Anticonvulsant Property of Substituted 5-Aryltetrazol-2-ylacetylcarbamides

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Eight 1-(5-aryltetrazol-2-ylacetyl)3-substituted carbamides were synthesized as possible anticonvulsants. The anticonvulsant activity possessed by these substituted tetrazolylacetylcarbamides was reflected by their ability to provide 10-50% protection against pentylenetetrazol(1,5-pentamethylenetetrazol)-induced convulsions in mice. These substituted tetrazolylacetylcarbamides possessed low monoamine oxidase inhibitory activity, and the degree of enzyme inhibition ranged from 22-47% at a final concentration of 1 mmole using kynuramine as the substrate.

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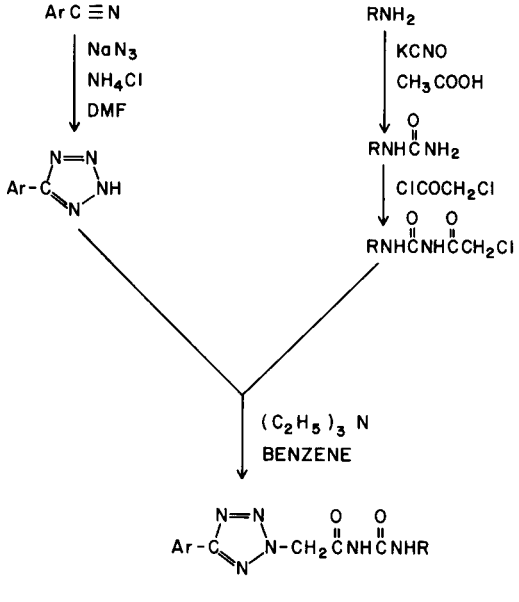
Earlier studies have shown that various aryloxy alkylcarbamides affect the central nervous system activity (3) and that substituted carbamides possess anticonvulsant activity (4). In other investigations substituted phenylpiperidino carbamides have also been reported to possess anticonvulsant activity and monoamine oxidase inhibitory activity (5,6). In addition, introduction of a tetrazolyl moiety in the benzodiazepine nucleus led to the synthesis of tetrazolylbenzodiazepines as central nervous system depressants (7,8). Furthermore, pronounced anticonvulsant activity has been reported to be associated with monoamine oxidase inhibitors (9). These observations prompted synthesis of 1-(5-aryltetrazol-2-ylacetyl)-3-substituted carbamides which were evaluated for their anticonvulsant activity and their ability to inhibit rat brain monoamine oxidase.

SCHEME I



Eight 1-(5-aryltetrazol-2-ylacetyl)-3-substituted carbamides (**1**−**8**) were synthesized from 5-aryltetrazoles by condensation with 1-chloroacetyl-3-substituted carbamides by following the steps outlined in Scheme 1.

The anticonvulsant activity possessed by substituted tetrazolylacetylcarbamides is recorded in Table II. All compounds at a dose of 100 mg/kg, i.p., were able to provide protection against convulsions induced by 90 mg/kg, s.c., pentylenetetrazol (1,5-pentamethylenetetrazol) in mice and the degree of protection ranged from 10−50%. The maximum anticonvulsant activity was possessed by 1-[5-(α-naphthyl)tetrazol-2-acetyl]-3-(4-methylphenyl)carbamide (**7**). It was observed that substituted tetrazolylacetylcarbamides with α-naphthyltetrazolyl moiety (5−7), in general, possessed greater anticonvulsant activity as compared to carbamides with substituted phenyl tetrazolyl moiety in their structure (**1**−**4**). As is evident from Table II, the protection observed with substituted tetrazolylacetylcarbamides against 24 hours pentylenetetrazol-induced mortality was not found to correspond with their anticonvulsant activity. All substituted tetrazolylacetylcarbamides (**1**−**8**) inhibited *in-vitro* monoamine oxidase activity of rat brain homogenates at a final concentration of 1 mM and the inhibition ranged from 22−44% (Table II). These results have indicated that low monoamine oxidase inhibition and anticonvulsant activity of substituted tetrazolylacetylcarbamides do not correlate.

EXPERIMENTAL

The melting points of 1-(5-aryl-2-acetyltetrazolyl)-3-substituted carbamides were taken in open capillary tubes with partial immersion thermometer and are corrected.

5-Aryltetrazoles.

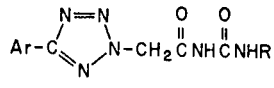
The method of Finnegan *et al* (10) was used for the synthesis of 5-(2-methylphenyl)tetrazole (mp 140−141°; yield 80%) and 5-α-naphthyltetrazole (mp 165°; yield 65%).

1-Chloroacetyl Substituted Carbamides.

The reaction of the appropriate arylamino hydrochloride with potassium cyanate led to the synthesis of substituted carbamides (11)

Table I

Physical Constants of 1-(5-Aryltetrazol-2-ylacetyl)-3-substituted Carbamides



Compound No.	Ar	R	Melting Point	Yield %	Formula	Analysis % Calculated C	H	N	Found C	H	N
1	*o*-$CH_3C_6H_4$	*o*-$CH_3C_6H_4$	191°	54	$C_{18}H_{18}N_6O_2$	61.71	5.14	24.00	61.52	4.96	24.22
2	*o*-$CH_3C_6H_4$	*m*-$CH_3C_6H_4$	202°	58	$C_{18}H_{18}N_6O_2$	61.71	5.14	24.00	61.66	5.13	24.32
3	*o*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	164°	46	$C_{18}H_{18}N_6O_2$	61.71	5.14	24.00	62.05	4.87	23.81
4	*o*-$CH_3C_6H_4$	*o*-$CH_3OC_6H_4$	140°	60	$C_{18}H_{18}N_6O_3$	59.01	4.91	22.95	59.21	4.69	22.88
5	α-$C_{10}H_7$	*o*-$CH_3C_6H_4$	178°	48	$C_{21}H_{18}N_6O_2$	65.28	4.66	21.76	65.45	4.46	21.83
6	α-$C_{10}H_7$	*m*-$CH_3C_6H_4$	137-138°	50	$C_{21}H_{18}N_6O_2$	65.28	4.66	21.76	64.96	4.88	21.39
7	α-$C_{10}H_7$	*p*-$CH_3C_6H_4$	177°	52	$C_{21}H_{18}N_6O_2$	65.28	4.66	21.76	65.51	4.28	21.56
8	α-$C_{10}H_7$	*o*-$CH_3OC_6H_4$	130°	48	$C_{21}H_{18}N_6O_3$	62.68	4.47	20.89	62.87	4.73	21.13

Table II

Anticonvulsant and Monoamine Oxidase Inhibitory Properties of 1-(5-Aryltetrazol-2-ylacetyl)-3-substituted Carbamides

Compound No.	Anticonvulsant Activity Protection, % (a)	Pentylenetetrazol Mortality % (b)	Inhibition of Monoamine Oxidase Activity, % (c)
1	30	60	43.3 ± 0.5
2	10	80	40.5 ± 1.3
3	20	60	28.2 ± 1.0
4	20	50	47.3 ± 1.0
5	40	50	32.7 ± 0.5
6	30	40	22.1 ± 0.2
7	50	10	36.9 ± 1.9
8	30	40	24.1 ± 1.6

(a) Compounds were administered at a dose of 100 mg/kg, i.p., 4 hours before the administration of pentylenetetrazol (90 mg./kg, s.c.). (b) Represents mortality in each group of animals administered pentylenetetrazol during the 24 hour period. (c) Each experiment was done in duplicate and the values are mean values of three separate experiments with ± standard error of the mean. All compounds were used at a final concentration of 1×10^{-3} *M*.

which were refluxed with chloroacetyl chloride (12) to obtain 1-chloroacetyl-3-substituted carbamides.

1-(5-Aryltetrazol-2-ylacetyl)-3-substituted Carbamides (**1—8**).

A mixture of 5-aryltetrazole (0.1 mole), 1-chloroacetyl-3-substituted carbamides (0.1 mole) and triethylamine (0.1 mole) were refluxed in dry benzene (50 ml) for 4 hours. The solution was filtered hot and concentrated under reduced pressure. The solid mass, which separated on cooling, was filtered, dried and recrystallized with benzene-petroleum ether (60 – 80°) to yield 1-(5-aryltetrazol-2-ylacetyl)-3-substituted carbamides where predominantly one isomer is obtained since the reaction was carried out in organic solvent while aqueous medium favors two isomers (13). The presence of the characteristic band of C=O attached to nitrogen (1670 cm^{-1}), C=N (1550 cm^{-1}) and NH group (3300 cm^{-1}) in the infrared spectra provided further support for the structure of 1-(5-aryl-2-acetyl tetrazolyl)-3-substituted carbamides (Table I).

Determination of Anticonvulsant Activity.

Anticonvulsant activity was determined against pentylenetetrazol-induced seizures in albino mice of either sex weighing 25 – 30 g. The mice were divided into groups of ten, keeping the group weights as equal as possible. All substituted tetrazolylcarbamides were suspended in 5% aqueous gum acacia to give a concentration of 0.25% (weight/volume). Each test compound was injected intraperitoneally into a group of ten mice at a dose of 100 mg/kg. Four hours after the administration of the test compounds, the mice were injected with pentylenetetrazol (90 mg/kg, s.c.). This dose of pentylenetetrazol was shown to produce convulsions in almost all untreated mice and the mice exhibited 100% mortality during the period of 24 hours. The mice were then observed for 60 minutes for the occurrence of seizures. An episode of clonic spasm persisting for at least 5 seconds was considered a threshold convulsion. Transient intermittent jerks and tremulousness were not counted. Animals devoid of threshold convulsions during 60 minutes were considered protected. The

number of animals protected in each group was recorded and the anticonvulsant activity of these substituted tetrazolylcarbamides was represented as the percent protection. The mice were then observed for 24 hours and their mortality was recorded.

Determination of Monoamine Oxidase Activity.

Monoamine oxidase activity was determined spectrophotofluorometrically using kynuramine as the substrate. The reaction mixture in a final volume of 2 ml contained 1 ml phosphate buffer (0.5 *M*, *p*H 7.4), suitable aliquots of enzyme preparation, 20 μg of kynuramine, substituted tetrazolylacetylcarbamides in a final concentration of 1×10^{-3} *M*, and water (14).

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