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Comparison of the Hypotensive Activities of Highly Hindered Open-Chain Amines and Their Cyclic Counterparts

NELSON R. EASTON, FRANCIS G. HENDERSON, WALTER J. MCMURRAY,[1,2] AND NELSON J. LEONARD

The Lilly Research Laboratories, Indianapolis, Indiana, and the Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

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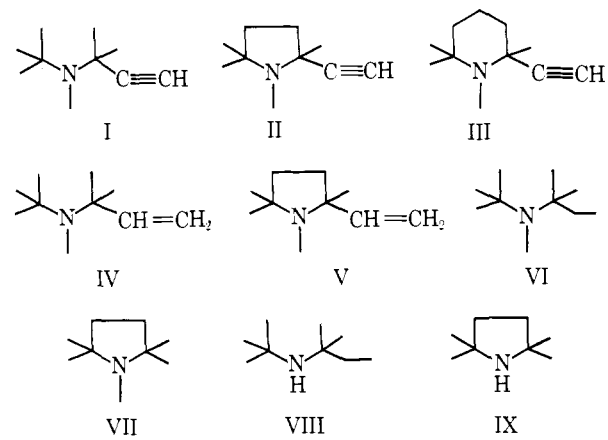
A number of cyclic hindered amines substituted on the α-carbon with ethynyl and vinyl groups have been prepared by the addition of Grignard reagents to ternary iminium salts including: 2-ethynyl-1,2,5,5-tetramethylpyrrolidine, 2-ethynyl-1,2,6,6-tetramethylpiperidine, 2-ethynyl-1,2,6-trimethylpiperidine, and 1,2,5,5-tetramethyl-2-vinylpyrrolidine. Together with 1,2,2,5,5-pentamethylpyrrolidine and 2,2,5,5-tetramethylpyrrolidine, these comprised a series of cyclic compounds which were compared in antihypertensive properties with a closely related series of open-chain compounds, including 3-(N-*t*-butylmethylamino)-3-methyl-1-butyne, (3-N-*t*-butylmethylamino)-3-methyl-1-butene, *t*-amyl-*t*-butylmethylamine, and *t*-amyl-*t*-butylamine. Within the two series studied, the open-chain compounds are generally more potent in their hypotensive effect than the cyclic compounds.

Change in pharmacological activity with difference in chemical structure is especially significant when the compounds differ only by ring formation, that is, one of the compounds is cyclic and the other is open chain. The Hennion synthesis of highly hindered acetylenic amines[3,4] and their hydrogenation products made available a large number of these compounds for pharmacological evaluation. At the same time, the synthesis of highly substituted pyrrolidines and piperidines by the mercuric acetate–iminium salt route[5,6] made it possible to obtain an analogous series of compounds in the monocyclic system. The purpose of this paper is to report on the pharmacological activities of these two series of compounds, especially with regard to their antihypertensive properties as found in rats made hypertensive by a modification of the Goldblatt procedure. The pyrrolidine II and the piperidine III can be visualized as the cyclic counterparts of 3-(N-*t*-butylmethylamino)-3-methyl-1-butyne (I). The vinylpyrrolidine V is analogous to the open-chain amine IV, and 1,2,2,5,5-pentamethylpyrrolidine (VII) is similar to the saturated open-chain tertiary amine VI. The final pair of compounds which were compared in this study were IX and VIII.

Chemistry.—The general reaction consisting of the attack of nucleophilic reagents on ternary iminium salts has been broadly applied.[7] Among the nucleophiles which have been utilized were representative Grignard reagents. The acetylenic-substituted pyrrolidine II, 2-ethynyl-1,2,5,5-tetramethylpyrrolidine, was made by the addition of ethynylmagnesium bromide to 1,2,5,5-tetramethyl-Δ^1-pyrrolinium perchlorate (X).[5] The reaction of an acetylenic Grignard reagent with a ternary iminium salt has also been exemplified by Ryan and Ainsworth[8] in the addition of ethoxyethynylmagnesium bromide to 1,2-dimethyl-Δ^1-tetrahydropyridinium perchlorate, and by Lednicer and Babcock[9] in the addition of ethynylmagnesium bromide to steroidal ternary iminium salts. The characterization of the product from X, 2-ethynyl-1,2,5,5-tetramethylpyrrolidine (II), was based on the infrared spectra of the base and its hydrochloride salt, both of which showed characteristic maxima associated with ≡C—H and C≡C stretching.



The addition of vinyl Grignard reagent to 1,2,5,5-tetramethyl-Δ^1-pyrrolinium perchlorate (X) represents the first example of this type of combination. The product of the reaction was 1,2,5,5-tetramethyl-2-vinylpyrrolidine (V), which was characterized by the infrared spectrum of the base and by the nmr spectrum of the corresponding perchlorate salt.

(1) Eli Lilly and Company Fellow, 1959–1960.
(2) U. S. Rubber Company Fellow, 1960–1961.
(3) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, **82**, 4908 (1960).
(4) C. Ainsworth and N. R. Easton, *J. Org. Chem.*, **26**, 3776 (1961).
(5) N. J. Leonard and A. G. Cook, *J. Am. Chem. Soc.*, **81**, 5627 (1959).
(6) N. J. Leonard and F. P. Hauck, Jr., *ibid.*, **79**, 5279 (1957).
(7) N. J. Leonard and A. S. Hay, *ibid.*, **78**, 1984 (1956), and references therein.
(8) C. W. Ryan and C. Ainsworth, *J. Org. Chem.*, **26**, 1547 (1961).
(9) D. Lednicer and J. C. Babcock, *ibid.*, **27**, 2541 (1962).

In the piperidine series, acetylenic-substituted compounds were made by the addition of acetylenic Grignard reagent to tetrahydropyridinium perchlorate salts. Specifically, 2-ethynyl-1,2,6-trimethylpiperidine (XII) was obtained by the addition of ethynylmagnesium bromide, prepared by the method of Jones, *et al.*,[10] to 1,2,6-trimethyl-Δ^1-tetrahydropyridinium perchlorate (XI).[6] Similarly, 2-ethynyl-1,2,6,6-tetramethylpiperidine (III) was prepared by the addition of ethynyl magnesium bromide to 1,2,6,6-tetramethyl-Δ^1-tetrahydropyridinium perchlorate (XIII). The presence of the acetylenic group in products XII and III was confirmed by the infrared absorption spectra of these compounds and their salts.

Experimental Section[11]

Grignard Reaction Products (Table I).—The general reaction of ethynylmagnesium bromide, prepared by the method of Jones, *et al.*,[10] with ternary iminium salts may be illustrated by the preparation of 2-ethynyl-1,2,5,5-tetramethylpyrrolidine (II). To 0.16 mole of ethynylmagnesium bromide in 50 ml of tetrahydrofuran (THF) was added 10 g (0.04 mole) of 1,2,5,5-tetramethyl-Δ^1-pyrrolinium perchlorate, and the contents was heated under reflux for 5 hr. The reaction mixture was decomposed with aqueous K_2CO_3 solution, and the resulting solid was removed by filtration. The THF was removed under reduced pressure. The residue was basified with NaOH and then extracted with ether. The ether extracts were dried ($MgSO_4$) and filtered, and the ether was removed under reduced pressure to give 6 g of residue, which was distilled *in vacuo*. In a similar manner, vinylmagnesium bromide in THF, prepared by the method of Fuson and Mon,[12] reacted with 1,2,5,5-tetramethyl-Δ^1-pyrrolinium perchlorate[5] to give 1,2,5,5-tetramethyl-2-vinylpyrrolidine (V). The preparations of the ternary iminium salts employed in these reactions are described below.

1,2,6,6-Tetramethyl-Δ^1-tetrahydropyridinium Perchlorate (XIII).—Oxidation of 38.1 g (0.27 mole) of 1,2,2,6-tetramethylpiperidine[13] with mercuric acetate according to the general procedure,[6] followed by preparation of the perchlorate salt and recrystallization from ethanol, furnished colorless needles, mp 199–200° (lit.[14] 201°), of 1,2,6,6-tetramethyl-Δ^1-tetrahydropyridinium perchlorate, ν_{max}^{Nujol} 1650 cm^{-1}, yield 29.7 g (49%). Refluxing the perchlorate salt in ethanol containing a drop of perchloric acid for 48 hr improved the melting point to 208–209° dec, ν_{max}^{Nujol} 1650 cm^{-1}, with no absorption above 3000 cm^{-1}.

Anal. Calcd for $C_9H_{18}ClNO_4$: C, 45.09; H, 7.57; N, 5.84. Found: C, 45.20; H, 7.71; N, 5.70.

It is noteworthy that the infrared spectrum of the base, 1,2,6,6-tetramethyl-Δ^2-tetrahydropyridine, in CCl_4 exhibited a miximum at 1652 cm^{-1}. The failure to observe a shift to higher frequency in the infrared in going from an α,β-unsaturated amine to the corresponding salt (C=N$^+$),[15,16] which has been taken to be characteristic of enamines,[17] is unusual. When other exceptions are found,[18] the basis of their behavior may be established and may then be of additional utility in enamine structural assignments.

Hydrogenation of 5-Methyl-5-nitrohexan-2-one.—A solution of 187.0 g (1.175 moles) of 5-methyl-5-nitrohexan-2-one[19] in 500

TABLE I
GRIGNARD REACTION PRODUCTS

Compd	Bp (mm) or mp, °C	n_D (°C)	Infrared maxima, cm^{-1}	Yield, %	Formula	C, % Calcd	C, % Found	N, % Calcd	N, % Found
2-Ethynyl-1,2,5,5-tetramethylpyrrolidine (II)	65–67 (32)	1.4471 (26)	3280, 2100	40	$C_{10}H_{17}N$	79.40	79.29	11.34	11.47	9.26	9.20
II·Hydrochloride	202–204 dec		3155, 2630, 2400, 2110	*b*	$C_{10}H_{18}ClN$	63.98	63.88	9.66	9.83	7.46	7.49
2-Ethynyl-1,2,6,6-tetramethylpiperidine (III)	93–95 (32)	1.4708 (25)	3285, 2100	30	$C_{11}H_{19}N$						
III·Hydrochloride	253–254 dec		3155, 2440, 2130	*b*	$C_{11}H_{20}ClN$	65.49	65.25	10.00	9.98	6.95	6.76
2-Ethynyl-1,2,6-trimethylpiperidine (XII)	*Ca.* 93 (35–40)	1.4683 (20)		Var.	$C_{10}H_{17}N$						
XII·Hydrochloride	217–218.5 dec		3315, 2340, 2125	*b*	$C_{10}H_{18}ClN$	63.98	63.89	9.66	9.78	7.46	7.40
1,2,5,5-Tetramethyl-2-vinylpyrrolidine (V)	69 (23)	1.4495 (25)	3100, 2700, 1643, 1602, 915	45	$C_9H_{17}N$	78.36	78.27	12.50	12.54	9.14	9.20
V·Perchlorate	264–265 dec			*b*	$C_9H_{18}ClNO_4$	47.33	47.06	7.95	7.81	5.52	5.66

[a] Liquids determined in carbon tetrachloride, solids in Nujol mull. [b] Conversions to salts were essentially quantitative.

(10) E. R. H. Jones, L. Skatteböl, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956).

(11) The boiling points and melting points are uncorrected. The infrared spectra were obtained on a Perkin-Elmer Model 21 spectrometer. The authors are indebted to Mr. Josef Nemeth and his associates for the microanalyses.

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(17) N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954).

(18) Dr. M. G. Reinecke of Texas Christian University has advised us of the unusual spectral behavior of several other enamine–enamine salt pairs: see footnote 13 in M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **30**, 3671 (1965).

(19) R. B. Moffett and J. L. White, *ibid.*, **17**, 407 (1952).

ml of absolute ethanol was hydrogenated with 28 g of Raney nickel (*not* freshly prepared) and 70 kg/cm² of hydrogen at 60° until no more hydrogen was taken up. The solution was then filtered and acidified with 12 *N* HCl. The ethanol and excess HCl were removed *in vacuo*, and the remaining solid was basified and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and filtered, and the ether was carefully removed. The solution remaining was fractionally distilled. A total of 86.8 g of product was collected with the range of physical constants for the cuts being bp 109–120°, $n^{24.5}D$ 1.4259–1.4265. The infrared spectra of all the cuts showed a band at 1642 cm^{-1} (C=N), indicating the presence of **2,5,5-trimethyl-Δ¹-pyrroline** along with the saturated base, 2,2,5-trimethylpyrrolidine. Incomplete hydrogenation results from the use of ordinary Raney nickel.[20,21]

Separation of 2,5,5-Trimethyl-Δ¹-pyrroline from 2,2,5-Trimethylpyrrolidine.—To 2 l. of a saturated solution of picric acid in absolute ethanol was added 40 g (0.28 mole) of a mixture of 2,5,5-trimethyl-Δ¹-pyrroline and 2,2,5-trimethylpyrrolidine. The precipitate which formed immediately gave 76.5 g (0.22 mole) of 2,5,5-trimethyl-Δ¹-pyrrolinium picrate, mp 163–165°, recrystallized twice from ethanol as yellow needles to mp 166–167°, ν_{max}^{Nujol} 1689 cm^{-1} ($C{=}N^+$).

Anal. Calcd for $C_{13}H_{16}N_4O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 46.07; H, 4.75; N, 16.24.

2,5,5-Trimethyl-Δ¹-pyrrolinium hydrochloride was made by bubbling dry HCl gas through an ether solution of the above mixture of amines. It was recrystallized twice from ethanol–ether as colorless needles, mp 173–174°, ν_{max}^{Nujol} 1683 cm^{-1} ($C{=}N^+$).

Anal. Calcd for $C_7H_{14}ClN$: C, 56.94; H, 9.56; N, 9.49. Found: C, 56.87; H, 9.46; N, 9.48.

Reduction of the Mixture of 2,5,5-Trimethyl-Δ¹-pyrroline and 2,2,5-Trimethylpyrrolidine.—The mixture of saturated and Schiff bases could be hydrogenated in absolute ethanol using Pt at 25° or reduced with $LiAlH_4$ in ether to give pure 2,2,5-trimethylpyrrolidine,[5,19] which served as the precursor of 1,2,2,5-tetramethylpyrrolidine, 1,2,5,5-tetramethyl-Δ²-pyrroline, and 1,2,5,5-tetramethyl-Δ¹-pyrrolinium perchlorate.[5]

2,2,5,5-Tetramethylpyrrolidine (IX).—2,2,5,5-Tetramethyl-3-pyrrolidone was prepared by the method of Sandris and Ourisson[22] in the sequence: bromination of triacetoneamine to give 3,5-dibromo-2,2,6,6-tetramethyl-4-piperidone hydrobromide, Favorskii rearrangement using ammonium hydroxide to 2,2,5,5-tetramethyl-Δ³-pyrroline-3-carboxamide, and conversion with sodium hypobromite to 2,2,5,5-tetramethyl-3-pyrrolidone, identified by comparison of spectral data[22] and by formation of the **picrate** derivative, mp 220–222° dec.

Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.59; H, 4.72; N, 14.90.

The 2,2,5,5-tetramethyl-3-pyrrolidone was converted to 2,2,5,5-tetramethylpyrrolidine[23] by the Huang-Minlon modification of the Wolff–Kishner reduction, as also used by Wragg and Bretherick,[24] in 56% yield, bp 124–125°, $n^{25}D$ 1.4202.

Anal. Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.36; H, 13.10; N, 10.74.

The **hydrochloride** crystallized from ether–ethanol as colorless needles, mp 307–308° dec.

Anal. Calcd for $C_8H_{18}ClN$: C, 58.70; H, 11.08; N, 8.56. Found: C, 58.64; H, 10.91; N, 8.55.

The **picrate** separated from ethanol in the form of fine yellow prisms, mp 267.5–269° dec.

Anal. Calcd for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.29; H, 5.62; N, 15.48.

The **perchlorate** crystallized from ethanol as colorless prisms, mp 296–297° dec.

Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 42.04; H, 7.74; N, 6.31.

1,2,2,5,5-Pentamethylpyrrolidine (VII).—Methylation of 35.0 g (0.274 mole) of 2,2,5,5-tetramethylpyrrolidine with 63 g of formic acid and 48 g of 37% formalin produced 36.1 g (93%) of VII,[24] bp 144–145°. The liquid when cooled to room temperature solidified into colorless prisms, mp 38–39°. It sublimed readily at room temperature.

Anal. Calcd for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92. Found: C, 76.18; H, 13.41; N, 9.40.

The **hydrochloride** crystallized from ether–ethanol as colorless prisms, mp 235–236° (lit.[24] 228–231°).

Anal. Calcd for $C_9H_{20}ClN$: C, 60.82; H, 11.34; N, 7.88. Found: C, 60.83; H, 11.24; N, 7.81.

The **picrate** crystallized from ethanol as yellow needles, mp 243–244° dec.

Anal. Calcd for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.73; H, 5.80; N, 15.32.

The **perchlorate** separated from ethanol in the form of colorless prisms, mp (starts to char at 302°) 325° dec.

Anal. Calcd for $C_9H_{20}ClNO_4$: C, 44.72; H, 8.34; N, 5.80. Found: C, 44.86; H, 8.27; N, 5.77.

Pharmacology. Methods.—The hypotensive effect of the open-chain and cyclic compounds was determined in renal hypertensive rats. The animals were surgically prepared by a modification of the procedure described by Goldblatt, *et al.*[25] Following surgery the animals were allowed to develop systolic blood pressures of 160 mm or higher prior to being used as test animals. Blood pressures were determined by the microphonic method of Friedman and Freed.[26] Three hypertensive rats were used to test each dose of the experimental compound. The substances were administered by stomach tube. Control blood pressures were determined prior to drug administration. Following dosage, blood pressures were obtained every hour for 7 hr. Results are expressed (Table II) as the mean per cent change from control during the 7-hr observation period.

General pharmacological studies were made on one compound of this series. A normotensive dog was anesthetized with sodium phenobarbital and prepared to record blood pressure from the carotid artery, respiration from the trachea, and standard lead II of the electrocardiogram. These parameters were recorded with a Grass polygraph.

The effect on ganglionic transmission was determined in the cat anesthetized with chloralose. Blood pressure was recorded from the carotid artery with a mercury manometer. Movements of the nictating membrane were recorded by a lever attached through a pulley to the membrane. The preganglionic portion of the cervical sympathetic trunk was stimulated to evoke contraction of the nictating membrane.

Results

In Table II are assembled the data on the blood pressure effects of the compounds studied. Among the pyrrolidines, only the tertiary amines showed activity in lowering blood pressure. Within the group of compounds I–III, the open-chain compound shows a mean average lowering of 11% at 5 mg/kg, while III shows a mean average lowering of 5% at the same dosage, and II shows a lowering of 6% at 20 mg/kg. In the next group, 3-(N-*t*-butylmethylamino)-3-methyl-1-butene (IV) shows a lowering of 15% at 20 mg/kg and 1,2,5,5-tetramethyl-2-vinylpyrrolidine (V), only 7% at the same dosage. The greatest difference between open-chain and cyclic analogs is for VIII and IX, the former being one of the most potent hypotensive agents in the series and the latter virtually ineffective at 20 mg/kg. These data indicate that the open-chain compounds are more potent in their hypotensive effect than the cyclic ones, at least than the corresponding substituted pyrrolidines. In the investigation of the congeners of pempidine, 1,2,2,6,6-pentamethylpiperidine, Bretherick, *et al.*,[27] found that the over-riding factor controlling activity (on the preganglionically stimulated nictitating membrane of the cat) was the shielding of the basic nitrogen atom provided by alkyl groups substituted on

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TABLE II
BLOOD PRESSURE RESPONSE IN HYPERTENSIVE RATS

Compd hydrochloride	Oral dose, mg/kg	Mean change of blood pressure, %	Side effects
3-(N-*t*-Butylmethylamino)-3-methyl-1-butyne (I·HCl)	1	−4.5	None
	5	−11.5	
	20	−15.7	
3-(N-*t*-Butylmethylamino)-3-methyl-1-butene (IV·HCl)	5	−6	None
	20	−15	Moderate to severe
t-Amyl-*t*-butylmethylamine (VI·HCl)	1	−7	
	5	−12	1 rat died
	20	−11	
t-Amyl-*t*-butylamine (VIII·HCl)	1	−11	None
	2.5	−12	None
2-Ethynyl-1,2,5,5-tetramethylpyrrolidine (II·HCl)	20	−5.7	None
	40	−7.5	None
2-Ethynyl-1,2,6,6-tetramethylpiperidine (III·HCl)	5	−5.4	Mild
	20	−13.6	Severe ganglionic block
1,2,5,5-Tetramethyl-2-vinylpyrrolidine (V·HCl)	20	−7	None
	40	−11.8	None
1,2,2,5,5-Pentamethylpyrrolidine (VII·HCl)	5	−12.5	None
	10	−13.5	Mild ganglionic block
	20	−13	Mild ganglionic block
2,2,5,5-Tetramethylpyrrolidine (IX·HCl)	20	−2.7[a]	None
2,2,5-Trimethylpyrrolidine ($C_7H_{15}N$·HCl)	20	−2.7[a]	None
2,5,5-Trimethyl-Δ^1-pyrroline ($C_7H_{13}N$·HCl)	20	+1.7[a]	None

[a] Not significant.

the two carbon atoms adjacent to it. They found that di-*t*-butylamine has an activity similar to that of pempidine, but greater than that of 2,2,5,5-tetramethylpyrrolidine (IX), which is in line with our comparison of VIII and IX.

In Table II, the only exceptional acyclic–cyclic pair is *t*-amyl-*t*-butylmethylamine (VI) and 1,2,2,5,5-pentamethylpyrrolidine (VII). Both show the same blood pressure lowering in the hypertensive rat at the same dose and appear to be nearly equivalent in potency. In this pair the greatest steric shielding of the nitrogen occurs for the series of compounds investigated, and, in models, there appears to be a close resemblance of the surface conformations of VI and VII.

To cite one example from another realm of pharmacological activity, Blicke and Krapcho[28] compared open-chain and cyclic analogs for analgesic action and found that substituted 3-piperidones which might be considered "cyclic amidones (methadones)" did not exhibit the analgesic activity of methadone and were quite toxic.

Additional pharmacological studies with 1,2,5,5-tetramethyl-2-vinylpyrrolidine (V) showed that intravenous administration of 2 mg/kg of the hydrochloride in the normotensive anesthetized dog produced a 20–40% decrease in arterial pressure, and 5 mg/kg, a 35–45% decrease in arterial pressure. There was a decrease in heart rate and an increase in respiratory rate. In the anesthetized cat this compound decreased the response of the nictitating membrane to electrical stimulation of the preganglionic nerve fibers indicating ganglionic blockade. There was 80% block with 1 mg/kg, 34% block with 0.5 mg/kg, and 11% block with 0.25 mg/kg. The duration of the blockade was less than 1 hr.

Finally, within each of the series studied, that is, open-chain and cyclic considered separately, no dramatic change in hypotensive activity is produced by substituting an alkyl for a vinyl for an ethynyl group, although differences are evident in the side effects of these compounds.

(28) E. F. Blicke and J. Krapcho, *J. Am. Chem. Soc.*, **74**, 4001 (1952).