in our earlier paper.[1] The results obtained are listed in Tables III and IV. Increasing the size of the substituent on the nitrogen atom resulted, in selected cases, in compounds having good potency. Compound (12), where *p*-aminophenethyl replaces methyl, has activity significantly greater than the reference compound. The *p*-nitrophenethyl compound (11), an intermediate in the synthesis of the *p*-aminophenethyl analog, would appear to be of interest with regard to its apparently low toxicity compared with other compounds in the series; with its retention of analgetic activity this gives the compound the highest rating in the potency–toxicity column of the tables. However, it is likely that full inherent toxicity was not manifest because of incomplete solution of the compound particularly at toxic dose levels. A strongly basic side chain (10), or an acidic one (20) effectively destroyed activity. None of the compounds with oxygenated side-chains (5,6,13,14,15,16,17,18) showed activity superior to the N-methyl compound. Isosteric replacement of the phenyl group at position 3 with *o*-pyridyl had an unsatisfactory result, while insertion of a methyl, methoxy or trifluoromethyl group effectively abolished activity.

Structure–Activity Relationships in a Series of Anticonvulsant and Hypnotic Bicyclic Carboxamides

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Received October 7, 1961

A series of stereoisomeric 5-substituted 2-norbornene-5-carboxamides was synthesized. The effect of alkyl, alkenyl, dialkylaminoalkyl, aryl and aralkyl substitution in the 5-position, halogenation, and N-alkylation upon electroshock- and pentylenetetrazol-induced convulsions and upon hypnotic activity is discussed. The norbornene derivatives are compared with their positional isomers, with bicyclo[2.2.2]oct-2-ene homologs and with several saturated and unsaturated monocyclic analogs.

Central nervous system depression is a characteristic pharmacodynamic response commonly observed upon administration of

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

aliphatic α-substituted acetic acids and more particularly of their amidic derivatives.[2] Alterations in the nature of the α-substituent and of the amide function may lead to manifestation of this depression as sedation, hypnosis, reduction in the response to pain, spasms, convulsions, etc. These differences have been attributed to a relative specificity for enzymatic receptor sites concerned with the mediation of nerve impulses.[3] The weak depressant action of the lower unbranched carboxamides is enhanced by lengthening and by branching of the alkyl chain.[4] α,α-Dialkylacetic acid derivatives are usually more effective than their monosubstituted analogs and activity reaches a maximum when the three α-hydrogen atoms of acetamide are substituted.[5,6] Hypnotic activity may at times be increased further by replacing alkyl by alkenyl[7] or halogen.[7,8]

As part of an investigation of the contribution of bridged bicyclic nuclei to pharmacodynamically active structures,[9] we synthesized a series of carboxamides from some 2-norbornene- and related carboxylic acids. These compounds may be regarded as highly compacted, three-dimensional, α-substituted acetamides whose fixed stereochemistry affords a unique opportunity to study the steric effects of the bicyclic ring and its substituents upon depressant activity. For comparison of pharmacodynamic activity both the bicyclic ring and its substituent alkyl groups were varied. The norbornene ring was replaced by bicyclo[2.2.2]oct-2-ene and by monocyclic saturated and unsaturated rings. The 2-alkyl substituent was modified to include alkenyl, dialkylaminoalkyl, aryl, aralkyl, and halogen. Finally, the effect of N-alkyl substitution of the carboxamide moiety was investigated.

The 5-*endo*-alkyl-2-norbornene-5-*exo*-carboxamides of this series were obtained by Diels–Alder condensation of cyclopentadiene with an appropriately substituted acrylic acid and conversion of the resulting 5-*endo*-alkyl-2-norbornene-5-*exo*-carboxylic acid to the carboxamide via the corresponding acid chloride. The stereoisomeric 5-*exo*-alkyl-2-norbornene-5-*endo*-carboxamides were obtained by alkylation of 5-*endo*-cyano-2-norbornene in the presence of sodamide fol-

(2) A. Burger, "Medicinal Chemistry," Interscience Publishers, Inc., New York, N. Y., 1960, p. 371.
(3) G. J. Martin, "Biological Antagonism," Blakiston Co., New York, N. Y., 1951, p. 476.
(4) H. P. Kaufmann, "Arzneimittel-Synthese," Springer-Verlag, Berlin, 1953, p. 30.
(5) S. Fränkel, "Die Arzneimittel-Synthese," Julius Springer, Berlin, 1919, p. 480.
(6) K. Junkmann, *Arch. exptl. Path. Pharmakol.*, **186**, 552 (1937).
(7) G. Ehrhart, *Med. u. Chem.*, **3**, 366 (1936).
(8) G. Ehrhart, *ibid.*, **2**, 338 (1934).
(9) For previous paper see: W. R. Boehme, M. L. Graeme, W. G. Scharpf, E. A. Siegmund, E. Schipper, and M. Tobkes, *J. Med. Pharm. Chem.*, **4**, 183 (1961).

lowed by saponification of the intermediate 5-*exo*-alkyl-5-*endo*-cyano-2-norbornenes. The elucidation of the stereochemical configurations of some of these derivatives and the synthetic methods by which they were obtained have been reported in an earlier communication from these laboratories.[10]

5-Phenyl-5-cyano-2-norbornene was obtained by the Diels–Alder condensation of cyclopentadiene with troponitrile, an incipient dienophile which is dehydrated to atroponitrile at the reaction temperature. Hydrolysis of this intermediate gave 5-phenyl-2-norbornene-5-carboxamide (XXI) whose steric configuration was not determined. The N-substituted carboxamides were prepared from the bicyclic acid chlorides and the appropriate amines. 2-*exo*-Bromonorbornane-2-*endo*-carboxamide (XXXV) and its rearrangement product 2-*exo*-bromonorbornane-1-carboxamide (XXXVI) have been described previously.[11] 2-Bromobicyclo[2.2.2]octane-2-carboxamide (XXXVIII) was obtained by the method employed for the norbornane homolog. The related α-bromonorbornane-2-*endo*-acetamide (XXXVII) was prepared *via* the Hell-Volhard bromination of norbornane-2-*endo*-acetyl chloride and subsequent ammonolysis of the α-bromo-acid chloride. Finally, a dihalo derivative, 2-*exo*-methyl-5,7-dichloronorbornane-2-*endo*-carboxamide (XXXIX) was obtained by direct chlorination of 5-*endo*-methyl-2-norbornene-5-*exo*-carboxylic acid in chloroform, conversion to the acid chloride and subsequent ammonolysis.

Anticonvulsant activity against electroshock- and pentylenetetrazol- induced convulsions and hypnotic activity were determined in mice by the methods of Swinyard *et al.*[12] and P'an *et al.*,[13] respectively. Toxicity was measured by oral administration to mice and the LD_{50} values were calculated according to Litchfield and Wilcoxon.[14] The activities of several compounds of this series have been reported in a preliminary communication.[15]

Table III compares the anticonvulsant and hypnotic activities of a series of 2-norbornene-5-*endo*-carboxamides. 2-Norbornene-5-*endo*-carboxamide (I), which may be regarded as an α,α-disubstituted

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

(11) W. R. Boehme, *ibid.*, **81**, 2762 (1959).

(12) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

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

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

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

acetamide, was practically devoid of activity. A marked enhancement of activity accompanied the introduction of a 5-*exo*-alkyl substituent. Anticonvulsant and hypnotic activity of the 5-*exo*-alkyl-2-norbornene-5-*endo*-carboxamides, which are comparable to the α,α,α-trisubstituted acetamides, increased with the length of the alkyl group reaching a maximum in 5-*exo*-*n*-propyl-2-norbornene-5-*endo*-carboxamide (IV), and then decreased upon further lengthening of the chain. Unfortunately, neurological side effects which were manifested by drowsiness and sedation also increased with the length of the 5-substituent so that actually the lowest homolog, 5-*exo*-methyl-2-norbornene-5-*endo*-carboxamide (II), exhibited the optimum anticonvulsant protective index (P.I. = ED_{50}/NTD_{50} = 1.3) against pentylenetetrazol. However, the optimum hypnotic therapeutic index (T.I. = ED_{50}/LD_{50} = 2.6) was found in IV. It is of interest to note that in this series unbranched substituents gave more active compounds than their branched isomers (IV > V and VIII > IX) and that a compound with a saturated chain was more effective than its olefinic analog (IV > VI).

Introduction of a benzyl group into the 5-position of 2-norbornene-5-*endo*-carboxamide led to a fairly active CNS depressant (XV). Equivalent substitution by a phenyl group (XXI) or by dialkylaminoalkyl moieties (XII to XIV) abolished both anticonvulsant and hypnotic activity at the maximum dosage administered. When the carboxamide function of I or XXIII (Table III) was replaced by N-methylcarboxamide (XVI and XVII, respectively) activity was qualitatively unchanged. N,N-Dimethyl-5-*endo*-methyl-2-norbornene-5-*exo*-carboxamide (XVIII) also resembled its unmethylated primary amide (XXIII) in action. N,N-Diethyl-5-*endo*-methyl-2-norbornene-5-*exo*-carboxamide (XIX), however, elicited the characteristic stimulant response of many tertiary carboxamides in low doses and N,N-tetramethylene-2-norbornene-5-*endo*-carboxamide (XX) produced convulsions at high dosage levels.

The anticonvulsant and hypnotic activities of several stereoisomeric 2-norbornene-5-carboxamides are compared in Table IV. 2-Norbornene-5-*exo*-carboxamide (XXII), like its stereoisomer (I), exhibited a low order of anticonvulsant activity. 5-*endo*-Methyl- and 5-*endo*-ethyl-2-norbornene-5-*exo*-carboxamide (XXIII and XXIV, respectively) were more active as hypnotics and against electroshock-induced convulsions than their stereoisomers (II and III). Against pentylenetetrazol the differences were less marked. Neurotoxic dose and acute toxicity values of the alkylated 2-*exo*-carboxamides were

generally lower and may be related to differences in the rate of absorption.[9,16]

The effect of ring modification upon anticonvulsant and hypnotic activity is summarized in Table V. Replacement of the 2-norbornene nucleus of II by the bicyclo[2.2.2]oct-2-ene moiety (XXV) elicited a marked increase in hypnotic activity and an inhibition of electroshock-induced convulsions. Neurological effects and acute toxicity, however, also increased and the protective index against electroshock remained unchanged although the hypnotic therapeutic index rose to 3.0. Saturation of the double bond to form the bicyclo[2.2.2]octane derivative (XXVI) effected a reduction in activity analogous to that observed in the related series of norbornane-2-carbonylureas. The optimum hypnotic activity found in 5-*exo*-*n*-propyl-2-norbornene-5-*endo*-carboxamide (IV) led us to examine the homologous bicyclo-[2.2.2]oct-2-ene derivative (XXVII). This compound, although approximately equal in hypnotic potency to IV on a molar basis, possessed a more favorable therapeutic index. 1,4-Dimethyl-3-cyclohexene-1-carboxamide (XXVIII), a monocyclic isomer of the norbornene II, possessed less anticonvulsant activity, greater hypnotic activity and approximately the same acute toxicity as II. The hypnotic therapeutic index of XXVIII was approximately equal to that of the bicyclo[2.2.2]oct-2-ene derivative (XXVII). Removal of the methylene bridge of II gave a compound (1-methyl-3-cyclohexane-1-carboxamide, XXIX) which was at least as effective in anticonvulsant and hypnotic activity but slightly more toxic. 1-Methylcyclopentane-1-carboxamide (XXX), the fragment of II remaining after removal of the vinylene bridge, showed a marked reduction in both anticonvulsant and hypnotic activity.

Norbornane-1-carboxamide (XXXI), although an α,α,α-trisubstituted acetamide, was inactive at the 500 mg./kg. level. The two acetamides, 2-norbornene-5-*endo*-acetamide (XXXII) and its monocyclic analog, 3-cyclohexene-1-acetamide (XXXIII) and the acetoxy derivative (XXXIV) exhibited no activity of interest.

The well-known central nervous system depressant action of halogenated carboxamide derivatives led us to examine 2-*exo*-bromonorbornane-2-*endo*-carboxamide (XXXV) and its rearrangement product, 2-*exo*-bromonorbornane-1-carboxamide (XXXVI). Only the α-bromocarboxamide (XXXV) gave protection against electroshock-induced convulsions, although both isomers appeared to be approximately equal in activity against pentylenetetrazol. 2-

(16) Similar differences in anticonvulsant activity have also been observed in stereoisomeric spiro bicyclic carbonylureas (to be published).

Bromobicyclo[2.2.2]octane-2-carboxamide (XXXVIII) exhibited anticonvulsant activity of the same order as its norbornane homolog (XXXV). α-Bromonorbornane-2-*endo*-acetamide (XXXVII), as other acetamides of this series, was of no pharmacodynamic interest.

Experimental[17]

2-Norbornene-5-*endo*- and *exo*-carboxamides (I and XXII) were prepared by the published procedure.[10]

5-*exo*-Substituted-5-*endo*-cyano-2-norbornenes. General Procedure.—5-*endo*-cyano-2-norbornene[18] (1.0 mole) was added dropwise to a stirred suspension of sodamide prepared in the usual manner from 1 mole of sodium in 1000-1200 ml. of liquid ammonia with the aid of ferric nitrate as a catalyst. The alkyl chloride or bromide (1.25 mole) then was added dropwise with stirring and followed by approximately 200 ml. of dry toluene. Stirring was continued until most of the ammonia had evaporated (overnight) and the suspension was filtered through Celite. The filter cake was washed well with toluene and discarded. The combined filtrates were washed with dilute hydrochloric acid to remove the amidine by-products and dried superficially by shaking briefly with anhydrous potassium carbonate. The alkylated nitrile was separated by fractional distillation under reduced pressure (see Table I).

5-*exo*-Substituted-2-norbornene-5-*endo*-carboxamides.—The 5-*exo*-substituted-5-*endo*-cyano-2-norbornene (0.2 mole) was refluxed for 10 hr. with 1.0 mole of potassium hydroxide as a 40% solution in 95% ethanol. Most of the solvent was removed by distillation under reduced pressure through a Vigreux column on the steam-bath while 2 vol. of water was added gradually. The solid carboxamide which separated from the aqueous phase was filtered off, washed with cold water and purified by recrystallization from hexane or heptane. Carboxamides prepared by this method are listed in Table II. The preparation of 5-*exo*-methyl-2-norbornene-5-*endo*-carboxamide (II) and 5-*exo*-ethyl-2-norbornene-5-*endo*-carboxamide (III) by this method was reported previously.[10]

N-Methyl-2-norbornene-5-*endo*-carboxamide (XVI).—The reaction of 123 g. of 2-norbornene-5-*endo*-carbonyl chloride[10] and 72.5 g. of methylamine in dry benzene solution gave 99.0 g. (81%) of long, colorless needles, m.p. 99–102° (from hexane). For analysis a sample was recrystallized twice from hexane, m.p. 102–103.5°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.66; H, 8.54; N, 8.90.

N,N-Tetramethylene-2-norbornene-5-*exo*-carboxamide (XX).—The reaction of 2-norbornene-5-*exo*-carbonyl chloride[10] (32.3 g.) and pyrrolidine (29.8 g.) in dry benzene solution gave upon distillation 35.9 g. (91%) of colorless liquid, b. p. 100–102° (0.03 mm.).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.20; H, 9.04; N, 7.37.

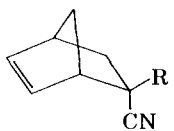
N-Methyl-5-*endo*-methyl-2-norbornene-5-*exo*-carboxamide (XVII).—5-*endo*-

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

(18) This compound was prepared by the method of H. A. Bruson (*J. Am. Chem. Soc.*, **64**, 2457 (1942)) with slight modifications to minimize formation of the *exo* isomer. The reaction temperature was maintained at 25° and ether was used as a solvent.

TABLE I

5-*exo*-SUBSTITUTED-5-*endo*-CYANO-2-NORBORNENES

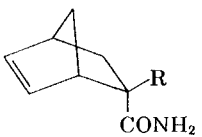


R	B.p. °C	B.p. mm.	Yield. %	$n^{25}D$	Analysis. % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$-CH(CH_3)_2$	99–102	6	63	1.4826	81.93	9.38	8.69	82.14	9.51	8.54
$-(CH_2)_2CH_3$	121–124	16	79	1.4798	81.93	9.28	8.69	81.69	9.19	8.49
$-(CH_2)_3CH_3$	136–140	21	67	1.4776	82.23	9.78	7.99	82.12	9.73	7.85
$-(CH_2)_4CH_3$	135–137	17	66	1.4776	82.48	10.12	7.40	82.29	10.29	7.28
$-(CH_2)_2CH(CH_3)_2$	148–152	25	65	1.4770	82.48	10.12	7.40	82.54	9.99	7.42
$-(CH_2)_5CH_3$	124–125	0.03	65	1.4762	82.70	10.41	6.89	82.86	10.64	6.74
$-(CH_2)_{11}CH_3$[a]	120–140	0.05	56	—	83.56	11.57	4.87	83.55	11.56	4.86
$-CH_2CH=CH_2$	108–112	8	42	1.4937	82.97	8.23	8.80	83.26	8.25	8.60
$-CH_2CH_2N(CH_3)_2$	139	8	40	1.4883	75.74	9.54	14.72	75.67	9.42	14.55
$-CH_2CH_2N(C_2H_5)_2$	79–84	0.07	45	1.4822	77.01	10.16	12.83	76.74	10.10	12.99
$-CH_2CH_2CH_2N(C_2H_5)_2$	95–97	0.07	54	1.4830	77.53	10.41	12.06	77.64	10.53	12.08
$-CH_2C_6H_5$[b]	92–94	0.02	39	—	86.08	7.22	6.69	87.26	7.40	5.08

[a] M.p. 44–45.5°. [b] The benzylated nitrile appeared to be contaminated with tetracyclopentadiene which gradually crystallized from the product and could not be separated by distillation.

TABLE II

5-*exo*-SUBSTITUTED-2-NORBORNENE-5-*endo*-CARBOXAMIDES

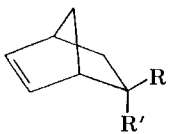


Compound	R	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IV	$-(CH_2)_2CH_3$	110–111	20	73.70	9.56	7.81	73.74	9.61	7.80
V	$-CH(CH_3)_2$[a]	129–130	70	73.70	9.56	7.81	73.81	9.67	7.75
VI	$-CH_2CH=CH_2$	98–99	75	74.54	8.53	7.90	74.72	8.32	7.67
VII	$-(CH_2)_3CH_3$	111–112	67	74.57	9.91	7.25	74.35	9.99	7.21
VIII	$-(CH_2)_4CH_3$	94–94.5	77	75.31	10.21	6.76	75.40	10.33	6.70
IX	$-(CH_2)_2CH(CH_3)_2$	96–97	46	75.31	10.21	6.76	75.50	10.19	6.66
X	$-(CH_2)_5CH_3$	93–94	51	75.97	10.47	6.33	76.17	10.73	6.34
XI	$-(CH_2)_{11}CH_3$	82–83.5	40	78.63	11.55	4.59	78.59	11.51	4.42
XII	$-(CH_2)_2N(CH_3)_2$	127–128	34	69.17	9.68	13.45	69.23	9.46	13.52
XIII	$-(CH_2)_2N(C_2H_5)_2$	108–109	76	71.14	10.24	11.85	70.86	10.38	11.78
XIV	$-(CH_2)_3N(C_2H_5)_2$	94.5–95.5	67	71.95	10.47	11.19	72.14	10.57	11.15
XV	$-CH_2C_6H_5$	119.5–120	67	79.26	7.54	6.61	79.06	7.67	6.21

[a] The time of hydrolysis was 36 hr.

TABLE III

GENERAL STRUCTURE–ACTIVITY RELATIONSHIPS



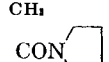
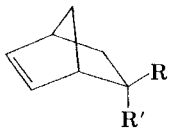
Compound	R	R′	Anticonvulsant activity (mg./kg.) ED50 MES	ED50 Pentylenetetrazol	ED50 Neurotoxic dose50	Protective index MES	Protective index Pentylene tetrazol	Hypnotic dose50 (mg./kg.)	LD50 (mg./kg.)	Therapeutic index MES	Therapeutic index Pentylene tetrazol	Therapeutic index Hypnotic
I	H	$CONH_2$	840	650	780	0.9	1.2	>1000	1600	1.9	2.5	<1.6
II	CH_3	$CONH_2$	280	245	315	1.1	1.3	595	1000	3.6	4.1	1.7
III	C_2H_5	$CONH_2$	290	190	182	0.6	1.0	490	790	2.7	4.2	1.6
IV	*n*-C_3H_7	$CONH_2$	125	125	~100	<1.0	<1.0	166	440	3.5	3.5	2.6
V	*i*-C_3H_7	$CONH_2$	~175	125	~100	<1.0	<1.0	300	~650	~3.7	5.2	~2.2
VI	$CH_2CH\text{-}CH_2$	$CONH_2$	~200	~300	~100	~1.0	<0.5	365	~550	2.8	1.8	~1.5
VII	*n*-C_4H_9	$CONH_2$	250	~200	~100	<0.5	~0.5	275	472	1.9	~2.4	1.7
VIII	*n*-C_5H_{11}	$CONH_2$	~100	>125	~100	~1.0	<1.0	368	>630			>1.7
IX	*i*-C_5H_{11}	$CONH_2$	~300	>250	<250	~1.0	<1.0	>500	>500			
X	*n*-C_6H_{13}	$CONH_2$	~400	~300	~300	<1.0	~1.0	~700	>1000			
XI	*n*-$C_{12}H_{25}$	$CONH_2$	inactive (800)	inactive (800)				inactive (800)				
XII	$(CH_2)_2N(CH_3)_2$	$CONH_2$										
XIII	$(CH_2)_2N(C_2H_5)_2$	$CONH_2$	inactive (800)	inactive (800)				inactive (800)				
XIV	$(CH_2)_3N(C_2H_5)_2$	$CONH_2$										
XV	$CH_2C_6H_5$	*CONH*$_2$	~200	>250	~300	>1.0	>1.0	~450	~750			
XVI	H	$CONHCH_3$	~500	~500	~500	~1.0	~1.0					
XVII	$CONHCH_3$	CH_3	~400	~200	<250			<500				
XVIII	$CON(CH_3)_2$	CH_3	~250		<250							
XIX	$CON(C_2H_5)_2$	CH_3			stimulation (25) convulsions (500)			~75				
XX	H											
XXI	$CONH_2$	C_6H_5	inactive (800)		inactive (800)				inactive (800)			
Tridione			—	460	720	—	1.6		2050	—	4.5	
Paradione			283	200	273	1.0	1.4		1174	4.1	5.9	
Methylparafynol								468	1000			2.1
Valmid								135	554			4.1
Phenobarbital								82	228			2.8
Butabarbital sodium								69	204			3.0

TABLE IV

STRUCTURE–ACTIVITY RELATIONSHIPS. COMPARISON OF STEREOISOMERS



Compound	R	R'	Anticonvulsant activity (mg./kg.) ED50 MES	ED50 Pentylenetetrazol	ED50 Neurotoxic dose50	Protective index MES	Protective index Pentylenetetrazol	Hypnotic dose50 (mg./kg.)	LD50 (mg./kg.)	Therapeutic index MES	Therapeutic index Pentylenetetrazol	Therapeutic index Hypnotic
XXII	$CONH_2$	H	560	597	610	1.1	1.0		1268	2.3	2.1	
I	H	$CONH_2$	840	650	780	0.9	1.2		1600	1.9	2.5	
XXIII	$CONH_2$	CH_3	220	250	230	1.0	0.9	475	667	3.0	2.7	1.6
II	CH_3	$CONH_2$	280	245	315	1.1	1.3	595	1000	3.6	4.1	1.7
XXIV	$CONH_2$	C_2H_5	250	208	180	0.7	0.9	355	584	2.3	2.8	1.6
III	C_2H_5	$CONH_2$	290	190	182	0.6	1.0	490	790	2.7	4.2	1.6

TABLE V

STRUCTURE–ACTIVITY RELATIONSHIPS. EFFECT OF RING ALTERATIONS

Compound	Anticonvulsant activity (mg./kg.) ED50 MES	ED50 Pentylenetetrazol	ED50 Neurotoxic dose50	Protective index MES	Protective index Pentylenetetrazol	Hypnotic dose50 (mg./kg.)	LD50 (mg./kg.)	Hypnotic index
II	280	245	315	1.1	1.3	595	1000	1.7
XXV	194	228	210	1.1	0.9	300	890	3.0
XXVI	~375	>250	~250	<1.0	<1.0	328	958	2.9
XXVII						190	600	3.2
XXVIII	~375	>250	<250	<1.0	<1.0	341	1063	3.1
XXIX	270	200	285	1.1	1.4	480	766	1.6
XXX	380	400	390	1.0	1.0	~900	1196	
XXXI	(500) inactive	(500)	~500			~1000		
XXXII	>500	>800	~650			800		
XXXIII	(1000) inactive	(1000)	500			>1000		
XXXIV	(800) inactive	(800)						

TABLE VI

STRUCTURE–ACTIVITY RELATIONSHIPS. EFFECT OF HALOGENATION

Compound	Anticonvulsant activity (mg./kg.) ED50 MES	Pentylenetetrazol	Neurotoxic dose50 (mg./kg.)	HD50 (mg./kg.)	LD50 (mg./kg.)	T.I. (hypn.)
XXXV	~200	~200	<200	~650	>800	
XXXVI	inactive (800)	157	~200	~1000		
XXXVII	inactive (500)	>500	~500		>1000	
XXXVIII	~300	~200	<125	360	1343	3.7
XXXIX	~250	~250	~250	~650		

Methyl-2-norbornene-5-*exo*-carbonyl chloride[19] (44.5 g.) was added dropwise to a stirred, ice-cold solution of 17.7 g. of methylamine in 200 ml. of dry benzene. The mixture was allowed to stand overnight at room temperature and washed successively with water, dilute hydrochloric acid and sodium bicarbonate solution. The benzene phase was then dried superficially by shaking briefly with anhydrous potassium carbonate and the solvent was distilled under reduced pressure. The residual solid (48 g., 98%) was crystallized twice from hexane to yield 34.5 g. of colorless crystals, m.p. 95–96°.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.66; H, 9.15; N, 8.48. Found: C, 72.25; H, 9.12; N, 8.32.

N,N-Dimethyl-5-*endo*-methyl-2-norbornene-5-*exo*-carboxamide (XVIII).—The reaction of 33.6 g. of 5-*endo*-methyl-2-norbornene-5-*exo*-carbonyl chloride and 27.0 g. of dimethylamine in dry benzene by the above procedure gave 33.5 g. (95%) of the crude product. Crystallization from pentane gave colorless crystals, m.p. 83–84°.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; Found: C, 73.70; H, 9.46.

N,N-Diethyl-5-*endo*-methyl-2-norbornene-5-*exo*-carboxamide (XIX).—The reaction of 44.5 g. of 5-*endo*-methyl-2-norbornene-5-*exo*-carbonyl chloride and 41.8 g. of diethylamine in dry benzene by the above procedure gave 52.0 g. (97%) of crude product as a light yellow liquid. The material was crystallized from pentane; m.p. 10–11°, $n^{25}D$ 1.4943.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.36; H, 10.11; N, 6.68.

5-Phenyl-2-norbornene-5-carboxamide (XXI).—A mixture of 93.0 g. of troponitrile[20] and 57 g. of dicyclopentadiene was heated in a sealed glass tube at 185–190° for 12 hr. The biphasic mixture was allowed to separate and the aqueous layer was discarded. The organic phase was taken up in benzene, dried over anhydrous sodium sulfate and distilled under reduced pressure to yield 17.2 g. of crude 5-phenyl-5-cyano-2-norbornene, b.p. 99–100° (0.04 mm.), contaminated with some tetracyclopentadiene, m.p. 208–209° (from ethanol, reported[21] m.p. 207°). A solution of 17.2 g. of the crude nitrile and 29.0 g. of potassium hydroxide

(19) 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).

(20) J. F. Walker, U. S. Patent 2,478,990 (1949).

(21) K. Alder, G. Stein, J. Reese, and W. Grassmann, *Ann.*, **496**, 204 (1932).

in 50 ml. of ethanol was refluxed for 10 hr. The solvent was distilled under reduced pressure and replaced by 75 ml. of water. The cooled suspension was filtered and the precipitate was washed with water. Three crystallizations of the crude product (8.0 g.) from toluene gave 2.5 g. of colorless needles, m.p. 243–244°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.80; H, 7.28; N, 6.63.

5-*exo*-Methylbicyclo[2.2.2]oct-2-ene-5-*endo*-carboxamide (XXV) and **2-methylbicyclo[2.2.2]octane-2-carboxamide (XXVI)** were prepared by the previously described procedure.[10]

5-*n*-Propyl-5-cyanobicyclo[2.2.2]oct-2-ene was prepared by the general alkylation procedure described above from 5-*endo*-cyanobicyclo[2.2.2]oct-2-ene[22] in 57% yield, b.p. 130–131° (15 mm.), $n^{25}D$ 1.4860.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.11; H, 9.79; N, 7.80.

5-*n*-Propylbicyclo[2.2.2]oct-2-ene-5-carboxamide (XXVII).—The above nitrile was hydrolyzed by the general procedure described for the substituted cyanonorbornenes in 32% yield, m.p. 88–90° (from pentane).

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25; Found: C, 74.59; H, 10.07; N, 7.06.

1,4-Dimethyl-3-cyclohexene-1-carboxylic Acid.—A solution of 95.0 g. of isoprene, 120.0 g. of methacrylic acid and 1.0 g. of hydroquinone in 100 ml. of dry toluene was heated in an autoclave at 150° for 12 hr. The clear, pale yellow liquid was fractionally distilled under reduced pressure to yield 163.3 g. (76%) of a viscous, colorless distillate (b.p. 135–141° (11–12 mm.)) which solidified on cooling. Crystallization from pentane gave 91.0 g. of colorless crystals, m.p. 64–66°. An analytical sample was recrystallized 5 times from pentane, m.p. 69.5–70° (reported[23] m.p. 62–63°).

1,4-Dimethyl-3-cyclohexene-1-carboxamide (XXVIII).—A solution of 46.2 g. of once-crystallized 1,4-dimethyl-3-cyclohexene-1-carboxylic acid in 47.6 g. of thionyl chloride was refluxed for 90 min. and fractionally distilled under reduced pressure. The acid chloride [27.6 g., 63%, b.p. 108–112° (22 mm.)] was dissolved in 250 ml. of dry benzene and a gentle stream of gaseous ammonia was passed into the solution for 30 min. The suspension was allowed to stand overnight, heated on the steam bath and filtered from ammonium chloride. The solvent was distilled from the filtrate and the solid residue was crystallized from hexane. The yield of colorless, glistening plates was 13.0 g., m.p. 115–116° (reported[23] m.p. 113–114°). Recrystallization of a sample from hexane did not change the melting point.

1-Methyl-3-cyclohexene-1-carboxamide (XXIX) was prepared by the method of Roberts and co-workers,[24] 1-methylcyclopentanecarboxamide (XXX) by the method of Mousseron *et al.*,[25] and norbornane-1-carboxamide (XXXI) by the method of Boehme.[11]

2-Norbornene-5-*endo*-acetic Acid.—A solution of 133.0 g. of 2-norbornene-5-*endo*-acetonitrile[26] and 280 g. of potassium hydroxide in 420 g. of 90% ethanol was refluxed for 8 hr. Most of the solvent was distilled under reduced pressure

(22) K. Alder, H. Krieger, and H. Weiss, *Chem. Ber.*, **88**, 144 (1955).

(23) I. N. Nazarov, A. I. Kuznetsova, and N. V. Kuznetsov, *Zhur. Obshchei Khim.*, **25**, 88 (1955).

(24) J. D. Roberts, A. K. Jeydel, and R. Armstrong, *J. Am. Chem. Soc.*, **71**, 3248 (1949).

(25) M. Mousseron, R. Jacquin, and A. Fontaine, *Compt. rend.*, **232**, 1562 (1951).

(26) K. Alder and E. Windemuth, *Ber.*, **71**, 1939 (1938).

while 2 vol. of water was added gradually. The clear solution was cooled, washed with ether and acidified carefully with hydrochloric acid. The precipitated oil was extracted with ether, the extracts were dried over anhydrous magnesium sulfate and distilled under reduced pressure. The yield of colorless, rather viscous liquid was 94.0 g. (62%), b.p. 124–125° (4 mm.) (reported[26] b.p. 137–139° (12 mm.)), $n^{25}D$ 1.4877.

2-Norbornene-5-*endo*-acetamide (XXXII).—A solution of 118 g. of 2-norbornene-5-*endo*-acetic acid and 119 g. of thionyl chloride in 125 ml. of chloroform was refluxed for 2 hr. and fractionally distilled under reduced pressure. The yield of 2-norbornene-5-*endo*-acetyl chloride was 69.2 g. (52%), b.p. 109–112° (2 mm.). A solution of 25.5 g. of the acid chloride in 500 ml. of absolute ether was saturated with gaseous ammonia with stirring and ice-bath cooling. Stirring was continued for 1 hr. longer and the solvent was allowed to evaporate. Two crystallizations of the solid residue from boiling water gave 16.0 g. (71%) of colorless plates, m.p. 146–147°. An analytical sample melted at 147.5–148.5° (from hexane).

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.35; H, 8.58; N, 9.14.

3-Cyclohexene-1-acetamide (XXXIII)[27] was prepared from 3-cyclohexene-1-carbonyl chloride *via* the Arndt–Eistert reaction, 5 (or 6)-acetoxynorbornane-2-*exo*-carboxamide (XXXIV) (m.p. 209–210°) by a published procedure,[10] and 2-*exo*-bromonorbornane-2-*endo*-carboxamide (XXXV) and 2-*exo*-bromonorbornane-1-carboxamide (XXXVI) were prepared by the procedure of Boehme.[11] Norbornane-2-*endo*-acetic acid was obtained in 86% yield by catalytic hydrogenation of 2-norbornene-5-*endo*-acetic acid in ethanol solution in the presence of palladium oxide catalyst, b.p. 138–142° (16 mm.) (reported[26] b.p. 141–142° (13 mm.)), $n^{25}D$ 1.4814.

α-Bromonorbornane-2-*endo*-acetamide (XXXVII).—A mixture of 42.0 g. of norbornane-2-*endo*-acetic acid and 100 ml. of thionyl chloride was heated slowly to the boiling point and refluxed for 2 hr. Bromine (43.6 g.) was added dropwise and the mixture was refluxed for 3 hr. longer. Fractional distillation of the solution through a short Vigreux column gave 37.0 g. (54%) of α-bromonorbornane-2-*endo*-acetyl chloride, b.p. 120–124° (15 mm.). A solution of 18.5 g. of the bromoacid chloride in 250 ml. of absolute ether was cooled in an ice-bath and saturated with ammonia. The suspension then was filtered, the precipitate washed with ether and the combined filtrates were allowed to evaporate. Several crystallizations of the crude product (9.3 g.) from toluene gave 4.2 g. of colorless crystals, m.p. 163–164°.

Anal. Calcd. for $C_9H_{14}BrNO$: C, 46.57; H, 6.08; N, 6.04. Found: C, 46.82; H, 6.18; N, 5.85.

2-*exo*-Methyl-5,7-dichloronorbornane-2-*endo*-carboxylic Acid.—5-*endo*-Methyl-2-norbornene-5-*exo*-carboxylic acid[19] (76.0 g.) was dissolved in 1200 ml. of chloroform and cooled to −70° in a Dry-Ice bath. Some microcrystalline material precipitated at this temperature and chlorine was passed into the suspension with stirring. Absorption of the chlorine appeared to be complete in 1 hr. and the reaction mixture was allowed to stand at room temperature overnight. The volume was reduced to 150 ml. by distillation and the residue was allowed to crystallize in the refrigerator. The colorless product (62.5 g.) was filtered off, washed with carbon tetrachloride and recrystallized several times from chloroform to yield

(27) W. R. Boehme, *J. Org. Chem.*, **26**, 2107 (1961).

29.6 g. (27%) of colorless prisms, m.p. 204–207°. An analytical sample melted at 205–207° (from chloroform).

Anal. Calcd. for $C_9H_{12}Cl_2O_2$: C, 48.45; H, 5.42. Found: C, 48.77; H, 5.69.

2-*exo*-Methyl-5,7-dichloronorbornane-2-*endo*-carboxamide (XXXIX).—The dichloro acid (22.0 g.) was refluxed for 3 hr. with 75 ml. of thionyl chloride and distilled through a short Vigreux column. The colorless acid chloride (21.6 g., 90%, b.p. 84–87° (0.03 mm.)) which crystallized as hard rosettes upon standing, was dissolved in 250 ml. of absolute ether. Gaseous ammonia was passed over the surface of the stirred solution for 1 hr. with ice-cooling. The suspension was allowed to stand overnight at room temperature, evaporated to dryness and the residue was washed well with water. The coarse crystalline product (19.5 g., 89%, m.p. 152–156°) was recrystallized twice from toluene to yield 15.8 g., m.p. 160–161°.

Anal. Calcd. for $C_9H_{13}Cl_2NO$: C, 48.67; H, 5.90; N, 6.31. Found: C, 48.46; H, 6.02; N, 6.26.

2-Bromobicyclo[2.2.2]octane-2-carboxamide (XXXVIII).—A solution of 16.0 g. of bicyclo[2.2.2]octane-2-carboxylic acid[28] and 50 g. of thionyl chloride in 500 ml. of chloroform was refluxed for 6 hr. and distilled under reduced pressure on a steam bath. The residue of bicyclo[2.2.2]octane-2-carbonyl chloride was dissolved in 100 ml. of thionyl chloride, heated to reflux and 17.0 g. of bromine was added dropwise in 4 hr. Refluxing was continued for 1 hr. longer and the solution was distilled. The 2-bromobicyclo[2.2.2]octane-2-carbonyl chloride (20.0 g., b.p. 132–134°(15 mm.)) was dissolved in ether, cooled in an ice bath, and saturated with gaseous ammonia. The ether was allowed to evaporate and the residue was washed well with water. Recrystallization from hexane gave 18.0 g. of colorless crystals, m.p. 107–108°.

Anal. Calcd. for $C_9H_{14}BrNO$: C, 46.57; H, 6.08; N, 6.04. Found: C, 46.82; H, 6.18; N, 5.85.

(28) C. A. Grob, H. Kny, and A. Gagnieux, *Helv. Chim. Acta*, **40**, 130 (1957).

The Synthesis and γ-Aminobutyric Acid Transaminase Inhibition of Aminoöxy Acids and Related Compounds

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Received November 4, 1961

A series of forty-six aminoöxy derivatives and thirty-six analogs of γ-aminobutyric acid was prepared and tested for inhibition of γ-aminobutyric acid transaminase and for protection against thiosemicarbazide-induced convulsions. Good *in vivo* activity in these tests was generally limited to certain α-aminoöxyacids or their easily hydrolyzed derivatives, such as esters. None of the compounds studied was superior to aminoöxyacetic acid.