

The Crystal Structure of the Dimeric Acid Product of 1-Methyl-1,4-dihydronicotinamide

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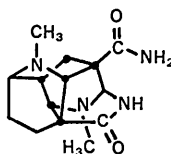
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One of the so-called 'acid products' of 1-methyl-1,4-dihydronicotinamide is a crystalline, colorless material with twice the molecular weight of the parent compound. The crystals are monoclinic, space group $P2_1/n$, with cell dimensions of $a=13.687$, $b=13.488$, $c=7.367$ Å, $\beta=98^\circ 58'$ and four molecules per unit cell. The structure of the dimer has been determined by a three-dimensional X-ray analysis, using Cu $K\alpha$ radiation. Phases were initially found for 224 reflections by the symbolic addition procedure and the subsequent refinement was carried out by full-matrix least squares with anisotropic temperature factors to an R of 0.049. Hydrogen atoms were included. The structure



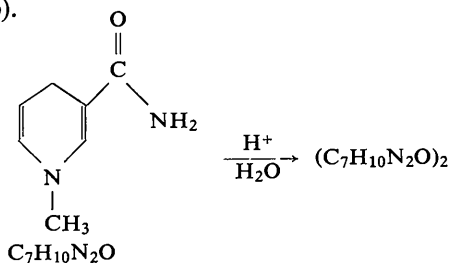
is analogous to two twistane molecules with one ring (solid circles) in common. There are several long C-C bonds. Both of the amide groups are involved in hydrogen bonding across centers of symmetry.

Introduction

Much of the work on the nature of the reactions of acids and other electrophiles with the reduced forms of nicotinamide-adenine dinucleotide (NAD) and nicotinamide-adenine dinucleotide phosphate (NADP) has been facilitated by use of the appropriate 1,3-disubstituted-1,4-dihydronicotinamide model compounds. (A review of this area has been published by Stock, Sann & Pfeleiderer, 1961.) Investigations of the acid reactions of 1-benzyl-3-acetyl-1,4-dihydropyridine by Anderson & Berkelhammer (1958) have conclusively demonstrated that the so-called 'primary acid reaction' involves addition of water to the 5,6 double bond. This reaction is readily characterized by a decrease in the 340–350 $m\mu$ absorption in the ultraviolet spectrum of the parent compound with concurrent formation of a new maximum at 290–300 $m\mu$.

The dihydro products obtained from the reaction of sodium hydrosulfite with pyridinium salts, which are identical with the enzymatic reduction products for the pyridine nucleotide coenzymes NAD and NADP, have now been definitely established as the 1,4-dihydro isomers. In the early studies of the dihydronicotinamide model compounds, the reduced materials were thought to have either the 1,2- or 1,6-dihydro structure. The treatment of the sodium hydrosulfite reduction product of nicotinamide methiodide with dilute, methanolic sulfuric acid resulted in a new 'acid product' which, on the basis of an empirical formula identical with that

of the starting material, was originally thought to be the unknown 1-methyl-1,4-dihydronicotinamide (Karrer, Schwartzbach, Benz & Solmssen, 1936; Karrer & Stare, 1937). However, further work (Kuhnis, Tarber & Karrer, 1957; Krebs, Rafter & Chaykin, 1956; Ammon, Berkelhammer & Anderson, 1962) has shown these new compounds to be dimeric, in that each molecule contains the elements of two molecules of starting material. The acid product may also be obtained from the reaction of 1-methyl-1,4-dihydronicotinamide with an acidic ion-exchange resin (Krebs, Rafter & Chaykin, 1956).

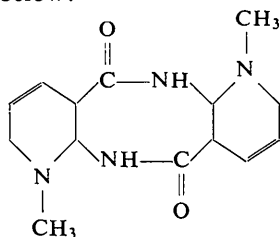


A brief summary of the most salient data from chemical and spectroscopic investigations (Ammon, Berkelhammer & Anderson, 1962) follows:

1. The high melting, dimeric compounds exhibited no absorption in the ultraviolet, indicating the absence of both the α,β -unsaturated carbonyl and enamine functions originally present in the starting materials.
2. Two points of unsaturation were indicated by catalytic hydrogenation in glacial acetic acid. The

amide carbonyl functions were retained (infrared) in the reduced material. The colorless starting material gave a yellow acetic acid solution (no hydrogen uptake in other solvents) and the initial rate of hydrogen absorption depended on the incubation period in this solvent. This could be interpreted as decomposition of the dimer followed by hydrogenation of the degradation product.

3. The degree of substitution of the amide nitrogen was examined by active hydrogen analysis with lithium aluminum hydride. The release of two moles of hydrogen indicated either two secondary, or one primary and one tertiary, amide nitrogens. Similar dimeric compounds could not be isolated from dihydronicotinamides with secondary amide nitrogen atoms, indicating that both of the amide nitrogen atoms were probably utilized for bonding in the dimer. The structure which seemed to best fit all of the available information is shown below:



Experimental

The dimeric acid product of 1-methyl-1,4-dihydronicotinamide crystallizes as large, colorless parallelepipeds from methanol (a preliminary communication has been made by Ammon & Jensen, 1966). In fact, it is often difficult to obtain crystals which are sufficiently small for X-ray diffraction studies. Cell constants were measured from rotation and Weissenberg photographs ($\text{Cu } K\alpha$, $\lambda = 1.5418 \text{ \AA}$, calibrated with NaCl , $a = 5.6396 \text{ \AA}$) of crystals mounted along their b and c axes. The material crystallizes in the monoclinic system and the unit cell parameters are

$$a = 13.687 \pm 0.007 \text{ \AA}$$

$$b = 13.448 \pm 0.007$$

$$c = 7.367 \pm 0.005$$

$$\beta = 98^\circ 58' \pm 4';$$

$Z = 4$, $\rho_{\text{x-ray}} = 1.371 \text{ g.cm}^{-3}$, $\rho_{\text{meas}} = 1.368 \text{ g.cm}^{-3}$. Systematic absences for $0k0$, k odd, and $h0l$, $h+l$ odd, are consistent with space group $P2_1/n$.

A single crystal rotated about the c axis, with dimensions of ca. 0.1×0.1 mm in cross-section by 0.15 mm long, was used for all intensity measurements. The levels $hk0$ – $hk6$ were recorded with Ni-filtered $\text{Cu } K\alpha$ radiation on equi-inclination Weissenberg photographs. The spots were integrated (0.9 mm) at right angles to the crystal rotation axis and measured by scanning with a microdensitometer (logarithmic slide wire) in a direction parallel to the rotation axis. The

areas under the photometer tracings, which are proportional to the diffraction intensities, were measured with a planimeter. The longest exposure time for each of the levels was 100 hours. Of the 2581 reflections accessible on film, 611 (24%) were unobserved. These reflections were assigned a value equal to the minimum observed intensity on the appropriate level. The hll level of a second crystal, rotated about the b axis, was photographed and the intensities used for scaling the c axis data. Structure factors were obtained from the intensities in the usual fashion. No absorption corrections were applied.

Solution of the structure

A three-dimensional, sharpened Patterson function was calculated and preliminary work on the solution of the structure centered about interpretation of the Harker section at $u, \frac{1}{2}, w$. This section was well resolved and its most outstanding feature was a textbook example of three equally spaced collinear peaks (of heights 1:2:1) resulting from the interaction of two different atoms with identical y coordinates (Lipson & Cochran, 1957). The x and z coordinates of the atoms were calculated from these peaks and a search of the Patterson map produced reasonable values for the y coordinates. These two positions were then used as the basis for a long series of Patterson superpositions. Despite much determined effort, no real progress was ever made in this direction. In retrospect, a comparison of the Harker section with one calculated from the known atomic positions showed not only that the original interpretation was wrong, but also that more than half of the maxima on the section were non-Harker peaks.

Our attention was next directed to the symbolic addition procedure (Karle & Karle, 1963) for phase determination. Overall scale and temperature factors and normalized structure factors, E_{hkl} (Hauptman & Karle, 1953), were calculated with the *Crystal Structure Calculations System, X-ray 63* (1964) subprogram DAT-FIX. The PHASER system of programs (Ammon, 1964) was utilized to list the Σ_2 relationships for each reflection and to calculate the associated probabilities (Karle & Karle, 1963). Initially, the 351 E 's ≥ 1.5 were used but this list was subsequently reduced to a more manageable set containing the 246 E 's ≥ 1.7 . Eleven reflections were chosen as a starting set for the phase determination: three were used to specify the origin, a fourth was known from a strong Σ_1 relationship and a fifth was known in terms of the other members of the starting set.

The 64 (2^6) starting phase combinations of the six unknown symbols were formed by PHASER and the 64 phase pyramids calculated. For each of the solutions, this option of the program only outputs the number of phases determined as +, the number determined as –, the number undetermined and the number of agreements and discrepancies in the Σ_2 relationships. It is usually true that the correct combination

of starting phases will result in a pyramid with a relatively small number of undetermined phases and a fairly even distribution of + and - phases. The opposite is generally found for a pyramid constructed from an incorrect starting combination. These criteria pointed to combination no. 40 as the most probable solution and this set of the arbitrary symbols was the same found from an interrelation of the symbols by the program SIGNIE (Ammon, 1964). Several of the solutions, which would have represented 'second choices', differed from no. 40 in only one of the phases of the starting reflections.

An E map (Karle, Hauptman, Karle & Wing, 1958), computed with the 224 phases of solution 40, revealed twenty strong peaks in a totally unsuspected arrangement. It was immediately thought that an incorrect solution (*i.e.* 40) had been chosen. However, a structure factor calculation using only the eighteen 'most reasonable' positions and 1025 reflections ($\sin \theta \leq 0.7$) gave the very encouraging R of 0.39 and a difference synthesis showed the remaining two atoms in exactly the positions predicted by the original E map. An F_c calculation gave an R of 0.26 with carbon scattering factors used for all twenty atoms.

The full set of data and individual isotropic temperature factors were then used in a few cycles of least-squares refinement. Consideration of the resulting bond lengths, temperature factors and peak heights of an F_o Fourier synthesis readily led to the identification of the two oxygen and four nitrogen atoms ($R=0.15$ at this point). The refinement proceeded *via* full-matrix least-squares with anisotropic temperature factors for the carbon, nitrogen and oxygen atoms. A Hughes (1941) weighting scheme (w) was used from the start of the anisotropic refinement. The unobserved data were included in the refinement and given $w=0$ if $F_o > F_c$ and $w=1$ if $F_o \leq F_c$. The F_c 's for 108 of the 611 unobserved

reflections were greater than their respective F_o 's following the last cycle of anisotropic refinement. The average and maximum shifts in this cycle were 0.11σ and 0.76σ . Hydrogen atoms were easily located from a difference map and were refined with isotropic temperature factors.

The final R index is 0.049. Fractional coordinates and temperature parameters for the carbon, nitrogen and oxygen atoms and for the hydrogen atoms are given in Tables 1 and 2 respectively. Observed and calculated structure factors are listed in Table 3.

Table 2. Fractional coordinates and isotropic temperature factors (\AA^2) for the hydrogen atoms

Estimated standard deviations are given in parentheses.

	x	y	z	B
H(2)	1.029 (1)	1.222 (1)	0.781 (3)	2.1 (4)
H(4a)	1.205 (1)	1.333 (1)	0.919 (3)	1.7 (4)
H(4b)	1.250 (1)	1.388 (1)	0.751 (3)	2.0 (4)
H(5)	1.354 (2)	1.247 (2)	0.918 (3)	2.3 (4)
H(6)	1.298 (2)	1.086 (2)	0.838 (3)	3.0 (5)
H(7a)	1.121 (2)	1.008 (2)	0.861 (3)	4.8 (6)
H(7b)	1.183 (2)	1.042 (2)	1.048 (4)	5.4 (7)
H(7c)	1.062 (2)	1.078 (2)	0.999 (4)	5.9 (7)
H(10a)	1.174 (2)	1.418 (2)	0.426 (4)	4.5 (6)
H(10b)	1.077 (2)	1.489 (2)	0.427 (4)	5.5 (7)
H(2')	1.161 (1)	1.236 (1)	0.368 (3)	1.5 (4)
H(4a')	1.327 (2)	1.020 (2)	0.538 (3)	3.3 (5)
H(4b')	1.309 (1)	1.092 (2)	0.362 (3)	2.2 (4)
H(5a')	1.452 (2)	1.166 (2)	0.486 (3)	3.6 (5)
H(5b')	1.447 (2)	1.130 (2)	0.692 (3)	4.0 (6)
H(6')	1.418 (2)	1.307 (2)	0.667 (3)	2.7 (5)
H(7a')	1.337 (2)	1.243 (2)	0.248 (3)	3.8 (6)
H(7b')	1.270 (2)	1.330 (2)	0.220 (4)	5.6 (7)
H(7c')	1.376 (2)	1.357 (2)	0.319 (3)	4.6 (6)
H(10')	0.996 (2)	1.089 (2)	0.578 (4)	5.7 (7)

Of the 224 phases used from solution 40, only one was incorrect by comparison with the phases from the fully refined structure. The E map from solution 40 contained twelve peaks greater than 300, seven greater

Table 1. Fractional coordinates and anisotropic temperature factors (\AA^2) for the carbon, oxygen and nitrogen atoms

Estimated standard deviations are given in parentheses.

The anisotropic thermal parameters are in the form $\exp[-0.25(h^2B_{11}a^{*2} + \dots + 2klB_{23}b^*c^*)]$.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	1.16454 (12)	1.15552 (12)	0.86829 (25)	2.71 (7)	2.32 (6)	2.77 (9)	0.55 (5)	1.06 (6)	0.88 (5)
C(2)	1.09079 (13)	1.19892 (13)	0.72529 (28)	2.12 (7)	1.50 (6)	3.02 (10)	0.11 (5)	0.83 (6)	0.08 (6)
C(3)	1.14455 (12)	1.28509 (12)	0.64179 (27)	1.72 (6)	1.33 (6)	2.50 (9)	-0.04 (5)	0.26 (6)	0.03 (5)
C(4)	1.22825 (14)	1.32474 (14)	0.79174 (28)	2.39 (8)	2.01 (7)	2.43 (10)	-0.08 (6)	-0.03 (6)	-0.32 (6)
C(5)	1.30998 (14)	1.24553 (15)	0.80059 (28)	2.03 (7)	2.65 (8)	2.24 (10)	0.25 (6)	-0.27 (6)	0.09 (6)
C(6)	1.25387 (14)	1.14539 (14)	0.78134 (29)	2.28 (7)	2.10 (7)	2.89 (11)	0.49 (6)	0.65 (6)	0.70 (6)
C(7)	1.13190 (19)	1.06493 (18)	0.95049 (39)	4.58 (11)	3.07 (10)	5.53 (15)	0.79 (8)	2.53 (6)	2.01 (9)
C(8)	1.07568 (13)	1.36958 (13)	0.57124 (28)	1.92 (7)	1.54 (6)	2.96 (10)	0.07 (8)	0.13 (6)	-0.13 (6)
O(9)	0.99376 (11)	1.38008 (11)	0.61844 (25)	2.33 (6)	2.46 (6)	6.02 (10)	1.05 (5)	1.42 (6)	1.13 (6)
N(10)	1.11107 (12)	1.43245 (12)	0.45735 (27)	2.42 (7)	1.80 (6)	4.59 (10)	0.49 (5)	0.57 (6)	1.04 (6)
N(1')	1.28974 (11)	1.29649 (11)	0.48530 (23)	1.75 (6)	2.03 (6)	2.48 (8)	-0.23 (5)	0.34 (5)	0.52 (5)
C(2')	1.20001 (12)	1.23811 (12)	0.49445 (26)	1.68 (6)	1.41 (6)	2.31 (9)	-0.10 (5)	0.14 (5)	0.12 (5)
C(3')	1.22653 (13)	1.13034 (13)	0.56871 (28)	1.99 (7)	1.48 (6)	2.84 (10)	1.06 (5)	0.81 (6)	0.09 (6)
C(4')	1.31765 (14)	1.09087 (14)	0.49719 (32)	2.54 (8)	2.00 (7)	3.95 (12)	0.34 (6)	1.28 (7)	0.03 (7)
C(5')	1.40552 (14)	1.15747 (16)	0.58101 (34)	1.88 (7)	3.10 (9)	4.50 (13)	0.48 (6)	0.84 (7)	0.60 (8)
C(6')	1.38470 (13)	1.25806 (14)	0.63431 (30)	1.60 (7)	2.54 (8)	3.25 (11)	-0.24 (6)	0.04 (6)	0.21 (7)
C(7')	1.32075 (17)	1.30498 (18)	0.30699 (35)	3.23 (9)	3.90 (10)	3.67 (13)	0.25 (7)	1.27 (8)	1.14 (8)
C(8')	1.13092 (14)	1.07451 (13)	0.51798 (30)	2.40 (7)	1.48 (7)	3.77 (11)	-0.18 (5)	0.85 (7)	-0.27 (6)
O(9')	1.12046 (12)	0.99731 (11)	0.42750 (25)	3.50 (7)	2.02 (6)	5.56 (10)	-0.84 (5)	1.66 (6)	1.55 (6)
N(10')	1.05709 (11)	1.12419 (11)	0.58190 (26)	1.84 (6)	1.71 (6)	4.29 (10)	-0.33 (5)	0.90 (6)	-0.49 (6)

Table 3. Final structure factor table for the 'dimeric acid product' of 1-methyl-1,4-dihyronicotinamide

The data are listed in groups of constant k and l. The three columns within each group are h, 10F0 and 10 Fc. Those data not included in the refinement are marked with an E and the unobserved data are indicated with an asterisk.

Table with multiple columns (h, 10F0, 10 Fc) and rows grouped by k and l values (e.g., h=0, l=0; h=1, l=0; etc.).

Table 3 (cont.)

A large table of numerical data with multiple columns and rows, organized into sections labeled H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, H18, H19, H20, H21, H22, H23, H24, H25, H26, H27, H28, H29, H30, H31, H32, H33, H34, H35, H36, H37, H38, H39, H40, H41, H42, H43, H44, H45, H46, H47, H48, H49, H50, H51, H52, H53, H54, H55, H56, H57, H58, H59, H60, H61, H62, H63, H64, H65, H66, H67, H68, H69, H70, H71, H72, H73, H74, H75, H76, H77, H78, H79, H80, H81, H82, H83, H84, H85, H86, H87, H88, H89, H90, H91, H92, H93, H94, H95, H96, H97, H98, H99, H100. Each section contains a list of numbers, some with signs, and some with sub-labels like H1, H2, etc. The numbers are arranged in a grid-like pattern across the page.

Table 3 (cont.)

H10,5	-2 77 75	-2 70 -81	1 53 -44	-8 95 89	-2 19* 22	-12 54 48	8 23*	-4	-7 49 -50
5 57 63	-7 18* -11	4 80 61	-1 140 -148	9 36 -34	3 36* -16	-13 16*	-7	-8 23 -27	-8 91 -86
-5 155 155	-3 92 93	-4 107 -107	2 233 239	-9 76 -33	-3 30 -36	-10 35 33	-9	35 33	-9 85 -79
6 38 50	4 51 50	6 131 134	-2 63 -63	10 26*	-14	4 144 -133		-10 135 122	-17 27 -21
6 44 44	4 28 29	-6 355 385	3 30* 27	-10 92 91	-4 157 -161			-11 16*	-4
-7 17*	-5 33 -33	-8 82 77	5 51 -43	-11 62 -74	-5 177 175	0 51 -55		-12 27 -24	H11,6
-7 91 -60	6 14* 21	10 98 101	4 72 71	-12 97 83	6 34* 13	-1 74 -74			0 54 -57
4 15* 13	-6 18* 18	-10 80 -75	6 61 41	-13 53 49	-6 165 160	2 63 -58		0 38 -28	1 51 -47
-4 20* 12	-7 17* 14	-12 64 -67	-5 140 -147	-14 31 -23	7 108 -101	-2 65 -37		1 39 -34	-1 20* -1
-9 11* -9	-8 53 -53	-14 50 55	6 61 -59	-6 45 -44	-7 107 -97	3 85 82		-1 76 -70	2 93 91
-1 59 52	-7 6* -6		-6 45 -44	H4,6	8 45 -36	-3 224 -17		-1 76 -70	-2 62 -67
11 49 47			7 61 -66		-6 0* -94	4 34* 7		2 37*	3 43 40
12 56 -55	H13,5		-7 25 21	0 173 175	-9 27*	-2		-4 127 129	-2 41 40
	0 29 -25	0 194 206	8 33* 6	1 133 -129	-9 55 -59	5 55 -55		3 33* 26	4 28 30
H11,5	-1 32 -28	-1 75 -73	9 47 -38	2 44 -40	10 22* 20	-5 53 -53		3 22 19	-4 19* 23
0 34 -31	-1 18*	0 2 84 -78	-9 115 -98	-2 40 -43	11 33 -23	-6 92 -93		4 92 91	5 62 -66
1 87 80	-2 98 92	3 29* 2	-10 22* 2	-3 18*	10 42 28	6 78 -75		4 92 91	5 63 60
-1 22* -22	3 37 -35	-3 25 25	4 111 110	4 111 110	14 14* -19	8 27* 6		6 30 35	-8 38 35
2 91 70	-3 25 -29	4 75 71	-11 22* 4	-4 90 81		-8 224 9		28 30 -9	22 -19
-2 95 45	4 14* 22	-4 54 55	-12 31 25	5 34* 36	H5,6	9 22* -15		7 23*	-17
3 4* -64	-4 17* -5	5 34* 19	-13 71 -63	-5 39 -34		-9 96 -93		7 39 -30	H12,6
-3 49 45	5 11* -9	-5 78 -68	-14 16* -12	6 76 -77	0 179 -182	-10 78 -70		8 23 37	8 23 37
4 35 -39	-5 44 -44	6 134 136	-15 26 28	6 103 -93	1 33* 25	-11 100 94		-8 20*	0 86 82
-4 77 -75	-6 54 -53	-6 58 -50	7 34* -2	7 34* -2	-1 74 -69	-12 56 -51		-9 7 36	-1 25* 17
5 19* 2	-7 64 59	7 34* 6		-7 23 -13	2 34* 31	-13 41 39		-10 33 -35	-1 32 -27
-5 65 -66	-8 71 77	-7 20* 17	H3,6	8 32* -26	-2 70 66			-11 14*	-2
0 50 48		8 33* -2	0 118 -117	-8 113 -106	3 56 62				-2 17* 5
7 12* -120	-8 147 141	-8 147 141	1 82 79	-3 42 -42	-3 42 -42				32 -32
-7 112 -127	9 31* 11	-1 182 -213	9 64 -62	4 35* 17					-3
8 118 -118	-9 42 -32	2 167 159	10 25* 14	-4 94 95	1 33* 36				4 44 65
-8 148* 3	1 138* 2	10 29* -18	-2 86 83	-10 22* -7	5 54 57	-1 40 -38			4 16* -3
-9 54 53	2 33 31	11 22* 2	-3 88 83	-11 28 -18	-5 241 251	2 62 -62			-5 15* 20
10 115 112	-3 33 -33	-12 54 -36	4 33* 21	-12 40 41	7 36* 4	-3 69 70			-7 23 -21
11 42 41	-4 45 -46	-13 42 39	5 62 -52	-14 14* 16	-7 22* 4	4 33* 8			-3 25 -27
H12,5	-5 30 -29	-14 28 27	-5 110 102	6 155* 0	8 29* -12	-4 46 -46			4 28* -8
0 64 -60		-15 11* 20		H5,6	-8 22* 15	5 68 -59			6 35 60
1 131 -132			7 40 39	0 132 129	-9 53 56	-6 53 49			-5 30 -25
-1 37 -34	0 17* -2	H12,6	7 40 39	1 131 130	-7 36 -37	-6 50 42			-2 13* 7
2 17* 10	2 265 -275	0 133 -131	8 37 43	-1 83 82	10 131 -117	7 27* 25			-6 20* 16
				3 57 -57	11 20* 1	-7 51 45			7 4* -61
									-4 81 81

than 200 and one of 175 on an arbitrary scale. The largest 'noise' peak, *ca.* 122, was at the position of a hydrogen atom. The scattering factors used were the following: C, N and O, Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955); H, Stewart, Davidson & Simpson (1965).

Discussion

The molecule is shown in Fig. 1. A re-examination of the chemical data is necessary on two counts. First, the hydrogen absorption in acetic acid must now be interpreted as arising from the reduction of an acid-catalyzed degradation product of the dimer. Second, the failure of the dimer to show three active hydrogen atoms could be explained by the precipitation of a dianion from the reaction solution (tetrahydrofuran), making the third amide hydrogen atom unavailable for reaction.

The two 'monomeric' 6-rings in the dimer have been turned up down relative to each other and are roughly parallel. Three C-C bonds [C(3)-C(2'), C(5)-C(6') and C(6)-C(3')] and one C-N [C(2)-N(10')] bond connect the original molecules. The structure contains nine different six-membered rings, the conformations of which can be best described as distorted twist or skew boat, and very closely resembles the geometry assumed by two twistane molecules (Whitlock, 1962) with one ring [C(3)-C(4)-C(5)-C(6)-C(3')-C(2')] in common. This ring shows the least deviation from the twist conformation.

The hydrocarbon 'parent' of the compound would have a twofold axis passing through C(3')-C(4), although the molecule itself does not possess this symmetry. Fig. 2, a view parallel to the C(3')-C(4) direction, readily shows this pseudo twofold axis. Another analogy can be drawn in that the skeleton bears the same relationship to twistane as congressane (Cupas, Schleyer & Tecker, 1965) does to adamantane (Landa,

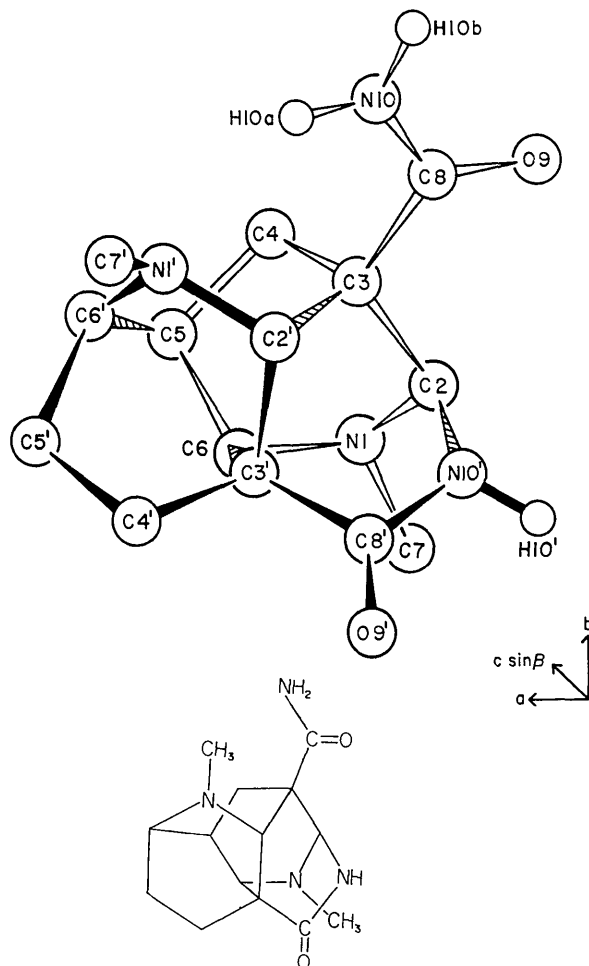


Fig. 1. A drawing of the molecule viewed normal to the *ab* plane. The dark and light lines are used to indicate the original 'monomers'. Hydrogen atoms are shown only for the amide groups. A regular line drawing of the molecule is also shown.

1962; Nowacki, 1945). We are grateful to a referee for bringing the above points to our attention.

Bond lengths and angles for the carbon, nitrogen and oxygen atoms are given in Tables 4 and 5. The method of Busing & Levy (1964) for bond length corrections resulting from the librational motion of a center of mass (Cruickshank, 1956) was applied to the 14 endocyclic atoms. Distances involving the 6 exocyclic atoms have been corrected for the 'riding motion' (Busing & Levy, 1964) of one atom on another. The corrected average, 1.553 ± 0.004 Å, of the eleven C-C bonds (presumably of sp^3-sp^3 hybridization) is significantly greater than the value of 1.533 ± 0.003 Å, which is generally accepted as the 'normal' length for bonds of this type (Bartell, 1959). This lengthening is not too surprising considering the polycyclic nature of the molecule and the large number of nonbonded, cross-cage interactions. A further example is the CH_2-CH_2 bond in 4,12-dimethyl[2.2]-*m*-cyclophane, 1.573 Å (Hanson, 1962), which is presumably lengthened by such interactions between the two aromatic rings.

An examination of the individual $C(sp^3)-C(sp^3)$ bond lengths shows that $C(3')-C(6)$ (1.572 ± 0.003 Å) and $C(2')-C(3')$ (1.577 ± 0.002 Å) are quite long. In each case, however, the bonded atoms have a total of seven non-hydrogen substituents, a situation which furnishes the conditions for several nonbonded *gauche* interactions. The important influence of nonbonded interactions on bond distances has been emphasized by Bartell (1959, 1962) and the available data suggest that bond lengthening becomes noticeable in the $CX_2H-CX_3^*$ case and appreciable in the $CX_3-CX_3^*$ case (Sundara-

* The X's refer to substituents other than hydrogen.

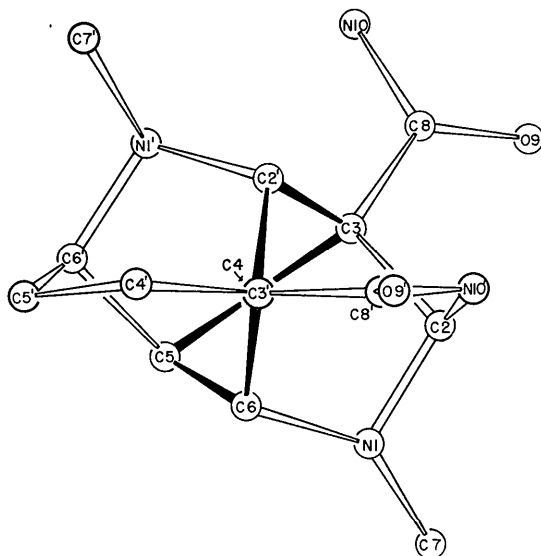


Fig. 2. A drawing of the molecule looking along a line connecting $C(3')$ and $C(4)$. This view emphasizes the pseudo twofold axis from $C(3')$ to $C(4)$ and shows the well defined twist-boat conformation of the central six membered ring [dark lines, $C(2')-C(3)-C(4)-C(5)-C(6)-C(3')$].

Table 4. Bond lengths involving carbon, nitrogen and oxygen atoms

	Length	e.s.d.	Corrected length*
N(1)-C(7)	1.461 Å	0.003 Å	1.482 Å <i>r</i>
N(1)-C(2)	1.462	0.002	1.468
N(1)-C(6)	1.472	0.003	1.476
C(2)-C(3)	1.550	0.003	1.555
C(2)-N(10')	1.479	0.002	1.484
C(3)-C(4)	1.557	0.002	1.562
C(3)-C(8)	1.516	0.002	1.519 <i>r</i>
C(3)-C(2')	1.553	0.003	1.557
C(4)-C(5)	1.539	0.002	1.544
C(5)-C(6)	1.546	0.003	1.551
C(5)-C(6')	1.541	0.003	1.546
C(6)-C(3')	1.566	0.003	1.572
C(8)-O(9)	1.233	0.002	1.255 <i>r</i>
C(8)-N(10)	1.334	0.003	1.345 <i>r</i>
N(1')-C(7')	1.447	0.003	1.463 <i>r</i>
N(1')-C(2')	1.468	0.002	1.472
N(1')-C(6')	1.474	0.002	1.480
C(2')-C(3')	1.571	0.002	1.577
C(3')-C(8')	1.504	0.003	1.509
C(3')-C(4')	1.523	0.003	1.527
C(4')-C(5')	1.549	0.003	1.554
C(5')-C(6')	1.538	0.003	1.543
C(8')-O(9')	1.230	0.002	1.248 <i>r</i>
C(8')-N(10')	1.356	0.003	1.360

* Bond lengths between the 14 endocyclic atoms were corrected (Busing & Levy, 1964) for the librational motion about a center of mass. Distances involving the 6 exocyclic atoms have been corrected for the riding motion described by Busing & Levy (1964); an *r* is used to indicate these corrections. We are grateful to Dr R.A. Alden for computing the riding motion corrections (High & Alden, 1965).

Table 5. Bond angles involving carbon, nitrogen and oxygen atoms

		e.s.d.
C(2)-N(1)-C(6)	104.50°	0.16°
C(2)-N(1)-C(7)	114.21	0.16
C(6)-N(1)-C(7)	115.56	0.17
N(1)-C(2)-C(3)	105.50	0.14
N(1)-C(2)-N(10')	110.30	0.14
C(3)-C(2)-N(10')	109.82	0.17
C(2)-C(3)-C(4)	108.47	0.15
C(2)-C(3)-C(8)	112.84	0.14
C(2)-C(3)-C(2')	106.69	0.14
C(4)-C(3)-C(8)	109.65	0.14
C(4)-C(3)-C(2')	104.46	0.14
C(8)-C(3)-C(2')	114.27	0.16
C(3)-C(4)-C(5)	104.05	0.15
C(4)-C(5)-C(6)	104.58	0.15
C(4)-C(5)-C(6')	109.31	0.16
C(6)-C(5)-C(6')	108.56	0.16
N(1)-C(6)-C(5)	108.29	0.16
N(1)-C(6)-C(3')	111.22	0.15
C(5)-C(6)-C(3')	104.02	0.16
C(3)-C(8)-O(9)	122.25	0.18
C(3)-C(8)-N(10)	115.05	0.16
O(9)-C(8)-N(10)	122.69	0.17
C(2')-N(1')-C(6')	105.57	0.14
C(2')-N(1')-C(7')	116.73	0.16
C(6')-N(1')-C(7')	115.80	0.16
N(1')-C(2')-C(3)	108.55	0.14
N(1')-C(2')-C(3')	111.08	0.13
C(3)-C(2')-C(3')	104.09	0.15
C(6)-C(3')-C(2')	103.61	0.14
C(6)-C(3')-C(4')	108.07	0.15
C(6)-C(3')-C(8')	112.09	0.17

Table 5 (cont.)

		e.s.d.
C(2')-C(3')-C(4')	110.99	0.16
C(2')-C(3')-C(8')	103.24	0.13
C(4')-C(3')-C(8')	117.88	0.16
C(3')-C(4')-C(5')	106.70	0.16
C(4')-C(5')-C(6')	108.67	0.15
C(5')-C(6')-N(1')	105.20	0.15
C(5')-C(6')-C(5')	110.34	0.17
N(1')-C(6')-C(5')	110.89	0.17
C(3')-C(8')-O(9')	125.39	0.18
C(3')-C(8')-N(10')	109.54	0.16
O(9')-C(8')-N(10')	125.04	0.17
C(2)-N(10')-C(8')	114.62	0.15

lingam, 1964). Calculations (similar to those made by Bartell (1959) for diamond) considering only *gauche* interactions for the C(3')-C(6) and C(2')-C(3') bonds predicted increases of 0.040 and 0.039 Å, respectively, over the 'normal' 1.533 Å bond.

The polycyclic nature of the structure makes justification of all bond length variations quite difficult. A comparison of the projected angles between substituents for each of the bonds in question provides little help in explaining the differences. For example, the next longest C-C bonds are C(3)-C(4) (1.562 ± 0.002 Å, 6 non-H substituents), C(3)-C(2') (1.557 ± 0.003 Å, 7 non-H's) and C(2)-C(3) (1.555 ± 0.003 Å, 7 non-H's). The two nitrogen substituents on C(2), however, would be expected to make the C(2)-C(3) bond shorter than in a similar situation with all carbon substituents. A diversion of *s* character at C(2) away from the two more electronegative nitrogen atoms (relative to carbon) would increase the *s* character in the orbital to C(3) and result in bond shortening (Bent, 1961).

The lengths of the two carbon-carbon bonds with presumably *sp*³-*sp*² hybridization, C(3)-C(8), 1.519 ± 0.002 Å, and C(3')-C(8'), 1.509 ± 0.003 Å, are compatible with other bonds of this type, 1.506-1.516 Å (Tables of Interatomic Distances, 1958, 1965). Bond length differences between the two are probably the result of their exo- and endocyclic environments and, in the case of the latter, a slight increase in *s* character of the C(3') orbital to C(8') as shown by the C(6)-C(3')-C(8'), 112.09°, and C(4')-C(3')-C(8'), 117.88°, bond angles.

Bond angles involving the carbon, nitrogen and oxygen atoms are given in Table 5. The average of the nine C-C(*sp*³)-C angles* is 106.7° and that for all of the eighteen C(or N)-C(*sp*³)-C(or N) angles* is 107.84°; both are less than the tetrahedral value. This would be expected if it is assumed that relief of strain caused by the nonbonded interactions has resulted in a slight, general increase in *p* character of the carbon and nitrogen orbitals within the rings. The angle range is from 103.61 to 117.88°.

The seven C(*sp*³)-N bond lengths are in fair agreement with each other and with similar bonds (average

* Both sets of six angles about C(3) and C(3') have been omitted from this average.

1.472 Å, Tables of Interatomic Distances). The riding motion corrections have had considerable effect upon the two CH₃-H bonds, C(7')-N(1') and C(7)-N(1). The quite short C(7')-N(1') bond length of 1.447 Å has been corrected to 1.463 Å, still a bit short, and the C(7)-N(1) bond length has been corrected from 1.461 to 1.482 Å (from a little short to a little long). The C(7')-N(1') case is a good example of the desirability of applying thermal motion corrections to atoms bonded to only one other 'heavy' atom.

Projected angles for the two CH₃-N bonds are shown in Fig. 3. The methyl groups have rotated in order to achieve almost perfect staggering of their hydrogen atoms with respect to the nitrogen substituents.

C-O and C-N distances within the two carboxamido groups are consistent with similar distances in other molecules. The correction for the exocyclic amide C-N bond (+0.011 to 1.345 Å) is greater than that for its endocyclic counterpart (+0.004 to 1.360 Å) and has reduced the apparent difference between the two. Relatively large corrections for the two carbonyl groups [+0.018 to 1.248 Å for C(8')-O(9') and +0.022 to 1.255 Å for C(8)-O(9)] have made these distances a little longer than those normally found for amide carbonyls. It should be mentioned that most bond length data in the literature are uncorrected. Thermal motions in the two oxygen atoms are quite anisotropic and the principal axes of the vibration ellipsoids are almost normal to the amide planes (angles of 19.2 and 18.5°, respectively, with the normals to these planes). Bond angles about C(8) and C(8') are compatible with those usually observed in amides.

The average of the seventeen C-H bonds (Table 6), 1.003 Å, corresponds with that usually found in X-ray determinations, *ca.* 1.02 Å; X-ray measurements of bond lengths involving hydrogen atoms are generally shorter than spectroscopic values (Stewart, Davidson & Simpson, 1965). In spite of this shortening, the difference of *ca.* 0.07 Å between the N-H, average 0.935 Å, and C-H bond lengths is of the same magnitude as that found for spectroscopic measurements of similar bonds.

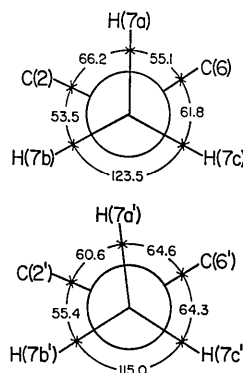


Fig. 3. Views down the two CH₃-N bonds showing projected angles (°).

Table 6. Bond lengths for the hydrogen atoms

	Uncorrected*	Corrected†
H(2)—C(2)	1.04 (2) Å	1.06 Å
H(4a)—C(4)	1.04 (2)	1.06
H(4b)—C(4)	0.96 (2)	0.99
H(5)—C(5)	0.98 (2)	1.00
H(6)—C(6)	1.05 (2)	1.09
H(7a)—C(7)	1.01 (3)	1.09
H(7b)—C(7)	0.97 (3)	1.06
H(7c)—C(7)	1.08 (3)	1.17
H(10a)—N(10)	0.94 (3)	1.03
H(10b)—N(10)	0.90 (3)	1.00
H(2')—C(2')	1.00 (2)	1.02
H(4a')—C(4')	1.00 (2)	1.04
H(4b')—C(4')	0.99 (2)	1.01
H(5a')—C(5')	1.02 (3)	1.07
H(5b')—C(5')	0.98 (2)	1.05
H(6')—C(6')	0.99 (2)	1.02
H(7a')—C(7')	0.98 (3)	1.04
H(7b')—C(7')	0.93 (3)	1.04
H(7c')—C(7')	1.03 (3)	1.10
H(10')—N(10')	0.96 (3)	1.07

* Estimated standard deviations are given in parentheses.

† Corrected for the riding motion of one atom upon another (Busing & Levy, 1964).

The C—H and N—H bond lengths were corrected for the riding motion of one atom on another by the method of Busing & Levy (1964). The average correction for the six methyl hydrogen atoms, 0.08 Å, produced a mean distance of 1.08 Å. The remaining eleven C—H bonds were corrected an average of 0.03 to 1.04 Å. Although the extent of the correction should be larger in the former case as a result of the greater motion of CH₃ relative to that of CH₂ and CH, it is probable that the correction has been overestimated for these distances.

A table of bond angles involving the hydrogen atoms, and the carbon and nitrogen atoms, may be obtained from the authors on request.

Both of the amide carbonyl groups are planar within the limits of the determination (Table 10). The N(10') group has been twisted, about the C(8')—N(10') bond, from coplanarity (*ca.* 15.6°) with the carbonyl group. In addition, N(10') is at the apex of a shallow pyramid with its substituents, C(8'), C(2) and H(10'), forming the base. These features are nicely illustrated by the projected angles H(10')—N(10') → C(8')—O(9'), 14.03°, and C(2)—N(10') → C(8')—C(3'), 17.21°, and by the sum of the angles around N(10'), 352.7 ± 2.6°. The presence of this amide function in a ring is, in all likelihood, responsible for these characteristics and for the lengthening of the C—N bond, 1.360 Å, relative to C(8)—N(10), 1.345 Å. The exocyclic amide nitrogen

N(10) and its substituents are planar (the sum of the angles about N(10) is 359.6 ± 3.6°) and the group is twisted *ca.* 5.4° from coplanarity with the C(8) carbonyl group.

A rigid body analysis (Cruickshank, 1956) of the thermal vibration ellipsoids of the 14 endocyclic atoms was made with the program DIAGUS (Stewart, 1966). The 6 exocyclic atoms C(7), C(7'), C(8), O(9), O(9') and N(10) were included only for a determination of the molecular center of mass. The B_{ij} 's were converted into U_{ij} 's and all calculations were performed in the orthogonal E vector system (Patterson, 1952). Table 7 gives the translational (τ) and librational (ω) tensors of the center of mass together with their estimated standard deviations relative to the E axial system; and the observed and calculated U_{ij} 's are given in Table 9. The principal axes of the τ and ω tensors and their direction angles are given in Table 8 relative to the crystal axes, a , b and c .

Table 8. Principal axes of the τ and ω tensors relative to the crystal axes

R.m.s. amplitude of translation	Direction angles			
	0.13 Å	77.6°	162.4°	79.7°
0.17	85.5	101.6	167.6	
0.14	13.2	76.9	96.9	
R.m.s. angular oscillation	2.46°	66.1°	78.5°	35.0°
	4.03	23.9	94.7	122.3
	3.19	89.6	167.6	77.8

The amplitudes of the principal axes of τ are essentially isotropic. The major and intermediate axes of ω are roughly parallel to a and b respectively. These motions are in directions which provide a minimum amount of distortion of the intermolecular hydrogen bonding system. A torsional motion, somewhat in the plane of the amide hydrogen bonds, is represented by the minor axis of ω . If the hydrogen bonds are assumed to be primarily responsible for restricting molecular movement, a shearing motion in the plane of these bonds would be less favorable than a bending motion of the planes, and it should be represented by the minor axis of the librational tensor.

A view of part of the structure, normal to the ab plane, is shown in Fig. 4. Both of the amide groups are involved in the formation of centrosymmetric, hydrogen bonded 'dimers', which have been observed in many other amides [*e.g.* 1-benzyl-1,4-dihydronic-

Table 7. The translational (10^{-2} Å²) and librational (deg²) tensors and their estimated standard deviations relative to the orthogonal E vector system*

$$\tau = \begin{bmatrix} 2.00 & 0.09 & -0.04 \\ & 1.64 & 0.24 \\ & & 2.75 \end{bmatrix} \quad \omega = \begin{bmatrix} 14.16 & -0.81 & -4.03 \\ & 10.03 & -0.49 \\ & & 8.27 \end{bmatrix}$$

$$\sigma(\tau) = \begin{bmatrix} 0.09 & 0.09 & 0.09 \\ & 0.12 & 0.10 \\ & & 0.13 \end{bmatrix} \quad \sigma(\omega) = \begin{bmatrix} 1.70 & 0.86 & 1.03 \\ & 1.02 & 0.81 \\ & & 0.99 \end{bmatrix}$$

* Patterson (1952).

Table 9. A comparison of the observed U_{ij} 's with those calculated from a rigid body analysis of the 14 endocyclic atoms (in 10^{-2} \AA^2)*

	U_{11}		U_{22}		U_{33}		U_{12}		U_{13}		U_{23}	
	obs	calc	obs	calc	obs	calc	obs	calc	obs	calc	obs	calc
N(1)	3.27	3.22	2.94	3.01	3.43	3.14	0.59	0.27	0.82	0.39	1.09	0.87
C(2)	2.56	2.26	1.90	2.20	3.77	3.44	0.13	0.08	0.54	0.37	0.10	0.35
C(3)	2.19	2.26	1.68	1.73	3.19	3.25	0.06	0.23	0.11	0.13	0.05	0.23
C(4)	3.13	3.13	2.54	2.51	3.14	3.78	0.06	0.25	0.53	0.03	-0.40	-0.66
C(5)	2.73	2.58	3.36	3.39	2.92	3.53	0.30	0.12	0.78	0.63	0.10	-0.08
C(6)	2.81	2.62	2.65	2.60	3.64	3.25	0.53	0.42	0.31	-0.16	0.85	0.79
N(1')	2.20	2.58	2.57	2.24	3.14	4.00	0.36	-0.12	0.00	0.55	0.68	0.59
C(2')	2.17	2.25	1.78	1.93	2.95	2.82	-0.15	0.13	0.23	0.03	0.16	0.36
C(3')	2.40	2.37	1.87	1.71	3.55	3.35	0.06	0.20	0.53	0.17	0.11	0.16
C(4')	3.00	3.01	2.53	2.43	4.91	4.80	0.43	0.71	0.96	0.82	0.02	0.03
C(5')	2.27	2.20	3.93	3.62	5.67	5.56	0.54	0.65	0.37	0.40	0.73	0.55
C(6')	2.11	2.09	3.22	3.06	4.18	4.67	-0.33	-0.26	0.49	-0.04	0.28	0.14
C(8')	2.94	3.05	1.88	2.08	4.73	4.52	-0.20	-0.41	0.44	0.19	0.33	-0.45
N(10')	2.20	2.38	2.17	2.52	5.39	4.50	-0.35	-0.48	0.48	0.04	0.61	0.04

* Relative to the E vector system (Patterson, 1952).Table 10. Deviations (\AA) from least-squares planes*Exocyclic amide: $3.9294x + 7.5509y + 5.3181z = 17.612$

Atom	Deviation
C(3)	-0.002
C(8)	0.006
O(9)	-0.002
N(10)	-0.002
H(10a)	0.026*
H(10b)	-0.129*

Endocyclic amide: $-0.7347x + 7.0689y - 6.1167z = 3.6075$

Atom	Deviation
C(3')	-0.003
C(8')	0.011
O(9')	-0.004
N(10')	-0.003
C(2)	0.370*
H(10')	0.182*

* Asterisks indicate atoms not included in the plane calculations.

tinamide (Karle, 1961) and benzamide (Penfold & White, 1959)]. The $N \cdots O$ distances (Fig. 5) for the hydrogen bonded atoms agree well with previous examples (Pimentel & McClellan, 1960a). The normals to the two dimer planes make angles of 29.32° (endocyclic) and 33.60° (exocyclic) with c^* and an acute angle of 48.42° with each other. In the dimers, the planes of the amide groups which are required to be parallel by symmetry, are separated by 0.663 and 0.605 \AA for the endocyclic and exocyclic cases, respectively.

A close examination of bond lengths, angles and planes in the amide dimers reveals several interesting features. $H(10')$ is 0.182 \AA (Table 10) out of the least-squares plane of the endocyclic amide, $C(3')-C(8')-O(9')-N(10')$, while it is only 0.036 \AA from the plane of $O(9')-N(10') \cdots O(9')_c-N(10')_c$ † defining the dimer. A similar, although less pronounced, alteration is observed for the exocyclic amide group. The hydrogen involved in dimer formation, $H(10b)$, is 0.129 \AA from

the amide plane (Table 10) but only 0.060 \AA from the dimer plane defined by $O(9)-N(10) \cdots O(9)_c-N(10)_c$. Additional evidence for the importance of these $H \cdots O$ interactions is seen from consideration of the small angles between the $H-N$ and O_c-N vectors, $H(10')-N(10')-O(9')_c$, 3.84° , and $H(10b)-N(10)-O(9)_c$, 3.82° (Fig. 5).

An interesting question can be raised concerning the oxygen atom hybridization from examination of the $C-O \cdots H$ angles, 122.23 and 119.17° respectively (Fig. 5), for the endo- and exocyclic amide groups. The angles are consistent with each other and remarkably close to 120° . This agreement with 120° might simply be fortuitous or imply a great deal of sp^2 character in the unshared electron pair orbitals of the oxygen atoms. In a simple situation, one would expect the lone pair orbitals to retain a good deal of s character providing very little for the carbon-oxygen bonds.

The second amide hydrogen atom on $N(10)$ is not involved in the centrosymmetric amide dimers but instead participates in an intramolecular $N-H \cdots N$ hydrogen bond to $N(1')$. The $N(10) \cdots N(1')$ distance of 3.035 \AA is shorter than the average of 37 $N-H \cdots N$ hydrogen bonds, $3.10 \pm 0.13 \text{ \AA}$, reported by Pimentel & McClellan (1960b). The $N(1') \cdots H(10a)$ distance of 2.266 \AA is considerably less than the $H \cdots N$ van der Waals approach of 2.7 \AA . This hydrogen bond may in part account for the short $C(7')-N(1')$ bond by increasing the positive character of the tertiary nitrogen. The twist of the $H(10a)-N(10)-H(10b)$ group from planarity with the $C(8)$ carbonyl is in a direction which favors the $N(1) \cdots H(10a)$ interaction.

Translations of $b/2$ relate the centers of symmetry of the two amide dimers formed by a single molecule; there is no change in the a and c components. The amide groups extend essentially from the same side of the molecule and, in conjunction with $C(7')$, form an almost flat surface. The remainder of the molecule protrudes from the flat amides to form a 'hump'. This shape, upon inversion through each of the hydrogen

† The c 's refer to atoms in the other half on the centrosymmetric dimer.

bonding centers, produces a well-defined herring-bone ribbon of molecules parallel to the b axis. The twofold screw and n -glide relate adjacent herring-bones, in the a direction, to fit the peaks of one into the troughs of another.

The mechanism of formation of this compound is consistent with the general mechanism for the acid

reactions of dihydronicotinamides and has been previously discussed by Ammon & Jensen (1966).

The authors are grateful to Mrs J.W. Ammon for many of the intensity measurements, Dr I. L. Karle for advice on the application of the symbolic addition procedure, Professor J.M. Stewart for help in the initial

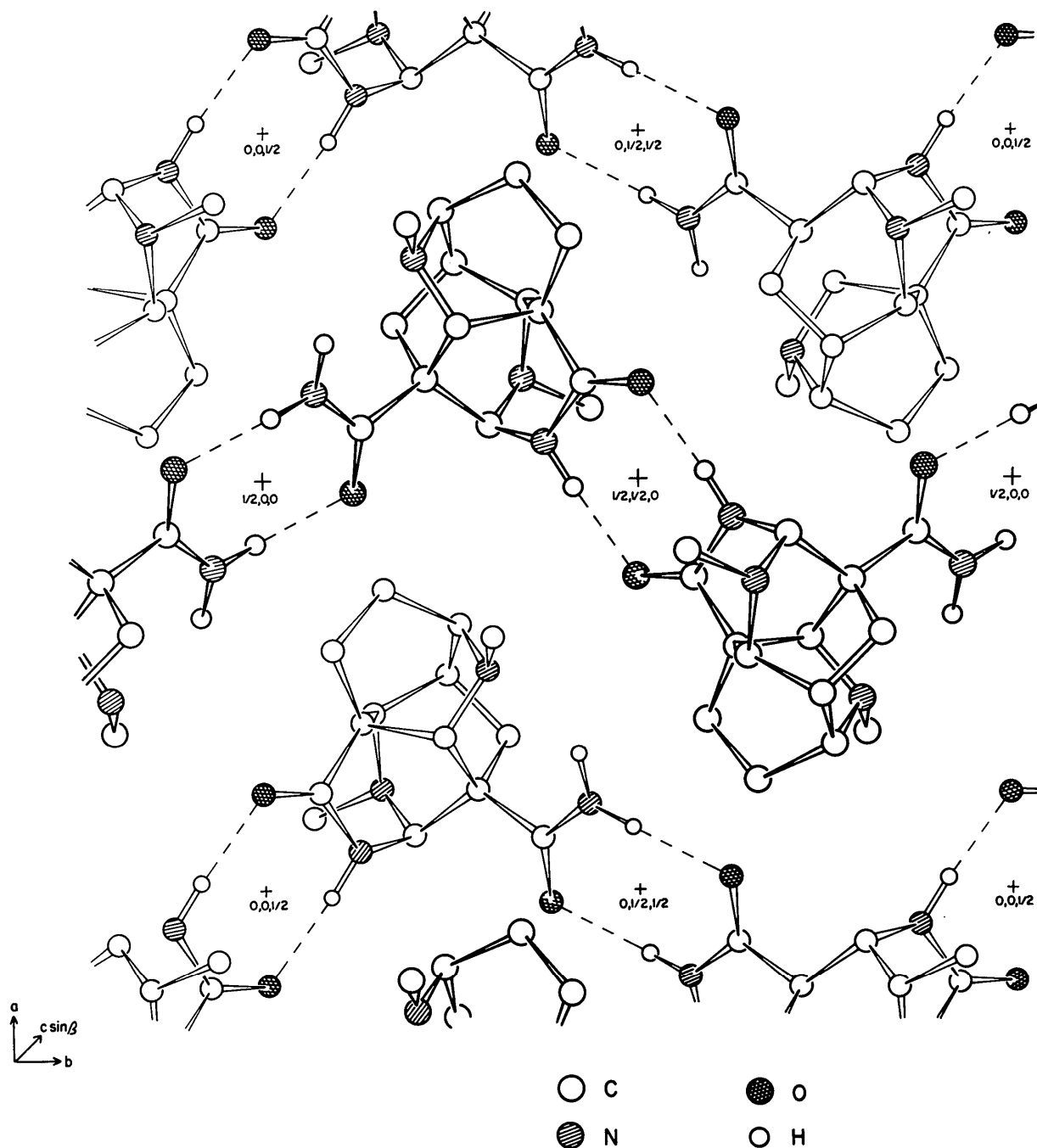


Fig. 4. Drawing of part of the crystal structure viewed normal to the ab plane. The dotted lines indicate intermolecular hydrogen bonds.

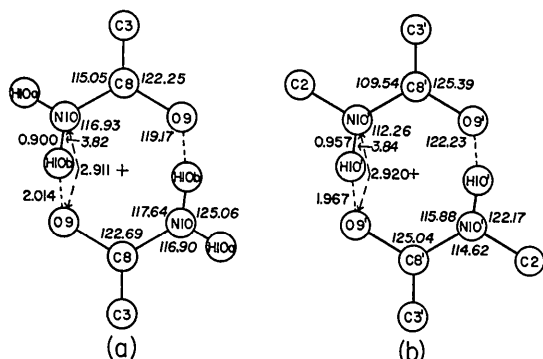


Fig. 5. Drawings of the two amide hydrogen bonded 'dimers'. Some bond lengths (Å) and angles ($^{\circ}$) are shown.

stages of the phase pyramid, Professor A. G. Anderson, Jr., for his constant interest, the National Institutes of Health for financial support (GM-10828) and the University of Washington Research Computer Laboratory for a generous grant of computer time. H. L. Ammon wishes to thank the National Institutes of Health for fellowships GF-13028 and GPD-13028 under which portions of this work were done.

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