SYNTHESIS AND SPECTROSCOPIC STUDIES ON SOME NEW SUBSTITUTED 2-QUINOXALINECARBOXAMIDES AND THEIR N-OXIDES

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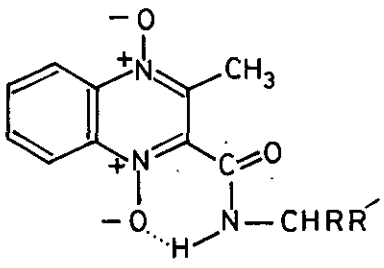
Abstract ——— Series of new 2-(N-phenylcarbamoyl)-3-methylquinoxaline 1,4-dioxides(I), monoxides(II,III) and their non-oxygenated analogues(IV), as well as the corresponding series lacking the C_3-methyl(V-VIII) have been prepared, and their ^{1}H-nmr spectral data analyzed. The C_3-Me protons in the di-N-oxides(I) resonate at higher field (δ2.45-2.80) than in the corresponding non-oxygenated analogues(IV) (δ ≃ 3.0). The observed upfield shift for the C_3-Me protons in the di-N-oxides(I) is maximum when two methylene carbons would separate to the "interacting" phenyl and quinoxaline rings. A comparable trend is observed for the quinoxaline-1-oxides(II), whereas the isomeric 4-oxides(III) closely resemble the parent quinoxalines(IV). This behavior might be due to the predominance of the intramolecular H-bonded conformation (A) in the di-N-oxides(I) and the N-1-oxides(II). Comparative nmr study of compounds(V-VIII) is also noted.

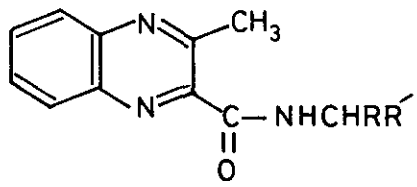
INTRODUCTION

Recent interest in the chemistry and biological activity of quinoxaline-N-oxides was spurred by the finding that these heterocycles can be synthesized in one step from benzofuroxan (BFO) and enamines[1], or enolate anions[2], and the subject has been reviewed[3]. Following this route, we have prepared series of quinoxaline-amino acids and esters[4,5], -amino alcohols and -amines[6], and their N-oxides. The di-N-oxides show an interesting conformational behaviour as displayed by their cd[4] and nmr[4-6] spectral data. In the aromatic amino derivatives (A, R=benzyl ; R' = CO_2Me or CH_2OH), the C_3-CH_3 protons resonate at a higher magnetic field (δ ≃ 2.4) than in the corresponding aliphatic analogues (A: R = Alkyl; R' = CO_2Me

or CH_2OH) ($\delta \simeq 2.6$)[4-6]. This upfield shift was attributed to aryl-heteroaryl "interaction" in the di-N-oxides that exist predominantly in the intramolecular H-bonded conformation (A)[4,5]. This phenomenon was, however, not observed in the corresponding non-oxygenated quinoxaline series[4-6]. In the latter series, conformation (B) might prevail where specific intramolecular H-bonding is lacking.



(A)



(B)

We now investigated the effect, on the C_3-CH_3 chemical shift, of changing the side chain length (of the amino component in I) in such a fashion as to modify the distance between the phenyl ring and the quinoxaline moiety. We also extended this study to include the corresponding monoxides II,III, and the parent quinoxalines IV (Chart 1). The nor C_3-CH_3 analogues V-VIII (R = H, Chart 1) were also prepared for comparative study.

RESULTS AND DISCUSSION

A. SYNTHESIS

The 2-(N-substituted carbamoyl)-3-methylquinoxaline 1,4-dioxides (Ia-e) were synthesized via interaction between BFO and the appropriate acetoacetamides following the reported procedures[2,6]. The desired acetoacetamides were prepared by the reaction of diketene with the appropriate amine[6,7]. Selective monodeoxygenation of (I) with trimethyl phosphite[8] furnished the corresponding 4-oxides (III), while the isomeric N-1-oxides (II) were obtained from the reaction between (I) and phosphorus trichloride[8,9]. The parent quinoxalines (IV) were obtained by complete deoxygenation

of (I) using excess sodium dithionite[4-6,10].

The 2-(N-substituted carbamoyl) quinoxaline 1,4-dioxides (Va-e) were synthesized by coupling of 1,4-dioxido-quinoxaline-2-carboxylic acid[11] with the appropriate amines using diphenylphosphoryl azide (DPPA) as the coupling reagent[12]. The corresponding 4-oxides (VII) were likewise prepared by the DPPA-coupling of 4-oxido-quinoxaline-2-carboxylic acid[5] with the appropriate amines, while the isomeric 1-oxide analogues (VI) were obtained by the selective removal of the 4-oxygen from the respective di-N-oxides (V) using trimethyl phosphite[5]. The parent quinoxalines(VIII) were prepared by the reaction of 2-quinoxalinecarbonyl chloride with the appropriate amines, following the reported procedures for related systems[13]. The physical and analytical data of compounds I-VIII are presented in Table 1.

B. ^{1}H-NMR SPECTRA

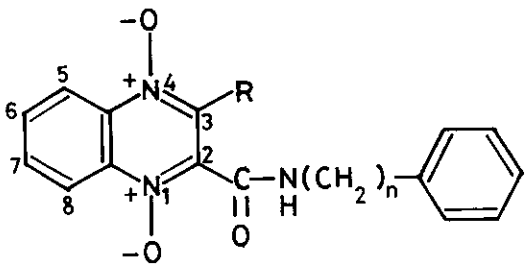
1. C_3-Me Quinoxalines (I-IV):

(1) 1,4-Dioxides (Ia-e):

These compounds show two multiplets centered at δ 8.50(2H) and 7.95(2H) assigned to the aromatic protons H-5/H-8 and H-6/H-7, respectively. There is a progressive decrease in the δ -value of the amide N-H (9.30 ⟶ 8.30 for Ia ⟶ Ie), probably as a result of the decrease in inductive effect of the phenyl group which is distant from the N-H.

The C_3-CH_3 protons' chemical shifts in $CDCl_3$ are: δ 2.70, 2.73, 2.45, 2.56 and 2.66 for compounds Ia, Ib, Ic, Id and Ie, respectively. Thus, the maximum shielding of the C_3-CH_3 protons is observed for compound Ic in which two methylene units separate the "interacting" quinoxaline and phenyl rings (Table 2). The same trend is also observed in the solvent DMSO-d_6 (Table 3). However, when a mixed solvent system of DMSO-d_6 and benzene-d_6 is used, the δ -value of the C_3-CH_3 protons in Ia-e is almost the same (δ ≈ 2.55) at C_6D_6/DMSO-d_6 ratio of 4:1, v/v (Table 3). This might indicate that the aromatic solvent C_6D_6 competes favorably with the phenyl side-chain in I for "interaction" with the hetero ring. This situation seems to disfavor any special intramolecular aryl-heteroaryl"interaction".

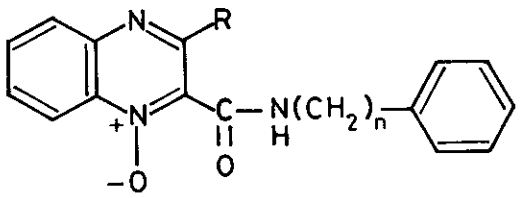
Chart 1



I : R = CH_3

V : R = H

No	a	b	c	d	e
n	0	1	2	3	4

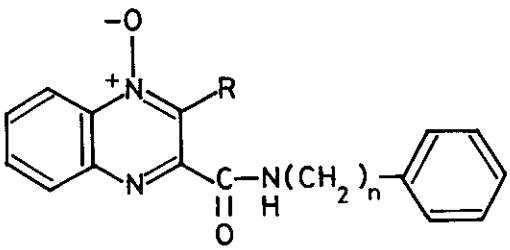


II : R = CH_3

No	b	c	d	e
n	1	2	3	4

VI : R = H

No	b	c
n	1	2

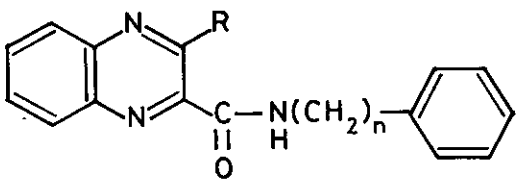


III : R = CH_3

No	b	c	d	e
n	1	2	3	4

VII : R = H

No	b	c
n	1	2



IV : R = CH_3

VIII : R = H

No	b	c
n	1	2

Table 1. Physical and Analytical Data of Compounds I - VIII

Compd No.	Yield (%)[f]	mp (°C)	Molecular formula	Analyses (%) Calcd/Found C	H	N
Ia	85	232-233	$C_{16}H_{13}N_3O_3$	65.08	4.44	14.23
				64.95	4.41	14.25
Ib	80	224-225	$C_{17}H_{15}N_3O_3$	66.01	4.89	13.59
				65.87	4.88	13.52
Ic	75	206-207	$C_{18}H_{17}N_3O_3$	66.86	5.30	13.00
				66.82	5.25	13.02
Id	80	154-155	$C_{19}H_{19}N_3O_3$	67.64	5.68	12.46
				67.68	5.71	12.38
Ie	80	162-163	$C_{20}H_{21}N_3O_3$	68.36	6.02	11.96
				67.99	6.02	11.89
IIb	45	140-141	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
				69.32	5.29	13.95
IIc	40	130-131	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67
				69.96	5.65	13.59
IId	45	134-135	$C_{19}H_{19}N_3O_2$	71.01	5.96	13.08
				70.59	5.79	12.91
IIe	35	136-137	$C_{20}H_{21}N_3O_2$	71.62	6.31	12.53
				71.60	6.25	12.48
IIIb	70	116-117	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
				69.23	5.10	14.17
IIIc	65	92-93	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67
				70.46	5.37	13.64
IIId	65	94-95	$C_{19}H_{19}N_3O_2$	71.01	5.96	13.08
				70.76	5.84	12.88
IIIe	60	72-73	$C_{20}H_{21}N_3O_2$	71.62	6.31	12.53
				71.53	6.21	12.50
IVb	75	152-153	$C_{17}H_{15}N_3O$	73.63	5.45	15.15
				73.44	5.36	15.08

cont. Table 1

IVc	70	146-147	$C_{18}H_{17}N_3O$	74.20	5.88	14.42
				74.15	5.71	14.24
Va	70	186-187	$C_{15}H_{11}N_3O_3$	64.05	3.94	14.94
				63.83	3.74	14.85
Vb	60	176-177	$C_{16}H_{13}N_3O_3$	65.08	4.44	14.23
				64.79	4.38	14.18
Vc[g]	60	169-170	$C_{17}H_{15}N_3O_3$	66.01	4.89	13.59
				65.88	4.81	13.46
Vd	65	158-160	$C_{18}H_{17}N_3O_3$	66.86	5.30	13.00
				66.73	5.22	12.85
Ve	60	136-137	$C_{19}H_{19}N_3O_3$	67.64	5.68	12.46
				67.51	5.56	12.28
VIb	60	164-165	$C_{16}H_{13}N_3O_2$	68.81	4.69	15.05
				68.53	4.58	14.86
VIc[h]	55	161-162	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
				69.33	5.08	14.16
VIIb	65	172-173	$C_{16}H_{13}N_3O_2$	68.81	4.69	15.05
				68.72	4.58	14.90
VIIc	60	168-169	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
				69.29	5.02	14.16
VIIIb[1]	70	155-156	$C_{16}H_{13}N_3O$	72.99	4.98	15.96
				72.65	4.90	15.88
VIIIc	75	150-151	$C_{17}H_{15}N_3O$	73.63	5.45	15.15
				73.38	5.42	15.02

[f] The yields refer to the isolated products.

[g] Previously prepared by treatment of methyl 1,4-dioxido-quinoxaline-2-carboxylate with 2-phenylaminoethane[14].

[h] Previously prepared by treatment of methyl 1-oxido-quinoxaline-2-carboxylate with 2-phenylaminoethane[14].

[1] Previously prepared by pyrolysis of 2-(N-benzylcarbamoyl)-3-quinoxalinecarboxylic acid in refluxing xylene for 1 h (mp 150-152°C, from methanol)[15].

Table 2. Chemical Shifts of the C_3-CH_3 Protons for I-IV in $CDCl_3$

Compd	δ	Compd	δ	Compd	δ	Compd	δ
Ia	2.70						
Ib	2.73	IIb	2.78	IIIb	3.03	IVb	3.02
Ic	2.45	IIc	2.65	IIIc	3.01	IVc	3.04
Id	2.56	IId	2.74	IIId	3.03		
Ie	2.66	IIe	2.76	IIIe	3.04		

Table 3. Chemical Shifts (δ) of the C_3-CH_3 for (I) in the Presence of Benzene-d_6

Compd No.	DMSO-d_6	C_6D_6/DMSO-d_6 (2:1, v/v)	C_6D_6/DMSO-d_6 (4:1, v/v)
Ia	2.44	2.45	2.52
Ib	2.43	2.46	2.53
Ic	2.25	2.33	2.52
Id	2.43	2.46	2.55
Ie	2.45	2.47	2.55

(ii) Non-Oxygenated Quinoxalines (IVb , c):

These compounds exhibit two multiplets centered at about δ 8.04 and 7.80 assigned to the aromatic quinoxaline protons H-5/H-8 and H-6/H-7, respectively. The amide N-H proton resonates at δ 8.40 for IVb, and at δ 8.10 for IVc.

The C_3-CH_3 protons' chemical shift is almost the same for IVb and IVc (δ 3.02 and 3.04, respectively). This might be due to the predominance of conformation (B) (vide supra) where any special "interaction" between the quinoxaline ring and the side-chain phenyl group is minimal.

(iii) N-4-Oxides (IIIb-e):

The aromatic quinoxaline protons appear as three multiplets centered at about δ 8.51 (H-5), 7.98 (H-8) and 7.75 (H-6/H-7). The amide N-H proton resonates in the range δ 8.00-8.40.

The C_3-CH_3 protons in IIIb-e have almost the same chemical shift (δ ≈ 3.00), and is comparable to that of the parent quinoxalines (IV) (Table 2). This indicates the absence of any special aryl-heteroaryl "interaction" as was noted above for the non-oxygenated quinoxalines (IV).

(iv) N-1-Oxides:

The aromatic protons appear as two multiplets centered around δ 8.35 (H-8) and 7.76 (H-5/H-6/H-7). The N-H proton resonates in the range δ 8.56-9.15.

The δ -value of the C_3-CH_3 protons for this series is lowest in compound IIc (Table 2). This indicates, as in the case of the 1,4-dioxides I, that the maximum shielding effect of the phenyl group is observed when it is separated from the 2 - carbamoyl - quinoxaline moiety by two methylene units.

It is worth noting that the shielding effect, exerted by the side-chain phenyl group, in the 1,4-dioxides (I) is more pronounced than in the corresponding N-1-oxides (II) (Table 2). It seems, therefore, reasonable to assume that both N-oxide functions are essential, together with two carbons separating the carbamoyl - quinoxaline and phenyl rings, in order to obtain maximum aryl-heteroaryl "interaction".

2. The C_3-H Quinoxalines (V-VIII):

The chemical shifts and multiplicity pattern of the aromatic protons H-5/H-6/H-7 and H-8 in these derivatives are comparable to those noted above for the corresponding C_3-CH_3 quinoxalines (I-IV). The amide N-H proton in the 1,4-dioxides (Va-e) and 1-oxides (VIb,c) has larger δ-value (~10.85) than in the 4-oxides (VIIb, c) and non-oxygenated quinoxaline analogues (VIIIb,c)(~ 8.10). This is due to the prevalence of an intramolecular H-bridging conformation, similar to (A) (vide supra), in the N-oxides (V-VI).

As expected[5], the C_3-H proton in the 1,4-dioxides (Va-e) and the 4-oxides (VIIb,c) has almost the same chemical shift (δ≈ 9.10). This δ -value is smaller

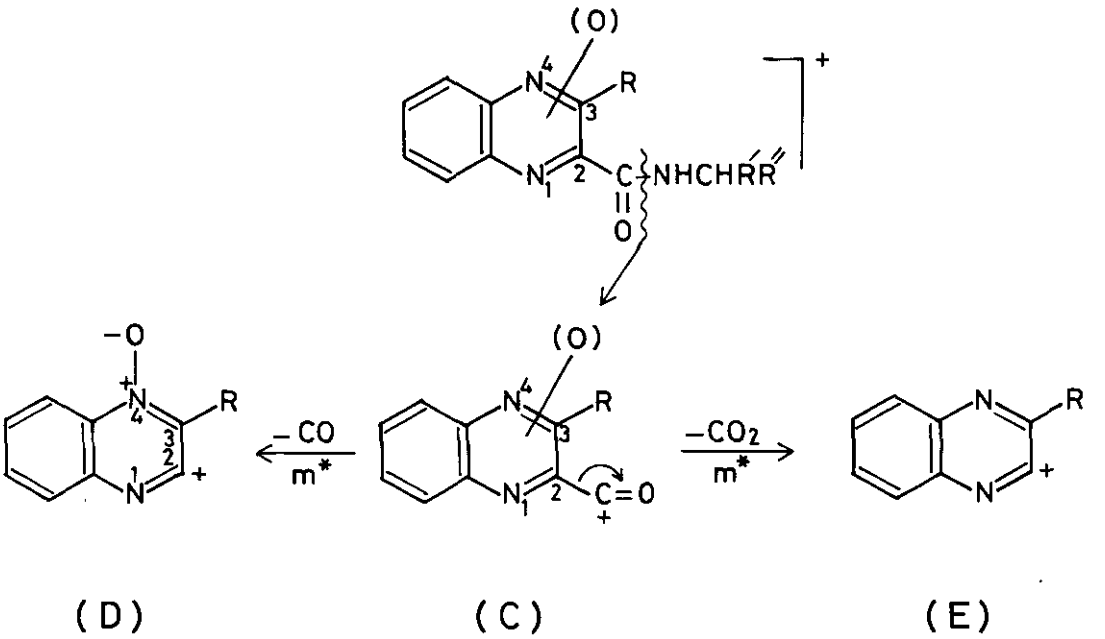
than that for the C_3-H proton in the corresponding 1-oxides (VIb,c) and non-oxygenated quinoxalines (VIIIb,c) ($\delta \simeq 9.70$).

As noted previously[5,6], it can be seen from the above data that ^{1}H-nmr spectroscopy can be used to differentiate between the isomeric quinoxaline monoxides (II/III and VI/VII). The criteria employed are the N-H and C_3-CH_3/C_3-H chemical shifts.

C. MASS SPECTRA

The mass spectra of compounds (I-VIII) display the correct molecular ions $[M]^+$ expected for the molecular formulae. The fragmentation patterns are in accord with the assigned structures. As noted previously [4,5], the primary cleavage of the molecular ion occurs at the amide bond (Chart 2) giving rise to the acylium ion $[C]^+$ (m/z = 187/173) in the ms of the monoxides (II,III/VI,VII). The prominance of fragment $[D]^+$ identifies the monoxides as the 4-oxides (III/VII). This ion is completely absent from the ms of the isomeric 1-oxides. In all cases, the quinoxalinium ion $[E]^+$ prevails.

Chart 2



EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. ^{1}H-nmr spectra were recorded on Bruker WH-90 spectrometer equipped with Fourier transform facilities, using TMS as internal standard. Mass spectra were obtained on a Varian MAT CH5 spectrometer using the direct inlet technique (70 eV). Elemental analyses were carried out in the laboratory of the Late Drs. F. and E. Pascher (Bonn). Chromatographic purification of a number of the target compounds was performed on preparative tlc plates coated with silica gel $HF_{254+366}$ (Merck), using chloroform as the developing solvent.

2-Quinoxalinecarbonyl chloride, 4-phenyl-1-aminobutane, 3-phenyl-1-aminopropane and acetoacetanilide, used in this study, were purchased from Aldrich. BFO was prepared by hypochlorite oxidation of o-nitroaniline, according to standard procedure[16].

General Procedures.

N-Substituted Acetoacetamides.

Redistilled diketene (0.12 mol, Fluka) was added gradually, during 40 min, to a stirred solution of the appropriate aliphatic amine (0.1 mol) in methanol (50 ml) cooled to 0-5°C. Stirring was continued at ambient temperature for 2-3 h. The solvent and excess diketene were then evaporated, leaving crude residue of the title compound. These intermediates were used as such for the following reaction step.

N-Substituted 3-Methyl-1,4-dioxido-2-quinoxalinecarboxamides (Ia-e).

A solution of the appropriate acetoacetamide (0.1 mol) in methanol (100 ml) was added to a solution of BFO (0.1 mol) in triethylamine (100 ml). The resulting reaction mixture was set at room temperature for 5-10 h. The yellow solid separated was collected and recrystallized from methanol.

N-Substituted 3-Methyl-1-oxido-2-quinoxalinecarboxamides(IIb-e).

Phosphorus trichloride (10 ml) was added to a solution of an quinoxaline-1,4-dioxide (I, 0.01 mol) in dry chloroform (40 ml). The reaction mixture was stirred for 8-10 h at room temperature, then poured onto cold water (60 ml) and treated with excess saturated aqueous sodium carbonate solution. The desired product was

isolated in the conventional manner[8,9], purified on preparative tlc plates, and finally recrystallized from chloroform-petroleum ether (bp 40-60°C).

N-Substituted 3-Methyl-4-oxido-2-quinoxalinecarboxamides (III-e).

A mixture of a quinoxaline-1,4-dioxide (I, 0.01 mol) and trimethyl phosphite (0.02 mol, Merck) in n-propanol (40 ml) was refluxed for 4-5 h. The resulting clear solution was cooled, and the precipitated monoxide (III) was collected and recrystallized from chloroform-petroleum ether.

N-Substituted 3-Methyl-2-quinoxalinecarboxamides(IVb-e).

To a boiling solution of a quinoxaline-1,4-dioxide (I, 0.01 mol) in 60% aqueous ethanol (100 ml) was added portionwise, with stirring, a saturated solution of sodium dithionite in hot water until a red colouration persisted[4-6,10]. The mixture was further refluxed for 3-5 h, diluted with water (100 ml) and cooled to 5°C. The white precipitate was collected and recrystallized from aqueous ethanol (Norit).

N-Substituted 1,4-Dioxido-2-quinoxalinecarboxamides(Va-e).

An appropriate amine (0.01 mol) and triethylamine (0.02 mol) were added successively to a stirred solution of 1,4-dioxido-quinoxaline-2-carboxylic acid (0.01 mol)[11] and DPPA (0.01 mol, Aldrich) in dimethylformamide (60 ml) at 0 to -5°C. The resulting solution was further stirred at room temperature for 5-8 h and then diluted with cold water (100 ml). The precipitated yellow solid was collected, purified on preparative tlc plates, and finally recrystallized from ethanol.

N-Substituted 1-Oxido-2-quinoxalinecarboxamides (VIb,c).

The parent quinoxaline-1,4-dioxide (V, 0.01 mol) and trimethyl phosphite (0.02 mol) in n-propanol (40 ml) were refluxed for 4-5 h. The resulting clear solution was cooled. The title monoxides thus precipitated were collected and recrystallized from chloroform-petroleum ether.

N-Substituted 4-Oxido-2-quinoxalinecarboxamides (VIIb,c)

These monoxides were prepared via DPPA-coupling between 4-oxido-quinoxaline-2-carboxy-

lic acid (0.01 mol)[5] and the appropriate amine (0.01 mol) as noted for the parent quinoxaline-1,4-dioxide (V)(vide supra). The product was purified on preparative tlc plates, and finally crystallized from chloroform-petroleum ether.

N-Substituted 2-Quinoxalinecarboxamides(VIIIb,c).

2-Quinoxaloyl chloride (0.01 mol) was added portionwise to a stirred solution of the appropriate amine (0.01 mol) and triethylamine (0.02 mole) in dry benzene (50 ml) at 10-12°C. After addition, stirring was continued for 2-3 h at room temperature . The resulting benzene solution was then filtered, the filtrate was washed successively with 10% aqueous $NaHCO_3$ solution (2 x 30 ml), and with water (30 ml) and dried ($MgSO_4$). Benzene was then evaporated and the solid residue was collected and recrystallized from aqueous methanol.

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