NEW METHOD OF SYNTHESIS OF 3-ALKYL-4-PIPERIDONES

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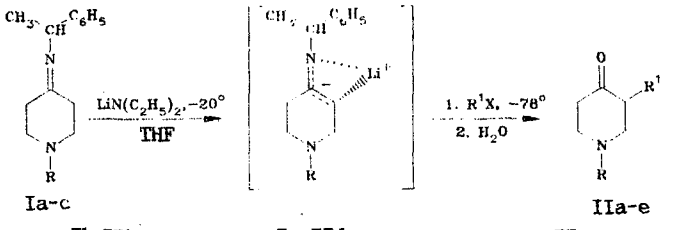
UDC 547.824'34:543.422

A new method is presented for the synthesis of 3-substituted 4-piperidones by alkylation of lithium derivatives of 4-(α-phenylethylimino) piperidines using alkyl halides.

Racemic derivatives of 3-substituted 4-piperidones possess analgesic and anaesthetic properties [1, 2]. We have studied the possible synthesis of chiral members of this series by asymmetric α-alkylation of the lithium salts of 4-piperidone imines (analogous to known derivatives of cycloalkanones [3, 4]).

The N-substituted 4-piperidone imines (Ia-c) were obtained in 70-90% yield by refluxing 4-piperidones with 1.2 equivalents of (±) or (–) α-phenylethylamine in benzene and azeotropic distillation of water. Ia-c are quite unstable compounds and sensitive to atmospheric moisture. They may be stored for an extended period under an inert atmosphere in the cold. Chromatography on silica gel caused decomposition to the starting materials. The structures of Ia-c were confirmed by a C=N stretching band in the IR spectrum at 1670 cm^{-1} and by signals for the phenylethyl fragment in the PMR spectrum. Imines Ia-c were α-alkylated in conditions analogous to those used for cyclohexanone imines [4].



Ia-c IIa-e

Ia, IIa R=CH_3, Ib, IIb,c R=p-C_4H_9, Ic, IId,e R=$CH(CH_3)C_6H_5$; IIa,c,e R^1=$CH_2C_6H_5$, b,d R^1=CH_3

Optimum yields of piperidones IIb, d were achieved by metallation of imines Ib, d at –20°C over 1 h with 1.5 equivalents of lithium amide followed by 3-4 equivalents of methyl iodide at –70°C for 2-3.5 h. After decomposition of the reaction mixture with water of hydrochloric acid the 3-substituted 4-piperidones were passed through a short silica gel column. Benzyl piperidones (IIa, c, e) were obtained similarly in 52-60% yields. The PMR spectrum of IId shows two doublets for the protons of the 3-methyl group at 0.93 and 0.98 ppm of equal integrated area which points to the formation of a mixture of two diasteroisomers in equal amounts. Introduction of the 3-benzyl group is confirmed in IIa,c by the appearance of two phenyl signals at 7.23 and 7.20 ppm respectively in their PMR spectra. The presence of two phenyl proton signals at 7.17 and 7.27 ppm in the spectrum of 1-α-phenylethyl-3-benzyl-4-piperidone also points to the formation of two pairs of diastereoisomers in equal amounts. Thus asymmetric alkylation of the lithium salts of piperidone imines under the given conditions is not observed. However, the developed method of synthesis of 3-alkyl substituted 4-piperidones by alkylation of lithium derivatives of 4-(α-phenylethylimino)piperidones can be recommended for synthesizing 3-substituted 4-piperidones which are difficult to obtain by other routes.

M. V. Lomonosov State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 372-374, March, 1986. Original article submitted April 4, 1985.

 0009-3122/86/2203-0304$12.50

TABLE 1. Properties of I-R-3-R'-4-Piperidones (IIa-e)

Piperidone*	R_f †	mp, °C (from ethanol)	Piperidone picrates: found, % C	H	N	Empirical formula	Calculated, % C	H	N	IR spectrum, C=O, cm^{-1}	PMR spectrum, δ, ppm, (J, Hz), 3-R'	Yield, %
IIa	0,5	175—176‡	52,8	4,6	12,2	$C_{13}H_{17}NO \cdot C_6H_3N_3O_7$	52,8	4,7	13,0	1720	7,23, s, 5H, C_6H_5	60
IIb	0,5	153—155	47,9	5,5	14,1	$C_{10}H_{19}NO \cdot C_6H_3N_3O_7$	48,2	5,6	14,1	1720	0,92, d (6), 3H, CH_3	77
IIc	0,4	91—92	56,1	5,5	11,8	$C_{16}H_{23}NO \cdot C_6H_3N_3O_7$	55,7	5,5	11,8	1725	7,20, s, 5H, C_6H_5	52
IId	0,7	163—165	53,1	5,2	12,6	$C_{14}H_{19}NO \cdot C_6H_3N_3O_7$	53,8	5,0	12,6	1730	0,92, d (6), 0,97, d (6), 3H, CH_3	67
IIe	0,7	155—157	59,5	5,1	11,0	$C_{20}H_{23}NO \cdot C_6H_3N_3O_7$	59,8	5,0	10,7	1730	7,17, s, 5H, C_6H_5	57

*IIa) R = CH_3; b,c) R = p-C_4H_9, d,e) R = $CH(CH_3)C_6H_5$; a,c,e) R' = $CH_2C_6H_5$; b, d) R' = CH_3.
†Silufol-254. IIa in benzene:acetone (3:1):IIb in benzene: acetone:chloroform (6:2:1, saturated with ammonia); IIc-e in benzene:acetone (6:1).
‡Lit mp picrate = 169.5-171°C (from ethanol) [3].

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer as films in paraffin oil and PMR spectra on a T-60 instrument in $CDCl_3$.

4-Piperidone imines (Ia-c) were obtained by refluxing 4-piperidones with 1.25 equivalents of α-phenylethylamine in absolute benzene (argon stream) using a Dean and Stark apparatus with subsequent vacuum distillation.

Ia. Yield 90%, bp 148-149°C (7 mm), n_D^{20} 1.5397. IR spectrum (film): 1670 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 2.27 (3H, s, N-CH_3), 2.47-2.53 (8H, m, piperidine ring protons), 1.45 (3H, d, J = 6.6 Hz, CH_3CH), 4.72 (1H, q, J = 6.6 Hz, CH_3CH), 7.37 ppm (5H, m, CHPh), Found: C 77.2; H 9.2; N 12.6%. $C_{14}H_{20}N_2$. Calculated: C 77.7; H 9.3; N 13.0%.

Ib. Yield 70%, bp 108-110°C (1 mm), n_D^{20} 1.5251. IR spectrum (film): 1670 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 0.9-1.5 and 2.2-2.6 (8H and 9H, two multiplets, piperdine ring and n-butyl protons), 1.34 (3H, d, J = 6.6 Hz, CH_3CH) 4.56 (1H, q, J = 6.6 Hz, CHPh), 7.1 ppm (5H, s, CHPh). Found: C 79.1; H 10.2; N 10.4%. $C_{17}H_{26}N_2$. Calculated: C 79.0; H 10.1; N 10.8%.

Ic. Yield 90%. IR spectrum (film): 1670 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 1.31 (3H, d, J = 6.6 Hz, 1-$CHPhCH_3$), 2.3-2.8 (8H, m, piperidine ring), 3.43 (1H, q, J = 6.6 Hz, 4-$CHCH_3Ph$), 7.2 ppm (10H, s). Found: C 82.6; H 8.5; N 8.3%. $C_{21}H_{26}N_2$. Calculated: C 82.3; H 8.6; N 9.1%. Analogously from (-) α-phenylethylamine (with $[\alpha]_D^{20}$ −41°, no solvent) there were obtained imines Ib with $[\alpha]_D^{20}$ −42.5° (c 1.4, benzene) and Ic with $[\alpha]_D^{20}$ −49.1° (c 9.2, benzene).

1-Methyl-3-benzyl-4-piperidone (IIa). 1-Methyl-4- (α-phenylethylimino)piperidine (Ia, 0.54 g, 2.5 mmoles) in absolute THF (2.5 ml) at −23°C was added dropwise to a solution of lithium diethylamide (previously prepared at −10°C from diethylamine (0.55 g, 7.5 mmoles) in absolute THF (10 ml) and an ethereal solution of methyl lithium (5.1 ml, 7.5 mmoles, 1470 mmoles/liter). After one hour the reaction mixture was cooled to −75°C and benzyl bromide (1.27 g, 10 mmoles) added dropwise. After holding for 1 h at −75°C, the temperature was slowly raised to 0°C. Water (5 ml) was added and the product was extracted with ether (10 × 20 ml) and dried with 4Å molecular sieve. Following removal of ether, the oil (2.3 g) was column chromatographed on silica gel using benzene:acetone (5:1) as eluent. Combination of the homogeneous chromatographic fractions gave 1-methyl-3-benzyl-4-piperidone (IIa, 0.3 g, 60%) as a pale yellow oil.

Piperidones IIb-e were obtained similarly. The properties of all of the piperidones IIa-e are presented in Table 1.

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MASS SPECTROMETRY OF STEREOISOMERIC 3-HYDROXY-4-PIPERIDONES

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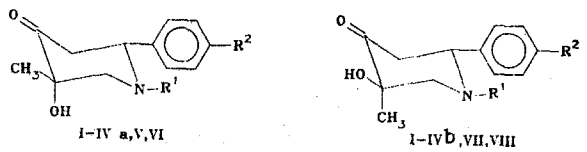
UDC 547.723:543.51

The existence of several sites of charge localization upon the mass spectrometric decomposition of stereoisomeric 3-hydroxy-4-piperidones leads to a large number of fragmentation products both with retention and destruction of the piperidine ring. Analysis of the mass spectra of the compounds studied showed that the appearance of $[M - CO]^+$ ion peaks for isomers with an axial hydroxyl group may serve as a method for determining the configuration of the carbinol site of such cyclic structures.

A mass spectrometric study was carried out on the major characteristic pathways for the decomposition of the molecular ions (M^+) of stereoisomeric 3-hydroxy-4-piperidones in order to establish correlations between the structure of these compounds and their mass spectra and possible analytical applications. The mass spectra of the compounds studied are published for the first time although Ermakov [1, 3, 4] and Bartanyan [2] have already discussed the fragmentation of alkyl derivatives of 4-piperidone and 4-piperidol.

3-Hydroxy-4-piperidones (I)-(VIII) contain a tertiary nitrogen atom, carbonyl, hydroxyl and phenyl groups, which may serve as positive charge localization sites in M^+. Thus, these mass spectra were interpreted assuming predominant charge localization on one of these sites. The concept of charge localization on individual molecular sites is used in mass spectrometry to explain pathways for the decomposition of organic compounds, including piperidine compounds [1-6]. The decomposition of piperidones Ia, IIb, IIIa, IIIb and IVa was studied using high-resolution mass spectrometry. The fragmentation sequence for several of these derivatives was studied using metastable ions by the DADI method.



Ia, b, V R^1=H, IIa, b, IIIa, b, VII, VIII R^1=CH_3, IVa, b, VI R^1=CH_2Ph; Ia, b, IIa, b, IVa, b R^2=H, IIIa, b, V, VI R^2=F, VII R^2=CH_3, VIII R^2=Cl

These compounds are characterized by an M^+ peak with intensity $\geqslant$10% of the maximal peak (Table 1). Analysis of the mass spectra showed that two competing pathways obtain upon charge localization in M^+ on the piperidine ring nitrogen atom (scheme 1) involving both opening and retention of the piperidine ring. One of the major decomposition processes of previously studied derivatives of piperidine [1-4, 7] and 3,4-dihydroxypiperidines [6] containing a substituent in the α-position relative to the nitrogen atom is loss of this substituent. How-

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 0009-3122/86/2203-0306$12.50