4-(Arylaminothiocarbonyl)-1-(1-*o*-methoxyphenylcarbamido)-ethylpiperazines as Anticonvulsants

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Several 4-(arylaminothiocarbonyl)-1-(1-*o*-methoxyphenylcarbamido)ethylpiperazines were synthesized and evaluated for their anticonvulsant activity against pentylenetetrazol-induced seizures in mice. The ability of substituted piperazines to inhibit *in vitro* respiratory activity of rat brain homogenates was also determined to study their structure-activity relationship.

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Amongst a large number of *N*-(substituted-benzyl)-*N'*-(substituted-benzoyl)piperazine derivatives found to possess CNS depressant properties, *N*-(2-chlorobenzyl)-*N'*-(2-chlorobenzoyl)piperazine was found to be the most potent compound (2). Marked anticonvulsant and anti-reserpine properties have been observed with *N*-(3-amino-4-pyridyl)-*N'*-phenylpiperazines (3). Several *N,N'*-bis-3-(3'-substituted-thiourea)propylpiperazines reported as anticonvulsants (4) were found to exhibit selective inhibition of respiratory activity of rat brain (5). Recently, a series of 4-nitrobenzoyl-1-(1-arylthiocarbamido)ethylpiperazines were synthesized as anticonvulsants and were investigated for their inhibitory effects on the cellular respiratory activity of rat brain homogenates (6). These observations led to the synthesis of 4-(arylaminothiocarbonyl)-1-(1-*o*-methoxyphenylcarbamido)ethylpiperazines. The anticonvulsant activity of these substituted piperazines was investigated against pentylenetetrazol-induced seizures in albino mice. Inhibitory effects of substituted piperazines on NAD-dependent oxidations of pyruvate, α-ketoglutarate and $NADH_2$ were also determined to study the biochemical mechanism of action for their anticonvulsant activity.

The reaction of 1-(2-aminoethyl)-piperazine **1** with *o*-methoxyphenyl isocyanate in absolute ethanol yielded 1-(1-*o*-methoxyphenylcarbamido)ethylpiperazine **2** which on treatment with the appropriate aryl isothiocyanate gave various 4-(arylaminothiocarbonyl)-1-(1-*o*-methoxyphenylcarbamido)ethylpiperazines **3-13**.

All substituted piperazines **3-13** were found to inhibit the *in vitro*, NAD-dependent oxidation of pyruvate, α-ketoglutarate and $NADH_2$ while NAD-independent oxidation of sodium succinate remained unaltered. The degree of inhibition ranged from 30-89% with pyruvate, 25-69% with α-ketoglutarate and 19-83% with $NADH_2$. These results have indicated the selectivity of the inhibition of respiratory activity of rat brain homogenate by substituted piperazines, since the NAD-independent oxidation of sodium succinate was found to be unaltered. Furthermore, the ability of **3-13** to inhibit the oxidation of $NADH_2$, unlike anticonvulsant quinazolones (7,8), provides evidences regarding their possible inactivation of the process of electron transfer in the electron-transport chain by presumably acting at the site of transfer of electrons from $NADH_2$ to flavine adenine dinucleotide (FAD).

All compounds **3-13** exhibited protection against pentylenetetrazol-induced seizures which ranged from 10-80%. Maximum degree of protection was observed with **12** while minimum protection was afforded by **8** and **9**. These studies, in spite of exhibiting selective inhibition of NAD-dependent oxidations, have failed to provide a biochemical basis for the anticonvulsant activity of the substituted piperazines.

EXPERIMENTAL

All compounds were analyzed for their carbon, hydrogen and nitrogen contents. Melting points were taken in open capillary tubes with partial immersion thermometer.

1-(1-*o*-Methoxyphenylcarbamido)ethylpiperazine (**2**).

1-(2-Aminoethyl)piperazine **1** (0.01 mole) and *o*-methoxyphenyl isocyanate (0.01 mole) were mixed in 25 ml. of absolute ethanol and the mixture was refluxed on a steam bath for 2 hours. The reaction mixture was concentrated under reduced pressure. On cooling the solid mass which separated out was filtered, washed with ether, dried and recrystallized from ethanol, m.p. 92°, yield 80%.

Anal. Calcd. for $C_{14}H_{22}N_4O_2$: C, 60.43; H, 7.91; N, 20.14. Found C, 60.67; H, 8.12; N, 20.38.

4-(Arylaminothiocarbonyl)-1-(1-*o*-methoxyphenylcarbamido)ethylpiperazines (**3-13**).

Suitable aryl isothiocyanate (0.01 mole) and 1-(1-*o*-methoxyphenylcarbamido)ethylpiperazine (0.01 mole) were mixed in 20 ml. of dry benzene and the reaction mixture was refluxed on a steam bath for 2 hours. The reaction mixture was concentrated under reduced pressure. On cooling the solid mass which separated out was filtered, washed with ether, dried and recrystallized from dimethylformamide. The various 4-(arylaminothiocarbonyl)-1-(1-*o*-methoxyphenylcarbamido)ethylpiperazines were characterized by their sharp melting points and elemental analyses (Table I). The presence of the characteristic bands -NH (3300 cm^{-1}), C=O (1660 cm^{-1}) and C=S (1510 cm^{-1}) in the infrared spectrum of 4-(4-ethoxyphenylaminothiocarbonyl)-1-(1-*o*-methoxyphenyl-

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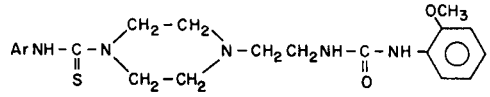
Table I

Physical Constants of 4-(Arylaminothiocarbonyl)-1-(1-*o*-methoxyphenylcarbamido)ethylpiperazines



Compound	Ar	Melting Point	Yield %	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3	C_6H_5	270°	80	$C_{21}H_{27}N_5O_2S$	61.06	6.53	16.94	61.36	6.55	16.71
4	$2\text{-}CH_3C_6H_4$	178°	78	$C_{22}H_{29}N_5O_2S$	61.82	6.79	16.39	61.53	6.58	16.11
5	$3\text{-}CH_3C_6H_4$	174°	75	$C_{22}H_{29}N_5O_2S$	61.82	6.79	16.39	62.00	6.71	16.68
6	$4\text{-}CH_3C_6H_4$	154°	76	$C_{22}H_{29}N_5O_2S$	61.82	6.79	16.39	61.63	6.51	16.40
7	$2,4\text{-}(CH_3)_2C_6H_3$	177°	85	$C_{23}H_{31}N_5O_2S$	62.58	7.02	15.87	62.82	6.99	15.76
8	$2\text{-}OCH_3C_6H_4$	170°	80	$C_{22}H_{29}N_5O_3S$	59.59	6.54	15.80	59.87	6.58	15.99
9	$4\text{-}OCH_3C_6H_4$	187°	83	$C_{22}H_{29}N_5O_3S$	59.59	6.54	15.80	59.35	6.31	16.18
10	$2\text{-}OC_2H_5C_6H_4$	158°	70	$C_{23}H_{31}N_5O_3S$	60.39	6.78	15.31	60.16	6.69	15.43
11	$4\text{-}OC_2H_5C_6H_4$	148°	76	$C_{23}H_{31}N_5O_3S$	60.39	6.78	15.31	60.55	7.00	15.61
12	$4\text{-}ClC_6H_4$	130°	87	$C_{21}H_{26}ClN_5O_2S$	56.31	5.81	15.64	56.52	5.87	15.78
13	$4\text{-}BrC_6H_4$	118°	85	$C_{21}H_{26}BrN_5O_2S$	51.21	5.28	14.22	51.42	5.31	14.19

carbamido)ethylpiperazine (**11**) further supported the chemical structure of **3-13**.

Assay of Respiratory Activity of Rat Brain Homogenate.

The respiratory activity of various substituted piperazines was determined by measuring oxygen consumption by conventional Warburg manometric method at 37° using rat brain homogenates as a source of enzymes and air as the gas phase (6). The final concentration of various substrates, *i.e.*, pyruvate, α-ketoglutarate, reduced nicotinamideadenine dinucleotide ($NADH_2$) and succinate was 10 m*M*. All substituted piperazines **3-13** were used at a final concentration of 2 m*M*.

Anticonvulsant Activity.

The anticonvulsant activity of these compounds **3-13** was determined in albino mice of either sex weight 25-30 g. against pentylenetetrazol-induced seizures (6). The substituted piperazines **3-13** were administered intraperitoneally at a dose of 100 mg./kg. The convulsions were produced by the subcutaneous injection of pentylenetetrazol (90 mg./kg.).

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