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On the Conformation of Naloxone, a Narcotic Antagonist

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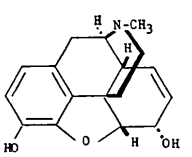
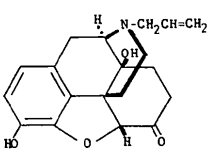
The narcotic antagonist naloxone ($C_{19}H_{21}NO_4$), the *N*-allyl derivative of oxymorphone, appears to be 100 to 1000 times more potent than its agonist oxymorphone in enhancing receptor binding in the brain. The conformation of the *N*-allyl chain, the pertinent feature in this molecule, is not completely extended but has an N–C–C=C torsional angle of $-98°$, reminiscent of the N–C–C–C torsional angle of $+97°$ in the cyclopropyl methyl chain in cycloazocine. The conformation of the ring system in naloxone is similar to that in morphine and codeine. Hydrogen bonding does not occur directly between alkaloid moieties as in morphine and codeine. The naloxone molecules are separated by layers of Cl^- ions and water molecules. The space group for naloxone.$HCl.2H_2O$ is $P2_12_12_1$ with $a=13{\cdot}293 \pm 0{\cdot}003$, $b=18{\cdot}592 \pm 0{\cdot}015$ and $c=7{\cdot}852 \pm 0{\cdot}002$ Å and $Z=4$. The R index for 1789 observed reflections is 6·0%.

Morphine, the standard, accepted analgesic, causes addiction with repeated doses. The search for a better analgesic without disturbing side effects has been reviewed by Eddy & May (1973). Parallel research projects spurred by the recent upsurge of addiction by drug abuse have led into the area of nonaddictive antagonists to morphine (I) and its derivatives, *e.g.* codeine (phenolic methyl ether of morphine) and heroin (diacetylmorphine) (see *e.g. Chem. Eng. News*, 1973). Cyclazocine (III), with an abbreviated morphine nucleus, showed promise from several points of view. It is a potent analgesic, and an effective nonaddicting antagonist to morphine, but it has a drawback in that it is hallucinogenic at therapeutic doses (Eddy & May, 1973). Methadone (IV) contains the alleged chemical essentials for activity; *i.e.* the benzene nucleus, the quaternary carbon and the tertiary nitrogen removed by two CH_2 groups from the quaternary carbon. It is an effective analgesic and the drug of choice to ameliorate the distress of withdrawal of other narcotics, but is itself habit-forming. Naloxone (II), on the other hand, although it does not have analgesic properties, is a potent nonaddictive antagonist to narcotics and is also very effective in counteracting undesirable side effects from narcotic antagonist analgesics. Its limited use has been due to its short duration of action. Experiments are underway which show that this difficulty may be overcome by imbedding naloxone in a biodegradable plastic pellet which is inserted surgically under the skin. The naloxone is released slowly and one application is effective over a period of months.



(I)



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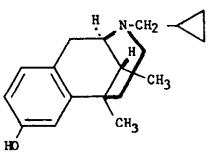

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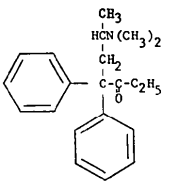

(IV)

Naloxone binds specifically to physiologically significant receptor sites in the corpus striatum (Pert & Snyder, 1973). Only drugs that present a high degree of molecular complementarity toward the site at which they act are believed to be able to form a drug-receptor complex (Korolkovas, 1970). Narcotic antagonists are 10 to 1000 times more potent than their corresponding agonists* in enhancing receptor binding (Pert, Pasternak & Snyder, 1973).

The detailed molecular structure of naloxone (II) was determined by X-ray diffraction analysis with the immediate objective of elucidating the structural features of an effective, nonaddicting narcotic antagonist, as well as the long-range objective of clarifying the nature of the drug–receptor complex in the nervous system. The geometry of the molecule can be compared with that of morphine (I) (Mackay & Hodgkin, 1955; Gylbert, 1973), codeine (Lindsey & Barnes, 1955; Kartha, Ahmed & Barnes, 1962), cyclazocine (III) (Karle, Gilardi, Fratini & Karle, 1969) and methadone (IV) (Bürgi, Dunitz & Shefter, 1973). This X-ray study has provided accurate parameters for quantum-chemical calculations on naloxone (J. Kaufman, in preparation) to determine charge distribution and the possible attracting sites which bind the receptor to the nervous system.

* An agonist is a compound which interacts with a receptor to cause a reaction. An antagonist competes with the agonist for the receptor site and prevents the agonist from acting.

Experimental

Crystals of naloxone.HCl.$2H_2O$ from water were provided by Dr Joyce Kaufman of the Johns Hopkins University. Diffraction data were collected from an irregular fragment (maximum dimension 0·5 mm) aligned along an optical extinction. Pertinent crystal data are: $C_{19}H_{21}NO_4$.HCl.$2H_2O$, M.W. 381·8, $P2_12_12_1$, $a=13{\cdot}293\pm0{\cdot}003$, $b=18{\cdot}592\pm0{\cdot}015$, $c=7{\cdot}852\pm0{\cdot}002$ Å, $V=1940{\cdot}6$ Å^3, $Z=4$, $D_x=1{\cdot}307$ g cm^{-3}. The data, 1797 observed reflections ($2\theta_{max}=126°$), were measured on a four-circle automatic diffractometer with Cu $K\alpha$ radiation, $\lambda=1{\cdot}54178$ Å, using the θ–2θ scan technique with a scan of $2{\cdot}0°+2\theta(\alpha_2)°-2\theta(\alpha_1)°$ at a speed of 2° min^{-1}. Background counts for 10 s were made at either end of the scan. Intensities were corrected for Lorentz and polarization factors and normalized structure factors $|E|$ were derived.

Phases were determined from the normalized structure factor magnitudes by means of the symbolic addition procedure (see *e.g.* Karle & Karle, 1966). The origin was specified by assigning the value of $+\pi/2$ to the phases of reflections 1,10,0, 055 and 407 and the enantiomorph was arbitrarily chosen by assigning $+\pi/2$ to reflection 11,0,5. Three additional phase assignments were made by using symbols a, b and m for reflections 10,0,2, 026 and 1,14,6. From multiple indications in the phase determination, it was clear that $a=\pi$, $m=-\pi/2$ and b was probably equal to π. The complete structure was visible in the first E map, including the two molecules of water of crystallization per asymmetric unit. The molecule, however, corresponded to the mirror image of the absolute configuration of codeine (Kartha, Ahmed & Barnes, 1962). Therefore all z coordinates were transformed to $z'=1-z$. The correct enantiomorph would have resulted if the phase for 11,0,5 had been chosen to be $-\pi/2$ instead of $+\pi/2$ (see above). All but four hydrogen atoms were found in a difference map computed after one cycle of refinement with anisotropic thermal factors for the 27 heavy atoms. Thermal parameters for the hydrogen atoms were assumed to be the same as for the heavy atoms to which they are attached. The weighting function was based on counting statistics. Refinement of the heavy atoms with the parameters for 22 hydrogen atoms kept constant resulted in an R value of 6·7% for all the data. The reflections 011, 022, 102, 103, 121, 200, 212 and 401, all of low index and with large $|F_o|$, are too small by a significant amount as compared to the calculated structure factors. These

Table 1. *Fractional coordinates and thermal parameters*

The thermal parameters are of the form $T=\exp[-\frac{1}{4}(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{12}hka^*b^*+2B_{13}hla^*c^*+2B_{23}klb^*c^*)]$. The standard deviations are those calculated by the least-squares program.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	0·6661	0·1881	0·1847	3·42	4·75	3·36	0·29	0·59	0·26
C(2)	0·6679	0·2634	0·1896	3·16	3·84	3·52	−0·42	0·36	−0·03
C(3)	0·6036	0·3025	0·2942	2·97	3·18	3·12	−0·41	−0·27	0·25
C(4)	0·5364	0·2648	0·3921	2·75	3·16	2·97	−0·01	0·37	−0·35
C(5)	0·3926	0·2302	0·5242	2·89	2·94	3·61	−0·14	0·56	−0·14
C(6)	0·3106	0·2323	0·3853	2·78	3·72	4·31	0·39	0·31	0·11
C(7)	0·2693	0·1615	0·3257	3·16	3·88	4·60	−0·12	−0·54	0·06
C(8)	0·3539	0·1077	0·2864	3·33	3·83	3·19	0·31	−0·38	−0·12
C(9)	0·5047	0·0412	0·4131	2·83	2·59	3·78	−0·07	−0·03	−0·24
C(10)	0·5837	0·0688	0·2845	3·50	3·52	4·40	0·26	0·95	−0·39
C(11)	0·5991	0·1499	0·2382	2·80	3·12	3·43	0·06	0·39	0·01
C(12)	0·5391	0·1897	0·3929	2·20	3·28	2·83	−0·07	0·10	−0·09
C(13)	0·4614	0·1620	0·5179	2·88	2·90	2·84	0·09	0·51	−0·10
C(14)	0·4154	0·0940	0·4471	2·89	3·23	2·97	−0·11	0·26	0·02
C(15)	0·5107	0·1474	0·6902	3·37	3·54	3·20	−0·01	0·23	−0·03
C(16)	0·5912	0·0893	0·6727	3·16	3·43	4·04	−0·43	−0·57	−0·17
C(17)	0·6258	−0·0367	0·5837	3·06	3·91	6·00	0·72	−0·32	−0·13
C(18)	0·5881	−0·1033	0·4973	4·89	4·69	6·92	1·18	−1·38	−0·05
C(19)	0·5505	−0·1567	0·5754	8·32	5·87	9·37	−0·28	−3·04	1·84
N	0·5481	0·0250	0·5851	2·67	3·10	3·88	−0·03	−0·20	0·30
O(1)	0·6081	0·3764	0·2909	3·85	3·13	4·29	−0·86	0·70	0·33
O(2)	0·4610	0·2916	0·4961	2·62	2·72	4·01	−0·12	0·74	−0·47
O(3)	0·2817	0·2890	0·3315	4·15	4·01	8·05	0·63	−1·79	0·58
O(4)	0·3534	0·0631	0·5750	2·65	3·64	3·38	−0·23	0·19	0·42
W(5)	0·3264	0·4310	0·4730	3·44	4·26	9·87	0·16	−1·48	−0·26
W(6)	0·2412	0·0535	0·9373	3·51	4·11	5·06	−0·11	−0·65	0·77
Cl^-	0·5498	0·4739	0·5717	3·43	4·34	4·35	−0·41	0·15	−1·17
Standard deviations									
C(1–17)	0·0004	0·0003	0·0007						
C(18–19)	0·0005	0·0004	0·0011						
O, N	0·0003	0·0002	0·0005						
Cl^-	0·0001	0·0001	0·0002						

reflections may be affected by extinction effects. When these reflections were omitted from the least-squares refinement, the R value was reduced to 6·0%.*

Fractional coordinates and thermal parameters for the heavy atoms are listed in Table 1 and the approximate coordinates for the hydrogen atoms as derived from the difference map are listed in Table 2. Bond lengths and angles are shown in Fig. 1 and torsional angles are listed in Table 3.

Table 2. *Approximate coordinates for hydrogen atoms as determined from a difference map*

	x	y	z
H(1)	0·6985	0·1654	0·0841
H(2)	0·7137	0·3987	0·0976
H(5)	0·3640	0·2335	0·6564
H(7)1	0·2194	0·1495	0·4351
H(7)2	0·2263	0·1827	0·2157
H(8)1	0·4093	0·1170	0·1869
H(8)2	0·3159	0·0566	0·2469
H(9)	0·4689	−0·0099	0·3803
H(10)1	0·6584	0·0504	0·3002
H(10)2	0·5596	0·0502	0·1482
H(15)1	0·5414	0·1955	0·7415
H(15)2	0·4662	0·1339	0·7784
H(16)1	0·6541	0·1093	0·5778
H(16)2	0·6013	0·0647	0·8076
H(17)1	0·6427	−0·0490	0·7110
H(17)2	0·6972	−0·0102	0·5509
H(18)	0·5582	−0·0964	0·3592
H(N)	0·4823	−0·0007	0·6506
H($W5$)1	0·3251	0·3943	0·3995
H($W5$)2	0·3865	0·4358	0·4992
H($W6$)1	0·3153	0·0508	0·9241

Structure

Molecule

Rings A, B and C in naloxone and morphine are identical chemically and corresponding bond lengths and angles in these rings in naloxone, Fig. 1, and morphine (Gylbert, 1973) do not show any significant differences except for C(13)–C(14) which is 0·04 Å longer in morphine. Ring D differs in the two compounds in that in naloxone C(7)–C(8) is saturated and a carbonyl oxygen rather than an OH group is attached to C(6); hence some of the bond lengths and angles are necessarily different. The attachments to ring E differ in the two compounds in the substitution of a hydroxyl group for a hydrogen atom on C(14) in naloxone, and the substitution of an allyl chain for the methyl group on the N atom. The three C–N distances are unequal in both compounds; however, C(9)–N is the longest bond in morphine and codeine whereas C(17)–N is the longest in naloxone.

* A table of observed and calculated structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30415 (8 pp.). Copies of this table may be obtained through The Exectuive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Torsional angles for naloxone*

Ring A	C(1)C(2)C(3)C(4)	−0·9°
	C(2)C(3)C(4)C(12)	4·3
	C(3)C(4)C(12)C(11)	−6·7
	C(4)C(12)C(11)C(1)	4·8
	C(12)C(11)C(1)C(2)	−1·1
	C(11)C(1)C(2)C(3)	−0·8
Ring B	C(4)O(2)C(5)C(13)	31·0
	O(2)C(5)C(13)C(12)	−31·1
	C(5)C(13)C(12)C(4)	21·3
	C(13)C(12)C(4)O(2)	−3·5
	C(12)C(4)O(2)C(5)	−17·6
Ring C	C(9)C(10)C(11)C(12)	−4·1
	C(10)C(11)C(12)C(13)	4·4
	C(11)C(12)C(13)C(14)	−32·7
	C(12)C(13)C(14)C(9)	56·2
	C(13)C(14)C(9)C(10)	−60·4
	C(14)C(9)C(10)C(11)	33·1
Ring D	C(5)C(6)C(7)C(8)	−47·5
	C(6)C(7)C(8)C(14)	60·6
	C(7)C(8)C(14)C(13)	−58·8
	C(8)C(14)C(13)C(5)	43·6
	C(14)C(13)C(5)C(6)	−28·8
	C(13)C(5)C(6)C(7)	31·0
Ring E	NC(9)C(14)C(13)	64·8
	C(9)C(14)C(13)C(15)	−64·6
	C(14)C(13)C(15)C(16)	58·2
	C(13)C(15)C(16)N	−51·7
	C(15)C(16)NC(9)	57·2
	C(16)NC(9)C(14)	−63·3
Chain	C(9)NC(17)C(18)	−51·0
	C(16)NC(17)C(18)	−179·6
	NC(17)C(18)C(19)	−97·9

The conformations of the morphine, codeine and naloxone molecules are similar. The T-shape can be characterized by the angle between the two least-squares planes containing atoms in rings A, B and C for one plane and atoms in rings D and E plus O(3)

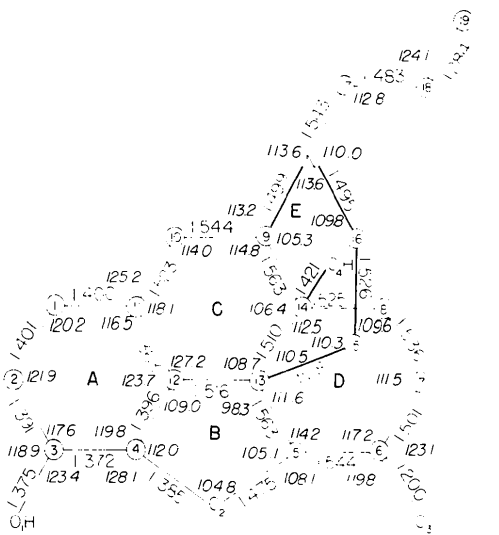

Fig. 1. Bond lengths and angles for naloxone. The standard deviations for the bond lengths are near 0·007 Å and 0·6° for the bond angles. C(5)–C(13)–C(14) 117·0°, C(12)–C(13)–C(15) 110·0°, C(8)–C(14)–C(9) 111·8°, O(4)–C(14)–C(8) 109·9°, O(4)–C(14)–C(9) 107·8°, O(4)–C(14)–C(13) 108·3°.

and C(17) for the other plane. In morphine, the angle between these two planes is 90·9° while in naloxone the value for the same angle is 82·6°. The differences in the chemical bonding in rings *D* of the two compounds chiefly account for the difference in this angular value. The benzene ring (*A*) is essentially planar with the largest deviation from the least-squares plane for the six atoms in the ring being 0·029 Å. Deviations from planarity in ring *A* have the same pattern and magnitudes as in morphine (Gylbert, 1973). The deviations of atoms in rings *B* and *C* from the least-squares plane of ring *A* are shown in Table 4. Ring B is in the envelope conformation, E_5, with a pseudo-torsion angle $\Delta = 28°$ [if φ_0 is assigned to the rotation about C(5)–C(13)] (Altona, Geise & Romers, 1968) and ring *C* has five atoms roughly in a plane with C(14) 0·75 Å out of the plane. Rings *D* and *E* are in the chair conformation (ring *D* somewhat flattened) as indicated by the torsional angles in Table 3.

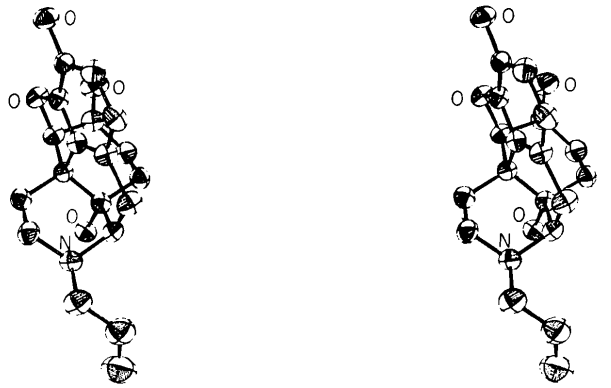

Fig. 2. Stereodiagram of the naloxone molecule. The thermal ellipsoids are at the 50% probability level.

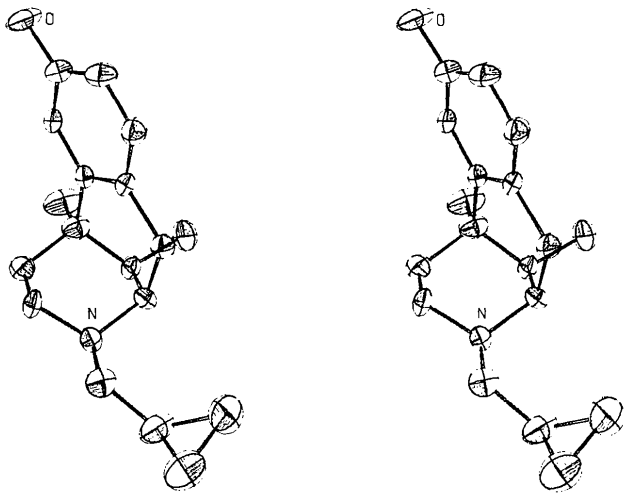

Fig. 3. Conformation of cyclazocine.

Table 4. *Deviations* (Å) *of atoms in rings A, B and C from the least-squares plane based on six atoms* in ring A*

The equation of the plane is: $9{\cdot}09252x - 0{\cdot}36935y + 5{\cdot}72571z = 7{\cdot}05249$ where x, y and z refer to the fractional coordinates.

Ring *A*	O(1)	+0·003			
	C(1)*	−0·008			
	C(2)*	+0·009			
	C(3)*	+0·009			
	C(4)*	−0·027	C(5)	−0·567	Ring *B*†
	C(11)*	−0·010	O(2)	−0·128	
	C(12)*	+0·029			
Ring *C*	C(13)	+0·048			
	C(14)	−0·750			
	C(9)	−0·113			
	C(10)	−0·142			

† Ring *B* also contains atoms C(4), C(12), C(13).

The atoms in the cyclazocine molecule (III), as illustrated in Fig. 3 (Karle, Gilardi, Fratini & Karle, 1969), can be directly superimposed upon naloxone, Fig. 2. Except for the atoms which are missing in cyclazocine (as compared to the morphine nucleus), the only significant difference between naloxone and cyclazocine occurs at the end of the side chain where the torsional angle N–C–C=C in naloxone is −98° while the equivalent torsional angle N–C–C–C in cyclazocine is +97°.

Packing

The packing of naloxone.HCl.$2H_2O$ is shown in the stereodiagram in Fig. 4. The Cl^- ion and the water molecules occur in layers near $b = 0$ and $\frac{1}{2}$. Seven hydrogen bonds, listed in Table 5, link the molecules into a three-dimensional network. The crystals of morphine.HI.$2H_2O$, codeine.HBr.$2H_2O$ and morphine.HCl.$3H_2O$ have very similar packing with NH···O hydrogen bonds between the alkaloid molecules, and halide ion is hydrogen-bonded only to water molecules. In naloxone, on the other hand, there is no direct hydrogen bonding between the alkaloid molecules. The N^+ atom forms an NH···Cl^- linkage.

Table 5. *Hydrogen bonds in naloxone.*HCl.$2H_2O$

Donor	Acceptor		Symmetry equivalents of acceptor
N	Cl^-	3,14 Å	$1-x, -\frac{1}{2}+y, 1\frac{1}{2}-z$
O(1)	Cl^-	2·96	x, y, z
W(5)	Cl^-	3·17	x, y, z
W(6)	Cl^-	3·15	$1-x, -\frac{1}{2}+y, 1\frac{1}{2}-z$
W(6)	O(1)	2·83	$-\frac{1}{2}+x, \frac{1}{2}-y, 1-z$
W(5)	O(3)	2·92	x, y, z
O(4)	*W*(6)	2·73	$\frac{1}{2}-x, y, -\frac{1}{2}+z$

Discussion

As expected from the similarities of the molecular formulas, naloxone and morphine have very similar conformations for the ring system. The point of importance in naloxone is the conformation of the side chain on the N atom. Recent experiments on receptor binding have shown naloxone to be 100 to 1000 times more

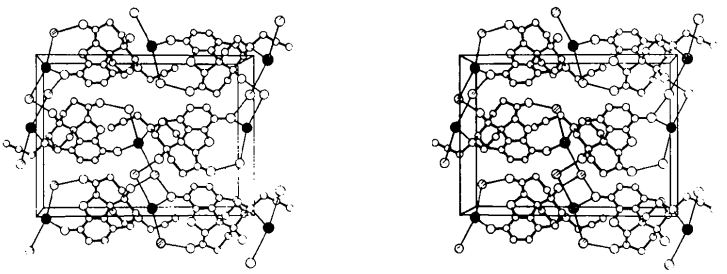

Fig. 4. Packing of naloxone.HCl.$2H_2O$. The solid circles represent the Cl^- ions while the shaded circles represent the O atoms in the H_2O molecules. The directions of the axes are $a \downarrow$, $b \rightarrow$ and c directed toward the viewer.

potent than the corresponding agonist oxymorphone (Pert, Pasternak & Snyder, 1973) where the only chemical difference in the molecules is the substitution of an allyl side chain for the methyl group on the N atom.

The substitution of CH_2–◁ for $CH_2CH=CH_2$ in naloxone yields compound EN-1639 in which some of the favorable properties of naloxone are increased. The conformation of EN-1639 can be predicted by combining the conformational parameters of naloxone with those of the N–CH–◁ moiety in cyclazocine (see the previous section).

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The Crystal and Molecular Structure of Hexakis(pyridine-*N*-oxide)nickel(II) Bis(tetrafluoroborate)

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Crystals of $Ni(PyNO)_6(BF_4)_2$ are rhombohedral, with $a = 12{\cdot}487$ (5) and $c = 18{\cdot}92$ (1) Å for the hexagonal cell (rhombohedral cell: $a = 9{\cdot}579$ Å, $\alpha = 81{\cdot}36°$); $Z = 3$. Diffractometer data (Mo $K\alpha$ radiation) were collected up to $\theta = 35°$. Anisotropic refinement was carried out with 2163 observed independent reflexions. Two models were refined, one in space group $R3$, the other in $R\bar{3}$. The final R_w values are 0·037 and 0·046 for space groups $R3$ and $R\bar{3}$ respectively. Both models contain disordered BF_4 groups. The ambiguity in choice of space group is discussed. Atomic parameters of both models are given. Geometrical data are based on the centrosymmetric model. The coordination of the Ni cation is nearly octahedral. Each $Ni(PyNO)_6$ group is surrounded by eight tetrafluoroborate groups. Lattice dimensions of a number of isomorphous complexes are presented.

Introduction

Complexes M(II) $(PyNO)_6(Anion)_2$ (PyNO = pyridine-*N*-oxide) of metals of the first transition series with the anions BF_4^- and ClO_4^- have been investigated by several authors. Reviews on the coordination chemistry of aromatic *N*-oxide compounds have been given by Garvey, Nelson & Ragsdale (1968) and Karayannis,