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Benzimidazolyl-1,2,4(*H*)-triazoles as Central Nervous System Depressants

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Pellizzari, *et al.*,[1] have reported the ability of 4-phenyl-1,2,4(*H*)-triazoles to produce convulsions while 1-phenyl-1,2,4(*H*)-triazole was found to exhibit anticonvulsant properties.[2] Diverse pharmacological properties such as analgetic,[3] antiinflammatory,[4] tranquilizing,[5] and anticonvulsant[6] possessed by various benzimidazoles as well as CNS activity exhibited by hydrazides[7] led us to synthesize 5-(2'-benzimidazolyl)ethyl-4-substituted-3-mercapto-1,2,4(*H*),-5-(2'-benzimidazolyl)ethyl-4-substituted-3-ethoxycarbonylmethylthio-1,2,4(*H*)-, and 5-(2'-benzimidazolyl)ethyl-4-substituted-3-hydrazinocarbonylmethylthio-1,2,4(*H*)-triazoles. The CNS depressant property of these benzimidazolyltriazoles was reflected by their ability to possess anticonvulsant activity and to potentiate sodium pentobarbital sleeping time. Most of these triazoles produced behavioral depression. All triazoles (Table I) were found to exhibit anticonvulsant activity which ranged from 30 to 80%. Substitution of an SH group by either a CH_2CO_2Et or $CH_2CONHNH_2$ moiety in no way altered their anticonvulsant property. Introduction of substituents on the Ph nucleus attached to the N atom at position 1 of the triazole ring was found to enhance anticonvulsant activity. Results shown in Table II indicate that benzimidazolyltriazoles possessing a MeO group para to the Ph nucleus (**4**, **10**, **16**) exhibit greater anticonvulsant activity than unsubstituted triazoles (**1**, **7**, **13**). The anticonvulsant property was found to correspond with the ability of these compounds to protect against death in animals treated with pentylenetetrazol during a 24-hr period. All of these benzimidazolyltriazoles were found to quicken the effect of sodium pentobarbital hypnosis in mice by a factor of from 11.66 to 87.10 min. However, unlike the results obtained for anticonvulsant activity, no structure-activity relationship could be determined for the phenobarbital hypnosis potentiation results.

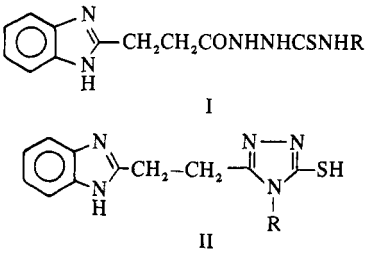
Experimental Section

Determination of Anticonvulsant Activity. Albino mice of either sex weighing 20–25 g in groups of ten were used. Substituted triazoles were injected ip in aqueous suspension in 5% gum acacia at a dose level of 100 mg/kg. Pentylenetetrazol was administered sc (80 mg/kg) after 4 hr under the loose skin of the back. The animals were observed for a period of 60 min for the occurrence of seizures.[8] The number of animals protected in each group was recorded and per cent protection was calcd. The mortality was recorded after 24 hr in pentylenetetrazol-treated animals.

Potentiation of Sodium Pentobarbital Sleeping Time. Mice weighing 20–25 g were taken in groups of 6 animals. One group was used for each compound and one group served as control. Sodium pentobarbital, when administered ip in a dose of 30 mg/kg to the control group, was found to produce ataxia and no sleep whereas an increase in the dose was found to produce sleep. The test compounds were administered ip at a dose of 100 mg/kg 1 hr prior to the administration of sodium pentobarbital. The animals were observed regularly for sleep as evidenced by the observance of the loss of righting reflex.[9] The mean average sleeping time in each group was calcd.

Chemistry.† **5-(2'-Benzimidazolyl)ethyl-4-substituted-3-mercapto-1,2,4(*H*)-triazoles (II).** A soln of 1-benzimidazole-2-propionyl-4-substituted thiosemicarbazide (I) in 2 *N* NaOH was refluxed for 2–3 hr. After cooling, the soln was filtered, and the filtrate was acidified with dil HCl until complete precipitation occurred.[10,11] The solid which sepd out was filtered, washed (H_2O), and recrystd (EtOH); yield 70–80%.

5-(2'-Benzimidazolyl)ethyl-4-substituted-3-ethoxycarbonylmethylthio-1,2,4(*H*)-triazoles (III). Equimolecular quantitites of



I

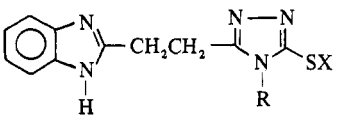
II

(II), $ClCH_2COOEt$, and anhyd K_2CO_3 were refluxed in dry Me_2CO for 8 hr. The soln was filtered, and the filtrate was concd. The solid which sepd out was collected by filtration and recrystd (EtOH); yield 50–60%.

5-(2'-Benzimidazolyl)ethyl-4-substituted-3-hydrazinocarbonyl-

†The melting points were taken in open capillary tubes with a partial immersion thermometer and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical value.

Table I. 5-(2'-Benzimidazolyl)ethyl-4-alkyl/aryl-3-substituted-1,2,4(*H*)-triazoles



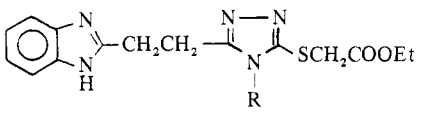
No.	R	X	Yield, %	Mp, °C	Formula	Analyses
1	C_6H_5	H	75	190	$C_{17}H_{15}N_5S$	C, H, N
2	*m*-$CH_3C_6H_4$	H	70	162	$C_{18}H_{17}N_5S$	C, H, N
3	*o*-$OCH_3C_6H_5$	H	75	203	$C_{18}H_{17}N_5OS$	C, H, N
4	*p*-$OCH_3C_6H_4$	H	75	284	$C_{18}H_{17}N_5OS$	C, H, N
5	C_6H_{11}	H	80	220	$C_{17}H_{21}N_5S$	C, H, N
6	$CH_2CH{=}CH_2$	H	70	260	$C_{14}H_{15}N_5S$	C, H, N
7	C_6H_5	CH_2COOEt	60	210	$C_{21}H_{21}N_5O_2S$	C, H, N
8	*m*-$CH_3C_6H_4$	CH_2COOEt	55	200	$C_{22}H_{23}N_5O_2S$	C, H, N
9	*o*-$OCH_3C_6H_4$	CH_2COOEt	55	178	$C_{22}H_{23}N_5O_3S$	C, H, N
10	*p*-$OCH_3C_6H_4$	CH_2COOEt	55	200	$C_{22}H_{23}N_5O_3S$	C, H, N
11	C_6H_{11}	CH_2COOEt	60	168	$C_{21}H_{27}N_5O_2S$	C, H, N
12	$CH_2CH{=}CH_2$	CH_2COOEt	50	153	$C_{18}H_{21}N_5O_2S$	C, H, N
13	C_6H_5	$CH_2CONHNH_2$	65	200	$C_{19}H_{19}N_7OS$	C, H, N
14	*m*-$CH_3C_6H_4$	$CH_2CONHNH_2$	70	208–210	$C_{20}H_{21}N_7OS$	C, H, N
15	*o*-$OCH_3C_6H_4$	$CH_2CONHNH_2$	65	212	$C_{20}H_{21}N_7O_2S$	C, H, N
16	*p*-$OCH_3C_6H_4$	$CH_2CONHNH_2$	65	190–192	$C_{20}H_{21}N_7O_2S$	C, H, N
17	C_6H_{11}	$CH_2CONHNH_2$	70	90	$C_{19}H_{25}N_7OS$	C, H, N
18	$CH_2CH{=}CH_2$	$CH_2CONHNH_2$	60	120	$C_{16}H_{19}N_7OS$	C, H, N

Table II. Biological Activity of Benzimidazolyltriazoles

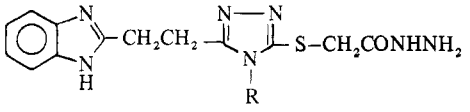
Compd no.[a]	Approx LD_{50}, mg/kg ip	Anticonvulsant activity[b]		Potentiation[b] of pentobarbital sleeping time, min ± std dev
		Protection, %	24-hr mortality, %	
1	>1000	30	40	11.66 ± 6
2	>1000	70	10	23.16 ± 6
3	>1000	60	20	57.56 ± 14
4	>1000	70	10	45.83 ± 20
5	>1000	60	20	26.83 ± 7
6	>1000	50	40	24.50 ± 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

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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