Crystal and Molecular Structure of the One to One Complex of Rotenone and Carbon Tetrachloride

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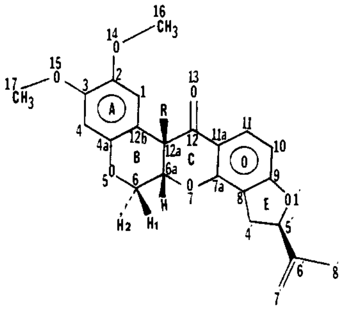
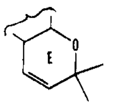
Abstract: The crystal structure of the 1:1 complex of the natural insecticide *l*-rotenone and carbon tetrachloride ($C_{23}H_{22}O_6 \cdot CCl_4$) becomes the first rotenoid structure to be solved by X-ray techniques. The space group is orthorhombic, $P2_12_12_1$. Cell dimensions are $a = 21.137$ (7), $b = 12.861$ (5), $c = 9.516$ (3) Å, and $Z = 4$. The structure has been refined to $R = 0.063$. Three of the four chlorine atoms in the carbon tetrachloride molecule are disordered. The results confirm the 6a*S*, 12a*S*, 5′*R* configurations deduced for rotenone by Büchi and coworkers and the V-shaped conformation found for rotenone in solution by Carlson and coworkers. The packing consists of stacks of nested V's of rotenone molecules, with CCl_4 molecules filling the tunnels between the stacks. The failure of some rotenoids with six-membered E rings to crystallize is apparently due to steric inhibition of this type of stacking.

Structural investigations of the widely used insecticide *l*-rotenone, which occurs in members of Leguminosae, culminated in the proposal 1 by Büchi et al.[2a] More recently, Carlson et al.[2b] have through detailed NMR studies gained considerable evidence regarding the preferred conformation of rotenone and other rotenoids in solution. To check these findings, to learn the detailed conformation of rotenone 1 in its crystalline 1:1 complex with carbon tetrachloride (used in the purification of the insecticide), and in the hope of finding an explanation why only certain rotenoids form such complexes, an X-ray study of the latter complex was undertaken.

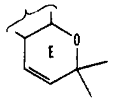


1 R = H

2 R = H,



3 R = OH,



Experimental Section

Crystals of the title compound were grown by evaporation from carbon tetrachloride. Oscillation and Weissenberg photographs of a needle 0.2 × 0.3 mm indicated orthorhombic space group $P2_12_12_1$. The cell parameters were found by least-squares fitting of the settings for the four angles of seven reflections on a Picker FACS-1 diffractometer (Cu Kα, λ 1.54178 Å, graphite monochromator) to be $a = 21.137$ (7) Å, $b = 12.861$ (5) Å, $c = 9.516$ (3) Å, $\rho_{\text{calcd}} = 1.37$ g/ml, $\rho_{\text{obsd}} = 1.34$ g/ml (flotation in $CHCl_3$-heptane), and $Z = 4$. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan, 2°/min scan rate, 10-sec background counts, attenuators when the count rate exceeded 10^4 counts/sec, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 2263 independent reflections measured, 1843 > $3\sigma(I)$ were considered observed. Three standard reflections were monitored every 50 measurements; no decrease in the intensity of the standards was observed. Lorentz and polarization corrections were applied, but no correction was made for absorption.

Attempts to locate the chlorine atoms by Patterson methods failed. Efforts to solve the structure by direct methods were unsuccessful until scaling factors were employed to build up the reflections with *l* odd, and several origins had been tried. Using MULTAN[3] with the origin and enantiomorph fixed by reflections 7 0 4(0), 7 9 0 ($\pi/2$), 15 0 1 ($\pi/2$), and 4 2 3 ($-\pi/4$), the *E* map from the phase set with the highest combined figure of merit revealed 32 of the 34 nonhydrogen atoms in the asymmetric unit. The other two nonhydrogen atoms were located from a difference map. Two cycles of full-matrix isotropic least-squares refinement of nonhydrogen atoms reduced *R* to 0.171. A difference map at this stage revealed that three chlorine atoms of the carbon tetrachloride molecule were disordered. The occupancy factors for these three chlorines were accordingly reduced and their secondary positions were included. Refinement of occupancy factors for these disordered chlorines and two cycles of anisotropic refinement reduced the *R* value to 0.099. A difference map revealed the locations of all of the hydrogen atoms and showed no significant further chlorine positions. Two more cycles of full-matrix least-squares refinement, in which nonhydrogen atoms were refined anisotropically and hydrogen atoms isotropically, reduced *R* to 0.068. Refinement to this point had been with the nonliterature[2a] absolute configuration (enantiomeric with 1); changing to the literature configuration gave $R = 0.067$ and one more cycle of refinement brought *R* down to 0.063. Refinement was terminated at this stage since the average ratio of shifts in parameters to standard deviations was less than 0.3. Unit weights were used, and refinement was based on F_o with $\Sigma w(F_o - F_c)^2$ minimized. The scattering factors used were those of Hanson et al.[4] No correction was applied for extinction. Tables of temperature factors, bond distances and angles involving hydrogens, and structure factors will appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.

Results and Discussion

The final atomic coordinates are given in Table I. As can be seen in the ORTEP[5] drawing in Figure 1, the rotenone configurations are 6a*S*, 12a*S*, 5′*R*, as proposed by Büchi et al.[2a] rather than as suggested earlier by Miyano and Matsui.[6] The conformation found is essentially that deduced from proton-proton NMR coupling constants for rotenone in solution by Carlson et al.[2b] Except for the isopropenyl group, the nonhydrogen atoms lie close to the plane of aromatic ring A and/or D, resulting in an approximately V-

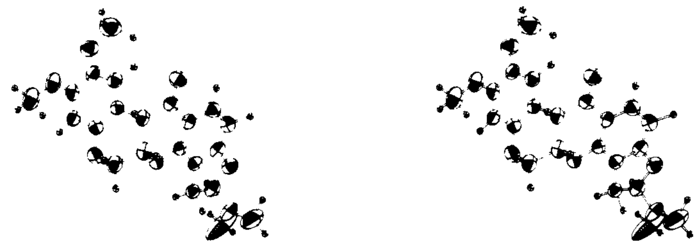


Figure 1. Stereoscopic view of a rotenone molecule. Hydrogen atoms are depicted as spheres and other atoms as 50% probability ellipsoids.

Table I. Fractional Coordinates and Estimated Standard Deviations. All Chlorines Except Cl1 Had Occupancies Less Than 1 as Discussed in the Text

Atom	*x/a*	*y/b*	*z/c*
Cl1	0.1365 (3)	0.6307 (4)	−0.2115 (6)
Cl2	0.2680 (4)	0.6041 (7)	−0.1056 (10)
Cl3	0.1922 (4)	0.4347 (5)	−0.1909 (9)
Cl4	0.1543 (5)	0.5395 (10)	0.0488 (7)
Cl2′	0.2681 (7)	0.3626 (14)	0.4605 (20)
Cl3′	0.2794 (22)	0.5244 (38)	0.2671 (36)
Cl4′	0.1595 (21)	0.4499 (26)	0.0077 (52)
C1	0.8286 (4)	0.3241 (6)	−0.8420 (9)
C2	0.8777 (4)	0.3087 (7)	−0.9389 (10)
C3	0.9101 (4)	0.3951 (7)	−0.9889 (9)
C4	0.8927 (4)	0.4925 (7)	−0.9483 (9)
C4a	0.8422 (4)	0.5075 (7)	−0.8546 (8)
O5	0.8289 (3)	0.6098 (4)	−0.8252 (6)
C6	0.7873 (4)	0.6271 (7)	−0.7066 (9)
C6a	0.7348 (4)	0.5525 (7)	−0.7007 (8)
O7	0.6960 (2)	0.5729 (4)	−0.8234 (6)
C7a	0.6504 (4)	0.5022 (6)	−0.8549 (8)
C8	0.6012 (4)	0.5348 (6)	−0.9423 (9)
C9	0.5549 (4)	0.4636 (7)	−0.9771 (9)
C10	0.5530 (4)	0.3623 (7)	−0.9284 (9)
C11	0.6022 (4)	0.3324 (7)	−0.8419 (10)
C11a	0.6505 (4)	0.4005 (7)	−0.8065 (9)
C12	0.7038 (4)	0.3641 (7)	−0.7186 (9)
C12a	0.7565 (4)	0.4404 (7)	−0.6981 (9)
C12b	0.8100 (4)	0.4240 (6)	−0.8032 (8)
O13	0.7062 (3)	0.2757 (5)	−0.6707 (7)
O14	0.9001 (3)	0.2155 (5)	−0.9788 (7)
O15	0.9583 (3)	0.3709 (6)	−1.0801 (7)
C16	0.8679 (6)	0.1248 (9)	−0.9252 (15)
C17	0.9992 (5)	0.4535 (9)	−1.1218 (12)
C18	0.1887 (8)	0.5550 (12)	−0.1125 (14)
O1′	0.5087 (3)	0.5064 (5)	−1.0595 (7)
C4′	0.5840 (4)	0.6393 (7)	−1.0009 (9)
C5′	0.5303 (4)	0.6086 (8)	−1.1017 (9)
C6′	0.4767 (5)	0.6826 (10)	−1.1110 (10)
C7′	0.4733 (9)	0.7432 (17)	−1.2204 (19)
C8′	0.4333 (7)	0.6881 (12)	−0.9987 (17)
HC1	0.797 (3)	0.258 (5)	−0.813 (8)
HC4	0.915 (3)	0.555 (5)	−0.971 (7)
H1C6	0.813 (3)	0.623 (6)	−0.634 (8)
H2C6	0.770 (3)	0.729 (5)	−0.717 (8)
HC6a	0.710 (3)	0.560 (6)	−0.647 (8)
HC10	0.505 (3)	0.308 (5)	−0.940 (8)
HC11	0.609 (3)	0.253 (5)	−0.814 (8)
HC12a	0.777 (3)	0.439 (5)	−0.622 (8)
H1C16	0.811 (4)	0.136 (7)	−0.946 (10)
H2C16	0.896 (4)	0.066 (7)	−0.983 (10)
H3C16	0.888 (4)	0,126 (7)	−0.841 (10)
H1C17	1.044 (4)	0.424 (8)	−1.175 (10)
H2C17	1.021 (4)	0.512 (8)	−1.040 (10)
H3C17	0.963 (4)	0.502 (8)	−1.141 (10)
H1C4′	0.619 (3)	0.679 (5)	−1.013 (7)
H2C4′	0.556 (3)	0.706 (5)	−0.937 (8)
HC5′	0.542 (3)	0.589 (5)	−1.146 (8)
H1C7′	0.440 (5)	0.760 (8)	−1.237 (10)
H2C7′	0.501 (4)	0.711 (8)	−1.275 (11)
H1C8′	0.391 (5)	0.731 (8)	−1.026 (11)
H2C8′	0.420 (4)	0.603 (8)	−1.007 (10)
H3C8′	0.452 (4)	0.691 (8)	−0.926 (11)

Table II. Bond Lengths and Angles in the Carbon Tetrachloride Molecule

Atoms	Distance (Å)	Atoms	Distance (Å)
C18–Cl1	1.747 (12)	C18–Cl4	1.710 (12)
C18–Cl2	1.793 (13)	C18–Cl2′	1.563 (18)
C18–Cl3	1.720 (13)	C18–Cl3′	1.677 (25)
		C18–Cl4′	1.876 (24)
Atoms	**Angle (deg)**	**Atoms**	**Angle (deg)**
Cl1–C18–Cl2	114.5 (0.9)	Cl2–C18–Cl4′	122.6 (0.9)
Cl1–C18–Cl3	107.2 (0.8)	Cl3–C18–Cl4	107.7 (0.9)
Cl1–C18–Cl4	106.3 (0.9)	Cl3–C18–Cl2′	141.0 (1.2)
Cl1–C18–Cl2′	103.3 (0.9)	Cl3–C18–Cl3′	29.7 (1.4)
Cl1–C18–Cl3′	102.7 (1.0)	Cl3–C18–Cl4′	68.3 (1.5)
Cl1–C18–Cl4	121.5 (1.4)	Cl4–C18–Cl2′	85.9 (0.9)
Cl2–C18–Cl3	107.0 (0.9)	Cl4–C18–Cl3′	135.2 (1.0)
Cl2–C18–Cl4	113.9 (0.9)	Cl4–C18–Cl4′	39.5 (1.5)
Cl2–C18–Cl2′	36.6 (1.5)	Cl2′–C18–Cl3′	119.6 (0.9)
Cl2–C18–Cl3′	82.9 (1.0)	Cl2′–C18–Cl4′	114.3 (0.9)
		Cl3′–C18–Cl4′	95.9 (0.9)

shaped molecule with 105.3° between rings A and D. Ring B has a typical cyclohexene-like monoplanar conformation[7] with torsion (dihedral) angles starting from the C12b-C4a bond and proceeding clockwise around the ring of −3.4, 17.2, −42.7, 56.0, −40.7, and 14.7°. Carlson and coworkers[2b] deduced torsion angles of 55 and 65° for H1C6-C6-C6a-HC6a and H2C6-C6-C6a-HC6a, respectively; these agree well with our findings of 54.2 and 69.4°. Ring C adopts a 1,2-diplanar conformation[7] with torsion angles clockwise starting with the C7a-C11a bond of −1.8, −19.1, 45.3, −50.0, 30.8, and −4.6°. The torsion angles in the five-membered ring E, clockwise from C8-C9, are 2.8, 9.6, −17.8, 18.2, and −12.9°, indicating an envelope conformation[7] with the isopropenyl group equatorial as proposed earlier.[2] The methoxyl groups are almost coplanar with ring A; the angles between the plane of ring A and planes C2-O14-C16 and C3-O15-C17 have normal values[8] of 9.1 and 2.9°, respectively. Torsion angle C4′-C5′-C6′-C7′ is found to be 103.0°; from the failure to observe long range coupling between HC5′ and H2C7′ (cis to C5′) in the ^{1}H NMR spectrum of **1**,[2] it can be deduced that the isopropenyl group is not rotated this way in solution a very large fraction of the time.[9]

Figure 2 shows the bond lengths and bond angles in the rotenone molecule. The average estimated standard deviations in C-C and C-O distances are 0.011 and 0.009 Å, respectively, and in C-C-C and C-C-O angles, 0.7 and 0.6°, respectively. The average values of bond lengths in benzene rings A and D are each 1.385 Å, while the average values of angles in these rings are 119.9 and 120.0°, respectively.

The bond lengths and bond angles in the carbon tetrachloride molecule are given in Table II, and the ORTEP drawing of the molecule is shown in Figure 3. The blackened bonds go to major chlorine atoms Cl2 (occupancy factor 0.65), Cl3 (0.70), and Cl4 (0.73); the other bonds go to minor chlorines Cl2′ (0.25), Cl3′ (0.20), and Cl4′ (0.17). Distortion of the carbon tetrachloride molecule in the crystal from ideal tetrahedral geometry seems likely from the wide variation in bond lengths and bond angles in the major chlorine molecule; a similar conclusion was reached in an-

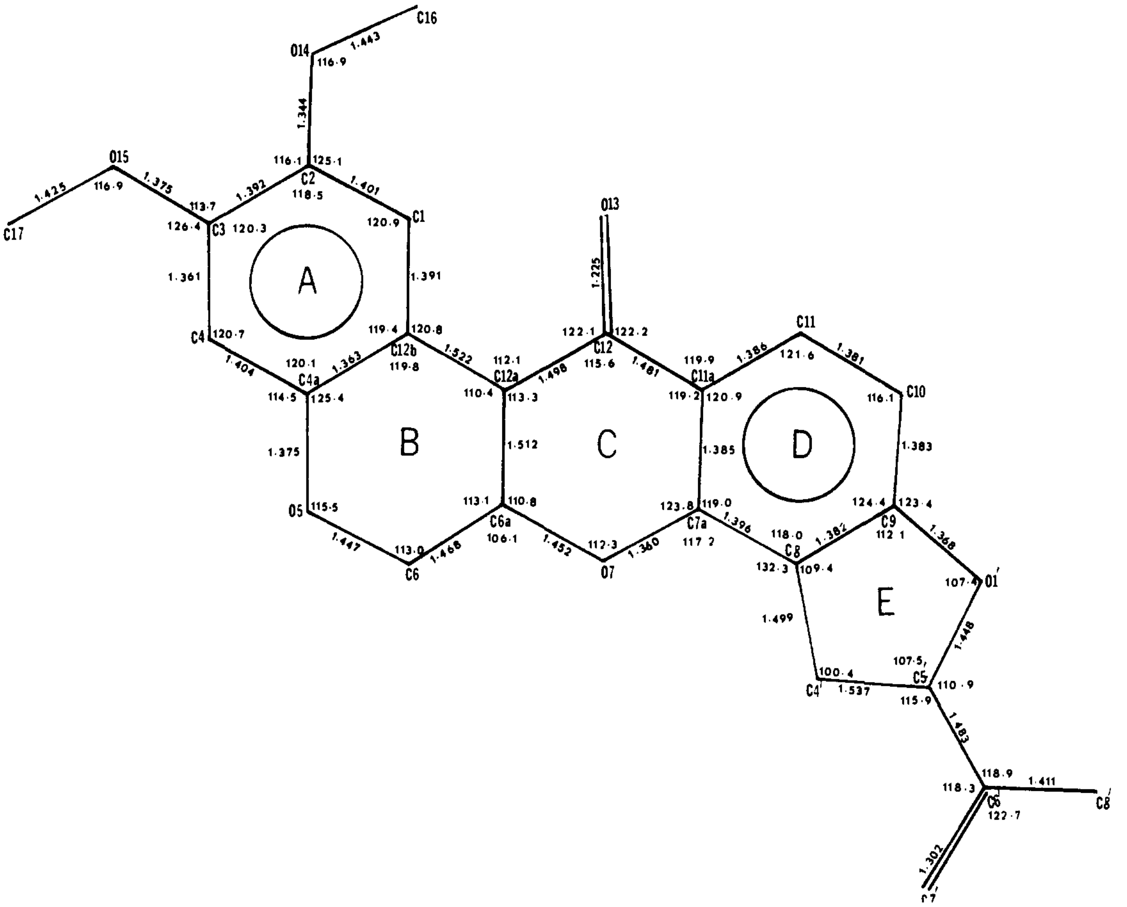


Figure 2. Bond lengths (Å) and bond angles (deg) in rotenone.

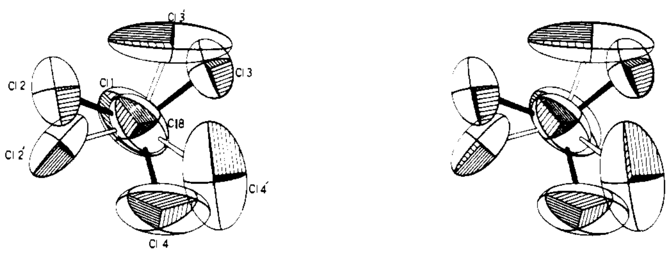


Figure 3. Stereoscopic view of a carbon tetrachloride molecule looking down the C18–Cl1 bond. Atoms are shown as 50% probability ellipsoids.

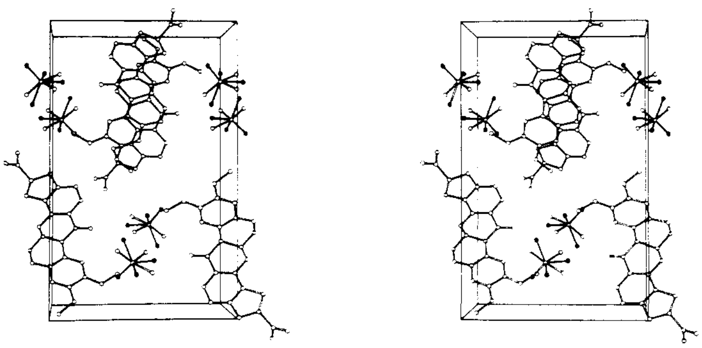
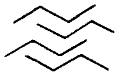


Figure 4. Stereoscopic view of a unit cell, *c* axis projection, *a* axis vertical, *b* axis horizontal.

other X-ray study of a carbon tetrachloride complex.[10] As can be seen in Figure 3, the disorder in the carbon tetrachloride involves 35° rotation about the C18–Cl1 bond. The final difference map did reveal some diffuse electron density near the disordered chlorine positions, but attempts to place and refine further partial chlorine atoms were fruitless.

Figure 4 shows the packing arrangement, with the V-shaped rotenone molecules nested like



to form stacks in the c direction (the small extra line represents the isopropenyl group); the carbon tetrachloride molecules (with major occupancy chlorines blackened) lie in tunnels between the stacks of rotenone molecules. From efforts to stack molecular models of other rotenoids in this way, it seems clear why the related rotenoids *l*-deguelin[11,12] (**2**) and *l*-tephrosin[12] (**3**) fail to crystallize; the *gem*-dimethyl group sterically interferes with the methoxyl groups in the molecule above and/or below in the stack. This unfavorable interaction is not serious in *l*-millettone[12] (like **2**, but with a methylenedioxy group replacing the two methoxyls) and *l*-dihydrodeguelin[11] (like **2**, but no double bond in ring E), both of which have been crystallized. In the latter compound, the greater flexibility of the E-ring presumably permits a conformation satisfactory for stacking.

The only intermolecular contacts less than 3.5 Å were C13-O13 (3.022 Å, surprisingly short) and C12-O13 (3.475 Å).

Acknowledgments. We thank the Public Health Service (Grant No. CA-10944) for financial aid and the University of Arizona Computer Center for computer time.

Supplementary Materials Available. Tables of temperature factors, bond distances and angles involving hydrogens, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$4.50 for photocopy or \$2.50 for microfiche, referring to code number JACS-75-5752.

References and Notes

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Applications of Artificial Intelligence for Chemical Inference. XVII. An Approach to Computer-Assisted Elucidation of Molecular Structure[1,2]

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Abstract: An interactive computer program for assisting in molecular structure elucidation is described. The program is supplied with information in the form of inferred structural fragments of an unknown together with a variety of constraints on desired and undesired structural features. The program generates all structural isomers, without duplication, consistent with this information. Our approach employs a method of atom and superatom assembly in which superatoms are imbedded within intermediate structures to yield final structures. This method permits a stepwise solution of a problem during which intermediate results can be examined interactively and constrained further during the course of generation of final structures. The program suggests solutions to a structure problem and provides a guarantee that no plausible alternatives have been overlooked.

Automation of tasks related to elucidation of molecular structure has been the focus of many, diverse research groups. Automation of analytical instrumentation, e.g., NMR spectrometers, X-ray diffractometers, represents one area of effort. Sophisticated computer programs for analysis of data in terms of molecular structure represent another broad area. This report is concerned with the latter area and describes a computer program for assisting in molecular structure elucidation based on structural features of unknown molecules derived from physical, chemical, and/or spectroscopic information.

Our program is designed to model some aspects of manual approaches to structure elucidation. These manual approaches normally involve piecing together structural fragments of arbitrary complexity, inferred from a variety of sources of information. As structures are constructed in this way, chemical knowledge and intuition serve to constrain the structural types considered plausible. Knowledge of the sample results in early elimination of unstable species, unlikely functional groupings, and so forth. Knowledge of symmetry helps prevent consideration of equivalent (duplicate) structures. We know that people well versed in the "art" of structure elucidation are capable of making intuitive leaps from data to plausible structures with surprising accuracy. Such leaps rely on broad chemical experience, reasoning by analogy, and intelligent guessing, none of which can easily be modeled in current computer programs. The task of assembly of inferred structural units into complete structures, however, is amenable to systematic treatment, as we have demonstrated for assemblies of atoms without constraints[3b] and which we discuss in this report for assemblies of structural units of arbitrary complexity (may be atoms) under constraints.

Our program, which we call CONGEN (for *CON*strained

Carhart, et al. / Computer-Assisted Elucidation of Molecular Structure