Synthesis, crystal and molecular structure of methyl[(4-acetamidophenyl)sulfonyl]carbamate, precursor of herbicide Asulam

Patricio Castillo, Ariel Gómez,* Heiddy Márquez, Ana M. Plutín,** Margarita Morales,** Ramón Pomés,* Yolanda I. Rodríguez,** Graciela Punte*** y Gustavo Echeverría.****

Laboratorio de Investigaciones Aplicadas, Dpto. de Ciencias Nucleares, Escuela Politécnica Nacional, P.O. Box 17-01-2759, Quito, Ecuador. E-mail: pesd@yahoo.com. *Laboratorio de Rayos X, Centro Nacional de Investigaciones Científicas, P.O. Box 6414, Ciudad de La Habana, Cuba. **Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de La Habana, Cuba. ***LANADI e IFLP, Departamento de Física, Universidad Nacional de La Plata, La Plata, Argentina. E-mail: gustavo@ayelen.fisica.unlp.edu.ar. ****Facultad de Ingeniería, Departamento de Físico-Matemática, Universidad Nacional de La Plata, La Plata, Argentina.

Recibido: 24 de octubre de 2000. Aceptado: 12 de octubre de 2001.

Palabras clave: estructura, síntesis, sulfonilcarbamato, herbicida, cristal.
Key words: structure, synthesis, sulfonylcarbamate, herbicide, crystal.

RESUMEN. El metil-[(4-aminofenil)sulfonil]carbamato es conocido comercialmente como Asulam, el nombre más común de un herbicida sistémico y sinergístico, que es incorporado a las plantas a través de sus hojas y de sus raíces y que se utiliza extensamente contra las malezas y los helechos en el cultivo de las gramíneas, los cítricos, el plátano y la caña de azúcar, entre otros. La obtención industrial de este compuesto carbámico incluye la hidrólisis básica del metil-[(4-acetamidofenil)-sulfonil]carbamato. En este trabajo se presenta un método sencillo y convencional para la síntesis del intermediario del Asulam y la caracterización de su estructura cristalina y molecular, mediante el empleo de técnicas de Difracción de Rayos-X y de espectroscopia IR, NMR ^{1}H y ^{13}C. El precursor sintético será utilizado como sustrato de una enzima hidrolítica para el desarrollo de un nuevo procedimiento de obtención biocatalítica del herbicida Asulam. Por tanto, determinar su estructura ayudará no solo a establecer las características físicas de su conformación más estable, sino que permitirá predecir la compatibilidad entre las posibles enzimas a utilizar y el sustrato, de acuerdo con las propiedades de sus centros catalíticos. El compuesto fue sintetizado a partir de la 4-acetamidofenilsulfonamida y el cloroformiato de metilo, en presencia de K_2CO_3 anhidro y acetona, extraído con éter etílico y recristalizado desde metanol. El producto final se obtuvo como un sólido cristalino, con un rendimiento del 62 %. Los cristales de este compuesto se obtuvieron mediante evaporación lenta desde una disolución de metanol. Los cristales son monoclínicos, el grupo espacial $P2_1/n$; a = 8,681(4), b = 8,174(3), c = 17,583(3) Å, ß = 92,40(1)°, Z = 4. El empaquetamiento cristalino es asistido por un arreglo bidimensional de puentes de hidrógeno. Esta información podría emplearse en la modelación del enlazamiento de la molécula del intermediario al centro catalítico de la enzima hidrolítica que se utilice.

ABSTRACT. The methyl[(4-aminophenyl)sulfonyl]carbamate is commercially known as Asulam. It is the most common trade name for a systemic and synergistic herbicide, which is incorporated by the plants through their foliage and roots, and is extensively used against weeds and brackens in the cultivation of gramineous, citric, banana and sugarcane, among others. The industrial procedure for obtaining this carbamic compound includes the base-catalyzed hydrolysis of the methyl[(4-acetamidophenyl)sulfonyl]carbamate. In this work a simple and conventional method for the synthesis of the Asulam intermediate and the characterization of its crystal and molecular structure utilizing X-Ray Diffraction and IR, NMR ^{1}H and ^{13}C spectroscopic techniques is presented. The synthetic precursor will be used as substrate of the hydrolytic enzyme in the development of a new biocatalytic preparation of the herbicide Asulam. Therefore, the knowledge of its structure will help not only to define the physical characteristics of its more stable conformation, but also will allow predicting the compatibility between the possible enzymes to be used and the substrate, according to the properties of their catalytic centers. The title compound was synthesized from 4-acetamidophenylsulfonamide and methylchloroformate in the presence of anhydrous K_2CO_3 and acetone, extracted with ethyl ether and recrystallized from methanol. The studied compound was obtained as crystalline solid in 62 % yield. The crystals of intermediate were grown by slow evaporation from methanol solution. They are monoclinic, space group $P2_1/n$; a = 8.681(4), b = 8.174(3), c = 17.583(3) Å, ß = 92.40(1) °, Z = 4. The molecular packing shows a bidimensional hydrogen bond network. These results might be employed for modeling the linking of intermediate molecule to the catalytic center of hydrolytic enzime, which will be used.

INTRODUCTION

The methyl[(4-acetamidophenyl)-sulfonyl]carbamate (I) is a precursor in the synthesis of Asulam.[1] The latter is the most common trade name for the herbicide methyl[(4-aminophenyl)sulfonyl]carbamate (II) (Fig. 1), which is incorporated by the plants through their foliage and roots,[2] presents very low toxicity and accumulation, and does not produce genetic mutations.[3] For its systemic and synergistic action,[4] this herbicide is extensively used

against weeds and brackens in the cultivation of gramineous, citric, banana and sugarcane; as well as in hill farming, conservation, and forestry.[5]

The synthetic precursor will be used as substrate of an enzyme in the procedure to obtain the herbicide Asulam. Therefore, the knowledge of its structure will help not only to define the physical characteristics of its more stable conformation, but also allow to predict the compatibility between the enzyme and the substrate, according to the properties of the catalytic center of the enzyme to be used (Fig. 1).[6]

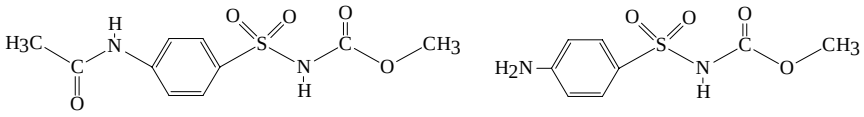
In this work, it is presented the synthesis of **I**, from 4-acetamidophenylsulfonamide and methyl chloroformate; and its characterization by means of melting point, TLC, spectroscopic methods (NMR-^{1}H, -^{13}C, and IR), and single crystal X-Ray Diffraction.

MATERIALS AND METHODS

The synthesis of methyl[(4-acetamidophenyl)sulfonyl]carbamate **(I)** was performed by means of the conventional method. In a flask were placed 0.032 mol of 4–acetamidophenylsulfonamide, or its salt, 0.078 mol of anhydrous K_2CO_3, 0.034 mol of methylchloroformate, and 40 mL of acetone. The mixture was heated and refluxed during two hours. Then, it was cooled down in the flask and poured onto 150 mL of water. The filtrate was acidified to pH 2 with HCl and the product was extracted with ethyl ether and recrystallized from methanol.

The melting point was determined with an Electrothermal 9100 equipment and it was not corrected. The IR spectrum was registered with a Philips Analytical PU 9600 FTIR spectrometer in KBr pellets. The spectra of RMN-^{1}H and -^{13}C were registered with a Bruker AC F spectrometer (250-^{1}H; 62.0-^{13}C) using TMS as internal standard and DMSO-d_6 as solvent. Thin layer chromatography (TLC) was carried out employing silicagel-G-60 plates as stationary phase, and acetonitrile- chloroform (0.6:1.3) (v/v) mixture as mobile phase.

Crystals suitable for X-ray analysis were obtained by slow evaporation from a methanol solution. The crystal structure was solved by direct methods using SHELXS-86 program[7] and refined on F^2 with SHELXL-93 program.[8] The refinement was performed on F^2 (hkl) by a full matrix least squares procedure, originally with isotropic and in the later stages with anisotropic temperature factors. The H-atoms were geometrically located and allowed to ride on the corresponding bound atom. Program PARST was used for the interpretation of the crystallographic results.[9] Data collection and structure refinement details are listed below (Table 1).



(I) **(II)**

Fig. 1*. Structures of the methyl[(4-acetamidophenyl)sulfonyl]carbamate (**I**) and methyl[(4-aminophenyl)sulfonyl]carbamate (**II**).*

Table 1. Crystal data and details of data collection and structure refinement for methyl[(4-acetamidophenyl)sulfonyl]carbamate.

Crystal data		
Empirical formula: $C_{10}H_{12}N_2O_5S$.		Mo K_α radiation.
Formula weight = 272.275.		λ = 0.710 730 0 Å .
Crystal system: monoclinic.		μ = 2.75 cm^{-1} .
Space group: $P2_1/n$.		
Unit cell dimension:	a = 8.681(4) Å .	Cell parameters
	b = 8.174(3) Å .	from 25 reflections
	c = 17.583(3) Å .	θ = 6.37 – 15.05° .
	β = 92.40(1)° .	
V = 1 246.6(8) $Å_3$.		T = 293 K .
Z = 4		Prismatic.
		(0.30X0.20X0.16) mm .
		Colorless.
Data Collection		
Diffractometer Enraf Nonius CAD 4.		
$\theta/2\theta$ scan.		Angle $2\theta_{max.}$ = 55.78° .
Analytical absorption correction.[10]		–11 ≤ h ≤ 11.
$T_{max.}$ = 0.966 1. $T_{min.}$ = 0.886 4.		
3 051 measured reflections.		0 ≤ k ≤ 10.
2 960 independent reflections.		0 ≤ l ≤ 23.
		Three standard reflections monitored every 1 800 s .
		Intensity decay: < 2 %.
Refinement		
Refinement on F2.		$(\Delta/\sigma)_{max.}$ = 0
R = 0.060.		$\Delta\rho_{max.}$ = 0.62 e $Å^{-3}$
WR = 0.154.		$\Delta\rho_{min.}$ = –0.38 e $Å^{-3}$
S = 1.013.		Extinction correction: none.
1 903 observed reflections [F > 4σ (F)].		Atomic scattering factors from international tables.[12]
163 refined parameters.		
H atoms were allowed to ride on the heavier atom.		
Weighting scheme:		
$w = 1/[\sigma^2(Fo^2) + (0.0756P)^2 + 1.43P]$.		
$P = [max (Fo^2,0) + 2Fc^2]/3$.		

RESULTS

The compound **(I)** was synthesized from methylchloroformate

and 4-acetamidophenylsulfonamide dissolved in dry acetone and in presence of anhydrous K_2CO_3, and obtained as crystalline solid in 62 % yield from methanol.

Melting point: 175-178 °C . R_f = 0.77 cm (TLC).

IR (KBr); $\nu_{max.}$ (cm^{-1}): 3 300 (NH); 3 250 (NH); 1 750 (C=O); 1 680 (C=O); 1 580, 1 500 (C=C); 1 250, 1 160 (SO_2).

NMR-^{1}H (DMSO-d_6); δ(ppm): 10.3 (1H, s, NH); 7.82 (2H, o, ArH); 7.79 (2H, m, ArH); 7.74 (1H, s, NH); 3.6 (3H, s, CH_3); 2.1 (3H, s, CH_3).

NMR-^{13}C (DMSO-d_6); δ(ppm): 169.1 (CO); 151.9 (CO_2); 143.8 (C_{ipso}); 132.5 (C_p, Ar); 128.8 (C_o, Ar); 118.5 (C_m, Ar); 52.8 (CH_3); 24.1 (CH_3).

Chemical analysis calculated $C_{10}H_{12}N_2O_5S$ (272.23): C: 44.11; H: 4.41; N: 10.29. Found: C: 43.95; H: 5.19, N: 9.43.

The FTIR spectrum of the title compound mainly presents the carbonyl groups at 1 750 and 1 680 cm^{-1}, which correspond to carbamic and amido groups. The NH groups appear at 3 300 and 3 250 cm^{-1} as are usual for secondary amides and carbamates, respectively.

The NMR-^{1}H studies show that the signals of the protons from the benzene ring appear at 7.82 and 7.79 ppm, while that ones corresponding to the protons of the methyl groups are at 3.6 and 2.1 ppm . The proton signals of the NH groups are observed at 10.3 and 7.74 ppm. The values are usual for this kind of compound in DMSO-d_6.

The NMR-^{13}C spectrum shows signals, which correspond to the benzene ring, in the range between 143.8 and 118.5 ppm . The signals of the methyl groups appear at 52.8 and 24.1 ppm. Signals from carbonyl carbons are observed at 169.1 ppm (CO) and 151.9 ppm (CO_2), respectively.

The geometry of the methyl[(4-acetamidophenyl)sulfonyl]carbamate molecule in the crystalline state, as well as the crystal data, the atomic coordinates and the temperature factors were obtained from the X-Ray Diffraction study (Fig. 2, Tables 1 and 2).

DISCUSSION

The bond lengths, bond angles, and torsion angles are within expected values (Table 3). According to these X-ray data, **I** presents a nearly planar region located from S to C_2 atoms (S-C_{11}-C_{12}-C_{13} and C_2-N_2-C_{14}-C_{13} torsion angles: 179.8 and 178.7°, respectively).

The analysis of the molecular packing indicates the existence of two intermolecular hydrogen bonds (Fig. 3). These bonds (Table 4) link neighbor molecules building bidimensional puckered layers parallel to the (011) plane. The layers are held together in the crystal by Van der Waals interactions.

The obtained results allow to predict the compatibility between the precursor molecular structure and the active site of the enzyme, which will be used in its hydrolysis.

Taking into account the conformation of **I**, obtained from the single crystal study (Fig. 2), and the structure of the hydrolase active site, it is possible to develop a model for the interaction between **I** and the enzyme. In this sense, the position, as well as the orientation of main functional groups of the substrate molecule are important.[6]

The precursor molecule presents several functional groups such as the acetyl, carbonyl, amide, carbamoyl and phenyl ones. The carbonylic group plays a decisive role in the mechanism of the amidasic bond hydrolysis, which has to be located at the catalytic center of enzyme, in the appropriate way.

In order to define the compatibility of the substrate and the enzyme structures, the hydrophobic end of acetyl group and the benzene ring might interact with two hydrophobic subsites of the enzyme active center, and the carboxylate group, present in the carbamic end of the intermediate molecule, would be linked with the hydrophilic subsite of the enzyme.

ACKNOWLEDGMENTS

To the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), to the Agencia de Promoción Científica y Tecnológica (PICT97-1135), to the Comisión de

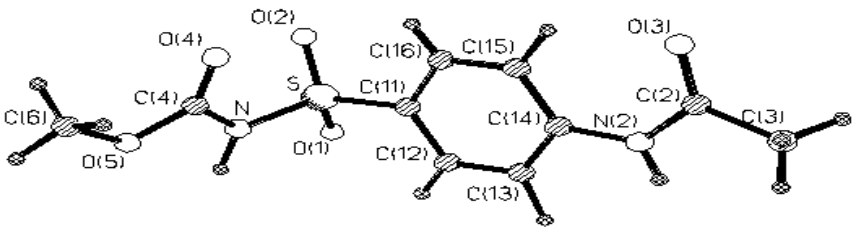


***Fig. 2**. ORTEP plot,[11] showing atoms labels, of the XRD conformation f methyl[(4-acetamidophenyl)sulfonyl]carbamate .*

Table 2. Fractional atomic coordinates (10^{-4}) and equivalent isotropic displacement parameters ($Å^2 \cdot 10^{-4}$).

Atom	X/a	Y/b	Z/c	U_{eq}
O(4)	–902(3)	3 165(4)	985(2)	76(1)
N(1)	218(3)	2 010(4)	2 055(1)	54(1)
C(4)	–604(4)	3 193(5)	1 660(2)	60(1)
O(5)	–1 007(3)	4 380(4)	2 128(2)	88(1)
C(6)	–1 853(6)	5 845(9)	1 806(4)	124(2)
S	944(1)	364(1)	1 651(1)	56(1)
O(2)	–209(4)	–341(4)	1 156(2)	82(1)
O(1)	1 574(4)	–563(3)	2 282(1)	73(1)
N(2)	6 178(3)	2 856(4)	–65(2)	57(1)
C(2)	6 362(4)	2 914(4)	–815(2)	53(1)
O(3)	5 353(3)	2 914(4)	–1 306(1)	68(1)
C(3)	7 872(4)	3 979(6)	–977(2)	68(1)
C(11)	2 459(4)	1 085(4)	1 119(2)	47(1)
C(12)	3 840(4)	1 458(5)	1 489(2)	65(1)
C(13)	5 048(4)	2 031(6)	1 086(2)	69(1)
C(14)	4 895(4)	2 233(4)	297(2)	47(1)
C(15)	3 509(4)	1 822(5)	–70(2)	55(1)
C(16)	2 293(4)	1 261(5)	341(2)	58(1)

Table 3. Selected bond lengths, bond angles and torsion angles.

Bond lengths (Å)		Bond Angles (°)		Torsión Angles (°)	
	Length		Angle		Angle
O(4)-C(4)	1.206(4)	C(4)-N(1)-S	123.7(2)	C(14)-N(2)-C(2)-O(3)	–4.2(7)
N(1)-C(4)	1.372(5)	O(4)-C(4)-N(1)	124.8(4)	C(14)-N(2)-C(2)-O(3)	175.5(4)
N(1)-S	1.657(3)	O(4)-C(4)-O(5)	124.8(4)	O(2)-S-C(11)-C(12)	–164.7(3)
C(4)-O(5)	1.328(5)	N(1)-C(4)-O(5)	111.0(4)	O(1)-S-C(11)-C(12)	–32.2(4)
O(5)-C(6)	1.503(6)	C(4)-O(5)-C(6)	119.1(4)	N(1)-S-C(11)-C(12)	78.4(4)
S-O(2)	1.421(3)	N(1)-S-O(2)	108.7(2)	O(2)-S-C(11)-C(16)	14.3(4)
S-O(1)	1.432(3)	N(1)–S–O(1)	103.8(2)	O(1)-S-C(11)-C(16)	146.8(3)
S-C(11)	1.748(3)	N(1)-S-C(11)	105.3(2)	N(1)-S-C(11)-C(16)	–102.6(3)
N(2)--C(2)	1.365(4)	O(2)-S-O(1)	119.8(2)	C(16)-C(11)-C(12)-C(13)	1.2(7)
N(2)--C(14)	1.401(4)	O(2)-S-C(11)	109.6(2)	S-C(11)-C(12)-C(13)	–179.8(4)
C(2)-O(3)	1.228(4)	O(1)-S-C(11)	108.7(2)	C(11)-C(12)-C(13)-C(14)	–0.5(7)
C(2)-C(3)	1.494(5)	C(2)-N(2)-C(14)	129.9(3)	C(12)-C(13)-C(14)-C(15)	–0.9(7)
C(11)-C(12)	1.374(5)	N(2)-C(2)-O(3)	122.1(3)	C(12)-C(13)-C(14)-N(2)	178.9(4)
C(11)-C(16)	1.378(4)	N(2)-C(2)-C(3)	114.4(3)	C(2)-N(2)-C(14)-C(15)	1.1(7)
C(12)-C(13)	1.372(5)	O(3)-C(2)-C(3)	123.6(3)	C(2)-N(2)-C(14)-C(13)	–178.7(4)
C(13)-C(14)	1.399(4)	S-C(11)-C(12)	118.9(2)	C(13)-C(14)-C(15)-C(16)	1.7(6)
C(14)-C(15)	1.383(4)	S-C(11)-C(16)	121.1(3)	N(2)-C(14)-C(15)-C(16)	–178.1(4)
C(15)-C(16)	1.382(5)	C(12)-C(11)-C(16)	120.0(3)	C(12)-C(11)-C(16)-C(15)	–0.5(6)
		C(11)-C(12)-C(13)	120.1(3)	S-C(11)-C(16)-C(15)	–179.4(3)
		C(12)-C(13)-C(14)	120.7(3)	C(14)-C(15)-C(16)-C(11)	–1.0(6)
		N(2)-C(14)-C(13)	116.7(3)		
		N(2)-C(14)-C(15)	124.7(3)		
		C(13)-C(14)-C(15)	118.6(3)		
		C(14)-C(15)-C(16)	120.4(3)		
		C(11)-C(16)-C(15)	120.2(3)		

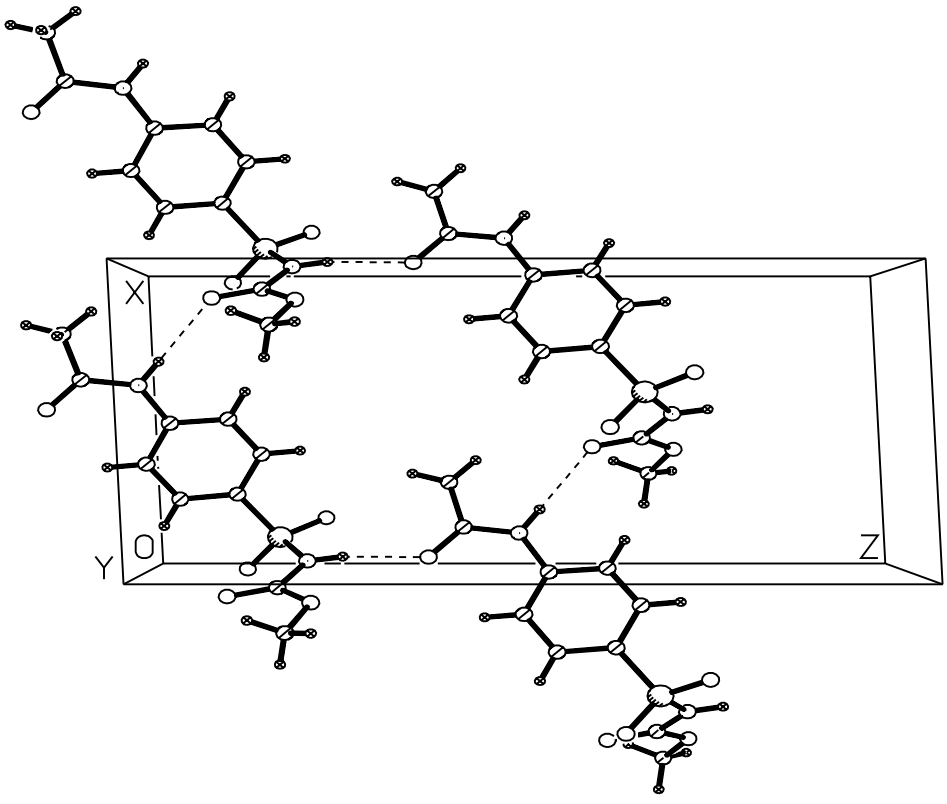


Fig. 3. *View of the unit cell of the title compound. Hydrogen bonds are shown with dashed lines.*

Table 4. Relevant geometrical parameters‡ for the intermolecular hydrogen bonds observed in the crystal structure of methyl[(4-acetamidophenyl)sulfonyl]-carbamate.

Donor-H (Å)	Donor ... Acceptor (Å)	H ... Acceptor (Å)	Donor-H ... Acceptor (Å)
N_1-H_1	N_1 ... O_3*	H ... O_3*	N_1-H_1 ... O_3*
0.860	2.885(4)	2.038(4)	168.0(4)
N_2-H_2	N_2 ... O_4**	H_2 ... O_4**	N_2-H_2 ... O_4**
0.860	3.087(4)	2.234(4)	171.8(4)

* x–1/2, –y+1/2, +z+1/2.
** x+1, +y, +z.
‡ Supplementary chemical and crystalographic data of this paper are available from the X-ray Laboratory of the National Center for Scientific Research, Havana, Cuba.

Investigaciones Científicas de la Provincia de Buenos Aires, and to the Facultad de Ciencias Exactas de la Universidad de La Plata from Argentina. To the Instituto de Catálisis y Petroleoquímica (CSIC) from Spain. To the International Program for the Physical Sciences from Uppsala University, Sweden, by financial support for P. Castillo. G. P. is member of the CONICET.

BIBLIOGRAPHY

1. Carpenter K., Heywood B., Parnell E., Metivier J. y Boesch R. Herbicidal compositions, Patent GB1040541, 1966.
2. Martin H., Asulam, in Pesticide Manual. British Corp. Protection Council, 22, 1974.
3. Hu Y., Jiang Y., Zhao and Wang G. **Journal of West China University of Medical Sciences, 23**, 190, 1992.
4. Fisher J. and Tice C., Synergistic herbicidal compositions. Patent EP 0813811 A2 971229, 1997.
5. Burge M. and Kirkwood R., **Critical reviews in Biotechnology, 12,** 299, 1992.
6. Boyer R. Conceptos de Bioquímica, International Thomson Editores, SA, México, 154, 2000.
7. Sheldrick G.M., **Acta Cryst., A46**, 467, 1990.
8. Sheldrick G.M. SHELXL93, Program for the Refinement of Crystal Structures. University of Götingen, Germany, 1993.
9. Nardelli M., **Comput. Chem.**, **7**, 95, 1983.
10. Alcock N.W., **Cryst. Computing**, 271, 1970.
11. Johnson C.K., ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA, 1976.
12. Brown R.T. Coherent and Incoherent X-Ray Scattering by Bound Electrons. III. Five-Electron Atoms. International Tables for X-ray Crystallography, Vol. IV, 1974.

ACTIVIDADES CIENTIFICAS
MINISTERIO DE EDUCACION SUPERIOR DE CUBA

CONFERENCIA 50 ANIVERSARIO DE LA UNIVERSIDAD CENTRAL DE LAS VIILAS ''LA CIENCIA EN EL SIGLO XXI''

Universidad Central de Las Villas ''Marta Abreu''

Del 27 al 29 de noviembre del 2002.

TEMATICAS: *Impacto socio-cultural, psicológico y filosófico del desarrollo científico en el hombre del Siglo XXI. Globalización de la ciencia, la tecnología, y la Educación Superior. Tecnología del Siglo XXI, bioinformática, nanotecnologías, neurociencias y nuevos materiales. Agricultura sostenible - Agricultura tradicional (química). Sociedad de la información.*

CUOTA DE INSCRIPCION: 120.00 USD. Se pagará en el momento de la acreditación en el evento.

COMITE ORGANIZADOR: Dr. Andrés Olivera Ranero.
Fax: (5342) 28-1608. E-mail: arubio@uclv.etecsa.cu

XVII CONFERENCIA DE QUÍMICA

Universidad de Oriente

Santiago de Cuba, Cuba.

Del 4 al 6 de diciembre de 2002.

TEMATICAS: *Química Orgánica, Inorgánica, Analítica, Química Física. Biotecnología. Enseñanza de la Química. Ingeniería Química y Química del Medio Ambiente.*

CUOTA DE INSCRIPCION: 130.00 USD. Se pagará en el momento de la acreditación en el Seminario.

COMITE ORGANIZADOR: Dr. Marcos Cortina Vegas.
Fax: (53226) 63-268. E-mail: marcos@rect.uo.edu.cu