The Anticonvulsant Activity of 4a,8a-Naphthalenedicarboximide and Its Derivatives[1]

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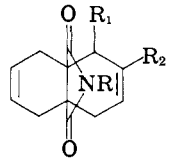
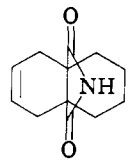
1,4,5,8-Tetrahydro-4a,8a-naphthalenedicarboximide (I) has been found to have anticonvulsant activity against pentylenetetrazole-induced convulsions in mice and low toxicity. A structure–activity study was made revealing that N-substitution destroyed this activity as did saturation of the double bonds. Increasing the degree of ring unsaturation as in 4a,8a-naphthalenedicarboximide (VII) produced a compound with half of the activity of I. An hypothesis has been suggested to explain the structure–activity relationship in these compounds. This led to the synthesis of 4,7-dihydro-3a,7a-indandicarboximide (XIV), which also proved to be active.

Many substituted succinimides have been studied for anticonvulsant activity and several of these are clinically useful in the treatment of petit mal epilepsy. These compounds manifest themselves in pharmacological testing by preventing the clonic convulsions induced by administration of pentylenetetrazole to mice. The most active succinimides possess α,α-dialkyl or α-alkyl-α-phenyl substitution with nitrogen unsubstituted or methylated. Alkyl-substituted compounds show little or no activity in the maximal electroshock test, which indicates compounds potentially effective against grand mal epilepsy; phenyl substitution, however, specifically increases activity against electroshock, and α,α-diphenylsuccinimides are electroshock active and pentylenetetrazole inactive.[2] Although some trisubstituted succinimides are highly active in the pentylenetetrazole test, few tetrasubstituted derivatives have been tested.[3] Surprisingly, however, $\alpha,\alpha,\beta,\beta$-tetramethylsuccinimide has been shown to be a pentylenetetrazole-like convulsant.[4]

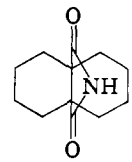
We have found that 1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide (I), which is, in effect, a tetrasubstituted succinimide, displayed significant activity against pentylenetetrazole convulsions. It has an ED_{50} of 22 mg/kg and relatively low toxicity (LD_{50} = 620 mg/kg) and thus possessed a high therapeutic ratio. Typical of alkyl-substituted succinimides, it was inactive against maximal electroshock.



I, $R = R_1 = R_2 = H$
IX, $R = H$; $R_1 = CH_3$; $R_2 = H$
X, $R = R_1 = H$; $R_2 = CH_3$

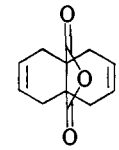


II

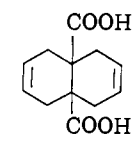


III

The first preparation of I was reported by Snatzke and Zanati,[5] although the corresponding hexahydro and octahydro derivatives II and III had been prepared earlier by Brigl and Herrmann.[6] Dicarboximide I was prepared from the corresponding anhydride IV by refluxing in aqueous ammonia. The anhydride was formed, along with diacid V and 3,6-dihydrophthalic anhydride (VI), from a Diels–Alder addition of 2 moles of butadiene to 1 mole of acetylenedicarboxylic acid.



IV

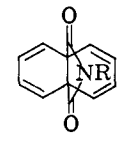


V

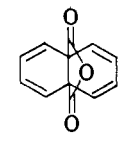
To determine a structure–activity relationship for this unique tricyclic dicarboximide system, a number of N-substituted derivatives of I were prepared by treatment of the anhydride IV with the corresponding amine (see Table I). The N-methyldicarboximide showed markedly reduced activity, but it and the N-benzyl compound were still weakly active. However, a variety of other substituents destroyed the activity altogether (see Table II).

Since N-substitution did not appear fruitful, attempts were made to modify the carbocyclic system. The most obvious change involved saturation of the double bonds. The monounsaturated derivative, 1,4,5,6,7,8-hexahydro-4a,8a-naphthalenedicarboximide (II), was prepared by addition of butadiene to 3,4,5,6-tetrahydrophthalic anhydride. The resulting anhydride was converted to the diacid for isolation and treated with urea in ethylene glycol at 200° to produce the imide II. This proved to be considerably less active than I; methylation with diazomethane formed the N-methyl derivative which was also inactive. Catalytic hydrogenation of II as described by Brigl and Herrmann[6] produced III which was void of all biological activity in the pharmacodynamic screen.

The next attempt was to move in the opposite direction, *i.e.*, to introduce more double bonds into the rings. The goal was to prepare 4a,8a-naphthalenedicarboximide (VII), the parent compound. Although the



VII



VIII

(1) Presented before the Division of Medicinal Chemistry at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) A. Spinks and W. S. Waring, *Progr. Med. Chem.*, **3**, 261 (1963).

(3) W. J. Close and M. A. Spielman in "Medicinal Chemistry," Vol. V, W. H. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 1.

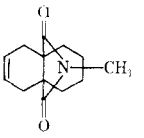
(4) G. Chen and B. Bohner, *J. Pharmacol. Exptl. Therap.*, **123**, 212 (1958).

(5) G. Snatzke and G. Zanati, *Ann.*, **684**, 62 (1965).

(6) P. Brigl and R. Herrmann, *Ber.*, **71B**, 2280 (1938)

TABLE I

4a,8a-NAPHTHALENEDICARBOXIMIDE AND DERIVATIVES

No.	Structure no.	Mp,[c] °C	Formula	Calcd, %: C	H	N	Found, %[d]: C	H	N	Yield,[e] %
1	III[a]	184–189	$C_{12}H_{17}NO_2$	69.53	8.27	6.76	69.77	8.27	6.95	78
2	II[a]	173–174	$C_{12}H_{15}NO_2$	70.22	7.37	6.82	70.44	7.37	6.86	84
3		79–80	$C_{13}H_{17}NO_2$	71.20	7.81	6.39	71.42	7.91	6.52	77
4	I, R = H[b]	217–219	$C_{12}H_{13}NO_2$	70.92	6.45	6.89	71.09	6.80	6.77	65
5	I, R = CH_3	161–162	$C_{13}H_{15}NO_2$	71.87	6.96	6.45	72.11	7.04	6.45	85
6	I, R = C_6H_5	130–132	$C_{18}H_{17}NO_2$	77.40	6.13	5.01	77.60	6.02	5.28	50
7	I, R = $CH_2C_6H_5$	129–130	$C_{19}H_{19}NO_2$	77.79	6.53	4.77	77.92	6.66	4.80	65
8	I, R = $CH_2CH_2C_6H_5$	96–97	$C_{20}H_{21}NO_2$	78.15	6.89	4.56	77.98	6.89	4.36	26
9	I, R = 2,3-$Cl_2C_6H_3$	178–179	$C_{18}H_{15}Cl_2NO_2$	62.08	4.34	4.02	62.32	4.37	4.14	Low
						Cl, 20.36			Cl, 20.32	
10	I, R = cyclopropyl	133–134	$C_{15}H_{17}NO_2$	74.05	7.04	5.76	74.06	7.06	5.76	Low
11	I, R = $(CH_2)_3N(CH_3)_2$	71–72	$C_{17}H_{24}N_2O_2$	70.80	8.39	9.71	70.75	8.30	9.51	12
12	VII, R = H	164–165	$C_{12}H_9NO_2$	72.35	4.55	7.04	72.27	4.63	7.27	5
13	VII, R = CH_3	151–152	$C_{13}H_{11}NO_2$							47
14	X	180–182	$C_{13}H_{15}NO_2$	71.87	6.96	6.45	71.98	6.97	6.50	13[f]
15	IX	190–193	$C_{13}H_{15}NO_2$	71.87	6.96	6.45	72.06	7.05	6.35	4[f]
16	XI	228–230	$C_{12}H_{13}NO_3$	65.74	5.98	6.38	65.79	6.14	6.30	11
17	XII	230–231	$C_{12}H_{15}NO_3$	65.14	6.83	6.33	65.20	6.91	6.51	43
						O, 21.69			O, 21.53	
18	XIV, R = H	162–164	$C_{11}H_{13}NO_2$	69.09	6.85	7.33	68.71	6.87	7.14	5[f]
19	XIV, R = CH_3	84–87	$C_{12}H_{15}NO_2$							65

[a] See ref 6. [b] See ref 5. [c] All melting points were uncorrected. [d] All microanalyses were determined by Midwest Micro Laboratories. [e] No effort was made to maximize yields; yields were calculated from the immediate precursor. [f] Over-all yield calculated from the Diels–Alder reactants.

TABLE II

PHARMACOLOGICAL SCREENING RESULTS

No.	Test no.	Screening dose, mg/kg ip	HST[a]	MES[b]	SLT[c]	MET[d]	ED_{50}, mg/kg	LD_{50}, mg/kg
1	III	50	42/51	0/4	0/4	0/4		
2	II	50	60/48	2/4 0/10	0/4	1/4		
3		100	...	1/10	...	2/10		
4	I	100	55/48	1/4	4/4, 6/10	4/4, 8/10	SLT 86 (79–94) MET 22 (12–38)	620 (500–775)
5		200	84/48	1/4	0/4	3/4, 5/10		
6		400	>162/47	0/4	0/4	0/4		
7		100	67/48	0/4	0/4	2/4, 3/10		
8		100	57/48	0/4	0/4	1/4		
9		100	...	0/4	0/4	1/4		
10		200	155/37	0/4	0/4	1/4		
11		50	49/47	0/4	0/4	0/4	[e]	
12	VII	50	114/51	0/4	0/4	3/4, 7/10	42 (34–52)	
13		100	...	0/10	...	0/10		
14	X	50	...	...	...	4/10		
15	IX	50	...	...	...	2/10		
16	XI	50	54/26	0/4	0/4	1/4		
17	XII	100	45/36	0/4	0/4	1/4		
18	XIV	50	78/54	0/4	0/4	4/4, 6/10	46 (36–59)	
19		100	...	0/10	...	3/10		

[a] Hexobarbital sleep time in minutes; experimental animals/controls. [b] Maximal electroshock test; animals protected/animals tested. [c] Strychnine lethality test; animals protected/animals tested. [d] Pentylenetetrazole test; animals protected/animals tested. [e] Recent work has shown that this compound was active against oxotremorine-induced tremors in mice: ED_{50} = 27.8 mg/kg. However, it was also fairly toxic: LD_{50} = 121 mg/kg.

corresponding anhydride VIII had been obtained previously by Vogel, *et al.*,[7] the dicarboximide was unknown. Following Vogel's procedure, VIII was prepared from IV in reasonable yield, but it could not be converted to the dicarboximide with aqueous ammonia as in the case of IV. The anhydride VIII dissolved in the ammonia slowly at room temperature but acidification regenerated the anhydride and refluxing produced only naphthalene as a crystalline product.[8] The dicarboximide was finally produced in low yield from I *via* Vogel's procedure: bromination with N-bromosuccinimide and dehydrobromination in quinoline at 140°. The crude product was purified by chromatog-

(7) E. Vogel, W. Mecke, and W. Grimme, *Angew. Chem.*, **76**, 786 (1964).

(8) J. J. Bloomfield and J. R. Smiley Irelan, *Tetrahedron Letters*, 2971 (1966).

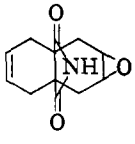
raphy on silicic acid. It showed typical dicarboximide absorption bands in the infrared and its nmr spectrum displayed only vinyl proton peaks centered at 5.8 ppm similar to those reported by Vogel, *et al.*,[9] and by Bloomfield and Smiley Irelan[8] for 4a,8a-bridged naphthalenes.

Biologically VII proved to be active against pentylenetetrazole, with an ED_{50} of 42 mg/kg, or half as active as its precursor I. The N-methyl derivative, prepared with diazomethane, was not active.

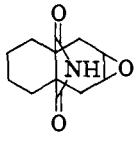
Two C-methyl-substituted derivatives of I were prepared by treating 3,6-dihydrophthalic anhydride (VI) with piperylene and isoprene. The resulting anhydrides were converted to the dicarboximides with ammonia. These products, 1-methyl- (IX) and 2-methyl-1,4,5,8-tetrahydro-4a,8a naphthalenedicarboximide (X), were only weakly active against pentylenetetrazole.

Epoxidation of one of the double bonds in I or of the single double bond in II with *m*-chloroperbenzoic acid produced the epoxides XI and XII in which almost all of the activity against pentylenetetrazole convulsions was absent.

A study of models indicated that a possible reason for this structure–activity relationship might involve steric hindrance around the dicarboximide group. Those compounds which showed very little activity also sterically blocked one or both sides of the heterocyclic ring. The tetrahydro-4a,8a-naphthalenedicarboximide I probably exists in the symmetrical *exo–exo* configuration XIII, as indicated by the nmr splitting patterns of the methylene protons and as suggested by the work of Kallos and Deslongchamps[10] on the configuration of the adduct of furan and acetylenedicarboxylic acid. In this form, the four vinyl protons lie on a plane at the base of and perpendicular to the plane of the heterocyclic ring. In the case of II, III, XI, and XII, all of which were inactive, protons lie above this

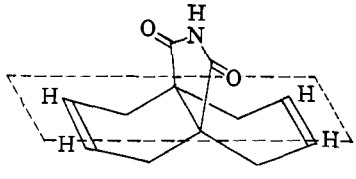


XI



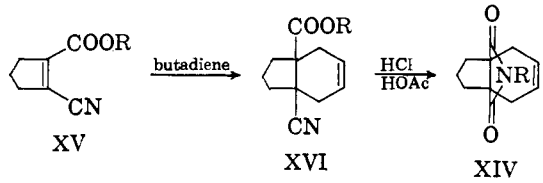
XII

plane blocking one or both sides of the center ring. However, in I and VII the protons lie below this plane and the compounds were active.



XIII

This hypothesis led to the preparation of the corresponding unknown indandicarboximide XIV. By the steric hindrance argument XIV should be active since the five-membered ring would be completely below the hypothetical "plane." Activity in this compound would also indicate that the presence of two double bonds was not required. Following literature procedures,[11] 2-cyanocyclopentene-1-carboxylic ester (XV) was obtained in good yield, and its adduct with butadiene prepared XVI. The cyano ester was cyclized to dicarboximide XIV by the method of Horning and Schock.[12]



XV XVI XIV

As predicted, XIV was active against pentylenetetrazole convulsions with an ED_{50} of 46 mg/kg. Also as expected, the N-methyl derivative was of much lower activity.

Although it was useful in predicting activity of XIV, the hypothesis did not explain the lack of activity in a large number of other unhindered succinimides, nor the activity found in some trisubstituted compounds which must be hindered at least as much as some of these.[13] In addition, IX and X were less active than one would have predicted since the steric hindrance of the methyl groups appears to be slight.[14]

Unfortunately none of the modifications of the 4a,8a-naphthalenedicarboximides could match the anticonvulsant activity of the tetrahydro derivative I. Compound I was also effective in protecting mice from a lethal dose of strychnine sulfate. The ED_{50} value of I against strychnine was found to be 86 (79–94) mg/kg ip. None of the compounds in this series protected against the seizures induced by maximal electroshock, but several appeared to possess central nervous system depressant properties. Compound VII and the N-phenyl and N-cyclopropyl derivatives of I were found to potentiate the sleeping time induced by hexobarbital (a greater than twofold increase in sleeping time was considered to be significant).

Experimental Section[15]

1,4,5,8-Tetrahydro-4a,8a-naphthalenedicarboxylic anhydride (IV) was prepared by a modification of the procedure described by Alder and Backendorf.[16] A mixture of 250 g of acetylenedicarboxylic acid (2.19 moles), 750 ml of dioxane, and 550 ml of liquid butadiene was heated in a bomb at 170° for 20 hr. The reaction was cooled and the dioxane was removed *in vacuo*. The resulting brown oil, which weighed 489 g, crystallized on standing.

Instead of distilling the residue, the product was suspended in 2 l. of CCl_4 and the insoluble dicarboxylic acid V was isolated by filtration. Some viscous polymer separated on dilution of the filtrate to 4 l. with CCl_4. A mixture of anhydrides IV and VI was obtained by concentration of the CCl_4 solution and these

(9) E. Vogel, W. Maier, and J. Eimer, *ibid.*, 655 (1966).

(10) J. Kallos and P. Deslongchamps, *Can. J. Chem.*, **44**, 1239 (1966).

(11)(a) S. C. Sen-Gupta and A. J. Bhattacharyya, *J. Indian Chem. Soc.*, **17**, 183 (1940); (b) B. R. Baker, M. V. Querry, S. Bernstein, S. R. Safir, and Y. Subbarow, *J. Org. Chem.*, **12**, 167 (1947); (c) G. Biglino, *Farmaco* (Pavia), *Ed. Sci.*, **17**, 377 (1962); *Chem. Abstr.*, **58**, 5684*g* (1963).

(12) E. C. Horning and R. U. Schock, Jr., *J. Am. Chem. Soc.*, **70**, 2945 (1948).

(13) G. Chen, R. Portman, C. Ensor, and A. C. Bratton, Jr., *J. Pharmacol. Exptl. Therap.*, **103**, 54 (1951).

(14) These unsymmetrical dicarboximides must occur as racemic mixtures and it could be that only one of the optical isomers is active. However, stereo- or geometrical configuration may not be too important since C. A. Miller, H. I. Schell, and L. M. Long (*J. Am. Chem. Soc.*, **73**, 5608 (1951)) found no differences in the activity between *cis* and *trans* isomers in some substituted succinimides they studied.

(15) All microanalyses were performed by Midwest Microlab., Inc., Indianapolis, Ind. All melting points were obtained on a Thomas–Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer grating infrared spectrophotometer Model 337. Nmr spectra were obtained using a Varian A-60 nmr spectrometer.

(16) K. Alder and K. H. Backendorf, *Ber.*, **71B**, 2199 (1938).

could be separated readily by fractional crystallization from $CHCl_3$.

When no more crystalline material could be obtained from the syrupy mother liquors, they were reduced to dryness and hydrolyzed by treatment with 20% NaOH on the steam bath for 0.5 hr. The reaction mixture was filtered and acidified and the resulting crude naphthalenedicarboxylic acid was recrystallized from acetone.

The total amounts of each of the three major products (about 90% purity) separated from the reaction are shown in Table III. This amounts to a 39% recovery of the acetylenedicarboxylic acid used.

TABLE III

Product	g	mole
3,6-Dihydrophthalic anhydride	29.5	0.197
1,4,5,8-Tetrahydro-4a,8a-naphthalenedicarboxylic anhydride	69.6	0.341
1,4,5,8-Tetrahydro-4a,8a-naphthalenedicarboxylic acid	70.6	0.318
	169.7	0.856

1,4,5,8-Tetrahydro-4a,8a-naphthalenedicarboximide (I) could be best prepared by the method of Snatzke and Zanati[5] from the anhydride (see Table I for properties of analytical samples).

N-Substituted 1,4,5,8-Tetrahydro-4a,8a-naphthalenedicarboximides. N-Methyl-1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide could be prepared by refluxing a mixture of the anhydride (10 g, 0.05 mole) and excess aqueous 40% methylamine until the anhydride dissolved and the dicarboximide precipitated (4 hr). The product isolated in 85% yield (9.0 g) was recrystallized from ethanol.

N-Alkyl-1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximides were prepared by adding the amine, dropwise, to a stirred ether solution of the anhydride. The resulting precipitate was filtered and dried *in vacuo* and then fused at 210°. The melt was cooled and triturated with ethanol whereupon the dicarboximides crystallized. They were recrystallized from ethanol.

The dimethylaminopropyl derivative was best separated from the crude reaction as its hydrochloride and the free base regenerated from the partially purified salt.

N-Phenyl- and N-dichlorophenyl-1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximides could be prepared by direct heating of a mixture of the anhydride and the excess aniline to 210° for 10 min. Crystals formed when the residue was cooled and treated with ethanol. The dicarboximides were recrystallized from ethanol.

1,4,5,6,7,8-Hexahydro-4a,8a-naphthalenedicarboximide (II).—The corresponding diacid was obtained by the method of Brigl and Herrmann[6] using commercially available (Aldrich) 3,4,5,6-tetrahydrophthalic anhydride. The diacid cyclized to the dicarboximide in 84% yield using the urea procedure described by Kondrat'eva and Huang.[15]

N-Methyl-1,4,5,6,7,8-hexahydro-4a,8a-naphthalenedicarboximide.—The N-methyl derivative was prepared by treating the methanolic solution of the unsubstituted dicarboximide with an excess of ethereal CH_2N_2. Removal of the solvents left a crystalline residue which was recrystallized from ethanol.

4a,8a-Naphthalenedicarboximide (VII).—The route to this compound follows that used by Vogel[7] to prepare VIII. A mixture of 10 g of 1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide, 14.8 g of N-bromosuccinimide, and 600 ml of CCl_4 was refluxed for 0.5 hr. It was cooled and filtered and the clear filtrate was reduced to dryness *in vacuo*. The glassy residue was heated at 140° for 15 min in 30 ml of quinoline. The resulting black solution was poured into 1 l. of water, and the mixture was acidified with 10% H_2SO_4 and filtered to separate an amorphous precipitate which formed. This precipitate was dissolved in 300 ml of $CHCl_3$ and the solution was washed once with 10% H_2SO_4 and twice with water. The $CHCl_3$ solution was dried (Na_2SO_4) and taken to dryness *in vacuo*. The dark residue weighed 8.3 g. It was chromatographed on 75 g of silicic acid (acetone washed and dried, Mallinckrodt Chromatography Grade 200 mesh) using $CHCl_3$ as a solvent. When the first material began to move off the column, 200-ml fractions were collected. The second fraction reduced to dryness was decolorized with Darco, and the solvent was removed. The 3-g residue was taken up in CH_2Cl_2 and CCl_4 and filtered and the filtrate was concentrated to about 2 ml and refrigerated overnight. The crystals that formed were filtered, washed, dried, and weighed to yield 0.6 g, mp 156–161°. The infrared spectrum (1710 and 1770 cm^{-1}) and the nmr spectrum (multiplet centered at 5.75 ppm) of this material were consistent with the structure VII. It was twice recrystallized from CCl_4, after another treatment in methanol with Darco, to yield 321 mg, mp 164–165°.

N-Methyl-4a,8a-naphthalenedicarboximide.—A methanolic solution of 147 mg of 4a,8a-naphthalenedicarboximide was treated with excess ethereal CH_2N_2. The solution was filtered, the solvent was removed, and the product was crystallized from CCl_4 to produce 74 mg of material, mp 151–152°. The infrared and nmr spectral data were consistent with the proposed structure.

2-Methyl-1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide (X).—A mixture of 10 g of 3,6-dihydrophthalic anhydride, 25 ml of dioxane, and 50 ml of isoprene was heated to 150° for 22 hr in a bomb. After the bomb was cooled and opened, the yellow, oily residue was poured into 250 ml of water and extracted three times with $CHCl_3$. The combined extracts were washed twice with water, dried (Na_2SO_4), and evaporated to dryness. The oil remaining was heated with 250 ml of 20% NaOH for 0.5 hr on the steam bath. The mixture was cooled and extracted twice with $CHCl_3$. Acidification of the aqueous layer produced a white solid which was collected, washed, and dried. The crude diacid (8 g) was refluxed in 100 ml of acetyl chloride for 45 min. The excess acetyl chloride was removed *in vacuo* and the oil was poured into 300 ml of water. It was extracted into $CHCl_3$ which was washed, dried, and taken to dryness. A yellow oil (3.4 g) remained which crystallized on cooling. It was triturated with 1 ml of CCl_4 and filtered to leave 3.2 g of waxy solid.

This solid was refluxed for 4 hr in 50 ml of concentrated aqueous ammonia. The white solid which precipitated after formation of a clear solution was filtered, washed, and dried to weigh 3.0 g, mp 179–81°. It was recrystallized several times from ethanol to a constant melting point 180–182°. The infrared spectrum showed the typical dicarboximide absorption and the nmr spectrum displayed an eight-proton complex in the region 1.9–3.0 ppm similar to that of the unsubstituted dicarboximide. A three-proton, slightly broadened doublet (J = 1.5 cps) at 1.7 ppm corresponded to the vinyl methyl group. A complex one-proton multiplet appeared at 5.5 ppm adjacent to the two-proton vinyl proton multiplet of the unsubstituted ring at 5.9 ppm.

1-Methyl-1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide (IX) was prepared with piperylene in essentially the same manner as the 2-methyl derivatives above. It was recrystallized several times from ethanol to mp 190–193°. Again the infrared and nmr spectra were consistent with the proposed structure. In the latter, the methyl group appeared as a doublet at 1.3 ppm (J = 7 cps).

2-Cyanocyclopentene-1-carboxylic acid ester (XV) was prepared according to the general route used by Sen-Gupta and Bhattacharyya.[16a] To a mixture of 400 g of 2-cyclopentanone carboxylic acid ester (a mixture of methyl and ethyl esters obtained from Aldrich) and 190 ml of liquid HCN at 0° was added 1 ml of 50% KOH as suggested by the work of Baker, *et al.*[16b] The solution was stirred gently and the temperature rose briefly to 55° while some HCN boiled away, but it dropped again rapidly and the reaction was refrigerated overnight. The solution was treated with 1 ml of 90% H_3PO_4 and the excess HCN was removed through a NaOH trap. Traces were removed *in vacuo*. The dried (Na_2SO_4) oil weighed 450 g. It was mixed with 500 ml of anhydrous pyridine as according to Biglino,[16c] and with stirring and cooling, 330 ml of $SOCl_2$ was added dropwise over a 1-hr period. The mixture turned brown and a precipitate formed. It was stirred at room temperature for 2 hr longer and then allowed to stand overnight. The partially solid mass was poured onto 1 kg of ice and extracted four times with ether. The ether (2 l.) was filtered to remove a fine insoluble black solid and then washed twice with 600-ml portions of 10% NaOH, three times with 600-ml portions of 10% HCl, and three times with water. It was dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The resulting red oil weighed 377 g. Its infrared spectrum was consistent with that expected for the desired product.

The oil distilled over a 5° range 140–145° (22 mm) with only a small forerun. The distilled ester weighed 334 g (84% yield) and nmr analysis indicated it contained about 10% of the Δ^2 isomer.

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4,7-Dihydro-3a,7a-indandicarboximide (XIV).—A mixture of 100 g of 2-cyanocyclopentene-1-carboxylate and 250 ml of butadiene was heated at 175° in a bomb for 22 hr. On cooling, the contents of the bomb were poured into 8 l. of acetone. The cloudy solution was filtered and taken to dryness *in vacuo* to leave 150 g of dark oil. This was poured into 2 l. of 95% ethanol and filtered again through Super-Cel. The clear yellow solution was taken to dryness and the resulting oil distilled *in vacuo*.

The first fraction weighing 59 g boiled over a range from below 100 to 115° (0.7 mm). The next fraction weighing 15 g boiled from 115 to 125° (0.6 mm) and contained the desired nitrile ester as indicated by infrared and nmr analysis.

This nitrile ester was cyclized by the procedure of Horning and Schock.[11] The mixture of 5 g of cyano ester, 25 ml of glacial acetic acid, and 25 ml of concentrated HCl was heated on the steam bath for 2 hr. The resulting solution was cooled and poured into 250 ml of water, and the oil which separated was extracted three times with 50-ml portions of $CHCl_3$. The extracts were dried (Na_2SO_4) and evaporated to dryness. The resulting yellow oil weighed 4.8 g and crystallized on standing. Recrystallized from CCl_4, it weighed 0.86 g, mp 152–156°. The infrared spectrum showed typical dicarboximide absorption. The dicarboximide was recrystallized twice more from CCl_4 to a melting point of 162–164°.

4,7-Dihydro-N-methyl-3a,7a-indandicarboximide was prepared by treating 166 mg of dicarboximide with excess ethereal CH_2N_2. It was recrystallized from petroleum ether (30–60°) to yield 116 mg, mp 84–87°. Its infrared spectrum was consistent.

2,3-Epoxy-1,2,3,4,5,6,7,8-octahydro-4a,8a-naphthalenedicarboximide (XII).—To a solution of 10 g of II in 200 ml of CH_2Cl_2, was added 10 g of *m*-chloroperbenzoic acid and the resulting solution was stirred at room temperature overnight. The reaction solution was washed three times with $NaHCO_3$ solution, dried (Na_2SO_4), and taken to dryness. The white crystalline residue was recrystallized from $CHCl_3$ to yield 4.6 g, mp 225–226°. Further crystallizations raised the melting point to 230–231°. The infrared and nmr spectra were consistent with the proposed structure.

2,3-Epoxy-1,2,3,4,5,8-hexahydro-4a,8a-naphthalenedicarboximide (XI) was prepared in the same manner as XII using only 1 mole of *m*-chloroperbenzoic acid/mole of dicarboximide I. The product proved to be a mixture of starting material and monoepoxide. The epoxy compound was finally obtained in pure form (11% yield) by fractional crystallization and silicic acid chromatography. It had mp 228–230°, and its spectra were consistent.

Pharmacology.—Adult male mice weighing 18–24 g were used in all the pharmacological testing. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[18]

Hexobarbital Sleeping Time (HST).—Groups of four mice were injected intraperitoneally with the test compound 30 min before the intraperitoneal injection of 100 mg/kg of hexobarbital. The time in minutes between the injection of the hexobarbital and the regaining of the righting reflux was measured and compared to that of the control group.

Maximal Electroshock Test (MES).—The compounds to be tested were injected intraperitoneally to groups of four mice, 1 hr prior to being subjected to supramaximal electroshock as per the method of Swinyard, *et al.*[19] The results are expressed as a ratio of the number of animals protected from the hind limb extensor phase of the seizure to the number shocked.

Strychnine Lethality Test (SLT).—Groups of four or ten mice were administered the test compounds 30 min prior to the intraperitoneal injection of 2 mg/kg of strychnine sulfate. The animals were observed for death during the 30 min following strychnine. The results are expressed as a ratio of the number of animals surviving strychnine to the number of animals tested.

Pentylenetetrazole Test (MET).—Thirty minutes following the injection of the test compound, groups of four to ten mice were injected subcutaneously with 85 mg/kg of pentylenetetrazole. The results are expressed as a ratio of the number of animals protected from the clonic convulsions induced by pentylenetetrazole to the number of animals tested.

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Preparation and Anticonvulsant Activity of Some Aryldialkylsuccinimides

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A series of substituted succinimides related to α-methyl-α-phenyl-β-ethylsuccinimide has been prepared and examined for anticonvulsant properties.

The interesting tranquilizing properties of α-methyl-α-phenyl-β-ethylsuccinimide[2] prompted us to prepare a series of closely related compounds. Many of these showed activity against pentylenetetrazole-induced convulsions and some showed activity against electrically induced convulsions.

Most of the compounds were synthesized by the method of Miller and Long[3] as modified by Miller and Hull[2] in which a ketone is condensed with ethyl cyanoacetate to yield an α-cyanocinnamate. This is then treated with KCN, followed by an alkyl halide, and thus converted to an α,β-dicyanopropionate which was hydrolyzed directly to a succinimide with KOH in aqueous alcohol.

Neither Scheme I nor the sequence[4] arylacetonitrile → alkylarylacetonitrile → ethyl α-aryl-α,β-dialkylsuccinic-α-nitrile β-ester → succinic acid → succinimide was found convenient for the preparation of aryldialkylsuccinimides with larger or functional α substituents. The desired compounds were prepared by condensing the appropriate arylacetonitrile with an aldehyde in the presence of NaCN to give an arylalkylsuccinonitrile[5] which was then alkylated with an alkyl halide using NaH in tetrahydrofuran (THF) (Scheme II). The resulting aryldialkylsuccinonitrile was hy-

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