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The Crystal and Molecular Structure of 6,9-Diaza-5,10-dioxotricyclo[7.3.0.$0^{1,6}$]dodecane, a Molecule Designed to Contain Non-planar Amide Bonds

BY S. E. EALICK AND DICK VAN DER HELM*

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73069, *USA*

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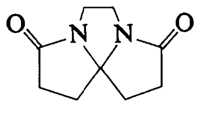
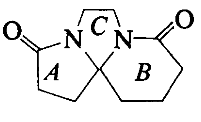
The crystal structure of 6,9-diaza-5,10-dioxotricyclo[7.3.0.$0^{1,6}$]dodecane, $C_{10}H_{14}N_2O_2.H_2O$, a molecule designed to contain non-planar amide bonds, has been determined and refined with three-dimensional least-squares techniques. The molecule crystallizes in space group $P2_1/c$ with unit-cell dimensions $a = 13{\cdot}4455$ (7), $b = 7{\cdot}3448$ (4), $c = 10{\cdot}7919$ (5) Å and $\beta = 99{\cdot}410$ (3)°. The crystal form is a monohydrate with the water molecule bridging the carbonyl groups of symmetry-related amide functions. The constraints of the tricyclic system result in highly non-planar amide groups, less so in the six-membered ring ($\chi_N = -16{\cdot}7$, $\tau' = 17{\cdot}8°$) than in the five-membered ring ($\chi_N = -41{\cdot}2$, $\tau' = 20{\cdot}8°$). The final R value for all 2160 reflections is 0·058 with standard deviations in non-hydrogen atomic parameters ranging from 0·0012 to 0·0024 Å.

Introduction

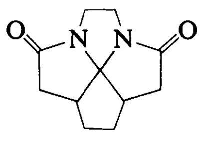
The structure of 6,9-diaza-5,10-dioxotricyclo[7.3.0.$0^{1,6}$]dodecane was determined as the fourth compound in a series of polycyclic spirodilactams. The results of three of the structures (I, III, IV) have been published (Ealick & van der Helm, 1975; Ealick, Washecheck & van der Helm, 1976), while a preliminary report of this structure (II) has also been reported (van der Helm, Ealick & Washecheck, 1975). In addition, the synthesis and IR spectra of this series of molecules have been published (Smolíková, Koblicová & Bláha, 1973). This group of molecules is interesting structurally because the restrictions of the polycyclic system determine the conformation of the amide group. By changes of the ring sizes in the molecule a large variety of conformations is possible. A study to determine conformations of amide groups in medium-ring compounds has also been published (Dunitz & Winkler, 1975). Systematic studies of non-planar amides and peptides are important in light of the increasing number of examples of such groups in biological systems.



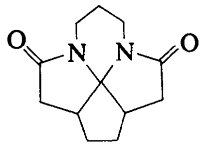
$C_9H_{12}N_2O_2$
(I)



$C_{10}H_{14}N_2O_2$
(II)



$C_{11}H_{14}N_2O_2$
(III)



$C_{12}H_{16}N_2O_2$
(IV)

Experimental

A crystalline sample of (II) was kindly provided by Professor K. Bláha, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague. Large colorless crystals suitable for a diffraction experiment were obtained by adding water dropwise to an ethanolic solution of the compound. A plate-like crystal with approximate dimensions

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0·3 × 0·4 × 0·07 mm was selected for intensity collection. Crystallographic data (Table 1) and integrated X-ray intensity data were collected on a Nonius CAD-4 automatic diffractometer. For intensity data Ni-filtered Cu $K\bar{\alpha}$ radiation ($\lambda = 1{\cdot}5418$ Å) was used and for unit-cell parameters Cu $K\alpha_1$ radiation ($\lambda = 1{\cdot}54051$ Å) was used. The space group was determined uniquely as $P2_1/c$ from systematic absences. A total of 2160 independent reflections with $2\theta < 150°$ were measured using θ–2θ scan techniques. A variable scan width was used and was calculated as $(1{\cdot}0 + 0{\cdot}1 \tan\theta)°$. A variable receiving aperature was used with a width of $(4{\cdot}0 + 0{\cdot}86 \tan\theta)$ mm while the height was constant at 6·0 mm. The maximum scan time for each intensity was 120 s with 80 s used for scanning the peak and 20 s used for scanning each of the left and right backgrounds. A total of 368 intensities having $I \leq 1{\cdot}4\sigma(I)$ were considered indistinguishable from background and were assigned a value of $1{\cdot}0\sqrt{T}$, where T is the peak count plus twice the left and right background (the value of 1·0 was experimentally verified by comparing ΣF_c and ΣkF_o for this type of reflection). A criterion for excluding these reflections from the least-squares sum was applied in a separate logical routine in the structure factor refinement program (van der Helm & Nicholas, 1970), but all reflections were included in the calculation of standard deviations. The discrepancy in observed and calculated densities can be attributed to a loss of water from the solid state which was also reflected in a slight decrease (about 9%) in the monitor intensity. Lorentz, polarization and absorption corrections ($\mu = 8{\cdot}47$ cm^{-1}) were applied. For the absorption correction, the program of Coppens, Leiserowitz & Rabinovich (1965) was used. The program employs the numerical integration method of Gauss; 216 sampling points were taken. Values for the transmission coefficients ranged from 0·766 to 0·943. Each amplitude was assigned an experimental weight, based on counting statistics, from a weighting scheme which has been described previously (Ealick & van der Helm, 1975).

Table 1. *Crystallographic data*

Unit-cell dimensions were determined by least-squares fit to the $+2\theta$ and -2θ values of 49 reflections taken from all quadrants of reciprocal space, at 21·5 ± 0·5 °C.

Formula $C_{10}H_{14}N_2O_2$ H_2O	F.W. 242·27
Space group $P2_1/c$	$V = 1051{\cdot}4$ Å^3
$a = 13{\cdot}4455$ (7) Å	$Z = 4$
$b = 7{\cdot}3448$ (4)	$D_{\rm obs} = 1{\cdot}316$ g cm^{-3}
$c = 10{\cdot}7919$ (5)	$D_{\rm calc} = 1{\cdot}341$
$\beta = 99{\cdot}410$ (3)°	

Structure determination and refinement

The intensities were placed on an absolute scale with the results of a Wilson plot (Wilson, 1942) and normalized structure factors, $|E|$, were derived. The signs for 290 individual E's with $|E| > 1{\cdot}5$ were derived with the program *MULTAN* (Germain, Main & Woolfson, 1971) leading to an E map which revealed the positions of all non-hydrogen atoms. The water molecule was not included in the initial structure factor calculation which yielded an $R = \Sigma\,|kF_o - F_c|/\Sigma|kF_o|$ of 0·52. After several cycles of least-squares refinement a difference Fourier map was calculated from which the coordinates of the O atom of the water molecule were determined. This O atom was present in the original E map but was not recognized at that time. After this O atom was included in the refinement the R value converged at 0·17 for the isotropic model and 0·10 for the anisotropic model. At this point a second difference Fourier map was calculated from which the positions of all 16 H atoms were located. Least-squares refinement, with isotropic temperature factors for H atoms and anisotropic temperture factors for C, N and O atoms, was terminated when all shifts for non-hydrogen atoms were less than 0·6 of the corresponding estimated standard deviation. The R value based on the

Table 2. *Positional* (×10^4) *and thermal* (Å^2 × 10^4) *parameters for* C, O *and* N *atoms*

Calculated standard deviations are given in parentheses. Thermal parameters are of the form:
$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$.

	x	y	y	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	2099 (1)	1909 (2)	4313 (1)	433 (7)	360 (7)	396 (7)	−4 (6)	−1 (6)	−20 (6)
C(2)	1471 (1)	3156 (2)	5035 (2)	583 (10)	474 (9)	509 (9)	100 (8)	3 (8)	−109 (8)
C(3)	406 (1)	3022 (2)	4303 (2)	545 (9)	522 (10)	543 (10)	145 (8)	54 (8)	25 (8)
C(4)	379 (1)	1154 (2)	3724 (1)	436 (7)	561 (10)	392 (7)	35 (7)	12 (6)	9 (7)
N(5)	1343 (1)	675 (2)	3639 (1)	414 (6)	443 (7)	440 (7)	−5 (5)	36 (5)	−94 (6)
C(6)	1711 (1)	−1201 (2)	3725 (2)	462 (8)	453 (9)	670 (11)	−20 (7)	54 (8)	−178 (8)
C(7)	2357 (1)	−1217 (2)	5020 (2)	442 (8)	358 (8)	752 (11)	−25 (7)	3 (8)	1 (8)
N(8)	2773 (1)	634 (2)	5106 (1)	379 (6)	349 (6)	473 (7)	−11 (5)	26 (5)	5 (5)
C(9)	3733 (1)	997 (2)	5593 (2)	395 (7)	426 (8)	463 (8)	−13 (6)	49 (6)	−44 (7)
C(10)	4146 (1)	2808 (3)	5289 (2)	571 (11)	493 (10)	783 (13)	−156 (8)	−54 (9)	28 (9)
C(11)	3587 (2)	3913 (3)	4258 (2)	784 (13)	657 (13)	764 (13)	−293 (11)	−78 (10)	212 (11)
C(12)	2705 (1)	2927 (3)	3463 (2)	637 (11)	589 (11)	490 (9)	−103 (9)	33 (8)	108 (8)
O(1)	6147 (1)	3623 (2)	2601 (1)	517 (7)	722 (9)	913 (11)	−53 (7)	−62 (7)	106 (8)
O (4)	−363 (1)	219 (2)	3386 (1)	439 (6)	774 (9)	636 (8)	−40 (6)	1 (5)	−103 (7)
O(9)	4271 (1)	−119 (2)	6257 (1)	431 (5)	516 (7)	669 (8)	13 (5)	−46 (5)	48 (6)

final parameters (Tables 2 and 3) is 0·058 for all 2160 data and 0·042 for the 1702 reflections included in the least-squares refinement. This discrepancy is probably due to the presence of minor secondary extinction effects for which no correction was made.

Atomic scattering factors for C, N and O atoms were taken from *International Tables for X-ray Crystallography* (1962) and those for H atoms from Stewart, Davidson & Simpson (1965). A final difference Fourier map showed no peaks larger than 0·2 e Å^{-3}. In the structure factor analysis the average value of $\omega_F \Delta F^2$ did not show a significant variation with either $|F_o|$ or $\sin \theta/\lambda$, thus validating the weighting scheme used.*

Description and discussion of the structure

A stereo view of a single molecule is given in Fig. 1. The molecule contains a five-membered lactam ring (*A*) and a six-membered lactam ring (*B*) joined at the spiro C atom. The ethano bridge from N(5) to N(8) forms a second five-membered ring (*C*); thus, the molecule is best classified as a tricyclic spirodilactam. Torsion angles for rings *A*, *B*, and *C* are given in Fig. 2. Ring *A* is approximately in the twist (C_2) conformation while ring *C* is intermediate between the envelope (C_s) and twist conformations. This can most easily be seen from the pseudo-rotation parameter Δ (Altona, Geise & Romers, 1968) where $\Delta = \pm 36$ for C_s conformation and $\Delta = 0°$ for the C_2 conformation. The experimental values for Δ are 4·7° for ring *A* and 16·2° for ring *C*. The most noticeable feature in the six-membered ring is that the smallest value for a torsion angle occurs for the rotation about C(9)—N(8) which has not been true in general for the five-membered lactam rings in this series.

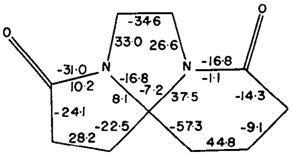

Fig. 2. Torsion angles (°) for rings *A*, *B* and *C*. Other angles are C(3)—C(4)—N(5)—C(6) = 149·0, O(4)—C(4)—N(5)—C(1) = −169·8, C(7)—N(8)—C(9)—C(10) = 162·3 and C(1)—N(8)—C(9)—O(9) = 179·7°.

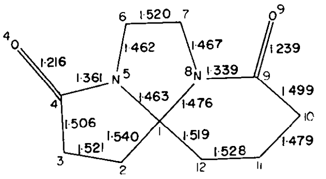

Fig. 3. Bond distances (Å). Standard deviations range from 0·002–0·003 Å.

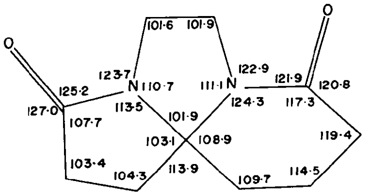

Fig. 4. Bond angles (°). Other angles are C(2)—C(1)—N(8) = 114·8 and C(12)—C(1)—N(5) = 113·7°. Standard deviations are between 0·1 and 0·2°.

Table 3. *Positional parameters* (×10^3) *and isotropic temperature factors for* H *atoms*

Standard deviations are given in parentheses.

	x	y	z	β (Å^2)
H(C2)*A*	149 (1)	271 (3)	591 (2)	6·0 (5)
H(C2)*B*	174 (1)	437 (3)	514 (2)	6·1 (5)
H(C3)*A*	−11 (1)	316 (2)	485 (2)	5·1 (4)
H(C3)*B*	28 (2)	396 (3)	367 (2)	5·6 (5)
H(C6)*A*	113 (1)	−201 (3)	362 (2)	5·2 (4)
H(C6)*B*	209 (1)	−146 (2)	304 (2)	5·3 (4)
H(C7)*A*	196 (1)	−142 (2)	568 (2)	4·8 (4)
H(C7)*B*	289 (1)	−206 (3)	511 (2)	5·6 (5)
H(C10)*A*	430 (2)	338 (3)	600 (2)	8·1 (6)
H(C10)*B*	485 (2)	252 (4)	512 (3)	10·0 (7)
H(C11)*A*	336 (2)	500 (4)	472 (3)	10·8 (9)
H(C11)*B*	401 (2)	447 (3)	374 (3)	8·9 (7)
H(C12)*A*	229 (1)	382 (2)	291 (2)	5·3 (4)
H(C12)*B*	296 (1)	192 (3)	287 (2)	5·9 (5)
H(O1)*A*	562 (1)	407 (3)	210 (2)	6·2 (5)
H(O1)*B*	597 (2)	252 (4)	293 (2)	8·7 (6)

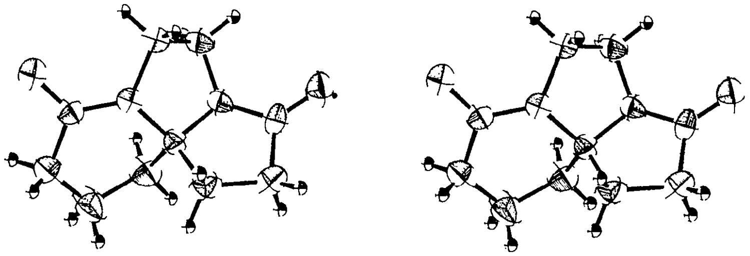

Fig. 1. Stereo view of a single molecule (Johnson, 1965).

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32020 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Bond distances are listed in Fig. 3 and bond angles in Fig. 4. The apparent shortening in C(10)–C(11) can be associated with the high thermal motion of atom C(11). The most notable features, however, are the bond distances in the amide groups. Most recent compilations of crystallographic data show the average bond distances in a peptide group to be 1·33 Å for the C′–N bond and 1·23 Å for the C′–O bond (Ramachandran, Kolaskar, Ramakrishnan & Sasisekharan, 1974). Marsh & Donohue (1967) list these values as 1·32 and 1·24 Å. The amide bond length in the five-membered ring C(4)–N(5) is lengthened by about 20 standard deviations from the expected value while the carbonyl bond distance C(4)–O(4) is shortened. This can be correlated with a non-planar deformation of the amide group. In the six-membered lactam ring the amide bond is only slightly lengthened as a result of a relaxation of ring strain compared to the five-membered ring. The bond angle C(3)–C(4)–N(5) is found to be 107·7°, a value very close to those found for the same angle in compounds I, III and IV. As the ring is changed to six atoms the equivalent bond angle, C(10)–C(9)–N(8), increases to 117·3°, resulting in angles more closely resembling those expected for the sp^2-hybridized C′ atom in a peptide. The relation between non-planarity of the amide group and the amide bond length is summarized in Table 4 for this series of compounds. The parameters used for describing the non-planar amide group are χ_N, χ_C and τ' (Winkler & Dunitz, 1971). The values of χ_N and χ_C describe the non-planar arrangement of bonds about the N and C atoms respectively while τ' describes a rotation about the C–N bond.

Table 4. *Geometrical parameters for the amide groups*

	χ_N (°)	χ_C (°)	τ' (°)	d(C′–N) (Å)	d(C′–O) (Å)
I*	−42·0	−0·3	21·3	1·362	1·223
II*a*	−41·2	0·0	20·8	1·361	1·216
II*b*	−16·7	0·9	17·8	1·339	1·239
III†	−43·7	−0·2	20·5	1·372	1·222
IV†	−19·1	−0·6	7·3	1·351	1·220

* Ealick & van der Helm (1975).

† Ealick, Washecheck & van der Helm (1976).

It can be seen from Table 4 that as the non-planarity increases (seen primarily in the values of χ_N and τ') the amide bond length increases and carbonyl bond length decreases. A qualitative explanation is that as the amide group becomes more non-planar the π-overlap in the C–N bond decreases and the bond length increases. A second feature is that the values of χ_C are all very near zero which is consistent with the predicted energy requirements of the modes of deformation (Winkler & Dunitz, 1971). Such an explanation is also consistent with IR data for these compounds (Smolíková *et al.*, 1973) in which a correlation is seen between the stretching frequency, ν(C′–N), and the torsion angle ω_3 as measured from Dreiding models.

A packing diagram is shown in Fig. 5. Two hydrogen bonds are formed in which the water molecule bridges amide groups related by the twofold screw axis. This arrangement results in infinite spirals about the twofold screw axis in which four hydrogen bonds are required to complete one full turn. The hydrogen bonds formed are O(9)···H(O1)*A*′–O(1)′ [H(O1)*A* and O(1) transformed by $x, \frac{1}{2}-y, \frac{1}{2}+z$] and O(9)···H(O1)*B*′–O(1)′ [H(O1)*B* and O(1) transformed by $1-x, -y, 1-z$]. The O···O distances are 2·912 and 2·947 Å, the O···H distances 2·04 and 2·02 Å and the O···H–O angles 169 and 174° respectively. A short intermolecular contact is also observed between H(C3)*B* and O(4)′ of 2·42 Å and between C(3) and O(4)′ of 3·312 Å [O(4) transformed by $-x, \frac{1}{2}+y, \frac{1}{2}-z$].

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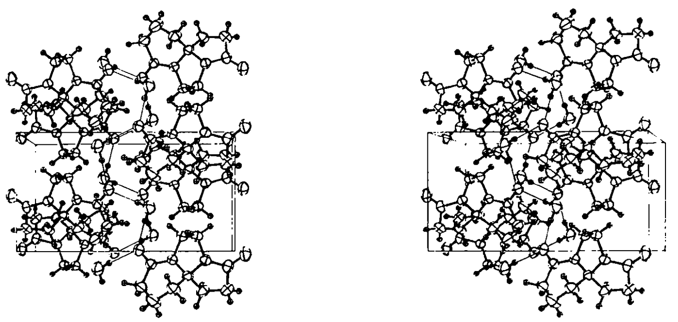

Fig. 5. Packing diagram (Johnson, 1965). The orientation of axes is $\mathbf{a}\nearrow\mathbf{b}\uparrow\mathbf{c}\rightarrow$.

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The Crystal and Molecular Structure of 2-Thiouridine

BY STUART W. HAWKINSON*

The University of Tennessee–Oak Ridge Graduate School of Biomedical Sciences, and Biology Division, Oak Ridge National Laboratory,† Oak Ridge, Tennessee 37830, *USA*

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The 'minor' nucleoside 2-thiouridine, $C_9H_{12}O_5N_2S$, crystallizes in a monoclinic cell, space group $P2_1$ with $a = 5{\cdot}049$ (2), $b = 7{\cdot}526$ (2), $c = 14{\cdot}050$ (3) Å, $\beta = 90{\cdot}17$ (2)°, and $d = 1{\cdot}619$ g cm^{-3} (for $Z = 2$) at 22 ± 2°C. The structure was derived from 1334 unique intensities measured with an Oak Ridge computer-controlled diffractometer to a limit of $\sin\theta/\lambda = 0{\cdot}65$ Å^{-1} with Nb-filtered Mo $K\alpha$ radiation. Atomic parameters were obtained by a combination of Patterson and Fourier techniques and refined by full-matrix least squares to a final $R(F)$ value of 0·023 for all data. The bond lengths and angles in the molecule agree well with those of other thiopyrimidines [C(2)–S = 1·677 Å]. The conformation of the sugar ring relative to the base is *anti* with a torsion angle χ[O(1')–C(1') → N(1)–C(6)] of 17°. The sugar exists in the 3'-*endo* conformation. The O(5')–C(5') bond is *gauche* to C(4)–O(1') and *trans* to C(4')–C(3') [torsion angles of 74 and −169° respectively]. The molecules are linked together in the crystal by hydrogen bonds in an intricate network which is identical to that inferred by Kojić-Prodić, Liminga, Šljukić & Ružić-Toroš [*Acta Cryst.* (1974), B**30**, 1550–1555] for the crystal structure of 5,6-dihydro-2-thiouridine.

Introduction

2-Thiouridine is a minor nucleoside of transfer RNA, derivatives of which have been isolated from several tRNA species (Baczynsky, Biemann & Hall, 1968; Carbon, David & Studier, 1968). A derivative of 2-thiouridine has also been found in the anticodon sequence of GAA-specific, glutamic acid tRNA from yeast (Yoshida, Takeishi & Ukita, 1970), where its role may be to prevent recognition of nonspecific codons. This study was undertaken to determine whether the 2-thio substitution on uridine confers any unusual conformational aspects to the nucleoside and to examine its potentialities for hydrogen bonding.

Since the beginning of this work, the structure of 5,6-dihydro-2-thiouridine has been determined (Kojić-Prodić, Liminga, Šljukić & Ružić-Toroš, 1974); the similarities of the structures as well as the details of the hydrogen bonding will be discussed.

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* Postdoctoral investigator supported by subcontract No. 3322 from the Biology Division of Oak Ridge National Laboratory to The University of Tennessee. Present address: Department of Biochemistry, The University of Tennessee, Knoxville, Tennessee 37916, USA.

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