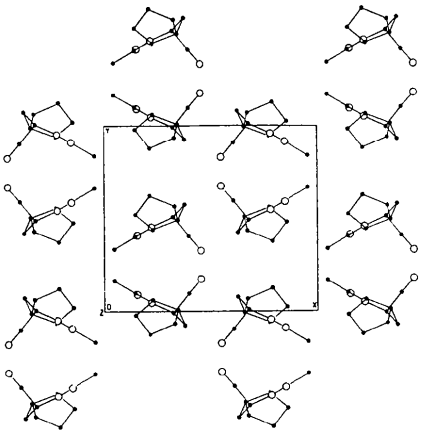

Fig. 3. Projection of the crystal structure of (I) at room temperature along the *c* axis.

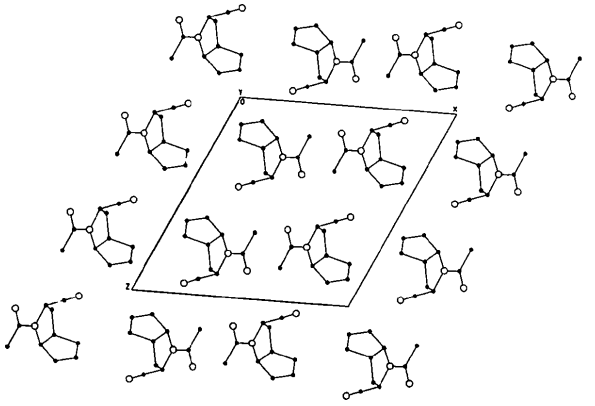

Fig. 4. Projection of the crystal structure of (II) at room temperature along the *b* axis.

The rows C6 and C7 of Table 4 give details of the conformation of the cyclopentane ring. The differences are much larger than in the pyrrolidine ring: (I) has an envelope conformation with C7 0·551 Å out of the plane of the other four atoms, (II) and (III) are disordered in this ring and (IV) has a twist conformation. This again indicates that the conformation of the cyclopentane ring is quite sensitive to the substituents of the ring system. In the line Δ(cp) the Δ values for the four compounds are shown. These emphasize that the cyclopentane ring has an envelope conformation in (I) and a twist conformation in (IV). The formal results for the disordered compound (II) at low temperature are twist in both forms and also twist for the disordered compound (III). Because always only one atom in the ring is disordered, one can conclude that in both disordered compounds there is in reality an envelope conformation. In the last row the angles of the plane of the acetyl group with the plane of the pyrrolidine ring can be found; these are rather small.

Plots of the crystal structures of (I) and (II) are given in Figs. 3 and 4. The various symmetry elements can be recognized quite easily. The structure of compound (II) shown in Fig. 4 is that at room temperature.

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Structures of Two Active Inotropic Cardiac Agents: Milrinone [5-Cyano-2-methyl-(3,4′-bipyridin)-6(1*H*)-one] (I) and Amrinone [5-amino-(3,4′-bipyridin)-6(1*H*)-one] (II)

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(*Received* 10 *August* 1986; *accepted* 24 *March* 1987)

Abstract. Milrinone (I), $C_{12}H_9N_3O$, $M_r = 211{\cdot}22$, $P2_1/c$, $a = 7{\cdot}067$ (1), $b = 10{\cdot}089$ (1), $c = 15{\cdot}477$ (2) Å, $\beta = 100{\cdot}74$ (1)°, $V = 1082{\cdot}2$ (3) Å^3, $Z = 4$, $D_x = 1{\cdot}29$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54018$ Å, $\mu = 6{\cdot}67$ cm^{-1}, $F(000) = 440$, $T = 257$ K, $R = 0{\cdot}060$ for 1969 unique reflections. Amrinone (II), $C_{10}H_9N_3O$, $M_r = 187{\cdot}2$, $P2_1/c$, $a = 9{\cdot}257$ (5), $b = 17{\cdot}064$ (6), $c = 22{\cdot}845$ (6) Å, $\beta = 99{\cdot}71$ (1)°, $V = 3557{\cdot}2$ (4) Å^3, $Z = 16$, $D_x = 1{\cdot}39$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}89$ cm^{-1}, $F(000) = 1568$, $T = 257$ K, $R = 0{\cdot}091$ for 3255 unique

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reflections. The orientation of the two pyridine rings of (I) is twisted 42·3 (5)° (C2–C1–C1′–C6′), whereas this angle in the four independent molecules in (II) is −13·4 (9), −11·8 (10), −8·7 (10) and −21·7 (10)°, respectively. These conformations differ from those reported for other structures of milrinone and amrinone.

Introduction. Milrinone (I) and amrinone (II) are members of a new class of nonglycosidic positive inotropic bipyridines which are useful in the treatment of congestive heart failure (Alousi, Farah, Lesher & Opalka, 1979; Endoh, Yamashita & Taira, 1982). Milrinone is approximately 30 times more potent than amrinone and also acts as a vasodilator. In addition, structure–activity relationship data indicate that the 2-methyl substituent of milrinone, rather than the 5-nitrile moiety, is primarily responsible for this increased potency (Robertson *et al.*, 1986). Recent observations have also shown that milrinone, but not amrinone, stimulates Ca^{2+}-ATPase activity in rabbit myocardial membrane in a manner similar to that observed for thyroid hormones (Mylotte, Cody, Davis, Davis, Blas & Schoenl, 1985). These data suggest that these inotropic agents show structural homologies with the thyroid hormones. To elucidate the structure–activity relationships of these inotropic agents, the crystal structures of milrinone (I) and amrinone (II) (Fig. 1) were studied and their conformations are compared with those of the thyroid hormones. The molecular conformations of milrinone and amrinone differ from those reported for their salt and hydrate, respectively (Robertson *et al.*, 1986).

Experimental. Samples were obtained from Sterling–Winthrop (Rensselaer, NY) and crystals of both compounds were obtained from ethanol solutions at room temperature; cell dimensions from least-squares refinement of 25 reflections, 2θ range 60·28 to 69·86° for (I); 25 reflections, 2θ range 11·86 to 27·49° for (II); Enraf–Nonius CAD-4 diffractometer, Ni-filtered Cu $K\alpha$ radiation, ω–2θscan, $\theta_{max} = 77°$ ($-19 < h < 0$, $0 < k < 12$, $-8 < l < 8$) for (I): for (II), Nicolet *P*3 diffractometer, Nb-filtered Mo $K\alpha$ radiation, θ–2θ scan, $\theta_{max} = 50°$ ($0 < h < 9$, $-1 < k < 17$, $-22 < l < 22$); (I) 0·16 × 0·32 × 0·54 mm, (II) 0·08 × 0·28 × 0·40 mm; 4 standard reflections monitored at intervals of 14 400 s (I), every 96 reflections for (II); no crystal decomposition; no correction for extinction or absorption; 2248 unique reflections (I), 1969 with $I > 3\sigma(I)$; 6274 unique reflections (II), 3255 with $I > 4\sigma(I)$; direct methods [*MULTAN*: Germain, Main & Woolfson (1971); *NQEST*: DeTitta, Edmonds, Langs & Hauptman (1975)]; refinement of *F* by full-matrix least squares; anisotropic thermal parameters; H-atom positions located in difference Fourier syntheses, positions not refined; final difference Fourier map for (I) and (II) showed no peaks > 0·15 e Å^{-3}, $\sum w(|F_o| - |F_c|)^2$ minimized, $w = 1/\sigma(F)^2$ (Stout & Jensen, 1968), final $R = 0{\cdot}060$, $wR = 0{\cdot}079$, max. Δ/σ 0·01 for 1969 data for (I); final $R = 0{\cdot}101$, $wR = 0{\cdot}091$, max. Δ/σ 0·02 for 3255 data (II); the relatively high *R* indices are attributable to the very thin crystals used for data collection. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974); all calculations performed on a VAX 11/780 computer using the Enraf–Nonius crystallographic package.

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* (Å^2 × 10) *for milrinone* (I)

$B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}(\mathbf{a}_i\mathbf{a}_j)$.

	x	*y*	*z*	B_{eq}
C(1)	−247 (2)	1232 (2)	8505 (1)	35 (1)
C(2)	1648 (2)	1559 (2)	8849 (1)	37 (1)
C(4)	2294 (2)	−627 (2)	9513 (1)	35 (1)
C(5)	365 (2)	−984 (2)	9105 (1)	34 (1)
C(6)	−846 (2)	−67 (2)	8633 (1)	35 (1)
C(21)	2617 (3)	2848 (2)	8725 (2)	51 (1)
C(51)	−261 (2)	−2313 (2)	9222 (1)	42 (1)
C(1′)	−1661 (2)	2181 (2)	8018 (1)	37 (1)
C(2′)	−2917 (3)	1783 (2)	7262 (1)	42 (1)
C(3′)	−4307 (3)	2653 (2)	6846 (1)	46 (1)
C(5′)	−3276 (3)	4269 (2)	7840 (1)	48 (1)
C(6′)	−1862 (3)	3470 (2)	8309 (1)	43 (1)
N(3)	2797 (2)	643 (1)	9332 (1)	37 (1)
N(52)	−798 (3)	−3364 (2)	9302 (1)	60 (1)
N(4′)	−4510 (2)	3893 (2)	7118 (1)	51 (1)
O(4)	3445 (2)	−1362 (1)	9992 (1)	43 (1)

Discussion. Final fractional coordinates and equivalent *B* values for the two structures are listed in Tables 1 and 2.* The molecular conformations of these structures are illustrated in Figs. 1 and 2. The conformation of these bipyridines is described by the torsion angle [C(2)–C(1)–C(1′)–C(6′)] between the two pyridine rings. As shown (Table 3), there is more conformational flexibility in the amrinone structure than the milrinone where the 2-methyl substituent causes the two rings to adopt a twist conformation. This flexibility was also noted in solution NMR studies (Robertson *et al.*, 1986). The geometry of the pyridinone ring reflects the nonaromaticity of this ring system compared to that of the pyridine ring as the average C–C bond length is 1·358 (8) and 1·425 (8) Å for alternating bonds of the four amrinone molecules; the average C–C bond distance is 1·380 (8) Å for the pyridine ring. A similar pattern is observed for milrinone. The pyridine rings in each molecule are planar.

The hydrogen-bonding patterns differ significantly between these two structures. Milrinone (I) forms

* Lists of structure factors, geometry and hydrogen bonding, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43830 (66 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

N(3)—H···O(4) [2·76 (2) Å] hydrogen bonds between inversion-related molecules, whereas the four independent molecules of amrinone form a more complex pattern involving the 5-amino, 4-keto and 4′-pyridine N atoms. The 5-amino group preferentially forms hydrogen bonds to the 4′-pyridine N atom, while the 3-pyridone N atom forms stronger hydrogen bonds to the keto function.

To understand the thyromimetic potential of milrinone and amrinone, the molecular conformations of these compounds were compared with that observed for thyroxine (Mylotte *et al.*, 1985). As illustrated (Fig. 3), computer graphics studies show that the best fit of the two structures results from the superposition of the milrinone-substituted ring with the iodophenolic ring of thyroxine. This superposition provides the best structural homology between the chemical and electronic properties of these two classes of molecules. There is even less structural homology between amrinone and thyroxine since the amino group of amrinone does not occupy the same volume as the cyano group, nor does it have the same electrochemical potential.

Table 2. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($Å^2 \times 10$) *for amrinone* (II)

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j \beta_{ij}(\mathbf{a}_i\mathbf{a}_j).$$

	x	y	z	B_{eq}
C(1)	1931 (7)	5969 (4)	7898 (3)	31 (2)
C(6)	3368 (7)	5906 (4)	8227 (3)	33 (2)
C(5)	3975 (7)	5175 (4)	8381 (3)	32 (2)
C(4)	3153 (7)	4486 (4)	8205 (3)	33 (2)
C(2)	1195 (7)	5300 (4)	7742 (3)	32 (2)
C(1′)	1243 (7)	6745 (3)	7769 (3)	27 (2)
C(2′)	−91 (7)	6825 (3)	7371 (3)	32 (2)
C(3′)	−730 (8)	7548 (4)	7260 (3)	42 (2)
C(5′)	1140 (8)	8146 (4)	7872 (4)	45 (2)
C(6′)	1850 (7)	7434 (4)	8013 (3)	36 (2)
N(3)	1794 (6)	4585 (3)	7886 (2)	36 (2)
N(51)	5323 (6)	5068 (3)	8723 (3)	44 (2)
N(4′)	−138 (6)	8219 (3)	7504 (3)	42 (2)
O(4)	3641 (5)	3805 (3)	8333 (2)	48 (2)
C(1′2)	2104 (7)	831 (4)	4657 (3)	31 (2)
C(2′2)	2848 (8)	145 (4)	4814 (3)	42 (2)
C(3′2)	2189 (8)	−558 (4)	4640 (3)	45 (2)
C(5′2)	127 (8)	36 (5)	4199 (3)	47 (2)
C(6′2)	683 (8)	759 (4)	4348 (3)	42 (2)
C(12)	2788 (7)	1614 (4)	4827 (3)	33 (2)
C(62)	4154 (7)	1669 (4)	5228 (3)	32 (2)
C(52)	4788 (8)	2384 (4)	5357 (3)	33 (2)
C(42)	4088 (8)	3080 (4)	5105 (3)	38 (2)
C(22)	2132 (7)	2282 (3)	4592 (3)	36 (2)
N(4′2)	838 (6)	−643 (3)	4333 (3)	43 (2)
N(521)	6146 (6)	2475 (3)	5716 (2)	39 (2)
N(32)	2792 (6)	2984 (3)	4731 (3)	41 (2)
O(42)	4628 (6)	3759 (3)	5211 (2)	46 (1)
C(13)	10854 (7)	−1591 (4)	1038 (3)	30 (2)
C(63)	12307 (7)	−1670 (4)	1350 (3)	34 (2)
C(53)	12919 (7)	−2393 (4)	1493 (3)	31 (2)
C(43)	12079 (7)	−3086 (4)	1323 (3)	34 (2)
C(23)	10103 (7)	−2247 (4)	873 (3)	33 (2)
C(1′3)	10162 (7)	−810 (4)	920 (3)	35 (2)
C(2′3)	8797 (9)	−716 (4)	569 (4)	52 (2)
C(3′3)	8197 (9)	18 (5)	479 (4)	57 (3)
C(5′3)	10122 (9)	571 (4)	1048 (4)	55 (3)
C(6′3)	10818 (8)	−126 (4)	1164 (4)	50 (2)
N(33)	10712 (6)	−2978 (3)	1013 (2)	36 (2)
N(513)	14284 (6)	−2498 (3)	1820 (2)	40 (2)
N(4′3)	8823 (7)	672 (3)	705 (3)	45 (2)
O(43)	12566 (5)	−3764 (3)	1438 (2)	41 (1)
C(14)	4677 (7)	985 (4)	1483 (3)	32 (2)
C(64)	5604 (7)	828 (4)	2035 (3)	34 (2)
C(54)	6325 (7)	130 (4)	2125 (3)	33 (2)
C(44)	6064 (7)	−477 (4)	1691 (3)	35 (2)
C(24)	4513 (8)	426 (4)	1067 (3)	39 (2)
C(1′4)	3919 (6)	1761 (4)	1386 (3)	32 (2)
C(2′4)	3635 (9)	2216 (4)	1851 (3)	52 (2)
C(3′4)	2990 (10)	2930 (5)	1745 (4)	60 (3)
C(5′4)	2758 (10)	2787 (5)	762 (4)	64 (3)
C(6′4)	3420 (9)	2046 (4)	824 (3)	50 (2)
N(34)	5189 (6)	−280 (3)	1178 (2)	38 (2)
N(514)	7392 (7)	−22 (3)	2614 (3)	47 (2)
N(4′4)	2569 (8)	3233 (4)	1207 (4)	61 (2)
O(44)	6609 (5)	−1151 (3)	1763 (2)	48 (2)

Table 3. *Conformational comparisons*

Structure	C(6′)—C(1′)—C(1)—C(2)(°)	Reference
Milrinone (I)	42·4	This work
Milrinone .HCl	52·2	Robertson *et al.* (1986)
Amrinone .H_2O	1·3	Robertson *et al.* (1986)
Amrinone (II)		This work
molecule 1	−13·4	
molecule 2	−11·8	
molecule 3	−8·7	
molecule 4	−21·7	

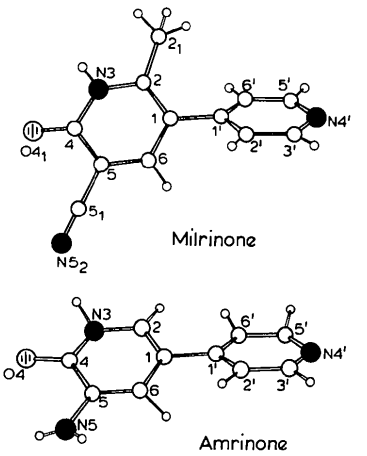

Fig. 1. Molecular conformation of milrinone and amrinone with their numbering schemes.

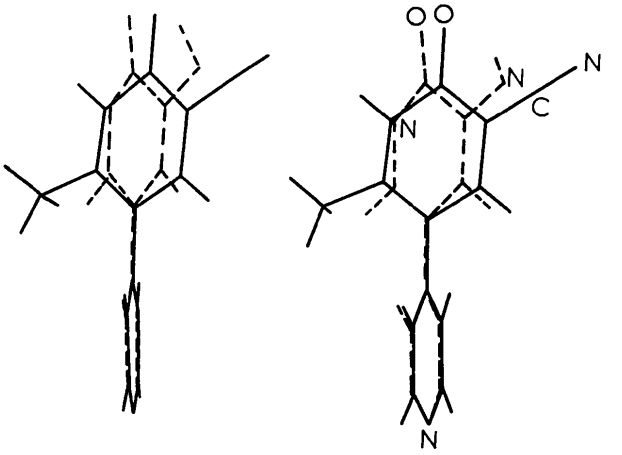

Fig. 2. Stereo superposition of amrinone, molecule 3 (dashed), and that of milrinone (solid).

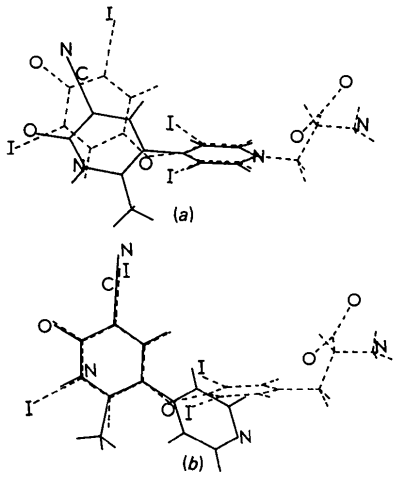

Fig. 3. (*a*) Superposition of the pyridine ring of milrinone (solid lines) on the tyrosyl ring of thyroxine (dashed lines). (*b*) Superposition of the pyridinone ring of milrinone (solid lines) on the phenolic ring of thyroxine (dashed lines). Note that the cyano group occupies the same space as the 5′-iodo group and that the keto and phenolic O atoms overlap in this orientation.

This research was supported in part by Grant AM-15051. The author thanks Walter Pangborn and Joe Luft for their technical assistance.

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Structure of the Diastereoisomeric Salt of (+)-2-Hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane and (1*R*,2*S*)-(−)-α-[(1-Methylamino)ethyl]benzyl Alcohol

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(*Received* 17 *September* 1986; *accepted* 23 *February* 1987)

Abstract. $C_{21}H_{30}NO_5P$, $M_r = 407{\cdot}445$, monoclinic, $P2_1$, $a = 13{\cdot}842$ (2), $b = 7{\cdot}804$ (2), $c = 10{\cdot}168$ (1) Å, $\beta = 92{\cdot}952$ (9)°, $V = 1096{\cdot}9$ Å^3, $Z = 2$, $D_x = 1{\cdot}234$ Mg m^{-3}, Cu $K\alpha$ radiation (graphite-crystal monochromator, $\lambda = 1{\cdot}54178$ Å), μ(Cu $K\alpha$) = 1·348 mm^{-1}, $F(000) = 436$, $T = 290$ K, final conventional R factor = 0·031, $wR = 0{\cdot}044$ for 2700 'observed' reflections and 342 variables. The structure contains phosphorinane cations and ephedrine anions which are linked in a three-dimensional network by N—H···O and O—H···O hydrogen bonds. The phosphorinane ring is in the usual chair conformation. The ephedrine is in the usual extended form.

Introduction. The present compound, denoted INAM, is the first of a series of crystal structure investigations on phosporinane ephedrine salts. The other compounds (INAP, CLINAM, CLINAP) are presented in the three following papers. These structural investigations are part of a study on crystallization properties of diastereoisomers. INAM and the following compound INAP (Smits, Beurskens, Kok & Wynberg, 1987; paper II) form a pair of diastereoisomers.

The synthesis of the dioxaphosphorinane, a novel chiral acidic resolving agent, has recently been described by ten Hoeve & Wynberg (1985). The crystal structure of the diastereoisomeric *n*-salt with ephedrine has been determined in order to discover significantly different structural features as an aid in a resolution protocol. Studies related to this subject have been published by Brianso (1981) and Gould & Walkinshaw (1984).

0108-2701/87/071328-04$01.50