Synthesis of New Hydrazidines with Vasoconstrictor Activity

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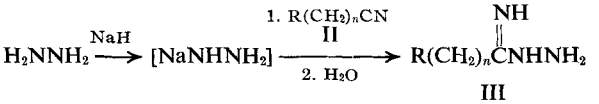
Abstract □ A series of hydrazidines with a structural similarity to the guanidines of the guanethidine series was synthesized. The observation that the hydrazidines raised blood pressure led to their screening as nasal decongestants. The most active compound, 3-(*hexahydro-1H-azepino*)*propionimidic* acid hydrazide dihydrochloride, was less potent than phenylephrine hydrochloride.

Keyphrases □ Hydrazidines—synthesis □ Vasoconstrictive activity—hydrazidines □ Hypertensive activity—hydrazidines

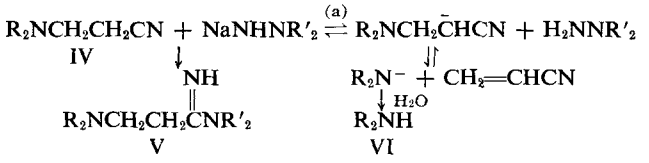
A series of hydrazidines with a structural similarity to the guanidines of the guanethidine series (1) was prepared for screening as antihypertensive compounds. The observation that the amino-substituted imidic acid hydrazides (III) raised blood pressure led to the screening of these compounds as nasal decongestants. In this paper the name hydrazidine refers to the general class of compounds, $-C(=N)N-N=$; specific types are named according to the system of *Chemical Abstracts*.

Several disubstituted aminoacetimidic acid hydrazides (III*a–c*, Table I) were prepared by a modification (Method *A*) of Kauffmann's procedure (2) for the synthesis of aliphatic hydrazidines.

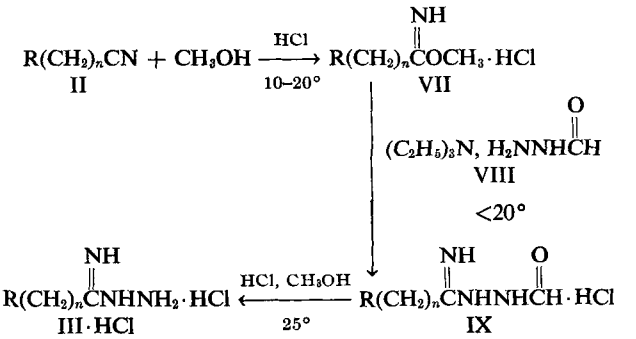


Method A

Certain limitations to Method *A* have been observed. The reaction did not occur with acetonitriles possessing a labile α-hydrogen atom which could yield a resonance stabilized anion, as in the case of 2-phenyl-2-(2-pyridyl)-acetonitrile. In the case of 3-aminopropionitriles (IV), the competitive retrograde Michael reaction (a) was dependent upon the nature of the amino substituent (R_2N^-). When R_2N^- was incapable of resonance stabilization, competition was nil, and the desired hydrazidine V was formed. With R_2N^- capable of resonance stabilization, *e.g.* $C_6H_5N^-Et$, however, the amine VI was a primary product of the reaction.



A variety of substituted imidic acid hydrazides (III*d–i*, Table I) has been prepared *via* a modified procedure (Method *B*) of Westermann *et al.* (3), through the intermediate *N*-formamidoalkylamidines (IX*a–f*, Table II). Method *B* affords a safer preparation of the hydrazides (III) than Method *A*, where metastable sodium hydrazides are formed as intermediates.



Method B

PHARMACOLOGIC RESULTS

All of the hydrazidines that were tested (Table II) for their effect on nasal volume were less active than phenylephrine hydrochloride. The most active compound was III*g* which caused marked changes in nasal volume with relatively little effect on systemic blood pressure. Although these studies are preliminary in nature and involve few animals, a tentative order of decreasing potency of the compounds may be listed as III*g* > III*f* ≥ III*h* ≥ III*c* ≥ III*i* > III*b* > III*d*. Thus, the 3-disubstituted aminopropionimidic acid hydrazides appear to be the most potent compounds prepared.

EXPERIMENTAL

Chemistry

2-(Hexahydro-1H-azepino)acetimidic Acid Hydrazide Dihydrochloride, IIIc—(*Method A*)—The reaction was conducted with special equipment and precautions as described by Kauffmann *et al.* (2). The main modification was the substitution of sodium hydride for sodamide in the generation of sodium hydrazide (I), affording a more rapid and reliable reaction with acetonitrile (II, $n = 1$).

Thus, to a mixture of 50% NaH (14.4 g., 0.30 mole) dispersed in mineral oil and dry ether (300 ml.) was added dropwise a solution of anhydrous hydrazine (9.6 g., 0.30 mole) in dry ether at 0–5°; this then was warmed to 10–15° over a 2-hr. period. The gray suspension was cooled to 0–5°, and treated dropwise with a solution of azepinoacetonitrile (41.4 g., 0.30 mole) in dry ether. The resultant creamy white suspension was warmed to 15° for 1.5 hr., cooled to 0–5° and treated with H_2O (14 ml.). The reaction mixture was stirred for 1 hr., and then filtered. The ethereal filtrate was dried (Na_2SO_4), concentrated, and distilled to give 17.4 g. (29%) of the free base; b.p. 114–126° (0.3–0.5 mm.).

The dihydrochloride (III*c*) was prepared by treating the free base in acetonitrile at 60° with a saturated solution of hydrogen chloride in acetonitrile. The salt suspension was heated to boiling, cooled, and filtered. Recrystallization from ethanol gave white crystals.

Method B—The method of Westermann *et al.* (3) was employed with several modifications. The methyl imidates VII rather than ethyl imidates were used since the intermediate nitrile hydrochlorides encountered in the preparation of the imidates were readily soluble in methanol. To ensure anhydrous conditions the semistable imidates were stored in a vacuum desiccator overnight. The commercially available formic acid hydrazide (VIII), which contained water, was unacceptable for the preparation of Compounds IX. Anhydrous VIII was prepared as follows.

Formic Acid Hydrazide (VIII)—To a solution of anhydrous hydrazine (960 g., 30 moles) in anhydrous ethanol (3.7 l.) was added ethyl formate (2220 g., 30 moles) at 20–25° during 2 hr. with mechanical stirring. The stirring was continued an additional

Table I—Amino-Substituted Hydrazidines

No.	R	*n*	Method	Yield, %	M.p., °C.[a]	Formula	Anal., % Calcd.	Found
III								
$R(CH_2)_nC(=NH)NHNH_2$								
a	$(C_2H_5)_2N$	1	A	46[b]	175–177	$C_6H_{16}N_4 \cdot 2HCl$	C, 33.19	33.26
							H, 8.36	8.46
							N, 25.80	25.84
b	$(C_5H_{10})N$	1	A	20[b]	200–201	$C_7H_{16}N_4 \cdot 2HCl$	C, 36.73	36.65
							H, 7.98	7.92
							N, 24.52	24.38
c	$(C_6H_{12})N$	1	A	29[b]	195–196	$C_8H_{18}N_4 \cdot 2HCl$	C, 39.51	39.51
							H, 8.29	8.55
							N, 23.04	22.99
d	$3,4\text{-}(CH_3O)_2C_6H_3$	1	B	68[c]	199–201	$C_{10}H_{15}N_3O_2 \cdot HCl$	C, 48.90	49.07
							H, 6.52	6.49
							N, 17.12	17.13
e	$(CH_3)_2N$	2	B	47[c]	158–159	$C_5H_{14}N_4 \cdot 2HCl$	C, 29.56	29.82
							H, 7.94	7.99
							N, 27.58	27.58
	$(C_5H_{10})N$	2	B	90[c]	179–180	$C_8H_{18}N_4 \cdot 2HCl$	C, 39.63	39.74
							H, 8.31	8.29
							N, 23.11	23.00
g	$(C_6H_{12})N$	2	B	73[c]	182–184	$C_9H_{20}N_4 \cdot 2HCl$	C, 42.02	42.32
							H, 8.62	8.55
							N, 21.78	21.83
h	$(C_7H_{14})N$	2	B	36[c]	164–166	$C_{10}H_{22}N_4 \cdot 2HCl$	C, 44.30	44.32
							H, 8.92	8.84
							N, 20.65	20.92
i		2	B	72[c]	180–181	$C_7H_{16}N_4O \cdot 2HCl$	C, 34.30	34.33
							H, 7.40	7.40
							N, 22.82	22.60
IX								
$R(CH_2)_nC(=NH)NHNHCH(=O)$								
a	$(CH_3)_2N$	2		32[d]	118–120	$C_6H_{14}N_4O \cdot HCl$	C, 37.02	36.90
							H, 7.77	7.83
							N, 28.78	28.81
b	$(C_5H_{10})N$	2		29[d]	157–159	$C_9H_{18}N_4O \cdot 2HCl$	C, 39.86	39.90
							H, 7.43	7.42
							N, 20.66	20.53
c	$(C_6H_{12})N$	2		45[d]	159–160	$C_{10}H_{20}N_4O \cdot 2HCl$	C, 42.10	42.27
							H, 7.78	7.62
							N, 19.64	19.48
d	$(C_7H_{14})N$	2		35[d]	165–167	$C_{11}H_{22}N_4O \cdot 2HCl$	C, 44.15	44.23
							H, 8.08	8.11
							N, 18.72	18.75
e		2		40[d]	166–167	$C_8H_{16}N_4O_2 \cdot 2HCl$	C, 35.18	35.15
							H, 6.64	6.79
							N, 20.51	20.35
	$3,4\text{-}(CH_3O)_2C_6H_3$	1		42[b]	126–128	$C_{11}H_{15}N_3O_3$	C, 55.68	55.54
							H, 6.37	6.15
							N, 17.71	17.77

[a] Melting points were determined on a Fisher-Johns (hot stage) apparatus and are uncorrected. [b] Yield of free base; based on nitrile (II). [c] Yield based on *N*-formamidoamidine (IX). [d] Yield of hydrochloride; based on nitrile (II).

0.5 hr. The product was filtered on cloth (S/26 Jaybeeco Chain Weave); and the cake was kept wet with cold, anhydrous ethanol until all of the slurry was on the filter, after which it was protected from air with a rubber dam. The product was dried in a vacuum desiccator over $CaCl_2$ and finally over P_2O_5; m.p. 55–56°, yield: 1150–1330 g. (64–74%). A second crop was obtained by concentrating the mother liquor under N_2 to about 500 ml.; m.p. 54–56° [lit. (4) m.p. 54°], yield: 305–470 g. (17–26%).

Methyl 3-Dimethylaminopropionimidate Dihydrochloride—A solution of 3-dimethylaminopropionitrile (88.0 g., 1.05 moles) in absolute methanol (700 ml.) was treated with dry hydrogen chloride at 10–20° over 3 hr. until saturated. The reaction was diluted with dry ether, and the resultant white crystalline product was collected by filtration and washed with dry ether (1 l.); m.p. 99–100° [lit. (5) m.p. 100° dec.], yield: 118 g. (55%). Both dilution and filtration operations were conducted in a dry box.

N-Formamido-3-dimethylaminopropionamidine Hydrochloride (IXa)—To a mixture of methyl 3-dimethylaminopropionimidate dihydrochloride (105.0 g., 0.52 mole) and absolute ethanol was added dropwise triethylamine (78 ml., 0.57 mole) at 2–4° with rapid stirring, under an atmosphere of dry N_2. Then formic acid hydrazide (35.0 g., 0.58 mole) was added at 4–7° during 1 min. The temperature was held at 5–7° for 15 min., and allowed to rise gradually to 13° over 25 min., and finally to 23° over 2.5 hr. The mixture was cooled to 10°, and the solid product was collected and washed with ethanol and ether. Recrystallization from 95% ethanol (300 ml.) gave white crystals.

3-Dimethylaminopropionimidic Acid Hydrazide Dihydrochloride, IIIe—To *N*-formamido-3-dimethylaminopropionamidine hydrochloride (90.0 g., 0.46 mole) was added 270 ml. of a cold solution of dry hydrogen chloride in methanol. The reaction mixture was allowed to warm to room temperature over 40 min. The solid product was collected, and washed with ethanol and ether. Recrystallization from methanol (300 ml.) gave white crystals.

Pharmacology

Volume changes in the nasal cavity were measured utilizing a modification of the method of Jackson (6). Mongrel dogs were anesthetized with sodium pentobarbital, 35 mg./kg., i.v., and a

Table II—Vasoconstrictor-Hypertensive Activity

No.[a]	Dose, mg./kg. i.v.	Nasal Volume: Δ mm.[3]	Nasal Volume: Duration, min.	Blood Pressure: Δ mm. Hg	Blood Pressure: Duration, min.	Blood Pressure: Dose, mg./kg. i.v.	Blood Pressure: Change, %	Blood Pressure: Duration, min.
III								
a			[b]			10	+25	5
b	1.0	+300	6	+15	6			
c	1.0	+500	14	+45	5			
d	5.0	+80	14	−25[c]	>14			
e	1.0	+240	10	+5	5	10	+22	45
f	1.0	+580	17	+50	>17			
g	0.5	+680	9	+20	9			
h	1.0	+600	13	+20	13	10	+100	45
i	5.0	+530	36	+37	20			
Phenylephrine hydrochloride	0.01	733	9	+30	9			

[a] Refers to compound numbers in Table I and in the text. [b] Nasal volume changes were not measured for this compound. [c] Doses of 10 to 100 mg./kg. did not produce consistent blood pressure effects.

tracheotomy performed. A femoral artery was cannulated for blood pressure recording. A 22.9-cm. (9-in.) metal rod fitted with a small rubber ball was passed into the dog's mouth to the soft palate so that the ball pressed against the wall of the nasopharynx. A glass nose cannula was then inserted into a nostril, and a clamp was applied to hold the cannula in place and to seal the other nostril. The cannula was connected to a Grass PT-5A volumetric low pressure transducer, and the volume (pressure) changes of this cavity were measured. In some experiments only blood pressure was monitored. All compounds were administered intravenously

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Gas Chromatographic Determination of Chlorphenesin in Plasma

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Abstract □ A procedure is described for the determination of chlorphenesin in plasma. Chlorphenesin is extracted from plasma with chloroform, reacted with bis-(trimethylsilyl)-acetamide, and the silylated derivative is measured quantitatively by gas chromatography. The technique is reproducible and accurate in the range of 1–10 mcg./ml. Dibutyl phthalate is used as internal standard for quantitation by the relative peak height method.

Keyphrases □ Chlorphenesin in plasma—determination □ Plasma, analysis—chlorphenesin □ GLC—analysis □ Dibutyl phthalate—internal standard

Chlorphenesin (3-*p*-chlorophenoxy-1,2-propanediol) has been shown to suppress immunological response in a number of animal systems (1–3) and to inhibit the release of histamine from sensitized human leucocytes by ragweed antigen (4). Although chlorphenesin has been known since 1949 and a number of procedures have been described in the literature for the analysis of chlorphenesin (5, 6) or chlorphenesin carbamate (7), none are sufficiently sensitive to measure the presence of chlorphenesin in biological fluids after therapeutic doses. Procedures for the quantitative analysis in plasma of a closely related compound, mephenesin [3-(*o*-tolyloxy)-1,2-propanediol], have been reported by Titus *et al.* (8) and by Wyngaarden *et al.* (9). However, these analyses depend upon diazotization or nitration of mephenesin at the *para* position of the phenol ring and are not applicable to chlorphenesin which contains a chlorine atom at this location.