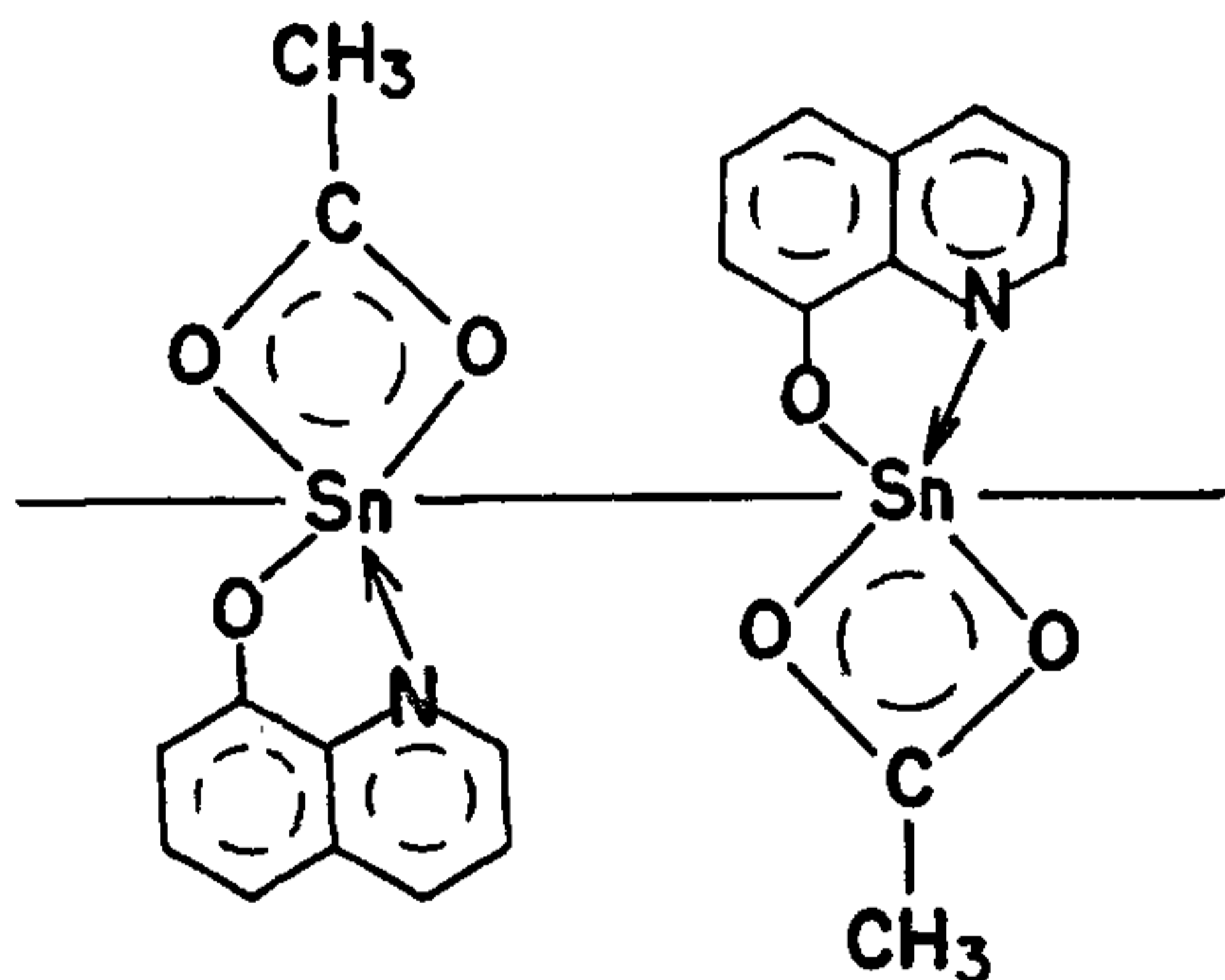


to insufficient solubility of the compound in cyclohexane. But in the chloroform solution this compound shows absorption maxima at 259 nm ($\log \epsilon_{\max} = 4.79$) and a broad band at 385 nm ($\log \epsilon_{\max} = 3.50$) the compound in UV and visible region of the spectra in CHCl_3 solution clearly demonstrates the presence of the chelating oxinate groups¹³ in the present compound.

Hence, the present compound can be assumed to have a structure (figure 1) consisting chelating acetate and oxinate groups in conforming with the analytical data.



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SYNTHESIS AND ANTHELMINTIC ACTIVITY OF 1-(5'-SUBSTITUTED PHENOXY METHYL, 1',3',4'-THIADIAZOL-2'-YL), 2-METHYL-4-SUBSTITUTED BENZYLIDENE IMIDAZOL-5-ONES

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ABSTRACT

A number of 1-5'-substituted phenoxy methyl 1',3',4'-thiadiazol-2'-yl), 2-methyl-4-substituted benzylidene imidazol-5-ones have been prepared by the condensation of 2-amino-5-substituted phenoxy methyl 1,3,4-thiadiazole with 2-methyl-4-substituted benzylidene azlact-5-ones. They have been screened for their cestodicidal activity against *H. nana* infection in rats.

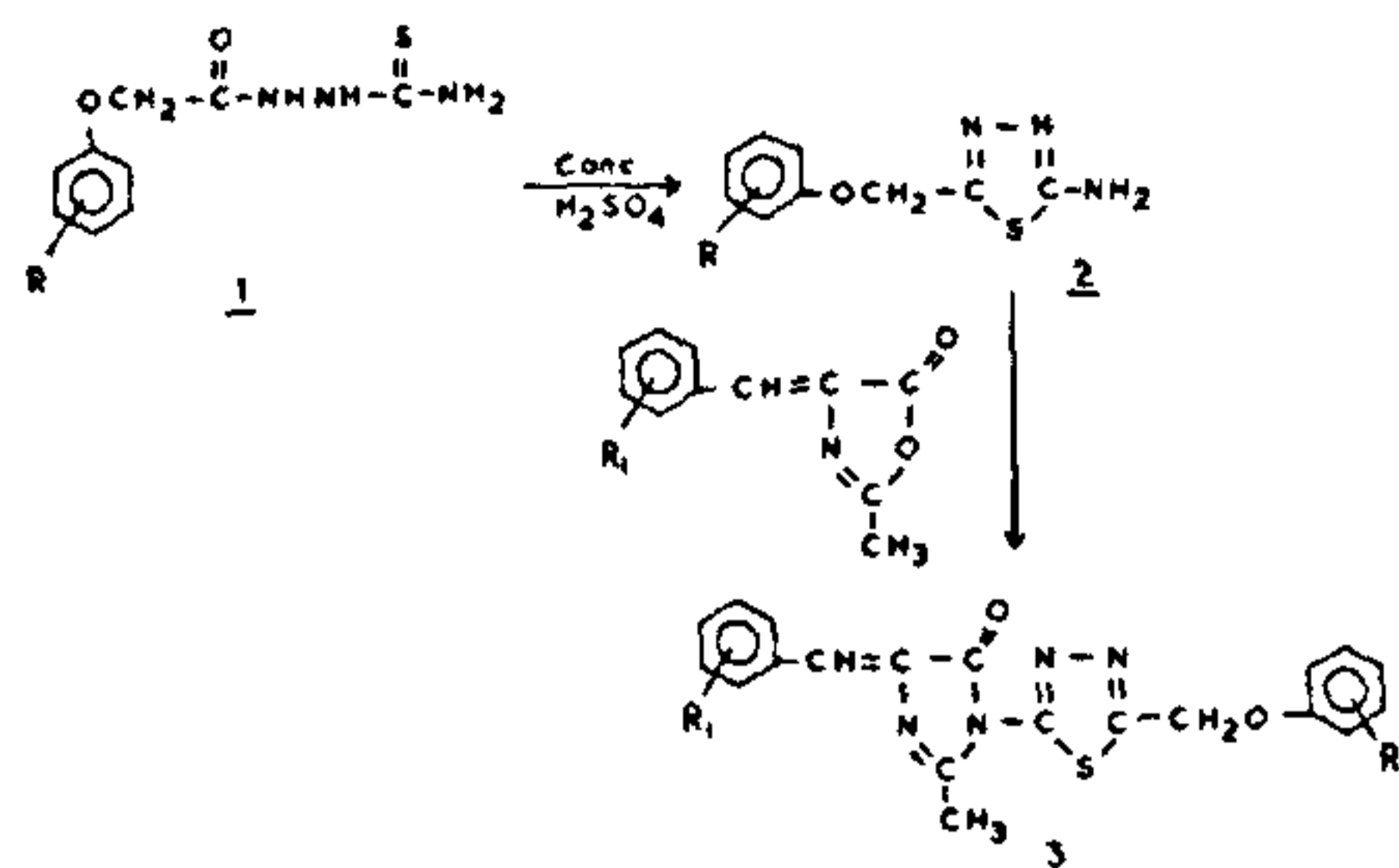
INTRODUCTION

THE therapeutic properties of a number of thiadiazoles¹⁻⁴ and imidazolones⁵⁻⁹ against infection in gastro-intestinal tract are well documented. In view of the important cestodicidal activity displayed by thiadiazole derivatives, it was considered worthwhile to prepare the compounds containing both the thiadiazole and imidazole nucleus. The present communication describes the synthesis of various 1-(5'-substituted

phenoxy methyl 1',3',4'-thiadiazol-2'-yl), 2-methyl-4-substituted benzylidene imidazol-5-ones.

1-Substituted phenoxy methyl thiosemicarbazide(1) on cyclodehydration with conc. H_2SO_4 gives the corresponding 2-amino-5-substituted phenoxy methyl 1,3,4-thiadiazole(2) which on condensation with various 2-methyl-4-substituted benzylidene azlact-5-ones yields the corresponding 1-(5'-substituted phenoxy methyl 1',3',4'-thiadiazol-2'-yl),

2-methyl-4-substituted benzylidene imidazol-5-ones(3). (Scheme I).



SCHEME-I

EXPERIMENTAL

All m.p.s were recorded in H_2SO_4 bath and are uncorrected. IR spectra ($\gamma_{\text{max}} \text{ cm}^{-1}$) were recorded on a Perkin-Elmer 135, 157 infracord spectrophotometer and PMR on varian A-60D and Perkin-Elmer R-32 Spectrometer using TMS as internal reference (chemical shifts in δ ppm). The purity of all the compounds was checked on silica-gel G-plates.

Synthesis of 2-amino-5-substituted phenoxy methyl 1,3,4-thiadiazole

Thiosemicarbazide, substituted phenoxy acetic acid and conc. H_2SO_4 (all 0.01 mole) were heated at $60-80^\circ$ for 4 hr. The resulting mixture was allowed to stand at 25° for 1 hr, then poured into ice cold water and neutralized with ammonia solution. The solid thus obtained was filtered and recrystallized from ethyl alcohol (table 1).

Synthesis of 2-methyl-4-substituted benzylidene-azlact-5-ones

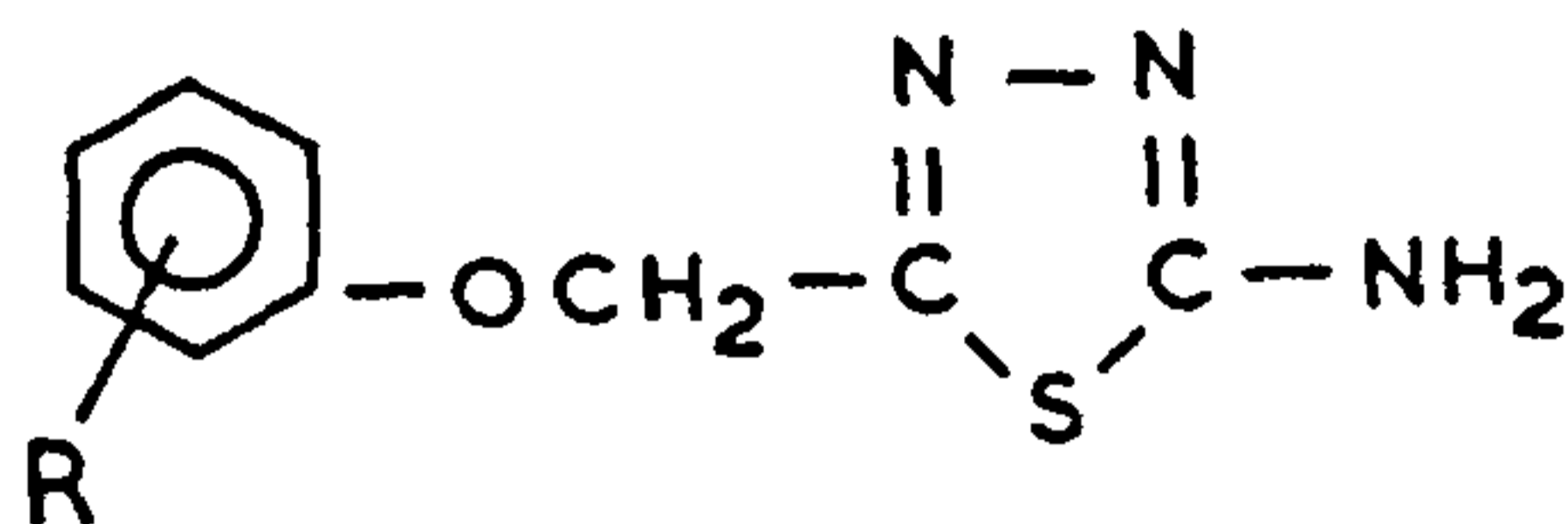
These were synthesized using standard procedures¹⁰⁻¹³.

Synthesis of 1-(5'-o-methyl phenoxy methyl 1',3',4'-thiadiazol-2'-yl)2-methyl-4-p-chloro-benzylidene imidazol-5-ones

2-amino-5-o-methyl phenoxy methyl 1,3,4-thiadiazole and (0.01 mole) 2-methyl-4-(p-chloro-benzylidene)-azlact-5-one were taken in pyridine (15 ml) and the mixture was refluxed for about 6 hr on a sand bath. The excess of pyridine was distilled off at reduced pressure and the residue was cooled at 25°C .

TABLE I

2-Amino-5-substituted
phenoxy methyl 1,3,4-
thiadiazoles



| R | m.p. $^\circ\text{C}$ |
|------------------------|-----------------------|
| p-Cl | 200 |
| o-Cl | 224 |
| o-CH ₃ | 214 |
| m-CH ₃ | 202 |
| p-CH ₃ | 208 |
| p-Cl-m-CH ₃ | 196 |

(a) The elemental analyses of (C, H and N) are within the range of $\pm 0.4\%$. (b) The compounds were obtained in about 60-65% yield.

It was then poured into a mixture of 50 ml conc. HCl and 50 g ice and left overnight. The solid separated was filtered and recrystallised with ethanol. m.p. 232°C . IR(KBr) $\gamma_{\text{max}} \text{ cm}^{-1}$: 1660 (for C = C stretch trisubstituted); 1680 (for ring N—C—O group of imidazolone moiety), 1640 (for ring C = N bonding), 1215 for (C—O—C), PMR (CDCl_3): 7.08 (d, J = 9 Hz, 2H, H-3'-3'), 8.15 (d, J = 9 Hz, 2H, H-2'-6'), 8.13 (d, 1H, C-2'-H), 7.64-6.82 (m, 2H, C-3'-4'-H), 7.80 (d, 1H, J = 7 Hz, C5'-H), 2.5 (s, 3H, CH₃), 3.82 (t, 2H, J = 6 Hz, OCH₂).

Similarly other 1-(5'-substituted phenoxy methyl 1',3',4'-thiadiazol-2'-yl) 2-methyl-4-substituted benzylidene imidazol-5-ones were prepared and are described in table 2.

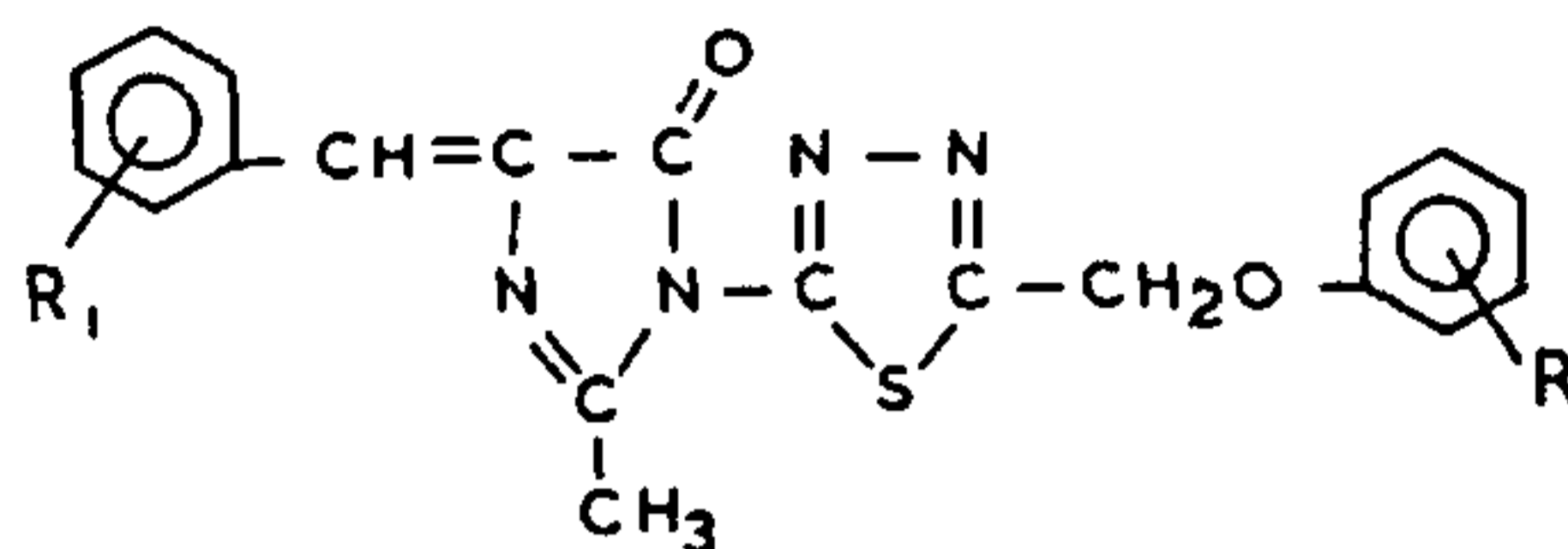
Similarly other 1-(5'-substituted phenoxy methyl 1',3',4'-thiadiazol-2'-yl) 2-methyl-4-substituted benzylidene imidazol-5-ones were prepared and are described in table 2.

Anthelmintic activity

The compounds were screened for their cestodicidal activity against *H. nana* infection in rats by the technique of Steward¹⁴ with slight modifications at dosages 500, 400 and 250 mg/kg using 3 rats per experimental group. Niclosamide was used as the standard drug which cleared 100% of the above infection at a single oral dose of 50 mg/kg. The results are summarised in table 2.

TABLE 2

1-(5'-substituted phenoxy methyl, 1',3',4'-thiadiazol-2'-yl), 2-methyl-4-substituted benzylidene imidazolo-5-ones



| R | R ₁ | m.p. °C | Cestodicidal activity against <i>H. nana</i> infection | |
|---|----------------------------|---------|--|------------|
| | | | Dose mg/kg | % Efficacy |
| <i>o</i> -CH ₃ | <i>p</i> -Cl | 232 | 500 | Inactive |
| <i>p</i> -CH ₃ | <i>p</i> -Cl | 228 | 250 | 65.0 |
| <i>o</i> -Cl | <i>p</i> -Cl | 240 | 250 | 61.0 |
| <i>m</i> -CH ₃ | <i>p</i> -Cl | 220 | 250 | 38.0 |
| <i>p</i> -Cl | <i>p</i> -Cl | 218 | 250 | 76.0 |
| <i>p</i> -Cl- <i>m</i> -CH ₃ | <i>p</i> -Cl | 250 | 400 | 18.8 |
| <i>p</i> -Cl | <i>o</i> -OH | 232 | 250 | 32.1 |
| <i>p</i> -CH ₃ | <i>o</i> -OH | 250 | 250 | Inactive |
| <i>p</i> -Cl- <i>m</i> -CH ₃ | <i>o</i> -OH | 222 | 400 | 12.0 |
| <i>o</i> -CH ₃ | <i>o</i> -OH | 208 | 500 | 11.2 |
| <i>m</i> -CH ₃ | <i>o</i> -OH | 260 | 400 | Inactive |
| <i>p</i> -Cl | <i>o</i> -OH | 208 | 250 | 48.2 |
| <i>o</i> -Cl | H | 240 | 250 | 32.0 |
| <i>p</i> -CH ₃ | H | 236 | 250 | 28.5 |
| <i>o</i> -CH ₃ | H | 238 | 500 | 22.5 |
| <i>p</i> -Cl- <i>m</i> -CH ₃ | H | 218 | 500 | Inactive |
| <i>m</i> -CH ₃ | H | 215 | 500 | — |
| <i>p</i> -Cl | H | 224 | 250 | 54.0 |
| <i>p</i> -Cl | <i>p</i> -OCH ₃ | 158 | 250 | 55.0 |
| <i>p</i> -CH ₃ | <i>p</i> -OCH ₃ | 228 | 250 | 42.0 |
| <i>o</i> -CH ₃ | <i>p</i> -OCH ₃ | 230 | 250 | 18.8 |
| <i>o</i> -Cl | <i>p</i> -OCH ₃ | 204 | 400 | 21.2 |
| <i>p</i> -Cl- <i>m</i> -CH ₃ | <i>p</i> -OCH ₃ | 178 | 400 | Inactive |
| <i>m</i> -CH ₃ | <i>p</i> -OCH ₃ | 260 | 400 | 31.8 |

(a) The elemental analyses of (C, H and N) are within the range of $\pm 0.5\%$. (b) The compounds were obtained in about 58–62% yield.

In this test compounds 2–5 showed 65–76% reduction in worms at a dose of 250 mg/kg given for three days while compounds 7, 12–14, 18–21, 24 also showed reduction in worm population from 22.5–61 at a dose of 250×3 mg/kg. The rest of compounds was either found inactive or showed insignificant activity at a dose of 500 and 400 mg/kg.

The cestodicidal activity reported in this paper clearly demonstrates that the substitution of chloro group at the para position of benzene ring increases the activity while the methoxy group decreases the activity. Substitution of methyl group at the ortho position of phenyl moiety produced less activity where as at *m*- and *p*-position induced higher activity.

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SYNTHESIS OF SOME NEWER. 1-HETEROCYCLIC AMINO/IMINOMETHYL-2-SUBSTITUTED BENZIMIDAZOLES AS A POTENT CNS; ANTICONVULSANT AND MONOAMINEOXIDASE INHIBITORY AGENTS

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ABSTRACT

A series of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles (4-23) were synthesised and screened for their neuropharmacological and monoamineoxidase inhibitory properties. A number of such compounds showed CNS stimulant, anticonvulsant and monoamineoxidase inhibitory activity.

INTRODUCTION

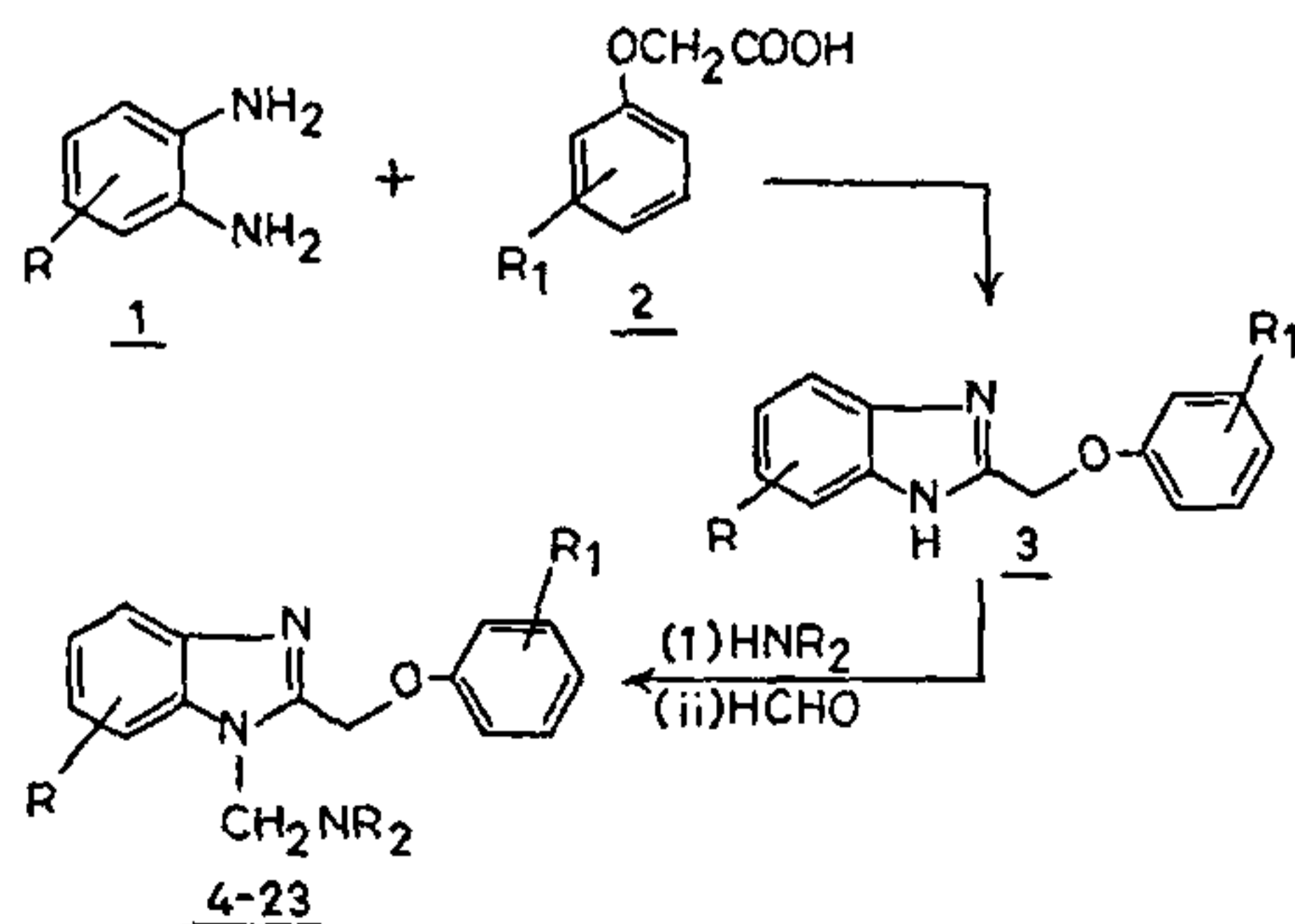
BENZIMIDAZOLE derivatives have become increasingly important due to their psychotropic properties¹⁻³. Heterocyclic amines are also reported to have chemotherapeutic value^{4,5}. Hence it was anticipated that the combination of benzimidazole and

heterocyclic amines may result in compounds of better CNS and monoamineoxidase inhibitory activity. The present paper describes the synthesis of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles and their CNS, anticonvulsant and monoamineoxidase inhibitory activity.

Condensation of *o*-phenylenediamine (1) with different substituted phenoxy acetic acid (2)⁶ gave 2-substituted phenoxy methyl benzimidazoles (3)⁷. Reaction of 3 with heterocyclic amines in presence of formaldehyde resulted in the formation of respective 1-heterocyclic amino/iminomethyl-2-substituted phenoxy methyl benzimidazoles (4-23) (Scheme 1).

EXPERIMENTAL

Melting points were recorded in an open capillary tube and are uncorrected. The IR spectra of the compounds were taken in Perkin-Elmer 137 and 177 spectrophotometers in KBr pellets and the mass spectra of the compounds were taken on JEOL-JMS-D-300 instrument.



SCHEME-1