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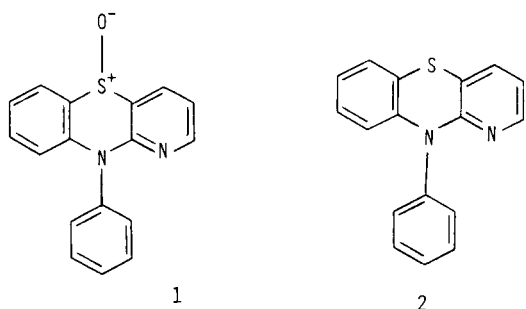
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The compound 10-phenylpyrido[3,2-*b*][1,4]benzothiazine 5-oxide, **1**, has been obtained in nearly quantitative yield oxidation of 10-phenylpyrido[3,2-*b*][1,4]benzothiazine with oxygen in dioxane solution. The ^{13}C nmr chemical shift assignments of **1** are reported. Its structure has been determined by X-ray single crystal methods. The crystals of **1** are monoclinic, space group $P2_1/n$. There are four molecules in a unit-cell of dimensions $a = 12.347(3)$, $b = 12.947(3)$, $c = 8.987(1)\text{ \AA}$, $\beta = 106.73(1)^\circ$ and $V = 1375.8(5)\text{ \AA}^3$. The central ring is in a boat conformation and the sulfoxide oxygen atom occupies the axial position. The folding angle between the planes of the pyrido and the benzo planes is $161.55(9)^\circ$.

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Introduction.

It is known that in substituted phenothiazine 5-oxides the sulfoxide oxygen occupies the axial position. This has been shown by several crystal structure determinations, for example those of chlorpromazine sulfoxide [1], *N*-methylchlorpromazine sulfoxide [2] and 10-methylphenothiazine 5-oxide [3]. In the absence of any structural data concerning the azaphenothiazine 5-oxides, we have initiated an investigation of these compounds in order to ascertain the position of the sulfoxide group. This paper reports the synthesis, ^{13}C nmr spectrum and the crystal structure of 10-phenylpyrido[3,2-*b*][1,4]benzothiazine 5-oxide, **1**.



EXPERIMENTAL

Synthesis and ^{13}C nmr Spectrum of **1**.

Initially we investigated the synthesis of **1** by hydrogen peroxide oxidation of 10-phenylpyrido[3,2-*b*][1,4]benzothiazine, **2**, in various solvents, since Gilman *et al* [4] have reported that some phenothiazines can be oxidized selectively to their respective sulfoxides or sulfones by varying the polarity of the solvent. Hydrogen peroxide oxidation of **2** in absolute ethanol gave **1** (yield 60%) whereas in acetic acid **1** was obtained in 40% yield along with oxidation products which were not identified. A much better method to prepare **1** in almost quantitative manner was found

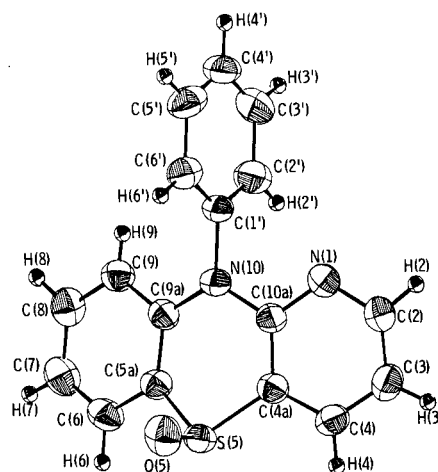


Figure 1. ORTEP drawing of **1**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary size.

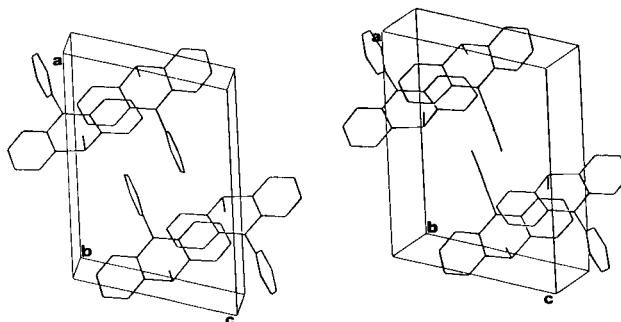


Figure 2. Stereoscopic drawing of the molecular packing of **1** in the unit cell. The hydrogen atoms have been excluded for clarity.

Table 1

¹³C Chemical Shifts of Some Phenothiazine Sulfoxides in Deuteriochloroform

Atom	CMPD No 1	$\delta^{13}\text{C}$ [a,b]	
		3	4
C(1)	—	115.33 (+1.40)	117.24 (+1.14)
C(2)	151.86 (+7.02)	130.66 (+3.71)	131.13 (+4.48)
C(3)	118.19 (+1.10)	121.58 (-0.70)	121.97 (-0.45)
C(4)	140.47 (+6.62)	132.49 (+5.22)	132.42 (+5.66)
C(4a)	117.35 (+1.95)	124.56 (+1.26)	122.53 (+2.20)
C(5a)	122.21 (+3.28)		
C(6)	132.64 (+5.63)		
C(7)	122.65 (-0.21)		
C(8)	131.50 (+5.15)		
C(9)	117.79 (-0.15)		
C(9a)	139.04 (-5.06)	139.64 (-6.03)	139.37 (-4.85)
C(10a)	148.11 (-5.92)		
C(1')	138.78 (-1.39)	—	138.88 (-2.25)
C(2'), C(6') [c]	130.14 (-0.81)	—	130.41 (-0.26)
C(3'), C(5') [c]	130.03 (+0.30)	—	131.77 (+1.10)
C(4')	128.71 (+0.96)	—	129.41 (+1.36)
CH ₃	—	35.03 (-0.04)	—

[a] $\delta^{13}\text{C}$ in ppm downfield from TMS, using deuteriochloroform as the internal reference at 77.0 ppm. [b] $\Delta > \text{S}^+ - \text{O}^-$ given in parentheses and defined as $\delta^{13}\text{C}_{\text{sulfoxide}} - \delta^{13}\text{C}_{\text{parent phenothiazine}}$. [c] Pairs of equivalent carbon atoms.

Table 2

Crystal and Experimental Data for 1

Chemical Formula	C ₁₇ H ₁₂ N ₂ OS
Formula Weight	292.36
Crystal System	Monoclinic
Space Group	P2 ₁ /n
Unit Cell Parameters	a = 12.347(3) Å b = 12.947(3) c = 8.987(1) β = 106.73(1)° V = 1375.8(5) Å ³
Number of molecules per unit cell	4
Density (calculated)	1.411 g cm ⁻³
X-radiation used for data collection	λ(MoKα) = 0.7107 Å
Linear absorption coefficient	μ(MoKα) = 2.23 cm ⁻¹
Total number of reflection with 3° < 2θ < 50°	2442
Number of reflections with I > 3σ(I)	1984
Maximum residual electron density	0.43 e Å ⁻³
Disagreement index, R for 1984 observed reflections	0.034
Weighted disagreement index, wR for 1984 observed reflections	0.038
Crystal size	0.82 x 0.61 x 0.58 mm

later. A stream of oxygen was bubbled into a refluxing solution of dioxane (100 ml) containing 1.38 g (4.7 mmoles) of 2 for 2 hours. The solvent was then evaporated to yield 1.43 g (98%) of 1, mp 211–212°.

Anal. Calcd. for C₁₇H₁₂N₂OS: C, 69.84; H, 4.14; N, 9.58. Found: C, 69.62; H, 4.23; N, 9.40.

The ¹³C nmr chemical shifts of 1 were assigned using 10-methylphenothiazine 5-oxide, 3, and 10-phenylpyrido[3,2-b][1,4]benzothiazine 5-oxide,

4, as model compounds. They are summarized in Table 1.

The ¹³C spectra were obtained using 1.2–1.5 M solutions in deuteriochloroform or d₆-DMSO using the solvent and TMS as double reference standard (deuteriochloroform:77.0 ppm, d₆-DMSO:39.5 ppm). The spectra were recorded on a WP 200-SY Bruker spectrometer operating at the frequency of 50.327 MHz. Spectral widths of 200 ppm were employed using 2 second relaxation delay and pulse width of 10 microseconds (corresponds to a tip angle of 33°). Data collection was carried out with 16K data point memory (8K after FT transformation) with digitation rate of 1.25 Hz/point.

Crystal Data and Structure Determination.

The crystals of 1 are colorless prisms. A crystal of approximate size 0.82 x 0.61 x 0.58 mm was selected for the determination of unit-cell parameters and the intensity measurements. The unit-cell parameters were obtained by least-squares fit of 15 reflections with 2θ values ranging from 20° to 30°, measured on a Syntex P2, automatic diffractometer with graphite monochromatized MoKα radiation. The crystal is monoclinic with space group P2₁/n deduced from systematic absences (h0l absent with h + l = 2n + 1, Ok0 absent with k = 2n + 1). The crystal data are summarized in Table 2. The intensity data were collected as 295°K with the θ/2θ scanning mode. A total of 2442 independent reflections with h: -14 - 13; k: 0 - 15; and l: 0 - 10 were measured with 2θ in the range of 3° to 50°, of which 1984 reflections were considered as observed by the criterion I > 3σ(I), where σ(I) was determined by counting statistics. The intensity data were reduced to structure amplitudes by application of the Lorentz and polarization factors, and no absorption correction was applied.

The structure was solved by direct methods using MULTAN78 [5] which showed the positions of all non-hydrogen atoms. Full-matrix least-squares refinements were carried out using SHELX76 [6]. The non-hydrogen atoms were refined with anisotropic temperature factors. All hydrogen atoms were located in a difference Fourier map and were allowed to refine with isotropic temperature factors. The weighting scheme used in the least-squares was w = 1/[σ²(Fo) + 2.2 x 10⁻⁴Fo²] and the quantity minimized was Σw(|F_o| - |F_c|)². The final agreement factors are R = 0.034 and R_w = 0.038 for the 1984 observed reflections. The final difference Fourier map showed a maximum residual electron density of 0.42 e/Å³ in the vicinity of the sulfur atom. The scattering factors for all atomic species were taken from the International Tables for X-ray Crystallography [7]. The final atomic coordinates and temperature factors are given in Table 3.

Results and Discussion.

The identification of the atoms and the configuration of the molecule are shown in ORTEP [8] drawing in Figure 1. The bond lengths and bond angles, with their standard deviations, are listed in Table 3. The least-squares planes of the benzo and the pyrido rings, together with the deviations of the atoms from the planes are given in Table 5. The tricyclic ring is folded along the line S(5)-N(10). The central ring system is in a boat conformation as shown by

the Cremer and Pople puckering parameters [9] and the torsion angles in Table 4. The 10-phenyl substituent is in an axial position with respect to the central ring as shown in the stereoscopic drawing in Figure 1. The folding angle between the least-squares planes (given in Table 5) of the pyrido and benzo rings of 161.55(9)° is within the range of magnitudes observed in other pyridobenzothiazine derivatives [10,11]. The plane of the phenyl ring nearly bisects the pyridobenzothiazine moiety as shown by the dihedral angles of 86.09(8)° between the planes of the phenyl ring

Table 3

Fractional atomic coordinates and thermal parameters ($\times 10^4$) for non-hydrogen and ($\times 10^3$) for hydrogen atoms. (The estimated standard deviations are given in parentheses and refer to the last positions of respective values.)

The expression for the thermal parameters with U values in \AA^2 is:

$$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b + 2U_{13}hla^*c^* + 2U_{23}kfb^*c^*)]$$

Atom	x	y	z	U11	U22	U33	U12	U13	U23
N(1)	4492(1)	4117(1)	13019(2)	458(9)	671(12)	403(9)	16(8)	138(8)	-65(9)
C(2)	5500(2)	3926(2)	14034(2)	491(12)	654(14)	401(11)	18(10)	86(10)	-57(11)
C(3)	6383(2)	3451(2)	13673(3)	426(12)	562(14)	516(13)	0(10)	35(10)	1(10)
C(4)	6196(2)	3112(2)	12175(2)	375(11)	446(12)	548(13)	34(10)	138(10)	1(9)
C(4A)	5162(2)	3266(1)	11092(2)	386(10)	380(10)	440(11)	-46(8)	168(9)	-21(8)
S(5)	4895(0)	2619(0)	9297(1)	413(3)	436(3)	459(3)	11(2)	181(2)	-57(2)
O(5)	4333(1)	1632(1)	9439(2)	661(9)	406(8)	665(9)	-57(7)	142(8)	-17(7)
C(5A)	3844(1)	3461(1)	8227(2)	392(10)	398(10)	426(11)	-45(8)	183(8)	-5(8)
C(6)	3649(2)	3445(2)	6617(2)	570(13)	518(13)	459(12)	-31(10)	264(11)	-33(11)
C(7)	2748(2)	3949(2)	5652(3)	714(15)	613(14)	364(11)	-38(10)	189(11)	43(12)
C(8)	2015(2)	4479(2)	6283(2)	573(13)	461(12)	452(12)	23(10)	85(10)	67(11)
C(9)	2197(2)	4516(2)	7862(2)	443(11)	437(12)	463(12)	53(9)	143(9)	-9(9)
C(9A)	3117(1)	4023(1)	8874(2)	398(10)	384(10)	390(10)	-50(8)	158(8)	-21(8)
N(10)	3308(1)	4089(1)	10484(2)	361(8)	552(10)	381(8)	57(7)	152(7)	-49(7)
C(10A)	4328(1)	3816(1)	11537(2)	362(10)	432(10)	393(10)	-34(8)	153(8)	-21(8)
C(1')	2485(2)	4639(2)	11067(2)	377(10)	564(12)	370(10)	55(9)	138(8)	-40(9)
C(2')	2596(2)	5681(2)	11333(3)	549(14)	587(15)	740(16)	-32(12)	253(12)	-163(12)
C(3')	1811(2)	6191(2)	11895(3)	718(17)	669(18)	777(18)	119(14)	164(14)	-287(14)
C(4')	927(2)	5658(2)	12177(3)	531(14)	1000(21)	450(12)	259(13)	157(11)	-109(15)
C(5')	823(2)	4627(2)	11898(3)	425(12)	918(20)	505(13)	120(12)	210(10)	122(13)
C(6')	1602(2)	4105(2)	11329(2)	447(12)	559(14)	466(11)	65(10)	159(9)	65(10)
H(2)	557(2)	416(2)	1509(3)	72(7)					
H(3)	707(2)	338(2)	1442(3)	59(6)					
H(4)	677(2)	277(2)	1196(3)	55(6)					
H(6)	416(2)	306(2)	623(2)	53(6)					
H(7)	261(2)	395(2)	462(3)	77(8)					
H(8)	135(2)	482(2)	564(2)	48(5)					
H(9)	177(2)	488(2)	822(3)	58(7)					
H(2')	322(2)	600(2)	1119(3)	63(7)					
H(3')	189(2)	688(2)	1206(3)	83(9)					
H(4')	41(2)	603(2)	1256(3)	78(8)					
H(5')	21(2)	425(2)	1211(3)	73(7)					
H(6')	153(2)	339(2)	1113(2)	58(7)					

Table 4

Bond lengths (\AA) and bond angles ($^\circ$) with estimated standard deviations in parenthesis

Bond lengths in \AA (E. s. d. 's in parentheses)

N(1)	-	C(2)	1.337 (3)
N(1)	-	C(10A)	1.346 (2)
C(2)	-	C(3)	1.370 (3)
C(3)	-	C(4)	1.371 (3)
C(4)	-	C(4A)O	1.379 (3)
C(4A)	-	S(5)	1.763 (2)
C(4A)	-	C(10A)	1.402 (2)
S(5)	-	O(5)	1.477 (2)
S(5)	-	C(5A)	1.755 (2)
C(5A)	-	C(6)	1.397 (3)
C(5A)	-	C(9A)	1.405 (3)
C(6)	-	C(7)	1.364 (3)
C(7)	-	C(8)	1.381 (3)
C(8)	-	C(9)	1.372 (3)
C(9)	-	C(9A)	1.389 (3)
C(9A)	-	N(10)	1.400 (2)

Table 4 (Continued)

N(10)	-	C(10A)	1.386 (2)
N(10)	-	C(1')	1.456 (3)
C(1')	-	C(2')	1.370 (3)
C(1')	-	C(6')	1.367 (3)
C(2')	-	C(3')	1.383 (4)
C(3')	-	C(4')	1.375 (4)
C(4')	-	C(5')	1.357 (4)
C(5')	-	C(6')	1.388 (3)

Bond angles ($^\circ$) (E. s. d. 's in parentheses)

C(2)	-	N(1)	-	C(10A)	117.8(2)
N(1)	-	C(2)	-	C(3)	124.7(2)
C(2)	-	C(3)	-	C(4)	117.1(2)
C(3)	-	C(4)	-	C(4A)	120.5(2)
C(4)	-	C(4A)	-	S(5)	117.9(2)
C(4)	-	C(4A)	-	C(10A)	118.6(2)
S(5)	-	C(4A)	-	C(10A)	122.9(1)
C(4A)	-	S(5)	-	O(5)	107.5(1)
C(4A)	-	S(5)	-	C(5A)	96.9(1)

Table 4 (Continued)

O(5)	—	S(5)	—	C(5A)	107.0(1)
S(5)	—	C(5A)	—	C(6)	116.0(1)
S(5)	—	C(5A)	—	C(9A)	123.7(1)
C(6)	—	C(5A)	—	C(9A)	119.8(2)
C(5A)	—	C(6)	—	C(7)	121.2(2)
C(6)	—	C(7)	—	C(8)	119.2(2)
C(7)	—	C(8)	—	C(9)	120.7(2)
C(8)	—	C(9)	—	C(9A)	121.4(2)
C(5A)	—	C(9A)	—	C(9)	117.8(2)
C(5A)	—	C(9A)	—	N(10)	121.4(1)
C(9)	—	C(9A)	—	N(10)	120.7(2)
C(9A)	—	N(10)	—	C(10A)	122.7(1)
C(9A)	—	N(10)	—	C(1')	118.3(1)
C(10A)	—	N(10)	—	C(1')	118.0(1)
N(1)	—	C(10A)	—	C(4A)	121.1(1)
N(1)	—	C(10A)	—	N(10)	116.8(1)
C(4A)	—	C(10A)	—	N(10)	122.2(1)
N(10)	—	C(1')	—	C(2')	119.9(2)
N(10)	—	C(1')	—	C(6')	119.2(2)
C(2')	—	C(1')	—	C(6')	120.8(2)
C(1')	—	C(2')	—	C(3')	119.2(2)
C(2')	—	C(3')	—	C(4')	120.3(2)
C(3')	—	C(4')	—	C(5')	119.8(2)
C(4')	—	C(5')	—	C(6')	120.5(2)
C(1')	—	C(6')	—	C(5')	119.3(2)

Table 5

Torsion Angles and Ring Puckering Parameters

Torsion angles (°) around the central ring

N(10)	—	C(10a)	—	C(4a)	—	S(5)	—14.8(2)
C(10a)	—	C(4a)	—	S(5)	—	C(5a)	31.2(2)
C(4a)	—	S(5)	—	C(5a)	—	C(9a)	—29.6(2)
S(5)	—	C(5a)	—	C(9a)	—	N(10)	11.3(2)
C(5a)	—	C(9a)	—	N(10)	—	C(10a)	14.8(2)
C(9a)	—	N(10)	—	C(10a)	—	C(4a)	14.8

Torsion angles around the N(10) — C(1') bond

C(9a)	—	N(10)	—	C(1')	—	C(2')	—88.8(2)
C(9a)	—	N(10)	—	C(1')	—	C(6')	90.8(2)
C(10a)	—	N(10)	—	C(1')	—	C(2')	80.3(3)
C(10a)	—	N(10)	—	C(1')	—	C(6')	—100.2(2)

Puckering parameters of central ring

Central	ring	Ideal boat conformation
Q	0.371(1) Å	
q ₂	0.345(1)	q ₂ = 0
q ₃	—0.136(2)	q ₃ = 0
θ	111.5(2)°	θ = 90°
φ ₂	356.8(3)°	φ = 360

Table 6

Deviations (Å) of atoms from the least-squares planes
(* refers to atoms not included in the least-squares planes.)

	Pyrido ring	Benzo ring	Phenyl ring		
N(1)	—0.010(2)	C(5a)	—0.009(2)	C(1')	0.006(3)
C(2)	—0.012(3)	C(6)	0.005(3)	C(2')	—0.003(3)
C(3)	0.022(3)	C(7)	0.009(3)	C(3')	—0.001(3)
C(4)	0.002(3)	C(8)	—0.008(3)	C(4')	0.002(3)
C(4a)	—0.030(3)	C(9)	—0.006(3)	C(5')	0.001(3)
C(10a)	0.021(2)	C(9a)	0.010(2)	C(6')	—0.005(3)
S(5)*	—0.349(3)	S(5)*	—0.278(3)	N(10)	0.012(4)
N(10)*	0.122(3)	N(10)*	0.045(3)		

Angles between the Pyrido and Benzo rings: 161.55(8)°; Pyrido and Phenyl rings: —75.65(9); Benzo and Phenyl rings: 86.09(8).

and the benzo ring and 75.65(9)° between the planes of the phenyl ring and the pyrido ring. The packing of the molecule in the unit cell is shown in the stereoscopic drawing in Figure 2. There is no intermolecular distance less than van der Waals separation.

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REFERENCES AND NOTES

- [1] E. Hough, M. Hjorth and S. G. Dahl, *Acta Cryst.*, **C41**, 383 (1985).
- [2] E. Hough, E. Wold, and S. G. Dahl, *Acta Cryst.*, **C41**, 386 (1985).
- [3] S. S. C. Chu, P. de Meester, M. V. Jovanovic and E. R. Biehl, *Acta Cryst.*, **C41**, 1111 (1985).
- [4] H. Gilman, R. K. Ingham, J. F. Champaigne, J. W. Diehl and R. O. Ranck, *J. Org. Chem.*, **19**, 560 (1954).
- [5] P. Main, S. E. Hull, L. Lessiner, G. Germain, J. P. Declercq, and M. M. Wolfson, MULTAN78. A system of computer programs for the automatic solution of crystal structure from X-ray diffraction data. Universities of York, England and Louvain, Belgium, 1978.
- [6] G. M. Sheldrick, SHELX76. Programs for crystal structure determination, University of Cambridge, England, 1976.
- [7] International Tables for X-ray Crystallography, Vol IV, Birmingham, Kynoch Press, 1974.
- [8] C. K. Johnson, ORTEP Report ORNL-3784. Oak Ridge, National Laboratory, Tennessee, 1965.
- [9] D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1354 (1975).
- [10] M. V. Jovanovic, E. R. Biehl, P. de Meester and S. S. C. Chu, *J. Heterocyclic Chem.*, **21**, 1425 (1984).
- [11] P. de Meester, S. S. C. Chu, M. V. Jovanovic and E. R. Biehl, *Acta Cryst.*, **C41**, 1246 (1985).