Chemistry of Heterocyclic Compounds, Vol. 33, No. 6, 1997

SYNTHESIS OF SUBSTITUTED 4-ACETYLAMINO-4-PHENYLPIPERIDINES FROM THE CORRESPONDING 4-PIPERIDOLS UNDER RITTER REACTION CONDITIONS

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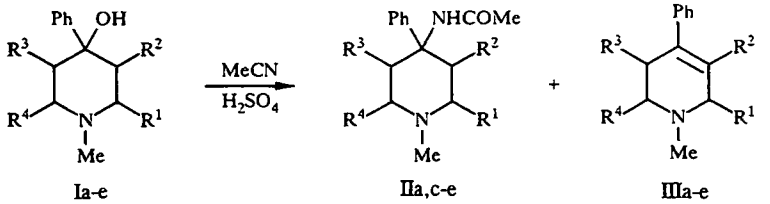
The reaction of substituted 4-phenyl-4-piperidols with acetonitrile under Ritter reaction conditions leads to formation of mixtures of the corresponding 4-acetylamino-4-phenylpiperidines and 1,2,5,6-tetrahydropyridines, from which we isolated the target amides by fractional crystallization.

The Ritter reaction of 4-alkyl-4-piperidols with acetonitrile in the presence of conc. H_2SO_4, leading to formation of substituted 4-acetylaminopiperidines, is described in [1]. Compounds of this type, belonging to the aminoamide class, are of interest as potential biologically active substances [2].

We have studied the possibility of synthesis of 4-acetylaminopiperidines from 1-methyl- [3], 1,3-dimethyl- [4], 1,2,5-trimethyl- [5], -4-phenyl-4-piperidols (Ia-c), and also 1,3(1,5)-dimethyl-2,4-diphenyl-4-piperidols (Id, e) [6]. Phenols Ia-e without preliminary separation into individual stereoisomers were reacted with acetonitrile in the presence of conc. H_2SO_4 (~20°C, 12-24 h). As a result, the corresponding substituted 4-acetylamino-4-phenylpiperidines IIa, c-e were obtained in the form of individual stereoisomers and dehydration products of 4-piperidols: 4-phenyltetrahydropyridines IIIa-e.

4-Phenyl-4-piperidol (Ia) is practically completely converted to the desired 4-acetylamino-4-phenylpiperidine (IIa); the yield of amides IIc, d is 32% and 67% respectively; from 1,3-dimethyl-4-phenyl-4-piperidol (Ib) under these conditions, 1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (IIIb) is formed exclusively; amide IIe could be isolated in pure form in ~3.5% yield. The different behavior of the phenols Ia-e under Ritter reaction conditions is probably connected with the spatial structure of the molecules and with the stability of the intermediate carbocation, which is formed according to the generally accepted Ritter reaction mechanism [7].



Ia-e IIa,c-e IIIa-e

I—III a $R^1 = R^2 = R^3 = R^4 = H$; b $R^2 = Me$, $R^1 = R^3 = R^4 = H$; c $R^2 = R^4 = Me$, $R^1 = R^3 = H$; d $R^2 = Me$, $R^1 = Ph$, $R^3 = R^4 = H$; e $R^4 = Ph$, $R^2 = Me$, $R^1 = R^3 = H$

The 4-phenyltetrahydropyridines IIIa-e were identified using TLC by comparison with compounds described earlier [8-10] having R_f ~ 0.8 (system B), while amides IIa, c-e in all cases have a lower value of R_f. The structure of the undescribed tetrahydropyridine IIId is supported by the PMR spectrum, in which signals are present from the protons of two structural isomers formed in about equal amounts: 1,3-dimethyl-2,4-diphenyl-1,2,5,6-tetrahydropyridine (IIId) [1.24 (s, 3-CH_3); 2.20 (s, N−CH_3); 3.64 ppm (broad s, 2-H)] and 1,5-dimethyl-4,6-diphenyl-1,2,5,6-tetrahydropyridine [0.77 (d, 5-CH_3); 2.06 (s, N−CH_3); 3.01 (d, 6-H); 3.38 (m, 2-H); 5.89 ppm (m, 3-H)].

M. V. Lomonosov State Academy of Fine Chemical Technology, Moscow 117571. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 776-780, June, 1997. Original article submitted December 27, 1996.

 0009-3122/97/3306-0676$18.00

TABLE 1. Characteristics of Substituted 4-Acetylamino-4-phenylpiperidines (IIa, c-e)

Compound	Empirical formula	Found / Calculated, %			T_{mp}, °C (hexane)	Yield, %
		C	H	N		
IIa	$C_{14}H_{20}N_2O$	72,36 / 72,38	8,63 / 8,68	11,86 / 12,06	143...144	86
IIc	$C_{16}H_{24}N_2O$	74,13 / 73,81	9,55 / 9,29	10,44 / 10,76	177...179 (eth.-chlf.)	32
IId	$C_{21}H_{26}N_2O \cdot 1/2\ H_2O$	76,84 / 76,10	7,91 / 8,21	8,09 / 8,45	195...196	67
IIe	$C_{21}H_{26}N_2O \cdot H_2O$	73,80 / 74,08	7,47 / 8,29	8,19 / 8,23	174...175	3

TABLE 2. PMR Spectra of Substituted 4-Acetylamino-4-phenylpiperidines IIa, c-e

Compound	Chemical shifts, d, ppm	Proton spin-spin coupling constants, J, Hz
IIa	2,0 (3H, s, $COCH_3$); 2,31 (3H, s, N—CH_3); 2,1...2,4 and 2,73 (m, ring protons) 5,63 (1H, br. s., NH); 7,2...7,3 (5H, m, 4-C_6H_5)	
IIc	0,59 (3H, m, 5-CH_3); 1,12 (3H, d, 2-CH_3); 1,89 (1H, d.d.d., 3*a*-H); 2,13 (3H, c, $COCH_3$); 2,18 (3H, m, 2*a*-H, 5*a*-H, 6*a*-H); 2,32 (3H, s, N—CH_3); 2,77 (1H, m, 6*e*-H); 3,02 (1H, d.d, 3*e*-H); 5,47 (1H, br. s, NH); 7,4...7,2 (5H, m, 4-C_6H_5)	$J_{5a,CH3}$ = 6,6; $J_{2a,CH3}$ = 6,1; $J_{3a,3e}$ = 14,1; $J_{3a,2a}$ = 11,2; $^4J_{3a,NH}$ = 0,7; $J_{3e,2e}$ = 2,2
IId	0,26 (3H, d, 3-CH_3); 2,01 (1H, d.q, 3*a*-H); 2,10 (3H, s $COCH_3$); 2,39 (1H, d.d.d.d, 5*a*-H); 2,51 (1H, d.d.d, 6*a*-H); 2,86 (1H, d.d.d, 6*e*-H); 3,15 (1H, d, 2*a*-H); 3,15 (1H, d.d.d.d 5*e*-H)	$J_{3a,CH3}$ = 7,08; $J_{3a,2a}$ = 10,25; $J_{5a,5e}$ = 12,5; $^4J_{5a,NH}$ = 0,5; $J_{6a,6e}$ = $J_{6a,5a}$ = 12,5; $J_{6e,5a}$ = = $J_{6a,5e}$ = 3,42; $J_{5e,6e}$ = 2,0
IIe	0,72 (3H, d, 5-CH_3); 1,81 (3H, s, N—CH_3); 2,13 (3H, s, $COCH_3$); 3,09 (1H, d.d.q, 5*a*-H); 3,19 (1H, d.d, 3*e*-H); 3,37 (1H, d.d.d, 3*a*-H); 3,60 (1H, d.d, 6*e*-H); 4,04 (1H, d.d 6*a*-H); 4,70 (1H, d.d, 2*a*-H); 7,21...7,45 (C_6H_5 protons); 7,72 (1H, br. s, NH)	$J_{5a,CH3}$ = 7,30; $J_{5a,6a}$ = 12,20; $J_{5a,6e}$ = 3,4; $J_{3e,3a}$ = 14,30; $J_{3e,2a}$ = 2,40; $J_{3a,2a}$ = 11,90; $^4J_{3a,NH}$ = 0,60; $J_{6e,6a}$ = 12,20

*Solvent, $(CD_3)_2CO$.

TABLE 3. Mass Spectra* of Compounds IIa, c-e

Compound	*m/z* values (intensity, %)
IIa	232 (8), 174 (11), 173 (100), 172(55), 96 (21), 91 (12), 71 (14), 70 (12), 44 (13), 43 (33), 42 (44)
IIc	260 (9), 245 (12), 201 (16), 200 (7), 187 (15), 186 (100), 85 (14), 71 (8), 56 (6), 43 (5), 42 (7)
IId	322 (9), 248 (53), 204 (100), 161 (39), 160 (36), 146 (31), 133 (33), 132 (97), 118 (51), 117 (22), 91 (25)
IIe	322 (4), 263 (32), 248 (100), 218 (47), 186 (32), 146 (37), 132 (38), 118 (49), 104 (33), 91 (43), 42 (43)

*The molecular ion peak and the ten most intense peaks are given.

The properties and yields of the synthesized substituted 4-acetylamino-4-phenylpiperidines IIa, c-e are given in Table 1. In the IR spectra of compounds IIa, c-e absorption bands are present at ~3500-3300 cm^{-1} (NH stretch), ~1640 cm^{-1} ("amide I" band), and ~1530 cm^{-1} ("amide II" band). The parameters of the PMR spectra of amides IIa, c-e are given in Table 2.

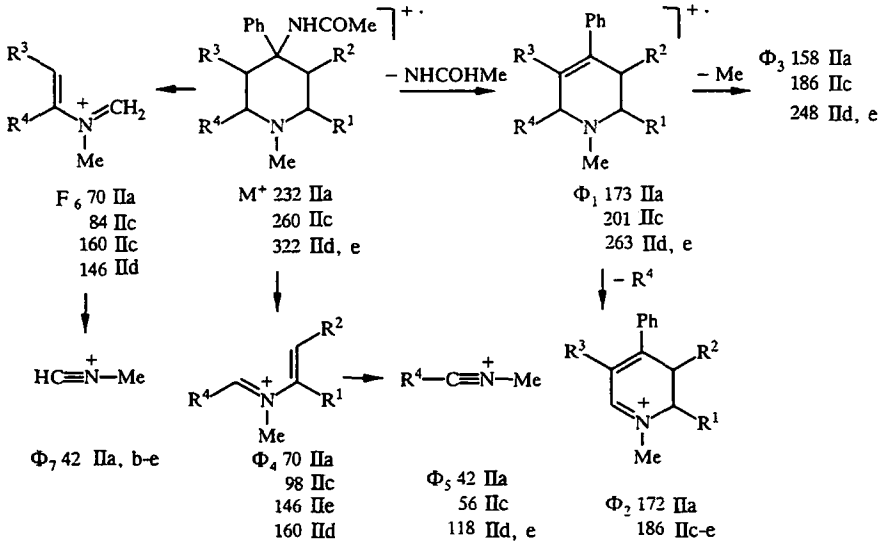
Based on the PMR spectra, from the values of the spin–spin coupling constants for protons 2-H, 3-H, 5-H, and 6-H of the piperidine ring we determined the relative configuration of the substituents at the $C_{(2)}$, $C_{(3)}$, $C_{(5)}$ atoms of amides IIc-e. All the substituents in the indicated positions of the piperidine ring are equatorial. Determination of the orientation of the geminal phenyl and acetylamino groups at the $C_{(4)}$ atom of the ring is the most difficult. We know [11]

that comparison of the half-widths of signals from the $C_{(1)}$ atoms of the phenyl ring in the ^{13}C NMR spectra of two stereoisomers is used to solve such problems. We observed the long-range spin–spin coupling of the 3-H_a proton with the proton of the acetylamino group with spin–spin coupling constant ^4J = 0.5-0.7 Hz. According to known stereochemical requirements for the ^4J constants [12], we can conclude that the acetylamino group has an axial orientation. It is interesting to note that the long-range spin–spin coupling ^4J in this case is transferred along the W-shaped chain of atoms, one of which is nitrogen: NH–C–C–H. We noted such coupling including an oxygen atom earlier for isomers of alcohols with an axial hydroxyl group [6].

Thus the synthesized compounds have the following configurations: IIc 4*r*-acetylamino-1,2*t*,5*c*-trimethyl-4-phneyl-; IId 4*r*-acetylamino-1,3*c*-dimethyl-2*t*,4-diphenyl; IIe 4*r*-acetylamino-1,5*c*-dimethyl-2*t*,4-diphenylpiperidines.

The structure of compounds IIa, c-e is supported by their mass spectra (Table 3). The intensity of the molecular ion M^+ peaks in the spectra of these compounds is no greater than 10%, and the main process for decomposition of the M^+ ions is sequential detachment of a neutral acetamide molecule and the substituent R^4 or methyl radical with formation of the ions F_1-F_3 (see Scheme). Opening of the piperidine ring in the M^+ ions, typical for substituted piperidines, leads to the appearance in the spectra of compounds IIa, c-e of rather intense peaks for ions F_4-F_7.

Scheme



The numbers given on the Scheme indicate the mass to charge ratio *m/z* of the ion.

In contrast to the mass spectra of 2-phenyl-4-piperidones [13] and 4-piperidols [6] we studied earlier, for compounds IId, e we see practically no fragmentation of the M^+ ions connected with detachment of a phenyl radical. We noted a similar difference in the decomposition processes for M^+ ions when studying the mass spectra of 4,4-diacetylaminopiperidines [14].

EXPERIMENTAL

The PMR spectra of the investigated compounds were recorded on a Bruker WM-250 spectrometer for 2% solutions in $CDCl_3$. The proton chemical shifts were measured with respect to the internal standard HMDS. The mass spectra were obtained on a Finnigan MAT-90 with ionizing electron energy 70 eV by direct injection of the sample into the source. The temperature of the ionization chamber was 200°C, the vaporization temperature of the samples was 35-135°C. The IR spectra of the synthesized compounds were recorded on a Shimadzu IR-435 in Vaseline oil. Thin-layer chromatography was done on plates with a nonadherent layer of aluminum oxide (standard activity II) in the solvent system hexane–ethylacetate, 1:1 (A); ether–methanol, 10:0.5 (B); ether (C).

The substituted 4-phenyl-4-piperidols were synthesized according to the procedures in the following references: Ia [3], Ib [4], Ic [5], Id, e [6].

4-Acetylamino-4-phenylpiperidine (IIa). Concentrated H_2SO_4 (1.1 ml) was added to a mixture of 0.63 g (0.0033 moles) 1-methyl-4-phenyl-4-piperidol (Ia) and 0.27 g (0.0066 mole) acetonitrile with stirring; the addition rate was such that the temperature of the reaction mixture did not go above 60-70°C. The reaction mass was allowed to stand for 24 h at ~20°C and then was poured over ice (~10 g) and then extracted with ether (2 × 50 ml). Then it was alkalized with a saturated potassium carbonate solution, extracted with ether and then chloroform, and then dried. The solvents were driven off and 0.8 g were obtained of a mixture of 4-acetylamino-4-phenylpiperidine (IIa) and 4-phenyl-1,2,5,6-tetrahydropyridine (IIIa), R_f 0.2 and 0.7 (system A) respectively. Compound IIa (0.65 g) was isolated by fractional crystallization from hexane, R_f 0.2 (system A).

4-Acetylamino-1,2,5-trimethyl-4-phenylpiperidine (IIc). Using a similar procedure, from 4 g (0.018 moles) 1,2,5-trimethyl-4-phenyl-4-piperidol (Ic), 1.6 g (0.036 moles) acetonitrile, and 6 ml conc. H_2SO_4 we obtained 4.59 g of a mixture containing the starting piperidol Ic, 4-acetylamino-1,2,5-trimethyl-4-phenylpiperidine (IIc), and 1,3,6-trimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (IIIc), R_f 0.7, 0.6, and 0.8 respectively (system B). Amide IIc (1.3 g) was obtained by fractional crystallization from hexane followed by recrystallization from a mixture of ether with chloroform.

4-Acetylamino-1,3-dimethyl-2,4-diphenylpiperidine (IId). Using a similar procedure, from 1.1 g (0.004 moles) 1,3-dimethyl-2,4-diphenyl-4-piperidol (Id), 0.3 g (0.008 moles) acetonitrile, and 1.33 ml conc. H_2SO_4 we obtained 1.09 g of a mixture of amide IId and tetrahydropyridine IIId, R_f 0.15 and 0.8 respectively (system C). Amide IId (0.86 g) was isolated by fractional crystallization from hexane, R_f 0.15 (system C).

4-Acetylamino-1,5-dimethyl-2,4-diphenylpiperidine (IIe). Using a similar procedure, from 2.7 g (0.0096 moles) 1,5-dimethyl-2,4-diphenyl-4-piperidol (Ie), 0.79 g (0.0192 moles) acetonitrile, and 3.2 ml conc. H_2SO_4 we obtained 2.96 g of a mixture of compounds with R_f 0.8, 0.6, 0.3, 0.1 (system C). The mixture was chromatographed on a column with Al_2O_3 (~60 g) and we isolated 1.59 g tetrahydropyridine IIIe, R_f 0.8 (system C), using hexane as the eluent, and a mixture of compounds with R_f 0.6, 0.3, and 0.1 (ether as the eluent), from which we obtained 0.1 g 4-acetylamino-1,5-dimethyl-2,4-diphenylpiperidine (IIe) by fractional crystallization from hexane, R_f 0.3 (system C).

1,3-Dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (IIIb). Using a similar procedure, we reacted 0.9 g (0.0044 moles) 1,3-dimethyl-4-phenyl-4-piperidol (Ib), 0.36 g (0.0088 moles) acetonitrile, and 1.4 ml conc. H_2SO_4. After 12 h, according to TLC the reaction mixture contained the starting Ib and IIIb, R_f 0.3 and 0.6 respectively (system A). Heating the reaction mixture at 30-40°C for 8 h led to formation of exclusively tetrahydropyridine IIIb, R_f 0.6 (system A).

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