TABLE 1: Physical and Spectral Data of ω, ω-Diacetylstyrene Derivatives

Derivaties	mp (°C)	max(nm)	IR (cm^{-1})	NMR (ppm)
H	168–170	282	1690	2.10 (*s*)
			1940	2.30 (*s*)
			1600	7.25 (*s*)
				7.30 (*s*)
p-CH_3	41–42	294	1690	2.33 (*s*)
			1640	2.40 (*d*)
			1600	7.25 (*s*)
				7.45 (s)
p-CH_3O	67–68	318	1690	2.30 (*d*)
			1640	3.85 (*s*)
			1580	6.90 (*s*)
				7.40 (*d*)
p-Cl	72–73	286	1700	2.30 (*d*)
			1640	7.35 (*s*)
			1600	7.40 (*s*)

gave white precipitate, whose recrystallization from CCl_4 afforded s-[2,2-diacetyl-1-(chloro)-phenylethyl]-thioglycolic acid (2.4g, 78.8 %): mp 115–116 °C: UV(CH_3OH) λ_{max} 286nm: IR(KBr disc) 1670, 2500–3300 cm^{-1}: NMR ($CDCl_3$) 1.90(3H, *s*), 2.35(3H, *s*), 3.00(2H, *s*), 4.20(1H, *d*), 4.80(1H, *d*), 7.30(4H, *s*).

Neutralization equivalent. Calculated for $C_{14}H_{15}O_4SCl$: 314.78. Found: 308.21. Anal. Calcd for $C_{14}H_{15}O_4SCl$: C, 53.44 %; H, 4.77 % Found: C, 53.12 %; H, 4.86 %

References

(1) E. D. Bergman, D. Ginsberg and R. Pappo, *Org. React.*, **10**, 179 (1955).

(2) R. K. Boeckman, Jr., *J. Amer. Chem. Soc.*, **96**, 6179 (1974).

(3) G. Stork and J. Singh, *J. Amer. Chem. Soc.*, **96**, 6181 (1974).

(4) R. A. Alarcon and J. Meinhofer, *Nature*, **233**, 250 (1971).

(5) H. Zoller, *Biochem. Pharmacol.*, **22**, 1171 (1973).

(6) R. W. Kims and D. R. Morris, *Biochem. Biophys. Acta*, **228**, 235 (1971).

(7) P. J. Conroy, J. T. Nodes, T. F. Slator and G. W. White, *Europ. J. Cancer*, **11**, 231 (1971).

(8) T. R. Kim and S. Y. Choe, *Bull. Korean Chem. Soc.*, **2**, 4, 125 (1981).

(9) T. R. Kim, T. S. Huh and I. S. Han, *J. Korean Chem. Soc.*, **25**, 6, 390 (1981).

(10) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957).

(11) E. P. Kohler and H. M. Chadwell, "Org. Syn., Coll." Vol. I,78, (1958).

(12) Handbook of Chemistry and Physics, CRC, 55, 72 (1974–1975).

The Crystal and Molecular Structure of Phthalylsulfacetamide

Whanchul Shin†, Young Chang Kim and Chung Hoe Koo

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151, Korea

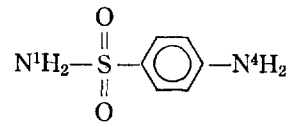
(Received September 10, 1983)

The crystal structure of phthalylsulfacetamide, one of the long-acting 'sulfa' drugs, has been determined by the X-ray diffraction methods. The crystal is monoclinic with cell dimensions of $a = 7.980(3)$, $b = 12.784(2)$, $c = 18.064(7)$ Å and $\beta = 112.94(2)°$, space group $P2_1/c$ and $Z=4$. The structure was solved by the direct methods and refined to $R = 0.048$. The sulfonylacetamide moiety is folded with respect to the central phenyl ring and the benzamide and benzoyl planes are nearly perpendicular to each other. This conformation is consistent with those of the relevant molecules containing the corresponding moieties. All of the molecules in the crystal lattice are connected by a three-dimensional hydrogen bonding network.

Introduction

Phthalylsulfacetamide (PSA), N^1-acetyl-N^4-phthalylsulfanilamide, is one of the long-acting 'sulfa' drugs where both N^1 and N^4 of sulfanilamide (I) are substituted.[1]

Although numerous crystal structures of 'sulfa' drugs usually designated for the N^1-substituted sulfanilamide derivatives have been determined,[2] only one crystal structure of an N^1, N^4-substituted 'sulfa' drug, succinylsulfathiazole (SST), has been determined to date.[3] We now report the first crystal structure of an N^4-phthalyl derivative of a 'sulfa' drug.



(I)

Experimental

Transparent, prismatic crystals of PSA(Sigma) were obtained by slow evaporation of an ethanol solution at room temperature. The crystals were monoclinic as determined from oscillation and Weissenberg photographs. The space group $P2_1/c$ was determined uniquely from the systematic absences. The unit cell parameters were determined by a least-squares fit of 2θ angles for 25 centered reflections measured with CuK_α radiation on an automated Rigaku AFC diffractometer. Crystal data are as follows:

$C_{16}H_{14}N_2O_6S$; Mol. Wt. 362.36, F(000)=752,
a=7.980(3), b=12.784(2), c=18.064(7)Å,
β=112.94(2)°, V=1697.0Å^3, Space group $P2_1/c$,
z=4, μ=19.01 cm^{-1}, d_m=1.40 g·cm^{-3} by flotation in $CH_3I/(CH_3CH_2)_2O$, d_c=1.42 g·cm^{-3}.

The reflection data from a crystal with dimensions of 0.2×0.3×0.6 mm were collected with graphite-monochromated CuK_α radiation using the 2θ-ω scan technique with the scan width of (1.0+0.5 tan θ)° in ω at a scan rate of 4°/min. The background was counted for 10 sec at each end of the scan range. Three standard reflections were monitored after each 50 data reflections and did not show any noticeable change during the data collection. The intensities were corrected for Lorentz and polarization effects and then converted to structure factors. Of the 2577 independent reflections measured within the range of $2° \leq 2\theta \leq 122°$, 345 were considered unobserved as defined by $F \leq 6\sigma(F)$. No correction for the absorption and extinction effects was made.

Structure Determination and Refinement

The structure was solved by direct methods using the program SHELX 76.[4] Three origin and twelve multisolution reflections were used for tangent refinement of 299 reflections with $E \geq 1.5$. From the initial E map calculated with the phase set having the highest reliability index, it was possible to identify the positions of 22 atoms among the 25 nonhydrogen atoms. One cycle of isotropic full-matrix least-squares refinement reduced the conventional R value($R=\sum||F_o|-k|F_c||/\sum|F_o|$ where k is a single scale factor) to 0.32 and a subsequent difference Fourier map gave the positions of the remaining nonhydrogen atoms. After one cycle of isotropic and one cycle of anisotropic refinements with all nonhydrogen atoms which lowered the R value to 0.084, all of the hydrogen atoms were found in a subsequent difference Fourier map. Futher two cycles of anisotropic refinement with all of the atom lowered the R value to 0.069, but some of the hydrogen atoms moved to unacceptable positions. At this stage it was noticed that a strong reflection, (-1 0 4), was significantly affected by extinction and this was excluded in further calculations. Using the weighting scheme final two cycles of anisotropic refinements converged the R value to 0.048 for the 2231 observed reflections. The weighted R_ω ($R_\omega=\sum\sqrt{\omega}||F_o|-k|F_c||/\sum\sqrt{\omega}|F_o|$) was 0.061. The function minimized in least-squares refinements was $\sum\omega(|F_o|-k|F_c|)^2$ where $\omega=1.0/(\sigma^2(F)+0.0042(F)^2)$ in the last cycle of refinement. Refinements were done using the program SHELX 76. The final difference Fourier map showed no peaks greater than 0.24 eÅ^{-3}. All of the atomic scattering factors were taken from the International Tables for X-ray Crystallography.[5] The final atomic parameters are tabulated in Table 1.*

Results and Discussion

A schematic drawing of the PSA molecule with the atomic

TABLE 1: Atomic Coordinates (×10^4, H atoms×10^3) and Thermal Parameters (Å^2×10^3)

	x	y	z	U_{eq}*/U_{iso}
S	−2392.2(9)	3855.8(5)	3013.6(4)	40
C(1)	−68(4)	3754(2)	3607(2)	36
C(2)	586(4)	3881(2)	4429(2)	46
C(3)	2426(4)	3811(3)	4891(2)	47
C(4)	3617(4)	3569(2)	4529(2)	37
C(5)	2952(4)	3473(3)	3691(2)	54
C(6)	1117(4)	3561(3)	3232(2)	53
O(1)	−3284(3)	4306(2)	3481(1)	54
O(2)	−2618(3)	4304(2)	2257(1)	55
N(1)	−3106(3)	2638(2)	2788(1)	41
C(7)	−3116(4)	1912(2)	3347(2)	44
O(3)	−2731(3)	2154(2)	4040(1)	61
C(8)	−3596(7)	827(3)	3041(3)	77
N(2)	5487(3)	3398(2)	4954(1)	41
C(9)	6325(3)	3120(2)	5739(1)	38
O(4)	5670(3)	3238(2)	6237(1)	51
C(10)	8209(3)	2698(2)	5958(1)	40
C(11)	9671(4)	3349(2)	6357(2)	54
C(12)	11430(4)	3017(3)	6542(2)	60
C(13)	11772(4)	2019(3)	6332(2)	61
C(14)	10333(4)	1347(3)	5965(2)	50
C(15)	8547(3)	1670(2)	5779(2)	40
C(16)	7012(4)	935(2)	5422(2)	44
O(5)	7476(3)	19(2)	5246(2)	67
O(7)	5455(2)	1175(1)	5310(1)	53
H(1)	−22(5)	404(3)	465(2)	57(11)
H(2)	279(4)	395(2)	541(2)	43(9)
H(3)	385(5)	326(3)	347(2)	62(9)
H(4)	70(5)	336(3)	263(2)	68(10)
H(5)	−322(5)	241(3)	239(2)	60(11)
H(6)	−407(5)	54(3)	338(2)	83(12)
H(7)	−407(6)	85(3)	258(3)	98(14)
H(8)	−253(5)	67(3)	290(2)	134(12)
H(9)	597(5)	326(3)	463(2)	65(10)
H(10)	946(5)	390(3)	654(2)	70(11)
H(11)	1,244(5)	351(3)	680(2)	91(10)
H(12)	1,295(5)	185(3)	637(2)	79(10)
H(13)	1,052(4)	64(3)	583(2)	86(10)
H(14)	643(5)	−48(3)	502(2)	87(10)

* $U_{eq}=\frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*(a_i, a_j)$

*Tables for the anisotropic temperature factors of the nonhydrogen atoms, the final observed and calculated structure factors and the bond angles involving the hydrogen atoms are available as supplementary materials from the author.

numbering scheme is given in Figure 1. The bond distances and angles are tabulated in Table 2. The corresponding molecular dimensions of sulfonylacetamide moieties in PSA, sulfacetamide[6] and sulfacetamide-caffeine salt[7] agree well within experimental error (3σ). The N(1)–C(7) amide bond is significantly longer than that in the peptide bond (1.374(4) Å as compared to 1.33Å).[8] This indicates that the $2p\pi$ electron of the nitrogen atom is delocalized through the N–S bond as well as the C–N bond. The N(2)–C(9) amide bond is also longer by *ca.* 0.02Å than the peptidyl N–C bond. The exocyclic C(4)–N(2) bond [1.403(3)Å] is nearly same as found in SST (1.406Å) but longer by 0.02Å than those usually found in sulfanilamide and its N^1–derivatives.[9-11] The fact that the C(4)–N(2) bond is shorter than the expected value of 1.43Å for a single bond between sp^2–hybridized atoms[8] is indicative of π delocalization between the amide group and the phenyl ring (I). However, there seems to be no π delocalization between the amide group and the phenyl ring (II) since the C(9)–C(10) bond shows a single bond character and the two planes are almost perpendicular (dihedral angle; 103°) to each other. In contrast, the amide plane is almost coplanar with the phenyl ring(I) to permit effective delocalization of the π electrons (dihedral angle; 22 °). The bond distances in the phthalylamino moiety of PSA agree within 2σ with those in N-(*p*-chlorophenyl) phthalamic acid (CPA).[12] The bond distances involving the sulfur atom are normally found ones in the sulfa drugs.[13] The two benzene rings are planar within experimental error with the maximum deviation of 0.023 (1)Å in each as listed in Table 3. The sulfonylacetamide moiety except the oxygen atom O(1) is also planar within 0.05Å. The carboxyl group shows a good planarity.

The conformation of the sulfacetamide part of the PSA molecule is similar to those of the sulfacetamide molecules in the free and caffeine-salt forms,[6,7] as can be seen in similarity of the corresponding torsion angles in Table 4. The sulfonylacetamide moiety, which is nearly coplanar, is in a folded rather than an extended form with respect to the phenyl ring. The dihedral angle between the two planar groups is 94 °.

From the analysis of the crystal structures of *ca.* 120 N^1–substituted arylsulfonamides A. Kalman *et al.* have observed that the rotations about the S–C (ring) and S–N bonds show a marked directional preference despite apparent lack of steric hindrance.[2] The majority of the rotamers have the torsion angles of τ_1[C(2)–C(1)–S–N(1)] = (50–100°) and τ_2[C(1)–S–N(1)–C(7)] = (60–90 °) which represent the folded form.

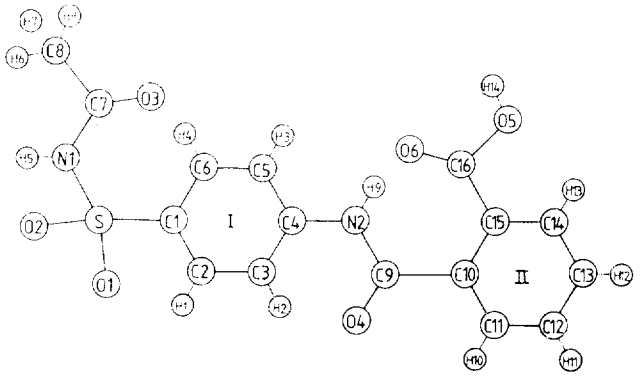


Figure 1. Atomic numbering scheme for phthalylsulfacetamide.

TABLE 2: Bond Distances (Å) and Angles (°) with e.s.d.'s in Parenthese

S –O(1)	142.1(3)	C(4)–N(2)	1.404(3)
S –O(2)	1.426(2)	N(2)–C(9)	1.358(3)
S –N(1)	1.653(3)	C(9)–O(4)	1.214(4)
N(1)–C(7)	1.374(4)	C(9) –C(10)	1.499(4)
C(7)–C(8)	1.488(5)	C(10)–C(11)	1.385(4)
C(7)–O(3)	1.207(4)	C(11)–C(12)	1.378(5)
S –C(1)	1.748(3)	C(12)–C(13)	1.388(5)
C(1)–C(2)	1.379(4)	C(13)–C(14)	1.379(4)
C(2)–C(3)	1.380(4)	C(14)–C(15)	1.393(4)
C(3)–C(4)	1.383(5)	C(15)–C(10)	1.404(4)
C(4)–C(5)	1.400(4)	C(15)–C(16)	1.478(4)
C(5)–C(6)	1.378(4)	C(16)–O(5)	1.305(4)
C(6)–C(1)	1.384(5)	C(16)–O(6)	1.218(4)
N(1)–H(5)	0.75(4)	C(6)–H(4)	1.03(4)
C(8)–H(6)	0.92(5)	N(2)–H(9)	0.84(4)
C(8)–H(7)	0.77(4)	C(11)–H(10)	0.82(4)
C(8)–H(8)	1.00(5)	C(12)–H(11)	0.99(4)
C(2)–H(1)	0.91(5)	C(13)–H(12)	0.94(4)
C(3)–H(2)	0.89(4)	C(14)–H(13)	0.96(4)
C(5)–H(3)	0.99(4)	O(5)–H(14)	1.00(4)
O(1)–S–O(2)	120.1(1)	C(4)–N(2)–C(9)	126.7(3)
O(1)–S–C(1)	108.9(1)	N(2)–C(4)–C(5)	116.9(3)
O(2)–S–C(1)	109.0(1)	N(2)–C(9)–O(4)	124.3(2)
O(1)–S–N(1)	108.9(1)	N(2)–C(9)–C(10)	113.8(3)
O(2)–S–N(1)	103.9(1)	O(4)–C(9)–C(10)	121.8(2)
C(1)–S–N(1)	105.2(1)	C(9)–C(10)–C(11)	118.4(2)
S –N(1)–C(7)	123.7(2)	C(9)–C(10)–C(15)	122.7(2)
N(1)–C(7)–C(8)	115.6(3)	C(10)–C(11)–C(12)	120.8(3)
N(1)–C(7)–O(3)	121.1(3)	C(11)–C(12)–C(13)	120.5(3)
C(8)–C(7)–O(3)	123.3(3)	C(12)–C(13)–C(14)	119.2(3)
S –C(1)–C(2)	121.2(3)	C(13)–(14)–C(15)	120.9(3)
S –C(1)–C(6)	118.5(2)	C(14)–C(15)–C(10)	119.5(2)
C(1)–C(2)–C(3)	120.7(3)	C(15)–C(10)–C(11)	119.0(3)
C(2)–C(3)–C(4)	119.6(3)	C(14)–C(15)–C(16)	120.9(3)
C(3)–C(4)–C(5)	119.3(3)	C(16)–C(15)–C(10)	119.6(2)
C(4)–C(5)–C(6)	120.7(3)	C(15)–C(16)–O(5)	114.3(2)
C(5)–C(6)–C(1)	119.2(3)	C(15)–C(16)–O(6)	122.1(3)
C(6)–C(1)–C(2)	120.3(3)	O(5)–C(16)–O(6)	123.7(2)
C(3)–C(4)–N(2)	123.8(3)		

TABLE 3: Deviations from Least-Squares Planes

(A) Phenyl ring (I)

0.1649X + 0.9810Y − 0.1023Z = 3.6769

C (1)* : −0.013 Å	C (2)* : 0.009	C (3)* : 0.009
C (4)* : −0.023	C (5)* : 0.020	C (6)* : −0.002
N (2) : −0.114	S : −0.021	H (1) : 0.03
H (2) : 0.10	H (3) : −0.07	H (4) : −0.13

(B) Phenyl ring (II)

−0.3229X − 0.3263Y + 0.8884Z = 6.9417

C (10)* : −0.023Å	C (11)* : 0.010	C (12)* : 0.011
C (13)* : −0.019	C (14)* : 0.006	C (15)* : 0.015
C (16) : 0.108	O(5) : 0.070	O(6) : 0.218
C (9) : −0.087	H (10) : 0.14	H (11) : −0.02
H (12) : −0.19	H (13) : 0.03	

*Atoms used to define the planes.

TABLE 4: Selected Torsion Angles (°) in PSA and Relevant Molecules

	I	II	III	IV	V*	
τ_1	77.9	66.0	85.1	75.4		
τ_2	65.1	55.8	70.0	87.7		
τ_3	−172.9	−172.0	176.5			
τ_4	21.8				−27.0	4.4
τ_5	163.2				172.1	177.2
τ_6	−78.5				−84.9	−90.3
τ_7	−5.2				−2.1	5.1
τ_8	176.8				−0.1	168.6

τ_1=C(2)−C(1)−S−N(1) , τ_2=C(1)−S−N(1)−C(7)
τ_3=S−N(1)−C(7)−C(8) , τ_4=C(9)−N(2)−C(4)−C(3)
τ_4=C(10)−C(9)−N(2)−C(4) , τ_6=C(15)−C(10)−C(9)−N(2)
τ_7=C(16)−C(15)−C(10)−C(9) , τ_8=O(5)−C(16)−C(15)−C(10)

I: present study; II: sulfacetamide[6]; III: sulfacetamide-caffein salt[7] IV: succinylsulfathiazole[3]; V: N-(p-chlorophenyl) phthalamic acid[10] * two molecules in the asymmetric unit.

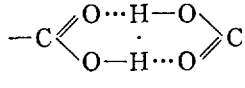
TABLE 5: Hydrogen Bonds in Phthalylsulfacetamide

a	*b*	*c*	*a*–*c*(Å)	*b*–*c*(Å)	<*abc*(°)	Position of *c*
N(1)—H(5)···O(4)		2.815	2.09	163	$-1+x, \frac{1}{2}-y, -\frac{1}{2}+z$	
N(2)—H(9)···O(3)		3.017	2.25	153	$1+x, y, z$	
O(5)—H(14)···O(6)		2.642	1.65	172	$1-x, -y, 1-z$	

This observation strongly indicates that there is some kind of common intramolecular effect at work since the fragments are in quite different environments from crystal to crystal. From the present study it has been confirmed that substitution of a bulky group at the N^4 position does not exert any long range effect on the conformational property of arylsulfonamides.

The conformation of the phthalylamino moieties in both the PSA and CPA molecules are very similar especially in that the benzamide planes are nearly perpendicular to the benzoyl planes. The dihedral angles between the amide plane and the phenyl rings are 22° and 103° for the phenyl rings (I) and (II) respectively. This conformation is quite different from that of phthalic acid and may be a characteristic solid state conformation for phthalamic acid whose crystal structure has not been reported yet. In crystalline phthalic acid, the two keto oxygen atoms are juxtaposed and the two carboxyl groups are almost coplanar with the dihedral angle of only 20°.[14]

There are three unique hydrogen bonds in the structure as tabulated in Table 5. The molecules are connected by the two kinds of the N—H···O=C hydrogen bonds between the phthalylamide and sulfonylamide moieties in an alternating fashion as shown in Figure 2. These hydrogen bonds make two-dimensionally hydrogen-bonded molecular sheets. The molecules related by the centers of symmetry at (1/2,1/2, 0) and (1/2, 0, 1/2) form molecular dimers through a



hydrogen bonding scheme.

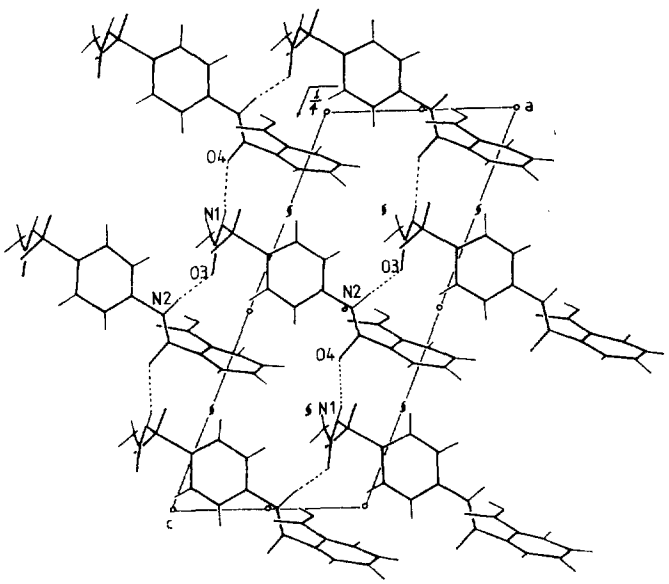


Figure 2. Crystal packing diagram projected along the *b* axis.

These hydrogen bonds interweave the molecular sheets to form a three-dimensional hydrogen bonding network. Sulfonyl oxygen atoms are not involved in the hydrogen bonds.

Acknowledgement. This research was supported by Grant No. ED82-312 of the Ministry of Education.

References

(1) N. Anand, "Antibiotics," (J. W. Cocoran and F. E. Hahn eds.) Vol. 3,pp. 668–698, Springer, Berlin, 1975.
(2) A. Kalman, M. Czugler, and G. Argay, *Acta Cryst* **B37,** 868–877 (1981).
(3) P. N. Rodier, A. Chauvet and J. Masse, *Acta Cryst.* **B34,** 218–221 (1978).
(4) G. M. Sheldrick, SHELX. A Program for X-ray Crystal Structure Determination. University Chemical Laboratory, Cambridge, England, 1976.
(5) International Tables for X-ray Crystallography. Vol. IV. Kynoch Press, Birmingham, England, 1974.
(6) A. K. Basak and S. K. Mazumdar, *Cryst. Struct. Comm.* **11,** 1609–1616 (1982).
(7) P. J. M. Leger, S. Alberola, and A. Carpy, *Acta Cryst.* **B33,** 1455–1459 (1977).
(8) Molecular Structures and Dimensions, Vol. A1, Utrecht: Oosthoek, 1972.
(9) G. P. Bettinetti, F. Giordano, A. La Manna, G. Giuseppetti and C. Tadini, *Cryst. Struc. Comm.* **11,** 821–828 (1982).
(10) G. J. Kruger nad G. Gafner, *Acta Cryst.* **B27,** 326–333 (1971).
(11) C. H. Koo, Y. J. Chung, H. S. Shin and J. S. Suh, *Bull. Korean. Chem. Soc.,* **3,** 9 (1982).
(12) P. J. P. Mornon, *Acta Cryst.,* **B26,** 1985–1999 (1970).
(13) M. Alleaume, A. Gulko, M. Kapon and R. E. Marsh, *Acta Cryst.,* **B32,** 669–682 (1976).
(14) O. Ermer, *Helv. Chim. Acta,* **64,** 182, 1902–1909 (1981).