Monatshefte für Chemie 130, 1129–1136 (1999)

Monatshefte für Chemie
Chemical Monthly

Synthesis and Structural Characterization of the Two Epimeric O-Cholesteryl-O-phenyl-*N*-phenylphosphoramidates

Raymundo Cea-Olivares[1,*], **Marcela López-Cardoso**[2], and **Rubén A. Toscano**[1]

[1] Instituto de Química, Universidad Nacional Autónoma de México, México 04510, D.F.
[2] Centro de Investigaciones Químicas, Universidad Autónoma de Morelos, Cuernavaca, México

Summary. O-Cholesteryl-O-phenyl-*N*-phenylphosphoramidate was synthesized as intermediate for the stereoselective synthesis of organophosphates and phosphorothioates. Single crystal X-ray diffraction discerned four independent P-epimeric phosphoramidates cocrystallizing in the triclinic P1 space group. They were found to be selectively paired in the crystal forming *pseudo*-centrosymmetric dimers *via* hydrogen bonds between the amide group of one epimer and the phosphinoyl group of the other.

Keywords. P-Epimeric phosphoramidates; O-Cholesteryl derivatives; X-Ray structure determination.

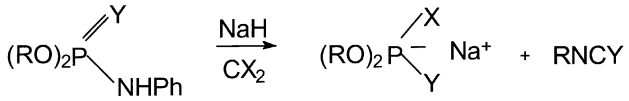
Synthese und strukturelle Charakterisierung zweier epimerer O-Cholesteryl-O-phenyl-*N*-phosphoramidate

Zusammenfassung. O-Cholesteryl-O-phenyl-*N*-phosphoramidat wurde als Zwischenprodukt für die stereoselektive Synthese von Organophosphaten und Phosphorthioaten dargestellt. Die Einkristallröntgenstrukturanalyse ergab vier unabhängige P-epimere Phosphoramidate, die in der triklinen Raumgruppe P1 kristrallisieren. Sie liegen im Kristall selektiv gepaart in From von *pseudo*-zentrosymmetrischen Dimeren vor, die über Wasserstoffbrücken zwischen der Amidgruppe des einen Epimers und der Phosphinoylgruppe des zweiten aneinander gebunden sind.

Introduction

Phosphoramidates have found considerable biological interest as anticancer agents [1]. Besides, they have been widely used in organic synthesis as the key intermediate in the *Wadsworth-Emmons* reaction [2], and their treatment with base followed by CO_2, CS_2, or CSe_2 provides a general method to synthesize organophosphates and phosphorothioates. *Stec et al*. [3] have shown that replacement of the anilino group by O, S, or Se proceeds with retention of configuration, thus allowing the stereospecific synthesis of phosphates and phosphorothioates containing chiral phosphor atoms [4]. With this aim in mind we present in this

* Corresponding author



X=O, S, Se; Y=O, S,Se

Scheme 1

work the synthesis and structure characterization of O-Cholesteryl-O-phenyl-*N*-phenylphosphoramidate.

Results and Discussion

Spectroscopy

The mass spectrum confirms the formula proposed for compound **3** by observation of the molecular ion at $m/z = 617$ (M^+). Beside the resonance signals ascribed to the cholesteryl moiety (0.67–2.6, 4.4, and 5.3 ppm) and to phenyl groups (6.8–7.3 ppm), the most striking feature in the ^{1}H NMR spectrum was the couple of doublets at $\delta = 5.8$ ppm ($^2J_{PH} = 9.6$ Hz) whose total area accounts for a single hydrogen. It is assigned to the amide proton from its coupling with the phosphorous atom and suggest the presence of an equimolecular mixture of epimers at P. On trying to solve this ambiguity, the ^{31}P NMR spectrum was of limited utility, since it showed a single signal at -3.11 ppm, although diastereoisomeric phosphates display ^{31}P shift differences in the order of 0.06 ppm [5, 6]. In order to clarify this point we decided to perform a single crystal structure determination of **3**.

Structure

The solid state structure agrees with conclusions obtained from NMR data in solution, indicating the presence of both diastereoisomeric phosphoramides of **3**. The crystal used for the X-ray measurement was found to contain four crystallographically independent molecules, *i.e.* the two pairs of epimers at the P-atom which differ in some conformational features as well as in bond lengths and, to some lesser extent, bond angles. The ORTEP view of the molecules showing also the absolute configuration is displayed in Fig. 1. Selected bond lengths, angles, and other significant data are listed in Table 1.

The geometry of the phosphoramidate group is similar to that observed in related compounds [7–9]. The four values of the P=O bond lengths are not significantly different (within experimental error) from the mean value of 1.459(4) Å. The P1–O2 (phenyl) bonds are significantly shorter than those of the typical single bond P1–O3 (cholesteryl), possible due to some resonance effect. The phosphorus tetrahedron in all four molecules is deformed as usually observed showing increased O1–P1–O2 and O1–P1–O3 angles and compressed O2–P1–O3 angles.

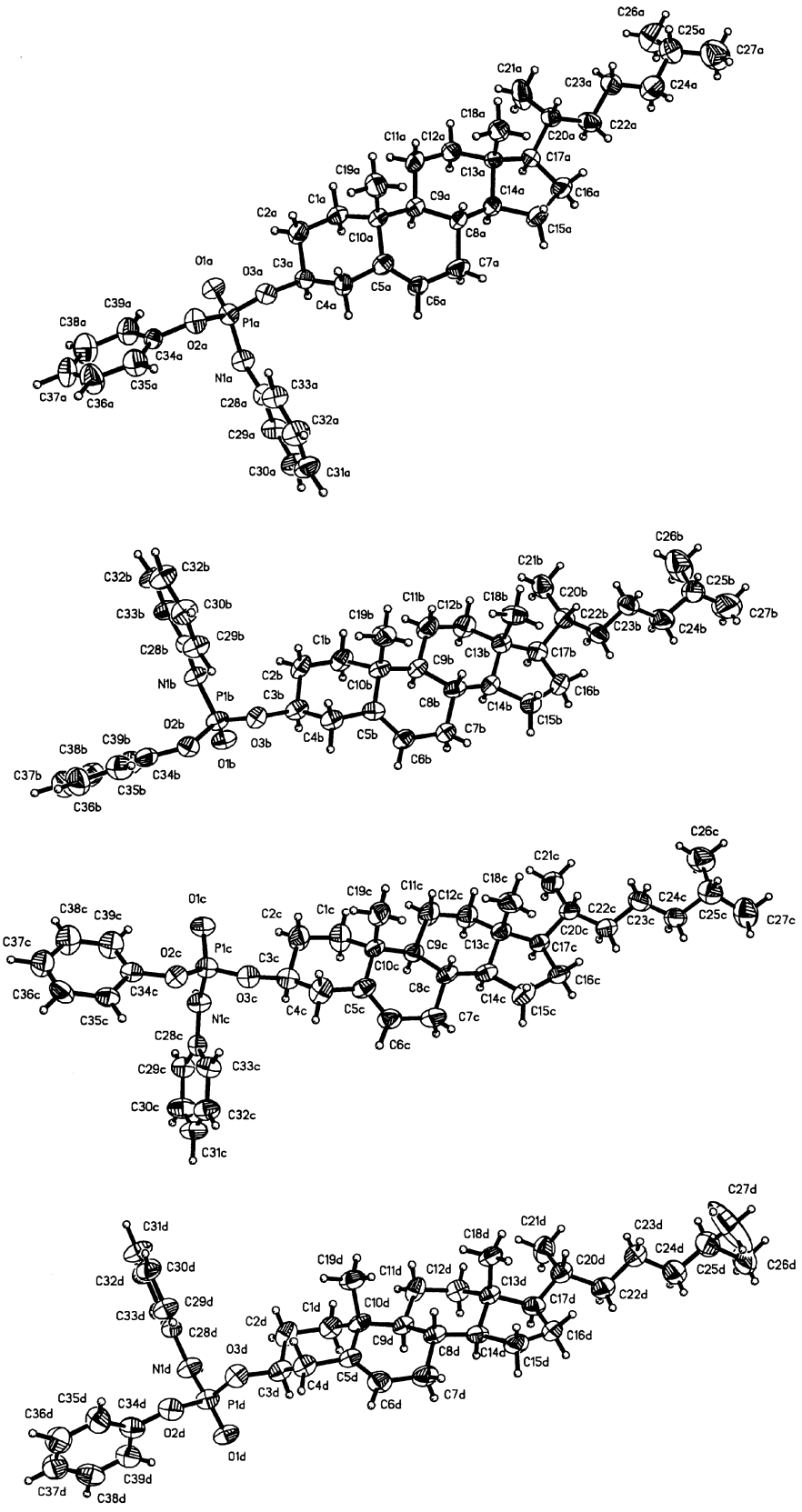


Fig. 1. ORTEP-like view of the four independent molecules; thermal ellipsoids at 30% probability level

Table 1. Selected geometric parameters (distance/Å, angle/°)

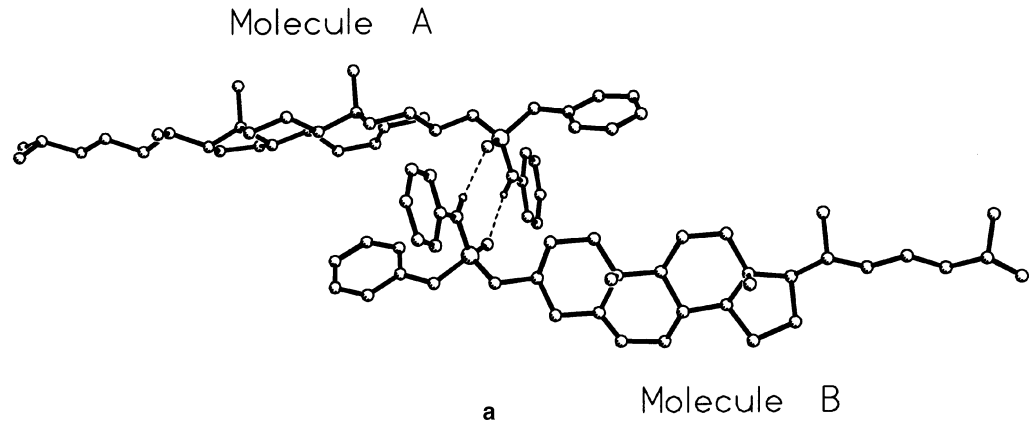
Bond	Molecule A	Molecule B	Molecule C	Molecule D
P1=O1	1.462(5)	1.464(6)	1.471(5)	1.470(6)
P1–O2	1.594(5)	1.590(6)	1.577(6)	1.588(6)
P1–O3	1.551(5)	1.543(6)	1.555(6)	1.571(6)
P1–N1	1.615(7)	1.622(6)	1.629(7)	1.621(7)
Angle	Molecule A	Molecule B	Molecule C	Molecule D
O1–P1–O2	115.1(3)	115.9(3)	115.6(3)	116.5(3)
O1–P1–O3	115.7(3)	115.4(3)	116.6(4)	115.1(4)
O2–P1–O3	96.1(3)	96.8(3)	95.5(3)	95.5(3)
O1–P1–N1	110.4(3)	109.9(3)	110.4(3)	110.7(3)
O2–P1–N1	108.6(3)	106.9(3)	108.3(3)	107.9(4)
O3–P1–N1	110.1(3)	111.2(3)	109.5(3)	110.0(4)
C28–N1–P1	130.0(5)	129.8(5)	129.0(5)	131.8(5)
O1–P1–O3–C3	−54.9(6)	35.8(6)	−65.7(7)	38.4(6)
N1–P1–O3–C3	71.1(6)	−90.2(6)	60.4(7)	−87.6(6)
O2–P1–O3–C3	−176.6(5)	158.7(5)	172.1(6)	161.2(2)
O1–P1–N1–C28	173.1(7)	−175.6(6)	−175.6(7)	−175.1(8)
C17–C20–C22–C23	−176.1(8)	−171.6(9)	−170.0(9)	−164.4(9)
C22–C23–C24–C25	175(1)	−177(1)	−176(1)	−178(1)

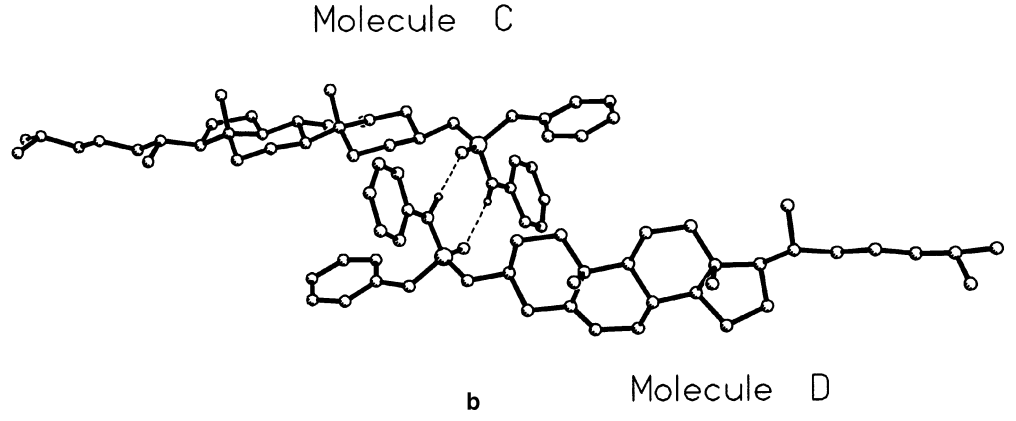
Table 2. Hydrogen bonding data (distance/Å, angle/°)

D–H···*A*	*D*–H	H···*A*	*D*···*A*	(*D*H*A*)
N1A–H1A···O1B	0.81(5)	2.01(5)	2.818(6)	174(8)
N1B–H1B···O1A	0.77(5)	2.10(5)	2.863(5)	171(8)
N1C–H1C···O1D	0.80(4)	2.04(5)	2.824(6)	168(8)
N1D–H1D···O1C	0.84(4)	1.97(5)	2.798(6)	169(7)

X-Ray results (Table 2) show that two pairs of hydrogen bonded P-epimers form pseudo-centrosymmetric dimers (Fig. 2a,b). The *syn*-coplanar conformation of N–H and P=O groups required for dimerization results in an enlargement of the P1–N1–C28 bond angle (Table 1). In the crystal, dimer packets are stacked alternately along the *a* direction, causing in turn the stacking of molecules A and C and B and D, respectively, into parallel infinite columns (Fig. 2c).

The side chains afford the most significant differences among the otherwise very similar cholesteryl moieties, and although the full extended conformation is the common feature, significant differences in the torsion angle C17–C20–C22–C23 are observed. In molecule D, the orientational disorder observed at the terminal isopropyl group is probably precluded by steric hindrance around the C27 carbon atom and C21C ($2+x$, $-1+y$, $-1+z$) and C15B ($1+x$, $-1+y$, z), caused by neighboring molecules, forcing the terminal C25–C27 bond to point into two different directions (C23D–C24D–C25D–C27D: 77(3); C23D–C24D–C25D–C26D7: −65(3)°).





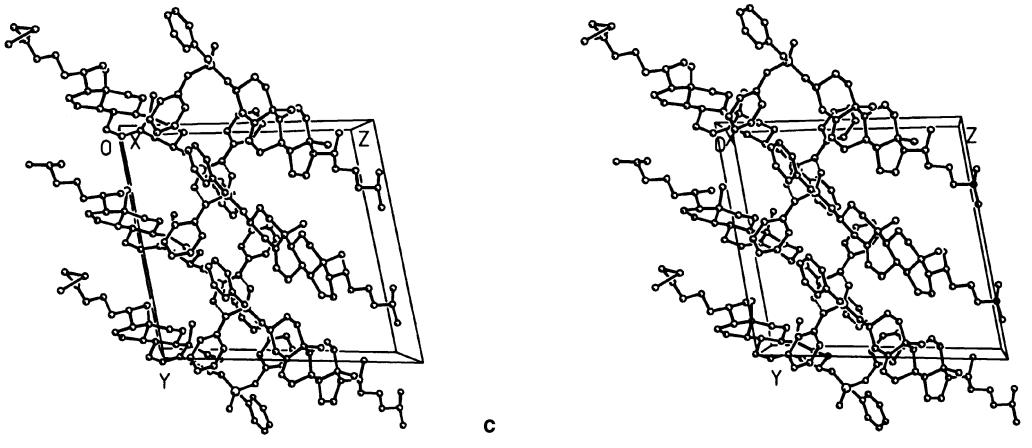


Fig. 2. Dimers and stereoscopic view of the unit cell

Experimental

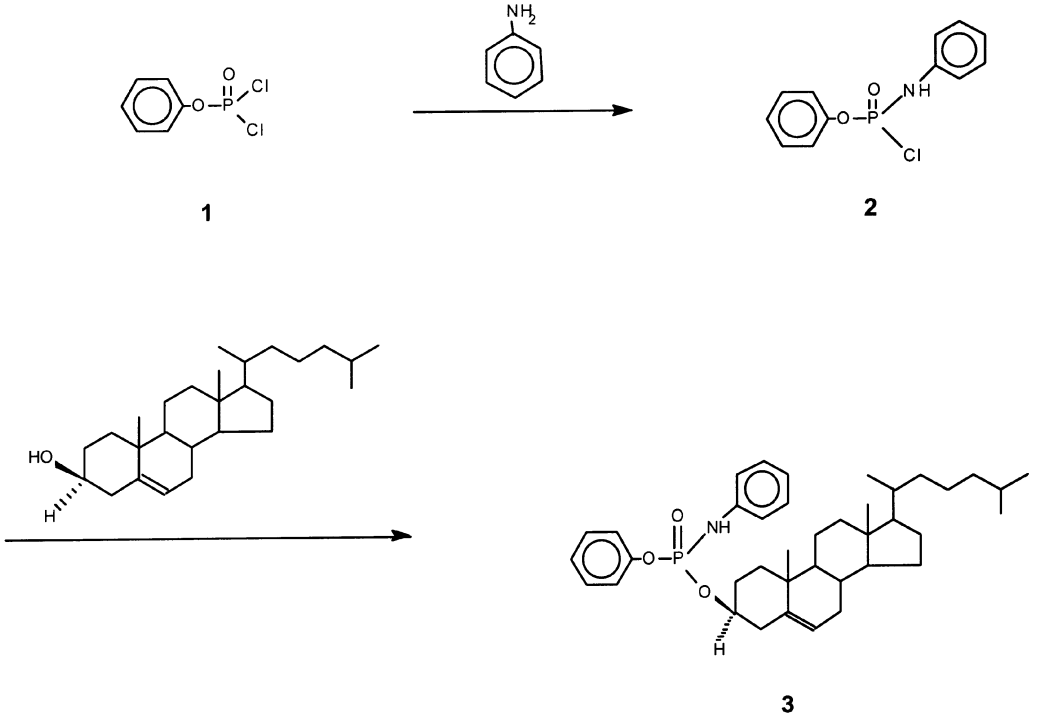
Synthesis and NMR spectroscopy

Column chromatography and thin layer chromatography (TLC) were performed on Kieselgel 60 (230–400 mesh) and on HPTLC plates from E. Merck. All reagents and solvents were of commercial grade and were thoroughly dried and distilled before use. The NMR spectra were recorded on a Varian VXR-300 spectrometer operating at 299.949 MHz for ^{1}H, 75.3 MHz for ^{13}C, and 121.4 MHz for ^{31}P using $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to *TMS* (internal) for ^{1}H and ^{13}C and 85% H_3PO_4 (external) for ^{31}P. Mass spectroscopy was performed on a Jeol JSM-SX 102A instrument by means of the FAB technique. An elemental analysis gave satisfactory results.

O-Cholesteryl-O-phenyl-N-phenylphosphoramidate (**3;** $C_{39}H_{56}O_3PN$)

A solution of 3.86 g (10 mM) cholesterol in 10 cm^3 of pyridine was added dropwise to a freshly prepared solution of 2.94 g (11 mM) *O*-phenyl-*N*-phenylphosphoramidochloridate (**2**) [10] in 10 cm^3 of pyridine at 0°C. After completion of the addition, the temperature was slowly raised to 25°C, and the mixture was allowed to react during 3 h under an N_2 atmosphere. Pyridine was evaporated, and the residue was coevaporated with toluene and finally extracted with CH_2Cl_2. The combined extracts were evaporated, and the residue was chromatographed on a column (hexane: AcOEt = 85:15). The column chromatography was followed by TLC. The fractions containing product **3** were pooled and evaporated to give 4 g of a white solid (64.8%).

^{31}P NMR ($CDCl_3$, δ, 121.4 MHz): −3.11 ppm; ^{1}H NMR ($CDCl_3$, δ, 299.949 MHz): 0.67 (s, 3H), 0.82 (d, $J = 6.6$ Hz, 6H), 0.91 (d, $J = 6.3$ Hz, 3H), 1.01 (s, 3H), 1.01–2.6 (m, 28H), 4.4 (m, 1H), 5.3



Scheme 2

Table 3. Data collection parameter for **3**[a]

Space Group	P1
Cell constants	$a = 14.370(2)$ Å
	$b = 15.880(2)$ Å
	$c = 17.904(2)$ Å
	$\alpha = 77.360(1)^\circ$
	$\beta = 66.750(1)^\circ$
	$\lambda = 83.270(1)^\circ$
Cell volume	3660.7(8) Å^3
Molecular formula	$C_{39}H_{56}NO_3P$
Molecular weight	617.82 g
Density (calc; $Z = 4$ mol/cell)	1.121 g · cm^{-3}
Radiation employed	MoK_α($\lambda = 0.71073$ Å)
Absorption coefficient	0.110
Data collection range	$3 \leq 20 \leq 50^\circ$
Total data collected	13406
$R = \sum(\|F_o\| - \|F_c\|)/\sum\|F_o\|$	0.0668[b]
$wR = (\sum(w\|F_o^2 - F_c^2\|)^2/\sum(wF_o^2)^2)^{1/2}$	0.1905
Weights used	$w = (\sigma^2(F_0^2) + (0.0740P)^2 + 0.7731P)^{-1}$,
	$P = (F_0^2 + 2F_c^2)/3$

[a] Coordinates were deposited at the Cambridge Crystallographic Data Center (CDC-No. 114651);
[b] Conventional *R*-factor based on *F*, with threshold expression of $F_0^2 \int 2\sigma(F_0^2)$

(dd, $J = 4.8$, 5.1 Hz, 1H), 5.8 (dd, $J = 9.6$, 9.3 Hz, 1H), 6.8–7.3 (m, 10H) ppm; ^{13}C ($CDCl_3$, δ, 75 MHz): 11.9, 18.7, 19.3, 21.1, 22.5, 22.8, 23.9, 24.3, 28.0, 29.6, 31.9, 35.8, 36.2, 36.4, 37.0, 39.5, 39.8, 39.9, 42.4, 50.1, 56.2, 56.7, 78.7, 117.9, 118.0, 120.5, 122.0, 123.1, 124.9, 129.2, 129.5, 139.5, 150.5 ppm; MS: $m/z = 617$ (M^+); m.p.: = 162–163°C.

X-Ray diffraction analysis

Crystals of *O*-Cholesteryl-*O*-phenyl-*N*-phenyl-phosphoramidate suitable for X-ray analysis were obtained by vapor diffusion of hexanes into a chloroform solution. Data were collected with a Siemens P4/PC diffractometer operating with the XSCANS software package [11]. The crystal was centered using data in the $15 \leq 20 \leq 25^\circ$ range, and examination of cell constants and the *Niggli* matrix [12] clearly showed **3** to crystallize in a primitive, triclinic lattice.

Details of the data collection are summarized in Table 3. The intensity data were corrected for *Lorentz* and polarization effects but not for absorption. The structure was solved by direct methods [13] and refined [14] by block-matrix least-squares procedure based on F^2. Conversion of the heavy atoms to anisotropic positions and inclusion of the hydrogen atoms at idealized positions (except for those bonded to N-atoms which were refined in a restrained fashion) with a common isotropic temperature factor $U = 0.08$ Å^2 resulted in a refinement of the overall structure to final $R(F)$ and $wR(F^2)$ factors as listed in Table 1.

Acknowledgments

We thank the *Mexican National Council of Science and Technology* (CONACyT, Grant No. 47-3100-5-1428P-N) for financial support.

References

[1] Pankiewicz K, Kinas R, Stec WJ, Foster AB, Jarman M, Van Maanen JMS (1979) J Am Chem Soc **101**: 7712
[2] Wadsworth WS, Emmons WD (1964) J Org Chem **29**: 2816
[3] Stec WJ, Okruszek A, Lesiak K, Uznanski B, Michalski J (1976) J Org Chem **41**: 227
[4] Frey PA (1982) Tetrahedron **38:** 1541
[5] Gorestein DG, Rowell R (1979) J Am Chem Soc **101**: 4925
[6] Gorestein DG, Rowell R, Findlay J (1980) J Am Chem Soc **102**: 5077
[7] Du Plessis MP, Modro TA, Nassimbeni LR (1982) Acta Cryst **B38**: 1504
[8] Du Plessis MP, Modro TA, Nassimbeni LR (1985) J Crystallogr Spectrosc Res **15**: 663
[9] Blaszczyk J, Wieczorek MW, Okruszek AO, Sierzchala A, Kobylanska A, Stec WJ (1996) J Crystallogr Spectrosc Res **26**: 33
[10] Zielinski WS, Lesnikowski Z (1976) Synthesis 185
[11] Siemens (1993) XSCANS Users Manual Version 2.1 Siemens Analytical X-Ray Instruments Inc., Madison, Wisconsin, USA
[12] Roof RB (1969) A Theoretical Extension of the Reduced Cell Concept in Crystallography. Report LA-4038, Los Alamos Scientific Laboratory
[13] Altomare A, Cascarano G, Giacovazzo C, Guagliardi A, Burla MC, Palordi G, Camalli M (1994) J Appl Cryst **27**: 435
[14] Sheldrick GM (1997) SHELXL97. Program for Refinement of Crystal Structures. University of Göttingen, Germany

Received December 11, 1998. Accepted (revised) February 17, 1999