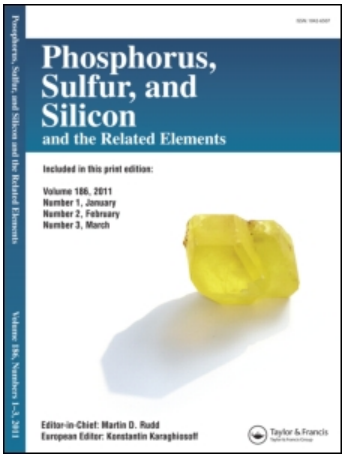

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND BIOLOGICAL STUDIES OF α-ARYL-N-(2-PHENYLTHIOPHENYL)NITRONES

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To cite this Article Sivasubramanian, S. , Ravichandran, K. , Ponnusamy, A. , Muthusubramanian, S. and Mahendran, V.(1992) 'SYNTHESIS AND BIOLOGICAL STUDIES OF α-ARYL-N-(2-PHENYLTHIOPHENYL)NITRONES', Phosphorus, Sulfur, and Silicon and the Related Elements, 66: 1, 165 — 170
To link to this Article: DOI: 10.1080/10426509208038343
URL: http://dx.doi.org/10.1080/10426509208038343

Phosphorus, Sulfur, and Silicon, 1992, Vol. 66, pp. 165–170
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SYNTHESIS AND BIOLOGICAL STUDIES OF α-ARYL-N-(2-PHENYLTHIOPHENYL)NITRONES

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(Received May 28, 1991; in final form September 12, 1991)

Fourteen new α-aryl-N-(2-phenylthiophenyl)nitrones have been synthesized. The spectral features reveal that the α-aryl and N-aryl rings are *trans* to each other and deviate from the $\rangle C{=}\overset{\oplus}{N}{-}\overset{\ominus}{O}$ plane. (2-Hydroxyphenyl)-N-(2-phenylthiophenyl)nitrone has a conformation in which the hydroxy group is closer to nitrone oxygen and other α-2-substituted phenyl-N-(2-phenylthiophenyl)nitrones prefer a conformation in which the 2-substituent of the α-aryl ring is away from the nitrone oxygen. The antimicrobial studies of these compounds reveal that while α-(2-methoxyphenyl)-N-(2-phenylthiophenyl)nitrones is moderately active against *Shigella flexneri* and the α-(2-hydroxyphenyl)-N-(2-phenylthiophenyl)nitrone is moderately active against *Staph. aureus, Shigella flexneria* and *S. typhi* "*H*".

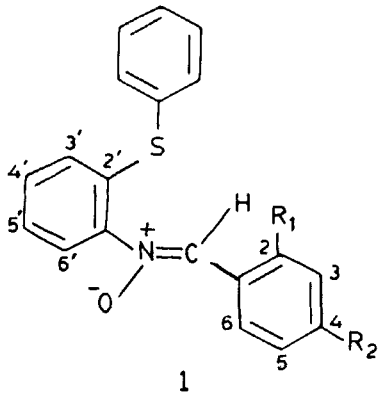
Key words: Synthesis; antimicrobial activities; α-aryl-N-(2-phenylthiophenyl)nitrones; conformation.

INTRODUCTION

In continuation of our studies on the chemistry of nitrones,[1–9] we embarked upon a program to synthesize α-aryl-N-(2-phenylthiophenyl)nitrones with the expectation that these nitrones may be biologically active. This expectation is based on the fact that even simple ortho-substituted diphenyl sulphides are biologically active.[10] Furthermore, configurational and conformational study of these compounds also assume importance owing to the expectation that they may not exist in a planar configuration due to the ortho substitution in the N-phenyl ring which will inhibit through resonance throughout the molecule.

RESULTS AND DISCUSSION

Several hitherto unknown α-aryl-N-(2-phenylthiophenyl)nitrones, fourteen in all, along with the parent, -phenyl (**1a**) having methyl (**1b**), methoxy (**1c**), chloro (**1d**), dimethylamino (**1e**), methylthio (**1f**), methylsulphonyl (**1g**), nitro (**1h**), phenylthio (**1i**) and 4-methylphenylthio (**1j**) substituent in the **4** position of the α-aryl ring and



1

a) R_1=R_2=H

b) R_1=H, R_2=Me

c) R_1=H, R_2=OMe

d) R_1=H, R_2=Cl

e) R_1=H, R_2=NMe_2

f) R_1=H, R_2=SMe

g) R_1=H, R_2=SO_2Me

h) R_1=H, R_2=NO_2

i) R_1=H, R_2=SPh

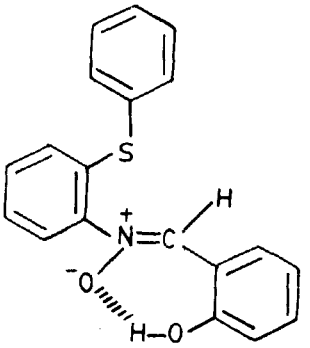
j) R_1=H, R_2=S.p-tolyl

k) R_1=OH, R_2=H

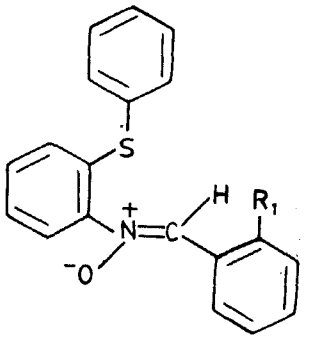
l) R_1=OMe, R_2=H

m) R_1=Cl, R_2=H

n) R_1=NO_2, R_2=H



(X)



(Y)

hydroxy (**1k**), methoxy (**1l**), chloro (**1m**) and nitro (**1n**) at 2 position of the α-aryl ring have been synthesized by the condensation of ortho- and para-substituted benzaldehydes with 2-phenylthiophenylhydroxylamine following the literature procedure.[4] The molecular formula, m.p., UV, IR and ^{1}H NMR data of these compounds are given in Table I.

As in the case of simple α,N-diaryl nitrones,[11] three bands were observed in the electronic spectra of **1**. Though the absorption maximum appearing above 300 nm

TABLE I

Yields and physical constants of α-aryl-N-(2-phenylthiophenyl)nitrones **1**

Entry	Mol. formula	Yield %	M.P. °C	UV λ_{max} nm	IR cm^{-1} $\nu_{C=N}$	IR cm^{-1} ν_{N-O}	IR cm^{-1} α-H	^1H NMR (δ-scale) 2,6	^1H NMR (δ-scale) other aromatic hydrogens	^1H NMR (δ-scale) others
1a	$C_{19}H_{15}NOS$	77	85–7	196, 238 355	1560	1070	7.45	8.40	720–7.70	—
b	$C_{20}H_{17}NOS$	76	92–4	197, 231 349	1565	1075	7.45	8.40	7.00–7.70	2.40 (Me)
c	$C_{20}H_{17}NO_2S$	74	138–40	196, 237 316	1565	1065	7.55	8.30	6.95–7.60	3.85 (OMe)
d	$C_{19}H_{14}NOSCl$	74	124–26	197, 233 304	1575	1080	7.50	8.40	7.30–7.70	—
e	$C_{21}H_{20}N_2OS$	72	144–46	196, 240 360	1580	1060	7.50	8.35	6.80–7.60	3.00 (Me)
f	$C_{20}H_{17}NOS_2$	82	152–53	197, 239 338	1575	1075	7.55	8.30	7.10–7.60	2.55 (Me)
g	$C_{20}H_{17}NO_3S_2$	83	160–62	195, 239 319	1570	1070	7.75	8.50	7.10–8.00	3.10 (Me)
h	$C_{19}H_{14}N_2O_3S$	78	78–81	194, 245 342	1580	1090	7.90	8.60	7.30–8.40	—
i	$C_{25}H_{19}NOS_2$	70	133–34	196, 237 309	1565	1070	7.60	8.35	7.10–8.00	—
j	$C_{26}H_{21}NOS_2$	76	145–47	197, 240 337	1570	1060	7.50	8.30	7.10–7.60	2.40 (Me)
k	$C_{19}H_{15}NO_2S$	70	97–8	202, 233 341	1580	1050	7.90	*[a]	6.90–7.90	12.60 (OH)
l	$C_{20}H_{17}NO_2S$	73	102–04	197, 227 336	1570	1080	8.20	9.60[b]	6.90–7.70	3.80 (OMe)
m	$C_{19}H_{14}NOSCl$	70	108–10	198, 237 301	1565	1090	8.30	9.70[b]	7.30–7.80	—
n	$C_{19}H_{14}N_2O_3S$	72	110–12	195, 243 342	1570	1090	8.30	9.40[b]	7.00–8.00	—

[a]The C_6—H appears along with other aromatic hydrogens.
[b]C_6—H only.

is affected by the change of substituents in aryl ring, there is no direct correlation between λ_{max} and the electron-withdrawing and electron-releasing nature of the substituents. This is in contrast to what has been observed in simple α,N-diaryl nitrones[11] and α-aryl-N-(4-phenylthiophenyl)nitrones.[9] This absorption maximum (K band) is, in general, attributed to the excitation of the whole molecule where both the α and N-aryl rings along with their substituents are expected to be planar or nearly planar. Evidently, the planar conformation and hence the through resonance, is absent in these compounds (**1a–1n**) as a result of the presence of the phenylthio group at the ortho position of the N-aryl ring. How far the N-aryl ring has gone out the plane from the fragment $-O\diagdown\!\diagup N^+=C\diagup\!\diagdown$ ie., the dihedral angle between the N-aryl ring and this fragment, can be worked out for these compounds following the relationship[12]

$$\cos^2\phi = \frac{\varepsilon_{ortho}}{\varepsilon_{para}}$$

where ε_{ortho} is the value for the longest wavelength band of **1** and ε_{para} is that for the corresponding α-aryl-N-(4-phenylthiophenyl)nitrone.[9] This angle varies depending on the nature of the substituent in the α-aryl ring and ranges between 30° to 45°. It is also to be noticed that the other two bands have not undergone any appreciable change in their λ_{max} values due to the different substitution. All the nitrones exhibit their characteristic IR absorption bands at 1570 ± 10 cm^{-1} (C=N stretching) and at 1075 ± 15 cm^{-1} ($\overset{+}{N}$—$\bar{O}$ stretching).

In the ^1H NMR spectra of **1a–1f**, the α-H appears at 7.50 ± 0.05 ppm (δ-scale). Thus the azomethine hydrogen is shielded compared to the corresponding α-aryl-N-(4-phenylthiophenyl)nitrones by 0.35 ppm. This may be due to the ortho substituent viz. phenylthio group in the N-phenyl ring. However, in the case of **1g** and **1h**, the same α-H appears a bit downfield as expected due to the presence of strong electron withdrawing substitution in the α-aryl ring. It is interesting to note that in the ortho substituted α-aryl systems **1l–1n**, the α-H is more deshielded than their para counterparts (**1a–1g**). This can be ascribed as due to van der Walls deshielding in its preferred conformation (vide infra).

In general, the 2,6-hydrogens, which are deshielded due to the anisotropic effect of nitrone oxygen[13] which is equally felt by both these hydrogens because of C_α—C_1 free rotation, appears around 8.35 ppm in **1a–1f** and at 8.50 and 8.60 ppm for **1g** and **1h**, respectively. This proves the *trans* orientation of the aryl rings. It is to be noted that C_6—H of **1k** appears somewhere in between 6.90 to 7.80 along with other aromatic hydrogens while the C_6 of **1l–1n** appear far downfield, above 9.50 ppm. Apparently there is no deshielding due to anisotropic effect of nitrone oxygen in the former, but strongly felt exclusively on C_6 in the latter cases. This can only be explained if **1k** prefers a conformation (X) wherein the ortho substituted hydroxyl group forms a hydrogen bonded structure with the nitrone oxygen pushing the C_6 hydrogen away from it and with the latter compounds (**1l–1n**) prefer a different conformation (Y) wherein the C_2 substituent is away from the nitrone oxygen.

TABLE II

Antimicrobial activity of nitrones **1**

Entry	Micro-organisms tested					
	Staph.[a] *aureus*	*Strep.*[a] *aureus*	*K. aerogens*[b]	*Shigella*[b] *flexneria*	*S. typhi* "*H*"[b]	*P. mirabilis*[b]
1c	NA	NA	NA	[d]	NA	NA
e	NA	NA	NA	NA	NA	NA
f	NA	NA	NA	NA	NA	NA
h	NA	NA	NA	NA	[c]	NA
j	NA	NA	NA	NA	NA	NA
k	[d]	NA	NA	[d]	[d]	NA
n	[c]	NA	NA	[c]	NA	NA

[a]Gram positive Cocci.
[b]Gram negative bacilli.
[c]Less active.
[d]Moderately active.
NA No activity.

Antimicrobial Activity

The antimicrobial activity of a few compounds (**1c, e, f, h, j, k** and **n**) were tested against a variety of gram negative and gram positive bacteria *Proteus mirabilis, Shigella flexneria, Salmonella typhi "H", Klebsiella aerogenes, Staphylococcus aureus* and *Streptococcus aureus* based on the disc diffusion method (100 μg of the sample/disc) in acetone.[14-16] The cultures were made in nutrient agar and the discs were placed on the cultures. The agar plates were incubated for 24 hours at 37°C. The results are shown in Table II. It could be seen from the table that **1k** is moderately active (4 to 6 mm) against *S. flexneri, S. typhi "H"* and *Staph. aureus*. **1n** is less active (2 mm) against *S. flexneri* and *Staph. aureus*. **1e** is moderately active against *S. flexneri*. **1h** showed less activity against *S. typhi "H"* while all other organisms (*P. mirabilis, Strep. aureus* and *K. aerogenes*) are resistant towards all the compounds tested.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded in Perkin Elmer 557 instrument as KBr pellets. UV spectra were recorded in PU 8800 UV/visible spectrophotometer (Philips) using ethanol (95%) as the solvent. ^{1}H NMR spectra were measured in $CDCl_3$ with TMS as an internal standard on a R32 Perkin-Elmer instrument (90 MHz) at 27°C. All the new compounds gave satisfactory analysis.

General procedure for the preparation of nitrones **1**: A mixture of 2-(phenylthio)nitrobenzene[17] (4.60 gm, 0.02 mol) in warm ethanol (50 ml) and ammonium chloride (2.00 gm) in distilled water (30 ml) was taken in a round bottomed flask and stirred well. Zinc dust (4.00 gm) was added to it in small portions with stirring during a period of 15 minutes. The stirring of the reaction mixture at 60–70°C was continued for a further period of 30 minutes. The zinc oxide formed was filtered off at the pump and washed with chloroform (50 ml). The filtrate was extracted immediately with chloroform (2 × 30 ml). The combined extract of 4-phenylthiophenylhydroxylamine in chloroform was concentrated to 50 ml and used as such. The hydroxylamine thus obtained (~0.02 mol) was added with aryl aldehyde (0.015 mol) and refluxed for 1 hour, which resulted in a viscous liquid upon removal of the solvent. This liquid was triturated with ether to give crystals of nitrone **1**. In the case of **1b**, the resulted liquid was triturated with n-hexane instead of ether to get the solid. Nitrones were then recrystallized from 95% ethanol.

ACKNOWLEDGEMENTS

The authors thank USIC, M. K. University for the IR and NMR spectra and also thank Dr. S. Puratchimani and Mr. P. V. Kumar, Bose Research and Diagnostic Centre, Madurai, for their technical assistance.

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