

## Structure of the Cardiotonic Drug 2-[(2-Methoxy-4-methylthio)phenyl]-1*H*-imidazo[4,5-*b*]pyridine, AR-L 113BS

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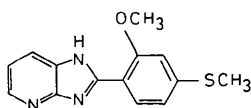
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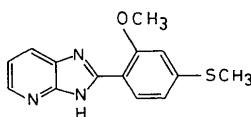
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**Abstract.** C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>OS,  $M_r=271.34$ , monoclinic,  $P2_1/c$ ,  $a=9.184$  (2),  $b=12.056$  (3),  $c=11.759$  (3) Å,  $\beta=92.02$  (3)°,  $V=1301.2$  (5) Å<sup>3</sup>,  $D_m=1.380$  (7),  $D_x=1.385$  (1) g cm<sup>-3</sup>,  $Z=4$ ,  $\lambda(\text{Cu } K\alpha)=1.5418$  Å,  $\mu=21.10$  cm<sup>-1</sup>,  $F(000)=568$ ,  $T=295$  K,  $R=4.7\%$  ( $wR=5.9\%$ ) for 1917 observed reflections. The totally planar molecule is present in its 1*H*-tautomer in the crystal with the methoxy group in a *cis* position with the imidazole nitrogen proton. This conformation is stabilized by an intramolecular hydrogen bond between the NH and the oxygen function.

**Introduction.** Several years ago we became involved in a research project aimed at finding new cardiotonic drugs that were devoid of the usual shortcomings encountered with conventional agents such as cardiac glycosides and beta adrenergic compounds. Our work led to the discovery of a new class of cardiotonic compounds which compared favourably with the conventional agents (Kutter & Austel, 1981). A representative of the most interesting members of this class is AR-L 113BS (1).



(1)



(2)

Structure–activity relationships have shown that both the free imidazole –NH and the oxygen function in

the 2-position of the phenyl ring are necessary for high potency. The most obvious interpretation of these findings in terms of the binding mode to a putative receptor would be that the compounds have to adopt a coplanar conformation. Stabilization of this conformation *via* hydrogen bonding between the NH and the oxygen function would favour such a conformation and thereby enhance potency. In order to find out whether such a hydrogen-bonded coplanar conformation is indeed preferred we carried out an X-ray analysis. A second objective of this analysis was to determine which of the two tautomeric forms, *i.e.* (1) (1*H* tautomer) or its 3*H* tautomer (2), would be more favourable, both allowing the expected intramolecular hydrogen bond.

**Experimental.** Small prismatic crystals from acetone by slow evaporation, one specimen 0.2 × 0.2 × 0.45 mm, sealed in glass capillary, since unstable in open air, DEC PDP 15/40 controlled Siemens-AED diffractometer, Ni-filtered Cu  $K\alpha$  radiation, lattice constants from 25 high-order reflections. One quadrant ( $hkl$  and  $h\bar{k}l$ ) of independent reflections measured,  $\omega$ – $2\theta$  scan  $[(\sin\theta)/\lambda]_{\max}=0.583$  Å<sup>-1</sup>, 2213 reflections, 296 unobserved [ $I < 2\sigma(I)$ ]. Two standard reflections showed long-time variation of less than 2%. No absorption correction,  $D_m$  by flotation.  $h$  0→10,  $k$  0→14,  $l$  –13→13.

Phase problem solved with direct methods (*MULTAN*; Main, Lessinger, Woolfson, Germain & Declercq, 1977). Least-squares refinement with isotropic, then with anisotropic temperature factors for non-hydrogen atoms; hydrogens, all located from a difference synthesis, isotropic (*XRAY76*; Stewart, Machin, Ammon, Dickinson, Heck & Flack, 1976). Quantity minimized  $\sum w(|F_o| - |F_c|)^2$ , with  $w=xy$ ,  $x=1$  for  $\sin\theta > 0.6$ ,  $x=(\sin\theta)/0.6$  for  $\sin\theta \leq 0.6$ ,  $y=1$  if  $|F_o| < 5.0$  and  $y=5.0/|F_o|$  otherwise. Parameters for  $w$  were chosen so as to make  $\langle w\Delta F \rangle$  almost independent of  $|F_o|$  and  $\sin\theta$ . Unobserved

Table 1. Atomic parameters and isotropic or equivalent isotropic thermal parameters ( $\text{\AA}^2 \times 10^2$ )

$U_{eq}$  values were calculated according to Hamilton (1959).

	x	y	z	$U_{eq}/U$
S1	0.0462 (1)	0.16288 (6)	0.04972 (7)	8.23 (3)
C01	0.1409 (4)	0.1211 (3)	-0.0723 (3)	7.8 (1)
C1	-0.0459 (3)	0.2846 (2)	0.0073 (2)	5.20 (7)
C2	-0.0460 (3)	0.3305 (2)	-0.1017 (2)	5.37 (7)
C3	-0.1259 (3)	0.4254 (2)	-0.1242 (2)	5.05 (7)
C4	-0.2061 (2)	0.4787 (2)	-0.0415 (2)	4.42 (6)
C5	-0.2014 (2)	0.4330 (2)	0.0689 (2)	4.58 (6)
O5	-0.2760 (2)	0.4877 (1)	0.1500 (1)	5.98 (5)
C51	-0.2620 (4)	0.4499 (3)	0.2648 (2)	7.2 (1)
C6	-0.1235 (3)	0.3368 (2)	0.0918 (2)	5.14 (7)
C7	-0.2912 (2)	0.5770 (2)	-0.0749 (2)	4.31 (6)
N8	-0.3074 (2)	0.6112 (2)	-0.1818 (1)	5.13 (6)
C9	-0.3968 (2)	0.7025 (2)	-0.1766 (2)	4.72 (6)
N10	-0.4422 (2)	0.7650 (2)	-0.2657 (2)	6.03 (7)
C11	-0.5311 (3)	0.8479 (2)	-0.2389 (2)	6.17 (8)
C12	-0.5744 (3)	0.8730 (3)	-0.1308 (2)	6.73 (9)
C13	-0.5260 (3)	0.8100 (2)	-0.0387 (2)	6.47 (9)
C14	-0.4351 (2)	0.7224 (2)	-0.0646 (2)	4.71 (6)
N15	-0.3665 (2)	0.6415 (2)	-0.0014 (2)	4.85 (6)
H011	0.085 (6)	0.107 (4)	-0.140 (5)	13 (2)
H012	0.206 (6)	0.175 (4)	-0.098 (4)	13 (2)
H013	0.197 (5)	0.059 (4)	-0.047 (4)	12 (1)
H2	0.008 (3)	0.297 (3)	-0.161 (3)	6.9 (8)
H3	-0.128 (3)	0.458 (2)	-0.198 (2)	6.0 (7)
H511	-0.317 (4)	0.497 (3)	0.308 (3)	10 (1)
H512	-0.155 (4)	0.451 (3)	0.289 (3)	8.1 (9)
H513	-0.297 (4)	0.369 (4)	0.269 (3)	10 (1)
H6	-0.123 (3)	0.305 (2)	0.165 (2)	5.7 (7)
H11	-0.568 (3)	0.890 (3)	-0.303 (3)	7.1 (8)
H12	-0.633 (4)	0.933 (3)	-0.120 (3)	7.8 (9)
H13	-0.554 (4)	0.824 (3)	0.034 (3)	9 (1)
H15	-0.368 (3)	0.633 (2)	0.072 (3)	5.9 (7)

Table 2. Bond angles ( $^\circ$ ) with e.s.d.'s in parentheses

C(01)-S(1)-C(1)	104.6 (1)	C(4)-C(7)-N(15)	124.6 (2)
S(1)-C(1)-C(2)	125.2 (2)	N(8)-C(7)-N(15)	112.3 (2)
S(1)-C(1)-C(6)	115.3 (2)	C(7)-N(8)-C(9)	104.7 (2)
C(2)-C(1)-C(6)	119.5 (2)	N(8)-C(9)-N(10)	125.7 (2)
C(1)-C(2)-C(3)	119.2 (2)	N(8)-C(9)-C(14)	110.5 (2)
C(2)-C(3)-C(4)	122.6 (2)	N(10)-C(9)-C(14)	123.8 (2)
C(3)-C(4)-C(5)	117.5 (2)	C(9)-N(10)-C(11)	114.3 (2)
C(3)-C(4)-C(7)	118.4 (2)	N(10)-C(11)-C(12)	125.5 (2)
C(5)-C(4)-C(7)	124.2 (2)	C(11)-C(12)-C(13)	120.4 (3)
C(4)-C(5)-O(5)	117.0 (2)	C(12)-C(13)-C(14)	115.2 (2)
C(4)-C(5)-C(6)	120.4 (2)	C(9)-C(14)-C(13)	120.8 (2)
O(5)-C(5)-C(6)	122.6 (2)	C(9)-C(14)-N(15)	105.3 (2)
C(5)-O(5)-C(51)	118.4 (2)	C(13)-C(14)-N(15)	133.9 (2)
C(1)-C(6)-C(5)	120.9 (2)	C(7)-N(15)-C(14)	107.2 (2)
C(4)-C(7)-N(8)	123.1 (2)		

reflections included only if  $|F_c| > |F_o|$ ; atomic scattering factors from the standard routine of XRAY76 (Cromer & Mann, 1968; Stewart, Davidson & Simpson, 1965); complex anomalous-dispersion correction for sulfur (*International Tables for X-ray Crystallography*, 1974). After convergence  $R = 3.8\%$ ,  $wR = 5.9\%$  for observed reflections;  $(\Delta/\sigma)_{\max} = 0.15$ ,  $(\Delta/\sigma)_{\text{ave}} = 0.014$ ;  $\Delta\rho < |0.37| \text{ e \AA}^{-3}$  in final difference synthesis. All calculations on a CDC Cyber 175 computer (Wissenschaftliches Rechenzentrum, WRB, Berlin).\*

\* Lists of observed and calculated structure factors and of anisotropic thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44026 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

**Discussion.** Fractional coordinates of the title compound are listed in Table 1. Bond lengths and the chosen atomic numbering scheme can be taken from Fig. 1, bond angles are in Table 2.

The two major questions of this structure determination could definitely be resolved. Since an H atom could certainly be located at N15 but definitely *not* at N8 the heterocyclic system exists in the 1H form. Moreover, the methoxy group at C5 was found in the *cis* position to N15-H15. Further proof is provided by the bond length of 1.326(3) Å between C7 and N8, which is in accord with a C=N double bond in an aromatic system, as was found, for example, in the structure of benzimidazole (Escande & Galigné, 1974; Dix-Edixhoven, Schenk & van der Meer, 1973).

To check whether the pyridine N was at position 10 or 13 both possibilities were examined. If atom 13 was chosen as N, its temperature factor increased, whereas the temperature factor of atom 10 became unusually small, the  $R$  value was 7.9% and neither at atom 10 nor at atom 13 could an H atom be detected. In the opposite assignment, atom 10 as N, 13 as C, both thermal parameters were refined to normal values, the  $R$  value (in a non-final stage of refinement) dropped to 6.1% and an H atom could clearly be located at C13 but there was no residual density at N10. The latter assignment was therefore correct and it was clear that the molecular structure was as given in Fig. 1.

Bond lengths and angles are as expected and need no special discussion. The whole molecule is practically planar. If a least-squares plane is calculated through all

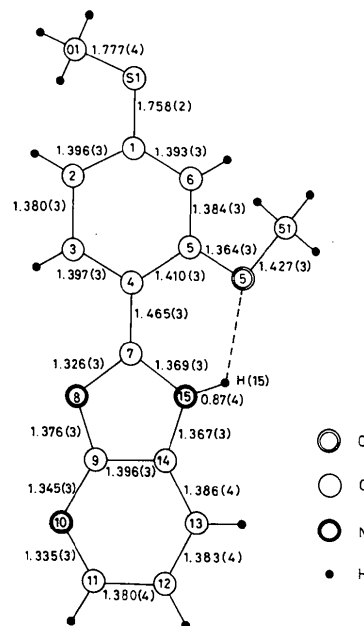


Fig. 1. Schematic drawing of the molecular skeleton displaying bond lengths (Å, e.s.d.'s in parentheses) and the numbering scheme used.

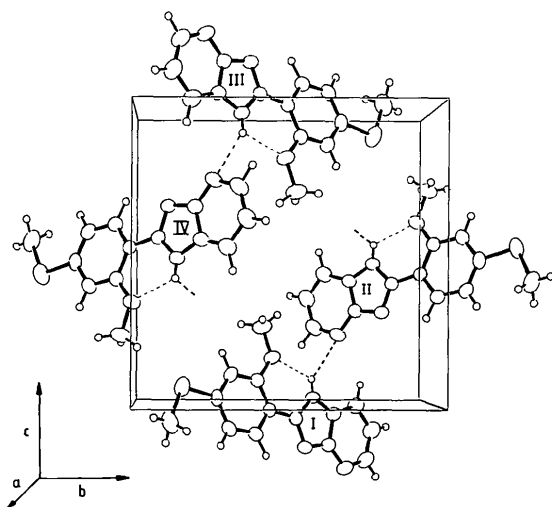


Fig. 2. Unit cell of the title compound projected down *a*. Dotted lines indicate hydrogen bonds. Molecules generated by the following symmetry operations are drawn: (I)  $x, y, z$ ; (II)  $x, \frac{1}{2}-y, \frac{1}{2}+z$ ; (III)  $-x, 1-y, 1-z$ ; (IV)  $-x, -\frac{1}{2}+y, \frac{1}{2}-z$ .

non-hydrogen atoms, the plane is fitted within  $\sigma = 0.07$  Å. Separate least-squares planes through the phenyl ring C1–C6 and through the five/six-membered ring system C7–N15 are fitted within  $\sigma = 0.009$  and  $\sigma = 0.007$  Å respectively. The angle between these two planes is then  $7.3$  ( $8^\circ$ ).

From the *cis* arrangement of N15–H15 and O5 and the planarity of the molecule an intramolecular hydrogen bond N15–H15...O5 results with intra-

molecular contacts N15...O5 = 2.682 (2) and H15...O5 = 2.13 (3) Å.

The crystal structure is shown in Fig. 2 as a projection of the unit cell down *a*. An additional relatively weak intermolecular hydrogen bond N15–H15...N10<sup>i</sup> exists [symmetry operation (i):  $x, \frac{3}{2}-y, \frac{1}{2}+z$ ; N15...N10<sup>i</sup> = 3.094 (3), H15...N10<sup>i</sup> = 2.39 (3) Å], connecting the molecules in the *c* direction. No further intermolecular contacts of interest were observed.

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## Structure of an Oxatriquinane: *cis,anti,cis*-7b-Methylperhydrodicyclopenta[*b,d*]furan-1,6-dione

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**Abstract.** C<sub>11</sub>H<sub>14</sub>O<sub>3</sub>, *M<sub>r</sub>* = 194.23, orthorhombic, *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 8.644 (2), *b* = 9.749 (3), *c* = 11.461 (3) Å, *Z* = 4, *V* = 965.8 (5) Å<sup>3</sup>, *D<sub>x</sub>*(85 K) = 1.34 g cm<sup>-3</sup>, Mo *K*α, λ = 0.71069 Å, μ = 0.64 cm<sup>-1</sup>, *T* = 85 K, 1296 independent reflections, *F*(000) = 416, *R* = 0.047 for 1161 observed reflections with *I* > 2.5σ(*I*). The compound, whose connectivity could not be determined from spectroscopic and chemical

information alone, is an oxa analogue of a linearly fused triquinane, with two *cis* ring fusions and an *anti* disposition of the rings at each end. All three rings possess slightly folded configurations typical of cyclopentanone and tetrahydrofuran systems.

**Introduction.** In the course of a study aimed at the preparation of highly functionalized hydrazulene systems for use in natural-product synthesis, we were exploring the reactions of a series of tricyclic pre-

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