^{13}C DYNAMIC NMR STUDIES ON RESTRICTED ROTATION ABOUT C-N BOND IN 2-ARYL-1-FORMYL-4-PIPERIDONES

Mario Rubiralta* and M. Pilar Marco

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain

Miguel Feliz and Ernest Giralt

Department of Organic Chemistry, Faculty of Chemistry, University of Barcelona, 08028 Barcelona, Spain

Abstract — The synthesis of 1-formyl-2-(3-indolyl)-4-piperidone (**7**), trans-1-formyl-2-(3-indolyl)-3-methyl-4-piperidone (**8**), and their 4,4-ethyleneacetals **5** and **6** is described. The introduction of a formyl group on the piperidone nitrogen induces a change in the piperidine ring conformation such that the 2-indolyl group is axial. However, in the 1-formyl-2-indolyl-4-piperidone 4,4-ethyleneacetals the indolyl group adopts an equatorial disposition due to a severe steric syn-diaxial interaction with the C-4 substituent. ^{13}C-Dnmr is used to investigate the amide rotational barriers in a series of 2-aryl-1-formyl-4-piperidones.

In the context of our studies about the use of 2-aryl-4-piperidones as synthetic intermediates,[1,2] we have reported the favourable conformational effect that the N-formyl substituent of 2-(3-methoxyphenyl)-4-piperidone **1** exerts in the synthesis of B-nor-benzomorphans.[1] The interest of 2-indolyl derivatives as intermediates in the synthesis of indole alkaloid ervitsine analogues[3] has prompted us to carry out the preparation and

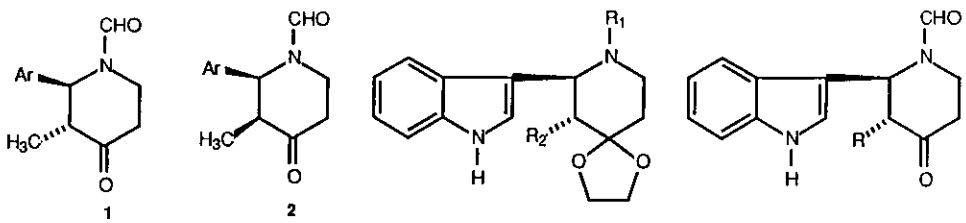

Figure 1

conformational studies of 1-formyl-2-(3-indolyl)-4-piperidone (**7**) and trans-1-formyl-2-(3-indolyl)-3-methyl-4-piperidone (**8**). In this paper we report the synthesis and the studies on *the pseudoallylic strain effect of piperidines* **5-8**, *as well as the determination* of amide rotational barriers of 1-formyl-4-piperidones **1**, **2**, **7**, and **8** by ^{13}C dynamic nmr spectroscopy.

1-Formyl-2-(3-methoxyphenyl)-3-methyl-4-piperidones (**1a** and **2a**) , and 1-formyl-2-(3,4,5-trimethoxyphenyl)-3-methyl-4-piperidone (**1b**) have previously been synthesized by us.[1] In addition, the required N-formyl-2-(3-indolyl)-4-piperidones **7** and **8** were prepared in good yields by initial cyclization of 3,3-ethylenedioxy-N-(3-indolylmethylidene)-butylamine (**9**) and –pentylamine (**10**) with p-toluenesulfonic acid in dry benzene,[4,5] followed by acylation of the piperidine nitrogen atom of acetals **3** and **4** with an equimolecular mixture of acetic anhydride and formic acid,[6] and final selective deprotection of the keto group with a hydrochloric acid-acetone mixture. In turn, imine **9** was obtained by condensation of indole-3-carbaldehyde and 4-amino-2-butanone ethylene acetal.[4]

N-Formylpiperidine **5** was observed by nmr as a single (E)-rotamer[7] with the indolyl group in an equatorial disposition. Thus, the chemical shift of the C-2 methine proton (δ 4.89) and the magnitude of its coupling constant (J=11.2 Hz) was indicative of its axial orientation. The non observation of a piperidine conformation in which the indolyl substituent is axial, as would be expected due to the $A^{(1,3)}$ strain effect[8] in C-2 substituted N-acylpiperidines,[9] was accounted for by considering the great steric hindrance that the axial C-4 substitution would provoke. [10,11] The existence of an equatorial α-substituent respect the amide function gives rise to a single (E)-rotamer, in which the carbonyl oxygen is disposed anti to the bulkier group.[11] This relative configuration was established from the chemical shift of the equatorial C-6 proton (δ 4.53).[12]

Similarly, piperidine **6** was observed by nmr as a single (E)-rotamer with a ring conformation in which the indolyl group adopts an equatorial disposition and a trans relationship respect the C-3 methyl group. The equatorial C-3 methyl group disposition was confirmed by its characteristic chemical shift (δ 0.77) and by the trans-diaxial coupling constant (J=11 Hz) between C-2 and C-3 protons.[13]

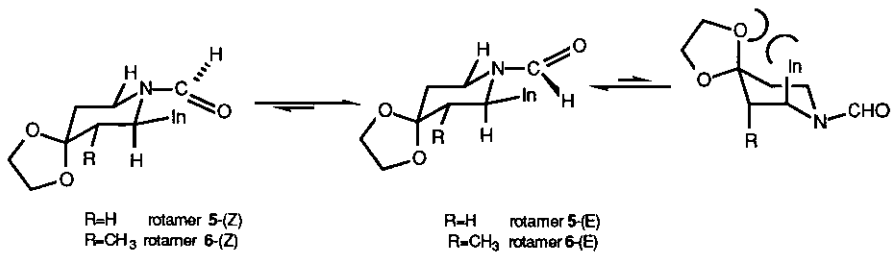

Figure 2

N-Formyl-4-piperidone **7** was obtained as a mixture of (E)- and (Z)-rotamers by deprotection of **5** without removal of the formyl group. In this case the conformation of piperidine ring shows an axial disposition of the indolyl group as a consequence of the pseudoallylic $A^{(1,3)}$ strain[8] that would exist if equatorial. The presence of two rotamers was clearly deduced by the splitting of the signals in the ^{1}H-nmr spectrum. The equatorial methine proton on C-2 appears more deshielded in the (Z)-rotamer (δ_Z 6.40; δ_E 5.54) as a consequence of the anisotropic effect of the carbonyl group, and its coupling constant (J=6 Hz) indicates its equatorial disposition.

Similarly, piperidone **8** was observed as a mixture of two rotamers with a ring conformation in which both the indolyl and methyl groups are in an axial disposition.

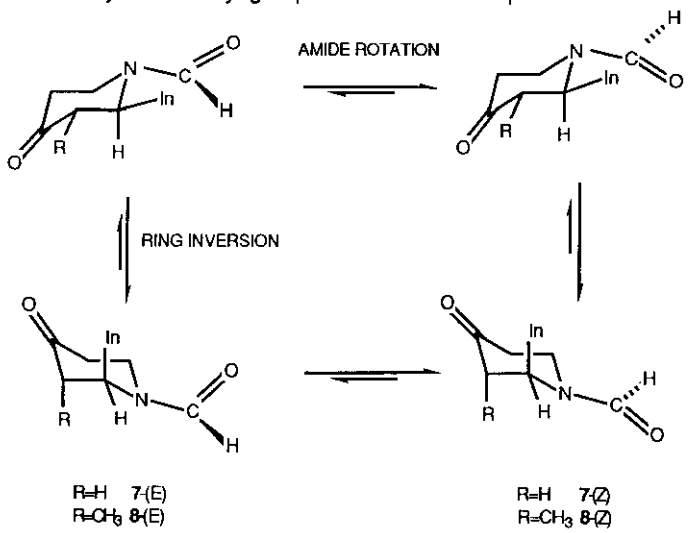

Figure 3

This fact demonstrates the larger magnitude of the $A^{(1,3)}$ effect respect the diaxial interaction between the methyl and the C-5 proton. The major (Z)-rotamer presents two signals at δ 6.08 and 3.61 assigned to the equatorial protons on C-2 and C-6 , respectively.[14] The chemical shift of C-2 equatorial proton is shielded (Δδ ~0.3 ppm) in comparison to piperidone **7,** due to the effect of the adjacent axial methyl group.[17] In both piperidines (**7** and **8**) the formyl proton is more deshielded (Δδ~0.1-0.3 ppm) in the E-rotamer which is in agreement with reported precedents.[10,12]

Table 1. ^{13}C Nmr Spectra[a] of 1-Formyl-2-arylpiperidines

Carbon	Compounds												
	1a-(Z)	**1a-(E)**	**2a-(Z)**	**2a-(E)**	**1b-(Z)**	**1b-(E)**	**6**[b]	**7-(Z)**	**7-(Z)**[c]	**7-(E)**	**7-(E)**[c]	**8-(Z)**	**8-(E)**
C-2	57.7	62.1	56.1	62.2	58.0	62.7	60.2	45.0	43.5	52.6	50.6	49.6	56.8
C-3	46.5	46.7	45.5	46.6	46.6	46.9	45.0	44.8	43.8	46.3	45.2	47.7	47.8
C-4	209.7	209.8	209.8	209.4	210.0	209.8	109.7	208.8	207.6	208.5	207.6	208.7	207.9
C-5	37.4	38.1	38.4	38.0	39.4	37.8	39.4	41.9	39.9	40.6	40.4	37.7	37.0
C-6	35.3	40.8	39.3	34.3	40.9	35.6	35.1	40.9	39.6	35.3	33.9	40.1	34.9
CMe	14.1	13.5	11.1	11.0	13.6	13.8	11.0	----	----	----	----	16.0	14.8
CHO	162.3	162.2	161.3	161.1	162.3	162.3	163.5	162.0	160.8	162.8	161.1	162.0	161.7
C´1	141.9	141.1	139.9	139.6	136.9	136.8	----	----	----	----	----	----	----
C´2	112.5	113.0	112.7	113.0	104.7	104.9	126.7	124.7	123.9	124.8	124.0	124.1	124.6
C´3	159.3	159.6	159.2	159.1	152.8	153.2	109.7	111.9	112.3	111.7	111.8	111.4	112.6
C´3a	----	----	----	----	----	----	126.8	125.9	125.1	125.7	125.0	125.5	125.3
C´4	113.2	113.1	114.5	114.4	136.0	135.0	120.7	119.9	121.5	120.2	118.9	118.7	118.6
C´5	129.6	130.0	129.8	129.6	152.8	153.2	119.8	119.3	118.9	118.8	118.2	121.7	121.7
C´6	119.4	119.3	120.3	120.0	104.7	104.9	123.2	122.8	121.5	122.8	121.5	121.7	121.7
C´7	----	----	----	-----	----	----	113.0	112.3	112.4	112.7	111.7	111.9	111.6
C´7a	----	----	----	----	----	----	138.5	137.2	136.1	137.4	136.4	136.3	136.6
OMe	55.0	54.9	56.1	55.2	56.0	56.9	66.4[d]	----	----	----	----	----	----
					60.1	60.0							

a. Recorded at 50.3 MHz in $CDCl_3$. Assignments were aided by "off resonance" experiments. Chemical shifts are given in δ units (downfield from TMS). b. Recorded in $CDCl_3$-CD_3OD. Only one rotamer was detected. c. Recorded in DMSO-d_6. d. Value due to CH_2O group.

The ^{13}C chemical shifts of piperidones **1**, **2**, **7** and **8** are reported in Table 1. As expected, the chemical shifts of α-carbons syn to the carbonyl oxygen atom are shielded relative to the corresponding carbon with an anti disposition.[18,19] In benzene series this effect (Δδ~ 4 ppm) is lower than in indole derivatives (Δδ~7 ppm). The solvent effect upon the chemical shift was studied on indolylpiperidone **7**. No significant differences were observed on the formyl carbon due to the existence of rotamers.

Finally, the rotational barriers of 3-(methoxyphenyl)piperidones **1a** and **2a** were calculated at the coalescence temperature by ^{13}C-dnmr (see Table 2). The higher barrier observed for compound **2a** ($\Delta\Delta G^{\neq}$ ~5.9 KJ mol^{-1}) probably results from the steric effect arising from the cis substituents at C-2 and C-3.[20] For indolylpiperidone **7** the calculated barrier ($\Delta G^{\neq}$~82 KJ mol-1) is similar to the previously reported for trans-1-formyl-2-(3-indolyl)-3-ethyl-4-piperidone[11] and N-formyl-norreticuline.[21]

We can conclude that the 2-indolylpiperidines behavior is similar to that of 2-substituted phenylpiperidines from the amide rotation point of view.

Table 2. Spectral Data and Free Energies of Activation ($\Delta G^{\neq}_c$) Estimated at the Coalescence Temperature (Tc)[a]

Compound	Observed Nucleus	δ_E	δ_Z	Δδ(Hz)	T_c(°K)	kc (s^{-1})	$\Delta G^{\neq}$(KJ/mol)
1a	C-CH3	14.06	13.46	29.8	352	66.7	74.4 (77.6)[b]
2a	C-CH3	10.99	11.10	5.7	357	12.7	80.3 (89.3)[b]
7	C=O	207.29	207.55	12.7	377	28.4	82.5
7	CHO	161.07	160.84	11.3	377	25.3	82.8
7	In-C3	111.77	112.34	28.5	377	63.8	79.9
7	In-C7	111.56	111.36	10.0	377	22.4	83.2

a. Measured in a DMSO-d_6 solution at 50.3 MHz. b. From ref. 1 (determined by ^1H-dnmr).

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- and ^{13}C-Nmr spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Varian XL-200 spectrometer or, when indicated, on a Perkin-Elmer 24B (60 MHz) instrument, using TMS as internal standard . Chemical shifts are reported in ppm downfield (δ) from TMS. Ir spectra were taken with a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Tlc was carried out on SiO2 (silica gel 60, Merck 0.063-0.200 mm), and the spots were located with uv light or iodoplatinate reagent. Drying of organic extracts during the work up of reactions was performed over anhydrous sodium sulfate. Microanalyses were performed on a Carlo Erba 1106 analyzer by Departamento de Química Orgánica Biológica, Barcelona.

1-Formyl-2-(3-indolyl)-4-piperidone Ethylene Acetal (**5**). A solution of 4-amino-2-butanone ethylene acetal[5] (71 g, 540 mmol) and indole-3-carbaldehyde (76 g, 520 mmol) in dry benzene (900 ml) was stirred at room temperature for 30 min and under reflux for 4 h with removal of water by a Dean-Stark trap. The benzene was evaporated to give 3,3-ethylenedioxy-N-(3-indolylmethylidene)butylamine (**9**) (127 g, 92%); ir (NaCl) 3470 (NH), 1630 (C=N); ^{1}H-nmr (60 MHz) 1.36 (s, 3H, CH_3) , 2.06 (t, J=7 Hz, 2H, $COCH_2$) , 3.66 (t, J=7 Hz, 2H, NCH_2), 3.86 (s, 4H, OCH_2), 6.80-7.50 (m, 5H, indole), 8.15 (s, 1H, NH), 8.33 (s, 1H, N=CH). The imine thus obtained (35 g, 120 mmol) and anhydrous p-toluenesulfonic acid (45 g, 180 mmol) in benzene (200 ml) were refluxed under nitrogen atmosphere for 1 h. The cooled mixture was poured into a 20% aqueous potassium carbonate solution and extracted with dichloromethane. The organic extracts were washed with the basic solution, dried, and evaporated to give 2-(3-indolyl)-4-piperidone (**3**) (24 g, 60%) which was added to a cooled mixture of anhydrous formic acid (10 ml, 265 mmol) and acetic anhydride (25 ml, 265 mmol), previously stirred at 60 °C for 30 min. The resulting solution was stirred at room temperature overnight, concentrated and dissolved in dichloromethane. The organic phase was washed with an aqueous potassium carbonate solution and evaporated to dryness to obtain piperidone **5** (20 g, 78%). A sample was purified by preparative tlc (SiO_2, 9:1 ether-acetone as eluent); mp 129-130 °C (acetone); ir ($CHCl_3$) 3480 (NH), 1650 (C=O); ^{1}H-nmr 1.70-1.80 (m, 2H, 5-H), 2.09 (ddd, J=13.6, 3.2 and 1.6 Hz, 1H, 3-He), 2.28 (dd, J=13.6 and 11.2 Hz, 1H, 3-Ha), 3.11 (ddd, J=13.6, 11.2, and 4.8 Hz, 1H, 6-Ha), 4.00 (br s, 4H, OCH_2), 4.53 (dt, J=13.6 and 4.8 Hz, 1H, 6-He), 4.89 (dd, J=11.2 and 3.2 Hz, 1H, 2-Ha), 7.10-7.30 (m, 3H, indole), 7.32 (d, J=7 Hz, 1H, In-7H), 7.52 (d, J=7 Hz, 1H, In-4H), 7.81 (s, 1H, CHO), 8.88 (br s, 1H, NH); ms (m/z; %) 286 (M^+, 29), 269 (10), 206 (56), 189 (24), 167 (24), 149 (58), 120 (37), 119 (54), 43 (100). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, C, 67.24; H, 6.26; N, 9.40.

1-Formyl-2-(3-indolyl)-3-methyl-4-piperidone Ethylene Acetal (**6**). Operating as above from the 3,3-ethylenedioxy-N-(3-indolylmethylidene)pentylamine (**10**)[4] (30 g, 110 mmol) and p-toluenesulfonic acid (30 g, 150 mmol) in benzene (200 ml) piperidine **4** was obtained. Treatment of **4** with anhydrous formic acid (8.5 ml, 225 mmol) and acetic anhydride (21.2 ml, 225 mmol) gave piperidone ethylene acetal **6** (32 g, 95%). A sample was purified by flash chromatography

(4:1 ether-acetone as the eluent): mp 200-201 °C (ether-acetone); ir (KBr) 3250 (NH), 1645 (CHO); ^{1}H-nmr ($CDCl_3$-CD_3OD) 0.77 (d, J=6.7 Hz, 3H, CCH_3), 1.78 (td, J=12.8 and 4.8 Hz, 1H, 5-Ha), 2.07 (dt, J=12.8 and 3.2 Hz, 1H, 5-He), 2.67 (dq, J=11.2 and 6.7 Hz, 1H, 3-Ha), 3.13 (td, J=12.8 and 3.2 Hz, 1H, 6-Ha), 4.10 (m, 4H, OCH2), 4.56 (ddd, J= 12.8, 4.8, and 3.2 Hz, 1H, 6-He), 4.65 (d, J=11.2 Hz, 1H, 2-Ha), 6.90-7.10 (m, 3H, indole), 7.27 (dt, J=7 and 1.3 Hz, 1H, In-7H), 7.38 (dt, J=7 and 1.3 Hz, 1H, In-4H), 7.86 (s, 1H, CHO). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.32. Found: C, 67.83; H, 6.54; N, 9.12.

1-Formyl-2-(3-indolyl)-4-piperidone (**7**). A solution of **5** (20 g, 87 mmol), 2N hydrochloric acid (200 ml) and acetone (200 ml) was stirred at 45 °C for 2 h. After cooling, the organic solvent was evaporated; the resulting aqueous residue was basified with solid potassium carbonate and extracted with chloroform. The organic phase was dried and evaporated to give piperidone **7** (10 g, 60%); mp 157-159 °C (acetone-ether); ir (KBr) 3310 (NH), 1715 (CO), 1660 (CHO); ^{1}H-nmr 3.66* (major rotamer) and 4.30 (ddt, J=13.2, 7.2, and 1.8 Hz, and dddd, J=13.8, 7.2, 3.0, and 1.2 Hz, 1H, 6-He), 6.40* and 5.54 (dd, J=6 and 1.2 Hz, and ddd, J= 6, 3, and 1.2 Hz, 1H, 2-He), 7.00-7.26 (m, 3H, indole), 7.38 (dt, 1H, J=7.8 and 1 Hz, In-4H), 7.55 and 7.42 (dt, J=7.8 and 1 Hz, 1H, In-7H), 8.30* and 8.58 (s, 1H, CHO); ms (m/z, %) 242 (M^+, 12), 174 (2), 169 (4), 146 (12), 145 (73), 144 (100), 115 (45), 89 (66), 49 (56) 43 (25). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.44; H, 5.78; N, 11.56. Found: C, 69.79; H, 5.72; N, 11.23.

1-Formyl-2-(3-indolyl)-3-methyl-4-piperidone (**8**). Operating as above from **6** (32 g, 0.11 mol), 2N hydrochloric acid (250 ml) and acetone (250 ml), piperidone **8** was obtained (26 g, 90%); ir (KBr) 3300 (NH), 1710 (C=O), 1655 (CHO); ^{1}H-nmr 1.40* and 1.32 (d, J=7.2 Hz, 3H, CH_3), 3.61* and 4.22 (ddt, J=13.5, 8.1 and 0.9 Hz, and ddd, J=13.5, 7.2, and 1.2 Hz, 1H, 6-He), 6.08* and 4.99 (br s and d, J=3 Hz, 1H, 2-He), 7.10 and 7.30 (m, 3H, indole), 7.38 (dt, J=8 and 1 Hz, 1H, In-4H), 7.66* and 7.46 (dd, J=8 and 1 Hz, In-7H), 8.43* and 8.54 (2 s, 1H, CHO). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29 ; H, 6.29 ; N, 10.93. Found: C, 70.36 ; H, 6.12 ; N, 11.23.

ACKNOWLEDGMENT

We wish to thank the Fondo de Investigaciones Sanitarias (projects 87/1252 and 88/1949).

REFERENCES AND NOTES

1. J. Bosch, M. Rubiralta, M. Moral, and J. Bolós, J. Chem. Soc., Perkin Trans I, 1984, 1459.
2. (a) J. Bosch, M. Rubiralta, M. Moral, and J. Ariño, J. Chem. Soc., Perkin Trans I, 1986, 1533; (b) M. Rubiralta, A. Diez, A. Balet, and J. Bosch, Tetrahedron, 1987, **43**, 3021.
3. J. Bosch, M. Rubiralta, J. Bolós, and J. Trapé, " Fifth International Conference on Organic Synthesis", Freiburg i. Br., Germany, 1984.
4. J. Bosch, M. Rubiralta, M. Moral, and M. Valls, J. Heterocycl. Chem., 1983, **20**, 595.
5. For a general synthesis of 2-aryl-4-piperidones by Mannich-type cyclization of imino acetals, see: (a) J. Bosch, M. Rubiralta, and M. Moral, Heterocycles, 1982, **19**, 473; (b) E. Giralt, M. Feliz, M. Rubiralta, and J. Bosch, J. Heterocycl. Chem., 1984, **21**, 715; (c) M. Rubiralta, M. Feliz, C. Jaime, and E. Giralt, Tetrahedron, 1986, **42**, 3957; (d) ref. 4.
6. C. W. Huffman, J. Org. Chem., 1958, **23**, 727.

7. The rotamer containing the C(2)-N and the formyl C=O bonds in a relative transoid conformation is called E.
8. F. Johnson, Chem. Rev., 1968, **68**, 375.
9. (a) R. A. Johnson, J. Org. Chem., 1968, **33**, 3627; (b) R. R. Fraser and T. B. Grindley, Tetrahedron Lett., 1974, 4169.
10. The same conformational change was observed in 3-ethyl-4-ethynyl-1-formyl-2-(3-indolyl)-4-piperidinol : G. Büchi, S. J. Gould, and F. Näf, J. Am. Chem Soc., 1971, **93**, 2492.
11. This result contrasts with that observed in cis - and trans-[(tert-butyl)carbonyl]-4-methyl-4-phenylpipecolic acids, an example of 2,4,4-trisubstituted N-acylpiperidine , in which the carbamoyl moiety induces a change in the piperidine ring conformation such that the C- 2 group is axial, despite a cis-diaxial interaction with the C-4 substituent: E. E. Sugg, J. F. Griffin, and P. S. Portoghese, J. Org. Chem., 1985, **50**, 5032.
12. L. A. LaPlanche and M. T. Rogers, J. Am. Chem. Soc., 1963, **85**, 3728.
13. (a) T. M. Moyenehan, K. Schofield, R. A. Y. Jones, and R. A. Katritzky, J. Chem. Soc., 1962, 2637; A. F. Casy, Tetrahedron, 1966, **22**, 2711.
14. In dimethylformamide the methyl group cis to the carbonyl oxygen appears at higher magnetic fields,[13,15] but in N-acylpiperidines the effect of the magnetic anisotropy of the amide group upon the equatorial and axial α-protons depends on their orientation respect the plane of the amide group: the equatorial and axial protons cis to the carbonyl oxygen are deshielded and shielded, respectively, compared to the trans ones.[16]
15. W. E. Stewart and T. H. Siddall, III, Chem. Rev., 1970, **70**, 517.
16. (a) H. Dietrich and H. Dierks, Angew. Chem., Int. Ed., 1966, **5**, 899; (b) M. Lynch and W. Cole, J. Org. Chem., 1966, **31**, 3337; (c) A. M. Monro and M. J. Sewell, Tetrahedron Lett., 1969, 595.
17. An axial methyl group shields the vicinal equatorial protons ($\Delta\delta$~ -0.4 ppm) and deshields the vicinal axial protons ($\Delta\delta$~ +0.2 ppm): H. Booth, Tetrahedron, 1966, **22**, 615.
18. For ^{13}C nmr studies on N-acylpiperidines, see: (a) J. A. Hirsch, R. L. Augustine, G. Koletar, and H. G. Wolf, J. Org. Chem., 1975, **40**, 3547; (b) M. Pinto, T. B. Grindley, and W. A. Szarek, Mag. Res. Chem., 1986, **24**, 323.
19. For ^{13}C nmr studies on N-acyl-3- and 4-piperidones, see: (a) J. A. Hirsch and E. Havinga, J. Org. Chem., 1976, **41**, 455; (b) J. A. Hirsch, J. Org. Chem., 1979, **44**,3225.
20. The repulsion between the N-acyl group and the vicinal equatorial hydrogens leads to a lower rotational barrier of the amide function in piperidines than in the acyclic analogues.[9a,18b]
21. C. Szántay, G. Blaskó, M. Bárczai-Beke, G. Dörnyei, and L. Radics, Heterocycles, 1980, **14**, 1127

Received, 4th August, 1989