Pesticidal Mannich Bases Derived from Isatinimines

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Mannich bases from isatinimines and isatin hydrazones are synthesized for evaluation of their pesticidal activities. Among all the prepared Mannich bases only *N*-dimethylaminomethyl-3-(*p*-bromophenyl)iminoindol-2-one exhibited herbicidal activity in pre- and post-emergent tests.

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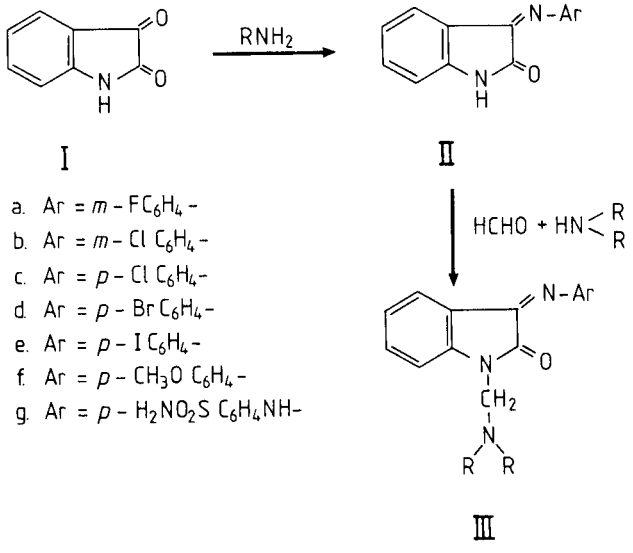
The diverse biological activities associated with isatin derivatives are well documented [1]. The importance of this nucleus is well established in pharmaceutical chemistry as its corresponding derivatives are used as analgetic, antipyretic, anticonvulsant, antibacterial, and antidepressant agents [2-4]. The isatin hydrazones and *N*-isatin Mannich bases are known to have potential antiviral [5], antifungal and antibacterial activities [6]. Structure-activity relationship studies of isatin derivatives have demonstrated that substitution in the aromatic ring commonly led to reduction or complete loss of activity, while substitution at the 1-position with alkyl chains not longer than two carbon atoms produced a conspicuous rise in the biological activity [5]. The broad range of biological activities of Mannich bases aroused considerable interest to synthesize iminoisatin Mannich bases and to evaluate their pesticidal activities. Since not much work has been done on the herbicidal properties of iminosatin Mannich bases, we have taken up this project for investigation.

SCHEME I



I

II

III

a. Ar = *m*-FC_6H_4-
b. Ar = *m*-ClC_6H_4-
c. Ar = *p*-ClC_6H_4-
d. Ar = *p*-BrC_6H_4-
e. Ar = *p*-IC_6H_4-
f. Ar = *p*-$CH_3OC_6H_4$-
g. Ar = *p*-$H_2NO_2SC_6H_4NH$-

Chemistry.

Reaction of isatin (I) with a number of aromatic and aliphatic amines gave the previously reported Schiff's bases except IIg in quantitative yield [7-9].

The Mannich bases were prepared by refluxing a mixture of the corresponding isatinimine IIa-g, formaldehyde and a primary or secondary amine in alcohol. The structures of the Mannich bases were confirmed by spectroscopic studies.

The nmr spectra of the isatinimines IIa-g showed chemical shifts for the aromatic protons in the range of δ 6.9-7.95 and the NH proton at δ 8-8.5, while in the isatinimine Mannich bases the chemical shift for the NH proton disappeared and a new peak appeared at δ 4.25 due to the $-CH_2-N$ protons.

The ir spectra of the Mannich bases showed an intense peak due to the carbonyl group in the range of 1765-1725 cm^{-1}. The absorption due to the imino function appeared in the range of 1640-1600 cm^{-1}.

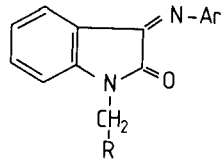
Peaks in the range of 3150-3300 cm^{-1} for IIg and its Mannich bases were assigned to the NH stretching frequency.

Pesticidal Evaluation.

All the compounds prepared were screened for their potential antifungal, antibacterial and herbicidal activities. In the antifungal screening the prepared compounds were tested *in vivo* against a variety of soil and foliage disease organisms with the exception of *Botrytis cinerea*, which was assayed *in vitro*. The soil pathogens used included *Pythium aphanodermatum, Ihielaviopsis basicola* and *Sclerotinea sclerotiorum*. None of the test chemicals were found to be active against any of the said pathogens. The antibacterial activity was evaluated *in vitro* against *Escherichia coli, Salmonella choleraesuris, Streptococcus faecalis, Staphylococcus aureus, Pseudomonas aeruginosa* and *Proteus mirabilis*, but none of the compounds showed even marginal activity. For the determination of the herbi-

Table I

N-Alkylaminomethyl-3-iminophenyl/*p*-Sulphonamidophenylhydrazonoisatins



Compound No.	R	MP °C	Molecular Formula	Elemental Analysis (%) Calcd. C	Calcd. H	Found C	Found H
		Ar = *m*-Fluorophenyl					
1	Dimethylamino-	75	$C_{17}H_{16}F_3FO$	68.69	5.38	68.32	5.45
2	Morpholino-	176	$C_{19}H_{18}N_3FO_2$	67.26	5.31	67.38	5.65
3	Piperidino-	145	$C_{20}H_{20}N_3FO$	71.21	5.93	70.85	5.83
4	γ-Morpholinopropylamino-	160	$C_{22}H_{25}N_4FO_2$	66.66	6.31	66.85	5.96
5	Diethanolamino-	147	$C_{19}H_{20}N_3FO_3$	63.86	5.60	63.75	5.35
		Ar = *m*-Chlorophenyl					
6	Piperidino-	165	$C_{20}H_{20}N_3ClO$	67.89	5.66	68.36	5.82
7	Morpholino-	200	$C_{19}H_{18}N_3ClO_2$	64.13	5.06	63.89	5.23
8	γ-Morpholinopropylamino-	215	$C_{22}H_{25}N_4ClO_2$	64.00	6.06	64.13	6.45
9	Di-*n*-propylamino-	108	$C_{21}H_{24}N_3ClO$	68.20	6.49	68.43	6.71
10	*n*-Butylamino-	225	$C_{19}H_{20}N_3ClO$	66.76	5.86	66.82	5.62
		Ar = *p*-Chlorophenyl					
11	Dimethylamino-	120	$C_{17}H_{16}N_3ClO$	65.07	5.10	65.32	5.38
12	Diethylamino-	152	$C_{19}H_{20}N_3ClO$	66.76	5.86	66.58	5.92
13	Piperidino-	145	$C_{20}H_{20}N_3ClO$	67.89	5.66	68.12	5.26
14	Morpholino-	152	$C_{19}H_{18}N_3ClO_2$	64.13	5.06	64.35	5.29
15	Diethanolamino-	260	$C_{19}H_{20}N_3ClO_3$	61.04	5.35	61.43	5.28
		Ar = *p*-Bromophenyl					
16	Dimethylamino-	122	$C_{17}H_{16}N_3BrO$	56.98	4.47	56.85	4.53
17	Piperidino-	150	$C_{20}H_{20}N_3BrO$	60.30	5.02	60.12	5.35
18	Morpholino-	135	$C_{19}H_{18}N_3BrO_2$	57.00	4.50	57.23	4.71
19	Diethylamino-	145	$C_{19}H_{20}N_3BrO$	59.06	5.18	58.85	5.23
20	Diethanolamino-	252	$C_{19}H_{20}N_3BrO_3$	54.54	4.78	54.23	4.98
		Ar = *p*-Iodophenyl					
21	Dimethylamino-	125	$C_{17}H_{16}N_3IO$	50.37	3.95	50.08	4.28
22	Di(n-)Propylamino-	90	$C_{21}H_{24}N_3IO$	54.66	5.21	54.82	5.35
23	Ethanolamino-	248	$C_{17}H_{16}N_3IO_2$	48.46	3.80	48.57	3.76
24	Diethanolamino-	255	$C_{19}H_{20}N_3IO_3$	49.03	4.30	49.45	4.36
25	Piperidino-	145	$C_{20}H_{20}N_3IO$	53.93	4.49	54.12	4.98
26	Morpholino-	153	$C_{19}H_{18}N_3IO_2$	51.01	4.03	51.25	4.33
27	γ-Morpholinopropylamino-	260	$C_{22}H_{25}N_4IO_2$	52.38	4.96	52.46	5.12
		Ar = *p*-Methoxyphenyl					
28	Piperidino-	100	$C_{21}H_{23}N_3O_2$	72.20	6.59	72.46	7.02
29	Morpholino-	130	$C_{20}H_{21}N_3O_3$	68.38	5.98	68.63	5.46
30	γ-Morpholinopropylamino-	210	$C_{23}H_{28}N_4O_3$	67.65	6.86	67.83	6.53
		Ar = *p*-Sulphonamidophenylamino					
31	Dimethylamino-	>300	$C_{17}H_{19}N_5O_3S$	54.69	5.09	54.34	5.21
32	Piperidino-	>300	$C_{20}H_{23}N_5O_3S$	58.11	5.57	58.38	5.69
34	Diphenylamino-	>300	$C_{27}H_{23}N_5O_3S$	65.19	4.63	65.33	4.51
34	Diethanolamino-	285 dec	$C_{19}H_{23}N_5O_5S$	52.66	5.31	52.31	5.62

Table II

Herbicidal Activity of Mannich Bases at 8 kg/ha

Compound* [a] No.	In Pre-emergent conditions		In Post-emergent conditions	
	Pw	Mu	Pw	Mu
3,4	0	0	10	0
5	0	0	10	10
6	0	0	20	10
7	0	0	10	0
8	20	10	30	10
9-12	0	0	20	0
13-15	0	0	10	10
16	0	0	90	70
19	10	0	20	10
20	0	0	10	10
21	20	0	10	10
22,23	0	0	10	10
28	0	0	20	40
29-32	0	0	10	10
34	20	0	0	0

[a] Other compounds whose activity is not presented in the table were found completely inactive in pre- and post- emergent tests.
PW = Pigweed; Mu. = Wild mustard; Ha; Hectare.

cidal activity, the compounds were evaluated in pre- and post-emergent conditions at the rate of 8 kg/ha. In the pre-emergent screening the compounds were applied to a flat of soil, which contained the seeds of a representative variety of weeds, while in the post-emergent screen the compounds were sprayed on two week old weeds. After two weeks of growth, the pre- and post-emergent flats were examined for the percent control of weeds. The compounds showing herbicidal activity are listed in Table II with their percent control in pre- and post-emergent tests. Among all of the screened compounds only one compound *viz.* 1-dimethylaminomethyl-3(*p*-bromophenyl)iminoisatin (No. **16**) was found to be effective by controlling pigweed (90%) and wild mustard (70%) at a concentration of 8 kg/ha in post-emergent conditions. The other compounds were found to be almost inactive. Many of the compounds with a *N,N*-dimethylaminomethyl substituent have some herbicidal activity (10-20%).

EXPERIMENTAL

All melting points are uncorrected. The nmr spectra were recorded on a Varian-T-60 spectrophotometer in DMSO-d_6 using TMS as the internal standard. The ir spectra were measured on a Perkin-Elmer Model 700 in potassium bromide.

3-Aryliminoisatins IIa-f.

These compounds were prepared by following the literature procedures [7,8] and isolated in a quantitative yield.

3-*p*-Sulphonamidophenylhydrazonoisatin (IIg).

This compound was prepared by refluxing an equimolar mixture of isatin and *p*-sulphonamidophenylhydrazine in ethanol for 2 hours. The precipitate thus formed was filtered off, washed with ethanol and crystallized from a DMF:water mixture, mp >280°.

Anal. Calcd. for $C_{14}H_{12}N_4O_3S$: C, 53.16; H, 3.80; N, 17.72. Found: C, 53.45; H, 3.55; N, 17.62.

N-Substituted-3-aryliminoisatins III.

To a solution of 3-aryliminoisatin (IIa-g, 0.01 mole) in 25-40 ml of ethanol, formaldehyde (0.015 mole) and amine (0.01 mole) were added. The resulting mixture was refluxed for half an hour and cooled. The precipitate thus separated was filtered off, washed with cold ethanol and finally crystallized from ethanol. All the compounds prepared by the above procedure are listed in Table I (No. **1-30**) along with their relevant data.

N-Substituted-3-(*p*-sulphonamidophenyl)hydrazonoisatins III.

A mixture of hydrazone (IIg, 0.01 mole), formaldehyde (0.015 mole) and amine (0.01 mole) in ethanol (30-40 ml) was refluxed for 1-2 hours. The yellow precipitate separated after cooling was filtered off, washed with ethanol and crystallized from ethanol/methanol or a DMF-water mixture.

The compounds prepared are listed in Table I (No. **31-34**) along with their relevant data.

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