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Structure–Activity Relationships in a Series of Antiarrhythmic and Local Anaesthetic Bicyclic Glycinamides

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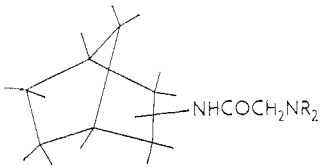
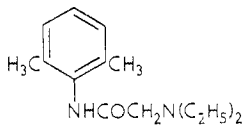
Antiarrhythmic as well as local anaesthetic activities have been reported in a wide variety of synthetic amines, amino esters and amino amides. Noteworthy among these are procaine,[1] procainamide[2] and lidocaine,[3] although there is little apparent correlation of antiarrhythmic activity with chemical structure[4] or with other pharmacodynamic responses.[5] The relationship of chemical structure to local anaesthetic activity, however, has been studied extensively and the literature of basic esters related to procaine[6, 7] and of basic amides related to lidocaine[7, 8] has been reviewed.

As part of an investigation of the contribution of bridged bicyclic nuclei to pharmacodynamically active compounds, we synthesized some basic amides of aminobicycloheptanes as potential antiarrhythmic and local anaesthetic agents. Optimum anaesthetic activity by the infiltration technique is achieved in the lidocaine series when both 2- and 6- positions of the aniline moiety are substituted. The prolonged duration of action and reduced rate of hydrolysis have been attributed to the steric hindrance introduced by the two *ortho* substituents of lidocaine.[7, 9] It has been shown that certain carboxamides of bridged bicyclic acids are highly resistant to hydrolysis[10] and it appeared probable that a highly hindered three-dimensional bicyclic ring such as bicyclo[2,2,1]heptane might, therefore, provide a more effective shield over the amide function than the planar 2,6-xylidine moiety of lidocaine. The hindering effect of the hydrocarbon

bridges in the norbornylglycinamides (A) may be compared with that of the 2,6-dimethyl substituents of lidocaine (B).



(A)



(B)

A series of bridged bicyclic glycinamides (Table II) was synthesized by the reaction of a bicyclic amine with a chloroacyl chloride and subsequent ammonolysis of the resulting chloroacylamides (Table I) with a primary or secondary amine. Structural modifications included alterations in the position of glycinamide substitution, introduction of alkyl substituents in the bicyclic ring, in the α-position of the side-chain and on the amide nitrogen, modification of the terminal amino group and lengthening of the side-chain. Ring modifications included enlargement of norbornane to bicyclo[2,2,2]octane, removal of the methylene bridge to form the simpler cyclohexane analogue and the introduction of unsaturation into the norbornane ring. Since reactive functions can often be modified with retention of pharmacodynamic activity, the amide group was reversed and also replaced by carboxylate ester and carbamate linkages.

The bicyclic primary amines were obtained from the corresponding carbonyl azides as volatile, fuming liquids or solids which rapidly absorbed moisture and carbon dioxide from the air. 2-*Endo*methylaminonorbornane was prepared from 2-*endo*aminonorbornane via the chloral formylation reaction of Blicke and Lu[12] and subsequent reduction with lithium aluminium hydride. The Ritter[13] reaction between (*r*)-camphene and chloroacetonitrile gave 2-*exo*chloroacetamidoisocamphane, and 2-*exo*chloroacetoxynorbornane was prepared via the acid-catalyzed addition of chloroacetic acid to norbornene.

Antiarrhythmic activity was determined by measuring the reduction in duration of methacholine-induced auricular arrhythmia in dogs. This method has been applied to several bicyclic

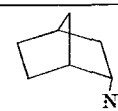
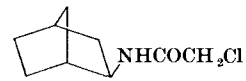
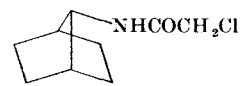
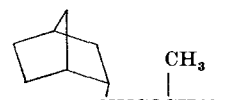
glycinamides and reported in a preliminary communication.[14] Pharmacodynamic activities are summarized in Table III. Antiarrhythmic activity increased with the size of the terminal amino group of 2-*endo*-(*t*-aminoacetamido)-norbornanes from *N*,*N*-dimethyl (ERL-361) to a maximum at *N*,*N*-diethyl (ERL–239). Further increase in the size of the terminal tertiary amino group to *N*,*N*-di-*n*-propyl (ERL–413) caused the activity to fall off. Branched substituents (ERL–411 and 414) on the terminal amino group were slightly more active than their unbranched chain isomers (ERL–412 and 413). When the dialkylamino group was replaced by 1-pyrrolidyl (ERL–360), antiarrhythmic activity was practically abolished. The *exo*-isomer (ERL–381) of ERL–239 showed a marked reduction in antiarrhythmic activity, an observation that is in agreement with the less hindered configuration of 2-*exo*substituted norbornanes. The quaternary methiodide of 2-*endo*diethylaminoacetamidonorbornane (ERL–362), however, was somewhat more active than the corresponding hydrochloride (ERL–239).

Antiarrhythmic activity was markedly reduced when only one substituent was present on the terminal nitrogen atom. Thus, the *N*-isopropyl analogue (ERL–359) was inactive and the *N*-(2-diethylaminoethyl) (ERL–385) and *N*-benzyl (ERL–387) derivatives elicited only a very low order of activity.

The introduction of alkyl substituents in proximity to the amide nitrogen permits a comparison of varying degrees of steric hindrance with antiarrhythmic activity. When a methyl group was introduced into ERL–239 either on the amide nitrogen (ERL–367) or in the 2-*exo*position (ERL–437), a moderate loss in activity was observed. As anticipated, inversion of the 2-*exo*methyl and 2-*endo*diethylaminoacetamido groups in ERL–437 to the stereoisomer (ERL–382) was accompanied by a further loss in activity. Introduction of a methyl group in the α-position of the side-chain (ERL–368) of ERL–239 also resulted in a marked loss of activity. The introduction of three methyl groups into the norbornane ring of ERL–381 to form the isocamphane analogue (ERL–389) practically abolished antiarrhythmic activity.

Isomerization of the side-chain of ERL–239 from the 2-*endo* position to the bridgehead (ERL–406) considerably reduced the degree of amide shielding and gave, as anticipated, a markedly

Table I. Chloracylamides

Structure	m.p., °C (b.p./mm)	Yield, %	Recrystn. solvent	Formula	Analysis, % Calcd. C	H	N	Found C	H	N
	110–111	43–54	C_7H_8	$C_9H_{14}ClNO$	57·60	7·52	7·46	57·70	7·30	7·35
	126·5–127	45	C_7H_8	$C_9H_{14}ClNO$	57·60	7·52	7·46	57·74	7·73	7·46
	115–116 (108–112°/0·4)	47	C_7H_{16}	$C_9H_{14}ClNO$	57·60	7·52	7·46	58·02	7·71	7·32
	84–85 (106-110°/0·25 mm)	64	C_7H_{16}	$C_9H_{14}ClNO$	57·60	7·52	7·46	57·88	7·50	7·30
	130·5–131·5	47	C_7H_{16}	$C_{10}H_{16}ClNO$	59·54	8·00	6·94	59·77	8·07	6·91

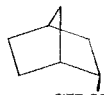
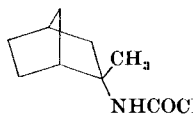
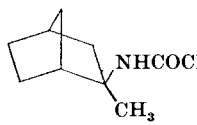
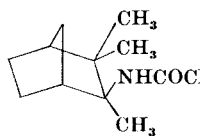
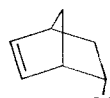
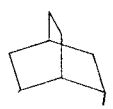
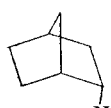
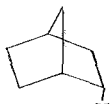
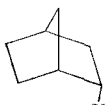
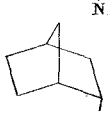
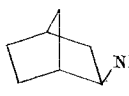
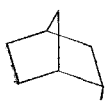
 CH_3NCOCH_2Cl	(120–122°/0·15 mm)	89	—	$C_{10}H_{16}ClNO$	59·54	8·00	6·94	59·40	7·79	7·13
 CH_3 $NHCOCH_2Cl$	107·5–108·5 (116–121°/0·5–1)	26	C_7H_{16}	$C_{10}H_{16}ClNO$	59·54	8·00	6·94	59·42	7·92	6·88
 $NHCOCH_2Cl$ CH_3	83·5–84·5	32	C_6H_{14}	$C_{10}H_{16}ClNO$	59·54	8·00	6·94	59·33	7·88	6·90
 CH_3 CH_3 $NHCOCH_2Cl$ CH_3	82–85	42	C_6H_{14}, C_2H_5OH	$C_{12}H_{20}ClNO$	62·73	8·77	6·10	63·04	8·63	6·22
 $NHCOCH_2Cl$	79–81	59	C_6H_{14}	$C_9H_{12}ClNO$	58·22	6·52	7·56	57·84	6·69	7·45
 $NHCOCH_2Cl$	129–130	75	C_6H_{14}	$C_{10}H_{16}ClNO$	59·54	8·00	6·94	59·28	8·09	6·79
 $NHCOCH_2CH_2Cl$	98·5–99	44	C_6H_6–C_6H_{14}	$C_{10}H_{16}ClNO$	59·54	8·00	6·94	59·84	7·96	6·97

Table II. Glycinamides

ERL No.	Structure	b.p., °C/mm of base	n_D^{25}	Yield, %	m.p. of hydrochloride, °C	Recrystn. solvent	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
361	 NHCOCH$_2$N(CH$_3$)$_2$·HCl	87–89/0·03	1·4944	89	238–240	$(CH_3)_2CO$	$C_{11}H_{21}ClN_2O$	56·76	9·10	12·04	56·89	8·95	12·17
409	 NHCOCH$_2$N(CH$_3$)(C$_2$H$_5$)·HCl	83–85/0·03	1·4915	88	187–188	C_7H_8	$C_{12}H_{23}ClN_2O$	58·40	9·39	11·35	58·53	9·25	11·20
239	 NHCOCH$_2$N(C$_2$H$_5$)$_2$·HCl	107–110/0·08	1·4875	88	194–195	C_6H_6	$C_{13}H_{25}ClN_2O$	59·86	9·66	10·74	59·92	9·72	10·66
362	 NHCOCH$_2$N(C$_2$H$_5$)$_2$·CH$_3$I (m.p. 151–152°)					$CH_3COOC_2H_5$	$C_{14}H_{27}IN_2O$	45·90	7·43	7·65	46·09	7·60	7·52
381													
412	 NHCOCH$_2$N(C$_2$H$_5$)$_2$·HCl	112–116/0·05	1·4873	91	183–184·5	C_7H_8	$C_{13}H_{25}ClN_2O$	59·86	9·66	10·74	59·74	9·93	10·90
	 NHCOCH$_2$N(C$_2$H$_5$)(*n*-C$_3$H$_7$)·HCl	110–119/0·04	1·4853	90	150·5–152·5	C_7H_8	$C_{14}H_{27}ClN_2O$	61·18	9·90	10·20	60·96	9·89	10·05

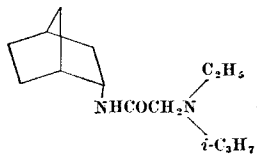
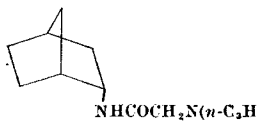
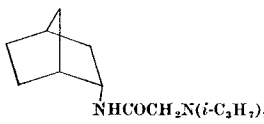
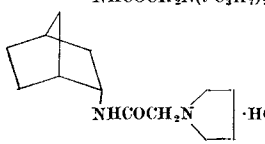
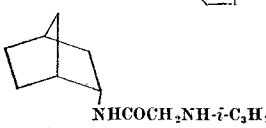
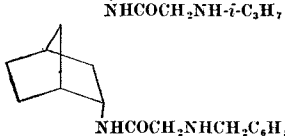
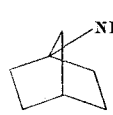
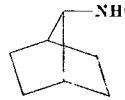
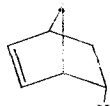
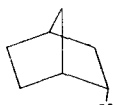
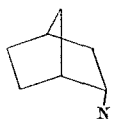
411		110–114/0·04	1·4855	87	188·5–190·5	C_7H_8	$C_{14}H_{27}ClN_2O$	61·18	9·90	10·20	61·38	9·75	10·07
413		99–102/0·03	1·4836	84	159·5–161·5	C_7H_8	$C_{15}H_{29}ClN_2O$	62·36	10·12	9·70	62·82	10·16	9·60
414		110–114/0·04	1·4853	76	157·5–158·5	C_7H_8	$C_{15}H_{29}ClN_2O$	62·36	10·12	9·70	62·32	10·03	9·52
360		125–126/0·1	1·5111	91	199–200	$(CH_3)_2CO$	$C_{13}H_{23}ClN_2O$	60·35	8·96	10·83	60·10	8·97	10·88
359		112–116/0·02	1·4933	75	223–225	i-C_3H_7OH	$C_{12}H_{23}ClN_2O$	58·40	9·39	11·35	58·65	9·53	11·41
387		200–210/0·05	1·5529	82	246–248	H_2O	$C_{16}H_{23}ClN_2O$	65·18	7·86	9·50	65·41	7·96	9·42

Table II—*continued*

ERL No.	Structure	b.p., °C/mm of base	n_D^{25}	Yield, %	m.p. of hydrochloride, °C	Recrystn. solvent	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
406	 NHCOCH$_2$N(C$_2$H$_5$)$_2$·HCl	108–110/0·25	1·4829	79	172–174	C$_7$H$_8$	C$_{13}$H$_{25}$ClN$_2$O	59·86	9·66	10·74	59·71	9·60	10·60
407	 NHCOCH$_2$N(C$_2$H$_5$)$_2$·HCl	112–115/0·25	1·4862	91	156–157	C$_7$H$_8$	C$_{13}$H$_{25}$ClN$_2$O	59·86	9·66	10·74	59·62	9·81	10·58
436	 NHCOCH$_2$N(C$_2$H$_5$)$_2$·HCl	122–126/1·0	1·4908	82	148·5–150	(CH$_3$)$_2$CO	C$_{13}$H$_{23}$ClN$_2$O	60·35	8·96	10·83	60·53	8·86	10·80
368	 NHCOCHN(C$_2$H$_5$)$_2$·HCl (CH$_3$)	118–120/0·15	1·4863	93	167–168	CH$_3$COOC$_2$H$_5$	C$_{14}$H$_{27}$ClN$_2$O	61·18	9·90	10·20	61·64	10·06	10·21
367	 CH$_3$ N COCH$_2$N(C$_2$H$_5$)$_2$·HCl	116–118/0·05	1·4918	92	193·5–194·5	C$_2$H$_5$COCH$_3$	C$_{14}$H$_{27}$ClN$_2$O	61·18	9·90	10·20	61·32	9·94	10·10

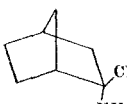
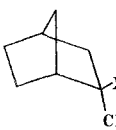
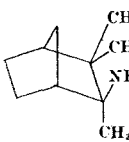
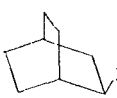
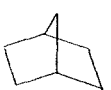
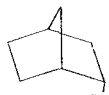
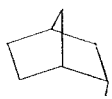
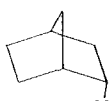
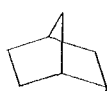
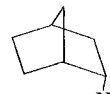
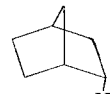
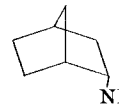
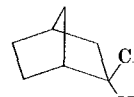
437		116–120/0·08	1·4825	97	189·5–190·5 (Metastable form 147°)	$CH_3COOC_2H_5$	$C_{14}H_{27}ClN_2O$	61·18	9·90	10·20	060·98	9·42	10·20
382		109–111/0·15	1·4839	78	174–174·5	$CH_3COOC_2H_5$	$C_{14}H_{27}ClN_2O$	61·18	9·90	10·20	61·43	10·14	10·15
389		102·109/0·08	solid	68	177–178	C_6H_6-C_6H_{12}	$C_{16}H_{31}ClN_2O$	63·44	10·32	9·25	63·45	10·20	9·12
358		120–125/0·02	1·4915	87	198–200	C_2H_5OH-$(C_2H_5)_2O$	$C_{14}H_{27}ClN_2O$	61·18	9·90	10·20	61·43	9·82	10·15
385		145–150/0·1	1·4873	64	217–219	*i*-C_3H_7OH	$C_{15}H_{31}Cl_2N_3O$	52·93	9·18	12·35	52·87	9·17	12·38
271[11]		93–98/0·08	m.p. 34–35	80	134–135	$CH_3COOC_2H_5$	$C_{12}H_{24}ClN_2O$	57·93	10·13	11·26	58·01	9·90	10·91

Table III. Structure–activity relationships

ERL No.	Structure	Antiarrhythmic activity[a] 5 mg/kg	10 mg/kg	20 mg/kg	Infiltration[b] anaesthesia	Irritant ratio[c]	LD_{50}, mg/kg[d]
361	 $NHCOCH_2N(CH_3)_2 \cdot HCl$	0	—	—	++		400
409	 $NHCOCH_2N(CH_3)(C_2H_5) \cdot HCl$	15 (increase)	46	—	++	3	320
239	 $NHCOCH_2N(C_2H_5)_2 \cdot HCl$	80	—	—	++	2	338
412	 $NHCOCH_2N(C_2H_5)(n\text{-}C_3H_7) \cdot HCl$	12	35	—	+++	3	315
411	 $NHCOCH_2N(C_2H_5)(i\text{-}C_3H_7) \cdot HCl$	32	70	—	++	1	—

413		$NHCOCH_2N(n\text{-}C_3H_7)_2 \cdot HCl$	14	12 (increase)	—	+++	1	250
414		$NHCOCH_2N(i\text{-}C_3H_7)_2 \cdot HCl$	31	85	--	++	1	282
360		$NHCOCH_2N \cdot HCl$	7	—	--	++	3	348
362		$NHCOCH_2N(C_2H_5)_2 \cdot CH_3I$	95	—	--	0 to +	—	272
381		$NHCOCH_2N(C_2H_5)_2 \cdot HCl$	29	53	--	+ to ++	1 to 2	342
359		$NHCOCH_2NH\text{-}i\text{-}C_3H_7 \cdot HCl$	0	—	—	++	2	313

Table III—*continued*

ERL No.	Structure	Antiarrhythmic activity[a] 5 mg/kg	10 mg/kg	20 mg/kg	Infiltration[b] anaesthesia	Irritant ratio[c]	LD_{50}, mg/kg[d]
385	 $NHCOCH_2NHCH_2CH_2N(C_2H_5)_2 \cdot 2HCl$	19	31	61	0	—	645
387	 $NHCOCH_2NHCH_2C_6H_5 \cdot HCl$	16	48	—	++	< 1	138
368	 $NHCOCHN(C_2H_5)_2 \cdot HCl$ (CH_3)	—	58	—	++	3	320
437	 $NHCOCH_2N(C_2H_5)_2 \cdot HCl$ (CH_3)	12	86	—	+	—	355

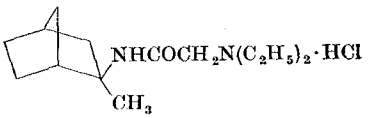
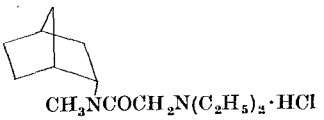
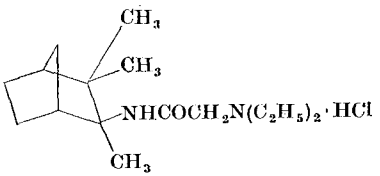
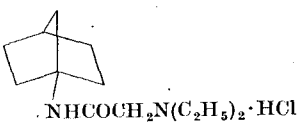
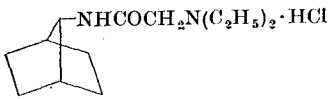
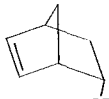
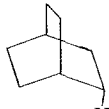
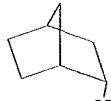
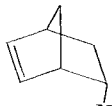
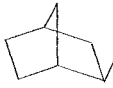
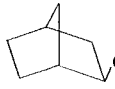
382		0	64	—	+	—	335
367		25	75	—	++	3	216
389		19	12	—	0 to ±	< 1	300
406		28	29	83	+	1 to 2	220
407		71	—	—	++	2	330

Table III—*continued*

ERL No.	Structure	Antiarrhythmic activity[a] 5 mg/kg	10 mg/kg	20 mg/kg	Infiltration[b] anaesthesia	Irritant ratio[c]	LD_{50}, mg/kg[d]
436	 $NHCOCH_2N(C_2H_5)_2 \cdot HCl$	40	—	82	++	—	405
271	 $NHCOCH_2N(C_2H_5)_2 \cdot HCl$	24	—	—	+	—	280
358	 $NHCOCH_2N(C_2H_5)_2 \cdot HCl$	84	—	—	++	1–2	200
439	 $NHCOCH_2CH_2N(C_2H_5)_2 \cdot HCl$	10	—	72	++	—	310

390	 $NHCOOCH_2N(C_2H_5)_2 \cdot HCl$	22	90	—	++	<1	150
376	 $OOCCH_2N(C_2H_5)_2 \cdot HCl$	33 (increase)	82 (increase)	—	+	1	—
377	 $OOCCH_2N(C_2H_5)_2 \cdot CH_3I$	0	58	—	+	1	150
483	 $CONHCH_2CH_2N(C_2H_5)_2 \cdot HCl$	22	81	91	+	—	280
	Lidocaine hydrochloride	56	—	—	++++	5–10	140, 175
	Quinidine Sulphate	47	—	—			
	Procainamide hydrochloride	34 (increase)	38	—			

[a] Antiarrhythmic activity is expressed as percentage reduction in the duration of methacholine-induced auricular arrhythmia in dogs compared with the average control period established for each animal.[14]

[b] Approximate anaesthetic concentration $dose_{50}$ ($\sim AD_{50}$) ratings: 0·1–0·25%=++++, 0·26–0·50%=+++, 0·51–1·0%=++, >1·1%=+.

[c] Irritant Ratio is expressed as $TIC/\sim AD_{50}$. The threshold irritant concentration (TIC) is that concentration expressed in per cent which produces no more than a mild irritation.

[d] LD_{50} was determined intraperitoneally in mice.

less active compound. The 7-isomer (ERL–407), however, which is only slightly less hindered than ERL–239, was almost as active as ERL–239 itself.

Unsaturation of the norbornane ring of ERL–239 reduced the degree of shielding over the amide linkage and markedly decreased antiarrhythmic activity (ERL–436). The bicyclo[2,2,2]octane homologue (ERL–358) has approximately the same degree of amide shielding and was approximately equal to ERL–239 in activity. When the methylene bridge of the norbornane ring is removed, however, the six-membered ring is no longer held in the boat form over the amide linkage through a quasi-axial bond, and the cyclohexyl analogue (ERL–271) (joined equatorially to the side chain) was much less active than ERL–239.

Increasing the distance between the terminal amino group and the amide function from diethylaminoacetamido to β-diethylaminopropionamido (ERL–439) greatly reduced antiarrhythmic activity. A similar reduction in activity was observed when an oxygen atom was inserted into the side chain of ERL–436 to form the carbamate analogue (ERL–390). The ester analogue, diethylaminoethyl norbornane-2-*endo*carboxylate (ERL–376), increased the duration of auricular arrhythmias although its methiodide (ERL–377) was weakly antiarrhythmic. Inversion of the amide function of ERL–439 to *N*-(2-diethylaminoethyl)-norbornane-2-*endo*carboxamide (ERL–483) did not appreciably increase antiarrhythmic activity.

Under the conditions employed in this investigation, 2-*endo*-diethylaminoacetamidonorbornane hydrochloride (ERL–239) was more active than lidocaine hydrochloride, quinidine sulphate and procainamide hydrochloride as an auricular antiarrhythmic agent. In the chloralose-anaesthetized dog, intravenously administered ERL–239 has been shown to increase coronary flow at dosage levels which had no effect upon either arterial blood pressure, cardiac output or cardiac oxygen consumption.[15]

Unlike lidocaine hydrochloride, none of the compounds of this series exhibited topical anaesthetic activity[16] in rabbits when applied to the cornea as 2 per cent aqueous solutions. The majority of the compounds were slightly to moderately active when administered intradermally[17] to guinea pigs. The irritant ratio (threshold irritant concentration/approximate anaesthetic

concentration dose$_{50}$) as determined by the Trypan blue method[18] was in all instances lower than that of lidocaine hydrochloride.

Experimental*

2-Endoaminonorbornane. This procedure is a modification of the general method of Oesterlin.[19] Sodium azide (78·0 g, 1·2 moles) was added in small portions to a stirred mixture of norbornane-2-*endo*carboxylic acid[20] (140·0 g, 1·0 mole) (m.p. 65–66°), concentrated sulphuric acid (280 ml) and chloroform (800 ml) to maintain the reaction temperature at 40–45°. The addition required about 2 h. The mixture was maintained at 40–45° for 2·5 h longer, cooled and hydrolyzed with ice and water. The chloroform phase was separated and washed with water. The combined aqueous layers were cooled, made alkaline with 25 per cent sodium hydroxide solution and extracted three times with ether. The extracts were dried over solid potassium hydroxide and distilled through a Vigreux column to yield 60·0 g (54 per cent) of a colourless, fuming liquid (b.p. 155–158°, reported[21] b.p. 156–157°) which solidified on cooling. A sample of the hydrochloride melted at 296–297° (reported[22] m.p. 295°).

2-Exo*aminonorbornane*† Norbornane-2-*exo*carboxylic acid[23] (113·0 g), chloroform (650 ml) concentrated sulphuric acid (22·4 ml) and sodium azide (64·1 g) were allowed to react by the above procedure. The yield of 2-*exo*aminonorbornane was 70·5 g (79 per cent), b.p. 151–154°.

1-Aminonorbornane.‡ This compound was prepared by the above procedure from norbornane-1-carboxylic acid[24] (12·9 g), chloroform (75 ml), concentrated sulphuric acid (26·0 ml) and sodium azide (7·2 g). The yield was 8·8 g (86 per cent) of colourless liquid (b.p. 142–145°) which solidified on cooling.

7-Aminonorbornane. This compound was prepared by the above procedure from norbornane-7-carboxylic acid[25] (10·8 g), chloroform (60 ml), concentrated sulphuric acid (22·0 ml) and

* Analyses by Mr. E. R. Hoffmann and staff of these laboratories. Melting points are uncorrected.

† The hydrochloride of 2-*exo*aminonorbornane has been described by K. Alder and G. Stein, *Liebigs Ann.*, **514**, 224 (1934).

‡ The hydrochloride of 1-aminonorbornane has been reported by W. P. Whelan, Jr., Dissertation, Columbia University, 1952.

sodium azide (6·0 g) in 56 per cent yield (4·8 g) as a colourless liquid (b.p. 147–152°) which solidified on cooling.

*2-Norbornene-5-*endo*isocyanate.* A mixture of 2-norbornene-5-*endo*carbonyl chloride (107·0 g, 0·68 mole)[10, 26] and sodium azide (65·0 g, 1·0 mole) in dry xylene (300 ml) was refluxed with stirring for 6 h. Filtration of the suspended solid and distillation of the filtrate gave 42·9 g (47 per cent), b.p. 67–68°/8 mm. The halide test was negative.

*5-*Endo*amino-2-norbornene.* A mixture of 2-norbornene-5-*endo*isocyanate (26·8 g, 0·199 mole), carbon tetrachloride (125 ml), water (75 ml) and concentrated sulphuric acid (21·0 ml) was refluxed with stirring for 72 h. The layers were separated and the organic phase was washed with water. The combined aqueous solutions were made alkaline with sodium hydroxide solution and extracted with ether. The extracts were dried over solid potassium hydroxide and distilled to yield 11·8 g (54 per cent) of colourless liquid boiling at 152–156° (reported[26] b.p. 150–160°).

*2-*Exo*methyl-2-*endo*aminonorbornane.** This procedure is essentially that of Komppa and Beckmann.[21] A mixture of 2-*exo*methylnorbornane-2-*endo*carbonyl chloride[27] (51·0 g, 0·295 mole), technical sodium azide (21·8 g, 0·335 mole) and dry xylene (130 ml) was refluxed with stirring for 5 h. The cooled mixture was filtered, the precipitate washed with xylene, and the filtrates were refluxed an additional 5 h with 115 ml of concentrated hydrochloric acid. The layers were separated and the xylene phase was washed with water. The combined aqueous solutions were made alkaline with sodium hydroxide and extracted with ether. The ether extracts (dried over solid potassium hydroxide) upon distillation gave 33·1 g (90 per cent) of a colourless fuming liquid, b.p. 162–164°.

*2-*Endo*methyl-2-*exo*aminonorbornane.** This compound was prepared by the procedure employed above for its isomer from 2-*endo*methylnorbornane-2-*exo*carbonyl chloride[27] in 77 per cent yield as a colourless liquid (b.p. 163°) which solidified on cooling (m.p. 65–68°).

*2-*Endo*formamidonorbornane.* A solution of freshly distilled chloral (44·1 g, 0·30 mole) was added dropwise in 1 h with stirring

* The hydrochloride of this compound has been described by S. Beckmann, R. Schaber and R. Bamberger, *Chem. Ber.*, 87, 997 (1954).

to 2-*endo*aminonorbornane (33·3 g, 0·30 mole) in chloroform (200 ml) at 0°. The solution was allowed to stand overnight at room temperature and distilled under reduced pressure. The colourless, viscous liquid weighed 38·8 g (93 per cent), b.p. 104–108°/0·05 mm, n_D^{25} 1·5075.

Anal. Calcd. for $C_8H_{13}NO$: C, 69·03; H, 9·41; N, 10·06. Found: C, 69·00; H, 9·54; N, 9·95.

2-Endo*methylaminonorbornane.* A solution of 2-*endo*formamidonorbornane (38·0 g, 0·274 mole) in anhydrous ether (100 ml) was added dropwise with cooling to a stirred suspension of lithium aluminium hydride (10·5 g, 0·276 mole) in anhydrous ether (400 ml) during 1 h. The suspension was then refluxed for 2 h and decomposed with aqueous sodium hydroxide solution. The ether layer was separated, dried over solid potassium hydroxide and distilled through a short Vigreux column. The yield of colourless, fuming liquid was 27·6 g (80 per cent), b.p. 75–77°/33 mm, n_D^{25} 1·4722. A sample of the base was converted to the hydrochloride, m.p. 193–194° (from 2-propanol–ether).

Anal. Calcd. for $C_8H_{16}ClN$: C, 59·43; H, 9·98; N, 8·66. Found: C, 59·50; H, 10·02; N, 8·55.

2-Aminobicyclo[2,2,2]octane was prepared according to Seka and Tramposch.[28]

Chloroacetamides. General procedure. A solution of the chloroacyl chloride (0·1 mole) in dry benzene (20 ml) was added dropwise with stirring during ½ h to a solution of the amine (0·1 mole) and dry pyridine (0·105 mole) in dry benzene (100 ml at −10 to 0°). Stirring was continued for 2 h longer without cooling. The precipitated pyridine hydrochloride was filtered off and washed with benzene. The filtrates were washed successively with dilute hydrochloric acid, water and sodium bicarbonate solution and dried superficially by shaking briefly with anhydrous magnesium sulphate. The solvent was removed by distillation and the product was isolated either by distillation or by crystallization.

2-Exo*chloroacetamidoisocamphane.* A solution of (*r*)-camphene (136·2 g, 1·0 mole) and chloroacetonitrile (75·5 g, 1·0 mole) in acetic acid (200 ml) was added slowly to a stirred, ice-cooled solution of 98 per cent sulphuric acid (100 g, 1·0 mole) in acetic acid (500 ml), maintaining the temperature below 30°. The brown solution was allowed to stand overnight at room

temperature and poured into cold water. The precipitate which separated initially as an oil was filtered off, washed well with water and air dried; yield: 95·4 g (41 per cent), m.p. 82–88°. For analysis a sample was recrystallized several times from aqueous ethanol, m.p. 82–85°.

2-Endo-(*β-chloropropionamido*)-*norbornane.* This compound was prepared by the general procedure for the chloroacetamides above.

Chloracetamidocyclohexane. This compound was obtained by a modification of the procedure of Speziale and Hamm,[29] m.p. 106–107° (from 50 per cent ethanol) (reported m.p. 105–106°[30], 108·5–109·5°[27]).

Glycinamides. General procedure. The chloroacylamide (0·1 mole) and the amine (0·2 mole) were dissolved in ethanol (50 ml) and heated in a sealed tube at 130° for 16 h. The solvent was removed by distillation on a steam bath under reduced pressure. The residue was taken up in dilute hydrochloric acid, washed with ether and the aqueous solution made alkaline with potassium carbonate solution. The precipitated oil was extracted with ether, the extracts were dried over anhydrous potassium carbonate and the ether was evaporated. The product was purified either by distillation or by crystallization.

2-Exo*chloroacetoxynorbornane.* A mixture of norbornene (94·2 g, 1·0 mole),[31] chloroacetic acid (94·5 g, 1·0 mole) and 40 per cent sulphuric acid (5·0 g) was heated with stirring on a steam bath under an efficient reflux condenser. An exothermic reaction took place, the solution began to boil and heating was interrupted. When the reaction subsided, heating was continued on the steam bath for 5 h longer. The cooled solution was poured into ice-water and extracted with ether. The extract was washed successively with water, sodium bicarbonate solution and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. Distillation under reduced pressure gave 150·7 g (80 per cent) of a colourless liquid, b.p. 101–106°/4·4 mm, n_D^{25} 1·4821. For analysis a sample was redistilled through a packed column, b.p. 120°/13 mm, n_D^{25} 1·4817 (reported[32] b.p. 83–85°/0·5 mm).

Anal. Calcd. for $C_9H_{13}ClO_2$: C, 57·30; H, 6·94. Found: C, 57·40; H, 6·76.

2-Exo*diethylaminoacetoxynorbornane.* A solution of *2-exo-*

chloroacetoxynorbornane (47·2 g, 0·25 mole) and diethylamine (36·6 g, 0·5 mole) in ethanol (50 ml) was heated in a sealed tube at 113° for 16 h. The solvent was removed by distillation, the residue dissolved in dilute hydrochloric acid and the solution was washed with ether. The aqueous phase was made alkaline with potassium carbonate solution and extracted with ether. The extract was dried over anhydrous potassium carbonate and distilled under reduced pressure to give 37·5 g (67 per cent) of colourless liquid, b.p. 129·5–130°/5·8 mm, n_D^{25} 1·4657.

The hygroscopic hydrochloride was obtained in 79 per cent yield, m.p. 131–131·5° (from ethyl acetate).

Anal. Calcd. for $C_{13}H_{24}ClNO_2$: C, 59·62; H, 9·24; N, 5·35. Found: C, 59·57; H, 9·40; N, 5·50.

The dihydrogen citrate was prepared from a solution of citric acid monohydrate (6·25 g) and the base (6·3 g) in absolute ethanol. The solvent was distilled and the residual gum was recrystallized from acetone–ethyl acetate to yield 8·1 g (69 per cent) of colourless crystals, m.p. 120–122° (d.). For analysis it was recrystallized from acetone, m.p. 120–121·5° (d.).

Anal. Calcd. for $C_{19}H_{31}NO_9$: C, 54·66; H, 7·49; N, 3·36. Found: C, 54·41; H, 7·65; N, 3·22.

The methiodide was prepared in absolute ethanol solution from methyl iodide (2·84 g) and the base (4·51 g), distillation of the solvent and recrystallization of the semi-solid residue from acetone–ethyl acetate. The product (6·0 g, 79 per cent, m.p. 94–96°) was recrystallized several times from absolute ethanol–ether yielding 4·9 g of colourless crystals, m.p. 98·5–99°.

Anal. Calcd. for $C_{14}H_{26}INO_2$: C, 45·78; H, 7·14; N, 3·81. Found: C, 45·91; H, 7·09; N, 3·98.

*2-Diethylaminoethyl 2-norbornene-5-*endo*carbamate.* A solution of 2-norbornene-5-*endo*isocyanate (13·5 g, 0·1 mole) and 2-diethylaminoethanol (11·7 g, 0·1 mole) in dry benzene (100 ml) was refluxed for 1 h, allowed to stand overnight at room temperature and distilled on the steam bath under aspirator vacuum. The colourless, viscous residue was taken up in anhydrous ether and the hydrochloride was precipitated with anhydrous hydrogen chloride. The crude salt [24·7 g, 86 per cent, m.p. 158–161° (d.)] was recrystallized twice from methyl ethyl ketone to yield 18·7 g of colourless crystals, m.p. 166·5–167·5° (d.).

Anal. Calcd. for $C_{14}H_{25}ClN_2O_2$: C, 58·22; H, 8·73; N, 9·70. Found: C, 58·14; H, 8·78; N, 9·85.

N-(*2-Diethylaminoethyl*)-*norbornane-2*-endo*carboxamide.* A solution of 2-diethylaminoethylamine (22·4 g, 0·193 mole) in dry toluene (200 ml) was added dropwise during 1·5 h to a stirred, ice-cooled solution of norbornane-2-*endo*carbonyl chloride (30·6 g, 0·193 mole) in dry toluene (50 ml). The mixture was then refluxed for 1 h and diluted with heptane. The brown oily product which precipitated solidified to tan crystals upon cooling overnight in the refrigerator. The crude ester hydrochloride (50·4 g, 95 per cent, m.p. 85–92°) was recrystallized three times from ethyl acetate with charcoaling to give colourless, hygroscopic crystals, m.p. 94–95°.*

Anal. Calcd. for $C_{14}H_{27}ClN_2O$: C, 61·18; H, 9·90; N, 10·20. Found: C, 61·43; H, 10·05; N, 10·03.

2-Endo-(*β-diethylaminopropionamido*)-*norbornane.* This compound was prepared by the general procedure for glycinamides in 90 per cent yield, b.p. 133–135°/0·08 mm. The hydrochloride melted at 134·5–136·5° (from toluene).

Anal. Calcd. for $C_{14}H_{27}ClN_2O$: C, 61·18; H, 9·90; N, 10·20. Found: C, 60·96; H, 10·05; N, 10·20.

Summary. The synthesis of a series of bicyclic glycinamides is reported. These compounds were obtained by the reaction of a chloroacyl chloride with a bicyclic amine and subsequent ammonolysis of the resulting chloroacylamides with a primary or secondary amine.

Screening data against methacholine-induced auricular arrhythmias in dogs are presented and the relationship of chemical structure to pharmacodynamic activity is discussed. The steric effects of the bicyclic ring in these structures is compared with that of the 2,6-xylyl group of lidocaine.

Several compounds were found to possess a high order of antiarrhythmic activity but local anaesthetic activity was generally rather low.

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* An isomer of unspecified steric configuration (m.p. 90–94°) has been reported by W. W. Jenkins, U.S. Patent 2,681,931 (1954).

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