CARBON-13 NMR STUDIES ON SOME QUINOXALINE AMINO ESTERS AND THEIR N-OXIDES

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Abstract —— Carbon-13 chemical shift assignments are reported for a series of N-(2-quinoxaloyl)- α-amino esters, their mono- and di-N-oxides as well as their C-3 methyl analogues. The influences of substituents at C-2 and/or C-3 on the N-oxidation shifts are discussed in terms of mesomeric states and intramolecular hydrogen bridging.

INTRODUCTION

Quinoxaline-amino esters and dipeptides as well as their mono and di-N-oxides attracted our attention, since some quinoxaline-peptides are naturally occurring antibiotics (quinomycins)[1]. In recent publications we reported[2,3] on the syntheses, and spectral characterisation of model quinoxaline derivatives (2-7) as depicted in Chart 1. ^{13}C-chemical shift data for some quinolines have also been reported[4,5,6], and are in agreement with our early findings[3].

In this study we wish to present a detailed ^{13}C-nmr investigation of these compounds with special emphasis on the effects of N-oxidations. There are few studies on this topic published recently[5,6] reporting N-oxidation effects on neighbouring carbon atoms in various aza-aromatic heterocycles. We wish to demonstrate that these N-oxidation effects on the ^{13}C-chemical shifts ($\Delta\delta$) and on carbon-hydrogen coupling constants ($^{n}J_{C-H}$) may strongly depend on the presence of certain substituents at C-2 and C-3.

RESULTS AND DISCUSSION

A. ASSIGNMENTS:

The ^{13}C-chemical shifts for compounds 2-7 are listed in Table 1. The assignments are based on data reported earlier for the parent quinoxalines (1a-1d)[5], on coupling information and substituent effects. These assignments are discussed as follows:

COMPOUNDS 2a - 2d :

The two carbonyl signals (C-9 and C-11) are readily distinguished; the ester carbonyl is less shielded (172-173 ppm) than the amide (157-163 ppm) which is conjugated to the quinoxaline moiety. The signals of the quaternary atoms C-4a and C-8a are differentiated from C-2 by their shape in the ^{1}H-coupled spectra; they appear as broadened singlets, while those of C-2 are doublets due to coupling with H-3. Furthermore, calculations using the characteristic N-oxidation effects[5] confirmed these assignments (vide infra). The signals of C-3 are easily identified by their large $^{1}J_{C-H}$ values ranging from 189 to 194 Hz. The tertiary carbon atoms of the benzenoid ring (C-5 to C-8) can be recognized as two sets (C-5/C-8 and C-6/C-7) which are distinguishable in the ^{1}H-coupled spectra by Günther's "finger-print" rule[7]. The assignments of C-5 and C-8 in 2a and 2d are tentative due to their very close chemical shifts. In 2b and 2c they are well-separated from each other because of the pronounced diamagnetic shielding effect of N-oxidation upon peri-positioned carbon atoms. Changes of the $^{1}J_{C-H}$ values[5] of the signals of C-5 and C-8 were also helpful (vide infra). N-oxidation shifts were also useful in assigning the C-6 and C-7 signals. As Günther demonstrated[5], the effect of introducing one oxygen atom at N-1 causes a stronger deshielding for C-7 compared to C-6. Since both carbon atoms have the same chemical shift (133.0) in the di-N-oxide 2d, we attributed the signal with the larger chemical shift value in the spectrum of 2b to C-7 (and vice versa to C-6 in 2c). The signals of C-6 and C-7 in 2a were assigned by comparison with the corresponding values for the C_3-methyl analogue 3a. In the spectra of the other pairs (2b/3b, 2c/3c and 2d/3d) we found that the C-6 signal is more shielded by methyl introduction than that of C-7. These assignments are also confirmed by differences in $^{1}J_{C-H}$ values of the C-6 and C-7 signals (vide infra). Assignments of the remaining side chain carbon atoms are straightforward.

Table 1

^{13}C - Chemical Shifts(a) of Compounds 2 - 7

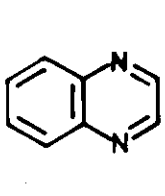
No	C-2	C-3	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9
2a	143.1	143.8	144.0	129.5(e)	130.3	131.7	129.7(e)	140.2	162.9
2b	130.3	148.1	145.7	130.3	131.1	132.8	119.4	136.3	159.1
2c	146.7	128.4	138.1	119.1	132.4	131.5	130.5	143.7	161.5
2d	133.0	131.7	138.7(e)	120.6(f)	133.0	133.0	121.0(f)	138.2(e)	157.3
3a	142.8	154.3	143.1	129.4	129.7	131.7	128.6	139.2	164.3
3b	134.0	155.2	143.5	130.0	129.3	132.3	118.7	134.4	160.5
3c	146.0	141.7	137.0	118.8	131.0	131.4	130.1	141.1	163.6
3d	137.3	141.1	136.8	119.2(e)	131.6	132.4	119.7(e)	135.7	158.7
4a	142.9	143.7	144.0	129.3(e)	130.8	131.7	129.8(e)	140.3	162.9
4b	130.3	148.1	145.7	130.3	131.0	132.8	119.4	136.2	159.2
4c	146.5	128.6	138.2	119.2	132.3	131.5	130.6	143.8	161.6
4d	132.9	131.6	138.2(e)	120.4	132.9(f)	132.7(f)	120.9	138.7(e)	157.5
5a	142.7	154.1	143.0	129.3	129.6	131.5	128.5	139.1	164.2
5b	133.2	155.9	143.6	129.8	129.2	132.4	119.1	134.0	160.7
5c	145.8	141.8	137.1	118.9	131.4	131.0	130.2	141.2	163.6
5d	136.1	141.3	136.8	119.6(e)	131.6	132.4	119.8(e)	136.1	159.0
6a	142.9	143.8	144.0	129.5(e)	130.9	131.5	129.8(e)	140.3	162.8
7d	136.8	141.4	136.8	119.5	131.4(e)	132.4(e)	119.5	135.9	158.7

(a) In ppm, relative to internal TMS; values marked (e) or (f) may be interchanged pairwise.

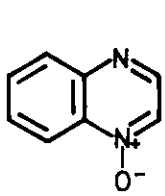
Table 1 (continued)

No	C-10	C-11	C-12	R^1	R^2
2a	48.3	173.1	52.6		18.4
2b	48.7	172.5	52.6		18.1
2c	48.5	172.8	52.6		18.3
2d	48.9	172.3	52.7		18.1
3a	48.4	173.4	52.6	24.7	18.4
3b	48.6	172.7	52.5	23.6	17.7
3c	48.5	173.0	52.5	13.6	18.1
3d	48.8	172.5	52.6	14.4	17.3
4a	53.5	171.7	52.4		38.2(t), 135.9(s), 129.3(2d), 128.6(2d), 127.2(d)
4b	54.3	171.3	52.4		37.9(t), 136.1(s), 129.2(2d), 128.7(2d), 127.2(d)
4c	53.6	171.5	52.4		38.2(t), 135.7(s), 129.3(2d), 128.7(2d), 127.3(d)
4d	54.5	171.0	52.5		37.8(t), 135.8(s), 129.2(2d), 128.6(2d), 127.2(d)
5a	53.5	171.8	52.3	24.5	38.2(t), 136.0(s), 129.4(2d), 128.6(2d), 127.2(d)
5b	54.0	171.5	52.4	24.3	38.0(t), 136.1(s), 129.4(2d), 128.7(2d), 127.2(d)
5c	53.7	171.6	52.4	13.6	38.1(t), 135.9(s), 129.4(2d), 128.7(2d), 127.3(d)
5d	54.0	171.3	52.0	14.4	37.6(t), 136.2(s), 129.4(2d), 128.6(2d), 127.2(d)
6a	56.7	171.0	52.9		136.3(s), 129.8(d), 129.1(2d), 127.5(2d)
7a	57.3	170.5	52.8	14.4	135.1(s), 129.0(2d), 128.8(d) , 127.7(2d).

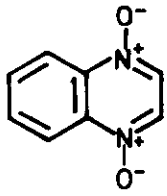
Chart 1



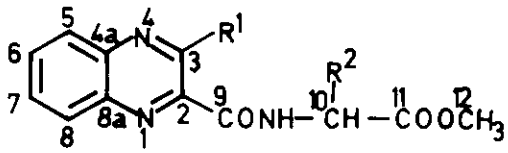
1 a



1 b ≡ 1 c



1 d



No	2	3	4	5	6	7
R^1	H	CH_3	H	CH_3	H	CH_3
R^2	CH_3	CH_3	CH_2Ph	CH_2Ph	Ph	Ph

a: Reduced

b: N^1— oxide

c: N^4— oxide

d: N^1,N^4— dioxide

COMPOUNDS 3a - 3d :

The introduction of a methyl group at C-3 causes a pronounced deshielding of C-3 (+7 to +10.5 ppm), while its influence on C-2 is either negligible (2a/3a and 2c/3c) or moderate deshielding (about +4 ppm) in 2b/3b and 2d/3d. Similar observations were reported for methylated quinoline and isoquinoline derivatives as

well as their N-oxides[4]. Further evidence for the C-2/C-3 assignment is found in the signal intensities: the C-2 signal is very small in the spectra of 3a/3d because it is far away from any proton in the molecule resulting in a long relaxation time (T_1) and a low nuclear Overhauser enhancement (NOE)[8]. Assignments of the remaining carbon atoms agree with the arguments outlined above.

COMPOUNDS 4a-4d, 5a-5d, 6a and 7d :

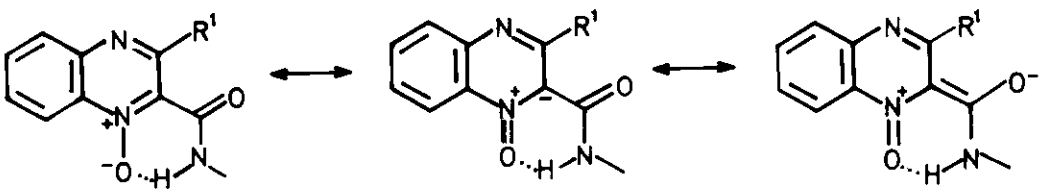
The chemical shifts of all quinoxaline carbon atom signals are very close to those of the corresponding analogues 2a-2d and 3a-3d discussed above. Hence, assignments of the ring carbons as well as of the side chain carbon atoms in the title compounds are straightforward.

B. EFFECTS OF N-OXIDATION

In the following discussion we are mainly confined with the representative compounds 2 and 3 , comparing them with series 1. All arguments are valid as well for the corresponding derivatives 4 to 7 .

In agreement with Gunther's findings[5] the tertiary α -carbon atoms are more shielded by N-oxidation than the quarternary α'-carbons. Their magnitudes, however, depend on the substituents at C-2 and C-3. If the amide group is attached to C-α (entry 2, Table 2), the Δδ -value for this C-α becomes smaller. This may be due to the fact that the mesomeric state I (Chart 2) is more favoured now due to the

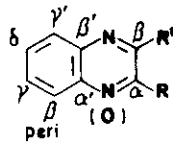
Chart 2

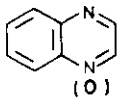
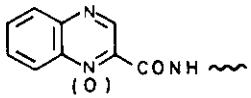
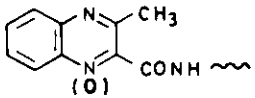
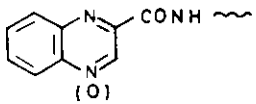
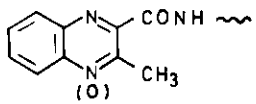


I II III

Table 2

N-Oxidation Effects ($\Delta\delta$) on ^{13}C-Chemical Shifts (a) of Compounds 1 - 3 in the Absence of a Second N-Oxide.



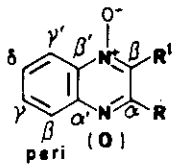
Entry		C-α	C-α'	C-β	C-β'	C-β_{peri}	C-γ	C-γ'	C-δ	C^9=O	$CH_3(R^1)$
1	 (1a→1b) (b)	-14.9	-5.5	+1.1	+2.9	-10.6	+2.0	+0.7	+0.5	-	-
2	 (2a→2b)	-12.8	-3.9	+4.3	+1.7	-10.2 (±0.1)(c)	+1.1	+0.7 (±0.1)(c)	+0.3	+0.3	-
3	 (3a→3b)	-8.8	-4.8	+0.9	+0.4	-9.9	+0.6	+0.6	-0.4	-3.8	-0.9
4	 (2a→2c)	-15.4	-5.9	+3.6	+3.5	-10.5 (±0.1)(c)	+1.6	+0.9 (±0.1)(c)	-0.2	-1.4	-
5	 (3a→3c)	-12.6	-6.1	+3.2	+1.9	-10.6	+1.3	+1.5	-0.3	-0.7	-11.1

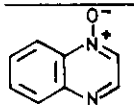
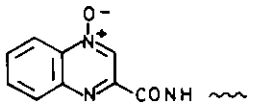
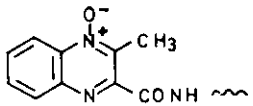
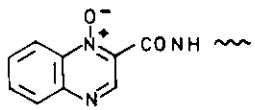
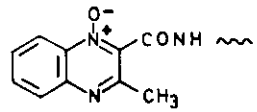
(a) Positive values correspond to deshielding, negative values to shielding.

(b) Taken from reference 5. (c) Due to uncertainty in peak assignment.

Table 3

N-Oxidation Effects ($\Delta\delta$) on ^{13}C-Chemical Shifts (a) of Compounds 1 - 3 in the Presence of a Second N-Oxide.



Entry		C-α	C-α'	C-β	C-β'	C-β_{peri}	C-γ	C-γ'	C-δ	C^9=O	$CH_3(R^1)$
1	 (O) (1b → 1d) (b)	-15.7	-7.3	+0.3	+1.1	-9.6	+1.9	+1.7	+0.4	-	-
2	 (O) (2c → 2d)	-13.7	-5.3 (±0.3)(c)	+3.3	+0.3 (±0.1)(c)	-9.7	+1.5	+1.7 (±0.2)(c)	+0.6	-4.2	-
3	 (O) (3c → 3d)	-8.7	-5.4	-0.6	-0.2	-10.7 (±0.3)(c)	+1.0	+0.6 (±0.2)(c)	+0.6	-4.9	+0.8
4	 (O) (2b → 2d)	-16.4	-7.3 (±0.3)(c)	+2.7	+2.1 (±0.2)(c)	-9.5 (±0.2)(c)	+1.9	+1.4 (±0.2)(c)	+0.2	-1.8	-
5	 (O) (3b → 3d)	-14.1	-6.7	+3.3	+1.3	-10.6 (±0.3)(c)	+2.3	+0.7 (±0.2)(c)	+0.1	-1.8	-9.2

(a) Positive values correspond to deshielding, negative values to shielding.

(b) Taken from reference 5. (c) Due to uncertainty in peak assignments.

presence of strong intramolecular hydrogen bridging[3]. Furthermore, the contribution of the mesomeric state III will cause state II to be less pronounced. The same is valid for C- α', the Δδ of which is also decreased by the introduction of the amide group at C- α. This interpretation is supported by the finding that an amide group at the β-carbon atom has virtually no influence on the N-oxidation effects on C-α and C- α' (entry 4).

Additional introduction of a methyl group at C- β (entry 3) causes a further decrease of the Δδ for C- α, while its influence on C- α' is negligible. This cannot be rationalized on the basis of the arguments discussed above. It is conceivable that the methyl group is practicing steric interference onto the amide moiety, disturbing its coplanarity with the hetero-ring, and thus weakening the hydrogen bridge[3,9]. Using this argument, however, one would expect increased shielding. Therefore, we feel that the above arguments are insufficient to explain the N-oxidation effects on the α- and α'- carbon atoms quantitatively[5]. The presence of a methyl group at C-α (entry 5) also causes a decrease of the shielding (Δδ) for this carbon atom. A similar observation, though to a lesser extent, was reported previously for the 2-methylquinoline system[4]. The amide group at C- α causes increased deshielding of C-β but decreases the deshielding of C- β' (entry 2). The additional methyl group at C- β (entry 3) cancels the former and reinforces the latter effect. This might be due to variations in the extent of the intramolecular hydrogen bridge which is now weakened by the steric interaction of the methyl and the amide group[3]. In the system with the amide group at C- β, where no comparable hydrogen bridging is possible (entries 4 and 5), these changes are less pronounced. Thus the dependence of inductive and mesomeric effects of the amide group on conformational changes may be responsible for the alteration of the Δδ -values at C-β and C- β'.

The N-oxidation effects on the C- β_{peri}, C- γ, C- γ' and C-δ are very similar to those reported by Günther[5]. The amide carbon atom is slightly shielded when this group is attached to C-β. As expected, when the amide group is at C-α, the existence of the intramolecular hydrogen bridge reinforces this shielding. The methyl carbon is shielded considerably only if it is attached to C- β, the magnitude of this shielding being virtually the same as that of C- β_{peri}. This suggests that the effects have the same origin for both carbon atoms, e.g. steric interactions between the solvated N ⟶ O group and the methyl C - H bonds[5].

The methyl protons, however, are not deshielded[3] and the $^{1}J_{C-H}$ for the methyl carbon signal is only increased by approximately 2 Hz when comparing 3a and 3c (129.4 and 131.8 Hz, respectively).

The N-oxidation effects on the ^{13}C-chemical shifts in presence of an already oxidized nitrogen atom (Table 3) are related to those in absence (Table 2). Only the C- α' atoms are slightly more shielded by 0.6 to 1.8 ppm.

Oxidizing a nitrogen atom in quinoxaline systems has certain effects on carbon-hydrogen coupling constants:

$^{1}J_{C-H}$ of peri-positioned carbon atom signals are increased by approximately 5-7 Hz in our compounds in accordance with Günther's findings[5]. The coupling constants of more remote carbon signals are affected as well. Thus, we found that $^{1}J_{C-H}$ of C- δ atoms are generally larger than those of C-γ by about 2 Hz in the monoxides[5]. This might be useful in signal assignments of other related compounds.

There is an interesting dependence of $^{2}J_{C2-H3}$ on the N-oxidation: Due to signal overlapping, it was not possible to identify all signals of one individual series (e.g. 2a to 2d), but those of the corresponding compounds in the series 4 and 6 can be taken into account also. In the reduced quinoxalines 4a and 6a, the $^{2}J_{C2-H3}$ values are 8.8 and 8.1 Hz, respectively. A similar value is found for the N^{1}-oxide 2b (10.0 Hz); oxidation of N^{4}, however, leads to considerably smaller couplings (3.1 Hz for 2c and 4.9 Hz for 4c). In the dioxide 2d, the C-2 signal in the ^{1}H-coupled spectrum is only a broadened singlet implying that the coupling constant is very small.

In the methylated compounds 3 and 5, the two-bond coupling constant (C - 3 with methyl protons) are invariant (6-7 Hz). This is in accordance with the corresponding $^{2}J_{C-H(methyl)}$ in toluene[10]. The $^{3}J_{C2-H(methyl)}$, however, are negligible in the reduced compounds (3a and 5a), being 2.1 and 2.9 Hz for 3c and 5c, respectively, and 4.4 Hz for 3d. Although a number of coupling constants in this series again cannot be identified unequivocally due to signal overlapping, there is a clear trend: N-Oxidation increases these $^{3}J_{C-H}$ values, but they never exceed the $^{2}J_{C3-H(methyl)}$. Ernst et al reported 5.8 Hz for the corresponding $^{3}J_{C-H}$ in toluene[10]. These values are relatively small compared to three-bond coupling to aromatic protons[11]. This is understandable, since the methyl group is rotating; thus, the bonds between the coupling nuclei are not within a rigid coplanar configuration.

EXPERIMENTAL

The ^{13}C-nmr spectra were recorded in the PFT mode (16 K data points for the FID) at ambient temperature with internal deuterium lock using Bruker WH-90 spectrometer (22.64 MHz). The pulse duration was 5-8 μsec. Sweep width was 6000 Hz in all cases. ^{1}H-coupled spectra were recorded in the "gated-decoupling" mode. The samples were 0.1 - 0.2 molar solutions in deuterochloroform. The chemical shifts were determined on the δ -scale relative to internal tetramethylsilane and are accurate to about 0.05 ppm. The coupling constants are accurate to 0.5 - 1 Hz.

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REFERENCES

1. H.T. Cheung, J. Feeney, G.C.K. Roberts, D.H. Williams, G. Ughetto and M.J. Waring, J. Am. Chem. Soc., 1978, 100, 46, and references cited therein.
2. M.M. El-Abadelah, S.S. Sabri, M.Z. Nazer and M.F. Za'ater, Tetrahedron., 1976, 32, 2931; M.M. El-Abadelah, S.S. Sabri, H.D. Tabba' and H. Duddeck, J. Heterocyclic Chem., 1977, 14, 871.
3. M.M. El-Abadelah, S.S. Sabri and H.I. Tashtoush, Tetrahedron., 1979, 35, 2571.
4. Ja-An Su, E. Siew, E.V. Brown and S.L. Smith, Org. Magn. Resonance., 1978, 11, 565, and references cited therein.
5. H. Günther and A. Gronenborn, Heterocycles., 1978, 11, 337, and references cited therein.
6. A.F. Kluge, M.L. Maddox and G.S. Lewis, J. Org. Chem., 1980, 45, 1909.
7. H. Günther, H. Schmickler and G. Jikeli, J. Magn. Resonance., 1973, 11, 344; G. Jikeli, W. Herrig and H. Günther, J. Am. Chem. Soc., 1974, 96, 323.
8. J.R. Lyerla, Jr. and G.C. Levy, "Carbon-13 Nuclear Spin Relaxation" in "Topics in Carbon-13 NMR Spectroscopy", G.C. Levy, ed., Wiley-Interscience, New York, 1, 1974, p. 79.

9. G.A. Baramki, G. Derdall and J.T. Edward, Can J. Spectroscopy., 1973, 18, 160.

10. L. Ernst, V. Wray, V.A. Chertkov and N.M. Sergeyev, J. Magn. Resonance., 1977, 25, 123.

11. E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy", 2nd ed., Verlag Chemie, Weinheim/Bergstr, 1978.

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