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SYNTHESIS AND STERIC STRUCTURE OF 1,3(1,5)-DIMETHYL-2-PHENYL- AND -2,4-DIPHENYL-4-PIPERIDOLS

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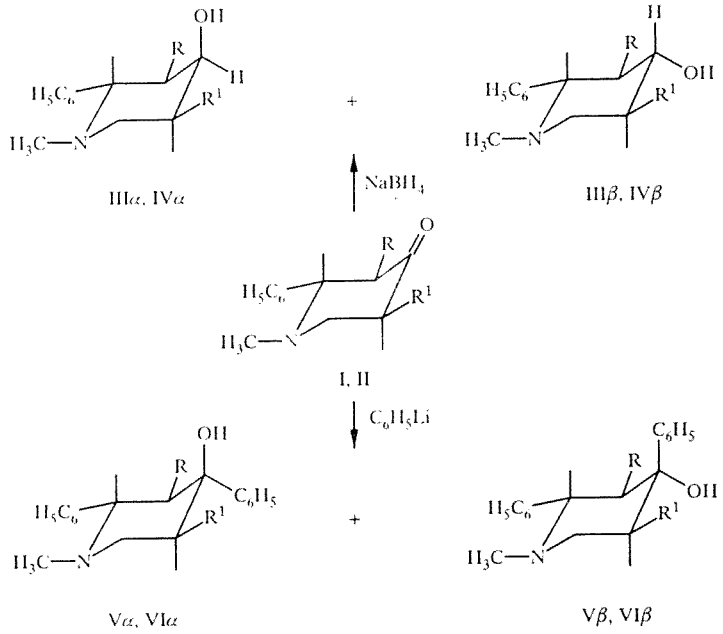
1,3(1,5)-dimethyl-2-phenyl- and -2,4-diphenyl-4-piperidols were respectively obtained with the reaction of 1,3- and 1,5-dimethyl-2-phenyl-4-piperidones with sodium borohydride and phenyllithium. The steric isomers of the compounds obtained were separated and identified by spectral methods.

4-Piperidols are of interest as the starting compounds for synthesis of functional derivatives of piperidine with different biological activity.

Mixtures of two steric isomers of secondary alcohols: 4r-hydroxy-1,3c-(1,5c)-dimethyl-2t-phenylpiperidines (IIIα, IVα) and 4r-hydroxy-1,3t(1,5t)-dimethyl-2c-phenylpiperidines (IIIβ, IVβ), with predominance of isomers IIIβ and IVβ, were obtained by reduction of 1,3-dimethyl-2-phenyl-4-piperidone (I) and 1,5-dimethyl-2-phenyl-4-piperidone (II) [1] with sodium borohydride at room temperature. The quantitative ratio of stereoisomers was established with the PMR spectra The mixture was separated into individual isomers by fractional crystallization from hexane. The properties and yields of piperidols III and IV are reported in Table 1.



I, III, V R = CH_3, R^1 = H; II, IV, VI R = H, R^1 = CH_3

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TABLE 1. 1,3(1,5)-Dimethyl-2-phenyl- and -2,4-Diphenyl-4-piperidols (III-VI)

Compound	Empirical formula	mp, °C (hexane)	R_f (system of solvents)	Yield of mixture of stereoisomers, %/concentration of predominant isomer
IIIα	$C_{13}H_{19}NO$	152...153	0,32(A)	90/70β
IIIβ		74...75*	0,19(A)	
IVα	$C_{13}H_{19}NO$	111...112	0,42(B)	89/75β
IVβ		103...104	0,12(B)	
Vα	$C_{19}H_{23}NO$	109...110*[2]	0,35(A)	100/80α
Vβ		—	0,10(A)	
VIα	$C_{19}H_{23}NO$	151...152	0,5(C)	94/70α
VIβ		T_{bp} 145/0,8	0,1(C)	

*Published data: mp = 91-92°C [2].

*[2]Published data: mp = 12-113°C [2].

The relative configuration of the substituents at the $C_{(2)}$, $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ atoms in the piperidine ring in piperidols III and IV was determined from the data in the PMR spectra using the SSCC of the piperidine ring 2-, 3-, 4-, 5-, and 6-H vicinal protons (Table 2). Isomers of the α series IIIα and IVα are in the ground conformation with equatorial phenyl and methyl groups and axial OH group. Isomers IIIβ and IVβ differ from the α-isomers by the position of the hydroxyl group alone (4e-OH).

Mixtures of phenyl alcohol steric isomers were obtained by the reaction of phenyllithium and 4-piperidones I and II — 4r-hydroxy-1,3c(1,5c)-dimethyl-2t,4-diphenylpiperidines (Vα, VIα) and 4r-hydroxy-1,3t(1,5t)-dimethyl-2c,4-diphenylpiperidines (Vβ, VIβ).

Isomers of alcohols Vα,β were obtained in the ratio of 85:15 in [2], and in our opinion, it was insufficiently demonstrated with the IR and TLC spectra that the isomers differed by the configuration at the $C_{(4)}$ atom of the piperidine ring. We isolated individual phenyl alcohol Vα by fractional crystallization from hexane and VIα and VIβ by chromatography of a stereoisomeric mixture in a column with aluminum oxide. The steric arrangement of the substituents at the $C_{(2)}$, $C_{(3)}$, and $C_{(5)}$ atoms of alcohols Vα and VIα, β was established in the same way as for secondary alcohols III and IV (Table 2). It was much more difficult to determine the configuration at the $C_{(4)}$ atom. It was previously shown that isomers with axial or equatorial position of the phenyl group in the ring could be assigned based on the width of the signal of the phenyl radical $C_{(1)}$ atom in the ^{13}C NMR spectra [3]. We were able to assign the α- and β-isomers of alcohol VI due to the long-range spin-spin interaction of the axial proton at the $C_{(3)}$ atom with the proton of the hydroxyl group with SSCC of ^4J = 1.2 Hz found in the PMR spectrum. Piperidol VIα thus has the configuration of 4r-hydroxy-1,5c-dimethyl-2t,-4-diphenylpiperidine, while alcohol VIβ has the configuration of 4r-hydroxy-1,5t-dimethyl-2c,4-diphenylpiperidine. The relative configuration of the substituents at the $C_{(4)}$ atom of phenyl alcohol V was determined by comparing the experimental chemical shift and the chemical shift of the methyl group at the $C_{(3)}$ atom calculated with the rule of the additive effect of substituents. The additive increments of the substituents were obtained as follows. It follows from a comparison of the spectra of secondary alcohols IIIα with IIIβ and IVα with IVβ that the axial or equatorial orientation of the hydroxyl group has little effect on the chemical shift of the vicinal CH_3 group ($\Delta\delta = 0.04 \pm 0.01$ ppm). The examination of the spectra of pairs of isomers IIIα, IVα and IIIβ, IVβ shows that the existence of a C_6H_5 vicinal equatorial group shifts the signal of the CH_3 group at the $C_{(3)}$ atom to the strong field by 0.34 ± 0.01 ppm. A comparison of the chemical shifts of the CH_3 group at the $C_{(5)}$ atom in alcohols VIα and β suggests that the equatorially oriented 4-C_6H_5 group shifts the signal of the vicinal CH_3 group by 0.2 ppm to a stronger field than the axial group. The experimentally found chemical shift of the CH_3 group at the $C_{(3)}$ atom of alcohol V is 0.30 ppm. Excluding the effect of the equatorial 2-C_6H_5 group on the chemical shift of the CH_3 group at the $C_{(3)}$ atom, we obtained a value of 0.30 + 0.35 = 0.65 ppm, which agrees with the chemical shift of the 5-CH_3 group of alcohol VIα in consideration of the effect of the hydroxyl group (±0.04 ppm). As a consequence, the isomer has an α-configuration with a high probability, i.e., it is 4r-hydroxy-1,3c-dimethyl-2t,4-diphenylpiperidine.

TABLE 2. Parameters of the PMR Spectra of 1,3(1,5)-Dimethyl-2-phenyl- and -2,4-Diphenyl-4-piperidols (III-VI)

Compound	Chemical shifts, δ, ppm	SSCC of protons, J, Hz
IIIα	2,89 d (2a-H), 1,88 m (3a-H), 3,93 d.d.d (4e-H), 2,08 d.d.d.d (5a-H), 1,88 m (5e-H), 2,60 d.d (6a-H), 2,77 d.d.d (6e-H), 1,94 s (N—CH$_3$), 0,63 d (3-CH$_3$, J = 7,1 Hz), 7,28 m (2-C$_6$H$_5$)	J_{2a3a} = 10,7, J_{3a4e} = 2,7, J_{4e5a} = 2,7, J_{5a5e} = 13,9, J_{5a6a} = 13,0, J_{5a6e} = 4,9, J_{5e6a} = 2,9, J_{5e6e} = 2,7, J_{6a6e} = 11,7
IIIβ	2,44 d (2a-H), 1,64 m (3a-H), 3,25 d.d.d (4a-H), 1,85 d.d.d.d (5a-H), 2,01 d.d.t (5e-H), 2,20 d.d.d (6a-H), 3,01 d.d.d (6e-H), 1,90 s (N—CH$_3$), 7,26 m (2-C$_6$H$_5$), 0,68 d (3-CH$_3$, J = 6,3 Hz)	J_{2a3a} = 10,0, J_{3a4a} = 10,0, J_{4a5a} = 11,0, J_{4a5e} = 4,7, J_{5a5e} = 12,5, J_{5a6a} = 12,9 J_{5a6e} = 3,9, J_{5e6a} = 2,9, J_{5e6e} = 2,9, J_{6a6e} = 12,0
IVα	3,19 d.d (2a-H), 1,90 m (3a-H), 1,83 m (3e-H), 3,90 d.d.d (4e-H), 2,06 m (5a-H), 2,27 d.d (6a-H), 2,65 d.d (6e-H), 2,00 s (N—CH$_3$), 0,99 d (5-CH$_3$), 7,31...7,24 m (C$_6$H$_5$)	J_{2a3a} = 9,5, J_{2a3e} = 5,4, J_{4e3a} = J_{4e3e} = 2,7, J_{4e5a} = =2,4, J_{5a6a} = 11,7, J_{5a6e} = 4,0, J_{6a6e} = 11,7, $J_{5,CH3}$ = 6,8
IVβ	2,86 d.d (2a-H), 1,67 d.d.d (3a-H), 1,99 d.d.d (3e-H), 3,24 d.d.d (4a-H), 1,79 m (5a-H), 1,88 d.d (6a-H), 2,92 d.d (6e-H), 1,96 s (N—CH$_3$), 1,02 d (5-CH$_3$), 7,28 m (2-C$_6$H$_5$)	J_{2a3a} = 11,7, J_{2a3e} = 2,7, J_{3a3e} = 12,8, J_{3a4a} = 11,3, J_{3e4a} = 4,5, J_{4a5a} = 9,5, J_{5a6a} = 11,2, J_{5a6e} = 2,9, $J_{5,CH3}$ = 6,3, J_{6a6e} = 11,0
Vα	3,01 d (2a-H), 2,27 d.q (3a-H), 2,39 d.d.d (5a-H), 1,79 d.d.d (5e-H), 2,71 d.d.d (6a-H), 2,92 d.d.d (6e-H), 2,01 s (N—CH$_3$), 0.305 d (3-CH$_3$, ^3J = =6,8 Hz), 7,2...7,5 m (C$_6$H$_5$)	J_{2a3a} = 10,2, J_{5a5e} = 13,9, J_{5a6a} = 12,9, J_{5a6e} = 4,6, J_{5e6a} = 2,7, J_{5e6e} = 2,7, J_{6a6e} = 11,5
VIα	3,34 d.d (2a-H), 2,10 d.d.d (3a-H) 1,81 d.d (3e-H), 2,48 m (5a-H), 2,44 d.d (6a-H), 2,86 d.d (6e-H), 2,08 s (N—CH$_3$), 0,69 d (5-CH$_3$), 7,15...7,45 (C$_6$H$_5$), 1,75 d (OH)	J_{2a3a} = 11,7, J_{2a3e} = 2,9, J_{3a3e} = 14,2, J_{3aOH} = 1,2, J_{5a6a} = 11,0*, J_{5a6e} = 3,7, J_{6a6e} = 11,0***
VIβ	3,43 d.d (2a-H), 2,21 d.d (3a-H), 2,34 d.d (3e-H), 2,45 m (5a-H), 2,30 d.d (6a-H), 2,89 d.d (6e-H), 2,07 s (N—CH$_3$), 0,89 d (5-CH$_3$), 7,2...7,7 m (C$_6$H$_5$), 3,75 b.s (OH)	J_{2a3a} = 11,6, J_{2a3e} = 3,8, J_{3a3e} = 13,7, J_{5a6a} = 11,6, J_{5a6e} = 4,3, J_{6a6e} = 11,9

*Additional splitting from the hydroxyl group proton of ^4J = 1.2 Hz.

**Determined in recording the spectrum in deuteroacetone.

The structure of compounds IIIα, β, IVβ, Vα, and VIα was confirmed by the mass spectra (Table 3). Separation of the phenyl radical and consequent retrodiene decomposition of ions* 128 (compounds IIIα,) and 204 (compounds Vα, VIα) formed is characteristic of electron-impact fragmentation of these compounds, as for the 2-phenyl-4-piperidones in [4]. Alternative processes of separation of a hydrogen atom from molecular ions of compounds IIIα, Vα, VIα, and retrodiene decomposition of $[M-H]^+$ ions cause the formation of ions 146 (compounds IIIα, β, Vα) and 160 (compounds IVβ, VIα).

The ratio of the intensities of the peaks of ions $[M-C_6H_5]^+$ and 118 is a distinctive feature of the mass spectra of compounds IIIα, Vα, and VIα. Although the peaks of $[M-C_6H_5]^+$ ions have the maximum intensity in the spectra of compounds IVβ and VIα, the peaks of ions 118 are most intense in the spectra of compounds IIIα, β. The high-resolution mass spectra showed that the nitrogen-containing $[C_8H_8N]^+$ ion makes the basic contribution to the intensity of ions 118 for compounds IVβ and VIα. On the contrary, in the spectra of compounds IIIα, β and Vα, ions 118 are compound and correspond to two structures $[C_8H_8N]^+$ and $[C_9H_{10}]^+$ with a 5:1 ratio of intensities. This difference in the ratio of the intensities of the peaks of ions $[M-C_6H_5]^+$ and 118, also observed in the spectra of 2-phenyl-4-piperidones [4], is probably common to all 2-phenyl-3-methyl- and 2-phenyl-5-methylpiperidines and allows easily distinguishing these structural isomers. However, the mass spectra of the α- and β-isomers of compound III were almost identical.

EXPERIMENTAL

The PMR spectra of the compounds were recorded on a Bruker WM-250 spectrometer for 2% solutions in $CDCl_3$. The chemical shifts of the protons were measured relative to HMDS internal standard (δ 0.055 ppm). The low-resolution mass

*The values of m/z are reported in the text here and below.

TABLE 3. Mass Spectra* of Compounds IIIα, β, IVβ, Vα, and VIα

Compound	m/z (intensity, %)
IIIα	205(61), 188(62), 146(61), 132(41), 128(93), 120(26), 119(30), 118(100), 117(22), 91(41), 42(28)
IIIβ	205(56), 188(67), 146(57), 132(40), 128(88), 120(27), 119(29), 118(100), 117(22), 91(38), 42(27)
IVβ	205(27), 204(9), 160(10), 132(13), 128(100), 119(12), 118(38), 104(25), 91(10), 70(11), 42(9)
Vα	281(54), 204(35), 146(60), 133(62), 132(96), 120(49), 118(100), 105(31), 91(38), 77(31), 44(35)
VIα	281(64), 204(100), 160(25), 133(26), 132(43), 119(26), 118(51), 105(37), 91(24), 77(30), 70(44)

*The peak of the molecular ion and 10 most intense peaks are reported.

spectra were made on a Finnigan MAT-90 with 70 eV ionizing electron energy by direct introduction of the sample into the source. The ionization chamber temperature was 200°C, and the sample evaporation temperature was 25°C. The resolution was M/ΔM = 10,000. Thin-layer chromatography was conducted on plates with an unattached layer of aluminum oxide with grade II activity in the system of solvents: ether (A), ether—methanol, 9:1 (B), and ether—hexane, 4:1 (C).

1,3(1,5)-Dimethyl-2-phenyl-4-piperidones were synthesized as described in [1].

1,3-Dimethyl-2-phenyl-4-piperidol (IIIα, β). While cooling with ice water and stirring, 1.85 g (0.049 mole) of sodium borohydride was added to a solution of 10 g (0.049 mole) of 1,3-dimethyl-2-phenyl-4-piperidone (I) in 30 ml of methanol. The reaction mixture was stirred for 1.5 h, acidified with concentrated hydrochloric acid, and then alkalized with a solid base, extracted with ether, and dried. The solvent was distilled off, and 9.1 g of a mixture of isomers of 1,3-dimethyl-2-phenyl-4-piperidol (IIIα, β) was obtained. Individual piperidols IIIα and IIIβ were separated by fractional crystallization from hexane.

1,5-Dimethyl-2-phenyl-4-piperidol (IVα, β). Similarly, 3.5 g of a mixture of isomers of 1,5-dimethyl-2-phenyl-4-piperidol (IVα, β) was obtained from 3.9 g (0.02 mole) of 1,5-dimethyl-2-phenyl-4-piperidone (II) in 12 ml of methanol and 0.8 g (0.02 mole) of sodium borohydride. Individual piperidols IVα and IVβ were separated by fractional crystallization from hexane.

1,3-Dimethyl-2,4-diphenyl-4-piperidol (V). Here 10 g (0.048 mole) of 1,3-dimethyl-2-phenyl-4-piperidone (I) in 10 ml of dry ether was added by drops to a solution of phenyllithium prepared from 1.36 g (0.196 g-atom) of lithium and 15.5 g (0.098 mole) of bromobenzene in dry ether. The reaction mixture was held for 24 h at room temperature, acidified with dilute hydrochloric acid (1:1), the neutral products were extracted with ether, alkalized with saturated potash solution, extracted with ether and chloroform, and dried. The solvents were distilled off, and 13 g of a mixture of 1,3-dimethyl-2,4-diphenyl-4-piperidol isomers (IVα, β) was obtained. Individual alcohol Vα was isolated by fractional crystallization from hexane.

1,5-Dimethyl-2,4-diphenyl-4-piperidol (VIα, β). In a similar manner, 6.33 g of a mixture of 1,5-dimethyl-2,4-diphenyl-4-piperidol isomers (VIα, β) was obtained from 0.64 g (0.092 g-atom) of lithium, 7.22 g (0.046 mole of bromobenzene, and 4.85 g (0.023 mole) of 1,5-dimethyl-2-phenyl-4-piperidone (II). Individual VIα was isolated from part of a mixture of isomers VIα, β by fractional crystallization from hexane. Column chromatography (d = 10 mm, 60 g of Al_2O_3 with grade II activity per 1 g of isomer mixture, petroleum ether—ether eluent, 1:1) was used for isolation of individual isomer VIβ.

The basic characteristics of the synthesized substances are reported in Table 1.

The data from elemental analysis agreed with the calculated data.

REFERENCES

1. M. Yu. D'yakov, T. D. Sokolova, A. V. Peretokin, A. S. Moskovkin, and B. V. Unkovskii, Khim. Geterotsikl. Soedin., No. 2, 224 (1991).
2. B. T. Sydykov, Zh. I. Isin, and D. V. Sokolov, Izv. Akad. Nauk KazSSR, Ser. Khim., No. 3, 54 (1973).

3. V. B. Rozhnov, O. V. Agashkin, T. D. Sokolova, B. V. Unkovskii, and Yu. F. Malina, Zh. Org. Khim., **21**, 1097 (1985).
4. A. S. Moskovkin, M. Yu. D'yakov, T. D. Sokolova, and B. V. Unkovskii, Khim. Geterotsikl. Soedin., No. 5, 634 (1994).