Synthesis of 5-Phenoxy-1,3-disubstituted Benzimidazolin-2-thiones as biologically active agents*

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Summary: 5-Phenoxy-1,3-disubstituted benzimidazolin-2-thione obtained from 4-phenoxy-O-phenylenediamine has been successfully utilised to synthesise a variety of N-Mannich bases.

Introduction

Benzazoles [1-3] have been found to be effective as antimicrobial, antiviral, anthelmintic and CNS active agents. Recent literature survey reveals that substituted 5-phenoxy benzimidazolin-2-thiones have exhibited anthelmintic activity and are also of use in veterinary medicine [4,5] against "Fasiola hepatica". In addition to these observations certain phenoxy substituted heterocyclic and other related compounds have also been reported as bactericidal [6], fungicidal [7], anti-inflammatory [8] and insecticidal [9] agents. In view of these reports the syntheses of the title compounds have been undertaken.

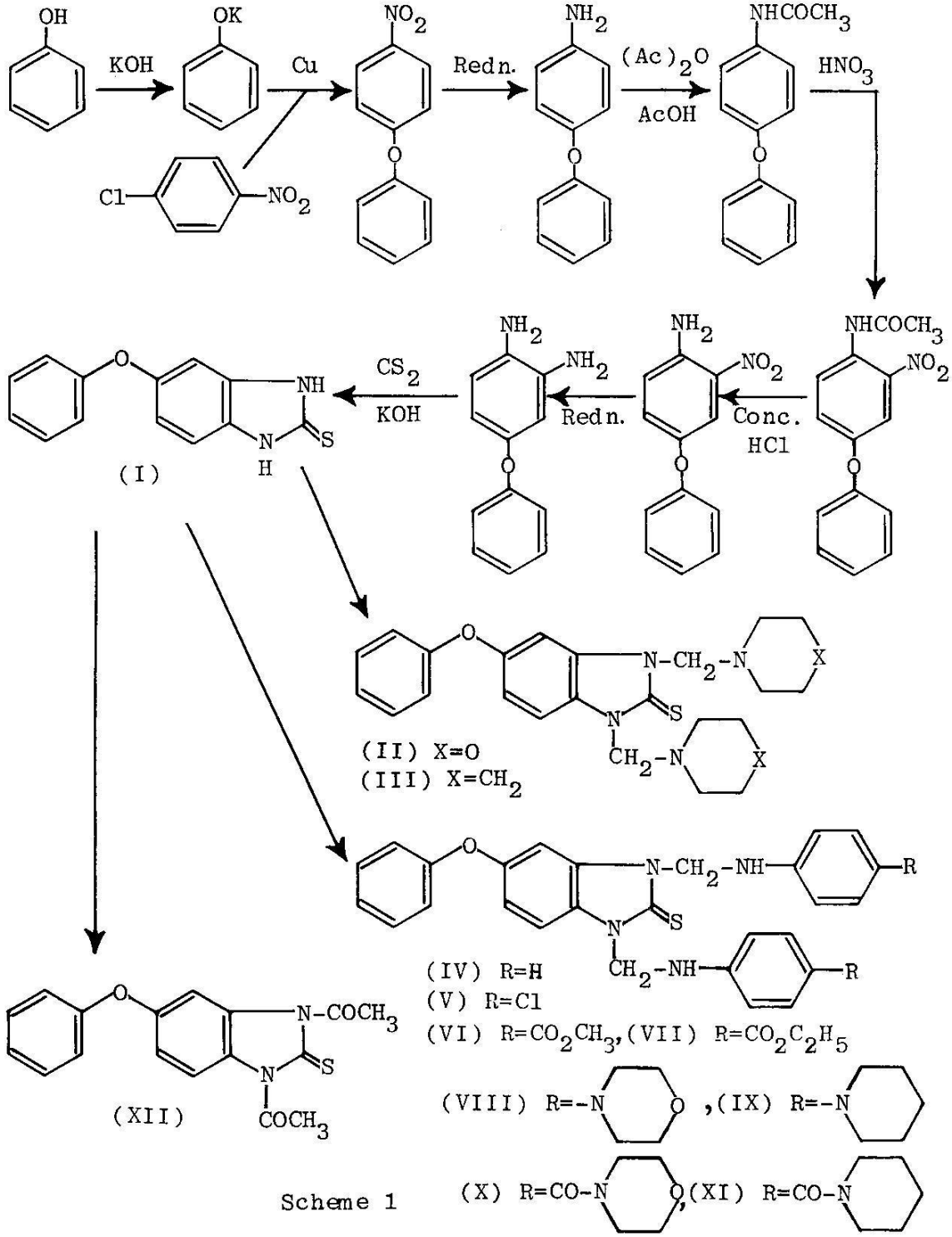
The synthesis of 5-phenoxy benzimidazolin-2-thionel [4,5] was done by the reaction of 4-phenoxy-*o*-phenylenediamine [10-13] and CS_2 in presence of ethanolic KOH. 4-Phenoxy-*o*-phenylenediamine has been prepared by the reduction [13] of 4-phenoxy-*o*-nitroaniline

For the synthesis of title compounds 5-phenoxy benzimidazolin-2-thione was treated with 40% aqueous formaldehyde solution and various anilines under the conditions of the Mannich reaction [2]. 5-Phenoxybenzimidazolin-2-thione was also acylated to give (XII). All the synthesised compounds were characterised by correct elemental analysis and spectral data.

The mass spectrum of IV (Scheme 2) has been examined. The compound undergoes cleavage at the 5 position leading to intense ion at m/e 358 $(1)_+$ The ion 2 m/e 242 obtained from M^+ loses phenyl radical to give ion 3 (m/e 165). Ion 2 could also lose sulfer atom giving ion 4 at m/e 210. The ion 5 at m/e 105 generated from M^+ loses a H radical to give ion 6 at m/e 104 from which a molecular of HCN is lost to yield ion 7 at m/e 77.

An examination of the mass spectrum of compound II further confirmed the assigned structures of the synthesised compounds. The molecular ion observed at m/e 440 as an intense peak undergoes McLafferty rearrangement leading to ion 2 at m/e 341 from which emerges ion 3 at m/e 242; loss of a phenyl radical from 3 could yield ion 4 (m/e 165). Whereas removal of a sulfide radical generates ion 5 (m/e 210). Ion 6 at m/e 100 (base peak) arises from M^+ by a simple cleavage (Scheme 3)

*Part XLI of the series Potential Biologically active agents.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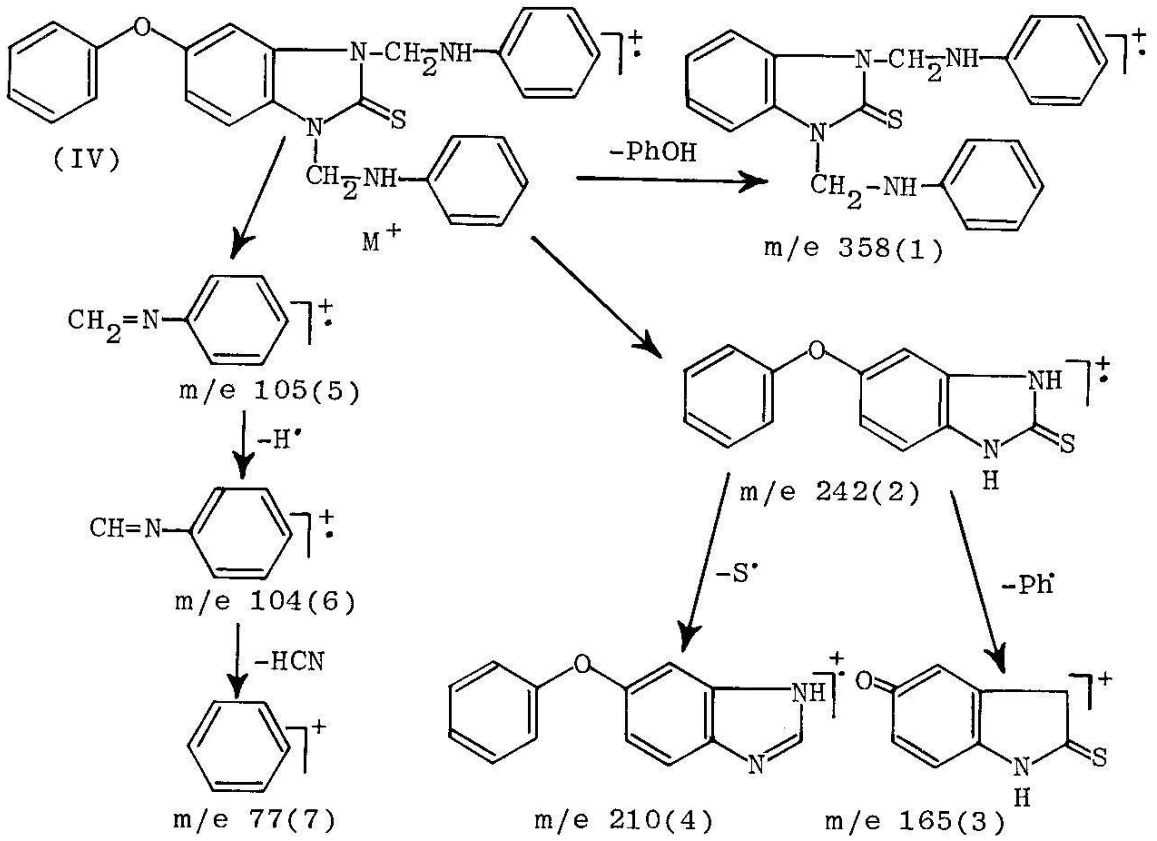
Conc.
HCl
NH2
NO2
Redn.
NH2
NH2
CS2
KOH
NH
N
H
S
(I)
N-CH2-N
X
N
S
CH2-N
X
(II) X=O
(III) X=CH2
N-CH2-NH
R
N
S
CH2-NH
R
(IV) R=H
(V) R=Cl
(VI) R=CO2CH3, (VII) R=CO2C2H5
N-COCH3
N
S
COCH3
(XII)
(VIII) R=-N O ,(IX) R=-N
(X) R=CO-N O ,(XI) R=CO-N

Scheme 1



Scheme 2

Experimental

All melting points were taken in open capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin Elmer 157 spectrophotometer in KBr and the characteristic bands are given in Table 1. The NMR spectra were recorded in $CDCl_3$ and TFA on a Varian A-60D instrument and the characteristic signals are given in Table 1. The mass spectra were obtained on a Hitachi RMU-6 at 70 eV.

5-Phenoxybenzimidazolin-2-thione (I)

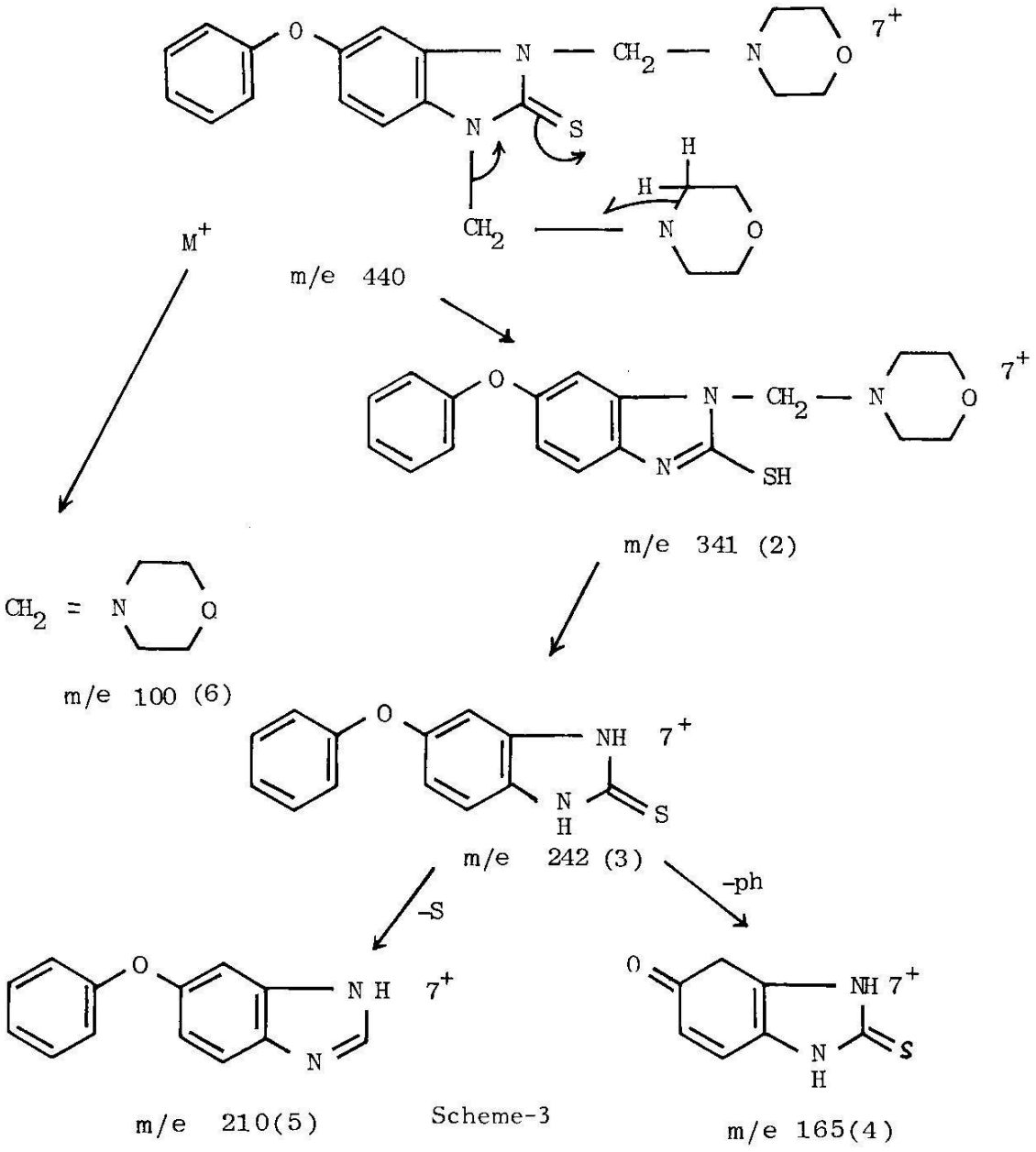
4-Phenoxy-O-phenylenediamine (10 g) was dissolved in 45 ml of methanol and diluted with 10 ml of water, 3 g of KOH and 4 ml of CS_2 were added. The contents were refluxed for 4 hours. The contents were filtered and filtrate was acidified with 10% acetic acid. The mixture was refrigerated over night for complete crystallisation. The product was recrystallised from methanol m.p. 235, yield (90%)

1,3-Bis (morpholino/piperidinomethyl)-5-phenoxy benzimidazolin-2-thiones (II,III)

I (1.20 g) was taken in 10 ml of methanol, 1 ml of formalin and 1 ml of morpholine/piperidine were added to it with warming and shaking. The product which separated on scratching the side of the flask was recrystallised from methanol (Table 1).

1,3-Bis (arylaminomethyl) 5-phenoxybenzimidazolin-2-thiones (IV-XI)

To I (1.20 g) in 20 ml of methanol, 1 ml of formalin and an appropriate



Scheme-3

Table-1: Substituted 5-Phenoxybenzimidazoline-2-thiones

Compound No.	Mol.Formula	m.p.°C	Calculated	Found	Yiled %
II*	$C_{23}H_{28}N_4O_3S$	125-126	C 62.70 H 6.30	62.45 6.35	65
III*	$C_{25}H_{32}N_4OS$	105-106	C 68.80 H 7.30	68.10 6.97	65
IV*	$C_{27}H_{24}N_4OS$	160	C 71.60 H 5.30	71.60 5.60	60
V*	$C_{27}H_{22}N_4OCl_S$	126-127	C 62.18 H 4.20	61.60 4.46	60
VI*	$C_{31}H_{28}N_4O_5S.H_2O$	200	C 63.48 H 5.11	63.60 5.18	65
VII*	$C_{33}H_{32}N_4O_5S$	186-187	C 66.44 H 5.36 N 9.38	66.30 5.41 8.95	65
VII*	$C_{35}H_{38}N_6O_3S$	100-112	C 67.50 H 6.10	66.80 6.01	55
IX*	$C_{37}H_{42}N_6OS$	108-110	C 71.80 H 6.78	70.50 6.85	55
X*	$C_{37}H_{38}N_6O_5S$	155-156	C 65.60 H 5.60	65.60 5.41	60
XI*	$C_{39}H_{42}N_6O_3S$	153-155	C 69.40 H 6.20	69.05 6.49	60
XII*	$C_{17}H_{14}N_2O_3S$	155	C 61.60 H 4.29 N 8.59	61.20 4.81 7.97	60

* See Scheme 1.

IR in KBr (cm^{-1})

II 2860 (CH_2), 1224 (C=S), 1118 (C-O-C).
III 2925 (CH_2), 1223 (C=S), 1139 (C-O-C)
IV 3400 (NH), 1230 (C=S) 1139 (C-O-C).
VI 3325 (NH), 1685 (C=O), 1245 (C=S), 1138 (C-O-C).
IX 3325 (NH), 2900 (CH_2), 1220 (C=S), 1120 (C-O-C).
X 3325 (NH), 2900 (CH_2), 1065 (C=O), 1210 (C=S), 111) (C-O-C).
XI 3290 (NH), 2900 (CH_2), 1660 (C=O), 1245 (C=S), 1100 (C-O-C).
XII 1700 (C=O), 1220 (C=S), 1093 (C-O-C).

NMR (δ)

II (in $CDCl_3$) - 2.7 ($-N-(CH_2)_2$), 3.6 ($O-(CH_2)_2$), 5.0 ($N-CH_2-N$) and 6.6-7.5 (aromatic protons)
VI (in TFA) - 3.6 ($-CH_2$), 5.2 ($-N-CH_2-N-$), 6.6-7.9 (aromatic & NH protons)
XI (in $CDCl_3$) - 1.5 ($-C-CH_2-C$), 3.4 ($-N-(CH_2)_2$), 5.5 ($N-CH_2-N$, 6.7-7.3 (aromatic & NH protons).

aromatic amine (0.01 mole) were added with stirring. The reaction mixture was warmed on a water bath. The product that separated on standing at room temperature was recrystallised from chloroform - petroleum ether (60-80°) (Table-1).

1,3-Bis-(aceto)-5-phenoxybenzimidazolin-2-thione (XII)

I (1.50 g) was refluxed with 5 ml of acetic anhydride for 1 hour. The contents were poured in water (100 ml). Recrystallisation from methanol, yielded pure XII, m.p. 155°, yield (60%).

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