NEWER INDOLE DERIVATIVES AS MONOAMINE OXIDASE INHIBITORS

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INDOLE containing compounds have been reported to possess a wide spectrum of biological activities. Their effect on central nervous system is well documented and several indole compounds have been found to be potential psychotropic agents and possess marked MAO inhibitory activity[1-4]. In continuation of our work on such compounds, we have synthesized substituted indolyl thiosemi carbazides and substituted indolyl thiazolidones and evaluated them for their biochemical and various pharmacological properties.

EXPERIMENTAL

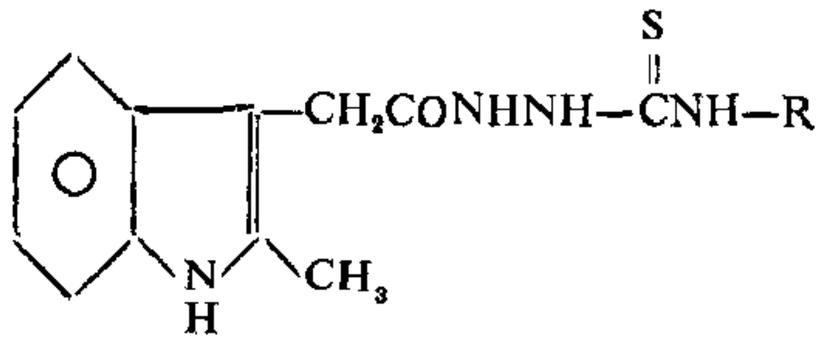
2-Methyl-indole-3-acetate[5], 4-chloro-2-carboxylate[6] and 2-methyl-indole-3-acetyl hydrazide[4] were prepared according to the literature methods.

Substituted indolyl thiosemicarbazides

These were prepared by refluxing the appropriate hydrazide with substituted iso-thiocyanates in dry ethanol; the solid obtained was recrystallized with appropriate solvents. M.Ps. and analytical data are reported in Table I.

TABLE I

Substituted indolyl thiosemicarbazides



Compd. No.	R	mp. °C	Molecular formula	Analytical data % N calcd.	Analytical data % N found	% MAO inhibitory activity 1×10^{-4}	% MAO inhibitory activity 1×10^{-5}
1.	m-F-C_6H_4	174	$C_{18}H_{17}ON_4SF$	15·73	15·42	32·94	..
2.	*p*-ClC_6H_4	130	$C_{18}H_{17}N_4OSCl$	15·05	15·38	21·05	..
3.	C_2H_5	112	$C_{14}H_{18}N_4OS$	19·31	19·68	36·32	..
4.	C_6H_5	168	$C_{16}H_{13}N_4OSCl$	16·23	16·25	82·62	50·0
5.	O-$OCH_3C_6H_4$	180	$C_{17}H_{15}N_4O_2ClS$	14·93	14·23	90·15	58·6
6.	*p*-$OCH_3C_6H_4$	165	$C_{17}H_{15}N_4O_2ClS$	14·93	14·48	89·39	55·25
7.	C_2H_5	200	$C_{12}H_{13}OClSN_4$	18·85	18·92	66·86	..

Substituted indolyl thiazolidones

These were prepared by refluxing indolyl thiosemicarbazides (0·01 M), chloroacetic acid (0·01 M), and sodium acetate (0·015 M) in glacial acetic acid (15 ml) for 6 hrs. After pouring in cold water, the solid obtained was washed and recrystallized from sthanol (Table II).

BIOLOGICAL METHODS

Determination of monoamine oxidase (MAO) inhibition

MAO activity was determined by the spectrophotofluorometric method of Krazl[8] using partially purified

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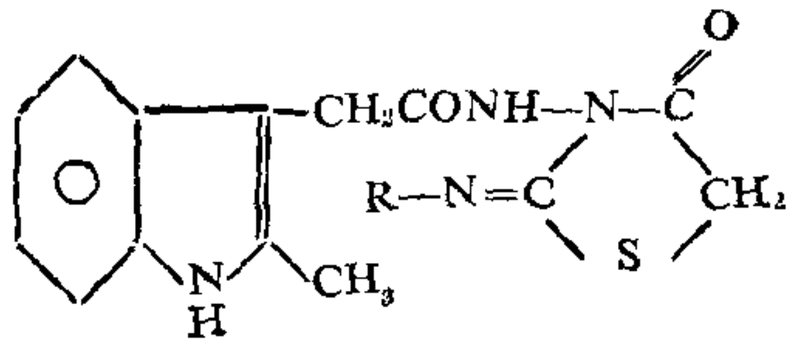
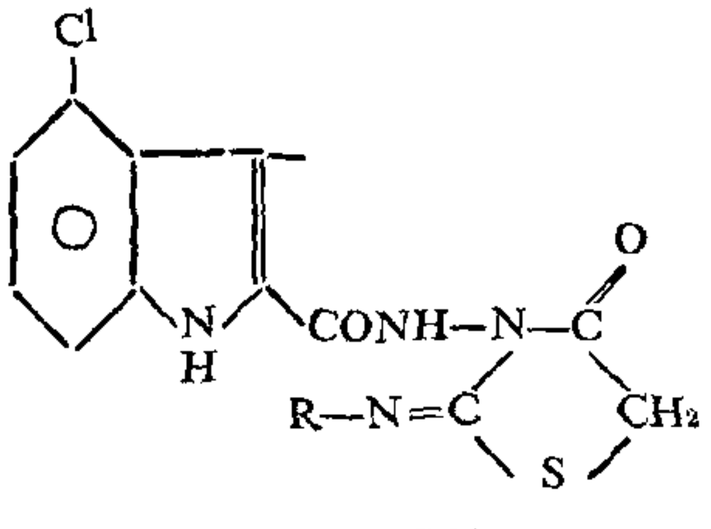
TABLE II

Substituted indolyl thiazolidones



Compd. No.	R (*d*)	m.p. °C (*a*)	Molecular formula	Analytical data % N calcd.	Analytical data % N found	% MAO inhibitory activity (*b*, *c*) 1×10^{-4}	% MAO inhibitory activity (*b*, *c*) 1×10^{-5}
8.	C_6H_5	188	$C_{20}H_{16}N_4O_2S$	14·81	14·91	20·12	..
9.	O-$OCH_3C_6H_4$	185	$C_{21}H_{20}O_3N_4S$	13·72	13·58	18·78	..
10.	*p*-$OCH_3C_6H_4$	215	$C_{21}H_{20}O_3N_4S$	13·72	13·42	48·0	..
11.	*m*-F-C_6H_4	180	$C_{20}H_{17}O_2SFN_4$	14·14	14·51	54·0	..
12.	*p*-ClC_6H_4	185	$C_{20}H_{17}O_2SCl$	13·58	13·62	..	..
13.	C_2H_5	162	$C_{16}H_{18}N_4O_2S$	16·98	16·78	11·95	..



14.	C_6H_5	215	$C_{18}H_{13}N_4O_2SCl$	14·54	14·56	71·46	41·28
15.	O-$OCH_3C_6H_4$	200	$C_{19}H_{15}N_4O_3SCl$	13·49	13·82	41·34	..
16.	*p*-$OCH_3C_6H_4$	175	$C_{19}H_{15}N_4O_3SCl$	13·49	13·54	58·95	..
17.	C_2H_5	224	$C_{14}H_{13}N_4O_2SCl$	16·58	16·42	82·56	11·05

(*a*) Melting points were taken in open capillary tubes and are uncorrected.

(*b*) Compounds were dissolved in propylene glycol.

(*c*) Each experiment was done in duplicate. Values in the table are mean of two separate experiments.

(*d*) All the compounds were routinely checked, by T.L.C. on silicagel G for their homogenicity.

rat brain preparation (16,000 × g sedimented particles) as an enzyme source and kynuramine as a substrate at a final concentration of 4×10^{-6} *M* at pH8 Compounds were tested at 10^{-4} and 10^{-5} *M* concentrations. After suitable dilution, optical density was recorded at 315 nm and fluorescence at 380 nm.

Pharmacological studies

The compounds were tested for the following pharmacological activities and the results are reported in Table III.

1. *MAO inhibition*: MAO inhibitory activity *in vivo* was determined by Reserpine Reversal Test (Chessin *et al.*)[9] and L-dopa potentiation Test (Everett *et al.*)[11].

2. *Anticonvulsant activity* : Maximal Electro shock test and pentylenetetrazol seizures test (Swinyard *et al.*)[12], were used for the determination of anticonvulsant activity.

3. *Analgesic activity* : Analgesic activity was determined by Haffner's clip method (Haffner)[13].

Results and Discussion

All the compounds were assayed for their *in vitro* MAO inhibitory activity as reported in Tables I and II. Five compounds (4, 5, 6, 14, 17) of the series showed more than 80% inhibition at concentration of 1×10^{-4} *M*. Therefore, the MAO inhibitory activity of these five compounds was determined at lower concentration (1×10^{-5} *M*) and is reported in Tables I-II.

An examination of enzyme inhibitory activity in relation to their chemical structure showed that the compounds having a chloro substituent at position 4 or were unsubstituted resulted in an increase of MAO inhibitory activity. Cyclisation of thiosemicarbazides into thiazolidones resulted in compounds possessing decreased MAO inhibitory activity.

TABLE III

Test compound 100 mg kg i.p.	Behavioural effects (in mice)	Reserpine reversal (in rats)		L-dopa potentiation (in mice)			ALD_{50} mg/kg i.p. (in mice)
		Ptosis scores	Locomotor activity	Piloerection	Locomotor activity	Stereotypy	
Control	..	4	+	1	+	0	..
4	Moderate increase in spontaneous locomotor activity, slight increase in respiratory rate	2·1	+++	3	+++	1	>1000
5	Slight increase in spontaneous locomotor activity	3·3	++	3	+++	1	>1000
6	No prominent effects	3·3	++	2	+	0	>1000
14	No prominent effects	2·6	++	1	+	0	>1000
17	No prominent effects	2·1	+++	1	+++	0	>1000

— Test compounds were administered in aqueous suspension with gumacacia intraperitoneally.
— Observations were made 4 hrs after administration of test compounds.
— ALD_{50} was determined by observing the mortality 24 hrs after the administration of compounds.
— Degree of ptosis was determined by the method of Rubin[10] *et al.*
— Reserpine 5 mg/kg i.p.
— L-dopa 100 mg/kg i.p.

The above five compounds which showed promising *in vitro* MAO inhibitory activity were studied for their ability to inhibit MAO *in vivo*, anticonvulsant activity and analgesic activity. Their ALD_{50} values were also determined (Table III).

Out of the compounds studied for their CNS effects, compounds 4 and 17 showed reversal of reserpine induced ptosis to a greater extent as compared to that observed with other compounds, (5, 6 and 14) (Table III). Compounds 5 and 6 showed potentiation of L-dopa effects, such as piloerection and increased locomotor activity whereas the other compounds, *viz.*, 6, 14 and 17 potentiated to a mild degree (Table III). The compounds 4 and 5 produced some behavioural effects such as increase in spontaneous locomotor activity and an increase in respiratory rate, whereas compounds 6, 14 and 17 were without any prominent behavioural effects in mice. All the 5 compounds were devoid of anticonvulsant activity both against maximal electroshock seizures and pentylenetetrazol induced seizures and showed no analgesic activity. All the compounds possess a wide margin of safety as is indicated by their high approximate LD_{50} values.

Reversal of reserpine effects and potentiation of L-dopa effects by compound 4 correlate well with its *in vitro* MAO inhibitory activity, thereby indicating that this compound in the series may possess antidepressant activity.

ACKNOWLEDGEMENT

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