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THE CRYSTAL AND MOLECULAR STRUCTURES OF EUPALMERIN ACETATE, EUPALMERIN ACETATE DIBROMIDE, A DIMER KETONE, A TRIMER DIKETONE AND FOUR NON-PLANAR SPIRODILACTAMS.

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THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

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A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

DOCTOR OF PHILOSOPHY

By

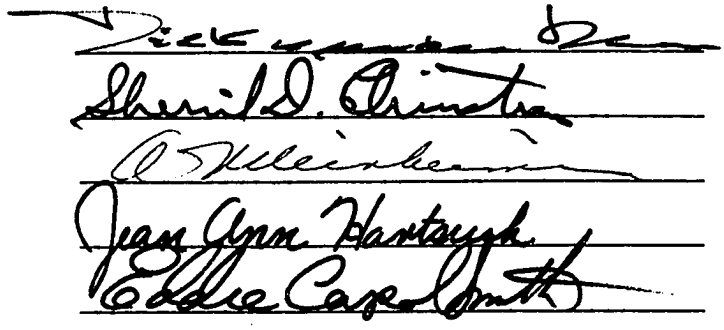
STEVEN EDWARD EALICK

Norman, Oklahoma

1976

THE CRYSTAL AND MOLECULAR STRUCTURES OF EUPALMERIN ACETATE, EUPALMERIN ACETATE DIBROMIDE, A DIMER KETONE, A TRIMER DIKETONE AND FOUR NON-PLANAR SPIRODILACTAMS

By



DISSERTATION COMMITTEE

Dedication

To Donna

ACKNOWLEDGEMENTS

The author wishes first of all to extend his sincere thanks to Dr. Dick van der Helm. Integrity in research, the perseverance to continue a problem to the end, responsibility and leadership in the laboratory, a thorough understanding of crystallography, and a personal interest in each of his students are but a few of the qualities I have seen in him. The role he has played in shaping both my personal and professional life will forever be remembered.

The author wishes to thank his parents, for without their continued support and encouragement this work would not have been possible. The author would also like to thank his wife. The role of a graduate student wife requires a type of understanding and devotion above and beyond the ordinary which will always be appreciated. The support of my mother-in-law, Mrs. J. A. Doctor, has not gone unnoticed nor unappreciated.

To Steve Holbrook I owe a very special thanks. Without his friendship this work would have been much more difficult. Dr. Eric Enwall has played an important role. The author wishes to thank him for the many very useful discussions. I would also like to thank John Burks, Don Washecheck and Jim Ekstrand for both contributions in the laboratory and friendships which have helped me through the difficult

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15(R)-ACETOXY-6(S),10(S)-DIBROMO-3a(S),4,7,8,11,12,13,14(S),15,15a(R)-DECAHYDRO-6,10,14-TRIMETHYL-3-METHYLENE-5(R),9(R)-EPOXYCYCLOTETRADECA[b]2-FURANONE, $C_{22}H_{32}Br_2O_5$

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Norman, Oklahoma, 73069, USA

Preliminary information. The crystal structure of 15(R)-Acetoxy-6(S),10(S)-dibromo-3a(S),4,7,8,11,12,13,14(S),15,15a(R)-decahydro-6,10,14-trimethyl-3-methylene-5(R),9(R)-epoxycyclotetradeca[b]2-furanone (Eupalmerin acetate-dibromide) was determined in a general study of naturally occurring marine diterpene lactones. The natural product, Eupalmerin acetate, was isolated from the Caribbean gorgonian Eunicea palmeri Bayer (Rehm, 1971) and was converted to the addition product $C_{22}H_{32}Br_2O_5$ for the purpose of x-ray studies.

Crystal data. (All data taken on a Nonius automatic diffractometer, CuK_α = 1.54178Å) Z=4, F.W.=536.32, space group: $P2_12_12_1$ (No. 19). At t=25°C: a=13.0971(7)Å, b=16.603(1)Å, c=10.6758(3)Å, V=2321.5Å^3, D_o=1.537 g cm^{-3}, D_c=1.534 g cm^{-3}. At t=-110±5°C: a=12.967(2)Å, b=16.392(2)Å, c=10.5605(8)Å, V=2244.7Å^3, D_c=1.587 g cm^{-3}.

Intensity data, structure determination and refinement. Intensity data were measured with a Nonius automatic diffractometer (CuK_α=1.54178Å, t=-110± °C). A total of 2184 independent reflections were collected, with θ<72°, of which 2155 were considered observed having I>1.4σ(I). The

data were collected using four different crystals because of difficulty with adhesives and icing. Absorption corrections were applied (μ=53.4 cm^{-1}) with subsequent merging of the four data sets. The two bromine atoms were located from the three Harker sections of a sharpened Patterson map. A difference synthesis, based on the refined positions of these atoms, showed all carbon and oxygen atoms. Anomalous dispersion corrections were made for the bromine atoms. All hydrogen atoms were located from a difference synthesis based on the refined positions of all non hydrogen atoms. The absolute configuration was determined by comparing observed values of I_{hkl} and $I_{\bar{h}\bar{k}\bar{l}}$ with calculated values of F^2_{hkl} and $F^2_{\bar{h}\bar{k}\bar{l}}$. A total of twenty-four pairs of reflections were used and no discrepancies occurred. The structure was refined by block diagonal least-squares using experimental weights. All atoms were included in the refinement with carbon, oxygen and hydrogen atoms given isotropic temperature factors and bromine atoms given anisotropic temperature factors. The final R index for all data was 0.023.

Atomic coordinates ($x10^4$) and thermal parameters ($x10^2$) for non-hydrogen atoms

	x/a(σ)	y/b(σ)	z/c(σ)	B(Å^2)(σ)
Br(1)	4917.4(.3)	1790.2(.2)	5410.0(.4)	*
Br(2)	3566.5(.3)	5295.6(.2)	1561.3(.4)	*
O(1)	3969(2)	839(1)	-509(3)	117(4)
C(2)	3782(3)	112(2)	52(4)	118(6)
C(3)	3723(3)	227(2)	1450(4)	117(6)
C(3a)	3988(3)	1111(2)	1706(4)	119(6)
C(4)	3459(3)	1478(2)	2869(4)	111(6)
C(5)	3849(3)	2337(2)	3223(4)	115(6)
C(6)	3865(3)	2519(2)	4655(4)	130(6)
C(7)	4266(3)	3392(2)	4846(4)	151(6)
C(8)	3606(3)	4005(2)	4117(4)	153(6)
C(9)	3523(3)	3746(2)	2731(4)	120(6)
C(10)	2794(3)	4259(2)	1895(4)	121(6)
C(11)	2564(3)	3856(2)	620(4)	110(6)
C(12)	3497(3)	3520(2)	-87(4)	108(6)

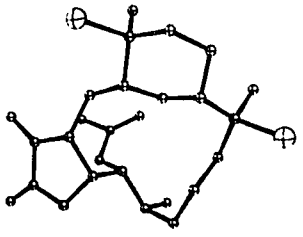
	x/a(σ)	y/b(σ)	z/c(σ)	B($A^{\circ 2}$)(σ)
C(13)	3262(3)	3006(2)	-1266(4)	108(6)
C(14)	2558(3)	2236(2)	-1105(4)	95(6)
C(15)	2702(3)	1834(2)	185(4)	95(6)
C(15a)	3794(3)	1499(2)	393(4)	103(6)
C(16)	3465(3)	-377(2)	2226(4)	179(7)
C(17)	2836(3)	2349(2)	5292(4)	181(7)
C(18)	1786(3)	4497(2)	2527(4)	169(7)
C(19)	1423(3)	2447(2)	-1361(4)	137(6)
C(20)	1198(3)	1192(2)	1084(4)	143(6)
C(21)	744(3)	371(2)	1322(4)	208(7)
O(22)	3700(2)	-512(2)	-551(3)	181(5)
O(23)	3149(2)	2920(1)	2653(3)	95(4)
O(24)	2038(2)	1123(1)	309(3)	108(4)
O(25)	902(2)	1836(2)	1499(3)	193(5)

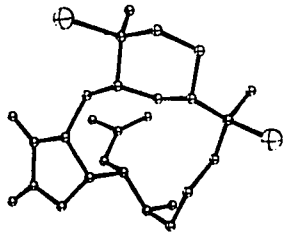
Anisotropic temperature factors ($x10^5$) for bromine atoms

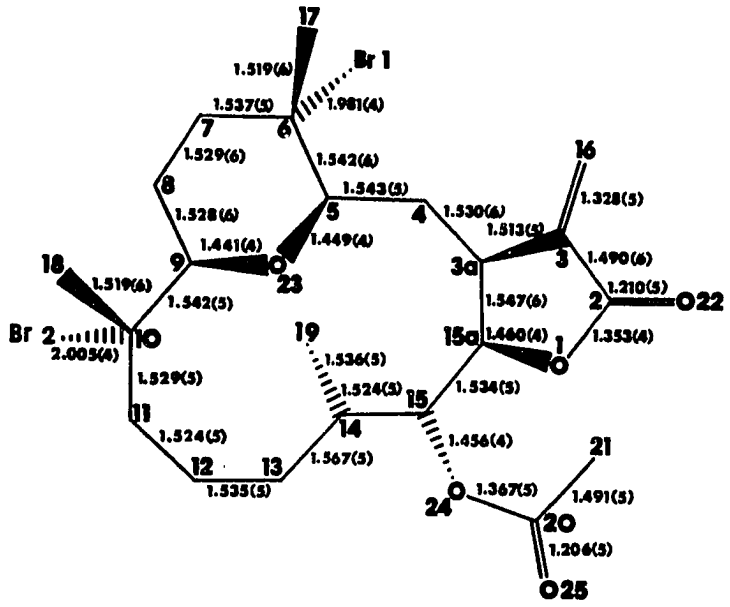
	b_{11}(σ)	b_{22}(σ)	b_{33}(σ)	b_{12}(σ)	b_{13}(σ)	b_{23}(σ)
Br(1)	360(2)	124(1)	499(4)	27(3)	-444(6)	38(3)
Br(2)	286(2)	74(1)	370(3)	-44(3)	-125(5)	14(4)

Atomic coordinates ($x10^3$) for hydrogen atoms

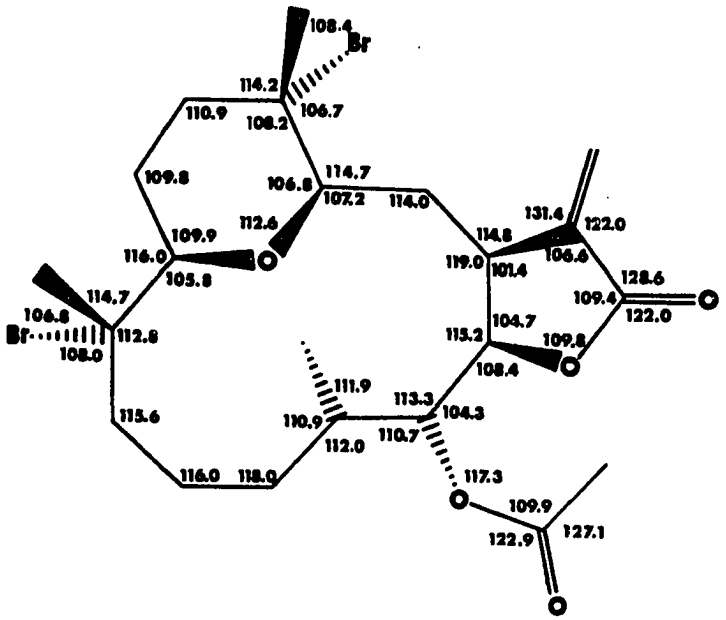
	x/a(σ)	y/c(σ)	z/c(σ)		x/a(σ)	y/b(σ)	z/c(σ)
H(3a)	471(3)	113(2)	193(4)	H(15)	255(3)	220(2)	92(4)
H(4A)	370(3)	110(2)	363(5)	H(15a)	431(3)	190(2)	21(4)
H(4B)	265(3)	150(2)	279(4)	H(16A)	346(3)	-27(2)	311(4)
H(5)	454(3)	240(2)	288(4)	H(16B)	328(3)	-94(3)	182(5)
H(7A)	497(3)	342(2)	452(4)	H(17A)	267(3)	177(2)	519(4)
H(7B)	422(3)	354(2)	574(5)	H(17B)	291(4)	249(3)	613(7)
H(8A)	391(3)	458(2)	419(4)	H(17C)	231(3)	262(2)	483(4)
H(8B)	293(3)	401(2)	450(4)	H(18A)	186(3)	484(2)	315(4)
H(9)	422(3)	379(2)	230(4)	H(18B)	144(3)	403(3)	283(5)
H(11A)	210(3)	345(2)	80(4)	H(18C)	132(4)	481(3)	205(6)
H(11B)	213(3)	426(2)	10(4)	H(19A)	97(3)	196(2)	-126(4)
H(12A)	390(2)	319(2)	50(4)	H(19B)	140(3)	264(3)	-230(5)
H(12B)	395(3)	398(2)	-46(5)	H(19C)	122(3)	284(2)	-77(4)
H(13A)	389(3)	282(2)	-162(5)	H(21A)	69(3)	20(2)	70(4)
H(13B)	293(3)	334(2)	-192(4)	H(21B)	15(4)	44(3)	199(5)
H(14)	279(3)	186(2)	-177(4)	H(21C)	128(4)	-5(3)	184(6)







Bond distances.



Bond angles. Standard deviations are between 0.2° and 0.4°

Additional bond angles

C(5) C(6) C(17)	112.8°	C(11) C(10) C(18)	109.3°
C(7) C(6) Br(1)	106.0	C(9) C(10) Br(2)	104.8

Comments. During the solution of the structure it was found that the reaction of Eupalmerin acetate with bromine was not a simple addition to the isolated double bond (C(9) - C(10)), but had involved transannular participation by the epoxide function (C(5) - C(6)), resulting in the formation of an ether bridge (C(5) - C(9)) and incorporation of bromine at the methyl-substituted carbon atoms C(6) and C(10). This fact renders a structure assignment to Eupalmerin acetate itself impossible except by inference. Nevertheless, the absolute configurations found for positions 3a, 15a, 14 and 15 are in part unexpected. The substitution patterns at these positions in Eupalmerin acetate are closely related to those of two other cembranolides in this series: Eunicin (Hossain, Nicholas and van der Helm) and Jeunicin (van der Helm, Enwall, Karns and Weinheimer). Although the configurations at 3a and 15a are identical in all three compounds, those at 14 and 15 in Eupalmerin acetate are both opposite to those of the comparable positions in Eunicin and Jeunicin.

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The Molecular Structures and Absolute Configurations of Eupalmerin Acetate and Eupalmerin Acetate Dibromide at Low Temperature

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The crystal structures of eupalmerin acetate dibromide, $C_{22}H_{32}O_5Br_2$, and eupalmerin acetate, $C_{22}H_{32}O_5$, have been determined and refined by three-dimensional least-squares techniques. Eupalmerin acetate dibromide crystallizes in space group $P2_12_12_1$, $Z=4$, with $a=12{\cdot}967$ (2), $b=16{\cdot}392$ (2) and $c=10{\cdot}5605$ (8) Å at $T=-110$°C. The final R value for 2184 reflections, collected at -110°C, is 0·023. The absolute configuration was determined from the anomalous contribution of the bromine atoms. Eupalmerin acetate also crystallizes in space group $P2_12_12_1$, $Z=4$, with $a=10{\cdot}693$ (6), $b=18{\cdot}842$ (7) and $c=10{\cdot}321$ (4) Å at $T=-110$°C. The final R value for 2433 reflections, collected at -110°C, is 0·033. The absolute configuration of eupalmerin acetate was determined from the anomalous contribution of the five oxygen atoms and was in agreement with the absolute configuration of its heavy-atom derivative. The bromine addition reaction involves transannular participation of the epoxide function and does not reveal the absolute configuration of the epoxide except by inference. The absolute configuration of atoms C(3) and C(4) is the opposite of that in other similar compounds determined in this laboratory, while the lactone fusion is the same.

Introduction

Eupalmerin acetate (EPA) is a diterpene lactone isolated from the gorgonian *Eunicea palmeri* Bayer (Rehm, 1971).

The gorgonians are a prominent group of marine invertebrates (coelenterates) in the Caribbean region and have been the subject of considerable study in these laboratories. A number of terpenoids and other organic compounds isolated from gorgonians have shown various levels of biological activity (*e.g.* Ciereszko, Sifford & Weinheimer, 1960; Ciereszko,

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1962; Weinheimer & Spraggins, 1970; Schmitz & Lorance, 1971; Rehm, 1971). The general structure for one group of these compounds, the cembranolides, is shown in Fig. 1. The structures have the following features in common: (1) a 14-membered carbocyclic ring, (2) a γ-lactone or δ-lactone fused at C(1) and C(2) or C(1) and C(13) respectively, (3) methyl substitution at C(4), C(8) and C(12) typical of a regular isoprenoid diterpene structure, (4) an isolated endocyclic double bond, C(8)–C(9), and (5) various types of oxygenation at atoms C(3), C(12) and C(13). The molecules differ primarily in the type of oxygenation and the stereochemistry at atoms C(3), C(4), C(12) and C(13). Fig. 2 shows the structures of five of these compounds. Of these structures, four have been determined crystallographically. They are EPA, eunicin (Hossain, Nicholas & van der Helm, 1968), jeunicin (Enwall, van der Helm, Karns & Weinheimer, to be published) and crassin acetate (Hossain & van der Helm, 1969). In addition the structure of ceunicin acetate, as shown, has been proposed from n.m.r. analysis and chemical transformations (Gross, 1974). The original structural investigation of EPA was carried out on the bromine addition product, eupalmerin acetate dibromide (EPA-Br_2), and a preliminary report has been published (van der Helm, Ealick & Weinheimer, 1974). The numbering scheme used in the present publication for both EPA and EPA-Br_2 is the common numbering scheme. In the preliminary report of the structure of EPA-Br_2 (van der Helm *et al.*, 1974) the IUPAC nomenclature and numbering was required. The relationship of the common numbering scheme and the IUPAC numbering scheme is given in Table 1. Because the epoxide ring was involved in the addition reaction the stereochemistry of atoms C(12) and C(13) in EPA could not be determined. For this reason the structural investigation of the natural product, EPA itself, was undertaken.

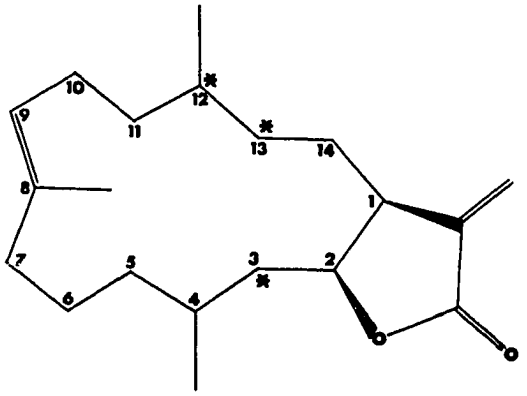

Fig. 1. General structure for a group of diterpene lactones isolated from gorgonians. Asterisks indicate possible sites for oxidation.

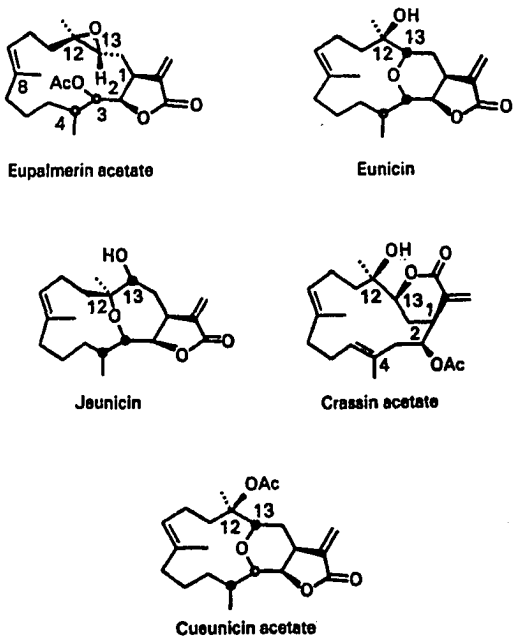

Fig. 2. Structures of five diterpene lactones.

Table 1. *Relationship of the two numbering schemes for* EPA-Br_2

This publication	IUPAC	This publication	IUPAC
Br(1)	Br(2)	C(14)	C(4)
Br(2)	Br(1)	C(15)	C(21)
C(1)	C(3a)	C(16)	C(20)
C(2)	C(15a)	C(17)	C(22)
C(3)	C(15)	C(18)	C(17)
C(4)	C(14)	C(19)	C(15)
C(5)	C(13)	C(20)	C(16)
C(6)	C(12)	C(21)	C(18)
C(7)	C(11)	C(22)	C(19)
C(8)	C(10)	O(1)	O(1)
C(9)	C(9)	O(2)	O(24)
C(10)	C(8)	O(3)	O(23)
C(11)	C(7)	O(4)	O(22)
C(12)	C(6)	O(5)	O(25)
C(13)	C(5)		

Experimental

The bromine addition product of EPA was prepared by treating EPA with one molar equivalent of bromine in CCl_4 solution at 0°, followed by chromatographic purification (Florisil, benzene). It was recrystallized from benzene/hexane, m.p. 184–185·5°, and was shown to possess the molecular formula expected for the adduct, $C_{22}H_{32}O_5Br_2$, by elemental analysis and mass spectrometry. After the solution of the structure it was discovered that formation of the addition product had involved transannular participation of the epoxide function and not simply addition to the isolated double bond.

Purified EPA-Br_2 was dissolved in benzene and slowly cooled. Large colorless crystals of suitable quality for a diffraction experiment were obtained. During preliminary investigation of the crystals it was found that the crystals decomposed rapidly in an X-ray

beam. For this reason data were collected at low temperature where no significant decomposition was observed. Crystallographic data (Table 2) and integrated X-ray intensity data were collected at −110 °C using a Nonius CAD-4 automatic diffractometer and a Nonius low-temperature apparatus.

Table 2. *Crystallographic data for* EPA-Br_2

Formula $C_{22}H_{32}O_5Br_2$	F.W. 536·30
Systematic absences $h00$, $h=2n+1$	
$0k0$, $k=2n+1$	
$00l$, $l=2n+1$	
Space group $P2_12_12_1$	$Z=4$
$T=25$ °C	$T=-110$ °C
$a=13·0971$ (7) Å	$a=12·967$ (2) Å
$b=16·603$ (1)	$b=16·392$ (2)
$c=10·6758$ (3)	$c=10·5605$ (8)

(determined by least-squares fit to the $+2\theta$ and -2θ values of 32 reflections)

$V=2321·5$ Å^3	$V=2244·7$ Å^3
$D_c=1·534$ g cm^{-3}	$D_c=1·587$ g cm^{-3}
$D_o=1·537$ g cm^{-3}	

(measured by flotation in CCl_4/C_6H_{14})
$F(000)=1096$

The 2184 data, comprising all unique reflections with $2\theta<144°$, were measured using Cu $K\alpha$ radiation ($\lambda=1·5418$ Å) and θ–2θ scans. The θ scan width was calculated as $1·0+0·1\tan\theta$. The maximum scan time was 90 s with $\frac{2}{3}$ of the time used in scanning the peak and $\frac{1}{6}$ of the time used in scanning each the high and low-θ backgrounds. Four different crystals were used in the collection of data because of difficulties with adhesives and formation of ice. Through our experience we have found that any epoxy glue serves as an adequate low-temperature adhesive. There were 19 reflections which could not be distinguished from the background on the basis that the net count was less than $1·4\sigma(I)$. These reflections were assigned intensities equal to the square root of the total count for the purpose of least-squares refinement. The observed intensities were corrected for Lorentz and polarization factors and for absorption ($\mu=53·4$ cm^{-1}). For the absorption corrections the program uses the numerical integration method of Gauss and in this case eight sampling points were used along each axis (Coppens, Leiserowitz & Rabinovich, 1965).

For the crystallization of EPA a purified sample was dissolved in benzene and a few drops of hexane were added to aid crystallization. Block-like, colorless crystals were obtained which were suitable for data collection. Preliminary photographs indicated high thermal motion and for this reason data were collected at low temperature. Crystallographic data (Table 3) and integrated X-ray intensities were collected at −110 °C. The 2433 reflections, comprising all unique data with $2\theta<150°$ were measured using Cu $K\alpha$ radiation ($\lambda=1·5418$ Å) and θ–2θ scans. The scan widths and scan times were calculated in the same way as for EPA-Br_2. In total, 128 reflections were measured with a net intensity less than $1·4\sigma(I)$ and were assigned intensities

Table 3. *Crystallographic data for* EPA

Formula $C_{22}H_{32}O_5$	F.W. 376·48
Systematic absences $h00$, $h=2n+1$	
$0k0$, $k=2n+1$	
$00l$, $l=2n+1$	
Space group $P2_12_12_1$	$Z=4$
$T=25$ °C	$T=-110$ °C
$a=10·834$ (2) Å	$a=10·694$ (6) Å
$b=19·041$ (2)	$b=18·842$ (7)
$c=10·4237$ (8)	$c=10·321$ (4)

(determined by least-squares fit to the $+2\theta$ and -2θ values of 52 and 44 reflections, respectively)

$V=2150·3$ Å^3	$V=2079·6$ Å^3
$D_c=1·163$ g cm^{-3}	$D_c=1·202$ g cm^{-3}
$D_o=1·166$ g cm^{-3}	

(measured by flotation in CCl_4/C_6H_{14})
$F(000)=816$

equal to the square root of the total count. The observed intensities were corrected for Lorentz and polarization effects and absorption ($\mu=6·86$ cm^{-1}).

Structure determination and refinement

The positions of the two bromine atoms of EPA-Br_2 were located from the three Harker sections of a sharpened Patterson map. The bromine atoms were given anisotropic temperature factors and after several cycles of least-squares refinement the R ($\sum||kF_o|-|F_c||/\sum|kF_o|$) was 0·27. A difference Fourier map was calculated from which the positions of all 27 carbon and oxygen atoms were located. The five oxygen atoms were identified as the five largest peaks in the difference Fourier. After several more cycles of refinement a difference Fourier map was calculated which indicated that anisotropic effects for carbon and oxygen atoms were not significant. In addition all but three hydrogen atom positions were clearly defined. The absolute configuration was determined using the method of Bijvoet, Peerdeman & van Bommel (1951). The observed values of I_{hkl} and $I_{\overline{hkl}}$ were compared with calculated values of F^2_{hkl} and $F^2_{\overline{hkl}}$ for 24 pairs of enantiomorph-sensitive reflections. All 24 pairs indicated the absolute configuration reported. At this point the observed structure factors were corrected for anomalous dispersion of bromine (Patterson, 1963). A subsequent difference Fourier calculation revealed the positions of the remaining three hydrogen atoms. Least-squares refinement of the bromine atoms using anisotropic temperature factors, and carbon, oxygen and hydrogen atoms using isotropic temperature factors, was terminated when all shifts for non-hydrogen atoms were less than $\frac{1}{3}$ the corresponding standard deviation. A difference Fourier map based on the final parameters showed a large amount of detail. Several peaks between 0·2 and 0·3 e Å^{-3} which seemed to be associated with the areas of bonding electrons were observed. Two peaks of about 0·5 e Å^{-3} associated with each bromine atom were the most significant features. The peaks were located at a distance of about 1·0 Å from the bromine atoms. The unweighted R value based on the final

parameters (van der Helm *et al.*, 1974) is 0·023 for all data.

The structure of EPA was solved by direct methods using the program *MULTAN* (Germain, Main & Wolfson, 1971). The phases for 284 normalized structure factors greater than 1·5 were used in generating and *E* map. Reflections in the starting set were 1,14,0, 081, 870, 051, 1,20,0, 508 and 521. The first three reflections were used to define the origin with the fourth reflection being used as the enantiomorph-defining reflection. The *E* map calculated from one of four sets of phases showing high figures of merit (1·18–1·19) and similar residuals (27·7–27·8) revealed the position of all 27 carbon and oxygen atoms. The other three *E* maps were not investigated. The five highest peaks in the *E* map were consistent with the expected locations of the five oxygen atoms. The initial structure-factor calculation resulted in an *R* of 0·34. After several cycles of least-squares refinement all carbon and oxygen atoms were given anisotropic temperature factors. After several more cycles the *R* was 0·10 and had appeared to converge. A difference Fourier map was then calculated from which the position of all hydrogen atoms were located. Least-squares refinement of the non-hydrogen atoms using anisotropic temperature factors, and hydrogen atoms using isotropic temperature factors, was terminated when all shifts for the non-hydrogen atoms were less than $\frac{1}{3}$ of the corresponding standard deviation. A final difference Fourier map was calculated in which all electron densities were between $-0{\cdot}20$ and $0{\cdot}20$ e Å^{-3}. The unweighted *R* based on final parameters (Tables 4, 5 and 6) is 0·033 for all data.

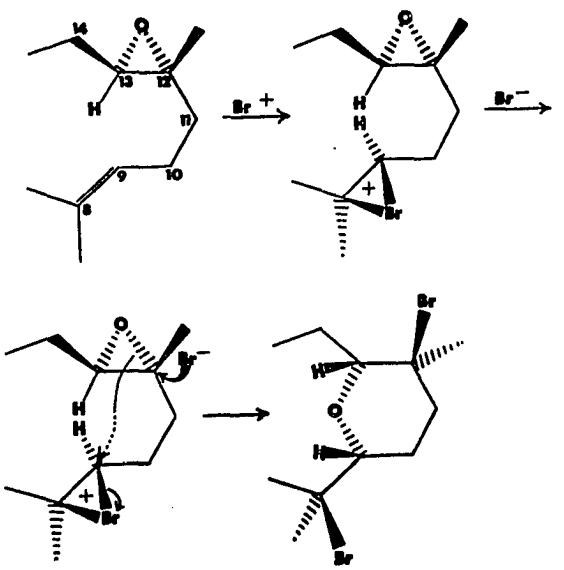

Fig. 3. Proposed reaction mechanism for the conversion of EPA to EPA-Br_2.

All least-squares refinements for both EPA and EPA-Br_2 were carried out using the block-diagonal least-squares program of Ahmed (1966). The atomic scattering factors for Br, O and C atoms and the anomalous scattering factors for Br atoms were taken from *International Tables for X-ray Crystallography* (1962). The scattering factors for hydrogen atoms were those of Stewart, Davidson & Simpson (1965). A weighting scheme was used for each compound which assigns an experimental weight, W_F, to each structure factor as defined below:

$$W_F = \frac{1}{\sigma_F^2},$$

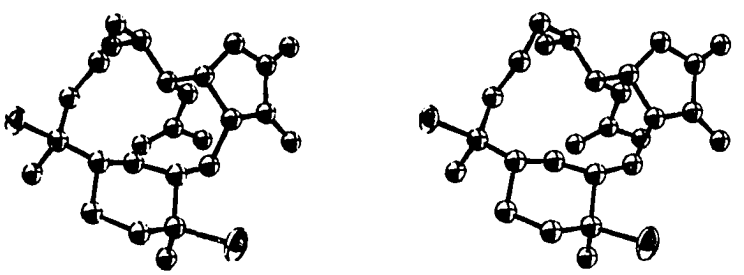

Fig. 4. Stereo view of a single molecule of EPA-Br_2 (Johnson, 1965).

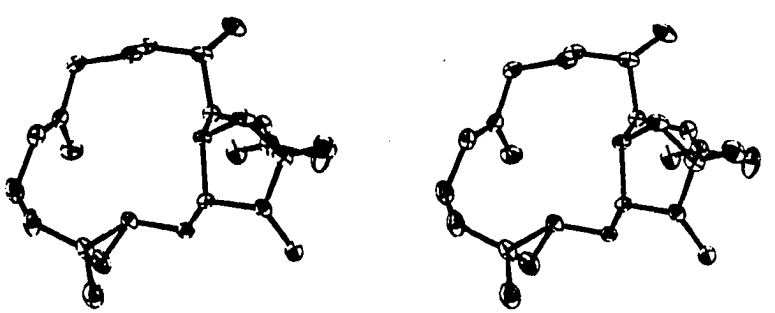

Fig. 5. Stereo view of a single molecule of EPA (Johnson, 1965).

Table 4. *Positional parameters of carbon and oxygen atoms for* EPA

Calculated standard deviations for the last digit are listed in parentheses.

	x	*y*	*z*
C(1)	0·5483 (2)	0·47367 (8)	0·3730 (2)
C(2)	0·5603 (2)	0·39728 (8)	0·4265 (2)
C(3)	0·5496 (2)	0·33697 (8)	0·3286 (2)
C(4)	0·5764 (2)	0·26438 (9)	0·3922 (2)
C(5)	0·7191 (2)	0·25226 (9)	0·3885 (2)
C(6)	0·7700 (2)	0·22879 (8)	0·2566 (2)
C(7)	0·9122 (2)	0·24153 (9)	0·2436 (2)
C(8)	0·9446 (2)	0·31687 (9)	0·2060 (2)
C(9)	0·9836 (2)	0·36500 (10)	0·2919 (2)
C(10)	1·0280 (2)	0·43900 (10)	0·2648 (2)
C(11)	0·9620 (2)	0·49976 (10)	0·3379 (2)
C(12)	0·8371 (2)	0·52496 (9)	0·2859 (2)
C(13)	0·7433 (2)	0·47445 (8)	0·2381 (2)
C(14)	0·6040 (2)	0·48796 (8)	0·2391 (2)
C(15)	0·4107 (2)	0·48751 (8)	0·3885 (2)
C(16)	0·3653 (2)	0·43772 (9)	0·4900 (2)
C(17)	0·3369 (2)	0·53341 (9)	0·3283 (2)
C(18)	0·5035 (2)	0·20309 (10)	0·3311 (2)
C(19)	0·9305 (2)	0·33180 (10)	0·0636 (2)
C(20)	0·8004 (2)	0·59731 (11)	0·3354 (3)
C(21)	0·4137 (2)	0·33774 (9)	0·1445 (2)
C(22)	0·2797 (2)	0·34542 (14)	0·1043 (2)
O(1)	0·4576 (1)	0·39090 (6)	0·5190 (1)
O(2)	0·4242 (1)	0·34068 (6)	0·2752 (1)
O(3)	0·8171 (1)	0·51500 (8)	0·1474 (1)
O(4)	0·2653 (1)	0·43643 (7)	0·5436 (2)
O(5)	0·5004 (1)	0·33169 (8)	0·0722 (1)

Table 5. *Anisotropic temperature factors for carbon and oxygen atoms*

Temperature factors are of the form $\exp[-(b_{11}h^2+b_{22}k^2+b_{33}l^2+b_{12}hk+b_{13}hl+b_{23}kl)]$. The parameters and standard deviations are multiplied by 10^4.

	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	31 (1)	8·1 (4)	26 (1)	0 (1)	0 (2)	3 (1)
C(2)	36 (1)	8·3 (4)	28 (1)	0 (1)	7 (2)	4 (1)
C(3)	38 (1)	9·3 (4)	28 (1)	0 (1)	3 (2)	−3 (1)
C(4)	57 (2)	8·0 (4)	33 (2)	−1 (1)	22 (3)	1 (1)
C(5)	59 (2)	8·5 (4)	34 (2)	8 (1)	1 (3)	3 (1)
C(6)	50 (2)	8·3 (4)	40 (2)	2 (1)	7 (3)	−5 (1)
C(7)	45 (1)	10·7 (4)	42 (2)	11 (1)	−7 (3)	3 (1)
C(8)	33 (1)	12·2 (4)	38 (2)	6 (1)	−8 (2)	−2 (1)
C(9)	34 (1)	15·2 (5)	45 (2)	3 (1)	−8 (3)	−10 (2)
C(10)	36 (1)	14·4 (5)	74 (2)	−5 (1)	14 (3)	−26 (2)
C(11)	34 (1)	16·4 (5)	75 (2)	−4 (1)	1 (3)	−34 (2)
C(12)	36 (1)	12·8 (4)	44 (2)	−12 (1)	21 (3)	−13 (1)
C(13)	35 (1)	10·6 (4)	34 (1)	−6 (1)	9 (2)	−2 (1)
C(14)	34 (1)	8·9 (4)	29 (1)	−3 (1)	−4 (2)	6 (1)
C(15)	33 (1)	8·4 (4)	35 (1)	−6 (1)	8 (2)	−9 (1)
C(16)	46 (1)	10·5 (4)	36 (2)	−4 (1)	16 (3)	−10 (1)
C(17)	34 (1)	11·9 (4)	60 (2)	−3 (1)	−4 (3)	1 (2)
C(18)	68 (2)	9·6 (5)	59 (2)	−12 (2)	40 (3)	−8 (2)
C(19)	72 (2)	13·9 (5)	41 (2)	−6 (2)	−15 (3)	2 (2)
C(20)	44 (2)	13·9 (5)	114 (3)	−5 (2)	5 (4)	−35 (2)
C(21)	48 (1)	13·1 (4)	40 (2)	−2 (1)	−5 (3)	−15 (1)
C(22)	50 (2)	32·8 (8)	63 (2)	14 (2)	−21 (3)	−32 (2)
O(1)	54 (1)	9·4 (3)	29 (1)	−1 (1)	25 (2)	1 (1)
O(2)	37 (1)	12·9 (3)	36 (1)	−2 (1)	8 (2)	−11 (1)
O(3)	47 (1)	20·5 (4)	42 (1)	−14 (1)	34 (2)	2 (1)
O(4)	54 (1)	16·1 (4)	64 (1)	−4 (1)	56 (2)	−3 (1)
O(5)	52 (1)	21·0 (4)	37 (1)	−8 (1)	10 (2)	−13 (1)

Table 6. *Positional parameters and isotropic temperature factors for the hydrogen atoms*

Standard deviations in the last digits are given in parentheses

	x	*y*	*z*	B (Å^2)
H(C1)	0·591(2)	0·504 (1)	0·437 (2)	1·3 (4)
H(C2)	0·635 (2)	0·389 (1)	0·473 (2)	0·9 (3)
H(C3)	0·608 (2)	0·344 (1)	0·254 (2)	0·9 (3)
H(C4)	0·544 (2)	0·268 (1)	0·493 (2)	2·1 (4)
H(C5)*A*	0·743 (2)	0·216 (1)	0·455 (2)	2·6 (5)
H(C5)*B*	0·763 (2)	0·295 (1)	0·412 (2)	2·2 (4)
H(C6)*A*	0·725 (2)	0·254 (1)	0·186 (2)	1·8 (4)
H(C6)*B*	0·754 (2)	0·176 (1)	0·248 (2)	2·6 (5)
H(C7)*A*	0·945 (2)	0·208 (1)	0·173 (2)	2·5 (5)
H(C7)*B*	0·956 (2)	0·230 (1)	0·331 (2)	2·6 (5)
H(C9)	0·994 (2)	0·350 (1)	0·388 (2)	2·4 (5)
H(C10)*A*	1·118 (2)	0·443 (1)	0·286 (3)	3·1 (5)
H(C10)*B*	1·025 (2)	0·449 (1)	0·172 (2)	2·0 (4)
H(C11)*A*	0·948 (3)	0·488 (2)	0·429 (3)	4·8 (7)
H(C11)*B*	1·020 (2)	0·543 (1)	0·334 (3)	3·5 (6)
H(C13)	0·764 (2)	0·422 (1)	0·240 (2)	3·0 (5)
H(C14)*A*	0·590 (2)	0·537 (1)	0·214 (2)	1·3 (4)
H(C14)*B*	0·564 (2)	0·459 (1)	0·170 (2)	2·0 (4)
H(C17)*A*	0·249 (2)	0·534 (1)	0·354 (2)	1·8 (4)
H(C17)*B*	0·366 (2)	0·566 (1)	0·259 (2)	2·3 (5)
H(C18)*A*	0·931 (3)	0·383 (1)	0·044 (3)	4·8 (7)
H(C18)*B*	0·847 (3)	0·313 (2)	0·033 (3)	4·4 (6)
H(C18)*C*	0·997 (3)	0·307 (2)	0·020 (3)	4·7 (7)
H(C19)*A*	0·520 (2)	0·199 (1)	0·237 (2)	2·4 (5)
H(C19)*B*	0·530 (2)	0·158 (1)	0·374 (2)	2·9 (5)
H(C19)*C*	0·410 (2)	0·209 (1)	0·345 (2)	3·2 (5)
H(C20)*A*	0·806 (3)	0·596 (1)	0·434 (3)	4·4 (6)
H(C20)*B*	0·715 (2)	0·615 (1)	0·306 (3)	3·5 (6)
H(C20)*C*	0·859 (3)	0·633 (2)	0·309 (3)	4·8 (7)
H(C22)*A*	0·227 (2)	0·321 (1)	0·159 (3)	3·7 (6)
H(C22)*B*	0·256 (3)	0·397 (2)	0·104 (3)	5·0 (7)
H(C22)*C*	0·270 (3)	0·325 (1)	0·010 (3)	4·3 (6)

where

$$\sigma_F=\tfrac{1}{2}\left[\frac{\sigma^2+(CP)^2}{(P)\,(\mathrm{Lp})}\right]^{1/2},$$

in which $\sigma=T^{1/2}\nu$, ν=scan speed, $T=Pk+2(R+L)$, $P=[Pk-2(R+L)]\nu$, R=right background, L=left background, Lp=Lorentz and polarization corrections, C=0·05 for EPA and 0·02 for EPA-Br_2.

In the structure-factor analysis for both EPA and EPA-Br_2 the average values of $W_F\Delta F^2$ did not show a significant variation with either F_o or $\sin\theta/\lambda$, indicating that the weighting scheme used was reasonable.*

Determination of the absolute configuration of EPA

Because of the close agreement of observed and calculated structure factors in EPA, it was thought that it might be reasonable to attempt to determine the absolute configuration using the anomalous contribution of the oxygen atoms. In addition the results should

* Lists of structure factors for EPA and EPA-Br_2 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30905 (26 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars. Chester CH1 1NZ, England.

be consistent with the absolute configuration of EPA-Br_2, thus providing a test of our procedure. Already there are a number of examples in the literature in which absolute configurations of light-atom structures have been determined (*e.g.* Hope & De la Camp, 1969; Thiessen & Hope, 1970; Wetherington, Ament & Moncrief, 1974). In addition Engel (1972) has published an analysis of the determination of the absolute configuration of seven light-atom compounds in which he concluded that the 'Bijvoet method' was more effective than the '*R* method'. The Bijvoet method involves measurement of Bijvoet differences while the *R* method is a variation of the Hamilton (1965) *R* test in which the *R* comparisons are restricted to a set of enantiomer-sensitive reflections.

With this as background we chose to use the Bijvoet method with 15 pairs of reflections. Our goal then was to select the 15 reflections most sensitive to the choice of enantiomer. We chose to do this by selecting the reflections for which the absolute value of difference in the calculated values of F_+^2 and F_-^2 was largest compared to the corresponding value $\sigma(F^2)$. That is we chose reflections for which the sensitivity factor [$SF = |F_+^2 - F_-^2|/(F_o^2)$] was the largest. The values of F_+^2 and F_-^2 are calculated according to the method of James (1948) and $\sigma(F_o^2)$ may be derived from the value of σ_F mentioned previously in which $\sigma(F_o^2) = 2F_o\sigma_F$. Using this method we have chosen the reflections in which the difference to be observed is most likely to be significant compared with the standard deviation of the values to be measured. After the 15 enantiomorph-sensitive reflections were chosen the values of I_{hkl} and $I_{\bar{h}\bar{k}\bar{l}}$ were measured ten times each. The results are summarized in Table 7. Of the 15 pairs of reflections chosen, 11 indicated the absolute configuration derived from EPA-Br_2, one indicated the opposite configuration, and three pairs showed no difference in intensity. It may be important to point out that intuitively the value of ΔI compared with $\sigma(I)$ might appear to be of questionable significance. However, this is not the statistically important feature, which is the consistency of the measurements. Although each individual measurement is associated with a relatively low probability, the fact that 11 measurements indicate one absolute configuration, while only one measurement indicates the opposite configuration, allows one to accept one configuration and reject the other at a high probability. It might also be noted that the reflection which indicated the opposite configuration (634) has the smallest value of F_c^2 of all the reflections measured. It is apparent that the use of the anomalous contribution of oxygen atoms in determining absolute configuration is limited by the inherent errors of the model from which F_+^2 and F_-^2 are derived. We believe that our method of selection of enantiomer-sensitive reflections is reasonable and has the advantage of requiring very little computer time. The anomalous scattering factors used for the oxygen atoms were those of Cromer & Liberman (1970).

Table 7. *Comparison of observed and calculated Bijvoet differences*

The values are $\Delta I_o = I_{hkl} - I_{\bar{h}\bar{k}\bar{l}}$, $\Delta F_c^2 = F_{hkl}^2 - F_{\bar{h}\bar{k}\bar{l}}^2$, $\sigma(I_o)$ = internal estimation of the standard deviation of I_o and $\sigma(F_c^2)$ = external estimation of the standard deviation of F_c^2. The consistent agreement of observed and calculated differences indicates the configuration reported.

h	k	l	F_c^2	ΔI_o	$\sigma(I_o)$	$\frac{\Delta I_o}{\overline{I_o}}$	ΔF_c^2	$\sigma(F_c^2)$	$\frac{\Delta F_c^2}{\overline{F_c^2}}$
1	2	4	290	13·0	4·0	5%	11·8	8·5	4%
1	11	10	210	0·0	4·8	0	−7·8	7·3	−4
2	8	4	355	4·1	3·9	2	11·4	11·2	3
2	10	3	135	−0·2	2·7	−0	6·7	6·0	5
2	15	2	140	−1·3	2·3	−2	−5·8	5·7	−4
2	15	4	300	4·5	2·7	4	13·3	10·5	4
3	8	5	110	−1·7	2·5	−3	−7·1	4·6	−6
4	8	3	250	−1·2	3·9	−1	−8·3	8·4	−3
4	9	9	70	−0·1	2·7	−0	−3·5	3·4	−5
5	4	4	100	−1·4	2·7	−2	−4·0	4·1	−4
5	20	1	40	0·9	2·3	4	2·3	2·2	5
6	3	4	20	0·9	2·4	7	−2·8	2·5	−13
7	9	1	95	2·6	2·8	7	4·3	3·9	5
7	12	3	265	−2·3	3·3	−2	−10·0	8·7	−4
8	9	2	65	−2·5	1·7	−9	−5·5	3·8	−8

Description and discussion of the structures

As mentioned above, the conversion of EPA to EPA-Br_2 proceeded with participation of the epoxide oxygen in the addition to the double bond. The proposed reaction mechanism is shown in Fig. 3. The first step involves the formation of a bromonium ion intermediate. The stereochemistry of this intermediate is determined by the fold of the molecule with the configuration shown being favored. The second step involves the concerted attack by the epoxide oxygen on the bromonium ion, forming the ether bridge [C(9)–C(13)], and attack by the bromide ion at the epoxide function [C(12)]. This mechanism was proposed prior to the solution of the structure of EPA and is consistent with the observed stereochemistry of both reactant and product molecules.

Considering the relative positions of the epoxide and isolated double-bond functions, it is not surprising that the epoxide participated in the addition reaction. Such participation is not unprecedented, and reaction of the sensitive epoxide function with the proximate electrophilic bromonium ion intermediate in the addition reaction can be considered normal. Of interest is the fact that the participation reaction showed complete stereospecificity in both the intramolecular attack by oxygen at the bromonium ion, and attack by external bromide at the epoxide function. The configurations at C(8) and C(9), and C(12) and C(13) in the dibromide all reflect the occurrence of the mechanistically normal *trans* addition and ring opening at these sites. A slightly unusual feature of the reaction at the double bond is the attack by the nucleophilic oxygen at the secondary carbon atom [C(9)]. In additions to isolated double bonds, nucleophilic opening of the bromonium ion normally occurs by attack at the tertiary center. In this case, steric factors favor the formation of the six-

membered oxygen-containing ring rather than the seven-membered possibility.

A stereo view of a single molecule of EPA-Br_2 is shown in Fig. 4 and a stereo view of EPA in Fig. 5. The natural product, EPA, consists of a 14-membered, cembrane-type ring (Drew, Templeton & Zalkin, 1969). A γ-lactone is fused at carbons C(1) and C(2). The molecule contains an epoxide function [C(12)–C(13)] and an acetoxy group [C(3)]. The only double bond in the ring is C(8)–C(9) and its geometry with respect to the ring is *trans*. The conversion to EPA-Br_2 results in bromination at C(8) and C(13) and the loss of the double bond. The epoxide function is converted to an ether bridge [C(9)–C(13)]. All other chemical features of the molecules are identical. The most noticeable feature of both molecules is the relative flatness of the cembrane (saturated cembrene) rings.

The bond distances for EPA are shown in Fig. 6 and bond angles in Fig. 7. The bond distances and angles for EPA-Br_2 have been published in a preliminary publication (van der Helm *et al.*, 1974). For the purpose of comparison, bond distances for EPA and EPA-Br_2 have been listed in Table 8. There are several differences in bond distances which appear to be significant. Three of these distances are for carbon–carbon single bonds [C(3)–C(4), C(4)–C(5), C(6)–C(7)] in which case there is no chemical explanation for the differences (about four standard deviations based on EPA-Br_2) and may tend to indicate some underestimation of the standard deviations. A second group of distances where differences occur is as expected because they involve carbons C(8) and C(9) which are converted from sp^2 hybridized atoms in EPA to sp^3 hybridized atoms in EPA-Br_2. The final group of bond distances with differences are those associated with the epoxide

Table 8. *Comparison of bond distances for* EPA *and* EPA-Br_2

Standard deviations in the last digits are given in parentheses.

	EPA	EPA-Br_2
C(1)—C(2)	1·547 (2)	1·547 (6)
C(1)—C(14)	1·529 (2)	1·530 (6)
C(1)—C(15)	1·503 (2)	1·513 (5)
C(2)—O(1)	1·460 (2)	1·460 (4)
C(2)—C(3)	1·525 (2)	1·534 (5)
C(3)—O(2)	1·451 (2)	1·456 (4)
C(3)—C(4)	1·544 (3)	1·524 (5)
C(4)—C(5)	1·544 (3)	1·567 (5)
C(4)—C(18)	1·529 (3)	1·536 (5)
C(5)—C(6)	1·532 (3)	1·535 (5)
C(6)—C(7)	1·545 (3)	1·524 (5)
C(7)—C(8)	1·512 (3)	1·529 (5)
C(8)—C(9)	1·335 (3)	1·542 (5)
C(8)—C(19)	1·504 (3)	1·519 (6)
C(9)—C(10)	1·499 (3)	1·528 (6)
C(10)—C(11)	1·542 (3)	1·529 (6)
C(11)–C(12)	1·515 (3)	1·537 (5)
C(12)–C(13)	1·469 (2)	1·542 (6)
C(12)–C(20)	1·508 (3)	1·519 (6)
C(13)–O(3)	1·443 (2)	1·449 (4)
C(13)–C(14)	1·511 (2)	1·543 (5)
C(15)–C(16)	1·488 (2)	1·490 (6)
C(15)–C(17)	1·325 (3)	1·328 (5)
C(21)–O(2)	1·354 (2)	1·367 (5)
C(21)–O(5)	1·196 (2)	1·206 (5)
C(21)–C(22)	1·498 (3)	1·491 (5)

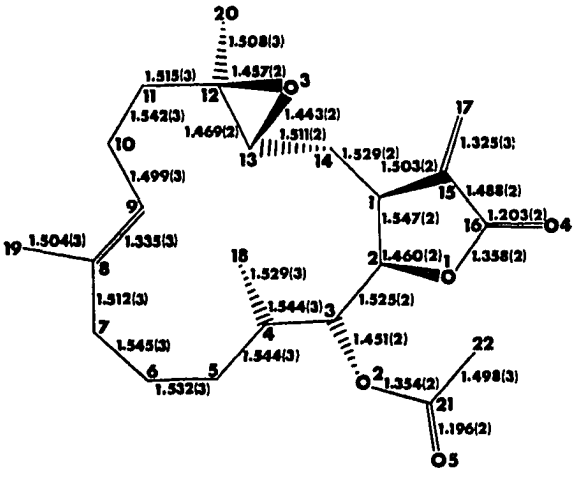

Fig. 6. Bond distances in EPA (Å).

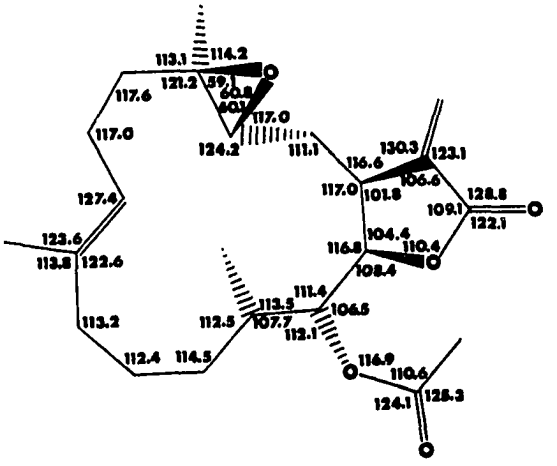

Fig. 7. Bond angles in EPA (°).

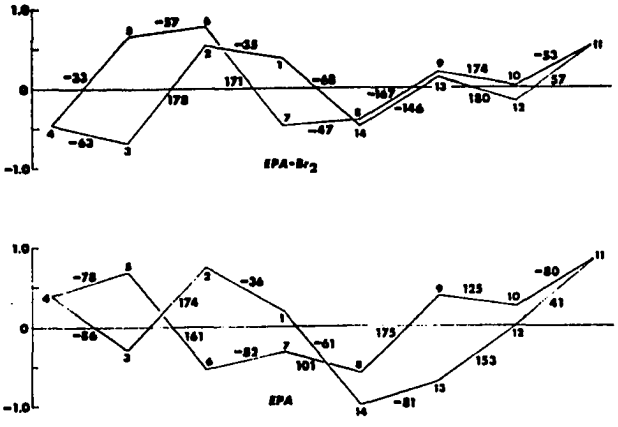

Fig. 8. Least-squares planes and torsion angles for 14-membered ring of EPA and EPA-Br_2.

function in EPA. The C(12)–C(13) bond in the epoxide ring is seen to be extremely short compared with the expected value for a bond between two sp^3 hybridized carbon atoms. In addition, bonds C(11)–C(12) and C(13)–C(14) show shortening as a result of being adjacent to the epoxide function. In EPA-Br_2 all three of these bond distances are observed as not being significantly different from the value expected for a carbon–carbon single bond.

The differences in bond angles of the two structures may serve as an approximation to the relative degree of ring strain. If the potential-energy function for deformation of a bond angle is assumed to be proportional to the difference in the observed angle and an equilibrium value for that angle, squared [*i.e.* $V(\theta)=k\Delta\theta^2$], then the sum of $\Delta\theta^2$ for the interior angles of the cembrane ring may be taken as an indication of ring strain. The equilibrium values for bond angles are taken to be 109·5° and 120° for angles subtended at an sp^3 and sp^2 carbon atom respectively. The values of $\sum\Delta\theta^2$ calculated for EPA and EPA-Br_2 are 50·2 deg^2 and 28·4 deg^2 respectively. This is expected, as the inclusion of a double bond and epoxide group in EPA will provide large contributions to ring strain.

Torsion angles in the cembrane rings along with the least-squares planes through the ring, are given in Fig. 8 for EPA and EPA-Br_2. The flatness of the cembrane ring for each molecule is easily seen as the maximum deviation of a ring atom for either molecule from the least-squares plane is less than 1·0 Å. The torsion angles serve as a further indication of the ring strain. An investigation of the angles shows a larger deviation from the minimum energy conformations (60, 180, 300°) in the case of EPA. Again the epoxide function is responsible for a large amount of the strain while the ether bridge C(9)–O(3)–C(13) plus atoms C(10), C(11) and C(12) in EPA-Br_2 form a relatively low-energy chair conformation.

At least some mention should be made of the intermolecular contacts in these structures. Neither EPA nor EPA-Br_2 contains active hydrogens (*i.e.* –O–H or $-NH_2$ groups) and no hydrogen bonding is anticipated. There are, however, several intermolecular contacts which are less than the sum of the van der Waals radii of the atoms involved. In EPA the distances H(C1)–O(3) and H(C4)–H(C7)*A* are 2·41 and 2·05 Å. In both cases the C–H bonds are directed generally towards the center of the contact such that systematic errors in the C–H bond length tends to increase the error in the intermolecular distance. In EPA-Br_2 intermolecular distances of 3·03 and 3·06 Å were observed for Br(2)–H(C19)*B* and Br(1)–H(C3) respectively. Although these intermolecular interactions observed in both EPA and EPA-Br_2 apparently provide little in stabilization energy it is interesting to note that the atoms involved in three of these are the epoxide oxygen, O(3), in EPA and the two bromine atoms of EPA-Br_2.

It is of interest to discuss the possible biogenetic relationship of the diterpene lactones isolated from gorgonians. There have been four such compounds isolated for which X-ray crystallographic analyses have been completed. They are EPA, eunicin (Hossain *et al.*, 1968), jeunicin (Enwall *et al.*, to be published) and crassin acetate (Hossain & van der Helm, 1969). Of these EPA, eunicin and jeunicin have the same general structural features (Fig. 2) while crassin acetate has a δ-lactone. In addition the stereochemistry of the lactone is identical for all three compounds containing γ-lactones.

Based upon the gross structure of EPA deduced by chemical methods (Rehm, 1971), and without the knowledge of stereochemical detail provided by this work, it was attractive to consider EPA as the direct biogenetic precursor of eunicin and jeunicin. The configuration of the oxygenated centers C(12) and C(13) in these two oxa-bridged compounds is compatible with their formation from a single *trans* epoxide function, such as is present in EPA. Attack at the epoxide at either C(12) or C(13) by the oxygen function at C(3) would establish the oxa-bridge from C(3) to C(13) (eunicin) or to C(12) (jeunicin). Stereospecific ring opening of the epoxide in each of these attacks, occurring with the mechanistically preferred inversion at the epoxide sites, would generate precisely the configurations which exist in eunicin and jeunicin. However, EPA cannot be the precursor of the other two cembranolides because it possesses the opposite configurations at both C(3) and C(4).

Nevertheless, this speculation appears reasonable, and suggests that there remains to be found in the *Eunicea* gorgonians an 'iso' EPA which will indeed possess configurations at C(3) and C(4) corresponding to those in eunicin and jeunicin. It further suggests that an 'iso' eunicin and an 'iso' jeunicin remain to be found, in which the configurations at C(3) and C(4) are common with those present in EPA.

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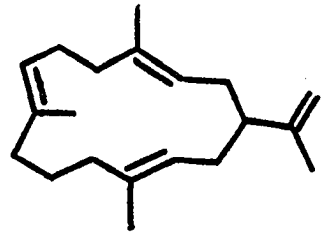
A SUMMARY OF THE CRYSTALLOGRAPHIC STUDIES OF MARINE CEMBRANES

Introduction

Cembranes are a class of diterpenes having the carbon skeleton of the compound cembrene (I). All cembranes have a regular isoprenoid structure characterized by a fourteen-membered carbocycle. The compounds



I

differ in the extent of oxygenation at (or allylic to) the double bonds. A lactone function occurs in many of the known compounds in which case the compound is referred to as a cembranolide. Marine life serves as a rich source of cembranes and cembranolides although similar compounds are also found in various forms of plant life. In particular a large number of cembranes studied in this department[1] have been isolated from various species of gorgonians. The gorgonians are a group of marine invertebrates (coelenterates) occurring in the Caribbean region. Interest in these particular compounds arises from the fact that many show some level of biological activity. Because the cembran-

olides are toxic to certain other marine life it has been suggested that the organism produces these compounds as part of its defense mechanism.[1]

Because some of the cembranolides have shown activity in KB tests for anticancer agents the structures and absolute configurations are important. Such methods as NMR, IR, etc. have been used with some success in structure determination. Their disadvantage lies in the fact that these methods are slow and time consuming and, in addition, the results are ambiguous for many of the structures having the complexity of a cembrane. The most powerful method for the determination of molecular structure is x-ray crystallography. In the past one of its major disadvantages was that structures containing 25 or more non-hydrogen light atoms (such as the cembranolides) could be attempted with only limited chances of success. Recent developments in the area of x-ray crystallography have now made it possible to determine these structures, at least in many cases, routinely. Specifically these developments fall in three major areas as follows: 1) the development of automated instruments with low temperature capabilities for fast, accurate measurement of intensity data 2) advances in direct methods for the solution of medium difficulty structures (40 or 50 light atoms) in non-centrosymmetric space groups and 3) the development of faster and larger computer systems allowing rapid processing of data. Although the number of structural determinations is still limited and success is not guaranteed these developments have increased many-fold the effectiveness of x-ray crystallography in structure determination.

Methods of Structure Determination

Two of the most common problems related to data collection for cembranes are high thermal motion resulting in a limitation on the amount of observable data and decomposition caused by the bombardment of sample with x-radiation during the data collection process. Both of these problems can be resolved by measuring the data at low temperature. In the case of high thermal motion, collection of data at low temperature results in a large increase in the number of observed data points (as opposed to unobserved data points in which the peak height is indistinguishable from the backgrounds). This is advantageous both in determining the trial structure and in refining the parameters obtained for the trial structure. In the case of decomposition, the kinetic processes resulting in decomposition can be slowed to the point that data is not affected. Problems which may arise in attempting to collect low temperature data are weakening of the crystal from thermal shock and phase transitions caused by the change in temperature.

Possibly the most dramatic changes have come in the evolution of mathematical methods for solving crystal structures. Highly automatic computer programs such as MULTAN[2] can start with the reduced x-ray data along with basic input parameters and produce a line printer plot of the molecule. In some cases, this process requires little or no operator intervention. Further developments such as the use of quartet relationships among phases[3] and the magic integer representation of phases[4] have shown the potential of being even more powerful than the present techniques. Structures having between

100 and 200 non-hydrogen atoms are now being attempted using these methods.

Computing power has steadily increased at the University of Oklahoma from the IBM 1620 to the current machine which is the IBM 370/158 having two million bytes of core memory. Computer programs requiring hours on the 1620 require only minutes on the 370. The result is that structure solutions restricted by large requirements of computer time and memory may now be determined and refined.

The way in which these factors have influenced the structure determination of natural products can be seen in the increased number of structures reported each year. Not only has the number of reported structures increased but the complexity of the structures attempted has also increased. In addition the former requirement of a heavy atom derivative for solving structures is no longer essential.

Determination of Absolute Configuration

Because most natural products contain asymmetric carbon atoms it is desirable to determine the absolute configuration of the molecule as well as the gross chemical structure. In x-ray crystallography this is normally accomplished through consideration of the anomalous scattering of a heavy atom in the compound.[5] The introduction of a heavy atom such as bromine, iodine, etc. is effected by making appropriate derivatives of the natural product. Although the presence of a heavy atom facilitates the structure solution it is objectionable because the accuracy of the light atom locations is decreased and the process of synthesizing the derivative may alter the structure of the natural product. There-

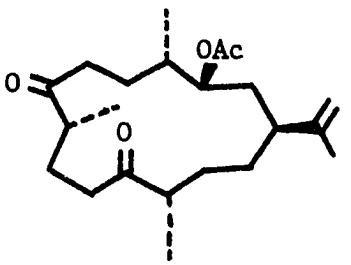
fore, in recent years a number of researchers have begun developing methods for determining absolute configurations based only on the anomalous dispersion of oxygen (and sometimes carbon).[6] Because the effect for these atoms is very small (usually of the magnitude of one or two times the standard deviation of the measurement for CuK_{α} radiation) accurate values for the intensities must be obtained. This can be accomplished by multiple determinations and subsequent averaging. Even so the errors within the sets of measurements lead to discrepencies such that typically 75-80% of the observations indicate one absolute configuration and the remainder indicate the opposite absolute configuration. Since this method involves the measurement of Friedel pairs of reflections, instead of the Hamilton R test,[7] the reflections must be selected so that only those most sensitive to changes in enantiomorph are used. One of the most important factors in determining absolute configuration is the recognition of the enantiomorph sensitive reflections. The method may be improved by determining a better set of criteria for recognizing the enantiomorph sensitive reflections.

Another factor for improving the ability to determine absolute configuration is the correct choice of radiation. The normal radiation is CuK_{α} having anomalous scattering factors of $\Delta f' = 0.047$ and $\Delta f'' = 0.032$ for oxygen atoms. On the other hand CrK_{α} radiation has values for oxygen atoms of $\Delta f' = 0.090$ and $\Delta f'' = 0.073$. The disadvantage is that because CrK_{α} radiation has a longer wavelength the number of accessible reflections is smaller. For example, on

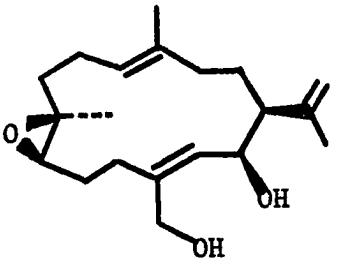
the Nonius CAD-4 diffractometer the largest theta value allowed by the instrument is 75°. Therefore when using CrK_{α} radiation only those reflections can be measured which have $\theta < 41°$ when using CuK_{α} radiation. This limitation will in general be outweighed by the increase in $\Delta f''$ when using CrK_{α} radiation so that one can expect agreement of perhaps 95% or better.

Biogenetic Implications of the Known Cembrene Structures

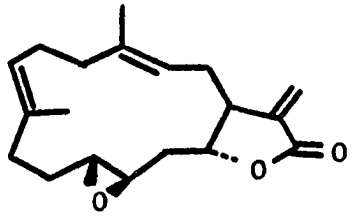
A total of ten structures of marine cembranes have been determined using x-ray crystallography.[8-17] Eight of these have been solved in this laboratory. A summary of these ten compounds is given in table 1. One of the most interesting features is the relationships among these compounds. For example, all ten compounds can be derived from cembrene by various oxygenation reactions. One can then imagine various pathways in which cembrene is converted to a final product with a variety of intermediate structures. Such a biogenetic pathway may be a part of the evolutionary process by which the gorgonian adapts to defend itself against the environment. Figure 1 shows a possible pathway by which eunicin (VII) might have been generated from cembrene. The first step involves oxygenation at an allylic position. Step two is the epoxide formation resulting in a compound quite similar in level of development to 320(III). This is followed by formation of the lactone at which point a number of possibilities exist. The lactone may be cis or trans for which V, VI, VII and VIII are examples of the former and IV, IX are examples of



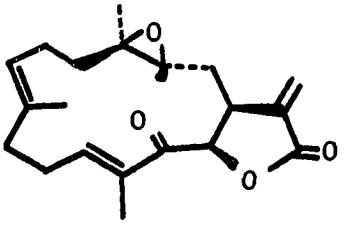
II
B-1 ACETATE[8]



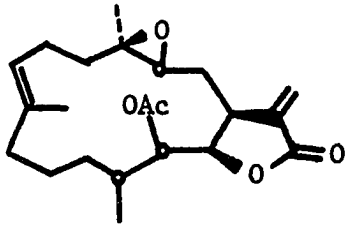
III
"320"[9]



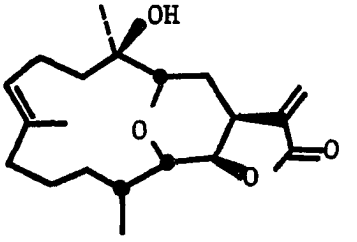
IV
LOBOPHYTOLIDE[10]



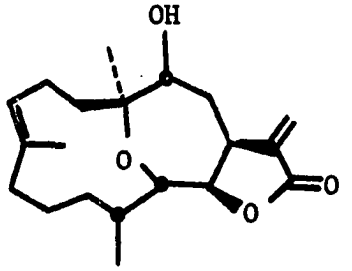
V
PEUNICIN[11]



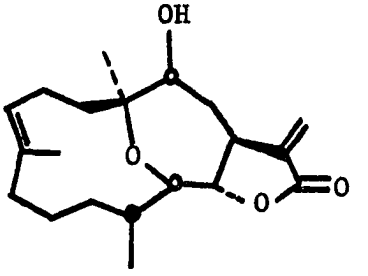
VI
EUPALMERIN ACETATE[12]



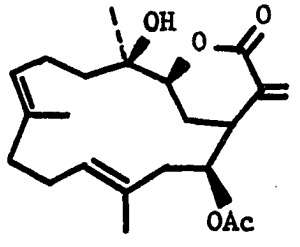
VII
EUNICIN[13]



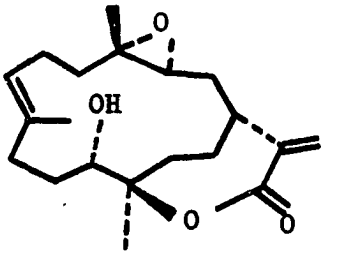
VIII
JEUNICIN[14]



IX
"ISO-JEUNICIN"[15]



X
CRASSIN ACETATE[16]



XI
SINULARIOLIDE[17]

Table 1. Summary of the x-ray structures of cembrane type molecules

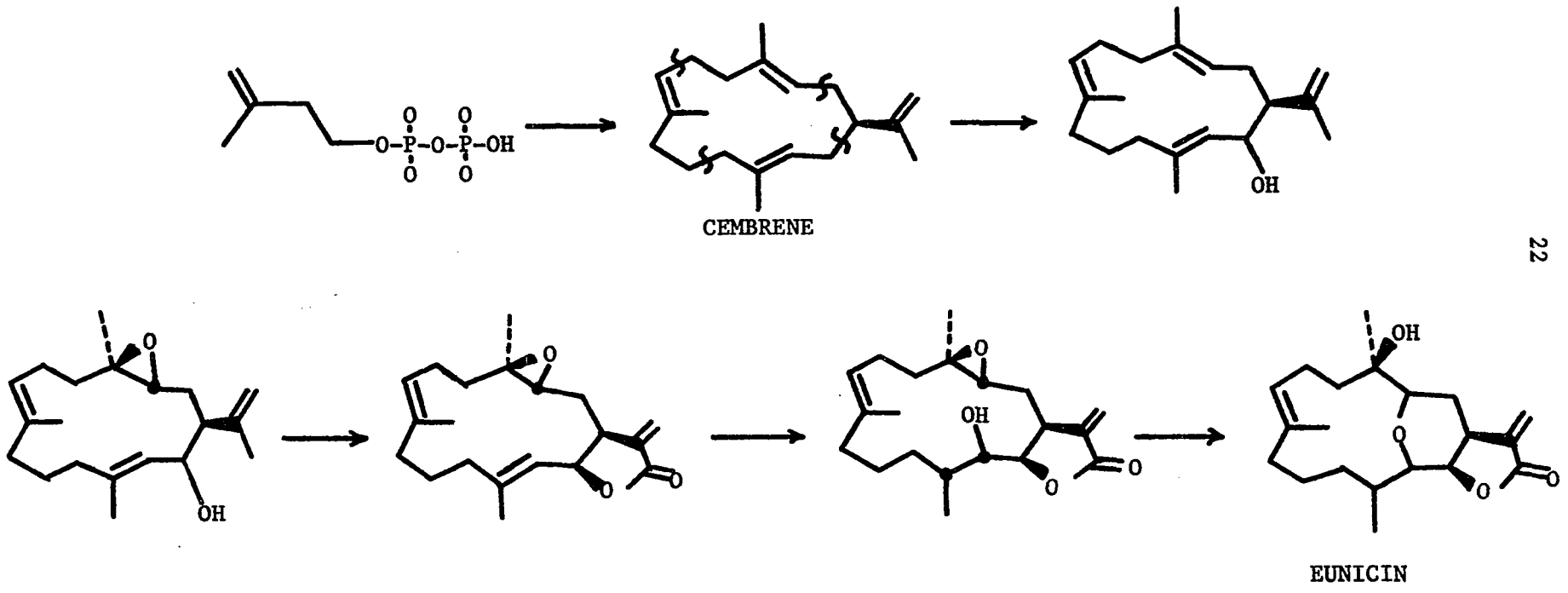


Figure 1. Possible pathway for the conversion of cembrene to eunicin.

the latter. In addition the γ-lactone is most common but a δ-lactone is observed for X and a ε-lactone is found in XI. The next to last step is oxygen addition at another double bond resulting in a compound differing from eupalmerin acetate (VI) only in configuration at two asymmetric carbon atoms. This suggests the possible existence of an "iso" eupalmerin acetate. The final step is the bridging of the fourteen membered ring to form the ether group and the final product. If the bridging had occurred in such a way as to form a seven-membered ring the product would be jeunicin (VIII). One may therefore conclude that eunicin (VII) and jeunicin (VIII) are very closely related and share a common precursor. The existence of eupalmerin acetate (VI) may suggest the possibility of an "iso" eunicin and another "iso" jeunicin which are consistent with the stereochemistry of VI. The task of proving such a biogenetic pathway is awesome. To find all of the missing links may not be possible because these compounds may no longer exist. A laboratory simulation may be difficult because most of the reactions are enzymatically catalyzed. Nonetheless such speculation is reasonable and further determinations of structures may contribute to the overall picture of biogenetic development.

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1,4,4aα,4bβ,5,8aβ,9aα-OCTAHYDRO-*anti*,*anti*-10,11-DI-*t*-BUTOXY-1,4:5,8-DIMETHANOFLUORENE-9-ONE, $C_{23}H_{32}O_3$

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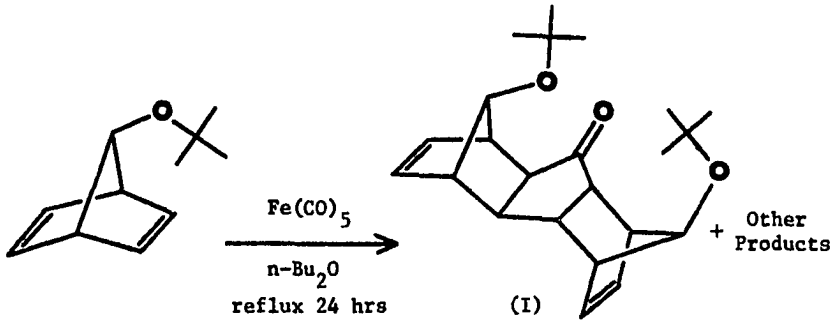
Norman, Oklahoma, 73069, USA

Preliminary information. In an effort to elucidate the mechanism of iron carbonyl induced coupling of strained olefins with carbon monoxide the following reaction was carried out (Marchand, Hayes, van der Helm, Neely).

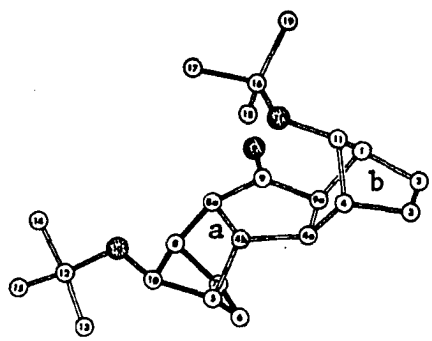


(I)

The title compound (I) was isolated from the reaction mixture as a white crystalline solid, m.p. 95-6°C (uncorr.). The structure determination of (I) was undertaken to confirm the structure and its stereochemistry.

Crystal data. (All data collected on a Nonius CAD-4 automatic diffractometer, CuK_α=1.5418Å) $C_{23}H_{32}O_3$, F.W.=356.5, space group=Pbcn (No.60) with a=29.248(1), b=12.2059(5), c=11.6621(6)Å, V=4163.3Å^3, Z=8, D_{calc}= 1.137g cm^{-3}.

Intensity data, structure determination and refinement. Intensity data were measured on a Nonius CAD-4 automatic diffractometer using CuK_α radiation (λ=1.5418Å). All 3538 independent reflections with $\theta<65^o$ were measured of which 416 were considered indistinguishable from the background having $I<1.4\sigma(I)$. The data were corrected for Lorentz and polarization effects but absorption corrections were not applied. The structure was solved by direct methods using the program MULTAN (Germain, Main and Woolfson, 1971). All hydrogen atoms were located from a difference Fourier based on the refined positions of the carbon and oxygen atoms. All atoms were included in the refinement with carbon and oxygen atoms given anisotropic temperature factors. The final unweighted R value for all data is 0.057.



Atomic coordinates ($x/a \times 10^5$, y/b and $z/c \times 10^4$) for carbon and oxygen atoms. Standard deviations for last digit in parentheses.

	x/a(σ)	y/b(σ)	z/c(σ)		x/a(σ)	y/b(σ)	z/c(σ)
C(1)	36431(6)	5532(1)	-1416(1)	C(10)	44490(5)	1776(1)	0702(2)
C(2)	36292(7)	6570(1)	-0711(2)	C(11)	32429(5)	4926(1)	-0854(1)
C(3)	34999(7)	6303(1)	0341(2)	C(12)	40502(7)	0124(1)	1380(2)
C(4)	34293(5)	5080(1)	0374(1)	C(13)	40619(11)	0492(2)	2628(2)
C(4a)	39179(5)	4568(1)	0294(1)	C(14)	35902(9)	-0399(2)	1068(3)
C(4b)	39543(5)	3309(1)	0414(1)	C(15)	44335(10)	-0665(2)	1137(2)
C(5)	43436(5)	2907(1)	1231(1)	C(16)	27628(6)	3321(2)	-1227(2)
C(6)	47748(6)	3495(1)	0910(2)	C(17)	28611(8)	2152(2)	-1553(3)
C(7)	49088(5)	3121(2)	-0108(2)	C(18)	25534(8)	3386(2)	-0036(2)
C(8)	45709(5)	2257(1)	-0476(1)	C(19)	24592(8)	3839(2)	-2143(3)
C(8a)	41072(5)	2842(1)	-0756(1)	O(9)	42690(5)	3721(1)	-2560(1)
C(9)	41537(5)	3796(1)	-1556(1)	O(10)	40720(4)	1051(1)	0619(1)
C(9a)	40608(5)	4864(1)	-0951(1)	O(11)	32094(3)	3836(1)	-1254(1)

Anisotropic thermal parameters ($x10^4$) for carbon and oxygen atoms. The anisotropic temperature factors are expressed in the form:

$$\exp\left[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)\right]$$

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	555(9)	369(8)	461(9)	5(7)	-40(7)	93(7)
C(2)	702(13)	335(8)	781(12)	17(8)	-84(10)	34(8)
C(3)	706(13)	387(8)	704(12)	126(8)	-87(10)	-128(8)
C(4)	498(9)	392(8)	455(8)	74(7)	41(7)	-18(7)
C(4a)	425(9)	373(8)	393(8)	6(6)	-33(7)	-32(6)
C(4b)	368(9)	374(8)	371(8)	23(6)	-11(6)	9(6)
C(5)	451(9)	507(9)	397(8)	53(7)	-46(7)	43(7)
C(6)	442(9)	567(11)	630(11)	-18(8)	-136(8)	26(9)
C(7)	360(9)	621(11)	692(11)	17(7)	-10(8)	91(9)
C(8)	429(9)	457(8)	531(9)	99(7)	22(7)	9(8)
C(8a)	390(9)	390(8)	418(8)	44(6)	-14(6)	-36(6)
C(9)	438(9)	536(9)	386(8)	90(7)	5(7)	18(7)
C(9a)	416(9)	406(8)	426(8)	-48(6)	6(6)	52(6)
C(10)	416(9)	472(8)	614(10)	71(7)	-56(8)	90(8)
C(11)	425(9)	361(8)	506(8)	70(6)	-30(6)	6(7)
C(12)	732(13)	408(9)	641(12)	91(8)	143(10)	106(8)
C(13)	1469(26)	782(16)	717(15)	-1(16)	277(16)	73(13)
C(14)	919(17)	602(12)	1288(22)	-174(13)	264(16)	65(14)
C(15)	1096(17)	581(12)	1122(19)	339(13)	283(16)	180(13)
C(16)	416(9)	522(10)	833(12)	-77(7)	4(9)	-65(9)
C(17)	676(13)	523(11)	1566(25)	-174(10)	48(15)	-171(14)
C(18)	689(13)	1117(20)	1197(21)	-327(14)	346(15)	-94(17)
C(19)	676(13)	883(17)	1497(25)	-47(13)	-513(16)	-102(16)
O(9)	984(9)	812(9)	390(6)	303(8)	148(7)	71(6)
O(10)	524(9)	432(6)	826(9)	6(5)	-82(6)	176(6)
O(11)	364(4)	386(5)	587(7)	0(5)	-19(5)	-43(5)

Atomic coordinates (x/a $x10^4$, y/b and z/c $x10^3$) and isotropic temperature factors ($Å^2$) for hydrogen atoms.

	x/a(σ)	y/b(σ)	z/c(σ)	B(σ)		x/a(σ)	y/b(σ)	z/c(σ)	B(σ)
H(1)	3627(5)	563(1)	-224(1)	3.2(3)	H(13)C	4019(9)	-18(2)	310(2)	9.6(7)
H(2)	3727(6)	731(1)	-102(2)	5.4(4)	H(14)A	3310(7)	13(2)	120(2)	8.8(6)
H(3)	3483(6)	679(2)	102(1)	5.5(4)	H(14)B	3609(8)	-68(2)	24(2)	9.9(7)
H(4)	3242(5)	480(1)	93(1)	4.0(4)	H(14)C	3537(9)	-102(2)	151(2)	9.5(7)
H(4a)	4121(5)	495(1)	79(1)	4.3(4)	H(15)A	4432(8)	-81(2)	32(2)	8.2(6)
H(4b)	3649(5)	297(1)	70(1)	2.9(3)	H(15)B	4388(8)	-137(2)	166(2)	8.4(6)
H(5)	4268(5)	291(1)	202(1)	4.2(4)	H(15)C	4783(9)	-32(2)	125(2)	12.0(8)
H(6)	4905(7)	409(2)	134(2)	6.1(5)	H(17)A	2595(7)	174(2)	-166(2)	7.5(5)
H(7)	5160(6)	336(2)	-59(2)	6.3(5)	H(17)B	3041(7)	179(2)	-89(2)	7.2(5)
H(8)	4671(5)	173(1)	-108(1)	3.7(3)	H(17)C	3072(9)	209(2)	-224(2)	10.2(7)
H(8a)	3883(5)	232(1)	-107(1)	3.8(3)	H(18)A	2283(7)	299(2)	-7(2)	9.2(7)
H(9a)	4335(5)	527(1)	-104(1)	3.9(3)	H(18)B	2810(8)	306(2)	62(2)	10.2(7)
H(10)	4728(6)	144(1)	102(1)	5.2(4)	H(18)C	2484(10)	417(2)	19(2)	10.6(7)

Atomic coordinates and temperature factors for hydrogen atoms (cont.)

H(11)	2950(5)	532(1)	-99(1)	3.4(3)	H(19)A	2174(8)	339(2)	-210(2)	9.1(7)
H(13)A	4373(7)	89(2)	283(2)	7.1(5)	H(19)B	2392(10)	461(2)	-197(2)	11.4(8)
H(13)B	3803(8)	104(2)	276(2)	9.4(7)	H(19)C	2611(9)	382(2)	-306(2)	10.6(8)

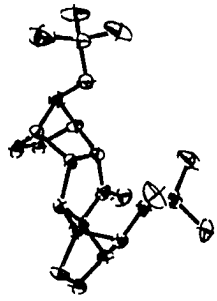
Bond distances (Å) involving non-hydrogen atoms.

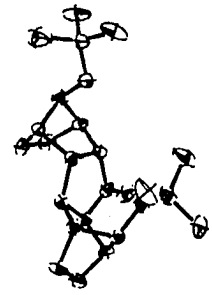
C(2)-C(3)	1.324(3)	C(8a)-C(9)	1.499(2)	C(9)-O(9)	1.222(2)
C(6)-C(7)	1.331(3)	C(9a)-C(9)	1.507(2)		
				C(4a)-C(9a)	1.552(2)
C(1)-C(9a)	1.566(2)	C(1)-C(11)	1.532(2)	C(4b)-C(8a)	1.545(2)
C(8)-C(8a)	1.567(2)	C(8)-C(10)	1.535(2)	C(4a)-C(4b)	1.547(2)
C(4)-C(4a)	1.562(2)	C(4)-C(11)	1.544(2)		
C(5)-C(4b)	1.564(2)	C(5)-C(10)	1.543(2)	C(12)-C(13)	1.525(3)
				C(12)-C(14)	1.533(3)
C(1)-C(2)	1.510(2)	C(10)-O(10)	1.417(2)	C(12)-C(15)	1.505(3)
C(3)-C(4)	1.508(2)	C(11)-O(11)	1.413(2)	C(16)-C(17)	1.504(3)
C(5)-C(6)	1.499(2)			C(16)-C(18)	1.520(3)
C(7)-C(8)	1.508(2)	C(12)-O(10)	1.440(2)	C(16)-C(19)	1.526(3)
		C(16)-O(11)	1.450(2)		

Bond angles involving non-hydrogen atoms. Standard deviations are between 0.1 and 0.2°.

C(2)-C(1)-C(9a)	105.6	C(5)-C(6)-C(7)	107.8	C(10)-O(10)-C(12)	118.9
C(2)-C(1)-C(11)	98.7	C(6)-C(7)-C(8)	107.6	C(1)-C(11)-C(4)	93.9
C(9a)-C(1)-C(11)	101.3	C(7)-C(8)-C(8a)	108.0	C(1)-C(11)-O(11)	111.5
C(1)-C(2)-C(3)	107.8	C(7)-C(8)-C(10)	99.5	C(4)-C(11)-O(11)	116.4
C(2)-C(3)-C(4)	107.8	C(8a)-C(8)-C(10)	99.2	C(11)-O(11)-C(16)	117.6
C(3)-C(4)-C(4a)	105.6	C(4b)-C(8a)-C(8)	103.6	O(10)-C(12)-C(13)	110.9
C(3)-C(4)-C(11)	98.3	C(4b)-C(8a)-C(9)	106.8	O(10)-C(12)-C(14)	102.7
C(4a)-C(4)-C(11)	102.7	C(8)-C(8a)-C(9)	113.9	O(10)-C(12)-C(15)	110.8
C(4)-C(4a)-C(4b)	117.0	C(8a)-C(9)-C(9a)	111.4	C(13)-C(12)-C(14)	111.7
C(4)-C(4a)-C(9a)	102.1	C(8a)-C(9)-O(9)	124.3	C(13)-C(12)-C(15)	110.6
C(4b)-C(4a)-C(9a)	107.3	C(9a)-C(9)-O(9)	124.3	C(14)-C(12)-C(15)	110.0
C(4a)-C(4b)-C(5)	114.7	C(1)-C(9a)-C(4a)	103.6	O(11)-C(16)-C(17)	103.5
C(4a)-C(4b)-C(8a)	107.9	C(1)-C(9a)-C(9)	115.4	O(11)-C(16)-C(18)	111.1
C(5)-C(4b)-C(8a)	102.2	C(4a)-C(9a)-C(9)	106.6	O(11)-C(16)-C(19)	109.2
C(4b)-C(5)-C(6)	108.0	C(5)-C(10)-C(8)	93.6	C(17)-C(16)-C(18)	111.0
C(4b)-C(5)-C(10)	100.5	C(5)-C(10)-O(10)	115.5	C(17)-C(16)-C(19)	109.1
C(6)-C(5)-C(10)	99.2	C(8)-C(10)-O(10)	111.0	C(18)-C(16)-C(19)	112.5

Comments. The structure contains a five-membered ring(C(4a)-C(4b)-C(8a)-C(9)-C(9a)) which is very nearly planar. The distances from the least-squares plane calculated through these five atoms and the carbonyl oxygen (O(9)) are -0.017,-0.002,0.015,-0.011,0.024 and -0.009 Å respectively. This is not unexpected because the constraints of the norbornene rings require





the torsion angles C(5) - C(4b) - C(8a) - C(8) and C(1) - C(9a) - C(4a) - C(4) to be close to 0°. This in turn forces the five bonds of the five-membered ring to be co-planar. The two norbornene rings are attached to this five-membered ring in an anti-arrangement. A great deal of strain is present in the molecule which is evident in the lengthening of the four carbon-carbon single bonds attached directly to the five-membered ring. In addition, large deviations from the expected bond angle of 109.5° for a tetrahedral carbon are observed. The range of the C-H bond lengths is from 0.92(2) Å to 1.16(3) Å with the average distance being 1.00 Å. It is interesting to note that there is a systematic difference in the bond lengths of C(10) - O(10) and C(11) - O(11) as one type, and C(12)-O(10) and C(16) - O(11) as the other kind. This is probably correlated with the small bond angles C(5) - C(10) - C(8) and C(1) - C(11) - C(4), giving for the sp^3 hybridization of C(10) and C(11) a larger than normal amount of s-character to the C(10) - O(10) and C(11) - O(11) bonds and thus shortening these two bonds.

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Marchand, A.P., Hayes, R.R., van der Helm, D. and Neely, S.C. To be published.

Received: 25 February 1975

anti,anti,anti-13,14,15-TRI(1,1-DIMETHYLETHOXY)-1,4:

6,12:7,10-TRIMETHANO-1,4,4aα,5aβ,6,6aβ,6bα,7,

10,10aα,11aβ,12,12aβ,12bα-TETRADECAHYDROINDENO

[1,2-b]FLUOREN-5,11-DIONE.

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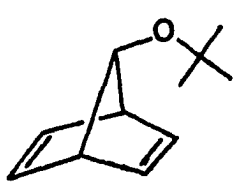
Norman, Oklahoma, 73069, USA

Preliminary information. As part of a general investigation of the mechanism of iron carbonyl induced coupling of strained olefins with carbon monoxide the following reaction was carried out (Marchand, Hayes, van der-Helm, Neely).



$\xrightarrow[\text{n-Bu}_2\text{O}]{\text{Fe(CO)}_5}$
reflux 24 hrs

I Cage Dimer

II Linear Dimer Ketone

III Linear Trimer Diketone

IV Cyclic Trimer Ketone

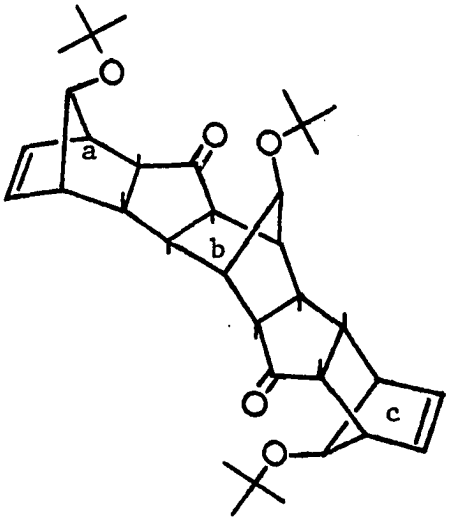
V Teloner

The title compound (III) was isolated from the reaction mixture as a white crystalline solid, m.p. 226-227°C (uncorr.). The structures of I (Neely, van der Helm, Marchand and Hayes, 1976) and II (Ealick and van der Helm, 1975) have been published while the structure of III is reported here.

Crystal data. (All data collected on a Nonius CAD-4 automatic diffractometer, CuKα=1.5418Å) $C_{35}H_{48}O_5$, F.W.=548.73, space group=$P2_{1/c}$ (No. 14),

$a=10.5378(8)$, $b=27.084(3)$, $c=12.7897(6)\mathring{A}$ and $\beta=120.928(5)°$, $V=3131.2\mathring{A}^3$ $Z=4$, $\rho_{calc}=1.164 g\cdot cm^{-3}$.

Intensity data, structure determination and refinement. Large single crystals of III were obtained by slow evaporation from acetone. The crystal used for the diffraction experiment was cut to a more suitable size (.52x.26x.17mm) from one of the larger crystals. Crystallographic data and integrated x-ray intensity data were collected using a Nonius CAD-4 automatic diffractometer. The 6520 data comprising all reflections with $2\theta<150°$ were measured using θ-2θ scan techniques. The scan width was calculated as $(1.1+0.11\ \tan\theta)°$. A variable receiving aperture was used with a horizontal width of $(4.0+0.86\ \tan\theta)$mm and a constant height of 6.0mm. The maximum scan time spent on each reflection was 60s with 40s used for scanning the peak and 10s used for scanning each the left and right backgrounds. A total of 401 reflections were considered indistinguishable from the background having $I\leq 2\sigma(I)$ and were assigned an intensity equal to 1.4 times the total count.



The structure was determined using direct methods and the program MULTAN (Germain, Main and Woolfson, 1971). The structure was refined using block-diagonal least-squares methods (Ahmed, 1966) in which the quantity $\Sigma w_F(kF_o-F_c)^2$ was minimized. Hydrogen atoms were located in a difference Fourier map and were refined with isotropic temperature factors. All carbon and oxygen atoms were refined with anisotropic temperature factors. The $R(\Sigma|kFo-Fc|/\Sigma|kFo|)$ based on the final parameters

is 0.068 for all data. Atomic scattering factors for C and O atoms were taken from the International Tables for X-ray Crystallography and those for H atoms from Stewart, Davidson and Simpson (1965). A final difference Fourier map showed no peaks larger than 0.2 e.A^{-3}. In the structure factor analysis the value of $w_F \Delta F^2$ did not show a significant variation with either $|Fo|$ or $\sin\theta/\lambda$, thus validating the weighting scheme which was used.

Positional parameters for carbon and oxygen atoms. Estimated standard deviations are listed in parentheses. ($x,z \times 10^4$, $y \times 10^5$)

	x	y	z
C(1)	7099(2)	13193(6)	1185(2)
C(2)	6575(2)	13110(8)	2529(2)
C(3)	5948(2)	17402(8)	2995(2)
C(4)	6029(2)	20530(7)	1985(1)
C(4a)	4961(2)	18106(6)	1624(1)
C(5)	4884(2)	20715(6)	0602(1)
C(5a)	5342(2)	17305(5)	0472(1)
C(6)	4040(2)	15560(5)	0617(1)
C(6a)	4739(2)	12780(5)	1848(1)
C(6b)	3712(2)	11416(5)	2341(1)
C(7)	4410(2)	12317(6)	3743(1)
C(8)	5913(2)	09915(7)	4383(2)
C(9)	5726(2)	05078(7)	4282(2)
C(10)	4091(2)	04076(6)	3578(2)
C(10a)	3472(2)	05770(6)	2232(1)
C(11)	4352(2)	03779(6)	1695(1)
C(11a)	5239(2)	07856(5)	1542(1)
C(12)	4868(2)	08514(5)	0219(1)
C(12a)	5894(2)	12438(5)	0180(1)
C(12b)	5667(2)	12998(6)	-1112(1)
C(13)	7535(2)	18676(7)	-0940(1)
C(14)	3411(2)	11404(5)	-0336(1)
C(15)	3573(2)	08406(6)	4049(1)
C(16)	8987(2)	24114(6)	0810(2)
C(17)	8488(3)	28670(8)	0012(2)
C(18)	0495(2)	22354(10)	1086(2)
C(19)	9000(2)	25117(8)	1985(2)
C(20)	1158(2)	06455(7)	-1459(2)
C(21)	0208(2)	10290(9)	-2405(2)
C(22)	1905(2)	03061(8)	-1933(2)
C(23)	0233(2)	03434(9)	-1095(2)
C(24)	1310(2)	10405(7)	4039(2)
C(25)	1903(3)	15397(10)	4627(3)
C(26)	1485(3)	06489(13)	4950(2)
C(27)	-0305(2)	10814(8)	3044(2)

Positional parameters for carbon and oxygen atoms (cont.)

O(5)	4459(2)	24902(5)	-0663(1)
O(11)	4374(2)	-00521(4)	1441(1)
O(13)	7909(1)	20176(4)	0248(1)
O(14)	2232(1)	08881(4)	-0334(1)
O(15)	2017(1)	08840(5)	3394(1)

Anisotropic temperature factors and standard deviations (x 10^4) for carbon and oxygen atoms. Temperature factors are of the form $\exp(-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+U_{12}hka^*b^*+U_{13}kla^*c^*+U_{23}klb^*c^*))$.

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	471(9)	539(11)	474(9)	- 69(7)	335(8)	- 71(8)
C(2)	626(12)	743(11)	520(10)	-185(10)	429(8)	-157(9)
C(3)	618(11)	847(15)	399(9)	-213(11)	326(9)	- 44(9)
C(4)	556(10)	539(11)	423(9)	-105(8)	297(8)	45(8)
C(4a)	449(9)	450(7)	393(8)	- 60(7)	243(7)	27(7)
C(5)	525(10)	353(7)	502(9)	- 47(7)	324(8)	31(7)
C(5a)	452(8)	301(7)	409(8)	- 35(6)	278(7)	- 19(6)
C(6)	421(8)	290(7)	413(8)	18(6)	278(7)	2(6)
C(6a)	433(8)	305(7)	374(8)	- 8(6)	264(7)	- 21(6)
C(6b)	447(8)	316(7)	369(7)	11(6)	274(7)	- 8(6)
C(7)	515(10)	439(7)	385(9)	- 29(7)	288(8)	- 47(7)
C(8)	488(10)	728(11)	401(9)	- 17(9)	261(8)	40(8)
C(9)	588(11)	673(11)	491(10)	194(9)	335(9)	208(9)
C(10)	659(11)	398(7)	499(10)	32(8)	411(10)	82(8)
C(10a)	526(9)	331(7)	420(9)	- 24(7)	329(8)	- 7(6)
C(11)	679(11)	312(7)	485(9)	45(7)	416(9)	32(7)
C(11a)	437(8)	316(7)	400(8)	56(6)	275(7)	39(6)
C(12)	407(8)	290(7)	390(8)	6(6)	272(7)	- 16(6)
C(12a)	383(7)	353(7)	368(7)	- 11(6)	244(7)	- 17(6)
C(12b)	415(8)	416(7)	385(8)	- 68(6)	264(7)	- 41(6)
C(13)	477(9)	583(11)	427(9)	-137(8)	306(8)	- 59(8)
C(14)	384(7)	320(7)	378(7)	- 19(6)	258(7)	6(6)
C(15)	505(10)	528(11)	368(8)	4(7)	290(8)	- 5(7)
C(16)	484(10)	465(11)	554(10)	-113(7)	290(9)	- 84(8)
C(17)	1094(19)	513(11)	823(16)	-207(12)	521(15)	5(11)
C(18)	518(12)	1081(19)	845(16)	-156(12)	369(12)	-266(14)
C(19)	730(13)	613(11)	599(13)	-135(11)	375(11)	-192(10)
C(20)	416(9)	531(11)	469(10)	-100(7)	228(8)	- 17(8)
C(21)	538(12)	870(15)	706(14)	- 12(11)	185(11)	166(13)
C(22)	688(13)	661(11)	634(13)	-203(11)	361(11)	-264(11)
C(23)	623(13)	910(15)	771(15)	-331(12)	404(12)	- 57(13)
C(24)	523(10)	665(11)	503(10)	56(9)	337(9)	- 35(9)
C(25)	617(14)	1055(22)	1046(21)	66(14)	263(14)	-568(17)
C(26)	791(17)	1709(30)	841(18)	199(18)	590(15)	485(19)
C(27)	500(11)	721(15)	781(15)	- 22(10)	303(11)	- 64(11)
O(5)	1117(12)	353(7)	829(10)	125(7)	668(10)	129(7)

Anisotropic temperature factors and standard deviations (x 10^4) for carbon and oxygen atoms (cont.)

O(11)	1263(13)	290(7)	1023(12)	7(7)	922(11)	- 25(7)
O(13)	491(7)	513(7)	417(6)	-151(6)	280(6)	- 79(5)
O(14)	414(6)	450(7)	421(6)	- 81(5)	283(5)	- 29(5)
O(15)	486(7)	773(7)	403(6)	- 35(6)	289(6)	- 65(6)

Positional parameters and isotropic temperature factors ($Å^2$) for hydrogen atoms (x,z x 10^3, y x 10^4). Standard deviations are listed in parentheses. Each hydrogen atom is given the number of the carbon atom to which it is attached.

	x	y	z	B
H(1)	786(2)	1079(6)	- 62(2)	4.3(4)
H(2)	665(2)	1009(7)	-296(2)	6.3(5)
H(3)	548(2)	1867(7)	-381(2)	5.7(5)
H(4)	582(2)	2417(6)	-215(2)	4.2(4)
H(4a)	391(2)	1799(6)	-233(2)	4.0(4)
H(5a)	613(2)	1900(6)	125(1)	3.9(4)
H96)	334(2)	1819(6)	53(1)	3.6(4)
H(6a)	563(2)	1469(5)	251(1)	3.0(3)
H(6b)	276(2)	1326(5)	191(1)	2.9(3)
H(7)	439(2)	1589(6)	394(2)	4.4(4)
H(8)	684(2)	1164(7)	474(2)	5.5(5)
H(9)	653(2)	280(7)	457(2)	5.3(5)
H(10)	375(2)	72(7)	363(2)	4.8(4)
H(10a)	241(2)	493(6)	171(1)	3.4(4)
H(11a)	629(2)	715(5)	212(1)	2.8(3)
H(12)	486(2)	547(6)	- 19(1)	3.2(3)
H(12a)	695(2)	1173(6)	76(1)	3.1(3)
H(12b)	504(2)	1036(6)	-163(1)	3.5(4)
H(13)	837(2)	1953(6)	-110(1)	3.6(4)
H(14)	308(2)	1267(5)	-118(1)	2.2(3)
H(15)	400(2)	818(6)	499(2)	3.6(4)
H(17A)	849(2)	2822(8)	- 74(2)	7.0(6)
H(17B)	744(3)	2958(9)	- 3(2)	9.2(7)
H(17C)	916(2)	3142(8)	43(2)	7.8(6)
H(18A)	126(2)	2483(8)	162(2)	7.9(6)
H(18B)	73(3)	1901(9)	154(2)	9.1(7)
H(18C)	55(2)	2178(8)	36(2)	7.2(6)
H(19A)	799(2)	2622(8)	181(2)	7.3(6)
H(19B)	926(2)	2203(8)	252(2)	6.8(6)
H(19C)	979(2)	2758(7)	247(2)	6.6(5)
H(21A)	86(3)	1230(8)	-264(2)	7.7(6)
H(21B)	- 56(2)	866(8)	-308(2)	8.2(7)
H(21C)	- 21(2)	1270(8)	-202(2)	7.1(6)
H(22A)	112(2)	150(8)	-265(2)	6.9(6)
H(22B)	254(2)	512(7)	-217(2)	6.4(5)
H(22C)	253(2)	44(8)	-127(2)	6.5(5)

Positional parameters and isotropic temperature factors ($Å^2$) for hydrogen atoms (cont.).

H(23A)	- 9(2)	544(8)	- 68(2)	7.6(6)
H(23B)	97(2)	82(8)	- 40(2)	7.2(6)
H(23C)	- 65(2)	180(7)	188(2)	6.1(5)
H(25A)	298(2)	1502(8)	529(2)	6.7(5)
H(25B)	137(3)	1636(10)	502(2)	10.4(8)
H(25C)	177(3)	1780(11)	400(3)	12.5(9)
H(26A)	81(3)	678(10)	520(3)	12.6(9)
H(26B)	250(3)	693(8)	564(2)	8.0(6)
H(26C)	121(3)	312(11)	443(3)	12.6(9)
H(27A)	70(1)	753(8)	261(1)	6.9(6)
H(27B)	44(2)	1348(8)	241(2)	7.1(6)
H(27C)	94(3)	1165(9)	343(2)	9.1(7)

Results. The right two-thirds of the molecule is stereochemically identical to the dimer ketone with the formation of III resulting from the addition of the left most 7-t-butoxynorbornadiene residue as viewed in the stereoview. The carbonyl groups are found to be in an anti-periplanar configuration (i.e. parallel but pointed in opposite directions) and all t-butoxy groups are approximately in the staggered configuration. The most interesting feature in the structure of III is the observed shortening of the C-O bond distances from the norbornane bridge atoms to the O atom of the t-butoxy group (C(13)-O(13), C(14)-O(14), C(15)-O(15)) compared to the C-O bond distances in the t-butoxy group (C(16)-O(13), C(20)-O(14), C(24)-O(15)). This shortening has also been observed in the crystal structures of the cage dimer (I) (Neely, et.al., 1976) and the dimer ketone (II) (Ealick and van der Helm, 1975) and can be labeled as a hybridization effect. A qualitative argument is that as the angle at the norbornane bridge decreases the p-character of those orbitals increases resulting in an increase in s-character in the orbital involved in the C-O bond. This increase in s-character can be directly associated with a decrease in the observed bond length. The bridge angles of the norbornane units are observed to be considerably smaller than 109.5°.

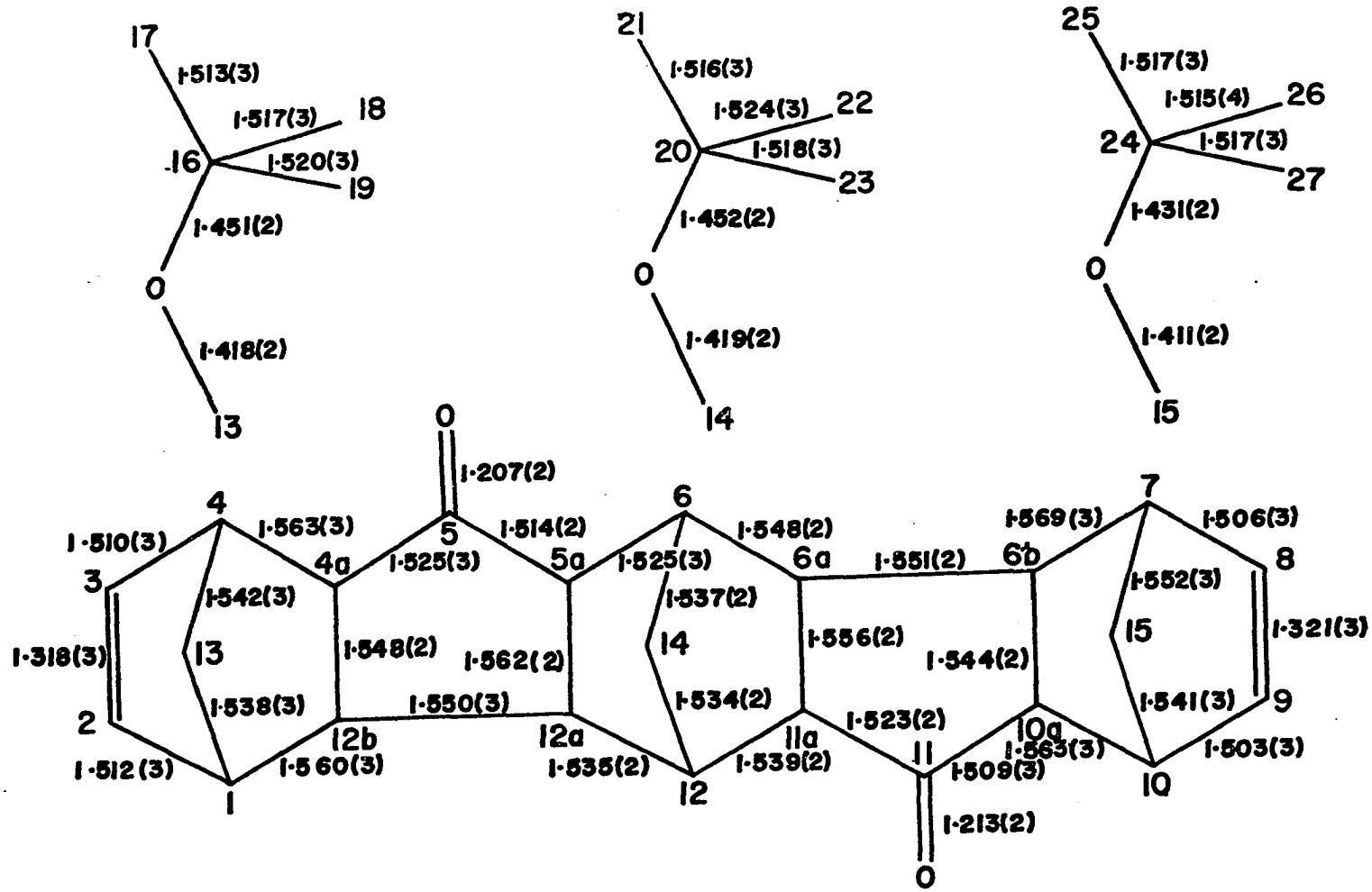
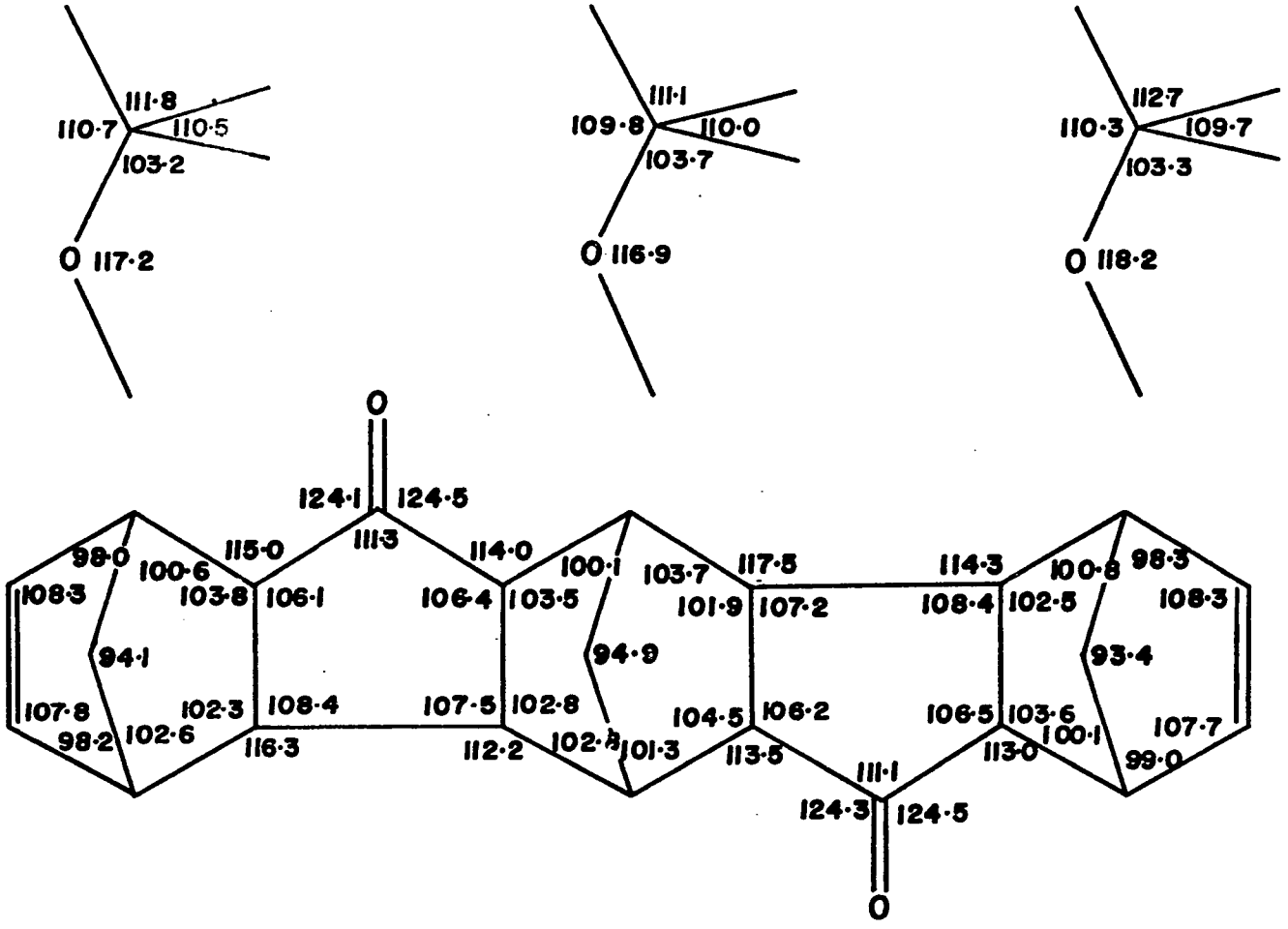


Figure 2. Bond distances for the trimer diketone.



C1-C2-C3=106·5	C5-C6-C7=106·4	C8-C9-C10=107·4
C18-C19-C20=105·6	C15-C16-C17=109·3	C11-C12-C13=107·9
C2-C21-O21=115·5	C6-C22-O22=111·8	C9-C23-O23=115·5
C19-C21-O21=112·6	C16-C22-O22=115·0	C12-C23-O23=111·6
O21-C24-C26=110·1	O22-C28-C30=111·6	O23-C32-C34=110·0
C25-C24-C27=110·2	C29-C28-C31=110·4	C33-C32-C35=110·5

Figure 3. Bond angles for the trimer diketone.

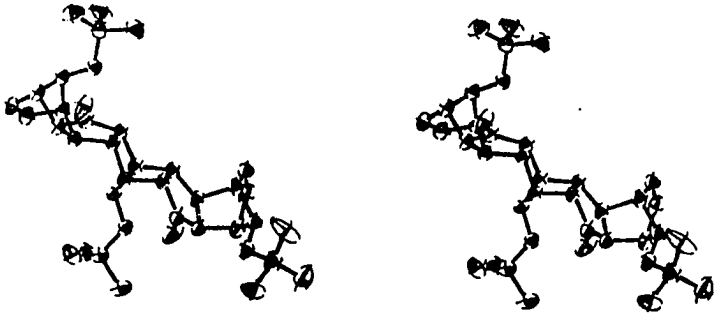


Figure 4. Stereoview of the trimer diketone.

In addition many other areas of strain are evident in the generally large deviations from the expected value of 109.5° for sp^3 hybridized atoms.

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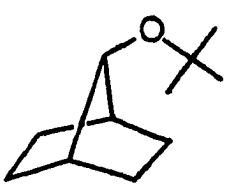
A SUMMARY OF THE CRYSTALLOGRAPHIC STUDIES OF THE REACTION PRODUCTS OF 7-t-BUTOXYNORBORNADIENE WITH IRON CARBONYL

Introduction

One of the research projects of Dr. A. P. Marchand is a study of the reactions of strained olefins with $Fe(CO)_5$. As a part of this study 7-t-butoxynorbornadiene was reacted with $Fe(CO)_5$ as shown below.



$\xrightarrow[n\text{-}Bu_2O]{Fe(CO)_5}$

reflux 24 hrs

I Cage Dimer
II Dimer Ketone
III Trimer Diketone
IV Cyclic Trimer Ketone
V Telomer

The details of this reaction and spectroscopic and chemical data for the products have been discussed in the dissertation of R. R. Hayes.[1] Because of the complexity of the NMR spectra of these compounds, assignment of molecular structure was not possible. Therefore an x-ray crystallographic study of I, II and III was undertaken.

The structure of the cage dimer, which has been previously reported,[2] is shown in Fig. 1. It should be pointed out that the observed structure is one of the three possible structures shown below.

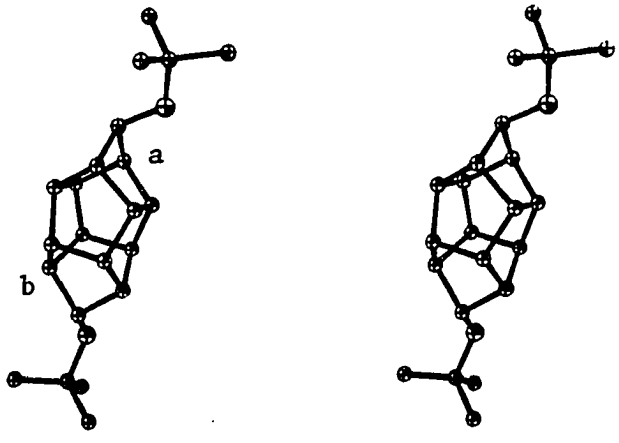
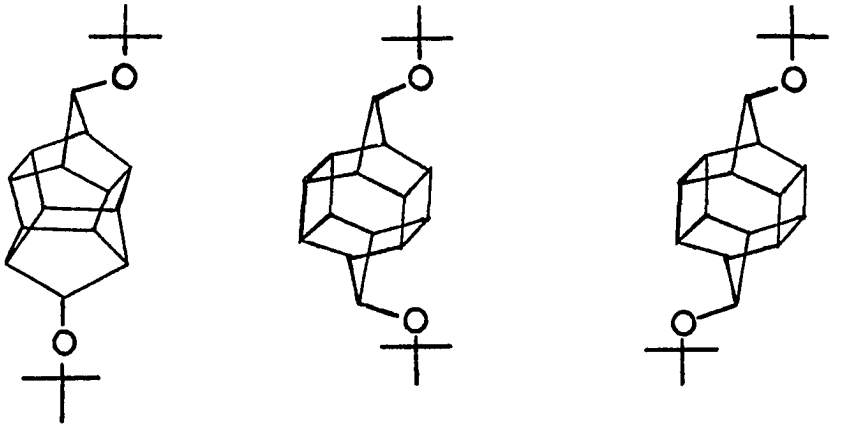


Figure 1. Stereoview of the cage dimer.



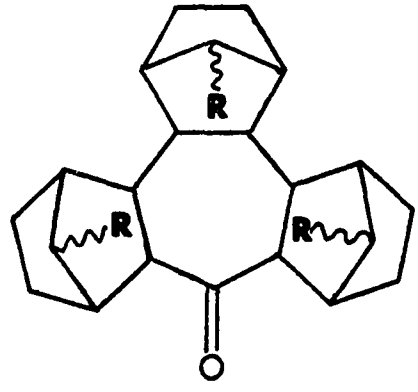
No detectable amount of either of the remaining two isomers was found in the reaction mixture.

The structure of II has been reported in a communication[3] and is discussed in Chapter 4 of this dissertation. The structure is linear with two 7-t-butoxynorbornadiene moieties joined by a cyclopentanone ring. In the case of the dimer ketone 2^5 or 32 possible isomers exist. These correspond to combinations of the possibilities of cis or trans fusion at the cyclopentanone ring, endo or exo conformation for each 7-t-butoxynorbornadiene group and the t-butoxy group being syn or anti for each group. The isomer observed as shown on page 26 can be described in these terms as syn-exo-trans-endo-syn going from left to right. The fact that only one out of 32 possible isomers is observed is an indication of the involvement of the iron atom in the stereospecific mechanism. Although the mechanism is still somewhat unclear the transition state probably involves the chelation of the iron atom to the double bond and possibly the oxygens in the t-butoxy groups.

The structure of III is reported in Chapter 5 of this dissertation. The trimer diketone is also linear in which two cyclopenta-

none groups join three 7-t-butoxynorbornadiene groups in an alternating fashion. In this case 2^{10} or 1024 possible isomers exist. These isomers correspond to the combinations of endo and exo for each of the three 7-t-butoxynorbornadiene groups, syn and anti for each of the three t-butoxy groups, cis and trans for the fusion about each cyclopentanone ring, cis or trans fusion about the middle 7-t-butoxynorbornadiene group and periplanar or antiperiplanar for the conformation of the carbonyl groups. The observed isomer can be designated as syn-endo-trans-exo-syn-cis-trans-exo-syn-antiperiplanar going from left to right in the schematic on page 31. Even though the formation of many of the 1024 isomers is sterically possible the fact that only one is observed is a further indication of the stereospecificity invoked by the mechanism. It is also interesting to note that the trimer diketone is simply an extension of the dimer ketone. As seen from the stereochemical designations the left two-thirds of the trimer diketone is identical to the dimer ketone.

The structure of IV has not been determined at this time. A likely structure consists of three 7-t-butoxynorbornadiene groups and a carbonyl group joined in a cyclic fashion as shown below. Unfortunately the NMR spectra is again complex and suitable crystals are



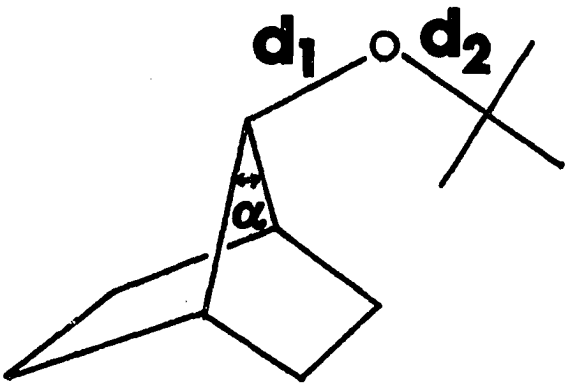
not available for single crystal X-ray diffraction work. It is again interesting to point out that only one of 512 possible isomers is observed.

The final product (V) is the telomer. The exact molecular weight is unknown but mass spectrometer evidence indicates that probably 10 or more 7-t-butoxynorbornadiene residues are involved. As the trimer diketone is an extension of the dimer ketone the telomer is probably an extension of the trimer diketone.

Hybridization and Bond Lengths

One of the most interesting structural features in the 7-t-butoxynorbornadiene moiety is the observation that the C-O bond length from the oxygen atom to the bridgehead atom is systematically shorter than the C-O bond length from the same oxygen atom to the t-butyl group. From the three structures which have been determined using x-ray crystallography there are a total of seven such observations which are summarized in Table 1. This effect can best be explained on the basis of hybridization models. A normal sp^3 hybridized atom has bond angles of 109.5°. In the case of norbornadiene the restrictions of the cyclic system force the bridgehead angle, α, to be less than 109.5° (ranging from 93.4 to 95.2°). As this angle decreases the p-character in the associated bonds increases and the s-character in the bonds not involved in angle α increases. That is, the bonds within the cyclic system have sp^x hybridization with $x > 3$ at the bridgehead atom while the bonds directed outside the cyclic system have sp^x hybridization with $x < 3$. The resulting increase in s-

Table 1. Comparison of bond lengths in the cage dimer, dimer ketone and trimer diketone



I Cage Dimer
II Dimer Ketone
III Trimer Diketone

	α(°)	d_1(Å)	d_2(Å)
Ia	95.1(2)	1.420(3)	1.432(3)
Ib	95.2(2)	1.421(3)	1.435(3)
IIa	93.6(1)	1.417(2)	1.440(2)
IIb	93.9(1)	1.413(2)	1.450(2)
IIIa	94.1(1)	1.418(2)	1.451(2)
IIIb	94.9(1)	1.419(2)	1.452(2)
IIIc	93.4(1)	1.411(2)	1.431(3)

character causes an increase in overlap and therefore a shortening of bond d_1 with respect to the average value of about 1.47 Å. Figure 2 shows a plot of d_1 versus α for these seven norbornadiene groups. The result is approximately a straight line having the equation $d_1 = 0.0042\ \alpha + 1.018$ where d_1 is in angstroms and α is in degrees. The maximum deviation of any point from the line is 0.004 Å or about two standard deviations of a bond distance. By extrapolation one can calculate a value of 1.481 Å for $\alpha = 109.5°$ which is in fairly good agreement with the expected value of 1.47 Å. In summary, differences in bond lengths exist in the 7-t-butoxynorbornadiene groups which in this case can be explained using only hybridization as a model.

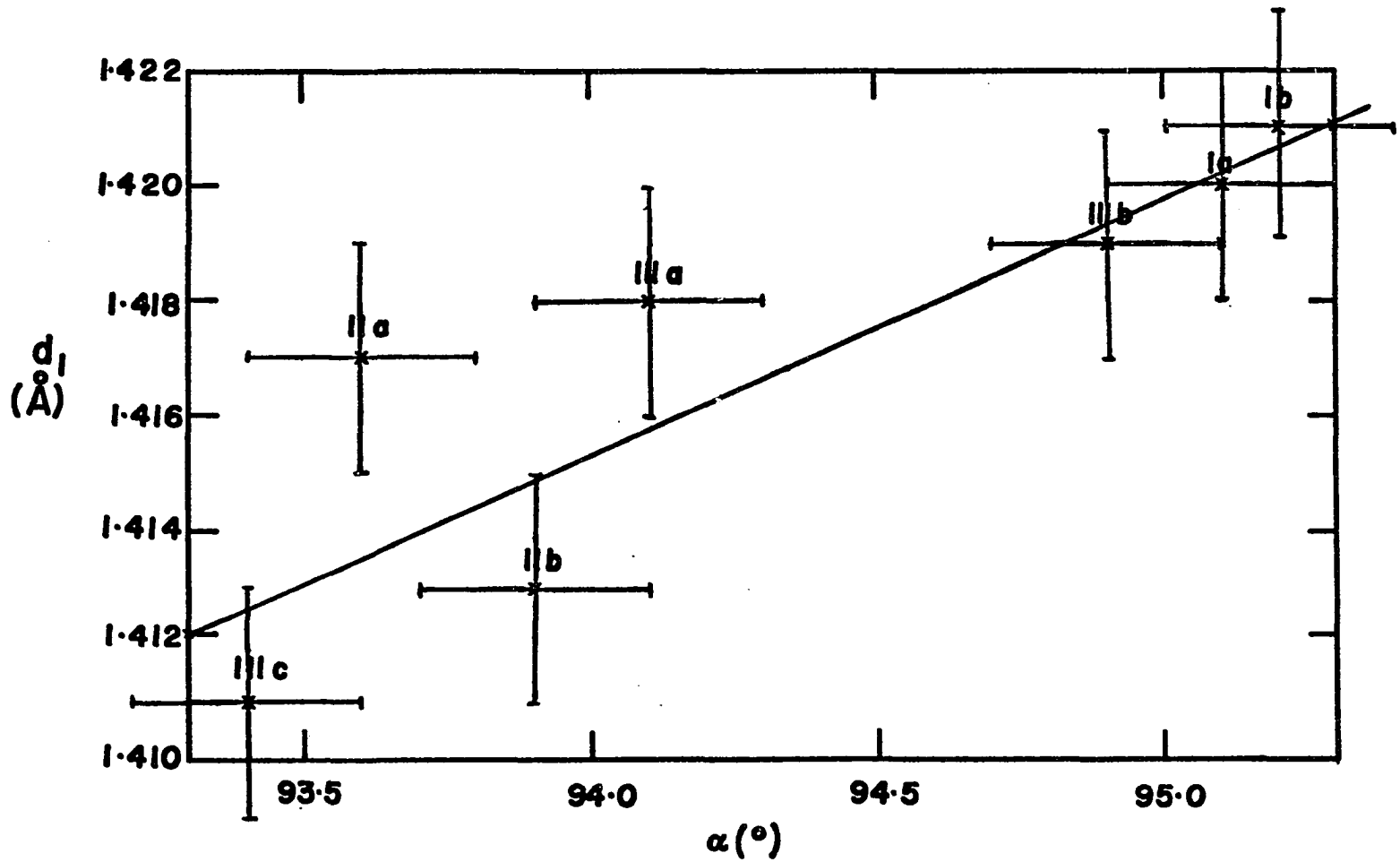


Figure 2. Plot of d_1 versus α for the cage dimer(I), the dimer ketone(II) and the trimer diketone(III).

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The Crystal and Molecular Structure of 5,8-Diaza-4,9-dioxotricyclo-[6,3,0,$0^{1,5}$]undecane, a Non-Planar Tertiary Amide

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The crystal structure of 5,8-diaza-4,9-dioxotricyclo[6,3,0,$0^{1,5}$]undecane, $C_9H_{12}N_2O_2$, a molecule designed to contain a non-planar amide bond, has been determined and refined by three-dimensional least-squares techniques. The crystals are monoclinic, space group $C2/c$, $Z=4$, with $a=12{\cdot}1576$ (8), $b=7{\cdot}4193$ (4), $c=10{\cdot}9614$ (7) Å and $\beta=118{\cdot}437$ (6)°. The final R value for 868 reflections is 0·037. The standard deviations are between 0·001 and 0·002 Å for all C, N and O atom positions. The space group utilizes the twofold rotation axis of the molecule in the crystal structure. The structure solution indicates that the N atom of the amide group is pyramidal while the twist about the amide bond is 21·3°. Significant lengthening of the C–N bond in the amide group is observed.

Introduction

The structure of 5,8-diaza-4,9-dioxotricyclo[6,3,0,$0^{1,5}$]-undecane (DDTU) was determined as the first of a series of molecules designed to contain non-planar amide bonds. This series of tricyclic and tetracyclic amides is illustrated in Fig. 1. The synthesis of DDTU, along with several other tricyclic and tetracyclic analogs, has been reported and a correlation has been shown between the wave number ν(C′–N) and the *cis* rotation angle, ω(C$^{\alpha}$–N–C′–O), as measured from Dreiding models (Smolikova, Koblicova & Blaha, 1973). The purpose of the present investigation is to determine accurate conformational parameters for DDTU and to examine them in light of the correlation with spectroscopic data.

Experimental

Large colorless crystals of DDTU were obtained by equilibrating a saturated ethanolic solution of the compound with hexane. The crystal used for the diffraction experiment was cut to a more suitable size (0·5 × 0·1 × 0·06 mm) from one of the larger crystals.

Crystallographic data (Table 1) and integrated X-ray intensity data were collected on a Nonius CAD-4 automatic diffractometer. These 868 data, comprising all unique reflections with $2\theta<144°$, were measured using Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å) and θ–2θ scan techniques. The θ scan width was calculated as 0·8 + 0·08 tan θ. The maximum scan time was 180 s with 120 s used for scanning the peak and 30 s used for scanning both the high-θ and low-θ backgrounds. 77 reflections were considered indistinguishable from the background having a net count less than 1·4 times the square root of the total count. For the purposes of least-squares refinement these reflections were assigned a value equal to 0·63 times the square root of the total count. Lorentz, polarization and absorption corrections ($\mu=8{\cdot}25$ cm^{-1}) were applied. For the absorption corrections, the program of Coppens, Leiserowitz & Rabinovich (1965) was used. The program employs the numerical integration method of Gauss, and in this case 216 sampling points were used. The weight assigned to each structure amplitude (w_F) is given by $w_F=1/\sigma_F^2$

Table 1. *Crystallographic data*

$C_9H_{12}N_2O_2$, F.W. 180·21
Systematic absences: hkl, $h+k=2n+1$; $h0l$, $l=2n+1$, ($h=2n+1$); $0k0$, ($k=2n+1$)
Space group: $C2/c$
$a=12{\cdot}1576\pm0{\cdot}0008$ Å
$b=7{\cdot}4193\pm0{\cdot}0004$
$c=10{\cdot}9614\pm0{\cdot}0007$
$\beta=118{\cdot}437\pm0{\cdot}006°$
(determined by least-squares fit to the $+2\theta$ and -2θ values of 30 reflections at 26°C)
$V=869{\cdot}4$ Å^3
$Z=4$
$D_c=1{\cdot}377$ g cm^{-3}
$D_o=1{\cdot}376$ g cm^{-3} (measured by flotation in CCl_4–C_6H_{12} mixture at 25°C)
$F(000)=384$

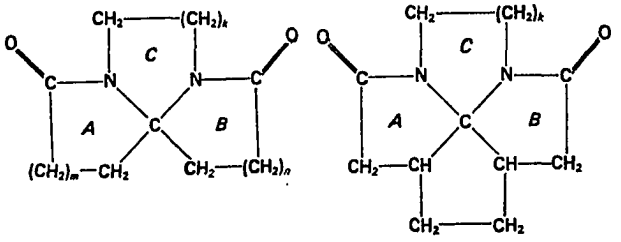


Fig. 1. Schematic structures of a series of tricyclic and tetracyclic non-planar amides. DDTU is the tricyclic compound with $k=m=n=1$.

* Supported by N.I.H. Development Award K4-GM-42572.

where σ_F is the standard deviation of the structure factor. The value of σ_F is calculated as:

$$\sigma_F = 1/2 \left(\frac{\sigma^2 + (0{\cdot}05P)^2}{(P)\,(\mathrm{Lp})} \right)^{1/2}$$

where $\sigma = T^{1/2}\nu$, ν = scan speed, $T = \mathrm{Pk} + 2(R+L)$, $P = [\mathrm{Pk} - 2(R+L)]\nu$, Pk = peak count, R = right background count, L = left background count, Lp = Lorentz–polarization factor.

Structure determination and refinement

The intensities were placed on an absolute scale using the results of a Wilson plot and normalized structure factors, $|E|$, were derived. The E statistics indicated a center of symmetry and the space group was assigned as $C2/c$ rather than Cc. The signs for 117 individual $|E|$'s greater than 1·5 were derived using the symbolic addition procedure for centrosymmetric space groups (Karle & Karle, 1966) leading to an E map that revealed the seven non-hydrogen atom positions.

The initial structure factor calculation had an $R = (\sum||kF_o| - |F_c||/\sum|kF_o|)$ of 0·34. The structure was refined by block-diagonal least-squares methods in which the quantity $\sum w_F(|kF_o| - |F_c|)^2$ was minimized. All non-hydrogen atoms were given anisotropic temperature factors. After several cycles of least-squares refinement R decreased to 0·10. At this point a difference map yielded the positions of the six hydrogen atoms. The hydrogen atoms were included in the refinement with isotropic temperature factors. After several further cycles of refinement inspection of observed and calculated structure factors revealed the presence of secondary extinction effects. The observed intensities were corrected for secondary extinction as follows: $I_c = I_o \exp[-(\mathrm{CEXT} \times \mathrm{NET\ COUNT})]$ where I_c is the corrected intensity, I_o is the observed intensity and $\mathrm{CEXT} = -2{\cdot}91 \times 10^{-8}$. Least-squares refinement was terminated when the shifts for all non-hydrogen atom parameters were less than $\frac{1}{6}$ of the corresponding standard deviation. The R value based on final parameters (Tables 2 and 3) is 0·037 for all data.

Atomic scattering factors for C, N and O atoms were taken from *International Tables for X-ray Crystallography* (1962). The scattering factors for hydrogen atoms were those of Stewart, Davidson & Simpson (1965). A logical routine (Van der Helm & Nicholas, 1970), which may exclude certain reflections from least-squares refinement, was used during the refinement. A final difference Fourier showed no peaks larger than 0·2 e Å^{-3}. In the structure factor analysis the average value of $w_F \Delta F^2$ did not show a significant variation with either $|F_o|$ or $\sin\theta/\lambda$, validating the weighting scheme which was used.*

Table 3. *Positional parameters and isotropic temperature factors for hydrogen atoms (standard deviations in parentheses)*

	x	y	z	B (Å^2)
H(C2)A	0·041 (2)	0·683 (2)	0·373 (2)	5·3 (3)
H(C2)B	0·075 (1)	0·496 (2)	0·462 (1)	4·8 (3)
H(C3)A	0·219 (1)	0·651 (2)	0·342 (2)	5·0 (3)
H(C3)B	0·276 (1)	0·568 (2)	0·499 (2)	6·1 (4)
H(C5)A	−0·004 (1)	0·124 (2)	0·118 (2)	5·2 (3)
H(C5)B	0·117 (1)	0·059 (2)	0·264 (2)	4·9 (3)

* The final F_o, F_c tables have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31094 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Positional and thermal parameters* (Å$^2 \times 10^4$) *for carbon, oxygen and nitrogen atoms*

Calculated standard deviations for the last digit are listed 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	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	0·0	0·4508 (2)	0·25	374 (8)	437 (8)	457 (8)	0	236 (7)	0
C(2)	0·0757 (1)	0·5615 (2)	0·3821 (1)	474 (6)	521 (7)	533 (7)	−21 (5)	263 (6)	−100 (5)
C(3)	0·2082 (1)	0·5554 (2)	0·4003 (1)	451 (6)	532 (7)	528 (7)	−76 (5)	233 (6)	−60 (5)
C(4)	0·2126 (1)	0·3716 (2)	0·3431 (1)	383 (6)	549 (7)	453 (6)	−12 (5)	223 (5)	−9 (5)
C(5)	0·0447 (1)	0·1432 (2)	0·2189 (1)	460 (6)	460 (6)	592 (8)	6 (5)	228 (6)	−60 (5)
N	0·0935 (1)	0·3272 (1)	0·2477 (1)	384 (5)	465 (5)	460 (5)	1 (4)	219 (4)	−39 (4)
O	0·3050 (1)	0·2780 (1)	0·3747 (1)	416 (5)	731 (6)	647 (6)	81 (4)	228 (4)	−47 (5)

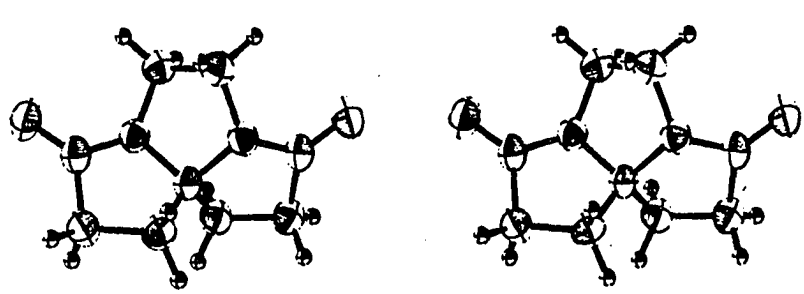


Fig. 2. Stereo view of DDTU (Johnson, 1965).

Description and discussion of the structure

A stereo view of a single molecule of DDTU is shown in Fig. 2. The molecule consists of three five-membered rings fused together at a central quaternary carbon atom. A twofold axis passes through the quaternary carbon atom and bisects the C(5)–C(5′) bond of ring *C*. This twofold axis is a symmetry element of the space group.

All three five-membered rings are in the twist conformation. Table 4 lists the values for the torsion angles in the two types of rings together with the theoretical values for a cyclopentane ring in the twist conformation (Ouannes & Jacques, 1965). The comparison shows that both types of rings are flattened compared with cyclopentane. This can be attributed to changes in bond distances and angles created by the presence of the two amide groups and by the tendency of these two groups to be planar.

Bond distances and angles, along with the numbering scheme for DDTU, are given in Fig. 3. Bond distances and angles involving hydrogen atoms are given in Table 5. It seems reasonable to expect the thermal ellipsoids of DDTU to be consistent with a rigid-body model for thermal motion. Such a calculation was carried out using the method of Schomaker & Trueblood (1968) with the appropriate restrictions imposed for a molecule of point symmetry C_2. The r.m.s. ΔU_{ij} was 0·0018 Å^2 whereas the r.m.s. σU_{ij} from the least-squares refinement was 0·0006 Å^2. Because the average ΔU_{ij} is three times the average σU_{ij} we conclude that the acceptance of the rigid-body model is at the limit of statistical significance. The corrected bond distances calculated from the rigid-body model are given in Table 6. The most notable bond distances are those for the C(4)–N and C(4)–O bonds. The former is shortened while the latter is lengthened from the value expected for a normal amide bond (Marsh & Donohue, 1967). The bond distances will be discussed later in the text.

One very short intermolecular contact was observed in the crystal structure. This weak interaction occurs between O and H(C3)*A* related by the symmetry operation $\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$. The calculated distances are 3·374 Å for O···C(3) and 2·44 Å for O···H(3), both shorter than the sum of the corresponding van der Waals radii of 3·4 and 2·6 Å, respectively.

The non-planar amide group

The primary reason for the structural investigation of DDTU was to obtain conformational parameters for the amide groups in this molecule. The conformation of the amide bond is determined by the conformations of rings *A*, *B* and *C*. By changing the ring size of *A*, *B* and *C* it is possible to produce various conformations

Table 5. *Bond lengths and angles involving hydrogen atoms*

Standard deviations are 0·02 Å for bond lengths and 1° for bond angles.

C(2)–H(C2)*A*	0·98 Å	C(1)–C(2)–H(C2)*A*	111°
		C(3)–C(2)–H(C2)*A*	114
C(2)–H(C2)*B*	1·00	C(1)–C(2)–H(C2)*B*	108
		C(3)–C(2)–H(C2)*B*	108
C(3)–H(C3)*A*	1·01	C(2)–C(3)–H(C3)*A*	110
		C(4)–C(3)–H(C3)*A*	109
C(3)–H(C3)*B*	1·00	C(2)–C(3)–H(C3)*B*	114
		C(4)–C(3)–H(C3)*B*	111
C(5)–H(C5)*A*	0·99	N——C(5)–H(C5)*A*	110
		C(5′)–C(5)–H(C5)*A*	109
C(5)–H(C5)*B*	0·99	N——C(5)–H(C5)*B*	108
		C(5′)–C(5)–H(C5)*B*	115

Table 6. *Bond distances corrected for rigid-body thermal motion*

	Uncorrected	Corrected
C(1)–C(2)	1·533 Å	1·538 Å
C(1)–N	1·470	1·475
C(2)–C(3)	1·526	1·530
C(3)–C(4)	1·512	1·519
C(4)–N	1·362	1·365
C(4)–O	1·223	1·226
C(5)–C(5′)	1·534	1·540
C(5)–N	1·462	1·467

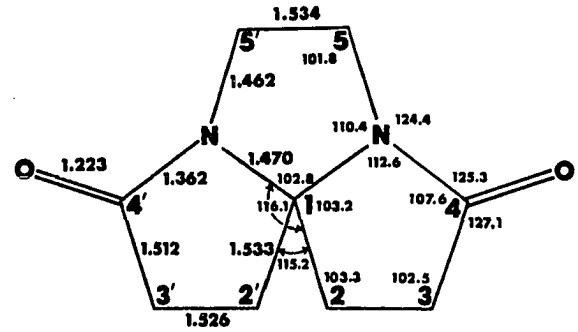


Fig. 3. Bond distances and angles for DDTU. Standard deviations for bond distances are between 0·0014 and 0·0021 Å for uncorrelated atoms and 0·0029 Å for C(5)–C(5′) bond. Standard deviations for bond angles are 0·1°.

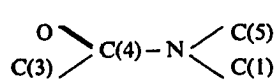
Table 4. *Comparison of conformational angles* (°) *in five-membered rings of DDTU and theoretical values for cyclopentane* (*Ouannes & Jacques*, 1965)

Ring *A* or *B*		Ring *C*		Cyclopentane	
C(4)–N——C(1)–C(2)	−10·7	N′——C(1)–N——C(5)	12·1	C(1)–C(2)–C(3)–C(4)	15·1
N——C(1)–C(2)–C(3)	26·9	C(1)–N——C(5)–C(5′)	−29·7	C(2)–C(3)–C(4)–C(5)	−39·4
C(1)–C(2)–C(3)–C(4)	−32·6	N——C(5)–C(5′)–N′	34·8	C(3)–C(4)–C(5)–C(1)	48·1
C(1)–C(3)–C(4)–N	27·2	C(5)–C(5′)–N′——C(1)	−29·7	C(4)–C(5)–C(1)–C(2)	−39·4
C(3)–C(4)–N——C(1)	−10·5	C(5′)–N′——C(1)–N	12·1	C(5)–C(1)–C(2)–C(3)	15·1

of the amide group (Smolikova *et al.*, 1973). Normally the atoms of this group are planar or nearly so, but non-planarity can occur *via* three types of distortions. They are a rotation about the C′–N bond and a non-planar arrangement of bonds about either the N or C′ atoms. It appears that the first two have about the same energy requirements while the last requires a relatively large amount of energy (Winkler & Dunitz, 1971). Such distortions have been observed in cyclic systems (*e.g.* Winkler & Dunitz, 1971; Sweet & Dahl, 1970; Simon, Morin & Dahl, 1972; Sletten, 1970; Groth, 1973) and also for at least one acyclic tertiary amide (Pedone, Beneditti, Immirzi & Allegra, 1970).

In order to describe the non-planarity of an amide bond three independent parameters are required. We shall follow Warshel, Levitt & Lifson (1970) in taking χ_C and χ_N to describe the non-planar arrangement of bonds about C′ and N respectively. For the third parameter we shall choose τ' as defined by Winkler & Dunitz (1971). The definitions of the four torsional angles about the amide bond and their relationship to χ_N, χ_C and τ' are summarized in Table 7. It can also be seen that χ_N is the dihedral angle between the planes defined by C(4)–N–C(5) and C(4)–N–C(1) while χ_C is the dihedral angle between planes N–C(4)–O and N–C(4)–C(3). One would therefore expect the values of χ to be equal to 0 and $\pm 60°$ for a planar and tetrahedral atom respectively.

Table 7. *Definition of conformational parameters in the non-planar amide group (Winkler & Dunitz, 1971)*



Parameter	Definition	Value for DDTU
ω_1	C(3)-C(4)-N-C(5)	−148·5
ω_2	O—C(4)-N-C(1)	169·8
ω_3	O—C(4)-N-C(5)	31·8
ω_4	C(3)-C(4)-N-C(1)	−10·5
$\tau'=2\tau=\omega_1+\omega_2$	(mod 2π)	21·3
$\chi_C=\omega_1-\omega_3+\pi$	(mod 2π)	−0·3
$\chi_N=\omega_2-\omega_3+\pi$	(mod 2π)	−42·0

The calculated values for the conformational parameters for DDTU are given in Table 7 from which it can be seen that the surrounding of C(4) is almost perfectly planar whereas the nitrogen atom is definitely pyramidal, in agreement with the predicted energy requirements given by Winkler & Dunitz (1971). The angle of twist (τ') about the amide bond is 21·3°. Ramachandran & Kolaskar (1973) have compiled the results of several crystal structures of non-planar peptides and shown the experimental data to be consistent with theoretical calculations (Ramachandran, Lakshminarayanan & Kolaskar, 1973). The theoretical prediction is that χ_N ($\equiv\theta_N$) has the highest probability of falling in the range of $-1{\cdot}5$ to $-2{\cdot}0$ times $\Delta\omega$ ($\equiv\omega_1+180$). In the case of DDTU $\chi_N=-1{\cdot}33\Delta\omega$, which is within the range of experimental values reported.

As the magnitude of χ_N, χ_C and τ' increases the amount of π overlap in the amide bond decreases and the amide bond length should increase. This phenomenon should be observed in the bond lengths derived from crystallographic data as well as in the infrared spectra. The amide bond length [C(4)–N] in DDTU is $1{\cdot}362\pm0{\cdot}002$, about 20 standard deviations longer then the value for the standard peptide bond (Marsh & Donohue, 1967). From infrared spectra observed for DDTU and analogous compounds, the wave number ν(C′–N) appears to correlate with the angle $\omega_3=\omega${[O–C(4)–N–C(5)]} as estimated from Dreiding models (Smolikova *et al.*, 1973). Their estimated value of ω_3 for DDTU is 25°, somewhat smaller than the observed value of 31·8° but of the right order of magnitude.

From the results of this structure and others containing non-planar amide groups it is evident that the deformation about N provides a significant contribution to the non-planarity of the amide group and that a single rotation angle (ω_1) is not always sufficient to describe the conformation of these groups.

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The Crystal Structures of Two Tetracyclic Spirodilactams Containing Non-Planar Amide Bonds

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The crystal structures of 1,4-diaza-5,12-dioxotetracyclo[5,5,1,$0^{4,13}$,$0^{10,13}$]tridecane, $C_{11}H_{14}N_2O_2$, and 1,5-diaza-6,13-dioxotetracyclo[6,5,1,$0^{5,14}$,$0^{11,14}$]tetradecane, $C_{12}H_{16}N_2O_2$, have been determined and refined by three-dimensional least-squares techniques. Both molecules crystallize in space group $C2/c$ and have similar unit-cell dimensions. Unit-cell dimensions for the former are $a=13{\cdot}6008$ (4), $b=8{\cdot}3177$ (2), $c=10{\cdot}0596$ (2) Å and $\beta=120{\cdot}563$ (2)° while those for the latter are $a=13{\cdot}7523$ (3), $b=8{\cdot}9985$ (2), $c=10{\cdot}2316$ (2) Å and $\beta=120{\cdot}527$ (1)°. The final R values are 3·7% for the tridecane derivative and 3·9% for the tetradecane derivative. Each molecule lies on the twofold rotation axis of space group $C2/c$. The amide group in each molecule is non-planar even though the conversion of a five-membered ring to a six-membered ring in the tetradecane derivative releases a certain amount of the strain.

Introduction

The geometry of the non-planar amide group (or the non-planar peptide group in biological systems) has been the subject of several theoretical and experimental studies in the last few years (Warshel, Levitt & Lifson, 1970; Winkler & Dunitz, 1971; Ramachandran, Lakshminarayanan & Kolaskar, 1973; Ramachandran & Kolaskar, 1973; Dunitz & Winkler, 1975). The present study deals with two compounds of a series of polycyclic spirodilactams. The syntheses and infrared spectra of these compounds have been published (Smolikova, Koblicova & Bláha, 1973). The first compound of this series, a tricyclic spirodilactam, and a preliminary study of the present tetracyclic compounds have been reported (Ealick & van der Helm, 1975; van der Helm, Ealick & Waschecheck, 1975). The occurrence of both *cis* and *trans* non-planar peptide groups has been observed in cyclic and acyclic molecules (*e.g.* Sletten, 1970; Winkler & Dunitz, 1971; Pedone, Benedetti, Immirzi & Allegra, 1970). One must also consider the occurrence of the non-planar peptide group in protein molecules. In the present paper we present the description of the structures of two molecules containing non-planar amide bonds.

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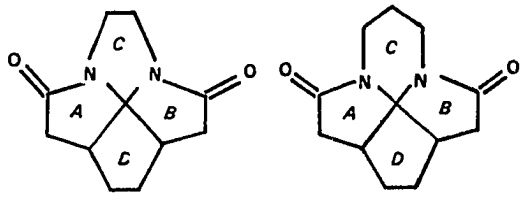
Experimental

Crystalline samples of 1,4-diaza-5,12-dioxotetracyclo-[5,5,1,$0^{4,13}$,$0^{10,13}$]tridecane (I) and 1,5-diaza-6,13-dioxotetracyclo[6,5,1,$0^{5,14}$,$0^{11,14}$]tetradecane (II) were supplied by Professor K. Bláha, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague. Suitable crystals of (I) were obtained by slow cooling of an ethanolic solution of the compound. The crystal used for the diffraction experiment was in the shape of an octahedron with maximum dimensions 0·55 × 0·45 × 0·30 mm. Crystals of (II) were obtained by equilibrating a saturated benzene solution of the compound with hexane. The crystal selected for data collection had the shape of a rectangular prism with dimensions 0·32 × 0·24 × 0·12 mm. Integrated intensity data and crystallographic data (Table 1) 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 determination of unit-cell parameters Cu $K\alpha_1$ radiation ($\lambda = 1{\cdot}54051$ Å) was used. 1011 intensities for (I) and 1129 for (II), comprising all unique data with $2\theta < 150°$, were measured by θ–2θ scans. The θ-scan width was calculated as $(1{\cdot}0 + 0{\cdot}1 \tan\theta)°$. A variable receiving aperture was used with a width of $(4{\cdot}0 + 0{\cdot}4 \tan\theta)$ mm; the height was constant at 6 mm.



(I) (II)

Table 1. *Crystallographic data*

	(I)	(II)
Formula	$C_{11}H_{14}N_2O_2$	$C_{12}H_{16}N_2O_2$
F.W.	206·25	220·27
Space group	*C*2/*c*	*C*2/*c*
a	13·6008 (4) Å	13·7523 (3) Å
b	8·3177 (2)	8·9985 (2)
c	10·0596 (4)	10·2316 (2)
β	120·563 (2)°	120·527 (1)°
V	979·91 Å^3	1090·66 Å^3
Z	4	4
D_o	1·400 g cm^{-3}	1·336 g cm^{-3}
D_c	1·398	1·341

The cell dimensions were determined from the least-squares fit to $+2\theta$ and -2θ values of 38 reflections for (I) and 48 reflections for (II) at 27 °C. The reflections were taken from all quadrants of reciprocal space.

For each structure three data sets were collected with a variable scan speed so that a maximum time of 60 s was spent on each individual intensity with $\frac{2}{3}$ of the time used for scanning the peak and $\frac{1}{6}$ of the time used for scanning each of the high-θ and low-θ backgrounds. An intensity was considered indistinguishable from the background when $I < 1{\cdot}4\sigma(I)$ and was assigned a value equal to the square root of the total count (peak plus twice the left and right background) for the purpose of least-squares refinement. The three separate data sets for each compound were averaged together, a reflection being excluded if it differed from the average by more than three standard deviations [$\sigma(I)$]. The *R* values ($= \sum|\Delta I|/\sum I$) for the data sets were 0·0079, 0·0069 and 0·0095 for compound (I), and 0·0083, 0·0083 and 0·0086 for compound (II). Absorption corrections were applied to the averaged intensities [$\mu = 8{\cdot}080$ cm^{-1} for (I) and $\mu = 7{\cdot}598$ cm^{-1} for (II)]. Lorentz and polarization corrections were made and

Table 2. *Positional parameters* ($\times 10^5$) *and thermal parameters* (Å$^2 \times 10^4$) *for carbon, oxygen and nitrogen atoms of* (I) *and* (II)

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

(I)	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	0	42182 (17)	25000	269 (6)	282 (6)	296 (6)	0	150 (5)	0
C(2)	8072 (9)	53363 (13)	38520 (12)	297 (5)	343 (5)	318 (5)	−39 (4)	144 (4)	−34 (4)
C(3)	19552 (9)	51265 (15)	39303 (14)	270 (5)	425 (6)	450 (6)	−30 (4)	140 (5)	19 (5)
C(4)	18840 (9)	34933 (16)	32305 (14)	305 (6)	476 (6)	404 (6)	69 (5)	190 (5)	57 (5)
C(5)	3062 (11)	14811 (15)	20347 (15)	458 (6)	330 (5)	404 (6)	33 (5)	187 (5)	−31 (4)
C(6)	2764 (11)	70095 (15)	33803 (16)	404 (6)	329 (5)	528 (7)	−28 (4)	215 (6)	−89 (5)
N	7517 (8)	31221 (12)	22877 (10)	315 (4)	338 (4)	347 (5)	51 (4)	170 (4)	7 (4)
O	26793 (8)	26322 (15)	34421 (14)	385 (5)	712 (7)	681 (6)	182 (4)	281 (5)	11 (5)
(II)									
C(1)	0	38972 (14)	25000	391 (6)	300 (6)	422 (7)	0	244 (6)	0
C(2)	8150 (9)	49276 (12)	38181 (11)	475 (6)	378 (5)	428 (5)	−74 (4)	254 (4)	−34 (4)
C(3)	19416 (10)	47461 (14)	38752 (15)	411 (6)	508 (6)	654 (7)	−72 (5)	242 (5)	−22 (5)
C(4)	18420 (9)	33193 (14)	30465 (15)	420 (6)	518 (6)	635 (7)	63 (5)	286 (5)	54 (5)
C(5)	3004 (11)	15151 (13)	15147 (15)	597 (6)	396 (6)	619 (7)	63 (5)	270 (6)	−112 (5)
C(6)	0	5645 (17)	25000	560 (9)	317 (7)	631 (10)	0	97 (8)	0
C(7)	2919 (11)	64727 (12)	33638 (14)	650 (7)	357 (5)	637 (7)	−52 (5)	406 (6)	−90 (5)
N	7374 (7)	29518 (10)	22313 (11)	421 (4)	357 (4)	546 (5)	45 (3)	259 (4)	−38 (4)
O	26111 (8)	26116 (13)	30786 (14)	505 (5)	849 (7)	1079 (9)	176 (5)	430 (6)	−47 (7)

individual structure factor amplitudes were derived. Each amplitude was assigned an experimental weighting scheme, based on counting statistics, that has been described previously (van der Helm, Ealick & Burks, 1975).

Structure determination and refinement

The structure of (II) was determined by the symbolic addition procedure (Zachariasen, 1952; Karle & Karle, 1966). The intensities were placed on an absolute scale using the results of a Wilson plot (Wilson, 1942) and normalized structure factors, $|E|$, were derived. An analysis of the distribution of $|E|$'s indicated a center of symmetry and the space group was taken to be $C2/c$ rather than Cc. The signs of 159 E's with $|E|>1\cdot5$ were generated leading to an E map which revealed the positions of all nine non-hydrogen atoms.

The structure was refined by block-diagonal (9×9) least-squares methods in which the quantity $\sum w_F(kF_o-F_c)^2$ was minimized. The non-hydrogen atoms were given anisotropic temperature factors and the refinement proceeded to an $R=\sum||kF_o|-|F_c||/\sum|kF_o|$ of 0·11. At this point a difference Fourier map was calculated in which the positions of the eight H atoms were located. After several further cycles of least-squares refinement a comparison of F_o's and F_c's indicated the presence of minor secondary extinction effects. The observed intensities were corrected for secondary extinction as follows: $I_c=I_o\exp(-CI_o)$, where $I_c=$ corrected intensity, $I_o=$observed intensity and $C=8\cdot2\times10^{-7}$. The least-squares refinement was terminated when all shifts for non-hydrogen atoms were small fractions of the corresponding estimated standard deviation. The R value based on final parameters (Tables 2 and 3) for all data is 0·039.

The present two structures have very similar unit-cell dimensions (Table 1) and the molecular structures differ by only one $-CH_2-$ group. Therefore the structure of (I) was determined by assuming that the molecule had the same orientation and location as structure (II). Idealized coordinates were calculated using (II) as a template and a structure factor calculation was made. Although the initial R value was 0·65 the refinement proceeded quickly and converged at $R=0\cdot15$ for the isotropic model. The non-hydrogen atoms were made anisotropic and after several more cycles of refinement a difference Fourier map revealed positions of the seven H atoms. After refinement converged corrections were made for secondary extinction effects ($C=2\cdot91\times10^{-6}$). The refinement was terminated when all shifts for non-hydrogen atoms were small fractions of the corresponding estimated standard deviations. The R value based on final parameters (Tables 2 and 3) is 0·037.

Table 3. *Positional parameters* ($\times10^3$) *and isotropic thermal parameters for hydrogen atoms in* (I) *and* (II)

(I)	x	y	z	B (Å^2)
H(C2)	87 (1)	498 (2)	482 (1)	3·3 (3)
H(C3)*A*	262 (1)	509 (2)	502 (2)	4·8 (4)
H(C3)*B*	208 (1)	596 (2)	331 (2)	3·7 (3)
H(C5)*A*	95 (1)	70 (2)	245 (2)	4·9 (4)
H(C5)*B*	−24 (1)	126 (2)	96 (2)	3·8 (3)
H(C6)*A*	−36 (2)	718 (2)	363 (2)	4·9 (4)
H(C6)*B*	84 (2)	788 (2)	389 (2)	4·5 (4)
(II)				
H(C2)	89 (1)	460 (2)	481 (2)	5·0 (3)
H(C3)*A*	208 (1)	556 (2)	336 (2)	5·7 (3)
H(C3)*B*	259 (1)	463 (2)	495 (2)	6·0 (4)
H(C5)*A*	−42 (1)	164 (2)	47 (2)	5·6 (3)
H(C5)*B*	86 (1)	104 (2)	137 (2)	5·8 (4)
H(C6)	−66 (1)	−9 (2)	184 (2)	6·3 (4)
H(C7)*A*	87 (1)	726 (2)	387 (2)	4·9 (3)
H(C7)*B*	−28 (1)	664 (2)	368 (2)	5·0 (3)

Final difference Fourier maps for structures (I) and (II) showed no peaks larger than 0·2 e Å^{-3} nor less than −0·2 e Å^{-3}. All least-squares refinements were done with the block-diagonal least-squares program of Ahmed (1966). The absorption correction program was that of Coppens, Leiserowitz & Rabinovich (1965). The atomic scattering factors for O, N and C were from *International Tables for X-ray Crystallography* (1962) while scattering factors for H atoms were those of Stewart, Davidson & Simpson (1965).

In the structure factor analysis for both structures (I) and (II) the average values of $w_F\Delta F^2$ did not show a

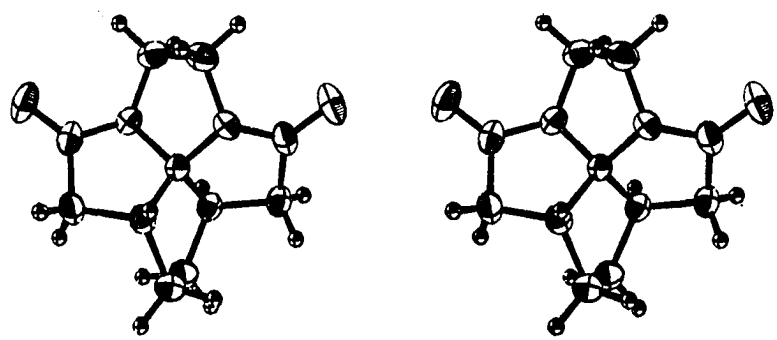


Fig. 1. Stereo view of (I) (Johnson, 1965).

significant variation with either $|F_o|$ or $\sin\theta/\lambda$ indicating that the weighting scheme used was reasonable.*

Description and discussion of the structure

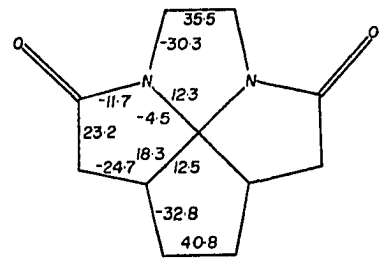
Stereo views of single molecules of (I) and (II) are shown in Figs. 1 and 2 respectively. (I) consists of four five-membered rings fused together at a central quaternary C atom. The molecule contains a twofold axis which is a symmetry element of the space group and which passes through atom C(1) and bisects the bonds C(5)–C(5′) and C(6)–C(6′). (II) also has point symmetry $C2$ with the twofold axis passing through atoms C(1) and C(6) and bisecting bond C(7)–C(7′).

In (I) rings C and D are in the twist conformation as required by the presence of a twofold axis passing through the rings. The conformation of ring $A(B)$ is intermediate between twist (C_2) and envelope (C_s). This can best be seen through the use of the pseudorotation parameter Δ (Altona, Geise & Romers, 1968) for which $\Delta=0°$ for the C_2 conformation and $\Delta=\pm36°$ for the C_s conformation. The value of Δ for ring $A(B)$ of (I) is 17·5°. In (II) all five-membered rings are in the C_2 conformation. Ring D lies on the twofold axis while the value of Δ for ring $A(B)$ is 1·6°. The conformation of the six-membered ring (C) is best described as twist-boat. Comparison of the $A(B)$ rings indicates a release of strain in (II). As the C ring is changed from a five-membered to a six-membered ring, ring $A(B)$ adopts a more normal twist conformation and the amide group becomes more planar. Fig. 3 lists the values of the torsion angles for both molecules and Table 4 lists the theoretical values for cyclopentane in the twist and envelope conformations (Ouannes & Jacques, 1965) and cyclohexane in the twist-boat conformation

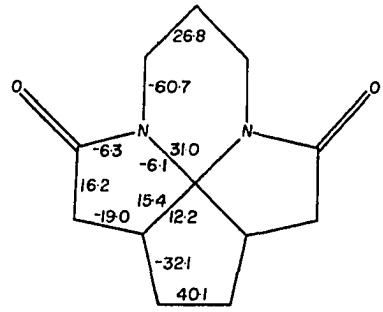
* The final F_o, F_c tables for (I) and (II) have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31333 (13 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1 NZ, England.

Table 4. *Theoretical values for the twist and envelope conformations of cyclopentane (Ouannes & Jacques, 1965) and the twist-boat conformation of cyclohexane (Hendrickson, 1961)*

	Cyclopentane		Cyclohexane
	Twist (C_2)	Envelope (C_s)	Twist-boat
φ_1	15·1	46·1	33·2
φ_2	−39·4	−28·6	−70·6
φ_3	48·1	0	33·2
φ_4	−39·4	28·6	33·2
φ_5	15·1	−46·1	−70·6
φ_6			33·2



(I)



(II)

Fig. 3. Torsion angles for (I) and (II). Standard deviations range from 0·10° for torsion angles involving uncorrelated atoms to 0·24° for angles containing a twofold axis.

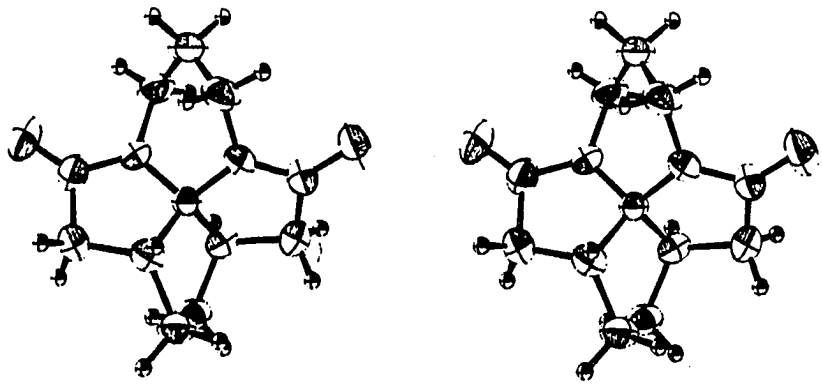


Fig. 2. Stereo view of (II) (Johnson, 1965).

(Hendrickson, 1961). Considerable flattening of all rings is observed compared to the expected conformations of the carbocyclic analogs. The flattening results from changes in bond distances and angles brought about by the inclusion of the amide group in the ring and the tendency for this group to be planar.

Bond distances and angles for (I) and (II) are given in Figs. 4 and 5 respectively. The most interesting distances are those involving atoms of the amide groups. The amide bond distance [C(4)–N] is lengthened while the carbonyl bond distance [C(4)–O] is shortened from the expected values for planar amide groups (Ramachandran, Kolaskar, Ramakrishnan & Sasisekharan, 1974). The C–H bond distances range from 0·97 to 1·03 Å with an average value of 1·00 Å for (I) and from 0·96 to 1·03 Å with an average value of 1·00 Å for (II).

Rigid-body corrections were carried out for each molecule by the method of Schomaker & Trueblood (1968) with the appropriate restrictions imposed for a molecule of point symmetry $C2$. The average ΔU_{ij} was 0·0016 Å^2 and r.m.s. U_{ij} 0·0005 Å^2 for (I) and the average ΔU_{ij} was 0·0024 Å^2 and r.m.s. U_{ij} 0·0006 Å^2 for (II). The rigid-body model for both molecules is acceptable only at the limits of statistical significance. It should be noted, however, that the carbonyl O atoms show some independent thermal motion in both compounds. The bond distances corrected for rigid-body thermal motion are given in Table 5.

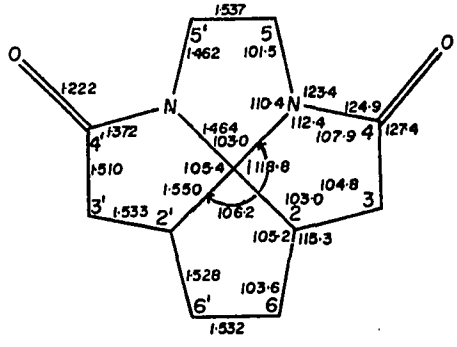


Fig. 4. Bond distances and angles for (I). Standard deviations are 0·0014–0·0018 Å for bond distances involving uncorrelated atoms and 0·0032 Å for the C(5)–C(5′) and C(6)–C(6′) bonds. Standard deviations for bond angles are 0·1°.

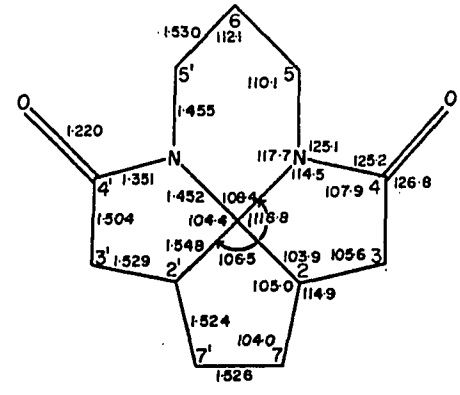


Fig. 5. Bond distances and angles for (II). Standard deviations are 0·0012–0·0019 Å for bond distances involving uncorrelated atoms and 0·0028 Å for the C(7)–C(7′) bond. Standard deviations for bond angles are 0·1°.

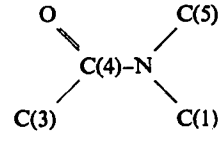
Table 5. *Bond distances corrected for rigid-body thermal motion*

	(I)	(II)
C(1)–C(2)	1·555	1·555
C(1)–N	1·470	1·460
C(2)–C(3)	1·538	1·536
C(2)–C(6)	1·532	–
C(2)–C(7)	–	1·530
C(3)–C(4)	1·516	1·512
C(4)–N	1·375	1·356
C(4)–O	1·225	1·224
C(5)–C(5′)	1·543	–
C(5)–C(6)	–	1·537
C(5)–C(N)	1·467	1·462
C(6)–C(6′)	1·537	–
C(7)–C(7′)	–	1·532

There are three short intermolecular contacts which should be pointed out: O···H(C3)B ($\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$) of 2·40 Å in (I) and O···H(C5)A ($\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$) of 2·52 Å and H(C5)$B$···H(C7)$B$ ($\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$) of 2·23 Å in (II). The corresponding sums of the van der Waals radii are 2·6, 2·6 and 2·4 Å respectively.

Table 6. *Conformational parameters for non-planar amide groups of* (I) *and* (II)

For further definition of symbols see Winkler & Dunitz (1971).



Parameter	Definition		(I)	(II)
ω_1	C(3)–C(4)–N–C(5)		−148·0 (1)	−167·1 (1)
ω_2	O—C(4)–N–C(1)		168·5 (1)	174·4 (1)
ω_3	O—C(4)–N–C(5)		32·2 (2)	13·5 (2)
ω_4	C(3)–C(4)–N–C(1)		−11·7 (1)	−6·3 (1)
τ'	$2\tau=\omega_1+\omega_2$		20·5	7·3
χ_C	$\omega_1-\omega_3+\pi$	(mod 2π)	−0·2	−0·6
χ_N	$\omega_2-\omega_3+\pi$		−43·7	−19·1

The non-planar amide group

Conformational parameters for the non-planar amide groups are given in Table 6, following the convention outlined by Winkler & Dunitz (1971). By comparison it can be seen that the amide group of (II) is more planar than that of (I). This also appears to be reflected in bond distances as lengthening of the amide bond

occurs to a greater extent in (I), thus substantiating the expected correlation between non-planarity and the amide bond length. In addition the N–C(1) and N–C(5) bonds also become shorter as the amide group becomes more planar. It might also be pointed out that the values of χ_C in each molecule are very small while the major contribution to non-planarity comes from χ_N and τ' which is consistent with the predicted energy requirement for deformation of the amide group (Winkler & Dunitz, 1971).

The primary interest in this series of compounds is the predicted correlation of non-planarity with the wave number ν(C′–N) (Smolikova *et al.*, 1973). From the results of these two structures and the first member of the series (Ealick & van der Helm, 1975) it appears that the suggested correlation of ω_3 and ν(C′–N) is a reasonable one and as more data become available the quantitative nature of these relationships will be explored.

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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.

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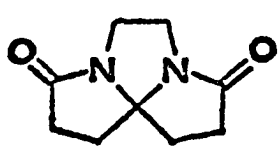
ABSTRACT

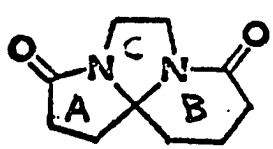
The crystal structure of 6,9-diaza-5,10-dioxotricyclo[7,3,0,$0^{1,6}$]dodecane, $C_{10}H_{14}N_2O_2 \cdot H_2O$ a molecule designed to contain non-planar amide bonds, has been determined and refined using three-dimensional least-squares techniques. The molecule crystallizes in space group $P2_1/c$ with unit cell dimensions a= 13.4455(7), b=7.3448(4), c=10.7919(5) Å and β=99.410(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 (χ_N=-16.7, τ'=17.8) than in the five-membered ring (χ_N=-41.2, τ'=20.8). The final R value for all 2160 reflections is 0.058 with standard deviations in nonhydrogen atomic parameters ranging from 0.0012 to 0.0024 Å.

INTRODUCTION

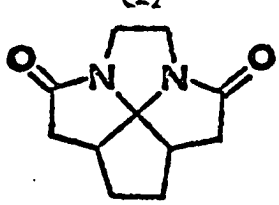
The structure of 6,9-diaza-5,10-dioxotricyclo[7,3,0,$0^{1,6}$]dodecane was determined as the fourth compound in a series of polycyclic spirodilactams. The results of three of the structures (I, III, IV) have been published (Ealick and van der Helm (1975); Ealick, Washecheck and van der Helm (1976)), while a preliminary report of this structure (II) has also been reported (van der Helm, Ealick and Washecheck (1975)). In addition the synthesis and infrared spectra of this series of molecules have been published (Smoliková, Koblicová and Blahá, 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 are possible. A study to determine conformations of amide groups in medium ring compounds has also been published (Dunitz and 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.



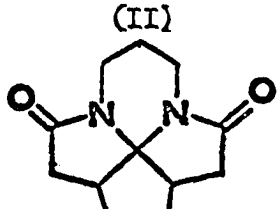
$C_9H_{12}N_2O_2$
(I)



$C_{10}H_{14}N_2O_2$
(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. Blåha, 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 platelike crystal with approximate dimensions 0.3 x 0.4 x 0.07mm 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 $CuK\bar{\alpha}$ radiation (λ=1.5418Å) was used and for unit cell parameters $CuK\alpha_1$ radiation (λ=1.54051Å) 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 $(1.0+0.1\tan\theta)$ degrees. A variable receiving aperature was used with a width of $(4.0+0.86\tan\theta)$mm while the height was constant at 6.0mm. The maximum scan time for each intensity was 120 s with 80s used for scanning the peak and 20s used for scanning each the left and right backgrounds. A total of 368 intensities having $I\leq1.4\sigma(I)$ were considered indistinguishable from background and were assigned a value of $1.0\sqrt{T}$, 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 and 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 (μ=8.47cm^{-1}) were applied. For the absorption correction, the program of Coppens, Leiserowitz and Rabinovich (1965) was used.

Table 1. Crystallographic Data

Formula: $C_{10}H_{14}N_2O_2 \cdot H_2O$

F.W.: 242.27

Space group: $P2_1/c$

a= 13.4455(7) Å

b= 7.3448(4)

c= 10.7919(5)

β= 99.410(3)°

(determined by least-squares fit to the +2θ and -2θ values of 49 reflections taken from all quadrants of reciprocal space, at 21.5±0.5°C.

V= 1051.4 $Å^3$

Z= 4

D_{obs} = 1.316g.cm^{-3}

D_{calc} = 1.341g.cm^{-3}

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 and van der Helm, 1975).

STRUCTURE DETERMINATION AND REFINEMENT

The intensities were placed on an absolute scale using the results of a Wilson plot (Wilson, 1942) and normalized structure factors, $|E|$, were derived. The signs for 290 individual E's with $|E|>1.5$ were derived using the program MULTAN (Germain, Main and 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 yeilded an $R = \Sigma|kFo-Fc|/\Sigma|kFo|$ of 0.52. After several cycles of least-squares refinement a difference Fourier map was calculated from which the coordinates of the oxygen atom of the water molecule were determined. This oxygen atom was present in the original E-map but was not recognized at that time. After this oxygen 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, using isotropic temperature factors for H atoms and anisotropic termperature 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 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.

Table 2. Positional and thermal parameters ($Å^2 \times 10^4$) for carbon, oxygen and nitrogen 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/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	0.2099(1)	0.1909(2)	0.4313(1)	433(7)	360(7)	396(7)	-4(6)	-1(6)	-20(6)
C(2)	0.1471(1)	0.3156(2)	0.5035(2)	583(10)	474(9)	509(9)	100(8)	3(8)	-109(8)
C(3)	0.0406(1)	0.3022(2)	-0.4303(2)	545(9)	522(10)	543(10)	145(8)	54(8)	25(8)
C(4)	0.0379(1)	0.1154(2)	0.3724(1)	436(7)	561(10)	392(7)	35(7)	12(6)	9(7)
N(5)	0.1343(1)	0.0675(2)	0.3639(1)	414(6)	443(7)	440(7)	-5(5)	36(5)	-94(6)
C(6)	0.1711(1)	-0.1201(2)	0.3725(2)	462(8)	453(9)	670(11)	-20(7)	54(8)	-178(8)
C(7)	0.2357(1)	-0.1217(2)	0.5020(2)	442(8)	358(8)	752(11)	-25(7)	3(8)	1(8)
N(8)	0.2773(1)	0.0634(2)	0.5106(1)	379(6)	349(6)	473(7)	-11(5)	26(5)	5(5)
C(9)	0.3733(1)	0.0997(2)	0.5593(2)	395(7)	426(8)	463(8)	-13(6)	49(6)	-44(7)
C(10)	0.4146(1)	0.2808(3)	0.5289(2)	571(11)	493(10)	783(13)	-156(8)	-54(9)	28(9)
C(11)	0.3587(2)	0.3913(3)	0.4258(2)	784(13)	657(13)	764(13)	-293(11)	-78(10)	212(11)
C(12)	0.2705(1)	0.2927(3)	0.3463(2)	637(11)	589(11)	490(9)	-103(9)	33(8)	108(8)
O(1)	0.6147(1)	0.3623(2)	0.2601(1)	517(7)	722(9)	913(11)	-53(7)	-62(7)	106(8)
O(4)	-0.0363(1)	0.0219(2)	0.3386(1)	439(6)	774(9)	636(8)	-40(6)	1(5)	-103(7)
O(9)	0.4271(1)	-0.0119(2)	0.6257(1)	431(5)	516(7)	669(8)	13(5)	-46(5)	48(6)

Table 3. Positional parameters and isotropic temperature factors for hydrogen atoms (standard deviation in parentheses)

	x/a	y/b	z/c	$\beta(\text{Å})^2$
H(C2)A	0.149(1)	0.271(3)	0.591(2)	6.0(5)
H(C2)B	0.174(1)	0.437(3)	0.514(2)	6.1(5)
H(C3)A	-0.011(1)	0.316(2)	0.485(2)	5.1(4)
H(C3)B	0.028(2)	0.396(3)	0.367(2)	5.6(5)
H(C6)A	0.113(1)	-0.201(3)	0.362(2)	5.2(4)
H(C6)B	0.209(1)	-0.146(2)	0.304(2)	5.3(4)
H(C7)A	0.196(1)	-0.142(2)	0.568(2)	4.8(4)
H(C7)B	0.289(1)	-0.206(3)	0.511(2)	5.6(5)
H(C10)A	0.430(2)	0.338(3)	0.600(2)	8.1(6)
H(C10)B	0.485(2)	0.252(4)	0.512(3)	10.0(7)
H(C11)A	0.336(2)	0.500(4)	0.472(3)	10.8(9)
H(C11)B	0.401(2)	0.447(3)	0.374(3)	8.9(7)
H(C12)A	0.229(1)	0.382(2)	0.291(2)	5.3(4)
H(C12)B	0.296(1)	0.192(3)	0.287(2)	5.9(5)
H(O1) A	0.562(1)	0.407(3)	0.210(2)	6.2(5)
H(O1) B	0.597(2)	0.252(4)	0.293(2)	8.7(6)

Atomic scattering factors for C, N and O atoms were taken from the International Tables for X-ray Crystallography (1962) and those for H atoms from Stewart, Davidson and Simpson (1965). A final difference Fourier map showed no peaks larger than 0.2 e.A^{-3}. In the structure factor analysis the average value of $\omega_F \Delta F^2$ did not show a significant variation with either $|Fo|$ or $\sin\theta/\lambda$, thus validating the weighting scheme used.*

DESCRIPTION AND DISCUSSION OF THE STRUCTURE

A stereoview of a single molecule is given in Figure 1. The molecule contains a five-membered lactam ring (A) and a six-membered lactam ring (B) joined at the spiro carbon 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 spiro-dilactam. Torsion angles for rings A, B, and C are given in Figure 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 and 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 the C(9)-N(8) which has not been true in general for the five-membered lactam rings in this series.

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* The final Fo, Fc tables have been deposited with the British Library Lending Division as Supplementary Publication No. SUP00000 (9 pp., 1 microfiche). Copies may be obtained through Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

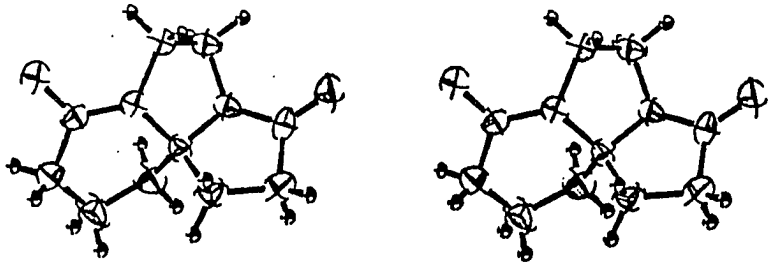

Figure 1. Stereoview of a single molecule.

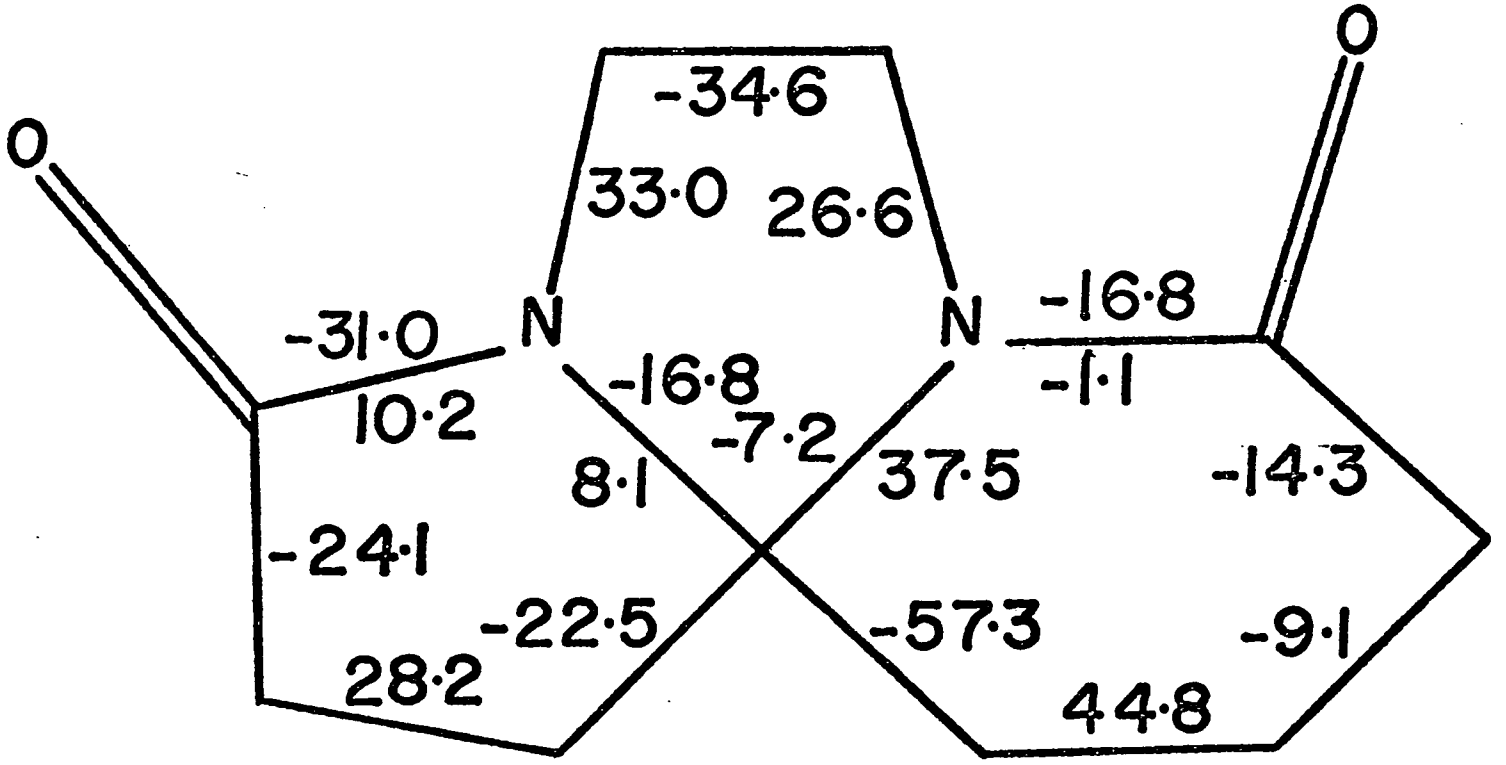

Figure 2. Torsion angles.

Bond distances are listed in Figure 3 and bond angles in Figure 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 1.23Å for the C'-O bond (Ramachandran, Kolaskar, Ramakrishnan and Sasisekharan, 1974). Marsh and Donohue (1967) list these values as 1.32Å and 1.24Å. 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 relationship between nonplanarity 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 and 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.

It can be seen from Table 4 that as the nonplanarity 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

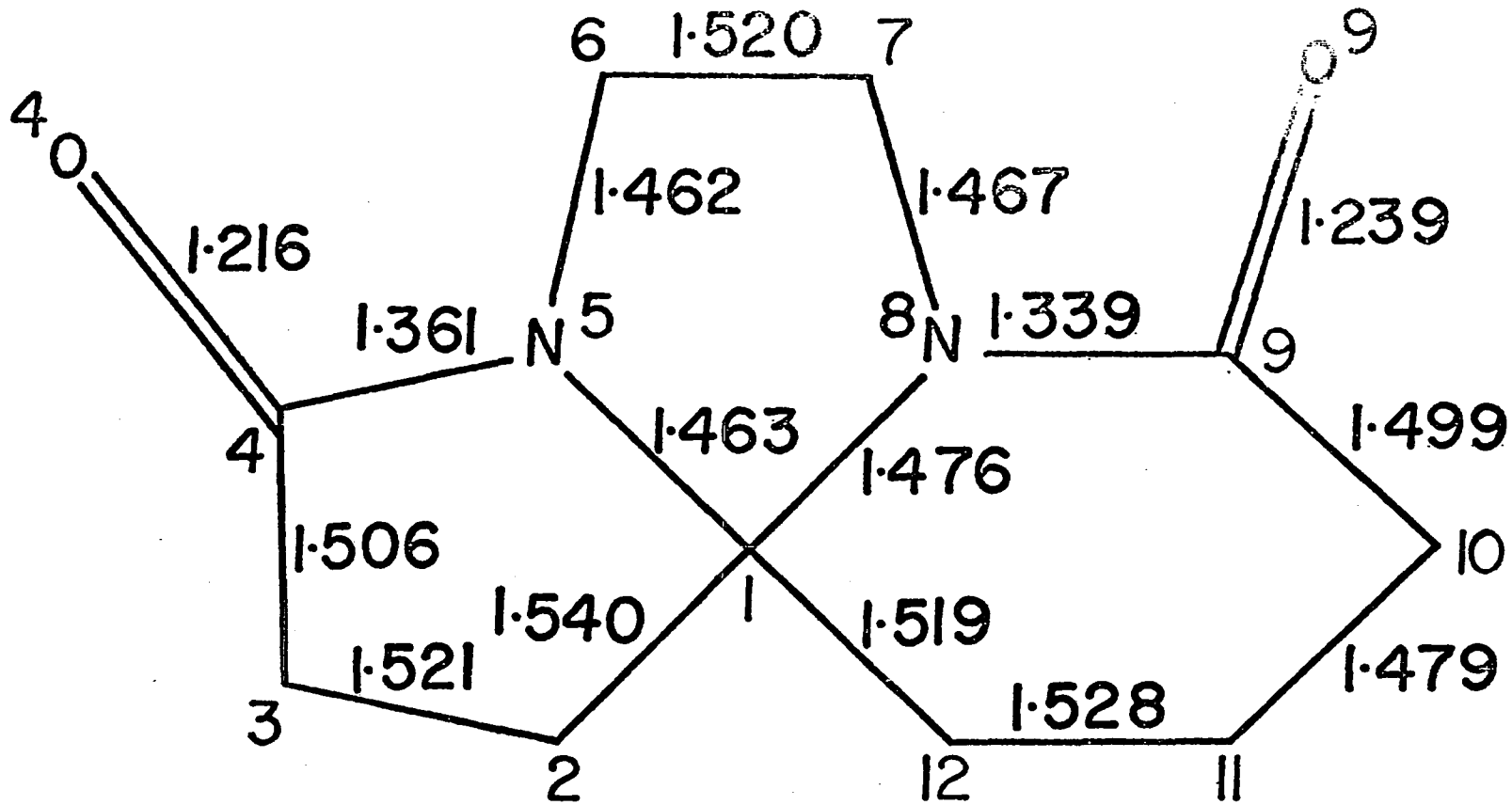

Figure 3. Bond distances.

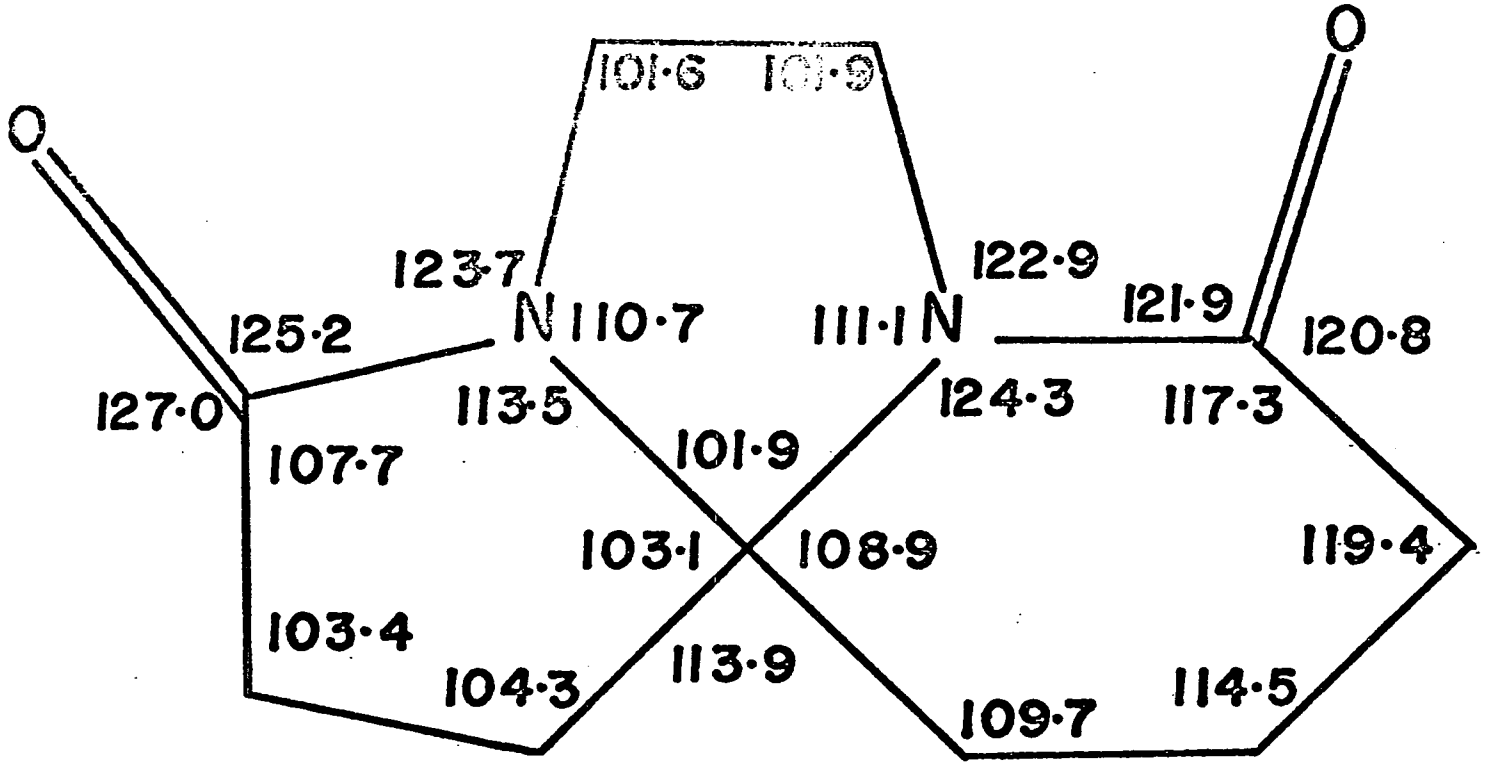

Figure 4. Bond angles.

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
IIA	-41.2	0.0	20.8	1.361	1.216
IIB	-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 and van der Helm (1975).

* Ealick, et.al. (1976).

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 and Dunitz, 1971). Such an explanation is also consistent with infrared 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 Figure 5. Two hydrogen bonds are formed in which the water molecule bridges amide groups related by the two-fold screw axis. This arrangement results in infinite spirals about the two-fold screw axis in which four hydrogen bonds are required to complete one full turn. The hydrogen bonds formed are O(9)...H(01)A'---O(1)' (H(01)A and O(1) transformed by x, 1/2-y, 1/2+z) and O(9)...H(01)B'---O(1)' (H(01)B and O(1) transformed by 1-x, -y, 1-z). The O...O distances are 2.912Å and 2.947Å, the O...H distances are 2.04Å and 2.02Å and the O....H-O angles are 169° and 174° respectively. A short intermolecular contact is also observed between H(C3)B and O(4)' of 2.42Å and between C(3) and O(4)' of 3.312Å (O(4)' transformed by -x, 1/2+y, 1/2-z).

ACKNOWLEDGEMENTS

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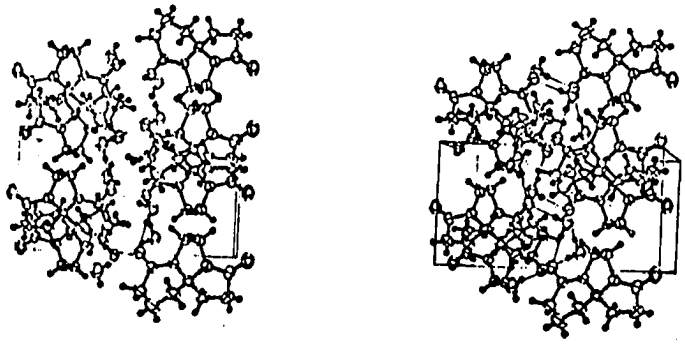

Figure 5. Packing diagram illustrating the chains of hydrogen bonds.

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A SUMMARY OF THE CRYSTALLOGRAPHIC STUDIES OF SPIRODILACTAMS CONTAINING NON-PLANAR AMIDE BONDS

Introduction

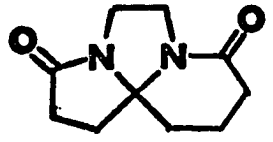
The non-planar amide group (or peptide group) has been the subject of increasing interest over the past few years. In particular structural studies have revealed the presence of a large number of compounds containing these non-planar groups. Because the conformation of the amide group helps to determine the tertiary structure of an enzyme two of the most important questions are how much energy does it require to deform an amide group and in what ways can an amide group be deformed. The protein crystallographers have found that in fitting the protein backbone to the observed electron density many peptide groups must be allowed to become non-planar. The amide group can become non-planar in three ways. The group can rotate about the C'-N bond, the nitrogen atom surroundings can change from planar to pyrimidal and the carbon atom surroundings can change from planar to pyramidal. The first two have been shown to require the least amount of energy while the latter normally contributes very little to the non-planarity.[1]

In order to study the non-planar amide bond a series of tricyclic and tetracyclic spirodilactams was investigated.[2-4] These

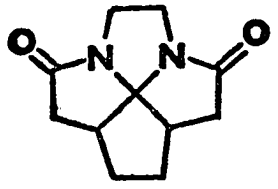
compounds were chosen because the constraints of the fused cyclic system forces the amide group to be non-planar. In addition the degree of non-planarity can be controlled by varying the size of rings in the compound. The crystal structures of the four compounds shown below were determined to obtain accurate parameters for the conforma-



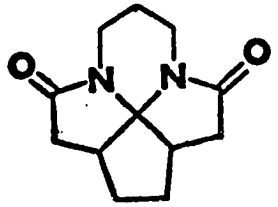
$C_9H_{12}N_2O_2$
(I)



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



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



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

tion of the amide groups. A summary of the crystallographic data for these four compounds is given in table 1. The most notable feature is the similarity of unit cell dimensions. The molecules do in fact pack in a similar fashion in their respective unit cells thus indicating that each molecule has the same general shape. Molecules I, III and IV lie on the two-fold axis in space group C2/c and belong to point group C_2 in the solid state. The four molecules contain a total of five crystallographically independent non-planar amide groups.

Description of the Non-planar Amide Group

One of the most important considerations is how to properly describe the non-planar amide group. In general 18 parameters are

Table 1. Summary of unit cell parameters for the series of spirodilactams

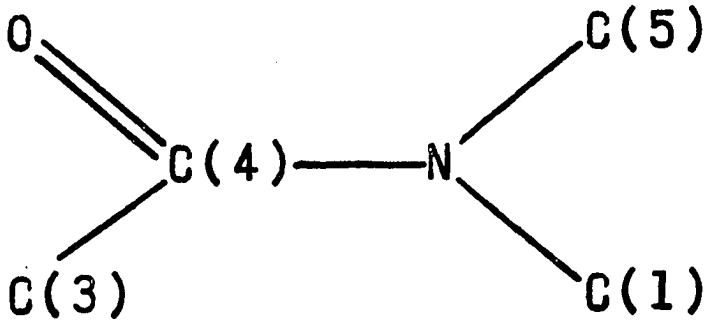
	I	II	III	IV
a(Å)	12.1576	13.4455	13.6008	13.7523
b	7.4193	7.3448	8.3177	8.9985
c	10.9614	10.7919	10.0596	10.2316
β(°)	118.437	99.410	120.563	120.527
V($Å^3$)	869.5	1051.4	979.9	1090.7
D($g.cm^{-3}$)	1.376	1.341*	1.398	1.341
M. Wt.	180.21	242.27*	206.33	220.27
Space group	C2/c	$P2_1/c$	C2/c	C2/c

*One molecule of H_2O is included in this calculation.

required to describe the arrangement of the six atoms in an amide group. If the amide group is planar only 15 parameters are required (3 to describe the plane and 12 to describe the locations of the six atoms in the plane). Consequently, the three remaining parameters describe the deviation of the amide group from planarity. The four torsion angles ω_1, ω_2, ω_3 and ω_4 as defined in table 2 and illustrated in figure 1 can be used for this purpose. It should be pointed out that any one of the ω_i is necessarily linearly dependent on the other three (i.e., $\omega_1 + \omega_2 + \omega_3 + \omega_4 = 0 \pmod{2\pi}$). As a matter of convenience we have chosen three other parameters χ_N, χ_C and τ' which are functions of the ω_i as the three linearly independent parameters.[5] The definitions in terms of ω_i are given for these parameters in table 2. Physically χ_N and χ_C are a measure of the non-planar arrangement of bonds about the N and C' atoms respectively, while τ' is a measure of pure rotation about the C'-N bond. The values of χ_N and χ_C are defined such that $\chi = 0°$ for a planar sp^2 hybridized atom while $\chi = 60°$ for a tetrahedral sp^3 hybridized atom. Similarly $\tau' = 0°$ for the cis planar amide group and 180° for the trans planar amide group. By using these three parameters the non-planar deformation of the amide group can be partitioned into the three modes discussed earlier.

Conformational Parameters for the Spirodilactams

The results for the conformational parameters of the four compounds studied are given in table 3. In the case of II the parameters for the γ lactam are listed under IIA while those for the δ-lactam are under IIB. One of the most notable features is the

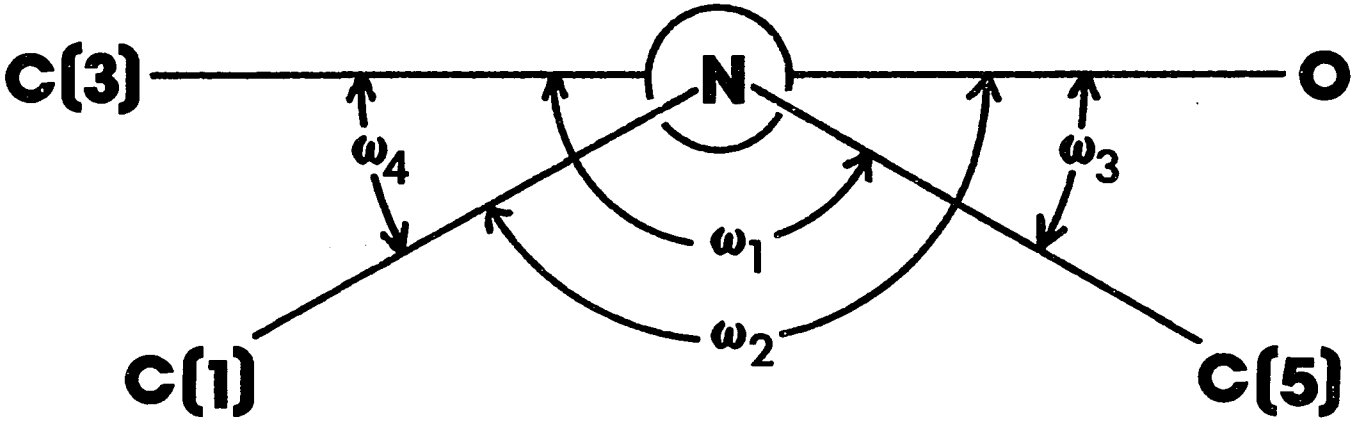


$$\omega_1 = C(3)\text{-}C(4)\text{-}N\text{-}C(5)$$
$$\omega_2 = O\text{-}C(4)\text{-}N\text{-}C(1)$$
$$\omega_3 = O\text{-}C(4)\text{-}N\text{-}C(5)$$
$$\omega_4 = C(3)\text{-}C(4)\text{-}N\text{-}C(1)$$

$$\left.\begin{aligned} X_C &= \omega_1 - \omega_3 + \pi \\ &= -\omega_2 + \omega_4 + \pi \\ X_N &= \omega_2 - \omega_3 + \pi \\ &= -\omega_1 + \omega_4 + \pi \\ \tau &= \tfrac{1}{2}(\omega_1 + \omega_2) \\ \tau' &= 2\tau = \omega_1 + \omega_2 \end{aligned}\right\} \text{Mod } 2\pi$$

Table 2. Definitions of conformational parameters for the non-planar amide group.

Figure 1. Illustration of the torsion angles (ω_i) for the non-planar amide group.



$$X_N = \omega_2 - \omega_3 + \pi$$
$$= -\omega_1 + \omega_4 + \pi$$

Table 3. Summary of conformational parameters in the series of spirodilactams

	I	IIA	IIB	III	IV
ω_1(°)	-148.5	-149.0	-162.3	-148.0	-167.1
ω_2(°)	169.8	169.8	180.1	168.5	174.4
ω_3(°)	31.8	31.8	16.8	32.2	13.5
ω_4(°)	-10.5	-10.2	1.1	-11.7	-6.3
X_N(°)	-42.0	-41.2	-16.7	-43.7	-19.1
X_C(°)	-0.3	-0.0	-0.9	-0.2	-0.6
τ'(°)	21.3	20.8	17.8	20.5	7.3
d(C'-N)(Å)	1.362	1.361	1.339	1.372	1.351
d(C'-O)(Å)	1.223	1.216	1.239	1.222	1.220

similarity of amide groups I, IIA and III. All three groups occur in a five-membered ring with at least one other five-membered ring fused to the first. In the case of IIb and IV the introduction of a six-membered ring relaxes molecular strain and allows the amide group to become more planar. Another observation is that χ_C is generally small ranging from -0.6 to 0.9°, while χ_N and τ' are large. This is consistent with the predicted energy requirements for the three modes of amide group deformation.

Perhaps the most interesting result is seen in the values of the C'-N and C'-O bond lengths. For each amide group the C'-N bond is longer than the expected value of 1.32 Å while the C'-O bond is shorter than the expected value of 1.24 Å.[6] This can be explained on the basis that as the amide group becomes non-planar the delocalization of electrons into the C'-N bond decreases because the π overlap decreases. One therefore may predict that as the non-planarity of the amide group increases (i.e., χ_N and τ' increase) the value of d(C'-N) also increases. An examination of the results indicate that this statement is, at least, approximately true.

Correlations of Structural Parameters

Initially, the research group responsible for the synthesis of these compounds suggested a relationship between $\bar{\nu}$(C'-N) and ω_3.[7] The stretching frequency obtained from infrared data was plotted against ω_3 as measured from Dreiding models. Figure 2 shows the results along with the experimental points determined from X-ray diffraction. The plot is essentially linear although the points are not well distributed.

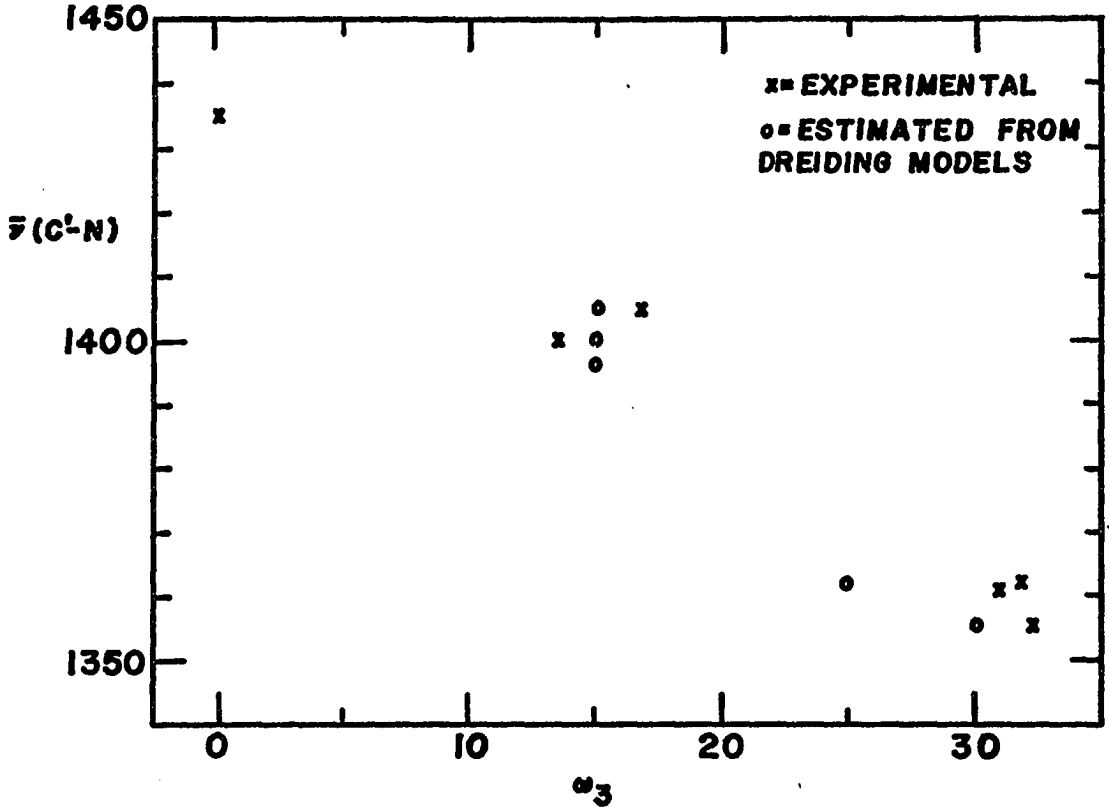


Figure 2. Plot of $\bar{\nu}$(C'-N) versus ω_3 for the series of spirodilactams. The correlation coefficient, r, is 0.988.

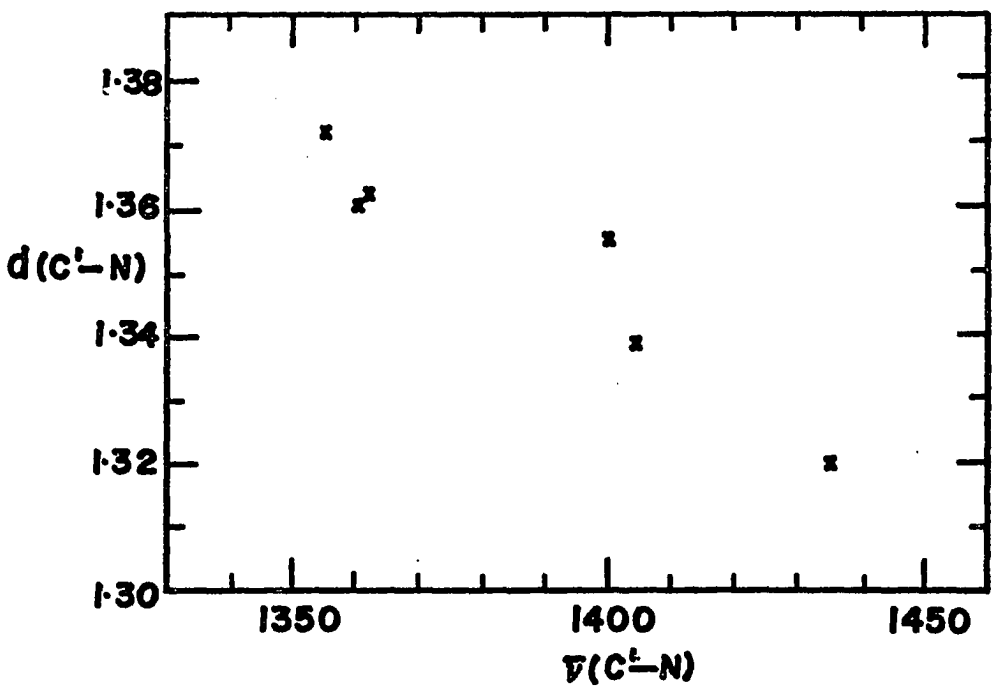


Figure 3. Plot of d(C'-N) vs $\bar{\nu}$(C'-N). (r=0.967)

A second relationship which should hold true is that $\bar{\nu}$ decreases as d(C'-N) increases. This plot is shown in figure 3 and is approximately linear. Figure 4 shows a plot of d(C'-N) vs d(C'-O). Based on the explanation given for lengthening of the C'-N one would predict that the C'-O bond shortens as the C'-N bond length increases. Although this general trend is seen to hold true, the correlation is not particularly good. Because the oxygen atom, in general, shows high thermal motion in these four structures a rigid-body model for thermal motion was fitted to each molecule. The bond distances corrected for rigid-body thermal motion are also shown in figure 4. The result shows no improvement and suggests that an alternate model for thermal motion, such as independent riding motion of the oxygen atom, should be applied.

The relationship of bond length to the parameters of non-planarity (χ_N and τ') is shown in figures 5 and 6. Although χ_N and τ' contribute independently to amide group deformation the correlations (with χ_N in particular) are good. The most reasonable correlation, however, should be one in which some function of χ_N and τ' together determine d(C'-N). Figure 7 shows a plot of d(C'-N) vs $|\chi_N|\cos\tau'$. Although this relationship holds well, resulting in a straight line, it should be pointed out that it is purely empirical.

The τ', χ_N Energy Surface

Recently Dunitz and Winkler have published a τ', χ_N energy surface based on experimental data and several assumptions.[8] Although this potential energy surface is in many ways unrefined, it does provide a model for the way in which the amide group become non-planar.

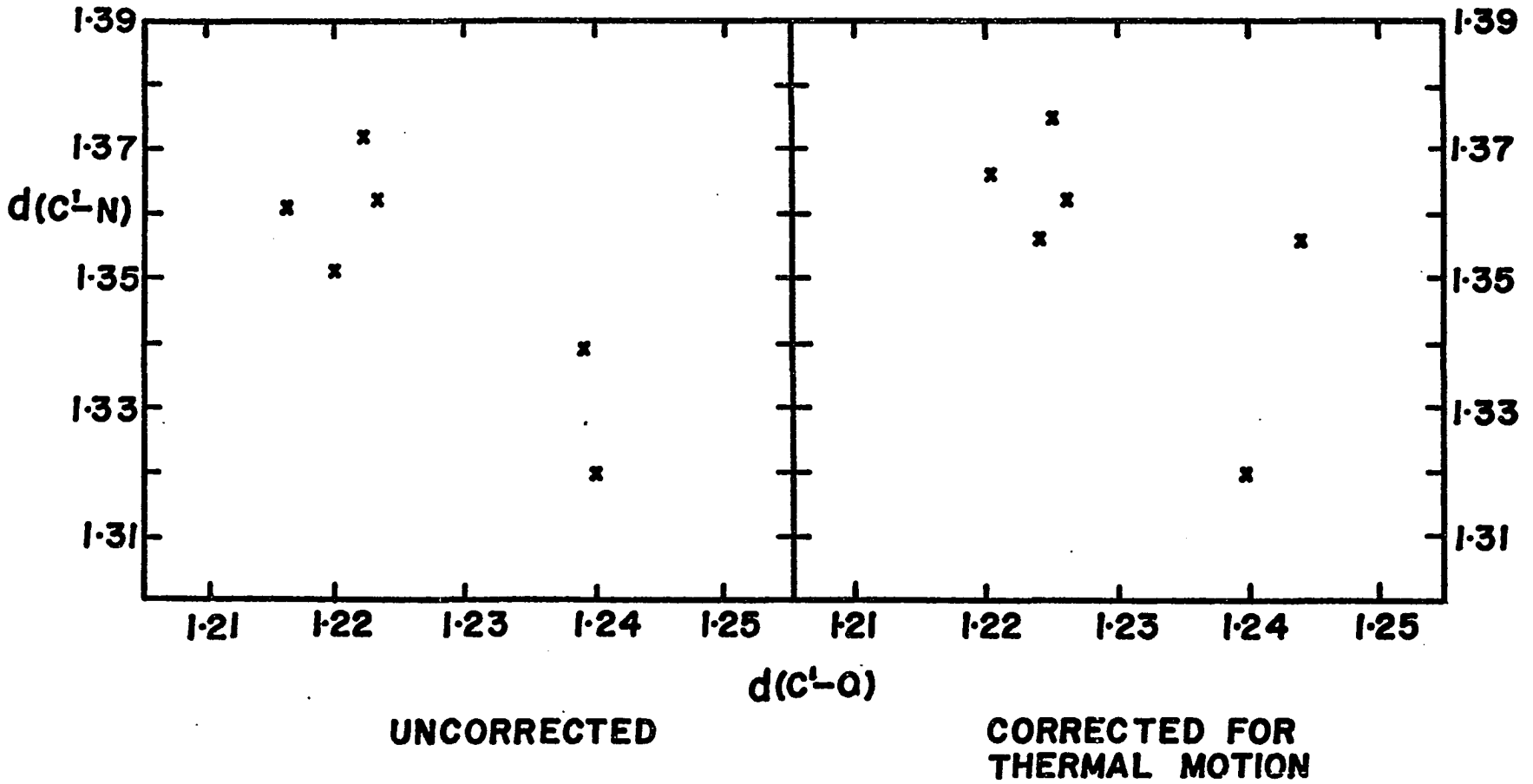


Figure 4. Plot of d(C'-N) vs d(C'-O). (r=0.839 for uncorrected and 0.871 for corrected data)

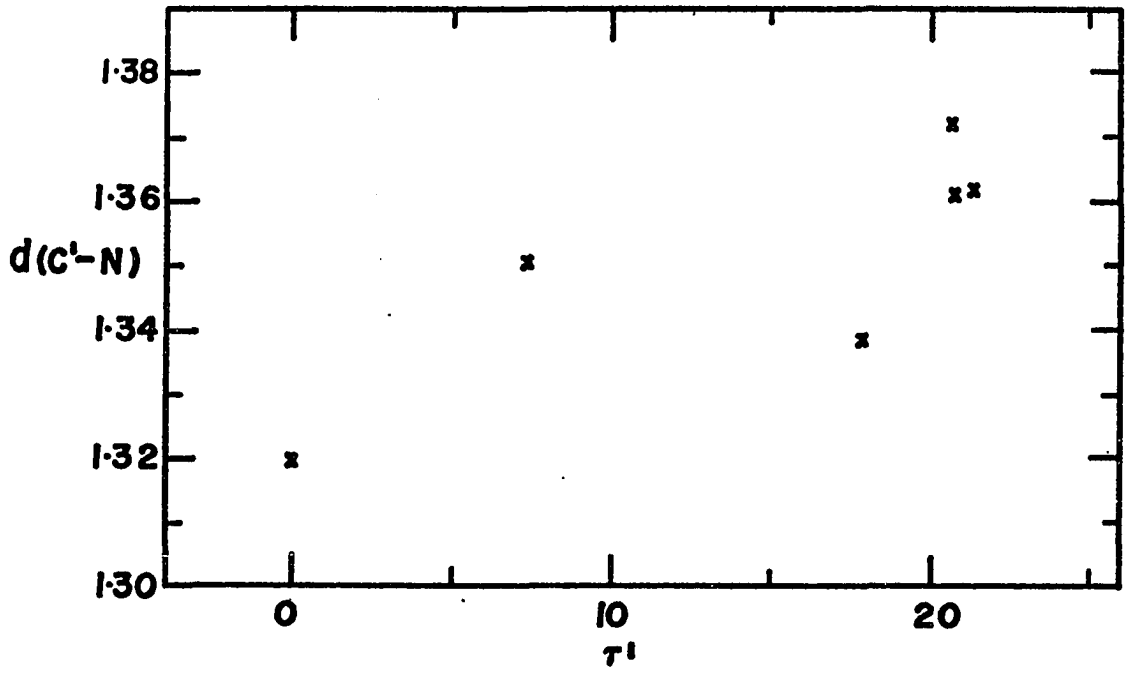


Figure 5. Plot of d(C'-N) vs τ'. (r=0.807)

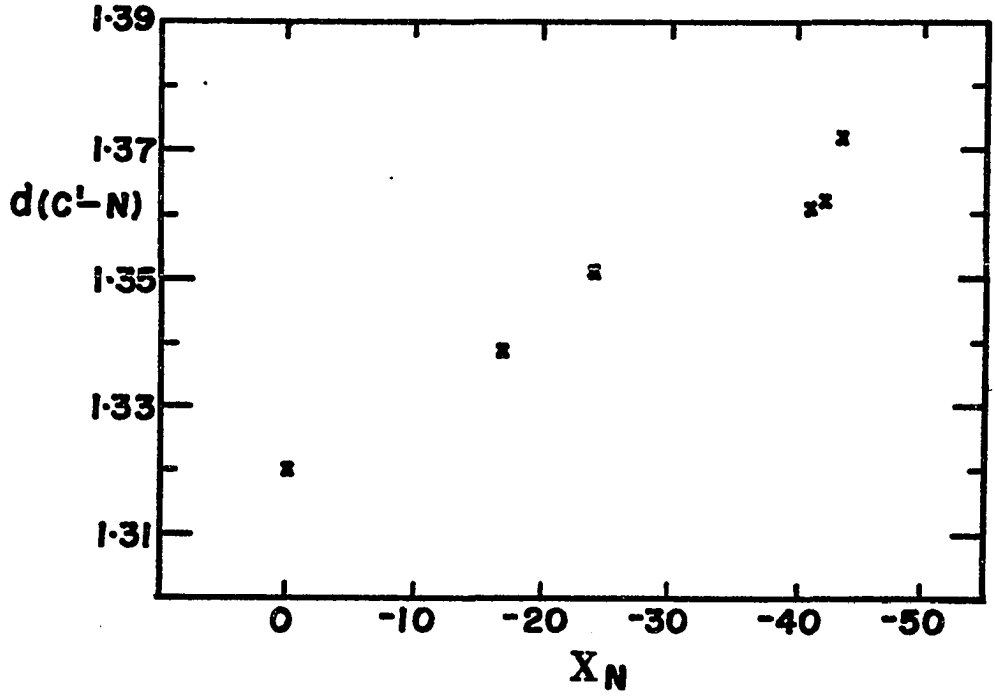


Figure 6. Plot of d(C'-N) vs χ_N. (r=0.962)

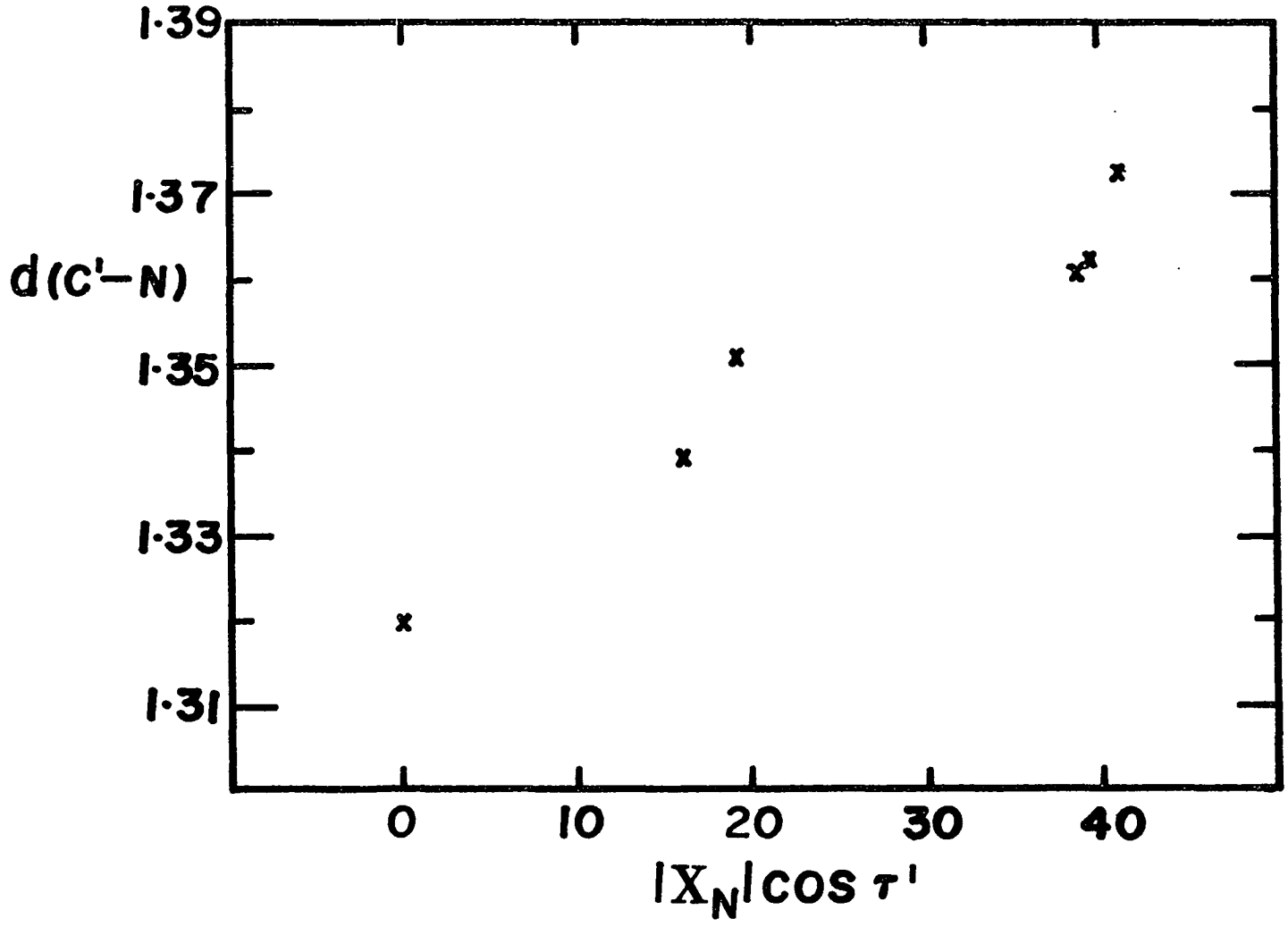


Figure 7. Plot of d(C'-N) vs $|\chi_N|\cos\tau'$. (r=0.934)

Based on this potential energy surface a minimum energy profile can be established in which for low or moderate values $\chi_N \approx 2\tau'$. The polycyclic spirodilactams, in particular compound III, provide an interesting test for the validity of the potential energy surface. By considering the restrictions imposed by the tetracyclic system which apply to the amide group a small area on the energy surface can be probed.

The way in which the amide group is constrained can best be examined in terms of the pseudo-symmetry of the molecule. Figure 8 illustrates the various point groups which III may approximate. If one assumes, for example, that the point symmetry is D_{2d} only a very limited number of combinations of τ' and χ_N are allowed. In other words, the pseudo-symmetry of the tetracyclic system constrains the molecule to certain areas of the energy surface. The condition which must hold in any case is that the (τ', χ_N) coordinates must correspond to the minimum energy point on the restricted portion of the surface. In this manner it is possible to test the validity of the proposed energy surface.

If one assumes that the very complex set of constraints imposed by the molecule can be approximated by assigning a point group then the molecule is no longer allowed to move along the minimum energy profile line. Instead, as energy is added to the molecule, it will follow a pathway which allows the molecule to maintain its point symmetry. The point at which this pathway intersects the minimum energy profile line should correspond to the experimentally observed τ' and χ_N values. In order to test the above argument a computer program was written to randomly generate molecules having the gross

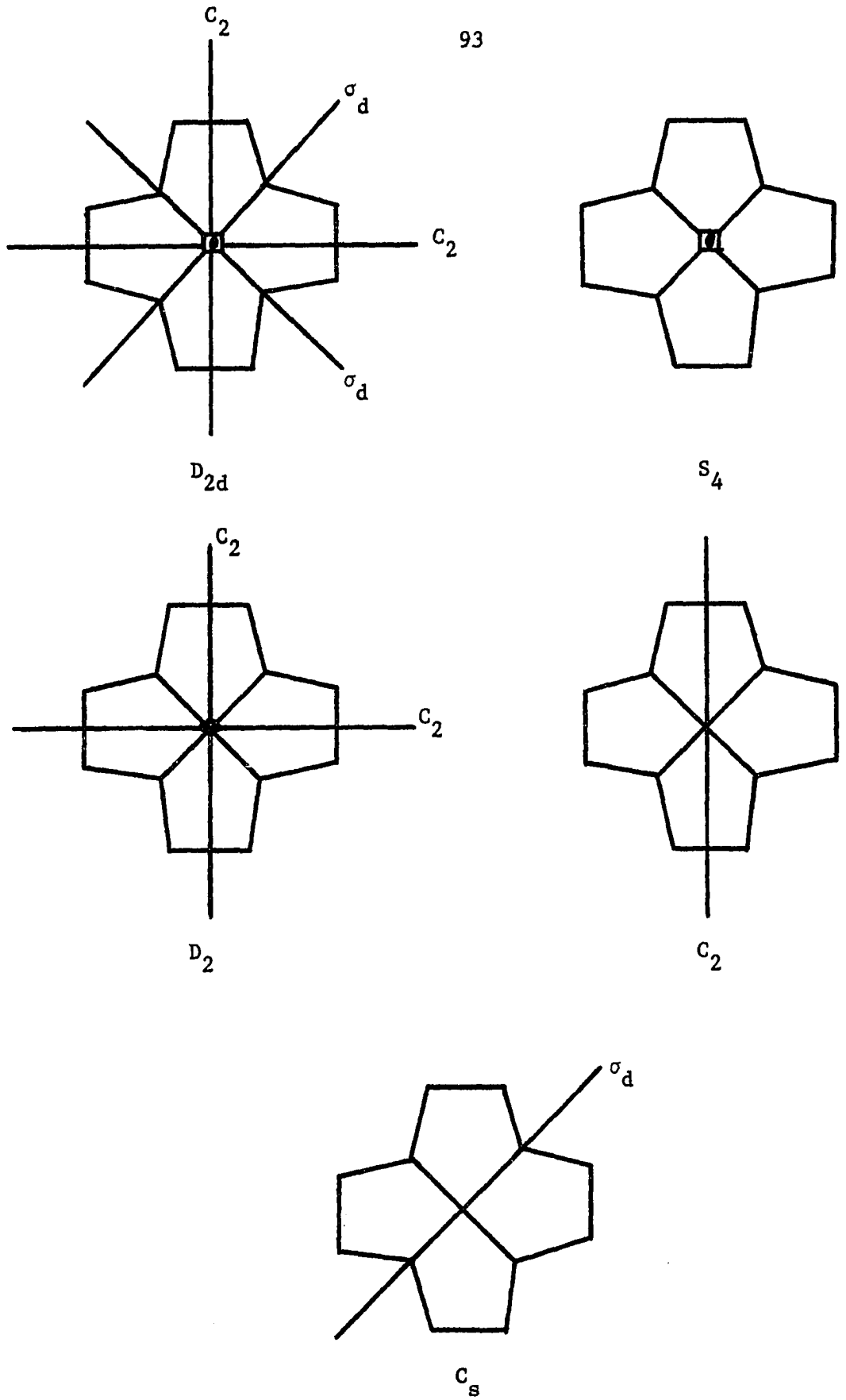


Figure 8. Possible symmetries for spirodilactam III.

chemical structure of III and a specific point symmetry.

The first point group attempted was D_{2d} because it requires the fewest number of parameters (5) to entirely describe the molecule. Three parameters were fixed by assuming normal bond distances and complete connectivity of the atoms. The remaining two parameters were allowed to vary in the form of bond angles. The generated molecules seemed to in general have unreasonable values of χ_N and τ' and it was concluded that point group D_{2d} (in particular the σ_d mirror planes) was too restrictive and a less symmetrical point group should be assumed.

The next point group attempted was D_2 which requires 9 parameters to specify molecule III. Five of these parameters were fixed by defining bond lengths while two other parameters were used to constrain the central atom to perfect sp^3 hybridization (i.e., all angles equal 109.5°). The remaining two parameters were allowed to vary by translating the two independent bonds lying on the two-fold axes along their respective two-fold axis. The initial result was again unreasonable values for χ_N and τ' and a plot of τ' versus χ_N failed to give many points which lie on the base of the potential energy surface shown in figure 9.

At this point no further data was analyzed but the problem was reevaluated resulting in suggestions for further modifications. The possibility of again lowering the molecular symmetry is unattractive because the number of independent parameters would no longer describe the restrictions on the molecular geometry. A better possibility is to remove the restriction of 109.5° bond angles at the central

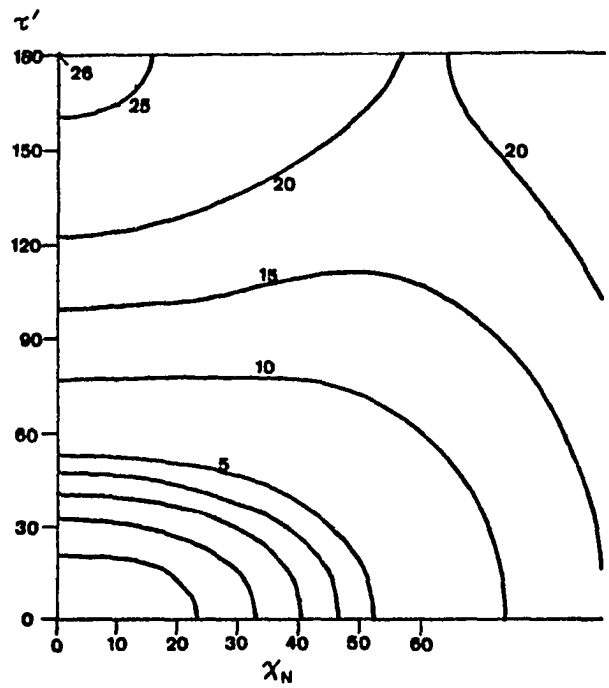


Figure 9. The χ_N,τ' energy surface for the amide group.[8] The contour levels are 1Kcal from 0 to 5 and every 5Kcal greater than 5.

carbon atom. A preliminary examination of the results of flattening of the molecular center does indicate that reasonable values of χ_N and τ' are attainable. The flattening of the central atom also renders a molecule more similar to the experimentally observed molecular geometry of III. That is, the angles interior to a five-membered ring decreases from 109.5° while the remaining two angles increase (the observed value for III is 118.8°). Another factor which must be considered is the credibility of the overall molecular structure. Molecules having the proper symmetry but unreasonable bond angles may provide anomalous values of χ_N and τ'. A criterion should be established to test for unreasonable molecules and exclude them from further consideration.

In conclusion the observation of molecular structures of the polycyclic spirodilactams may provide an interesting and unique test for the potential energy surface of Dunitz and Winkler. These molecular structures also contribute to the understanding of the deformation of the amide group and the relationship between χ_N and τ'. Such a relationship may prove valuable in such areas as protein crystallography in which amide group deformation is essential in fitting the backbone structure to the observed electron density map.

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