

Structure of 3-ethyl-6-phenyl-4-carbomethoxy-1·H-2-pyridone, an anti-tubercular metabolite[†]

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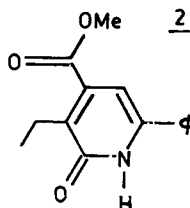
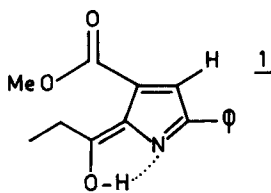
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Abstract. C₁₅H₁₅NO₃, *M_r* = 257.28, rhombohedral, *R*3̄, *a* = 40.510(4), *c* = 4.5456(3) Å, *V* = 6460(2) Å³, *Z* = 18, *d_c* = 1.1905(3) g/cm³, CuKα(*λ* = 1.5418 Å), *μ* = 6.5 cm⁻¹, *F*(000) = 2448, *T* = 295 K, final *R*(*F*) = 0.091, *wR* = 0.141 for 1425 significant reflections, *I* ≥ 2.5σ(*I*). The molecules are stacked along the *c* axis and are stabilized in the unit cell by N–H...O and C–H...O types of hydrogen bonds. Centrosymmetrically related molecules form dimers about the centre of inversion, and the hydrogen bond pattern is reminiscent of pyrimidine-purine base pairing in nucleotides.

Keywords. Anti-tubercular metabolite; dimers; crystal structure.

1. Introduction

Pyridine is generally used in the synthesis of vitamins and drugs, and pyridine derivatives like isonicotinyl hydrazide are used in the treatment of tuberculosis (Metzler 1977; Smith 1977). The title compound 3-ethyl-6-phenyl-4-carbomethoxy-1·H-2-pyridone is a metabolite of the anti-tubercular drug ethambutol [(*R*)-2,2'-(1,2,ethane-diyldiimino) *bis*-1-butanol]. The structure solution was undertaken to verify the chemical structure as proposed by the chemists (1) while the structure obtained by crystallographic study is 2.



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2. Experimental

Greenish transparent crystals of size $0.5 \times 0.3 \times 0.25 \text{ mm}^3$, rectangular in shape, were obtained from methanol + water, and the three dimensional intensity data collected on a Picker four-circle automated diffractometer in the scan mode $\theta/2\theta$ for the limit $2\theta \text{ max} = 110^\circ$ with graphite monochromated $\text{CuK}\alpha$ radiation in the hexagonal system. The data were corrected for direct beam polarisation and Lorentz effects, and not for absorption ($\mu t < 1$). The unit cell parameters were refined from least squares refinement of measured angle values of 45 reflections in the range $100 \leq 2\theta \leq 110^\circ$. A total of 1804 unique reflections were collected in the limit $-35 \leq h \leq 36$, $0 \leq k \leq 41$, $0 \leq l \leq 4$. 1425 reflections were considered observed with $I \geq 2.5\sigma(I)$. Three standard reflections monitored every 100 reflections showed no significant variation. The structure solution was obtained after considerable difficulty by direct methods using MULTAN80 (Main *et al* 1980). The structure was refined using a full matrix least squares refinement on I_{obs} in SHELX76 (Sheldrick 1976). Hydrogen positions were located from ΔF syntheses and checked against stereochemically fixed positions. The non-hydrogens were refined anisotropically and the hydrogens isotropically. Final cycles of refinement were done using a structure-determination package of ENRAF-NONIUS (1987) with unit weighting scheme. The refinement converged to a final $R(F) = 0.091$, and $wR = 0.141$. The last cycle of refinement had (shift/e.s.d.) $\text{max} = 0.02$, (shift/e.s.d.) $\text{mean} = 0.001$. Goodness of fit $S = 8.29$. The final electron density map had no peaks greater than $0.25 \text{ e}\text{\AA}^{-3}$. Scattering factors are as in SDP, ENRAF-NONIUS (1987).

3. Discussion

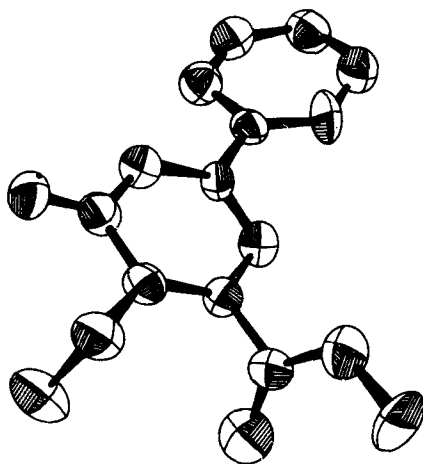
Atomic positions and equivalent temperature factors for non-hydrogen atoms are given in table 1. The ORTEP (Johnson 1965) diagram drawn at 50% probability level is shown in figure 1. Figure 2 shows the stereo view of the molecule. The bond lengths and bond angles involving non-hydrogen atoms are given in table 2. The average e.s.d. in bond lengths and angles are 0.008 \AA and 0.5° respectively. The average distance $1.391(6) \text{ \AA}$ and angle $120.0(5)^\circ$ around the phenyl ring are comparable with that of $1.376(3) \text{ \AA}$ and $120.5(3)^\circ$ of 5,5'-dichloro-3,3'-dinitro-2,2'-biphenyl diol (Hay and Mackay 1981). C(12)=O(15) bond is elongated [$1.242(6) \text{ \AA}$] and the actual bond distance is reported to be dependent on the hydrogen bond interaction with this atom (table 3) (Kvick and Booles 1972). Angles C(4)–C(3)–C(13) [$126.5(5)^\circ$] and C(4)–C(16)–O(17) [$124.1(5)^\circ$] are widened due to the steric repulsion between the two bulky substituents (Brown 1966). Widening of the angle C(5)–C(6)–C(7) [$123.7(5)^\circ$] and the rotation of the phenyl ring about C(6)–C(7) by $24.0(4)^\circ$ with respect to the pyridine-ring plane minimise the steric interaction between the hydrogens HC(5) and HC(8). The terminal atoms C(14), O(17), O(18) and C(19) exhibit high thermal vibrations leading to large liberations about C(3)–C(13) and C(4)–C(16) bonds.

The nitrogen atom of the pyridine ring is protonated. The molecules are stacked along the *c* axis and are stabilised in the unit cell by N–H...O and C–H...O type of hydrogen bonds. Centrosymmetrically related molecules form dimers about the centres of inversion and the hydrogen bond formation is reminiscent of pyrimidine-purine base pairing in nucleotides. The oxygen O(15) is hydrogen-bonded to N(1) and C(12) forming a bifurcated hydrogen bond, where one acceptor is hydrogen-bonded to

Table 1. Table of positional parameters and their estimated standard deviations.

Atom	x	y	z	$B_{eq}(\text{\AA}^2)$
N1	0.2883(1)	0.1204(1)	0.038(1)	4.0(1)
C2	0.2752(1)	0.1378(1)	0.225(1)	4.1(2)
C3	0.2351(1)	0.1178(1)	0.290(1)	4.1(1)
C4	0.2131(1)	0.0831(1)	0.166(1)	4.2(2)
C5	0.2279(2)	0.0661(2)	-0.021(2)	4.6(2)
C6	0.2664(1)	0.0853(1)	-0.083(1)	4.0(1)
C7	0.2850(1)	0.0701(1)	-0.278(1)	4.0(1)
C8	0.2678(2)	0.0308(2)	-0.318(2)	5.1(2)
C9	0.2850(2)	0.0156(2)	-0.502(2)	5.8(2)
C10	0.3184(2)	0.0397(2)	-0.647(2)	5.4(2)
C11	0.3354(2)	0.0785(2)	-0.607(2)	5.0(2)
C12	0.3191(2)	0.0939(1)	-0.421(1)	4.4(2)
C13	0.2219(2)	0.1379(2)	0.502(2)	5.3(2)
C14	0.2155(2)	0.1673(2)	0.344(2)	7.4(2)
O15	0.2982(1)	0.1695(1)	0.329(1)	5.5(1)
C16	0.1712(2)	0.0611(2)	0.217(2)	6.2(2)
O17	0.1510(1)	0.0746(2)	0.208(2)	12.8(3)
O18	0.1574(1)	0.0259(1)	0.260(2)	11.1(2)
C19	0.1168(2)	0.0030(2)	0.315(3)	13.2(4)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $B_{eq} = (4/3) \times [a^2 \times B(1, 1) + b^2 \times B(2, 2) + c^2 \times B(3, 3) + ab(\cos \gamma) \times B(1, 2) + ac(\cos \beta) \times B(1, 3) + bc(\cos \alpha) \times B(2, 3)]$.

**Figure 1.** ORTEP diagram.

two donors. This type of hydrogen bond is commonly observed in urea complexes (Vaughan and Donohue 1952). Values as determined are N(1)...O(15) 2.82(1), N(1)-HN(1) 1.14(7), HN(1)...O(15) 1.70(7) Å and N(1)-HN(1)...O(15) 167(4)°, and C(12)...O(15) 3.176(5), C(12)-HC(12) 1.10(7), HC(12)...O(15) 2.39(4) Å and C(12)-HC(12)...O(15) 128(4)° at the symmetry position $\frac{2}{3} - x, \frac{1}{3} - y, \frac{1}{3} - z$. The hydrogen bond geometry is shown in figure 3.

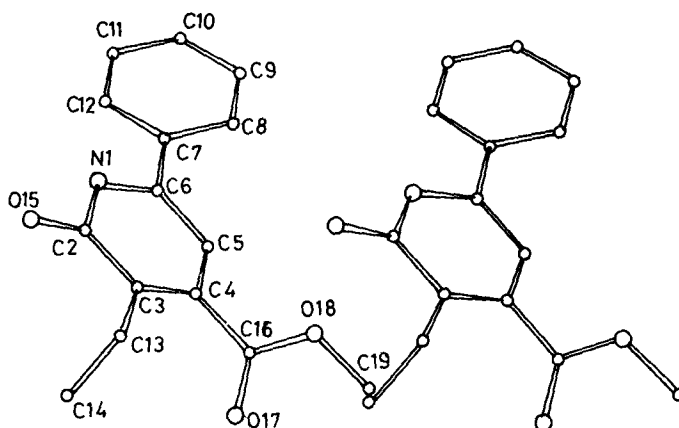


Figure 2. Stereo view of the molecule in the asymmetric unit.

Table 2a. Table of bond distances in angstroms.

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
N1	C2	1.371(9)	C7	C8	1.394(8)
N1	C6	1.359(6)	C7	C12	1.386(7)
C2	C3	1.440(7)	C8	C9	1.41(1)
C12	O15	1.242(6)	C9	C10	1.380(8)
C3	C4	1.356(7)	C10	C11	1.377(8)
C3	C13	1.52(1)	C11	C12	1.40(1)
C4	C5	1.40(1)	C13	C14	1.52(1)
C4	C16	1.488(7)	C16	O17	1.19(1)
C5	C6	1.381(7)	C16	O18	1.262(8)
C6	C7	1.483(9)	O18	C19	1.450(9)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2b. Table of bond angles in degrees.

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C2	N1	C6	124.9(4)	C6	C7	C8	118.9(5)
N1	C2	C3	117.2(4)	C6	C7	C12	121.9(5)
N1	C2	O15	119.2(5)	C8	C7	C12	119.2(6)
C3	C2	O15	123.7(6)	C7	C8	C9	120.2(6)
C2	C3	C4	117.9(6)	C8	C9	C10	119.7(6)
C2	C3	C13	115.5(4)	C9	C10	C11	119.9(7)
C4	C3	C13	126.5(5)	C10	C11	C12	120.7(5)
C3	C4	C5	122.9(5)	C7	C12	C11	120.2(5)
C3	C4	C16	121.0(6)	C3	C13	C14	111.3(6)
C5	C4	C16	116.1(5)	C4	C16	O17	124.1(5)
C4	C5	C6	119.1(5)	C4	C16	O18	115.4(6)
N1	C6	C5	118.0(6)	O17	C16	O18	120.4(5)
N1	C6	C7	118.3(4)	C16	O18	C19	118.0(7)
C5	C6	C7	123.7(5)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 3. Comparison of C=O distance with H-bond strength.

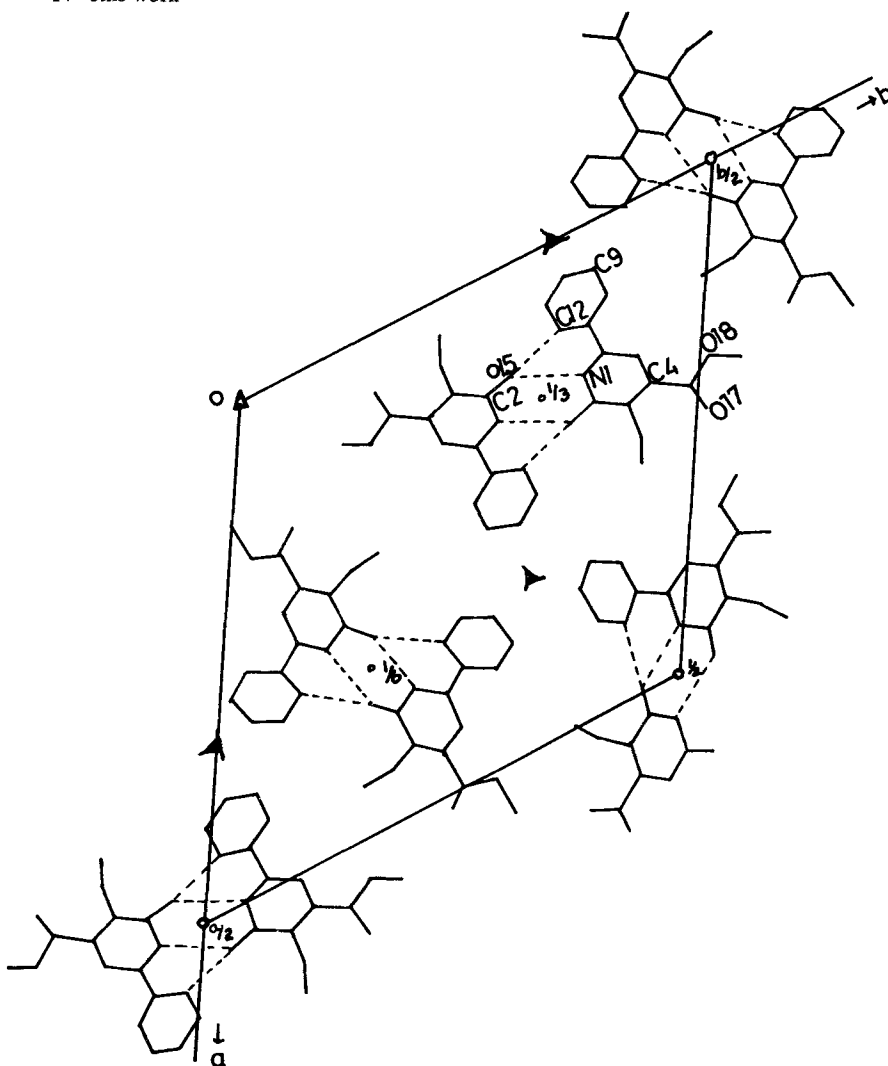
Distance (Å) C=O	Type of H-bond	Distance (Å) N-H...O	Reference
1.262(4)	O-H...O	2.570(4)	I
1.250(3)	N-H...O	2.796(3)	II
1.244(4)	N-H...O	2.808(5)	III
1.242(6)	N-H...O	2.82(1)	IV

*Compound name and references*I 6-Chloro-2-hydroxy pyridine: pyridone (Almlöf *et al* 1971)

II 5-Chloro-2-pyridone (Kvick and Booles 1972)

III 3,6-Phenyl-4-carbomethoxy-1·H-2-pyridone (Nethaji and Vasantha Pattabhi 1988)

IV This work

**Figure 3.** Packing diagram with hydrogen-bond geometry down the *c* axis.

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