Table II—Oogram Findings in Liver and Small Intestine of Infested Mice 9 d After Treatment with Experimental Compounds

Compound	Liver				Small Intestine			
	Mean Eggs/ Mouse (Range)	Total Immature Eggs, %	Mature Eggs, %	Dead Eggs %	Mean Eggs/ Mouse (Range)	Total Immature Eggs, %	Mature Eggs, %	Dead Eggs, %
Control	25–30	76	18	6	27–31	70	28	2
Hycanthone	23–29	—	—	—	25–30	0	48	52
IIId	26–31	35	30	35	28–32	16	34	50
IIIh	28–30	32	38	30	24–30	20	60	20
IVf	25–30	20	40	40	25–31	2	55	43
IVh	27–32	15	47	38	26–30	13	60	27
IVj	26–30	10	42	48	25–32	2	68	30

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Synthesis and Anticonvulsant Evaluation of *N*-Aminosuccinimides

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Abstract □ Twelve new *N*-aminosuccinimides were synthesized by the condensation of hydrazines with succinic anhydrides in glacial acetic acid. The compounds were evaluated in the maximal electroshock seizure and subcutaneous pentylenetetrazol seizure threshold tests for anticonvulsant activity and in the rotorod test for neurotoxicity in mice. The lowest dose at which several of the compounds exhibited anticonvulsant activity was 300 mg/kg.

Keyphrases □ *N*-Aminosuccinimides—synthesis, anticonvulsant and neurotoxic potential, mice □ Anticonvulsants—potential, *N*-aminosuccinimides, synthesis, neurotoxicity, mice

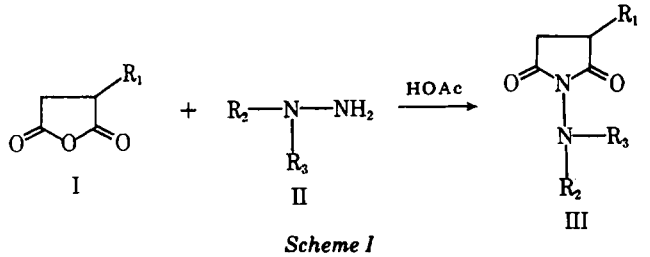
Potential anticonvulsants and hydrazine-derived drugs in general have been a principal interest of ours over several years. Anticonvulsant activity has been found among the 3,5-pyrazolidinediones (1), semicarbazides (2–4), and hydrazino urethans (5, 6). Because of the effectiveness of the succinimides such as phensuximide, methsuximide, and ethosuximide for the treatment of the petit mal condition and the paucity of information (7) concerning *N*-aminosuccinimides, an investigation in this area appeared warranted. A related compound, *N*-amino-3-(*m*-bromophenyl)succinimide, has been shown to possess potent maximal electroshock seizure activity (8). A decrease in spontaneous motor activity by *N*-arylaminosuccinimides has been noted (9).

This paper reports on the synthesis and anticonvulsant activity of a series of *N*-aminosuccinimides. The compounds vary in the nature of the amino nitrogen (alkylated or arylated) and in the α-position of the succinimide ring (unsubstituted, methyl, or phenyl).

RESULTS AND DISCUSSION

The synthesis of the aminosuccinimides (III) was accomplished by treating various succinic anhydrides (I) with substituted hydrazines (II) in glacial acetic acid (Scheme I) (Table I). Others (10) have used a mixture of equal volumes of glacial acetic acid and concentrated sulfuric acid to effect this condensation.

Compounds IIIa–IIIn were tested in the maximal electroshock seizure and subcutaneous pentylenetetrazol seizure threshold tests for anticonvulsant activity and in the rotorod test for neurotoxicity in male mice[1] by reported procedures (2). None of the compounds showed activity at 100 mg/kg in either test. In the maximal electroshock seizure test, IIIc, IIId, IIIf, IIIk, and IIIm exhibited activity at 300 mg/kg at 30 min with no indication of toxicity. One compound, IIIg, showed activity at this same dose at 4 h. In the pentylenetetrazol seizure test, IIIb, IIIl, and IIIm displayed activity at 300 mg/kg at 30 min with no toxicity. Overall, this



Scheme I

[1] No. 1, Carworth Farms.

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Table I—Physical Properties of *N*-Aminosuccinimides

Compound	R_1	R_2	R_3	Melting Point, °C	Yield, %	Formula
IIIa	H	H	$C(CH_3)_3$	98–99.5[a]	22	$C_8H_{14}N_2O_2$
IIIb	C_6H_5	CH_3	CH_3	86–87[b]	70	$C_{12}H_{14}N_2O_2$
IIIc	C_6H_5	H	$C(CH_3)_3$	123–124[b]	64	$C_{14}H_{18}N_2O_2$
IIId	C_6H_5	—$CH_2(CH_2)_3CH_2$—		101–102[c]	80	$C_{15}H_{18}N_2O_2$
IIIe	C_6H_5	—$CH_2CH_2OCH_2CH_2$—		152.5–153.5[b]	50	$C_{14}H_{16}N_2O_3$
IIIf	H	H	C_6H_5	160–161.5[d,e]	37	$C_{10}H_{10}N_2O_2$
IIIg	H	H	p-ClC_6H_4	155–157[d]	29	$C_{10}H_9ClN_2O_2$
IIIh	H	H	p-$O_2NC_6H_4$	268–270[f]	59	$C_{10}H_9N_3O_4$
IIIi	H	H	o-$O_2NC_6H_4$	203.5–205[f,g]	68	$C_{10}H_9N_3O_4$
IIIj	H	CH_3	C_6H_5	150–151[d]	50	$C_{11}H_{12}N_2O_2$
IIIk	H	H	o-$CH_3C_6H_4$	138–139.5[d]	44	$C_{11}H_{12}N_2O_2$
IIIl	H	H	2,4-$Cl_2C_6H_3$	156–157[h]	75	$C_{10}H_8Cl_2N_2O_2$
IIIm	CH_3	H	C_6H_5	111–112[i]	63	$C_{11}H_{12}N_2O_2$
IIIn	C_6H_5	H	o-$CH_3C_6H_4$	121–122[d]	73	$C_{17}H_{16}N_2O_2$

[a] Cyclohexane–toluene. [b] 70% Ethanol. [c] 60% Ethanol. [d] 95% Ethanol. [e] Reported mp 158°C [A. Michaelis and R. Hermens, *Chem. Ber.*, **25**, 2750 (1892)]. [f] Glacial acetic acid. [g] Reported mp 206–208°C (Ref. 9). [h] 80% Ethanol. [i] Toluene.

group of compounds does not display anticonvulsant activity comparable with currently available drugs.

EXPERIMENTAL[2]

Compound IIId was prepared by the dropwise addition of 3.15 g (0.0315 mol) of *N*-aminopiperidine to a solution of 5.28 g (0.030 mol) of phenylsuccinic anhydride (11) in 15 mL of glacial acetic acid. The initially exothermic reaction mixture was refluxed under nitrogen for 1.5 h, and the acetic acid was evaporated under reduced pressure. Water (10 mL) was added to the residue, and the pH was adjusted to 8 by addition of 5% NaOH solution. The product was extracted into chloroform, dried over magnesium sulfate, the solvent evaporated, and the residue recrystallized from 60% ethanol, affording 6.11 g (79%) of white crystals, mp 101–102°C. The reflux period for arylhydrazines was 3 h, and the NaOH neutralization in the workup was omitted.

[2] Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The IR spectra were taken on a Perkin-Elmer 700 spectrophotometer as either liquid films or as potassium bromide pellets. NMR spectra were recorded on a Varian EM-360 or T-60 spectrometer, using tetramethylsilane as the internal reference. Mass spectra were obtained on a RMU-7 double-focusing spectrometer by Hitachi/Perkin-Elmer. Elemental analyses for C, H, and N were performed by Baron Consulting Co., Orange, Conn.; values for all compounds were within ± 0.4% of theoretical. All compounds exhibited ^{1}H-NMR and mass spectra consistent with the structures shown.

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