*

p-Nitrobenozates of Substituted 4-Hydroxypiperidines (I, IIβ, γ-IVβ, γ). A 14-mmole sample of p-nitrobenzoyl chloride was added to 12 mmole of the appropriate stereoisomer of 4-hydroxypiperidine, after which the mixture was heated at 120° for 1-1.5 h. The end of the reaction was monitored by thin-layer chromatography

*The PMR spectra were obtained in the laboratory of physicochemical methods of investigation of the Institute of Chemical Sciences of the Academy of Sciences of the Kazakh SSR by senior scientific-co-worker V. I. Artyukhin, to whom the authors express their thanks.

(TLC). The crystalline acylation product was triturated and washed repeatedly with dry ether. The residue was dissolved in 30 ml of water, and the solution was saturated with potassium carbonate and extracted with five 20-ml portions of ether. The extract was dried with calcined $MgSO_4$, and the ether was removed by distillation. The residual crystalline base of the p-nitrobenzoate was recrystallized from ether. The hydrochloride of the p-nitrobenzoate was obtained by bubbling hydrogen chloride into an ether solution of the p-nitrobenzoate, after which it was recrystallized from alcohol. The methiodides were obtained by the addition of an equimolecular amount of methyl iodide to the corresponding p-nitrobenzoate, after which they were recrystallized from methanol.

1,3-Dimethyl-4-benzoxypiperidines (VIβ, γ). A mixture of 1.56 g (12 mmole) of the γ isomer of 1,3-dimethyl-4-hydroxypiperidine [5] and 5 ml (35 mmole) of benzoyl chloride was heated at 100-130° for 30 min. The end of the reaction was monitored by TLC. The excess benzoyl chloride was removed by vacuum distillation, and the crystalline hydrochloride was triturated in ether and washed repeatedly with dry ether to give 2.54 g (78%) of benzoate VIγ with mp 186-186.5° (from acetone). Found %: C 62.5; H 7.6; Cl 13.1. $C_{14}H_{19}NO_2 \cdot HCl$. Calculated %: C 62.3; H 7.5; Cl 13.1.

Benzoate VIβ, with mp 213-214° (from acetone), was similarly obtained in 70% yield. Found %: C 62.4; H 7.6; Cl 12.8. $C_{14}H_{19}NO_2 \cdot HCl$. Calculated %: C 62.3; H 7.5; Cl 13.1.

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