Indole Derivatives as Agrochemicals

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The synthesis of indole derivatives prepared as potential agrochemicals is reported. The 1-carbamoyl-2-indolinones **5** showed moderate nematicidal activity while the acylureas **8** were weak insecticides. The 2,4-dinitrophenyl oxime **11c** proved to be a potent herbicide with a narrow spectrum of activity.

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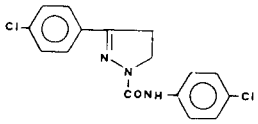
Introduction.

There is no need to stress the importance of finding new compounds for the control of weeds as well as new insecticides, nematicides, and acaricides that are more active or less toxic for humans than those available now.

In this paper we describe the synthesis of indole derivatives as potential insecticides, (related to PH 60-41 **1** [1,2] and diflubenzuron **2** [2-4]) and herbicides (related to bromofenoxim **3** [4]).



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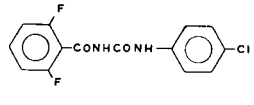

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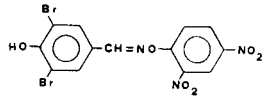

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Chemistry.

The first group of compounds consists of 1-carbamoyl derivatives **5** (see Scheme 1) prepared by treating a 2-indolinone **4** with *p*-chlorophenyl isocyanate.

The second group of compounds was prepared as shown in Scheme 1. The carboxylic acid **6** was refluxed with thionyl chloride and the resulting crude chloride was treated with ammonium hydroxide. The amide thus formed, **7**, was refluxed in xylene with *p*-chlorophenyl isocyanate to yield the acylureas **8**. The 2,4-dinitrophenyloximes **11** were prepared by reacting the oxime **10** (which, in turn, was obtained from the aldehyde **9**) with 2,4-dinitrochlorobenzene in sodium ethoxide. The new structures were confirmed by elemental analysis (Table III), ir and ^{1}H-nmr spectra (Table II). The 2,4-dinitrophenyloximes **11a-c**, due to their poor solubility, did not give good nmr spectra thus in Table II, ir and ms data are reported.

Biological Results.

The biological activity of compounds **5**, **8** and **11** is summarized in Table I. The carbamoyl derivatives **5a-d** were inactive as insecticides but the appearance of a moderate nematicidal activity could be useful for the development of a new lead in this field. The insecticidal activity of the acylureas **8a-f** was tested against the house fly and the flour beetle. Table I shows that a slight activity was shown by all the compounds under test. The 2,4-dinitrophenyl oximes **11a-c**, prepared as new herbicidal agents, were tested against weeds under paddy field conditions. The *N*-alkyl

Scheme 1

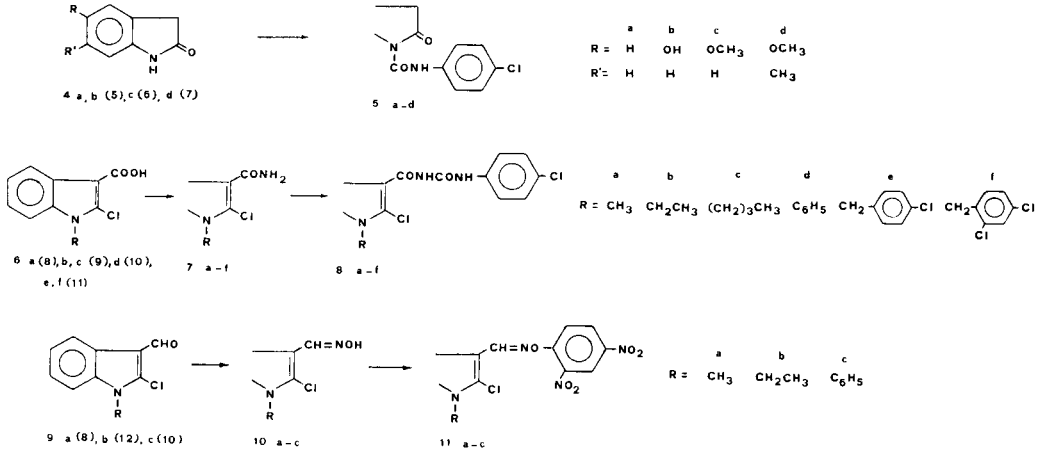

Table I

Indole Derivatives as Agrochemicals

Compound	Formula (MW)	Mp (°C)	Biological Activity (0 = no activity 10 = perfect control)		
			Nematicidal Activity		
			In vitro test		Pot test
5a	$C_{15}H_{11}ClN_2O_2$ (286.7)	180-181	3		3
5b	$C_{15}H_{11}ClN_2O_3$ (302.7)	205-207	3		0
5c	$C_{16}H_{13}ClN_2O_3$ (316.7)	172-174	3		0
5d	$C_{17}H_{15}ClN_2O_3$ (330.8)	215-218	3		2
			Insecticidal Activity		
			House fly		Flour beetle
8a	$C_{17}H_{13}Cl_2N_3O_2$ (362.2)	170-174	3		3
8b	$C_{18}H_{15}Cl_2N_3O_2$ (376.2)	184-186	2		0
8c	$C_{20}H_{19}Cl_2N_3O_2$ (404.3)	188-190	0		2
8d	$C_{22}H_{15}Cl_2N_3O_2$ (424.3)	203-207	2		3
8e	$C_{23}H_{16}Cl_3N_3O_2$ (472.7)	214-216	0		2
8f	$C_{23}H_{15}Cl_4N_3O_2$ (507.2)	227-229	2		3
			Herbicidal Activity		
			Barnyard grass	*Monochoria*	*Ammannia*
11a	$C_{16}H_{11}ClN_4O_5$ (374.7)	186-188 dec	6	0	0
11b	$C_{17}H_{13}ClN_4O_5$ (388.8)	192-194 dec	6	0	0
11c	$C_{21}H_{13}ClN_4O_5$ (436.8)	202-203 dec	2	10	10

derivatives **11a-b** were active against barnyard grass and inactive against broadleaf weeds (*monochoria* and *ammannia*). It is interesting to point out that the spectrum of activity of the *N*-phenyl derivative **11c** was the opposite; it was almost inactive against barnyard grass whereas the control of broadleaf weeds was perfect.

EXPERIMENTAL

A) Chemistry.

The melting points are uncorrected. Bakerflex plates (Silica gel IB2-F) were used for tlc; the eluent was a mixture of petroleum ether/acetone in various proportions. The ir were recorded in Nujol on a Perkin-Elmer 298. The ^{1}H-nmr were recorded on a Varian EM390 (90 MHz) using TMS as an internal standard; the solvent was pyridine-d_5 for compound **8f** and DMSO-d_6 for all the others. The mass (ms) spectra were recorded on an analytical mass spectrometer VG 7070E.

Synthesis of the 1-(*p*-Chlorophenylcarbamoyl)-2-indolinones **5a-d**.

2-Indolinone (**4a**) is commercially available. The substituted 2-indolinones **4b-d** were prepared according to the literature as reported in Scheme 1. The appropriate 2-indolinone **4** (10 mmoles) was dissolved in xylene and refluxed for 2 hours with 12 mmoles of *p*-chlorophenyl isocyanate. The expected carbamoyl derivative precipitated on cooling; an additional amount could be recovered by evaporating the solvent under reduced pressure. Compound **5** was crystallized from ethanol with a yield of 65-70% (see Table I, II, and III).

Synthesis of the Amides **7a-f**.

The acid **6** (20 mmoles) was refluxed for 6 hours with 40 ml of thionyl chloride. The unreacted thionyl chloride was evaporated under reduced pressure and the residual crude acid chloride was treated with 40 ml of 32% ammonium hydroxide. The reaction mixture was stirred at room temperature for 1-48 hours, depending on the tlc test. The crude amide thus formed was collected and crystallized from ethanol with a yield of 80-85% (see Tables II and III).

Compound **7a** had mp 247-251°; **7b** had mp 193-195°; **7c** had mp 174-177°; **7d** had mp 183-185°; **7e** had mp 248-250°; and **7f** had mp 217-220°.

Synthesis of the Acylureas **8a-f**.

The amide **7** (10 mmoles) was refluxed for 6 hours in xylene (150 ml) with 11 mmoles of *p*-chlorophenyl isocyanate and set aside overnight. If a precipitate of *N,N'*-bis-(*p*-chlorophenyl)urea [13] was present, it was removed by filtration. The filtrate was evaporated under reduced pressure and the residue crystallized from ethanol (yield 70-80%) see Tables I, II, and III.

Synthesis of the Oximes **10a-c**.

The aldehyde **9** dissolved in ethanol was refluxed for 30 minutes with one equivalent of hydroxylamine hydrochloride. The crude oxime, precipitated by the addition of water, was collected and crystallized with a yield of 85-90%, see Tables II and III.

Compound **10a** had mp 156-158° dec (dilute ethanol).

Compound **10b** had mp 152-154° (ethanol).

Compound **10c** had mp 155-157°, lit [14] 154-155° (2-propanol).

Synthesis of the 2,4-Dinitrophenyloximes **11a-c**.

The oxime **10** (5 mmoles) was treated with absolute ethanol (25 ml),

Table II

IR, NMR and MS Spectroscopic Data of Compounds **5**, **7**, **8**, **10**, **11** (ind = indole)

Compound	IR ν max (cm^{-1})	^1H NMR, δ (ppm) or MS, m/z
5a	3180, 1740, 1600, 1555, 1155	3.93 (2H, s, CH_2), 7.35 (3H, m, ind), 7.48 (2H, d, ar, J = 9 Hz), 7.70 (2H, d, ar, J = 9 Hz), 8.08 (1H, d, ind), 10.80 (1H, s, NH)
5b	3430, 3180, 1730, 1600, 1560	3.82 (2H, s, CH_2), 6.75 (2H, m, ind), 7.40 (2H, d, ar, J = 9 Hz), 7.65 (2H, d, ar, J = 9 Hz), 7.90 (1H, d, ind), 9.44 (1H, s, OH), 10.75 (1H, s, NH)
5c	3220, 1725, 1600, 1550, 1480	3.76 (3H, s, OCH_3), 3.92 (2H, s, CH_2), 6.95 (2H, m, ind), 7.47 (2H, d, ar, J = 9 Hz), 7.71 (2H, d, ar, J = 9 Hz), 8.0 (1H, d, ind), 10.70 (1H, s, NH)
5d	3200, 1735, 1595, 1550, 1225	2.20 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 3.92 (2H, s, CH_2), 7.05 (1H, s, ind), 7.48 (2H, d, ar, J = 9 Hz), 7.72 (2H, d, ar, J = 9 Hz), 7.93 (1H, s, ind), 10.75 (1H, s, NH)
7a	3370, 3180, 1630, 1610, 1510	3.78 (3H, s, CH_3), 7.25 (2H, m, ind + 2H, NH_2), 7.56 (1H, m, ind), 8.08 (1H, m, ind)
7b	3365, 3170, 1640, 1610, 1520	1.28 (3H, t, CH_3, J = 7.5 Hz), 4.30 (2H, q, CH_2, J = 7.5 Hz), 7.25 (2H, m, ind + 2H, NH_2), 7.60 (1H, m, ind), 8.05 (1H, m, ind)
7c	3365, 3180, 1640, 1610, 1515	0.85 (3H, t, CH_3 J = 7.5 Hz), 1.30 (2H, m, CH_2), 1.65 (2H, m, CH_2), 4.25 (2H, t, N-CH_2, J = 7.5 Hz), 7.27 (2H, m, ind + 2H, NH_2), 7.60 (1H, m, ind), 8.08 (1H, m, ind)
7d	3415, 3165, 1635, 1605, 1500	7.05 (1H, m, ar), 7.45 (4H, m, ar + 3H, ind + 2H, NH_2), 8.15 (1H, m, ind)
7e	3380, 3180, 1640, 1610, 740	5.58 (2H, s, CH_2), 7.18 (2H, d, ar, J = 9 Hz), 7.30 (2H, m, ind + 2H, NH_2), 7.45 (2H, d, ar, J = 9 Hz), 7.60 (1H, m, ind), 8.08 (1H, m, ind)
7f	3370, 3180, 1640, 1610, 735	5.60 (2H, s, CH_2), 6.42 (1H, d, ar, J = 8.5 Hz), 7.40 (3H, m, ind + 2H, NH_2), 7.50 (1H, dd, ar, J = 8.5 Hz, J = 2.0 Hz), 7.76 (1H, d, ar, J = 2.0 Hz), 8.10 (1H, m, ind)
8a	3340, 1695, 1655, 1590, 1220	3.78 (3H, s, CH_3), 7.35 (2H, m, ind), 7.40 (2H, d, ar, J = 9 Hz), 7.61 (1H, m, ind), 7.68 (2H, d, ar, J = 9 Hz), 7.90 (1H, m, ind), 10.20 (1H, s, NH), 10.90 (1H, s, NH)
8b	3330, 1700, 1655, 1590, 1220	1.33 (3H, t, CH_3, J = 7.5 Hz), 4.40 (2H, q, CH_2, J = 7.5 Hz), 7.40 (2H, m, ind), 7.45 (2H, d, ar, J = 9 Hz), 7.69 (1H, m, ind), 7.71 (2H, d, ar, J = 9 Hz), 7.95 (1H, m, ind), 10.30 (1H, s, NH), 10.90 (1H, s, NH)
8c	3350, 1695, 1650, 1590, 1490	0.90 (3H, t, CH_3, J = 7.5 Hz), 1.32 (2H, m, CH_2), 1.68 (2H, m, CH_2), 4.33 (2H, t, N-CH_2, J = 7.5 Hz), 7.40 (2H, m, ind), 7.44 (2H, d, ar, J = 9 Hz), 7.69 (1H, m, ind), 7.70 (2H, d, ar, J = 9 Hz), 7.95 (1H, m, ind), 10.32 (1H, s, NH), 10.90 (1H, s, NH)
8d	3390, 1715, 1590, 1545, 1215	7.15 (1H, m, ar), 7.40 (2H, m, ind + 2H, ar), 7.45 (2H, d, ar, J = 9 Hz), 7.65 (2H, m, ar + 1H, ind), 7.70 (2H, d, ar, J = 9 Hz), 8.01 (1H, m, ind), 10.55 (1H, s, NH), 10.90 (1H, s, NH)
8e	3335, 1705, 1590, 1550, 1490	5.65 (2H, s, CH_2), 7.27 (2H, d, ar, J = 9 Hz), 7.40 (2H, m, ind), 7.48 (2H, d, ar, J = 9 Hz), 7.50 (2H, d, ar, J = 9 Hz), 7.70 (1H, m, ind), 7.72 (2H, d, ar, J = 9 Hz), 7.97 (1H, m, ind), 10.50 (1H, s, NH), 10.90 (1H, s, NH)
8f	3260, 1705, 1660, 1590, 1510	5.52 (2H, s, CH_2), 6.42 (1H, d, ar, J = 8.5 Hz), 7.0 (1H, dd, ar, J = 8.5 Hz, J = 2.0 Hz), 7.38 (3H, m, ind), 7.40 (2H, d, ar, J = 9 Hz), 7.55 (1H, d, ar, J = 2.0 Hz), 7.87 (2H, d, ar, J = 9 Hz), 8.40 (1H, m, ind), 11.30 (1H, broad, NH), 11.40 (1H, s, NH)
10a	3280, 1635, 955, 840, 745	3.74 (3H, s, CH_3), 7.27 (2H, m, ind), 7.58 (1H, m, ind), 8.05 (1H, m, ind), 8.28 (1H, s, CH), 9.13 (1H, s, NOH)
10b	3250, 1640, 970, 940, 740	1.28 (3H, t, CH_3, J = 7.5 Hz), 4.30 (2H, q, CH_2, J = 7.5 Hz), 7.30 (2H, m, ind), 7.60 (1H, m, ind), 8.10 (1H, m, ind), 8.30 (1H, s, CH), 11.10 (1H, s, NOH)
10c	3270, 1535, 1500, 940, 740	7.25 (2H, m, ind + 1H, ar), 7.60 (4H, m, ar + 1H, ind), 8.20 (1H, m, ind), 8.40 (1H, s, CH), 11.30 (1H, s, NOH)
11a	1610, 1510, 1310, 1265, 750	374 (M^+, 11), 193 (16), 192 (38), 191 (49), 190 (100), 189 (18), 184 (35), 156 (12), 114 (13)
11b	1610, 1595, 1525, 1340, 1245	388 (M^+, 27) 218 (26), 207 (33), 206 (36), 205 (100), 204 (83), 189 (84), 184 (63), 176 (40)
11c	1610, 1595, 1365, 1340, 1270	436 (M^+, 12), 255 (28), 254 (50), 253 (74), 252 (100), 217 (19), 184 (25), 77 (20), 51 (20)

Table III

Analytical Data

Compound	Formula (MW)	Calcd. C (Found)	Calcd. H (Found)	Calcd. N (Found)
5a	$C_{15}H_{11}ClN_2O_2$ (286.7)	62.83 (63.21)	3.87 (3.90)	9.77 (9.97)
5b	$C_{15}H_{11}ClN_2O_3$ (302.7)	59.51 (59.23)	3.66 (3.98)	9.26 (9.11)
5c	$C_{16}H_{13}ClN_2O_3$ (316.7)	60.67 (61.00)	4.14 (4.20)	8.85 (8.82)
5d	$C_{17}H_{15}ClN_2O_3$ (330.8)	61.73 (61.59)	4.57 (4.52)	8.47 (8.53)
7a	$C_{10}H_9ClN_2O$ (208.6)	57.56 (57.56)	4.35 (4.51)	13.43 (13.23)
7b	$C_{11}H_{11}ClN_2O$ (222.7)	59.33 (59.40)	4.98 (5.01)	12.58 (12.49)
7c	$C_{15}H_{15}ClN_2O$ (250.7)	62.27 (62.20)	6.03 (6.05)	11.17 (11.33)
7d	$C_{15}H_{11}ClN_2O$ (270.7)	66.54 (66.35)	4.10 (3.95)	10.35 (10.18)
7e	$C_{16}H_{12}Cl_2N_2O$ (319.2)	60.20 (59.98)	3.79 (4.03)	8.78 (8.52)
7f	$C_{16}H_{11}Cl_3N_2O$ (353.6)	54.34 (54.03)	3.14 (3.13)	7.92 (7.81)
8a	$C_{17}H_{13}Cl_2N_3O_2$ (362.2)	56.40 (56.63)	3.62 (3.51)	11.60 (11.38)
8b	$C_{16}H_{15}Cl_2N_3O_2$ (376.2)	57.46 (57.32)	4.02 (3.92)	11.17 (11.13)
8c	$C_{20}H_{19}Cl_2N_3O_2$ (404.3)	59.41 (59.11)	4.74 (4.81)	10.39 (10.38)
8d	$C_{22}H_{15}Cl_2N_3O_2$ (424.3)	62.28 (62.27)	3.56 (3.47)	9.90 (9.82)
8e	$C_{23}H_{16}Cl_3N_3O_2$ (472.7)	58.43 (58.16)	3.41 (3.36)	8.89 (8.78)
8f	$C_{23}H_{15}Cl_4N_3O_2$ (507.2)	54.46 (54.06)	2.98 (2.90)	8.28 (8.20)
10a	$C_{10}H_9ClN_2O$ (208.6)	57.56 (57.42)	4.35 (4.26)	13.43 (13.29)
10b	$C_{11}H_{11}ClN_2O$ (222.7)	59.33 (59.53)	4.98 (4.90)	12.58 (12.20)
10c	$C_{15}H_{11}ClN_2O$ (270.7)	66.54 (66.72)	4.10 (3.97)	10.35 (10.20)
11a	$C_{16}H_{11}ClN_4O_5$ (374.7)	51.28 (51.67)	2.96 (2.91)	14.95 (15.04)
11b	$C_{17}H_{13}ClN_4O_5$ (388.8)	52.52 (52.61)	3.37 (3.32)	14.41 (14.75)
11c	$C_{21}H_{13}ClN_4O_5$ (436.8)	57.74 (57.80)	3.00 (2.98)	12.83 (12.86)

sodium ethoxide (5.2 mmoles) and 2,4-dinitrochlorobenzene (5 mmoles). The reaction mixture was stirred at room temperature for 5 hours, then it was treated with water and the yellow precipitate was collected (yield 95-98%). An analytical sample was crystallized from ethanol, see Tables I, II, and III.

B) Biology.

a) Nematicidal Activity.

Assessment *in vitro* (dosage = 50 ppm): an aqueous suspension containing both the compound under test and nematodes (Southern root-knot nematode *Meloidogyne incognita*) was mixed efficiently and poured into a small petri dish, which was placed in an air-conditioned room at 25°. The mortality of the nematodes was assessed by counting the dead nematodes with a microscope 24 hours after treatment.

Assessment in a pot test (dosage = 30 Kg/ha): the appropriate amount of 10% wettable powder of the compound under test was incorporated into the nematode-settled soil. Cucumber was seeded 24 hours after packing the mixed soil in a pot which was placed under good watering conditions in a greenhouse for 3 weeks. The activity was assessed by observing the degree of infestation of the roots of the cucumber seedlings.

b) Insecticidal Activity.

House fly (dosage = 160 mg/m^2): 10 mg of compound under test was dissolved in 10 ml of acetone. One ml of this solution was poured into a petri dish, which was tilted in order to cover all the bottom surface and it was dried in a room at 25°. Then 15 adult house flies, paralyzed with carbon dioxide, were placed in the dish which was covered after placing a piece of filter paper containing milk solution on the brim of the petri dish. The knock-down effect and the mortality of house fly were assessed 2 and 24 hours after the release, respectively.

Flour beetle (dosage = 20 mg/g of wheat flour): adult flour beetles were placed in a covered plastic cup which contained a sufficient amount of wheat flour incorporated with 10% wettable powder of the compound under test. After placing the cup in an air conditioned room at 25° for 1 month, insecticidal and IGR activities were assessed by counting the number of adults, larvae and pupae.

c) Herbicidal activity (paddy rice field treatment): weeds and rice at the 2nd true-leaf stage were planted together in a small pot at the same time. One day after planting, an adequate volume of suspension of the compound under test (corresponding to 4 Kg/ha as the final dose) was poured into the water. The pot was placed in a greenhouse under no leakage conditions for 21 days. The activity was determined using a rating scale of 0 (inactive) to 10 (completely killed).

Acknowledgement.

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