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SYNTHESIS OF N-[2-PHENOXY AND CHLOROSUBSTITUTED PHENOXY ACETYL] MORPHOLINES AND THEIR PLANT GROWTH REGULATORY AND PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

Phenoxy and some chlorophenoxy acetic acids have been synthesized and condensed with morpholine through their chlorides in alkaline medium; the amides thus obtained were found to be CNS depressant but none showed cardiovascular properties. Results of Anti-inflammatory and Antiallergic activities are also reported. A few were also found to possess plant growth promoting properties.

THE versatility of phenoxy acetic acid, substituted phenoxy acetic acids and their derivatives particularly the amides, is demonstrated by the fact that some of these compounds possess herbicidal[1–4], bactericidal[1] and diuretic[5] activities, and are also selective herbicides[6–9]. A few have also been used as local anaesthetics[10,11], tranquilizers and sedatives[12].

The present work, records the synthesis of heterocyclic amides of phenoxy acetic acid and chloro substituted phenoxy acetic acids.

The synthesized acids were converted into their acid chlorides by thionyl chloride and the acid chlorides were condensed with tetrahydro-1: 4-oxazine in alkaline medium to get the respective amides.

The pharmacological and plant growth regulatory properties were studied and are reported here.

EXPERIMENTAL PROCEDURE

Phenoxy acetic acid and chlorophenoxy acetic acids were synthesized by condensing sodium salt of appropriate phenols with $ClCH_2COONa$[13,14].

The aryloxy acids (0·02 M) were refluxed with thionyl chloride (0·04 M) for 3–4 hours under anhydrous conditions on a steam bath. Subsequently, after distilling off the excess of thionyl chloride under reduced pressure, the acid chlorides were added dropwise to the ice cooled solution of Morpholine (0·03 M) and 30 ml of 1N NaOH (as acid acceptor) in about 30 min. The separated amides were filtered, washed with sodium bicarbonate solution and then with water to remove any unreacted acid and recrystallized from petroleum-ether (40–60°).

The homogeneity of the products was tested by thin-layer-chromatography. Each compound gave a single spot on chromatoplates of silica gel 'G'.

The melting points and analytical data of the compounds are given in Table I.

Structures of amides have also been supported by their IR spectra which showed prominent peaks around 2900 cm^{-1} (C–H str.); 1650 cm^{-1} (C=O str.); 1600, 1580, 1500 and 1450 cms $^{-1}$ (Aromatic C=C in plane vibrations); 1470 cm^{-1} ($-CH_2-$bending); 1225 and 1025 cm^{-1} (Ar–O–); and 1115 cm^{-1} (CH_2-O-CH_2).

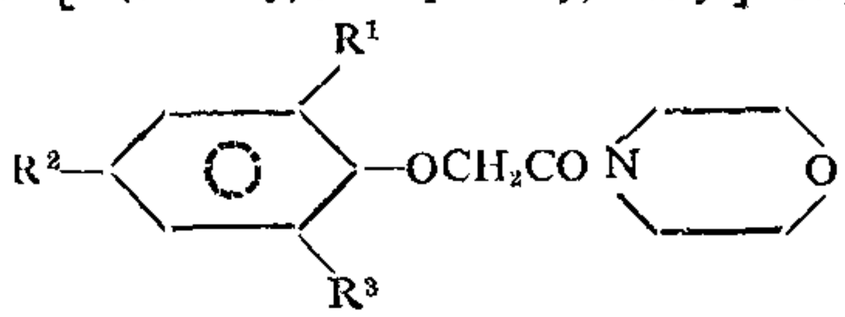
PLANT GROWTH REGULATING PROPERTIES

Compound Nos. 1, 3 and 4 of Table I were found to possess plant growth promoting properties. A solution of 50 mg of any of the above compounds in 100 ml of water when applied to the germinating seeds of Zea mays showed following shoot-length after four days.

Compound No. (Table I)	Control	1	2	3	4	5
Length in cm	5	6·2	5·1	6·2	6·3	4·9

TABLE I

N- [2-(*Phenoxy/Chlorophenoxy*) *Acetyl*] *Morpholine*



Compound No.	R^1	R^2	R^3	Molecular formula	m.p. °C	Yield %	Composition % Calculated C	H	N	Cl	Found C	H	N	Cl
1.	H	H	H	$C_{12}H_{15}NO_3$	89–91	82	65·15	6·78	6·33	..	65·1	6·55	5·82	..
2.	Cl	H	H	$C_{12}H_{14}NO_3Cl$	120–1	84	56·36	5·47	5·47	13·89	56·14	5·22	5·16	13·64
3.	H	Cl	H	$C_{12}H_{14}NO_3Cl$	141–2	82	56·36	5·47	5·47	13·89	55·96	5·38	5·24	13·52
4.	Cl	Cl	H	$C_{12}H_{13}NO_3Cl_2$	98–9	81	49·65	4·48	4·82	24·48	49·5	4·16	4·53	24·22
5	Cl	Cl	Cl	$C_{12}H_{12}NO_3Cl_3$	126–8	87	44·37	3·69	4·31	32·81	43·92	3·42	4·18	32·52

Note : (i) All the melting points are uncorrected. (ii) All are recrystallised from petroleum–ether (40–60°).

PHARMACOLOGICAL PROPERTIES

All the amides have LD_{50} (mice) > 1000 mg/kg (intra-peritoneal) except compound No. 4 (Table I) which has LD_{50} (mice) > 681 mg/kg (i.p.). $\frac{1}{5}$ of LD_{50} doses (i.p.) of all amides showed Central Nervous System depressant activity in mice. No cardiovascular activity was observed when tested on cats. The percentage inhibition of inflammation (Anti-inflammatory) and Passive Cutaneous Anaphylaxis (Antiallergic) were found as follows :— [$\frac{1}{5}$ of LD_{50} doses (peroral) in mice].

TABLE II

Compound No. (Table 1)	Anti-inflammatory	Passive cutaneous Anaphylaxis
1	11·4	60
2	..	54
3	34·2	54
4	3·4	58
5	..	54

ACKNOWLEDGEMENT

The authors express their thankfulness to the Director, CDRI, Lucknow, for pharmacological tests and Dr. D. S. Bhakuni of CDRI, Lucknow, for microanalysis and I.R. spectra of the compounds and Dr. P. N. Singh of Botany Department, Allahabad University, for studying plant growth regulating properties. AKG thanks CSIR, New Delhi, for financial assistance in the form of a Junior Research Fellowship.

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