Synthesis of 10-(Substituted Phenylhydrazonoacetyl)phenothiazines as Possible Anticonvulsants

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Some 10-(substituted phenylhydrazonoacetyl)phenothiazines were synthesized as possible anticonvulsants. These compounds were investigated for their anticonvulsant activity and inhibitory effects on the oxidation of pyruvic acid by rat brain homogenates.

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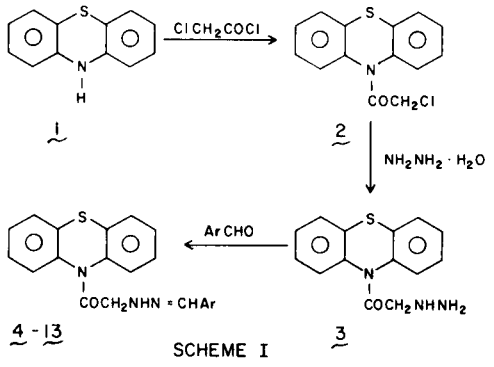
Earlier investigations have revealed that a wide variety of central nervous system (CNS) activities including tranquilizing (2), antispasmodic (3), hypnotic and sedative (4), muscle relaxant (5), and antihistaminic (6) properties are associated with phenothiazine derivatives. Inhibition of certain metabolic processes has been shown to be the property of various CNS depressants (7,8) and a parallelism has been shown to exist between *in vitro* and *in vivo* effects. Furthermore, the structure activity relationship of various pharmacological agents has been shown to be due to their interaction with receptor surfaces (9). In addition, several 10-(1-acetyl-4-arylthiosemicarbazido)phenothiazines and 10-(2-arylimino-3-acetylamino-4-thiazolidonyl)phenothiazines have recently been reported to possess anticonvulsant activity and ability to inhibit respiratory activity of rat brain homogenates (10). These observations prompted the synthesis of some 10-(substituted phenylhydrazonoacetyl)phenothiazines according to the steps outlined in Scheme I.

The reaction of chloroacetyl chloride with phenothiazine **1** yielded 10-chloroacetyl phenothiazine **2**. This compound on refluxing with hydrazine hydrate gave 10-hydrazinoacetyl phenothiazine **3**. The various 10-(substituted phenylhydrazonoacetyl)phenothiazines **4** to **13** were synthesized by the condensation of **3** with suitable aromatic aldehydes.

All 10-(substituted arylhydrazonoacetyl)phenothiazines were investigated for their anticonvulsant activity against pentylenetetrazol-induced seizures in albino mice (10). The degree of protection ranged from 20 to 60% where two compounds, 10-(3,4-dimethoxy phenyl hydrazonoacetyl)phenothiazine (**9**) and 10-(4-*N*,*N*-dimethylamino phenylhydrazonoacetyl)phenothiazine (**12**) afforded 60% protection against pentylenetetrazol-induced seizures. These phenothiazines were also found to inhibit the *in vitro* oxidation of pyruvic acid using rat brain homogenates as the source of the enzyme (10). The degree of inhibition by these phenothiazines at a final concentration of 2 *mM* ranged from 7-65%, where maximum inhibition was observed with 10-(3-methoxy-4-hydroxyphenylhydrazonoacetyl)phenothiazine (**10**).



1 2 3 4-13

SCHEME I

EXPERIMENTAL

All compounds were analyzed for carbon, hydrogen and nitrogen content. Melting points were taken in an open capillary tube with an immersion therometer and are corrected.

10-Chloroacetylphenothiazine (**2**).

A mixture of phenothiazine **1** (0.3 mole) and chloroacetylchloride (0.45 mole) in 100 ml. of dry benzene was refluxed on a steam bath for 4 hours. The benzene was removed under reduced pressure and the crude product was washed several times with water to remove excess of chloroacetyl chloride. The crude **2** (11) thus obtained was recrystallized from benzene; m.p. 114° (reported m.p. 115-116°).

10-Hydrazinoacetylphenothiazine (**3**).

The hydrazine hydrate (99%, 0.45 mole) was added to a solution of **2** (0.3 mole) in 100 ml. of absolute ethanol and the reaction mixture was refluxed for 18 hours on a steam bath. Excess of ethanol was removed under reduced pressure. The crude product **3** (10) thus obtained was recrystallized from ethanol; m.p. 180° (reported m.p. 180°).

10-(Substituted phenylhydrazonoacetyl)phenothiazines (**4** to **13**).

Equimolar quantities of **3** (0.01 mole) and suitable aromatic aldehyde (0.01 mole) in 25 ml. of ethanol containing few drops of acetic acid was refluxed on a steam bath for 6 hours. The reaction mixture was concentrated by distilling off the excess of ethanol under reduced pressure. The solid product thus obtained was recrystallized from ethanol. The various 10-(substituted phenylhydrazonoacetyl)phenothiazines were characterized by their sharp melting points and elemental analyses (Table I).

Anticonvulsant Activity.

The anticonvulsant activity was determined in albino mice by following the method reported earlier (10). The various substituted phenothiazines were injected intraperitoneally at a dose of 100 mg./kg. to evaluate their ability to provide protection against

Table I

Physical Constants of 10-(Substituted phenylhydrazonoacetyl)phenothiazines

Compound No.	Ar	M.p. °C	Yield %	Molecular Formula	Analyses % Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
4	C_6H_5	170	80	$C_{21}H_{17}N_3Os$	70.19	4.73	11.69	70.42	4.61	11.50
5	$2\text{-}HOC_6H_4$	160	60	$C_{21}H_{17}N_3O_2S$	67.20	4.53	11.20	67.31	4.51	11.46
6	$3\text{-}HOC_6H_4$	168	70	$C_{21}H_{17}N_3O_2S$	67.20	4.53	11.20	67.30	4.26	10.89
7	$4\text{-}HOC_6H_4$	210	85	$C_{21}H_{17}N_3O_2S$	67.20	4.53	11.20	67.41	4.67	10.92
8	$4\text{-}CH_3OC_6H_4$	178	82	$C_{22}H_{19}N_3O_2S$	67.86	4.88	10.79	67.63	5.07	10.96
9	$3,4\text{-}(CH_3O)_2C_6H_3$	176	75	$C_{23}H_{21}N_3O_3S$	65.87	5.01	10.02	65.66	5.28	9.85
10	$3\text{-}CH_3O,4\text{-}HOC_6H_3$	177	65	$C_{22}H_{19}N_3O_3S$	65.18	4.93	10.37	65.45	5.01	10.52
11	$4\text{-}O_2NC_6H_4$	285	83	$C_{21}H_{16}N_4O_3S$	62.37	3.96	13.86	62.65	4.18	13.63
12	$4\text{-}(CH_3)_2NC_6H_4$	174	72	$C_{23}H_{22}N_4OS$	68.65	5.47	13.93	68.41	5.67	14.06
13	$4\text{-}ClC_6H_4$	178	85	$C_{21}H_{16}ClN_3OS$	63.87	4.05	10.64	63.99	3.85	10.92

convulsions induced by subcutaneous injection of pentylenetetrazol (90 mg./kg.).

Assay of Respiratory Activity of Rat Brain Homogenates.

The respiratory activity was determined by measuring oxygen consumption by the conventional Warburg manometric method at 37°, with air as the gas phase (10). Rat brain homogenates were used as the source of the enzyme. The final concentrations of sodium pyruvate and 10-(substituted phenylhydrazonoacetyl) phenothiazines used were 10 and 2 *mM*, respectively.

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