X-Ray Crystal Structures of a 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethanol Intermediate and the 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethene Dehydration Compound Obtained from the Condensation Reaction of 2-Methylpyridine and *p*-Fluorobenzaldehyde

M. Judith Percino*[,1], Víctor M. Chapela[1], Ling-Fa Montiel[1] and Cecilia Rodríguez-Barbarín[2]

[1]*Centro de Química, Instituto de Ciencias, Universidad Autónoma de Puebla, Complejo de Ciencias, ICUAP, Edif. 194, 22 Sur y San. Claudio, C.P. 72570, Puebla, Puebla, México*

[2]*División de Estudios de Posgrado, Facultad de Ciencias Químicas, U.A.N.L., Guerrero y Progreso S/N, Col. Treviño, C.P. 64570 Monterrey, N.L., México*

Abstract: The compound 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethanol and its corresponding dehydration compound 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethene were obtained from the Knoevenagel condensation reaction between 2-methylpyridine with *p*-fluorobenzaldehyde. The X-ray structure determined for 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethanol reveals that the compound crystallizes in the monoclinic system space group, $P2_1/n$, containing four molecules in each crystal unit cell [a = 5.3664(15) Å, b = 8.343(2) Å, c = 25.056(6) Å, and β = 93.837(15)°]. The crystal structure shows the formation of an intermolecular hydrogen bond O-H···N between the oxygen atom of the O–H and the nitrogen atom of a pyridine group of the next molecule. The condensation product 1-(*p*-fluorophenyl)-2-(2-pyridyl)ethene crystallizes in the monoclinic system, in the *Cc* space group, with unit cell dimensions a = 22.920(7) Å, b = 5.9149(14) Å, c = 7.8544(15) Å, and β = 104.16(2)°. The molecular structure shows the *p*-fluorophenyl ring attached to the double bond and located *trans* to the pyridine ring. The crystallography data give evidence that the intermediary compound is actually the alcohol just before the dehydration process that yields the *trans* double bond of the 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethene.

INTRODUCTION

The reaction of an aromatic aldehyde with a methylpyridine, classified as a Knoevenagel condensation, gives stable products with *trans* configuration identified as styrylpyridines, also known as stilbazoles [1]. The Knoevenagel condensation has been generally defined as the reaction between an aldehyde or ketone with any compound having an active methyl and methylene group catalyzed by an organic base or ammonia or their salts [2]. The activation of the methylene group is due to the direct attachment of one group such as nitro, cyano or acyl; in most cases two such groups are required to provide sufficient activation [3]. Drawing from previous knowledge of the condensation reactions of methylpyridines with aromatic aldehydes, we have applied this method under catalyst-free and solvent-free conditions to synthesize new conjugated compounds (styrylpyridines) with light emitting properties. The method used in this work is a straightforward and clean process for obtaining various styrylpyridines [4]. Several compounds, such as the intermediate 1-phenyl-2-(4-pyridyl)ethanol, 2-styrylpyridine and 2,6-distyrylpyridine, have been previously obtained and characterized by X-ray single crystal diffraction [5-7].

The identification of an intermediate from the condensation of 2-methylpyridine with benzaldehyde to form 2-styrylpyridine is reported to proceed in two stages [8-10]. First is the formation of the alkines (-CH_2-CHOH- group), a reversible reaction. When benzaldehyde and 2-methylpyridine are allowed to boil for 10 hours, 1-phenyl-2-(α-pyridyl)-ethanol (alkines) and the corresponding stilbazole are produced simultaneously [10]. The alkines, when heated with water at 140 to 200 °C, are partially converted into methylpyridine and the aldehyde. The second stage is the dehydration of the alkines to yield the stilbazoles (-CH=CH- group) using a condensing agent. The condensation of 2-methylpyridine with *p*-nitrobenzaldehyde in N,N-DMF or DMSO in the presence of acetic acid gives 1-(4'-nitrophenyl)-2-(α-pyridyl)ethanol, which is readily converted to 2-(4'-nitrostyryl)pyridine by heating at 115 °C in acetic acid and acetic anhydride.

Solvent-free and catalyst-free conditions have been successfully employed in several cases. For example, kinetic studies [11] of the reaction between 2-methylpyridine and benzaldehyde, along with HPLC and UV detection, have identified the intermediates 1-phenyl-2-(α-pyridyl)ethanol and 2-styrylpyridine just 20 minutes after the start of the reaction. The products of 4-methylpyridine and benzaldehyde, in the absence of a condensing agent, are the model compound 4-styrylpyridine and the intermediates 1-phenyl-2-(4-pyridyl)ethanol or (4-[2-(1-hydroxy-1-phenyl)ethyl] pyridine), as characterized by X-ray crystallography [5]. A 5-ethyl-2-(4-nitro-7-ol-styryl)-pyridine intermediate is obtained from ethyl-2-methylpyridine and *p*-nitrobenzaldehyde, but in this case benzoic anhydride is used as a condensing agent [12].

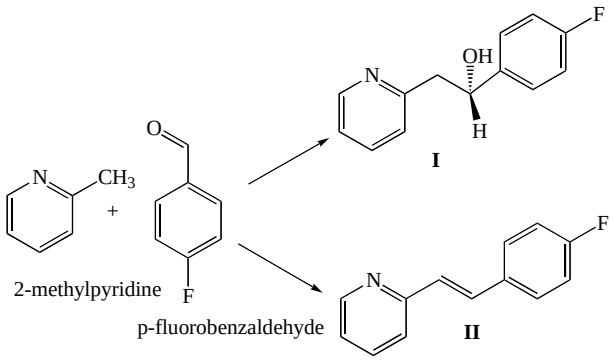
*Address correspondence to this author at the Centro de Química, Instituto de Ciencias, Universidad Autónoma de Puebla, Complejo de Ciencias, ICUAP, Edif. 194, 22 Sur y San. Claudio, C.P. 72570, Puebla, Puebla, México; E-mail: jpercino@siu.buap.mx

1874-8465/08

Using the condensation reaction of 2-methylpyridine and *p*-fluorobenzaldehyde without catalyst or solvent, as in the studies described above, we obtained 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethanol and the dehydration compound 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethene. The temperature used for each condensation reaction determined which compound was produced. To the best of our knowledge, this is the first report of the crystal structures of both compounds.

EXPERIMENTAL

Crystallization of 1-(*p*-fluorophenyl)-2-(α-pyridyl) ethanol (**I**) and 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethene, (**II**).



Scheme 1.

The condensation reaction was made according to Scheme **1**. The compounds **I** and **II** were obtained from 2-methylpyridine (50 mmol) and *p*-fluorobenzaldehyde (50 mmol), at reflux in the absence of a condensing agent and at a temperature of 120 °C for **I** and 140 °C for **II.** In both cases, the reaction mixtures appeared oily and brown in color. The brown mixture was distilled to evaporate the chemical reagents that did not react. The mixture was treated with a solution of NaOH 2N (643 mL) to precipitate a powder. The products were purified by recrystallization with hexane and characterized by IR and NMR spectroscopy. The structure of the intermediary and the dehydration compounds were confirmed by X-ray single crystal crystallography. Crystals of **I** were obtained by dissolving 30 mg of **I** in 1 ml of $CHCl_3$ and keeping at 4 °C; after 12 days, colorless crystals were formed. For the crystals of **II**, 30 mg of compound **II** were dissolved in 20 ml of ethanol. The solution was kept at 4 °C and allowed to slowly evaporate; after 47 days, light brown crystals were formed.

X-Ray Crystallography

All diffraction data were collected on a Bruker P4 diffractometer (graphite monochromated Mo-Kα radiation, λ = 0.71073 Å) using XSCAnS, release 2.3 for reflections collection. An appropriate single crystal of **I**, with approximate dimensions 0.40 × 0.24 × 0.06 mm, was selected for X-ray structure determination.. The structure was solved by direct methods and refined by the full-matrix least-squares technique using an anisotropic approximation for all non-hydrogen atoms by the SHELXL-*Plus* program [17]. Hydrogen atoms were included in calculated positions and refined in the riding mode with an isotropic factor related to the bonded atoms, except for H of the OH group. The hydroxyl H atom was found from the difference Fourier maps and its position parameters were freely refined.

The crystal structure of **II** has been also determined by the single crystal X-ray diffraction technique using a suitable single crystal with approximate dimensions of 0.30 × 0.20 × 0.06 mm.

Experimental details of the X-ray analyses are provided in Table **1** for both compounds **I** and **II**.

Table 1. Experimental Details of the X-Ray Analyses of the Title Compounds

	I	**II**
Empirical formula	**C13H12FNO**	**C13H10FN**
Color, habit	Colorless, plates	Colorless, plates
Crystal system	Monoclinic	Monoclinic
Space group	P 2_1/n	Cc
a, *b*, *c* (Å) parameters	5.3664(15), 8.343(2), 25.056(6)	22.920(7), 5.9149(14), 7.8544(15)
β (°)	93.837(15),	104.16(2)
Volume (Å^3)	1119.3(5)	1032.4(4)
Z	4	4
Formula weight	217.24	199.22
D_x(g cm^{-3})	1.289	1.282
μ (mm^{-1})	0.093	0.088
F(000)	456	416
Temperature (K)	297(2)	298(2)
2θ Range (°)	3.5 - 50.0	
Data collection method	Ω scans	θ/2θ scans
No. of measured, independent (a) and observed reflections	3818, 1971, 1178	1847, 906, 482
Criterion for observations	Fo > 4 σ(Fo)	Fo > 4 σ(Fo)
Coverage (%)	99.7 to 2θ = 50.0 º	99.8 to 2θ = 25.04 º
R_{int} (%)	4.14	10.80)
< I / σ(I) > (all data)	10.91	6.70
Absorption correction	None	
Wilson's statistics	< | E2 - 1| > = 1.035	< | E2 - 1| > = 0.939
Structure solution	Direct methods and difference Fourier maps	
Refinement method	Full matrix least-squares	
Refinement on	F^2	

(Table 1). Contd…..

Extinction correction	None	
H-atom treatment	Riding model, fixed isotropic U. For H1B their position parameters were refined	Riding model, fixed isotropic U
Restraints, constraints [(b)]	0	2
Weighting scheme	$w = [\sigma^2 (F_o^2) + (0.0733\ P)^2 + 0.14\ P]^{-1}$ where $P = (\max [F_o^2,0] + 2\ F_c^2) / 3$	$w = [\sigma^2 (F_o^2) + (\#\ P)^2 + \#\ P]^{-1}$ where $P = (\max [F_o^2,0] + 2\ F_c^2) / 3$
R_1, wR_2 (%) ($I > 2\ \sigma(I)$) [(a)]	5.31, 13.25	5.85, 14.24
R_1, wR_2 (%) (all data) [(a)]	9.81 , 15.80	12.20, 16.95 %
Goodness of fit[(a)]	S= 1.029	S= 1.026
$(\Delta/\sigma)_{max}$	0.000	
Data-to-parameters ratio	13.31	6.66
$\Delta\rho_{max}$(e Å^{-3})	0.286	0.118
$\Delta\rho_{min}$(e Å^{-3})	-0.179	-0.143

$$R_{int} = \frac{\sum |F_o^2 - \langle F_o^2 \rangle|}{\sum F_o^2}, R_1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}, wR_2 = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2}}, S = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{m-n}}$$

(a)
For R_{int}, both summations involve all input reflections for which more than one symmetry equivalent is averaged. For S, m is the number of observed reflections and n is the number of parameters refined.
(b) For non-hydrogen atoms.

RESULTS AND DISCUSSION

A molecular representation for both molecular structures **I** and **II**, including the atomic numbering scheme, is showed in Fig. (**1**). Table **2** gives selected bond lengths with estimated standard deviations for both compounds.

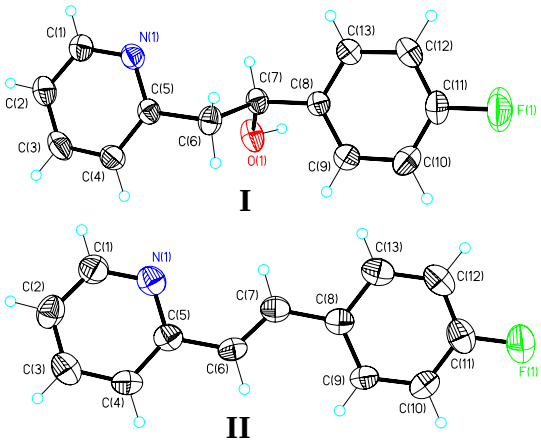


Fig. (1). Molecular structures of **I** and **II.** Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

Table 2. Bond Lengths (Å) for I and II Compounds

Bond	I Length (Å)	II Length (Å)
O(1)-C(7)	1.410(3)	-
N(1)-C(5)	1.330(3)	1.332(9)
F(1)-C(11)	1.356(3)	1.346(11)
C(2)-C(3)	1.354(4)	1.322(13)
C(4)-C(5)	1.382(3)	1.377(9)
C(6)-C(7)	1.509(3)	1.323(9)
C(8)-C(9)	1.371(3)	1.382(10)
C(9)-C(10)	1.386(3)	1.362(10)
C(11)-C(10)	1.354(4)	1.368(11)
O(1)-H(1B)	0.93(4)	-
N(1)-C(1)	1.335(3)	1.328(10)
C(1)-C(2)	1.369(4)	1.361(12)
C(3)-C(4)	1.372(4)	1.395(11)
C(5)-C(6)	1.505(3)	1.471(10)
C(7)-C(8)	1.515(3)	1.459(11)
C(8)-C(13)	1.375(3)	1.419(12)
C(11)-C(12)	1.352(4)	1.357(12)
C(12)-C(13)	1.381(3)	1.380(12)

Molecule I

The X-ray structure refinement shows that the molecule **I** possesses a chiral carbon atom, C(7), but the crystal structure belongs to a centrosymmetric space group, *P2₁/n*. This result indicates that **I** is a racemic mixture, as expected. All molecular geometry is within normal ranges [13]. The $-CH_2$-CHOH- moiety of the molecule shows a typical distance of 1.509(3)Å for the single carbon-carbon C(6)-C(7) bond. This bond length is similar to the analogous distances for two intermediates, 1-phenyl-2-(4-pyridyl)ethanol and 5-ethyl-2-(4-nitro-7-ol-styryl)-pyridine, reported in the literature as 1.508(8)Å and 1.517(9) Å, respectively [5,12]. The distances of F(1)-C(11), 1.356(3) and 1.346(11) Å for **I** and **II,** respectively, are similar to other phenyl rings bonded to a fluorine atom [14, 15]. Bond angles for **I** and **II** are shown in Table **3**. We find that the bonds angles in the $-CH_2$-CHOH- group are typical of sp^3 hybridization for C(6) and C(7)**.** The pyridine and phenyl rings are planar (r.m.s. deviations 0.0028 and 0.0017 Å, respectively) and are mutually inclined, making an angle of 7.1º.

The molecular crystal packing of **I** is shown in Fig. (**2**), illustrating the intermolecular H-bonding between the OH group of one molecule and the nitrogen atoms of a symmetry-related pyridine ring [O1-H1B…N1 1.932 Å, O1…N1 2.858(3) Å, O1-H1B…N1 174.93°, symmetry code: -x+3/2, y+1/2, -z+1/2]. Two independent parallel molecular chains

Table 3. Bond Angles (º) for Molecules I and II

	I	II
	Angle(º)	**Angle(º)**
C(7)-O(1)-H(1B)	109(2)	
C(5)-N(1)-C(1)	118.4(2)	117.5(7)
N(1)-C(1)-C(2)	123.1(3)	123.9(9)
C(3)-C(2)-C(1)	118.3(2)	119.4(9)
C(2)-C(3)-C(4)	119.8(3)	118.8(9)
C(3)-C(4)-C(5)	119.1(3)	119.1(8)
N(1)-C(5)-C(4)	121.3(2)	121.4(7)
N(1)-C(5)-C(6)	116.4(2)	116.9(7)
C(4)-C(5)-C(6)	122.3(2)	121.7(8)
C(5)-C(6)-C(7)	113.68(19)	125.9(6)
O(1)-C(7)-C(6)	107.3(2)	
O(1)-C(7)-C(8)	112.45(18)	
C(6)-C(7)-C(8)	111.20(18)	125.4(6)
C(9)-C(8)-C(13)	118.3(2)	118.3(8)
C(9)-C(8)-C(7)	121.3(2)	125.3(7)
C(13)-C(8)-C(7)	120.4(2)	116.4(8)
C(8)-C(9)-C(10)	121.2(3)	120.8(8)
C(11)-C(10)-C(9)	118.3(3)	120.2(9)
C(12)-C(11)-C(10)	122.4(2)	121.0(9)
C(12)-C(11)-F(1)	118.9(3)	119.3(9)
C(10)-C(11)-F(1)	118.7(3)	119.7(10)
C(11)-C(12)-C(13)	118.7(3)	120.1(9)
C(8)-C(13)-C(12)	121.0(3)	119.5(9)

are thus formed along the *b*-axis. The intermediate compound provided evidence of the condensation mechanism proposed decades ago [2], which states that an alcohol must dehydrate to produce a double bond in the final compound [1, 2, 10].

Molecule II

From the molecular structure of **II,** it is observed that the *p*-fluorophenyl ring is located *trans* to the pyridine ring in relation to the double bond. The bond lengths between C(5)-C(6) [1.471(10) Å], C(6)-C(7) [1.323(9) Å], and C(7)-C(8) [1.459(11) Å] (Table **2**) indicate a delocalization of the π electrons of the two rings through the C(6)-C(7) bond. Similar distances have been observed in 2-styrylpyridine [6], 2,6-distyrylpyridine [7], and 5-ethyl-2-pyridylvinylbenzene [16]. Also compound **II** is a planar molecule with an r.m.s. deviation of 0.0119 Å, with the F atom -0.0243 Å out of planarity. The partial π character of the C5−C6 and C7−C8 bonds (Table **2**), helps to explain the aromatic planar nature of the molecule.

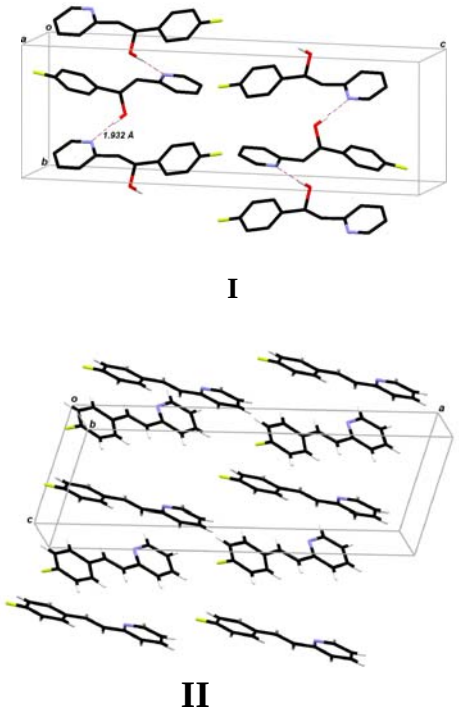


Fig. (2). Molecular crystal packing of **I**, showing the H-bonding scheme with two parallel molecular chains along the [010] direction, and the molecular packing structure of **II** viewed along the *b*-axis.

The molecular packing of **II** does not present regular hydrogen bonding between molecules (Fig. **2**). Instead, weaker intermolecular C−H…π(arene) interactions exist, one with H(1A)…Cg(1) (2.96 Å) and C(1)Å−H(1A)…Cg(1) (125º) [where Cg(1) is the centroid of ring {N1, C1, C2, C3, C4, C5}]. A similar interaction also occurs between C(10)−H(10A)… Cg(2) (2.96 Å) and C(10)Å−H(10A)… Cg(2) (127º) [where Cg(2) is the centroid of ring {C8, C9, C10, C11, C12, C13}].

CONCLUSIONS

The molecule 1-(*p*-fluorophenyl)-2-(α-pyridyl)-ethanol and its corresponding dehydration compound 1-(*p*-fluorophenyl)-2-(α-pyridyl)ethene were obtained and characterized by X-ray analysis. The crystallographic data gave evidence that the intermediary compound is actually the alcohol just before the dehydration process that yields the *trans* double bond. The 1-(*p*-fluorophenyl)-2-(α-pyridyl) ethanol crystal structure shows the formation of an intermolecular hydrogen bond O-H···N between the oxygen atom of the O–H and the nitrogen atom of a pyridine group of the next molecule. The 1-(*p*-fluorophenyl)-2-(2-pyridyl)ethane molecular structure shows the *p*-fluorophenyl ring attached to the double bond and located *trans* to the pyridine ring.

ACKNOWLEDGEMENTS

The authors acknowledge CONACYT for financial support (Projects No. 44237 and 46360).

SUPPLEMENTARY MATERIAL

Supplementary material can be viewed at www.bentham.org/open/tocryj

REFERENCES

[1] Acheson RM. An introduction of the chemistry of heterocyclic compounds. John Wiley and Sons, New York 1976; pp. 246-7.

[2] Krauch H, Kunz W. Reaktionen der organischen Chemie. Alfred Hüthig Verlag, Heidelberg 1969.

[3] Boucard V. Kinetic study of Knoevenagel condensation applied to the synthesis of poly [bicarbazolylene-alt-phenylenebis(cyanovinylene)]s. Macromolecules 2001; 34: 4308-13.

[4] Percino MJ, Chapela VM, Sánchez A, Maldonado-Rivera JL. Condensation reactions of methylpyridines and aromatic aldehydes under catalyst and solvent free conditions. CAIJ 2006; 3(9-10): 262-7.

[5] Percino MJ, Chapela VM, Salmón M, Toscano RA. Unexpected crystallization and X-ray crystal structure of recemic 1-phenyl-2-(4-pyrididyl)etanol intermediate. J Chem Cryst 2000; 30: 385-8.

[6] Percino MJ, Chapela VM, Salmon M, Espinoza-Pérez G, Herrera AM, Flores A. X-ray cristal structure of 2-styrylpyridine. J Chem Cryst 1997; 27: 9.

[7] Chapela VM, Percino MJ, Rodríguez de Barbarín C. Crystal structure of 2,6-distyrylpyridine. J Chem Cryst 2003; 33: 77-83.

[8] Ogata Y, Kawasaki A, Hirata H. Kinetic of the condensation of picoline with aromatic aldehydes in acetic anhydride. J Org Chem 1970; 35 (9): 2199-03.

[9] Beneš J, Kaválek J, Bartošek J, Churáček J. Kinetic and mechanism of non-catalysed condensation of picoline with bnezaldehyde. Collect Czech Chem Commun 1969; 34: 819-32.

[10] Shaw BD, Wagstaff EA. The reaction between 2-picoline and aromatic aldehydes. J Chem Soc 1933; 77-9.

[11] Chapela VM, Elizalde MP, Geissler G, Herrera AM, Percino MJ. High performance liquid chromatography in the synthesis of styrylpyridine. 21st International Symposium on Chromatography Stuttgart, Germany. September 1996.

[12] Chavarín C, Bernès S, Manero O. Synthesis and structural investigations of derivatives of 5-ethyl-2-styryl-pyridine. J Chem Cryst 1999; 29(6): 653-7.

[13] Allen FH, Kennard O, Watson DG, *et al*. Tables of bond lengths determined by X-ray and neutron diffraction. Part 1. Bond lengths in organic compounds. J Chem Soc Perkin Trans 1987; 2: S1-19.

[14] Clegg W, Watson DG. 5-(4-fluorobenzylidene)-imidazolidine-2,4-dione. Acta Cryst 2005; E61: 2784-6.

[15] Clegg W, Watson DG. 4-fluorobenzaldehyde salicylhydrazone. Acta Cryst 2006; E62: 119-20.

[16] Soriano-García M, Pannerselvam K, Jiménez-Estrada M, Chavarín C, Manero O. Crystal structure of 5-ethyl-2-pyridylvinylbenzene. Anal Sci Jpn Soc Anal Chem 1996; 12: 1001-2.

[17] SHELXTL Plus PC User's Manual; Siemens Analytical X- Ray Instruments; Madison, Wi 1990.

Received: May 14, 2008 Revised: July 24, 2008 Accepted: August 07, 2008