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Hydroacridines

Part 17†—Stereospecific Influence of the N^+—O^- Group on $^1J_{C,C}$ Couplings in Non-aromatic Amine Oxides

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ABSTRACT: The $^1J_{C,C}$ coupling constants of *N*-epimeric pairs of amine oxides derived from (4aα, 8aβ, 9aβ, 10aα)- and (4aα, 8aα, 9aβ, 10aα)-tetradecahydro-10-methylacridine, 1-*cis*-2,6-trimethylpiperidine and tropine were investigated and compared with those for the parent amines. For C—C bonds adjacent to the N^+—O^- group, the couplings depend on the mutual orientation of the N^+—O^- bond and the C—C bond of interest: with the N^+—O^- bond oriented *syn* (*gauche*), the couplings are essentially as large as those in the parent amines, whereas with the N^+—O^- bond oriented *anti*, the couplings are about 4–5 Hz smaller. The ^{13}C NMR chemical shifts of the *N*-CH_3 carbons, from which the configurations of the *N*-epimeric amine oxides can be derived, are also reported.

KEYWORDS: ^{13}C NMR; carbon–carbon coupling; non-aromatic amine oxides; tetradecahydroacridines; piperidines; tropane alkaloids; configuration

INTRODUCTION

A large number of $^1J_{C,C}$ coupling constants have been determined to obtain an insight into the bonding of carbon compounds.[2–6] $^1J_{C,C}$ coupling increases (a) with increasing s-character of the carbon orbitals involved in the C—C bond,[7] (b) with increasing π-bond order in olefinic and aromatic compounds[8,9] and (c) with increasing electronegativity of the substituents linked with the two carbons.[10,11]

Here we report on $^1J_{C,C}$ coupling constants in some *N*-epimeric pairs of *N*-oxides derived from saturated azaheterocyclic compounds and on stereochemical implications. The ^{13}C NMR chemical shifts of the *N*-CH_3 carbons, from which the configurations of the *N*-epimeric amine oxides can be derived, are also reported. NMR data were obtained by standard ^{13}C NMR and by two-dimensional INADEQUATE. The full ^{13}C NMR chemical shift assignments of the compounds will be given and discussed in a later paper.

RESULTS

The *N*-oxides **3**, **4**, **7**, **8**, **12** and **13** were measured as pure compounds. *N*-Oxides **10** and **11** were measured as an epimeric mixture; analysis of this mixture by 2D-INADEQUATE posed no problem because the ^{13}C NMR signals of the components are well separated.

The configurational assignment within the epimeric *N*-oxide pairs **3–4**, **7–8**, **10–11** and **12–13** was easily possible on the basis of the ^{13}C chemical shifts of their *N*-CH_3 carbons. Owing to additional *γ-gauche* interactions, axial *N*-methyl groups give signals shifted upfield by 6–13 ppm as compared with equatorial *N*-methyl groups:

3: $\delta^{13}C_{N\text{-Me(eq)}} = 51.5$ ppm *vs.* **4**: $\delta^{13}C_{N\text{-Me(ax)}} = 41.8$ ppm

7: $\delta^{13}C_{N\text{-Me(eq)}} = 53.6$ ppm *vs.* **8**: $\delta^{13}C_{N\text{-Me(ax)}} = 47.8$ ppm

10: $\delta^{13}C_{N\text{-Me(eq)}} = 51.7$ ppm *vs.* **11**: $\delta^{13}C_{N\text{-Me(ax)}} = 38.7$ ppm

12: $\delta^{13}C_{N\text{-Me(eq)}} = 57.2$ ppm *vs.* **13**: $\delta^{13}C_{N\text{-Me(ax)}} = 50.5$ ppm

These ^{13}C shifts data agree well with earlier configurational assignments, through ^1H NMR, for the epimeric pairs **3–4**[12] and **12–13**.[13]

Table 1 gives the $^1J_{C,C}$ values; the most important of these values, together with the relevant ^{13}C shifts data, are also given in the formulae.

Several coupling constants over more than one C—C bond, measured for **1**, **9** and **13**, are presented in Table 2. As emerges from the coupling paths shown in Table 2, all observed vicinal couplings occur via a coplanar zig-zag path, *i.e.* exclusively between mutually antiperiplanar-oriented carbon atoms. Several of the vicinal carbon–carbon couplings occur even through the nitrogen atom. These examples provide new experi-

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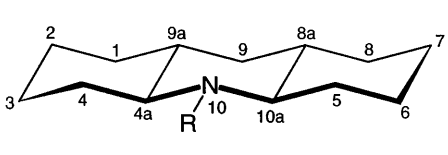

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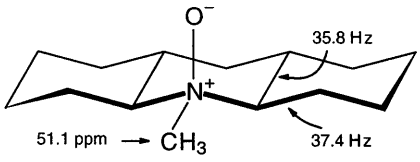

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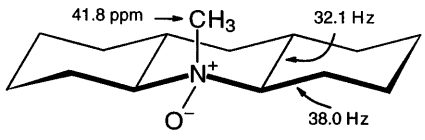

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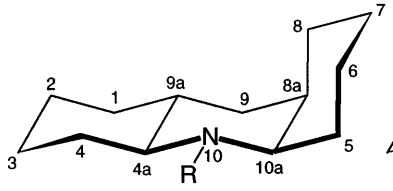

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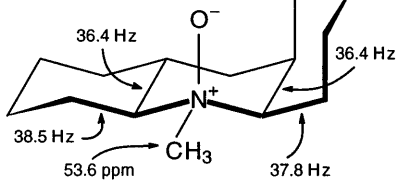

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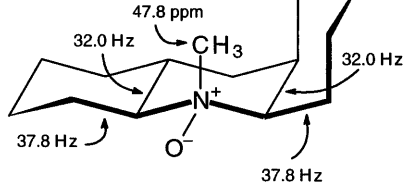

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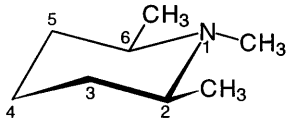

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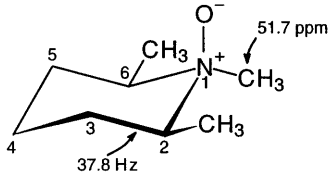

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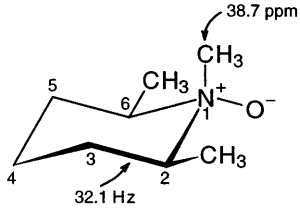

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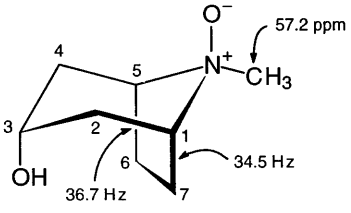

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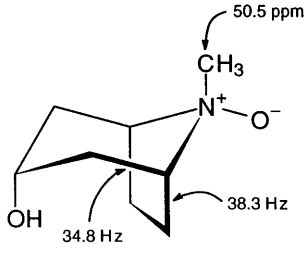

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mental support for conclusions of previous investigations.[14]

DISCUSSION

Within compounds **1–13** there are three features of one-bond carbon–carbon coupling constants to be distinguished and discussed.

$^1J_{C,C}$ couplings between C—C units not attached to the nitrogen

These couplings show magnitudes situated between 32 and 34 Hz in secondary and tertiary amines and *N*-oxides. No important influence of the degree and type of *N*-substitution or of stereochemical features on these couplings occurs.

Table 1. One-bond carbon–carbon coupling constants in compounds **1–13** (±0.8 Hz).

Bond	1	2	3	4	5	6	7	8	9	10	11	12	13
C(1)—C(2)	32.9	33.0	33.0	32.9	33.6	33.2	33.8	33.9	—	—	—	36.7	34.8
C(2)—C(3)	33.4	33.0	33.0	—[a]	33.0	31.6	32.6	—[a]	39.2	37.8	32.1	35.6	36.0
C(3)—C(4)	32.9	33.0	33.0	32.0	33.0	32.4	—[a]	—[a]	32.6	33.0	32.1	35.6	36.0
C(5)—C(6)	32.9	33.0	33.0	32.0	33.0	33.3	34.2	34.0	39.2	37.8	32.1	34.5	38.3
C(6)—C(7)	33.4	33.0	33.0	—[a]	33.0	32.4	32.8	33.9	—	—	—	a	a
C(7)—C(8)	32.9	33.0	33.0	32.9	33.0	31.6	33.5	32.6	—	—	—	—	—
C(8)—C(8a)	33.9	33.0	33.0	33.6	34.2	33.3	34.6	34.5	—	—	—	—	—
C(8a)—C(9)	33.4	33.7	33.7	32.9	33.6	33.3	34.0	33.9	—	—	—	—	—
C(9)—C(9a)	33.4	33.7	33.7	32.9	34.2	33.3	34.0	33.9	—	—	—	—	—
C(9a)—C(1)	33.9	33.0	33.0	33.6	33.6	33.3	34.2	33.3	—	—	—	—	—
C(4)—C(4a)	36.4	38.0	37.4	38.0	36.9	36.7	38.5	37.8	—	—	—	—	—
C(4a)—C(9a)	34.4	35.8	35.8	32.1	34.2	38.4	36.4	32.0	—	—	—	—	—
C(8a)—C(10a)	34.4	35.8	35.8	32.1	34.2	35.0	36.4	32.0	—	—	—	—	—
C(10a)—C(5)	36.4	38.0	37.4	38.0	36.3	36.7	37.8	37.8	—	—	—	—	—
C(2)—CH_3	—	—	—	—	—	—	—	—	39.2	39.7	38.7	—	—

[a] Could not be determined (strongly coupled AB system).

$^1J_{C,C}$ couplings between carbons, one of which is bonded to nitrogen, in the secondary and tertiary amines

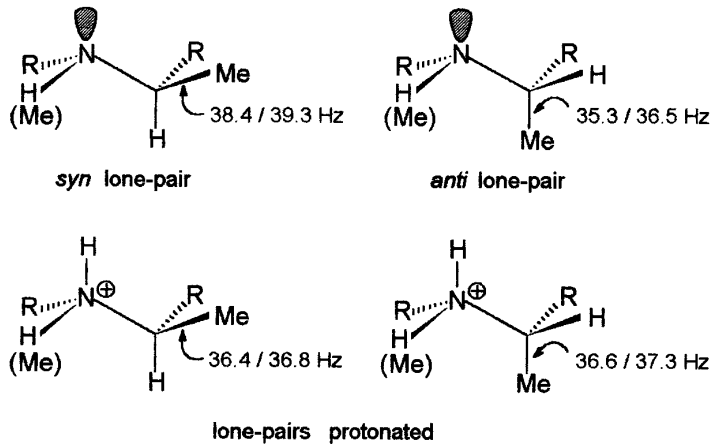
The magnitudes of these couplings range between 34 and 39 Hz. This increase in magnitude, compared with the above couplings, is attributable in part to the electronegativity of the nitrogen (enhancement of $^1J_{C,C}$s by attached electronegative substituents is well documented [10,11,15]), but mainly to the 'lone-pair effect' of the sp^3-hybridized nitrogen lone-pair: sp^2-hybridized heteroatom lone-pairs specifically enhance the $^1J_{C,C}$s of adjacent C—C bonds, if oriented closely (*Z* or *cis*, *syn* or *gauche*, or *ortho*) to each other. This is well demonstrated for sp^2 nitrogen lone-pairs in oximes,[16] imines[16] and aza-aromatics,[17] and has been rationalized in terms of the additional positive lone-pair term induced by the proximity of the heteroatom lone-pair.[6,17] For sp^3-hybridized nitrogen lone-pairs, the effect has been verified for the C(2)—CH_3 bonds in diastereomeric 4-*tert*-butyl-2-methyl- and 4-*tert*-butyl-1,2-dimethylpiperidines[18] (see Scheme 1). As can be seen in Scheme 1, the enhancing effect of the *syn*-oriented lone-pairs disappears on unfavourable (*anti*) orientation or on protonation of the lone-pairs; the *anti*-oriented lone-pairs, however, give even lower $^1J_{C,C}$s by 0.8–1.1 Hz compared with the corresponding protonated forms.

According to investigations on *C*,*N*-dimethyldecahydroquinolines,[19] sterically related to our amines, the share of the conformer with an axial lone-pair (*i.e.* equatorial *N*-methyl group) in tertiary amines **2**, **6** and

Table 2. Two- and three-bond carbon–carbon coupling constants in compounds **1**, **9** and **13** (± 0.8 Hz)[a]

Compound	Coupling path	Coupling constant
1	C(1)—C(9a)—C(9)	2.5
	C(1)—C(9a)—C(9)—C(8a)	3.5
	C(2)—C(1)—C(9a)—C(9)	3.5
	C(4)—C(4a)—N—C(10a)	3.5
9	C(2)—N—C(6)—CH_3	4.1
	C(3)—C(2)—N—CH_3	3.3
	C(4)—C(3)—C(2)—CH_3	6.5
13	C(1)—C(2)—C(3)	3.5

[a] The signs of these coupling constants are unknown.



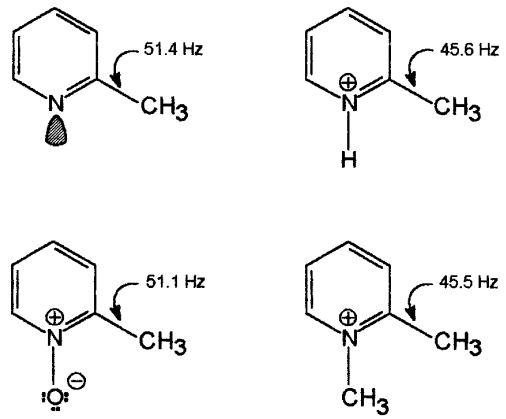
Scheme 1. The lower J values belong to the secondary amines and the higher values to the corresponding N-methylated tertiary amines. Data compiled from Ref. 18.

Table 3. $^1J_{C,C}$ values of C—C bonds adjacent to the nitrogen in amines **1**, **2**, **5**, **6** and **9**, depending on the degree of alkylation of the nitrogen and of the carbon atoms involved (± 0.8 Hz)[a]

Type of amine	Type of C—C bond		
	C_{tert}—C_{tert}	C_{tert}—C_{sec}	C_{tert}—C_{prim}
Secondary	34.2–34.4 (3)	36.3–36.9 (3)	38.4 (1)[b]
Tertiary	35.0–35.8 (2)[c]	36.7–39.2 (4)	39.2–39.3 (2)[d]

[a] The figures in parentheses indicate the number of occurrences.
[b] This occurrence is taken from Ref. 18 (see Scheme 1).
[c] The large value of 38.4 Hz found for the C(4a)—C(9a) bond in **6** (see Table 1) cannot be explained and is not included here.
[d] The value of 39.3 Hz is taken from Ref. 18 (see Scheme 1).

9 should be at least 95%. Hence the nitrogen lone-pairs in **2**, **6** and **9** are practically oriented entirely *syn* (or *gauche*) with respect to either adjacent C—C bond. The $^1J_{C,C}$ values of these bonds, within amines **1**, **2**, **5**, **6** and **9**, can be differentiated in terms of degree of substitution of the nitrogen atom and of carbon atoms (see Table 3). As can be seen in Table 3, the magnitudes of the $^1J_{C,C}$s increase as the degree of alkylation of the nitrogen increases (this is true also in Scheme 1), but decrease as the degree of alkylation of the carbons involved



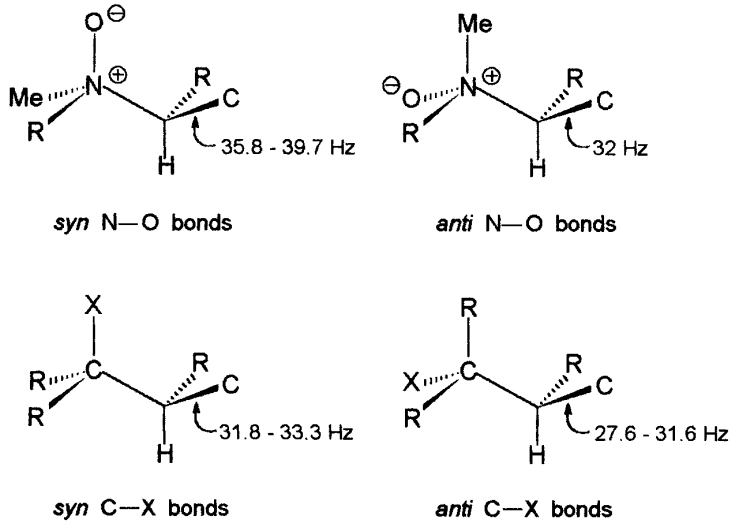
Scheme 2. J values taken from Refs 6 and 17.

increases. The generally lower $^1J_{C,C}$ values in secondary than in the corresponding tertiary amines can be rationalized by the lower electronic density of the nitrogen lone-pair (hence weaker 'lone-pair effect') in the secondary amines. In addition, for the C_{tert}—C_{tert} bonds [*i.e.* C(4a)—C(9a) and C(8a)–C(10a)], the difference between tertiary and secondary amines may be increased owing to the higher share of the equatorial lone-pair conformer (with the lone-pair oriented *anti* to these bonds) in secondary amines.

$^1J_{C,C}$ couplings between carbons, one of which is bonded to nitrogen, in the amine oxides

These couplings exhibit a marked dependence on the mutual orientation between the N^+—O^- bond and the C—C bond of interest. The ^1J values of C—C bonds oriented *syn* (*gauche*) to the N^+—O^- bond (35.8–39.7 Hz) are fairly close to those of the parent tertiary amines and also parallel their dependence on the degree of alkylation of the carbons (compare with Table 3): C_{tert}—C_{tert} 35.8–36.4 Hz (two occurrences), C_{tert}—C_{sec} 37.4–38.7 Hz (eight occurrences) and C_{tert}—C_{prim} 38.7–39.7 Hz (two occurrences). On the other hand, C—C bonds oriented *anti* to the N^+—O^- bond show clearly smaller ^1J values, which seem not to depend on the degree of alkylation of the carbons: C_{tert}-C_{tert} 32.0–32.1 Hz (three occurrences), C_{tert}—C_{sec} 32.1 Hz (1 occurrence).

Hence the sp^3-hybridized oxygen lone-pairs of the N^+—O^- group in aliphatic amine oxides produce essentially the same effect, in terms of stereospecificity and magnitude, as the sp^3-hybridized nitrogen lone-pair in the parent tertiary amines. A similar parallelism has been observed between the effects of the sp^2-hybridized nitrogen lone-pair and the oxygen lone-pairs in 2-methylpyridine and its *N*-oxide, respectively;[17] as can be seen in Scheme 2, on replacing the N^+—O^- oxygen by a methyl group, the 'lone-pair effect' also disappears



syn N—O bonds *anti* N—O bonds

syn C—X bonds *anti* C—X bonds

(X = OH, OMe, NH_2, F, Cl, Br, I)

Scheme 3. J values compiled from present work and Refs 10 and 20.

as on protonation of the nitrogen lone-pair in the amine. A parallel can also be drawn between the 'lone-pair effect' in *N*-oxides **3**, **4**, **7**, **8** and **10**–**13** and that observed in 2-X-substituted adamantanes[10] and 1-X-substituted diamantanes,[20] where X is a heteroatom bearing unshared sp^3-hybridized electron lone-pairs (see Scheme 3).

The observed effect can be useful in determining the configurations of *N*-bridged azabicyclic amine oxides, especially with symmetrical bicyclic skeleton (such as 7-azabicyclo[2.2.1]heptane or 9-azabicyclo[3.3.1]nonane derivatives), where ^1H and ^{13}C chemical shift arguments are expected to fail. Thus, for example, the configurations of **12** and **13**, which once created problems,[13] could be derived solely straight from the observed $^1J_{C,C}$ values: in **12**, because $^1J_{C(1),C(2)} > {}^1J_{C(1),C(7)}$, it emerges that the N^+—O^- bond is *gauche* to C(1)—C(2). In **13**, convesely, because $^1J_{C(1),C(2)} < {}^1J_{C(1),C(7)}$, the N^+—O^- bond is *gauche* to C(1)—C(7).

EXPERIMENTAL

The synthesis and separation of compounds **1**, **5**,[21] **2**, **6**,[22] **3**, **4**[12] and **9**[23] have been described elsewhere. The new compounds **7** (m.p. 164 °C, decomp.) and **8** (m.p. 136–138 °C) were prepared by *N*-oxidation of **6** with perhydrol and separated as described for **3** and **4**.[12] A mixture of the epimers **10** + **11**, prepared by *N*-oxidation of **9** with perhydrol, also as described for **3** and **4**,[12] resulted as a hygroscopic, thick syrup, and was measured without separation. The epimeric mixture **12** + **13** was prepared by essentially the same procedure as described in the literature[24] and the separation into the isomers was performed according to Ref. 25.

The 2D-INADEQUATE experiments, using a composite pulse sequence[26] and quadrature detection if f_1 and f_2, were performed on a JEOL GX 400 spectrometer. Solutions ranging from 1–1.5 M (**1**–**4**, **9**–**13**) to 2.5 M (**5**–**8**) in $CDCl_3$ with internal TMS (for **1**–**11**) or D_2O with internal DSS (for **12** and **13**) were used. The instrumental settings were as follows: 1792 scans (64 h measurement time), $\tau = 3/4\ J = 21.4$ ms (for $J = 35$ Hz), 32 data points in f_1 with zero filling to 64, 16 384 data points in f_2 (digital resolution 0.8 Hz).

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