Antihypertensives. 1. Syntheses of Thiazino-, Thiazepino-, and Thiazoninoethylguanidines

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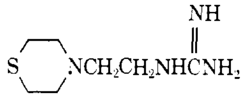
The discovery of guanethidine[1] has generated considerable interest in compounds which exert their antihypertensive effects by blockade of the adrenergic neurone. Subsequent structure–activity studies have demonstrated that the azocino ring of guanethidine can be altered without loss of antihypertensive activity.[2] The results of modification of the heterocyclic ring by incorporation of a sulfur atom are described in this paper. Two approaches were selected—insertion of the sulfur atom directly into the ring, guanidines 1 and 2, and bridging of the ring with a sulfur atom, guanidine 3.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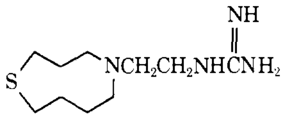
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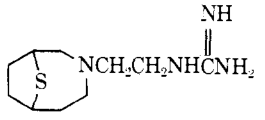
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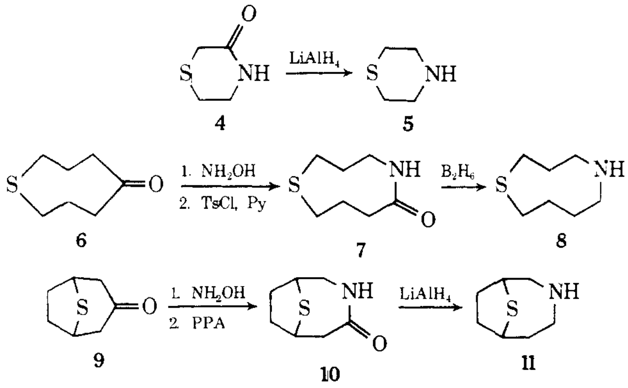
Chemistry. The synthetic approach to these compounds consisted of preparation of the heterocycle followed by attachment of the guanidinoethyl side chain. The thiomorpholine 5 was obtained from the $LiAlH_4$ reduction of thiomorpholinone 4 by a modified procedure of Horrom and Sommers.[3] The perhydro-1,5-thiazonine 8 was prepared from thiacyclooctan-5-one (6).[4] Beckmann rearrangement of the oxime of 6 with tosyl chloride–pyridine afforded amide 7 which was reduced by $LiAlH_4$ to the desired 8. By a similar sequence 8-thiabicyclo[3.2.1]octan-3-one[5] (9) was converted to 11. However, in this case PPA was used for the Beckmann rearrangement.



In each case the *N*-guanidinoethyl side chain was attached by the same synthetic route. Alkylation of the heterocyclic amine with chloroacetonitrile followed by reduction with $LiAlH_4$ gave the corresponding ethylenediamine. The guanidines 1–3 were obtained by treatment of the diamines with 3,5-dimethylpyrazole-1-carboxamidine nitrate.

Pharmacology. Effect on Cat Nictitating Membrane. Methods. Each test compound was examined for its ability to cause relaxation (prolapse) of the nictitating membrane when administered subcutaneously to a separate conscious cat (2–4 kg) of either sex in the manner described by McLean, *et al.*[6]

Results (Table I). Relaxation of the membrane was observed with 2 (10 and 30 mg/kg) and 3 (10 mg/kg) and persisted up to 54 hr with the large dose of 2. By comparison, a greater degree and more prolonged duration of relaxation was produced by smaller doses of guanethidine 12. None of the compounds caused mydriasis. Compound 1 had no noticeable effect on the nictitating membrane in doses up to 30 mg/kg.

Effect on Hypertensive Rats. Methods. Test compounds (contained in 1% tragacanth) were tested for antihypertensive activity after intragastric (oral gavage) administration to conscious Wistar renal (Grollman)[7] or spontaneously hypertensive rats (Carworth, New City, N. Y.). Systolic blood pressure was measured indirectly by means of a pulse transducer (Narco Bio-Systems, Inc., Houston, Texas) applied on the ventral surface of the tail artery distal to an occluding cuff.[8] Recordings were made on an E & M physiograph. Each dose of test compound was examined in two rats.

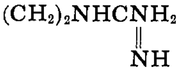
Results (Table I). Good antihypertensive activity ($\Delta\downarrow$ 40–70 mm) was obtained with 2 at 100 mg/kg; guanethidine, however, exhibited a greater po milligram potency. Compounds 1 and 3 (each at 100 mg/kg) were inactive ($\Delta\downarrow$ less than 25 mm).

Effect on Anesthetized Dogs. Methods. Test compounds were administered *via* a cannulated saphenous vein to anesthetized (barbital, 300 mg/kg iv combined with pentobarbital sodium, 120–240 mg iv total dose) mongrel dogs of either sex (8–10.5 kg). Reserpine-pretreated animals were anesthetized with sodium pentobarbital (15 mg/kg iv). A bilateral vagotomy was performed in order to minimize reflex changes in heart rate. Blood pressure was taken from a femoral artery with cannulae connected to a Statham P23AA high-pressure transducer. Heart rates were obtained using a cardiotachometer triggered by the R wave of the lead II ECG. Tracheae were intubated and respiration was maintained artificially with a Bird Mark 8 respirator. All parameters were monitored on a Beckman type R dynograph. The pressor responses to various autonomic drugs and to a 30–45-sec bilateral carotid artery occlusion (BCO) were determined before and after accumulated doses of each test compound (1, 3, and 10 mg/kg).

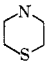
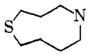
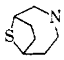
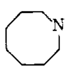
Results (Table II). Each test compound caused a pronounced rise in blood pressure and tachycardia that, in the case of 2 and 3, was preceded by a brief depressor response and followed by a fall in pressure to or slightly below the initial level. The pressor activity of 2 and 3 waned with subsequent dosing. The reflex pressor response to BCO was reduced or abolished while the responses to DMPP (dimethylphenylpiperazinium), norepinephrine, and epinephrine were usually enhanced after administration of test compounds. The tyramine pressor response was either unaffected or slightly augmented after the 1 and 3 mg/kg doses and reduced after the 10 mg/kg dose of test compound. The hypertension and tachycardia of 1 and 2 (each 1 and 3 mg/kg) were markedly reduced or abolished in dogs pretreated with reserpine (1 mg/kg ip 48 and 24 hr prior to experiment). This dose schedule of reserpine produced a nearly complete inhibition of the usual pressor response to tyramine (100 μg/kg iv), while the response to norepinephrine (0.1 μg/kg iv) appeared to be unaltered.

In summary, the cardiovascular–autonomic profile of

Table I



$R(CH_2)_2NHC(=NH)NH_2$

Compd no.	R	Effect on cat nictitating membrane: Dose, mg/kg sc	Deg of relaxation[a]	Duration, hr	Effect on hypertensive rat blood pressure: Dose, mg/kg po	Decrease of systolic pressure[b]
1		3	0			
		10	0		100	0
		30	0			
2		10	+	24	100	++
		30	+++	54	30	0
3		10	+	24	100	0
12		3	++	30	100	++
		10	+++	>72	30	++

[a] 0, inactive; +, 25%; ++, 50%; +++, >50%. [b] 0, inactive; +, 25–39 mm; ++, 40–70 mm; +++, >70 mm.

Table II. Effect of Thioguanidines in Anesthetized Vagotomized Dogs

Compd no.	Dose, mg/kg iv	Mean arterial blood pressure, mm[a]	Duration, min	Heart rate, beats/min[a]	Duration, min	Effect on pressor responses to vasoactive agents[b]: Norepinephrine		Epinephrine		Tyramine		DMPP		Carotid occlusion	
1	1	+85	27	+68	53	P	2	P	2	P	1	P	2	N	
	3	+115	35	+96	120	P	3	P	2	N		P	3	N	
	10	+90	44	+60	>105	P	3	P	2	B	1	P	3	B	2
2	1	−10		0		P	1	N		N		P	1	B	2
	3	+48[c]	22	+50	22	P	2	N		P	1	P	2	B	3
	10	+29[c,d]	35	+45	30	P	2	N		B	2	P	2	B	3
3	1	+58[c]	8	+56	7	P	1	P	2	P	2	P	3	N	
	3	+59[c]	11	+80	60	P	3	P	3	P	1	P	3	B	2
	10	+19[c,d]	10	+52	>60	P	3	P	3	B	2	P	3	B	2
12	1	+47[c,d]	7	+40	5	P	3	P	3	P	3	P	3	B	3
	3	+76[c]	13	+72	29	P	3	P	3	P	1	P	2	B	3
	10	+5[c]	27	+40	24	P	3	P	3	B	2	P	1	B	3

[a] (+) increase; (−) decrease; (0) no change. [b] Code for response: P = potentiates, B = blocks, N = no change. Degree: 1 = minor (10–25%); 2 = moderate (26–75%); 3 = marked (>75%). [c] Pressor response preceded by a transient depressor response. [d] Pressor response followed by a prolonged slight fall in blood pressure.

the test compounds (especially 2 and 3) resembles that of the classical adrenergic neuron blocking agents.[9] Thus, relaxation of the nictitating membrane, in the absence of mydriasis, is considered to be evidence of adrenergic neuron blockade.[6] The initial sympathomimetic action (hypertension, tachycardia) observed in normal animals appeared to be dependent upon the presence of endogenous stores of catecholamines since this was not apparent in reserpinized animals. The initial release of catecholamines prior to neuronal blockade is typical of these types of drugs. Potentiation of the pressor responses to norepinephrine and to a lesser degree epinephrine is probably due to inhibition of the adrenergic neuron amine uptake mechanism while antagonism to the BCO and tyramine responses is related to inhibition of endogenous norepinephrine release.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are corrected. The ir spectra were obtained with a Baird Model 455 double-beam instrument, the uv spectra with a Beckman DKI spectrophotometer, and the nmr spectra with a Varian A-60 spectrometer using Me_4Si as an internal standard. All spectra are consistent with the assigned structures.

3,4,5,6-Tetrahydro-2*H*-1,4-thiazine-4-acetonitrile. A solution of 10.0 g (97.0 mmol) of thiomorpholine, 7.32 g (97.0 mmol) of chloroacetonitrile, and 75 ml of Et_3N was refluxed with stirring for 2 hr. The reaction mixture was poured into 100 ml of Et_2O and filtered. The mother liquor was evaporated to yield 13.0 g (94%) of a solid, mp 51–52°. *Anal.* ($C_6H_{10}N_2S$) C, H, N, S.

4-(2-Aminoethyl)thiomorpholine. To a solution of 12.9 g (0.340 mol) of $LiAlH_4$ in 200 ml of Et_2O was added 36.6 g (0.258 mol) of 3,4,5,6-tetrahydro-2*H*-1,4-thiazine-4-acetonitrile in 400 ml of Et_2O. The resulting solution was refluxed for 20 hr. The excess hydride was destroyed by cautious addition of H_2O. The mixture was filtered, and the solvent was evaporated. Distillation of the residue gave 27 g (72%) of an oil, bp 135–140° (11 mm).

The **dihydrochloride** formed in MeOH as a crystalline solid. Recrystallization from EtOH gave an analytical sample, mp 159–160°. *Anal.* ($C_6H_{14}N_2S \cdot 2HCl$) C, H, Cl, N, S.

1-[2-(Thiomorpholino)ethyl]guanidine Nitrate (1). A solution of 5.0 g (34.2 mmol) of 4-(2-aminoethyl)thiomorpholine and 6.90 g (34.2 mmol) of 3,5-dimethylpyrazole-1-carboxamidine nitrate in 125 ml of EtOH was refluxed for 5 hr. On cooling to 0° there was deposited 6.00 g (70%) of a solid, mp 132–134°. Recrystallization from *i*-PrOH–Et_2O gave an analytical sample, mp 133–134°. *Anal.* ($C_7H_{16}N_4S \cdot HNO_3$) C, H, N, S.

Hexahydro-1,5-thiazonin-6(5*H*)-one (7). A solution of 15.0 g (0.104 mol) of 1-thiacyclooctan-5-one, 9.40 g (0.135 mol) of hydroxylamine hydrochloride, and 11.9 g (0.145 mol) of NaOAc in 250 ml of EtOH was refluxed for 3 hr. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to afford 16.1 g of a solid, mp 89–91°.

To a solution of 16.1 g (0.101 mol) of the oxime in 37 ml of pyridine was added dropwise 25.7 g (0.135 mol) of *p*-toluenesulfonyl chloride in 55 ml of pyridine under N_2 while the temperature was held at 25°. After the addition had been completed, stirring was continued for 7 hr. The reaction mixture was poured into a solution of 14.7 ml of H_2SO_4 in 550 ml of ice H_2O. The resulting solution was stirred for 30 min at 25° and extracted with $CHCl_3$. The organic layer was washed with dilute HCl, dried over Na_2SO_4, and evaporated. Crystallization of the residue from *i*-Pr_2O gave 5.5 g (24%) of solid, mp 85–89°. Further recrystallization gave a pure sample, mp 92–93°. *Anal.* ($C_7H_{13}NOS$) C, H, N, S.

[2-(Octahydro-1,5-thiazonin-5-yl)ethyl]guanidine Nitrate (2). To a solution of 1.90 g (35.0 mmol) of B_2H_6 in 70 ml of THF was added a solution of 5.50 g (34.5 mmol) of hexahydro-1,5-thiazonin-6(5*H*)-one in 50 ml of THF over a 20-min interval. The resulting mixture was decomposed by addition of 100 ml of EtOH at 0°; HCl gas was added until the pH was acidic. The solvent was evaporated and the residue was crystallized from EtOH–Et_2O to yield 4.60 g of a solid, mp 145–148°.

A solution of the hydrochloride, 1.90 g (25.2 mmol) of chloroacetonitrile, 40 ml of Et_3N, and 40 ml of EtOH was refluxed for 20 hr. The solvent was removed *in vacuo*, and the residue was dissolved in $CHCl_3$. The organic solution was washed with H_2O, dried over Na_2SO_4, and evaporated. Distillation of the residue gave 3.40 g of an oil, bp 114–118° (0.1 mm).

A solution of the oil and 2.80 g (73.6 mmol) of $LiAlH_4$ in 70 ml of THF was refluxed for 20 hr. The excess hydride was destroyed by the cautious dropwise addition of H_2O. The mixture was filtered, and the filtrate was evaporated. Distillation of the residue gave 2.90 g of an oil, bp 108–115° (0.3 mm). The reduction procedure was repeated, and 2.90 g of an oil was isolated after removal of the solvent.

A solution of 2.90 g (15.4 mmol) of the oil and 3.10 g (15.4 mmol) of 3,5-dimethylpyrazole-1-carboxamidine nitrate in 40 ml of EtOH was refluxed for 4 hr. On standing there was deposited 2.50 g (28%) of a solid, mp 175–179°. Further recrystallization gave an analytical sample, mp 177–179°. *Anal.* ($C_{10}H_{22}N_4S \cdot HNO_3$) C, H, N, S.

8-Thiabicyclo[3.2.1]octan-3-one Oxime. A solution of 59.8 g (0.421 mol) of 8-thiabicyclo[3.2.1]octan-3-one, 29.3 g (0.422 mol) of hydroxylamine hydrochloride, and 34.6 g (0.422 mol) of NaOAc in 500 ml of 95% EtOH was refluxed for 2 hr. The reaction mixture was poured into 500 ml of H_2O and allowed to stand overnight. There was deposited 53.5 g (81%) of a solid, mp 89–90°. Sublimation gave an analytical sample, mp 89–90°. *Anal.* ($C_7H_{11}NOS$) C, H, N, S.

Hexahydro-2,7-ethano-1,4-thiazepin-5-one (10). To a solution of 630 g of P_2O_5 in 630 ml of H_3PO_4 was added 28.8 g (0.183 mol) of 8-thiabicyclo[3.2.1]octan-3-one oxime portionwise while the temperature was maintained at 42–45°. The resulting solution was heated at 125° for 15 min. The reaction mixture was poured onto 1 kg of ice, neutralized with NaOH, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and dried over Na_2SO_4, and the solvent was removed. There remained 21.9 g (76%) of a solid, mp 148–157°. Recrystallization from EtOAc followed by sublimation gave an analytical sample, mp 156–157.5°. *Anal.* ($C_7H_{11}NOS$) C, H, N, S.

Hexahydro-2,7-ethano-1,4-thiazepine (11). To a solution of 14.4 g (0.381 mol) of $LiAlH_4$ in 1.1 l. of THF was added a solution of 12.4 g (0.079 mol) of hexahydro-2,7-ethano-1,4-thiazepin-5-one in 400 ml of THF. The resulting solution was refluxed for 48 hr. The excess hydride was destroyed by the cautious addition of H_2O. The mixture was filtered and the solvent was removed. Distillation of the residue gave 7.7 g (68%) of viscous oil, bp 107–112° (13 mm). The hydrochloride formed in Et_2O. Recrystallization from *i*-PrOH gave an analytical sample, mp 259–260.5°. *Anal.* ($C_7H_{13}NS \cdot HCl$) C, H, N, S.

3-(2-Aminoethyl)-9-thia-3-azabicyclo[4.2.1]nonane. To a solution of 25 g (0.175 mol) of hexahydro-2,7-ethano-1,4-thiazepine in 150 ml of Et_3N was added 13.3 g (0.176 mol) of chloroacetonitrile in 15 ml of C_6H_6. The mixture was refluxed for 96 hr. An additional 2 g (0.026 mol) of chloroacetonitrile was added and reflux was continued for 24 hr. The reaction mixture was filtered and the solvents were removed. Distillation of the residue gave 21.5 g (68%) of an oil, bp 103–110° (13 mm). To a solution of 8.9 g (0.233 mol) of $LiAlH_4$ in 450 ml of THF was added a solution of the nitrile in 50 ml of THF. The resulting solution was refluxed for 4 hr. The excess hydride was destroyed by the dropwise addition of H_2O. The mixture was filtered and the solvent was removed. Distillation of the residue gave 18.9 g (86%) of an oil, bp 97–103° (5 mm).

The **dihydrochloride** formed in MeOH. Recrystallization from MeOH gave an analytical sample, mp 243–246°. *Anal.* ($C_9H_{18}N_2S \cdot 2HCl$) C, H, N, S.

[2-(9-Thia-3-azabicyclo[4.2.1]non-3-yl)ethyl]guanidine Nitrate (3). A solution of 4.0 g (21.4 mmol) of 3-(2-aminoethyl)-9-thia-3-azabicyclo[4.2.1]nonane and 4.3 (21.4 mmol) of 3,5-dimethylpyrazole-1-carboxamidine in 125 ml of EtOH was refluxed for 20 hr. The EtOH was removed *in vacuo*. Trituration of the residue with Et_2O afforded a solid. Recrystallization from *i*-PrOH gave an analytical sample, mp 173–175°. *Anal.* ($C_{10}H_{20}N_4S \cdot HNO_3$) C, H, N, S.

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Synthesis of a Norcannabinoid

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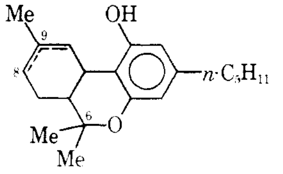
The major active constituents of marijuana have been shown to be the Δ^8- and Δ^9-tetrahydrocannabinols I.[1] The early work of Adams[2] and Todd[3] and their collaborators led to the synthesis of physiologically active $\Delta^{6a,10a}$ isomer IIa and eventually to the very potent dimethylheptyl compound IIe.[4]



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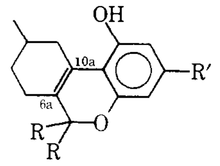

IIa, R = Me; R′ = C_5H_{11}
b, R = Et; R′ = C_5H_{11}
c, R = Pr; R′ = C_5H_{11}
d, R = Me; R′ = C_6H_{13}
e, R = Me;
R′ = $CH(CH_3)CH(CH_3)C_5H_{11}$

As part of a study of structure–activity relationships, Adams prepared the 6,6-diethyl and -dipropyl analogs IIb and IIc[5] and reported them to have a potency equivalent to only 0.05 and 0.02 times that of synhexyl† (IId) in the

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† For ready comparison of potency with other cannabinoids, it is convenient to state potency relative to IId (synhexyl, parahexyl, pyrahexyl) as standard and compared with respect to minimum dose po producing overt side effects.[6] In these terms IIa has a potency of about 0.5 relative to synhexyl in both the rat[6] and the dog[7] (the activity in the dog was incorrectly listed as 0.1 in the previous paper[6]); and IIe has an activity of 500.[6] Activities were determined as previously described.[6]