SYNTHESIS OF SUBSTITUTED 2-PHENYL-4-PIPERIDINONES FROM STYRYL β-DIMETHYLAMINOETHYL KETONES AND THEIR STERIC STRUCTURE

M. Yu. Dyakov, T. D. Sokolova, A. V. Peretokin, A. S. Moskovkin, and B. V. Unkovskii

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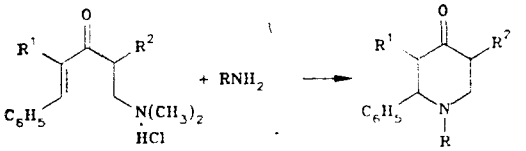
The difficultly obtainable substituted 2-phenyl-4-piperidinones were synthesized by the reaction of styryl β-dimethylaminoethyl ketone hydrochlorides with aqueous solutions of ammonia or alkylamines. It was found using ^1H and ^{13}C NMR spectroscopy methods that the cyclization process proceeds with the formation of pure stereoisomers of 4-piperidones with an equatorial disposition of all the substituents in the ring. The temperature for performing the cyclization is dependent on the number and position of the methyl substituents in the molecule of the starting substituted styryl β-dimethylaminoethyl ketones.

The synthesis of substituted 4-piperidinones and the study of their structure are of interest because of their physiological activity [1, 2] and their use in the preparation of physiologically active compounds [3]. However, no methods are available for the synthesis of substituted 4-piperidinones with a phenyl substituent at the $C_{(2)}$ atom and, therefore, they are difficultly available compounds [3-6] and their derivatives [7, 8] have practically not been investigated. One of the effective methods for the preparation of substituted 4-piperidinones is to heat alkenyl β-diethylaminoethyl ketone with aqueous solutions of ammonia or alkylamines [9], but this method could not be applied in the case of 5-diethylamino-1-phenyl-1-penten-3-one since this compound gives only undistillable products when reacted with an aqueous solution of methylamine [9].

We found that the method in [9] can also be used for the preparation of substituted 2-phenyl-4-piperidinones IIIa-i by changing the reaction conditions. The reaction of 5-dimethylamino-1-phenyl-1-penten-3-one hydrochloride (Ia) with aqueous solutions of lower alkylamines IIb-d leads to the formation of 1-alkyl-2-phenyl-4-piperidinones IIIa-c at room temperature [10], while upon heating the reaction mixture resinifies. The starting aminoketones Ib-d having even one methyl substituent in the styryl or β-dimethylaminoethyl groups react with aqueous solutions of ammonia or methylamine only on heating.



Ia-d IIa-d IIIa-i

I a $R^1=R^2=H$, b $R^1=CH_3$, $R^2=H$, c $R^1=H$, $R^2=CH_3$, d $R^1=R^2=CH_3$; II a R=H, b R=CH_3, c R=C_2H_5, d R=n-C_3H_7

We introduced the hydrochlorides of compounds Ia-d into the reactions instead of the free bases, as has been described in [9]. Thus, the previously described 1-methyl-, 3-methyl-, and 1,3-dimethyl-2-phenyl-4-piperidinones (IIIa, d, g) [4-6] were obtained, and also the unknown 2-phenyl-4-piperidinones IIIb, c, e, h, f, i (Table 1), the composition and steric structure of which was determined by means of PMR spectra from the SSCC values of protons at $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ in the ring (Table 2).

The 4-piperidinones IIId-i formed are pure stereoisomers.

By methylation of compounds IIId-f at the nitrogen atom by a mixture of formaldehyde and formic acid by a method described in [11], we obtained the corresponding compounds IIIg-i, the PMR spectra of which were identical

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TABLE 1. Characteristics of Substituted 2-Phenyl-4-piperidinones

Compound	Empirical formula	R	R¹	R²	Bp, °C (mm Hg)	mp, °C*	R_f	Yield, %
IIIa	$C_{12}H_{15}NO$	CH_3	H	H	122...126 (2,0)	59,5...61,5	0,54	76
IIIb	$C_{13}H_{17}NO$	C_2H_5	H	H	124...126 (3,0)	53...54	0,52	57
IIIc	$C_{14}H_{19}NO$	n-C_3H_7	H	H	114...116 (0,8)	—**	0,67	66
IIId	$C_{12}H_{15}NO$	H	CH_3	H	116...120 (0,8)	80,5...81,5 (83...84 [6])	0,44	66
IIIe	$C_{12}H_{15}NO$	H	H	CH_3	125...130 (1,0)	69...70	0,56	62
IIIf	$C_{13}H_{17}NO$	H	CH_3	CH_3	120...124 (0,8)	84...85	0,64	68
IIIg	$C_{13}H_{17}NO$	CH_3	CH_3	H	110...114 (0,9)	51,5...52,0 (60...61 [6])	0,51	91
IIIh	$C_{13}H_{17}NO$	CH_3	H	CH_3	115...117 (1,0)	30...31	0,63	64
IIIi	$C_{14}H_{19}NO$	CH_3	CH_3	CH_3	108...112 (0,8)	36...37	0,71	79

*After sublimation, compounds IIIa, b — after purification by column chromatography.
**n_D^{20} 1.5300.

TABLE 2. PMR Spectra of Substituted 2-Phenyl-4-piperidinones

Compound	Chemical shifts, δ, ppm*1								SSCC, J, Hz			
	N—CH_3 (NH)*2	2-H	3-H_a	3-H_e (3-CH_3)	5-H_a	5-H_e (5-CH_3)	6-H_a	6-H_e	$J_{2a,3a}$ ($J_{2a,3e}$)	$J_{5a,6a}$ ($J_{5a,6e}$)*3	J_{3a,CH_3}	J_{6a,CH_3}
IIIa	2,09	3,27	2,35...2,88 м (5H)					*3,20*	11,5	— (—)		
IIIb		3,48	2,38...2,82 м (5H)					3,36	10,8	— (—)		
IIIc		3,48	2,35...2,80 м (5H)					3,36	10,8	— (—)		
IIId	(1,91)	3,45	2,60	(0,77)	3,03	2,45	2,75	3,44	10,5	12,0 (6,5)	6,0	
IIIe	(1,92)	*3,93*	*2,56*		*2,64*	(1,04)	*2,68*	*3,47*		— (—)		6,2
IIIe*4		3,89	2,51	2,37	*2,58*	(0,94)	*2,58*	3,45	11,5	— (—)		6,1
IIIf	(1,91)	3,45	2,62	(0,76)	*2,68*	(1,04)	*2,68*	3,44	10,5 (3,4)	— (—)	6,4	6,0
IIIg	2,01	2,77	*2,66*	(0,70)	*2,90*	*2,47*	*2,47*	*3,28*	10,4	— (—)	6,4	
IIIh	2,05	3,18	2,66	2,42	2,89	(1,04)	2,19	3,25	11,9 (3,4)	11,9 (5,9)		6,6
IIIi	2,00	2,77	2,68	(0,70)	2,96	(1,04)	2,19	3,25	10,4	11,3 (5,8)	6,4	6,2

*1Signals of the aromatic protons are not shown; the numerals in italics represent a midpoint of a complex multiplet.
*2PMR spectrum of IIIb: 2.11 (1H, m, N—CH_2—CH_3); 0.96 ppm (3H, t, CH_3); IIIc: 2.00 (1H, m, N—CH_2—C_2H_5); 1.43 (2H, m, N—CH_2—CH_2—CH_3); 0.76 ppm (3H, t, CH_3).
*3A dash indicates superposition of signals of complex multiplets.
*4The spectrum was run in acetone-D_6.

TABLE 3. ^{13}C NMR of Substituted 2-Phenyl-4-piperidones

Compound	Chemical shifts, δ, ppm										
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$N-CH_3$	$C_{(3)}-CH_3$ / $C_{(5)}-CH_3$	$C_{(1')}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$
IIIa	69,3	49,2	207,1	41,0	55,1	42,4		141,9	126,8	128,3	127,2
IIId	69,1	46,0	209,1	42,2	51,8		9,7	141,4	127,0	128,0	127,3
IIIe	62,2	50,0	208,6	44,9	53,3		(10,4)	142,1	125,6	127,9	126,9
IIIf	69,9	51,4	210,8	45,4	54,0		9,8 (10,8)	141,5	126,9	127,9	127,3
IIIg	76,6	49,9	208,0	41,0	55,7	42,8	10,2	141,1	127,1	127,9	127,4
IIIh	70,0	48,7	207,4	41,7	62,8	43,5	(10,5)	140,5	127,0	128,2	127,4
IIIi	77,2	49,6	209,5	43,6	63,8	42,6	10,2 (10,8)	141,2	127,0	127,9	127,3

to the spectra of samples synthesized by the reaction of compounds Ib-d with methylamine. This shows that the orientation of the substituents in the ring of compounds IIId, g, IIIe, h, and IIIf, i is the same.

The phenyl substituent at the $C_{(2)}$ atom occupies an equatorial position in the molecules of compounds IIIa-i, as indicated by the large SSCC values of the vicinal protons at the $C_{(2)}$ and $C_{(3)}$ atoms – $^3J_{2,3}$ = 10.4-11.3 Hz (a trans-diaxial disposition of protons at $C_{(2)}$ and $C_{(3)}$). This shows that the methyl group at the $C_{(3)}$ atom in the molecules of compounds IIId, f, g, i also occupies an equatorial position.

In the PMR spectra of compounds IIIh, i, the signals of the axial proton at the $C_{(6)}$ atom are in the form of a quadruplet with SSCC $^2J_{6,6} = -11.5$ and $^3J_{6a,5a} = 11.9$ Hz in the spectrum of compound IIIh and, correspondingly, −11.2 and 11.3 Hz in the spectrum of compound IIIi. This indicates a trans-biaxial interaction of protons at the $C_{(5)}$ and $C_{(6)}$ atoms, which is possible only upon an equatorial orientation of the methyl group at the $C_{(5)}$ atom.

In the PMR spectra of compounds IIIe, f, the values of SSCC $^3J_{6,5}$ could not be determined because of the superposition of complex multiplet signals, but, since compounds IIIh, i, respectively, are formed during their methylation at the nitrogen atom, it can be concluded that the methyl group at the $C_{(5)}$ in these compound atoms also occupies an equatorial position. The identical orientation of the methyl groups of compounds IIIe, f, h, i is also confirmed by the identical values of the chemical shifts of their carbon atoms in the ^{13}C NMR spectra (Table 3). The structure of compounds IIId-i was also verified by the mass spectral data [12].

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) for 2% solutions in $CDCl_3$. The chemical shifts were measured relative to HMDS as internal standard. The ^{13}C NMR spectra were obtained on a Bruker WP-80 spectrometer (20.15 MHz) for 50% solutions in $CDCl_3$. The chemical shifts of the ^{13}C nuclei were measured under conditions of complete suppression of the spin–spin interaction with protons. The multiplicity of the signals was determined from spectra obtained with an incomplete uncoupling from protons.

Silufol UV-254 plates were used in a chloroform–methanol (10:1) system for the TLC, and silica gel 40/100 for the column chromatography with hexane–ether (1:1) as eluent.

The elemental analysis data for C and H correspond to the calculated values.

1-Methyl-2-phenyl-4-piperidinone (IIIa). A 43-ml portion of a 20% aqueous solution of methylamine IIb was added to a solution of 13.2 g (0.06 mole) of hydrochloride Ia [13] in 30 ml of water, and the mixture was stirred for 12 h at room temperature. It then was acidified by HCl, and extracted with ether. The aqueous layer was made alkaline with a sodium hydroxide solution and extracted with ether (3 × 100 ml). The combined ether extracts were dried over anhydrous $MgSO_4$, the ether was evaporated, and the residue (10.2 g) was subjected to a chromatographic separation on a column. Yield 7.2 g of compound IIIa.

Compounds IIIb, c were obtained in a similar way.

3-Methyl-2-phenyl-4-piperidinone (IIId). A 56-ml portion of a 20% aqueous solution of ammonia IIa was added to a solution of 52.3 g (0.21 mole) of 5-dimethylamino-2-methyl-1-phenyl-1-penten-3-one hydrochloride (Ib) [13] in 70 ml of water. The reaction mixture was heated to 85°C and stirred for 24 h, then cooled, acidified with HCl (1:1), and extracted with ether. The aqueous layer was made alkaline with a sodium hydroxide solution to a weakly alkaline reaction, and extracted with ether (3 × 100 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, the ether was evaporated, and the oily residue was dissolved in dry acetone and saturated with

gaseous HCl with cooling. The precipitate of the hydrochloride was separated and converted into the base by the action of alkali. Yield 25.76 g of compound IIId.

Compounds IIIe, f were obtained in a similar way.

Compounds IIIh, i were obtained from 5-dimethylamino-4-methyl-2-phenyl-1-penten-3-one hydrochloride (Ic) and 5-dimethylamino-2,4-dimethyl-1-phenyl-1-penten-3-one (Id) hydrochlorides, respectively [13], the temperature of cyclization being 70°C, and the treatment as described above.

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