

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.

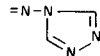
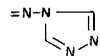
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It has been reported [1-7] that a number of compounds derived from isatin (I) exhibit anticonvulsant activity in the maximal electroshock seizure test [8] and/or the penty-

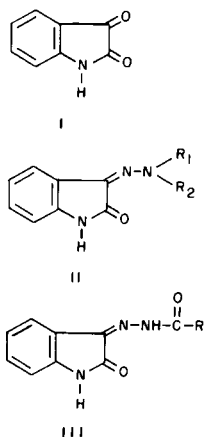
enetetrazol seizure threshold test [8]. Several hydrazones of indole-3-carboxaldehyde have also been reported [9] to have anticonvulsant activity in these screens.

Table I

Isatin Hydrazones and Related Compounds

R ₁	R ₂	R ₃	Mp °C [a]	Formula	Analysis, %		Anticonvulsant Activity, mg/kg [b]	
					Calcd./Found C	H	MES	Met
H	H	H	222-223 [c]	C ₈ H ₇ N ₃ O [d]	—	—	NA [e]	300
H	H	1-CH ₂ C ₆ H ₅	125-126 [f]	C ₁₅ H ₁₃ N ₃ O [d]	—	—	NA [e]	300
CH ₃	H	H	175-176	C ₉ H ₉ N ₃ O	61.70 61.69	5.18 5.13	100	300 [g]
CH ₃	H	5-Br	218-219	C ₉ H ₈ BrN ₃ O	42.53 42.27	3.17 3.15	NA [e]	NA [e]
CH ₃	H	4-Cl	222-223	C ₉ H ₈ ClN ₃ O	51.55 51.65	3.85 3.75	600 [g]	NA [e]
CH ₃	H	5-Cl	203-204	C ₉ H ₈ ClN ₃ O	51.55 51.54	3.85 3.89	600 [g]	NA [e]
CH ₃	H	7-Cl	195-196	C ₉ H ₈ ClN ₃ O	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 ₃ O	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 ₃ O	63.47 63.71	5.86 5.65	300	NA [e]
CH ₃	H	7-CH ₃	224-225	C ₁₀ H ₁₁ N ₃ O	63.47 63.41	5.86 5.79	300	600 [g]
CH ₃	H	5-NO ₂	229-230	C ₉ H ₈ N ₄ O ₃	49.09 49.01	3.66 3.79	NA [e]	NA [e]
CH ₃	H	4,7-Cl ₂	191-192	C ₉ H ₇ Cl ₂ N ₃ O	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 ₃ O	65.00 65.27	6.45 6.44	NA [e]	NA [e]
CH ₃	H	4-Cl-7-CH ₃ O	176-177	C ₁₀ H ₁₀ ClN ₃ O ₂	50.11 50.02	4.21 4.33	NA [e]	600
		H	225-226	C ₁₀ H ₇ N ₃ O	56.33 56.25	3.31 3.36	300 [h]	NA [e]
		5-NO ₂	176-177	C ₁₀ H ₆ N ₃ O ₂ [i]	43.48 43.88	2.92 2.88	NA [e,j]	NA [e,j]

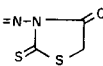
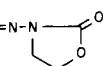
In view of these observations it was decided to prepare a series of isatin-3-hydrazones (II) and related compounds for screening as potential anticonvulsants.



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

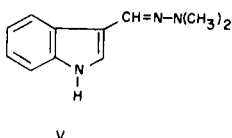
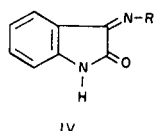
Table I continued

R_1	R_2	R_3	Mp °C [a]	Formula	Analysis, %		Anticonvulsant	
					Calcd./Found C	H	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.



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, %		Anticonvulsant	
					Calcd./Found C	H	Activity, mg/kg [b] MES	Met
(CH ₂) ₄		H	142-143	C ₁₂ H ₁₃ N ₃ O [n]	66.96	6.09	600 [g]	600 [g]
					66.78	6.30		
(CH ₂) ₂ -O-(CH ₂) ₂		H	186-188	C ₁₂ H ₁₃ N ₃ O ₂	62.32	5.67	300	300
					62.44	5.68		
(CH ₂) ₂ -O-(CH ₂) ₂		5-Br	208-209	C ₁₂ H ₁₂ BrN ₃ O ₂	46.47	3.90	NA [e]	NA [e]
					46.67	3.92		
(CH ₂) ₂ -O-(CH ₂) ₂		4-Cl	148-149	C ₁₂ H ₁₂ ClN ₃ O ₂	54.24	4.55	300 [h]	NA [e]
					54.20	4.50		
(CH ₂) ₂ -O-(CH ₂) ₂		7-Cl	180-181	C ₁₂ H ₁₂ ClN ₃ O ₂	54.24	4.55	NA [e]	NA [e]
					54.30	4.60		
(CH ₂) ₂ -O-(CH ₂) ₂		1-CH ₃	116-118	C ₁₃ H ₁₃ N ₃ O ₂	63.66	6.17	NA [e,j]	NA [e,j]
					63.85	6.16		
(CH ₂) ₂ -O-(CH ₂) ₂		5-CH ₃	214-215	C ₁₃ H ₁₃ N ₃ O ₂	63.66	6.16	NA [e]	NA [e]
					63.67	6.24		
(CH ₂) ₂ -O-(CH ₂) ₂		7-CH ₃	183-184	C ₁₃ H ₁₃ N ₃ O ₂	63.66	6.16	600	600
					63.73	6.43		
(CH ₂) ₂ -O-(CH ₂) ₂		5-NO ₂	237-238	C ₁₂ H ₁₂ N ₄ O ₄	52.17	4.38	NA [e]	NA [e]
					52.21	4.41		
(CH ₂) ₂ -O-(CH ₂) ₂		4-Cl-7-CH ₃ O	216-217	C ₁₃ H ₁₄ ClN ₃ O ₃	52.80	4.77	NA [e]	600
					52.82	4.66		
(CH ₂) ₂ -O-(CH ₂) ₂		5,7-(CH ₃) ₂	184-185	C ₁₄ H ₁₇ N ₃ O ₂	64.84	6.61	600 [j]	300 [g]
					64.73	6.42		
(CH ₃)C	H	H	164-165	C ₁₂ H ₁₃ N ₃ O	66.33	6.96	600	NA [e]
					66.47	6.99		
2-Pyridyl	H	H	293-294 [o]	C ₁₃ H ₁₂ N ₄ O	—	—	NA [e]	NA [e]
(CH ₂) ₅		H	141-142	C ₁₃ H ₁₅ N ₃ O	68.10	6.59	600	600
					68.14	6.58		
(CH ₂) ₅		5-CH ₃	196-197	C ₁₄ H ₁₇ N ₃ O	69.11	7.04	NA [e]	NA [e]
					69.16	7.10		

Table I continued

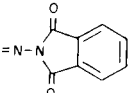
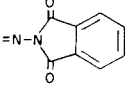
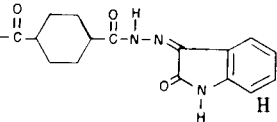
R ₁	R ₂	R ₃	Mp °C [a]	Formula	Analysis, %		Anticonvulsant	
					Calcd./Found	C	H	MES
-COCH ₂ -3-Pyridyl	H	H	237-238	C ₁₅ H ₁₂ N ₄ O ₂	64.28 63.99	4.32 4.45	NA [e]	NA [e]
-C ₆ H ₅	H	H	213-214 [p]	C ₁₄ H ₁₁ N ₃ O	—	—	NA [e]	100
CH ₂ CH ₂ CN	-CH ₂ CH ₂ CN	H	157-158	C ₁₄ H ₁₃ N ₅ O	62.91 62.70	4.90 5.01	NA [e,h]	NA [e,h]
-(CH ₂) ₆ -		H	134-135	C ₁₄ H ₁₇ N ₃ O	69.11 69.21	7.04 7.03	600	NA [e]
2-benzothiazolyl	H	H	238-239	C ₁₅ H ₁₀ N ₄ SO	61.20 61.32	3.42 3.40	NA [e]	NA [e]
2,4-C ₆ H ₃ (NO ₂) ₂	CH ₃	H	218-219	C ₁₈ H ₁₁ N ₅ O 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 ₄ O ₂	63.15 63.15	3.79 3.80	600 [g]	600 [g]
-C ₆ H ₅	CH ₃	H	172-174	C ₁₅ H ₁₃ N ₃ O	71.69 71.93	5.21 5.20	NA [e]	NA [e]
-C ₆ H ₅	CH ₃	5-Cl	208-209	C ₁₅ H ₁₂ ClN ₃ O	63.05 63.35	4.23 4.13	NA [e]	NA [e]
-C ₆ H ₅	CH ₃	5-CH ₃	186-187	C ₁₆ H ₁₅ N ₃ O	72.43 72.53	5.70 5.69	NA [e]	NA [e]
-C ₆ H ₅	CH ₃	5-NO ₂	264-265	C ₁₅ H ₁₂ N ₄ O ₃	60.80 60.85	4.08 4.02	NA [e]	NA [e]
-CH(CH ₃)(CH ₂) ₅ -(CH ₃)CH-		H	179-180	C ₁₅ H ₁₉ N ₃ O	70.01 69.95	7.44 7.69	NA [e]	NA [e]
		H	265-267	C ₁₆ H ₉ N ₃ O ₃	65.98 65.89	3.11 3.14	NA [e]	NA [e]
		5-Cl	232-233	C ₁₆ H ₈ ClN ₃ O ₃	59.00 59.17	2.48 2.00	NA [e]	NA [e]
COC ₆ H ₃ -2-OH-3-CH ₃	H	H	323-325	C ₁₆ H ₁₃ N ₃ O ₃	64.08 64.80	4.44 4.37	NA [e]	NA [e]
-CH ₂ CH ₂ C ₆ H ₅	H	H	158-159	C ₁₆ H ₁₅ N ₃ O	72.43 72.14	5.70 5.79	NA [e]	NA [e]
-CO(CH ₂) ₂ C ₆ H ₄ -4-NO ₂	H	H	224-227	C ₁₇ H ₁₄ N ₄ O ₄	60.35 60.25	4.17 4.07	NA [e]	NA [e]
C ₆ H ₅	-CH ₂ CH ₂ CH ₃	H	162-164	C ₁₇ H ₁₇ N ₃ O [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 ₄ O ₂	—	—	NA [e,s]	NA [e,s]
-CO(CH ₂) ₃ C ₆ H ₅	H	H	199-200	C ₁₈ H ₁₇ N ₃ O ₂	70.34 70.33	5.58 5.49	NA [e]	NA [e]
-C ₆ H ₅	-C ₆ H ₅	H	245-246	C ₂₀ H ₁₅ N ₃ O	76.66 76.57	4.82 4.87	NA [e]	NA [e]
-C ₆ H ₅	-C ₆ H ₅	5-Cl	305-306	C ₂₀ H ₁₅ ClN ₃ O	69.06 68.97	4.06 4.12	600 [g]	30 [h]
-C ₆ H ₅	-C ₆ H ₅	6-Cl	242-244	C ₂₀ H ₁₄ ClN ₃ O	69.06 69.26	4.06 4.17	NA [e,h]	600 [g]
-C ₆ H ₅	-C ₆ H ₅	7-CH ₃	239-240	C ₂₁ H ₁₇ N ₃ O	77.04 77.21	5.23 5.17	NA [e]	NA [e]
-CH ₂ C ₆ H ₅	-CH ₂ C ₆ H ₅	H	148-149	C ₂₂ H ₁₉ N ₃ O	77.39 77.37	5.61 5.56	NA [e]	NA [e]
		H	> 340	C ₂₄ H ₂₂ N ₆ O ₄ [t]	62.87 62.52	4.84 4.79	NA [e]	NA [e]

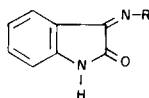
Table I continued

R ₁	R ₂	R ₃	Mp °C [a]	Formula	Analysis, %		Anticonvulsant	
					Calcd./Found C	H	Activity, mg/kg [b] MES	Met
6-Cl-4-quinazoliny	H	H	310-320 [v]	C ₁₆ H ₁₀ ClN ₅ O [v]	59.36 59.66	3.11 3.37	NA [e]	NA [e]
7-Cl-4-quinoliny	H	H	298-299	C ₁₇ H ₁₁ ClN ₄ O	63.26 63.23	3.44 3.49	NA [e]	NA [e]
-SO ₂ C ₆ H ₄ -CH ₃ -4 2-quinoliny	H H	H H	203-206 [w] 271-272	C ₁₅ H ₁₃ N ₃ SO ₂ C ₁₇ H ₁₂ N ₄ O [x]	— 70.82 70.82	— 4.20 4.26	NA [e] NA [e]	600 NA [e]
-COCH ₂ C ₆ H ₄ -NO ₂ -4	H	H	256-257	C ₁₆ H ₁₂ N ₄ O ₄	59.26 59.06	3.73 3.75	NA [e]	NA [e]
-C ₆ H ₅ NO ₂ -2	H	H	293-295 [y]	C ₁₄ H ₁₀ N ₄ O ₃	—	—	NA [e]	NA [e]
COC ₆ H ₄ NO ₂ -2	H	H	250-251 [z]	C ₁₅ H ₁₀ N ₄ O ₄	—	—	NA [e]	NA [e]
-C ₆ H ₅ NO ₂ -2	H	1-COCH ₃	238-239 [aa]	C ₁₅ H ₁₂ N ₄ O ₄	—	—	NA [e]	NA [e]
-COCH ₃	H	H	234-235 [bb]	C ₁₀ H ₆ N ₃ O ₂	—	—	NA [e]	NA [e]
COCH ₃	H	6,7-(CH ₃) ₂	247-248	C ₁₂ H ₁₃ N ₃ O ₂	62.32 62.38	5.66 5.68	NA [e]	NA [e]
-C ₆ F ₅	H	H	231-233 [cc]	C ₁₄ H ₆ F ₅ N ₃ O	—	—	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 protocol 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 C₁₀H₆N₃O₃·H₂O. [j] Toxic at 300 mg/kg. [k] N, Calcd.: 22.21. Found: 22.14. [l] MES ED₅₀ 59.25, Met ED₅₀ 90.93, TD₅₀ 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 ₉ N ₃ O	69.44 69.34	4.06 3.92
C ₆ HF ₄ -2,3,4,5	197-198	C ₁₄ H ₆ F ₄ N ₂ O	57.15 57.08	2.06 1.97
C ₆ H ₃ (CH ₂) ₃ -2,4	196-197	C ₁₆ H ₁₄ N ₂ O [d]	76.78 76.99	5.64 5.64
3-Quinolyl	303-304	C ₁₇ H ₁₁ N ₃ O [e,f,g]	73.12 73.52	4.21 4.22
5-Isoquinolyl	257-258	C ₁₇ H ₁₁ N ₃ O	74.71 74.50	4.06 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 H₂O. [f] Active at 600 mg/kg in MES screen. [g] N, Calcd. for C₁₇H₁₁N₃O·0.33H₂O: 15.05. Found: 15.01.

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