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Indole-3-carboxaldehyde and some additional aldehydes were condensed with various hydrazines, hydrazides, and related compounds. A number of the products exhibited low levels of anticonvulsant activity.

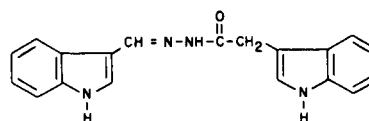
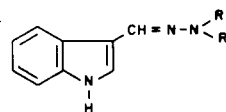
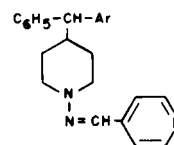
J. Heterocyclic Chem., **21**, 617 (1984).

In connection with other work in progress in this laboratory we had occasion to prepare **1** by the reaction of indole-3-carboxaldehyde with indole-3-acethydrizide [1]. On routine screening it was found that this compound has a low order of activity (600 mg/Kg) in both the maximal electroshock seizure test (MES) and the subcutaneous pentylenetetrazol seizure threshold test (Met) [2].

We now report on the synthesis and anticonvulsant activity of a series of compounds **2** from the reaction of indole-3-carboxaldehyde and various hydrazines and hydrazides. These compounds and their anticonvulsant activity are included in Table I. A number of the compounds showed activity, particularly in the MES test; however, only those derived from 1,1-dimethylhydrazine (**2**, R = R' = CH₃), 1-aminopiperidine, 6-chloro-4-hydrazinoquinazoline, and 1-amino-2,6-dimethylpiperidine had activity at 100 mg/Kg in the MES test. The latter compound was also active at 100 mg/Kg in the Met test, but exhibited neurotoxicity at that dose.

Several of the hydrazines that gave active compounds of the type **2** were also reacted with other aldehydes to give the compounds in Table II. The dimethylhydrazone of pyridine-4-carboxaldehyde was active at 100 mg/Kg in the MES test, while the dimethylhydrazones of both ferrocene-carboxaldehyde and pyrene-1-carboxaldehyde were inactive at 600 mg/Kg. Reaction of both pyridine-4-carboxaldehyde and pyrrole-2-carboxaldehyde with 1-aminopiperidine gave compounds active at 100 and 300 mg/Kg respectively in the MES test. It might be noted that pyridine hydrazones such as **3** have also been reported [3] to have MES activity.

The reaction of indole-3-acethydrizide with several substituted indole-3-carboxaldehydes and with pyrrole-2-carboxaldehyde gave compounds inactive at 600 mg/Kg in both tests. These are shown in Table III. Several products from aromatic aldehydes and 2-methylindole-3-acethydrizide have been reported [4] to have weak activity in the Met test.

**1****2****3**

EXPERIMENTAL

Condensations.

The indole-3-carboxaldehyde (or other aldehydes) (0.01 mole) and the hydrazine derivatives (0.01 mole) in 30-50 ml of absolute ethanol were heated at reflux on the steam bath for 30-60 minutes. In several cases a few drops of concentrated hydrochloric acid was added at the start of reflux. After standing for several days at room temperature, the products (Table I-III) were collected, in good yield, by filtration. All products gave spectra consistent with the structures assigned.

REFERENCES AND NOTES

- [1] F. D. Popp, *J. Med. Chem.*, **13**, 1017 (1970).
- [2] Anticonvulsant screenings were carried through the Antiepileptic Drug Development Program, N.I.H. The standard screening protocol of that group was followed. MES = Maximal electroshock seizure test and Met = Pentylenetetrazol seizure threshold test. We thank the ADD program for these results.
- [3] C. R. Craig, *Arch. Int. Pharmacodyn. Ther.*, **165**, 328 (1967).
- [4] S. Nagar, V. K. Agarwal and S. S. Parmar, *Curr. Sci.*, **41**, 215 (1972).
- [5] F. D. Popp, *J. Heterocyclic Chem.*, **11**, 79 (1974).

Table I
Hydrazones of Indole-3-carboxaldehyde

Hydrazine Used	R	Mp, °C [a]	Formula	Analysis, Calcd./Found			MES [b]	Met [b]
				C	H	N		
Cyanoacetylhydrazide	H	189-190	C ₁₂ H ₁₀ N ₄ O	63.70 63.32	4.46 4.49	— —	300	NA [c,d]
<i>N</i> -Aminorhodanine	H	208-209	C ₁₂ H ₉ N ₃ OS ₂	52.34 52.52	3.29 3.39	— —	NA [c,d]	NA [c,d]
1,1-Dimethylhydrazine	H	103-104	C ₁₁ H ₁₃ N ₃	70.56 70.58	7.00 7.01	— —	100 [e]	300 [d,e]
<i>N</i> -Aminomorpholine	H	138-140	C ₁₃ H ₁₅ N ₃ O	68.10 68.17	6.60 6.49	— —	300	600 [d]
Diaminomaleonitrile [f]	H	197-199 [g]	C ₁₃ H ₉ N ₅	— —	— —	— —	NA [c]	NA [c]
Diaminomaleonitrile [f]	7-CH ₃	245-246	C ₁₄ H ₁₁ N ₅	67.45 67.51	4.45 4.47	— —	NA [c]	NA [c]
2-Hydrazinopyridine	H	188-189	C ₁₄ H ₁₂ N ₄	71.16 71.28	5.12 5.11	— —	300	600 [d]
<i>N</i> -Aminopiperidine	H	126-127	C ₁₄ H ₁₇ N ₃	73.94 74.06	7.54 7.55	— —	100 [h]	600 [d]
Diaminomaleonitrile [f]	1-COCH ₃	243-244	C ₁₅ H ₁₁ N ₅ O	64.97 64.65	4.00 3.99	— —	NA [c]	NA [c]
4-Amino-1,2,4-triazole	H	303-304	C ₁₁ H ₉ N ₅	62.55 62.18	4.30 4.20	— —	NA [c]	NA [c]
<i>N</i> -Aminopiperidine	1-COCH ₃	132-133	C ₁₆ H ₁₉ N ₃ O	71.35 71.69	7.11 7.33	15.60 15.68	600	NA [c]
1-Amino-2,6-dimethylpiperidine	H	152-153	C ₁₆ H ₂₁ N ₃	75.25 75.37	8.29 8.34	16.46 16.46	100 [d]	100 [d]
<i>p</i> -Toluenesulfonylhydrazide	H	176-177	C ₁₆ H ₁₅ N ₃ O ₂ S	61.32 61.41	4.82 4.81	— —	NA [c]	NA [c]
2-Hydrazinobenzothiazole	H	260-261	C ₁₆ H ₁₂ N ₄ S	65.73 65.70	4.14 4.19	19.17 19.23	300	NA [c]
2-Hydrazinoquinoline	H	181-184	C ₁₈ H ₁₄ N ₄	75.50 75.33	4.93 4.68	— —	NA [c]	NA [c]
Diaminomaleonitrile [f]	1-C ₆ H ₅ CH ₂	214-215	C ₂₀ H ₁₅ N ₅	73.83 73.71	4.65 4.68	— —	NA [c]	NA [c]
Indole-3-acetylhydrazide	H	227-229 [i]	C ₁₉ H ₁₆ N ₄ O	— —	— —	— —	600	600
Indole-3-acetylhydrazide	1-COCH ₃	278-279	C ₂₁ H ₁₈ N ₄ O ₂	70.37 70.35	5.06 5.02	— —	NA [c]	NA [c]
Indole-3-acetylhydrazide	1-C ₆ H ₅ CH ₂	233-235	C ₂₆ H ₂₂ N ₄ O	— —	— —	13.78 13.47	NA [c]	NA [c]
Isonicotinylhydrazide	H	230-232	C ₁₅ H ₁₂ N ₄ O	68.17 67.82	4.58 4.92	21.20 20.85	NA [c]	NA [c]
7-Chloro-4-hydrazinoquinoline	H	283-284	C ₁₈ H ₁₃ ClN ₄	67.39 66.98	4.08 4.14	17.47 17.07	NA [c]	NA [c]
6-Chloro-4-hydrazinoquinazoline	H	247-249	C ₁₇ H ₁₂ ClN ₅	— —	— —	21.77 21.40	100 [j]	300
<i>N</i> -Aminopyrrolidine	H	173-175	C ₁₃ H ₁₅ N ₃	73.21 73.59	7.09 6.70	— —	300 [k]	NA [c]
1,1-Dimethylhydrazine	1-COCH ₃	116-117	C ₁₃ H ₁₅ N ₃ O	68.10 68.21	6.59 6.58	— —	600	NA [c]
1,1-Dimethylhydrazine	7-CH ₃	134-135	C ₁₂ H ₁₅ N ₃	71.61 71.51	7.51 7.59	— —	300	600 [d]
1,1-Dimethylhydrazine	5-F	131-132	C ₁₁ H ₁₂ FN ₃	64.37 64.24	5.89 5.81	— —	600 [d]	600 [d]
1,1-Dimethylhydrazine	5-C ₆ H ₅ CH ₂ O	84-86	C ₁₈ H ₁₉ N ₃ O	— —	— —	14.32 13.99	600	NA [c]
1-Methyl-1-phenylhydrazine	H	109-110	C ₁₆ H ₁₅ N ₃	77.08 76.95	6.06 6.03	— —	NA [c]	NA [c]

Table I continued

Hydrazine Used	R	Mp, °C [a]	Formula	Analysis, Calcd./Found			MES [b]	MET [b]
				C	H	N		
1-Methyl-1-(2,4-dinitrophenyl)-hydrazine	H	278-279	C ₁₆ H ₁₃ N ₅ O ₄	56.63 56.42	3.86 3.86	— —	NA [c]	NA [c]
<i>N</i> -Aminophthalimide	H	189-190	C ₁₇ H ₁₁ N ₃ O ₂	70.58 70.38	3.83 3.84	14.53 14.79	NA [c]	NA [c]
2-Phenylethylhydrazine sulfate	H	209-210	C ₁₇ H ₁₇ N ₃ ·0.5 H ₂ SO ₄	65.35 65.13	5.30 5.86	— —	600 [d]	NA [c]
2-Phenylethylhydrazine sulfate	COCH ₃	176-178	C ₁₈ H ₁₉ N ₃ O·0.5 H ₂ SO ₄	64.39 63.99	5.69 5.72	— —	300	NA [c]

[a] Recrystallized from ethanol. [b] See reference [2]. [c] Not active at 600 mg/Kg. [d] Toxic at this dose. [e] MES ED₅₀ 75.8, Met Ed₅₀ 102.7, TD₅₀ 141.7. [f] Thirty-one derivatives of diaminomaleonitrile and various aromatic aldehydes, prepared in connection with other work, were also screened. Most were inactive and the only one with activity greater than 600 mg/Kg was the derivative of 4-hydroxybenzaldehyde which was active at 300 mg/Kg in the MES screen. [g] Reported [5] mp 196-198°. [h] MES ED₅₀ 264, TD₅₀ 261.8. [i] Reported [1] mp 228-230°. [j] MES ED₅₀ 169.5, TD₅₀ 525.6. [k] MES ED₅₀ 96.3, TD₅₀ 222.7.

Table II
Hydrazones of Other Aldehydes

Aldehyde	Hydrazine	Mp, °C	Formula	Analysis, Calcd./Found		
				C	H	N
Pyridine-4-carboxaldehyde	1,1-Dimethylhydrazine	61-62	C ₈ H ₁₁ N ₃	64.40 64.18	7.43 7.38	— —
Pyrene-1-carboxaldehyde	1,1-Dimethylhydrazine	132-133	C ₁₉ H ₁₆ N ₂	83.79 83.71	5.92 5.92	— —
Ferrocenecarboxaldehyde	1,1-Dimethylhydrazine	68-69	C ₁₃ H ₁₆ FeN ₂	60.96 61.18	6.30 6.26	— —
Pyridine-4-carboxaldehyde	<i>N</i> -Aminopiperidine [a]	61-63	C ₁₁ H ₁₅ N ₃	69.80 69.26	7.99 7.92	22.20 22.06
Pyrrole-2-carboxaldehyde	<i>N</i> -Aminopiperidine	85-87	C ₁₀ H ₁₃ N ₃	67.76 68.00	8.53 8.22	23.71 23.88
Pyrrole-2-carboxaldehyde	Diaminomaleonitrile	212-213	C ₉ H ₇ N ₅	58.36 58.44	3.81 3.79	— —

[a] MES ED₅₀ 60.6, TD₅₀ 215.4.

Table III
Condensation of Aldehydes with Indole-3-acetylhydrazide

Aldehyde	Mp, °C	Formula	Analysis, Calcd./Found		
			C	H	N
Indole-3-carboxaldehyde	227-229 [a]	C ₁₉ H ₁₆ N ₄ O	— —	— —	— —
1-Acetylintole-3-carboxaldehyde	278-279	C ₂₁ H ₁₈ N ₄ O ₂	70.37 70.35	5.06 5.01	— —
1-Benzylindole-3-carboxaldehyde	233-235	C ₂₆ H ₂₂ N ₄ O	— —	— —	13.78 13.47
Pyrrole-2-carboxaldehyde	224-225	C ₁₅ H ₁₄ N ₄ O	67.65 67.73	5.30 5.32	— —
Pyrene-1-carboxaldehyde	260-262	C ₂₇ H ₁₉ N ₃ O	80.78 80.73	4.77 4.81	— —

[a] Reported [1] mp 228-230°.