

*Dedicated to the memory of
Professor Mircea D. Banciu (1941–2005)*

SATURATED AMINE OXIDES: Part 7.¹ HYDROACRIDINES: Part 26.² EFFECTS OF *N*-OXIDATION ON THE ¹³C NMR CHEMICAL SHIFTS OF SATURATED SIX-MEMBERED AZAHETEROCYCLIC TERTIARY AMINES. PREDICTION OF THE CHEMICAL SHIFTS OF THE AMINE OXIDES

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Received December 13, 2005

The ¹³C NMR chemical shifts of 38 saturated monocyclic, bicyclic and tricyclic piperidine-derived amine oxides are compared with those of their parent amines, and the stereostructural parameters accounting for the shift differences are identified and determined quantitatively by multilinear regression analyses. The results indicate that nitrogen electron lone-pairs in saturated tertiary amines exert γ -*gauche* effects of roughly the same magnitude as a *N*-methyl group, and γ -*anti* effects sizeable larger than a *N*-methyl group or a N⁺—O[−] oxygen atom. The obtained shift increments allow quite accurate chemical shift predictions for the amine oxide carbons located in the β -, γ -, and δ -positions with respect to the N⁺—O[−] oxygen, provided the molecular geometry (certain dihedral angles) of the amine oxide and of its parent amine is fairly well known.

INTRODUCTION

The ¹³C NMR chemical shifts data of a number of piperidine-derived azaheterocyclic tertiary amines and of their *N*-oxides, existing in the literature, show that *N*-oxidation produces considerable substituent effects on the chemical shifts of the carbon atoms located in the β and γ positions with respect to the N⁺—O[−] oxygen, and the magnitude and even the direction of the effects can be dramatically influenced by the geometry of the carbon skeleton and by the steric orientation (axial or equatorial) of the N⁺—O[−] bond: through the numerous compounds examined in this paper, the observed β -effects range from +1.22 to +18.15 ppm, and the γ -effects from −7.6 to +5.7 ppm (the + and − signs meaning a deshielding and a shielding effect, respectively). Multilinear regression analyses between various structural variables and the observed shift effects enabled to identify the stereostructural parameters involved in these effects, and to derive the associated shift increments, thus making possible quite accurate ¹³C chemical shift predictions for the β - and γ -carbons in monocyclic and condensed bi- and tricyclic piperidine-derived amine oxides. The piperidine ring carbons in δ position always show upfield *N*-oxidation shifts, that range from −0.67 to −3.3 ppm, and their chemical shifts also may be well predicted by a simple linear correlation with the shifts of the corresponding carbons in the parent amines.

RESULTS

For the regression analyses, the observed ¹³C chemical shift data of following 30 parent amines and 38 amine oxides were considered (for the structural formulae see Schemes 1 and 2): 1-methylpiperidine (**1**), 1-methylpiperidine-1-oxide (**1ax**), 1-ethylpiperidine (**2**), 1-ethylpiperidine-1-oxide (**2ax**), 1-*n*-propylpiperidine

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(**3**), 1-*n*-propylpiperidine-1-oxide (**3ax**), 1-isopropylpiperidine (**4**), 1-isopropylpiperidine-1-oxide (**4ax**), 1-*n*-butylpiperidine (**5**), 1-*n*-butylpiperidine-1-oxide (**5ax**), 1,2-dimethylpiperidine (**6**), (1 α ,2 β)-1,2-dimethylpiperidine-1-oxide (**6ax**), 1-ethyl-2-methylpiperidine (**7**), (1 α ,2 β)-1-ethyl-2-methylpiperidine-1-oxide (**7ax**), 1-*n*-propyl-2-methylpiperidine (**8**), (1 α ,2 β)-1-*n*-propyl-2-methylpiperidine-1-oxide (**8ax**), 1-*n*-butyl-2-methylpiperidine (**9**), (1 α ,2 β)-1-*n*-butyl-2-methylpiperidine-1-oxide (**9ax**), 1,3-dimethylpiperidine (**10**), (1 α ,3 α)- (**10ax**) and (1 α ,3 β)-1,3-dimethylpiperidine-1-oxide (**10eq**), 1-ethyl-3-methylpiperidine (**11**), (1 α ,3 α)-1-ethyl-3-methylpiperidine-1-oxide (**11ax**), 1-isopropyl-3-methylpiperidine (**12**), (1 α ,3 α)-1-isopropyl-3-methylpiperidine-1-oxide (**12ax**), 1-*n*-butyl-3-methylpiperidine (**13**), (1 α ,3 α)-1-*n*-butyl-3-methylpiperidine-1-oxide (**13ax**), 1,4-dimethylpiperidine (**14**), (1 α ,4 β)-1,4-dimethylpiperidine-1-oxide (**14ax**), 1-ethyl-4-methylpiperidine (**15**), (1 α ,4 β)-1-ethyl-4-methylpiperidine-1-oxide (**15ax**), 4-methyl-1-*n*-propylpiperidine (**16**), (1 α ,4 β)-4-methyl-1-*n*-propylpiperidine-1-oxide (**16ax**), 1-isopropyl-4-methylpiperidine (**17**), (1 α ,4 β)-1-isopropyl-4-methylpiperidine-1-oxide (**17ax**), 1-*n*-butyl-4-methylpiperidine (**18**), (1 α ,4 β)-1-*n*-butyl-4-methylpiperidine-1-oxide (**18ax**), 4-*t*-butyl-1-methylpiperidine (**19**), (1 α ,4 β)- (**19ax**) and (1 α ,4 α)-4-*t*-butyl-1-methylpiperidine-1-oxide (**19eq**), (2 α ,6 α)-1,2,6-trimethylpiperidine (**20**), (1 α ,2 β ,6 β)- (**20ax**) and (1 α ,2 α ,6 α)-1,2,6-trimethylpiperidine-1-oxide (**20eq**), (3 α ,5 α)-1,3,5-trimethylpiperidine (**21**), (1 α ,3 α ,5 α)- (**21ax**) and (1 α ,3 β ,5 β)-1,3,5-trimethylpiperidine-1-oxide (**21eq**), *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (**22**), (*endo,anti*)- (**22ax**) and (*endo,syn*)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol-8-oxide (**22eq**), (4 α ,8 $\alpha\beta$,9 $\alpha\beta$,10 α)-tetradecahydro-10-methylacridine (**23**), (4 α ,8 $\alpha\beta$,9 $\alpha\beta$,10 β ,10 α)- (**23ax**) and (4 α ,8 $\alpha\beta$,9 $\alpha\beta$,10 α ,10 α)-tetradecahydro-10-methylacridine-10-oxide (**23eq**), (4 α ,8 $\alpha\beta$,9 $\alpha\beta$,10 α)-10-ethyltetradecahydroacridine (**24**), (4 α ,8 $\alpha\beta$,9 $\alpha\beta$,10 β ,10 α)-10-ethyltetradecahydroacridine-10-oxide (**24ax**), (4 α ,8 $\alpha\alpha$,9 $\alpha\beta$,10 α)-tetradecahydro-10-methylacridine (**25**), (4 α ,8 $\alpha\alpha$,9 $\alpha\beta$,10 β ,10 α)- (**25ax**) and (4 α ,8 $\alpha\alpha$,9 $\alpha\beta$,10 α ,10 α)-tetradecahydro-10-methylacridine-10-oxide (**25eq**), (4 α ,8 $\alpha\alpha$,9 $\alpha\beta$,10 α)-10-ethyltetradecahydroacridine (**26**), (4 α ,8 $\alpha\alpha$,9 $\alpha\beta$,10 β ,10 α)-10-ethyltetradecahydroacridine-10-oxide (**26ax**), (4 α ,8 $\alpha\alpha$,9 $\alpha\alpha$,10 $\alpha\beta$)-tetradecahydro-10-methylacridine (**27**), (4 α ,8 $\alpha\alpha$,9 $\alpha\alpha$,10 α ,10 $\alpha\beta$)- (**27ax**) and (4 α ,8 $\alpha\alpha$,9 $\alpha\alpha$,10 β ,10 $\alpha\beta$)-tetradecahydro-10-methylacridine-10-oxide (**27eq**), myrrhine (**28**), myrrhine-*N*-oxide (**28ax**), precocinelline (**29**), coccinelline (**29ax**), hippodamine (**30**) and convergine (**30ax**). The experimentally observed chemical shifts of the amines and amine oxides, along with those predicted for the amine oxides are listed in Tables 1-3.

Table 1

¹³C NMR chemical shifts of the amines **1-22**, and of their *N*-oxides **1ax-22ax**, **10 eq**, and **19eq-22eq**^a

	Piperidine ring carbons					Exocyclic <i>N</i> -alkyl group carbons ^b				Other
	C(2)	C(3)	C(4)	C(5)	C(6)	C $_{\beta}$	C $_{\gamma}$	C $_{\delta}$	C $_{\epsilon}$	
1	56.7	26.3	24.3	26.3	56.7	47.0	-	-	-	-
1ax	66.1	21.1	21.7	21.1	66.1	59.6	-	-	-	-
	66.72	21.02	22.14	21.02	66.72	60.90	-	-	-	-
2	54.3	26.1	24.7	26.1	54.3	53.1	12.1	-	-	-
2ax	63.4	20.5	21.5	20.5	63.4	64.2	7.4	-	-	-
	63.64	20.15	22.55	20.15	63.64	-	-	-	-	-
3	54.8	26.1	24.7	26.1	54.8	61.7	20.2	12.1	-	-
3ax	63.9	20.8	21.5	20.8	63.9	71.2	15.5	11.1	-	-
	64.11	20.13	22.55	20.13	64.11	-	-	-	-	-
4	49.8	26.5	25.0	26.5	49.8	55.0	18.3	-	-	-
4ax	61.0	20.6	22.4	20.6	61.0	69.7	16.6	-	-	-
	60.16	21.23	22.86	21.23	60.16	-	-	-	-	-
5	54.8	26.1	24.6	26.1	54.8	59.5	29.3	21.0	14.0	-
5ax	63.9	20.8	21.5	20.8	63.9	69.4	24.1	20.0	13.8	-
	64.12	20.13	22.45	20.13	64.12	-	-	-	-	-

Table 1 (continues)

Table 1 (continued)

6	59.41	34.88	24.73	26.43	57.22	43.37	-	-	-	20.42
6ax	69.24	28.42	22.64	20.58	68.35	57.44	-	-	-	14.90
	70.00	28.68	22.58	20.51	67.35	58.71	-	-	-	-
7	55.5	35.0	24.4	26.4	51.6	47.6	10.2	-	-	19.3
7ax	67.1	28.6	22.0	20.5	62.2	62.0	9.0	-	-	14.8
	65.85	28.28	22.25	20.48	61.04	-	-	-	-	-
8	56.9	34.9	24.3	26.4	52.4	56.4	18.7	12.2	-	19.3
8ax	68.0	28.3	22.2	20.4	62.7	67.2	17.0	11.0	-	14.7
	67.26	28.17	22.15	20.47	61.84	-	-	-	-	-
9	56.1	35.0	24.3	26.5	52.4	54.1	27.9	21.1	14.1	19.2
9ax	68.3	28.5	22.9	20.5	63.8	66.6	25.6	20.3	13.8	14.8
	66.39	28.24	22.15	20.54	61.79	-	-	-	-	-
10	64.17	31.21	32.53	25.65	56.00	46.59	-	-	-	19.72
10ax	71.59	26.22	29.81	20.35	65.29	59.92	-	-	-	18.10
	72.71	26.47	30.51	20.37	66.00	60.49	-	-	-	-
10eq	74.61	29.45	30.35	22.85	68.27	53.84	-	-	-	18.53
	74.50	29.09	30.51	22.96	68.31	54.37	-	-	-	-
11	61.8	31.2	33.3	25.7	53.7	52.8	12.0	-	-	19.9
11ax	68.5	26.0	30.7	20.2	62.6	65.3	7.9	-	-	18.4
	69.42	25.79	31.29	19.75	63.00	-	-	-	-	-
12	57.3	31.6	33.6	26.1	49.1	54.7	18.3	-	-	20.0
12ax	64.4	26.0	30.9	20.2	58.5	71.6	16.9	-	-	18.6
	66.55	26.87	31.59	20.82	59.43	-	-	-	-	-
13	62.5	31.3	33.3	25.8	54.2	59.2	29.3	21.0	14.1	19.9
13ax	70.0	26.5	30.0	20.5	63.0	68.8	24.0	20.0	13.9	18.2
	70.05	25.87	31.29	19.82	63.49	-	-	-	-	-
14	56.07	34.48	30.23	34.48	56.07	46.49	-	-	-	21.86
14ax	66.39	28.40	28.64	28.40	66.39	61.39	-	-	-	20.78
	66.09	29.19	28.17	29.19	66.09	60.39	-	-	-	-
15	53.7	34.4	31.0	34.4	53.7	52.7	12.2	-	-	22.0
15ax	63.0	28.6	28.5	28.6	63.0	65.1	7.8	-	-	21.3
	63.01	28.44	28.95	28.44	63.01	-	-	-	-	-
16	54.2	34.6	31.0	34.6	54.2	61.3	20.3	12.1	-	22.0
16ax	63.4	28.6	28.4	28.6	63.4	71.6	15.7	11.0	-	21.3
	63.51	28.62	28.95	28.62	63.51	-	-	-	-	-
17	49.2	34.8	31.3	34.8	49.2	54.7	18.5	-	-	22.0
17ax	59.6	28.6	29.0	28.6	59.6	70.6	16.8	-	-	21.3
	59.59	29.53	29.26	29.53	59.59	-	-	-	-	-
18	54.2	34.6	31.1	34.6	54.2	59.0	29.5	21.0	14.1	22.0
18ax	64.0	28.5	29.3	28.5	64.0	70.8	24.5	20.1	13.8	21.1
	63.51	28.63	29.05	28.63	63.51	-	-	-	-	-

Table 1 (continues)

Table 1 (continued)

19	56.70	26.88	45.83	26.88	56.70	46.31	-	-	-	c
19ax	66.87	21.75	44.48	21.75	66.87	60.50	-	-	-	d
	<i>66.76</i>	<i>21.58</i>	<i>44.02</i>	<i>21.58</i>	<i>66.76</i>	<i>60.24</i>	-	-	-	-
19eq	69.06	24.85	44.32	24.85	69.06	52.79	-	-	-	e
	<i>69.10</i>	<i>24.22</i>	<i>44.02</i>	<i>24.22</i>	<i>69.10</i>	<i>56.41</i>	-	-	-	-
20	59.59	35.17	24.79	35.17	59.59	38.07	-	-	-	21.62
20ax	71.21	28.86	23.23	28.86	71.21	52.45	-	-	-	15.53
	<i>70.57</i>	<i>29.01</i>	<i>22.64</i>	<i>29.01</i>	<i>70.57</i>	<i>51.54</i>	-	-	-	-
20eq	74.52	31.27	22.99	31.27	74.52	39.29	-	-	-	15.27
	<i>74.18</i>	<i>31.73</i>	<i>22.64</i>	<i>31.73</i>	<i>74.18</i>	<i>39.56</i>	-	-	-	-
21	63.59	31.10	41.61	31.10	63.59	46.21	-	-	-	19.55
21ax	72.39	26.12	39.72	26.12	72.39	61.13	-	-	-	18.21
	<i>72.12</i>	<i>26.54</i>	<i>39.73</i>	<i>26.54</i>	<i>72.12</i>	<i>60.11</i>	-	-	-	-
21eq	74.86	29.48	39.89	29.48	74.86	54.58	-	-	-	18.46
	<i>73.83</i>	<i>29.15</i>	<i>39.73</i>	<i>29.15</i>	<i>73.83</i>	<i>51.62</i>	-	-	-	-
22^{f,g}	60.74	39.50	63.40	39.50	60.74	41.13	-	-	-	25.34
22ax^{g,h}	70.66	34.31	61.53	34.31	70.66	55.20	-	-	-	24.31
	<i>70.86</i>	<i>33.55</i>	<i>61.86</i>	<i>33.55</i>	<i>70.86</i>	<i>55.03</i>	-	-	-	-
22eq^{g,h}	72.75	37.25	60.86	37.25	72.75	48.40	-	-	-	26.32
	<i>72.45</i>	<i>37.81</i>	<i>61.86</i>	<i>37.81</i>	<i>72.45</i>	<i>47.79</i>	-	-	-	-

^a If not specified otherwise, the chemical shifts were measured in CDCl₃ solution, and are reported relative to TMS = 0 ppm. The predicted chemical shifts for the *N*-oxides are given in italics, in the second lines of the rows.

^b The notations C_β, C_γ, *etc.*, denote the positions relative to the oxygen atom in the *N*-oxides.

^c *tert*-Butyl group: quaternary carbon 32.03 ppm, methyl groups 27.31 ppm.

^d *tert*-Butyl group: quaternary carbon 32.03 ppm, methyl groups 27.16 ppm.

^e *tert*-Butyl group: quaternary carbon 31.85 ppm, methyl groups 27.07 ppm.

^f Chemical shifts measured at -70°C, in CFCl₃ + CH₃OH (2:1).

^g For ease of chemical shift comparison with the piperidines in this Table, the carbon numbering for the tropane derivatives is unconventional, and corresponds with that shown in Scheme 1.

^h Chemical shifts measured in D₂O with respect to internal 1,4-dioxane = 67.4 ppm,⁶ and referred to TMS = 0 ppm.

DISCUSSION

In a paper of Lebrun *et al.*,³ the ¹³C chemical shift differences between amine oxides and parent amines have been inadequately considered and discussed as an effect of the whole *N*-oxide function, and, consequently, the carbon atoms bonded directly to the nitrogen atom have been designated as α-carbons, carbons two bonds away from it as β-carbons, *etc.* In contrast to that, in the subsequent discussions we consider the shift differences between amine oxides and amines to be the substituent effects of solely the introduced oxygen atom (the nitrogen atom being, obviously, already present in the parent amine) and, accordingly, designate the α, β, γ, *etc.* positions with respect to the oxygen atom.

Table 2

¹³C NMR chemical shifts of the amines **23-27** and of their *N*-oxides **23ax-27ax**, **23eq**, **25eq**, **26ax** and **27eq** (± 0.1 ppm)^a

Compounds and chemical shifts													
	23	23ax	23eq	24	24ax	25	25ax	25eq	26	26ax	27	27ax	27eq
C(1)	33.46	33.32	33.78	33.26	33.32	33.71	33.61	33.98	33.66	33.50	32.09	30.51	30.21 ^b
C(2)	25.83	24.65	25.32	25.71	24.46	25.71	24.52	25.15	25.76	24.37	21.50	19.73	19.59
C(3)	26.10	25.50	25.59	25.98	25.38	26.07	25.44	25.46	26.09	25.27	26.24	25.81	25.61 ^c
C(4)	31.03	24.75	25.18	30.47	23.82	30.52	24.14	25.04	30.03	23.53	17.81	23.44	20.29
		24.67	24.70	24.56	24.56	23.54	24.68	23.77	23.77	23.77	23.31	23.31	19.90
C(4a)	69.28	79.75	82.48	63.98	73.73	70.21	80.20	82.33	64.38	74.08	63.87	79.51	78.83
		79.73	82.37	74.27	74.27	80.15	83.39	83.39	74.54	74.54	80.30	80.30	78.22
C(5)	31.03	24.75	25.18	30.47	23.82	30.74	28.04	23.64	30.18	27.16	31.31	24.24	25.33 ^c
		24.67	24.70	24.56	24.56	27.87	27.87	23.95	27.44	27.44	24.91	24.91	25.02
C(6)	26.10	25.50	25.59	25.98	25.38	19.74	21.72	22.16	20.40	20.89	26.33	25.51	25.46 ^c
C(7)	25.83	24.65	25.32	25.71	24.46	26.86	25.94	25.27	26.77	25.66	26.51	24.92	25.43 ^c
C(8)	33.46	33.32	33.78	33.26	33.32	27.37	27.75	27.48	27.02	27.89	33.21	33.08	33.51
C(8a)	40.99	34.78	37.63	41.37	34.00	37.55	36.34	36.16	37.47	35.91	42.81	35.48	38.74
		34.43	37.58	34.22	34.22	35.85	35.85	36.54	35.41	35.41	36.15	36.15	39.18

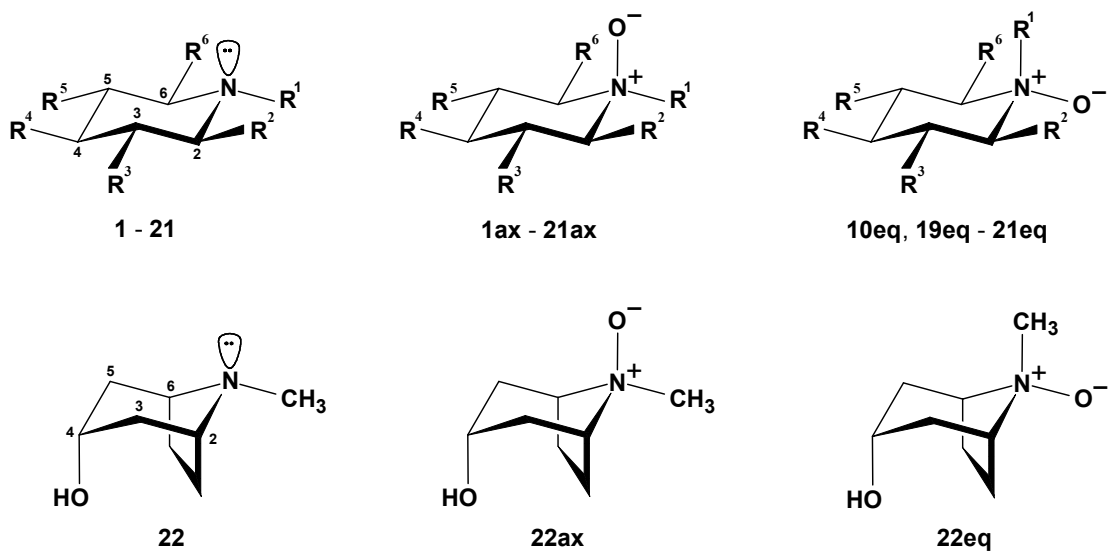
Table 2 (continues)

Table 2 (continued)

	23	23ax	23eq	24	24ax	25	25ax	25eq	26	26ax	27	27ax	27eq
C(9)	40.69	39.62 38.80	39.28 38.80	40.67	39.59 38.78	39.35	38.68 37.43	37.73 37.43	39.49	38.13 37.58	32.42	30.69 30.39	30.42 ^b 30.39
C(9a)	40.99	34.78 34.43	37.63 37.58	41.37	34.00 34.22	36.96	30.81 30.93	34.64 33.68	37.09	30.49 30.28	36.28	29.03 29.78	32.59 32.63
C(10a)	69.28	79.75 79.73	82.48 82.37	63.98	73.73 74.27	63.67	70.36 70.64	76.20 76.08	57.22	64.51 64.40	60.21	71.45 70.51	73.03 72.92
N-CH ₃	36.07	51.93 52.11	42.42 42.82	-	-	36.54	54.69 52.98	48.11 48.11	-	-	39.32	54.38 54.51	50.80 50.06
N-CH ₂ -	-	-	-	38.95	55.86	-	-	-	38.44	57.09	-	-	-
C-CH ₃	-	-	-	7.22	8.77	-	-	-	5.40	9.55	-	-	-

^a Chemical shifts measured in CDCl₃ relative to CDCl₃ = 77.0 ppm, and referred to TMS = 0 ppm. The predicted chemical shifts for the *N*-oxides are given in italics, in the second lines of the rows.

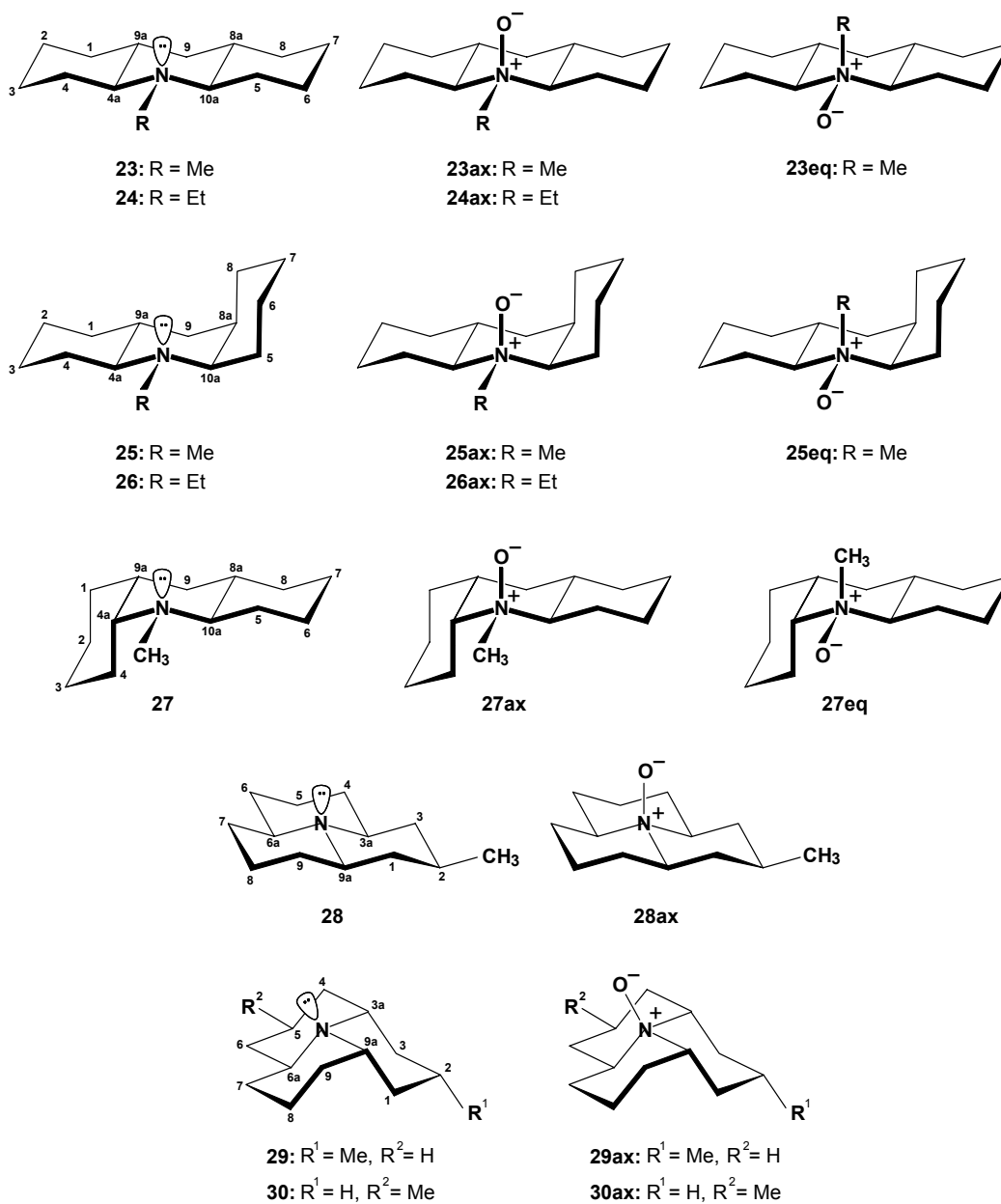
^{b,c} Chemical shift values with the same superscript may be interchanged.



	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
1, 1ax	Me	H	H	H	H	H
2, 2ax	Et	H	H	H	H	H
3, 3ax	<i>n</i> -Pr	H	H	H	H	H
4, 4ax	<i>i</i> -Pr	H	H	H	H	H
5, 5ax	<i>n</i> -Bu	H	H	H	H	H
6, 6ax	Me	Me	H	H	H	H
7, 7ax	Et	Me	H	H	H	H
8, 8ax	<i>n</i> -Pr	Me	H	H	H	H
9, 9ax	<i>n</i> -Bu	Me	H	H	H	H
10, 10ax, 10eq	Me	H	Me	H	H	H
11, 11ax	Et	H	Me	H	H	H
12, 12ax	<i>i</i> -Pr	H	Me	H	H	H
13, 13ax	<i>n</i> -Bu	H	Me	H	H	H
14, 14ax	Me	H	H	Me	H	H
15, 15ax	Et	H	H	Me	H	H
16, 16ax	<i>n</i> -Pr	H	H	Me	H	H
17, 17ax	<i>i</i> -Pr	H	H	Me	H	H
18, 18ax	<i>n</i> -Bu	H	H	Me	H	H
19, 19ax, 19eq	Me	H	H	<i>t</i> -Bu	H	H
20, 20ax, 20eq	Me	Me	H	H	H	Me
21, 21ax, 21eq	Me	H	Me	H	Me	H

Scheme 1

(For the convenience of chemical shift comparisons with the piperidines **1-21**, the carbon numbering in the tropane derivatives **22** is unconventional)



Scheme 2

Table 3

¹³C NMR chemical shifts of amines **28-30** and of their *N*-oxides **28ax-30ax**^a

	Compounds and chemical shifts								
	28	28ax		29	29ax		30	30ax	
	Obs.	Obs.	Pred.	Obs.	Obs.	Pred.	Obs.	Obs.	Pred.
C(1)	42.6	35.0	35.73	31.2	35.5	36.14	23.0	27.29	27.94
C(2)	30.3	29.6	28.24	32.6	29.8	30.58	26.0	23.5	23.87

Table 3 (continues)

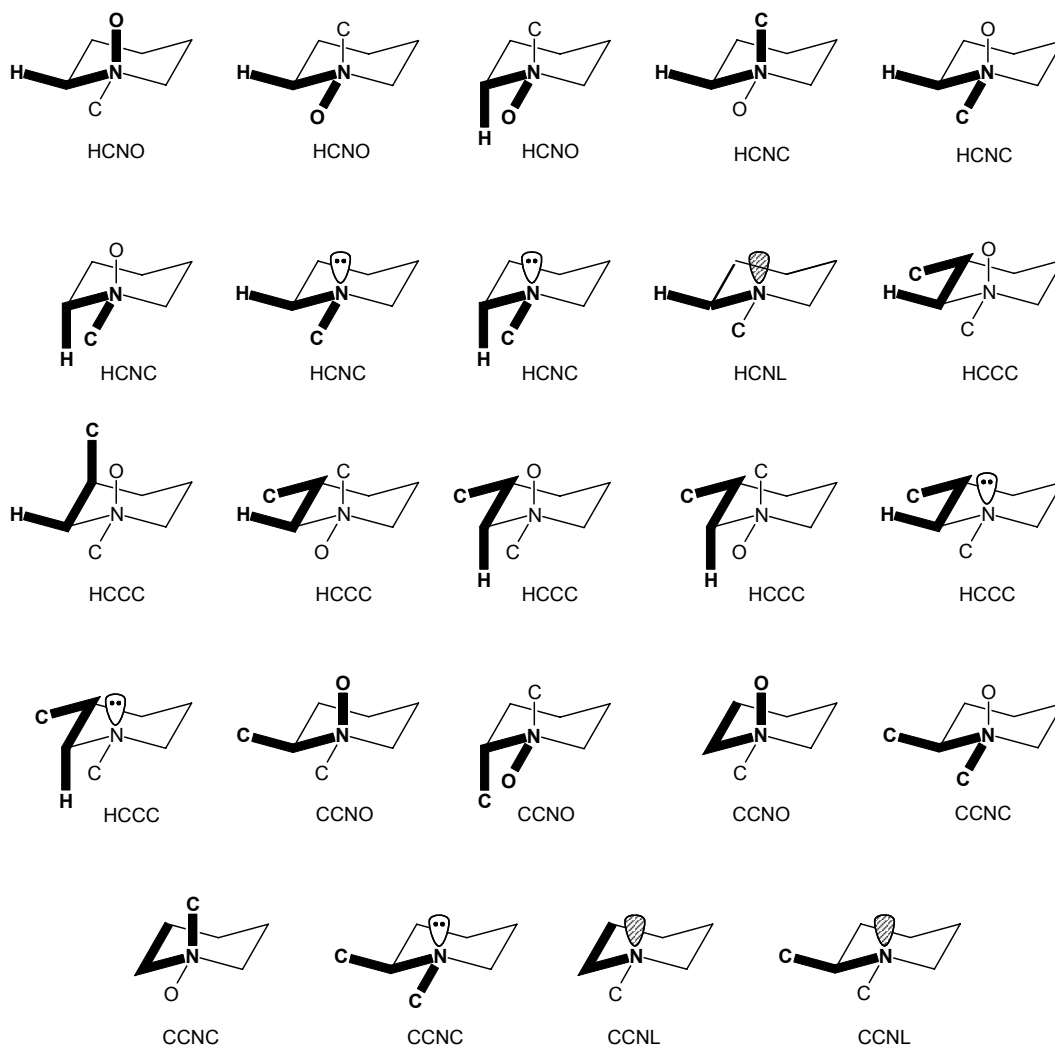
Table 3 (continued)

C(3)	42.6	35.0	35.73	31.2	35.5	36.14	22.3	28.0	27.24
C(3a)	62.2	74.2	73.95	58.1	72.7	73.35	58.0	74.3	73.25
C(4)	34.0	27.0	27.24	31.1	25.2	24.40	39.9	33.9	33.19
C(5)	24.3	22.5	22.14	19.8	17.5	17.57	25.6	24.5	23.47
C(6)	34.0	27.0	27.15	34.6	27.0	27.61	43.3	35.8	36.30
C(6a)	62.2	74.2	74.00	48.3	59.5	60.15	47.9	58.7	59.75
C(7)	34.0	27.0	27.15	34.6	27.0	27.61	34.5	27.33	27.52
C(8)	24.3	22.5	22.14	19.8	17.5	17.57	19.7	18.0	17.47
C(9)	34.0	27.0	27.24	31.1	25.2	24.40	31.3	25.6	24.61
C(9a)	62.2	74.2	73.95	58.1	72.7	73.35	58.8	73.7	74.05
CH ₃	22.0	21.0	–	22.7	21.0	–	22.4	21.5	–

^a All observed chemical shifts were measured in CDCl₃, from CDCl₃ = 77.10 ppm, and referred to TMS = 0 ppm.

Effects of *N*-oxidation on the endocyclic β -carbons

Multiple linear regression analysis allowed to select a number of nine structural parameters with significant contributions to the chemical shifts of the ring C $_{\beta}$ carbons in the amines and amine oxides, and to determine their shift effects quantitatively. Among these parameters there are seven types of *gauche* fragments involving H, C, N, O atoms and/or nitrogen lone-pairs (designated as “L”), in various sequences. To define these *gauche* arrangements unambiguously, in the subsequent discussion symbols of four letters will be used, as follows: “HCNO”- denoting a *gauche* arrangement between a hydrogen atom on the C $_{\beta}$ of interest, and the exocyclic oxygen atom of the N⁺—O[−] group; “HCNC”- denoting a *gauche* arrangement between a hydrogen atom on the C $_{\beta}$ of interest, and an exocyclic carbon atom linked to the nitrogen in the amine oxide or in the amine; “HCNL”- denoting a *gauche* arrangement between a hydrogen atom on the C $_{\beta}$ of interest, and the nitrogen lone-pair in the amine; “HCCC”- denoting a *gauche* arrangement between a hydrogen atom on the C $_{\beta}$ of interest, and an exocyclic carbon atom linked to an endocyclic carbon atom in the amine oxide or in the amine; “CCNO”- denoting a *gauche* arrangement between an endocyclic or exocyclic γ -carbon atom linked to the C $_{\beta}$ of interest, and the exocyclic oxygen atom of the N⁺—O[−] group; “CCNC”- denoting a *gauche* arrangement between an endocyclic or exocyclic γ -carbon atom linked to the C $_{\beta}$ of interest, and an exocyclic carbon atom linked to the nitrogen, in the amine oxide or in the amine; “CCNL”- denoting a *gauche* arrangement between an endocyclic or exocyclic γ -carbon atom linked to the C $_{\beta}$ of interest, and the nitrogen lone-pair in the amine. (An illustration of the possible occurrences of the seven mentioned types of *gauche* arrangements is given in Scheme 3). The remaining two structural parameters are whether the C $_{\beta}$ under consideration is a secondary or a tertiary carbon atom – designated as “C^{sec}” and “C^{tert}”, respectively. For quaternary C $_{\beta}$ carbons, so far no example was available. The quantitative results of the regression analysis for the nine parameters are presented in Table 4, along with the appropriate statistical summary. The values of the shift increments given in Table 4 are valid only for *gauche* arrangements showing dihedral angles (Φ) of exactly 60°. For distorted *gauche* fragments, where $\Phi \neq 60^\circ$, an angle correction has to be applied, by multiplying the parameter increment by $2\cos\Phi$ (e.g., HCNL $\cdot 2\cos\Phi_1$, CCNO $\cdot 2\cos\Phi_2$, etc.) which correction should be approximately valid for any dihedral angle $0 \leq \Phi \leq 90^\circ$. For the present study, the pertinent dihedral angles were determined on optimized-geometry models obtained by molecular mechanics (MM+ force field) calculations. It should be noted that, without angle corrections, the multiple correlation coefficient decreases to $r = 0.85$, the standard deviation rises to ± 1.24 ppm, and worse statistic indicators are obtained. To illustrate the use of the nine parameters, the derivation of the *N*-oxidation shifts of the carbons C(2) in **10eq**, and C(10a) in **25ax** is discussed below in detail.



Scheme 3

Definition and occurrences of the seven types of structural parameters influencing the ^{13}C NMR chemical shifts of C_β carbons in the amine oxides and their parent amines

In **10**, the chemical shift of $\text{C}(2)$ is affected by the following *gauche* arrangements (corresponding dihedral angles are given in parentheses): $\text{H}_{\text{eq}}-\text{C}(2)-\text{N}-\text{L}$ (61.39°), $\text{H}_{\text{ax}}-\text{C}(2)-\text{N}-\text{CH}_3$ (63.18°), $\text{H}_{\text{eq}}-\text{C}(2)-\text{N}-\text{CH}_3$ (55.86°), $\text{H}_{\text{ax}}-\text{C}(2)-\text{C}(3)-\text{CH}_3$ (57.82°), $\text{H}_{\text{eq}}-\text{C}(2)-\text{C}(3)-\text{CH}_3$ (60.64°), and $\text{C}(3)-\text{C}(2)-\text{N}-\text{L}$ (57.98°). On *N*-oxidation, these will be replaced with following *gauche* fragments in **10eq**: $\text{H}_{\text{ax}}-\text{C}(2)-\text{N}-\text{O}$ (50.56°), $\text{H}_{\text{eq}}-\text{C}(2)-\text{N}-\text{O}$ (66.68°), $\text{H}_{\text{eq}}-\text{C}(2)-\text{N}-\text{CH}_3$ (49.88°), $\text{H}_{\text{ax}}-\text{C}(2)-\text{C}(3)-\text{CH}_3$ (56.49°), $\text{H}_{\text{eq}}-\text{C}(2)-\text{C}(3)-\text{CH}_3$ (60.29°) and $\text{C}(3)-\text{C}(2)-\text{N}-\text{CH}_3$ (72.10°). Assuming that, on going from **10** to **10eq**, the geometry of all more remote parts of the molecule remains essentially unchanged, the chemical shift difference between $\text{C}(2)$ in **10eq** and in **10** should be given by the difference between the two corresponding sets of parameters, to whom also the parameter C^{sec} must be added: $\delta\text{C}(2)_{10\text{eq}} - \delta\text{C}(2)_{10} = \text{C}^{\text{sec}} + \text{HCNO}\cdot 2\cos 50.56^\circ + \text{HCNO}\cdot 2\cos 66.68^\circ + \text{HCNC}\cdot 2\cos 49.88^\circ + \text{HCCC}\cdot 2\cos 56.49^\circ + \text{HCCC}\cdot 2\cos 60.29^\circ + \text{CCNC}\cdot 2\cos 72.10^\circ - \text{HCNL}\cdot 2\cos 61.39^\circ - \text{HCNC}\cdot 2\cos 63.18^\circ - \text{HCNC}\cdot 2\cos 55.86^\circ - \text{HCCC}\cdot 2\cos 57.82^\circ - \text{HCCC}\cdot 2\cos 60.64^\circ - \text{CCNL}\cdot 2\cos 57.98^\circ = 10.44 \text{ ppm}$, i.e., $\text{C}^{\text{sec}} + 2.062 \text{ HCNO} - 0.736 \text{ HCNC} + 0.05 \text{ HCCC} + 0.614 \text{ CCNC} - 0.957 \text{ HCNL} - 1.06 \text{ CCNL} = 10.44 \text{ ppm}$.

The structural parameters affecting the carbons $\text{C}(10\text{a})$ in **25ax** and in **25** are: C^{tert} , $\text{H}_{\text{eq}}-\text{C}(10\text{a})-\text{N}-\text{CH}_3$ (61°), $\text{C}(5)-\text{C}(10\text{a})-\text{N}-\text{CH}_3$ (55.17°), and $\text{H}-\text{C}(10\text{a})-\text{N}-\text{CH}_3$ (68.39°),

C(5)—C(10a)—N—CH₃ (49.11°), respectively. Thereby, the effect of *N*-oxidation on $\delta\text{C}(10a)$, from **25** to **25ax**, is given by:

$$\delta\text{C}(10a)_{25\text{ax}} - \delta\text{C}(10a)_{25} = C^{\text{tert}} + 0.233 \text{HCNC} - 0.167 \text{CCNC} = 6.69 \text{ ppm}$$

It should be noted that carbons C(5) and C(8a) undergo *gauche* interactions with neither the oxygen in **25ax**, nor the nitrogen lone-pair in **25**, because they bear no hydrogen atom oriented parallel (*syn*-axial) to the N⁺—O[−] bond and to the lone-pair orbital, respectively.⁴⁻⁷ Similarly, the N—CH₃ groups in **22**, **22ax** and the N⁺—O[−] oxygen atom in **22eq** undergo no effective γ -*gauche* interaction with the pyrrolidine ring carbons, because these have no hydrogen atom oriented parallel to the N—CH₃ and N⁺—O[−] bond, respectively. (In a tentative regression analysis where such γ -*gauche* interactions were supposed to be effectual, again worse correlation parameters were attained). Interesting and unexpected is the large contribution of the nitrogen lone-pair, which practically equals that of a carbon atom linked to the nitrogen (compare, in Table 4, the magnitudes of HCNC and CCNC with those of HCNL and CCNL parameters, respectively). Excluding the HCNL and CCNL parameters from the regression analysis, or replacing the C^{sec} and C^{tert} parameters by a single constant term, or the attempt to differentiate the HCNC, HCCC and CCNC parameters in the amine oxides from those in the amines, led also to worse correlation data and worse statistics.

Table 4

Regression analysis of structural parameters determining the chemical shift differences between ring β -carbons in saturated six-membered azaheterocyclic amine oxides and the corresponding carbons in their parent amines

Number of observations: 53

Number of independent variables: 9

Multiple correlation coefficient, $r = 0.96$

Standard deviation in predicted *N*-oxidation shifts: ± 0.67 ppm

Constant term: nil

Parameter and value ^a	No. of occurrences	Student's <i>t</i> ratio
C ^{sec} : 5.25 \pm 0.67	26	6.56
C ^{tert} : 9.02 \pm 0.58	27	15.38
HCNO: −5.61 \pm 1.68	38	3.33
HCNC: −10.90 \pm 2.06	46	5.28
HCNL: −10.01 \pm 1.45	33	6.88
HCCC: −41.53 \pm 7.26	6	5.72
CCNO: −1.31 \pm 0.65	46	2.01
CCNC: −2.92 \pm 0.70	23	4.16
CCNL: −2.67 \pm 0.50	50	5.3

^a In ppm \pm standard error

Effects of *N*-oxidation on the exocyclic β -carbons

N-Methyl groups

The *N*-oxidation shifts of *N*-methyl groups with equatorial orientation, and undergoing no steric interaction in both amine oxide and parent amine, such as in **1ax**, **10ax**, **14ax**, **19ax**, **21ax**, are very similar to each other (14 ± 1 ppm), and also with that found for trimethylamine-*N*-oxide. This fact strongly suggests that, alike in trimethylamine-*N*-oxide, owing to free rotation of the *N*-methyl groups, all conformational effects are averaged to zero, and the sole effect experienced should be the angle- and, hence, conformation-independent inductive effect of the oxygen atom. In contrast, within the amine oxides with axial *N*-methyl

groups, and/or substituted 2- and 6-positions of the piperidine ring, the observed magnitudes of *N*-oxidation effects are scattered from +1.22 ppm through +18.15 ppm, due to combination of the inductive effect with the effects of the various γ -*gauche* interactions (and in **25eq** also a double δ -*syn*-axial interaction) that the *N*-methyl groups undergo. Earlier workers have found that the magnitudes of γ -*gauche* effects depend upon whether the perturbed γ -carbon atom is tertiary or secondary, upon the dihedral angle between the perturbed γ -carbon and the perturbing substituent, and upon the electronegativity of the perturbing substituent; however, in the present case all the perturbed carbons belong to N-CH₃ groups, whereas the perturbing γ -*gauche* substituents are secondary and/or tertiary ring carbons, and/or exocyclic primary carbons. Thus, to see whether and to which extent the magnitudes of the γ -*gauche* effects depend upon the degree of substitution at the perturbing carbon, in the regression analysis were introduced the structural parameters “gCH/CH₃”, “gCH₂/CH₃” and “gCH₃/CH₃” – denoting the γ -*gauche* effect exerted by a CH, a CH₂, and a CH₃ group, respectively, upon the N-CH₃ group of interest in the amine oxide, and “gCH₂/CH₃A” and “gCH₃/CH₃A” – denoting the same types of effects as above, but in the parent amine. The “ δ -*syn*CH₂/CH₃” parameter was included to account for the δ -*syn*-axial effect exerted by a CH₂ group upon the N-CH₃ group of interest, in the amine oxide. From the regression analysis resulted that, for good correlation and prediction results, besides these structural parameters also a constant term “Ct” is required. As for endocyclic β -carbons in the previous section, the use of these new structural parameters will also be illustrated by two examples, **20eq** and **25eq**.

On *N*-oxidation of **20** to **20eq**, the CH₃—C(2)—N—CH₃ (57.35°) and CH₃—C(6)—N—CH₃ (57.35°) *gauche* interactions in **20**, are replaced by the new CH₃—C(2)—N—CH₃ (55.72°), CH₃—C(6)—N—CH₃ (55.72°), C(3)—C(2)—N—CH₃ (69.9°) and C(5)—C(6)—N—CH₃ (69.9°) interactions in **20eq**. Thus, the chemical shift difference between the NCH₃ groups is derived as: $\delta(\text{NCH}_3)_{20\text{eq}} - \delta(\text{NCH}_3)_{20} = \text{Ct} + 2g\text{CH}_3/\text{CH}_3 \cdot 2\cos 55.72^\circ + 2g\text{CH}_2/\text{CH}_3 \cdot 2\cos 69.9^\circ - 2g\text{CH}_3/\text{CH}_3\text{A} \cdot 2\cos 57.35^\circ = 1.22 \text{ ppm}$, i.e., $\text{Ct} + 2.252 g\text{CH}_3/\text{CH}_3 + 1.375 g\text{CH}_2/\text{CH}_3 - 2.158 g\text{CH}_3/\text{CH}_3\text{A} = 1.22 \text{ ppm}$

When **25** is *N*-oxidized to **25eq**, the C(4)—C(4a)—N—CH₃ (53.51°) and C(5)—C(10a)—N—CH₃ (49.11°) *gauche* interactions in **25**, are replaced by the C(4)—C(4a)—N—CH₃ (49.55°) *gauche* interaction, and the C(6)—C(5)—C(10a)—N—CH₃ and C(8)—C(8a)—C(10a)—N—CH₃ δ -*syn* interactions in **25eq** (for δ -*syn* interactions no angle-correction was attempted). Thereby, for the chemical shift difference $\delta(\text{NCH}_3)_{25\text{eq}} - \delta(\text{NCH}_3)_{25}$, following equation emerges:

$$\text{Ct} + 1.297 g\text{CH}_2/\text{CH}_3 + 2 \delta_{\text{syn}}\text{CH}_2/\text{CH}_3 - 2.498 g\text{CH}_2/\text{CH}_3\text{A} = 11.57 \text{ ppm}$$

For the regression analysis, a set of 16 such equations was used, affording the data listed in Table 5. The constant term “Ct” (13.90 ppm) obviously accounts for the inductive effect of the oxygen; without this constant term, no correlation at all is achieved. If, on the other hand, the *gauche* interactions in the parent amines are not differentiated from those in the amine oxides, the multiple correlation coefficient drops to $r = 0.90$, and the standard deviation rises to ± 2.08 ppm.

N-Ethyl and higher *N*-alkyl groups

The attempts to predict *N*-oxidation shifts of β -carbons members of *N*-ethyl or higher *N*-alkyl groups, in the same way as shown above for *N*-methyl groups, in most cases have led to deviations higher than acceptable. This may be explained by the fact that higher *N*-alkyl groups exhibit a predominant conformation (rotamer), which can contribute substantially with the HCNO, HCNC, HCNL, CCNO, CCNC and CCNL parameters (see Table 4) to the *N*-oxidation shifts of these carbons. Thus, to achieve more exact predictions, for each particular case the conformation and the ratio of the predominant rotamer should be determined and taken into account.

Effects of *N*-oxidation on the γ -carbons

On *N*-oxidation, the C _{γ} carbons may experience both γ -*gauche* and/or γ -*anti* effects. The γ -*gauche* effect has been found to be always upfield, whereas the γ -*anti* effect can be either upfield or downfield shifting. The magnitudes of both γ -*gauche* and γ -*anti* effects have been found to depend on the

electronegativity of the perturbing substituent,⁸⁻¹⁴ on the torsion angle between the substituent and the perturbed γ -carbon,¹⁵⁻¹⁷ and on the extent of substitution and the nature of the substituents on the intervening α - and β -carbons^{9,11,14,18-20} and on the perturbed γ -carbon.^{5,10,11,14,18,19,21} However, for the γ -*gauche* upfield shift to be observed, the perturbed γ -carbons have to bear a hydrogen atom *syn*-axial or in an equivalent parallel orientation with respect to the perturbing group,^{4-6,22} and there are also indications^{11,14,18} that the presence of *syn*-axial hydrogens on both α - and γ -carbons could favour the transmission of γ -*anti* effects.

Table 5

Regression analysis of structural parameters determining the chemical shift differences between N-CH₃ β -carbons in saturated six-membered azaheterocyclic amine oxides and the corresponding carbons in their parent amines

Number of observations: 16

Number of independent variables: 6

Multiple correlation coefficient, $r = 0.984$

Standard deviation in predicted N-oxidation shifts: ± 0.95 ppm

Constant term, Ct: 13.90 ± 0.37

Parameter and value ^a	No. of occurrences	Student's <i>t</i> ratio
$g\text{CH}/\text{CH}_3$: -6.95 ± 0.70	4	9.95
$g\text{CH}_2/\text{CH}_3$: -3.05 ± 0.40	8	7.63
$g\text{CH}_2/\text{CH}_3\text{A}$: -3.63 ± 0.41	5	8.78
$g\text{CH}_3/\text{CH}_3$: -37.40 ± 6.07	3	6.16
$g\text{CH}_3/\text{CH}_3\text{A}$: -35.22 ± 5.99	3	5.88
$\delta_{\text{syn}}\text{CH}_2/\text{CH}_3$: -2.16 ± 0.56	2	3.83

^a In ppm \pm standard error

The results of the present study show that all these features apply to amine oxides, too. However, due to the presence of the nitrogen atom instead of a carbon atom in the α position of the transmission path, the mechanisms of the γ -effects occurring on *N*-oxidation of amines like **1-30** are additionally complicated by several features, not encountered within the systems investigated and reported so far. Thus, the results of the multilinear regression for γ -effects, presented in Table 6, confirm a suspicion of ours, that already in the parent amines, the nitrogen lone pair electrons exert sizeable γ -*gauche* effects (denoted as “gLNCC”) or γ -*anti* effects (denoted as “aLNCC”) upon the carbons of interest. On most of the affected carbons, the gLNCC acts in combination with the γ -*anti* effect of the *N*-alkyl carbons (denoted as “aCNCCA”; e.g., on the carbons C(3) and/or C(5) in **1-22**) or with the γ -*gauche* effect of the *N*-alkyl carbons (denoted as “gCNCCA”; e.g., on C(4) and/or C(5) in **23-27**, and on the $-\text{CH}_3$ carbons in the 2 or 6 positions of **6-9** and **20**), and the aLNCC in combination with gCNCCA (e.g., on C(4) in **27**). A “pure” (noncombined) gCNCCA effect and a “pure” aCNCCA effect are experienced only in **25** and **26**, by C(5) and C(8a), respectively, which carbons do not undergo the gLNCC effect since neither of them has a hydrogen atom oriented *syn*-axial (or equivalent) to the nitrogen lone-pair. For the amines **28-30** arose the question whether or not the carbons C(3a), C(6a) and C(9a) should be considered to be an *N*-alkyl substituent, each for that piperidine ring of which it is not a member; two parallel regression analyses revealed that a little bit better multiple correlation coefficient and standard error are attained if C(3a), C(6a) and C(9a) are considered not to be *N*-alkyl substituents, and, consequently, C(1), C(3), C(4), C(6), C(7), C(9) in **28**, and C(4), C(6), C(7), C(9) in **29** and **30** were considered to experience a “pure” gLNCC effect, and C(1), C(3) in both **29** and **30** - a “pure” aLNCC effect.

In the amine oxides, too, most of the γ -carbons experience combinations of the γ -*gauche* effect of the $\text{N}^+\text{—O}^-$ oxygen atom (“gONCC”) with either the γ -*anti* effect of the N^+ -alkyl carbons (“aCNCC”; e.g., the carbons C(3) and/or C(5) in **1ax-22ax**, C(9a) in **23ax-27ax**, and C(8a) in **23ax**, **24ax**, **27ax**), or the γ -*gauche* effect of the N^+ -alkyl carbons (“gCNCC”; e.g., the $-\text{CH}_3$ carbons at the 2 and/or 6 positions of **6ax-9ax**,

20ax, **20eq**, the C(4) carbons in **23ax-26ax**, **23eq**, **25eq**, and C(5) in **23ax**, **24ax**, **27ax**, **23eq**, **27eq**, or combinations of the γ -*anti* effect of the N⁺—O⁻ oxygen (“*a*ONCC”) with the *g*CNCC (e.g., C(3) and/or C(5) in **10eq**, **19eq-22eq**, C(9a) in **23eq**, **25eq**, **27eq**, and C(8a) in **23eq**, **27eq**). A “pure” *g*CNCC and a “pure” *a*CNCC effect are experienced in **25ax** and **26ax**, by C(5) and C(8a), respectively, which do not undergo the *g*ONCC effect, since they have no hydrogen atom oriented *syn*-axial to the N⁺—O⁻ oxygen. A “pure” *g*ONCC effect is experienced by C(5) in **25eq**, by C(1), C(3), C(4), C(6), C(7), C(9) in **28ax** and by C(4), C(6), C(7), C(9) in both **29ax** and **30ax**, and a “pure” *a*ONCC effect – by C(8a) in **25eq** and by C(1), C(3) in both **29ax** and **30ax**.

Table 6

Regression analysis of structural parameters determining the chemical shift differences between hetero- and carbocyclic ring γ -carbons in saturated monocyclic, bicyclic and tricyclic piperidine-derived amine oxides and the corresponding carbons in their parent amines

Number of observations: 74

Number of independent variables: 12

Multiple correlation coefficient, $r = 0.986$

Standard deviation in predicted *N*-oxidation shifts: ± 0.54 ppm

Constant term: nil

Parameter and value ^a	No. of occurrences	Student's <i>t</i> ratio
$\text{NC}_{\beta}^{\text{sec}}\text{C}\gamma^{\text{sec}}$: -1.47 ± 0.43	21	3.42
$\text{NC}_{\beta}^{\text{sec}}\text{C}\gamma^{\text{tert}}$: -0.87 ± 0.45	7	1.93
$\text{NC}_{\beta}^{\text{tert}}\text{C}\gamma^{\text{sec}}$: -2.60 ± 0.33	33	7.88
$\text{NC}_{\beta}^{\text{tert}}\text{C}\gamma^{\text{tert}}$: -2.28 ± 0.39	13	5.84
<i>g</i> ONCC : -1.46 ± 0.38	55	3.84
<i>g</i> CNCC : 2.38 ± 0.49	21	4.86
<i>g</i> LNCC : 3.02 ± 0.35	63	8.63
<i>g</i> CNCCA : 2.28 ± 0.50	13	4.56
<i>a</i> ONCC : -22.25 ± 5.93	15	3.75
<i>a</i> CNCC : -21.93 ± 5.74	38	3.82
<i>a</i> LNCC : -29.70 ± 5.71	5	5.20
<i>a</i> CNCCA : -22.56 ± 5.77	49	3.91

^a In ppm \pm standard error

For the γ -*anti* fragments in both amines and amine oxides, to correct the dihedral angle deviations from the standard 180°, multiplication of the corresponding structural parameters with the simple negative cosines of the measured angles was chosen, in order to preserve the accordance between the sign of the parameters and the real direction of the various γ -*anti* effects. For the γ -*gauche* fragments, the correction of the torsion angle deviations from the standard 60° is made by multiplication with the double cosine, as shown in the previous section. A sizeable improvement of the correlation fit is achieved when additionally four corrective parameters ($\text{NC}_{\beta}^{\text{sec}}\text{C}\gamma^{\text{sec}}$, $\text{NC}_{\beta}^{\text{sec}}\text{C}\gamma^{\text{tert}}$, $\text{NC}_{\beta}^{\text{tert}}\text{C}\gamma^{\text{sec}}$ and $\text{NC}_{\beta}^{\text{tert}}\text{C}\gamma^{\text{tert}}$) are introduced, to account for the degree of substitution of the β -carbons and the perturbed γ -carbons. For the γ -effects, too, two examples will illustrate the way these parameters are used. The first example is the equation regarding the *N*-oxidation shift of C(4), on going from **27** to **27ax**, which should be written as follows:

$$\delta C(4)_{27ax} - \delta C(4)_{27} = NC_{\beta}^{tert}C\gamma^{sec} + gCH_3NC(4a)C(4) \cdot 2\cos 51.79^\circ + aONC(4a)C(4) \cdot (-\cos 169.54^\circ) - gCH_3NC(4a)C(4)A \cdot 2\cos 57.39^\circ - aLNC(4a)C(4) \cdot (-\cos 173.33^\circ) = 5.63 \text{ ppm, i.e.,}$$

$$NC_{\beta}^{tert}C\gamma^{sec} + 1.237 gCNCC + 0.9834 aONCC - 1.078 gCNCCA - 0.9932 aLNCC = 5.63 \text{ ppm}$$

As a second example will serve the equation affording the shift of C(8a), on *N*-oxidation of **25** to **25ax**: $\delta C(8a)_{25ax} - \delta C(8a)_{25} = NC_{\beta}^{tert}C\gamma^{tert} + aCH_3NC(10a)C(8a) \cdot (-\cos 176.1^\circ) - aCH_3NC(10a)C(8a)A \cdot (-\cos 174.4^\circ) = -1.21 \text{ ppm, i.e.,}$

$$NC_{\beta}^{tert}C\gamma^{tert} + 0.9977 aCNCC - 0.9953 aCNCCA = -1.21 \text{ ppm}$$

From the 38 amine oxides, a number of 74 such equations were deduced and subjected to regression analysis, with the results presented in Table 6. If the parameters $NC_{\beta}^{sec}C\gamma^{sec}$, $NC_{\beta}^{sec}C\gamma^{tert}$, $NC_{\beta}^{tert}C\gamma^{sec}$ and $NC_{\beta}^{tert}C\gamma^{tert}$ are ignored, then the multiple correlation coefficient drops to $r = 0.976$, and the standard error raises to ± 0.69 ppm.

δ -Effects

Within the amine oxides examined, among the carbon atoms in δ -position to the $N^+—O^-$ oxygen may be distinguished δ -carbons members of the piperidine rings (in all compounds), δ -carbons members of several exocyclic *N*-alkyl groups (in **3ax**, **5ax**, **8ax**, **9ax**, **13ax**, **16ax**, **18ax**), and δ -carbons members of the carbocyclic side-rings (in **23ax-27ax**, **23eq**, **25eq**, **27eq**), and each of these groups is showing a different behaviour.

δ -Carbons members of the piperidine rings

On *N*-oxidation, all carbons in the 4 position of the piperidine rings exhibit upfield shifts, of magnitudes ranging from -0.67 ppm to -3.3 ppm, which do not correlate with the steric orientation of the $N^+—O^-$ bond. However, their chemical shifts show a good linear correlation with those of their counterparts in the parent amines, which can be used for prediction according to following equation: $\delta C_{\delta(N\text{-oxide})} = 1.016 \delta C_{\delta(A\text{mine})} - 2.54$ (No. of observations: 44; correlation coefficient, $r = 0.998$; standard deviation of predicted *N*-oxidation shifts: ± 0.65 ppm).

*δ -Carbons members of the *N*-alkyl groups*

All seven available examples of δ -carbons (3 primary and 4 secondary) in the *N*-alkyl groups show, on *N*-oxidation, very constant upfield shifts (-0.8 ppm to -1.2 ppm), which seem completely independent of the degree of substitution.

δ -Carbons members of the carbocyclic side-rings

In contrast to the previous two groups, which exhibit only upfield shifts, the *N*-oxidation shifts of δ -carbons in the side-rings may be either upfield or downfield, and of quite variable magnitudes (-0.10 to -1.88 ppm, and $+0.06$ to $+2.42$ ppm, respectively). Most of the observed downfield shifts (6 examples) belong to carbons that, on *N*-oxidation of the amine, undergo also a δ -*syn* axial interaction with the $N^+—O^-$ oxygen atom (see C(6) and C(8) in both **25ax** and **26ax**), or with the $N^+—CH_3$ group (see C(6) and C(8) in **25eq**), and could be explained by the additional contribution of the apparent deshielding effect of these δ -*syn* axial interactions. However, there are also 4 examples of (weak) downfield shifts (up to $+0.32$ ppm) of carbons experiencing no δ -*syn* interaction (see C(1,8) in both **23eq** and **24ax**, C(1) in **25eq**, and C(8) in **27eq**), which require another explanation.

EXPERIMENTAL

NMR spectra

The NMR spectra were measured on a JEOL GX 400 spectrometer (1H : 400 MHz, ^{13}C : 100.4 MHz), equipped with a LSI 11/73 computer and a JEOL JEC 32 dataprocessor. The ^{13}C chemical shifts of **19** were assigned on the basis of a DEPT-135

spectrum, of relative signal intensities, and of chemical shift comparisons with piperidines having chemical shifts already assigned. The signal assignments for **27** were achieved by a 2D-INADEQUATE experiment, using a pulse sequence and instrumental settings as described in a previous paper.²³ The ¹³C chemical shifts of all the other compounds are taken from the literature, as follows: **1-9**, **1ax-9ax**, **11-13**, **11ax-13ax**, **15-18** and **15ax-18ax**,²⁴ **10**, **14**, **20** and **21**,²⁵ **10ax**, **10eq**, **14ax**, **19ax-27ax**, **19eq-23eq**, **25eq** and **27eq**,² **22**,²⁶ **23-26**,²⁷ **28-30** and **28ax-30ax**.³

Compounds

The synthetic routes to the compounds **19**²⁸ and **27**²⁹ have already been indicated.

Calculations

The MM+ molecular mechanics calculations were performed using the program HyperChem Lite 1.1 for Windows (Hypercube, Gainesville, FL, USA).

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