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SYNTHESIS OF SUBSTITUTED 4,4-DIACETYLAMINOPIPERIDINES

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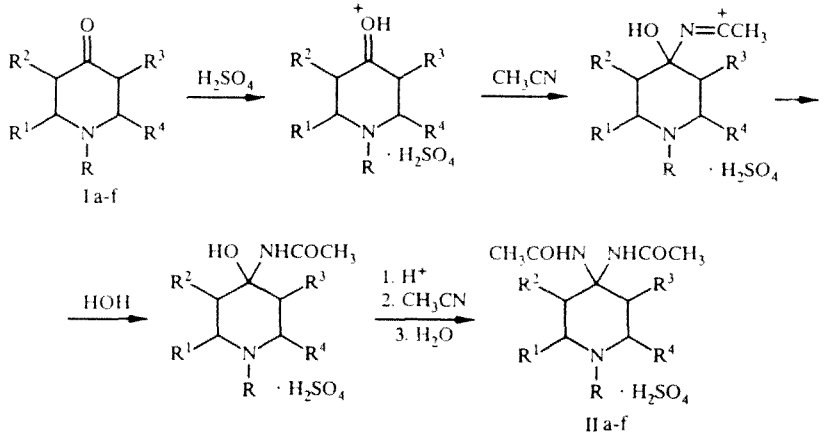
The synthesis of a series of 4,4-diacetylaminopiperidines has been achieved by the reaction of 4-piperidones, described earlier, with acetonitrile in the presence of concentrated sulfuric acid. The structure and the three-dimensional constitution of the compounds has been confirmed by IR, PMR, and mass spectrometric data.

It is known that compounds which contain an amide and an amino group in the molecule possess various biological activities [1]; The synthesis of similar bifunctional compounds of the piperidine series is therefore of considerable interest.

Data are available in the literature which show that some aldehydes react with acetonitrile and benzonitrile to form N,N^1-alkylidene bisamides [RCH(NHCOR^1)$_2$, where R, R^1 = H, C_6H_5]; however, analogous conversions of ketones are not known [2-4]. We have achieved the reaction of some substituted 4-piperidones with acetonitrile in the presence of concentrated H_2SO_4. The following piperidones served as the starting compounds: 1-methyl- (Ia) [5], 1,2,5-trimethyl- (Ib), an industrial product, 1,3(1,5)-dimethyl-2-phenyl- Ic, d), [6], 2,6-diphenyl- (Ie), and 1-methyl-2,6-diphenyl- (If) piperidones [7]. The reaction of the 4-piperidones (Ia-f) with acetonitrile was carried out in a acid medium at room temperature or at 60°C, giving the corresponding 4,4-diacetylaminopiperidones (IIa-f). It can be assumed that protonation of the carbonyl group of the piperidones (Ia-f) leads to the formation of the carbocation, which suffers nucleophilic attack by the acetonitrile molecule, leading to the formation of the amide group in analogy with the generally accepted mechanism of the Ritter reaction [3].



I, II a R = CH_3, $R^1 = R^2 = R^3 = R^4 = H$; b R = $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$; c R = $R^2 = CH_3$, $R^1 = C_6H_5$, $R^3 = R^4 = H$; d R = $R^3 = CH_3$, $R^1 = C_6H_5$, $R^2 = R^4 = H$; e R = $R^2 = R^3 = H$, $R^1 = R^4 = C_6H_5$; f R = CH_3, $R^1 = R^4 = C_6H_5$, $R^2 = R^3 = H$

The properties and yields of the synthesized compounds are given in Table 1. The three-dimensional constitution and structure of the compounds was confirmed by IR, PMR, and mass spectrometric data. IR spectra of the diamides (IIa-f) contain absorption bands at ~1650 cm^{-1} (I amide band) and ~1520 cm^{-1} (II amide band). The parameters of the PMR spectra of the diamides (IIa-f) are presented in Table 2. The data show that gemdiacetylamino groups produce an unusually strong unscreening effect on the vicinal protons.

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TABLE 1. Substituted 4,4-Diacetylaminopiperidines IIa-f

Compound	Empirical formula	mp, °C (hexane-acetone)	Yield, %
IIa	$C_{10}H_{19}N_3O_2$* · $C_6H_3N_3O_7$	173...174*	78
IIb	$C_{12}H_{23}N_3O_2$* · $C_6H_3N_3O_7$	142...143*[2]	81
IIc	$C_{17}H_{25}N_3O_2$	190...191	92
IId	$C_{17}H_{25}N_3O_2$	189...190	85
IIe	$C_{21}H_{25}N_3O_2$	235...235,5	56
IIf	$C_{22}H_{27}N_3O_2$	272...273*[2]	70

*Characterized as the picrates.

*[2]Purified by washing with ether.

TABLE 2. Parameters of the PMR Spectra of 4,4-Diacetylaminopiperidine IIa-f

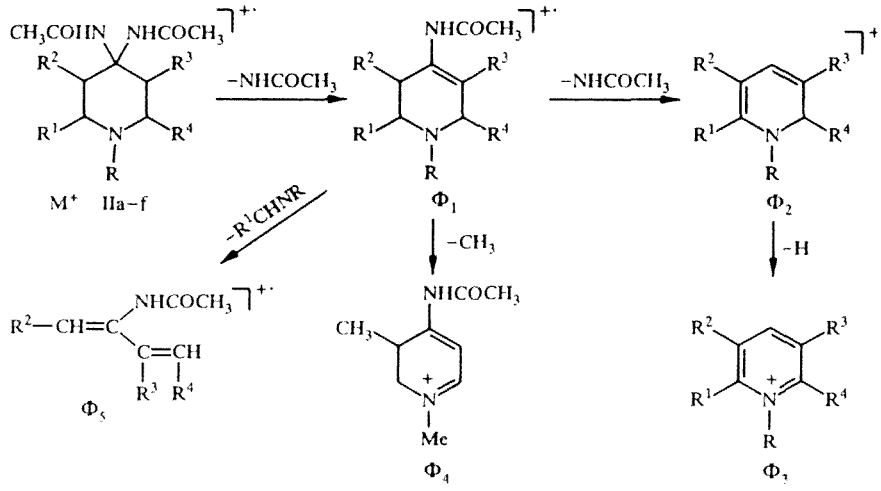
Compound	Chemical shifts, Δ, ppm	SSIC of protons, J, Hz
IIa	1,93 (6H, s, $COCH_3$), 2,26 (3H, s, N—CH_3), 2,40 (8H, broad s, ring protons), 6,79 (2H, s, NH)	—
IIb	0,91 (3H, d, 5-CH_3), 1,06 (3H, d, 2-CH_3), 1,94 (3H, broad s, $COCH_3$), 2,03 (3H, broad s, $COCH_3$), 2,03 (3H, m, 2a-H, 3a-H and 5a-H), 2,24 (3H, s, N—CH_3), 2,57 (1H, d.d., 3e-H), 2,70 (1H, d.d, 5e-H), 3,04 (1H, m, 5a-H)	J_{2aCH3} = 5,9, J_{2a3e} = =1,7, J_{3a3e} = 11,0, J_{5aCH3} = 7,1, J_{5a6a} = =11,7, J_{5a6e} = 4,2, J_{6a6e} = 12,5
IIc	0,56 (3H, d, 3-CH_3), 1,92 (3H, s, N—CH_3), 1,95 (3H, s, $COCH_3$), 2,11 (3H, s, $COCH_3$), 2,29 (1H, m, 6a-H), 2,60 (1H, d.d, 2a-H), 2,67 (2H, m, 5a-H and 5e-H), 2,91 (1H, d.t, 6e-H), 3,27 (1H, m, 3a-H), 5,73 (1H, broad s, NH), 7,26 (5H, m, 2-C_6H_5), 6,90 (1H, broad s, NH)	J_{2a3a} = 10,7, J_{3aCH3} = 7,1, J_{5a6e} = =J_{5e6e} = 3,4, J_{6a6e} = =12,0
IId	0,96 (3H, d, 5-CH_3), 1,91 (3H, s, $COCH_3$), 1,99 (3H, s, N—CH_3), 2,09 (1H, d.d, 6a-H), 2,10 (3H, s, $COCH_3$), 2,34 (1H, d.d, 3a-H), 2,71 (1H, d.d, 3e-H), 2,88 (1H, d.d, 6e-H), 2,93 (1H, d.d, 2a-H), 3,38 (1H, m, 5a-H), 5,84 (1H, broad s, NH), 6,88 (1H, broad s, NH), 7,2...7,3 (5H, m, 2-C_6H_5)	J_{2a3e} = 2,9, J_{2a3a} = =12,2, J_{3a3e} = 13,7, J_{5aCH3} = 6,5, J_{5a6a} = =12,0, J_{5a6e} = 4,1, J_{6a6e} = 12,0
IIe	1,65 (2H, broad d.d, 3a- and 5a-H), 1,86 (3H, s, $COCH_3$), 2,04 (3H, s, $COCH_3$), 3,14 (2H, broad d.d., 3e-H and 5e-H), 4,04 (2H, d.d, 2a-H and 6a-H), 6,19 (1H, broad s, NH), 6,57 (1H, broad s, NH), 7,26...7,44 (1H, m, 2-C_6H_5 and 6-C_6H_5)	J_{3a3e} = J_{5a5e} = 13,2, J_{2a3a} = J_{5a6a} = 12,0, J_{2a3e} = J_{5e6a} = 1,7
IIf	1,60 (3H, s, N-CH_3), 1,81 (2H, m, 3a-H and 5a-H), 1,85 (3H, s, $COCH_3$), 2,09 (3H, s, $COCH_3$), 3,06 (2H, broad. d, 3e-H and 5e-H), 3,30 (2H, d.d, 2a-H and 6a-H), 6,06 (1H, broad s, NH), 6,37 (1H, broad s, NH), 7,20...7,44 (1H, m, 2-C_6H_5 and 6-C_6H_5)	J_{3a3e} = J_{5a5e} = 12,7, J_{2a3a} = J_{5a6a} = 12,2, J_{2a3e} = J_{5e6a} = 2,2

TABLE 3. Mass Spectra* of Compounds IIa-f

Compound	*m/z* values (intensity, %)
IIa	213(14), 154(40), 153(12), 111(41), 96(32), 95(85), 94(100), 70(27), 44(15), 43(31), 42(24)
IIb	241(8), 182(38), 167(100), 139(13), 125(31), 124(24), 123(24), 108(30), 57(18), 43(26), 42(18)
IIc	303(8), 245(27), 244(76), 229(57), 186(40), 185(100), 170(52), 160(26), 142(32), 126(42), 118(44)
IId	303(5), 244(59), 229(41), 201(26), 186(39), 185(60), 184(100), 172(24), 170(62), 118(34), 43(33)
IIe	351(0,8), 247(17), 233(46), 232(100), 204(20), 194(22), 193(14), 189(26), 188(18), 104(27), 43(21)
IIf	365(2), 261(21), 247(41), 246(100), 232(32), 202(83), 189(30), 159(29), 118(56), 43(26)

*The molecular ion peak and the 10 strongest peaks are given.

The structure of compounds IIa-f is also corroborated by their mass spectra (Table 3). The main decomposition process of the molecular ions M^+ of these compounds is the consecutive splitting off of two neutral acetamide molecules and of an atom of hydrogen with the formation of $\Phi_1-\Phi_3$ ions (see scheme):



The Φ_3 ion peaks are the strongest peaks in the spectra of compounds IIa, d, e, f. For compound IIb the loss of the methyl radical by the Φ_1 ion is more probable.

A peculiar characteristic of compounds IIa-f is the presence of Φ_5 ion peaks in their mass spectra, formed by the retrodiene decomposition of Φ_1 ions. In distinction from the mass spectra of 2-phenyl-4-piperidones [8] and 4-piperidols [9], studied earlier, the fragmentation of the M^+ ions of compounds IIc-f, related to the splitting off of the phenyl radical, does virtually not occur.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker M-250 spectrometer for 2% solutions in $CdCl_3$. The chemical shifts of the protons were measured with respect to HMDS, serving an internal standard (0.055 ppm). The mass spectra were recorded on a Finnigan MAT-90 spectrometer at an energy of the ionizing electrons of 70 eV by direct introduction of the sample into the source. The temperature of the ionization chamber was 200°C and the vaporization temperature of the samples 75-240°C. The elemental analysis data for C, H, and N correspond to the calculated values. The substituted 4-piperidones were synthesized by the following procedures: Ia [5], Ic, d [6], Ie, f [7].

4,4-Diacetylamino-2,6-diphenylpiperidine (IIe). A mixture of 3 g (12 mmole) of 2,6-diphenyl-4-piperidone (Ie) and 2.51 ml concentrated sulfuric acid by cooling with ice water. The reaction mixture is then heated for 2 h at 60°C. About 20 g ice is added ad the neutral products extracted with ether. The residue is neutralized with a 15% K_2CO_3 solution, extracted with chloroform, and dried with $MgSO_4$. The solvent is stripped off, yield 2.34 of diamide IIe.

The diamides IIa, b, f are obtained in the same way.

4,4-Diacetylamino-1,3-dimethyl-2-phenylpiperidine (IIc). A mixturė of 0.5 g (2.5 mmole) of 1,3-dimethyl-2-phenyl-4-piperidone (Ic) and 0.52 ml (10 mmole) acetronitrile is treated dropwise with 1 7 ml concentrated sulfuric acid by cooling with ice water, and allowed to stand at room temperature for ~ 16 h. The product is treated as described above. Yield 0.7 g of diamide IIc.

The diamide IId is prepared in the same way. The main characteristics of the synthesized diamides IIa-f are given in Table 1.

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