[CONTRIBUTION FROM THE CHEMISTRY DIVISION, LAKESIDE LABORATORIES, INC.]

Hypotensive Agents. IV. Aminoalkylhydrazines

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The incorporation of a hydrazine moiety into a number of "bis-onium" hypotensive prototypes has yielded derivatives with inferior, comparable or superior hypotensive properties. While some of the hypotensive effect is attributable to ganglionic blockade, additional contributive mechanisms appear to be in evidence. Two of the acid addition salts produced a large increase in Na^+ output in normal and hyperaldosteronized dogs. The compounds were prepared by the reductive hydrazinolysis of the corresponding aminoaldehydes; lithium aluminum hydride was the preferred reducing agent.

The bis-ammonium alkanes have yielded a series of potent hypotensive agents[1-3] which exert their blood pressure lowering effect *via* ganglionic blockade (both sympathetic and parasympathetic). Many of the side effects encountered with these agents are directly attributable to the blockade of the parasympathetic nervous system, such as dry mouth, mydriasis, intestinal atony and urinary retention. Hence, an effort was made to modify the structure of "hexamethonium" and related compounds

$$Am\text{-}(CH_2)_n\text{-}Am\cdot 2CH_3X$$

Am = secondary amino group, n = 5 or 6, X = halogen

and to study the pharmacologic properties of the novel compounds.

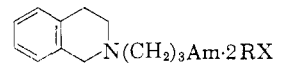
Previous work in our laboratories had dealt with the introduction of triple and double bonds into the bis-ammonium alkane structures[4,5] as well as with the insertion of piperidylcarboxylic acid moieties[6] into the alkylene chain without greatly altering the critical distance relationships between the "onium" nitrogens. The present work deals with further structural modifications of some hypotensive "prototypes."

The commercial availability of hydrazine prompted the synthesis of a number of hydrazine analogs of the prototypes shown (I, Ia, II, IIa, IIb, III, IIIa). The compounds in series Ia, IIa, IIb and IIIa represent nitrogen isosteres of compounds reputed to possess potent hypotensive properties in animals and in man.[7-9]

The choice of investigating hydrazine analogs of active hypotensive agents was based on several considerations: It has been demonstrated by Simpson, *et al.*,[10,11] that "aldosterone," an adrenal corticoid bearing an aldehyde group, was the most powerful salt-retaining hormone of all the mineral corticoids. Hence, we reasoned that hydrazines—by virtue of their reactivity with carbonyl compounds—might inactivate this steroid sufficiently

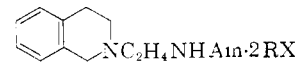
Prototype	Hydrazine analogs
$Am(CH_2)_nAm\cdot 2RX$	$Am_1C_2H_4NHNHC_2H_4Am_2\cdot 2RX$

I

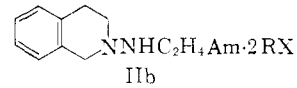


II

Ia



IIa



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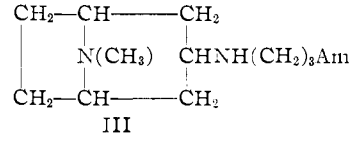
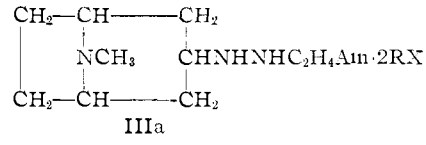


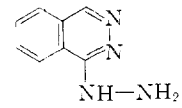
III



IIIa

Am, Am_1, Am_2 = secondary amino groups
n = 5 or 6
RX = alkyl or aralkyl halide groups

to promote the loss of sodium chloride and thus potentiate the hypotensive effect of the parent structures. Furthermore, another hydrazine-containing compound, 1-hydrazinophthalazine (Apresoline) already had been shown to be a potent blood



pressure lowering agent.[12,13] Hence, the incorporation of a hydrazine moiety into structural skeletons with an already high affinity for certain blood pressure regulating centers appeared to be a logical approach to the development of more versatile hypotensive drugs.

Structure–Activity Relationships.—The compounds were submitted in the form of their salts for pharmacologic testing. They were administered intravenously and introduodenally to the nembutalized, normotensive dog. The structure–activity data are summarized in Tables III–V.

In the *sym*-bis-(aminoalkyl)-hydrazine series the replacement of 'CH_2' or 'CH_2-CH_2' by a hydrazine moiety produced in several compounds (2,4,5,6,7,8) an increase in the duration and the intensity of the hypotensive response over the

(1) W. D. M. Paton and E. J. Zaimis, *Brit. J. Pharmacol.*, **6**, 155 (1951).
(2) R. Wien, *J. Pharmacol. Exptl. Therap.*, **110**, 53 (1954).
(3) R. Wien, D. F. J. Mason, N. D. Edge and G. T. Langston, *Brit. J. Pharmacol.*, **7**, 534 (1952).
(4) J. H. Biel and F. DiPierro, THIS JOURNAL, **80**, 4609 (1958).
(5) J. H. Biel and F. DiPierro, *ibid.*, **80**, 4614 (1958).
(6) J. H. Biel, E. P. Sprengeler and H. L. Friedman, *ibid.*, **79**, 6184 (1957).
(7) T. B. O'Dell, C. Luna and M. D. Napoli, *J. Pharmacol. Exptl. Therap.*, **144**, 317 (1955).
(8) H. E. Lape, D. J. Fort and J. O. Hoppe, *ibid.*, **116**, 462 (1956).
(9) W. M. Paton and E. J. Zaimis, *Brit. J. Pharmacol.*, **6**, 155 (1951).
(10) S. A. Simpson, J. F. Tait and I. E. Bush, *Lancet*, **2**, 226 (1952).
(11) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. VonEnw, O. Schindler and T. Reichstein, *Experientia*, **10**, 132 (1954).
(12) B. N. Craver, W. Barrett, A. Cameron and F. F. Yonkman, *J. Am. Pharm. Assoc.*, **11**, 559 (1951).
(13) H. A. Schroeder, *Circulation*, **V**, 28 (1952).

TABLE I

$Am_1C_2H_4NH-NHC_2H_1Am_2$

		Bases						Salts				
		B.p.			Nitrogen, %			Nitrogen, %		Anion, %		M.p.,[a]
Am_1	Am_2	°C.	Mm.	$n^{20}D$	Calcd.	Found[f]	Formula	Calcd.	Found[b]	Calcd.	Found	°C.
Me_2N	Me_2N	65	0.2	1.4540	32.15	31.94	$C_8H_{22}N_4$	10.72	10.53[i]			129
										55.44	55.14[j]	144
C_4H_8N[c]	C_4H_8N[c]	121	.05	1.4951	24.75	24.88	$C_{12}H_{26}N_4$	9.75	9.35[i]			127
										49.75	49.56[j]	154
$C_5H_{10}N$[d]	$C_5H_{10}N$[d]	127	.05	1.4980	22.02	21.88	$C_{14}H_{30}N_4$			47.23	47.13[j]	158
C_4H_8NO[e]	C_4H_8NO[e]	143	.02	1.5000	21.69	21.18[b]	$C_{12}H_{26}N_4O_2$	9.24	9.95[i]			102
$(Me_2CH)_2N$	$(Me_2CH)_2N$	123	.02	1.466	19.56	19.17	$C_{16}H_{38}N_4$					
Et_2N	Et_2N	93	.03	1.4609	24.32	24.72	$C_{12}H_{30}N_4$	9.06	9.25[i]			94
Me_2N	Et_2N	78	.06	1.462	13.84	13.81	$C_{10}H_{26}N_4$	7.63	7.49	63.24[j]	63.40	94
								5.76	5.87	52.20[j]	52.87	151
Me_2N	C_4H_8N[c]	99	.8	1.4870	13.98	14.12	$C_{10}H_{24}N_4$	7.66	7.85[i]			120
								5.79	5.92	52.42	52.50[j]	161
Me_2N	C_4H_8NO[e]	105	.025	1.487	12.95	12.99	$C_{10}H_{24}N_4O$	7.45	7.17	61.67	61.69[j]	95
Me_2N	$C_5H_{10}N$[d]	99	.25	1.4843	13.07	12.90	$C_{11}H_{26}N_4$	5.62	5.43	50.94	50.37[j]	146
Et_2N	C_4H_8N[c]	100	.02	1.4824	12.27	12.08	$C_{12}H_{28}N_4$	5.47	5.37	49.55	49.22[j]	147
Me_2N	$C_5H_{11}N_2$[g]	116	.06	1.4910	12.21	11.99	$C_{11}H_{27}N_5$	7.28	7.34[i]			178
Me_2N	DMP[h]	90	.03	1.4805	12.27	12.21	$C_{12}H_{28}N_4$					

[a] Corrected. [b] Unstable base. [c] Pyrrolidino. [d] Piperidino. [e] Morpholino. [f] Non-aqueous titration of non-hydrazine nitrogen. [g] 4-Methylpiperazino. [h] 2,5-Dimethylpyrrolidino. [i] Trimaleate salt. [j] Dimethiodide.

parent compounds (9 and 10) (Tables III and IV). Structures bearing a heterocyclic amino group were generally more potent and longer acting (*viz.*, 2,4 and 7). Further alkylation of one of the hydrazine nitrogens (3) did not alter the activity greatly. The effect of unsaturation in the chain (hydrazones 11 and 12) on the duration of the hypotensive effect was equivocal. Bis-quaternary ammonium salt formation was essential to hypotensive activity as shown by the inactivity of tertiary amine salts 13 and 14. However, the two compounds produced a potent diuretic effect in dogs upon oral administration. In hyperaldosteronized dogs compound 14 effected a large increase in sodium and water output.[14] In the tetrahydroisoquinoline (THIQ) series, activity was dependent upon the position of the hydrazine moiety. The N-amino-THIQ compounds (15–17) elicited only a fleeting hypotensive effect, whereas the N-β-(substituted hydrazino)-alkyl-THIQ derivatives (20 and 22) produced an intense and prolonged blood pressure lowering activity, especially upon introduodenal administration (Table V).

Of the substituted tropyl hydrazines, compounds 26 and 27 displayed potent hypotensive properties (Table V).

In conclusion, we may state that the replacement of a 'CH_2' or 'C_2H_4' group by a hydrazine radical in some standard hypotensives has yielded compounds of inferior, comparable or superior hypotensive potency and duration of action when tested in the normotensive, anesthetized dog. While some of the hypotensive effect is attributable to ganglionic blockade, additional contributive mechanisms may be involved as suggested by the potent diuretic and natriuretic properties of compounds 13 and 14.

Acknowledgment.—We wish to thank Dr. H. L. Friedman for his many helpful suggestions and Dr. H. L. Daiell for his continued interest throughout the course of this project. We are indebted to Mr. Elmer F. Kluchesky for supplying the analytical results and to Mr. P. A. Nuhfer of the Pharmacology Division for the hypotensive data.

(14) F. C. Bartter, private communication.

Experimental

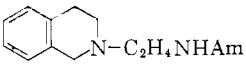
N,N'-Bis-(2-diethylaminoethylidenyl)-hydrazine (I).—To 1,600 g. of 38% aqueous hydrochloric acid was added 283.5 g. (1.5 moles) of diethylaminoacetal while cooling with ice-water. After 2 hours the excess of hydrochloric acid was removed by distillation *in vacuo* using a 60° water-bath and the residue was taken up in 1 liter of water. The excess of free hydrochloric acid was titrated with dilute alkali and to the crude diethylaminoacetaldehyde hydrochloride was added dropwise 44.1 g. (0.75 mole) of 85% hydrazine hydrate. After standing at room temperature for 24 hours, the solution was saturated with potassium carbonate and the azine extracted repeatedly with ether. The ethereal extracts were dried over potassium carbonate, filtered and the ether removed by distillation. The product was collected by fractional distillation; b.p. 109–110° (0.05 mm.), yield 127.9 g. (80%), $n^{20}D$ 1.4738. *Anal.* Calcd. for $C_{12}H_{26}N_4$: N, 24.78. Found: N, 24.22.

N,N'-Bis-(2-diethylaminoethylidenyl)-hydrazine Dimethiodide (II).—To a solution of 11.3 g. (0.05 mole) of N,N'-bis-(2-diethylamino-ethylidenyl)-hydrazine in 50 cc. of acetone was added a solution of 14.2 g. (0.10 mole) of methyl iodide in 50 cc. of acetone. After standing for 24 hours at room temperature, the solid was removed by filtration and recrystallized from boiling ethanol; yield 22.3 g. (87%) m.p. 185° dec. *Anal.* Calcd. for $C_{14}H_{32}I_2N_4$: I, 49.74. Found: I, 49.51.

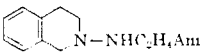
N,N'-Bis-(2-dimethylaminoethyl)-hydrazine (III).—A solution of 34.0 g. (0.2 mole) of N,N'-bis-(2-dimethylamino-ethylidenyl)-hydrazine in 100 cc. of dry ether was added dropwise to a solution of 19 g. (0.5 mole) of lithium aluminum ethylhydride in 600 cc. of dry ether at such a rate as to keep the ether solution at reflux. After the addition was completed, the solution was refluxed for an additional 6 hours, after which was added dropwise a 40% aqueous potassium hydroxide solution. The ethereal solution was decanted, dried over potassium carbonate and subjected to distillation; yield 28.8 g. (83%), b.p. 65° (0.2 mm.), $n^{20}D$ 1.4540. *Anal.* Calcd. for $C_8H_{22}N_4$: C, 55.12; H, 12.72; N, 32.15. Found: C, 55.51; H, 12.39; N, 31.94.

N,N'-Bis-(2-dimethylaminoethyl)-hydrazine Trimaleate (IV).—A solution of 8.5 g. (0.05 mole) of N,N'-bis-(2-dimethylamino-ethyl)-hydrazine in 25 cc. of ethanol was added to a solution of 17.4 g. (0.15 mole) of maleic acid in 100 cc. of ethanol. After standing for 24 hours at room temperature, the hygroscopic solid was removed by filtration and recrystallized once from ethanol; yield 18.1 g. (70%), m.p.

TABLE II

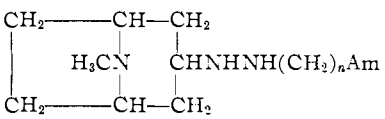


Am	n	Bases: B.p. °C.	Mm.	$n^{22}D$	Nitrogen, % Calcd.	Found	Formula	Salts: Nitrogen, % Calcd.	Found	Anion, % Calcd.	Found	M.p.,[a] °C.
NH_2		116	0 08	1.5594	21.97	21.33	$C_{11}H_{17}N_3$	13.24	13.46[e]			154
$(CH_3)_2N$		99	.03	1.5352	19.17	18.89	$C_{13}N_{21}N_3$			50.44	50.64[f]	211
$(C_2H_5)_2N$		131	.1	1.5350	16.89	17.29	$C_{15}H_{25}N_3$	7.90	8 07	47.78	46.64[f]	192
Pyrrolidino		160	.2	1.5551	17.13	16.76	$C_{15}H_{23}N_3$	7.90	7.89	47.96	47.03[f]	195
								8.80	8.79[e]			148
Morpholino		163	.04	1.5492	16.08	15.96	$C_{15}H_{23}N_3O$			46.55	46 22[f]	191
								8.52	8.52[e]			133
Piperidino		160	.05	1.5460	16.20	16.33	$C_{16}H_{26}N_3$	7.74	7.73	46.72	46.01[f]	216.5



$(CH_3)_2N$		105	0.025	1.5363	19.17	18.41[b]	$C_{13}H_{21}N_3$			50.44	49.57[f]	191
										24.26	23.82[g]	201
$(C_2H_5)_2N$		130	.06	1.5263	16.98	16.98	$C_{15}H_{25}N_3$	7.91	7.93	47.78	47.49[f]	190
Pyrrolidino		152	.07	1.5495	17.13	17.06	$C_{15}H_{23}N_3$	7.94	7.95	47.96	46.69[f]	200
								13.20	13.10	22.28	22.51[g]	207
Morpholino		139	.03	1.5489	16.08	16.01	$C_{15}H_{23}N_3O$	7.71	7.25[f]			190
								8.52	8.52[e]			133

$(CH_3)_2N$		113.5	0.025	1.5531	19.17	18.69	$C_{13}N_{21}N_3$			50.44	49.98[f]	161
										24.26	24.27[g]	168
$(C_2H_5)_2N$		135	.05	1.5419	16.98	16.62	$C_{15}H_{26}N_3$	7.91	8.53	47.77	46.63[f]	142
										47.96	47.58[f]	138



H	0	87	0.04	1.539	27.42	27.79	$C_3H_{17}N_3$	18.42	18.38	31.08	30.83[g]	245
$(CH_3)_2N$	2	105	.04	1.510	23.68	23 85	$C_{12}H_{26}N_4$	10.98	10.82	49.74	49.42[f]	224
$(C_2H_5)_2N$	2	132	.04	1.5099	22.03	20.80	$C_{14}H_{30}N_4$	10.40	10.42	47.16	46.43[f]	207
Pyrrolidino	2	139	.04	1.5229	23.31[c]	20.27	$C_{14}H_{28}N_4$	10.44	10.34	47.33	47.25[f]	210
Morpholino	2	145	.03	1.5247	20.86	20.48	$C_{14}H_{28}N_4O$	10.14	10.06	45.96	45.44[f]	208
4-$CH_3N_2C_4H_8$[d]	3	174	.08	1.5227	23.70	23.63	$C_{16}H_{33}N_5$					

[a] Corrected. [b] Unstable base. [c] Base decomposes on standing. [d] 4-Methylpiperazino. [e] Dimaleate. [f] Dimethiodide. [g] Dihydrochloride.

TABLE III

$Am_1C_2H_4NR-NHC_2H_4Am_2 \cdot 2CH_3I$

No.	Am_1	Am_2	R	Blood p. lowering, % I.v. dose 1.0 mg./kg.	I.d.[a] dose 10 mg./kg.	Duration, min. I.v.	I.d.
1	$(CH_3)_2N$	$(CH_3)_2N$	H	−28		25	
2	Piperidino	Piperidino	H	−31		120	
3	$(CH_3)_2N$	$(CH_3)_2N$	CH_3	−30		20	
4	Pyrrolidino	Pyrrolidino	H	−49	−28	120	300
5	$(CH_3)_2N$	Pyrrolidino	H	−26	−12	105	120
6	$(CH_3)_2N$	$(C_2H_5)_2N$	H	−32	− 6	120	90
7	$(CH_3)_2N$	Piperidino	H		−39		300
8	$(C_2H_5)_2N$	Pyrrolidino	H		−31		150
9	Hexamethonium			−34	−15	13	60
10	Pentolinium			−20		75	

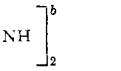
[a] Intraduodenal.

128°. *Anal.* Calcd. for $C_{20}H_{34}N_4O_{12}$: C, 45.97; H, 6.56; N, 10.72. Found: C, 46.66; H, 6.50; N, 10.53.

N,N'-Bis-(2-dimethylaminoethyl)-hydrazine Dimethiodide (V).—A solution of 28.4 g. (0.2 mole) of methyl iodide in 300 cc. of acetone was added to a solution of 17.4 g. (0.1 mole) of N,N'-bis-(2-dimethylaminoethyl)-hydrazine in 400 cc. of acetone. The solution was refrigerated, the solid removed by filtration and recrystallized from ethanol; yield 41.2 g. (90%), m.p. 143–144°.

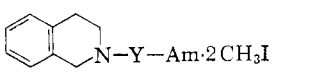
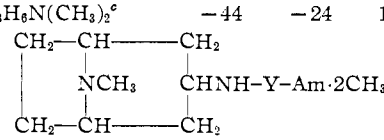
N-Methyl-N,N'-bis-(2-dimethylaminoethyl)-hydrazine (VI).—To a solution of 43.5 g. (0.25 mole) of N,N'-bis-(2-dimethylamino-ethyl)-hydrazine in 300 cc. of toluene was added 10.5 g. (0.27 mole) of sodamide. The mixture was refluxed for 4 hours, after which time the evolution of ammonia had ceased. Within a period of 1.25 hours there was added 37.8 g. (0.3 mole) of dimethyl sulfate and the mixture was stirred and refluxed for another 8 hours. After cooling there was added 100 cc. of water and the toluene layer

TABLE IV

No.	Structure	Blood p. lowering, %	I.v. dose, mg./kg.	Duration, min.
11	$[(CH_3)_2NCH_2CH{=}N{-}]_2$[a]	−33	2.0	5
12	$[(C_2H_5)_2NCH_2CH{=}N{-}]_2$[a]	−28	1.0	130
21	$[(CH_3)_2NCH_2CONH{-}]_2$[a]	0	5.0	
13	$[(CH_3)_2NC_2H_4NH{-}]_2$[b]	0	16.0	
14		−10	19.0	

[a] Dimethiodide. [b] Trimaleate.

TABLE V

No.	Y-Am	Blood p. lowering, % I.v. dose 1.0 mg./kg.	I.d. dose[a] 10.0 mg./kg.	Duration, min. I.v.	I.d.
					
15	$NHC_2H_4N(CH_3)_2$	−38		10	
16	$NHC_2H_4N(C_2H_5)_2$	− 7	0	10	
17	$NHC_2H_4NC_4H_8$	−30			
19	$C_2H_4NHN(CH_3)_2$	−37		30	
20	$C_2H_4NHNC_5H_{10}$	−23	−32	90	210
22	$C_2H_4NH{-}NC_4H_8$	−26	−36	50	210
23	$NHC_2H_4N(CH_3)_2$[b]	−32		30	
24	$NHC_2H_4NC_4H_8$[b]	−17		60	
25	$C_3H_6N(CH_3)_2$[c]	−44	−24	110	90
					
26	$NHC_2H_4N(CH_3)_2$	− 9	−31	105	150
27	$NHC_2H_4NC_4H_8O$		−26		150
28	$NHC_2H_4N(C_2H_5)_2$		0		
29	$NHC_2H_4NC_4H_8$	− 6	−10	Brief	75
30	$C_9H_4NHN(CH_3)_2$	0	0		
31	$C_2H_4N(C_2H_5)_2$[d]	−15[e]		120	

[a] Intraduodenal. [b] N-1,2,3,4-Tetrahydroquinolino. [c] I. N. 243; A. P. Gray, W. L. Archer, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, 77, 3536 (1955). [d] S. Archer, T. R. Lewis and M. J. Unser, *ibid.*, 79, 4194 (1957). [e] I.v. dose, 0.18 mg./kg.

separated. The toluene was removed by distillation and the residue was fractionated; yield 9.1 g. (19%), b.p. 60° (0.5 mm.), $n^{20}D$ 1.4707. *Anal.* Calcd. for $C_9H_{24}N_4$: N, 29.80. Found: N, 29.86.

N-Methyl-N,N'-bis-(2-dimethylaminoethyl)-hydrazine Dimethiodide (VII).—A solution of 3.76 g. (0.02 mole) of N-methyl-N,N'-bis-(2-dimethylaminoethyl)-hydrazine in 25 cc. of acetone was added to a solution of 8.5 g. (0.06 mole) of methyl iodide in 150 cc. of acetone. The precipitate weighed 8.1 g. (85%), m.p. 168–170°, and gave a negative reaction with bicarbonate solution. *Anal.* Calcd. for $C_{11}H_{30}I_2N_4$: I, 53.75. Found: I, 53.60.

2-(N-Formyl)-amino-1,2,3,4-tetrahydroisoquinoline (VIII).—A mixture of 21.0 g. (0.14 mole) of N-amino-1,2,3,4-tetrahydro-isoquinoline[15] and 210 g. of ethyl formate was refluxed for 4 hours on a steam-bath. The excess ethyl formate was removed by distillation leaving 27.2 g. of solid residue which was recrystallized from 55 cc. of ethanol; yield 13.8 g. (55.6%), m.p. 129°. *Anal.* Calcd. for $C_{10}H_{12}N_2O$: N, 15.90. Found: N, 15.74.

2-(N-Methyl)-amino-1,2,3,4-tetrahydroisoquinoline (IX).—A solution of 72.0 g. (0.41 mole) of N-formylamino-1,2,3,4-tetrahydroisoquinoline in 800 cc. of tetrahydrofuran was added dropwise to a stirred solution of 18.0 g. (0.47 mole) of lithium aluminum hydride in 800 cc. of THF. The reaction mixture was refluxed for 4 hours, after which there was added dropwise aqueous potassium hydroxide solution. The solution was decanted, dried over potassium carbonate, and distilled; yield 55.3 g. (83%), b.p. 74° (0.3 mm.), $n^{20}D$ 1.5577. *Anal.* Calcd. for $C_{10}H_{14}N_2$: N, 17.28. Found: N, 17.20.

The dihydrochloride was prepared in ethanol by the addition of ethereal hydrochloric acid; m.p. 185.5–186.5°. *Anal.* Calcd. for $C_{10}H_{16}ClN_2$: Cl, 17.85; N, 13.80. Found: Cl, 17.90; N, 14.10.

2-(N,N-Dimethyl)-amino-1,2,3,4-tetrahydroisoquinoline (X).—A mixture of 16.2 g. (0.1 mole) of N-methylamino-1,2,3,4-tetrahydroisoquinoline and 111 g. (1.5 mole) of ethyl formate was refluxed for 7 hours. The excess ethyl formate was removed by distillation leaving 19.2 g. of crude formylated amine, m.p. 85°. This was dissolved in 200 cc. of THF and added dropwise to a solution of 5.7 g. (0.15 mole) of lithium aluminum hydride in 300 cc. of THF. After a reflux period of 4 hours, the reaction mixture was cooled and potassium hydroxide solution added dropwise. The solution was decanted, dried over potassium carbonate, filtered and the solvent removed by distillation. On fractionation there was collected 13.65 g. (77%), b.p. 85° (0.5 mm.), $n^{20}D$ 1.5451. *Anal.* Calcd. for $C_{11}H_{16}N_2$: N, 15.90. Found: N, 16.02.

The hydrochloride was prepared in isopropyl alcohol with ethereal hydrochloric acid; m.p. 183–184°. *Anal.* Calcd. for $C_{11}H_{17}ClN_2$: N, 13.18. Found: N, 13.38.

1,2,3,4-Tetrahydroisoquinolinoacetal (XI).—A solution of 100 g. (0.75 mole) of 1,2,3,4-tetrahydroisoquinoline and 49.3 g. (0.25 mole) of bromoacetal in 500 cc. of ethanol was heated in an autoclave to 100° for 14 hours. The resulting solution was acidified with ethereal hydrochloric acid and taken to dryness; the residue was dissolved in 750 cc. of water and the solution clarified by filtration. After extraction with ether the aqueous solution was made alkaline with potassium hydroxide and the resulting oil extracted with ether. The ethereal extracts were dried over potassium carbonate, and the product collected by distillation; yield 53.3 g. (87%), b.p. 121° (0.05 mm.), $n^{20}D$ 1.5093. *Anal.* Calcd. for $C_{15}H_{19}NO_2$: N, 5.63. Found: N, 5.46.

N-[2-(1,2,3,4-Tetrahydroisoquinolino)-ethyl]-aminomorpholine (XII).—To an aqueous solution of crude N-1,2,3,4-tetrahydroisoquinolino-acetaldehyde hydrochloride (0.16 mole) was added dropwise at room temperature a solution of 16.1 g. (0.157 mole) of N-aminomorpholine in 100 cc. of water. After standing for 12 hours at room temperature the solution was saturated with potassium hydroxide and the resulting oil extracted repeatedly with ether. The combined ethereal extracts were dried over potassium carbonate and the ether was removed by distillation leaving 40.6 g. of crude hydrazone; 40.0 g. of this hydrazone was dissolved in 250 cc. of ether and this solution was added dropwise to a suspension of 5.3 g. (0.139 mole) of lithium aluminum hydride in 500 cc. of ether. After the addition was complete the solution was refluxed for another 5 hours after which there was added 60 cc. of 40% aqueous potassium hydroxide. The ethereal solution was decanted, dried over potassium carbonate and the product collected by distillation; yield 31.5 g. (79%), b.p. 163° (0.04 mm.), $n^{20}D$ 1.5492. The methiodide salt was prepared in acetonitrile; m.p. 191°.

N-(2-Diethylaminoethylidenyl)-amino-1,2,3,4-tetrahydroisoquinoline (XIII).—To an aqueous solution containing 0.17 mole of 2-diethylaminoacetaldehyde hydrochloride (prepared as described for compound I) was added dropwise at room temperature 25.3 g. (0.17 mole) of N-amino-1,2,3,4-tetrahydroisoquinoline. After standing for 12 hours, the solution was saturated with potassium hydroxide and the resulting red oil extracted by means of ether. The combined ethereal extracts were dried over potassium carbonate, filtered and the ether was removed by distillation. On fractionating the residue, there was obtained 35.9 g. (86%), b.p. 135° (0.06 mm.), $n^{20}D$ 1.5462. *Anal.* Calcd. for $C_{15}H_{23}N_3$: N, 17.11. Found: N, 17.25.

N-[(2-Diethylaminoethyl)-amino]-1,2,3,4-tetrahydroisoquinoline (XIV).—A solution of 35.0 g. (0.135 mole) of N-(2-diethylamino-ethylidenyl)-amino-1,2,3,4-tetrahydroisoquinoline in 200 cc. of ether was added dropwise to a stirred suspension of 4.0 g. (0.12 mole) of lithium aluminum hydride in 200 cc. of ether. After the addition was completed the solution was refluxed for 5 hours and the hydride complex decomposed by the addition of 20 cc. of 40% aqueous potas-

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sium hydroxide. The ethereal solution was decanted, dried over potassium carbonate, and the product collected by distillation; yield 28.5 g. (86%), b.p. 130° (0.06 mm.), $n^{20}D$ 1.5263.

The N-[(2-dialkylaminoethyl)-amino]-1,2,3,4-tetrahydroquinolines were prepared by essentially the same method as described for the corresponding isoquinolino derivatives.

Isoindolinoacetal (XV).—A solution of 32.5 g. (0.124 mole) of N-phthalimidoacetal[16] in 1 liter of dry ether was added dropwise with stirring to a slurry of 14.0 g. (0.37 mole) of lithium aluminum hydride in 500 cc. of ether. After the addition was completed, the solution was refluxed for 4 hours after which there was added 70 cc. of 40% aqueous potassium hydroxide. The ethereal solution was decanted, dried over potassium carbonate, filtered and the product collected by distillation; yield 18.4 g. (64%), b.p. 105° (0.04 mm.), $n^{20}D$ 1.5128. *Anal.* Calcd. for $C_{14}H_{21}NO_2$: N, 5.95. Found: N, 6.18.

N,N-Dimethyl-N'-2-(N-isoindolino)-ethylhydrazine (XVI).—N,N-Dimethylhydrazine (0.080 mole) was treated with N-isoindolinacetaldehyde (obtained from 0.074 mole of the acetal) in the usual manner; yield of hydrazone 9.75 g., b.p. 115° (0.05 mm.). A solution of 9.15 g. (0.045 mole) of this hydrazone in 50 cc. of ether was added dropwise to a slurry of 1.54 g. (0.04 mole) of lithium aluminum hydride in 100 cc. of ether. The solution was refluxed for another 4 hours after which there was added 10 cc. of 40% aqueous potassium hydroxide. The ethereal solution was decanted, dried over potassium carbonate, filtered and the product collected by distillation; yield 7.25 g. (56%), b.p. 114° (0.05 mm.), $n^{20}D$ 1.5366. *Anal.* Calcd. for $C_{12}H_{19}N_3$: N, 20.46. Found: N, 19.73.

N-Amino-4,7,8,9-tetrahydroisoindoline (XVII).—To a mixture of 49.3 g. (0.4 mole) of tetrahydroisoindoline[17] and 50 cc. of water was added 102 g. of 30% sulfuric acid. The solution was cooled to 5° at which temperature there was added dropwise a solution of 68 g. of sodium nitrite in 120 cc. of water. After stirring for another hour at room temperature, the supernatant oil was separated, dried and fractionated; yield 47.6 g., b.p. 115° (0.7 mm.), $n^{20}D$ 1.5352. A solution of 41.9 g. (0.275 mole) of this nitroso compound in 350 cc. of ether was added dropwise to a slurry of 15.6 g. (0.41 mole) of lithium aluminum hydride in 400 cc. of ether. After the solution was refluxed for another 5 hours there was added 200 cc. of 40% aqueous potassium hydroxide. The ethereal layer was decanted, dried over potassium carbonate and the product collected by distillation; yield 30.0 g. (63%), b.p. 65° (1.0 mm.), $n^{20}D$ 1.5173. *Anal.* Calcd. for $C_8H_{14}N_2$: N, 20.28. Found: N, 20.16.

N-[(2-Dimethylaminoethylidenyl)-amino]-4,7,8,9-tetrahydroisoindoline (XVIII).—To a solution of 0.2 mole of 2-dimethylaminoacetaldehyde hydrochloride, obtained by acid hydrolysis of dimethylaminoacetal, there was added 28.6 g. (0.21 mole) of N-amino-4,7,8,9-tetrahydroisoindoline. After standing at room temperature for 12 hours the solution was saturated with potassium hydroxide and extracted with ether. The ethereal solution was dried over potassium carbonate and the product collected by distillation; yield 35.7 g. (83%), b.p. 112° (0.7 mm.), $n^{20}D$ 1.5228. *Anal.* Calcd. for $C_{12}H_{21}N_3$: N, 20.28. Found: N, 20.25.

N-[(2-Dimethylaminoethyl)]-amino-4,7,8,9-tetrahydroisoindoline (XIX).—A solution of 33.2 g. (0.16 mole) of the above hydrazone in 200 cc. of ether was added dropwise to a slurry of 5.5 g. (0.144 mole) of lithium aluminum hydride in 300 cc. of dry ether. After a 5-hour reflux period there was added 50 cc. of 40% aqueous potassium hydroxide and the ethereal solution decanted, clarified by filtration and distilled; yield 26.8 g. (80%), b.p. 100° (0.7 mm.), $n^{20}D$ 1.5031. *Anal.* Calcd. for $C_{12}H_{23}N_3$: N, 20.07. Found: N, 19.58.

Dimethobromide.—A solution of 4.2 g. (0.02 mole) of the base in 25 cc. of acetonitrile was mixed with a solution of 4.8 g. (0.05 mole) of methyl bromide in 50 cc. of acetonitrile. After standing at room temperature there was collected 5.0 g. (63%) of solid, m.p. 201–203°. *Anal.* Calcd. for $C_{14}H_{29}N_3Br_2$: Br, 40.04. Found: Br, 40.36.

Tropinone-3-hydrazone (XX).—A solution of 77.0 g. (0.35 mole) of 3-tropinone hydrobromide in 350 cc. of methanol was added dropwise during 1.5 hours to a refluxing solution of 103 g. (1.7 moles) of 85% hydrazine hydrate in 400 cc. of methanol. After a 2-hour reflux period the methanol was removed by distillation and the residue taken up in 300 cc. of water. After saturating the solution with potassium hydroxide, the oil was extracted with chloroform, dried over potassium carbonate and fractionated. There were collected 33.0 g. (62%), b.p. 96° (0.03 mm.), $n^{20}D$ 1.543. *Anal.* Calcd. for $C_8H_{15}N_3$: N, 27.42. Found: N, 27.09.

3-Tropylhydrazine (XXI).—A solution of 35.2 g. (0.23 mole) of tropinone-3-hydrazone in 150 cc. of THF was added dropwise to a solution of 8.0 g. (0.21 mole) of lithium aluminum hydride in 250 cc. of THF. After a 4.5-hour reflux period the hydride complex was decomposed by addition of aqueous potassium hydroxide. The solution was decanted, dried over potassium carbonate and fractionated; yield 29.3 g. (82%), b.p. 87° (0.04 mm.), $n^{20}D$ 1.539. *Anal.* Calcd. for $C_8H_{17}N_3$: N, 27.42. Found: N, 27.79.

N-(2-Dimethylaminoethyl)-N'-3-tropylhydrazine (XXII). Method I.—A solution of 23.0 g. (0.15 mole) of 3-tropylhydrazine in 125 cc. of water was added dropwise at room temperature to an aqueous solution of 2-dimethylaminoacetaldehyde prepared by acid hydrolysis of 0.15 mole of dimethylaminoacetal. After standing at room temperature for 12 hours the solution was saturated with potassium hydroxide. The product was extracted with chloroform and dried over potassium carbonate. The chloroform was removed by distillation leaving 30.8 g. of crude hydrazone. A solution of 29.2 g. of this hydrazone in 100 cc. of THF was added dropwise to a solution of 4.8 g. (0.126 mole) of lithium aluminum hydride in 200 cc. of THF. After a 4.5-hour reflux period the hydride complex was decomposed by the addition of aqueous potassium hydroxide. The solution was decanted, dried over potassium carbonate, filtered and fractionated; yield 14.4 g. (40%), b.p. 105° (0.04 mm.), $n^{20}D$ 1.510.

The dimethiodide was prepared in ethanol solution giving a 93% yield of the salt with a m.p. of 224.°

Method II.—A solution of 22.7 g. (0.22 mole) of 2-dimethylamino-ethylhydrazine in 60 cc. of water was added dropwise at room temperature to a solution of 31.0 g. (0.22 mole) of 3-tropinone in 200 cc. of water. After standing for 12 hours at room temperature the solution was saturated with potassium hydroxide and extracted with ether. The ethereal extracts were dried over potassium carbonate, filtered and concentrated to 300 cc. The hydrazone in the ether solution was subjected to reduction by adding it dropwise to a slurry of 8.1 g. (0.21 mole) of lithium aluminum hydride in 300 cc. of ether. The product was worked up in the usual manner; yield 20.0 g. (41%), b.p. 105° (0.03 mm.), $n^{20}D$ 1.5098. The dimethiodide gave no melting point depression when mixed with the dimethiodide of the base prepared according to method I.

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