Cycloaddition Reactions of Nitrones with 4-Methylene-5-morpholino-3-phenyl-4,5-dihydroisoxazole. Structure and Stereochemical Assignments of the Products by Nuclear Magnetic Resonance and X-Ray Analysis

Piero Dalla Croce and Concetta La Rosa *
Dipartimento di Chimica Organica e Industriale; Centro CNR, Via Venezian 21, 20133 Milano, Italy
Riccardo Destro *
Dipartimento di Chimica Fisica ed Elettrochimica e Centro CNR, Via Golgi 19, 20133 Milano, Italy

4-Methylene-5-morpholino-3-phenyl-4,5-dihydroisoxazole (**1**) reacts with nitrones (**2**) to give a mixture of diastereoisomeric cycloadducts, namely spiro[isoxazolidine-5,4′-isoxazolines] (**3**) and (**4**). The structure and steric configuration of the spiro derivatives have been assigned on the basis of ^{1}H and ^{13}C NMR evidence and by X-ray analysis.

As part of our work concerning the reactivity towards nucleophiles[1] and 1,3-dipoles[2] of 5-amino-4-methylene-4,5-dihydroisoxazoles we report the cycloaddition reaction with nitrones. The [3 + 2] π cycloaddition reaction leads to the formation of a mixture of two spirocycloadducts (**3a–e**) and (**4a–e**) (Scheme 1). Some problems concerned with this reaction, such as the regioselectivity, the formation of the two diastereoisomers, and their relative steric configuration, are discussed.

Results and Discussion

Reaction of (**1**) with (**2**) in toluene at 80 °C for 24–48 h afforded in all cases, a *ca.* 3:1 mixture of two isomeric products (**3**) and (**4**) which were separated by column chromatography and further purified by crystallization. Analytical, physical, and spectroscopic data for products (**3**) and (**4**) are summarized in Table 1.

The reaction products can be considered as a mixture of the two possible regioisomers or of two diastereoisomers and the distinction between these possibilities was achieved by spectroscopic data. In the NMR spectra of (**3a–e**) and (**4a–e**) a singlet at δ 5.2–5.5 associated with H-5 and an ABX system pertaining to the two hydrogens in position 4′ and to the one in position 3′ are present. This observation precludes the possibility that this is a mixture of regioisomers and proves that both adducts result from the same kind of approach between dipole and dipolarophile which binds the carbon of the nitrone with the exocyclic carbon of the methyleneisoxazoline and the oxygen to the spiranic carbon. This is the only structure compatible with the spectroscopic data† and this confirms that the final products (**3**) and (**4**) are a pair of diastereoisomers.

The observed regioselectivity can be explained qualitatively by the FMO method. From the comparison between the energy values of the frontier orbitals for methyleneisoxazoline[2] and nitrones[3] a predominant interaction is not apparent. The values for the HOMO dipole/LUMO dipolarophile and LUMO dipole/HOMO dipolarophile interactions are, respectively, -9.0 and -9.1 eV and are, hence, rather close. This result is in agreement with other cases described in the literature[3] for cycloaddition reactions between nitrones and alkenes devoid of electron-rich and electron-poor substituents.

The regioselectivity is then controlled by the value of orbital coefficients of the nitrones and alkenes and the dominant interaction involves those atomic orbitals of the interacting atoms which have the greater coefficients. In the LUMO of the dipole, the coefficient of the carbon is greater than that of the oxygen, whereas in the HOMO of methyleneisoxazoline the greater coefficient is that associated with the exocyclic carbon and their interaction would lead to a 5-substituted isoxazoline derivative. Our experimental results support this prediction, as shown before.

The steric configurations of (**3**) and (**4**) contain three stereocentres from which the four stereoisomers A, B, C, and D, with the relative enantiomers, can be expected. From a coupled ^{13}C NMR spectroscopic analysis, the two isolated products (**3**) and (**4**) were assigned the structures **A** and **B**. As is known,[4,5] the long-range coupling constants $^3J_{CH}$ depend on the dihedral angle C–C–C–H and follow a Karplus-type curve. From molecular models of the four diastereoisomers, it can be seen that in **C** and **D** C-4′ must have a $^3J_{CH}$ with H-5, (dihedral angle *ca.* 0°), but not in **A** and **B** (dihedral angle *ca.* 90°). Only the two diastereoisomers (**3b**) and (**4b**) were considered because they were obtained in greater yield. As shown (Table 2) in ^{13}C NMR spectra of both adducts, C-4′ has a $^3J_{CH} = 0$ with H-5. Therefore, structures **C** and **D**, which result from the approach of dipole to dipolarophile from the same side of the morpholine residue, can be ruled out.

Compounds (**3**) and (**4**) are derived from the attack of the dipole on the side of the double bond opposite to the morpholino group. They have the same configuration at C-4 and C-5 and differ only in the stereochemistry at C-3′.

The structures and steric configurations assigned to (**3**) and (**4**) were confirmed by an X-ray analysis performed on compound (**3b**). This analysis also allowed us to ascribe to compounds (**3**) and (**4**) the structures (**A**) and (**B**), respectively.

Positional parameters for the 36 non-hydrogen atoms of (**3b**) are given in Table 3, while those of the 26 hydrogen atoms have been deposited at the Cambridge Crystallographic Data Centre.‡ A portion of the derived molecular geometry is reported in Table 4, and the configuration of the spiro compound, as observed in the crystal, is shown in the Figure, where the atoms are numbered according to the scheme

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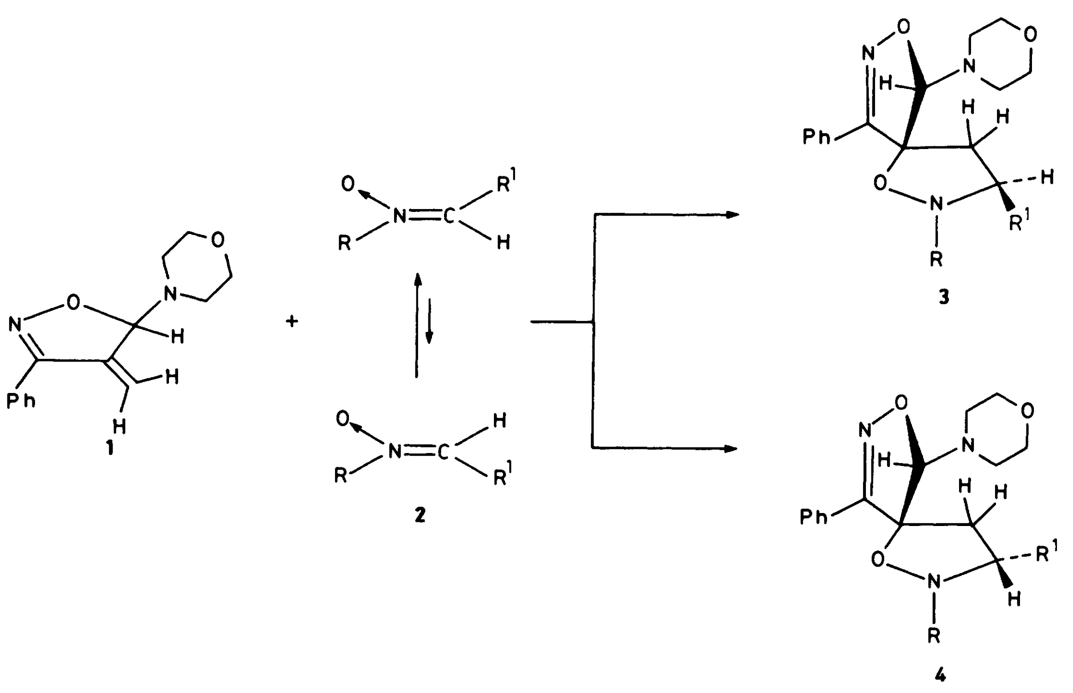
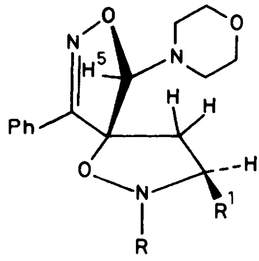
† The NMR spectrum of the reverse regioisomer (formation of a bond between *C*-nitrone and the spiro carbon and *O*-nitrone to the exocyclic methylene group) would have two singlets for H-3′ and H-5 and an AB system for the two C-5′ hydrogens.

‡ For details of the CCDC deposition scheme see 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans 2*, 1990, issue 1. Hydrogen-atom co-ordinates and thermal parameters have also been deposited at the Cambridge Crystallographic Data Centre.

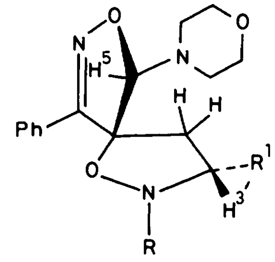


(2),(3),(4a) R = R¹ = C_6H_5
(2),(3),(4b) R = C_6H_5; R¹ = 4-NO_2-C_6H_4
(2),(3),(4c) R = C_6H_5; R¹ = 4-CH_3O-C_6H_4
(2),(3),(4d) R = CH_3; R¹ = C_6H_5
(2),(3),(4e) R = $C_6H_5CH_2$; R¹ = C_6H_5

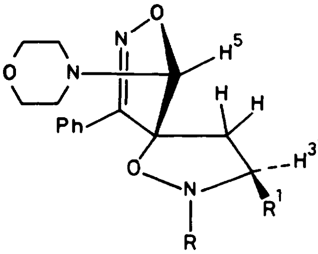
Scheme 1.



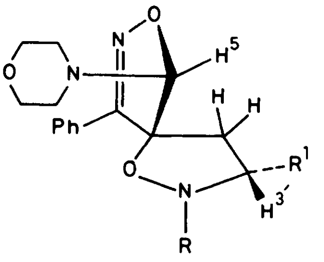
A



B



C



D

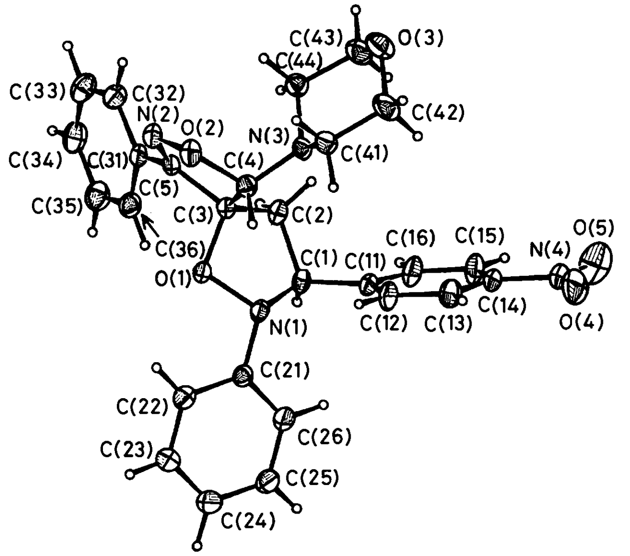


Figure. A perspective view of (3b) with the numbering scheme adopted for the X-ray analysis. The non-hydrogen atoms are represented by temperature-factor ellipsoids drawn[6] at a probability level of 0.20. Hydrogen atoms, represented by circles on an arbitrary scale, were numbered according to the carbon atom to which they are bonded.

adopted for the X-ray analysis. Compared with the values listed by Allen *et al.* in their extensive report[7] on bond lengths in organic compounds, most of those given in Table 4 fall within the expected ranges.

Both five-membered rings of (3b) are in an envelope (E) conformation, with 'flaps' at atoms C(4) in the ring including the C(5)=N(2) double bond, and at atom O(1) in the other. Puckering parameters[8] for the first ring, calculated for the sequence O(2) to C(4), are q_2 = 0.190(2) Å and φ_2 = 141.5(4)°, this latter quantity being only marginally different from the value, 144°, appropriate to one of the ten possible E forms. The other ring shows a larger puckering amplitude, q_2 = 0.419(1) Å, and is more distorted from a pure E form, with a phase φ_2 of −5.9(2)° for the sequence O(1) to C(3). This value indicates

Table 1. Physical, analytical, and ^{1}H NMR data of products (3) and (4).[a]

					Analysis (%)						
					Found				Required		
Compd.	M.p./°C	Solvent	Yield (%)[b,c]		C	H	N	Formula	C	H	N
(**3a**)[d]	143–145	Pr^{i}OH	28	2.7 (m, 4 H, CH_2NCH_2), 3.0 (d, 2 H, 2 × H-4′), 3.6 (t, 4 H, CH_2OCH_2), 4.4 (t, 1 H, H-3′), 5.5 (s, 1 H, H-5), 6.9–8.0 (m, 15 H, aromatic)	73.4	6.1	9.4	$C_{27}H_{27}N_3O_3$	73.45	6.2	9.5
(**3b**)	187–188	Pr^{i}OH	49	2.7 (m, 4 H, CH_2NCH_2), 3.0 (dd, 2 H, 2 × H-4′), 3.6 (t, 4 H, CH_2OCH_2), 4.6 (t, 1 H, H-3′), 5.4 (s, 1 H, H-5), 6.8–8.2 (m, 14 H, aromatic)	66.2	5.2	11.3	$C_{27}H_{26}N_4O_5$	66.65	5.4	11.5
(**4b**)	182–184	Pr^{i}OH	28	2.5–3.4 (m, 6 H, CH_2NCH_2 + 2 × H-4′), 3.7 (m, 4 H, CH_2OCH_2), 4.9 (t, 1 H, H-3′), 5.2 (s, 1 H, H-5), 6.9–8.5 (m, 14 H, aromatic)	66.7	5.5	11.7	$C_{27}H_{26}N_4O_5$	66.65	5.4	11.5
(**3c**)[d]	160–162	Pr^{i}OH	27	2.5–3.1 (m, 6 H, CH_2NCH_2 + 2 × H-4′), 3.6 (t, 4 H, CH_2OCH_2), 3.8 (s, 3 H, OCH_3), 4.4 (t, 1 H, H-3′), 5.5 (s, 1 H, H-5), 6.8–8.0 (m, 14 H, aromatic)	73.7	6.3	9.0	$C_{28}H_{29}N_3O_3$	73.8	6.4	9.2
(**3d**)	162–163	(Pr^i)$_2$O	31	2.5–3.1 (m, 9 H, CH_2NCH_2 + NCH_3 + 2 × H-4′), 3.7 (m, 5 H, CH_2OCH_2 + H-3′), 5.4 (s, 1 H, H-5), 7.2–7.9 (m, 10 H, aromatic)	69.5	6.4	11.0	$C_{22}H_{25}N_3O_3$	69.6	6.6	11.1
(**4d**)	142–143	(Pr^i)$_2$O	16	2.6–3.0 (m, 9 H, CH_2NCH_2 + NCH_3 + 2 × H-4′), 3.7 (m, 4 H, CH_2OCH_2 + H-3′), 5.3 (s, 1 H, H-5), 7.2–8.2 (m, 10 H, aromatic)	69.3	6.6	11.0	$C_{22}H_{25}N_3O_3$	69.6	6.6	11.1
(**3e**)	121–122	(Pr^i)$_2$O	22	2.5–3.0 (m, 6 H, CH_2NCH_2 + 2 × H-4′), 3.7 (t, 4 H, CH_2OCH_2), 3.9–4.3 (m, 3 H, CH_2Ph + H-3′), 5.3 (s, 1 H, H-5), 7.2–7.7 (m, 15 H, aromatic)	73.7	6.3	9.2	$C_{28}H_{29}N_3O_3$	73.8	6.4	9.2
(**4e**)	112–114	(Pr^i)$_2$O	11	2.5–3.2 (m, 6 H, CH_2NCH_2 + 2 × H-4′), 3.6 (t, 4 H, CH_2OCH_2), 3.8–4.1 (m, 3 H, CH_2Ph + H-3′), 5.0 (s, 1 H, H-5), 7.3–8.2 (m, 15 H, aromatic)	73.6	6.4	9.1	$C_{28}H_{29}N_3O_3$	73.8	6.4	9.2

[a] The crude reaction mixtures were examined (NMR) to exclude the presence of other regio- or diastereo-isomers. [b] Yield of pure isolated products. [c] A large amount of unchanged methylene isoxazoline was usually recovered using a molar ratio (1:1) between the reagents. This is due to the easy dimerization of nitrones [12] under the reaction conditions. [d] The diastereoisomers (**4a**) and (**4c**) were not isolated in a pure state.

Table 2. ^{13}C NMR data for compounds (**3b**) and (**4b**).[a]

Centre	δ(ppm)	J_{C-H}/Hz	Multiplicity
(**3b**) (structure **A**)			
C-4′	40.9	136.6	t
C-3′	69.1	141.5	d
C-4	92.5		s
C-5	104.2	164.0	d
(**4b**) (structure **B**)			
C-4′	42.2	137.5	t
C-3′	69.2	141.6	d
C-4	94.7		s
C-5	102.1	161.8	d

[a] Only the data necessary for discussion are reported.

that the distortion occurs towards a T form with twist axis through atom C(1).

The CCCH dihedral angle mentioned above corresponds, in the numbering of the Figure, to the torsion angle C(2)–C(3)–C(4)–H(4), and amounts to −99.7(8)°, further support to the spectroscopic findings that ruled out structures **C** and **D**.

In view of the interpretation of the ^{1}H NMR spectra of (**3**) and (**4**) it is interesting to note the positions of the substituents at atoms C(1) with respect to the phenyl ring at atom N(1). Distances from the ring least-squares plane in (**3b**) are: N(1) 0.049(1), C(1) −0.674(2), C(2) −1.224(2), C(11) 0.225(2), and H(1) −1.42(1) Å. This implies that in the other isomer (**4b**), the hydrogen atom at C(1) (H-3′ in **B**) would almost lie in the plane of the phenyl ring, provided that the torsion angle C(1)–N(1)–C(21)–C(26) in (**4b**) be not too different from that observed here in (**3b**), 36.4 (2)°.

In compound (**3b**) H-3′ resonates at higher field (δ 4.6) with respect to the values for the same proton in (**4b**) (δ 4.9) because, as shown before, it is shielded by the phenyl residue R at atom N. These considerations for products (**3b**) and (**4b**) can be extended to the products derived from (**2a–e**) as the mechanism is independent of the nitrone's substitution.

Products (**3**) and (**4**) differ only in the configuration at C-3′

Table 3. Fractional co-ordinates with esds in parentheses for the spiro compound (**3b**).

Atom	x	y	z
O(1)	0.232 99(6)	0.081 14(9)	0.821 92(6)
O(2)	0.152 15(7)	0.013 2(1)	0.621 61(7)
O(3)	−0.099 19(8)	0.254 1(1)	0.500 60(9)
O(4)	−0.256 90(9)	0.357 9(2)	0.865 3(1)
O(5)	−0.202 3(1)	0.537 8(2)	0.881 8(1)
N(1)	0.174 05(7)	0.116 5(1)	0.881 86(8)
N(2)	0.237 50(8)	0.061 6(1)	0.618 07(9)
N(3)	0.040 84(7)	0.161 7(1)	0.641 45(8)
N(4)	−0.194 1(1)	0.428 7(2)	0.875 1(1)
C(1)	0.162 3(1)	0.250 4(2)	0.871 5(1)
C(2)	0.182 1(1)	0.277 5(2)	0.778 7(1)
C(3)	0.196 96(9)	0.151 2(1)	0.742 07(9)
C(4)	0.113 6(1)	0.086 0(2)	0.685 7(1)
C(5)	0.263 76(9)	0.138 0(1)	0.682 5(1)
C(11)	0.067 9(1)	0.291 5(2)	0.876 8(1)
C(12)	−0.005 3(1)	0.213 2(2)	0.866 7(1)
C(13)	−0.091 1(1)	0.257 7(2)	0.866 6(1)
C(14)	−0.102 6(1)	0.380 1(2)	0.876 2(1)
C(15)	−0.031 6(1)	0.459 3(2)	0.887 0(2)
C(16)	0.053 6(1)	0.413 6(2)	0.888 1(1)
C(21)	0.212 84(9)	0.070 4(2)	0.969 1(1)
C(22)	0.267 0(1)	−0.032 5(2)	0.979 9(1)
C(23)	0.302 3(1)	−0.079 3(2)	1.064 1(1)
C(24)	0.283 4(1)	−0.026 5(2)	1.138 8(1)
C(25)	0.229 1(1)	0.075 2(2)	1.129 1(1)
C(26)	0.193 6(1)	0.124 3(2)	1.044 8(1)
C(31)	0.351 53(9)	0.201 1(1)	0.692 8(1)
C(32)	0.382 3(1)	0.237 6(2)	0.617 9(1)
C(33)	0.465 5(1)	0.293 9(2)	0.628 0(2)
C(34)	0.518 7(1)	0.314 8(2)	0.711 9(2)
C(35)	0.488 5(1)	0.279 8(2)	0.785 9(2)
C(36)	0.405 4(1)	0.224 2(2)	0.777 2(1)
C(41)	−0.043 7(1)	0.093 2(2)	0.607 7(1)
C(42)	−0.119 5(1)	0.180 7(3)	0.570 3(2)
C(43)	−0.019 6(2)	0.321 7(2)	0.534 7(2)
C(44)	0.060 3(1)	0.238 4(2)	0.569 8(1)

Table 4. Selected bond lengths/Å and angles/°, with their estimated standard deviations in parentheses, for compound (**3b**).

Bond lengths			
C(1)–C(11)	1.514(2)	C(3)–C(4)	1.532(2)
C(1)–C(2)	1.537(2)	C(4)–N(3)	1.420(2)
C(2)–C(3)	1.523(2)	C(4)–O(2)	1.475(2)
C(3)–O(1)	1.437(2)	O(2)–N(2)	1.406(2)
O(1)–N(1)	1.462(2)	N(2)–C(5)	1.282(2)
N(1)–C(1)	1.477(2)	C(5)–C(3)	1.507(2)
N(1)–C(21)	1.419(2)	C(5)–C(31)	1.471(2)
Bond angles			
C(2)–C(1)–N(1)	104.2(2)	C(1)–N(1)–O(1)	105.7(1)
C(2)–C(1)–C(11)	111.7(1)	C(1)–N(1)–C(21)	117.8(1)
N(1)–C(1)–C(11)	112.3(2)	O(1)–N(1)–C(21)	108.0(1)
C(1)–C(2)–C(3)	103.7(1)	C(3)–C(4)–O(2)	103.0(1)
C(2)–C(3)–C(4)	117.1(1)	C(3)–C(4)–N(3)	116.6(2)
C(2)–C(3)–C(5)	118.7(1)	N(3)–C(4)–O(2)	112.2(1)
C(2)–C(3)–O(1)	103.4(1)	C(4)–O(2)–N(2)	108.9(1)
C(5)–C(3)–O(1)	106.3(1)	O(2)–N(2)–C(5)	110.2(1)
C(4)–C(3)–O(1)	109.6(1)	C(3)–C(5)–N(2)	112.9(1)
C(4)–C(3)–C(5)	101.3(1)	C(3)–C(5)–C(31)	126.8(1)
C(3)–O(1)–N(1)	102.7(1)	N(2)–C(5)–C(31)	120.3(1)

and their formation starting from (*Z*)-nitrones[9] can be explained in terms of the possible *Z*→*E* isomerization of nitrones[9] under the reaction conditions. Taking into account the concerted nature of 1,3-dipolar cycloadditions[10,11] and the impossibility of interconversion of the two cycloadducts (**3**) and (**4**), as verified by suitable experiments, the formation of the two diastereoisomers is derived from the equilibrium of (*Z*)-nitrones with a small amount of the *E* form.

Experimental

M.p.s were measured with a Büchi apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) and ^{13}C NMR spectra on a Bruker WP-80-SY. All chemical shifts are expressed in δ values from tetramethylsilane as the reference. Compounds (**1**),[2] (**2a**),[12] (**2b**),[13] (**2c**),[14] (**2d**),[15] and (**2e**)[16] were prepared following the methods reported in the literature.

Cycloaddition Reactions: General procedure.—A mixture of (**1**) (10 mmol) and (**2**) (10 mmol) in toluene (40 cm^3) was heated at 80 °C for 24–48 h. The solvent was evaporated and the residue chromatographed on silica gel. Elution with toluene–ethyl acetate (9:1) gave the products (**3**) and (**4**).

X-Ray Crystal Analysis of (**3b**).—*Crystal data.* $C_{27}H_{26}N_4O_5$, $M = 486.5$. Monoclinic, $a = 15.106(2)$, $b = 10.920(2)$, $c = 15.226(2)$ Å, $\beta = 102.87(1)°$, $V = 2\,448.6(7)$ Å^3 (by least-squares refinement on diffractometer angles for 50 automatically centred reflections, $\lambda = 0.710\,73$ Å), space group $P2_1/n$ (alt. $P2_1/c$, No. 14), $Z = 4$, $D_x = 1.32$ g cm^{-3}. Approximate crystal dimensions: 0.4 × 0.3 × 0.2 mm, μ(Mo-K_α) = 0.87 cm^{-1}.

Data collection and processing.[17] Crystal quality was checked by film techniques. CAD4 diffractometer, ω mode with ω scan width = $1.0 + 0.35 \tan\theta$, ω scan speed = 2.0 deg min^{-1}, graphite-monochromated Mo-K_α radiation; 8 722 reflections measured ($1.0 \leqslant \theta \leqslant 25.0$, full hemisphere), 4 296 unique (merging $R = 0.019$), 4 151 with $I > 0$ classed as observed. Data were corrected for Lorentz and polarization effects but not for absorption.

Structure analysis and refinement. Direct methods (all non-H atoms) followed by difference maps to recover the positions of all 26 hydrogen atoms. Full-matrix least-squares refinement based on F; non-H atoms anisotropic, H atoms isotropic; 4 151 observations and 430 variables, including an isotropic extinction coefficient [final value = $8.9(3) \times 10^{-6}$]. Weighting scheme: $w = 4\ F_0{}^2/\sigma^2(F_0{}^2)$, with $\sigma^2(F_0{}^2)$ including, besides counting statistics, a term $(0.02\ S)^2$, where S is the scan count. Final R and wR values are 0.055 and 0.034, with goodness-of-fit = 1.63 [$R = 0.037$ on the 3 061 reflections with $1 > 2\sigma(I)$]. Programs and computers used and sources of scattering factors are given in ref. 17.

Acknowledgements

We thank MPI and CNR for financial support.

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Paper 9/04199K
Received 10*th October* 1989
Accepted 6*th November* 1989