Russian Journal of Organic Chemistry, Vol. 37, No. 12, 2001, pp. 1782–1785. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 12, 2001, pp 1863–1866.

Conformational Equilibrium of 4-Hydroxy- and 4-Acetoxy-4-(3-aryloxy-1-propynyl)-1-(2-ethoxyethyl)-piperidinium Salts in Solution

I. A. Poplavskaya, K. B. Bazhykova, and K. D. Praliev

Bekturov Institute of Chemical Science, Ministry of Education and Science of Kazakhstan Republic, ul. Ch. Valikhanova 106, Almaty, 480100 Kazakhstan

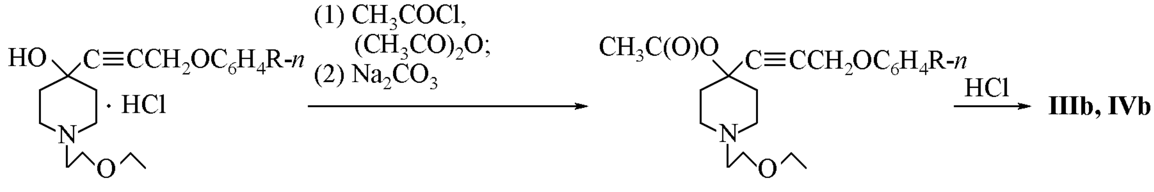
Received May 15, 2000

Abstract—4-Hydroxy- and 4-acetoxy-4-(3-aryloxy-1-propynyl)-1-(2-ethoxyethyl)piperidine hydroclorides in aprotic solvents give rise to equilibrium mixtures of two epimers. In the case of the acetoxy derivatives (in $CDCl_3$) the equilibrium is displaced toward the "less stable" epimer. This may be due to considerable contribution of the *skewed boat* conformer with intramolecular hydrogen bond.

4-(3-Aryloxy-1-propynyl)-1-(2-ethoxyethyl)-4-hydroxypiperidines **I** and **II** [1] and their acylation products were synthesized by us with the goal of obtaining new pharmacologically active substances. In the ^{1}H NMR spectra of some 4-aryloxypropynyl-4-hydroxypiperidines protons of the $–CH_2C≡$ appear as two singlets with an overall intensity of 2H. In order to elucidate the reason for the observed signal doubling we analyzed the ^{1}H NMR spectra of 1-(2-ethoxyethyl)-4-hydroxy-4-[3-(*p*-methylphenoxy)-1-propynyl]-piperidine (**Ia**), its hydrochloride **Ib**, 4-acetoxy-1-(2-ethoxyethyl)-4-[3-(*p*-methylphenoxy)-1-propynyl]-piperidine hydrochloride (**IIIb**), and 4-acetoxy-4-[3-(*p*-bromophenoxy)-1-propynyl]-1-(2-ethoxyethyl)-piperidine hydrochloride (**IVb**). Acetoxy derivatives **IIIa** and **IVa** were synthesized by acylation of hydrochlorides **Ib** and **IIb**, respectively, with acetyl chloride in acetic anhydride and, without isolation from the extract, were converted into hydrochlorides **IIIb** and **IVb** (Scheme 1).

The ^{1}H NMR parameters of compounds **I**–**IV** are summarized in Table 1. In the spectrum of base **Ia** the $CH_2C≡$ group gives a singlet at δ 4.68 ppm. Protons in positions *3*, *5* and *2*, *6* of the piperidine ring each give two groups of signals belonging to axial and equatorial protons; this may be due to slow inversion of the ring. Hydrochloride **Ib** shows in the ^{1}H NMR spectrum ($CDCl_3$) one signal only from the CH_3 group attached to the aromatic ring, while protons of the other fragments give rise to two sets of signals with an intensity ratio of ~1.2 : 1. The same compound in CD_3OD is characterized by a single set of signals, but signals from the piperidine ring protons are strongly broadened (no spin–spin coupling is observed. The ^{1}H NMR spectrum of hydrochloride **IIIb** in $CDCl_3$ contains two set of signals (intensity ratio ~1 : 3) from most protons. In going to DMSO-d_6, the signal intensity ratio changes to 1.1 : 1 (Table 1). Like hydrochloride **Ib**, compound **IIIb** in CD_3OD shows only one set of signals, and the piperidine ring

Scheme 1.



Ib, IIb **Ia, IVa**

I, **III**, R = CH_3; **II**, **IV**, R = Br.

1070-4280/01/3712-1782 $25.00 © 2001 MAIK "Nauka / Interperiodica"

Table 1. ^{1}H NMR spectra of compounds **Ia**, **Ib**, **IIIb**, and **IVb**, δ, ppm (*J*, Hz)

Compd. no.	Solvent	CH_3	$CH_3C(O)$	CH_3C arom.	3(5)-H_{ax}	3(5)-H_{eq}	2(6)-H_{ax}	2(6)-H_{eq}
Ia	$CDCl_3$	1.18 t (6.9)	–	2.27 s	1.77–1.89 m	1.87–1.96 m	2.34–2.44 m	2.65–2.74 m
Ib (1.2 : 1)[a]	$CDCl_3$	1.16 t (7)	–	2.27 s	2.37–2.51 m	2.05–2.17 m	2.51–2.65 m	3.10–3.17 m
		1.17 t (7)		2.27 s	2.72–2.87 m	2.05–2.17 m	3.14–3.29 m	2.9–2.97 m
Ib (1.6 : 1)[a]	DMSO-d_6	1.12 t (6.9)	–	2.26 s	2.19 m	1.9–2.0 m	3.11 m	3.21 m
		1.12 t (6.9)		2.26 s	2.01 m	1.9–2.0 m	2.83 m	3.12 m
Ib	CD_3OD	1.19 t (7)	–	2.29 s	1.99–2.18 m (4H)		3.1–3.3 m	3.3–3.47 m
IIIb (1 : 3)[a]	$CDCl_3$	1.17 t (7)	2.07 s	2.28 s	2.58–2.70 m	2.52–2.59 m	2.9–3.06 m	3.19[b]
		1.18 t (7)	2.03 s	2.28 s	2.52–2.62 m	2.39–2.48 m	2.72–2.87 m	2.89[b]
IIIb (1.1 : 1)[a]	DMSO-d_6	1.12 t (6.9)	2.02 s	2.22 s	2.3–2.42 m	2.45[b]	3.02–3.18 m	3.26[b]
		1.12 t (6.9)	2.01 s	2.22 s	2.3–2.42 m	2.48[b]	2.84–2.98 m	3.15[b]
IIIb	CD_3OD	1.20 t (7)	2.04 s	2.29 s	2.3–2.7 m (4H)		2.8–3.5 m (4H)	
IVb (1 : 2)[a]	$CDCl_3$	1.18 t (6.6)	2.07 s	–	2.60–2.75 m	2.50–2.60 m	3.05	3.2[b]
		1.19 t (6.6)	2.03 s		2.55–2.70 m	2.40–2.50 m	2.82 m	2.99[b]

Compd. no.	Solvent	CH_2N^+ (CH_2N)	OCH_2	CH_2O	$CH_2C≡$	H_{arom}	NH (OH)
Ia	$CDCl_3$	2.56 t (6)	3.49 q (6.9)	3.52 t (6)	4.68 s	6.48 d, 7.07 d (8.5)	–
Ib (1.2:1)[a]	$CDCl_3$	~3.5	3.46 q (7)	3.89 t (4.5)	4.63 s	6.81 d, 7.06 d (8.1)	11.8 (4)
		~3.5	3.47 q (7)	3.82 t (4.2)	4.72 s	6.84 d, 7.08 d (8.1)	11.6 (3.4)
Ib (1.6:1)[a]	DMSO-d_6	3.34[b]	3.45 q (6.9)	3.74[b]	4.76 s	6.86 d, 7.09 d (7.8)	10.95 s (5.9)
		3.34[b]	3.45 q (6.9)	3.74[b]	4.83 s	6.89 d, 7.09 d (7.8)	10.95 s (6.1)
Ib	CD_3OD	3.22[b]	3.53 q (7)	3.73 t (5)	4.75 s	6.86 d, 7.08 d (8.3)	–
IIIb (1:3)[a]	$CDCl_3$	~3.49	3.48 q (7)	3.93[b]	4.65 s	6.81 d, 7.07 d (8.4)	12.60 br.s
		~3.49	3.48 q (7)	3.86[b]	4.75 s	6.86 d, 7.1 d (8.4)	12.40 br.s
IIIb (1.1:1)[a]	DMSO-d_6	3.35[b]	3.45 q (6.9)	3.77[b]	4.77 s	6.85 d, 7.08 d (7.9)	11.52 br.s
		3.35[b]	3.45 q (6.9)	3.75[b]	4.86 s	6.92 d, 7.11 d (7.9)	11.37 br.s
IIIb	CD_3OD	3.22[b]	3.54 q (7)	3.74[b]	4.83 s	6.87 d, 7.07 d (6.7)	–
IVb (1:2)[a]	$CDCl_3$	~3.5	3.5 q (6.6)	3.94[b]	4.66 s	6.86 d, 7.41 d (8.4)	12.70 br.s
		~3.5	3.5 q (6.6)	3.90[b]	4.76 s	6.82 d, 7.37 d (8.4)	12.60 br.s

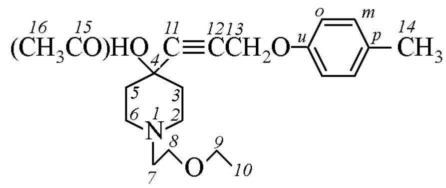
[a] For each compound, the upper line corresponds to epimer **A**, and the lower, to epimer **B**; the epimer ratio is given in parentheses.
[b] Unresolved signal.

protons appear as broadened unresolved signals. Two sets of signals are also observed in the ^{1}H NMR spectrum of hydrochloride **IVb** in $CDCl_3$; the intensity ratio is ~1 : 2.

The presence of two sets of signals in the spectra of hydrochlorides **Ib**, **IIIb**, and **IVb** can be explained by formation of two epimers **A** and **B** (Scheme 2) with different orientations of proton on the nitrogen atom. Casy and McErlane [2] studied the ^{13}C NMR spectra ($CDCl_3$) of isomeric 4-hydroxy-1,2,5-trimethyl-4-phenylpiperidines and esters derived therefrom and found a double set of signals in the spectra of hydrochlorides of the β-isomer and its acetoxy analog. The authors presumed that the β-isomer hydrochloride exists as a 1 : 1 mixture of two epimers with the following configurations of substituents in the piperidine ring: *t*-1-Me-*c*-2-Me-*t*-5-Me-*r*-4-OR (**C**) and *c*-1-Me-*c*-2-Me-*t*-5-Me-*r*-4-OR (**D**). In DMSO-d_6 the epimer ratio was 9 : 1. Therefore, epimer **C** with the equatorial hydroxy group was assumed to be more stable than epimer **D**; the authors also noted that the conformational equilibrium of epimer **D** is strongly contributed by conformer having equatorial phenyl group.

In the ^{13}C NMR spectra of hydrochlorides **Ib** and **IIIb** in CD_3OD we observed only one set of signals. In $CDCl_3$ and DMSO-d_6 the intensity ratio of signals belonging to different epimers was the same as in the

Table 2. ^{13}C NMR spectra (δ_C, ppm) of 1-(2-ethoxyethyl)-4-hydroxy-4-[3-(*p*-methylphenoxy)-1-propynyl]piperidine hydrochloride (**Ib**) and 4-acetoxy-1-(2-ethoxyethyl)-4-[3-(*p*-methylphenoxy)-1-propynyl]piperidine hydrochloride (**IIIb**)



Comp. no.	Solvent	C^2, C^6	C^3, C^5	C^4	C^7	C^8	C^9	C^{10}	C^{11}	C^{12}
Ib[a]	$CDCl_3$	48.31	34.75	61.38	59.80	66.38	64.07	14.71	89.02	78.70
		50.90	35.79	64.38	56.53	66.38	64.07	14.71	87.18	81.43
	DMSO-d_6	47.02	34.30	60.28	55.20	65.19	63.60	14.78	90.09	77.52
		49.46	35.37	63.40	55.20	65.19	63.60	14.78	88.05	80.51
Ib	CD_3OD	50.17	36.45	70.0	56.79	67.32	64.62	14.92	89.02	83.5
IIIb[a]	$CDCl_3$	48.08	32.47	68.42	56.30	66.42	64.70	14.72	84.07	81.95
		50.17	33.25	70.11	56.16	66.42	64.70	14.72	83.11	84.36
	DMSO-d_6	45.14	30.47	66.19	53.67	63.70	62.20	12.94	82.63	79.38
		47.33	31.19	68.73	53.56	63.70	62.20	12.94	81.50	83.41
IIIb	CD_3OD	50.96	34.32	71.21	56.85	67.40	64.56	14.92	86.11	83.90

Comp. no.	Solvent	C^{13}	C^{14}	C^{15}	C^{16}	C^i	C^o	C^m	C^p
Ib[a]	$CDCl_3$	55.93	20.14	–	–	155.1	14.4	129.6	130.5
		55.59	20.14	–	–	154.7	14.7	129.6	130.5
	DMSO-d_6	54.38	19.66	–	–	154.8	14.2	129.3	129.4
		53.96	19.66	–	–	154.6	14.4	129.3	129.4
Ib	CD_3OD	56.29	20.17	–	–	156.4	15.6	130.5	131.4
IIIb[a]	$CDCl_3$	55.80	20.11	168.3	21.32	154.6	14.5	129.5	130.5
		55.45	20.11	168.7	21.13	155.1	14.8	129.7	130.8
	DMSO-d_6	52.75	18.11	166.6	19.41	153.2	12.8	127.8	128.1
		52.59	18.11	166.7	19.32	153.0	13.1	127.8	128.2
IIIb	CD_3OD	56.20	20.17	170.1	21.15	156.3	15.8	130.5	131.6

[a] See note [a] to Table 1.

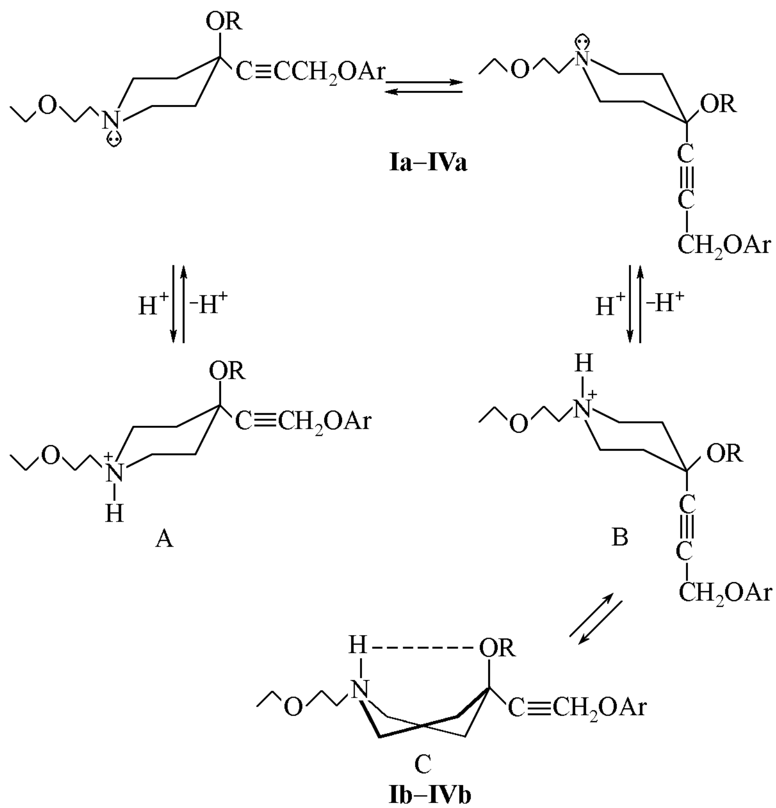
^{1}H NMR spectra (Table 2). The assignment of signals to epimers **A** and **B** is confirmed by the ^{13}C NMR data (monoresonance spectrum). The halfwidth of the C^{11} signal of epimer **A** (~30 Hz) is considerably smaller than the halfwidth of the corresponding signal of epimer **B** (~45 Hz). This allows us to speak with certainty that the aryloxypropynyl substituent in **A** occupies equatorial position [3].

It is known that conformational equilibria of 4-hydroxy-1,2,5-trimethyl-4-phenylpiperidines or their analogs, 4-hydroxy-1,2,5-trimethyl-4-organosilyl-piperidines, in aprotic solvents can involve a conformer having a structure of *skewed bath* which is stabilized by intramolecular hydrogen bond [4, 5]. In such structure, "heavy" substituent, e.g., phenyl or triphenylsilyl group, occupies equatorial position [4]. In our case structure **C** stabilized via H-bonding between the $\overset{+}{N}H$ proton and oxygen atom of the hydroxy or acetoxy group at C^4 is also possible. As a result, the aryloxypropynyl substituent in epimer **B** occupies the energetically favorable equatorial position. Probably, just this is the reason why conformer **B** of acetates **IIIb** and **IVb** strongly predominates in weakly polar chloroform and why the fraction of conformer **B** for acetate **IIIb** sharply decreases in going to more polar DMSO.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Mercury-300 spectrometer at 300 and 75 MHz,

Scheme 2.



respectively. The chemical shifts were measured relative to tetramethylsilane. Compounds **Ia** and **IIa** were synthesized as described in [1]; physical properties of the corresponding hydrochlorides (**Ib** and **IIb**) are also given therein.

Hydrochlorides IIIb and IVb (general procedure**).** To a solution of 0.005 mol of hydrochloride **Ib** or **IIb** in 0.05 mol of acetic anhydride we added 0.05 mol of acetyl chloride, and the mixture was kept for 24 h at 18–20°C. Excess acetic anhydride and acetyl chloride were distilled off under reduced pressure, the residue was dissolved in water, the solution was made alkaline by adding aqueous sodium carbonate, and free base **IIIa** or **IVa** was extracted into ethyl acetate. The extract was dried over anhydrous $MgSO_4$, and a solution of HCl in ether was added to isolate hydrochloride **IIIb** or **IVb**.

4-Acetoxy-1-(2-ethoxyethyl)-4-[3-(4-methylphenoxy)-1-propynyl]piperidine hydrochloride (IIIb). Yield 53%, mp 87–89°C (from alcohol–ether). Found, %: C 63.70; H 7.82; Cl 8.53; N 3.71. $C_{21}H_{30}ClNO_4$. Calculated, %: C 63.70; H 7.63; Cl 8.95; N 3.53.

4-Acetoxy-4-[3-(4-bromophenoxy)-1-propynyl]-1-(2-ethoxyethyl)piperidine hydrochloride (IVb). Yield 66%, mp 96–98°C (from alcohol–ether). Found, %: C 52.16; H 5.92; Br 17.13; Cl 7.61; N 3.02. $C_{20}H_{27}BrClNO_4$. Calculated, %: C 52.13; H 5.90; Br 17.34; Cl 7.69; N 3.03.

The authors are grateful to S.G. Klepikova for recording the ^1H and ^{13}C NMR spectra.

REFERENCES

1. Bazhykova, K.B., Praliev, K.D., and Poplavskaya, I.A., *Izv. Min. Nauki–Akad Nauk Resp. Kazakhstan, Ser. Khim.*, 1998, no. 3, pp. 112–120.
2. Casy, A.F. and McErlane, K.M.J., *Can. J. Chem.*, 1973, vol. 51, no. 11, pp. 1790–1796.
3. Rozhnov, V.B., Agashkin, O.V., Sokolova, T.D., Unkovskii, B.V., and Malina, Yu.F., *Zh. Org. Khim.*, 1985, vol. 21, no. 5, pp. 1097–1102.
4. Fomichev, A.A., Golovtsov, N.I., Rezakov, V.A., Varlamov, A.V., and Prostakov, N.S., *Khim. Geterotsikl. Soedin.*, 1986, no. 11, pp. 1496–1502.
5. Vlasova, T.F. and Sheinker, Yu.N., *Zh. Strukt. Khim.*, 1970, vol. 11, no. 4, pp. 640–645.