The inhibition by O-benzylhydroxylamine under these conditions was slightly lower than that reported by Creveling, *et al.*,[13] presumably through use of dopamine instead of tyramine as substrate in our studies.

The effect of **13** on the synthesis of norepinephrine from tyrosine in isolated guinea pig atria was investigated by the method of Merrills and Offerman.[66]

Acknoweldgments.—We wish to thank our colleagues in the Pharmacology Department of Pfizer Ltd. for the pharmacological results, Mr. P. R. Wood for the microanalysis, Mr. P. M. Brown for the spectroscopic measurements, Mr. R. W. Baldock for the pK_a measurements, and Messrs. J. A. Davidson, G. W. H. Potter, V. F. Voss, and J. A. Zoro for their competent assistance. We thank Dr. M. J. Sewell for some preliminary experiments and advice. This work was done during the tenure (by G. J. T. T.) of a D.S.I.R. Advanced Course Studentship.

(66) R. J. Merrills and J. Offerman, *Biochem. J.*, **99**, 538 (1966).

New Antihypertensive Aminoalkyltetrazoles

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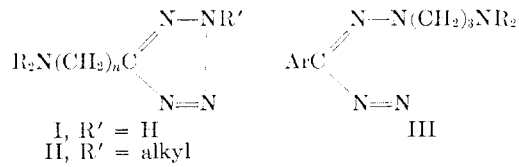
Received December 12, 1966

A series of 5-dialkylaminoalkyltetrazoles, 2-substituted 5-dialkylaminoalkyltetrazoles and 5-aryl-2-(3-dialkylaminopropyl)tetrazoles was prepared from the corresponding nitrile. These compounds showed varying degrees of antihypertensive activity; the 5-[2-(4-aryl-1-piperazinyl)ethyl]tetrazoles were the most active in experimental animals.

The antiadrenergic action of 1-phenylpiperazine and 1-phenyl-4-methylpiperazine were first mentioned by Bovet and Bovet-Nitti.[2] Numerous papers have since been published on the adrenergic blocking effects of 4-substituted 1-arylpiperazines.[3]

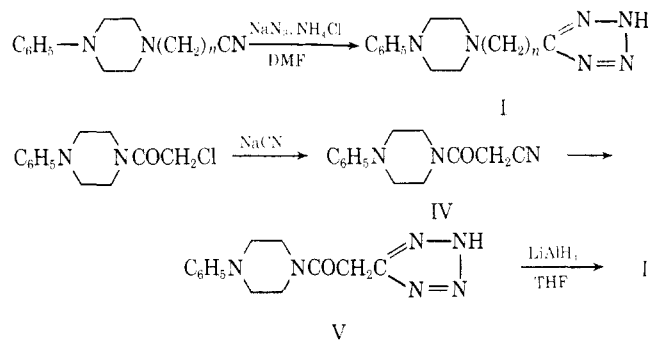
Some pharmacological activities of 1-aryl-5-dialkylaminomethyltetrazoles[4] and 5-aryl-1-alkyltetrazoles[5] have been reported. The chemistry of 2-dialkylaminoalkyl-5-aryltetrazoles[6] and 1-dialkylaminoethyl-5-aryltetrazoles[6] was described, but no pharmacological screening was carried out. These findings led us to prepare 5-dialkylaminoalkyltetrazoles (I), 2-substituted 5-dialkylaminoalkyltetrazoles (II), and 5-aryl-2-[3-dialkylaminopropyl]tetrazoles (III) for pharmacological screening as potential antihypertensive agents.



Some of the 5-[ω-(4-phenyl-1-piperazinyl)alkyl]tetrazoles were reported in a recent patent.[7]

Compounds of type I were prepared in high yield by reaction of the appropriate nitrile with hydrazoic acid according to Finnegan, *et al.*[8] (Scheme I). However, when n = 1 or 2, the yield of I was always less than 50% and 1-phenylpiperazine was obtained in *ca.* 50% yield.

SCHEME I



Alternatively, 1-phenyl-4-cyanoacetylpiperazine (IV) with hydrazoic acid gave 1-phenyl-4(5-tetrazolylacetyl)-piperazine (V) which was then reduced with lithium aluminum hydride to give I. The yield was 40% starting with IV.

Alkylation of 5-alkyltetrazoles is known to take place predominantly at position 2.[6] Therefore, the reaction of I (sodium salt) with an appropriate alkyl halide gave 2,5-disubstituted tetrazoles (II). Similarly, 5-aryl-2-substituted tetrazoles (III) were prepared from 5-aryltetrazoles and an alkyl halide (Scheme II).

Pharmacology.—Pharmacological tests in animals have shown that most of the compounds of this series

(1) To whom communications should be directed.

(2) D. Bovet and F. Bovet-Nitti, "Medicaments du Systeme Nerveux Vegetatif," Verlag S. Karger, Bale, 1948, p 247.

(3) (a) L. W. Roth, *J. Pharmacol. Exptl. Therap.*, **110**, 157 (1954); (b) R. K. S. Lim and R. L. Moffitt, *Federation Proc.*, **15**, 461 (1956); (c) B. B. Morphis, L. W. Roth, and R. K. Richards, *Proc. Soc. Exptl. Biol. Med.*, **101**, 174 (1959); (d) G. Quesnel, R. Chalaust, H. Schmitt, G. Kroneberg, and H. Schmitt, *Arch. Intern. Pharmacodyn.*, **128**, 17 (1960); (e) J. R. Boissier, C. Dumont, R. Ratouis, and J. Pagny, *ibid.*, **133**, 29 (1961); (f) J. R. Boissier, R. Ratouis, and C. Dumont, *J. Med. Chem.*, **6**, 29 (1963); (g) S. Hayao and R. N. Schut, *J. Org. Chem.*, **26**, 3414 (1961); (h) D. W. Wylie and S. Archer, *J. Med. Pharm. Chem.*, **5**, 932 (1962); (i) S. Hayao, R. N. Schut, and W. G. Strycker, *ibid.*, **6**, 133 (1963); (j) F. M. Da Costa and S. Spector, *Federation Proc.*, **22**, 447 (1963); (k) I. H. Page, R. W. Wolford, and A. C. Corcoran, *Arch. Intern. Pharmacodyn.*, **119**, 214 (1959); (l) S. Hayao, H. J. Havera, W. G. Strycker, T. J. Leipzig, R. A. Kulp, and H. E. Hartzler, *J. Med. Chem.*, **8**, 807 (1965).

(4) E. G. Gross and R. M. Featherstone, *J. Pharmacol. Exptl. Therap.*, **92**, 323 (1948).

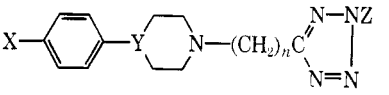
(5) E. G. Gross and R. M. Featherstone, *ibid.*, **92**, 330 (1948).

(6) B. Elpern, *J. Am. Chem. Soc.*, **75**, 661 (1953).

(7) W. G. Strycker and S. Hayao, U. S. Patent 3,231,574 (1966).

(8) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

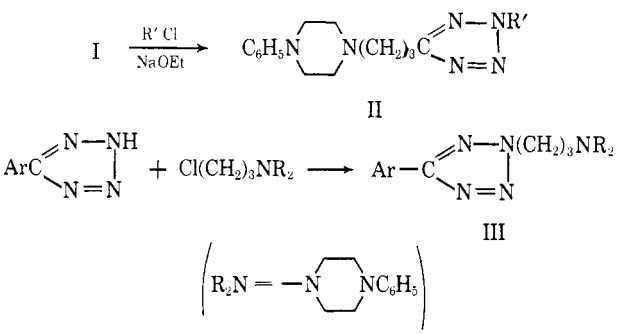
TABLE I



No.	X	Y	n	Z	Mp, °C dec	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H	N	0	H	230–231	$C_{11}H_{14}N_6$	57.4	6.09	36.5	57.0	6.10	36.8
					193–194	$C_{11}H_{14}N_6 \cdot 2HCl$			27.7			28.2
2	H	N	1	H	271	$C_{12}H_{16}N_6$	59.0	6.55	34.5	58.0	6.43	35.0
					200–202	$C_{12}H_{16}N_6 \cdot 2HCl$	45.4	4.90	26.5	44.8	4.90	26.4
3	H	N	2	H	200–201	$C_{13}H_{18}N_6 \cdot 2HCl$[a]	47.2	6.05	25.4	47.2	6.31	25.6
4	H	N	2	C_2H_5	202.4	$C_{15}H_{22}N_6 \cdot 2HCl$	50.1	6.69	23.4	49.9	6.89	23.2
5	4-CH_3	N	2	H	203.5–205.5	$C_{14}H_{20}N_6 \cdot 2HCl$	48.7	6.38	24.4	48.4	6.44	24.4
6	4-Cl	N	2	H	220–221	$C_{13}H_{17}ClN_6 \cdot HCl$[e]			25.6			26.1
7	4-F	N	2	H	194–196	$C_{13}H_{17}FN_6 \cdot 2HCl$	44.7	5.45	24.1	44.7	5.49	23.8
8	3-CF_3	N	2	H	184–186	$C_{14}H_{17}F_3N_6 \cdot 2HCl$	42.2	4.76	21.0	42.3	4.78	21.2
9	3,4-Cl_2	N	2	H	207–209	$C_{13}H_{16}Cl_2N_6 \cdot HCl$[f]			23.1			22.9
10	H	N	3	H	188–189	$C_{14}H_{20}N_6$	61.8	7.35	30.9	61.6	7.22	30.6
					254–256	$C_{14}H_{20}N_6 \cdot 2HCl$	48.7	6.38	24.4	48.7	6.41	24.6
11	3-Cl	N	3	H	165–166	$C_{14}H_{19}ClN_6$	54.7	6.20	27.4	54.7	6.47	27.4
12	H	CH	3	*b*	156–159	$C_{28}H_{38}FN_7 \cdot 2C_2H_2O_4$[c]	57.2	6.26	14.6	57.0	6.44	14.5
13	H	CH	3	H	244–245	$C_{15}H_{21}N_5$	66.5	7.75	25.8	67.0	7.82	26.0
					203–204	$C_{15}H_{21}N_5 \cdot HCl$	58.5	7.16	22.8	58.9	7.04	22.5
14	H	CH	3	*d*	218–220	$C_{29}H_{40}N_6 \cdot 2HCl$	64.2	7.75	15.5	63.8	7.80	15.4
15	H	N	4	H	195–196	$C_{15}H_{22}N_6 \cdot HCl$	55.7	7.12	26.0	55.6	7.12	26.0

[a] *Anal.* Calcd: Cl, 21.4; neut equiv, 110.3. Found: Cl, 21.2; neut equiv, 110.5. [b] 4-*p*-Fluorophenylpiperazinopropyl. [c] Dioxalate. [d] 4-Phenylpiperidinopropyl. [e] *Anal.* Calcd: HCl, 11.2; neut equiv, 164.5. Found: HCl, 11.2; neut equiv, 166.5. [f] *Anal.* Calcd: HCl, 10.0; neut equiv, 181.8. Found: HCl, 9.95; neut equiv, 183.2.

SCHEME II



possess potent α-antiadrenergic activity. They blocked aortic strip and nictitating membrane responses to epinephrine, antagonized the vasoconstrictor and pressor responses to norepinephrine, and produced reversal of blood pressure responses to epinephrine. Some 5-dialkylaminoalkyltetrazole derivatives appeared to be more potent *in vivo* than *in vitro* as compared with the commercially available adrenergic-blocking drugs. They also evoked proportionally greater blockade of sympathetic nerve stimulation. Furthermore, their action was much longer than that of drugs such as azapetine and phentolamine and, unlike that of phenoxybenzamine, immediate in onset and apparently of the competitive equilibrium type.

All of the compounds tested lowered the blood pressure acutely when injected in rats. Compound **3** (zolertine),[9] selected as the prototype, was found to be potent in lowering the blood pressure in anesthetized rats, dogs, and cats. The hypotensive action was apparent at doses of 0.01 mg/kg iv in the different species and was marked and prolonged at 1 mg/kg. This dose also produced a clear lowering of blood pressure in unanesthetized normotensive, renal hypertensive, and mecamylamine hypertensive dogs. The chronic oral administration at single daily doses of about 0.2 and 0.6 mg/kg of the drug-induced sustained lowering of the blood pressure in mecamylamine hypertensive dogs. The detailed pharmacology and the structure–activity relationships on these compounds were reported by our laboratory.[10]

(9) Proposed generic name for 5-[2-(4-phenyl-1-piperazinyl)ethyl]tetrazole hydrochloride.

Experimental Section[11]

The melting points and analyses for the compounds are given in Tables I–III.

5-[2-(4-Phenyl-1-piperazinyl)ethyl]tetrazole Hydrochloride (Method A).—A mixture of 4-phenyl-1-(2-cyanoethyl)piperazine (430 g, 2.0 moles), NH_4Cl (118 g, 2.2 moles), and NaN_3 (144 g, 2.2 moles) in 1.5 l. of DMF was heated at 125° for 20 hr. The reaction mixture was cooled to room temperature and the inorganic salts were removed by filtration. The filtrate was concentrated *in vacuo* and diluted with 1.5 l. of acetone. The mixture was stirred for 2 hr and the dark yellow product was collected on a filter and washed with acetone, yield 265 g, mp 160–170°. The crude solid was recrystallized from 4000 ml of hot water (with charcoal treatment) to give a light tan crystalline solid of mp 186–188°, yield 217 g (after drying at 35°). This solid was added to 1 l. of 2-propanol containing 100 g of concentrated HCl. The mixture was heated to boiling and just enough water was added to dissolve the solid. The hot solution was treated with charcoal and cooled in an ice bath to give a hydrochloride of mp 206–207°, yield 207 g (35.2%).

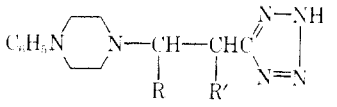
Anal. Calcd for $C_{13}H_{18}N_6 \cdot HCl$: HCl, 12.4; N, 28.5; neut equiv, 147.3. Found: HCl, 12.5; N, 28.5; neut equiv, 146.8.

5-[2-(4-Phenyl-1-piperazinyl)ethyl]tetrazole Hydrochloride (Method B). A. 4-Phenyl-1-cyanoacetylpiperazine.—To a mixture of 32.4 g (0.20 mole) of 1-phenylpiperazine in 150 ml of benzene and 50 ml of 20% NaOH was added 22.5 g (0.20 mole)

(10) R. Rodriquez, E. Hong, H. Vidrio, and E. G. Pardo, *J. Pharmacol. Exptl. Therap.*, **148**, 54 (1965).

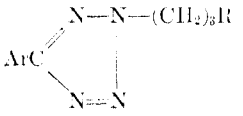
(11) All melting points are corrected and were determined using a Büchi capillary melting point apparatus (W. Büchi, Glasapparatefabrik, Flawil, Switzerland). Infrared spectra were determined with Perkin-Elmer Model 237 grating spectrophotometer. Titrations were carried out with a Sargent Model D recording titrator.

TABLE II



					Calcd, %			Found, %		
No.	R	R′	Mp dec, °C	Formula	N	HCl	Neut equiv	N	HCl	Neut equiv
16	H	CH_3	209–210	$C_{14}H_{20}N_6 \cdot 2HCl$	24.3	21.1	115.1	24.6	20.9	116.7
17	CH_3	H	208–209	$C_{14}H_{20}N_6 \cdot 2HCl$	24.3	21.1	115.1	23.9	20.7	117.5

TABLE III



					Calcd, %			Found, %		
No.	Ar	R	Mp, °C dec	Formula	C	H	N	C	H	N
18	C_6H_5	$C_4H_8NO^a$	143–144.5	$C_{14}H_{19}N_5O \cdot C_4H_4O_4{}^a$	55.5	5.91	18.0	55.6	5.89	17.9
19	C_6H_5	$C_{10}H_{18}N_2{}^f$	163–164	$C_{20}H_{24}N_6 \cdot C_4H_4O_4$	62.1	6.03	18.0	62.1	5.85	18.2
20	C_6H_5	$C_{10}H_{18}N_2$	162.5–163.5	$C_{21}H_{25}N_5 \cdot C_4H_4O_4$	64.8	6.26	15.1	64.9	6.39	15.2
21	$C_6H_5CH_2$	$C_{10}H_{18}N_2$	198–199.5	$C_{21}H_{26}N_6 \cdot 2HCl_4{}^b$	57.9	6.44	19.3	58.0	6.39	19.4
22	$C_6H_5CH_2$	$C_{10}H_{18}N_2$	158–161	$C_{22}H_{27}N_5 \cdot C_2H_2O_5{}^c$	63.9	6.43	15.5	63.9	6.47	15.4
23	$C_6H_5CH_2CH_2$	$C_{10}H_{18}N_2$	209–211	$C_{22}H_{28}N_6 \cdot 2HCl$	58.8	6.68	18.7	58.2	6.69	18.6
24	3-$C_5H_4N^d$	$C_{10}H_{18}N_2$	200.5–202	$C_{20}H_{24}N_6 \cdot C_4H_4O_4$	62.1	6.03	18.1	62.1	6.07	18.0

[a] Maleate. [b] *Anal.* Calcd: HCl, 16.8. Found: HCl, 16.9. [c] Oxalate. [d] 3-Pyridyl. [e] Morpholino. [f] 4-Phenylpiperazino.

of chloroacetyl chloride dropwise with stirring at 0°. After the addition was complete, the solution was stirred for 3 hr at 0–10°. The layers were separated and the benzene layer was washed with water and dried ($MgSO_4$). The benzene was concentrated *in vacuo* leaving a solid material which was collected and washed with ether, yield 28.0 g, mp 74–75°, $\nu_{max}^{CHCl_3}$ 1660 cm^{-1} (amide carbonyl). To 5.8 g (0.12 mole) of NaCN in 10 ml of water was added dropwise 28.0 g (0.11 mole) of the chloroamide in 200 ml of methanol. The solution was then heated on the steam bath for 4 hr and filtered while hot to remove NaCl. The methanol was concentrated *in vacuo* leaving a tan solid. The material was recrystallized from a methanol, $CHCl_3$, and ether mixture; yield 14.0 g; mp 130–132°; $\nu_{max}^{CHCl_3}$ 2260 (nitrile), 1660 cm^{-1} (amide carbonyl).

B. 4-Phenyl-1-(5-tetrazolylacetyl)piperazine.—To 18.0 g (0.078 mole) of the nitrile in 75 ml of DMF was added 5.85 g (0.09 mole) of NaN_3 and 4.8 g (0.09 mole) of NH_4Cl. The mixture was then heated in a wax bath at 125–130° with stirring for 6 hr. The DMF solution was concentrated *in vacuo* and the residual brown solid was recrystallized twice from a methanol–DMF mixture; yield 5.5 g, mp 132–134°.

Anal. Calcd for $C_{13}H_{16}N_6O$: C, 57.3; 5.92; N, 30.9. Found: C, 57.0; H, 5.93; N, 30.9.

C. 5-[2-(4-Phenyl-1-piperazinyl)ethyl]tetrazole Hydrochloride.—To 1.5 g of $LiAlH_4$ in 100 ml of dry THF was added 6.0 g (0.022 mole) of 4-phenyl-1-(5-tetrazolylacetyl)piperazine in 50 ml of THF with stirring. The reaction mixture was then refluxed for 6 hr. The excess $LiAlH_4$ was destroyed by adding 2 ml of a 10% aqueous THF solution, 2 ml of 20% NaOH, and 6 ml of water. The solution was filtered and the filtrate was concentrated *in vacuo* leaving a tan solid. The hydrochloride was prepared by adding excess 2.8 *N* HCl in 2-propanol to the free base in methanol. Upon addition of ether, a solid formed which was recrystallized twice from an aqueous methanol–ether mixture; yield 4.5 g, mp 206–207°.

Anal. Calcd for $C_{13}H_{19}ClN_6$: C, 53.0; H, 6.50; N, 28.5. Found: C, 52.7; H, 6.61; N, 28.6.

5-[2-(4-*p*-Fluorophenyl-1-piperazinyl)ethyl]tetrazole.—A mixture of 1-(2-cyanoethyl)-4-*p*-fluorophenylpiperazine (50.1 g, 0.215 mole), NaN_3 (29.4 g, 0.4 mole), and NH_4Cl (24.0 g, 0.45 mole) in 200 ml of DMF was refluxed with stirring for 7 hr to give a dark brown mixture which was filtered while hot. The inorganic salt residue was washed with acetone. The dark filtrate was concentrated *in vacuo*, diluted with water, and made basic with aqueous NaOH to give a clear solution which was extracted twice with chloroform and once with ether. The combined extracts were dried; the solvent was removed *in vacuo* and the remaining syrup, dissolved in methanol, was treated with dry HCl to give 13.1 g of solid. The hydrochloride was recrystallized from aqueous 2-propanol–ethyl acetal to give a product melting at 210–217°, yield 7.3 g. It was suspended in 20% NaOH solution and tosyl chloride (6.5 g, 0.034 mole) was added. The mixture with a little benzene was shaken vigorously to give a solid mass. After recrystallization from methanol–DMF, 1-*p*-fluorophenyl-4-*p*-toluenesulfonylpiperazine melted at 185–187°, yield 8.8 g.

Anal. Calcd for $C_{17}H_{19}FN_2O_2S$; N, 8.39. Found: N, 8.21.

Meanwhile, the aqueous alkaline solution was adjusted to pH 6 with dilute acetic acid and the clear solution was evaporated to dryness *in vacuo* to leave a tan solid mass. This was extracted with hot absolute ethanol and the insoluble solid was discarded. The dark brown filtrate was concentrated to a smaller volume to give more solid which was also discarded. The dark filtrate was saturated with dry HCl to give a light tan solid of mp 189–190° dec, yield 43.3 g. The solid was dissolved in hot aqueous methanol, filtered, and saturated with dry HCl to precipitate the hydrochloride. This process was repeated four times to obtain the pure dichloride, mp 194–196° dec, yield 23.0 g.

2,5-Bis[3-(4-phenyl-1-piperidyl)propyl]tetrazole.—To 150 ml of absolute ethanol was added 1.7 g (0.074 g-atom) of sodium. After the Na had reacted, 5-[3-(4-phenyl-1-piperidyl)propyl]-tetrazole (20.0 g, 0.074 mole) was added in one portion to give a clear solution. 1-(3-Chloropropyl)-4-phenylpiperidine (17.7 g, 0.074 mole) was added to the above solution immediately and the pale yellow solution was stirred under reflux for 7 hr. NaCl was removed and the solution was concentrated *in vacuo* to give a light amber syrup. This was extracted with chloroform, washed with water, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was dissolved in methanol. The methanolic solution was treated with dry HCl to give a clear solution. Ethyl acetate–ether mixture was added to give a colorless solid of mp 215–221° dec, yield 27.6 g. It was recrystallized twice from methanol–ether to give 21.6 g of dihydrochloride, mp 218–220° dec.

5-Phenyl-2-[3-(4-phenyl-1-piperazinyl)propyl]tetrazole Maleate.—5-Phenyltetrazole (16.3 g, 0.111 mole) was added to a solution of 2.57 g (0.111 g-atom) of Na in 350 ml of anhydrous ethanol and the solution was heated under reflux for 0.5 hr. 4-Phenyl-1-(3-chloropropyl)piperazine (26.6 g, 0.111 mole) was added and the solution was heated under reflux with stirring for 18 hr. The solvent was removed *in vacuo*, the concentrate was suspended in water, and the free base was extracted with several portions of $CHCl_3$. The extracts were concentrated *in vacuo* to give an oil. This base was dissolved in hot methanol and an aqueous–methanolic solution of maleic acid (13 g, 0.112 mole) was added. The solution was filtered and cooled to precipitate a crystalline salt which was collected and recrystallized from aqueous methanol, mp 163–164° dec, yield 37 g (72%).