Conformation of 1-Methyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]non-3-ene 7-Oxide

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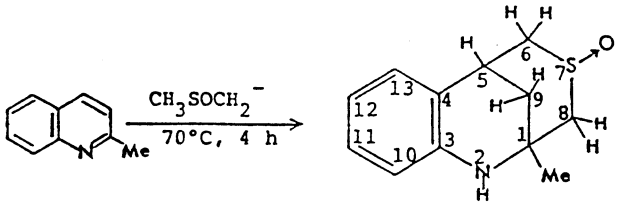
(Received April 12, 1990)

Synopsis. The crystal and molecular structures of 1-methyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]non-3-ene 7-oxide have been determined on the basis of three-dimensional X-ray data. The six-membered thiane ring in this novel tricyclic system has been elucidated to adopt a chair-type conformation with an axial-axial aza-phenyl substituent and an equatorial sulfinyl group. The conformation in the solid state was consistent with that previously proposed by molecular mechanics calculations.

The reaction of 2-methylquinoline with the methylsulfinylmethanide ion has been demonstrated[1] to produce a novel tricyclic compound, 1-methyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]non-3-ene 7-oxide (**1**), in high yields in addition to a small amount of the expected 2,4-dimethylquinoline. The chemical structure of this unexpected product has been determined[1,2] by means of elemental analysis as well as mass, infrared, and proton nuclear magnetic resonance (^{1}H NMR) spectroscopies, as shown in Scheme 1. The ^{1}H NMR spectrum had suggested that a probable conformation of the six-membered thiane ring is a boat,[1] whereas molecular mechanics calculations have predicted the chair-type conformer to be more stable in solution.[2]

In order to confirm the conformational details of the product, we carried out an X-ray single crystal analysis, which revealed that the thiane ring in the system adopts the chair form with an equatorial sulfinyl in the solid state. These results are reported herein, together with the stereochemical aspects of the compound. In a preliminary study concerning pharmacological activities, this compound has been reported[3] to show significant antispasmodic, muscle relaxant, and anodic effects.



Scheme 1.

Experimental

Preparation and CD Spectra of 1 Crystals. The synthesis and sundry physico-chemical data of **1** have been described previously.[1,2] Crystals of **1** obtained by recrystallization from benzene seemed to belong to a similar polymorphism. Several single crystals were collected for circular dichroism (CD) measurements. The CD spectra of the individual crystals dissolved in methanol were recorded on a JASCO J-600 spectropolarimeter. Three types of spectra were obtained from each crystal: positive and negative Cotton effects and no CD. The typical values of elliptical polarization, $[\theta]$, at 304 nm were 2.4×10^4 and -3.4×10^4 degree cm^2/decimol for a positive CD crystal and a negative one, respectively. It was thus indicated that natural asymmetric resolution took place in the crystallized procedure.

Crystal Structure Determination and Refinement. A crystal of **1** suitable for X-ray testing was picked up without

Table 2. Final Atomic Parameters and Equivalent Thermal Parameters with Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{eq}/Å^2
S	0.4418(1)	0.05452(8)	0.58376(8)	3.55(2)
O	0.6227(3)	0.1190(2)	0.5780(3)	5.36(7)
N	0.0066(4)	0.0098(3)	0.5405(2)	3.43(6)
C1	0.1253(5)	0.0372(3)	0.4507(3)	3.23(7)
C3	0.0358(5)	−0.0818(3)	0.6016(3)	2.78(6)
C4	0.1836(5)	−0.1540(3)	0.5804(3)	2.99(7)
C5	0.3095(5)	−0.1336(3)	0.4870(3)	3.63(8)
C6	0.4916(5)	−0.0734(3)	0.5181(3)	4.11(8)
C8	0.2896(5)	0.1115(3)	0.4843(3)	3.63(8)
C9	0.2024(5)	−0.0687(3)	0.4041(3)	3.69(8)
C10	−0.0859(5)	−0.1025(3)	0.6866(3)	3.44(7)
C11	−0.0571(6)	−0.1935(4)	0.7483(3)	4.27(9)
C12	0.0895(7)	−0.2647(4)	0.7293(3)	5.0(1)
C13	0.2082(6)	−0.2439(3)	0.6448(3)	4.07(8)
CM	0.0074(6)	0.0990(4)	0.3717(3)	5.0(1)
HN	−0.097(5)	0.053(3)	0.545(3)	2.8(9)[a]

a) Refined isotropically. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as:
$B_{eq}=(4/3)\sum_i\sum_j B_{ij}(\boldsymbol{a}_i\cdot\boldsymbol{a}_j)$.

Table 1. Summary of Crystal Data and Data Collection

Formula	$C_{12}H_{15}NOS$	$F(0\,0\,0)$	472
M_r	219.31	Temperature/K	296
Space group	$P2_12_12_1$	Crystal size/mm	0.27×0.15×0.90
a/Å	7.114(1)	Scan mode	ω-2θ
b/Å	12.251(1)	Scan width/°	$0.8+0.35\tan\theta$
c/Å	12.752(1)	Scan range/°	$2\theta<50.0$
V/Å^3	1111.3	No. of data with $\lvert F_o\rvert>3\sigma(\lvert F_o\rvert)$	1058
Z	4	No. of variables	141
D_c/g cm^{-3}	1.311	$R_F(R_{wF})$	0.036(0.038)
Radiation	Mo $K\alpha$	Absorption coefficient/cm^{-1}	2.5

any intention of selecting stereo-polymorphism. A pale-purple crystal in the form of a pillar was examined on an Enraf-Nonius CAD4 Kappa goniometer using Mo $K\alpha$ radiation. The preliminary examination established an orthorhombic system with four molecules in a unit cell. A summary of the crystal data and the intensity collection is given in Table 1. Intensity data were corrected for both Lorentz and polarization effects, but not for absorption (μ=2.5 cm^{-1}).

The structure was solved by a direct method and was refined by full-matrix least-squares techniques.[4] The most non-hydrogen atoms could be located in the initial E-map. After a few cycles of refinement and difference Fourier synthesis, a molecular model consistent with the chemical structure was established. The final model utilizing anisotropic thermal parameters for all non-hydrogen atoms and fixed (except H-N) hydrogen atoms parameters was carried to convergence by repeated least-squares refinements. A final difference Fourier analysis was judged to be essentially featureless: the largest peak had a height of 0.2 e Å^{-3} and was located near the S atom.

The final positional parameters with the estimated standard deviations and the isotropic equivalent temperature factors for the refined atoms are given in Table 2. The atomic labels are consistent with those in Scheme 1. Individual bond lengths and bond angles may be found in Table 3.[5]

Results and Discussion

The methylsulfinylmethanide ion adduct to 2-methylquinoline generates two asymmetric carbon centers in the molecule. The CD spectrum of each crystal suggested that the crystals were a mixture of the optically active forms (positive and negative at 304 nm) and a conglomerate or a racemic form. A crystal chosen for the X-ray examination must be either one of the optically active forms. With the non-centrosymmetric space group ($P2_12_12_1$) for this crystal, there might be a possibility to determine the absolute configuration of the two carbons (C1 and C5). Though the first molecular model given by the coordinates in Table 2 converged at an excellent agreement factor of R=3.6% after repeated refinements, the other enantiomorph did also at almost the same value. This equivocal result may be due to a small contribution of the imaginary term of anomalous scattering factors. We abandon further examinations of the absolute configurational analysis on the basis of the present data.[6] The first enantiomeric model plotted in Fig. 1 shows a (1(R),5(S)) configuration as the tentative choice for the accidentally selected **1** crystal. The six-membered thiane ring has a chair conformation with a planar central four-atom tetragon (C1, C5, C6, and C8) enlarging toward the sulfur side; consequently, the eight-membered azathiane ring displays a boat form with the sulfur atom located at the bow. The two mean planes of the central four-atoms (C1, C5, C6, and C8) and the aza-phenyl group intersect each other with a dihedral angle of 112.0°. The oxygen atom occupies the equatorial position in this chair conformation.

In order to numerically demonstrate the conformation and structure, a formal diagram of perpendicular displacement from the mean plane of the central 4-atoms of the thiane ring is shown in Fig. 2 (after an example for the diazepine rings.[7]). Figure 2 also provides a Newman projection along the C1-C8 and C5-C6 bonds with the torsional angles in degrees. The conformation of **1** in the solid state agrees well with that predicted by molecular mechanics calculations.[2]

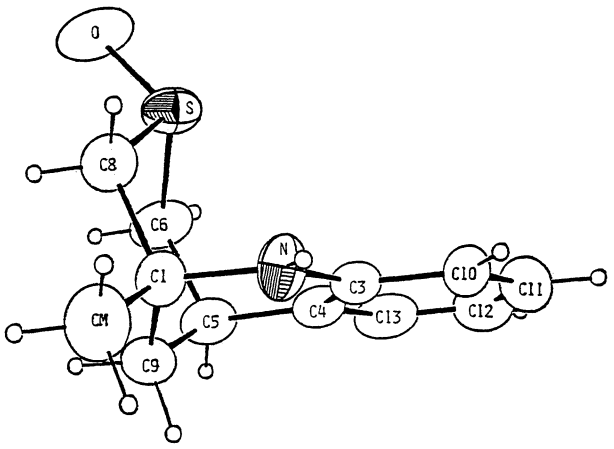


Fig. 1. Perspective view of **1** with thermal ellipsoids at 50% probability and the atomic numbering. Octant shading ellipsoids denote the sulfur and nitrogen atoms.

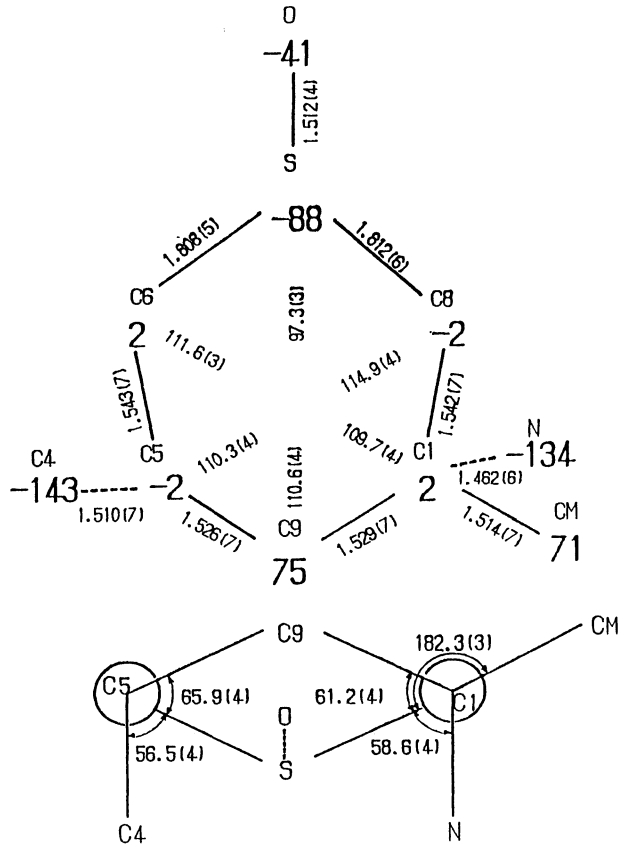


Fig. 2. Formal diagram of the thiane ring with a Newman projection along the C1-C8 and C5-C6 bonds: Illustrating displacement of each atom from the mean plane in units of 0.01 Å (thick letters), selected bond lengths in Å, and bond angles in degree (inside of the rings).

In a crystal analysis, a hydrogen bond between the oxygen and nitrogen atoms of the adjacent **1** molecules was also revealed. The intermolecular hydrogen bonds make a zigzag chain arrangement along the *a*-axis. The rather longer atomic distance of 3.079(5) Å between O and N′(1+*x*, *y*, *z*) suggests a smaller limit (ca. 10 kJ mol^{-1}) of the stabilization energy of the general hydrogen bonds. The hydrogen bonds in the solid state may not drastically change the stable conformation of the isolated molecule, since the free-energy difference between the chair and twist-boat forms has been calculated to be more than 25 kJ mol^{-1}.[2] Thus, the molecular conformation in the solid state must be maintained in the same way as in solution or in the isolated state, as has been predicted by molecular mechanics calculations.

The axial-axial substituent of the aza-phenyl group comprised 9-atoms (N, C1, C3, C4, C5, C10, C11, C12, and C13), showing a perfect planarity with the maximum deviation of 0.03 Å of C5 from their mean plane. With this planarity, the shortened C-N bond length (1.382 Å for C3-N) and the in-plane hydrogen position indicates the sp^2 hybrid character, i.e. a double-bond nature of the nitrogen atom.

All of the other bond lengths, bond angles, and thermal ellipsoids in the molecule are usual when compared with the standard values[8] and the related molecular structures reported.[9]

K. Hatano thanks Dr. Yoichi Iitaka, Emeritus Professor of the University of Tokyo, for a helpful discussion concerning the absolute structure determination.

References

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4) Programs of the Enraf-Nonius's SDP package were used. The package includes modified versions of Main, Hull, Lessinger, Germain, Declerg, Woolfson's MULTAN and Johnson's ORTEP II, and LSFM for full-matrix least-squares refinement.

5) Final tables of individual bond lengths and angles, hydrogen atomic positions, anisotropic thermal parameters for non-hydrogen atoms, and structure amplitudes (F_o and F_c) are deposited as Document No. 8940 at the Office of the Editor of the Bull. Chem. Soc. Jpn.

6) We are continuing to search methods collecting better reflections suitable to analyze the absolute configuration.

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