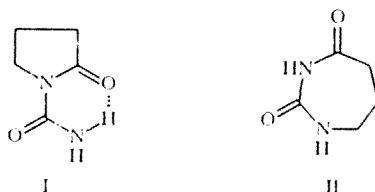


CYCLIZATION OF 4-UREIDOBUTANOIC ACIDS IN ACETIC ANHYDRIDE

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A simple method is proposed for synthesizing 1-carbamoyl-2-pyrrolidones by cyclization of 4-ureidobutanoic acids in acetic anhydride.

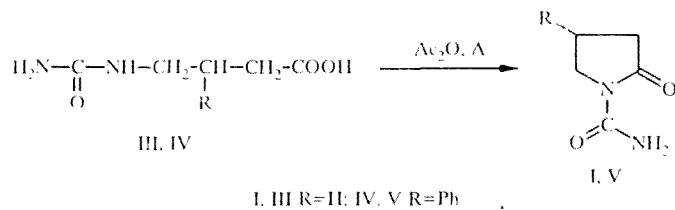
1-Carbamoyl-2-pyrrolidone (I) and 2,4-dioxohexahydro-1,3-diazepine (II) are structural isomers.



When separated from the *Annona squamosa*, the pyrrolidone I was initially given the diazepine structure II [1]. The synthesis of both compounds and the results of their structural investigations have been described [2]. However, there are no reports in the literature of their biological properties.

Two methods of preparing pyrrolidone I have been described. In the first 4-aminobutanoic acid is treated with potassium cyanate and the intermediate product with hydrochloric acid [2]. In the second 4-ureidobutanoic acid is cyclized in the presence of phosphorus oxychloride [2, 3]. The basic drawbacks of these methods are the need to carry out the reaction under a nitrogen atmosphere and the partial loss of the desired product by sublimation in the first method or twelve-fold extraction of the product with chloroform in the second.

We propose an improved method for preparing 1-carbamoyl-2-pyrrolidone by cyclization of 4-ureidobutanoic acid (III) in acetic anhydride. This gives both higher product yield and simplification of its extraction from the reaction mixture. Using this method 3-phenyl-4-ureidobutanoic acid (IV) gave 1-carbamoyl-4-phenyl-2-pyrrolidone (V).*



The presence of an intramolecular hydrogen bond in I causes the amino group protons to appear as two signals in the PMR spectrum, similar to the difference in signals for the protons on the two nitrogen atoms in II [2]. Thus PMR spectroscopy could not be used in this case as a reliable proof of structure. The same applies to mass spectrometry. Fragmentations of I and II are virtually identical, the spectra differing only in relative peak intensities [2]. We have shown that mass spectral fragmentation of pyrrolidone V differs significantly from the similar pyrrolidone I. Hence the maximum intensity occurs for

*The results of biological and other investigations on I and V will be reported in a separate publication.

the ion peak m/z 104 ($[\text{C}_6\text{H}_5-\text{CH}=\text{CH}_2]^+$) whereas the intensity of the m/z peak 161 ([M - HNCO]), base peak in I, amounts to only 2.3%. There are also differences in the intensities of the immonium ions with m/z 30 (69% in I and 4.1% in V). A characteristic of the fragmentation of pyrrolidone V is formation of a rearrangement ion with m/z 118



A similar decomposition leading to ions including an aryl substituent was observed previously in the mass spectrometric investigations of alkoxyphenylsuccinimides [4].

The structure of pyrrolidone V was proved using IR spectroscopy and x-ray analysis. The IR spectrum (KBr) showed absorption bands at 3210, 3370 (N - H stretching) and 1675 cm^{-1} (C=O group involved in the formation of intermolecular hydrogen bonds) and also bands at 3030 (NH) and 1705 cm^{-1} (C=O) identifying an intramolecular hydrogen bond. The intensity of a band at 1585 cm^{-1} corresponds to amide II type N - H deformation. In the IR spectrum of II this band is absent [2]. The spectrum of V taken in chloroform also shows the bands characterizing the intramolecular hydrogen bond but the bands corresponding to the intermolecular hydrogen bonds disappear and are replaced with free group bands at 1715 (C=O) , 3330, and 3490 cm^{-1} (NH).

The geometry of the V molecule is given in Fig. 1 together with bond lengths and intramolecular torsional angles in the pyrrolidone ring. Valence angles are given in Table 1. Overall, the bond lengths and valence angles have expected values and do not merit special comment. The pyrrolidone heterocycle has intramolecular torsional angles and the deviation of atom $\text{C}_{(4)}$ ($-0.497(2)\text{ \AA}$) from the mean square plane of the remaining ring atoms (Table 2). The phenyl substituent in the molecule occupies an equatorial position relative to the five membered heterocycle (deviation of atom $\text{C}_{(10)}$ from the mean plane formed by $\text{C}_{(3)}$, $\text{C}_{(2)}$, $\text{N}_{(1)}$, and $\text{C}_{(5)}$ being $-0.094(2)\text{ \AA}$). The dihedral angle between the mean plane of the phenyl ring and the plane of the 4-atom fragment fragment in the pyrrolidone ring is 12° .

The pyrrolidone ring in V forms a six membered pseudoheterocycle through intramolecular hydrogen bonding at $\text{N}_{(7)}-\text{H}_{(7a)}\dots\text{O}_{(9)}$ ($\text{N}\dots\text{O}$ 2.743(3), $\text{H}\dots\text{O}$ 2.04(2) \AA) involving the 1 and 2 substituents of the pyrrolidone ring. This heterocycle is virtually planar (maximum single deviation from the mean plane for $\text{H}_{(7a)}$ being 0.08(2) \AA) and coplanar with that of the fur atomic pyrrolidone fragment (dihedral angle between the mean planes being 2°).

The molecular geometry for the crystal is shown in Fig. 2. A second active hydrogen atom $\text{H}_{(7b)}$ at atom $\text{N}_{(7)}$ takes part in formation of an intermolecular hydrogen bond $\text{N}_{(7)}-\text{H}_{(7b)}\dots\text{O}_{(8)}$ ($1-x, -y, 1-z$) ($\text{N}\dots\text{O}$ 2.911(2), $\text{N}-\text{H}$ 0.93(3), $\text{H}\dots\text{O}$ 1.99(2) \AA , $\text{N}-\text{H}\dots\text{O}$ 168(2) $^\circ$) as a result of which the crystalline molecule forms a centrosymmetric dimer.

EXPERIMENTAL

IR Spectra were recorded on an IR-20 instrument using chloroform and KBr and mass spectra on an MK-1321-A spectrometer with direct introduction of the sample into the ionizing chamber, ionization intensity of 50 eV, and inlet temperature of 80°C. TLC was carried out using Armsorb VETLC-Si 10 plates and the system ether - chloroform (50:1). Spots were revealed using phosphomolybdic acid.

Elemental analytical data for C, H, and N for I and V corresponded to those calculated.

4-Ureidobutanoic (III) and 3-phenyl-4-ureidobutanoic acids (IV) were obtained by the method in [2].

X-Ray Investigation of V. Unit cell parameters and reflection intensities were measured at 20°C on a Hilger - Watts Y/290 automatic four-circle diffractometer ($\lambda_{\text{MoK}\alpha}$, graphite monochromator, $\theta/2\theta$ scanning, $\theta_{\text{max}} 28^\circ\text{C}$). Crystals of $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$ are monoclinic: $a = 5.437(2)$, $b = 8.716(3)$, $c = 20.874(6)\text{ \AA}$, $\beta = 90.94(2)^\circ$, $V = 981(1)\text{ \AA}^3$, $Z = 4$, $M = 204$, $d_{\text{calc}} = 1.37\text{ g/cm}^3$, space group $\text{P}2_1/\text{n}$. 1378 Independent reflections were measured by $\theta/2\theta$ scanning in the range of θ between 2° and 24° . The structure was solved by a direct method using the MULTAN program and refined by full matrix least squares analysis in the anisotropic approximation for nonhydrogen atoms. The positions of all hydrogen atoms were localized directly in a difference Fourier series and included in the refinement in the isotropic approximation. The final difference factors were $R = 0.039$ and $R_w = 0.047$ for 1202 reflections with $F^2 \geq 4.5\sigma$. All calculations were carried out on an Eclipse S/200 computer using the INEXTL program [5]. Atomic coordinates are given in Tables 3 and 4.

1-Carbamoyl-2-pyrrolidone (I, $\text{C}_5\text{H}_8\text{N}_2\text{O}_2$). Acid III (3.46 g, 24 mmole) was refluxed in acetic anhydride (17 ml) for 1 h. The solvent was distilled off *in vacuo* and the residue recrystallized from benzene to give I (2.09 g, 69%) with mp 147°C (according to [1-3] 145-146, 142-143, and 143-144°C respectively) and $R_f 0.66$.

TABLE 1. Valence Angles in Compound V

Angle	ω (σ)	Angle	ω (σ)
N ₍₁₎ C ₍₂₎ C ₍₃₎	107.5(2)	N ₍₁₎ C ₍₆₎ O ₍₈₎	119.0(1)
C ₍₂₎ C ₍₃₎ C ₍₄₎	105.0(2)	N ₍₇₎ C ₍₆₎ O ₍₈₎	124.3(1)
C ₍₃₎ C ₍₄₎ C ₍₅₎	102.4(2)	C ₍₆₎ N ₍₇₎ H _(7a)	117(1)
C ₍₄₎ C ₍₅₎ N ₍₁₎	103.2(2)	C ₍₆₎ N ₍₇₎ H _(7b)	118(1)
C ₍₅₎ N ₍₁₎ C ₍₂₎	111.7(2)	H _(7a) N ₍₇₎ H _(7b)	125(2)
N ₍₁₎ C ₍₂₎ O ₍₉₎	125.2(1)	C ₍₁₀₎ C ₍₁₁₎ C ₍₁₂₎	120.8(2)
C ₍₃₎ C ₍₂₎ O ₍₉₎	127.4(1)	C ₍₁₁₎ C ₍₁₂₎ C ₍₁₃₎	120.6(2)
C ₍₃₎ C ₍₄₎ C ₍₁₀₎	117.6(2)	C ₍₁₂₎ C ₍₁₃₎ C ₍₁₄₎	119.1(2)
C ₍₅₎ C ₍₄₎ C ₍₁₀₎	113.4(2)	C ₍₁₃₎ C ₍₁₄₎ C ₍₁₅₎	120.5(2)
C ₍₅₎ N ₍₁₎ C ₍₆₎	119.7(2)	C ₍₁₄₎ C ₍₁₅₎ C ₍₁₀₎	121.0(2)
C ₍₂₎ N ₍₁₎ C ₍₆₎	128.6(2)	C ₍₁₅₎ C ₍₁₀₎ C ₍₁₁₎	118.0(2)
N ₍₁₎ C ₍₆₎ N ₍₇₎	116.7(2)		

TABLE 2. Planar Molecular Fragments of Compound V:

a) Deviation of atoms (Δ) from the mean square plane coefficients of the density equation $Ax + By + Cz - D = 0$ in the orthogonal system coordinates, $\sigma = 0.0002$ Å

Plane	Atom	Δ , Å	Equation coefficient			
			A	B	C	D
I	C ₍₂₎	0.013	-0.6526	-0.7413	-0.1571	-3.1988
	C ₍₃₎	-0.007				
	N ₍₁₎	-0.008				
	C ₍₅₎	-0.008				
	C _{(4)*}	-0.497				
	C _{(10)*}	-0.094				
II	C ₍₉₎	-0.001	-0.6525	-0.7463	-0.1315	-2.9249
	C ₍₂₎	0.000				
	N ₍₁₎	0.002				
	C ₍₆₎	-0.005				
	N ₍₇₎	0.002				
	H _(7a)	0.08(2)				
III	C ₍₁₀₎	-0.002	-0.5439	-0.7672	-0.3401	-6.2249
	C ₍₁₁₎	0.001				
	C ₍₁₂₎	0.000				
	C ₍₁₃₎	-0.002				
	C ₍₁₄₎	0.002				
	C ₍₁₅₎	0.000				
IV	C _{(4)*}	-0.084				
	C ₍₂₎	-0.002	-0.6455	-0.7534	-0.1235	-2.8448
	N ₍₁₎	-0.002				
	C ₍₅₎	0.004				
	C ₍₆₎	0.009				
	N ₍₇₎	-0.002				

b) Dihedral angle between planes

Planes	Angle, °	Planes	Angle, °	Planes	Angle, °
I-II	2	I-IV	3	II-IV	1
I-III	12	II-III	14	III-IV	14

*Atoms not included in the calculation of the mean square plane.

TABLE 3. Coordinates of Nonhydrogen Atoms ($\times 10^4$) and their Equivalent Isotropic Temperature Parameters B_{iso} eq (\AA^2) in V

Atom	x/a (σ)	y/b (σ)	z/c (σ)	B_{iso} eq
N(1)	193(3)	2256(2)	5501(1)	2.0
C(2)	-1352(4)	3235(2)	5157(1)	2.0
C(3)	-3051(4)	3976(2)	5627(1)	2.1
C(4)	-1814(4)	3746(2)	6279(1)	2.3
C(5)	-403(4)	2234(2)	6187(1)	2.1
C(6)	2089(4)	1320(2)	5273(1)	2.1
N(7)	2467(3)	1348(2)	4645(1)	2.6
O(8)	3321(3)	564(2)	5660(1)	2.7
O(9)	1304(3)	3435(2)	4577(1)	2.7
C(10)	-3440(4)	3741(2)	6861(1)	2.1
C(11)	-5545(4)	4635(2)	6892(1)	2.4
C(12)	-6925(4)	4676(2)	7444(1)	2.6
C(13)	-6232(4)	3823(2)	7976(1)	2.7
C(14)	-4148(4)	2924(2)	7950(1)	2.6
C(15)	-2764(4)	2881(2)	7401(1)	2.4

TABLE 4. Coordinates of Hydrogen Atoms ($\times 10^3$) and their Isotropic Temperature Parameters B_{iso} (\AA^2) in V

Atom	x/a (σ)	y/b (σ)	z/c (σ)	B_{iso}
H(3a)	-457(3)	349(2)	561(1)	2.6
H(3b)	-338(4)	496(2)	551(1)	3.1
H(4)	-46(4)	461(2)	632(1)	3.6
H(5a)	-140(4)	136(2)	627(1)	2.8
H(5b)	114(4)	224(2)	642(1)	3.1
H(7a)	142(4)	189(2)	441(1)	3.0
H(7b)	382(4)	81(2)	449(1)	3.6
H(11)	-601(4)	521(2)	653(1)	3.0
H(12)	-841(4)	531(2)	747(1)	3.3
H(13)	-721(4)	388(2)	836(1)	3.2
H(14)	-362(4)	234(2)	830(1)	3.1
H(15)	-133(3)	224(2)	739(1)	2.5

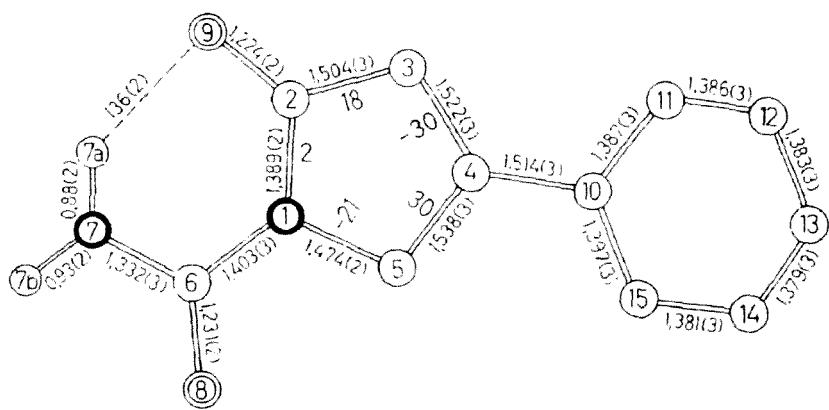


Fig. 1. Intramolecular torsional angle values for the pyrrolidine ring and bond lengths in molecule V.

1-Carbamoyl-4-phenyl-2-pyrrolidone (V, $C_{11}H_{12}N_2O_2$). A mixture of acid IV (1.7 g, 7 mmole) and acetic anhydride (8.5 ml) was heated on a steam bath for 1 h. Ice (10-15 g) was added to the product cooled to room temperature and then potassium hydroxide to pH 6. The crystalline product was filtered, washed with water, and recrystallized from 50% ethanol.

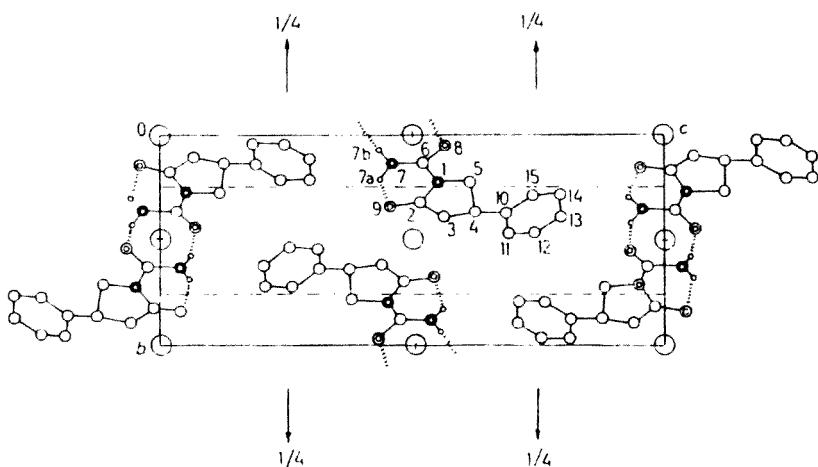


Fig. 2. Geometry of the crystalline molecule V.

The product (1.4 g, 93%) had mp 97-98°C and R_f 0.72. Mass spectrum, m/z , I_{rel} , %: 204 (57.2, M^{+}), 161 (2.3), 132 (4.2), 118 (23.1), 105 (15.2), 104 (100), 103 (10), 91 (10.8), 87 (5), 78 (6.7), 77 (8.8), 73 (3.8), 51 (6.7), 44 (7.9), 39 (3.2), 30 (4.1), 28 (5.9), 18 (7.8).

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