3-Hydroxypyrroles and 1*H*-Pyrrol-3(2*H*)-ones. Part 5.[1] Tautomerism of 1-Substituted and 1,2-Disubstituted Derivatives in the Solid State and in Solution: *X*-Ray Crystal and Molecular Structure of 1-Phenyl-1*H*-pyrrol-3(2*H*)-one

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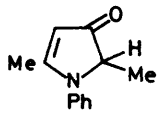
X-Ray crystallography of the typical derivative 1-phenyl-1*H*-pyrrol-3(2*H*)-one (**6**) has shown that the title compounds exist in the solid state as keto tautomers. In solution, the influence of solvent polarity, hydrogen bonding to solvent, and the steric and electronic demands of substituents on the position of the keto–enol equilibrium have been determined by n.m.r. spectroscopy for a number of examples.

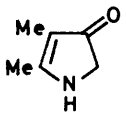
In the work described here, we have employed *X*-ray crystallographic and n.m.r. methods to study the keto–enol tautomerism of the 1*H*-pyrrol-3(2*H*)-one (pyrrolone) system in the solid state and in solution. The effect of alkyl and aryl groups in the 1- and 2-position of the five-membered ring on the position of the equilibrium is also considered.

Previous solution studies of this system are rare for derivatives lacking strongly electron-withdrawing or -donating substituents. However, in 1953, Davoll was able to conclude that the 2,5-dimethyl-1-phenyl derivative exists in the 3-pyrrolone (keto) form (**1**) by using u.v. spectroscopic methods.[2] More recently, Momose and co-workers have reached similar conclusions for other simple derivatives [*e.g.* (**2**)] using ^{1}H n.m.r. spectra,[3] though a pronounced solvent dependence on the equilibrium leads to significant quantities of the hydroxypyrrole (enol) tautomer in [$^2H_4$]methanol,[3] and, especially, in [$^2H_6$]DMSO.[4] *N*-Unsubstituted derivatives have been the subject of two theoretical studies, one of which predicts the keto[5] and the other the enol[6] tautomer to be favoured. The limited experimental evidence is equally equivocal: the 4,5-dimethyl compound entirely adopts the 3-pyrrolone form (**3**) in [$^2H_6$]DMSO,[7] while the parent 3-hydroxypyrrole is reported to exist as the enol (**4E**) in the same solvent.[4] The tautomeric form of the 1*H*-pyrrol-3(2*H*)-one–3-hydroxypyrrole system in the solid state is unknown. Previous crystallographic studies of pyrrolones[8] have been confined to 2,2-disubstituted examples in which tautomerism is impossible.

The 1-substituted and 1,2-disubstituted derivatives (**5**)—(**12**) used in this study were obtained, essential pure, by gas-phase pyrolysis of aminomethylene Meldrum's acid derivatives.[9] Though the *N*-phenyl derivative (**6**) is reported to be 'extremely unstable' and to 'resinify within several hours,'[3] crystalline samples are readily obtainable by the flash vacuum pyrolysis method,[9] and recrystallisation from methanol at −20 °C gave



(**1**)



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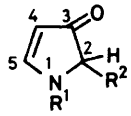
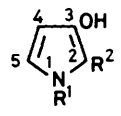


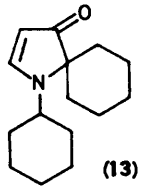
K



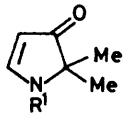
E

K = keto; **E** = enol

	R^1	R^2
(**2**)	Me	H
(**4**)	H	H
(**5**)	Bu^t	H
(**6**)	Ph	H
(**7**)	Et	Me
(**8**)	Me	Ph
(**9**)	CH_2Ph	Ph
(**10**)	Ph	Ph
(**11**)	Bu^t	Ph
(**12**)	Ph	Me



(**13**)



(**14**) R^1 = Pr^i
(**15**) R^1 = Ph

Table 1. Bond lengths (Å) with standard deviations

N(1)–C(2)	1.458 2(20)	C(6)–C(7)	1.396 7(22)
N(1)–C(5)	1.360 5(21)	C(6)–C(11)	1.394 1(22)
N(1)–C(6)	1.400 9(20)	C(7)–C(8)	1.382 2(24)
C(2)–C(3)	1.520 2(23)	C(8)–C(9)	1.383(3)
C(3)–O(1)	1.235 4(22)	C(9)–C(10)	1.378(3)
C(3)–C(4)	1.423 3(24)	C(10)–C(11)	1.383(3)
C(4)–C(5)	1.356 2(24)		

Table 2. Angles (°) with standard deviations

C(2)–N(1)–C(5)	108.70(13)	N(1)–C(6)–C(7)	121.57(13)
C(2)–N(1)–C(6)	124.39(13)	N(1)–C(6)–C(11)	119.60(14)
C(5)–N(1)–C(6)	126.77(13)	C(7)–C(6)–C(11)	118.83(14)
N(1)–C(2)–C(3)	103.42(13)	C(6)–C(7)–C(8)	119.76(15)
C(2)–C(3)–O(1)	123.17(15)	C(7)–C(8)–C(9)	121.32(16)
C(2)–C(3)–C(4)	106.50(14)	C(8)–C(9)–C(10)	118.85(17)
O(1)–C(3)–C(4)	130.33(17)	C(9)–C(10)–C(11)	120.88(17)
C(3)–C(4)–C(5)	108.46(15)	C(6)–C(11)–C(10)	120.36(16)
N(1)–C(5)–C(4)	112.89(15)		

Table 3. Torsion angles (°) with standard deviations

C(5)–N(1)–C(2)–C(3)	1.70(16)
C(6)–N(1)–C(2)–C(3)	−174.20(13)
C(2)–N(1)–C(5)–C(4)	−1.25(19)
C(6)–N(1)–C(5)–C(4)	174.52(15)
C(2)–N(1)–C(6)–C(7)	167.67(14)
C(2)–N(1)–C(6)–C(11)	−12.90(22)
C(5)–N(1)–C(6)–C(7)	−7.48(24)
C(5)–N(1)–C(6)–C(11)	171.95(15)
N(1)–C(2)–C(3)–O(1)	178.71(15)
N(1)–C(2)–C(3)–C(4)	−1.58(17)
C(2)–C(3)–C(4)–C(5)	0.93(19)
O(1)–C(3)–C(4)–C(5)	−179.39(18)
C(3)–C(4)–C(5)–N(1)	0.12(20)
N(1)–C(6)–C(7)–C(8)	179.19(15)
C(11)–C(6)–C(7)–C(8)	−0.24(24)
N(1)–C(6)–C(11)–C(10)	−179.09(15)
C(7)–C(6)–C(11)–C(10)	0.35(24)
C(6)–C(7)–C(8)–C(9)	0.0(3)
C(7)–C(8)–C(9)–C(10)	0.2(3)
C(8)–C(9)–C(10)–C(11)	0.0(3)
C(9)–C(10)–C(11)–C(6)	−0.2(3)

Table 4. Fractional co-ordinates of atoms with standard deviations

	x	*y*	*z*
N(1)	0.003 68(12)	0.087 99(13)	0.211 76(17)
C(2)	0.117 41(12)	0.154 54(18)	0.302 68(21)
C(3)	0.100 83(15)	0.309 23(16)	0.241 89(24)
O(1)	0.178 27(12)	0.401 94(14)	0.293 45(20)
C(4)	−0.015 26(15)	0.318 63(18)	0.121 30(24)
C(5)	−0.067 48(15)	0.187 94(16)	0.108 42(22)
C(6)	−0.027 63(13)	−0.053 24(16)	0.239 08(18)
C(7)	−0.145 26(14)	−0.102 83(17)	0.175 05(22)
C(8)	−0.172 10(15)	−0.243 47(20)	0.202 88(23)
C(9)	−0.084 52(16)	−0.337 07(19)	0.293 31(24)
C(10)	0.031 39(17)	−0.287 89(19)	0.356 8(3)
C(11)	0.060 38(14)	−0.147 57(19)	0.330 87(22)

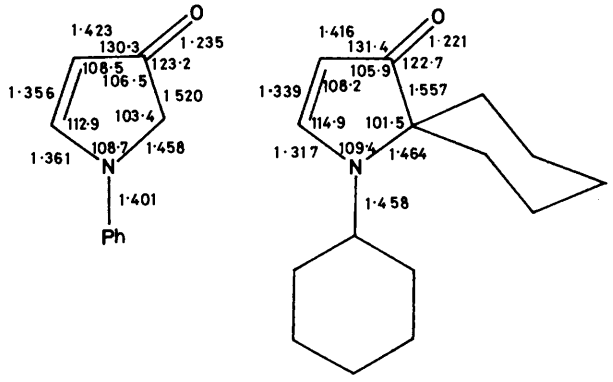


Figure 1. Selected structural parameters for the pyrrolones (**6**) and (**13**)

a suitable crystal for *X*-ray structure determination. Bond lengths, angles, and atomic co-ordinates are given in Tables 1—4 and are summarised in Figure 1; Figure 2 is an ORTEP plot showing the crystallographic numbering system. It is clear that the molecule adopts the keto tautomer (**6K**) in the solid state, and so the structure is closely related to that of the 2,2-disubstituted derivative (**13**) which we have published previously[8] (Figure 1). Indeed, almost all of the parameters of the five-membered rings are well within three standard deviations of each other (Figure 1). The sole exception is the length of the N(1)–C(5) bond which is significantly longer in the *N*-phenyl

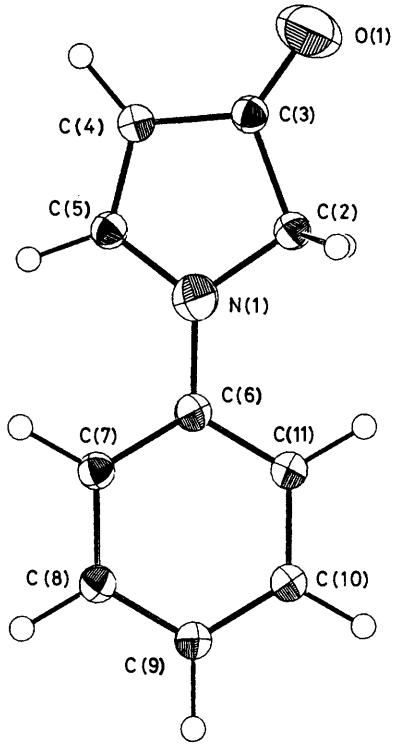


Figure 2. ORTEP plot of the pyrrolone (**6**) showing crystallographic numbering system

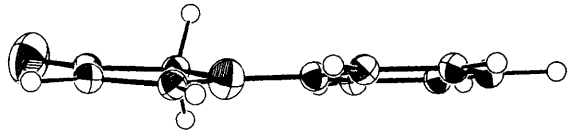


Figure 3. Side view of the pyrrolone (**6**)

derivative. This suggests that some electron density from the lone pair of the nitrogen atom is being diverted from the enaminone conjugated system into the phenyl group, and is supported by the approximate coplanarity of the two rings (dihedral angle just 12.6°) (Figure 3), and by the expected shortening of the *exo*cyclic N–C bond relative to the *N*-alkyl example. Parameters of both structures are in moderate agreement with a calculated[6] equilibrium geometry of the parent compound (**4K**).

In solution, the tautomers can be distinguished conveniently by n.m.r. spectroscopy. The keto tautomers display a widely spaced pair of doublets (δ *ca.* 5.0 and 8.0) due to 4-H and 5-H, characteristic of the enaminone system, and shown also by 2,2-disubstituted pyrrolones incapable of tautomerism.[10] In contrast, 2-, 4-, and 5-H of the enol tautomers resonate at δ 5.5—7.0 with ^3J and ^4J values of 2—3 Hz: these data are more typical of fully conjugated pyrroles in general, and 3-alkoxypyrroles in particular.[11] The keto and enol tautomers can be distinguished unambiguously by ^{13}C n.m.r. spectroscopy, most conveniently using the DEPT 3π/4 pulse sequence, since, for a given R^2, the state of C-2 (methylene, methine, or quaternary) is determined by the tautomerism. (This method will also be effective in cases where substituents more complex than these considered here might distort the ^1H n.m.r. chemical shifts.)

Because of indications from the literature[3,4] that the tautomerism might be solvent-dependent, we have studied the position of the equilibrium of the simple *N*-alkylpyrrole species [(**5K**) ⇌ (**5E**)] in a range of solvents (Table 5). The ratio of

Table 5. Solvent dependence of the tautomerism of the t-butylpyrrole (**5K**) ⇌ (**5E**)

Solvent	Keto:enol	$\Delta G°$/kJ mol^{-1} [a]
C[^{2}H]Cl$_3$	90:10	−5.4
[^{2}H$_4$]MeOH	74:26	−2.6
[^{2}H$_6$]Me$_2$CO	25:75	+2.7
[^{2}H$_8$]THF	17:83	+3.9
[^{2}H$_7$]DMF	16:84	+4.1
[^{2}H$_6$]DMSO	5:95	+7.3

[a] $\Delta G° = -8.314\ T \ln$ [keto/enol] (ref. 12); temperature in probe = 25 °C

Table 6. Substituent dependence of the tautomerism of the pyrroles (**5**)—(**12**) in [^{2}H]chloroform and [^{2}H$_6$]DMSO solution

Compound	R^1	R^2	[^{2}H]Chloroform Keto:enol	[^{2}H$_6$]DMSO Keto:enol
(**5**)	Bu^t	H	90:10	5:95
(**6**)	Ph	H	>99:1	5:95
(**7**)	Et	Me	88:12	12:88
(**8**)	Me	Ph	30:70	<1:99
(**9**)	CH_2Ph	Ph	45:55	<1:99
(**10**)	Ph	Ph	80:20	<1:99
(**11**)	Bu^t	Ph	>99:1	78:22
(**12**)	Ph	Me	>99:1	30:70

tautomers (measured from the integrals of the ^{1}H n.m.r. spectra) gives a measure of the free energy difference between them.[12] This varies dramatically from *ca.* 5 kJ mol^{-1} in favour of the keto tautomer (in chloroform solution) to *ca.* 7 kJ mol^{-1} in favour of the enol tautomer (in DMSO solution). In general, dipolar aprotic solvents (acetone, THF, DMF, and DMSO) favour the hydroxypyrrole form, while relatively non-polar solvents (chloroform) and protic solvents (methanol) favour the pyrrolone form. It is clear that the polarity of the substrate is not responsible for this behaviour; both calculations[6] and dipole moment studies of model pyrroles[13] and enaminones[14] suggest that the pyrrolone form is the more polar, and might therefore be expected to dominate in the solvents of high polarity. Instead, the ability of the tautomers to form hydrogen bonds with the solvent is a more likely explanation of the observed trends. In non-polar solvents, in the absence of hydrogen bonding, the pyrrolone form is favoured, as found in the solid state, while dipolar aprotic solvents can interact *only* with the hydroxypyrrole tautomer [Figure 4(a)], which is therefore lowered in energy. The situation is more complex in protic solvents in which hydrogen bonding to both tautomers is

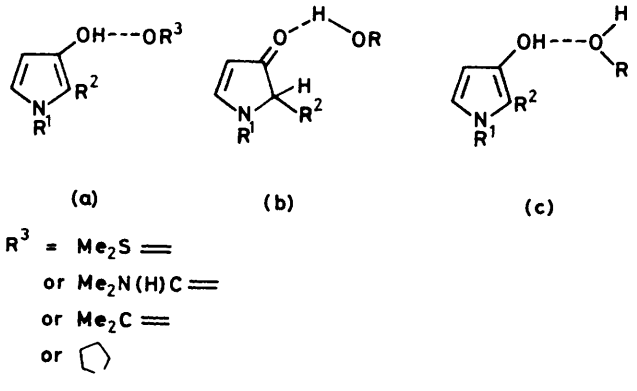
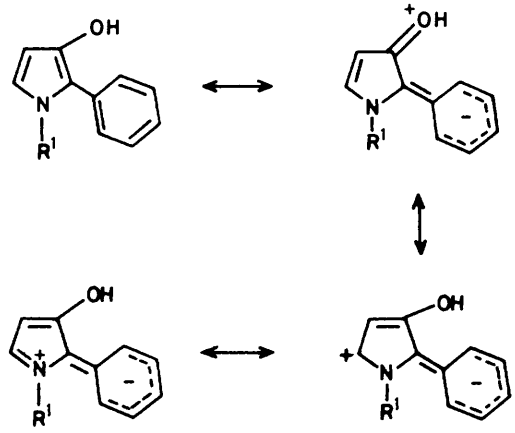


Figure 4. Solvent dependence of the tautomerism of 1,2-disubstituted pyrroles (a) in dipolar aprotic solvent, (b) and (c) in protic solvent

feasible [Figures 4(b) and (c)], and the results reflect a balance in which polarity assumes more importance.

It is clear from this dependence on external factors that there can be little difference in the *inherent* stability of the pyrrolone (**K**) and hydroxypyrrole (**E**) forms. In other words, the resonance energy of the planar, 6π-electron, push-pull enaminone in (**K**) is of the same order as the 6π-electron heteroaromatic stabilisation manifested by (**E**).

The effect of ring substituents on the tautomerism was examined using the 'extreme' solvents (chloroform and DMSO) found in the model study (Table 6). The *N*-phenyl example (**6**) and the 1,2-dialkyl derivative (**7**) show similar trends to those of the *N*-t-butyl compound (**5**); more significant effects are observed when the 2-position is substituted by phenyl groups. Thus, chloroform solutions of 2-aryl derivatives (**8**)—(**10**) show a significantly increased percentage of enol tautomer. This effect is also observed in derivatives with further polar substitution, and has been discussed by Momose.[3] The possibility, in the enol form, of enhanced stabilisation through resonance interaction with the pyrrole ring, and with electron pairs on the hydroxy function, and on the nitrogen atom is clearly responsible (see Scheme). In agreement with this, the effect is greater for the *N*-alkyl derivatives (**8**) and (**9**) than for the *N*-aryl compound (**10**), where delocalisation into the *N*-phenyl ring can partially compete.



Scheme.

The ability of the pyrrole ring and the 2-phenyl group to be approximately coplanar is an important requirement for enhanced stabilisation of the hydroxypyrrole (**E**) form. The steric demands of a bulky *N*-t-butyl substituent are incompatible with this, and indeed the crowding can be efficiently relieved in the pyrrolone (**K**) tautomer. Consequently the 2-phenyl-1-t-butyl derivative (**11**)[15] shows the smallest amount of enol tautomer of all the compounds studied (only 22% in [^{2}H$_6$]DMSO).

Similar factors are responsible for the reduced level of the enol tautomer of the 2-methyl-1-phenyl compound (**12**) in DMSO. The steric demands of the *N*-phenyl group (coplanarity) impose significant eclipsing strain on the 2-methyl substituent in the hydroxypyrrole form (**12E**) (or, alternatively, the steric demands of the 2-methyl substituent force the *N*-phenyl group out of plane) shifting the balance in favour of the less perturbed pyrrolone tautomer (**12K**).

Further information on the conjugative interactions (and hence planarity) of *N*-phenyl groups can be obtained from u.v. spectra. These were obtained in chloroform solution, in which the keto tautomer will dominate. The 'fixed' *N*-alkylpyrrolone (**14**) has an absorption maximum at 325 nm, typical of enaminones,[14] and this is shifted by *ca.* 30 nm to longer

wavelengths for pyrrolones with coplanar *N*-aryl groups [*e.g.* (**6**; $\lambda_{max.}$ 353 nm)]. Though one 2-methyl group has little effect (**12**; $\lambda_{max.}$ 350 nm), two adjacent methyl groups force the *N*-aryl substituent out of the plane causing a substantial reduction in the conjugation {*e.g.* (**15**; $\lambda_{max.}$ 330 nm); [**1**; $\lambda_{max.}$(MeOH) 324 nm^2]}. Very similar effects are well known in dihydrodiazepine chemistry.[16]

In conclusion, the results described here have the important consequence that *any* solution of a 3-hydroxypyrrole is liable to contain an equilibrium amount of the 1*H*-pyrrol-3(2*H*)-one tautomer, which may be substantial. Clearly, any systematic study of the chemistry of these compounds requires tautomerically fixed models so that the influence of the two forms can be identified. The preparation of 2,2-disubstituted pyrrolones has been previously described,[9] and the synthesis of 3-alkoxypyrroles will be the subject of a later Part of this series.[11]

Experimental

The pyrroles (**5**)—(**15**) were made by flash vacuum pyrolysis of aminomethylene Meldrum's acid derivatives.[8,9,15] ^{1}H N.m.r. spectra were recorded at 80 or 200 MHz, and ^{13}C n.m.r. spectra at 20 or 50 MHz.

X-Ray Structure Determination of $C_{10}H_9NO$ (**6**).—Crystals suitable for *X*-ray diffraction were grown by recrystallisation from methanol at −20 °C.

Crystal Data.—$C_{10}H_9NO$, M = 159.18, monoclinic, a = 11.491 5(18), b = 9.369 0(12), c = 7.698 3(16) Å, β = 104.577(15)°, U = 802.1 Å^3 (by least-squares refinement on diffractometer angles for 25 centred reflections with $11 < \theta < 15°$, $\bar{\lambda}$ = 0.710 69 Å), space group $P2_1/n$, Z = 4, $D_{calc.}$ = 1.318 g cm^{-3}. Yellow-brown columnar crystal, 0.65 × 0.36 × 0.40 mm, μ(Mo-K_α) = 0.80 cm^{-1}, F(000) = 336.

Data Collection and Processing.—CAD4 diffractometer, $\omega/2\theta$ mode with ω scan width (1.0 + 0.5 tan θ)°, graphite-monochromated Mo-K_α radiation, 1 615 reflections measured ($2\theta_{max.}$ = 50°, h −14 ⟶ 14, k 0 ⟶ 12, l 0 ⟶ 10), 1 411 unique ($R_{int.}$ = 0.0119), giving 1 144 with $F > 6\sigma(F)$. No significant crystal decay, no absorption correction.

Structure Analysis and Refinement.—Direct methods[17] revealed the positions of all non-H atoms. Full-matrix least-squares refinement[18] with H atoms in fixed, calculated positions and all non-H atoms anisotropic converged to R, wR = 0.0409, 0.0753, S = 0.752 for 109 refined parameters. The weighting scheme $w^{-1} = \sigma(F) + 0.009\,68\,F^2$ gave satisfactory agreement analysis and the final ΔF synthesis showed no feature above 0.19 e Å^{-3}. Molecular geometry calculations utilised CALC[19] and illustrations were produced using ORTEP;[20] selected molecular geometry parameters are listed in Tables 1—3 and refined fractional co-ordinates in Table 4.*

* *Supplementary data* (see section 5.6.3 of Instructions for Authors, in the January issue). Thermal parameters and hydrogen-atom co-ordinates have been deposited at the Cambridge Crystallographic Data Centre.

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References

1 Part 4. H. McNab, L. C. Monahan, and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1988, 759
2 J. Davoll, *J. Chem. Soc.*, 1953, 3802.
3 T. Momose, T. Tanaka, T. Yokota, N. Nagamoto, and K. Yamada, *Chem. Pharm. Bull.*, 1979, **27**, 1448.
4 B. Capon and F.-C. Kwok, *Tetrahedron Lett.*, 1986, **27**, 3275.
5 N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Am. Chem. Soc.*, 1970, **92**, 2329.
6 A. Karpfen, P. Schuster, and H. Berner, *J. Org. Chem.*, 1979, **44**, 374.
7 H. Bauer, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 734.
8 C. L. Hickson, E. M. Keith, J. C. Martin, H. McNab, L. C. Monahan, and M. D. Walkinshaw, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1465, and references therein.
9 H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1988, 863.
10 H. McNab and L. C. Monahan, following paper.
11 G. A. Hunter, H. McNab, and L. C. Monahan, unpublished work.
12 A. L. Weis and R. Vishkautsan, *Chem. Lett.*, 1984, 1773.
13 For example, R. A. Jones and G. P. Bean, 'The Chemistry of Pyrroles,' Academic Press, New York, 1977.
14 J. V. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277.
15 G. A. Hunter and H. McNab, unpublished work.
16 C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 1966, 93.
17 SHELX84, Program for crystal structure solution, G. M. Sheldrick, University of Göttingen, F.R.G., 1983.
18 SHELX76, Program for crystal structure refinement, G. M. Sheldrick, University of Cambridge, U.K., 1976.
19 CALC, Program for molecular geometry calculations, R. O. Gould and P. Taylor, University of Edinburgh, 1985.
20 ORTEPII, interactive version, P. D. Mallinson and K. W. Muir, *J. Appl. Crystallogr.*, 1985, **18**, 51.

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