NEWER INDOLYL ANTIPARKINSONIAN AGENTS

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ABSTRACT

Fourteen new indole derivatives were synthesized, characterized and screened for potential anti-parkinsonian activity. Some compounds have shown promising anti-parkinsonian activity with low toxicity.

INTRODUCTION

COMPOUNDS incorporating indole nucleus have shown anti-parkinsonian activity[1]. Of singular interest are the structures in which the variations have been done at position-3 of indole nucleus[2]. Earlier we have reported promising antiparkinsonian activity in indoles[3,4], with a view to examining the effect of other functional variants (at position-3 of indole nucleus) on the activity of these types of compounds. We have synthesized 3-[4'-(aryl propanonyl) phenylaldimino] indoles and 3-[4'-(N'-substituted propanonyl) phenylaldimino] indoles by the condensation of aryl aldehydes and mannich reaction with amines on 3-(acetylphenylaldimino) indole respectively. The compounds were screened for potential antiparkinsonian activity.

EXPERIMENTAL

All the compounds were checked by TLC on silica gel G. IR spectra were recorded on Perkin Elmer Infracord in KBr pellets. Mass spectrum was determined in JMS-D-300 double focussing with JMA-2000 data.

3-(Acetylphenyl aldimino) indole

A mixture of indole-3-aldehyde (0.01 mol) and *p*-amino acetophenone (0.01 mol) in ethanol (100 ml) was refluxed in the presence of 2–3 drops of glacial acetic acid for 6 hr. The excess solvent was distilled off. The solid obtained on cooling was filtered, dried and recrystallized from a mixture of ethanol/water (30:70). M.P. 99° C, yield 65%. IR(KBr) showed the characteristic bands of C=N (1640 cm^{-1}), C=O (1680 cm^{-1}) and NH (3100 cm^{-1}).

3-[4'-(p-methoxyphenyl propanonyl) phenylaldimino] indole

To a solution of 3-(acetylphenyl aldimino) indole (0.01 mol) and *p*-anisaldehyde (0.01 mol) in ethanol (50 ml), piperidine (4–5 drops) was added. The reaction mixture was refluxed for 8 hr. It was concentrated and cooled. The solid was filtered and recrystallized from a mixture of ethanol/water. Various compounds synthesized by the above method are reported in table 1. IR(KBr); 3200 cm^{-1} (–NH) 1640 cm^{-1} (C=N) and 1620 cm^{-1} (C=C).

3-[4'-(piperidino propanonyl) phenylaldimino] indole

A mixture of 3-(acetylphenyl aldimino) indole (0.01 mol), piperidine (0.01 mol) and formal dehyde solution (40%, 0.02 mol) in ethanol (50 ml) were refluxed for 3 hr. The solid obtained on cooling was filtered, washed with water and recrystallized from a mixture of ethanol/water. Analytical data of various compounds thus synthesized are given in table 2. IR(KBr); 3200 cm^{-1} (–NH), 1640 cm^{-1} (C=N) and 1700 cm^{-1} (C=O). MS:m/z 144 (41%), 116 (65%); 120 (23%), 98(77%), 89(34%) and 63(21%). This confirms the structure of the above compound.

Biological studies

These studies were carried out with albino mice weighing (20–30 g) and rats (200–250 g) of either sex. The compounds and l-dopa (standard drug) were administered at a dose of 100 mg/kg i.p. in aqueous suspension of gum accacia.

Gross behaviour–Effect of test compounds on motor, sensory and autonomic systems were studied in mice[5].

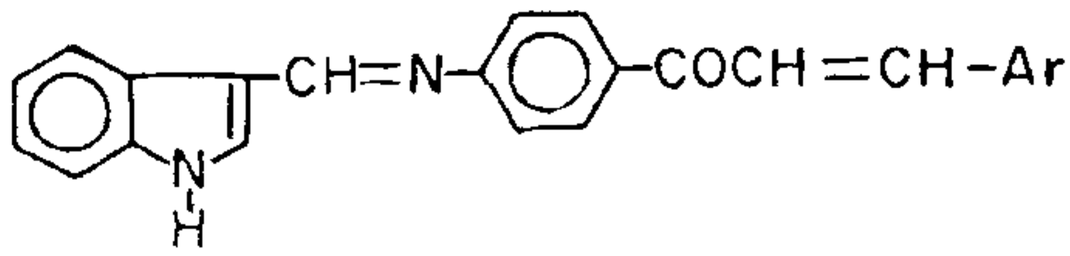
Antiparkinsonian activity

i) Tremor was produced in mice (20–30 g) by oxotremorine (0.5 mg/kg i.p.) given 1 hr after the administration of compounds. After 5 min of oxotremorine, tremor was scored (0–3)[6] in each mice of every group. Each group consisted f 5 mice and mean score (tremor index) of each group was calculated.

ii) Reserpine (5 mg/kg i.p.) was administered in rats to produce rigidity and after 15 min, test compounds were injected. Rigidity was measured 1 hr after reserpine according to Goldstein *et al*[7].

TABLE 1

Physical constants and antiparkinsonian activity of 3-[4'-(aryl propanonyl) phenyladimino] indoles

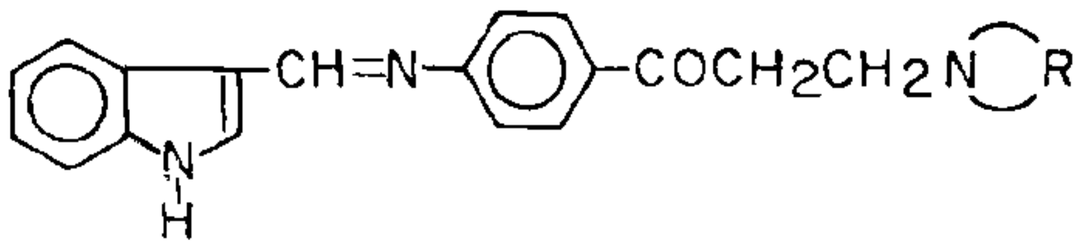


Compd. No.	Ar	M.P. ° C	Tremor index (Mean ± SE)	Rigidity %	Hypokinesia	Catatonia (Mean ± SE)	ALD_{50} mg/kg
	Control		3.0 ± 0	100	(−) 85.0	3.0 ±	—
1	4-OCH_3.C_6H_4	190	2.6 ± 0.2	100	(−) 81.3	3.0 ± 0	—
2	3-OCH_3,4-OH.C_6H_3	171	3.0 ± 0	80	(−) 86.9	2.8 ± 0.2	1000
3	2-OH.C_6H_4	137	3.0 ± 0	40	(−) 67.2*	2.2 ± 0.1*	750
4	3,4(OCH_3)$_2$,C_6H_3	154	3.0 ± 0	60	(−) 72.8	2.4 ± 0.2*	>1000
5	N-(CH_3)$_2$,C_6H_4	131	2.8 ± 0.1	80	(−) 83.1	2.8 ± 0.2	—
6	4-OH.C_6H_4	168	2.6 ± 0.2	40	(−) 70.0*	2.2 ± 0.2*	—
7	4-Cl.C_6H_4	149	2.8 ± 0.1	60	(−) 76.6	2.4 ± 0.2*	750
8	3-F.C_6H_4	142	2.4 ± 0.2*	40	(−) 64.4*	2.2 ± 0.1*	>1000
	l-dopa		2.6 ± 0.2	80	(−) 74.4	2.8 ± 0.1	—

(a) Elemental analyses were found within the limits
* Significant difference $P-<0.05$ from control values

TABLE 2

Physical constants and antiparkinsonian activity of 3-[4'-(N'-substituted propanonyl) phenylaldimino] indoles



Compd. No.	N R	M.P. ° C	Tremor index (Mean ± SE)	Rigidity %	Hypokinesia	Catatonia (Mean ± SE)	ALD_{50} mg/kg i.p.
	Control		3.0 ± 0	100	(−) 85.0	3.0 ± 0	—
9	p-tolyl-ethylamino	145	2.6 ± 0.2	60	(−) 75.7	2.4 ± 0.2*	750
10	2,4-dichloro benzylamino	298	2.4 ± 0.2*	40	(−) 75.4*	2.2 ± 0.1*	>1000
11	piperidino	139	2.8 ± 0.2	80	(−) 83.1	2.8 ± 0.2	—
12	2-methyl piperidino	140	3.0 ± 0	100	(−) 84.1	3.0 ± 0	1000
13	homopiperidino	301	2.8 ± 0.2	100	(−) 90.6	3.0 ± 0	—
14	morpholino	141	2.4 ± 0.2*	80	(−) 83.0	2.8 ± 0.2	>1000
	l-dopa		2.6 ± 0.2	80	(−) 74.4	2.8 ± 0.1	—

(a) Elemental analyses were found within the limits
* Significant difference $P< 0.05$ from control values

O = no resistance, 1 = normal resistance, 2 = complete resistance. A score of 2 was selected as criterion for rigidity.

iii) Hypokinesia was produced by reserpine (5 mg/kg i.p.) in rats. The test compounds were administered 15 min after reserpine. Locomotor activity was counted after 2 hr by placing each groups of rat in photoactometer, for 15 min and the total count was recorded. The percent increase or decrease in counts was calculated on the basis of count of untreated group.

iv) Catatonia–Reserpine (5 mg/kg i.p.) was administered in rats and after 4 hr catatonia was observed and scored according to Morpurgo[8]. The test compounds were administered after 15 minutes of reserpine.

Toxicity studies

Acute neurological toxicities were observed according to Swinyard *et al*[9]. ALD_{50} values were determined according to Smith[10].

Statistical analysis

The significance of difference between two mean values was determined by student *t* test. Significance of difference between percent change was determined by Chi square (Yates correction) test.

Results and Discussion

The results of antiparkinsonian activity are depicted in tables 1 and 2. Oxotremorine induced tremors were significantly antagonized by compounds 8, 10 and 14. Reserpine-induced rigidity was markedly antagonized (60%) by compounds 3, 6, 8, 10 whereas moderate (40%) inhibition of rigidity was observed in compounds 4, 7 and 9. Antihypokinetic activity was found in compounds, 3, 6, 8 and 10. Compounds 3, 4, 6, 7, 8, 9 and 10 showed significant reduction in catatonic score in comparison to control. However, compounds 1, 2, 5, 11, 12 and 13 were completely devoid of activity. None of the compound showed any marked effect on gross behaviour. The ALD_{50} values of the active compounds are reported in tables 1 and 2.

Compound No. 10 was active against all the parameters in which 2, 4-dichlorobenzylamino group was substituted at 4'-position of the acetophenone. Thus, it appears that substitution of 2, 4-dichlorobenzylamino group is beneficial for antiparkinsonian activity in the present series.

It is worthwhile to mention that compound No. 10 showed better pharmacological profile than l-dopa at similar dose against all the parameters.

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