Synthesis of 2-Substituted Benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)ones as Possible Anticonvulsants

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Several 2-substituted benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)ones were prepared by the condensation of 6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)one with suitable aryl aldehydes as possible anticonvulsants. Amongst these benzimidazoles, two compounds possessed anticonvulsant activity and provided 60% protection against pentylene-tetrazol-induced seizures in mice.

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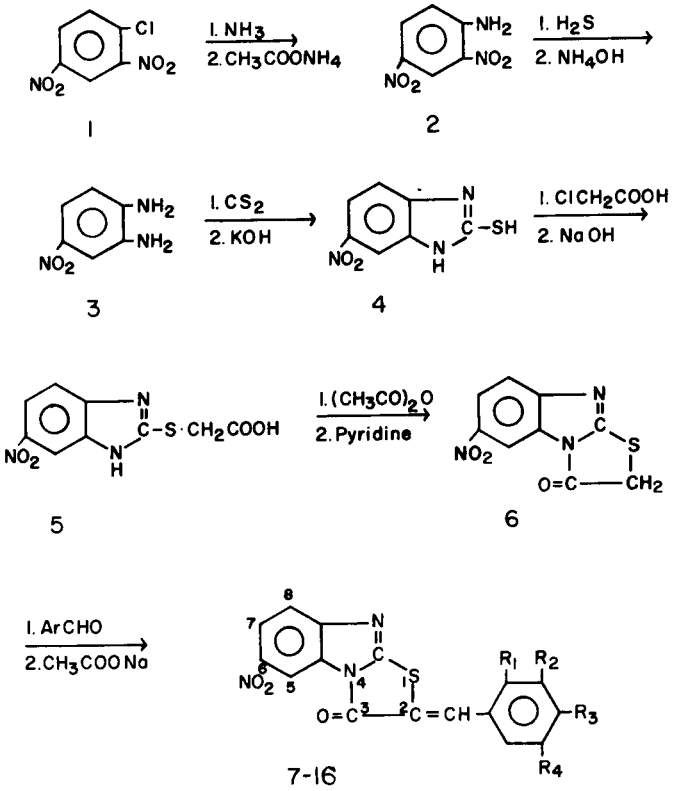
Diverse pharmacological properties have been shown to be associated with benzimidazole derivatives. These include anticonvulsant (1-4), analgesic (5), tranquilizing (6) and paralyzing (7) activities. Furthermore, thiazolidone derivatives have been reported to possess central nervous system (CNS) depressant properties (8,9). These observations prompted synthesis of benzimidazole derivatives having fused thiazolidone moiety at position 2,3 of the imidazole ring. The various 2-substituted benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)ones were synthesized according to steps outlined in Scheme 1.

2,4-Dinitroaniline (**2**), obtained from 2,4-dinitro-1-chlorobenzene (**1**) by reaction of ammonia in the presence of ammonium acetate, was reduced to 1,2-diamino-4-nitrobenzene (**3**) (11) with hydrogen sulfide and ammonium hydroxide and was further treated with carbondisulphide in alkaline medium to give 5-nitro-2-mercapto benzimidazole (**4**) (12). Reactions of **4** with monochloroacetic acid was used to synthesize 5-nitro-2-benzimidazolylthioacetic acid (**5**) (13) which was cyclized with acetic anhydride to yield 6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)one (**6**). The various 2-substituted benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)ones (**7-16**) were obtained by condensation of **6** with the appropriate aromatic aldehydes.



Scheme I

All substituted benzylidene thiazolidones were tested for their anticonvulsant activity in albino mice (14). The anticonvulsant activity ranged from 20-60% where two compounds, 2-(4-benzyloxy)benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)one (**15**) and 2-nitro-4,5-dimethoxybenzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)one (**16**), exhibited 60% anticonvulsant activity against pentylenetetrazol-induced seizures in mice.

EXPERIMENTAL

All compounds were analyzed for their carbon, hydrogen and nitrogen content. Melting points were taken in an open capillary tube with an immersion thermometer and are corrected. Infrared spectra were obtained using Beckman IR-12 Spectrophotometer. All compounds were examined as suspension in nujol mull in the range of 600-4000 cm^{-1}.

2,4-Dinitroaniline (**2**).

A mixture of ammonium acetate (0.4 mole) and 2,4-dinitro-1-chlorobenzene (0.4 mole) was placed in a round bottomed flask, fitted with a reflux condenser and inlet tube which was just above the surface of the reaction mixture. The flask was heated on an oil bath at 170° and ammonia gas was passed into the reaction mixture through a bubble counter at the rate of 3-4 bubbles per second for 6 hours. The reaction mixture was cooled and 150 ml. of water was added. The mixture was then heated to boiling and filtered while hot. The crude **2** (10) thus obtained was recrystallized from ethanol, m.p. 178° (reported m.p. 180°).

1,2-Diamino-4-nitrobenzene (**3**).

A solution of **2** (0.3 mole) in 600 ml. of 95% ethanol and 300 ml. of concentrated ammonium hydroxide (sp. gr. 0.90) was taken in a one liter 3-necked flask fitted with mechanical stirrer, a reflux

Table I

Physical Constants of 2-Substituted Benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)ones

Compound No.	R_1	R_2	R_3	R_4	M.p. °C	Yield %	Molecular formula	Analyses % Calculated C	H	N	Found C	H	N
7	H	H	H	H	295	85	$C_{16}H_9N_3O_3S$	59.44	2.78	13.00	59.46	2.75	13.08
8	H	H	OCH_3	H	267	84	$C_{17}H_{11}N_3O_4S$	57.78	3.12	11.89	57.78	3.16	11.85
9	H	OCH_3	OH	H	272	76	$C_{17}H_{11}N_3O_5S$	55.28	2.98	11.38	55.32	2.92	11.41
10	H	OCH_3	OCH_3	H	230	72	$C_{18}H_{13}N_3O_5S$	56.39	3.39	10.96	56.33	3.26	10.88
11	H	OCH_3	OC_2H_5	H	215	65	$C_{19}H_{15}N_3O_5S$	57.43	3.78	10.55	57.52	3.71	10.49
12	H	H	Cl	H	255	82	$C_{16}H_8ClN_3O_3S$	53.70	2.23	11.75	53.58	2.12	11.54
13	H	Cl	Cl	H	256	70	$C_{16}H_7Cl_2N_3O_3S$	48.98	1.78	10.71	48.88	1.57	10.67
14	H	OCH_2Ph	H	H	204	60	$C_{23}H_{15}N_3O_4S$	64.33	3.49	9.79	64.37	3.51	9.64
15	H	H	OCH_2Ph	H	243	66	$C_{23}H_{15}N_3O_4S$	64.33	3.49	9.79	64.32	3.47	9.89
16	NO_2	H	OCH_3	OCH_3	300	62	$C_{18}H_{12}N_4O_7S$	50.46	2.80	13.08	50.41	2.83	13.15

condenser, thermometer and inlet tube extending to the bottom of the flask. The mixture was heated to 45° with stirring and hydrogen sulfide was passed into the reaction mixture while its temperature was maintained between 45-50°. During this period **2** dissolved slowly to form an intensely red-colored solution. The reaction was completed when all the yellow particles had disappeared. After one hour, the reaction mixture was placed overnight in a refrigerator and the small deeply red-colored crystals of **3** (11) which separated were filtered, washed with 100 ml. of cold water, dried and recrystallized from ethanol, m.p. 197° (reported m.p. 197-198°).

5-Nitro-2-mercaptobenzimidazole (**4**).

The method of James and Turner (12) was used for the synthesis of **4**. A mixture of **3** (0.15 mole), carbon disulfide (0.20 mole), 300 ml. of 95% ethanol and 10 g. of potassium hydroxide in 60 ml. of water was refluxed for 3 hours on a water bath. The excess of carbon disulfide and ethanol were removed under reduced pressure. The product was acidified with acetic acid and the precipitate was filtered, washed with water and recrystallized from ethanol, m.p. 280-281° (reported m.p. 282°).

5-Nitro-2-benzimidazolylthioacetic acid (**5**).

The method of Rebstock, *et al.*, (13) was used for the synthesis of **5**. Equal molar quantities of **4** (0.1 mole) and monochloroacetic acid (0.1 mole) were refluxed for 2 hours in a 2 *N* aqueous sodium hydroxide solution. The solid mass which separated on cooling the solution was filtered and made acid to congo red with dilute hydrochloric acid. The precipitate was filtered, dissolved in a minimum volume of boiling ethanol and decolorized with charcoal. The filtered hot solution was diluted with water until a permanent cloudiness was obtained and kept in a refrigerator over night. The crystals of **5** were filtered and dried, m.p. 190° (reported m.p. 191-192°).

6-Nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)one (**6**).

To a mixture of acetic anhydride (15 ml.) and pyridine (22.5 ml.) was added **5** (0.06 mole) and the mixture was heated on a water bath for 5 minutes (14). The reaction mixture was kept over night in a refrigerator and the brown crystals which separated were filtered and recrystallized from benzene-alcohol, m.p. 220°, yield 70%; ir: (Nujol mull), C=N (1605 cm^{-1}) and C=O (1740 cm^{-1}).

Anal. Calcd. for $C_9H_5N_3O_3S$: C, 45.95; H, 2.12; N, 17.87. Found: C, 45.84; H, 2.16; N, 17.82.

2-Substituted-benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)ones (**7-16**).

A mixture of **6** (0.003 mole), suitable aldehyde (0.003 mole), fused sodium acetate (0.003 mole) and glacial acetic acid (30 ml.) was heated under reflux on an oil bath at 130-140° for 4 hours. On cooling, a yellow solid which separated was filtered, washed with water to remove sodium acetate and recrystallized from xylene. The physical properties of **7-16** are recorded in Table I. The frequencies and assignments of these compounds observed in their ir spectra are recorded in Table II. The OH stretching for **9** was 3460 cm^{-1}.

Anticonvulsant Activity.

The anticonvulsant activity was determined in mice by following the method reported earlier (15). All test compounds were used intraperitoneally at a dose of 100 mg./kg to evaluate their ability to provide protection against convulsions induced by subcutaneous administration of pentylenetetrazol (90 mg./kg).

Table II

Infrared Spectral Data of 2-Substituted Benzylidene-6-nitrothiazolo[3,2-*a*]benzimidazol-3(2*H*)ones

Compound Number	C=O (cm^{-1})	C=C and C=N (cm^{-1})	C-NO_2 (cm^{-1})
7	1730	1600	1350, 1510
8	1735	1600	1350, 1530
9	1730	1585	1345, 1535
10	1720	1585	1345, 1520
11	1740	1600	1360, 1540
12	1725	1610	1345, 1530
13	1740	1615	1350, 1515
14	1730	1615	1380, 1520
15	1725	1600	1345, 1525
16	1740	1615	1350, 1570

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