Synthesis, NMR Spectroscopic and X-ray Crystallographic Studies of Functionalized 2-Aminopyrrolin-4-ones

Anna Gola, Evangelia Samartzi, Vassilios Bardakos,
Margarita Petroliagi and Olga Igglessi-Markopoulou*

Laboratory of Organic Chemistry, Department of Chemical Engineering, National Technical University of Athens, Zografou Campus, 157 73 Athens, Greece

John Markopoulos

Laboratory of Inorganic Chemistry, Department of Chemistry, University of Athens, Greece

James V. Barkley

Department of Chemistry, University of Liverpool, United Kingdom

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Dedicated to the memory of Dr. Raymond N. Castle

An efficient method for the preparation of novel cyano derivatives of 4-amino-3-hydroxybutenoic acids **4-8** and *N*-substituted-2-aminopyrrolin-4-ones **9-18** is described; the structure of compound **13** has been elucidated with X-ray analysis.

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Recently, considerable attention has been focused on a structural class of cyano derivatives of 4-amino-3-hydroxybutenoic acids due to their increased pharmacological significance. These functionalized enols, possessing topographical similarities with statine, constitute a new class of medicinal agents for the construction of HIV-1 protease inhibitors [1].

In the course of our research program directed towards the synthesis of nitrogen heterocycles of chemical and biological interest [2], we have investigated a facile approach to 4-amino-3-hydroxy-2-cyano-butenoates **4-8** as useful synthons for the synthesis of 2-amino-pyrrolinones **9-13** and **14-18**. It is known that 2-amino-pyrrole analogues exhibit antiallergic, local anaesthetic, antiarrythmic, hypotensive and anticonvulsant properties [3]. We have introduced a strategy for the construction of 2-amino-pyrrolin-4-one system through an acylation reaction of an active methylene compound possessing an α-cyano group, with either the *N*-hydroxysuccinimide ester of *N*-acetyl sarcosine **1** and *N*-acetyl-*N*-phenylglycine **2** in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol. The isolated key intermediates **4-8** undergo a cyclization reaction (8% hydrogen chloride in ethanol) to *N*-substituted hydrochloric salts **9-13** through an intramolecular condensation mechanism. Transformation of **9-13** into the new free amines **14-18** is accomplished with sodium ethoxide in ethanol (Scheme 1).

The structure of the novel compounds **4-18** has been elucidated with nmr, ir spectroscopy and elemental analyses (Tables 1 and 2). Compound **13** has been also investigated with X-ray analysis.

Scheme 1

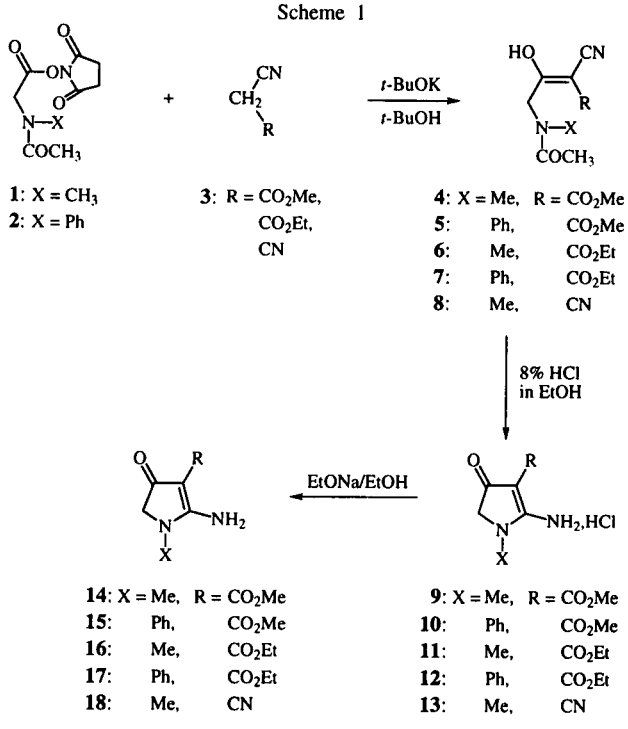


Table 1

Physical Properties and Spectral Data for Compounds **4-8**

Compound	Formula	Found/Calcd. (%) C	H	N	Mp (°C)	Yield (%)	^{1}H NMR (60 MHz, $CDCl_3$, δ ppm)
4	$C_9H_{12}N_2O_4$	50.92 (50.94)	5.69 (5.70)	13.19 (13.20)	oil	38	2.06 (s, $COCH_3$, 3H), 3.17 (s, NCH_3, 3H), 3.93 (s, CO_2CH_3, 3H), 4.47 (s, NCH_2C-, 2H)
5	$C_{14}H_{14}N_2O_4$	61.30 (61.31)	5.15 (5.15)	10.19 (10.21)	121-123	43	1.95 (s, $COCH_3$, 3H), 3.86 (s, CO_2CH_3, 3H), 4.8 (NCH_2C=, 2H), 7.36 (br, C_6H_5, 5H), 10.35 (br, OH, 1H)
6	$C_{10}H_{14}N_2O_4$	53.07 (53.09)	6.23 (6.24)	12.36 (12.38)	oil	71	1.33 (t, J = 8.0 Hz, CH_2CH_3, 3H), 2.16 (s, $COCH_3$, 3H), 3.1 and 3.16 (2s, NCH_3, 3H), 4.43 (s, NCH_2C-, 2H), 4.26 (q, J = 6.0 Hz, CH_2CH_3, 2H), 13.83 (br, OH, 1H)
7	$C_{15}H_{16}N_2O_4$	62.46 (62.49)	5.57 (5.59)	9.73 (9.72)	110-111	66	1.23 (t, J = 8.0 Hz, CH_2CH_3, 3H), 2.00 (s, $COCH_3$, 3H), 4.16 (q, J = 6.0 Hz, CH_2CH_3, 2H), 4.76 (s, NCH_2C=, 2H), 7.37 (br, C_6H_5, 5H), 10.03 (br, OH, 1H)
8	$C_8H_9N_3O_2$	53.61 (53.62)	5.04 (5.06)	23.44 (23.45)	oil	28	2.1 (s,$COCH_3$, 3H), 3.03 (s, NCH_3, 3H), 4.26 and 4.33 (two s, NCH_2C-, 2H), 6.16 (br, OH, 1H)

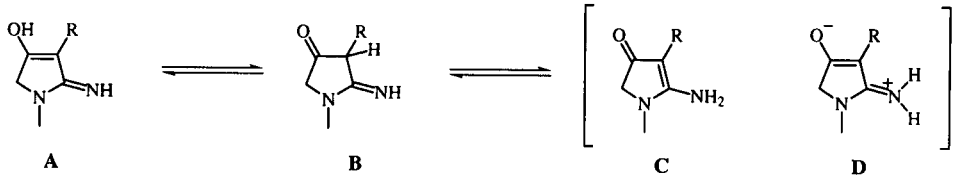
Table 2

Physical Properties and Spectral Data for Compounds **9-18**

Compound	Formula	Found/Calcd. (%) C	H	N	Mp (°C)	Yield (%)	IR (Nujol) (ν, cm^{-1})	^{1}H NMR (60 MHz, δ ppm) (DMSO-d_6 for **9-16,18**, $CDCl_3$ for **17**)
9	$C_7H_{11}N_2O_3Cl$	40.65 (40.68)	5.35 (5.36)	13.50 (13.56)	176-179	90	3390, 3280, 2300, 1700, 1650, 1600	3.03 (s, NCH_3, 3H), 3.6 (s, CO_2CH_3, 3H), 4.03 (2H, s, CH_2-ring, 2H) and 6.53, 7.43, 7.96, 8.26 (4s, NH_2, 2H)
10	$C_{12}H_{13}N_2O_3Cl$	65.28 (65.30)	5.91 (5.93)	12.60 (12.69)	166-170	63	3390, 3180, 2250, 1690, 1650, 1620, 1535	3.6 (s, CO_2CH_3, 3H), 4.2 (s, CH_2-ring, 2H), 7.36 (s, C_6H_5, 5H), 7.8 (m, NH_2, 2H)
11	$C_8H_{13}N_2O_3Cl$	55.60 (55.65)	7.52 (7.58)	16.20 (16.22)	156-160	90	3380, 3180, 2500, 1650, 1700, 1600	1.43 (t, J = 8.0 Hz, CH_2CH_3, 3H), 3.2 and 3.33 (two s, NCH_3, 3H), 4.43 (s, CH_2-ring, 2H), 4.33 (q, J = 6 Hz, CH_2CH_3, 2H), 7.7, 8.53 (two br, NH_2, 2H)
12	$C_{13}H_{15}N_2O_3Cl$	66.52 (66.51)	6.45 (6.44)	11.93 (11.93)	176-179	81	3350, 3150, 2260, 1680, 1650, 1620, 1540	1.2 (t, J = 8.0 Hz, CH_2CH_3, 3H), 4.1 (q, J = 6.0 Hz, CH_2CH_3, 2H), 4.13 (s, CH_2-ring, 2H), 7.3 (s, C_6H_5, 5H), 7.2 and 7.8 (two b-sh, NH_2, 2H)
14	$C_7H_{10}N_2O_3$	49.37 (49.40)	5.91 (5.92)	16.46 (16.46)	226-234	88	3390, 3380, 3110, 1680, 1640	3.06 (s, NCH_3, 3H), 3.7 (s, CO_2CH_3, 3H), 3.73 (s, CH_2-ring, 2H), 7.73 (4s, NH_2, 2H)
15	$C_{12}H_{12}N_2O_3$	62.00 (62.06)	5.18 (5.21)	12.16 (12.06)	245	63	3410, 3290, 3220, 1670, 1650, 1620 1545	3.5 (s, CO_2CH_3, 3H), 3.9 (s, CH_2-ring, 2H), 7.2 (m, C_6H_5, 5H), 7.7 (br, NH_2, 2H)
16	$C_8H_{12}N_2O_3$	52.00 (52.16)	6.58 (6.57)	15.20 (15.21)	217-221	78	3380, 3280, 1680, 1640	1.33 (t, J = 8.0 Hz, CH_2CH_3, 3H), 3.03 (s, NCH_3, 3H), 3.63 (s, CH_2-ring, 2H), 4.23 (q, J = 6.0 Hz, $CO_2CH_2CH_3$, 2H), 7.6 (br, NH_2, 2H)
17	$C_{13}H_{14}N_2O_3$	63.41 (63.40)	5.75 (5.73)	11.39 (11.38)	212-214	68	3400, 3290, 3220, 1670, 1650, 1620, 1545	1.36 (t, J = 8.0 Hz, CH_2CH_3, 3H), 4.1 (s, CH_2-ring, 2H), 4.3 (q, J = 6.0 Hz, CH_2CH_3, 2H), 7.1-7.7 (m, C_6H_5 and NH_2, 7H)
18	$C_6H_7N_3O$	52.50 (52.54)	5.14 (5.15)	30.61 (30.64)	234-238	40	3380, 3280, 2200, 1700, 1600	2.93 (s, NCH_3, 3H), 3.6 (s, CH_2-ring, 2H), 7.66 (s, NH_2, 2H)

2-Amino-pyrrolin-4-ones can occur in tautomeric forms AB [C/D] (Scheme 2).

Scheme 2



In order to confirm the structure of 2-amino-pyrrolin-4-ones in the solid state, a X-ray crystal structure determination was carried out. Figure 1 shows the molecular structure together with the atomic numbering scheme of **13**. Interatomic distances, selected fractional atomic coordinates and bond angles are given in Tables 3-6.

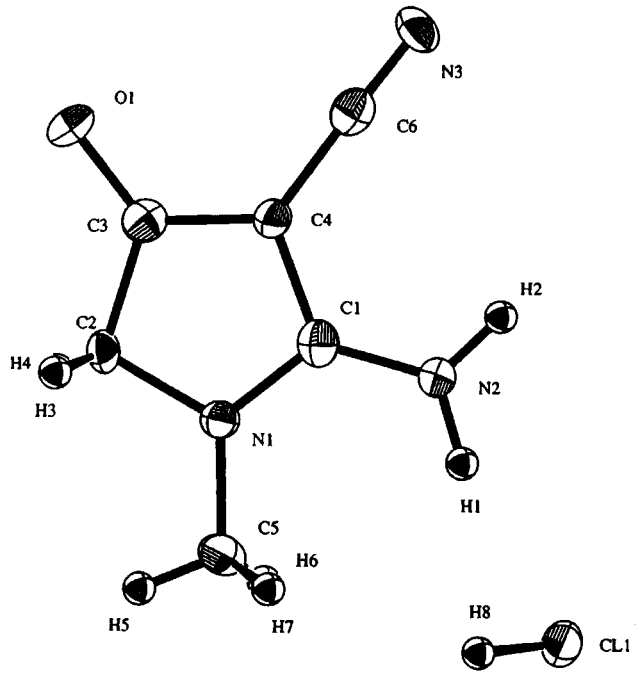


Figure 1. Molecular structure together with the atomic numbering scheme of **13**.

Table 3

Interatomic Distances (Å) in **13** with Standard Deviations in Parentheses

Atom	Atom	Distance
Cl(1)	H(8)	1.039
O(1)	C(3)	1.304(8)
N(1)	C(1)	1.328(8)
N(1)	C(2)	1.448(8)
N(1)	C(5)	1.452(9)
N(2)	C(1)	1.315(8)
N(2)	H(1)	0.962
N(2)	H(2)	0.961
N(3)	C(6)	1.135(8)
C(1)	C(4)	1.44(1)
C(2)	C(3)	1.496(9)
C(2)	H(3)	0.958
C(2)	H(4)	0.960
C(3)	C(4)	1.356(9)
C(4)	C(6)	1.430(9)
C(5)	H(5)	0.947
C(5)	H(6)	0.949
C(5)	H(7)	0.975

Table 4

Fractional Atomic Coordinates for **13**

Atom	X	Y	Z
Cl(1)	0.7415(2)	0.0783(3)	0.92595(9)
O(1)	1.4209(7)	1.0522(9)	0.8305(2)
N(1)	1.2158(7)	0.555(1)	0.9065(3)
N(2)	0.9192(8)	0.505(1)	0.8512(3)
N(3)	0.9274(8)	1.034(1)	0.7392(3)
C(1)	1.081(1)	0.616(1)	0.8620(3)
C(2)	1.378(1)	0.713(1)	0.9050(3)
C(3)	1.318(1)	0.879(1)	0.8502(3)
C(4)	1.141(1)	0.819(1)	0.8263(3)
C(5)	1.216(1)	0.368(1)	0.9554(4)
C(6)	1.025(1)	0.938(1)	0.7767(3)
H(1)	0.8876	0.3684	0.8758
H(2)	0.8276	0.5608	0.8177
H(3)	1.3960	0.7844	0.9490
H(4)	1.4953	0.6359	0.8936
H(5)	1.3318	0.3596	0.9813
H(6)	1.1098	0.3810	0.9857
H(7)	1.2009	0.2238	0.9307
H(8)	0.8901	0.0587	0.9262

Table 5

Special Contacts for **13** with Standard Deviations in Parentheses

Atom	Atom	Distance
Cl(1)	O(1)	2.886(5)
Cl(1)	N(2)	3.154(6)
N(1)	N(2)	2.348(8)

Table 6

Intramolecular Bond Angles (°) in **13** with Standard Deviations in Parentheses

Atom	Atom	Atom	Angle
C(1)	N(1)	C(2)	111.0(5)
C(1)	N(1)	C(5)	127.9(6)
C(2)	N(1)	C(5)	121.0(5)
C(1)	N(2)	H(1)	122.18
C(1)	N(2)	H(2)	120.12
H(1)	N(2)	H(2)	117.70
N(1)	C(1)	N(2)	125.3(6)
N(1)	C(1)	C(4)	109.2(6)
N(2)	C(1)	C(4)	125.5(6)
N(1)	C(2)	C(3)	102.8(5)
N(1)	C(2)	H(3)	110.70
N(1)	C(2)	H(4)	110.69
C(3)	C(2)	H(3)	112.55
C(3)	C(2)	H(4)	112.03
H(3)	C(2)	H(4)	108.00
O(1)	C(3)	C(2)	124.4(6)
O(1)	C(3)	C(4)	126.8(7)
C(2)	C(3)	C(4)	108.8(6)
C(1)	C(4)	C(3)	108.2(6)
C(1)	C(4)	C(6)	124.4(6)
C(3)	C(4)	C(6)	127.3(6)
N(1)	C(5)	H(5)	111.42
N(1)	C(5)	H(6)	111.03
N(1)	C(5)	H(7)	109.50
H(5)	C(5)	H(6)	109.76
H(5)	C(5)	H(7)	107.58
H(6)	C(5)	H(7)	107.41
N(3)	C(6)	C(4)	177.3(7)

The N(1)-C(1) and N(1)-C(2) bond lengths (Figure 1) are 1.328 (8) Å and 1.448 (8) Å, respectively, indicating that the bond N(1)-C(1) has partial double bond character. The bond length C(3)-C(4) [1.356(9) Å] is significantly shorter than the value for C(1)-C(4) [1.44(1) Å], whereas the mean value for the formal double bond in pyrrole is 1.374 Å. Therefore, for compound **13** the formal double bond can be assigned to C(3)-C(4) [1.356 Å]. Similarly the double bond character of the exocyclic group C(1)-N(2) [1.315(8) Å] is evident. The chlorine atom Cl(1) was assigned near N(2) and O(1) on the basis of the corresponding short contact distances Cl(1)-O(1) [2.886(5) Å] and Cl(1)-N(2) [3.154(6) Å]. Figure 2 shows the packing diagram of compound **13**, with a view along the y axis.

In conclusion, a methodology for the synthesis of new type *N*-substituted-2-aminopyrrolin-4-ones was developed, employing 4-amino-3-hydroxybutenoates **4-8** as building units. The preparation and nmr spectroscopic studies of chiral 4-amino-3-hydroxybutenoates, as well as their application to cyclization reactions are currently under investigation.

EXPERIMENTAL

Melting points were determined on a Gallenkamp MF13-595 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 267 spectrometer. The ^{1}H nmr spectra were recorded on a Varian EM-360 60 MHz spectrometer, using tetramethylsilane as the internal reference; Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); J values are given in Hz. Elemental analyses were obtained from the University of Liverpool, Chemistry Department.

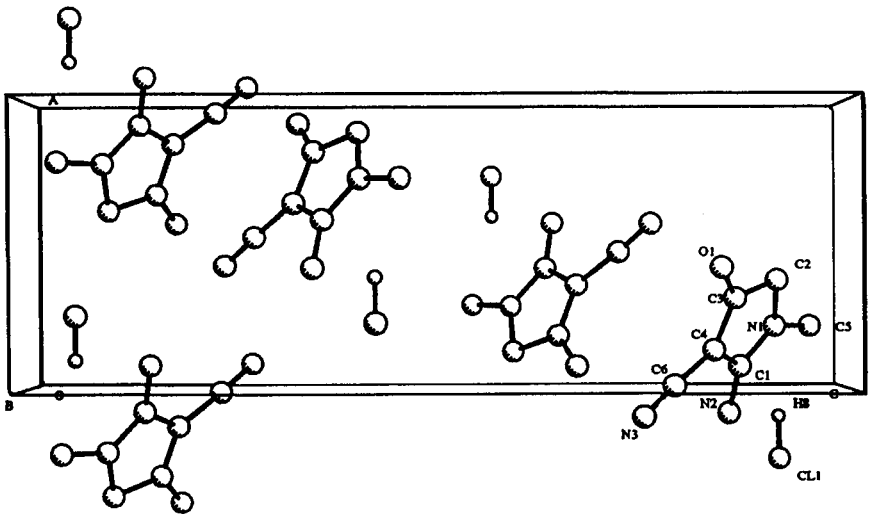


Figure 2. Packing diagram of compound **13**, with a view along the y axis.

N-Hydroxysuccinimide Esters of *N*-Acetylsarcosine **1** and *N*-Acetyl-*N*-phenylglycine **2**.

In a mixture of *N*-acetylsarcosine or *N*-acetyl-*N*-phenylglycine (30 mmoles), *N*-hydroxysuccinimide (3.5 g, 30 mmoles) and dimethoxyethane (60 ml) was added dropwise a solution of *N,N'*-dicyclohexylcarbodiimide (6.2 g, 30 mmoles) in dimethoxyethane (40 ml). The resulting mixture was stirred for 30 minutes after which it was refrigerated overnight. The precipitated *N,N'*-dicyclohexylurea was filtered off and the filtrate was concentrated *in vacuo* to give an oily residue (**1**) (7.4 g, 67%); ^{1}H nmr (deuteriochloroform): δ 2.16 (s, 3H), 2.8 (s, 4H), 3.05 and 3.13 (two s, 3H), 4.38 and 4.46 (two s, 2H), or a solid (**2**) (9.2 g, 71%), mp 102-105°; ^{1}H nmr (deuteriochloroform): δ 2.00 (s, 3H), 4.63 (s, 2H), 7.46 (m, 5H), 7.33 and 8.25 (two d, $A_2'B_2'$ system J = 9Hz, 4H).

General Method for the Preparation of Compounds **4-8**.

The active methylene compound **3** (72 mmoles) was added dropwise to a mixture of potassium *tert*-butoxide (5.4 g, 48 mmoles) in *tert*-butyl alcohol (55 ml) and the thick slurry thus formed was stirred at room temperature for 1 hour. A solution of **1** or **2** (24 mmoles) in 25 ml *tert*-butyl alcohol was then added to the mixture and stirring continued for 2 hours. Water was added to the reaction mixture and the aqueous layer was separated, washed with diethyl ether, acidified with 10% aqueous hydrochloric acid in an ice-water bath giving either a solid or an oily product that was extracted with chloroform.

General Method for the Preparation of Compounds **9-13**.

Compound **4-8** (14 mmoles) was added in a solution of 8% hydrochloric acid in ethanol [prepared from the addition of acetyl chloride (11 ml) in anhydrous ethanol (110 ml)]. The reaction mixture was stirred under reflux for 3 hours and set aside overnight at room temperature. The residue was evaporated *in vacuo* to give a solid product which was washed with diethyl ether and filtered off.

Preparation of Compound **13**.

The acidic water solution of the *C*-acylation compound **8** was evaporated *in vacuo* giving a brownish oily residue. This was treated with acetone affording sodium chloride which was filtered off. The filtrate was refrigerated overnight to afford a crystalline solid **13** (500 mg, 21%); ir (Nujol): ν max cm^{-1}, 3310, 3280, 2300, 2200, 1700, 16150; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.1 (s, 3H), 4.16 (s, 2H), 4.7 (s, 2H).

Anal. Calcd. for $C_6H_8N_3OCl$: C, 41.50; H, 4.61; N, 24.21. Found: C, 41.45; H, 4.58; N, 24.19.

General Method for the Preparation of Amines **14-18**.

Compound **14-18** (2 mmoles) was added to a solution (20 ml) of sodium ethoxide in ethanol [prepared from sodium (50 mg) in absolute ethanol (20 ml)]. After stirring for 1 hour, the reaction mixture was concentrated *in vacuo*, the resulting salt was filtered off and ethyl acetate was added to the filtrate solution. The solid product thus formed was filtered off and washed with small portions of ethanol and ethyl acetate.

X-ray Crystallographic Analysis of Compound **13**.

Crystallographic Data.

Molecular Formula: $C_6H_8N_3OCl$, M = [173.60], monoclinic, a = 6.950(6) Å, b = 5.866(5) Å, c = 19.400(4) Å, β = 90.65(4)°, V = 791(1) Å^3 (by least-squares refinement on twenty carefully centered reflections in the range $8.13<2\theta<17.2°$), λ = 0.71069 Å, space group $P2_1/n$ (# 14), Z = 4, D_x = 1.458 g cm^{-3}, colorless plates, dimensions of crystal used 0.3 x 0.1 x 0.3 mm, μ(MoK_α) = 4.25 cm^{-1}.

Data Collection and Processing.

The data were collected at a temperature of −120 ± 1° using the ω-2θ scan technique to a maximum 2θ value of 50.0°. Rigaku AFC6S diffractometer, graphite monochromated MoK_α radiation, ω-2θ scans to a maximum 2θ value of 50.0° with ω scan width (1.21 + 0.30 tan θ)°; 1671 reflections collected of which 1541 were unique (R_{int} = 0.094). The intensities of three representatives reflections which were measured after 150 reflections remained constant throughout data collection indicating crystal and electronic stability. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorenz and polarization effects.

Structure Solution and Refinement.

The structure was solved by direct methods [4]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the structure factor calculation in idealized positions (d_{C-H} = 0.95Å), and were assigned isotropic thermal parameters which are 20% greater than the $B_{equivalent}$ value of the atom to which they were bonded. The final cycle of full-matrix least-squares refinement was based on 875 observed reflections ($I > 3.00\sigma(I)$) and 100 variable parameters and converged (largest parameter shift was 0.03 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \mid |Fo| - |Fc| \mid / \Sigma |Fo| = 0.060$$

$$R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.078$$

The standard deviation of an observation of unit weight was 2.32. The weighting scheme was based on counting statistics and included a factor (p = 0.03) to downweight the intense reflections. Plots of $\Sigma w (|Fo| - |Fc|)^2$ *versus* |Fo|, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusal trends. The maximum and minimum peaks of the final difference Fourier map corresponded to 0.44 and -0.40 e$^-$/Å^3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber [5]. Anomalous dispersion effects were included in F_{calc} [6]; the values for Δf' and Δf" were those of Cromer [7]. All calculations were performed using the TEXSAN [8] crystallographic software package of Molecular Structure Corporation, including atom scattering factors and weighting scheme. The diagram was produced using PLUTO [9].

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