*Tetrahedron* Vol. 42, No. 17, pp. 4661 to 4670, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00


# SYNTHESIS, STRUCTURE, AND REDUCTIVE REARRANGEMENT OF A NOVEL TRICYCLIC ISOXAZOLIDINE

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(*Received in USA* 25 *June* 1986)

## ABSTRACT

*N-Oxidation of 2-methyl-3β-phenyl-2,3α,3aβ,6aβ-tetrahydrothieno[2,3-d]isoxazole-4,4-dioxide* (1) *gave a nitrone* (2) *which underwent an intramolecular 1,3-dipolar cycloaddition yielding a tricyclic isoxazolidine* (4). *A single-crystal X-ray analysis unequivocally established the structure of* 4 *as 9β-phenyl-2-oxa-6-thia-1-azatricyclo[3.3.1.0$^{3,7}$]nonan-4α-ol-6,6-dioxide. $LiAlH_4$ and $LiAlD_4$ reduced* 4 *exhaustively and rearranged it profoundly to isotopomers* 5 *and* 6, *respectively; a novel* Grob *fragmentation may have mediated the rearrangement.* Inter alia, *measurements of $^{13}C$-$^{13}C$ coupling constants and of m/z ratios of fragment ions yielded the complete structures of* 5 *and* 6. *They are 5β-phenyl-8-thia-6-azabicyclo[3.3.1]octan-2α-ol and its 3α-deuterio analog, respectively.*

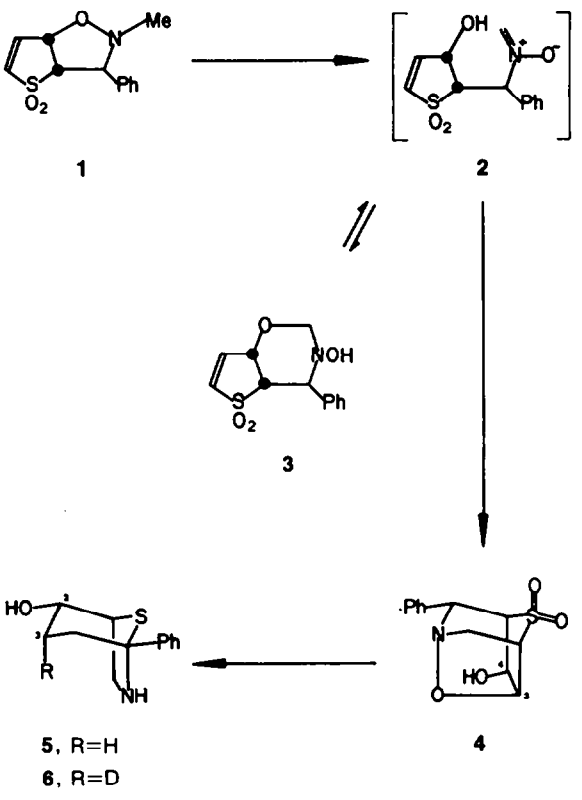
We carried out the present work[§] primarily to discover any useful biological activities of isoxazolidines like 1 and 4 (Scheme I). Secondarily, we planned to extend the scope of iterated nitrone cycloadditions[1-3] to an isoxazolidine-fused, unsaturated heterocycle (*e.g.*, 1) and to a C-aryl nitrone (*e.g.*, 8). Iterated cycloadditions of nitrones were extensible, but nevertheless the biological properties of the resulting isoxazolidines were disappointing. In the course of work we discovered a striking reaction (4 → 5), and hence report the synthesis, structure, and reductive rearrangement of tricyclic isoxazolidine 4.

Double dehydrobromination of dibromosulfolane 7 in the presence of N-methyl-C-phenylnitrone 8 gave isoxazolidine 1 (Scheme II). The cycloaddition was *cis*-

§ Presented at the Fifth International Conference on Organic Synthesis, Freiburg i.B., F.R.G., August 27th, 1984; Abstract No. W6.

stereospecific (C-3a,C-6a) and *trans*-diastereoselective (C-3,C-3a). Assignments of regio- and stereo-chemistry to 1 followed from those to tricyclic isoxazolidine 4 (*vide infra*). Neither crystallization nor chromatography isolated any other bicyclic isoxazolidine, but both techniques did separate the tricyclic diisoxazolidine 9. Yields of 1 (55%) and 9 (12%) were similar to those reported for products of analogous cycloadditions.[4]

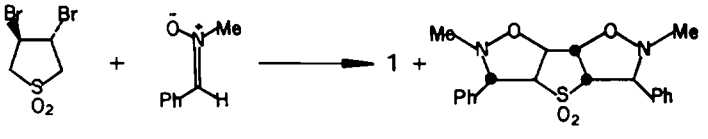
**SCHEME I**




1 2 3 4 5, R=H 6, R=D

Steric interactions may have determined the *trans*-diastereoselectivity of the cycloaddition forming 1.† Transition states leading to 1 lacked interactions which those leading to the unisolated, C-3,C-3a-*cis* diastereomer possessed. Models of the corresponding conformers presented forbidding repulsions between the sulfone and aryl groups (Scheme III). Development of these interactions in product-like transition states presumably would have slowed both *exo-trans* and *endo-cis* cycloadditions, compared respectively to *endo-trans* and *exo-cis* reactions. N-Methyl-C-phenylnitrone (8) also adds *trans*-diastereoselectively to cyclopentene,[5] but cycloadditions of N-phenyl-C-phenylnitrone to furan[6] and N-arylmaleimides[7] are *cis*- and non-diastereoselective, respectively.

**SCHEME II**

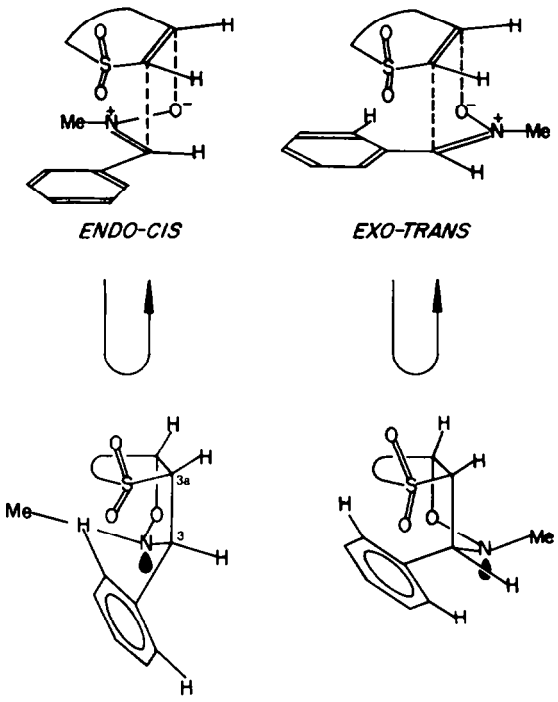



7 8 9

*m*-Chloroperbenzoic acid selectively oxidized the nitrogen atom of sulfolene-fused isoxazolidine 1 (Scheme I). Unisolated nitrone 2 resulted foreseeably[1-3] and cyclized intramolecularly, forming N-hydroxyoxazine 3 (62%). Heating a solution of 3 regenerated 2 which then exclusively formed the tricyclic isoxazolidine 4 (90%). Formation of the less substituted nitrone (2) was expected,[1-3] and frontier orbital interactions within 2 must have governed the precedented[8]

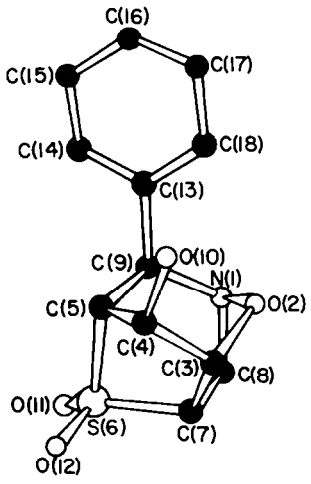
† Not knowing whether thiophenedioxide or 4-bromo-2-sulfolene mediated the cycloaddition yielding 1 may not affect our conclusion. Steric interactions in *Dreiding* models were similar regardless of which dipolarophile took part.

**SCHEME III**




regiochemistry of intramolecular cycloaddition.

**FIGURE 1**




Atom numbering scheme and solid-state conformation of **4**; hydrogen atoms have been omitted for clarity

A single-crystal *x*-ray analysis defined the complete structure of **4**, and, by implication, also established those of **1** and **3**. The crystal structure was solved by the heavy-atom method. Full-matrix least-squares refinement of atomic parameters converged to $R = 0.042$ over 1331 reflections. Final atomic coordinates for the two crystallographically independent molecules comprising the asymmetric crystal unit are in Table 1. Molecules of **4** are associated in the solid state by O-H ...O hydrogen bonds [O(2)...O(10') = 2.896 Å; O(10)...O(2') (at $x$, $-1+y$, $z$) = 2.829 Å]. The means of corresponding lengths and angles in the two molecules (Table II) are in accord with expected values, and, as would be anticipated with such a highly fused ring system, the overall molecular conformations are virtually identical. A view of the solid-state conformation of one molecule is provided in Figure 1. The five-membered N(1)-O(2)-C(3)-C(7)-C(8) and C(3)-C(4)-C(5)-S(6)-C(7) rings both have envelope forms with N(1) and C(5), respectively, as the out-of-plane atoms. The chair forms adopted by six-membered N(1)-O(2)-C(3)-C(4)-C(5)-C(9) and C(9)-C(5)-S(6)-C(7)-C(8)-N(1) rings are highly puckered around C(8) and C(7), respectively.

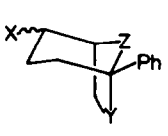
Isoxazolidine **4** defied two of three attempts to cleave its N-O bond. Attempted hydrogenolysis with Pearlman's catalyst (20% $Pd(OH)_2$ on C, 60psi of $H_2$, 25°, 15h) was ineffective, and educt **4** was recovered. We also recovered **4** from treatment with KOAm-*t* in boiling *t*-AmOH for 20h. Both failures were unanticipated, the latter because elimination under basic conditions typically breaks the N-O

bond of isoxazolidines.[9-10] A third trial succeeded, but the attendant net chemical change (4 → 5) seemed baroque.

Excess $LiAlH_4$ and $LiAlD_4$ in hot THF reduced 4 to 5 (41%) and 6 (30%), respectively. Chromatography followed by crystallization isolated only isotopomers 5 and 6, but $^1$H-NMR spectra of crude products did suggest the presence of other, unidentified components having ill-defined resonances. Peracetylation gave acetate-acetamide derivatives which (*inter alia*) characterized 5 and 6. Assignments of structure to compounds 5 and 6 rest largely on spectral data that the next six paragraphs present.

The respective empirical formulae of 5 and 6 were $C_{12}H_{15}NOS$ and $C_{12}{}^1H_{14}{}^2HNOS$. Microanalyses established the composition of 5 and confirmed that of the acetate-acetamide derivative of 6. Fast-atom bombardment (FAB) mass spectrometry yielded the molecular weights of 5 and 6, and, when combined with *in situ* deuterium labeling, also showed that both compounds bore two exchangeable protons. Compound 5, *e.g.*, formed ions of m/z 222 ($[M^+ + {}^1H_1]$) and 224 ($[M^+ - {}^1H_1 + {}^2H_2]$[¶]) from matrices of glycerol and $[^2H_3]$-glycerol, respectively. These results were consistent with those of IR and $^1$H-NMR spectroscopy and also with those of peracetylations. The presence of two exchangeable protons was unsurprising but implied that neither 5 nor 6 possessed an N-O bond nor any other heteroatom-heteroatom bond.

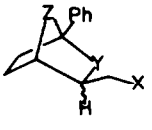
Three bridged, bicyclic structures (10-12) comprised all possible carbon skeletons of the reduction products. Structures 10-12 expressed interrelations and substitutions of all aliphatic carbons of 5 and 6, also relating aliphatic carbons to the quaternary aromatic carbons. The common connectivity followed from determinations of one-bond, $^{13}C$-$^{13}C$ coupling constants of 5, and from determination of degrees of substitution of certain carbon atoms of both compounds. One $^{13}C$-NMR resonance was especially important; the low-field, δ81.5ppm resonance of the quaternary, phenyl-substituted carbon (C-5) of 5 meant that C-5 bound two heteroatoms. Figure 11 illustrates results of the pertinent $^{13}C$-NMR measurements.




10


11

Substitution of heteroatoms in 10-12 formally yields a total of eighteen possible specific structures (10A-F through 12A-F; see Key). FAB mass spectrometry decisively eliminated seventeen of them, showing that the gross structure of the hydride reduction product (5) was that of 10A. Under fast-atom bombard-



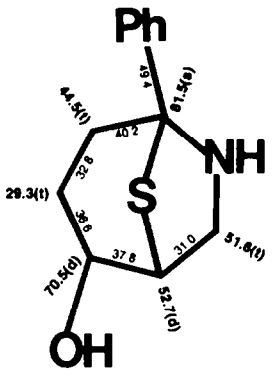

12

| Key | X | Y | Z |
|---|---|---|---|
| a | OH | NH | S |
| b | OH | S | NH |
| c | SH | O | NH |
| d | SH | NH | O |
| e | $NH_2$ | S | O |
| f | $NH_2$ | O | S |

¶ This algebraic expression represents the molecular ion that derived from addition of one proton and from exchange of two others for two deuterons.

ment compound 5 fragmented to ions 13 (m/z 162 (39%)) and 14 (m/z 170 (20%)) (Scheme IV). *Only* 10A *could have formed* both 13 *and* 14 *because none of the seventeen alternative structures contained* both *thiazolidine and hexahydroazepine units.* Exact mass measurements (Exptl.) and *in situ* deuterium labeling confirmed assignments of ion compositions. Ions $[^2H_1]$-13 (m/z 163 (65%)) and $[^2H_1]$-14 (m/z 171 (44%)) resulted from bombardment of 5 in a matrix of $[^2H_3]$-glycerol. Neither ion appeared in a FAB mass spectrum of 5 when the matrix was glycerol.

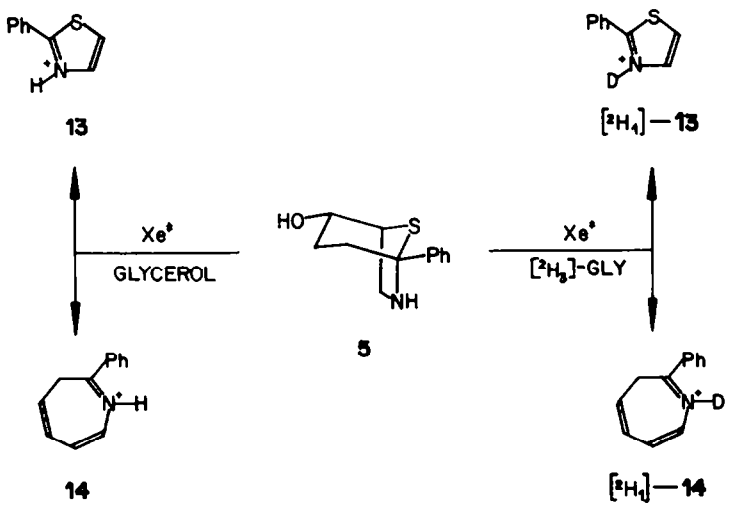
**FIGURE II**




$^1$J-values of selected, naturally-abundant $^{13}$C to $^{13}$C bonds and $^{13}$C-NMR δ-values (multiplicities) of selected resonances of **5**.

The alcohol groups of isotopomers 5 and 6 were equatorial. Two-dimensional proton-proton J-correlations showed that the carbinol proton of 5 coupled to the axial C-3 proton (δ1.78 ppm). It was shielded (Δδ = -0.4ppm) compared to the equatorial C-3 proton. Consequently, the associated J-value (10.2Hz) was due to axial coupling of H-2 to H-3ax. Equatorial stereochemistry of the hydroxyl group of 6 followed analogously and was verified independently (*vide infra*).

**SCHEME IV**

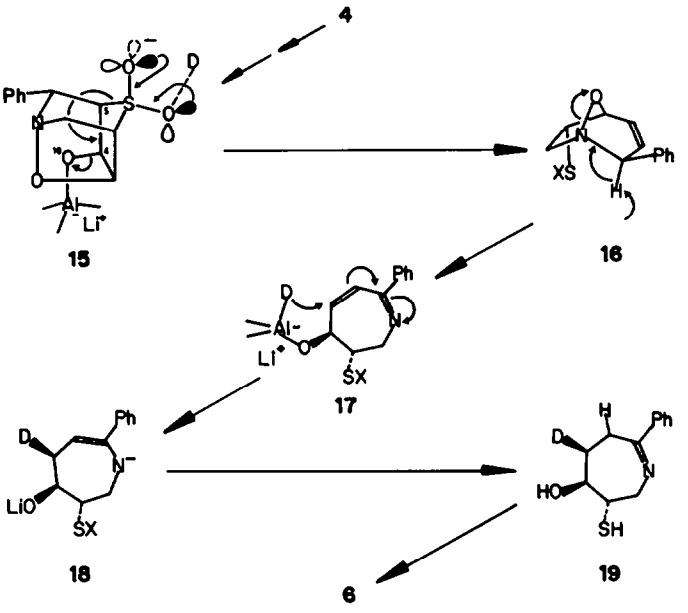



The deuterium atom of 6 was bound to carbon, and its locus was C-3. FAB of 6 in a matrix of glycerol produced a molecular ion (m/z 223 ($[M^+ + {}^1H_1]$, 100%)) which retained the deuteron of 6. Retention indicated that the deuteron was bound to carbon, a finding confirmed by an IR absorption (ν2150cm$^{-1}$). $^{13}$C-NMR experiments located the position of deuterium. Having been a singlet in the proton-decoupled $^{13}$C-NMR spectrum of 5, the C-3 resonance became a triplet in that of 6. In DEPT and APT experiments, C-3 of 5 and 6 resonated as a methylene and a methine carbon (δ29ppm), respectively. Two-dimensional correlation of spectra of 6 established that the carbon resonating at δ29ppm bore the proton resonating at δ1.78ppm. One proton and one deuteron thus substituted C-3 of 6.

Compound 6 formed stereoselectively. It was a single diastereomer since its $^2$H-NMR spectrum showed only one resonance. Also, the deuteron of 6 was axially substituted for two reasons. (*i*) The $^1$H-3ax resonance (δ1.78ppm) of 5 disappeared from the $^1$H-NMR spectrum of 6, whereas the $^2$H-3 signal of 6 appeared at δ1.78 ppm. (*ii*) Axial-axial coupling of $^1$H-2 absented itself from the $^1$H-NMR spectrum of 6, but presented itself in that of 5.

Scheme V offers one mechanism for reductive rearrangement of 4 to 6, explaining three associated deductions. They were that (*i*) C-3 or C-4 of 4 suffered deoxygenation, (*ii*) deuteration of 6 was axial and stereoselective, and (*iii*) C-2 and C-3 of 6 collectively retained the relative configurations of C-3 and C-4 of 4. An unusual *Grob* fragmentation (15 → 16) accounted for (*i*) and intramolecular reduction (17 → 18) explained both (*ii*) and (*iii*), we suggest. We conclude thinking that straightforward reduction of complex isoxazolidines cannot confidently be entrusted to $LiAlH_4$.

**SCHEME V**




## EXPERIMENTAL

General Information.-- Uncorrected melting points were measured on a Fisher Digital Melting Analyzer (Model 355). IR spectra were obtained with Perkin-Elmer 727B or 1320 Infrared Spectrophotometers, and were recorded using $CH_2Cl_2$ solutions unless otherwise noted. ν-Values are given in $cm^{-1}$. $^1$H-NMR spectra were recorded on Varian EM-390 or XL-200 Supercon instruments; chemical shifts were determined in $CDCl_3$ solution unless otherwise specified, and are cited in ppm downfield from TMS. Coupling constants are in Hz. High-resolution mass spectra were obtained using an AEI MS-9 double-focusing instrument. Medium-resolution mass spectra were obtained with a Varian CH5 spectrometer. E. Merck (Darmstadt) provided silica gel plates (F-254) for TLC. Developed plates were visualized in UV light, in $I_2$ vapor, or by spraying with phosphomolybdic acid followed by heating. Baker and Woelm respectively supplied silica gel and alumina for column chromatography; silica gel was 60-200 mesh, and alumina was deactivated to grade IV.

X-Ray Crystallography.-- *Crystal Data.* $C_{12}H_{13}NO_4S$ (4), mol wt = 267.31, Orthorhombic, $a$ = 19.151 (3) Å, $b$ = 6.188 (1) Å, $c$ = 19.255 (4) Å, $V$ = 2281.8 Å$^3$, $Z$ = 8, $D_{calc.}$ = 1.556 g $cm^{-3}$, μ (Cu-Kα radiation, λ = 1.5418 Å) = 25.5 $cm^{-1}$. Space group $Pna2_1$ ($C^9_{2v}$) or $Pnma$ ($D^{16}_{2h}$), with $b$ and $c$ axes interchanged, from the systematic absences: $Okl$ when $k + l \neq 2n$, $hOl$ when $h \neq 2n$; shown to be the former by structure solution and refinement. Sample dimensions: 0.05 x 0.05 x 0.30 mm.

*Crystallographic Measurements.* Preliminary unit-cell parameters and space group information

were obtained from oscillation, Weissenberg, and precession photographs. Intensity data for one octant of reciprocal space were recorded on an Enraf-Nonium CAD-4 diffractometer (Cu-$K\alpha$ radiation, incident-beam graphite monochromator; $\omega$-$2\theta$ scans, $\theta_{max.} = 67^0$). From a total of 2084 independent measurements, those 1331 reflections with $I > 3.00(I)$ were retained for the structure analysis and corrected for the usual Lorentz and polarization effects. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 25 reflections ($40^0 < \theta < 53^0$) widely separated in reciprocal space.

*Structure Analysis.* The crystal structure was solved by the heavy-atom approach. Initial coordinates for the sulfur atoms, derived from a three-dimensional Patterson map, were clearly incompatible with the centrosymmetric space group *Pnma* and thus all further calculations were based on the alternative choice, *i.e.* $Pna2_1$. Approximate coordinates for the remaining non-hydrogen atoms were obtained from a sulfur-phased $F_o$ Fourier synthesis. Hydrogen atoms were all located in a difference Fourier synthesis evaluated at a late stage in the analysis and were then included at their calculated positions in all subsequent structure-factor calculations. Full-matrix least-squares adjustment of the non-hydrogen atom positional and anisotropic thermal parameters converged to $R = 0.042$ ($R_w = 0.052$).[11] Neutral atom scattering factors used in the structure-factor calculations were taken from ref. 12. In the least-squares iterations, $\Sigma w\Delta^2$ ($\Delta = |F_o| - |F_c|$) was minimized with weights, $w$, assigned according to the scheme: $\sqrt{w} = 1$ for $|F_o| \leq 30.0$, $\sqrt{w} = 30.0/|F_o|$ for $|F_o| > 30.0$ to ensure no systematic dependence of $\langle w\Delta^2 \rangle$ when analyzed in ranges of $|F_o|$.

Final atomic positional parameters are in Table I. Tables of anisotropic thermal parameters, hydrogen atom positional and thermal parameters, bond lengths, bond angles, and torsion angles have been deposited with the Cambridge Crystallographic Data Centre. A list of observed and calculated structure amplitudes is available from the authors.

$^{13}$C-NMR Spectroscopy.-- Spectra were obtained with Varian CFT-20 or XL-200 Supercon instruments, and chemical shifts in ppm are referred to TMS. Unless otherwise specified, spectra were obtained using $CDCl_3$ solutions.

*DEPT Spectra.* DEPT spectra of 5 were obtained using a published, automated experiment taken from Varian software.[13] Four spectra were recorded with the last proton pulse set at $45^0$, $90^0$, $90^0$, and $135^0$. Four subspectra then contained resonances of all protonated carbons. Methine, methylene, and (any) methyl carbon resonances were obtained by linearly combining the four original spectra.

*APT Spectra.* APT spectra of 6 were obtained with a published pulse sequence, $90^0$-$\tau$-$180^0$-pulse-$\tau$-acq.[14]

*$^{13}$C-$^{13}$C Coupling Constants.* One-bond $^{13}$C-$^{13}$C coupling constants of naturally abundant carbon-thirteen atoms of 5 were obtained by an INADEQUATE experiment.[15] The delay $\tau$ was set at 6ms to select only one-bond couplings. Since $^1$J-values of the pairs of carbon atoms were quite different, the experiment also established the connectivity of neighboring carbon atoms. One-bond coupling constants of selected neighboring carbons appear in Figure II.

The connectivities were confirmed by a two-dimensional version of the INADEQUATE experiment.[16] The two-dimensional experiment was carried out on a Varian XL-400 instrument, operating at 100MHz for $^{13}$C and using a 200-mg sample of 5. The experiment required a total of 54h; and chromium (III) acetylacetonate was used to enhance the relaxation of the $^{13}$C nuclei.

*$^{13}$C-$^1$H Chemical Shift Correlations.* A published pulse sequence was used to make two-dimensional $^{13}$C-$^1$H chemical shift correlations of 5.[17] The sequence allowed quadrature detection in both frequency domains. Two-hundred fifty-six sets of free-induction decays (FID) each of 1K data points were obtained. In the second dimension -- the proton frequency domain -- the interferogram was zero-filled to 512 points for better digital resolution.

$^1$H-NMR Spectroscopy.-- *$^1$H-$^1$H Chemical Shift Correlations.* A two-dimensional $^1$H-$^1$H chemical shift correlation spectrum of 5 was obtained using the $90^0$-$\tau$-$90^0$-acq. pulse sequence with quadrature detection.[18] Two-hundred fifty-six FID each of 1K data points were collected. In the second dimension, interferograms were zero-filled to 512 points. In both dimensions, the FID were multiplied by two exponential functions which approximated a pseudo-echo. This resolution enhancement emphasized the cross peaks at the expense of the diagonal peaks.

2-Methyl-3$\beta$-phenyl-2,3$\alpha$,3a$\beta$,6a$\beta$-tetrahydrothieno[2,3-d]isoxazole-4,4-dioxide (1).-- 3,4-Dibromosulfolane 7 (52g, 19mmol), Py (45ml, 55mmol), and N-methyl-C-phenylnitrone (8) (13g, 9.3mmol) were heated at reflux in toluene (570ml) for 24h under $N_2$. The cooled soln was decanted from a dark, gummy ppt which was washed with toluene. Toluene was evaporated from combined solns and the residue was reserved. The ppt was partitioned between $Et_2O$ and $H_2O$. Combined extracts were washed with water and brine, and were united with the reserved residue. After evaporation of $Et_2O$, the residue crystallized to give monoadduct 1 (12.9g, 55%) as rods, mp 131.5-133$^0$ (MeOH). A $^1$H-NMR spectrum of 1 agreed with expectation.[4] EI-MS: m/z (relative intensity) 251 (24, $M^+$), 234 (64, M - OH), 141 (100). *Anal.* Calcd. for $C_{13}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76. Found: C, 57.09; H, 5.21; N, 5.39; S, 12.94%.

Mechanical separation of 1 from 9 (*vide infra*) facilitated purification in one preparation.

2,6-Dimethyl-3$\beta$,5$\alpha$-diphenyl-2,3$\alpha$,3a$\beta$,4a$\alpha$,5$\beta$,6,7a$\alpha$,7b$\beta$-octahydrothieno[2,3-d:5,4-d']diisoxazole-4,4-dioxide (9).-- The mother liquor from crystallization of 1 was concentrated to give diadduct 9 (4.3g, 12%), mp 144-145$^0$ (MeOH). A $^1$H-NMR spectrum of 9 agreed with expectation.[4] EI-MS: 386 (12, $M^+$), 160 (100). Exact mass: calcd. for $C_{20}H_{22}N_2O_4S$: 386.1300; found: 386.1299. *Anal.* Calcd.: C, 62.15; H, 5.74; N, 7.25; S, 8.65. Found: C, 62.14; H, 5.53; N, 6.84; S, 8.65%.

Mechanical separation of hexagonal plates of **9** from rods of **1** facilitated purification in one preparation.

4β-Phenyl-4aα,7aβ-dihydro-2H-thieno[2,3-d]-1,3-oxazin-3(4H)-ol-5,5-dioxide (**3**).-- A soln of *m*-CPBA (10.45g, 5.14mmol) in $CH_2Cl_2$ (116ml) was added over 6h to an ice-cooled soln of isoxazolidine **1** (12.9g, 5.14mmol) in $CH_2Cl_2$ (230ml). The reaction was monitored by starch-iodide tests. When reaction was complete, MeOH (16ml) was added, and crystals of **3** (4.4g, 32%, mp 215-218°) were collected by filtration. The yellow filtrate soln was passed through $Al_2O_3$ (500g) and $CHCl_3$ (3 l) eluted 8g of material. Crystallization of the 8-g sample gave another 4.1g (30%) of **3**, mp 214-215° ($Me_2CO$-EtOAc), bringing the total yield to 62%. IR (mineral oil): 3200br, 3080w, 3060w, 1290s, 1280s, 1170s, 1125s ($SO_2$), 1070s, 740. $^1$H-NMR (DMSO-$d_6$): 8.6 (s, O*H*, ex), 7.6-7.3 (m, 5 arom plus *H*-6), 7.01 (dd, *H*-7, J (6-7) = 6, J (7-7a) = 3), 5.12 (t, *H*-7a, J (7-7a) = 3), 4.79 (d, *H*-2β or *H*-2α, J (2α-2β) = 16.5), 4.69 (d, *H*-2α or *H*-2β, J (2α-2β) = 16.5), 4.14 (2H, overlapping signals of *H*-4a and *H*-4). Exact mass: calcd for $C_{12}H_{13}NO_4S$: 267.0565; found: 267.0559. *Anal.* Calcd.: C, 53.92; H, 4.90; N, 5.24; S, 11.99. Found: C, 54.13; H, 4.88; N, 5.00; S, 11.87%.

9β-Phenyl-2-oxa-6-thia-1-azatricyclo[3.3.1.0$^{3,7}$]nonan-4α-ol-6,6-dioxide (**4**).-- A stirred suspension of N-hydroxyoxazine **3** (6.86g, 2.5mmol) in a soln of toluene and *t*-BuOH (210ml, 5:1 by vol) was boiled 16h under reflux in $N_2$, and was cooled. Needles of **4** (mp 215-216°, 6.1g, 90.3%) were collected by filtration; recrystallization raised the mp to 216-217° ($Me_2CO$-EtOAc). IR (mineral oil): 3470, 1600, 1290, 1215, 1140, 1080. $^1$H-NMR (DMSO-$d_6$): 7.63 (m, 2H, arom), 7.26 (m, 3H, arom), 4.94 (d, O*H*, ex, J (O*H*-4) = 5), 4.82 (m, *H*-3), 4.53 (m, *H*-4, *H*-7, *H*-9), 4.27 (d, *H*-8β, J (8β-8α) = 12.6), 3.83 (br s, *H*-5), 3.53 (dd, *H*-8α, J (8α-8β) = 12.6, J 8α-7) = 6). EI-MS: 267 (74, $M^+$), 250 (99, M - OH). *Anal.* Found for $C_{12}H_{13}NO_4S$: C, 53.32; H, 5.00; N, 5.27; S, 11.77%

5β-Phenyl-8-thia-6-azatricyclo[3.2.1]octan-2α-ol (**5**).-- To a soln of **4** (0.60g, 2.2 mmol) in THF (200ml) was added $LiAlH_4$ (0.38g) during 30min. The mixture was boiled 20h under reflux in $N_2$, cooled, and treated with $H_2O$ (0.4ml), 15% aq NaOH (0.4ml), and $H_2O$ (1.2ml). The resulting mixture was filtered, THF was evaporated, and the residue was partitioned between $H_2O$ and $CHCl_3$. Extracts dried over $MgSO_4$ were filtered, and $CHCl_3$ was evaporated. The residue (0.42g) was chromatographed over silica gel (120g), and $CHCl_3$-MeOH (98:2 by vol) eluted compound **5** (0.2g, 41%), mp 98-100° ($CH_2Cl_2$-pet. eth.). IR: 3600m (OH), 3345 (NH), 3030, 2950s, 2650, 1490w, 1430br, 1100w, 1050m, 1020, 870. $^1$H-NMR (200MHz):7.56-7.37 (m, 5H, arom), 4.20 (octet, *H*-2, J (2-3α) = 10.2, J (2-1) or J (2-3β) = 2, J (2-3β) or J (2-1) = 5.8), 3.72 (br s, *H*-1), 3.71 (d, *H*-7α), J (7α-7β) = 11.2), 3.40 (dd, *H*-7β, J (7α-7β) =11.2, J (1-7β) = 5.6), 2.29 (br s, O*H* and N*H*, ex), 2.2-2.0 (complex m, *H*-3β, *H*-4α, *H*-4β), 1.78 (12-line m, *H*-3α). EI-MS: 221 (11, $M^+$), 204 (2, M - OH), 162 (100, $C_9H_8NS^+$ (**13**)). FAB-MS (glycerol): 223 (14), 222 (100), 205 (27), 204 (37), 172 (13), 170 (20), 162 (39); (glycerol-$d_3$): 225 (88), 224 (100), 223 (50), 222 (42), 205 (58), 202 (15), 172 (26), 171 (44), 170 (25), 164 (18), 163 (65), 162 (22). *Anal.* Calcd. for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; S, 14.49. Found: C, 65.02; H, 6.68; N, 6.17; S, 14.75%.

Compound **5** was further characterized as an acetate-acetamide derivative, mp 136-138° ($CHCl_3$-pet. eth.), prepared (73%) with excess $Ac_2O$-Py and eluted from silica gel by $CHCl_3$. IR: 1730 (ester CO), 1660 (amide CO). *Anal.* Calcd. for $C_{16}H_{19}NO_3S$: C, 62.92; H, 6.27; N, 4.59; S, 10.50. Found: C, 62.75; H, 6.28; N, 4.61; S, 10.89%.

5β-Phenyl-8-thia-6-azatricyclo[3.2.1]octan-3α-d-2α-ol (**6**).-- $LiAlD_4$ (2g) reduced **4** (3g, 11mmol) according to the foregoing procedure. After workup, chromatography, and crystallization, compound **6** (0.75g, 30%), mp 96-99° ($CHCl_3$-pet. eth.) was obtained. IR: 2150 (C-D). $^1$H-NMR (200MHz): 7.54 (m, 2H, arom), 7.34 (m, 3H, arom), 4.19 (br d, *H*-2, J (2-3β) or J (2-1) = 6), 3.76-3.66 (overlapping signals of *H*-7α and *H*-1), 3.40 (dd, *H*-7β, J (7α-7β) = 11.6, J (1-7β) = 7.5), 2.28-2.06 (complex m, O*H*, ex; N*H*, ex; *H*-3eq, 2*H*-4). $^2$H-NMR (200MHz): 1.78 (br s, D-3α). $^{13}$C-NMR: 143.0 (s, quat. arom.), 81.5 (s, *C*-5), 70.5 (d, *C*-2), 52.6 (d, *C*-1), 51.6 ( t, *C*-7), 44.4 (t, *C*-4), 28.7 (t, *C*H(D)-3). EI-MS: 222 (8, $M^+$), 205 (2, M - OH), 163 (100, $C_9{}^1H_7{}^2HNS^+$). FAB-MS (glycerol): 224 (75), 223 (100), 222 (26), 207 (20), 206 (44), 205 (35), 172 (20), 171 (28), 170 (10), 164 (11), 163 (22), 162 (54); (glycerol-$d_3$): 225 (100), 224 (84), 223 (58), 222 (38), 207 (78), 206 (75), 205 (26), 204 (8), 203 (7), 172 (44), 171 (37), 170 (16), 164 (28), 163 (71), 162 (73).

Compound **6** was further characterized as an acetate-acetamide derivative, mp 131-133° ($CHCl_3$-pet. eth.), prepared (89%) with excess $Ac_2O$-Py and eluted from silica gel by $CHCl_3$-pet. eth. IR: 2170w (C-D), 1720 (ester CO), 1650-1630br (amide CO). *Anal.* Calcd. for $C_{12}{}^1H_{11}{}^2HNO_3S$: C, 62.72; H, 5.92; N, 4.57; S, 10.46. Found: C, 62.43; H, 6.17; N, 4.25; S, 10.29%.

Exact Mass Measurements.-- *Ion* **13**. Calcd. for $C_9H_8NS^+$: 162.03774; found: 162.0393. *Ion* **14**. Calcd. for $C_{12}H_{12}N^+$: 170.09697; found: 170.0985.

## ACKNOWLEDGMENT

We are indebted to the staff of Analytical Research Services of Schering-Plough Corporation for microanalyses and spectra. We also thank *Dr. T. Kogan* (Schering-Plough Corp.) for a helpful discussion.

Table I: Non-hydrogen Atom Fractional Coordinates ($\times 10^4$) for **4**, with Standard Deviations in Parentheses

| Atom | $x$ | $y$ | $z$ | Atom | $x$ | $y$ | $z$ |
|---|---|---|---|---|---|---|---|
| N(1) | 3963(3) | 773(9) | 1060(3) | N(1') | 7281(3) | 6034(9) | 2209(3) |
| O(2) | 4647(2) | 1753(7) | 994(2) | O(2') | 6563(2) | 6835(8) | 2274(3) |
| C(3) | 4993(4) | 568(12) | 444(4) | C(3') | 6252(4) | 5511(12) | 2825(3) |
| C(4) | 5279(4) | -1496(12) | 790(3) | C(4') | 6036(4) | 3443(13) | 2475(4) |
| C(5) | 4611(4) | -2811(11) | 903(3) | C(5') | 6741(4) | 2298(12) | 2366(3) |
| S(6) | 4325(1) | -2961(3) | 0(-)[a] | S(6') | 7004(1) | 2185(3) | 3244(1) |
| C(7) | 4389(3) | -86(11) | -47(3) | C(7') | 6856(4) | 5065(12) | 3338(4) |
| C(8) | 3748(4) | 873(12) | 323(3) | C(8') | 7477(4) | 6140(12) | 2949(4) |
| C(9) | 4045(3) | -1497(11) | 1308(3) | C(9') | 7266(3) | 3769(12) | 1967(4) |
| O(10) | 5631(2) | -893(9) | 1399(3) | O(10') | 5673(2) | 3922(9) | 1851(3) |
| O(11) | 3620(3) | -3732(8) | -35(3) | O(11') | 7732(3) | 1643(9) | 3337(3) |
| O(12) | 4841(3) | -4008(9) | -412(3) | O(12') | 6507(3) | 945(9) | 3646(3) |
| C(13) | 4176(3) | -1650(11) | 2088(4) | C(13') | 7133(3) | 3596(12) | 1180(3) |
| C(14) | 4018(4) | -3656(12) | 2404(4) | C(14') | 7241(4) | 1599(11) | 868(4) |
| C(15) | 4214(4) | -3958(14) | 3094(4) | C(15') | 7131(4) | 1348(14) | 155(4) |
| C(16) | 4423(4) | -2220(15) | 3488(4) | C(16') | 6927(4) | 3060(15) | -238(3) |
| C(17) | 4509(4) | -2361(13) | 3201(5) | C(17') | 6825(4) | 5053(13) | 63(3) |
| C(18) | 4381(4) | 90(12) | 2486(4) | C(18') | 6924(4) | 5286(13) | 777(4) |

[a] The $z$-coordinate of S(6) was held constant throughout the analysis to define the origin in this direction

Table II: Mean Interatomic Distances (Å) and Angles (deg.) in **4**, with Estimated Standard Deviations in Parentheses

(a) Bond Lengths

| | | | | | |
|---|---|---|---|---|---|
| N(1)-O(2) | 1.458(7) | C(4)-O(10) | 1.411(9) | C(9)-C(13) | 1.533(9) |
| N(1)-C(8) | 1.477(9) | C(5)-S(6) | 1.795(7) | C(13)-C(14) | 1.392(10) |
| N(1)-C(9) | 1.485(9) | C(5)-C(9) | 1.561(10) | C(13)-C(18) | 1.371(10) |
| O(2)-C(3) | 1.458(9) | S(6)-C(7) | 1.800(8) | C(14)-C(15) | 1.382(11) |
| C(3)-C(4) | 1.523(11) | S(6)-O(11) | 1.440(6) | C(15)-C(16) | 1.368(12) |
| C(3)-C(7) | 1.547(10) | S(6)-O(12) | 1.435(6) | C(16)-C(17) | 1.367(12) |
| C(4)-C(5) | 1.536(10) | C(7)-C(8) | 1.547(10) | C(17)-C(18) | 1.404(10) |

(b) Bond Angles

| | | | | | |
|---|---|---|---|---|---|
| O(2)-N(1)-C(8) | 98.4(5) | S(6)-C(5)-C(9) | 107.6(5) | N(1)-C(9)-C(5) | 114.1(6) |
| O(2)-N(1)-C(9) | 109.2(5) | C(5)-S(6)-C(7) | 89.7(3) | N(1)-C(9)-C(13) | 112.7(6) |
| C(8)-N(1)-C(9) | 111.4(5) | C(5)-S(6)-O(11) | 112.0(3) | C(5)-C(9)-C(13) | 110.0(5) |
| N(1)-O(2)-C(3) | 105.1(5) | C(5)-S(6)-O(12) | 110.2(3) | C(9)-C(13)-C(14) | 117.6(6) |
| O(2)-C(3)-C(4) | 105.3(5) | C(7)-S(6)-O(11) | 112.4(3) | C(9)-C(13)-C(18) | 123.5(6) |
| O(2)-C(3)-C(7) | 104.4(6) | C(7)-S(6)-O(12) | 111.8(3) | C(14)-C(13)-C(18) | 119.0(7) |
| C(4)-C(3)-C(7) | 109.1(6) | O(11)-S(6)-O(12) | 117.4(3) | C(13)-C(14)-C(15) | 120.8(7) |
| C(3)-C(4)-C(5) | 102.0(6) | C(3)-C(7)-S(6) | 104.8(5) | C(14)-C(15)-C(16) | 119.6(8) |
| C(3)-C(4)-O(10) | 108.9(6) | C(3)-C(7)-C(8) | 101.6(6) | C(15)-C(16)-C(17) | 120.8(7) |
| C(5)-C(4)-O(10) | 114.7(6) | S(6)-C(7)-C(8) | 106.2(5) | C(16)-C(17)-C(18) | 119.8(8) |
| C(4)-C(5)-S(6) | 98.1(4) | N(1)-C(8)-C(7) | 103.3(6) | C(13)-C(18)-C(17) | 120.1(7) |
| C(4)-C(5)-C(9) | 111.7(6) | | | | |

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11. $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = \{\Sigma w(||F_o| - |F_c||)^2/\Sigma w|F_o|^2\}^{\frac{1}{2}}$.

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## NOTE

At the suggestion of a referee, we explain the terms *exo-trans* and *endo-cis*. *Exo* and *endo* denote transition-state relations between the nitrone N-Me group and the dipolarophile substituents. *Trans* and *cis* refer to geometries of the Me and Ph nitrone substituents.