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1-Substituted 2,5-Bischloromethylpyrrolidines. A New Class of Adrenolytic Agents

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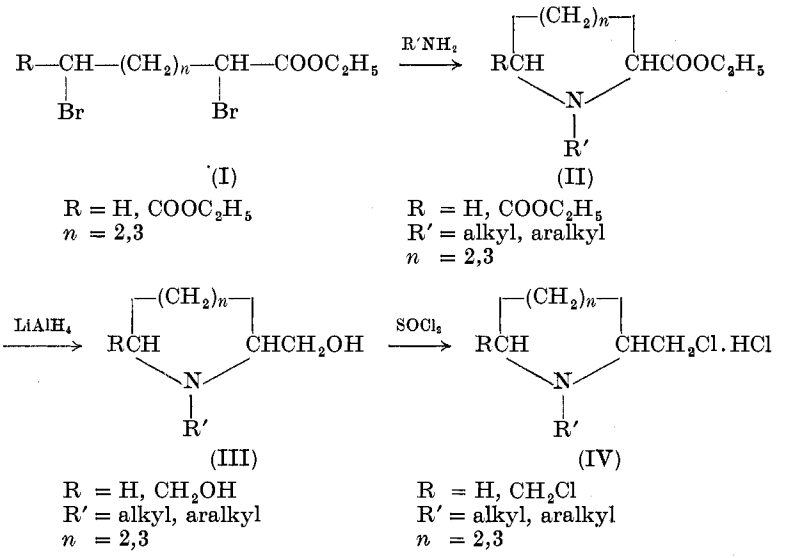
The remarkable adrenergic blocking activity of Dibenamine and its congeners has spurred chemists and pharmacologists alike to study the properties of a multitude of β-haloethylamines. In the ensuing sixteen years since Nickerson and Goodman[1] reported the pharmacodynamic activity of Dibenamine, upward of one thousand β-haloethylamines have been synthesized and screened as adrenergic blocking agents, and the literature has been reviewed[2] from the chemical as well as the pharmacological viewpoint.

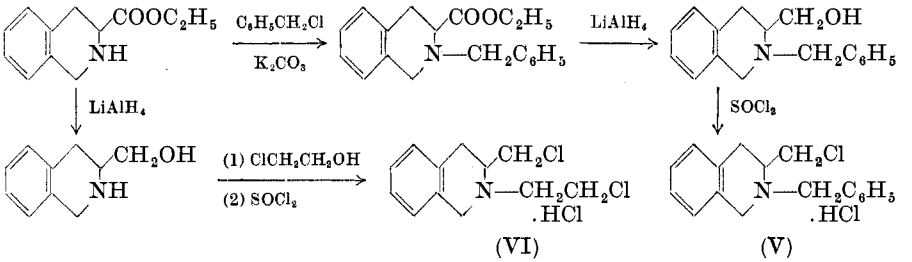
Our interest in the β-haloethylamines as adrenergic blocking agents was aroused when we prepared some 2-chloromethylpyrrolidines as intermediates in another research project. Structures of this type, in which the β-chloroethylamine chain is part of a heterocyclic ring, do not appear to have been studied previously as adrenergic blocking agents. These 2-chloromethylpyrrolidines may be regarded as β-chloroethylamines in which the nitrogen atom and the adjacent α-carbon atom are joined in a heterocyclic ring through a three-carbon alkylene chain. Relatively few α-substituted β-chloroethylamines have been synthesized and the reported adrenergic blocking activity of these derivatives is rather low.[2a]

This paper reports the synthesis and adrenolytic activity of a series of *N*-substituted 2-chloromethyl and 2,5-bischloromethylpyrrolidines. Several piperidine and tetrahydroisoquinoline analogues containing chloromethyl substituents adjacent to the nitrogen atom were also prepared for comparison. Monochloromethyl and bischloromethyl derivatives of pyrrolidine and piperidine were prepared by the following reaction sequence:



The condensation of the dibromoesters (I) with primary amines, first demonstrated by v. Braun and Seemann[3] and later modified by Hill and Maynard,[4] was investigated under a variety of conditions. In addition to the desired heterocyclic esters and diesters (II), a number of by-products were obtained whose isolation and characterization are the subject of another communication.[5] Lithium aluminium hydride reduction of II yielded the expected mono- and biscarbinols (III) which were converted to the hydrochlorides of the corresponding chloromethyl derivatives (IV) by means of thionyl chloride. The preparation of several bischloromethylpyrrolidines (IV; $n = 2$) has been reported recently by Cignarella and Nathansohn.[6] A number of the mono- and bischloromethylpyrrolidine derivatives (IV; $n = 2$) exhibited an anomalous melting point behaviour (liquefaction followed by rapid resolidification) which may be indicative of thermal rearrangement via an ethylenimmonium intermediate. The nature of the rearrangement has been elucidated by Fuson and Zirkle[7] (*vide infra*).

The chloromethyltetrahydroisoquinoline derivatives (V and VI) were obtained from ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate[8] via the following reactions:



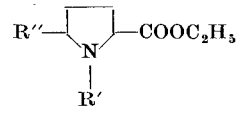
(VI) (V)

Adrenolytic activity is reported in anaesthetized dogs as the amount of drug administered intravenously which gave a 50 per cent or greater inhibition of the pressor response elicited by a standard dose of (−)epinephrine. Additional comparative studies for adrenolytic activity were performed in cats with Dibenamine and phenoxybenzamine as reference drugs. 1-Substituted pyrrolidines substituted by a single chloromethyl group (ERL-551, 548 and 547) were rather weak adrenolytic agents, inhibiting the pressor response of epinephrine in intravenous amounts of 5 mg/kg or more.

The introduction of a second chloromethyl substituent in the 5-position of 1-benzyl-2-chloromethylpyrrolidine (ERL-547) dramatically enhanced adrenolytic activity. Thus, 1-benzyl-2,5-bischloromethylpyrrolidine (ERL-491) was effective at 0·1 mg/kg in completely reversing the epinephrine response in dogs and even dose levels as low as 25–35 μg/kg produced partial blocks. The action developed over a 30 min period and persisted for several hours after a dose of 0·1 mg/kg. Compared to Dibenamine, ERL-491 is several hundred times as effective and has a considerably more favourable therapeutic index. The acute intravenous LD_{50} values of ERL-491 and Dibenamine in mice are 11 mg/kg, and 76 mg/kg respectively. In the pentobarbital-anaesthetized cat, doses of 50 μg/kg (i.v.) or 5·5 mg/kg (p.o.) of ERL-491 reversed the pressor response to 1·5 μg/kg of (−)epinephrine for approximately 90 min; 10–20 μg/kg (i.v.) or 5·0 mg/kg (p.o.) antagonized the response but did not reverse it. A detailed report of the pharmacodynamic activities of ERL-491 will be the subject of another communication.

Unexpectedly, 1-butyl-2,5-bischloromethylpyrrolidine (ERL-541) exhibited no adrenolytic activity at the 5 mg/kg level. The

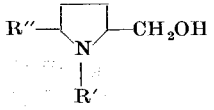
Table I. Derivatives of 2-carbethoxypyrrolidine



R′	R″	b.p. °C/mm	Yield, %	Refractive index, n_D°	Empirical formula	Analysis, %					
						Calcd.			Found		
						C	H	N	C	H	N
n-C_4H_9	H	60– 61/0·06	46	1·4460/24°	$C_{11}H_{21}NO_2$	66·29	10·62	7·03	65·92	10·51	7·20
$C_6H_5CH_2$	H	104–105/0·07	74	1·5120/25°	$C_{14}H_{19}NO_2$	72·07	8·21	6·00	72·36	8·03	6·11
CH_3[a]	$COOC_2H_5$	135–140/7	63	1·4512/25°							
n-C_4H_9[a]	$COOC_2H_5$	104–105/0·05	50	1·4520/25°							
$C_6H_5CH_2$[a]	$COOC_2H_5$	201–205/12	48	1·5035/26°							
$C_6H_5CH_2CH_2$[a]	$COOC_2H_5$	148–152/0·07	17	1·5024/24°							
1-$C_{10}H_7CH_2$	$COOC_2H_5$	193–195/0·4	11	1·5558/24°	$C_{21}H_{25}NO_4$	70·96	7·09	3·94	71·05	7·29	4·15
4-$CH_3C_6H_4CH_2$[a]	$COOC_2H_5$	140–142/0·07	51	1·5002/26°	$C_{18}H_{25}NO_4$	67·69	7·89	4·09	67·74	7·91	4·75
4-$ClC_6H_4CH_2$[a]	$COOC_2H_5$	155–158/0·08	25	1·5111/26°	$C_{17}H_{22}ClO_4N$	60·08	6·53	4·12	59·81	6·47	3·90
4-$CH_3OC_6H_4CH_2$	$COOC_2H_5$	168–170/0·5	46	1·5075/25°	$C_{18}H_{25}NO_5$	64·46	7·51	4·18	64·38	7·55	4·15
2-$BrC_6H_4CH_2$	$COOC_2H_5$	151–153/0·2	23	1·5260/22°	$C_{17}H_{22}BrNO_4$	53·13	5·77	3·65	53·62	6·12	4·13
$C_6H_5OCH_2CH_2$	$COOC_2H_5$	165–168/0·6	64	1·5040/33°	$C_{18}H_{25}NO_5$	64·46	7·51	4·18	64·20	7·44	4·45
$C_6H_5OCH_2CH(CH_3)$	$COOC_2H_5$	160–165/0·2	11	1·4950/24°	$C_{19}H_{27}NO_5$	65·31	7·79	4·01	65·13	8·01	4·16

[a] A. J. Hill, Jr. and J. T. Maynard, U.S. Patent 2,596,099 (1952).

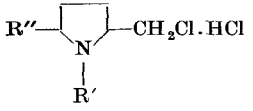
Table II. Derivatives of 2-hydroxymethylpyrrolidine



R′	R″	Yield, %	b.p. °C/mm	Refractive index, n_D°	Empirical formula	Analysis, %					
						Calcd.			Found		
						C	H	N	C	H	N
n-C_4H_9	H	82	67– 69/0·06	1·4641/24°	$C_9H_{19}NO$	68·74	12·18	8·91	68·68	12·19	8·98
$C_6H_5CH_2$	H	84	104–105/0·06	1·5401/24°	$C_{12}H_{17}NO$	75·35	8·96	7·32	75·62	8·70	7·58
CH_3[a]	CH_2OH	55	145–150/11	1·4895/27°							
n-C_4H_9	CH_2OH	72	105–108/0·07	1·4815/24°	$C_{10}H_{21}NO_2$	64·13	11·30	7·48	64·05	11·18	7·69
$C_6H_5CH_2$[a]	CH_2OH	77	120–125/0·04	1·5464/29°							
$C_6H_5CH_2CH_2$	CH_2OH	63	159–160/0·02	1·5470/25°	$C_{14}H_{21}NO_2$	71·45	9·00	5·95	71·48	8·99	6·13
1-$C_{10}H_7CH_2$	CH_2OH	87	195–200/0·05	1·6041/25°	$C_{17}H_{21}NO_2$	75·24	7·80	5·16	75·26	7·80	4·90
4-$CH_3C_6H_4CH_2$	CH_2OH	64	135–137/0·07	1·5428/27°	$C_{14}H_{21}NO_2$	71·45	9·00	5·95	71·17	9·21	6·03
4-$ClC_6H_4CH_2$	CH_2OH	73	170–172/0·08	1·5562/26°	$C_{13}H_{18}ClNO_2$	61·05	7·09	5·48	60·98	7·16	5·26
4-$CH_3OC_6H_4CH_2$	CH_2OH	85	190–193/0·5	1·5487/25°	$C_{14}H_{21}NO_3$	66·90	8·42	5·57	67·01	8·54	5·65
2-$BrC_6H_4CH_2$	CH_2OH	67	170–173/0·2	1·5641/25°	$C_{13}H_{19}BrClNO_2$[b]	46·32	5·69	4·16	46·63	5·89	4·33
$C_6H_5OCH_2CH_2$	CH_2OH	52	172–175/0·2	1·5402/23°	$C_{14}H_{21}NO_3$	66·90	8·42	5·57	66·78	8·57	5·92
$C_6H_5OCH_2CH(CH_3)$	CH_2OH	56	170–175/0·2	1·5250/25°	$C_{15}H_{23}NO_3$	67·89	8·74	5·28	68·07	9·00	5·47

[a] J. v. Braun and J. Seemann, *Ber. dtsch. chem. Ges.*, **56**, 1840 (1923). [b] Isolated as the hydrochloride, m.p. 198–200°.

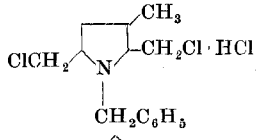
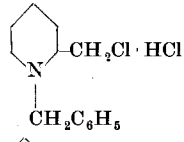
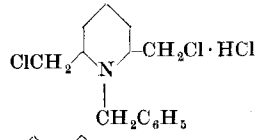
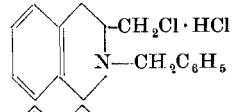
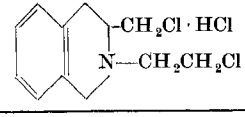
Table III. Derivatives of 2-chloromethylpyrrolidine hydrochloride



R′	R″	Yield, %	m.p., °C	Empirical formula	Analysis, %					
					Calcd.			Found		
					C	H	N	C	H	N
n-C_4H_9	H	74	186–188	$C_9H_{19}Cl_2N$	50·95	9·03	6·60	50·93	9·15	6·83
$C_6H_5CH_2$	H	42	133–135	$C_{12}H_{17}Cl_2N$	58·54	6·96	5·69	58·68	7·22	5·88
CH_3	CH_2Cl	32	147–150	$C_7H_{14}Cl_3N$	38·46	6·46	6·41	38·55	6·50	6·64
n-C_4H_9	CH_2Cl	85	155–157	$C_{10}H_{20}Cl_3N$	46·08	7·73	5·38	46·03	7·66	5·49
$C_6H_5CH_2$	CH_2Cl	60	153–156	$C_{13}H_{18}Cl_3N$	52·99	6·16	4·75	53·10	6·40	4·98
$C_6H_5CH_2CH_2$	CH_2Cl	24	[a]	$C_{20}H_{22}Cl_2N_4O_7$[a]	47·91	4·42	11·18	48·02	4·67	11·33
1-$C_{10}H_7CH_2$	CH_2Cl	56	154–156	$C_{17}H_{20}Cl_3N$	59·23	5·85	4·06	59·54	5·82	4·15
4-$CH_3C_6H_4CH_2$	CH_2Cl	85	168–170	$C_{14}H_{20}Cl_3N$	54·47	6·53	4·54	54·74	6·81	4·87
4-$ClC_6H_4CH_2$	CH_2Cl	65	174–175	$C_{13}H_{17}Cl_4N$	47·44	5·21	4·26	47·44	5·50	4·35
4-$CH_3OC_6H_4CH_2$	CH_2Cl	63	160–163	$C_{14}H_{20}Cl_3NO$	51·79	6·21	4·31	51·87	6·58	4·35
2-$BrC_6H_4CH_2$	CH_2Cl	61	126–129	$C_{13}H_{17}BrCl_3N$	41·79	4·59	3·75	42·04	4·80	4·01
$C_6H_5OCH_2CH_2$	CH_2Cl	64	126–128	$C_{14}H_{20}Cl_3NO$	51·79	6·21	4·32	51·77	6·40	4·53
$C_6H_5OCH_2CH(CH_3)$	CH_2Cl	53	140–141	$C_{15}H_{22}Cl_3NO$	53·19	6·55	4·13	52·90	6·82	4·24

[a] Isolated as picrate, m.p. 181–182°.

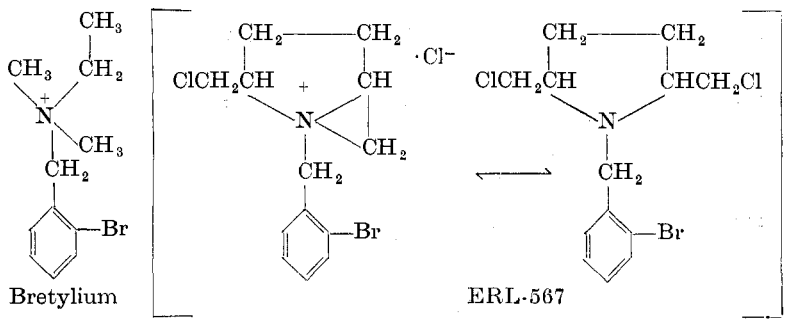
Table IV. Adrenolytic activity

ERL no.	R′	R″	Approximate ED_{50}[a], mg/kg (i.v.)	Approximate LD_{50}[b], mg/kg (p.o.)
551	CH_3	H	> 5	150
548	n-C_4H_9	H	5	300
547	$C_6H_5CH_2$	H	5	500
492	CH_3	CH_2Cl	> 5	500
541	n-C_4H_9	CH_2Cl	—	300
491	$C_6H_5CH_2$	CH_2Cl	0·1	500
561	1-$C_{10}H_7CH_2$	CH_2Cl	0·5	
552	4-$CH_3C_6H_4CH_2$	CH_2Cl	0·5	300
554	4-$ClC_6H_4CH_2$	CH_2Cl	5	> 600
560	4-$CH_3OC_6H_4CH_2$	CH_2Cl	1	
567	2-$BrC_6H_4CH_2$	CH_2Cl	0·1–0·2	
566	$C_6H_5OCH_2CH_2$	CH_2Cl	0·1	
570	$C_6H_5OCH_2CH(CH_3)$	CH_2Cl	0·2	
572			0·3	
558			10	
542			5	> 600
555			2	800
571			1	

[a] ED_{50} is expressed as the amount eliciting a 50 per cent or greater inhibition of the pressor response to 3 μg/kg (i.v.) of (−)epinephrine in allobarbital-urethane anaesthetized dogs.
[b] LD_{50} was determined in mice.

reason for the exception is not clear and may be related to the ease with which rearrangement and ring enlargement take place.

Nickerson and Gump[2b] have pointed out that the benzyl group of Dibenamine and related adrenolytic structures may be replaced by 1-naphthyl, 4-methylbenzyl or 4-methoxybenzyl without significant alteration of activity. Substitution of the benzyl group of ERL-491 by 1-naphthyl (ERL-561) or 4-methylbenzyl (ERL-552), however, led to a moderate loss in activity, and by 4-methoxybenzyl (ERL-560) to a marked loss in activity. As anticipated by analogy to the benzylaminoethyl halide series,[2b, 9, 10] the 4-chlorobenzyl analogue (ERL-554) exhibited but a low order of adrenolytic activity. The 2-bromobenzyl analogue (ERL-561) which bears a close similarity in its ethylenimmonium ion form to the non-adrenolytic hypotensive drug, bretylium,[11] however, was approximately as active as ERL-491.



A high level of adrenolytic activity in certain *N*-substituted *β*-phenoxyethylaminoethyl chlorides was reported by Nickerson and Gump in 1949[2b] and further modifications of these strucures[12, 13] led to the discovery of *N*-(2-phenoxyisopropyl)-*N*-benzylaminoethylchloride (phenoxybenzamine), a clinically useful drug. It was, therefore, not unexpected that 1-(2-phenoxyethyl)-2,5-bischloromethylpyrrolidine (ERL-566) and its 2-phenoxyisopropyl analogue (ERL-570) were approximately as active as ERL-491.

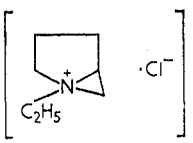
The correlation between adrenolytic activity and the rate at which certain *β*-chloroethylamines of the Dibenamine series are cyclized to the ethylenimmonium ion species has been reviewed by

Ullyot and Kerwin.[2a] It was of interest, therefore, to determine the steric effect of a substituent in the 3-position of the pyrrolidine ring upon adrenolytic activity. 1-Benzyl-3-methyl-2,5-bischloromethylpyrrolidine (ERL-572), however, was somewhat less active than ERL-491. The broad melting range of this compound is indicative of a mixture of *cis* and *trans* isomers, an aspect which is discussed below.

Uncertain stereochemistry may also be responsible for the much lower order of adrenolytic activity observed with 1-benzyl-2,6-bischloromethylpiperidine (ERL-542)—the piperidine analogue of ERL-491. The bicyclic analogues, 2-benzyl-3-chloromethyl-1,2,3,4-tetrahydroisoquinoline (ERL-555) and 2-(β-chloroethyl)-3-chloromethyl-1,2,3,4-tetrahydroisoquinoline (ERL-571), which may be viewed as chloromethyl piperidines in which an *N*-benzyl group forms a part of the heterocyclic ring, exhibited a considerable degree of adrenolytic activity.

At this point it may be of interest to speculate on the mechanism which mediates the potent adrenolytic activity of the pyrrolidine analogues of the nitrogen mustards. Belleau[14] has postulated a two-point attachment of adrenolytic β-haloalkylamines to the receptor surface of the enzyme system concerned with adrenolytic activity. The spatial requirements for an active moiety were defined as an aromatic group three interatomic distances removed from an electrophilic site.

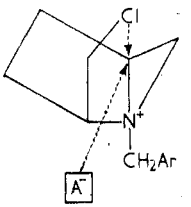
There can be little doubt that compounds of the type represented by ERL-491 readily fall into Belleau's[14] 'phenethylamine' pattern and some discussion of the factors which may contribute to the high degree of activity of these structures seems appropriate. It has been shown that ethylenimmonium ions undergo nucleophilic attack at the most substituted carbon atom.[15,16] Specifically, Fuson and Zirkle[7] demonstrated the rearrangement of 1-ethyl-2-chloromethylpyrrolidine to 1-ethyl-3-chloropiperidine via the intermediate ethylenimmonium ion:



Nucleophilic attack by the receptor site on this ionic species

should proceed similarly, and the release of ring strain in rearrangement of the bicyclic ethylenimmonium ion to the strainless piperidine ring should provide the driving force for an extremely facile reaction.

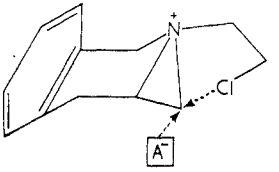
A second point worthy of discussion is the marked enhancement of adrenolytic activity observed upon introduction of an additional chloromethyl group into the pyrrolidine ring (i.e. ERL-491 *vs.* ERL-547). This effect, which is in direct contrast to previously observed activities of 'doubly armed' nitrogen mustards,[2a] may be related to any of the following phenomena: (*a*) A statistical increase of possible interactions between a chloromethyl group and the nitrogen atom leading to an increased ethylenimmonium ion concentration at the receptor site. This effect, however, should be operative in all bis(β-haloethyl)-amines, which is contrary to fact. (*b*) The formation of an additional link to the receptor surface, allowing the substrate to achieve a closer fit. While the stereochemistry of the second chloromethyl group (*cis* with respect to the ethylenimmonium moiety) should be favourable for interaction with the receptor protein, there is no evidence for the nature of this interaction. In this connection, it may even be argued that the bulky halogen group cannot be accommodated by the topography of the receptor surface and thus blocks the approach of the reactant to the active receptor site. (*c*) The potential anchimeric assistance provided by the chloromethyl moiety for nucleophilic attack on the ethylenimmonium ion.



This mechanism takes into consideration the favourable geometry of the chloromethyl group whose *cis* configuration places the nucleophilic halogen in the proximity of the site undergoing substitution. On the basis of this hypothesis, the relatively low order of activity of 1-benzyl-2,6-bischloromethylpiperidine (ERL-542) may be related to the stereochemistry of the 2- and 6-substi-

tuents. ERL-542 melts over a broad range and the range is independent of the rate of heating. This melting-point behaviour strongly suggests the presence of a mixture consisting of *cis* and *trans* isomers. This conclusion is supported by the heterogeneous nature of methyl α,α'-dibromopimelate,[17] used as an intermediate in the preparation of ERL-542, and by the reported facile isomerization of methyl scopolinate to methyl isoscopolinate.[18] Similar considerations may also be used to explain the lower degree of activity of 1-benzyl-3-methyl-2,5-bischloromethylpyrrolidine (ERL-572) referred to above.

Finally, the relatively high adrenolytic activity of 2-(β-chloroethyl)-3-chloromethyl-1,2,3,4-tetrahydroisoquinoline (ERL-571) may also be due to the neighbouring group effect discussed above. Indeed, the 2-benzyl analogue (ERL-555) in which this interaction cannot take place is physiologically somewhat less active.



Experimental*

Preparation of Amines. 1-Naphthylmethylamine was prepared by the method of Kochetkov and Dudykina;[19] and 1-phenoxy-2-aminopropane was synthesized according to the directions of Hurd and Perletz.[20] Since v. Braun's method[21] for the preparation of 2-phenoxyethylamine gave unsatisfactory yields, the compound was obtained by a modified Gabriel synthesis.[22] A mixture of 2-phenoxyethylbromide (305 g),[23] potassium phthalimide (299 g) and dimethylformamide (1200 ml) was heated at 125° for 5 h. The reaction mixture was poured into water, the solid was filtered off and recrystallized from acetone. Yield of *N*-(2-phenoxyethyl)-phthalimide, 300 g (79 per cent); m.p. 129–131° (reported[23] m.p. 129–130°). A solution of the above phthalimide (300 g), 85 per cent hydrazine hydrate (49·2 ml) and

* We are indebted to Mr. E. R. Hoffmann and staff for the analytical data reported in this paper. Melting points are uncorrected.

methanol (4 l.) was refluxed for 1 h. The solvent was removed under reduced pressure and 6N hydrochloric acid (4 l.) was added to the residue. After refluxing the mixture for 1 h, it was cooled to 0° and filtered. The filtrate was condensed to a volume of 200 ml, and after making the slurry basic with solid potassium hydroxide the precipitated oil was extracted with chloroform. The extract was dried and distilled; b.p. 77–79°/2 mm, n_D^{25} 1·5330. Yield, 122 g (69 per cent).

2-Bromobenzylamine was prepared by the reduction of 2-bromobenzonitrile. To a stirred suspension of lithium aluminium hydride (35 g) in ether (1·8 l.) was added dropwise a solution of 2-bromobenzonitrile (159 g).[24] The reaction mixture was refluxed overnight and the excess reagent was destroyed by the addition of 25 per cent sodium hydroxide. The ethereal solution was decanted and distilled; b.p. 115–117°/12 mm. Yield, 59·9 g (47 per cent).

Derivatives of 2-carbethoxypyrrolidine. General Procedure.—The compounds listed in Table I were prepared by the method of Hill and Maynard.[4] To a stirred solution containing one mole of amine, potassium iodide (1·6 g) and benzene (200 ml) was added in portions 0·5 mole of ethyl 2,5-dibromovalerate[25] or 0·33 mole of ethyl 2,5-dibromoadipate.[3] The mixture was stirred for 12 h at room temperature and refluxed for 2 h. The precipitate was filtered off and dissolved in 3N hydrochloric acid (500 ml). This solution was filtered and combined with a 3N hydrochloric acid extract of the original benzene filtrate. The combined acid solutions were made basic with 10 per cent potassium hydroxide and the resulting oil was extracted with ether. The extract was dried and distilled under reduced pressure.

Derivatives of 2-hydroxymethylpyrrolidine. General Procedure.—The compounds listed in Table II were prepared as follows: To a stirred suspension of lithium aluminium hydride (25 g) in ether (1 l.) was added dropwise a solution of 0·33 mole of the 2-carbethoxypyrrolidine derivative and ether (100 ml). The mixture was stirred and refluxed for 12 h and the excess hydride was destroyed by addition of 25 per cent sodium hydroxide. The supernatant ethereal solution was decanted and distilled *in vacuo*.

Derivatives of 2-chloromethylpyrrolidine hydrochloride. General Procedure.—The compounds listed in Table III were obtained in

the following manner. A solution of 0·1 mole of the 2-hydroxymethylpyrrolidine derivative in dry benzene (60 ml) was saturated with gaseous hydrogen chloride. After addition of thionyl chloride (15 ml) the mixture was heated at 60° for 3 h. The hydrochloride of the starting material gradually dissolved and the product started to crystallize. The solid was filtered off and purified by successive recrystallizations from anhydrous ethanol and acetone.

1-Methyl-2-chloromethylpyrrolidine hydrochloride. This compound was prepared by the procedure of Blicke and Lu;[26] m.p. 164–165° (reported[26] m.p. 151–153°).

Ethyl α,α′-dibromo-β-methyladipate. β-Methyladipic acid (96·0 g) was brominated and converted to the ethyl ester by the general method of v. Braun and Seemann[3] to yield 189 g (85 per cent) of a colourless liquid, b.p. 145–150°/1·5 mm (reported[27] b.p. 180°/10 mm); n_D^{25} 1·4880.

Anal. Calcd. for $C_{11}H_{18}Br_2O_4$: C, 35·30; H, 4·81; Br, 42·8. Found: C, 35·40; H, 5·04; Br, 42·5.

1-Benzyl-3-methyl-2,5-dicarbethoxypyrrolidine. A mixture of ethyl α,α′-dibromo-β-methyladipate (30 g) and benzylamine (125 g) was stirred at 40–50° for 3 h and at 80° for 2 h. The cooled reaction mixture was poured into water, acidified with hydrochloric acid and extracted with ether. The ether extract was then extracted with dilute hydrochloric acid, the acid extract made alkaline with sodium hydroxide and the liberated base taken up in ether. Distillation of the dried ether solution gave 39 g (36 per cent) of a colourless liquid, b.p. 176–179°/3 mm, n_D^{25} 1·4963.

Anal. Calcd. for $C_{18}H_{25}NO_4$: C, 67·67; H, 7·84; N, 4·38. Found: C, 67·44; H, 8·20; N, 4·67.

1-Benzyl-2-methyl-2,5-bishydroxymethylpyrrolidine. Reduction of 1-benzyl-3-methyl-2,5-dicarbethoxypyrrolidine (39 g) with lithium aluminium hydride by the general procedure above gave 25 g (88 per cent) of a colourless liquid, b.p. 171–173°/2 mm, n_D^{25} 1·5409.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71·49; H, 8·93; N, 5·96. Found: C, 71·70; H, 8·65; N, 5·97.

*1-Benzyl-3-methyl-2,5-bischloromethylpyrrolidine hydrochloride.**

* We are indebted to Dr. Glenn C. Morrison for the preparation of this compound and its intermediates.

Chlorination of 1-benzyl-3-methyl-2,5-bishydroxymethylpyrrolidine (20 g) with thionyl chloride by the general procedure above gave 7·0 g (27 per cent) of colourless crystals, m.p. 120–133° (after repeated crystallization from acetone).

Anal. Calcd. for $C_{14}H_{20}Cl_3N$: C, 54·45; H, 6·48; N, 4·51; Cl, 34·5. Found: C, 54·40; H, 6·69; N, 4·52; Cl, 34·6.

1-Benzyl-3-hydroxymethylpiperidine. This material was obtained by the lithium aluminium hydride reduction of 1-benzyl-2-carbethoxypiperidine (83·5 g)[28] according to the general procedure described above for the reduction of 2-carbethoxypyrrolidines. Yield, 60 g (87 per cent); b.p. 112–113°/0·5 mm, n_D^{25} 1·5430.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76·05; H, 9·33; N, 6·82. Found: C, 76·28; H, 9·08; N, 6·83.

1-Benzyl-2-chloromethylpiperidine hydrochloride. 1-Benzyl-2-hydroxymethylpiperidine (58 g) was converted to the *N*-mustard by treatment with thionyl chloride according to the procedure outlined for the corresponding conversion in the pyrrolidine series. The product was recrystallized from acetone. Yield, 45 g (61 per cent), m.p. 157–158°.

Anal. Calcd. for $C_{13}H_{19}Cl_2N$: C, 60·00; H, 7·36; N, 5·61. Found: C, 59·77; H, 7·43; N, 5·41.

1-Benzyl-2,5-bishydroxymethylpiperidine. 1-Benzyl-2,5-dicarbethoxypiperidine[30] (119 g) was reduced by lithium aluminium hydride according to the method described for the corresponding monoester. Yield, 73·5 g (86 per cent); b.p. 153–155°/0·08 mm, n_D^{25} 1·5535.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71·45; H, 9·00; N, 5·95. Found: C, 71·70; H, 9·28; N, 6·02.

1-Benzyl-2,5-bischloromethylpiperidine hydrochloride. This compound was prepared from 1-benzyl-2,5-bishydroxymethylpiperidine (73 g) by the procedure outlined for the synthesis of the corresponding monochloromethyl derivative. Yield, 29·5 g (33 per cent), m.p. 185–200°. The wide melting-point range, which remained unchanged even after numerous recrystallizations from ethanol and acetone, suggests the presence of *cis* and *trans* isomers.

Anal. Calcd. for $C_{14}H_{20}Cl_3N$: C, 54·47; H, 6·53; N, 4·54. Found: C, 54·68; H, 6·80; N, 4·67.

2-Benzyl-3-carbethoxy-1,2,3,4-tetrahydroisoquinoline. To a stirred and refluxing suspension consisting of 3-carbethoxy-1,2,3,4-tetra-

hydroisoquinoline (20·5 g),[8] anhydrous potassium carbonate (7·5 g) and dry benzene (125 ml) was added dropwise over a period of 1·5 h a solution of benzyl chloride (15 g) in dry benzene (25 ml). Stirring and refluxing was continued for 12 h, water was added to dissolve the salt, and the layers were separated. The benzene layer was washed with water and extracted with several portions of 3N hydrochloric acid. The extract was made basic with potassium carbonate and the precipitated oil was taken up in ether. The ether solution was dried and distilled. Yield, 10 g (34 per cent); b.p. 175–177°/1·3 mm, n_D^{27} 1·5590.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77·26; H, 7·17; N, 4·74. Found: C, 76·95; H, 7·15; N, 4·94.

2-Benzyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline. A solution of 2-benzyl-3-carbethoxy-1,2,3,4-tetrahydroisoquinoline (9·3 g) in ether (25 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (3 g) in ether (100 ml). The mixture was stirred and refluxed for 16 h and the excess hydride was destroyed by the addition of 25 per cent sodium hydroxide. The supernatant was decanted and distilled. Yield, 5·8 g (73 per cent); b.p. 168–170°/0·08 mm, n_D^{27} 1·5925.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80·57; H, 7·56; N, 5·53. Found: C, 80·51; H, 7·40; N, 5·63.

3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline. The above reduction procedure was applied to 20·3 g of 3-carbethoxy-1,2,3,4-tetrahydroisoquinoline.[8] After removal of the solvent under reduced pressure, the solid residue was crystallized from cyclohexane and ethyl acetate. Yield, 6·5 g (40 per cent), m.p. 105–107°.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73·59; H, 8·03; N, 8·58. Found: C, 73·56; H, 8·30; N, 8·80.

2-Benzyl-3-chloromethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride. A solution of 2-benzyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (5·4 g) and dry benzene (50 ml) was saturated with hydrogen chloride. Thionyl chloride (7·5 ml) was added and the mixture was heated for 2 h at 60–70°. The solvent and excess reagent were distilled under reduced pressure and the solid residue was taken up in absolute ethanol. The solution was refluxed for 5 min, the solvent was evaporated, and the residue was dissolved in hot ethyl acetate. The solution was refluxed

for 0·5 h; on cooling, the colourless crystals were collected by filtration. Yield, 4 g (61 per cent); m.p. 155–157°.

Anal. Calcd. for $C_{17}H_{19}Cl_2N$: C, 66·24; H, 6·21; N, 4·55. Found: C, 65·90; H, 6·30; N, 4·78.

2-(β-Chloroethyl)-3-chloromethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride. A mixture of 3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (6·5 g) and 2-chloroethanol (4·5 ml) was heated for 4 h at 130–140°. A solution of thionyl chloride (12 ml) in chloroform (19 ml) was added and the mixture was refluxed for 2 h. The solvent and excess reagent were removed under reduced pressure. Methanol (10 ml) was added to the residue and the solution was refluxed for 5 min. The solvent was evaporated and the residue recrystallized from acetone. Yield, 3 g (27 per cent), m.p. 147–150°.

Anal. Calcd. for $C_{12}H_{16}Cl_3N$: C, 51·35; H, 5·75; N, 4·99. Found: C, 51·30; H, 5·50; N, 5·09.

Summary. *N*-Substituted 2,5-bis(chloromethyl) pyrrolidines were shown to constitute a new class of compounds possessing significant adrenolytic activity. The most effective agent in this group—1-benzyl-2,5-bis(chloromethyl)pyrrolidine (ERL-491)—inhibited the pressor response to 3 μg/kg of (−)-epinephrine at dose levels of 25–100 μg/kg. A mechanism of action, based on the transition of a strained ethylenimmonium ion to a strainless piperidine conformation, has been proposed and the possibility of an anchimeric assistance by the second chloromethyl group towards nucleophilic attack by the receptor site has been discussed.

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