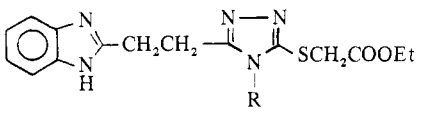
Table II. Biological Activity of Benzimidazolyltriazoles

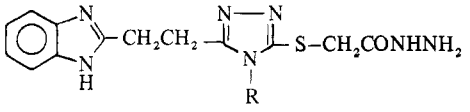
Compd no.[a]	Approx LD_{50}, mg/kg ip	Anticonvulsant activity[b]		Potentiation[b] of pentobarbital sleeping time, min ± std dev
		Protection, %	24-hr mortality, %	
1	>1000	30	40	11.66 ± 6
2	>1000	70	10	23.16 ± 6
3	>1000	60	20	57.56 ± 14
4	>1000	70	10	45.83 ± 20
5	>1000	60	20	26.83 ± 7
6	>1000	50	40	24.50 ± 15
7	1000	40	50	53.66 ± 4
8	>1000	40	40	35.00 ± 17
9	>1000	40	40	44.33 ± 12
10	750	80	20	35.83 ± 19
11	1000	60	40	52.00 ± 13
12	1000	50	30	43.66 ± 19
13	1000	30	50	87.10 ± 15
14	1000	50	50	55.16 ± 22
15	>1000	40	60	43.66 ± 9
16	1000	70	40	60.50 ± 10
17	>1000	50	40	57.33 ± 10
18	>1000	60	40	59.00 ± 17

[a] Compounds are numbered as in Table I. [b] Compounds were administered at a dose of 100 mg/kg ip.

methylthio-1,2,4(*H*)-triazoles (IV). To a soln of the ester (III) (0.01 mole) in EtOH was added $N_2H_4H_2O$ (0.015 mole), and the mixt was refluxed for 3-4 hr. Excess of EtOH was removed, and the solid thus obtained was collected by filtration, dried, and recrystd (EtOH); yield 60-70%.



III



IV

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Substituted Indolebenzylhydrazines as Anticonvulsants

V. K. Agarwal, T. K. Gupta, and Surendra S. Parmar*

Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow-3, India.
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The presence of a trimethoxy moiety has been shown to be responsible for pharmacological properties of reserpine[1-8] and other compounds associated with CNS activity. The MAO-inhibitory property exhibited by indolehydrazines[9] possessing CNS activity led to the synthesis of dimethoxy- and trimethoxyindolebenzylhydrazines with a view to evaluating their ability to afford protection against pentylenetetrazole-induced seizures.

Anticonvulsant activity was detd by injecting substituted indolebenzylhydrazines ip in a 5% aqueous suspension of gum acacia at a dose of 100 mg/kg in groups of 10 mice of either sex weighing 20-25 g. Four hours after the administration of the test compounds pentylenetetrazole was injected sc under the loose skin of the back in a dose of 80 mg/kg. This dose of pentylenetetrazole has been shown to cause convulsions within 1 hr of administration and to produce 100% mortality within 24 hr. The mice were observed for the next 60 min for occurrence of seizures. Animals devoid of even a threshold convulsion were considered protected.

Results and Discussion

As is evident from Table I anticonvulsant activity ranging from 10 to 50% was exhibited by the test compounds. Maximum protection against pentylenetetrazole-induced seizures, observed with **4**, was found to correspond with lowest mortality. The anticonvulsant properties of these compounds parallel their ability to protect against death in pentylenetetrazole-treated mice during a 24-hr period. Those indolebenzylhydrazines containing a trimethoxyphenyl group were found to exhibit greater anticonvulsant activity than those possessing a dimethoxyphenyl group. These results indicated that substitution at position 5 of an indole nucleus possessing a trimethoxyphenyl moiety influenced their anticonvulsant activity, in the order of $CH_3 > OCH_3 > H$. It is hoped that further detailed pharmacological studies with these and related indolebenzylhydrazines could ultimately lead to the development of therapeutic agents for diseases of the CNS.

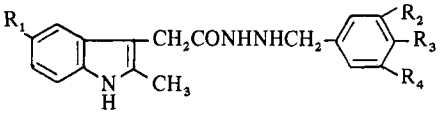
Experimental Section

Substituted Phenylhydrazines. *p*-Methylphenylhydrazine and *p*-methoxyphenylhydrazine were synthesized according to the methods reported earlier.[10]

Ethyl Substituted Indole-3-acetates. Ethyl substituted indole-3-acetates were synthesized by cyclization of substjtuted phenylhydrazines and ethyl levulinate in 2 *N* EtOH-HCl. The crude products were isolated with ether and washed with Na_2CO_3 soln and finally with H_2O. On distilling the solvent the esters were isolated.[9]

Substituted Indole-3-acetylhydrazines. Ethyl substituted indole-3-acetates (0.1 mole) were refluxed with $N_2H_4 \cdot H_2O$ (0.15 mole, 80%) in 25 ml of absolute EtOH for 8 hr. On distilling the excess of solvent

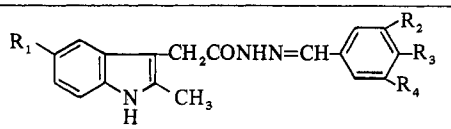
Table I. N^1-Substituted Indole-3-acetyl-N^2-(3′,4′-dimethoxy/3′,4′,5′-trimethoxybenzyl)hydrazines and Their Anticonvulsant Activity



No.	R_1	R_2	R_3	R_4	Mp,[a] °C	Yield, %	Solvent of crystn[b]	Formula[c]	Anticonvulsant activity: Protection, %	Anticonvulsant activity: Mortality, 24 hr, %
1	CH_3	CH_3O	CH_3O	H	225	60	EtOH	$C_{21}H_{25}N_3O_3$	30	30
2	H	CH_3O	CH_3O	H	220	70	EtOH	$C_{20}H_{23}N_3O_3$	10	40
3	CH_3O	CH_3O	CH_3O	H	215	75	PE	$C_{21}H_{25}N_3O_4$	20	50
4	CH_3	CH_3O	CH_3O	CH_3O	280	60	D	$C_{22}H_{27}N_3O_4$	50	20
5	H	CH_3O	CH_3O	CH_3O	120	40	D	$C_{21}H_{25}N_3O_4$	30	50
6	CH_3O	CH_3O	CH_3O	CH_3O	112	50	Et_2O	$C_{22}H_{27}N_3O_5$	10	70

[a]Melting points were taken in open capillary tubes. [b]PE = Petr ether; D = dioxane. [c]All compds were analyzed for C, H, and N and analyses were found within acceptable limits.

Table II. N^1-Substituted Indole-3-acetyl-N^2-(3′,4′-dimethoxy/3′,4′,5′-trimethoxybenzylidene)hydrazines



No.	R_1	R_2	R_3	R_4	Mp, °C[a]	Yield, %	Solvent[b]	Formula[c]
1	CH_3	CH_3O	CH_3O	H	198	65	EtOH	$C_{21}H_{23}N_3O_3$
2	H	CH_3O	CH_3O	H	192	60	PE	$C_{20}H_{21}N_3O_3$
3	CH_3O	CH_3O	CH_3O	H	191	70	PE	$C_{21}H_{23}N_3O_4$
4	CH_3	CH_3O	CH_3O	CH_3O	210	65	EtOH	$C_{22}H_{25}N_3O_4$
5	H	CH_3O	CH_3O	CH_3O	180	70	EtOH	$C_{21}H_{23}N_3O_4$
6	CH_3O	CH_3O	CH_3O	CH_3O	190	60	EtOH	$C_{22}H_{25}N_3O_5$

[a]Melting points were taken in open capillary tubes. [b]PE = petr ether. [c]All compds were analyzed for C, H, and N and analyses were found within acceptable limits.

the hydrazides which separated out were filtered and recrystd with appropriate solvents.

Substituted Indolebenzylidenehydrazines. A mixt of 0.01 mole of substituted indole-3-acetylhydrazine and substituted (dimethoxy- or trimethoxy)benzaldehyde (0.01 mole) in EtOH (50 ml) was refluxed for 2 hr. The reaction mixt was filtered hot and concd *in vacuo*. The solid compounds which sepd out on cooling were crystd from the appropriate solvents (Table II).

Substituted Indolebenzylhydrazines. A soln of 0.05 mole of substituted indolebenzylidenehydrazines in 100 ml of dioxane or THF was hydrogenated with 0.1 g of PtO_2 catalyst in a Parr hydrogenation apparatus at an initial pressure of 2.8 kg/cm². The required amount of hydrogen was absorbed in 15 hr. Filtration and removal of the solvent under reduced pressure left a residue which was crystd by dissolving in a minimum amount of EtOH and adding petroleum ether (bp 40–60°).

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Book Reviews

Search for New Drugs. Edited by Alan A. Rubin, with 12 contributors. Marcel Dekker, New York, N. Y. 1972. x + 452 pp. 16 × 24 cm. $19.50.

Fortuitous discovery of clinically useful drugs, so prevalent earlier in the century, is becoming less probable every day. The smaller number of clinical trials, dictated by more severe governmental restrictions, is the final pinacle protruding from an ocean of obstacles in drug research. These obstacles begin with the uncertainties of even the most sophisticated methods of drug design in the chemical laboratory. The most formidable difficulty is the predictability of the success of a drug in human medicine even if animal model experiments hold out promise. The book under discussion examines these pharmacological hurdles in several fields. In three of them drugs are known to suppress symptoms of the diseases, but with varying success only. They are antiinflammatory, antiulcer, and psychotropic drugs. The three chapters probe the possibility of discovering tests for curative agents.

Four other chapters deal with drugs–β-adrenergic blocking agents,