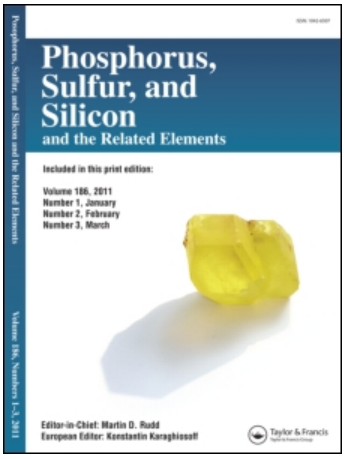


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-SUBSTITUTED MERCAPTO(4:5)-PHENAZINO OXAZOLE DERIVATIVES

R. Buchi Reddy[a]; E. Surender[a]; G. V. P. Chandra Mouli[a]; Y. D. Reddy[a]
[a] Department of Chemistry, Regional Engineering College, Warangal, India

To cite this Article Reddy, R. Buchi , Surender, E. , Mouli, G. V. P. Chandra and Reddy, Y. D.(1984) 'SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-SUBSTITUTED MERCAPTO(4:5)-PHENAZINO OXAZOLE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 20: 1, 49 — 53
To link to this Article: DOI: 10.1080/03086648408077610
URL: http://dx.doi.org/10.1080/03086648408077610

Phosphorus and Sulfur, 1984, Vol. 20, pp. 49–53
0308-664X/84/2001-0049/$18.50/0

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-SUBSTITUTED MERCAPTO(4:5)-PHENAZINO OXAZOLE DERIVATIVES

R. BUCHI REDDY, E. SURENDER, G. V. P. CHANDRA MOULI and Y. D. REDDY*

Department of Chemistry, Regional Engineering College, Warangal-506 004, India

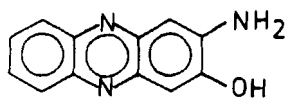
(*Received December 14, 1983; in final form January 25, 1984*)

2-Aminophenazin-3-ol (I) is treated with carbondisulfide in alkaline medium to furnish 2-mercapto(4:5)-phenazino oxazole (IIa). Treatment of IIa with alkyl/acyl halides gives the corresponding thioethers (IIb–i; k–o) and thioester (IIj). These are characterised by elemental, IR, PMR and mass spectral analysis. All the compounds synthesised have been screened for their antimicrobial activity.

Heterocyclic oxazoles have been found to be potential antibacterial,[1] antifungal[2] and fluorescent brightening agents.[3] Some of the phenazine derivatives have been reported to exhibit antitubercular activity in mice[4-6] and in vitro.[7] Anilinoapo-safranine, a derivative of phenazine has been claimed to exert a curative effect in lepromatous leprosy.[8] Many dyes on the market possess phenazine moiety. In an attempt to club both the properties of oxazoles and phenazines on to a single molecule we herewith report a brief synthesis of condensed phenazino oxazole derivatives.

2-Mercapto(4:5)phenazino oxazole (IIa) has been prepared by the condensation of 2-aminophenazin-3-ol[9] (I) with carbon disulfide in presence of ethanolic potassium hydroxide. In course of our present work we observed some deviations from the earlier report[10] on the synthesis of compound IIa. It was prepared[10] starting from compound I and potassium ethyl xanthate. The final product was described[10] as a black mass which did not melt below 300 °C and its structure was not confirmed by spectral data.

But we obtained the same compound in the form of yellowish-green crystals melting at 276–277 °C (decomposing). The structure has now been confirmed by its elemental, IR, PMR and mass spectral data.



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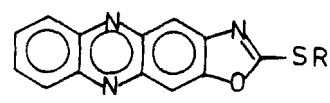


IIa R=H

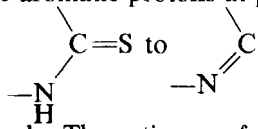
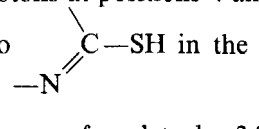
IIb–i, k–o R=alkyl

IIj R=$-COCH_3$

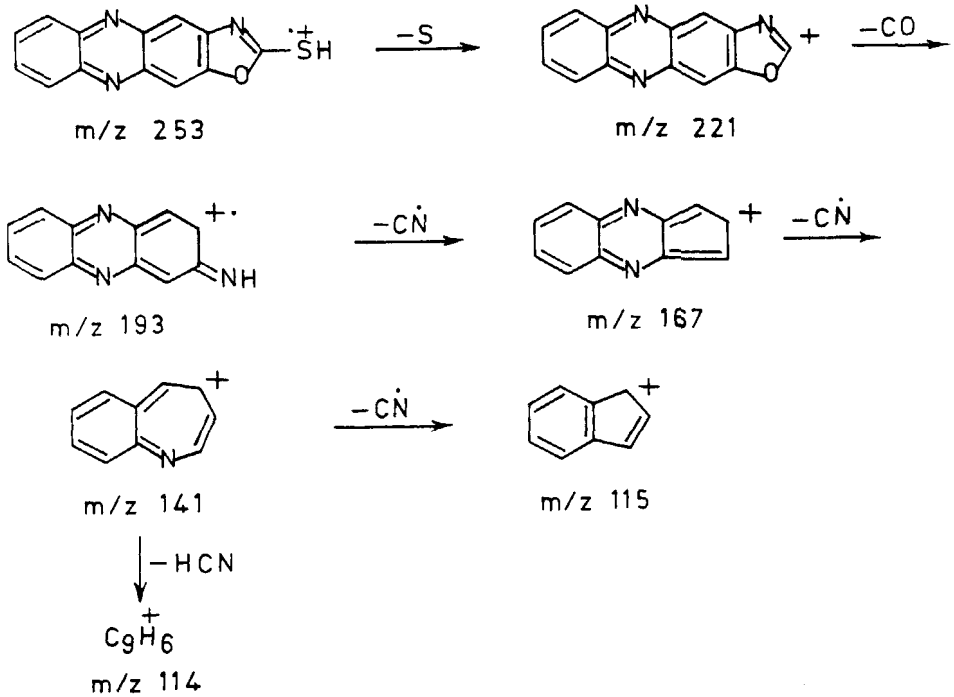
*Author to whom all correspondence should be addressed.

The weak but sharp IR absorption band at 2650 cm^{-1} reveals the presence of —SH group.[11] The —C—S—H bending vibrations are located in the regions of 850 and 750 cm^{-1}. The characteristic absorption bands for N—C=S are found at 1520 and 1480 cm^{-1} (amide II band); 1350 cm^{-1} (—C=S of amide I band) and 1300 cm^{-1} (amide III band). The C=S stretching vibrations[12] due to the tautomerisation of —SH are at 1100 cm^{-1}. The N—H stretching vibrations are observed in the region of 2800 cm^{-1}. The bands at 1650, 1590, 1360 and 1180 cm^{-1} are assigned to the vibrations arising from heterocyclic oxazole[13] system, which are totally absent in the IR spectrum of compound I.

The ^1H NMR spectrum offers further confirmation for the structure IIa. The —SH proton[14] is observed around δ 3.5 as a broad singlet. Another broad singlet around δ 6.0 indicates the —NH proton due to tautomerism, the aromatic protons of phenazine system are found in separate regions. The signals appearing at δ 7.8–8.1 indicate the aromatic protons at 6, 7, 8 and 9 positions.[15,16] The chemical shifts at δ 7.6–7.7 are for the aromatic protons at positions 4 and 11.[17]

The approximate ratio of  to  in the compound IIa was calculated from NMR integrals. The ratio was found to be 3.9 : 6.1 at the probe temperature of the instrument, indicating more —SH in the tautomeric mixture of IIa.

The mass fragmentation of IIa starts with ejection of sulfur atom giving phenazino oxazolium ion. Later, loss of CO takes place giving the fragment at m/z 193 which is followed by a further fragmentation by the loss of CN etc.[18] as shown below. The peaks of minor importance are omitted.



Reaction of IIa with alkyl/acyl halides in presence of pyridine in ethanol afforded the corresponding thioethers (IIb–i, k–o) and thioester (IIj) respectively. All these compounds have been confirmed by their elemental and spectral analysis.

Most of the IR absorptions for alkyl/acyl derivatives are similar to the 2-mercaptophenazino oxazole; except for the bands around 2800 and 1430 cm^{-1} (—S—CH_2—) and 1340 cm^{-1} (—S—CH_3) and 3000 cm^{-1} (allylic).

The NMR signals are also observed in the same regions as specified for compound IIa (δ 7.8–8.1 and δ 7.6–7.7).

The mass spectra of alkyl/acyl derivatives also indicate same types of fragmentation for the phenazine unit. The substituent upon sulfur is lost in the first step giving an ion at m/z 253 corresponding to IIa. The rest of the fragments are found at m/z values of 221, 193, 167, 141, 115, 114 etc.

BIOLOGICAL SCREENING

Antibacterial Activity

All the compounds were screened for their antibacterial activity by Vincent and Vincent[19] filter paper disc diffusion plate method. The gram +ve and gram −ve bacteria employed for the tests were *Bacillus pumilus*, *B.magaterium* and *Pseudomonas ovalis*, *Proteus vulgaris*, respectively. All the compounds exhibited potential antibacterial activity against all the above species except *P.ovalis*. They also exhibited higher activity on *B.magaterium* than on *B.pumilus*. Compound IIj was found to be more active than all the remaining compounds against gram +ve species, whereas IIj and IIm were more active against gram −ve species (*P.V*). The compound IIh was found to exhibit feeble activity against all the bacteria tried.

Antifungal Activity

The antifungal activity of the compounds synthesized was determined by adopting the food poisoning technique.[20] The fungi employed were *Fusarium oxysporum* and

TABLE I

Antibacterial activity

Compound	Conc. μg/ml	% of inhibition in mm			
		B.P.	*B.m.*	*P.V.*	*P.O.*
IIa	600	4.6	6.1	4.8	—
IIc	600	0.9	2.5	1.2	—
IIf	600	0.9	1.9	1.4	—
IIg	600	6.8	1.9	1.1	—
IIh	600	0.8	1.5	1.0	—
IIi	600	4.6	5.0	3.8	—
IIj	600	5.8	10.4	8.4	—
III	600	4.0	5.7	6.8	—
IIm	600	5.8	6.6	11.0	—
IIn	600	1.6	9.4	1.5	—
IIo	600	5.9	9.3	6.1	—

TABLE II

Antifungal activity

Compound	Conc μg/ml	% of germination inhibition	
		Fusarium	*Curvularia*
IIa	120	48.9	54.2
	240	100	91.2
IIb	120	83.6	72.1
	240	100	89.1
IIc	120	78.3	51.4
	240	100	80.9
IIe	120	47.2	45.8
	240	100	100
IIf	120	72.3	35.0
	240	100	83.7
IIh	120	48.9	47.2
	240	94.6	91.7
IIi	120	49.7	46.1
	240	94.5	83.6
III	120	47.2	45.8
	240	100	100
IIm	120	88.6	85.0
	240	100	100
IIn	120	100	48.1
	240	100	76.3
IIo	120	100	38.1
	240	100	100

TABLE III

Physical data of 2-substituted mercapto(4:5)phenazino oxazoles

Compound[a]	R	M.P.[b] °C	Mol. formula	N%[c]		S%	
				Found	Calc.	Found	Calc.
IIa	—H	276–277	$C_{13}H_7N_3OS$	16.59	16.6	12.63	12.65
IIb	—CH_3	157	$C_{14}H_9N_3OS$	15.69	15.73	11.52	11.99
IIc	—C_2H_5	222	$C_{15}H_{11}N_3OS$	14.61	14.95	11.47	11.40
IId	—$CH_2CH_2CH_3$	161	$C_{16}H_{13}N_3OS$	14.20	14.24	11.01	10.83
IIe	—$CH_2CH_2CH_2CH_3$	160	$C_{17}H_{15}N_3OS$	13.2	13.6	10.21	10.60
IIf	—CH_2—CH=CH_2	208	$C_{16}H_{11}N_3OS$	14.00	14.33	10.71	10.92
IIg	—CH_2—C_6H_5	205	$C_{20}H_{13}N_3OS$	12.10	12.24	9.42	9.33
IIh	—CH_2—CO—C_6H_4—NO_2(P)	266	$C_{21}H_{12}N_4O_4S$	13.09	13.46	7.52	7.70
IIi	—CH_2—CO—C_6H_4—CH_3(P)	230	$C_{22}H_{15}N_3O_2S$	10.50	10.91	8.10	8.31
IIj	—CO—CH_3	274	$C_{15}H_9N_3O_2S$	14.08	14.24	10.99	10.85
IIk	—$CH_2COOC_2H_5$	198	$C_{17}H_{13}N_3O_3S$	12.09	12.39	9.61	9.44
III	—$CH_2CH_2NMe_2$	283	$C_{17}H_{16}N_4OS$	17.01	17.28	9.59	9.88
IIm	—CH_2—CH_2—NC_4H_8O	289	$C_{19}H_{18}N_4O_2S$	14.99	15.30	8.92	8.74
IIn	—CH_2—CH_2—NC_5H_{10}	307	$C_{20}H_{20}N_4OS$	14.98	15.38	8.61	8.79
IIo	—$CH_2CH_2CH_2$—NC_5H_{10}	278	$C_{21}H_{22}N_4OS$	14.49	14.82	8.51	8.47

[a] Compounds were obtained in 50–70% yields.

[b] Compounds IIa, g were recrystallised from dioxane-water. Compounds IIb, d, e, j–n were recrystallised from alcohol. Compounds IIc, f, o were recrystallised from ethyl acetate. Compounds IIh, i were recrystallised from acetone.

[c] Satisfactory elemental analysis for C and H were also obtained, e.g. IIa C: 61.52 (61.66); H: 2.75 (2.77).

Curvelaria lunata. All these compounds caused more than 50% inhibition against both the fungi at 120 μg/ml. Compounds IIb, IIe and III exhibited remarkable activity (80% inhibition) at the same concentration.

EXPERIMENTAL

IR spectra were recorded in KBr discs and Nujol on Perkin-Elmer 283 instrument. PMR spectra were recorded on a Varian A 90-D instrument using TMS as an internal standard (chemical shifts in δ ppm) and mass spectra on a JMS-D 300 Mass spectrometer at 70 eV. Melting points were uncorrected.

2-Mercapto(4:5)phenazino oxazole (IIa). A mixture of I (0.013 mole), carbon disulfide (10 ml), potassium hydroxide (0.02 mole), alcohol (40 ml) and water (10 ml) was refluxed for 26 hrs and filtered hot. The filtrate was acidified. The separated solid was filtered, dried and recrystallised from dioxan (yield 85%). m.p. 276–277 °C (decomposing) (Table I). IR (KBr) 2800 cm^{-1}; 2650 cm^{-1}; 850 and 750 cm^{-1}; 1520 and 1480 cm^{-1}; 1350 cm^{-1}; 1300 cm^{-1}; 1100 cm^{-1}; 1650 and 1590 cm^{-1}; 1360 and 1180 cm^{-1}. NMR (DMSO-D_6) δ 3.5 s; δ 6.0 s; δ 7.8–8.1; δ 7.6–7.7. Mass: m/z values at 253 (87.7%), 221 (57%), 193 (47.7%), 167 (35.4%), 141 (10.8%), 115 (15%) and 114 (12%).

Alkylation/Acylation. Compound IIa (0.005 mole) was dissolved in ethanol (20 ml) in presence of pyridine (10 ml) and the appropriate alkyl/acyl halide (0.005 mole) was added and refluxed for $3\frac{1}{2}$ hours. Cooled, filtered and recrystallised from suitable solvent (Table I).

ACKNOWLEDGMENT

Authors are thankful to the Principal, Regional Engineering College, Warangal, for providing facilities. They are also grateful to Prof. S. R. Ramadas, IIT, Madras for his valuable suggestions. One of the authors (RBR) is thankful to CSIR, New Delhi (India) for the award of a Junior Research Fellowship.

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