the 7 isomer. Recrystallization of the product from EtOH yielded 4.0 g of white needles, mp 187.0–188.0°. *Anal.* ($C_{13}H_{18}BrNO_2$) C, H, Br, N.

5-Carbomethoxy-2-ethyldecahydroisoquinoline Hydrobromide.—5-Carbomethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline (1 g), AcOH (30 ml), and concentrated H_2SO_4 (0.1 ml) were hydrogenated (PtO_2, 1 g, 48 hr, 3.52 kg/cm²). The product was isolated in the usual manner, and the hydrobromide salt was prepared and recrystallized (EtOH–Et_2O) (0.3 g, mp 168.0–169.0°). The uv spectrum of this compound showed no absorption in the range 220–360 mμ. *Anal.* ($C_{13}H_{24}BrNO_2$) C, H, Br, N.

Acknowledgment.—The author is indebted to Marion Laboratories, Inc., Kansas City, Mo., for their financial assistance in the support of this project and to Dr. James G. Beasley for his assistance in the biological evaluations.

Diimides of Cyclobutane-1,1-dicarboxylic Acid[1a]

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Various imides of cyclobutanecarboxylic acid, particularly N-acetylcyclobutanecarboxamide, possess a structure-dependent ability to act as central nervous system depressants.[2] The phenomenon appears to be related to the cyclobutane ring system and is unique in that it is not subject to circadian rhythm variance, a finding contrary to the behavior of barbiturates. To further elucidate the biochemorphology of cyclobutane compounds we have expanded the original study to a group of cyclobutane-1,1-dicarboxylic acid derivatives. With the exception of **6**, a spirothiobarbiturate, these substances are di-N-acylimides and congeners of the compounds studied earlier.

When bioassayed the compounds were tested as reported previously[2] but dispersed in mineral oil, since they tended to agglomerate when ground in 0.25% methylcellulose. At a dose of 1000 mg/kg there was no loss of spontaneous activity nor were there any deaths. In addition to intraperitoneal administration, the compounds were also given orally as suspensions in gum tragacanth with the same lack of effect.

They were also tested as potentiators of barbiturate sedation[3,4] using pentobarbital sleeping time, judged by loss of the righting reflex, as a criterion. Using five mice and 50-mg/kg ip dose of the barbiturate, a mean sleeping time of 81 min was obtained. The only compound exhibiting potentiation was **6**. The mean sleeping time for five mice receiving 500 mg/kg of this compound orally 30 min before the standard dose of barbiturate was 147 min. A potentiation factor of 1.8 on the part of this compound at a dose which itself appears to have no depressant activity is of considerable practical and mechanistic interest.

(1) (a) Supported in part by research Grant NB-7548 of the National Institutes of Health, U. S. Public Health Service. (b) To whom inquiries should be directed.

(2) R. T. Buckler and C. H. Jarboe, *J. Med. Chem.*, **9**, 768 (1966).

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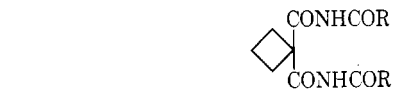
Experimental Section

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Preparation of Diimides.—A mixture of 20 g of $SOCl_2$ and 5 g (0.034 mole) of cyclobutane-1,1-dicarboxylic acid was refluxed for 1.5 hr (hood) and excess $SOCl_2$ was removed by flash evaporation. Crude cyclobutane-1,1-dicarbonyl chloride (1.6 g, 0.009 mole) was added dropwise to a stirred and cooled solution of the amide (0.018 mole) in 10 ml of neutral alumina washed and KOH-dried pyridine. In every case an exothermic reaction ensued; when it subsided the mixture was heated on the steam bath for 1 hr. The reaction mixture was then poured onto 100 g of crushed ice and the product precipitated. Solvents used in crystallization and yields of the respective compounds are in Table I.

TABLE I

DIIMIDES OF CYCLOBUTANE-1,1-DICARBOXYLIC ACID



No.	R	Yield, %	Mp, °C[a]	Crystn[b] solvent	Formula	Analysis[c]
1	CH_3	40	215	C	$C_{10}H_{14}N_2O_4$	N
2	C_2H_5	50	243	A	$C_{12}H_{18}N_2O_4$	N
3	$C(CH_3)_3$	60	215	A	$C_{16}H_{26}N_2O_4$	N
4	$(CH_2)_4CH_3$	50	175	E	$C_{18}H_{30}N_2O_4$	N
5		45	255	A	$C_{16}H_{22}N_2O_4$	N
6	>C=S	40	220	C	$C_7H_8N_2O_2S$	C, H, N

[a] Corrected. [b] A, acetone; B, benzene; C, chloroform; E, ethyl ether. [c] Analytical results obtained for the elements listed were within ±0.4% of the theoretical values.

Imidothiazoles

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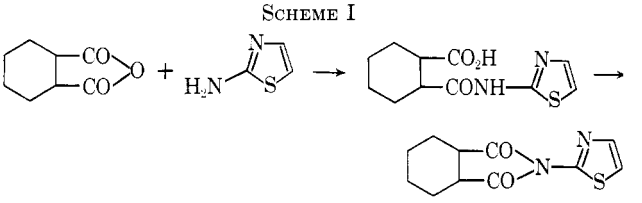
As part of a continuing study of various imides[2-4] and their reduction products as pharmacologically active compounds, we have prepared a limited series of imides derived from 2-aminothiazole and related thiazoles. These imides were obtained from a wide variety of compounds of diverse structure. An example employing 1,2-cyclohexanedicarboxylic anhydride illustrates the general method used (Scheme I). This reaction was either accomplished by heating an intimate

SCHEME I



(1) Deceased, June 1967.

(2) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

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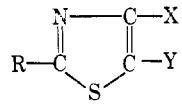
(4) C. H. Grogan and L. M. Rice, *J. Med. Chem.*, **6**, 802 (1963).

TABLE I

IMIDOTHIAZOLES

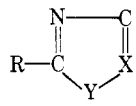


Compd	R	X	Y	Mp, °C	Formula	Analysis[b]	Method[c]	Yield, %
1	Maleimide	H	H	204–206	$C_7H_4N_2O_2S$	C, H, N	B	42
2	3,3-Dimethylglutarimide	H	H	180–181	$C_{10}H_{12}N_2O_2S$	C, H, N	B	46
3	Cyclopropane-1,2-dicarboximide	CH_3	H	197–198	$C_8H_6N_2O_2S$	C, H, N	B	55
4	Cyclobutane-1,2-dicarboximide	CH_3	H	113–115	$C_9H_8N_2O_2S$	C, H, N	B	54
5	*dl*-Camphorimide	H	H	125–126	$C_{15}H_{16}N_2O_2S$	C, H, N	B	38
6	Phthalimide	H	H	208–209	$C_{11}H_6N_2O_2S$	C, H, N	B	78
7	3,4,5,6-Tetrachlorophthalimide	H	H	225–226	$C_{11}H_2Cl_4N_2O_2S$	C, H, Cl, N	A	32
8	3,4,5,6-Tetrabromophthalimide	H	H	225–227	$C_{11}H_2Br_4N_2O_2S$	C, H, Br, N	A	35
9	3,4,5,6-Tetraiodophthalimide	H	H	233–235	$C_{11}H_2I_4N_2O_2S$	C, H, I, N	A	57
10	4-Cyclohexene-1,2-dicarboximide	H	H	108–110	$C_9H_{10}N_2O_2S$	C, H, N	B	60
11	5-Methyl-4-cyclohexene-1,2-dicarboximide	H	H	75–76	$C_{10}H_{12}N_2O_2S$	C, H, N	B	60
12	3-Nitrophthalimide	H	H	229–231	$C_{11}H_5N_3O_4S$	C, H, N	A	63
13	3-Nitrophthalimide	H	NO_2	196–197	$C_{11}H_4N_4O_6S$	C, H, N	A	27
14	Cyclohexane-1,2-dicarboximide	H	H	101–103	$C_9H_{12}N_2O_2S$	C, H, N	B	60
15	3,6-Endomethylene-4-cyclohexene-1,2-dicarboximide	H	H	148–150	$C_{10}H_8N_2O_2S$	C, H, N	B	51
16	3,6-Endomethylene-4-cyclohexene-1,2-dicarboximide	H	NO_2	175–177	$C_{10}H_7N_3O_4S$	C, H, N	B	49
17	3,6-Endoxycyclohexane-1,2-dicarboximide	H	H	187–188	$C_9H_{10}N_2O_3S$	C, H, N	A[d]	38
							B	43
18	3,6-Endoxycyclohexane-1,2-dicarboximide	CH_3	H	193–194	$C_{10}H_{12}N_2O_3S$	C, H, N	B	40
19	3-Methyl-3,6-endoxycyclohexane-1,2-dicarboximide	H	H	157–158	$C_{10}H_{12}N_2O_3S$	C, H, N	B	49
20	1,2-Dimethyl-3,6-endoxycyclohexane-1,2-dicarboximide	H	H	173–175	$C_{11}H_{14}N_2O_3S$	C, H, N	B	37
21	3,6-Dimethyl-3,6-endoxycyclohexane-1,2-dicarboximide	H	H	152–153	$C_{11}H_{14}N_2O_3S$	C, H, N	B	40
22	1,8-Naphthalimide	H	H	301–302	$C_{13}H_8N_2O_2S$	C, H, N	A	57
23	1,8-Naphthalimide	CH_3	H	262–263	$C_{14}H_{10}N_2O_2S$	C, H, N	B	98
24	3,6-Endoxycyclohexane-1,2-dicarboximide	5,6-Dimethylbenzo[e]		252–253	$C_{17}H_{16}N_2O_3S$	C, H, N	B	60
25	3,6-Endoxycyclohexane-1,2-dicarboximide	6-Ethoxybenzo[f]		212–213	$C_{17}H_{16}N_2O_4S$	C, H, N	B	41
26	4-Cyclohexene-1,2-dicarboximide	6-Methylbenzo[f]		186–187	$C_{14}H_{12}N_2O_2S$	C, H, N	B	52
27	3,6-Endoxycyclohexane-1,2-dicarboximide	Naphtho[2,3-*d*][g]		274–275	$C_{17}H_{12}N_2O_3S$	C, H, N	B	32
28	3,3-Pentamethyleneglutarimide	H	H	142–143	$C_{13}H_{16}N_2O_2S$	C, H, N	B	70

[a] See Experimental Section. [b] Solvent, xylene. [c] Solvent, DMF. [d] From 2-amino-5,6-dimethylbenzothiazole. [e] From 2-amino-6-ethoxybenzothiazole. [f] From 2-amino-6-methylbenzothiazole. [g] From 2-amino[2,3-*d*]naphthothiazole. [h] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

TABLE II

MISCELLANEOUS IMIDES

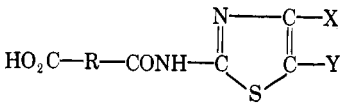


Compd	R	X	Y	Mp, °C	Formula	Analysis[d]	Method[c]	Yield, %
29	3,6-Endoxycyclohexane-1,2-dicarboximide	C–H	O	189–191	$C_{11}H_{10}N_2O_4$	C, H, N	B	20
30	3,6-Endoxycyclohexane-1,2-dicarboximide	N	N–H	339–340	$C_{10}H_{13}N_3O_3$	C, H, N	A[b]	80
31	1,8-Naphthalimide	N	N–H	>365	$C_{14}H_9N_3O_2$	C, H, N	A[b]	54
32	Cyclohexane-1,2-dicarboximide	*e*	N–H	265–266	$C_{13}H_{15}N_3O_2$	C, H, N	B	23

[a] See Experimental Section. [b] Solvent, DMF. [c] From 2-aminobenzimidazole. [d] See Table I, footnote *h*.

mixture of the reactants to 220° (method B) or refluxing the reactants in a high-boiling solvent (method A). This was particularly advantageous when a nitro group was present. In some cases, employing a low-boiling solvent, the intermediate amic acid was isolated. This compound could be cyclized to the imide by heating above its melting point or at 220°. Representative examples of the general procedures used are outlined in the Experimental Section and the compounds prepared are listed in Table I–III.

TABLE III
AMIC ACIDS



Compd	Starting acid	X	Y	Mp, °C	Formula	Analysis[d]	Yield, %
33	Maleic	H	H	153–154[a]	$C_7H_6N_2O_3S$	C, H, N	83
34	3,3-Dimethylglutaric	H	H	181–182[a]	$C_{10}H_{14}N_2O_3S$	C, H, N	91
35	3,4,5,6-Tetrachlorophthalic	H	H	183[a]	$C_{11}H_4Cl_4N_2O_3S$	C, H, Cl, N	62
36	Succinic	H	H	196–197[a]	$C_7H_8N_2O_3S$	C, H, N	88
37	Cyclohexane-1,2-dicarboxylic	H	H	193–194[a]	$C_{11}H_{14}N_2O_3S$	C, H, N	38
38	4-Cyclohexene-1,2-dicarboxylic	H	H	173–175[a]	$C_{11}H_{12}N_2O_3S$	C, H, N	51
39	3,4,5,6-Tetrabromophthalic	H	H	193[a]	$C_{11}H_4Br_4N_2O_3S$	C, H, Br, N	60
40	3-Nitrophthalic	H	NO_2	202–203[a]	$C_{11}H_6N_4O_7S$	C, H, N	81
41	3,6-Endoxycyclohexane-1,2-dicarboxylic	Naphtho[2,3-*d*][b]		270–272[a]	$C_{19}H_{16}N_2O_4S$	C, H, N	87
42	3,6-Endoxycyclohexane-1,2-dicarboxylic	6-Ethoxybenzo[c]		202–203[a]	$C_{17}H_{18}N_2O_5S$	C, H, N	52

[a] With decomposition. [b] From 2-amino[2,3-*d*]naphthothiazole. [c] From 2-amino-6-ethoxybenzothiazole. [d] See Table I, footnote *h*

TABLE IV
BIOLOGICAL DATA[a]

Compd	Dose, mg/kg	Survivors	% T/C[b]
16	160	6/6	21
	160	4/6	40
	160	6/6	*c*
	160	4/7	48
	160	5/6	51
	160	5/6	35
22	400	5/6	36
	400	2/6	*c*
	400	5/6	25
	400	5/7	26
	400	5/6	27
	400	6/6	46
	400	6/6	62

[a] Test system in all cases was Lewis lung carcinoma, with each test animal receiving a single daily injection for 11 days, the surviving animals being sacrificed on the 12th day. [b] Ratio of survival time of test animals to control animals, where 42% is considered acceptable. [c] Test data not reported.

Appropriate compounds were submitted to and screened under the auspices of the Cancer Chemotherapy National Service Center[5] in the primary rodent screens. Most of the compounds were also assayed for growth inhibitory activity against the KB cell line in tissue culture. In most cases the screens showed little activity in the following test systems: Sarcoma 180, Adenocarcinoma 755, L1210 lymphoid leukemia, Dunning leukemia, S91 Cloudman melanoma, Lewis lung carcinoma, and KB tissue culture. However, compounds **16** and **22** showed considerable activity in the screen against Lewis lung carcinoma. These significant data are summarized in Table IV.

Experimental Section

N-(2-Thiazolyl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide (17). Method A.—A mixture of 13.4 g (0.08 mole) of 3,6-endoxycyclohexane-1,2-dicarboxylic acid anhydride and 8.1 g (0.08 mole) of 2-aminoethiazole was dissolved in 100 ml of xylene and refluxed for 4 hr. After cooling, the product crystallized and was recrystallized (EtOH), yield 7.5 g, 38%, final mp 187–188°.

Method B.—An intimate mixture of 8.4 g (0.05 mole) of 3,6-endoxycyclohexane-1,2-dicarboxylic acid anhydride and 5 g (0.05 mole) of 2-aminothiazole was heated at 180° for 30 min. The temperature was raised to 220° and maintained for 10 min. After pouring the oil into water, the crude product which solidified was dried. Two recrystallizations (EtOAc) (charcoal) gave 5.6 g (43%) of analytically pure product, mp 187–188°.

Method C. 1-Cyclohexanecarboxylic Acid 2-(2-Thiazolyl)-amide (37).—A solution of 7.7 g (0.05 mole) of 1,2-cyclohexanedicarboxylic anhydride in CH_2Cl_2 was added 5 g (0.05 mole) of refluxing 2-aminothiazole. After 1 hr, the solvent was removed *in vacuo*, and the residue was washed (hot EtOAc). The crude product, 7.4 g, was dried, mp 179–182°. Two recrystallizations (MeOH) yielded 4.9 g (39%) of pure amic acid, mp 193–194° dec.

Acknowledgment.—The authors wish to thank Dr. Harry Wood of the National Cancer Institute for making the results of the screening data available.

(5) *Cancer Chemotherapy Rept.*, **1**, 43 (1959).

Some Hydrogenated Dibenz[*e*,*g*]isoindoline Derivatives

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For many years we have been interested in isoindoline types of compounds[2,3] and their pharmacological properties. Among these properties in particular have been the ganglionic blocking and hypotensive activity as well as their cytotoxicity. We now wish to report a small group of dibenz[*e*,*g*]isoindoline derivatives and some of their biological properties.

The key intermediate in our synthesis was the anhydride I, which was readily obtained from 1,1′-octahydrobiphenyl by means of the Diels–Alder reaction.[4] Preparation of the desired compounds was carried out by the reaction of the anhydride with an appropriate dialkylaminoalkylamine to produce an amic acid which on heating at 200° cyclized to yield the imide II. This product could be distilled easily and was reduced readily

(1) Deceased, June 1967.
(2) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).
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