

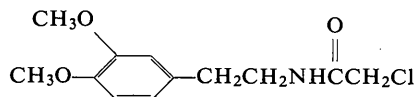
**The Identification and Crystal Structure of
1,2,5a,7b-Tetrahydro-5a,5b-dimethoxy-5bH-cyclobuta[1,4]cyclobuta[1,2,3gh]-pyrrolizin-
-4(5H)-one, a Photolysis Product from *N*-Chloroacetyl-3,4-dimethoxyphenethylamine**

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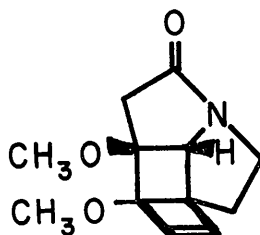
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Irradiation of



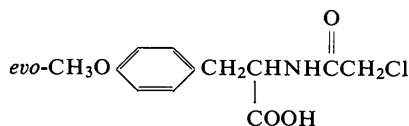
produces an unusual photocyclization product (m.p. 123.5°) which has been identified by an X-ray analysis of its crystal structure to be



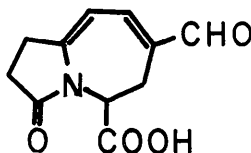
The material crystallizes in the orthorhombic system, space group $P2_12_12_1$ with cell parameters $a = 11.75 \pm 0.02$, $b = 6.27 \pm 0.02$, and $c = 14.70 \pm 0.03$ Å and four molecules in the unit cell. The structure was obtained by determining phases directly from the structure factor magnitudes by the use of the symbolic addition procedure for noncentrosymmetric space groups. Bond lengths in this highly strained molecule are quite normal. Each of the two four-membered rings is planar with a dihedral angle of 115.4° between their planes. In each of the five-membered rings, four atoms are coplanar and one is out of the plane.

Introduction

Irradiation of *N*-chloroacetyl derivatives of aromatic amino acids and amines results in photocyclization, often without changing the original chromophore (Yonemitsu, Cerutti & Witkop, 1966). By contrast, the irradiation of

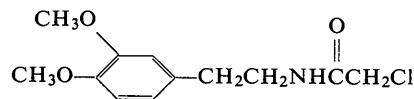


produced a drastically rearranged product,

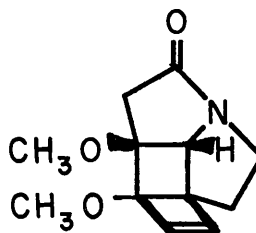


(Yonemitsu, Witkop & Karle, 1967) whose crystal structure has been reported (Karle, Karle & Estlin, 1967).

The irradiation of a closely related material



yielded several polycyclic products (Yonemitsu, Okuno, Kanaoka, Karle & Witkop, 1968). Among them was a product $C_{12}H_{15}NO_3$, in 10–12% yield (m.p. 123.5°), whose structural formula had not been deduced. The purpose of this investigation was to establish the structural formula and molecular configuration of this photolysis product. The X-ray analysis shows the unusual product to be



Experimental

The crystalline material was supplied by Dr B. Witkop of the National Institutes of Health. The compound crystallized in prisms elongated along the *b* axis and showed good optical extinctions. All of the data were taken on two crystals mounted along the *b* and *c* axes. The intensity data were collected on photographic films by means of the multiple-film equi-inclination Weissenberg technique and the intensities were read by means of visual comparison with a calibrated film strip. Corrections were made for spot size and Lorentz and polarization factors. The data were cross-correlated and placed on an absolute scale by means of a *K* curve (Karle & Hauptman, 1953). Both structure factor magnitudes $|F|$ and normalized structure factor magnitudes $|E|$ were computed. The values of the statistical averages for $\langle |E| \rangle$ and for $\langle ||E|^2 - 1 \rangle$ for the noncentrosymmetric reflections were 0.854 and 0.807 respectively, as compared with 0.886 and 0.736, the theoretical values for the noncentrosymmetric space groups. Cell parameters were measured by precession photographs. These along with other physical constants of the compound are listed in Table 1.

Table 1. Physical constants

Molecular formula	C ₁₂ H ₁₅ NO ₃
Molecular weight	221
Melting point	122–123.5 °C
Habit	prismatic <i>b</i>
Crystal size	~0.2 × 1.0 × 0.35 mm
Space group	P2 ₁ 2 ₁ 2 ₁
<i>a</i>	11.75 ± 0.02 Å

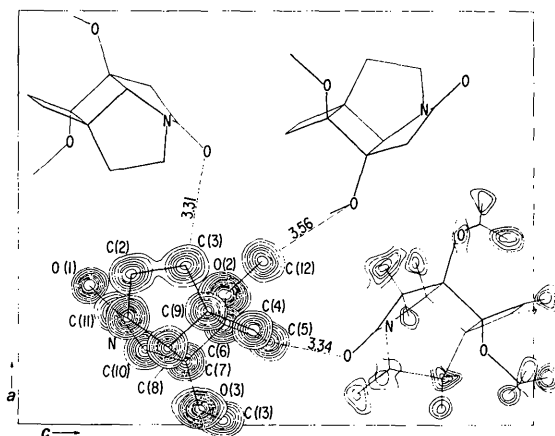


Fig. 1. Contents of the unit cell projected down along the *b* axis. On the lower left-hand side, sections of the final electron density map are plotted. The contours are spaced by 1 e.Å⁻³ beginning with the 1 e.Å⁻³ level. The difference map on the right shows the location of 14 of the 15 hydrogen atoms. The probable position of H(4) is shown by an X. The contours are spaced by 0.1 e.Å⁻³ beginning with the 0.3 e.Å⁻³ level. Also shown are some intermolecular distances of closest approach in Å units. Along the *b* direction two additional intermolecular distances of close approach are: C(3) to O(2), 3.56 Å, and C(4) to O(2), 3.50 Å.

Table 1 (cont.)

<i>b</i>	6.27 ± 0.02
<i>c</i>	14.70 ± 0.03
<i>V</i>	1082.2 Å ³
ρ_{calc}	1.246 g.cm ⁻³
Radiation	Cu K α , $\lambda = 1.5418$ Å
No. of independent reflections	1085
Molecules per asymmetric unit	1

Structure analysis

The symbolic addition procedure for determining phases in noncentrosymmetric space groups (Karle & Karle, 1964, 1966) was used to obtain an initial set of phases for about 60 reflections. These phases were refined and about 250 additional reflections with $|E| > 1.0$ were obtained by means of the tangent formula (Karle & Hauptman, 1956). A partial structure consisting of 12 atoms was chosen from the *E* map. The partial structure was used in a recycling procedure (Karle, 1968) employing the tangent formula in order to obtain the positions of 15 of the 16 heavy atoms in the molecule. A difference map revealed the position of the remaining atom. Inspection of the original *E* map showed that the 14 peaks of largest magnitude corresponded to 14 of the 16 heavy atoms of the molecule; however peaks for C(9) and C(12) were not present.

The phase determination, however, was not immediately successful for this crystal. Several different determinations were made by use of different sets of reflections for origin specification and symbol assignment which yielded incorrect *E* maps, usually characterized by one very large peak. The difficulty in each case arose from the existence of several combinations of reflections with large $|E|$ magnitudes which did not satisfy the sum of angles formula,

$$\Phi_h \sim \Phi_k + \Phi_{h-k}, \quad (1)$$

sufficiently well.

The assignments used to implement equation (1) in the successful trial are listed in Table 2. The most probable assignment for the symbols was $m = -\pi/2$ and $a + b = \pi$. Since *a* and *b* represent the phases of real structure factors, only two possibilities existed. For the correct set of phases, $a = \pi$ and $b = 0$.

Table 2. Phase assignments for specifying the origin and implementing equation (1)

$ E $	<i>h</i>	<i>k</i>	<i>l</i>	ϕ	
1.98	13	0	8	π	} origin assignment
2.85	9	3	0	$+\pi/2$	
2.10	4	0	5	$+\pi/2$	
2.38	1	1	1	$c \rightarrow +\pi/2$,	} enantiomorph assignment
3.05	0	4	14	<i>a</i> (0, π)	
1.93	10	2	0	<i>b</i> (0, π)	
2.47	7	1	0	<i>m</i> ($\pm\pi/2$)	

The coordinates and thermal factors for the 16 heavy atoms were refined by full-matrix least-squares. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 0.5$

Table 3 (cont.)

10 0 L	10 3 L	11 1 L	11 4 L	12 2 L	13 1 L	14 1 L
0 9.8 1 15.3 2 10.2 3 0.0 4 16.3 5 0.0 6 5.2 7 10.2 8 7.1 9 0.0 10 0.0 11 0.0 12 0.0 13 0.0 14 2.7	0 10.2 1 7.6 2 18.5 3 9.2 4 5.2 5 7.3 6 0.0 7 0.0 8 0.0 9 10.0 10 0.0 11 0.0 12 0.0 13 0.0 14 2.7	0 7.8 1 16.1 2 14.9 3 10.5 4 8.5 5 5.9 6 5.0 7 5.6 8 0.0 9 10.0 10 0.0 11 0.0 12 0.0 13 0.0 14 2.7	0 0.0 1 2.8 2 0.0 3 0.0 4 0.0 5 0.0 6 0.0 7 5.4 8 1.2 9 0.0 10 0.0 11 0.0 12 0.0 13 0.0 14 2.7	0 0.0 1 4.8 2 10.7 3 8.2 4 4.6 5 4.4 6 0.0 7 0.0 8 6.3 9 0.0 10 4.4 11 0.0 12 0.0 13 0.0 14 2.7	0 14.6 1 7.2 2 0.0 3 0.0 4 0.0 5 0.0 6 7.4 7 0.0 8 5.4 9 8.0 10 5.1 11 5.1 12 7.1 13 4.9 14 2.9	0 7.1 1 5.0 2 2.6 3 4.7 4 7.7 5 5.7 6 6.0 7 0.0 8 3.7 9 8.2 10 4.2 11 4.4 12 3.6 13 1.8 14 0.5

Table 4. Fractional atomic coordinates and thermal parameters for C₁₂H₁₅NO₃

Thermal parameters are of the form

$$T = \exp [- (\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$$

	x	y	z	β_{11} (Å ² × 10 ⁴)	β_{22} (Å ² × 10 ⁴)	β_{33} (Å ² × 10 ⁴)	β_{12} (Å ² × 10 ⁴)	β_{13} (Å ² × 10 ⁴)	β_{23} (Å ² × 10 ⁴)
N	0-2603	0-8650	0-2098	49	181	28	12	5	10
C(2)	0-3652	0-9949	0-2184	53	190	53	-8	17	-1
C(3)	0-3869	1-0024	0-3233	58	206	51	-30	10	4
C(4)	0-2293	1-0059	0-4573	57	232	36	-17	3	-28
C(5)	0-2035	0-8118	0-4844	46	319	27	22	0	-6
C(6)	0-2440	0-7021	0-3993	38	168	30	0	0	-13
C(7)	0-1528	0-6813	0-3233	20	186	35	-7	0	-6
C(8)	0-1863	0-9050	0-2891	42	194	25	12	-3	-8
C(9)	0-2755	0-9314	0-3661	40	265	31	-6	-4	-18
C(10)	0-1808	0-5251	0-2451	46	276	36	-15	-4	-17
C(11)	0-2697	0-6582	0-1910	50	235	38	0	0	10
C(12)	0-4001	0-5305	0-4738	67	356	33	24	-19	14
C(13)	0-0126	0-4777	0-3961	48	333	64	-10	1	-18
O(1)	0-3386	0-5757	0-1368	65	340	53	6	14	-47
O(2)	0-3178	0-5237	0-4013	42	137	42	16	-15	-7
O(3)	0-0375	0-6731	0-3512	23	222	52	-1	1	11
H(8)	0-105	1-058	0-270						
H(10-1)	0-117	0-492	0-208						
H(10-2)	0-237	0-408	0-255						
H(2-1)	0-425	0-925	0-155						
H(2-2)	0-383	1-150	0-200						
H(3-1)	0-390	1-183	0-328						
H(3-2)	0-458	0-875	0-320						
[H(4)	0-192	1-125	0-4831						
H(5)	0-192	0-783	0-525						
H(13-1)	0-050	0-425	0-450						
H(13-2)	0-033	0-342	0-355						
H(13-3)	0-042	0-475	0-400						
H(12-1)	0-367	0-308	0-483						
H(12-2)	0-425	0-675	0-450						
H(12-3)	0-383	0-508	0-545						

Standard deviations:

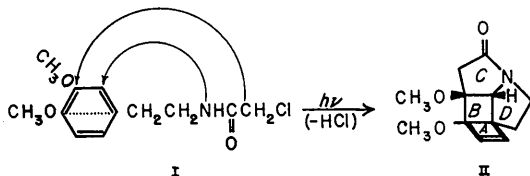
N	0-0006	0-0017	0-0005	5	37	3	10	4	9
C	0-0008	0-0019	0-0006	6	44	4	14	4	12
O	0-0005	0-0013	0-0005	4	29	3	9	3	9

for $|F_o|=0$, $w=1$ for $|F_o|<15$, and $w=15/|F_o|$ for $|F_o|>15$. The scattering factors used were those listed in *International Tables for X-ray Crystallography* (1962). A difference map computed after the anisotropic refinement, $R=11.3\%$, revealed the approximate positions of 14 of the 15 hydrogen atoms as may be seen on the lower right side of Fig. 1. Inclusion of the hydrogen atoms as constant parameters in the refinement reduced the R value to 10.0%.

Observed and calculated structure factors and phase angles expressed in radians are listed in Table 3. The refined coordinates and thermal factors of the heavy atoms and the approximate coordinates for the hydrogen atoms are listed in Table 4. An electron density map based on the refined structure is illustrated in Fig. 1.

Discussion

The X-ray analysis shows that the reaction is



A possible mechanism for this reaction has been proposed (Yonemitsu, Okuno, Kanaoka, Karle & Witkop, 1968). The starting material is optically inactive. Since the product contains asymmetric C atoms, it might be expected that the product would crystallize as a racemate. However, II crystallizes in space group $P2_12_12_1$, and hence the crystal consists of molecules of one hand only. Presumably separate crystals were formed of the D- and L-molecules. Unfortunately the crystal faces were not well enough developed to be able to recognize visually the right- and left-handed crystals.

The geometry of the molecule can be seen in the stereodiagram in Fig. 2. Ring C containing the peptide group is in the *trans*-configuration with respect to ring A. This configuration is forced by the cyclization pro-

cess. Similarly, the two methoxy groups are also *trans* with respect to each other.

Bond distances and angles are shown in Fig. 3. Standard deviations based solely on the least-squares fit are ~ 0.015 Å for the bond lengths and $\sim 1.2^\circ$ for the angles. Other sources of error would increase the standard deviations. Owing to the presence of the fused four- and five-membered rings the molecule is highly strained, especially at C(6) and C(9) were at each site two adjacent bond angles are only $85\text{--}90^\circ$, and at C(8) where three bond angles range from $92\text{--}105^\circ$. Consequently, at C(6) and C(9) there are bond angles as large as $126\text{--}127^\circ$ which would be expected to be near to a tetrahedral value in a less constrained molecule. Bond lengths, on the other hand, have normal values. For example, the peptide group in ring C has the same bond lengths, within the standard deviations, as peptide groups in various other molecules, e.g. L-leucyl-L-propylglycine (Leung & Marsh, 1958).

Least-squares planes have been computed for rings A, B, C and D (Schomaker, Waser, Marsh & Bergman, 1959). The equations and deviations of atoms from these planes are shown in Table 5. The two four-membered rings are both planar. Saturated four-membered rings are often found to be skewed as in e.g. C_4Cl_8 (Owen & Hoard, 1951), anemonin (Karle & Karle, 1966), the 5,5:6,6 *cis* photodimer of thymine (Camerman & Camerman, 1968), and *cis*-1,2-cyclobutane dicarboxylic acid (Van der Helm, Sims & Seigler, 1967). When compounds containing saturated four-membered rings have a center of symmetry and crystallize on a center of symmetry of the space group, then they necessarily possess a planar cyclobutane group, as in e.g. *trans*-1,3-cyclobutane dicarboxylic acid (Margulis & Fischer, 1967) and the 5,6:5,6 *trans* photodimer of thymine (Einstein, Hosszu, Longworth, Rahn & Wei, 1967). In the present case, with the constraints imposed by the fused-ring system upon the molecule, the planar configuration evidently prevails. The dihedral angle between the two four-membered rings is 115.4° .

Neither of the five-membered rings is planar. Like most saturated five-membered rings, four atoms are

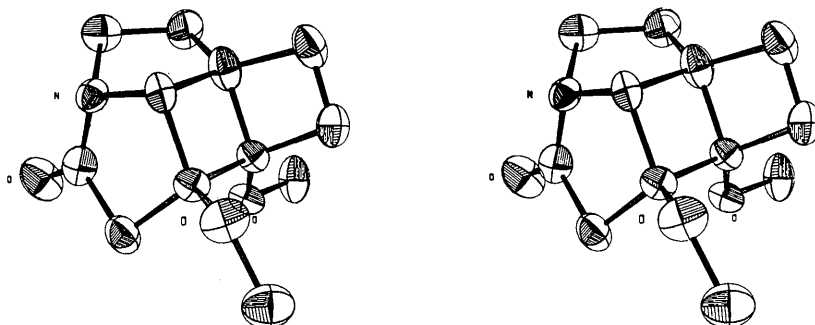


Fig. 2. A stereodiagram of the molecule (Johnson, 1965).

Table 5. *Least-squares planes and deviations*

The coordinates listed in Table 4 may be substituted directly into these equations.

Plane A		Plane B	
Atoms: C(4), C(5), C(6), C(9)		Atoms: C(6), C(7), C(8), C(9)	
Formula: $0.1070x - 0.6147y + 5.8984z = 4.5349$		Formula: $-8.1479x + 2.4848y + 8.8416z = 3.2968$	
Distances of atoms from plane:		Distances of atoms from plane:	
C(4)	-0.0004	C(6)	-0.010
C(5)	+0.0004	C(7)	+0.010
C(6)	-0.0003	C(8)	-0.010
C(9)	+0.0003	C(9)	+0.010
Plane C		Plane D	
Atoms: C(7), C(8), C(11), N		Atoms: C(2), C(3), C(8), C(9)	
Formula: $9.5222x - 0.2194y + 8.5949z = 4.0754$		Formula: $-2.9983x + 6.0509y + 0.6967z = 5.0979$	
Distances of atoms from plane:		Distances of atoms from plane:	
C(7)	+0.009	C(2)	-0.021
C(8)	-0.015	C(3)	+0.033
C(11)	-0.011	C(8)	+0.021
N	+0.017	C(9)	-0.033
C(10)	-0.362	N	-0.493
O(1)	+0.198		
Dihedral angles between planes: $A \wedge B$ 115.4°		$B \wedge D$ 126.0°	
$B \wedge C$ 103.0°		$C \wedge D$ 102.3°	

coplanar and one is significantly out of the plane. In ring C, C(10) is 0.36 Å out of the plane of the other four, and in ring D, N is 0.49 Å out of the plane.

In the unit cell, the molecules pack in such a manner as to have closest contacts between C...O pairs. The shortest intermolecular contacts are between the carbonyl oxygen O(1) and C(5') in the c direction, 3.34 Å, and O(1)...C(3') in the a direction, 3.31 Å. The next shortest approaches involve the oxygen atoms in the methoxy groups. They are O(2)...C(3') and O(2)...C(4') in the b direction and O(3)...C(12') along the c direction, with separations of 3.50 to 3.56 Å.

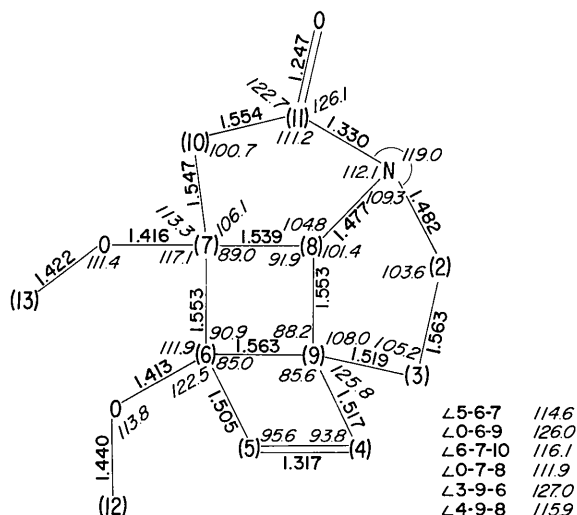


Fig. 3. Bond lengths in ångström units and bond angles in degrees. The e.s.d. as derived from the least-squares fit alone are ~ 0.015 Å for the bond lengths and $\sim 1.2^\circ$ for the angles.

We wish to thank Dr Bernhard Witkop of the National Institutes of Health for providing us with the crystals and for informative discussions.

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