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SYNTHESIS, CRYSTAL AND MOLECULAR STRUCTURES OF 2-METHYL-3-CARBOETHOXYQUINOXALINE 1,4-DIOXIDE

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ABSTRACT

2-Methyl-3-carboethoxyquinoxaline 1,4-dioxide (MCQO) was prepared and single crystals were grown out of the reaction mixture. The structure of MCQO was established by single-crystal X-ray crystallography using a direct method. The crystals are triclinic, space group $P\bar{1}$, with a = 6.928(1), b = 8.109(1), c = 10.552(1) Å, α = 83.445(8), β = 85.861(10), γ = 79.168 (8)°, V = 577.7 Å^3, Z = 2 and Dc = 1.428 g cm^{-3}. The structure was refined to R = 0.059 for 1454 reflections. The planar geometry of the parent quinoxaline ring is consistent with the aromaticity of the condensed heterocyclic system in the compound. The average N—O bond length is 1.297(5) Å, indicating a certain double-bond character. The X-ray analysis corroborates IR, NMR, and ESR spectroscopic evidence for the structure of this type of heteroaromatic N-oxides.

INTRODUCTION

The continuing interest in quinoxaline 1,4-dioxides stems partly from their antibacterial and animal growth promoting activities. By a facile synthetic method using benzofuroxans as reagents, known as the Beirut reaction, developed by Haddadin et al. [1—3], well over a thousand substituted quinoxaline 1,4-dioxides have been obtained. However, careful literature research reveals the lack of crystallographic data and systematic spectroscopic studies for these heterocyclic *N*-oxides. As a part of the series on the physicochemical studies of organic *N*-oxides, this paper presents the results of single-crystal and molecular structure studies and IR, NMR, and ESR spectral evidence for the structure of the heteroaromatic *N*-oxides with 2-methyl-3-carboethoxyquinoxaline 1,4-dioxide (MCQO) as a model compound.

EXPERIMENTAL

The synthesis of 2-methyl-3-carboethoxyquinoxaline 1,4-dioxide was carried out by the Beirut reaction (see eqn. 1) with some modification [4].

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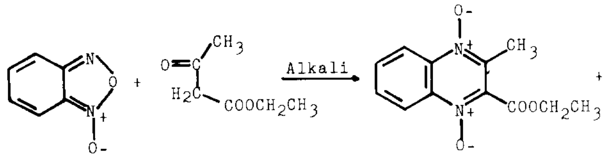
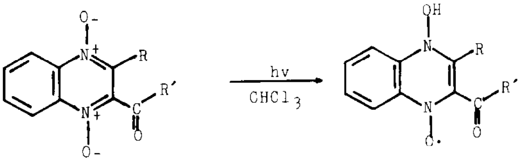


BFO MCQO (1)



Ia~c IIa~c (2)

	R	R′
a	CH_3	OCH_2CH_3
b	CH_3	CH_3
c	C_6H_5	C_6H_5

To a shaken solution of benzofuroxan (BFO, 1.00 g, 7.3 mmol) in ethylacetoacetate (4.0 ml) was added dropwise a solution of potassium hydroxide (1.0 g) in methanol (10 ml) at a temperature below 30°C. The container was covered with a watchglass and allowed to stand at room temperature (17°C) for 30 h. Acetone (5 ml) was then added, and the solution was allowed to stand for an additional 20 h, when the yellowish bar single crystals of MCQO of size about 2 × 2 × 10 mm formed, were collected and washed with water. The yield was 1.20 g (66%). M.p. was 138°C (lit. [1], 132—133°C). Analysis: calc. for $C_{12}H_{12}N_2O_4$ (248.24): C, 58.06; H, 4.87; N, 11.29; found: C, 58.00; H, 4.87; N, 11.28%. Infrared spectrum, 1735, 1520, 1330, 1280, 1240, 1050, 1010—1000, 765—775 cm^{-1}. Mass spectrum, *m/e*: 248.0795 (M^+ from high-resolution mass spectrum, the calculated formula is $C_{12}H_{12}N_2O_4$); 248 (M^+ 95%); 232 (M^+—O, 16%); 203 (M^+—OC_2H_5, 61%); 159 (M^+—O, $COOC_2H_5$, 100%).

For the X-ray crystallographic analysis the intensities were collected in the atmosphere and at room temperature on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated CuKa radiation ($\lambda = 1.5405$ Å). The relevant crystal and X-ray data are given in Table 1. The isotropic refinement leads to an *R* value of 0.059, so no absorption correction was applied. Phase problems were solved with a MULTAN 82 program. The missing non-hydrogen atoms were located in subsequent Fourier syntheses. Least square refinements were carried out for positional and anisotropic vibrational parameters for non-hydrogen atoms. Coordinates of hydrogen atoms were calculated but not refined anisotropically.

The grating infrared spectrum of a KBr pellet was recorded on a Perkin-Elmer model 325 spectrophotometer. MS spectral data were obtained with

TABLE 1

Crystal and relevant X-ray data, with estimated standard deviations (e.s.d.'s) given in parentheses referring to the least significant digits

Formula	$C_{12}H_{12}N_2O_4$	γ (degree)	79.168(8)
Molecular weight	248.24	V (Å3)	577.7
Space group	$P\bar{1}$	Dc (g cm^{-3})	1.428
a (Å)	6.928(1)	Z	2
b (Å)	8.109(1)	μ (cm^{-1})	8.7
c (Å)	10.552(1)	N (tot)	1603
α (degree)	83.445(8)	N (obs)	1454
β (degree)	85.861 (10)	R	0.059

a VG7070-E mass spectrometer operating at 70 eV. NMR spectra were run in $CDCl_3$ on a Varian FT-80 spectrometer with tetramethylsilane as internal standard. Electron spin resonance (ESR) measurements were recorded on a Varian E-115 X-band spectrometer at room temperature, with the radical samples prepared from quinoxaline 1,4-dioxides through photolysis of the dilute and deaerated chloroform solutions as described in ref. 5.

RESULTS AND DISCUSSION

Although we have prepared a number of 2,3-disubstituted quinoxaline 1,4-dioxides [6], only the present compound MCQO gives well-defined thick crystals from the reaction mixture. We have also failed in our efforts to grow suitable crystals for X-ray studies from saturated solutions of other 2,3-disubstituted quinoxaline 1,4-dioxides. Hence MCQO has been chosen as the first substituted quinoxaline 1,4-dioxide to be studied crystallographically. The results of these X-ray studies are of great assistance in corroborating the already established common structural properties of the vast number of substituted quinoxaline 1,4-dioxides.

The unit cell (Fig. 1) consists of two discrete molecules. No hydrogen bonding distance is less than 3.0 Å. Atomic positions are listed in Table 2. Bond distances and bond angles are summarised in Tables 3 and 4 respectively. The planar geometry of the quinoxaline ring is clearly shown in the ORTEP diagram of MCQO (Fig. 2) as has been indicated by the distances of relevant atoms to the least squares plane through the quinoxaline ring listed in Table 2. 0(1), 0(2), C(9) and C(10) are also in the plane. The average value of 1.297(5) Å for N—O bonds in MCQO was obtained which is very close to that of 1.303 Å for phenazine 5,10-dioxide [7].

Some molecular structural features appear in ESR studies. As shown in eqn. (2), the photolysis of Ia—c in chloroform gives persistent paramagnetic species IIa—c which are suitable for ESR studies. ESR investigations show that radical IIa, i.e., 1-hydroxy-2-methyl-3-carboethoxyquinoxalinyl-4-oxyl possess a poorly-resolved three-broad-line spectrum from which the parameters g (value about 2.0055) and a(N) (about 1.0 mT) were measured. A

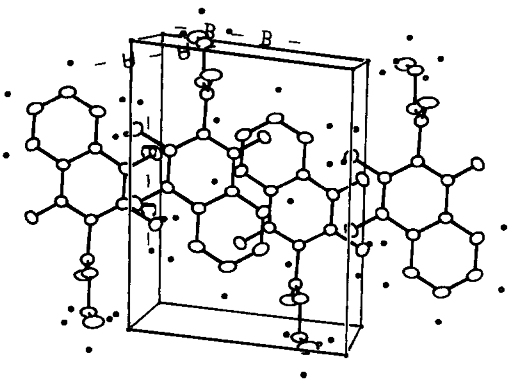


Fig. 1. Stereoscopic view of the molecular packing of MCQO.

TABLE 2

Fractional coordinates and B_{eq} (Å^2) for non-hydrogen atoms of MCQO and the distances of non-hydrogen atoms to the least-squares plane calculated from the positions of the atoms in the parent quinoxaline ring (e.s.d.'s in parentheses)

Atom	*x/a*	*y/b*	*z/c*	B_{eq}[a]	Distances to the plane (Å)
O1	0.2296(5)	−0.0055(4)	0.5741(3)	5.06(8)	−0.048(4)
O2	0.3207(5)	0.5716(4)	0.2908(3)	4.02(7)	−0.053(3)
O3	0.5253(4)	0.2583(4)	0.1332(3)	3.93(7)	−1.165(3)
O4	0.2076(5)	0.3352(5)	0.0906(3)	5.8(1)	1.061(3)
N1	0.2467(5)	0.1353(5)	0.5049(3)	3.39(8)	−0.015(4)
N2	0.2940(5)	0.4345(4)	0.3594(3)	2.91(8)	−0.020(3)
C1	0.2558(5)	0.4332(5)	0.4921(4)	2.81(9)	−0.017(4)
C2	0.2394(6)	0.5832(6)	0.5497(4)	3.5(1)	0.002(4)
C3	0.1999(7)	0.5788(6)	0.6791(5)	4.1(1)	0.020(5)
C4	0.1778(7)	0.4275(7)	0.7529(4)	4.2(1)	0.010(5)
C5	0.1938(6)	0.2805(6)	0.6965(4)	3.9(1)	−0.007(5)
C6	0.2332(6)	0.2829(5)	0.5642(4)	2.94(9)	−0.019(4)
C7	0.2761(6)	0.1408(6)	0.3771(4)	3.16(9)	0.032(4)
C8	0.3012(6)	0.2907(5)	0.3070(4)	2.83(9)	0.014(4)
C9	0.2804(8)	−0.0174(6)	0.3180(5)	4.7(1)	0.097(6)
C10	0.3351(6)	0.3006(6)	0.1643(4)	3.5(1)	0.059(5)
C11	0.5801(7)	0.2542(7)	−0.0033(4)	4.3(1)	−1.274(5)
C12	0.7978(8)	0.1951(9)	−0.0124(5)	6.4(2)	−2.728(6)

[a] $B_{eq} = (4/3) \times [a^2 \times B(1,1) + b^2 \times B(2,2) + c^2 \times B(3,3) + ab(\cos\gamma) \times B(1,2) + ac(\cos\beta) \times B(1,3) + bc(\cos\alpha) \times B(2,3)]$.

similar poorly-resolved spectrum has also been recorded for radical IIc, i.e., 1-hydroxy-2-phenyl-3-benzoylquinoxalinyl-4-oxyl. However, a well-resolved ESR spectrum has been observed for 1-hydroxy-2-methyl-3-acetylquinoxalinyl-4-oxyl IIb, from the system containing Ib which is quite similar to

TABLE 3

Bond distances (Å) in the molecule MCQO (e.s.d.'s given in parentheses)

O1—N1	1.303(5)	C2—C3	1.370(6)	C9—H91	1.020(5)
O2—N2	1.291(4)	C2—H2	1.091(4)	C9—H92	0.855(6)
O3—C10	1.325(5)	C3—C4	1.403(7)	C9—H93	1.058(5)
O3—C11	1.465(5)	C3—H3	1.184(5)	C11—C12	1.494(7)
O4—C10	1.192(6)	C4—C5	1.375(8)	C11—H111	1.071(5)
N1—C6	1.397(6)	C4—H4	1.115(4)	C11—H112	1.054(6)
N1—C7	1.346(5)	C5—C6	1.401(6)	C12—H121	1.034(5)
N2—C1	1.405(5)	C5—H5	1.072(5)	C12—H122	0.953(6)
N2—C8	1.337(6)	C7—C8	1.382(6)	C12—H123	1.028(7)
C1—C2	1.403(7)	C7—C9	1.483(7)		
C1—C6	1.389(6)	C8—C10	1.502(6)		

TABLE 4

Relevant bond angles (degree) in MCQO (e.s.d. values in parentheses)

C10—O3—C11	116.4(3)		
O1—N1—C6	119.5(3)	N1—C6—C1	120.2(4)
O1—N1—C7	120.9(4)	N1—C6—C5	120.1(4)
C6—N1—C7	119.6(4)	C1—C6—C5	119.7(4)
O2—N2—C1	120.4(4)	N1—C7—C8	119.5(4)
O2—N2—C8	121.5(3)	N1—C7—C9	117.5(4)
C1—N2—C8	118.2(3)	C8—C7—C9	123.0(4)
N2—C1—C2	119.8(4)	N2—C8—C7	123.3(4)
N2—C1—C6	119.3(4)	N2—C8—C10	116.0(4)
C2—C1—C6	120.9(4)	C7—C8—C10	120.7(4)
C1—C2—C3	118.6(4)	O3—C10—O4	125.3(4)
C3—C4—C5	120.5(4)	O3—C10—C8	110.2(4)
C4—C5—C6	119.3(4)	O4—C10—C8	124.5(4)
C2—C3—C4	120.9(5)	O3—C11—C12	106.0(4)

MCQO (Ia) in composition. Alternative forms of radicals from Ia—c could be 4-hydroxy-1-oxyl radicals, but INDO MO calculations show that IIa—c are more stable than the latter alternatives. As can be seen from the hyperfine coupling constants of the protons in the benzo-ring of IIb [5], the spin-density has been considerably distributed over the conjugated quinoxaline rings in II. This is an indication for the aromaticity of I, the precursors of II, and hence in accordance with the planar geometry of the quinoxaline rings in the molecule of MCQO as was detected by our X-ray analysis.

This structural property has also been demonstrated by the ^{1}HNMR spectrum (Fig. 3) where the 5,8-protons and the 6,7-protons show remarkably hyperfine interactions and have typical chemical shifts for hydrogen atoms attached to an aromatic ring.

The strong absorption bands in the IR spectra of heteroaromatic *N*-oxides which usually appear within the range 1320—1350 cm^{-1} should be assigned as the stretching vibration of the N—O functions [2]. Thus the band at

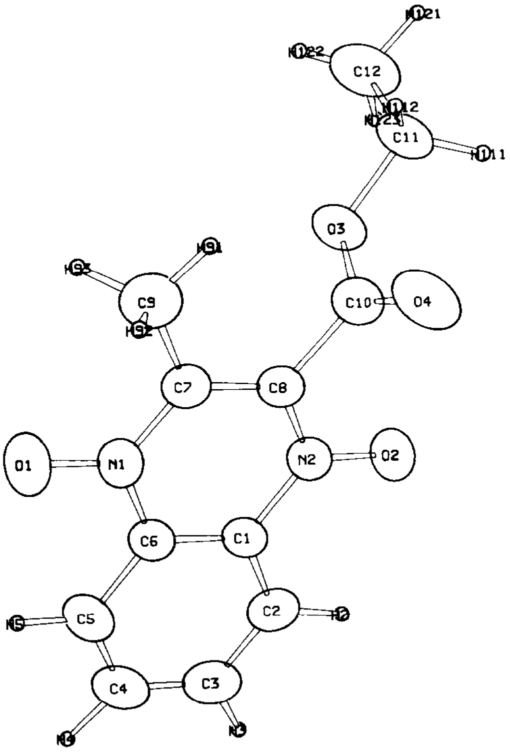
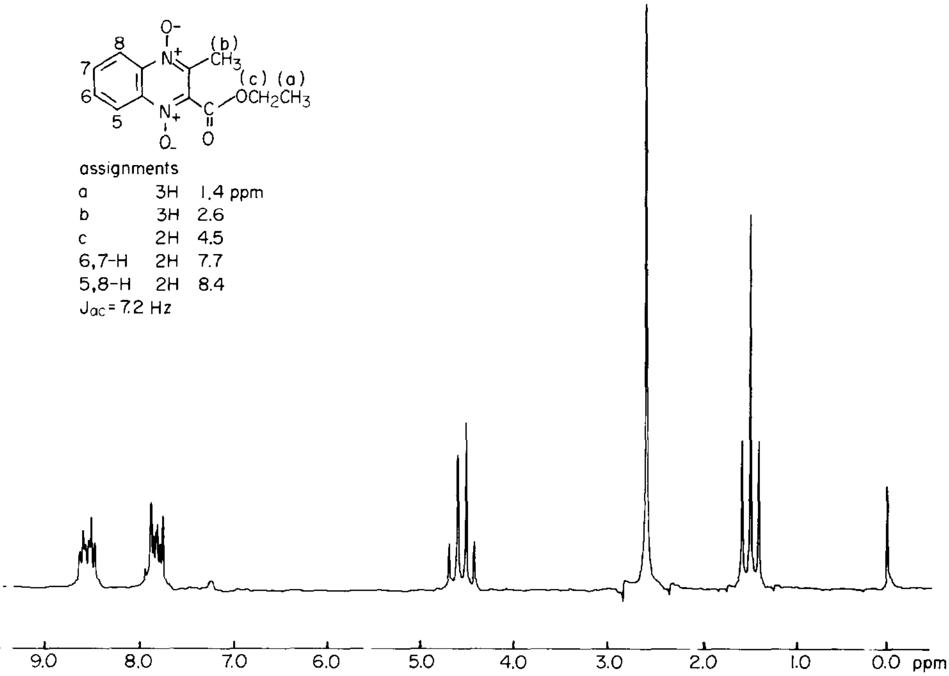


Fig. 2. ORTEP diagram of MCQO.

1330 cm^{-1} is assigned to N—O groups in MCQO. The N—O vibrations in these compounds usually have longer wavelength absorptions than those in C=O double bonds. Taking into account the heavier mass of the N atom in the N—O group compared with that of the C atom in the C=O group, the IR spectrum shows that N—O has certain double bond characteristics similar to C=O, even though the stretching vibration is located to lower wavenumber than that of C=O. Furthermore, our X-ray studies, in addition to the crystallographic X-ray structural determinations of other heterocyclic *N*-oxides [8], show that the N—O bond distances are longer than but close to the typical bond length of C=O in carbonyl compounds. In this case, the average bond length of 1.297(5) Å in MCQO is comparable with the C=O bond length of 1.21 Å in 1,4-naphthoquinone [9].

The structural similarities of these two categories of compounds of *N*-oxides and ketones seem obvious and will inexorably lead to similar properties and behaviour. Thus as has been demonstrated to be the case with some ESR studies, the photoreaction systems of quinoxaline 1,4-dioxides and of 1,4-naphthoquinone in certain solvents show similar hydrogen abstraction trends [10]. The aromatic di-*N*-oxides may have similar biological activities [11]. Some similarities have been noticed for decades [12]. Because many ketones (such as quinone compounds) have been very extensively studied in



assignments

a	3H	1.4 ppm
b	3H	2.6
c	2H	4.5
6,7-H	2H	7.7
5,8-H	2H	8.4

$J_{ac} = 7.2$ Hz

Fig. 3. ^{1}HNMR spectrum of MCQO in deuterated chloroform.

both theoretical and applied fields, the recognition of such similarities and the analogy between them in certain respects may be helpful in understanding the *para*diazine di-*N*-oxide compounds and the development in applied research of the heteroaromatic *N*-oxides in pharmaceutical and biological fields, and polymerization processes.

In conclusion, we have determined the crystal and molecular structures of MCQO through single crystal X-ray studies together with IR, NMR and ESR spectroscopic investigations. These initial results can be expected to be of considerable assistance in determining the structure of many more complicated substituted quinoxaline 1,4-dioxides and in elucidating the related biological functions and chemical reactivities.

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