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Ganglion Blocking Aminobicyclo [2. 2. 1] heptanes *

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Eight structural variations of 3-methylamino-2,2,3-trimethyl-norcamphane (mecamylamine) were prepared and studied.

In 1958 a communication from this laboratory [1] reported on the ganglion-blocking properties of some norbornane amines related to 3-methylamino-2,2,3-trimethylnorcamphane (mecamylamine), the first non-quaternary blocking agent discovered.[2]

Further structural variations were prepared and studied (*cf.* Ref.[3]), and in the meantime several of these, as well as some of the compounds presented earlier,[1] have been described and studied for biological effects by others.[4–9]

As a contribution to the study of the influence of the degree of steric hindrance on blocking potency it was thought of interest to report some related compounds bearing no methyl group in position 3, and in which either the alkyl groups in position 2 or the N-alkyl were varied in number and size.

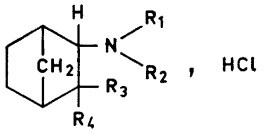
The compounds can be represented by the general formula given in Table 1. They were prepared by a modified Leuckart reaction [10] between norcamphor,[11] 3-methyl-norcamphor,[12] camphenilone,[13] and 3,3-diethyl-norcamphor,[12] and the formamide, appropriately substituted at nitrogen. The 3-dimethylamino-2,2-dimethylnorcamphane (Åsa 214/9) was obtained from Asa 214/1 by an Eschweiler-Clark methylation. The physical and biological data, and the IR-spectrum suggest that 214/1 is the *exo* form. This would then place the whole series in relation to the structure assignment of Stone *et al.*[8,9]

The pharmacological data on the ganglion blocking and hypotensive action of the compounds are shown in summary form in Table 2. It appears that a certain degree of steric hindrance is necessary for activity, which then disappears if too bulky substituents adversely affect solubility (phase distribution) or receptor approach.

A neurological syndrome (tremor, ataxia, motor stimulation) develops to a more or less pronounced degree after subacute feeding of the active compounds. This is absent when the substance is inactive and its appearance would thus indicate a central process mirroring the peripheral action and probably mediated by interference with central cholinergic transmission.

* Terpene amines III. Part II of this series: K. Rubinstein, K. Hermansen and N. Elming, *Acta Chem. Scand.* **17** (1963) 2069.

Table 1. Aminobicyclo [2.2.1] heptanes.



Code No. (ASA)	R_1	R_2	R_3	R_4	M.p./°C[a]	Recryst. solvent	Yield %	Formula	Carbon %[b]		Hydrogen %		Nitrogen %		Chlorine %	
									calc.	found	calc.	found	calc.	found	calc.	found
214/3	Me	H	H	H	199–201	MeCN	21	$C_8H_{15}ClN$	59.5	59.6	10.1	10.1	8.7	8.6	22.0	21.7
214/11	Me	H	Me	H	300–303 (dec.)	iPrOH-ether	13	$C_9H_{18}ClN$	61.5	61.7	10.3	10.3	8.0	8.0	20.2	19.4
214/1	Me	H	Me	Me	no definite m.p.	iPrOH	61	$C_{10}H_{20}ClN$	63.3	63.4	10.6	10.7	7.4	7.1	18.7	18.8
214/12	Me	H	Et	Et	no definite m.p.	EtOH	39	$C_{12}H_{24}ClN$	66.2	66.0	11.1	11.1	6.4	6.4	16.3	16.4
214/9	Me	Me	Me	Me	240–242	iPrOH-ether	53	$C_{11}H_{22}ClN$	64.9	64.1	10.9	10.8	6.9	6.6	17.4	17.0
214/2	Et	H	Me	Me	273–275	iPrOH-ether	15	$C_{11}H_{22}ClN$	64.9	65.0	10.9	10.9	6.9	6.8	17.4	17.5
214/7	n-Pr	H	Me	Me	255–257	EtOH	55	$C_{12}H_{24}ClN$	66.2	66.1	11.1	10.9	6.5	6.4	16.3	16.3
214/8	n-Bu	H	Me	Me	236–237	EtOH	45	$C_{13}H_{26}ClN$	67.5	67.3	11.3	11.2	6.0	6.0	15.3	15.3

a All melting points are uncorrected. *b* Microanalyses were carried out by Dr. W. Kirsten and his staff, Institute of Medical Chemistry, Uppsala, Sweden.

Table 2. Pharmacological properties of aminobicyclo [2.2.1] heptanes.

Code No. (ASA)	Ganglion blocking effect		Anti-ACh % atropin[c]	BP-effects[d] dose range/BP-drop/duration mg/kg mm Hg hours	COR[e]	LD 50 i.p. mg/kg	Remarks[f]
	S[a]	PS[b]					
214/3	(+)	10	0.02	inactive	norm.	352	
214/11	+++	176		1–5/25–50/>2	red.	73	
214/1	+++	300	0.006	0.5–1/5–65/>4	abol.	105	tremor, ataxia, hypermotility [1]
214/12	+++	289		1–10/10–40/>2	red.	47	tremor, ataxia
214/9	(+)	285		3/30/>1	red.	123	some tremor
214/2	+++	285	0.011	3/30/>1.5	red.	57	slight tremor
214/7	0	111		inactive	norm.	39	
214/8	0	116		inactive	norm.	36	

a Sympathetic, quantitative expression not possible due to length of action. For details of technique see[14]. *b* Parasympathetic, expressed in % of hexamethonium block. For details of technique see[14]. *c* Peripheral anti-acetylcholine action (isolated guinea pig ileum). *d* Chloralose-urethane anesthetized cats, i.v. injection, carotid blood pressure. *e* Carotis-occlusion reflex (*cf.* Ref.[14]). *f* Upon feeding of 50–75 mg/kg/day to rats for 14–60 days. Estimated by ability to walk on narrow horizontal square rod.

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