Synthesis of 3-Aryl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazones as Possible Anticonvulsants

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Several 3-aryl-4-oxo-thiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazones were synthesized and evaluated for their anticonvulsant activity. Three of these substituted hydrazones provided 80% protection against pentylenetetrazol-induced convulsions in mice.

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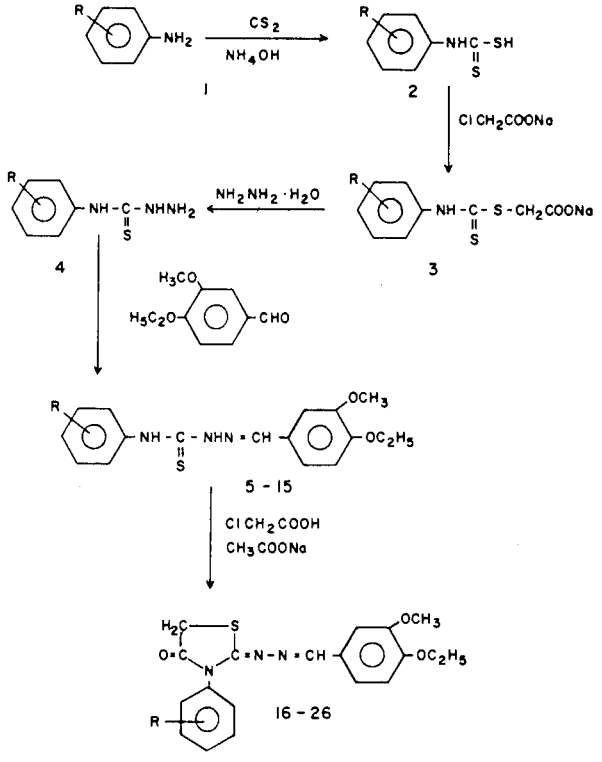
The wide variety of pharmacological properties have been shown to be associated with thiazolidone derivatives. These include anesthetic (1), anticonvulsant (2,3,4) and hypnotic (5) activities. Recent studies have reported reduced locomotor activity, ataxia, hind limb weakness and loss of righting reflex by some substituted thiazolidones (6). Anticonvulsant activity has also been reported in 3-(3,4-dimethoxyphenylethyl)-4-oxothiazolin-2-yl-substituted hydrazones (7). These observations prompted the synthesis of 3-aryl-4-oxo-thiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazones by following the steps outlined in Scheme I.

The reaction of the appropriate aromatic amines **1** with carbon disulphide in presence of concentrated ammonia yielded dithiocarbamates **2**. These compounds on treatment with the aqueous solution of sodium salt of monochloroacetic acid and followed by condensation with hydrazine hydrate gave 4-aryl-3-thiosemicarbazides **4**. The reaction of **4** with 4-ethoxy-3-methoxybenzaldehyde formed 1-(4-ethoxy-3-methoxy)phenyl-4-aryl-3-thiosemicarbazones **5** to **15**, which were cyclized with monochloroacetic acid in the presence of fused sodium acetate to the corresponding 3-aryl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)-phenyl hydrazones **16** to **26**.



SCHEME 1

All the substituted hydrazones were evaluated for their anticonvulsant activity against pentylenetetrazol-induced seizures in albino mice (7). The degree of protection, as a reflection of anticonvulsant activity, ranged from 20 to 80% where 3-(2-methyl)phenyl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazone **17**, 3-(3-methyl)phenyl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazone **18** and 3-(4-ethoxy)phenyl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazone **23**, exhibited 80% anticonvulsant activity.

EXPERIMENTAL

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

4-Aryl-3-Thiosemicarbazides (4).

To an ethanolic solution of the suitable aromatic primary amine (0.25 mole) was slowly added 40 ml. of concentrated ammonium hydroxide (sp. gr. 0.91). The reaction mixture was cooled below 30° and carbon disulphide (15 ml.) was added dropwise during a period of 15 minutes. After one hour, an aqueous solution of sodium salt of monochloroacetic acid (0.25 mole) was added to the reaction mixture and this was followed by the addition of hydrazine hydrate (0.25 mole, 80%). The mixture was cooled overnight in a refrigerator and the crude thiosemicarbazides which separated out were filtered and recrystallized from ethanol. The melting points of all thiosemicarbazides were in agreement with their melting points reported in the literature.

1-(4-Ethoxy-3-Methoxy)phenyl-4-aryl-3-thiosemicarbazones (5-15).

Equimolar quantities of the appropriate thiosemicarbazide **4** (0.05 mole) and 4-ethoxy-3-methoxybenzaldehyde (0.05 mole) in 100 ml. of ethanol was refluxed on water bath for 2 hours. The reaction mixture was concentrated under reduced pressure. The solid mass which separated out on cooling was separated by filtration and recrystallized from ethanol. The various 1-(4-ethoxy-3-methoxy)phenyl-4-aryl-3-thiosemicarbazones, recorded in Table I, were characterized by their sharp melting points and elemental analyses.

Table I

Physical Constants of 1-(4-Ethoxy-3-methoxy)phenyl-4-aryl-3-thiosemicarbazones

Compound No.	R	M.p. °C	Yield %	Molecular Formula	Analyses % Calculated C	H	N	Found C	H	N
5	C_6H_5	186	80	$C_{17}H_{19}N_3O_2S$	62.06	5.77	12.76	62.26	5.46	12.50
6	2-$CH_3C_6H_4$	192	75	$C_{18}H_{21}N_3O_2S$	62.97	6.12	12.24	62.90	6.01	12.51
7	3-$CH_3C_6H_4$	165	90	$C_{18}H_{21}N_3O_2S$	62.97	6.12	12.24	62.88	6.31	12.55
8	4-$CH_3C_6H_4$	180	80	$C_{18}H_{21}N_3O_2S$	62.97	6.12	12.24	62.70	6.28	12.44
9	2-$OCH_3C_6H_4$	178	65	$C_{18}H_{21}N_3O_3S$	60.16	5.84	10.69	59.90	5.44	10.40
10	3-$OCH_3C_6H_4$	200	80	$C_{18}H_{21}N_3O_3S$	60.16	5.84	10.69	60.30	5.65	10.58
11	4-$OCH_3C_6H_4$	176	90	$C_{18}H_{21}N_3O_3S$	60.16	5.84	10.69	60.22	5.75	10.72
12	4-$OC_2H_5C_6H_4$	153	80	$C_{19}H_{23}N_3O_3S$	61.12	6.16	11.26	61.42	6.21	11.50
13	4-$OC_3H_7C_6H_4$	138	75	$C_{20}H_{25}N_3O_3S$	62.01	6.45	10.85	61.82	6.85	10.72
14	4-ClC_6H_4	166	70	$C_{17}H_{18}ClN_3O_2S$	56.12	4.95	11.55	56.50	4.75	11.95
15	C_6H_{11}	165	60	$C_{17}H_{25}N_3O_2S$	60.89	7.45	12.55	60.57	7.40	12.52

Table II

Physical Constants of 3-Aryl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)phenyl Hydrazones

Compound No.	R	M.p. °C	Yield %	Molecular Formula	Analyses % Calculated C	H	N	Found C	H	N
16	C_6H_5	217	60	$C_{19}H_{19}N_3O_3S$	61.78	5.14	11.38	61.70	5.20	11.32
17	2-$CH_3C_6H_4$	140	50	$C_{20}H_{21}N_3O_3S$	62.66	5.48	10.96	62.58	5.44	10.76
18	3-$CH_3C_6H_4$	181	80	$C_{20}H_{21}N_3O_3S$	62.66	5.48	10.96	62.69	5.38	10.98
19	4-$CH_3C_6H_4$	210	60	$C_{20}H_{21}N_3O_3S$	62.66	5.48	10.96	62.63	5.56	10.82
20	2-$OCH_3C_6H_4$	146	50	$C_{20}H_{21}N_3O_4S$	60.15	5.23	10.52	60.15	5.53	10.21
21	3-$OCH_3C_6H_4$	223	70	$C_{20}H_{21}N_3O_4S$	60.15	5.23	10.52	60.2	5.08	10.63
22	4-$OCH_3C_6H_4$	180	80	$C_{20}H_{21}N_3O_4S$	60.15	5.23	10.52	60.33	5.48	10.38
23	4-$OC_2H_5C_6H_4$	185	70	$C_{21}H_{23}N_3O_4S$	61.01	5.56	10.16	60.90	5.23	10.40
24	4-$OC_3H_7C_6H_4$	174	60	$C_{22}H_{25}N_3O_4S$	61.82	5.83	9.83	61.43	5.62	9.70
25	4-ClC_6H_4	154	40	$C_{19}H_{18}ClN_3O_3S$	56.60	4.46	10.40	56.20	4.40	10.32
26	C_6H_{11}	171	50	$C_{19}H_{25}N_3O_3S$	60.80	6.66	11.20	60.75	6.46	11.10

3-Aryl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazones (**16**-**26**).

A mixture of substituted thiosemicarbazone (0.01 mole), monochloroacetic acid (0.01 mole) and fused sodium acetate (0.015 mole) in 15 ml. of glacial acetic acid was refluxed on a free flame for 6 hours. The reaction mixture was poured into ice-cold water and the mixture was stored overnight in a refrigerator. The crude product which separated out was filtered, washed several times with water, dried and recrystallized from ethanol. All compounds were characterized by their sharp melting points and elemental analyses (Table II). The presence of the characteristic bands at 1750 cm^{-1} (C = O) and 1640 cm^{-1} (C = N) and the absence of the characteristic bands for NH-group in the infrared spectra of 3-cyclohexyl-4-oxothiazolin-2-yl(4-ethoxy-3-methoxy)phenyl hydrazone (**26**) provided support for the structure of these substituted hydrazones.

Anticonvulsant Activity.

The anticonvulsant activity was determined in albino mice by following the method reported earlier (7). All test compounds were injected intraperitoneally at a dose of 100 mg./kg. to evaluate their ability to provide protection against convulsions induced by subcutaneous injection of pentylenetetrazol (90 mg./kg.).

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