Potential Anticonvulsants. IX. Some Isatin Hydrazones and Related Compounds

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A number of hydrazines, hydrazides, and related compounds have been condensed with isatin and substituted isatins. The anticonvulsant activity of these compounds is reported.

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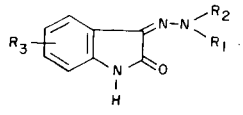
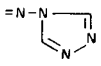
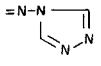
It has been reported [1-7] that a number of compounds derived from isatin (I) exhibit anticonvulsant activity in the maximal electroshock seizure test [8] and/or the pentylenetetrazol seizure threshold test [8]. Several hydrazones of indole-3-carboxaldehyde have also been reported [9] to have anticonvulsant activity in these screens.

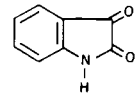
Table I

Isatin Hydrazones and Related Compounds

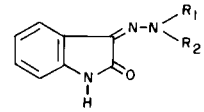


R_1	R_2	R_3	Mp °C [a]	Formula	Analysis, % Calcd./Found C	H	Anticonvulsant Activity, mg/kg [b] MES	Met
H	H	H	222-223 [c]	$C_8H_7N_3O$ [d]	—	—	NA [e]	300
H	H	1-$CH_2C_6H_5$	125-126 [f]	$C_{15}H_{13}N_3O$ [d]	—	—	NA [e]	300
CH_3	H	H	175-176	$C_9H_9N_3O$	61.70 61.69	5.18 5.13	100	300 [g]
CH_3	H	5-Br	218-219	$C_9H_8BrN_3O$	42.53 42.27	3.17 3.15	NA [e]	NA [e]
CH_3	H	4-Cl	222-223	$C_9H_8ClN_3O$	51.55 51.65	3.85 3.75	600 [g]	NA [e]
CH_3	H	5-Cl	203-204	$C_9H_8ClN_3O$	51.55 51.54	3.85 3.89	600 [g]	NA [e]
CH_3	H	7-Cl	195-196	$C_9H_8ClN_3O$	51.55 51.37	3.85 3.61	NA [e]	NA [e]
CH_3	H	1-CH_3	101-102	$C_{10}H_{11}N_3O$	63.47 63.19	5.86 5.75	300 [g]	NA [e]
CH_3	H	5-CH_3	201-202	$C_{10}H_{11}N_3O$	63.47 63.71	5.86 5.65	300	NA [e]
CH_3	H	7-CH_3	224-225	$C_{10}H_{11}N_3O$	63.47 63.41	5.86 5.79	300	600 [g]
CH_3	H	5-NO_2	229-230	$C_9H_8N_4O_3$	49.09 49.01	3.66 3.79	NA [e]	NA [e]
CH_3	H	4,7-Cl_2	191-192	$C_9H_7Cl_2N_3O$	44.28 44.01	2.89 3.01	NA [e]	NA [e]
CH_3	H	5,7-$(CH_3)_2$	218-219	$C_{11}H_{13}N_3O$	65.00 65.27	6.45 6.44	NA [e]	NA [e]
CH_3	H	4-Cl-7-CH_3O	176-177	$C_{10}H_{10}ClN_3O_2$	50.11 50.02	4.21 4.33	NA [e]	600
		H	225-226	$C_{10}H_7N_5O$	56.33 56.25	3.31 3.36	300 [h]	NA [e]
		5-NO_2	176-177	$C_{10}H_6N_6O_2$ [i]	43.48 43.88	2.92 2.88	NA [e,j]	NA [e,j]

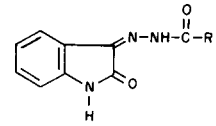
In view of these observations it was decided to prepare a series of isatin-3-hydrazones (II) and related compounds for screening as potential anticonvulsants.



I



II

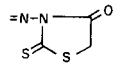
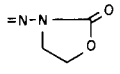


III

Isatin and a number of substituted isatins were condensed with a variety of mono and 1,1-disubstituted hydrazines, hydrazides, and other related compounds to give, as shown in Table I, compounds such as II and III. the results for these compounds in the maximal electroshock seizure test (MES) [8] and the pentylenetetrazol seizure threshold test (Met) [8] are also shown in Table I.

Compounds derived from isatin and methylhydrazine (II, R_1 = H, R_2 = CH_3) and from isatin and 1,1-dimethylhydrazine (II, R_1 = H, R_2 = CH_3) were active at 100 mg/kg in the MES screen and the former compound was also active at 300 mg/kg in the Met screen. In contrast the hydrazone derived from isatin and phenylhydrazine (II, R_1 = H, R_2 = C_6H_5) was active at 100 mg/kg in the Met screen and inactive in the MES screen. Generally the introduction of a substituent into the isatin portion of the molecule caused a decrease or loss of activity. An exception is the 1,1-diphenylhydrazone of 5-chloroisatin which was very active in the

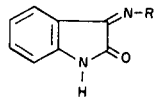
Table I continued

R_1	R_2	R_3	Mp °C [a]	Formula	Analysis, % Calcd./Found C	H	Anticonvulsant Activity, mg/kg [b] MES	Met
CH_3	CH_3	H	124-125	$C_{10}H_{11}N_3O$ [k]	63.47 63.69	5.86 6.02	100 [g,l]	300 [g,l]
CH_3	CH_3	5-Br	199-200	$C_{10}H_{10}BrN_3O$	44.79 44.72	3.76 3.69	600 [g]	NA [e]
CH_3	CH_3	4-Cl	273-274	$C_{10}H_{10}ClN_3O$	55.70 53.68	4.51 4.31	300 [g]	300 [g]
CH_3	CH_3	5-Cl	183-184	$C_{10}H_{10}ClN_3O$	53.70 53.77	4.51 4.54	300 [g]	600 [j]
CH_3	CH_3	6-Cl	146-147	$C_{10}H_{10}ClN_3O$	53.70 53.69	4.51 4.49	600 [j]	600 [j]
CH_3	CH_3	7-Cl	187-188	$C_{10}H_{10}ClN_3O$	53.70 53.91	4.51 4.73	NA [e]	600
CH_3	CH_3	5-CH_3	148-149	$C_{11}H_{13}N_3O$	65.00 65.06	6.45 6.49	300 [g]	NA [e]
CH_3	CH_3	7-CH_3	190-191	$C_{11}H_{13}N_3O$	65.00 64.91	6.45 6.34	600	600
CH_3	CH_3	5-NO_2	235-236	$C_{10}H_{10}N_4O_3$	51.28 51.33	4.30 4.27	NA [e]	NA [e]
CH_3	CH_3	4,7-Cl_2	213-214	$C_{10}H_9Cl_2N_3O$	46.53 46.72	3.51 3.49	600	300
CH_3	CH_3	5,7-$(CH_3)_2$	207-208	$C_{12}H_{15}N_3O$	66.33 66.14	6.96 6.69	NA [e]	NA [e]
		H	203-205	$C_{11}H_7N_3S_2O_2$	47.64 47.78	2.54 2.64	NA [e]	NA [e]
$COCH_2CN$	H	H	198-199	$C_{11}H_8N_4O_2$	57.89	3.53	NA [e]	NA [e]
		H	166-168	$C_{11}H_9N_3O_3$ [m]	57.14 56.77	3.92 4.22	600	NA [e]

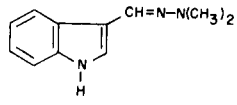
Met screen. None of the compounds derived from hydrazides III showed any appreciable activity.

A number of imines of isatin, obtained from the condensation of isatin and primary amines, IV were screened and found to be, in general, inactive in both screens. Several of these compounds are shown in Table II.

It is of interest to note that the 1,1-dimethylhydrazone of indole-3-carboxaldehyde (V) had the same activity [9] as the corresponding hydrazone (III, R_1 = H, R_2 = CH_3) in the isatin series. Other correlations between the two series are not as marked and no obvious structure to activity relationships appear to exist.



IV



V

EXPERIMENTAL [10]

Condensation of Isatin with Hydrazines and Related Compounds.

The compounds in Table I were prepared by heating a mixture of the isatin (0.01 mole) and the hydrazine (0.01 mole) in 30-50 ml of absolute ethanol on the steam bath for 30-60 minutes. After cooling, standing and in a few cases partial evaporation the solid products were collected by filtration and recrystallized from ethanol. A similar condensation of isatin and imines gave the imines shown in Table II.

Table I continued

R_1	R_2	R_3	Mp °C [a]	Formula	Analysis, % Calcd./Found C	H	Anticonvulsant Activity, mg/kg [b] MES	Met
-$(CH_2)_4$-		H	142-143	$C_{12}H_{13}N_3O$ [n]	66.96 66.78	6.09 6.30	600 [g]	600 [g]
-$(CH_2)_2$-O-$(CH_2)_2$-		H	186-188	$C_{12}H_{13}N_3O_2$	62.32 62.44	5.67 5.68	300	300
-$(CH_2)_2$-O-$(CH_2)_2$-		5-Br	208-209	$C_{12}H_{12}BrN_3O_2$	46.47 46.67	3.90 3.92	NA [e]	NA [e]
-$(CH_2)_2$-O-$(CH_2)_2$-		4-Cl	148-149	$C_{12}H_{12}ClN_3O_2$	54.24 54.20	4.55 4.50	300 [h]	NA [e]
-$(CH_2)_2$-O-$(CH_2)_2$-		7-Cl	180-181	$C_{12}H_{12}ClN_3O_2$	54.24 54.30	4.55 4.60	NA [e]	NA [e]
-$(CH_2)_2$-O-$(CH_2)_2$-		1-CH_3	116-118	$C_{13}H_{15}N_3O_2$	63.66 63.85	6.17 6.16	NA [e,j]	NA [e,j]
-$(CH_2)_2$-O-$(CH_2)_2$-		5-CH_3	214-215	$C_{13}H_{15}N_3O_2$	63.66 63.67	6.16 6.24	NA [e]	NA [e]
-$(CH_2)_2$-O-$(CH_2)_2$-		7-CH_3	183-184	$C_{13}H_{15}N_3O_2$	63.66 63.73	6.16 6.43	600	600
-$(CH_2)_2$-O-$(CH_2)_2$-		5-NO_2	237-238	$C_{12}H_{12}N_4O_4$	52.17 52.21	4.38 4.41	NA [e]	NA [e]
-$(CH_2)_2$-O-$(CH_2)_2$-		4-Cl-7-CH_3O	216-217	$C_{13}H_{14}ClN_3O_3$	52.80 52.82	4.77 4.66	NA [e]	600
-$(CH_2)_2$-O-$(CH_2)_2$-		5,7-$(CH_3)_2$	184-185	$C_{14}H_{17}N_3O_2$	64.84 64.73	6.61 6.42	600 [j]	300 [g]
$(CH_3)C$	H	H	164-165	$C_{12}H_{15}N_3O$	66.33 66.47	6.96 6.99	600	NA [e]
2-Pyridyl	H	H	293-294 [o]	$C_{13}H_{12}N_4O$	—	—	NA [e]	NA [e]
-$(CH_2)_5$-		H	141-142	$C_{13}H_{15}N_3O$	68.10 68.14	6.59 6.58	600	600
-$(CH_2)_5$-		5-CH_3	196-197	$C_{14}H_{17}N_3O$	69.11 69.16	7.04 7.10	NA [e]	NA [e]

Table I continued

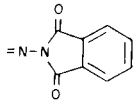
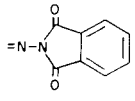
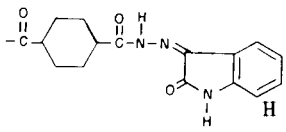
R_1	R_2	R_3	Mp °C [a]	Formula	Analysis, % Calcd./Found C	H	Anticonvulsant Activity, mg/kg [b] MES	Met
-$COCH_2$-3-Pyridyl	H	H	237-238	$C_{15}H_{12}N_4O_2$	64.28 63.99	4.32 4.45	NA [e]	NA [e]
-C_6H_5	H	H	213-214 [p]	$C_{14}H_{11}N_3O$	—	—	NA [e]	100
CH_2CH_2CN	-CH_2CH_2CN	H	157-158	$C_{14}H_{13}N_5O$	62.91 62.70	4.90 5.01	NA [e,h]	NA [e,h]
-$(CH_2)_6$-		H	134-135	$C_{14}H_{17}N_3O$	69.11 69.21	7.04 7.03	600	NA [e]
2-benzothiazolyl	H	H	238-239	$C_{15}H_{10}N_4SO$	61.20 61.32	3.42 3.40	NA [e]	NA [e]
2,4-$C_6H_3(NO_2)_2$	CH_3	H	218-219	$C_{15}H_{11}N_5O_5$	52.79 5.273	3.25 3.33	NA [e]	NA [e]
-CO-4-pyridyl	H	H	296-297	$C_{14}H_{10}N_4O_2$	63.15 63.15	3.79 3.80	600 [g]	600 [g]
-C_6H_5	CH_3	H	172-174	$C_{15}H_{13}N_3O$	71.69 71.93	5.21 5.20	NA [e]	NA [e]
-C_6H_5	CH_3	5-Cl	208-209	$C_{15}H_{12}ClN_3O$	63.05 63.35	4.23 4.13	NA [e]	NA [e]
-C_6H_5	CH_3	5-CH_3	186-187	$C_{16}H_{15}N_3O$	72.43 72.53	5.70 5.69	NA [e]	NA [e]
-C_6H_5	CH_3	5-NO_2	264-265	$C_{15}H_{12}N_4O_3$	60.80 60.85	4.08 4.02	NA [e]	NA [e]
-$CH(CH_3)$-$(CH_2)_3$-$(CH_3)CH$-		H	179-180	$C_{15}H_{19}N_3O$	70.01 69.95	7.44 7.69	NA [e]	NA [e]
		H	265-267	$C_{16}H_9N_3O_3$	65.98 65.89	3.11 3.14	NA [e]	NA [e]
		5-Cl	232-233	$C_{16}H_8ClN_3O_3$	59.00 59.17	2.48 2.00	NA [e]	NA [e]
COC_6H_3-2-OH-3-CH_3	H	H	323-325	$C_{16}H_{13}N_3O_3$	64.08 64.80	4.44 4.37	NA [e]	NA [e]
-$CH_2CH_2C_6H_5$	H	H	158-159	$C_{16}H_{15}N_3O$	72.43 72.14	5.70 5.79	NA [e]	NA [e]
-$CO(CH_2)_2C_6H_4$-4-NO_2	H	H	224-227	$C_{17}H_{14}N_4O_4$	60.35 60.25	4.17 4.07	NA [e]	NA [e]
C_6H_5	-$CH_2CH_2CH_3$	H	162-164	$C_{17}H_{17}N_3O$ [g]	73.09 73.11	6.14 6.07	NA [e]	NA [e]
-$COCH_2$-3-indolyl	H	H	252-254 [r]	$C_{18}H_{14}N_4O_2$	—	—	NA [e,s]	NA [e,s]
-$CO(CH_2)_3C_6H_5$	H	H	199-200	$C_{18}H_{17}N_3O_2$	70.34 70.33	5.58 5.49	NA [e]	NA [e]
-C_6H_5	-C_6H_5	H	245-246	$C_{20}H_{15}N_3O$	76.66 76.57	4.82 4.87	NA [e]	NA [e]
-C_6H_5	-C_6H_5	5-Cl	305-306	$C_{20}H_{15}ClN_3O$	69.06 68.97	4.06 4.12	600 [g]	30 [h]
-C_6H_5	-C_6H_5	6-Cl	242-244	$C_{20}H_{14}ClN_3O$	69.06 69.26	4.06 4.17	NA [e,h]	600 [g]
-C_6H_5	-C_6H_5	7-CH_3	239-240	$C_{21}H_{17}N_3O$	77.04 77.21	5.23 5.17	NA [e]	NA [e]
-$CH_2C_6H_5$	-$CH_2C_6H_5$	H	148-149	$C_{22}H_{19}N_3O$	77.39 77.37	5.61 5.56	NA [e]	NA [e]
	H	H	>340	$C_{24}H_{22}N_6O_4$ [t]	62.87 62.52	4.84 4.79	NA [e]	NA [e]

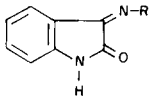
Table I continued

R_1	R_2	R_3	Mp °C [a]	Formula	Analysis, % Calcd./Found C	H	Anticonvulsant Activity, mg/kg [b] MES	Met
6-Cl-4-quinazolinyl	H	H	310-320 [v]	$C_{16}H_{10}ClN_5O$ [v]	59.36	3.11	NA [e]	NA [e]
					59.66	3.37		
7-Cl-4-quinolinyl	H	H	298-299	$C_{17}H_{11}ClN_4O$	63.26	3.44	NA [e]	NA [e]
					63.23	3.49		
$-SO_2C_6H_4-CH_3$-4	H	H	203-206 [w]	$C_{15}H_{13}N_3SO_3$	—	—	NA [e]	600
2-quinolinyl	H	H	271-272	$C_{17}H_{12}N_4O$ [x]	70.82	4.20	NA [e]	NA [e]
					70.82	4.26		
$-COCH_2C_6H_4-NO_2$-4	H	H	256-257	$C_{16}H_{12}N_4O_4$	59.26	3.73	NA [e]	NA [e]
					59.06	3.75		
$-C_6H_5NO_2$-2	H	H	293-295 [y]	$C_{14}H_{10}N_4O_3$	—	—	NA [e]	NA [e]
$COC_6H_4NO_2$-2	H	H	250-251 [z]	$C_{15}H_{10}N_4O_4$	—	—	NA [e]	NA [e]
$-C_6H_5NO_2$-2	H	1-$COCH_3$	238-239 [aa]	$C_{15}H_{12}N_4O_4$	—	—	NA [e]	NA [e]
$-COCH_3$	H	H	234-235 [bb]	$C_{10}H_9N_3O_2$	—	—	NA [e]	NA [e]
$COCH_3$	H	6,7-$(CH_3)_2$	247-248	$C_{12}H_{13}N_3O_2$	62.32	5.66	NA [e]	NA [e]
					62.38	5.68		
$-C_6F_5$	H	H	231-233 [cc]	$C_{14}H_6F_5N_3O$	—	—	NA [e]	NA [e]

[a] Recrystallized from ethanol, melting point uncorrected, spectral data consistent with structure. [b] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institute of Health. The standard screening protocal of the group was followed. MES = maximal electroshock seizure screen. Met = pentylenetetrazol seizures threshold test. [c] Literature [11] mp 219°. [d] Prepared by H. Pajouhesh [12]. [e] NA = No activity at 600 mg/kg. [f] Literature [13] mp 124°. [g] Toxic at this dose. [h] Toxic at 600 mg/kg. [i] Analysis for $C_{10}H_6N_6O_3 \cdot H_2O$. [j] Toxic at 300 mg/kg. [k] N, Calcd.: 22.21. Found: 22.14. [l] MES ED_{50} 59.25, Met ED_{50} 90.93, TD_{50} 88.47. [m] N, Calcd.: 18.18. Found: 18.17. [n] N, Calcd: 19.52. Found: 19.44. [o] Literature [14] mp 293-294°. [p] Literature [15] mp 211°. [q] Compound prepared in this laboratory by M. Rajopadhye (unpublished results). [r] Literature [14] mp 251-254°. [s] See reference [9]. [t] N, Calcd.: 18.33. Found: 17.93. [u] Could not be adequately purified. [v] N, Calcd.: 21.63. Found: 20.80. [w] Literature [16] mp 207-209°. [x] N, Calcd.: 19.44. Found: 19.31. [y] Literature [14] mp 294-295°. [z] Literature [14] mp 250-251°. [aa] Literature [14] mp 238-239°. [bb] Literature [17] mp 236-238°. [cc] Literature [14] mp 232-233°.

Table II

Isatin Imines [a]



R	Mp, °C [c]	Formula	Analysis, % Calcd./Found C	H
3-Pyridyl	227-228	$C_{13}H_9N_3O$	69.44	4.06
			69.34	3.92
C_6HF_4-2,3,4,5	197-198	$C_{14}H_6F_4N_2O$	57.15	2.06
			57.08	1.97
$C_6H_3(CH_2)_3$-2,4	196-197	$C_{16}H_{14}N_2O$ [d]	76.78	5.64
			76.99	5.64
3-Quinolyl	303-304	$C_{17}H_{11}N_3O$ [e,f,g]	73.12	4.21
			73.52	4.22
5-Isoquinolyl	257-258	$C_{17}H_{11}N_3O$	74.71	4.06
			74.50	4.16

[a] In addition to the imines in this table, imines from isatin and *o*-aminobenzhydrazide [14], 3-aminocarbazole [14], 3-amino-4-ethylcarbazole [14], cyclopentylamine [14], 2-phenylaniline [14], 4-acetylaniline [1], 4-methoxyaniline [18], 3-(2-aminoethyl)indole [b] [16], and 3,4-dimethylaniline [19] were screened for anticonvulsant activity. Except as noted below none of these imines were active at 600 mg/kg in the MES or Met screen. [b] Active at 600 mg/kg in Met screen. [c] Recrystallized from ethanol. Analyses by Spang Microanalytical Laboratory. [d] Active at 300 mg/kg in Met screen. [e] Analysis for 0.33 H_2O. [f] Active at 600 mg/kg in MES screen. [g] N, Calcd. for $C_{17}H_{11}N_3O \cdot 0.33H_2O$: 15.05. Found: 15.01.

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