

Synthesis of Secondary Alcohols and Their Esters from 4-Alkoxy-4-acetyl-1-(2-ethoxyethyl)piperidines

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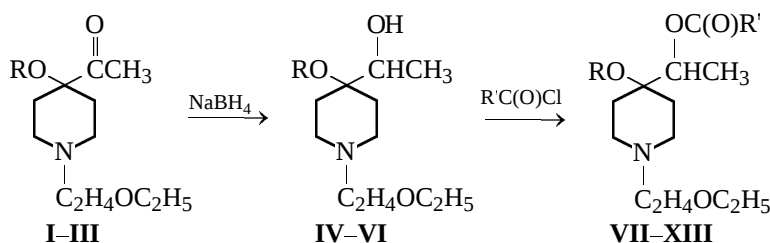
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Abstract—4-Alkoxy-4-(1-hydroxyethyl)-1-(2-ethoxyethyl)piperidines were prepared by reduction of 4-alkoxy-4-acetyl-1-(2-ethoxyethyl)piperidines. The esters of the hydroxyethyl derivatives were prepared. The presence of an asymmetric carbon atom in the molecules of the carbinols and their esters results in complication of their ^1H NMR spectra.

Some esters of N-substituted piperidin-4-ols exhibit analgetic activity [1–3]. To examine how replacement of the ester group by an alkoxy group will affect the properties of the compounds, we prepared methyl (IV), ethyl (V), and butyl (VI) ethers of 4-(1-hydroxy-

ethyl)-4-hydroxy-1-(2-ethoxyethyl)piperidine by reduction of the corresponding 4-acetyl derivatives I–III with NaBH_4 . Preparation of II [4] and III [5] was described previously. Methyl ether I was prepared similarly; its characteristics are given in the Experimental.



R = CH_3 (I, IV, VII, IX, XI), C_2H_5 (II, V, XII), C_4H_9 (III, VI, VIII, X, XIII); $\text{R}' = \text{CH}_3$ (VII, VIII), C_2H_5 (IX, X), C_6H_5 (XI–XIII).

Reduction of 4-acetyl derivatives I–III with NaBH_4 gave the corresponding secondary alcohols IV–VI whose structure was confirmed by ^1H NMR and IR spectra. In the IR spectra, the carbonyl absorption band ($\sim 1712\text{ cm}^{-1}$) disappears, and a hydroxyl absorption band (Table 1) appears at $3400\text{--}3700\text{ cm}^{-1}$.

By acylation of carbinols IV–VI with acyl halides, we prepared the corresponding acetates VII and X, propionates VIII and XI, and benzoates IX, XII, and XIII. Crystalline salts of these compounds were prepared (Table 1). The IR spectra of VII–XIII contain absorption bands of the ester group at $1708\text{--}1736\text{ cm}^{-1}$ ($\text{C}=\text{O}$) and $\sim 1190\text{--}1288\text{ cm}^{-1}$ (COC).

The ^1H NMR data for the compounds prepared are given in Table 2. In the spectra of the carbinols and their esters, the axial and equatorial protons at $\text{C}^3 +$

C^5 and $\text{C}^2 + \text{C}^6$ give two signals each. In the spectra of alcohols V and VI and of their esters VIII, X, XII, and XIII, containing the ethoxy and butoxy groups at C^4 , the OCH_2 protons give four signals (quartets and triplets, respectively).

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer (KBr pellets for crystalline samples, thin films for liquid samples). The ^1H and ^{13}C NMR spectra were taken on a Mercury-300 spectrometer (300 and 75 MHz, respectively). The chemical shifts are given relative to TMS. The reaction progress was monitored by TLC on Silufol UV-254 plates, eluent isopropyl alcohol–20% ammonia (9.3 : 0.7), development with iodine vapor.

Table 1. Yields, characteristic IR frequencies, and elemental analyses of secondary alcohols **IV–VI** and their esters **VII–XIII**

Comp. no.	Yield, %	mp, °C	IR spectrum, $\nu[\text{C}=\text{O}(\text{OH})]$, cm^{-1}	Found, %				Formula	Calculated, %			
				C	H	Cl	N		C	H	Cl	N
IV	82	^b	(3470)	62.18	10.87	–	6.34	$\text{C}_{12}\text{H}_{25}\text{NO}_3$	62.30	10.89	–	6.05
IVa	–	132–133	(3368)	52.30	8.60	–	4.30	$\text{C}_{14}\text{H}_{27}\text{NO}_7$	52.32	8.47	–	4.36
V	75	^b	(3408)	63.45	10.86	–	5.88	$\text{C}_{13}\text{H}_{27}\text{NO}_3$	63.64	11.09	–	5.71
VI	75	^b	(3456)	65.43	11.40	–	–	$\text{C}_{15}\text{H}_{31}\text{NO}_3$	65.89	11.43	–	–
VIa	–	132–134	–	58.16	10.43	11.10	4.50	$\text{C}_{15}\text{H}_{32}\text{ClNO}_3$	58.14	10.40	11.11	4.52
VIIa	68	146–148	1724	54.98	9.44	10.58	–	$\text{C}_{14}\text{H}_{28}\text{ClNO}_3$	54.87	9.21	10.46	–
VIII	67	^b	1736	64.52	10.46	–	4.42	$\text{C}_{17}\text{H}_{33}\text{NO}_3$	64.73	10.54	–	4.44
VIIIa	–	127–129	1736	58.40	8.69	–	–	$\text{C}_{21}\text{H}_{37}\text{NO}_8$	58.45	8.64	–	–
IX	62	^b	1736	62.95	10.39	–	–	$\text{C}_{15}\text{H}_{29}\text{NO}_4$	62.69	10.17	–	–
IXa	–	150–152	1736	54.43	8.22	–	4.00	$\text{C}_{17}\text{H}_{31}\text{NO}_8$	54.09	8.28	–	3.89
X	73	^b	1736	65.30	10.86	–	4.27	$\text{C}_{18}\text{H}_{35}\text{NO}_4$	65.61	10.70	–	4.25
Xa	–	130–132	1736	59.37	9.05	–	3.36	$\text{C}_{22}\text{H}_{39}\text{NO}_8$	59.30	8.82	–	3.17
XI	69	^b	1716	69.32	9.04	–	–	$\text{C}_{19}\text{H}_{29}\text{NO}_4$	68.02	8.71	–	–
XIa	–	168–170	1712	59.16	7.80	–	3.58	$\text{C}_{21}\text{H}_{31}\text{NO}_8$	59.28	7.34	–	3.29
XIIa	92	142–144	1720	62.24	8.64	9.46	3.81	$\text{C}_{20}\text{H}_{32}\text{ClNO}_4$	62.25	8.36	9.19	3.63
XIIIa	71	105–107	1708	64.05	8.55	8.18	–	$\text{C}_{22}\text{H}_{36}\text{ClNO}_3$	63.83	8.76	8.56	–

^a (**IVa**, **IXa**, **XIa**) Oxalates, (**VIa**, **VIIa**, **XIIa**, **XIIIa**) hydrochlorides, and (**VIIIa**, **Xa**) maleates. ^b Oil.

Table 2. ^1H NMR data for 4-alkoxy-4-(1-hydroxyethyl)-1-(2-ethoxyethyl)piperidines **IV–VI** and their esters **VII–XIII**, δ , ppm (J , Hz)

Comp. no. (solvent)	CH_3^a	$(\text{CH}_2)_2\text{C}$	$\text{C}^{3,5}\text{--H}$	$\text{C}^{2,6}\text{--H}$
IV (CDCl_3)	1.13 d, 1.20 d (3H, J 6.3), 1.18 t, 1.19 m (3H, J 7)	–	1.57–1.77 m (4H, H_a , H_e)	2.14–2.24 m, 2.26– 2.36 m (2H, H_a), 2.69–2.79 m (2H, H_e)
IV (C_6D_6)	0.99 t, 1.05 t (3H, J 7), 1.10 d, 1.29 d (3H, J 6.3)	–	1.49–1.58 m, 1.57–1.66 m (2H, H_e), 1.57–1.69 m, 1.70–1.82 m (2H, H_a)	2.17–2.27 m, 2.29–2.39 m, (2H, H_a), 2.59–2.67 m, (2H, H_e)
V (C_6D_6)	0.98 t (3H, J 7), 1.04 t (3H, J 7), 1.05 d (3H, J 6.3)	–	1.44–1.53 m, 1.53–1.62 m (2H, H_e), 1.52–1.63 m, 1.64–1.75 m (2H, H_a)	2.13–2.23 m, 2.31– 2.41 m (2H, H_a), 2.56– 2.64 m (2H, H_e)
VI (C_6D_6)	0.81 t (3H, J 7), 1.05 t (3H, J 6.9), 1.08 d (3H, J 6.6)	1.22–1.44 m (4H)	1.46–1.55 m, 1.56–1.65 m (2H, H_e), 1.55–1.66 m, 1.68–1.79 m	2.16–2.26 m, 2.31– 2.41 m (2H, H_a), 2.58– 2.66 m (2H, H_e)
VIa (CDCl_3)	0.92 t (3H, J 7.2), 1.18 d (3H, J 6.6)	1.37 m (2H), 1.54	1.87 m, 1.93 m (2H, H_e); 2.35 m, 2.40 m (2H, H_a)	2.96 m, 3.05 m (2H _a), 3.52 overlaps (2H _e)
VIIa (D_2O)	0.99 t J 7), 0.96 d, 1.03 d (3H, J 6.6)	–	1.63–1.76 m, 1.76–1.89 m (2H, H_a), 1.76–1.85 m, 2.00–2.09 m, 2H, H_e)	2.89–3.05 m (2H, H_a), 3.29–3.37 m (2H, H_e)
VIII (C_6D_6)	0.83 t (3H, J 7.2), 1.04 t (3H, J 7), 1.07 d (3H, J 6.5)	1.32 m (2H), 1.42 m (2H)	1.54–1.64 m (4H, H_a , 2H _e)	2.23–2.34 m (2H, H_a), 2.56–2.66 m (2H, H_e)

Table 2. (Contd.)

Comp. no. (solvent)	CH ₃ ^a	(CH ₂) ₂ C	C ^{3,5} -H	C ^{2,6} -H
VIIIa (DMSO- <i>d</i> ₆)	0.88 t (3H, <i>J</i> 7), 1.11 <i>d</i> (3H, <i>J</i> 6), 1.14 t (3H, <i>J</i> 6.7)	1.34 m (2H), 1.47 m (2H)	1.60–1.94 m (4H, H _a , H _e)	2.96 m (2H, H _a), 3.37 m (2H, H _e)
IXa (CDCl ₃)	1.16 t (3H, <i>J</i> 6.9), 1.15 <i>d</i> , 1.17 <i>d</i> (3H, <i>J</i> 6.5)	–	1.81–1.92 m, 1.85–1.96 m (2H, H _e), 2.03–2.17 m (2H, H _a)	2.94–3.07 m (2H, H _a), 3.53–3.63 m (2H, H _e)
X (C ₆ D ₆)	0.83 t (3H, <i>J</i> 7.2), 1.04 t (3H), <i>J</i> 7), 1.08 <i>d</i> (3H, <i>J</i> 6.3)	1.26–1.48 m (4H)	1.54–1.64 m (4H, H _a , H _e)	2.23–2.34 m (2H, H _a), 2.56–2.66 m (2H, H _e)
Xa (DMSO- <i>d</i> ₆)	0.88 t (3H, <i>J</i> 7), 0.96 <i>d</i> , 1.03 <i>d</i> (3H, <i>J</i> 6.6)	1.33 m (2H), 1.48 m (2H)	1.69–1.82 m, 1.74–1.87 m (2H, H _a), 1.78–1.87 m, 1.95–2.04 m (2H, H _e)	2.90–3.06 m (2H, H _a), 3.33–3.45 m (2H, H _e)
XIa (CDCl ₃)	1.15 t (3H, <i>J</i> 7), 1.17 <i>d</i> , 1.31 <i>d</i> (3H, <i>J</i> 6.3)	–	1.90–2.02 m, 1.94–2.06 m, (2H, H _e), 2.21–2.31 m (2H, H _a)	2.89–3.10 m, (2H, H _a), 3.56–3.67 m (2H, H _e)
XIIa (CDCl ₃)	1.17 t (3H, <i>J</i> 7), 1.18 t (3H, <i>J</i> 6.9), 1.33 <i>d</i> (3H, <i>J</i> 6.6)	–	1.91–2.00 m, 1.99–2.08 m (2H, H _e), 2.47–2.57 m, 2.52–2.62 m (2H, H _a)	3.00–3.11 m, 3.07– 3.18 m (2H, H _a), ~3.47–3.56 overlaps (2H, H _e)
XIIIa (CDCl ₃)	0.79 t (3H, <i>J</i> 7.2), 1.06 t (3H, <i>J</i> 6.9), 1.19 <i>d</i> (3H, <i>J</i> 6.3)	1.26 m (2H), 1.43 m (2H)	1.88 m (2H, H _e), 2.23 m (2H, H _a)	2.97 u/r (2H, H _a) 3.46 u/r (2H, H _e)

Comp. no. (solvent)	CH _{<i>n</i>} OC ^{4b}	CH ₂ N	CH ₂ O	C _{<i>as</i>} H	R'	OH (NH ⁺)
IV (CDCl ₃)	3.15 s, 3.22 s (3H)	2.57 t, 2.58 t (2H, <i>J</i> 6)	3.48 q (2H, <i>J</i> 7), 3.55 t (2H, <i>J</i> 6)	3.84 q (1H, <i>J</i> 6.3)	–	2.66 br ^c (1H)
IV (C ₆ D ₆)	2.95 s, 2.99 s (3H)	2.52 t (2H, <i>J</i> 6)	3.20 q, 3.23 q (2H, <i>J</i> 7; 3.43 t (2H, <i>J</i> 6)	3.63 q, 3.87 q (1H, <i>J</i> 6.3)	–	4.70 br (1H)
V (C ₆ D ₆)	3.04 q, 3.07 q, 3.16 q, 3.19 q (2H, <i>J</i> 7)	2.51 t (2H, <i>J</i> 6)	3.24 q (2H, <i>J</i> 7), 3.43 (2H, <i>J</i> 6)	3.58 q, 3.84 q (1H, <i>J</i> 6)	–	2.70 br (1H)
VI (C ₆ D ₆)	3.04 t, 3.07 t, 3.16 t, 3.19 t (2H, <i>J</i> 6.2)	2.52 t (2H, <i>J</i> 6)	3.23 q (2H, <i>J</i> 6.9), 3.42 t (2H, <i>J</i> 6)	3.63 q (1H, <i>J</i> 6.6)	–	2.98 br (1H)
VIa (CDCl ₃)	3.26 t, 3.28 t, 3.43 t, 3.45 t (2H, <i>J</i> 6.5)	3.17 u/r (2H)	3.51 q (6.9), 2H; 3.93 u/r ^c (2H)	~3.92 overlaps (1H)	–	2.85 r (11.75 br)
VIIa (D ₂ O)	3.06 s, 3.08 s, 3.11 s (3H)	3.15 t (2H, <i>J</i> 6.5)	3.41 q (2H, <i>J</i> 7), 3.62 t (2H, <i>J</i> 5.1)	3.83 q, 4.91 q (1H, <i>J</i> 6.6)	1.89 s, 1.92 s (3H)	–
VIII (C ₆ D ₆)	3.05 t, 3.08 t, 3.23 t, 3.26 t (2H, <i>J</i> 6)	2.52 t (2H, <i>J</i> 6)	3.24 q (2H, <i>J</i> 7), 3.42 t (2H, <i>J</i> 6)	5.08 q (1H, <i>J</i> 6.5)	1.61 s (3H)	–
VIIIa (DMSO- <i>d</i> ₆)	~3.35 overlaps (2H)	3.29 u/r (2H)	3.48 q (2H, <i>J</i> 6.7), 3.67 u/r (2H)	4.95 q (1H, <i>J</i> 6)	1.95 s, 2.02 s (3H)	9.17 br (OH, NH ⁺)

Table 2. (Contd.)

Comp. no. (solvent)	CH _n OC ^{4b}	CH ₂ N	CH ₂ O	C _{as} H	R'	OH (NH ⁺)
IXa (CDCl ₃)	3.23 s, 3.25 (3H)	3.22 u/r (2H)	3.46 q (2H, <i>J</i> 6.9), 3.74 u/r (2H)	5.04 q, 5.89 q (1H, <i>J</i> 6.5)	1.12 t (3H, <i>J</i> 7.5), 2.32 q (2H, <i>J</i> 7.5)	–
X (C ₆ D ₆)	3.07 t, 3.10 t, 3.25 t, 3.28 t (2H, <i>J</i> 6)	2.52 t (2H, <i>J</i> 6)	3.24 q (2H, <i>J</i> 7), 3.42 t (2H, <i>J</i> 7)	5.10 q (1H, <i>J</i> 6.3)	0.91 t (3H, <i>J</i> 7.5), 2.32 q (2H, <i>J</i> 7.5)	–
Xa (DMSO- <i>d</i> ₆)	3.25–3.40 overlaps (2H)	3.30 u/r (2H)	3.49 q (2H, <i>J</i> 7)	4.96 q (1H, <i>J</i> 6.6)	1.04 t (3H, <i>J</i> 7.5), 2.32 q (2H, <i>J</i> 7.5)	9.35 br (2H) (OH, NH ⁺) (9.33 br)
XIa (CDCl ₃)	3.24 s, 3.31 s (3H)	3.23 u/r (2H)	3.45 q (2H, <i>J</i> 7), 3.74 u/r (2H)	5.24 q, 5.89 q (1H, <i>J</i> 6.3)	7.46 t, 7.55 t, 8.00 d (5H, ³ <i>J</i> ~7.5)	(12.3 br)
XIIa (CDCl ₃)	3.41 q, 3.44 q, 3.53 q, 3.56 q (2H, 6.9)	3.20 t, 3.21 t (2H, <i>J</i> 4.5)	3.50 q (2H, <i>J</i> 7), 3.95 t (2H, <i>J</i> 4.5)	5.26 q, 5.90 q (1H, <i>J</i> 6.6)	7.45 t, 7.55 t, 8.09 d, 7.99 d (5H, ³ <i>J</i> ~7.2)	(12.3 br)
XIIIa (CDCl ₃)	3.23 t, 3.26 t, 3.32 t, 3.35 t (2H, <i>J</i> 6.3)	3.12 u/r (2H)	3.37 q (2H, <i>J</i> 6.9), 3.72 u/r (2H)	5.12 q, 5.75 q (1H, <i>J</i> 6.3)	7.36 t, 7.34 t, 7.92 d (5H, ³ <i>J</i> ~7.2)	11.39 br (2H) (OH, NH ⁺)

^a Here and hereinafter, the strongest signals in a given group are printed italic. ^b In **IV**, **VIIa**, **IXa**, and **XIa**, *n* = 3; in the other compounds, *n* = 2. ^c (br) Broadened singlet; (u/r) unresolved.

4-Acetyl-4-methoxy-1-(2-ethoxyethyl)piperidine I. A 2.1-g portion of 4-methoxy-4-ethynyl-1-(2-ethoxyethyl)piperidine [1] was added with stirring to a solution of 3.0 g of HgSO₄ in a mixture of 5 ml of H₂SO₄ (*d*₄²⁰ 1.83) and 60 ml of water. The mixture was heated at 85–90°C until the starting ether was completely consumed (6 h). After cooling, zinc dust was added, and the mixture was left overnight. The precipitate was filtered off, and the solution was alkalinized to pH ~10 and repeatedly extracted with benzene. The extract was dried over MgSO₄, the solvent was distilled off, and the residue was fractionated. Yield of **I** 2.01 g (88%), bp 79–80°C (1 mm Hg). ¹H NMR spectrum (CDCl₃), δ, ppm: 1.18 t (3H, CH₃, *J* 7 Hz), 1.74–1.82 m (2H, C^{3,5}H_e), 1.82–1.93 m (2H, C^{3,5}H_d), 2.17 s (3H, CH₃CO), 2.31–2.41 m (2H, C^{2,6}H_d), 2.57 t (2H, CH₂N, *J* 6 Hz), 2.63–2.71 m (2H, C^{2,6}H_e), 3.14 s (3H, OCH₃), 3.48 q (2H, CH₂O, *J* 7 Hz), 3.54 t (2H, CH₂O, *J* 6 Hz). Found, %: C 62.76; H 9.80. C₁₂H₂₃NO₃. Calculated, %: C 62.85; H 11.10.

Treatment of **I** with a solution of HCl in isopropyl alcohol gave hydrochloride **Ia**, mp 126–128°C (ethanol). Found, %: C 54.12; H 9.35; Cl 12.90; N 5.41. C₁₂H₂₄ClNO₃. Calculated, %: C 54.23; H 9.10; Cl 13.34; N 5.27.

4-(1-Hydroxyethyl)-4-methoxy-1-(2-ethoxyethyl)-

piperidine IV. A 0.15-g portion of NaBH₄ was added in small portions to a solution of 1.3 g of **I** in 30 ml of ethanol. The mixture was stirred at room temperature and then was kept at 60°C for 2 h (TLC monitoring). The solvent was distilled off, 5 ml of 6 M NaOH was added to the residue, and the mixture was extracted with chloroform. The extract was dried over MgSO₄, and the solvent was evaporated. Yield of **IV** (oil) 1.33 g (81%). Treatment of a solution of **IV** with a solution of oxalic acid in ethanol gave oxalate **IVa**; mp 132–133°C (ethyl acetate).

4-(1-Hydroxyethyl)-4-ethoxy-1-(2-ethoxyethyl)piperidine V was prepared similarly in 75% yield (Table 1).

4-Butoxy-4-(1-hydroxyethyl)-1-(2-ethoxyethyl)piperidine VI was prepared similarly in 75% yield; it was converted into hydrochloride **VIa** by treatment with a solution of HCl in isopropyl alcohol; mp 132–134°C (ethanol).

4-(1-Acetyloxyethyl)-4-methoxy-1-(2-ethoxyethyl)piperidine VII. A 3.34-g portion of acetyl chloride was added to a solution of 1.0 g of **IV** in 5 ml of chloroform; the mixture was allowed to stand for 48 h at room temperature (TLC monitoring). Then ether was added dropwise until the mixture became turbid, after which it was allowed to crystallize in a refrigerator.

The precipitate was filtered off and washed with ether. Yield of **VIIa** 0.8 g (68%), mp 146–148°C.

4-(1-Acetyloxyethyl)-6-butoxy-1-(2-ethoxyethyl)piperidine VIII was prepared similarly to **VII** from 0.5 g of **VI** and 0.14 g of acetyl chloride in 5 ml of chloroform. After alkalization and extraction, 0.36 g (67%) of **VIII** (oil) was obtained. Treatment of **VIII** with an equivalent amount of maleic acid gave maleate **VIIIa**, mp 138–140°C (ethanol).

4-Methoxy-4-(1-propionyloxyethyl)-1-(2-ethoxyethyl)piperidine IX. A 0.19-g portion of propionyl chloride was added to a solution of 0.5 g of **IV** in 5 ml of anhydrous chloroform. The mixture was allowed to stand at room temperature for 24 h (TLC monitoring). Excess reagents were distilled off, and the residue was alkalized with Na₂CO₃ to pH ~10 and extracted with benzene. The extract was dried over MgSO₄, and 0.4 g (62%) of **IX** (oil) was obtained; the product was converted into oxalate **IXa**, mp 150–152°C (ethyl acetate).

4-Butoxy-4-(1-propionyloxyethyl)-1-(2-ethoxyethyl)piperidine X was prepared similarly to **IX**. The oily product (yield 73%) was converted into maleate **Xa**, mp 130–132°C (ethanol).

4-(1-Benzoyloxyethyl)-4-methoxy-1-(2-ethoxyethyl)piperidine XI. A 1.8-g portion of benzoyl chloride was added to a solution of 1.0 g of **IV** in 5 ml of anhydrous chloroform; the mixture was allowed to stand at room temperature for 48 h (TLC monitoring). Then the solvent was distilled off, and the residue was acidified with HCl (1 : 1) to pH ~3 and extracted with benzene. The aqueous solution was alkalized and extracted with chloroform. The extract was dried over MgSO₄, and the solvent was evaporated. Yield of **XI** (oil) 1.0 g (69%). The product was converted into oxalate by treatment with oxalic acid in ethyl acetate; mp 150–152°C (ethyl acetate).

4-(1-Benzoyloxyethyl)-4-ethoxy-1-(2-ethoxyethyl)piperidine XIIa. A 1.6-g portion of benzoyl chloride was added to a solution of 1.0 g of **V** in 5 ml of pyridine. The mixture was allowed to stand at room

temperature for 24 h. Then the solvent was distilled off, and the residue was acidified with HCl (1 : 1) to pH ~3 and extracted with ether. The aqueous solution was alkalized with K₂CO₃ on cooling, the base was extracted with ether, and the extract was dried over MgSO₄. The desiccant was filtered off, the solvent was partially evaporated, and the residue was acidified with HCl in ether. Benzoate hydrochloride **XIIa** was obtained; yield 1.44 g (92%), mp 142–144°C (ethanol–ether).

4-(1-Benzoyloxyethyl)-4-butoxy-1-(2-ethoxyethyl)piperidine XIII. A 1.23-g portion of benzoyl chloride was added to a solution of 0.8 g of **VI** in 5 ml of chloroform. The mixture was allowed to stand at room temperature for 48 h. Then ether was added until the solution became turbid, and the mixture was left in a refrigerator to crystallize. The precipitate was filtered off and washed with ether. Yield of benzoate hydrochloride **XIIIa** 0.86 g (71%), mp 105–107°C (acetone–ether).

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