filtered and concentrated. The residue was distilled under reduced pressure. The above free base was dissolved in anhydrous ethanol and treated with an equivalent amount of anhydrous hydrogen chloride. The hydrochloride salt was obtained on diluting the solution with anhydrous ether to cloudiness and standing at 0°. Nine 3-acyloxy-3-aryl-1-methylpyrrolidines and one 1-ethylpyrrolidine and their hydrochlorides were prepared in this manner. Their physical constants are tabulated in Table II.

Acknowledgment.—We are indebted to Dr. John W. Kissel and his associates for the pharmacological data.

Structure-Activity Relationships in a Series of Anticonvulsant Bicyclic Acylureas

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The synthesis of a series of monocyclic and bicyclic carbonylureas is reported. The monocyclic carbonylureas containing a hydrogen atom in the *alpha*-position are of no interest as anticonvulsants. 2-Norbornene-5-*endo*-carbonylurea, however, afforded good protection against both electroshock- and pentylenetetrazol-induced convulsions. Introduction of a methyl group *alpha* to the carbonylurea chain of the monocyclic and bicyclic derivatives markedly enhanced anticonvulsant activity. Cycloalkenyl and bicycloalkenyl derivatives were more active than their saturated congeners. Anticonvulsant activity was abolished by the introduction of carboxyl, carbomethoxy or carboximide groupings. N^3-Acetylation reduced activity slightly but significantly increased the duration of action.

As part of an investigation of the contribution of bicyclic nuclei to pharmacodynamically active compounds[2] a series of acylureas derived from bridged bicyclic acids was synthesized. The acylurea radical has long been associated in medicinal chemistry with depression of the central nervous system[3] and Spielman and co-workers[4] have reported the anticonvulsant properties of an extensive series of acylureas derived from alkyl, aralkyl, aryl and heterocyclic carboxylic acids.

(1) Shulton, Inc., Clifton, N. J.

(2) For the previous paper of this series see: W. R. Boehme, E. A. Siegmund, W. G. Scharpf, and E. Schipper, *J. Med. Pharm. Chem.*, **5**, 451 (1962).

(3) H. P. Kaufmann, "Arzneimittelsynthese," Springer-Verlag, Berlin, 1953, p. 30.

(4) M. A. Spielman, A. O. Geiszler, and W. J. Close, *J. Am. Chem. Soc.*, **70**, 4189 (1948).

The bicyclic acylureas may be regarded as highly compacted, three-dimensional α-substituted acetylureas. The fixed stereochemistry of the bicyclic ring made it of interest to study the steric effects of *endo* and *exo* substitution upon anticonvulsant activity. For comparison several monocyclic acylureas were also synthesized.

The reaction of an acid chloride with urea in the presence of benzene[5] gave moderate yields of the acylureas (Method A). A somewhat better procedure (Method B), which was particularly applicable to bicyclic *gem*-methyl carbonyl chlorides, consisted of the ammonolysis of an acyl isocyanate (Table I), which in turn had been prepared from the corresponding acid chloride and silver cyanate.[6] The reaction of sodiourea[7] with bicyclic acid chlorides invariably led to partial epimerization and the resulting mixtures of isomers proved to be difficult to separate. The saturated bicyclic acylureas were obtained from the corresponding acid chlorides or, more conveniently, by catalytic hydrogenation (Method C) of the unsaturated analogs. Reaction of the isocyanate derived from 5-*endo*-methyl-2-norbornene-5-*exo*-carboxylic acid with acetamide,[8] methylamine and urea[6] gave the diacylurea XVIII, the N^3-methylated acylurea XVI and the acylbiuret XIX, respectively. Maleuric acid and several of its derivatives[9] were condensed with cyclopentadiene in the Diels–Alder reaction to give the 6-carboxyl substituted 2-norbornene-5-carbonylurea, its methyl ester and imide (Method D). Cyclopentane-, 3-cyclohexene- and 1-methyl-3-cyclohexene-carbonylurea were prepared by methods A and B for comparative activity studies.

Anticonvulsant activity was determined in mice against electroshock- and pentylenetetrazol-induced convulsions by the method of Swinyard and co-workers.[10] The procedure of P'an and co-

TABLE I

ACYL ISOCYANATES (RCONCO)

RCO	Yield, %	B.p. °C.	B.p. (mm.)
2-Norbornene-5-*exo*-carbonyl	73	82–85	14
5-*endo*-Methyl-2-norbornene-5-*exo*-carbonyl	89	106–109	30
5-*exo*-Methyl-2-norbornene-5-*endo*-carbonyl	82	107–108	26
3-Cyclohexene-1-carbonyl	89	100–102	30

(5) R. W. Stoughton, *J. Org. Chem.*, **2**, 514 (1938).
(6) A. J. Hill and W. M. Degnan, *J. Am. Chem. Soc.*, **62**, 1595 (1940).
(7) R. A. Jacobson, *ibid.*, **58**, 1984 (1936).
(8) R. Scholl, *Ber.*, **23**, 3515 (1890).
(9) P. O. Tawney, R. E. Snyder, C. E. Bryan, R. P. Conger, F. S. Dovell, R. J. Kelly, and C. H. Stiteler, *J. Org. Chem.*, **25**, 56 (1960).
(10) E. W. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 819 (1952).

workers[11] was employed to measure hypnotic activity in mice. Toxicity was determined by oral administration to mice and LD_{50} values were calculated by the method of Litchfield and Wilcoxon.[12] The activities of several compounds of this series have been reported in preliminary communications.[13,14]

An inspection of Table III permits some generalizations to be made with respect to the effect of substituent changes upon anticonvulsant activity: (a) Anticonvulsant activity is increased when the monocyclic ring is replaced by a bridged bicyclic structure. (b) The introduction of a methyl group α to the carbonylurea increases the anticonvulsant activity of both monocyclic and bicyclic acylureas. (c) Saturation of the double bond decreases anticonvulsant activity. (d) Ring enlargement of the norbornene ring to bicyclo[2.2.2]oct-2-ene does not significantly alter anticonvulsant activity. (e) Both *endo* and *exo* isomers of the norbornenecarbonylureas elicit approximately the same high order of anticonvulsant activity. In one instance, the *endo*-carbonylurea (VII) was considerably less toxic and longer acting than its stereoisomer (VIII). (f) N^3-Methylation, carbamoylation and acetylation of the bicyclic carbonylureas reduces anticonvulsant activity. N^3-Acetylation of compound VIII decreased activity slightly but significantly prolonged the duration of action. (g) The introduction of a second carboxylic function into the bicyclic ring abolishes anticonvulsant activity.

Compound VIII was administered orally to groups of 4 dogs each for periods of 24 to 31 weeks. No deleterious effects were observed at a level of 12.5 mg./kg. daily. Liver function tests (bromosulfalein dye retention), which indicated some damage at 62.5 mg./kg. daily, returned to normal within 5 weeks after withdrawal of the drug.[15]

Experimental[16]

Preparation of Acid Chlorides.—The published procedures were followed to obtain 2-norbornene-5-*endo*-carbonyl chloride,[17] 5-*exo*-methyl-2-norbornene-5-*endo*-carbonyl chloride,[18] 5-*endo*-methyl-2-norbornene-5-*exo*-carbonyl chloride,[18]

(11) S. Y. P'an, J. F. Gardocki, M. Harfenist, and A. Bavley, *ibid.*, **107**, 459 (1953).

(12) J. T. Litchfield, Jr., and F. Wilcoxon, *ibid.*, **96**, 99 (1949).

(13) E. A. Siegmund, R. A. Cadmus, A. H. Campbell, Jr., M. J. Penek, and G. Lu, *Federation Proc.*, **15**, 484 (1956).

(14) E. H. Jenney and C. C. Pfeiffer, *Ann. N. Y. Acad. Sci.*, **64**, 679 (1956).

(15) Data reported by Hazleton Laboratories, Falls Church, Va.

(16) Analyses were performed by Mr. E. R. Hoffmann and staff of these Laboratories. Melting points are uncorrected.

(17) W. R. Boehme, E. Schipper, W. G. Scharpf, and J. Nichols, *J. Am. Chem. Soc.*, **80**, 5488 (1958).

(18) S. Beckmann, R. Schaber, and R. Bamberger, *Chem. Ber.*, **87**, 997 (1954); J. S. Meek and W. B. Trapp, *J. Am. Chem. Soc.*, **79**, 3909 (1957).

TABLE II
ACYLUREAS

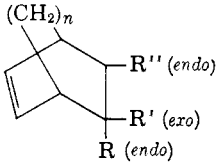
Compound no.	n	R	R′	R″	Method	Yield, %	Recrystn. solvent
a. Derivatives of Norbornene and Bicyclo[2.2.2]oct-2-ene							
IV	1	$CONHCONH_2$	H	H	A	30	EtOAc-MeOH
					B	36	
VI	1	H	$CONHCONH_2$	H	B	41	EtOAc
VII[a]	1	$CONHCONH_2$	CH_3	H	B	50	$C_6H_5CH_3$
VIII	1	CH_3	$CONHCONH_2$	H	B	56	$C_6H_5CH_3$
X	2	$CONHCONH_2$	H	H	A	37	EtOAc
XI	2	$CONHCONH_2$	CH_3	H	A	27	Et_2O
XIII[b]	1	$CONHCONH_2$	H	COOH	D	55	EtOH
XIV[b]	1	$CONHCONH_2$	H	$COOCH_3$	D	70	EtOH
XVI	1	CH_3	$CONHCONHCH_3$	H	B	56	C_6H_{14}
XVIII	1	CH_3	$CONHCONHCOCH_3$	H	B	40	EtOH, H_2O
XIX	1	CH_3	$CONHCONHCONH_2$	H	B	13	$C_6H_5CH_3$, EtOH
b. Derivatives of Norbornane and Bicyclo[2.2.2]octane							
V	1	$CONHCONH_2$	H		C	84	Me_2CHOH, $C_6H_5CH_3$
IX	1	CH_3	$CONHCONH_2$		C	91	Me_2CHOH
XII	2	$CONHCONH_2$	CH_3		A	28	EtOAc
XVII	1	CH_3	$CONHCONHCH_3$		C	88	EtOH
c. Miscellaneous Compounds							
I		Cyclopentanecarbonylurea			A	74	$CHCl_3$
II		3-Cyclohexene-1-carbonylurea			B	87	EtOH
III		1-Methyl-3-cyclohexene-1-carbonylurea			A	70	MeOH
XV[b]		N-Carbamyl-2-norbornene-5,6-dicarboximide			D	87	Acetone

[a] We are indebted to Mr. R. Kouhoupt for the preparation of this compound.

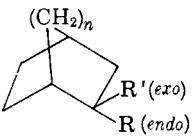
bicyclo[2.2.2]oct-2-ene-5-*endo*-carbonyl chloride,[19] 2-methylbicyclo[2.2.2]octane-2-carbonyl chloride,[17] 3-cyclohexene-1-carbonyl chloride,[20] 1-methyl-3-cyclohexene-1-carbonyl chloride,[21] and cyclopentanecarbonyl chloride.[22]

Preparation of Acyl Isocyanates.—The preparation of 2-norbornene-5-*endo*-carbonyl isocyanate is typical of the general procedure. Commercial silver cyanate (16.5 g., 0.11 mole) was added slowly to a stirred solution of 15.7 g. (0.1 mole)

(19) C. A. Grob, H. Kny, and A. Gagnieux, *Helv. chim. Acta*, **40**, 130 (1957).
(20) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).
(21) A. A. Petrov and N. P. Sopov, *Zhur. Obshchei Khim.*, **18**, 1781 (1948).
(22) R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, **65**, 99 (1894).



M.p., °C	Formula	Analysis, % Calcd. C	H	N	Found C	H	N
202–203	$C_9H_{12}N_2O_2$	59.98	6.71	15.55	60.16	6.86	15.30
197.5–198.5	$C_9H_{12}N_2O_2$	59.98	6.71		60.12	6.89	
164–165	$C_{10}H_{14}N_2O_2$	61.83	7.26		62.03	7.48	
148.5–149.5	$C_{10}H_{14}N_2O_2$	61.83	7.27	14.42	62.07	7.32	14.32
207–208	$C_{10}H_{14}N_2O_2$	61.83	7.27	14.42	61.98	7.23	14.71
197–199	$C_{11}H_{16}N_2O_2$	63.44	7.74	13.45	63.43	7.55	13.35
171–172	$C_{10}H_{12}N_2O_4$	53.57	5.39	12.50	53.51	5.53	12.38
194–195	$C_{11}H_{14}N_2O_4$	55.45	5.92	11.76	55.74	6.06	11.90
136–137	$C_{11}H_{16}N_2O_2$	63.44	7.74	13.45	63.54	7.75	13.53
161–162	$C_{12}H_{16}N_2O_3$	61.00	6.83	11.86	61.22	6.91	11.75
199–200	$C_{11}H_{16}N_2O_3$	55.68	6.37	17.71	55.62	6.21	17.55



210–210.5	$C_9H_{14}N_2O_2$	59.32	7.74	15.37	59.50	7.86	15.61
160–161	$C_{10}H_{16}N_2O_2$	61.20	8.22	14.28	61.10	8.22	14.10
202–204	$C_{11}H_{18}N_2O_2$	62.83	8.63	13.32	63.07	8.71	13.20
160–161	$C_{11}H_{18}N_2O_2$	62.83	8.63	13.32	62.70	8.61	13.25
207–208	$C_7H_{12}N_2O_2$	53.83	7.74	17.94	53.99	7.68	17.80
235–236	$C_8H_{12}N_2O_2$	57.13	7.19	16.66	57.40	7.31	16.60
134–135	$C_9H_{14}N_2O_2$	59.32	7.74	15.38	59.44	7.81	15.18
151.5–152.5	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.58	58.58	5.02	13.43

We are indebted to Mr. M. Tobkes for the preparation of these compounds.

of 2-norbornene-5-*endo*-carbonyl chloride[17] in 75 ml. of absolute ether or carbon tetrachloride. At times a noticeably exothermic reaction occurred during the addition and external cooling became necessary. The mixture was then refluxed with stirring for 4 hr., the silver chloride and excess silver cyanate filtered off and the filtrate distilled under reduced pressure through a short Vigreux column. The yield of colorless liquid was 12.9 g. (79%), b.p. 100–104° (22 mm.).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.25; H, 5.80; N, 8.44.

Acylureas. Procedure A—Reaction of an Acid Chloride with Urea.—A mixture of 0.1 mole of the acid chloride, 0.11 mole of well dried urea and 150 ml. of anhy-

TABLE III

STRUCTURE–ACTIVITY RELATIONSHIPS

Compound No.	Anticonvulsant activity: ED_{50} (mg./kg.) MES	ED_{50} (mg./kg.) Pentylenetetrazol	Neurotoxic $dose_{50}$	Protective Index MES	Protective Index Pentylenetetrazol	Hypnotic $dose_{50}$	LD_{50}
I	910	Inactive (1000)					
II	Inactive (1000)	Inactive (1000)					
III	270	240	550	2.0	2.3		1888
IV	260	88	225	0.9	2.6		>8000
V	260	145	220	0.8	1.5		>4000
VI	177	110	210	1.2	1.9		3100
VII	70	37	30	0.4	0.8	100	1300
VIII	75	31	46	0.6	1.5	142	355
IX	213	160	153	0.7	1.0	350	~1500
X	180	130	200	1.1	1.5		>2000
XII	~375	>500	~500				>1000
XIII	Inactive (1000)						
XIV	Inactive (1000)						
XV	Inactive (1000)						
XVI	~200	~500	~500				>1000
XVIII	93	42	93	1.0	2.2	125	290
XIX	~200	>250	~375 (convulsant)				>1000
Phenacetylurea	94	158	280	3.0	1.8		~5000

drous benzene was refluxed with stirring for 6 hr. and allowed to cool. Water (100 ml.) and sufficient potassium carbonate to give a slightly alkaline reaction were added to the crystalline suspension. The solid was removed by filtration, washed successively with benzene and water and air-dried. The crude product was purified by recrystallization.

Procedure B—Reactions with Acyl Isocyanates.—(a) Anhydrous ammonia or methylamine was passed into a stirred solution of 0.1 mole of the acyl isocyanate in 200 ml. of pentane for 2 hr. The solution, from which the product gradually separated, was allowed to stand overnight at room temperature. The crude material was removed by filtration and purified by recrystallization.

(b) A solution of 0.25 mole of the acyl isocyanate and 0.275 mole of acetamide or urea in 400 ml. of toluene was refluxed for 6 hr. The suspension was cooled in the refrigerator, filtered and the precipitate purified by recrystallization.

Procedure C—Hydrogenation.—A solution of 0.1 mole of the unsaturated acylurea in 300 ml. of dimethylformamide was hydrogenated in the presence of palladium oxide catalyst at 3.5 kg./cm.^{2} pressure. The absorption of hydrogen was complete in 45 min. The catalyst was filtered off, the solvent removed by distillation under reduced pressure and the residue was purified by recrystallization.

Procedure D—Diels-Alder Condensation.—Freshly distilled cyclopentadiene (0.35 mole) was added to a solution of 1.0 g. of hydroquinone and 0.25 mole of the dienophile in an appropriate solvent (maleuric acid[9] in 2 l. of acetic acid, methyl maleurate[9] in 500 ml. of acetone and N-carbamylmaleimide[9] in 1500 ml. of dioxane). The mixture was heated at 50–60° for 2 hr., an additional 0.15 mole of cyclopentadiene added and heating was continued for an additional 2 hr. The product, which was separated by filtration or by distillation of the solvent, was purified by recrystallization.

Some Aspects of the Chemistry of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione, an Anesthetic Agent

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The loss of potency of aqueous solutions of the sodium salt of 5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione was found to be due to hydrolysis to a linear product. Reactions carried out upon the dione established that it was stable enough so that derivatives could be prepared directly from it. Further, the sites where substitutions could be made without damage to the ring were established. Several derivatives and decomposition products were isolated and some preliminary pharmacological observations were made.