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Crystal Structure of a Non-stoichiometric Channel Inclusion Complex of 1-Benzyl-6-phenylpiperidin-2-one-5-carboxylic Acid with Acetonitrile

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Abstract. $C_{19}H_{19}NO_3 \cdot x\ CH_3CN$ ($x = 0.3$), $M_r = 643.35$, hexagonal, space group $P6_1$ (No. 169), $a = 23.027(5)$, $c = 5.775(1)$ Å, $V = 2652(1)$ Å^3, $Z = 6$. The structure was solved by direct methods and refined to $R = 0.077$ for 1562 observed Mo K_α reflections. The title heterocyclic carboxylic acid was established as the *trans* isomer, with the phenyl and carboxyl substituents occupying pseudo-equatorial and equatorial positions, respectively, of the piperidin-2-one ring in a half-chair conformation. Acid host molecules related by the 6_1 screw operation are linked by intermolecular O—H···O (cyclic amide) hydrogen bonds to generate an open channel bounded by coaxial intertwined helices each having a pitch of 5*c*. Within each channel of free diameter *ca.* 6.0 Å the acetonitrile molecules partially occupy highly disordered sites which do not lie on the *c* axis.

Key words. 1-Benzyl-6-phenylpiperidin-2-one-5-carboxylic acid, acetonitrile, inclusion compound, hydrogen bonding, disorder.

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. SUP 82067 (13 pages).

1. Introduction

The Perkin reaction of benzaldehyde with succinic anhydride to form γ-phenylparaconic acid (**1**) has been known for over a century [1]. A variant of this reaction using benzylideneamines as the electrophiles in place of benzaldehydes was reported by Castagnoli [2] to give pyrrolidin-2-one-4-carboxylic acids (**2**). As part of a program designed for the synthesis of new piperidine derivatives for broad pharmaceutical screening, one of us [3] has further extended Castagnoli's work to the condensation of Schiff bases with glutaric anhydride. As expected, these reactions have been found to provide a facile entry to the piperidin-2-one-5-carboxylic acid system (**3**), the details of which will be described elsewhere. An interesting aspect of this investigation is the formation of a non-stoichiometric acetonitrile adduct (**5**) by one of the products, namely 1-benzyl-6-phenylpiperidin-2-one-5-carboxylic acid (**4**), which was prepared from benzylidenebenzylamine and glutaric

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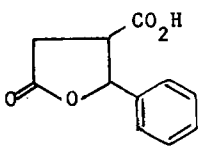
anhydride. In the present X-ray crystallographic study, we attempted to establish the isomeric form (namely whether the phenyl and carboxyl substituents are *cis* or *trans* with respect to each other) and the conformation of the host molecule (**4**), as well as the nature of the molecular association in the host-guest complex.



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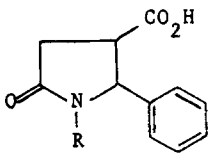

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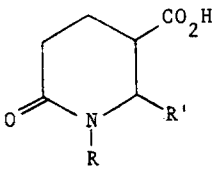

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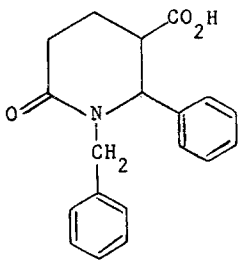

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2. Experimental

2.1. PREPARATION OF THE NON-STOICHIOMETRIC INCLUSION COMPLEX (5) OF 1-BENZYL-6-PHENLYPIPERIDIN-2-ONE-5-CARBOXYLIC ACID (4) WITH ACETONITRILE

A solution of 32.1 g (0.3 mole) of benzylamine and 31.8 g (0.3 mole) of benzaldehyde in 250 ml of freshly redistilled toluene was refluxed until the theoretical amount of water was collected through a Dean–Stark trap. The resulting benzylidenebenzylamine solution was cooled and 34.2 g (0.3 mole) of glutaric anhydride was added. The mixture was refluxed for 50 h after which period the solvent was removed under reduced pressure. The orange oily residue was taken up in 500 ml of 5% KOH and extracted with two portions of 100 mL of ether to remove non-acidic organic by-products. The aqueous alkaline solution was retained, warmed on a steam-bath to evaporate off the residual ether, cooled in an ice-bath, and acidified with conc. HCl. The white precipitate of (**4**) was collected, washed with water and recrystallized from acetonitrile to give 65.6 g (68%) of essentially pure inclusion complex (**5**) as white fluffy needles. During melting-point determination on a Koefler block, these crystals underwent visible expansion at temperatures higher than 150°C and melted with decomposition at 170–173°C. Further recrystallization from acetonitrile provided an analytical sample, m.p. 173–175°C dec. The mass spectrum of this substance showed prominent peaks at *m/e* 41 (M^+ of CH_3CN) and 309 (M^+ of host molecule). (Found: C, 73.16; H, 6.40; N, 5.44%. Calc. for $C_{19}H_{19}NO_3 \cdot x\ CH_3CN$ ($x = 0.3$): C, 73.18; H, 6.23; N, 5.66%). The value of x was established from repeated density measurements of freshly-prepared crystals of (**5**) by flotation in aqueous potassium iodide.

2.2. X-RAY CRYSTALLOGRAPHY

As compound (**5**) is slightly air-sensitive, a selected crystal was sealed in a Lindemann glass capillary for diffraction use. Determination of unit-cell dimensions, intensity data collection, and data processing were performed as described previously [4]. The results are summarized in Table I.

Structure solution was achieved by tangent refinement with random starting phase sets [5, 6]. All non-hydrogen atoms of host molecule (**4**) were subjected to anisotropic refine-

Table I. Data collection and processing parameters

Molecular formula	$2\,C_{19}H_{19}NO_3 \cdot x\ CH_3CN$ ($x = 0.6$)
Molecular weight	643.35
Cell constants	$a = 23.027(5)$ Å $Z = 3$
	$c = 5.775(1)$ Å $F(000) = 1023.5$
	$V = 2652(1)$ Å^3
Density (exptl)	1.205 g cm^{-3} (flotation in KI/H_2O)
Density (calcd)	1.208 g cm^{-3} (1.239 g cm^{-3} for $x = 1$)
Space Group	$P6_1$ (No. 169)
Radiation	graphite-monochromatized Mo $K\alpha$, $\lambda = 0.71069$ Å
Absorption coefficent	0.78 cm^{-1}
Crystal size	0.42 × 0.40 × 0.38 mm
Scan type and speed	ω-2θ; 2.02–8.37 deg min^{-1}
Scan range	1° below $K\alpha_1$ to 1° above $K\alpha_2$
Background counting	stationary counts for one-half of scan time at each end of scan range
Collection range	$h, \pm k, \pm l$; $2\theta_{max} = 54°$
Unique data measured	2142
Observed data with $\lvert F_o\rvert > 3\sigma(\lvert F_o\rvert)$, n	1562
Number of variables, P	232
$R = \Sigma\lvert\lvert F_o\rvert - \lvert F_c\rvert\rvert/\Sigma\lvert F_o\rvert$	0.077
Weighting scheme	$w = [\sigma^2(\lvert F_o\rvert) + 0.0018\lvert F_o\rvert^2]^{-1}$
$R_w = [\Sigma\, w(\lvert F_o\rvert - \lvert F_c\rvert)^2/\Sigma\, w\lvert F_o\rvert^2]^{1/2}$	0.092
$S = [\Sigma\, w(\lvert F_o\rvert - \lvert F_c\rvert)^2/(n-p)]^{1/2}$	1.557
Residual extrema in final difference map	+0.31 to −0.21 eÅ^{-3}

ment. The methine, methylene, and phenyl H atoms were generated geometrically (C—H bond length fixed at 0.96 Å) and assigned isotropic temperature factors. The acetonitrile molecule was so badly disordered that it was not possible to account for its X-ray scattering by a physically meaningful model. Accordingly the guest molecule was represented by six carbon atoms of variable site occupancy factors, namely G(1)–G(6) in Table II, all tied to the same isotropic thermal parameter. The carboxyl H atom did not show up in the final difference map. Computations were performed on a Data General Corporation Nova 3/12 minicomputer using the *SHELXTL* program package [7]. Analytic expressions of neutral-atom scattering factors were employed, and anomalous dipersion corrections were incorporated [8]. Blocked-cascade least squares refinement [9] coverged to the R indices listed in Table I. The refined atomic parameters are given in Table II. Anisotropic temperature factors, hydrogen atomic parameters, and structure factors are available as Supplementary Data.

3. Discussion

Figure 1 shows a stereo view of host molecule (**4**) along with atom labelling. Its measured molecular dimensions as given in Table III are not unusual, and planarity of the amide fragment [sum of bond angles equals nearly 360° about both N(1) and C(1)] leads to a highly distorted chair conformation of the piperidin-2-one ring, which resembles the half-chair of cyclohexene. The phenyl group on C(5) and the carboxyl function on C(4) occupy pseudo-equatorial and equatorial positions, respectively, thus bearing a *trans* relationship to each other. The relative orientation of these two ring substituents is described

Table II. Fractional coordinates ($\times 10^4$ for host molecule; $\times 10^3$ for guest molecule) and thermal parameters[a] ($Å^2 \times 10^3$) for non-hydrogen atoms of (**5**)

Atom	x	y	z	U_{eq}/U	K^b
Host molecule (4)					
O(1)	1889(2)	−1816(2)	2361(9)	77(2)	
O(2)	2676(2)	145(2)	−5742(8)	72(2)	
O(3)	3146(2)	944(2)	−3089(8)	67(2)	
N(1)	2691(2)	−1090(2)	0	40(2)	
C(1)	2082(2)	−1351(2)	963(11)	48(2)	
C(2)	1635(3)	−1072(3)	348(12)	57(2)	
C(3)	1819(2)	−661(3)	−1837(11)	51(2)	
C(4)	2566(2)	−176(2)	−1764(10)	41(2)	
C(5)	2950(2)	−565(2)	−1816(10)	37(2)	
C(6)	2792(2)	302(2)	−3756(11)	43(2)	
C(7)	3697(2)	−86(2)	−1608(10)	38(2)	
C(8)	3959(3)	340(3)	302(11)	51(2)	
C(9)	4637(3)	801(3)	388(12)	59(3)	
C(10)	5056(3)	854(3)	−1407(12)	58(2)	
C(11)	4799(3)	431(3)	−3242(13)	58(2)	
C(12)	4128(3)	−37(3)	−3355(11)	49(2)	
C(13)	3086(2)	−1414(2)	447(10)	42(2)	
C(14)	3055(2)	−1881(2)	−1459(11)	43(2)	
C(15)	3596(3)	−1954(3)	−1858(2)	55(2)	
C(16)	3586(3)	−2395(3)	−3604(14)	67(3)	
C(17)	3036(3)	−2732(3)	−4912(14)	63(3)	
C(18)	2467(3)	−2658(3)	−4539(14)	69(3)	
C(19)	2493(3)	−2234(3)	−2830(12)	57(3)	
Disordered CH_3CN guest molecule as represented by fractional C atoms					
G(1)	−108(2)	−7(3)	−124(11)	205(13)	0.40(3)
G(2)	−91(6)	−32(5)	30(27)	205(13)	0.19(3)
G(3)	−75(6)	−35(7)	243(27)	205(13)	0.18(3)
G(4)	−7(5)	77(5)	436(22)	205(13)	0.21(4)
G(5)	6(6)	71(4)	243(24)	205(13)	0.21(4)
G(6)	32(6)	82(4)	471(19)	205(13)	0.27(5)

[a] For atoms in the host molecule, equivalent isotropic temperature factor U_{eq} is calculated as one-third of the trace of the orthogonalized U_{ij} matrix. For the disordered atoms, the exponent of U takes the form $-8\pi^2 U \sin^2\theta/\lambda^2$.

[b] Site occupancy factors of disordered atoms.

by the torsion angle C(7)—C(5)—C(4)—C(6) = 60.4(5)°, which is in conformity with an idealized staggered arrangement.

In the crystal structure of (**5**), host molecules arranged about the 6_1 screw axis are linked by intermolecular hydrogen bonds of the type O(1)—H···O(3)′ [O(1)···O(3)′ = 2.52(1) Å; primed atom at $(y, -x+y, 5/6+z)$] to generate an open channel of free diameter *ca.* 6.0 Å directed along the *c* axis. The channel is bounded by coaxial intertwined helices each of pitch 5*c*, and the acetonitrile guest molecules (as represented by fractional carbon atoms) occupy disordered sites within it but do not lie on the channel axis (Fig. 2). The site occupancy factors of fractional carbon atoms G(1)–G(6) add up to 1.46, which is a reasonable value in view of the approximate nature of the disordered model.

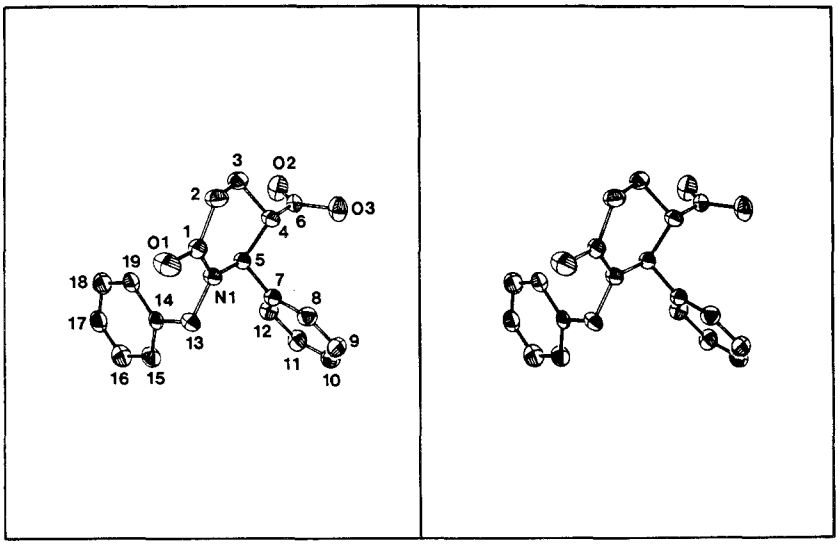

Fig. 1. Stereo view of the molecular structure of host molecule (**4**). The thermal ellipsoids are drawn at the 35% probability level.

Attempts to prepare good crystals of (**4**) and additional inclusion complexes using other guest species have so far been unsuccessful. We have also synthesized the methyl ester of (**4**), which is devoid of inclusion property in view of its inability to catenate through hydrogen bonding. Interestingly, an X-ray diffraction study has shown that the phenyl and carboxyl groups of the ester occupy pseudo-axial and axial positions, respectively, of the central piperidin-2-one ring [10].

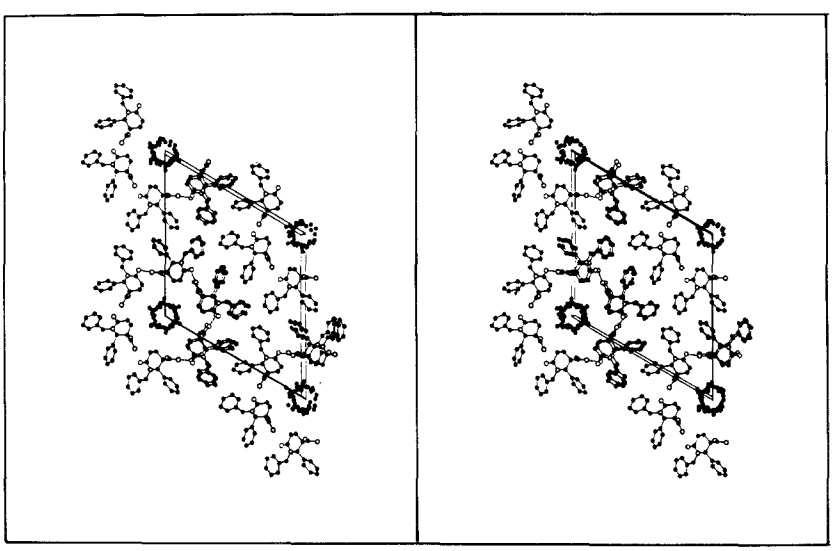

Fig. 2. Stereo view of the crystal structure of inclusion compound (**5**). The N and O atoms are represented by open circles, and the C and fractional atoms (of the guest molecule) by black dots. Hydrogen bonds are indicated by broken lines. The origin of the unit cell lies at the lower left corner, with *a* pointing from left to right at a downward slant, *b* upwards, and *c* towards the reader.

Table III. Bond lengths (Å), bond angles (°), and selected torsion angles (°) in host molecule (**4**)

O(1)—C(1)	1.233(7)	O(2)—C(6)	1.191(8)
O(3)—C(6)	1.340(6)	N(1)—C(1)	1.339(6)
N(1)—C(5)	1.482(6)	N(1)—C(13)	1.460(8)
C(1)—C(2)	1.502(10)	C(2)—C(3)	1.506(9)
C(3)—C(4)	1.513(6)	C(4)—C(5)	1.543(9)
C(4)—C(6)	1.494(8)	C(5)—C(7)	1.512(5)
C(7)—C(8)	1.397(8)	C(7)—C(12)	1.381(8)
C(8)—C(9)	1.382(7)	C(9)—C(10)	1.379(10)
C(10)—C(11)	1.358(9)	C(11)—C(12)	1.373(6)
C(13)—C(14)	1.516(8)	C(14)—C(15)	1.357(9)
C(14)—C(19)	1.383(8)	C(15)—C(16)	1.421(11)
C(16)—C(17)	1.338(9)	C(17)—C(18)	1.421(11)
C(18)—C(19)	1.368(10)		
C(1)—N(1)—C(5)	124.4(5)	C(1)—N(1)—C(13)	118.6(4)
C(5)—N(1)—C(13)	116.2(4)	O(1)—C(1)—N(1)	120.2(6)
O(1)—C(1)—C(2)	119.9(5)	N(1)—C(1)—C(2)	119.9(5)
C(1)—C(2)—C(3)	115.4(5)	C(2)—C(3)—C(4)	107.4(5)
C(3)—C(4)—C(5)	110.0(4)	C(3)—C(4)—C(6)	111.7(5)
C(5)—C(4)—C(6)	108.9(5)	N(1)—C(5)—C(4)	110.2(4)
N(1)—C(5)—C(7)	112.8(4)	C(4)—C(5)—C(7)	110.3(4)
O(2)—C(6)—O(3)	122.1(5)	O(2)—C(6)—C(4)	125.2(5)
O(3)—C(6)—C(4)	112.8(5)	C(5)—C(7)—C(8)	120.7(5)
C(5)—C(7)—C(12)	120.7(5)	C(8)—C(7)—C(12)	118.6(4)
C(7)—C(8)—C(9)	119.6(6)	C(8)—C(9)—C(10)	120.8(6)
C(9)—C(10)—C(11)	119.3(4)	C(10)—C(11)—C(12)	121.0(6)
C(7)—C(12)—C(11)	120.7(6)	N(1)—C(13)—C(14)	114.5(4)
C(13)—C(14)—C(15)	119.4(5)	C(13)—C(14)—C(19)	122.0(5)
C(15)—C(14)—C(19)	118.6(6)	C(14)—C(15)—C(16)	121.3(5)
C(15)—C(16)—C(17)	119.3(7)	C(16)—C(17)—C(18)	120.4(7)
C(17)—C(18)—C(19)	118.8(6)	C(14)—C(19)—C(18)	121.7(6)
C(1)—C(2)—C(3)—C(4)	−46.8(7)	C(2)—C(3)—C(4)—C(5)	64.3(6)
C(3)—C(4)—C(5)—N(1)	−51.7(6)	C(4)—C(5)—N(1)—C(1)	21.9(5)
C(5)—N(1)—C(1)—C(2)	−4.9(7)	N(1)—C(1)—C(2)—C(3)	17.8(7)
C(2)—C(3)—C(4)—C(6)	−174.7(6)	C(1)—N(1)—C(5)—C(7)	145.6(5)
N(1)—C(5)—C(7)—C(8)	−65.6(7)	C(7)—C(5)—C(4)—C(6)	60.4(5)
C(1)—N(1)—C(13)—C(14)	98.5(5)	N(1)—C(13)—C(14)—C(15)	148.4(5)

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References

1. R. Fittig and H. W. Jayne: *Ann.* **216**, 108 (1883).
2. N. Castagnoli: *J. Org. Chem.* **34**, 3187 (1969).
3. R. Kwok: unpublished results.
4. F. Toda, K. Tanaka, and T. C. W. Mak: *J. Incl. Phenom.* **3**, 225 (1985).

5. J.-X. Yao: *Acta Physica Sinica* **33**, 121 (1984). [In Chinese].
6. J.-X. Yao: *Acta Crystallogr.* **A37**, 642 (1981).
7. G. M. Sheldrick: in *Computational Crystallography* (Ed. D. Sayre), p. 506. Oxford University Press, New York (1982).
8. *International Tables for X-Ray Crystallography*, Vol. IV, pp. 55, 99, 149, Kynoch Press, Birmingham (1974). [Now distributed by Kluwer Academic Publishers, Dordrecht, The Netherlands].
9. J. W. Schilling: in *Crystallographic Computing* (Ed. F. R. Ahmed), p. 201. Munksgaard, Copenhagen (1970).
10. T.-L. Chan, R. Kwok and T. C. W. Mak: unpublished results.