Syntheses and Conformations of Some Cyclic Hydroxamates. X-Ray Crystal Structure of 2-(*p*-Nitrobenzoyl)tetrahydro-2*H*-1,2-oxazine

James Elver Johnson,* Richard Hodzi, and Susan L. Todd

Department of Chemistry, Texas Woman's University,
Denton, Texas 76204, U. S. A.

Patrice de Meester and Shirley S. C. Chu*

School of Engineering and Applied Science, Southern Methodist University,
Dallas, Texas 75275, U. S. A.

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Alkylation of potassium *p*-nitrobenzohydroxamate with 1,4-dibromobutane gave 2-(*p*-nitrobenzoyl)tetrahydro-2*H*-1,2-oxazine (**3**). The X-ray crystal structure of **3** has been determined. The crystals are monoclinic, space group $P2_1/n$ with a = 6.749(1), b = 7.644(1), c = 21.557(2) Å, β = 98.89(1), V = 1098.8(2) Å^3 and Z = 4. The structure, which was refined to R = 0.039 using 1340 observed reflections, shows the oxazine and carbonyl oxygen atoms *trans* to each other. Alkylation of potassium benzohydroxamate with 1,3-dibromobutane gave a mixture of 3-methyl-2-benzoyloxazolidine (**4**) and 5-methyl-2-benzoyloxazolidine (**5**). The ^{1}H and ^{13}C nmr spectra of the mixture of **4** and **5** indicates that these cyclic hydroxamates exist predominantly in the *s-trans* conformation.

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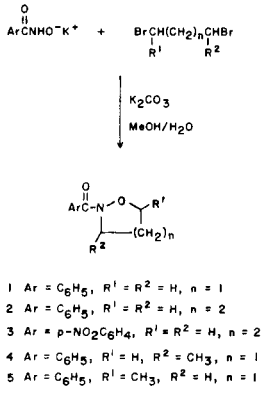
We have previously reported [1] the synthesis of two cyclic hydroxamates, 2-benzoyloxazolidine (**1**) and 2-benzoyltetrahydro-2*H*-1,2-oxazine (**2**), by the alkylation of potassium benzohydroxamate with 1,3-dibromopropane and 1,4-dibromopropane, respectively. The structural assignments for these compounds were based on spectroscopic correlations (^{1}H nmr, ir, and uv) established for open-chain hydroxamates [1]. Cyclic hydroxamates related to **1** and **2** have received limited attention [2], although Leclerc and coworkers [2b,2c] have reported some new examples of these ring systems which were synthesized by cyclization of *N*-[(haloalkyl)oxy]phthalimides in basic conditions.



1 Ar = C_6H_5, $R^1 = R^2$ = H, n = 1
2 Ar = C_6H_5, $R^1 = R^2$ = H, n = 2
3 Ar = p-$NO_2C_6H_4$, $R^1 = R^2$ = H, n = 2
4 Ar = C_6H_5, R^1 = H, $R^2 = CH_3$, n = 1
5 Ar = C_6H_5, $R^1 = CH_3$, R^2 = H, n = 1

To confirm our previous structural assignments based on spectroscopic evidence of **1** and **2**, which are both liquids at room temperature, we have obtained single crystals of compound **3** (the *p*-nitro derivative of **2**) and determined its structure. We also report on the reaction of potassium benzohydroxamate with 1,3-dibromobutane.

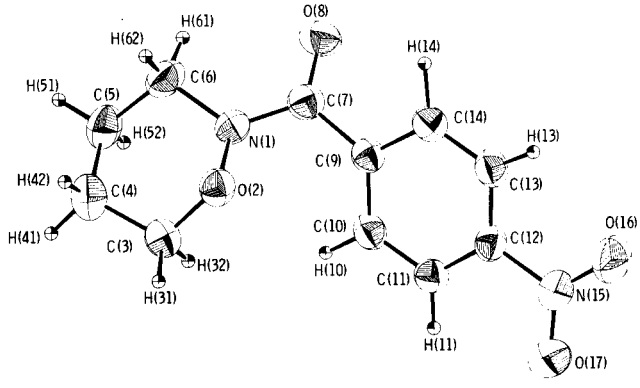


Figure 1. ORTEP drawing of one molecule of **3**. Thermal ellipsoids are scaled to the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radii.

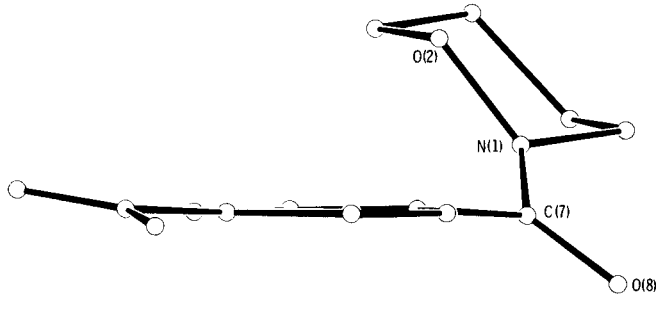


Figure 2. Side view of molecule **3** showing the chair conformation of the 1,2-oxazine ring.

Results and Discussion.

Alkylation of potassium *p*-nitrobenzohydroxamate with 1,4-dibromobutane gave 2-(*p*-nitrobenzoyl)tetrahydro-2*H*-

1,2-oxazine (**3**) as a crystalline solid. The crystal structure of **3** has been determined. The identification of the atoms and the conformation of the molecule are shown in the ORTEP [3] drawing in Figure 1. The bond lengths, bond angles, and some selected torsion angles are given in Table 3. Figure 2 shows that the tetrahydro-1,2-oxazine moiety is in the chair conformation. Thus, the crystal structure of **3** confirms our original structural assignment for **2** and substantiates the spectroscopic correlations used to assign the oxazolidine structure of **1**.

The crystal structures of open-chain hydroxamic acids, RC(=O)NROH, have shown the hydroxamic acid functional group to be in a planar *s-cis* conformation [4-6]. Dipole moment measurements [7] and infrared spectra [8] indicate this conformation is retained in solution. Two exceptions to this behavior are *N,N'*-diisopropyladipohydroxamic acid [8] and *N*-hydroxyurea [9] which exist in the planar *s-trans* conformation in the solid state. The X-ray structure of **3** shows that the carbonyl oxygen is *trans* to the 1,2-oxazine oxygen atom (Figure 1). The *s-trans* con-

Table 1

Crystal and Experimental Data of **3**

Chemical formula	$C_{11}H_{12}N_2O_4$
Formula weight	236.23
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 6.749(1) Å
	b = 7.644(1)
	c = 21.557(2)
	β = 98.89(1)°
	V = 1098.8(2) Å^3
Number of molecules per unit cell	4
Density (calculated)	1.428 g cm^{-3}
X-radiation used for data collection	λ(MoKα) = 0.71069 Å
Linear absorption coefficient	1.03 cm^{-1}
Total number of reflections with $2\theta < 50°$	1938
Number of reflections with $I > 3\sigma(I)$	1340
Maximum residual electron density	0.13 e Å^{-3}
R factors	R = 0.039
	R_w = 0.035
Crystal size	0.54 x 0.52 x 0.17 mm

Table 2

Atomic Coordinates and Temperature Factors
(anisotropic for non-H, isotropic for H atoms)

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	1.0539(3)	0.0746(3)	0.7714(1)	0.042(1)	0.059(1)	0.042(1)	0.009(1)	0.009(1)	−0.005(1)
O(2)	0.8896(2)	0.1911(2)	0.7581(1)	0.052(1)	0.046(1)	0.044(1)	0.007(1)	0.008(1)	−0.002(1)
C(3)	0.7364(3)	0.1092(3)	0.7126(1)	0.052(2)	0.052(2)	0.045(1)	0.002(1)	0.002(1)	0.003(1)
C(4)	0.8183(4)	0.0687(3)	0.6527(1)	0.076(2)	0.061(2)	0.044(1)	0.004(2)	0.005(1)	−0.002(1)
C(5)	1.0080(4)	−0.0404(3)	0.6663(1)	0.070(2)	0.058(2)	0.044(1)	0.005(2)	0.016(1)	−0.012(1)
C(6)	1.1556(3)	0.0452(3)	0.7171(1)	0.054(2)	0.062(2)	0.053(1)	0.003(1)	0.021(1)	−0.008(1)
C(7)	1.1452(3)	0.0660(3)	0.8320(1)	0.044(2)	0.044(2)	0.048(1)	−0.004(1)	0.007(1)	−0.006(1)
O(8)	1.3162(2)	0.0113(2)	0.8448(1)	0.043(1)	0.088(1)	0.062(1)	0.013(1)	0.002(1)	−0.012(1)
C(9)	1.0274(3)	0.1193(3)	0.8822(1)	0.042(1)	0.040(1)	0.038(1)	−0.001(1)	0.003(1)	0.002(1)
C(10)	0.8276(3)	0.0747(3)	0.8826(1)	0.045(1)	0.045(2)	0.038(1)	−0.005(1)	0.001(1)	0.000(1)
C(11)	0.7335(3)	0.1196(3)	0.9325(1)	0.039(1)	0.054(2)	0.043(1)	−0.005(1)	0.004(1)	0.005(1)
C(12)	0.8397(3)	0.2115(3)	0.9818(1)	0.047(2)	0.048(2)	0.036(1)	0.002(1)	0.009(1)	0.005(1)
C(13)	1.0382(4)	0.2557(3)	0.9835(1)	0.051(2)	0.053(2)	0.038(1)	−0.006(1)	0.002(1)	−0.003(1)
C(14)	1.1321(3)	0.2080(3)	0.9336(1)	0.043(1)	0.055(2)	0.043(1)	−0.004(1)	0.003(1)	0.001(1)
N(15)	0.7391(3)	0.2682(3)	1.0342(1)	0.059(1)	0.073(2)	0.045(1)	−0.001(1)	0.014(1)	−0.001(1)
O(16)	0.8410(3)	0.3277(3)	1.0810(1)	0.081(1)	0.108(2)	0.054(1)	−0.021(1)	0.018(1)	−0.029(1)
O(17)	0.5578(3)	0.2508(3)	1.0284(1)	0.054(1)	0.166(2)	0.066(1)	0.001(2)	0.017(1)	−0.022(1)
H(10)	0.756(3)	0.013(2)	0.846(1)	0.049(6)					
H(11)	0.597(3)	0.088(2)	0.934(1)	0.054(6)					
H(13)	1.096(2)	0.326(3)	1.018(1)	0.062(6)					
H(14)	1.288(3)	0.241(3)	0.930(1)	0.082(7)					
H(31)	0.621(3)	0.204(3)	0.709(1)	0.061(6)					
H(32)	0.685(3)	0.006(3)	0.733(1)	0.066(7)					
H(41)	0.710(3)	0.006(3)	0.621(1)	0.079(7)					
H(42)	0.850(3)	0.177(3)	0.633(1)	0.072(7)					
H(51)	1.063(3)	−0.061(3)	0.629(1)	0.056(6)					
H(52)	0.974(3)	−0.172(3)	0.682(1)	0.070(7)					
H(61)	1.269(3)	−0.024(3)	0.732(1)	0.060(6)					
H(62)	1.207(3)	0.167(3)	0.701(1)	0.079(7)					

The expression for the anisotropic thermal parameters is

$$T = \exp\{-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)\}$$

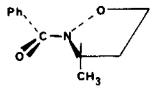
formation has been found to be the favored conformation in solution for *O,N*-dialkylated formohydroxamates [10,11] which are structurally related to the hydroxamate **3**.

Reaction of potassium benzohydroxamate with 1,3-dibromobutane gave a mixture of 3-methyl and 5-methyl-1-benzoyloxazolidine (**4** and **5** respectively). The ^{1}H nmr spectrum of the reaction product showed two methyl doublets in a ratio of 75:25 at δ 1.33 and δ 1.22. The hplc analysis of the mixture showed two peaks in approximately the same ratio, but unfortunately we were unable to separate the mixture on a preparative scale.

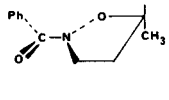
Since alkylation of the hydroxylamine oxygen of potassium benzohydroxamate is likely to be an S_N2 process, there should be preference for reaction at the primary carbon of 1,3-dibromobutane in the first step of the dialkylation process. Thus, 3-methyl-2-benzoyloxazolidine (**4**) would be expected to be the major product of the reaction.

The ^{13}C nmr spectrum of the reaction product is consistent with this expectation. Although every nonaromatic carbon absorption in the ^{13}C nmr spectrum is accompanied by a smaller absorption, the structural assignments can be made most readily from the OCH_2 (δ = 68.5 ppm) of **4** which is downfield from the NCH_2 (δ = 44.8 ppm) absorption of **5**. The OCH_2 absorption is the larger of the two and we conclude that 3-methyl-1-benzoyloxazolidine (**4**) is the major product of the alkylation reaction.

It is interesting that the methyl group in **4** is farther downfield in the ^{1}H and ^{13}C nmr spectra than the methyl group in **5**. We suggest that these isomers exist predominantly in the *s-trans* conformation [**4** (*s-trans*) and **5** (*s-trans*)] and the shielding effect of the carbonyl oxygen,



4 (s-trans)



5 (s-trans)

which is *cis* to the methyl group in **4**, causes the downfield shift in the ^{1}H and ^{13}C NMR absorptions of the methyl group in **4**.

An alternate interpretation of the ^{1}H and ^{13}C NMR spectra of the product obtained from the alkylation of potassium benzohydroxamate with 1,3-dibromobutane is that it is a mixture of slowly interconverting *s-cis* and *s-trans* isomers of **4**. This seems to be an unlikely explanation because the free enthalpy of activation for rotation around the C-N bond in open-chain *O,N*-dialkylated hydroxamic acids has been found to be only about 14 kcal/mole (coelescence temperatures of 0.5, −3.0 and −8.5° for three formohydroxamates) [10,11]. Furthermore, the ^{13}C nmr spectrum of this mixture is inconsistent with slowly interconverting conformers, because the separation between the absorptions for the OCH_2 of **4** (δ = 68.5 ppm) and the NCH_2 of **5** (δ = 44.8 ppm) is too large to be due to *s-cis* and *s-trans* conformers of **4**.

Table 3

Bond Lengths (Å), Bond Angles (°) and Selected Torsion Angles (°)
E.s.d.'s in parentheses

Bond lengths

N(1)−O(2)	1.417(3)	C(9) −C(10)	1.392(3)
N(1)−C(6)	1.463(3)	C(9) −C(14)	1.395(3)
N(1)−C(7)	1.357(3)	C(10)−C(11)	1.375(3)
O(2)−C(3)	1.452(3)	C(11)−C(12)	1.379(3)
C(3)−C(4)	1.513(3)	C(12)−C(13)	1.377(3)
C(4)−C(5)	1.518(3)	C(12)−N(15)	1.470(3)
C(5)−C(6)	1.511(3)	C(13)−C(14)	1.379(3)
C(7)−O(8)	1.218(3)	N(15)−O(16)	1.218(3)
C(7)−C(9)	1.495(3)	N(15)−O(17)	1.218(3)

Bond angles

O(2)−N(1)−C(6)	112.6(2)	C(7) −C(9) −C(14)	116.5(2)
O(2)−N(1)−C(7)	116.7(2)	C(10)−C(9) −C(14)	119.1(2)
C(6)−N(1)−C(7)	124.3(2)	C(9) −C(10)−C(11)	120.6(2)
N(1)−O(2)−C(3)	108.6(2)	C(10)−C(11)−C(12)	118.8(2)
O(2)−C(3)−C(4)	110.4(2)	C(11)−C(12)−C(13)	122.2(2)
C(3)−C(4)−C(5)	110.9(2)	C(11)−C(12)−N(15)	119.7(2)
C(4)−C(5)−C(6)	110.1(2)	C(13)−C(12)−N(15)	118.0(2)
N(1)−C(6)−C(5)	107.9(2)	C(12)−C(13)−C(14)	118.5(2)
N(1)−C(7)−O(8)	120.5(2)	C(9) −C(14)−C(13)	120.7(2)
N(1)−C(7)−C(9)	118.1(2)	C(12)−N(15)−O(16)	118.5(2)
O(8)−C(7)−C(9)	121.4(2)	C(12)−N(15)−O(17)	117.7(2)
C(7)−C(9)−C(10)	124.2(2)	O(16)−N(15)−O(17)	123.8(2)

Torsion angles

C(6)−N(1)−C(7)−O(8)	−9.1(4)	C(14)−C(9)−C(7)−O(8)	39.2(4)
C(6)−N(1)−C(7)−C(9)	173.1(2)	C(14)−C(9)−C(7)−N(1)	−142.9(3)
O(2)−N(1)−C(7)−O(8)	−158.9(3)	C(10)−C(9)−C(7)−C(8)	−135.8(3)
O(2)−N(1)−C(7)−C(9)	23.3(4)	C(10)−C(9)−C(7)−N(1)	42.0(4)

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. The high-performance liquid chromatography was carried out with a Model ALC-202 Waters Associates instrument equipped with a Varian Varichrome variable wavelength UV-VIS detector set at 254 nm. The hplc analyses were carried out on a Whatman Partisil 5 ODS-3 column with a 40:60 (V/V) acetonitrile-water solution as the mobile phase. Infrared spectra were determined with a Pye Unicam SP-1100 spectrophotometer and ^{1}H nmr spectra were obtained on a Varian EM-390 NMR spectrometer at 90 MHz. The ^{13}C nmr spectrum was measured with a JEOL FX-90Q at 22.6 MHz. The ultraviolet spectrum was measured on a Cary 15 spectrophotometer. Elemental analyses were performed at Atlantic Microlab.

2-(*p*-Nitrobenzoyl)tetrahydro-2*H*-1,2-oxazine (**3**).

A solution of potassium *p*-nitrobenzohydroxamate [12] (7.32 g), 1,4-dibromobutane (10.0 ml), and anhydrous potassium carbonate (11.6

g) in methanol (31 ml) and water (21 ml) was stirred for two days at 33°. The methanol was removed using a rotary evaporator at aspirator pressure; water (50 ml) was added to the residue, and the mixture was extracted with ether (2 x 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated to give a light yellow solid (6.80 g, 87%), mp 84-85°. Recrystallization of the crude product from 95% ethanol gave pale yellow needles, mp 84-85°; uv (acetonitrile): λ max 215 nm (ε = 4780), 261 nm (ε = 4550); ir (Nujol): 1665, 1610, cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.86 (m, 4, $CH_2CH_2CH_2CH_2$), 3.94 (m, 4, OCH_2 and NCH_2), 7.90 and 8.34 (two doublets, 4, aromatic H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.80; H, 5.16; N, 11.79.

3-Methyl-2-benzoyloxazolidine (**4**) and 5-Methyl-2-benzoyloxazolidine (**5**).

By the procedure described above (reaction time of three days), potassium benzohydroxamate [13] (14.7 g), 1,3-dibromobutane (20.0 g), and anhydrous potassium carbonate (23.2 g) in methanol (62 ml) and water (42 ml) yielded a mixture of **4** and **5** (8.80 g, 55%) as a colorless viscous liquid, bp 155-158° (2.8 torr); the hplc of the mixture showed two peaks in a ratio of 20:80; ^1H nmr (deuteriochloroform): δ 1.23 and 1.35 [two doublets integrating for a total of 3H, ratio of the two doublets is 25 (δ = 1.23); 75 (δ = 1.35), CH_3], 1.60-2.15 and 2.22-2.68 (two multiplets integrating for 1H each, $CH_2CH_2CHCH_3$), 3.55-4.85 (three multiplets integrating for a total of 3H, $CHCH_3$, OCH_2, and NCH_2, 7.30-7.70 (m, 3, aromatic H), 7.70-8.10 (m, 2, aromatic H). ^{13}C nmr (deuteriochloroform): δ 126.9, 127.3, 128.1, 130.1, 132.9, 133.0 (aromatic for both **4** and **5**), assignments for **4** δ 19.7 (q, CH_3), 34.7 (t, OCH_2CH_2), 51.9 (d, CH), 68.5 (t, OCH_2), 168.3 (s, C=O), assignments for **5** δ 17.2 (q, CH_3), 33.3 (t, NCH_2CH_2), 44.8 (t, NCH_2), 76.6 (d, CH), 167.9 (s, C=O).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.70; H, 6.92; N, 7.29.

Structure Determination of **3**.

Accurate unit-cell parameters were obtained by least-squares fit of 15 reflections in the range $17 < 2\theta < 25$ measured on a Syntex $P2_1$ diffractometer. The crystal data are summarized in Table 1. The intensity data were collected in the $\theta/2\theta$ scan mode using graphite monochromated MoKα radiation. Three standard reflections remeasured at intervals of every 100 reflections did not show any significant change during data collection. The intensity data were reduced to structure amplitudes by application of the Lorentz and polarization corrections. No absorption or extinction correction was applied. The structure was solved by direct methods using MULTAN [14] which showed the positions of all non-H atoms. Refinements were carried out by full matrix least-squares using SHELX76 [15]. Successive difference Fourier maps revealed the positions of all H atoms. All non-H atoms were refined anisotropically and the H atoms isotropically. In the final stages of refinement, a weighting scheme $w = 1/\sigma(F^2)$ was used. The quantity minimized in the least-squares was $\Sigma w(|F_o|-|F_c|)^2$. The final agreement factors are R = 0.039 and R_w = 0.035 for the 1340 observed reflections. The maximum shift in the final cycle of refinement was 0.03σ. The atomic scattering factors for C, H, N and O used were those stored in SHELX76. Positional and thermal parameters are given in Table 2.

Acknowledgments.

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REFERENCES AND NOTES

[1] J. E. Johnson, J. R. Springfield, J. S. Hwang, L. J. Hayes, W. C. Cunningham, and D. L. McClaugherty, *J. Org. Chem.*, **36**, 284 (1971).

[2a] L. Horner and M. Jordan, *Ann. Chem.*, 1518 (1978); [b] N. Amlaiky, G. Leclerc, and A. Carpy, *J. Org. Chem.*, **47**, 517 (1982); [c] M. Bouzouboa and G. Leclerc, *Tetrahedron Letters*, **25**, 3067 (1984).

[3] C. K. Johnson, ORTEP Report ORNL-3784, Oak Ridge National Laboratory, Tennessee (1965).

[4] S. Gottlicher and P. Ochsenreiter, *Chem. Ber.*, **107**, 391 (1974).

[5] I. K. Larsen, *Acta Crystallogr., Sect. B*, **34**, 962 (1978).

[6] B. H. Bracher and R. W. H. Small, *Acta. Crystallogr. Sect. B.*, **26**, 1705 (1970).

[7] O. Exner, *Collect. Czech. Chem. Commun.*, **30**, 652 (1965).

[8] W. L. Smith and K. N. Raymond, *J. Am. Chem. Soc.*, **102**, 1252 (1980).

[9] H. Bermon and S. H. Kim, *Acta Crystallogr.*, **23**, 180 (1967).

[10] T. Kolasa, *Tetrahedron*, **39**, 1753 (1983).

[11] W. Walter and E. Schaumann, *Ann. Chem.*, 743, 154 (1971).

[12] Prepared according to the procedure described for the synthesis of potassium benzohydroxamate (ref [13]).

[13] C. R. Hauser and W. B. Renfrow, Jr., "Organic Syntheses", John Wiley and Sons, New York, Collect Vol **2**, 1943, p 67.

[14] P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson. A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data (1978). Universities of York, England and Louvain, Belgium.

[15] G. M. Sheldrick SHELX76 Programs for Crystal Structure Determination, University of Cambridge, England (1976).