

Anomeric Effects Involving a Carbon–Sulphur Bond: The X-Ray Crystal Structure of Methyl (Z)-2-Methoxy-3-methyl-2-(*N*-methylanilino)-4-oxothiazolidin-5-ylidene-ethanoate

Anthony P. K. Orrell

Chemical Crystallography Laboratory, 9 Parks Road, Oxford OX1 3PD

John D. Wallis*†

Department of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD

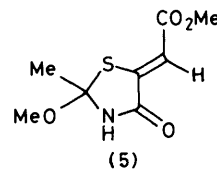
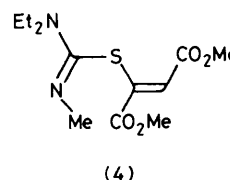
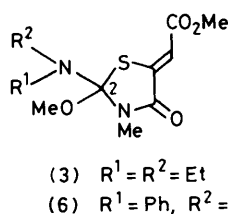
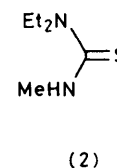
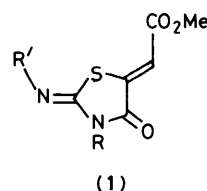
In the X-ray crystal structure of the title compound (6) the C(2)–S(1) bond is antiperiplanar to two lone pairs from the 2-methoxy- and 2-(*N*-methylanilino)-groups and is lengthened to 1.880(2) Å. The second lone pair on the 2-methoxy oxygen atom is antiperiplanar to the endocyclic C–N bond. The crystallographic evidence for anomeric interactions between oxygen or nitrogen lone pairs and C–S bonds is discussed and the latter appear to be stronger. Crystal data for (6): C₁₅H₁₈N₂O₄S, *M_r* = 322.4, triclinic, *P*1̄, *a* = 8.344(1), *b* = 10.045(5), *c* = 10.905(2) Å, α = 106.52(3), β = 109.99(1), γ = 97.10(2)°, *Z* = 2, *D_c* = 1.34 g cm⁻³, μ(Mo-Kα) = 0.59 mm⁻¹, final *R*-value = 0.039 for 1 981 reflections with *I* ≥ 3σ(*I*).

Dimethyl acetylenedicarboxylate reacts with *NN'*-disubstituted thioureas in methanol to give '1:1 molar – MeOH' adducts most of which have the thiazolidinone structure (1).¹ The trisubstituted thiourea (2) under similar conditions gives a '1:1 molar' adduct which has been assigned¹ the cyclic structure (3) rather than the open-chain structure (4) because the adduct's 'off-resonance' decoupled ¹³C n.m.r. spectrum has a singlet at δ 117.1. The chemical shift of this resonance is too small to be attributed to either of the carbons attached to sulphur in (4) and so is assigned to the quaternary carbon C(2) in structure (3) where the presence of four electronegative substituents would explain the rather large chemical shift for an *sp*³ carbon atom. The corresponding adduct (5) from thioacetamide, in which the quaternary carbon carries one less electronegative substituent, shows a singlet carbon resonance with a somewhat smaller chemical shift (δ 97.0). With four heteroatoms attached to C(2), compounds of type (3) are particularly interesting for investigating anomeric effects. The exocyclic nitrogen's lone pair of electrons could, in principle, be aligned with the anti-bonding orbital (σ*) of any of the three different C–X bonds to C(2) (X = N, O, or S), while the two lone pairs on the 2-methoxy oxygen could be aligned with the σ*s of two C–N bonds or with the σ*s of one of these C–N bonds and of the C–S bond. To investigate this further the X-ray crystal structure of the analogous compound (6) has been measured. Attempts to grow suitable crystals of (3) only gave powders and the ¹³C n.m.r. spectrum of (6) is in accord with that of (3) showing a singlet resonance at δ 115.3.

Discussion

The crystal structure determination confirmed that (6) was indeed a thiazolidinone derivative and not an open-chain isomer. Bond lengths and angles are given in Tables 1 and 2. This is the first structure determination on a substance containing a saturated carbon atom attached to a sulphur, an oxygen, and two nitrogen atoms. A few structures containing carbon surrounded by four nucleophilic heteroatoms have been reported² but in three of these cases the four heteroatoms are identical (all sulphur^{3,4} or all oxygen⁵) and in the other two cases^{6,7} only two types of heteroatom, nitrogen and oxygen, are involved.

† Present address: Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich.



In (6) the 2-OMe group is oriented so that the two oxygen lone pairs are antiperiplanar (*ap*) to the C–S and C–N bonds of the thiazolidinone ring (Figure 1). The exocyclic nitrogen is pyramidal and its lone pair is *ap* to the C–S bond, and the *N*-methyl group is oriented over the thiazolidinone ring (Figure 2). Thus two lone pairs overlap with the antibonding orbital of the C–S bond and, accordingly, the C(2)–S(1) bond is rather long [1.880(2) Å] compared with the normal value for organic sulphides [1.81(1) Å].² It is not clear how much the C(2)–N(1) bond is lengthened because there are no accurate crystallographic data for pyrrolidinones or thiazolidin-4-ones. However, it is clear that the exocyclic C(2)–O(1) and C(2)–N(2) bonds are both shortened by their anomeric interactions. The former [1.390(3) Å] is *ca.* 0.04 Å shorter than its expected value⁹ while the latter [1.435(3) Å] is shortened⁹ by *ca.* 0.03 Å. The thiazolidinone ring system is almost planar with the maximum deviation from the best plane through the ring being 0.028 Å by the amidic nitrogen N(1). This atom deviates by 0.037 Å from the plane of its three surrounding atoms so

Table 1. Bond lengths for (6) with e.s.d.s in parentheses

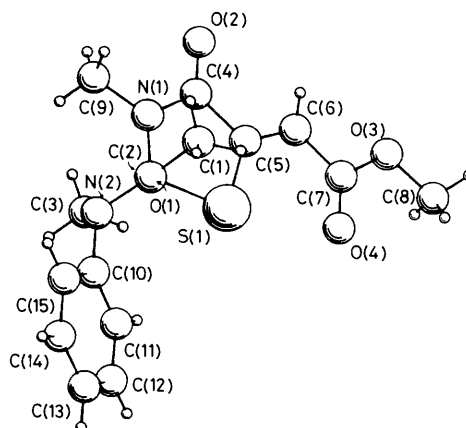
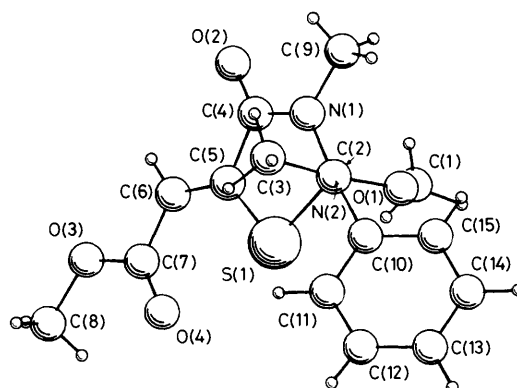
Bond	Length (Å)
S(1)-C(2)	1.880(2)
S(1)-C(5)	1.725(2)
O(1)-C(1)	1.425(3)
O(1)-C(2)	1.390(3)
O(2)-C(4)	1.217(3)
O(3)-C(7)	1.342(3)
O(3)-C(8)	1.445(4)
O(4)-C(7)	1.201(3)
N(1)-C(2)	1.453(3)
N(1)-C(4)	1.344(3)
N(1)-C(9)	1.455(3)
N(2)-C(2)	1.435(3)
N(2)-C(3)	1.458(4)
N(2)-C(10)	1.447(3)
C(4)-C(5)	1.493(4)
C(5)-C(6)	1.331(4)
C(6)-C(7)	1.451(4)
C(10)-C(11)	1.381(4)
C(10)-C(15)	1.381(4)
C(11)-C(12)	1.391(4)
C(12)-C(13)	1.364(5)
C(13)-C(14)	1.365(5)
C(14)-C(15)	1.388(4)

Table 2. Bond angles for (6) with e.s.d.s in parentheses

Bond	Angle (°)	Bond	Angle (°)
C(2)-S(1)-C(5)	92.9(1)	N(1)-C(4)-C(5)	111.7(2)
C(1)-O(1)-C(2)	116.7(2)	S(1)-C(5)-C(4)	111.5(2)
C(7)-O(3)-C(8)	115.8(3)	S(1)-C(5)-C(6)	127.1(2)
C(2)-N(1)-C(4)	119.4(2)	C(4)-C(5)-C(6)	121.5(2)
C(2)-N(1)-C(9)	118.9(2)	C(5)-C(6)-C(7)	122.3(2)
C(4)-N(1)-C(9)	121.5(2)	O(3)-C(7)-O(4)	123.6(3)
C(2)-N(2)-C(3)	113.8(2)	O(3)-C(7)-C(6)	111.4(2)
C(2)-N(2)-C(10)	114.1(2)	O(4)-C(7)-C(6)	125.0(3)
C(3)-N(2)-C(10)	114.4(2)	N(2)-C(10)-C(11)	121.7(2)
S(1)-C(2)-O(1)	111.2(2)	N(2)-C(10)-C(15)	119.0(2)
S(1)-C(2)-N(1)	104.4(2)	C(11)-C(10)-C(15)	119.3(2)
S(1)-C(2)-N(2)	112.6(2)	C(10)-C(11)-C(12)	119.3(3)
O(1)-C(2)-N(1)	111.9(2)	C(11)-C(12)-C(13)	121.3(3)
O(1)-C(2)-N(2)	106.1(2)	C(12)-C(13)-C(14)	119.3(3)
N(1)-C(2)-N(2)	110.9(2)	C(13)-C(14)-C(15)	120.6(3)
O(2)-C(4)-N(1)	123.9(3)	C(10)-C(15)-C(14)	120.1(3)
O(2)-C(4)-C(5)	124.5(3)		

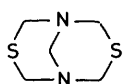
that the slightly developed sp^3 lone pair is *ap* to the C(2)-O(1) bond. However, this is a very small effect and this nitrogen's lone pair occupies just a slightly distorted *p* orbital. The sulphur lone pairs, however they are described, make no anomeric interaction with the exocyclic bonds at C(2). From the orientations of the exocyclic groups attached to C(2) one could conclude that oxygen and nitrogen lone pairs prefer to overlap with the anti-bonding orbital of a C-S bond than with that of a C-N bond. This is in accord with Stoddart's rough guide¹⁰ to the magnitude of anomeric interactions of an oxygen lone pair, which is based on solution conformational studies of 2-substituted tetrahydropyrans. However, such conclusions from crystallographic results should be based on data from a number of structures since, in some cases, the conformation favoured by anomeric interactions may be disfavoured by a more powerful steric or crystal-packing effect.

The crystallographic evidence for anomeric effects involving the C-S bond does not appear to have been examined. There are five reasonably accurate crystal structures,² (7)-(11),¹¹⁻¹⁵

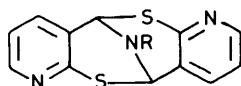
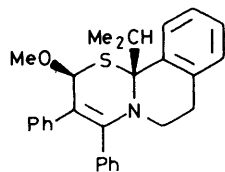
**Figure 1.** A plot of (6) looking down the O(1)-C(2) bond drawn with the graphics program SNOOPI⁸**Figure 2.** A plot of (6) looking down the N(2)-C(2) bond drawn with the graphics program SNOOPI⁸

where a nitrogen lone pair is within 20° of being *ap* to a C-S bond (Table 3). In all cases the C-S bond is lengthened to 1.85 Å or more. The C-N bond lengths lie in the narrow range 1.442-1.456 Å, slightly shorter (by 0.02 Å) than the normal value.⁹ The C-S bonds of (7)-(9) (1.85-1.86 Å) are probably more representative than the larger values of *ca.* 1.89 Å for (10) and (11). In (10), the dihydrothiophene ring is strained by steric factors and C(4)-C(5) is also long (1.563 Å). In the case of thiamine, (11), there is a second nitrogen, N(11), which may also be involved in an anomeric interaction with the C-S bond. This would be consistent with the rather short C(10a)-N(11) distance of 1.422 Å but N(11) is claimed to have planar bonding geometry. However, this depends on the N(11)-H atom being correctly positioned. It is not clear whether this was located from a difference Fourier map or placed geometrically, and no hydrogens were included in the final refinement.

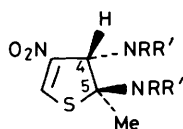
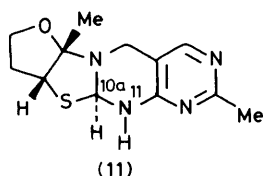
For the anomeric interaction of an oxygen lone pair with a C-S bond there appears to be a much smaller lengthening of the C-S bond. Thus for four accurate structures in which an oxygen lone pair is close to being *ap* to a C-S bond the average C-S bond length is only 1.818 Å and the C-O bonds are not especially short (Table 4). This suggests that the interaction of a nitrogen lone pair with a C-S bond is stronger than that of an oxygen lone pair and, furthermore, that the lengthening of the C-S bond in the title compound (6) is mainly due to the anomeric effect from nitrogen. This latter conclusion is supported by the structure of compound (15)¹⁹



(7)

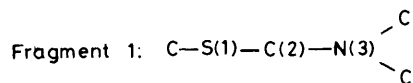
(8) R = C₆H₄-*p*-CN

(9)

(10) RR' = (-CH₂CH₂)₂O

(11)

Table 3. Parameters from *X*-ray crystallography for compounds containing the fragment 1 in which the nitrogen lone pair is approximately antiperplanar (*ap*) to the C-S bond



Compound	S(1)-C(2) (Å)	C(2)-N(3) (Å)	Deviation of the nitrogen lone pair from the <i>ap</i> position (°)	R-value
(7) ¹¹	1.850 ^a	1.453 ^a	7	0.039
	1.852 ^a	1.449 ^a	9	
(8) ¹²	1.855(6)	1.445(7)	1	0.063
(9) ¹³	1.860(2)	1.456(2)	18	0.036
(10) ¹⁴	1.892(3)	1.455(3)	5	0.041
(11) ¹⁵	1.895(2)	1.442(3)	14	0.030

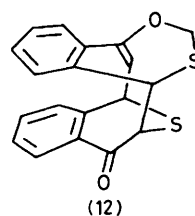
^a E.s.d.s ≤ 0.005 Å.

in which the hydroxy group attached to C(11) is oriented so that its lone pairs are *ap* to the S(1)-C(11) and N(4)-C(11) bonds. The S(1)-C(11) bond is slightly lengthened [1.832(2) Å] and the N(4)-C(11) bond is very similar in length to the equivalent bond in (6). The C(11)-OH bond is shortened to 1.397(6) Å, close to that in (6) (1.390 Å). (The position of the hydroxy hydrogen atom, which is crucial to this analysis, was located from a difference Fourier map.) Since the dominant anomeric interaction in (6) appears to be between the nitrogen lone pair and the σ* of the C(2)-S(1) bond it is possible that this also controls the orientation of the 2-methoxy group, which may prefer not to oppose the shortening of the C(2)-N(2) bond by an anomeric interaction with its anti-bonding orbital and so aligns its lone pairs *ap* to the other C(2)-S(1) and C(2)-N(1) bonds. The lengthening of the C-S bond to 1.880 Å by anomeric effects may be assisted by the conjugation of the sulphur with the acrylic ester function which should increase the polarisation of the C(2)-S(1) bond. A

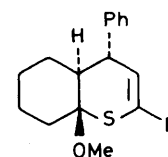
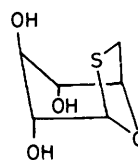
Table 4. Parameters from *X*-ray crystallography for compounds containing the fragment 2 in which an oxygen lone pair is approximately *ap* to the S(1)-C(2) bond

Compd.	Fragment 3: C-S(1)-C(2)-O(3)-C(4)			R-value
	S(1)-C(2) (Å)	C(2)-O(3) (Å)	S(1)-C(2)-O(3)-C(4) torsion angle (°)	
(9) ¹³	1.805(2)	1.423(2)	76	0.036
(12) ¹⁶	1.810(2)	1.437(3)	45	0.031
(13) ¹⁷	1.830 ^a	1.425 ^a	65	0.049
(14) ¹⁸	1.827(2)	1.423(2)	51	0.026

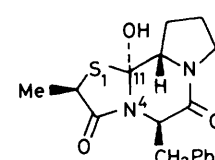
^a E.s.d.s ≤ 0.005 Å.



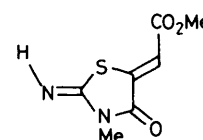
(12)

(13) R = C₆H₄-*p*-OMe

(14)



(15)



(16)

similar effect may be contributing to the long C-S bond in (10). The geometry of the rest of molecule (6) is similar to that of (16).²⁰

Experimental

Preparation of (6).—*NN'*-Dimethyl-*N*-phenylthiourea (3.0 g) and dimethyl acetylenedicarboxylate (2.4 g) were refluxed together in methanol (50 ml) for 3 h. The volume of solvent was reduced to 20 ml by evaporation *in vacuo* and the solution then cooled to -10 °C. The resulting precipitate was collected to yield *methyl (Z)-2-methoxy-3-methyl-2-(N-methylanilino)-4-oxothiazolidin-5-ylidene-ethanoate* (1.54 g, 29%), crystals (from methanol), m.p. 117–118 °C (Found: C, 55.7; H, 5.9; N, 8.6. C₁₅H₁₈N₂SO₄ requires C, 55.9; H, 5.6; N, 8.7%); ν_{\max} (CHCl₃) 1 690s, 1 612m, 1 600m, 1 497s, 1 440s, and 1 427m cm⁻¹; ¹H n.m.r. (τ, CDCl₃): Ar-H_s, 2.78 (s); 2-NCH₃, 7.07 (s); 2-OCH₃, 6.84 (s); 3-CH₃, 7.37 (s); =CH, 3.12 (s), and CO₂CH₃, 6.23 (s); ¹³C n.m.r. (δ, CDCl₃): 2-C, 115.3 (s); 4-C, 163.5 (s); 5-C, 146.2^a (s); 2-OCH₃, 51.8 (q); 2-NCH₃, 28.2 (q); 1'-C, 146.4^o; 2'-, 6'- and 3'-, 5'-C, 126.4 (d) and 128.6 (d); 4'-C, 125.7 (d); 3-CH₃, 27.5 (q); 5-CH, 113.4 (d); CO₂CH₃, 167.2 (s) and 51.8 (q) (^a assignments interchangeable); *m/z*,

Table 5. Fractional atomic co-ordinates and equivalent isotropic temperature factors for (6)

Atom	X/a	Y/b	Z/c	U _{eq.}
C(1)	-0.115 0(4)	0.214 4(3)	0.426 5(3)	0.058(2)
C(2)	0.145 6(3)	0.177 7(2)	0.389 2(2)	0.039(1)
C(3)	0.379 4(4)	0.135 7(3)	0.310 1(4)	0.058(2)
C(4)	0.320 6(3)	0.401 3(2)	0.573 7(3)	0.045(2)
C(5)	0.350 2(3)	0.301 7(2)	0.653 4(3)	0.042(1)
C(6)	0.454 2(4)	0.348 4(3)	0.788 3(3)	0.052(2)
C(7)	0.494 1(4)	0.252 1(3)	0.865 5(3)	0.050(2)
C(8)	0.660 5(6)	0.236 9(5)	1.082 8(4)	0.089(3)
C(9)	0.175 5(4)	0.405 9(3)	0.339 3(3)	0.057(2)
C(10)	0.106 0(3)	-0.049 3(2)	0.214 5(3)	0.042(2)
C(11)	0.187 7(4)	-0.150 1(3)	0.255 4(3)	0.053(2)
C(12)	0.100 6(5)	-0.294 4(3)	0.189 8(4)	0.066(3)
C(13)	-0.063 9(5)	-0.338 2(3)	0.086 4(4)	0.068(3)
C(14)	-0.142 5(4)	-0.238 7(4)	0.043 7(4)	0.069(2)
C(15)	-0.058 7(4)	-0.094 0(3)	0.107 3(3)	0.060(2)
N(1)	0.221 3(3)	0.330 7(2)	0.437 6(2)	0.041(1)
N(2)	0.191 2(3)	0.102 1(2)	0.277 9(2)	0.041(1)
O(1)	-0.037 2(2)	0.145 4(2)	0.336 2(2)	0.046(1)
O(2)	0.380 2(3)	0.530 5(2)	0.624 7(2)	0.060(2)
O(3)	0.602 8(3)	0.323 9(2)	0.999 1(2)	0.067(2)
O(4)	0.439 6(3)	0.124 2(2)	0.817 1(2)	0.057(1)
S(1)	0.237 9(1)	0.127 37(6)	0.548 15(7)	0.044 7(5)
H(11)	-0.0913	0.3105	0.4386	0.04
H(12)	-0.2408	0.1660	0.3797	0.05
H(13)	-0.0744	0.2024	0.5155	0.04
H(31)	0.4262	0.2281	0.3188	0.04
H(32)	0.4504	0.1166	0.3968	0.07
H(33)	0.3977	0.0795	0.2317	0.03
H(61)	0.5084	0.4431	0.8344	0.03
H(81)	0.6881	0.2951	1.1748	0.06
H(82)	0.5600	0.1754	1.0667	0.06
H(83)	0.7601	0.2162	1.0667	0.06
H(91)	0.1243	0.3404	0.2461	0.07
H(92)	0.0830	0.4491	0.3475	0.06
H(93)	0.2609	0.4795	0.3657	0.07
H(111)	0.3006	-0.1216	0.3297	0.02
H(112)	0.1636	-0.3563	0.2214	0.06
H(113)	-0.1221	-0.4394	0.0425	0.06
H(114)	-0.2650	-0.2618	-0.0255	0.06
H(115)	-0.1140	-0.0246	0.0781	0.04

(chemical ionisation with ammonia): 323 [(M + 1)⁺; 11], 216 [(M - 106)⁺, 100], 107 (17), 106(17), and 72 (30%).

Crystal Data for (6).—C₁₅H₁₈N₂O₄S, M_r = 322.4, triclinic, P $\bar{1}$, a = 8.344(1), b = 10.045(5), c = 10.905(2) Å, α = 106.52(3), β = 109.99(1), γ = 97.10(2)°, Z = 2, D_c = 1.34 g cm⁻³, μ(Mo-Kα) = 0.59 mm⁻¹, final R-value = 0.039 for 1981 reflections with I ≥ 3σ(I).

Crystal Structure Determination for (6).—A suitable crystal was obtained from a methanol solution stored at -10 °C. After preliminary Weissenberg photography, the crystal was mounted on a CAD-4F four-circle X-ray diffractometer and accurate cell parameters determined. X-Ray diffraction intensities were measured by ω-2θ scans out to θ = 27°. The data were transferred to a VAX 11/750 computer, Lorentz and

polarisation corrections applied, equivalent reflections merged and structure amplitudes derived for 2775 unique reflections. The structure was solved by the 'direct methods' program MULTAN 80²¹ and the positions of all non-hydrogen atoms were refined along with their isotropic temperature factors by full-matrix least-squares. After further blocked-matrix least-squares refinement using anisotropic temperature factors a difference Fourier map revealed the positions of all the hydrogen atoms. Weights for the final rounds of refinement were calculated from a Chebyshev series²² and the refinement converged at an R-value of 0.039. Crystallographic calculations were performed with the CRYSTALS²³ package. Final fractional atomic co-ordinates and equivalent isotropic temperature factors are given in Table 5. The anisotropic temperature factors and structure factor tables have been deposited in Supplementary Publication No. 23722 (21 pp).*

References

- 1 R. M. Acheson and J. D. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1981, 415, and references cited therein.
- 2 Information from the Cambridge Crystallographic Database.
- 3 K. Kato, *Acta Crystallogr.*, 1972, **B28**, 606.
- 4 W. G. Perdok and P. Terpstra, *Recl. Trav. Chim. Pays-Bas*, 1943, **62**, 687.
- 5 H. Meyer and G. Nagorsen, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 551.
- 6 S. David, G. de Sennyey, C. Pascard, and J. Guilhem, *J. Chem. Soc., Chem. Commun.*, 1981, 780.
- 7 E. Schaumann, S. Grabley, and G. Adiwidjaja, *Liebigs Ann. Chem.*, 1981, 264.
- 8 E. K. Davies, CHEMGRAF User Guide, Chemical Crystallography Laboratory, University of Oxford, 1981.
- 9 J. D. Dunitz, 'X-Ray Analysis and the Structure of Organic Molecules,' Cornell University Press, 1979, p. 338.
- 10 J. F. Stoddart, 'Stereochemistry of Carbohydrates,' Wiley-Interscience, 1971, p. 72.
- 11 K. A. Potekhin and E. N. Kurkutova, *Dokl. Akad. Nauk SSSR*, 1977, **235**, 813.
- 12 J. Becher, C. Dreier, and O. Simonsen, *Tetrahedron*, 1979, **35**, 869.
- 13 H. Preut, T. Eicher, D. Krause, and G. M. Sheldrick, *Acta Crystallogr.*, 1979, **B35**, 1285.
- 14 A. Mugnoli, C. Dell'Erba, G. Guanti, and M. Novi, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1764.
- 15 M. Shiro, H. Nakai, I. Makino, and A. Takamizawa, *Acta Crystallogr.*, 1978, **B34**, 3424.
- 16 D. H. Johansen, P. Groth, and K. Undheim, *Acta Chem. Scand., Ser. B*, 1980, **34**, 1.
- 17 S. V. Soboleva, O. A. D'Yachenko, L. O. Atovmyan, V. G. Kharchenko, and S. K. Klimenko, *Zh. Strukt. Khim.*, 1978, **19**, 499.
- 18 S. Takagi and G. A. Jeffrey, *Acta Crystallogr.*, 1978, **B34**, 816.
- 19 G. Lucente, F. Pinnen, G. Zanotti, S. Cerrini, W. Fedeli, and F. Mazza, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1499.
- 20 F. Adman, L. Jensen, and R. Warrender, *Acta Crystallogr.*, 1975, **B31**, 1915.
- 21 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, 'MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data,' Department of Physics, University of York, 1980.
- 22 J. R. Carruthers and D. J. Watkin, *Acta Crystallogr.*, 1979, **A35**, 698.
- 23 D. J. Watkin and J. R. Carruthers, CRYSTALS User Guide, Chemical Crystallography Laboratory, University of Oxford, 1981.

* For details of the Supplementary Publication Scheme see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.