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Notes

Molecular Geometry Studies. The Crystal and Molecular Structure of a 7-Spirocyclopentylbicyclo[2.2.1]heptene Anhydride[1]

Rhoda E. R. Craig,*[2] Arnold C. Craig, Raymond D. Larsen, and Charles N. Caughlan

Department of Chemistry, Montana State University, Bozeman, Montana.

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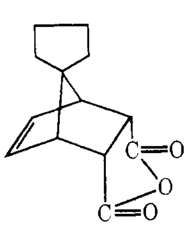
The conformation of the rigid bicyclo[2.2.1]heptane nucleus in various bifunctional derivatives (anhydrides, diacids, diesters) is essential to our study relating the molecular geometry in the solid state to the molecular geometry as determined in solution via NMR-LIS measurements.[3-5] Compound 1, which represents only the second bicyclo[2.2.1]heptane system containing a 7-spiro hydrocarbon substituent that has been reported, is one of the model compounds used in conformational equilibria determinations in the *cis*-1,2,3,6-tetrahydrophthalic anhydride series.[5]

In addition, compound 1 has been included in a series of kinetic studies on the mechanism of the endo–exo transformation.[3] Because compound 1 was the only endo compound in the series which did not thermally rearrange to the corresponding exo isomer, a knowledge of its molecular geometry in the solid state would indicate if steric requirements were too stringent to allow the reverse Diels–Alder reaction to proceed.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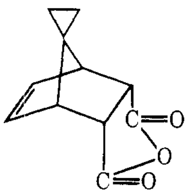
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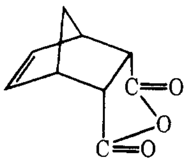
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In anhydrides 2 and 3 of the series, long carbon–carbon bonds (C_1–C_2, C_3–C_4) peculiar to some Diels–Alder adducts[6] occurred; hence we desired to further investigate this molecular asymmetry in compound 1.

Experimental Section

[3′aβ,4′α,7′α,7′aβ]-3′a,4′,7′,7′a-Tetrahydrospiro[cyclopentane-1,8′-[4,7]methanoisobenzofuran]-1′,3′-dione (1) was synthesized as previously described.[7] Colorless crystals with well-defined faces were obtained by recrystallization from solution in benzene by vapor diffusion of 60–110 °C petroleum ether into the benzene solution. Preliminary Weissenberg and precession photographs of a small crystal (ca. 0.21 × 0.24 × 0.24 mm) indicated an orthorhombic space group with systematic absences of $0kl$, $l \neq 2n$, and $h0l$, $h \neq 2n$. The choice of space group $Pca2_1$ with $Z = 4$ was confirmed by the eventual solution of the structure. Unit cell dimensions of $a = 12.3397$ (10), $b = 8.3315$ (5), and $c = 10.5058$ (11) Å were provided by least-squares refinement of 14 independent 2θ values obtained by automatic centering routines on a G.E. XRD-490 diffractometer with a scintillation counter detector using Ni filtered Cu Kα radiation. Intensity data were collected out to 120° 2θ using θ–2θ step scans with a 2° 2θ scan range for each reflection; backgrounds were counted at both extremes of each scan. Of the 854 reflections measured, 780 were considered observed by the criteria $I > 3\sigma(I)$ and were used for structure refinement. Lorentz and polarization factors were applied,[8] and the data were corrected for absorption by the method of Tompa[9] ($\rho_c = 1.342$ g cm^{-3}, μ(Cu Kα) = 7.848 cm^{-1}, transmission factor range 0.903–0.938). Weights were calculated by the method of Stout and Jensen,[10] $w(F) = [(k/4LpI)(\sigma^2(I) + (0.03I)^2)]^{-1}$. Scattering factors for nonhydrogen atoms were taken from Cromer and Mann;[11] the scattering factor curve for hydrogen was that of Stewart, Davidson, and Simpson.[12] No correction was made for extinction.

The structure was solved by direct methods using the program MULTAN.[8] Using phases chosen by the program for 80 reflections, an E map revealed the positions of 15 of the 16 nonhydrogen atoms in the asymmetric unit. These positions were refined isotropically by full-matrix least squares minimizing $\Sigma w \Delta F^2$, and a subsequent Fourier map revealed the remaining nonhydrogen atom. The structure was refined isotropically to an R factor of 10.7% ($R = \Sigma||F_o| - F_c||/\Sigma F_o$); further refinement, treating the vibration of all atoms anisotropically, reduced the R to 8.0%. A difference Fourier was calculated which revealed the positions of all hydrogen atoms. Hydrogen atoms were assigned the refined isotropic temperature factors of the atoms to which they were attached, and subsequent refinement of all positional parameters and anisotropic thermal parameters for nonhydrogen atoms reduced the R factor to 4.6%. The R for all data, including unobserved reflections, was 5.2%; the weighted R_w was 6.7% ($R_w = [\Sigma w \Delta F^2]^{1/2}/[\Sigma w F_o^2]^{1/2}$). The largest shift divided by the standard deviation was 0.3 for the last refinement cycle, and a final difference Fourier showed no areas higher than ±0.3 e Å^{-3}. A normal probability plot[13] was calculated which was essentially linear with a slope of 1.42 and an intercept of 0.06.

Results and Discussion

Figure 1 shows an ORTEP drawing of compound 1 with atom designations. Bond distances and bond angles for all atoms are given in Tables I and II, respectively. Characteristic bond lengths and bond angles are observed. Two important features of the data should be noted.

The long carbon–carbon bonds (C_1–C_2, C_3–C_4) typical of

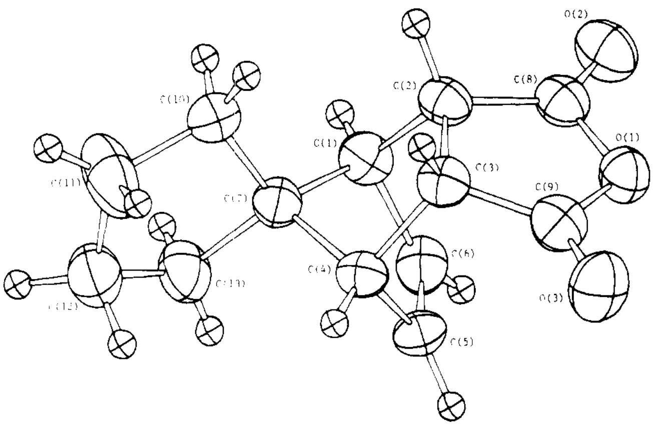


Figure 1.

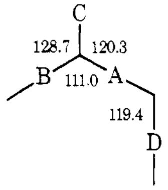
Table I. Bond Distances in Å with Standard Deviations in Parentheses

C(1)–C(2)	1.568 (6)	C(8)–O(1)	1.405 (6)
C(1)–C(6)	1.509 (7)	C(8)–O(2)	1.184 (5)
C(1)–C(7)	1.551 (6)	C(9)–O(1)	1.404 (5)
C(1)–H1	0.86 (5)	C(9)–O(3)	1.187 (7)
C(2)–C(3)	1.538 (6)	C(10)–C(11)	1.511 (8)
C(2)–C(8)	1.500 (6)	C(10)–H10(1)	0.82 (5)
C(2)–H2	1.04 (4)	C(10)–H10(2)	0.94 (4)
C(3)–C(4)	1.570 (6)	C(11)–C(12)	1.505 (9)
C(3)–C(9)	1.499 (7)	C(11)–H11(1)	0.91 (6)
C(3)–H3	0.96 (4)	C(11)–H11(2)	1.27 (6)
C(4)–C(5)	1.510 (7)	C(12)–C(13)	1.500 (8)
C(4)–C(7)	1.555 (7)	C(12)–H12(1)	1.03 (5)
C(4)–H4	1.00 (4)	C(12)–H12(2)	1.05 (5)
C(5)–C(6)	1.318 (7)	C(13)–H13(1)	0.97 (5)
C(5)–H5	0.96 (5)	C(13)–H13(2)	0.81 (5)
C(6)–H6	0.99 (5)		
C(7)–C(10)	1.532 (7)		
C(7)–C(13)	1.543 (6)		

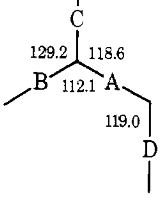
similar Diels–Alder adducts are present *but* in this case the two bonds are equivalent. This observation is in accord with chemical and spectroscopic properties. We suggest that the nonequivalence of the long bonds found in x-ray structure determination of similar adducts is artifact.[4,6]

The five-membered spiro ring imposes, by its bulk, subtle but consistent changes in the molecular architecture of **1** as compared to the unsubstituted and spirocyclopropyl substituted adducts. The dihedral angular relationships of several prominent atomic planes in the three adducts are shown below. In each case the planes are A = $C_1C_2C_3C_4$, B = $C_1C_4C_5C_6$, C = $C_1C_4C_7$, and D = $C_2C_3C_8C_9O_1$. The data for **2** are the averaged values for the two molecules of the asymmetric unit[4] and the values for **3** are due to Simonetta and co-workers.[6]

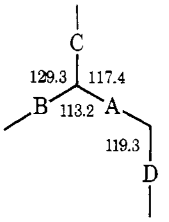
1 (7-spiro C_5)



2 (7-spiro C_3)



3 (7-diH)



Larger substituents at C_7 appear to cause only the A–C angle to become larger at the expense of the A–B angle. This certainly suggests that the π-bond/anhydride ring portion of the adducts are less repulsive/more compressible than the π-bond/bridge substituent or the bridge substituent/exo hydrogen portions. It is surprising that the A–D angle is essentially constant indicating no differential steric effects on the anhydride ring in any of the adducts.

Table II. Bond Angles with Standard Deviations in Parentheses

C(2)–C(1)–C(6)	105.6 (4)	C(4)–C(7)–C(13)	113.6 (4)
C(2)–C(1)–C(7)	100.1 (3)	C(10)–C(7)–C(13)	102.8 (4)
C(2)–C(1)–H1	114 (3)	C(2)–C(8)–O(1)	110.3 (4)
C(6)–C(1)–C(7)	101.1 (4)	C(2)–C(8)–O(2)	130.8 (4)
C(6)–C(1)–H1	120 (3)	O(1)–C(8)–O(2)	119.0 (4)
C(7)–C(1)–H1	113 (3)	C(3)–C(9)–O(1)	109.5 (4)
C(1)–C(2)–C(3)	103.1 (3)	C(3)–C(9)–O(3)	131.6 (5)
C(1)–C(2)–C(8)	113.8 (4)	O(1)–C(9)–O(3)	118.9 (4)
C(1)–C(2)–H2	111 (2)	C(7)–C(10)–C(11)	105.5 (4)
C(3)–C(2)–C(8)	104.3 (4)	C(7)–C(10)–H10(1)	112 (3)
C(3)–C(2)–H2	109 (2)	C(7)–C(10)–H10(2)	123 (3)
C(8)–C(2)–H2	114 (2)	C(11)–C(10)–H10(1)	115 (3)
C(2)–C(3)–C(4)	102.9 (3)	C(11)–C(10)–H10(2)	113 (3)
C(2)–C(3)–C(9)	105.5 (4)	H10(1)–C(10)–H10(2)	88 (4)
C(2)–C(3)–H3	114 (2)	C(10)–C(11)–C(12)	107.7 (5)
C(4)–C(3)–C(9)	113.0 (4)	C(10)–C(11)–H11(1)	130 (4)
C(4)–C(3)–H3	113 (2)	C(10)–C(11)–H11(2)	99 (3)
C(9)–C(3)–H3	109 (2)	C(12)–C(11)–H11(1)	116 (4)
C(3)–C(4)–C(5)	105.0 (4)	C(12)–C(11)–H11(2)	112 (3)
C(3)–C(4)–C(7)	100.3 (3)	H11(1)–C(11)–H11(2)	86 (5)
C(3)–C(4)–H4	114 (2)	C(11)–C(12)–C(13)	107.0 (5)
C(5)–C(4)–C(7)	100.9 (4)	C(11)–C(12)–H12(1)	115 (3)
C(5)–C(4)–H4	116 (2)	C(11)–C(12)–H12(2)	105 (3)
C(7)–C(4)–H4	118 (2)	C(13)–C(12)–H12(1)	114 (3)
C(4)–C(5)–C(6)	107.9 (4)	C(13)–C(12)–H12(2)	99 (3)
C(4)–C(5)–H5	126 (3)	H12(1)–C(12)–H12(2)	114 (4)
C(6)–C(5)–H5	126 (3)	C(7)–C(13)–C(12)	105.3 (4)
C(1)–C(6)–C(5)	107.8 (4)	C(7)–C(13)–H13(1)	104 (3)
C(1)–C(6)–H6	135 (3)	C(7)–C(13)–H13(2)	109 (3)
C(5)–C(6)–H6	117 (3)	C(12)–C(13)–H13(1)	110 (3)
C(1)–C(7)–C(4)	92.4 (3)	C(12)–C(13)–H13(2)	117 (3)
C(1)–C(7)–C(10)	117.7 (4)	H13(1)–C(13)–H13(2)	111 (4)
C(1)–C(7)–C(13)	115.7 (4)	C(8)–O(1)–C(9)	110.4 (4)
C(4)–C(7)–C(10)	115.2 (4)		

However, since the molecular geometries of the three adducts are very similar and whatever differences there are vary systematically from **3** to **2** to **1**, relatively faster endo → exo isomerization of **2** and the absence of isomerization in **1** cannot be rationalized by ground state geometrical differences.

Prior comparison via the program PDIGM[14,15] of experimental LIS and LIS calculated from partially idealized atomic coordinates for the anhydride **1** clearly showed that $Eu(fod)_3$ complexed at the carbonyl oxygen rather than the ether oxygen of the anhydride.[3]

Use of the actual x-ray determined coordinates confirmed this preference. The agreement factor, *R*, decreased by a factor of 2 (from 0.7 to 0.37) for the best fit at carbonyl oxygen, although in this case the best fit distance remained near 2.8 Å and the agreement factor contour was not as steep as in the spirocyclopropyl anhydride **2**.[4] The agreement factor for the best fit at ether oxygen remained an order of magnitude higher than that for the carbonyl oxygen fit.

Because the calculated/observed LIS data are in such good agreement and because the choice of coordination sites is so clear-cut for rigid bifunctional molecules, whose solution geometry must be nearly identical with their crystal geometry, we are convinced that assessment of solution geometry for conformationally flexible molecules by the analysis of LIS data is a fairly sensitive and, when applied with due caution, an appropriate procedure.

Acknowledgment. R.E.R.C. gratefully acknowledges financial support for chemicals associated with this project from the Eloise Gerry Fellowship Fund of Sigma Delta Epsilon, Graduate Women in Science. We also wish to thank the Montana State University Computing Center for a grant of computing time. We are grateful to Mr. Clarence Whitworth of Montana State University for modification of the PDIGM program.

Registry No.—1, 56587-28-1.

Supplementary Material Available. Table III, torsion angles excluding atoms C(8), C(9), O(1), O(2), O(3); Table IV, equations of planes and dihedral angles; Table V, crystal data for $C_{13}H_{14}O_3$; and Table VI, positional and thermal parameters and standard deviations for the structure of 1 (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) The *Chemical Abstracts* nomenclature for compound **1** is [3′aβ,4′α,7′α,7′aβ]-3′a,4′,7′,7′a-tetrahydrospiro{cyclopentane-1,8′-[4,7]methanoisobenzofuran}-1′,3′-dione.

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(8) Computer programs used were by F. R. Ahmed and co-workers (NRC-2, Data Reduction; NRC-8, Fourier for Distorted and Undistorted Nets; and NRC-12, Scan of Interatomic Distances and Angles; National Research Council, Ottawa, Ontario, Canada), Busing and Levy (ORFLS), Carrol K. Johnson (ORTEP), and Germaine, Main, and Woolfson (MULTAN, 1972 version). These programs were locally modified for use with the XDS Sigma 7 computer. Other programs were written locally by G. D. Smith, C. N. Caughlan, and R. D. Larsen.

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(15) The PDIGM program, using lanthanide positions selected by the user, calculates shift factors for all protons and assesses their agreement with experimental shifts. The ease of selection of lanthanide coordinates and the rapidity with which one can obtain the position best fit make the program useful.

Total Synthesis of (±)-Discretamine and (±)-Stepholidine

Hsüch-Ching Chiang and Einar Brochmann-Hanssen*[1a]

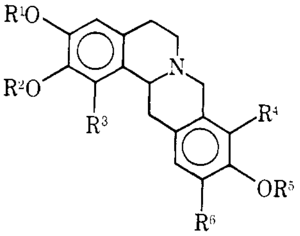
School of Pharmacy, National Taiwan University,
Taipei, Taiwan, Republic of China, and
Department of Pharmaceutical Chemistry, School of Pharmacy,
University of California, San Francisco, California 94143

Received March 8, 1977

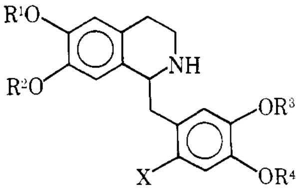
Discretamine, a tetrahydroprotoberberine alkaloid, was isolated in 1959 by Schmutz[1b] from *Xylopia discreta*. Elemental analysis gave the empirical formula $C_{19}H_{21}NO_4$ indicating the presence of two hydroxyl and two methoxyl groups in the cyclic moiety. Methylation with diazomethane gave (−)-tetrahydropalmatine (**1**), establishing absolute configuration and a 2,3,9,10-tetraoxygenated substitution pattern. Recently, structure **2** was proposed for discretamine based on mass spectroscopic evidence.[2]

Another diphenolic tetrahydroprotoberberine alkaloid, stepholidine, was isolated from *Stephania glabra* in 1968 and assigned structure **3** based on degradative evidence.[3] In 1975 stepholidine was discovered in opium[4] which also contains a third isomer, namely, scoulerine (**4**).[5] Neither discretamine nor stepholidine has been previously synthesized. The purpose of the investigation reported in the present communication was to confirm the structures of discretamine and stepholidine by synthesis, and to prepare these alkaloids in sufficient quantities for later use as cold carriers in biosynthetic studies.

Many approaches have been described for synthesis of protoberberines.[6,7] The oldest method which is still widely used is based on intramolecular Mannich condensation of an appropriately substituted 1-benzyltetrahydroisoquinoline with formaldehyde.[8,9] If the benzyltetrahydroisoquinoline carries a 3-hydroxy substituent in the benzyl moiety, cyclization occurs ortho and para to the phenolic hydroxyl group to afford a mixture of a tetrahydroprotoberberine and a tetrahydropseudoberberine, their relative proportion depending on steric factors and on reaction conditions such as pH and temperature. Applying this method to norreticuline (**9a**) at pH 6.3 and room temperature, Battersby et al.[10] obtained a mixture of scoulerine (**4**) and coreximine (**5**) in a ratio of approximately 2:1. When norreticuline was heated with formaldehyde in ethanol or in formic acid, Kametani et al.[11,12] and Tomita et al.[13] could isolate only coreximine. However, by blocking the para position with bromine (as in **9b**) ortho cyclization proceeded cleanly and debromination gave the 9,10-substituted tetrahydroprotoberberine.[14,15] With methoxy or benzyloxy groups in 3 and 4 positions of the benzyl moiety, only 10,11-substituted products could be obtained.[9,12,13,16,17]



1, $R^1 = R^2 = R^5 = Me; R^3 = R^6 = H; R^4 = OMe$
2, $R^1 = R^3 = R^5 = R^6 = H; R^2 = Me; R^4 = OMe$
3, $R^1 = Me; R^2 = R^3 = R^5 = R^6 = H; R^4 = OMe$
4, $R^1 = R^5 = Me; R^2 = R^3 = R^6 = H; R^4 = OH$
5, $R^1 = R^5 = Me; R^2 = R^3 = R^4 = H; R^6 = OH$
6, $R^1 = R^2 = Me; R^3 = R^5 = R^6 = H; R^4 = OMe$
7, $R^1 = R^2 = Me; R^3 = OH; R^4 = OMe; R^5 = R^6 = H$
8, $R^1 = R^2 = R^5 = Me; R^3 = R^4 = H; R^6 = OMe$



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a, $R^1 = R^4 = Me; R^2 = R^3 = X = H$
b, $R^1 = R^4 = Me; R^2 = R^3 = H; X = Br$