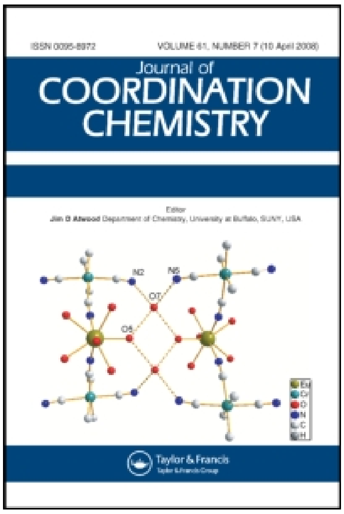

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THE CRYSTAL AND MOLECULAR STRUCTURE OF p-NITROPHENACETURIC ACID

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THE CRYSTAL AND MOLECULAR STRUCTURE OF p-NITROPHENACETURIC ACID

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The crystal and molecular structure of p-$NO_2C_6H_5CH_2CONHCH_2COOH$ or $C_{10}H_{11}N_2O_5$ has been determined by single crystal x-ray diffraction techniques. The compound crystallizes in the space-group $P2_1/c$ with four molecules in a unit cell of dimensions: $a = 11.8748(5)$A, $b = 11.2732(4)$A, $c = 8.8073(5)$A and $\beta = 112.966(4)°$. The structure was solved by direct methods and refined to a final value of $R = 0.042$. The molecule assumes a conformation similar to that found for the analogous side-chain in the penicillin G molecule and hence should be a convenient model system in studying copper catalyzed degradations of penicillin. The hydrogen bonding between the amide oxygen of one molecule to the carboxylic acid proton, 2.67(1)A, and the amide nitrogen, 2.91(1)A, of another molecule creates a three-dimensional network identical to that found for hippuric acid.

INTRODUCTION

The interest in the structure of p-nitrophenaceturic acid, or N-(p-nitrophenylacetyl)glycine, originated in the lack of data concerning simple α-amido-carboxylic acids which can be compared to penicillin's β-lactam-thiazolidine fused ring system (Figure 1). Perhaps the closest related system to date has been the proposed acyl-D-alanyl-D-alanine.[1,2] The crystal structure for this molecule has not been done. However, the p-nitrophenaceturic acid is a closer analogue to that portion of the penicillin G molecule. Finally, the formation of phenaceturic acid by the metabolism of phenylacetic acid in some mammals[3] adds biochemical impetus to this structure determination.

EXPERIMENTAL

A sample of the acid was recrystallized from water and a single crystal having no dimension greater than 0.25 mm was selected for the study. Using a General Electric XRD-5 diffractometer, extinctions were found when l was odd for the (h0l) reflections and k odd for the (0k0) reflections which uniquely determined the monoclinic space group as $P2_1/c$. Lattice

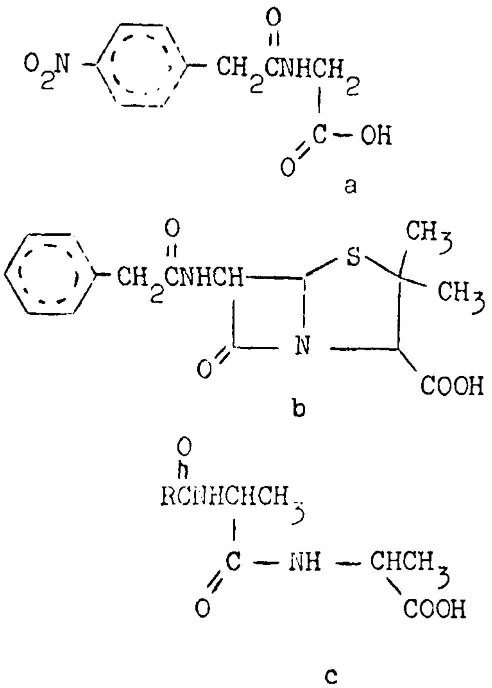

FIGURE 1 a. p-nitrophenaceturic acid; b. benzylpenicillin of "Pen G"; c. acylalanylalanine, R = alkyl constants were determined by a least-squares fit of 20 carefully measured 2θ values (1° take-off angle and 0.05° slit) of the Cu–K_{α_1} and Cu–K_{α_2} doublet for $2\theta > 66°$. The resultant lattice constants and their estimated standard deviations together with the derived quantities (cell volume and calculated density) are:

a = 11.8748(5) Å V = 1085.6 $Å^3$
b = 11.2732(4) Å S_{calc} = 1.463 g/cc
c = 8.8073(5) Å assuming four molecules/ unit cell
β = 112.966(4)° M.W. = 238

Intensity data were collected on a General Electric XRD-490 fully automated diffractometer by the stationary-crystal, stationary-counter method using balanced nickel and cobalt filters and copper K_α radiation. A total of 2458 independent reflections were measured to a 2θ maximum of 150° (d = 0.80 Å). Of these, 1678 reflections (68%) were considered statistically significant by the criteria;

$$|I_{Ni} - 2\sigma(I_{Ni})| - [I_{Co} + 2\sigma(I_{Co})] > 100$$

where the σ's were based entirely on counting statistics. The intensities were corrected for Lorentz-polarization effects, $K_{\alpha_1} - K_{\alpha_2}$ splitting, and absorption as a function of phi only with a maximum difference of 4.5% over the entire range of phi (linear absorption coefficient for Cu radiation is 10.3 cm^{-1}).

STRUCTURE DETERMINATION

Normalized structure magnitudes, | E | were calculated using a K-curve.[4] A total of 276 reflections with | E | values greater than 1.5 were used to solve the structure. An origin was chosen among the 10 largest | E | values, and five other reflections with large | E | values were then permuted. Of these 32 combinations, the correct one was among those which had a high consistency index and phased over 180 reflections. An | E | map was generated and all 17 anticipated non-hydrogen atoms were found in a chemically reasonable arrangement. All peaks were assigned with proper scattering factors based on the anticipated structure. Block-diagonal least-square isotropic refinement with $(1/\sigma)2$ weights, resulted in a reliability index[5] value of 0.14. Isotropic temperature factors were converted to anisotropic temperature factors and refinement was continued, resulting in a value of R = 0.08.

All hydrogen atoms were easily located on a difference electron-density map. Hydrogen atoms were then included in the refinement with both their coordinates and isotropic temperature factors being allowed to vary. The refinement was considered completed when all shifts in parameters were less than one-tenth of respective estimated standard deviations and the final $R = 0.04_2$.

TABLE IA
Final coordinates and anisotropic temperature factors[a]

	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O1	0.6543(1)	0.4688(1)	0.7780(2)	73(2)	78(2)	143(3)	1(1)	21(2)	−28(2)
C2	0.5603(2)	0.4150(2)	0.6641(3)	62(2)	56(2)	96(4)	0(2)	43(2)	11(2)
O3	0.4548(1)	0.4421(1)	0.6259(2)	59(2)	73(2)	162(3)	5(1)	66(2)	1(2)
C4	0.6029(2)	0.3134(2)	0.5858(3)	50(2)	68(2)	131(4)	4(2)	41(2)	−6(3)
N5	0.5018(2)	0.2597(2)	0.4520(2)	61(2)	69(2)	84(3)	4(1)	44(2)	3(2)
C6	0.4237(2)	0.1870(2)	0.4784(3)	59(2)	58(2)	84(3)	6(2)	42(2)	−6(2)
O7	0.4398(1)	0.1518(1)	0.6191(2)	97(2)	71(2)	92(3)	−7(1)	52(2)	11(2)
C8	0.3127(2)	0.1490(2)	0.3318(3)	69(2)	100(3)	104(4)	8(2)	47(3)	−28(3)
C9	0.1980(2)	0.1858(2)	0.3551(3)	56(2)	71(2)	78(3)	−5(2)	26(2)	−12(2)
C10	0.1166(2)	0.1028(2)	0.3672(3)	82(3)	55(2)	186(5)	3(2)	68(3)	−15(3)
C11	0.0133(2)	0.1367(2)	0.3938(3)	75(3)	59(2)	197(5)	−11(2)	73(3)	−7(3)
C12	−0.0056(2)	0.2553(2)	0.4084(3)	48(2)	66(2)	108(4)	2(2)	24(2)	−7(2)
C13	0.0723(2)	0.3412(2)	0.3944(3)	66(2)	53(2)	181(5)	1(2)	35(3)	−2(3)
C14	0.1745(2)	0.3055(2)	0.3684(3)	68(2)	66(2)	169(5)	−14(2)	49(3)	0(3)
N15	−0.1123(2)	0.2913(2)	0.4429(3)	55(2)	92(2)	171(4)	1(2)	31(2)	−28(3)
O16	−0.1458(2)	0.3947(2)	0.4195(3)	112(2)	96(2)	409(6)	40(2)	107(3)	−4(3)
O17	−0.1621(2)	0.2166(2)	0.4949(3)	96(2)	124(2)	329(5)	−16(2)	127(3)	−27(3)

[a] Anisotropic temperature factors of the form
$EXP\text{-}[\beta(11)h^2 + \beta(22)k^2 + \beta(33)l^2 + 2\beta(12)hk + 2\beta(13)hl + 2\beta(23)kl]$
Multiplied by $10.^4$

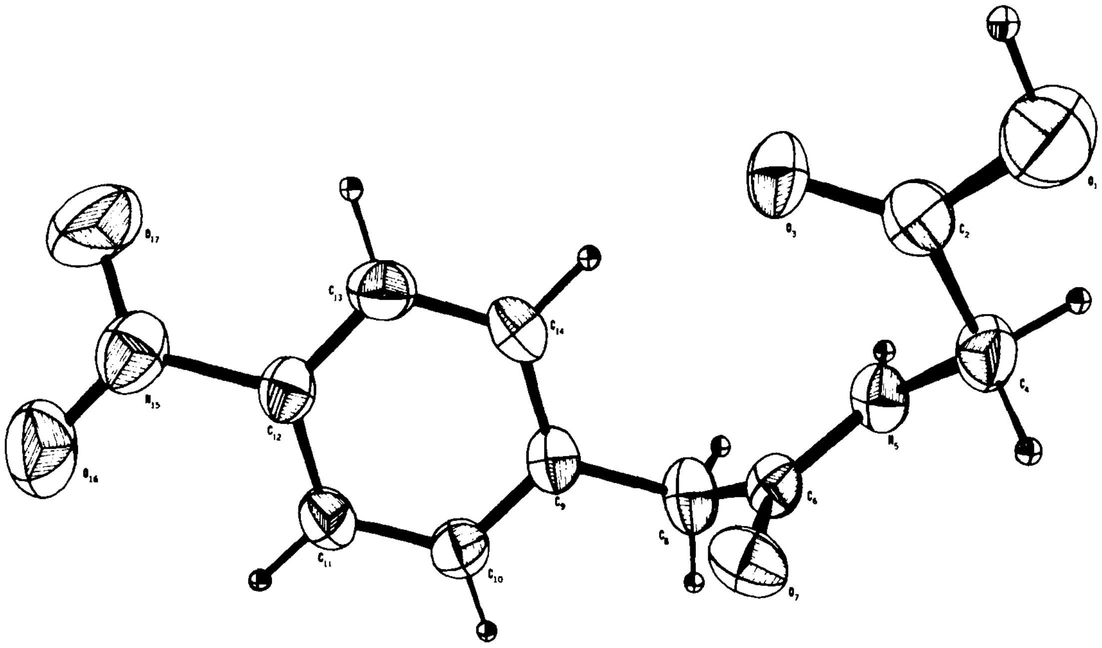

FIGURE 2 ORTEP drawing of molecule using thermal displacement ellipsoids.

RESULTS AND DISCUSSION

Table I lists the final coordinates and temperature factors (anisotropic for non-hydrogens and isotropic for hydrogens) with estimated standard deviations (ESDs) for each parameter. The labelling and thermal displacement ellipsoids of the atoms are shown in Figure 2.

The molecule does not extend to its full length folding back at the two methylene carbons, C4 and C8. This gives rise to three, essentially planar regions in the molecule as shown in Figure 3. Plane I is calculated from a least-square fit of the atoms of the carboxyl group, C4 and N5; Plane II from atoms C4,

TABLE IB
Hydrogen fractional coordinates

Atom[a]	X	Y	Z	β
H1	0.6278(25)	0.5315(24)	0.8193(35)	8.2(9)
H4	0.6492(18)	0.2528(19)	0.6786(25)	3.1(5)
H4′	0.6647(19)	0.3504(19)	0.5473(26)	3.9(6)
H5	0.4856(19)	0.2888(18)	0.3506(26)	3.8(6)
H8	0.3159(19)	0.0620(19)	0.3258(26)	4.2(6)
H8′	0.3131(20)	0.1813(20)	0.2343(26)	4.5(6)
H10	0.1340(21)	0.0178(20)	0.3560(29)	5.4(7)
H11	−0.0432(21)	0.0802(20)	0.4067(28)	5.2(7)
H13	0.0627(22)	0.4267(20)	0.4190(28)	5.3(7)
H14	0.2372(22)	0.3690(22)	0.3710(30)	6.1(7)

[a]Numbers refer to bonding atom.

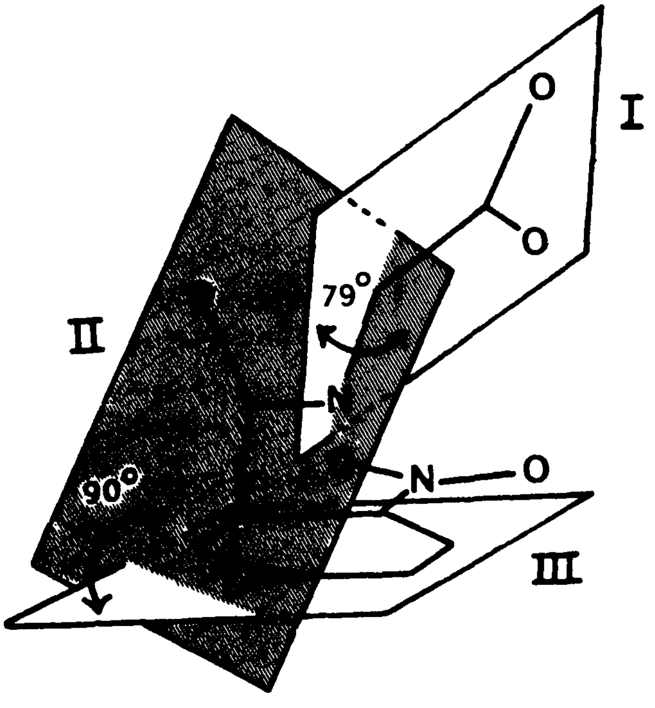

FIGURE 3 Folding of molecule.

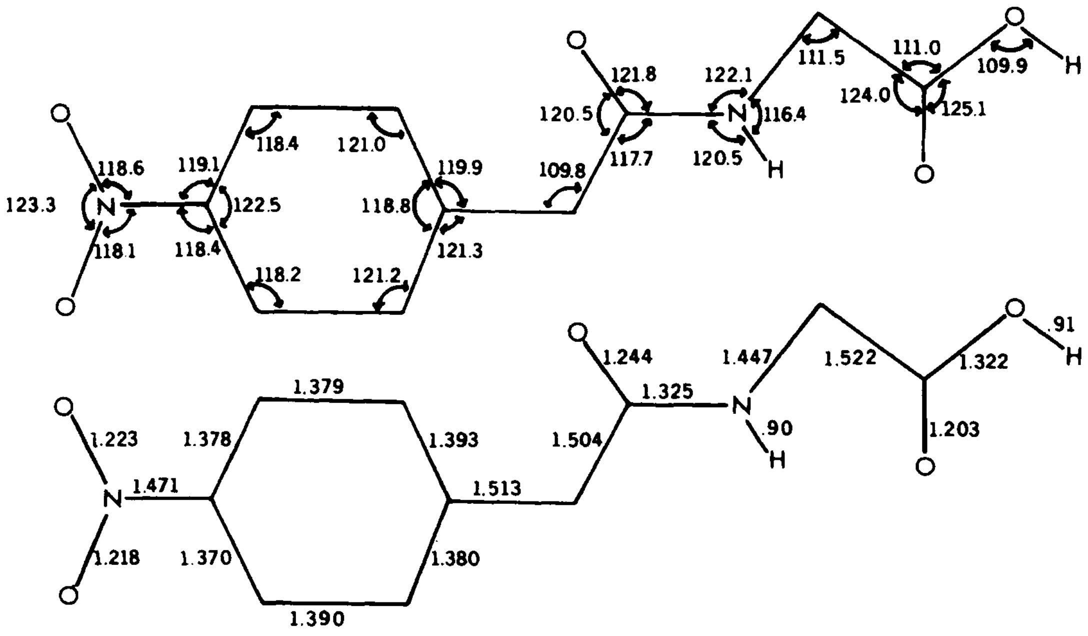

FIGURE 4 Schematic drawings of molecule with distances and angles indicated.

N5, C6, O7 and C8; and Plane III from C8 and the atoms of the phenyl ring. These planes are arranged such that the carboxyl group is bent back toward the ring. This bend is due to the hydrogen bonding between the proton on the acid of one molecule and the amide oxygen of another molecule related by the twofold screw axis. The complete scheme of hydrogen bonding is discussed later in detail.

Figure 4 shows a schematic drawing of the molecule with bond distances and angles indicated. The ESDs for the distances and angles involving hydrogen atoms are less than 0.03 Å and 1.9° while those of the non-hydrogen atoms do not exceed 0.004 Å and 0.2°, respectively. With the exception of the rotation of the carboxyl group about the C4–N5 bond, the parameters for the amide-acid portion of the molecule are in direct agreement with those found for acetylglycine and hippuric acid.[6–8] The acid group (O1, C2, O2, C4) is planar within the accuracy of our measurements, and the amide portion of the molecule (C4, N5, C6, O7 and C8) is planar within an ESD of 0.041 Å.

If one focusses on the carboxylic acid portion of this system, the molecular parameters appear anomalous, at first. Typically, in aliphatic systems[9,10,11] the C=O bond length is about 1.23 Å and the C–OH bond length varies from 1.29 Å (Di-acid) to 1.35 Å (Mono-acid). Corresponding angles are: $\angle$CCO-122.4°(Di)118°(Mono); $\angle$OCOH-122.1°(Di)-125°(Mono); $\angle$C–C–OH-115°(Di)117°(Mono). Aromatic carboxylic acids show similar values.

The title compound, the distances (C=O 1.20 Å and C–OH 1.32 Å) and the analogous angles (124.0°, 125.1° and 111.0°, respectively) are indicative of a very different environment to that just alluded. In the aforementioned cases,[9–11] and apparently as a relatively common occurrence in such systems, carboxylic acids can form head-to-head dimers. A different packing arrangement, where the carboxylic acid is intermolecularly hydrogen bonded instead, is observed in those system where an amide group is also present. Thus, in hippuric acid[8] and in acetylglycine[6,7] we observe a pattern similar to that found in this compound. Namely, distance (C=O–1.19 Å, C–OH–1.33 Å[8] and 1.31 Å[6,7]) and angles (124°, 124°, 112°, respectively) which are entirely comparable to ours.

No such difficulties arise in considering the nitro groups. The bond distances of N–O_{16} and N–O_{17} (1.22 Å each) are normal for aromatic nitro groups which fall in the range of 1.20–1.24 Å.[12,13] The dihedral angle formed between the plane of the nitro group and the adjacent aromatic ring may range from the planar case (p-nitro aniline with a dihedral angle of 1.9°); to small deviations from that plane (p-nitrophenol – 7.9° or p-nitrobenzoic acid 13.7°); or to cases of excess steric crowding. An example of the latter would be 2,3,4,6-tetranitroaniline with a dihedral angle of 64°(13). In the present study, the nitro group and the phenyl ring form a dihedral angle of 17.3°. This is not an unusually large deviation from planarity since calculations[14] show that the loss of "conjugation energy" for rotations of nitro groups up to 18° corresponds to only 0.6 kcal/mole, a number comparable to the energy of intermolecular interactions and less than the energy normally associated with thermal motion.

In a series of E. Coli strains the ability of penicillin acylase, an amidohydrolase, to cause rapid hydrolysis of phenaceturic acid is correlated with its ability to hydrolyze benzylpenicillin amides to corresponding acids.[15] Similarly, in a kinetic study of penicillin G, the proposed catalytic site of the metal complexation is the phenaceturic side chain.[16] Kinetic measurements indicate that the copper catalyzed degradation results from the copper coordinating to the side chain nitrogen and the β-lactam oxygen. That this molecule may serve as a model system for further studies of this kind is suggested by the close resemblance between this molecule and the analogous side chain of penicillin. Besides the obvious agreement in molecular parameters, the similarities in the overall conformation of the two systems, as suggested by the dihedral angles between the major planes, is striking. These dihedral angles in the structure determined by us are 90° between planes II and III; and 79°

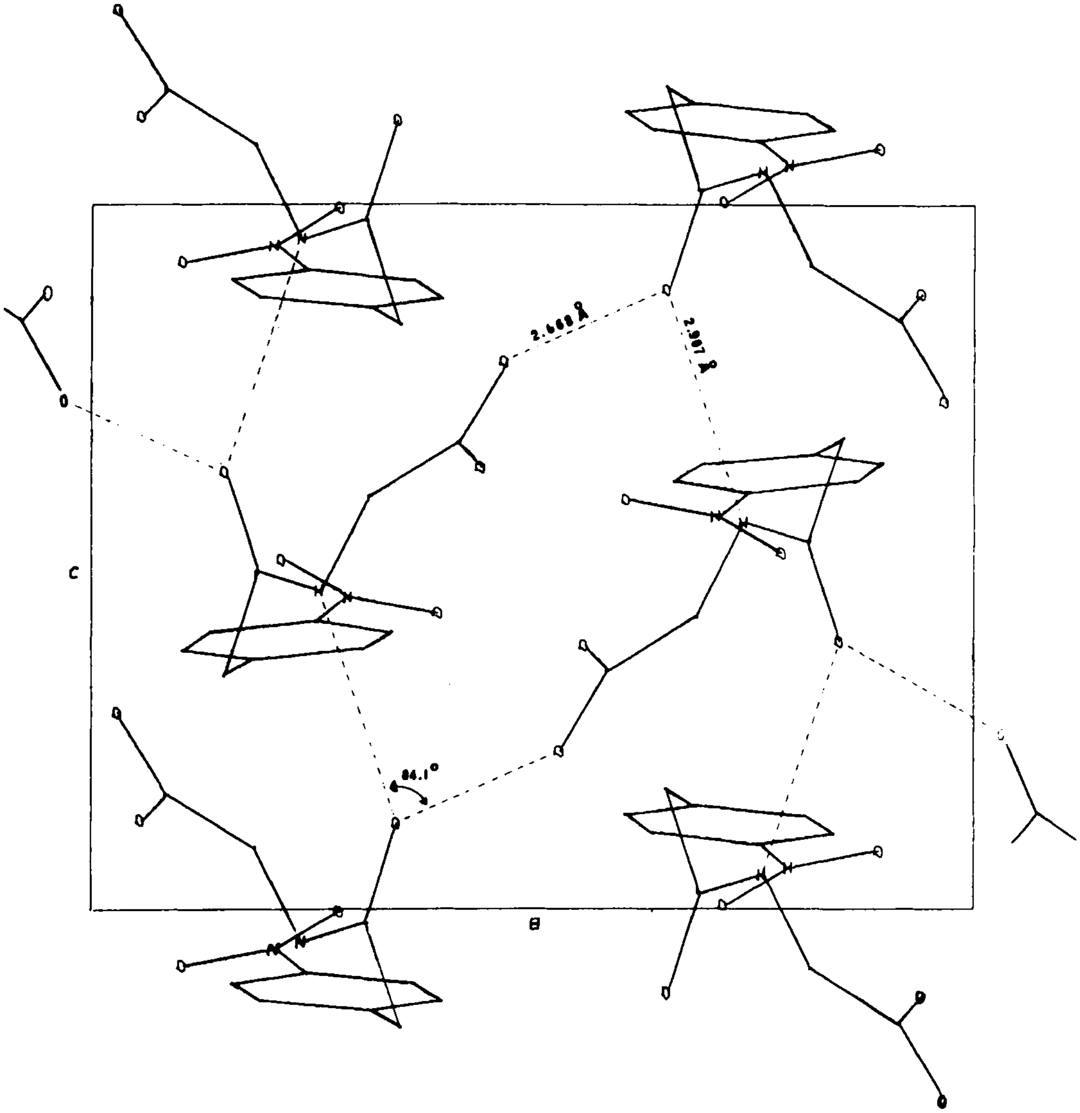

FIGURE 5 Projection of molecule down a-axis with intermolecular contacts indicated.

between planes II and I. The analogous angles[17] in Penicillin G[18] are 89° and 76°, respectively.

The hydrogen bonding system is indicated in the cell drawing, Figure 5. Each amide oxygen O(7) is intermolecularly hydrogen bonded to an adjacent acid proton,[19] O(7)-O(1′) distance 2.67 Å, and to an amide nitrogen, O(&)-N(5″) distance 2.91 Å of a different molecule. The O(1′)-O(7)–N(5″) angle is 84.1°. In this manner the molecules form a three dimensional network identical to that of the hydrogen bonding in hippuric acid. The nitro group and phenyl ring are relatively uninvolved in the scheme with the amide and acid portion of the molecule forming the major links. The O(17″)–O(91) distance 3.09 Å may indicate weak repulsion between the carboxyl oxygen and one of the nitro oxygens sufficient to account for the tilt of the nitro group mentioned earlier. The distance is comparable to 3.07 Å and 3.14 Å in O–NH intermolecular bonding in p-nitroaniline[20] but the acid proton is directed toward the adjacent amide carbonyl rather than toward the nitro group.

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