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Chemistry and Pharmacology of Monoamine Oxidase Inhibitors: Hydrazine Derivatives

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The preparations and some pharmacological properties of 70 aralkyl hydrazines and acylated hydrazines are described. From the data obtained attempts were made to correlate activity with structure. Several highly efficient monoamine oxidase inhibitors were uncovered and presently are undergoing additional laboratory and clinical tests.

During the early clinical testing of iproniazid as an antituberculous agent in 1951, the development of euphoria in patients was noted among the side effects of the drug.[2] In 1952, Zeller and co-workers found that iproniazid is an inhibitor of monoamine oxidase (MAO) *in vivo*[3] and *in vitro*[4] and suggested the potential antidepressant utility of such a compound which could result from potentiation of amines whose metabolism is normally catalyzed by this enzyme (MAO) in the central nervous system.[3] This possibility was dramatized by Brodie and his associates[5] and in our laboratory[6] with the demonstra-

(1) To whom all inquiries regarding this paper should be addressed.
(2) This experience is recalled by D. M. Bosworth, *Ann. N. Y. Acad. Sci.*, **80**, 809 (1959).
(3) E. A. Zeller and J. Barsky, *Proc. Soc. Exp. Biol. Med.*, **81**, 459 (1952).
(4) E. A. Zeller, J. Barsky, J. R. Fouts, W. F. Kirchheimer, and L. S. Van Orden, *Experientia*, **8**, 349 (1952).
(5) B. B. Brodie, A. Pletscher, and P. A. Shore, *J. Pharmacol. Exptl. Therap.*, **116**, 9 (1956).
(6) M. Chessin, B. Dubnick, E. R. Kramer, and C. C. Scott, *Federation Proc.*, **15**, 409 (1956).

tion that rabbits and mice pretreated with iproniazid and then injected with reserpine showed extreme "amphetamine-like" stimulation.[7] Clinical interest in MAO inhibitors *per se* as therapeutic agents had been awakened. The early experience of Zeller and others pointing toward alkyl and aralkyl substituted hydrazines as potent MAO inhibitors was presented in a recent symposium.[8] The National Heart Institute group, making use of iproniazid and some of the many compounds synthesized by Biel and his associates,[9,10] demonstrated that inhibition of MAO in the brain does indeed result in increased levels of endogenous amines such as serotonin, norepinephrine, tryptamine and possibly others.[11–14]

The compounds tabulated in this paper are a selection from over one hundred substituted hydrazines synthesized as part of a program covering a number of years of experience in our laboratory. This program was initiated by the discovery in our laboratories that phenethylhydrazine was an extremely efficient MAO inhibitor, which eventually resulted in a therapeutically successful antidepressant drug.[15,16]

Pharmacology: The "Reserpine-challenge Test."—This procedure has been useful for screening large numbers of potential MAO inhibitors in mice.[10,17] However, certain limitations should be noted. This test detects MAO inhibition only when it occurs in the brain. For example, although 1-acetyl-2-[1-(*p*-hydroxyphenyl)propyl]hydrazine and 1-acetyl-2-(*p*-hydroxybenzyl)hydrazine were negative at 150 and 100 mg./kg., respectively, both compounds inhibited mouse liver MAO about 50%, but brain MAO not at all, one hour after 50 and 30 mg./kg. i.p., respectively.

Selected successful MAO inhibitors have been compared in our lab-

(7) M. Chessin, E. R. Kramer, and C. C. Scott, *J. Pharmacol. Exptl. Therap.*, **119**, 453 (1957).

(8) "Amine Oxidase Inhibitors," *Ann. N. Y. Acad. Sci.*, **80**, 551–1045 (1959).

(9) J. H. Biel, A. E. Drukker, P. A. Shore, S. Spector, and B. B. Brodie, *J. Am. Chem. Soc.*, **80**, 1519 (1958).

(10) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway and A. Horita, *ibid.*, **81**, 2805 (1959).

(11) S. Udenfriend, H. Weissbach, and D. F. Bogdanski, *J. Pharmacol. Exptl. Therap.*, **120**, 255 (1957).

(12) S. Spector, D. Prockop, P. A. Shore, and B. B. Brodie, *Science*, **127**, 704 (1957).

(13) S. M. Hess, B. G. Redfield, and S. Udenfriend, *J. Pharmacol. Exptl. Therap.*, **127**, 178 (1959).

(14) A. Sjoerdsma, W. Lovenberg, J. A. Oates, J. R. Crout, and S. Udenfriend, *Science*, **130**, 225 (1959).

(15) L. E. Arnow, *Clin. Med.*, **6**, 1573 (1959).

(16) NARDIL,® Phenelzine (phenethylhydrazine dihydrogen sulfate).

(17) M. Chessin, B. Dubnick, G. Leeson, and C. C. Scott, *Ann. N.Y. Acad. Sci.*, **80**, 597 (1959).

oratory according to their ability to elevate brain serotonin; they exhibited a dose-response relationship.[17] Although for the most part the same order of potency prevailed in this test as in the reserpine challenge, occasionally differences were noted. For example, whereas it required 3.4 mg./kg. of α-methylphenethylhydrazine and 1.5 mg./kg. of α-methylbenzylhydrazine, to elevate whole mouse-brain serotonin by 50%, the two compounds were of equal potency[18] by reserpine-challenge.[19] That this apparent discrepancy may be the result of the "analpetic" component of α-methylphenethylhydrazine which α-methylbenzylhydrazine lacks, was shown in the following experiment: Normal mice were pretreated with amphetamine sulfate at a dose not sufficient to cause any visible excitation in these animals or to re-alert reserpine-depressed mice, 0.25–0.50 mg./kg., i.v. After fifteen minutes the amphetamine-pretreated mice were challenged with reserpine (5 mg./kg., i.v.). The animals became intensely hyperactive, *i.e.*, a positive reserpine-challenge test. However, the hyperactivity was of short duration, about 20 minutes, after which the animals became depressed. The endogenous amines released by reserpine when superimposed upon a subeffective level of amphetamine may have been sufficient to cause the observed response.

Experimental

The preparation of the seventy substituted hydrazines reported in this paper (see Tables I and II) required several synthetic approaches, as exemplified below:

Method A.—Eight compounds were prepared by direct reaction of an aralkyl halide with a large excess of hydrazine hydrate, with yields ranging from 25–78%. This is essentially the method outlined by Clark.[20]

***p*-Chlorophenethylhydrazine Hydrogen Sulfate.**—A solution of 25.9 g. (0.148 mole) of *p*-chlorophenethyl chloride in 50 ml. of isopropyl alcohol was added dropwise, over 0.5 hr., to a refluxing solution of 50 g. (1.0 mole) of hydrazine hydrate in 100 ml. of isopropyl alcohol. The mixture was refluxed for 10 hr., and the solvent and excess hydrazine were removed under vacuum. Potassium hydroxide solution (40%, 50 ml.) was added to the residue, the organic layer extracted with two 500 ml. portions of ether and the ether layer dried over anhydrous potassium carbonate. After filtering and removing the ether, the residue was distilled to yield 16.5 g. (65.8%) of *p*-chlorophenethylhydrazine as a colorless oil, b.p. 110–112° (1.0 mm.), $n^{25}D$ 1.5610. The sulfate salt, m.p. 152–155°, was prepared from aqueous sulfuric acid and recrystallized from isopropyl alcohol.

(18) B. Dubnick and M. Chessin, unpublished observations.

(19) The ED_{50}'s, significantly different (P = 0.95 by the statistical method previously employed), were calculated graphically from a dose-response curve.[17] The dose-related response was illustrated in that report with phenethylhydrazine as a reference compound.

(20) C. C. Clark, "Hydrazine," Mathieson Chem. Corp., New York, N. Y., 1953, p. 30.

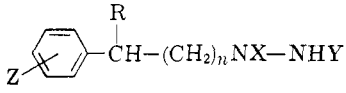
TABLE I

(A) Benzyl Derivatives, R = H, n = 0

Z	X	Y	M.p. (b.p.), °C.	Method of prepn.
H	H	H	111–113[a]	D[b,a]
H	H	$COCH_3$	80–81[b]	D
H	H	$COOC_2H_5$	(139 (0.5 mm.))	C[j]
H	H	$COOCH_3$	52–54[a]	C
p-CH_3	H	H	130–132[a]	D
p-Cl	H	H	194–196[a]	A
p-HO	H	$COCH_3$	111–113[c]	D
o-HO	H	$COOC_2H_5$	90–95[b]	C
p-NO_2	H	$COOC_2H_5$	87–88[a]	C
m-NH_2	H	$COCH_3$	108–109.5[c]	D
m-NH_2	H	$COOC_2H_5$	101–103[b]	C
p-$(CH_3)_2N$	H	$COCH_3$	75–76.5[b]	D
p-CH_3CONH	H	$COCH_3$	202–204[a]	D
p-C_4H_9O	H	H	176–177[a]	C
p-C_4H_9O	H	$COCH_3$	94.5–96[c]	D
p-C_4H_9O	$COCH_3$	$COCH_3$	89–91[b]	E
p-C_4H_9O	H	$COOC_2H_5$	58–60[a]	C
p-C_4H_9O	H	H	176–177[a]	C
p-$C_6H_{11}O$	H	$COCH_3$	88–90[b]	D
p-F_3C	H	H	138–139[d]	A
p-C_6H_5	H	H	256 dec.[a]	A

(B) α-Methylbenzyl Derivatives, R = CH_3, n = 0

H	H	H	167.5–170[d]	B, C, D[b,d]
H	H	$COOC_2H_5$	58.5–60[b]	C
H	H	$COOCH_3$	(130 (0.4 mm.))	C
H	$COOCH_3$	$COOC_2H_5$	(160–162 (0.7 mm.))	F
H	H	$COOC(CH_3)_3$	73–74[h]	C
p-F	H	H	160–161[d]	C
p-F	H	$COOC_2H_5$	92–93[b]	C
p-F	H	$COOCH_3$	71–72[b]	C
p-Cl	H	H	146–148[b]	D
p-Cl	H	$COCH_3$	119–121[b]	D
p-Cl	H	$COOC_2H_5$	86–88[a]	C
p-CH_3O	H	H	155–156[a]	B
p-CH_3O	H	$COCH_3$	95–96.5[b]	D
p-CH_3O	H	$COOC_2H_5$	71–72[a]	C
p-CH_3O	$COCH_3$	$COCH_3$	100–102[b]	E
p-C_2H_5O	H	H	175–176[a]	B
p-C_2H_5O	H	$COCH_3$	77–78[b]	D
p-C_2H_5O	$COCH_3$	$COCH_3$	94–96[b]	E
p-C_6H_5	H	H	154–156[a]	A
p-C_6H_5CH	H	$COOCH_3$	157–158[b]	C
p-C_6H_5O	H	H	111–112[a]	C
p-C_6H_5O	H	$COOCH_3$	155–156[b]	C
p-$C_6H_5SO_2$	H	$COOCH_3$	139–140[c]	C



Empirical formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Acute toxicity[p]	Reserpine-challenge test[q]
$C_7H_{10}N_2 \cdot HCl$	52.99	52.88	6.99	7.28	22.35	22.15	90	5
$C_9H_{12}N_2O$	65.83	65.93	7.37	7.69	17.06	17.26	550	15
$C_{10}H_{14}N_2O_2$	61.83	61.49	7.27	7.23	14.42	14.74	300	10–25
$C_9H_{12}N_2O_2$	59.98	60.15	6.71	6.71	15.55	15.44	375	10
$C_8H_{12}N_2 \cdot HCl$	55.64	56.19	7.59	7.50	20.53	20.72[m]	150	5–10
$C_7H_9ClN_2 \cdot HCl$	43.54	43.60	5.22	5.44	18.36	18.17[m]	200	25
$C_9H_{12}N_2O_2$	59.98	59.88	6.71	7.00	15.55	15.67	>1200	100
$C_{10}H_{14}N_2O_3$	57.13	57.28	6.71	6.64	13.33	13.20	>1000	100
$C_{10}H_{13}N_3O_4$	50.20	49.79	5.48	5.56	17.57	17.28	...	10–25
$C_9H_{13}N_3O$	60.31	59.59	7.31	7.31	23.45	23.83	>2000	>100–200
$C_{10}H_{15}N_3O_2$	57.40	58.08	7.23	7.02	20.08	19.81	>1000	>100
$C_{11}H_{17}N_3O$	63.74	63.75	8.27	8.56	20.27	19.88	>1000	>100
$C_{11}H_{15}N_3O_2$	59.71	59.69	6.83	6.90	18.99	19.26	1000	50
$C_{11}H_{18}N_2O \cdot C_2H_2O_4$	54.92	54.93	7.09	7.20	9.85	9.59	475	7
$C_{13}H_{20}N_2O_2$	66.07	66.03	8.53	8.56	11.86	12.23	1000	>100
$C_{15}H_{22}N_2O_3$	64.72	64.62	7.97	8.00	10.07	10.26	>1500	>200
$C_{14}H_{22}N_2O_3$	63.13	63.83	8.33	8.33	10.52	10.52	680	25
$C_{11}H_{18}N_2O \cdot C_2H_2O_4$	54.92	54.93	7.09	7.20	9.85	9.59	475	7
$C_{15}H_{22}N_2O_2$	68.67	68.67	8.45	8.55	10.68	10.77	250	25
$C_8H_9F_3N_2 \cdot HCl$	42.39	42.35	4.45	4.49	12.36	12.70	375	10
$C_{13}H_{14}N_2 \cdot HCl$	66.51	66.24	6.44	6.41	11.94	11.88	600	2.5–5
$C_8H_{14}N_2 \cdot {}^1/_2H_2SO_4$	...	...	...	...	15.12	14.94	265–360	5
$C_{11}H_{16}N_2O_2$	63.44	63.41	7.74	7.69	13.45	13.12	375	10
$C_{10}H_{14}N_2O_2$	61.83	62.01	7.27	7.32	14.42	14.24	375	10
$C_{13}H_{18}N_2O_4$	58.63	58.34	6.81	6.94	10.52	10.79	300	50
$C_{13}H_{20}N_2O_2$	66.07	66.30	8.53	8.76	11.86	11.62	400	10–25
$C_8H_{11}FN_2 \cdot C_2H_2O_4$	49.18	49.65	5.37	5.58	11.47	11.44	500	7.5
$C_{11}H_{15}FN_2O_2$	58.39	57.98	6.68	6.67	12.38	12.33	375	>100
$C_{10}H_{13}FN_2O_2$	56.59	57.34	6.17	6.43	13.20	13.11	400	25
$C_8H_{11}ClN_2 \cdot HCl$	46.39	46.31	5.84	6.05	17.17	16.84[m]	350	15
$C_{10}H_{13}ClN_2O$	56.47	56.41	6.16	6.40	13.17	13.24	300	>200
$C_{11}H_{15}ClN_2O_2$	54.34	54.79	6.23	6.13	11.54	11.87	300	>100
$C_9H_{14}N_2O \cdot C_2H_2O_4$	51.56	51.50	6.29	6.11	10.93	10.63	650	>15
$C_{11}H_{16}N_2O_2$	63.44	63.57	7.74	7.98	13.45	13.52	575	>50
$C_{12}H_{18}N_2O_3$	60.48	61.04	7.61	7.74	11.76	12.03	600	100
$C_{13}H_{18}N_2O_3$	62.38	62.74	7.25	7.38	11.19	11.62	>1500	>100
$C_{10}H_{16}N_2O \cdot C_2H_2O_4$	53.32	53.11	6.71	6.73	10.37	10.45	700	20
$C_{12}H_{18}N_2O_2$	64.84	64.82	8.16	8.08	12.60	12.66	375	20
$C_{14}H_{20}N_2O_3$	63.61	63.68	7.63	7.52	10.60	10.75	>2000	>200
$C_{14}H_{16}N_2 \cdot HCl$	67.59	67.43	6.89	7.19	11.26	11.17	340	5
$C_{17}H_{20}N_2O_2 \cdot HCl$	63.64	63.70	6.60	6.51	11.05	11.38[m]	240	25
$C_{14}H_{16}N_2O \cdot HCl$	63.51	63.50	6.47	6.43	13.40	13.57	400	2.5
$C_{16}H_{18}N_2O_3 \cdot HBr$	52.33	52.50	5.21	5.26	21.76	21.85[n]	240	10–25
$C_{16}H_{18}N_2O_4S$	57.47	57.32	5.42	5.39	8.38	8.22	1000	>25

TABLE I

Z	X	Y	M.p. (b.p.), °C.	Method of prepn.
		(C) α-Ethylbenzyl Derivatives, R = C_2H_5, n = 0		
H	H	H	130–131[d]	D[h,i]
H	H	$COCH_3$	63–64[b]	D[i]
H	H	$COOC_2H_5$	(138–139 (0.8 mm.))	C
p-Cl	H	H	195–197[c]	D
p-HO	H	$COCH_3$	153.5–154.5[b]	D
p-C_6H_5	H	H	175–177[n]	A
		(D) Phenethyl Derivatives, R = H, n = 1		
H	H	H	160–162[d]	A[h,i]
H	H	$COCH_3$	68–69[b]	D[i]
H	H	COC_6H_5	80–83[b]	D[i]
H	H	$COC_5H_4NH_2$-p	159–160[a]	D
H	H	COC_5H_4N[j]	178–180[d]	D
H	H	i-C_3H_7	120–121[c]	D[i]
H	H	$COOCH_3$	75–77[b]	C
H	H	$COOC_2H_5$	58–59[b]	C
H	H	$COO(CH_2)_2OH$	98–99[e]	C
H	H	$COO(CH_2)_2Cl$	163.5–164[b]	C
p-CH_3O	H	H	150–151[a]	A[k]
p-Cl	H	H	152–155[a]	A
p-C_6H_5	H	H	193–196[o]	A
		(E) γ-Phenylpropyl Derivatives, R = H, n = 2		
H	H	H	149–151[d]	D[i,l]
H	H	$COCH_3$	54–56[b]	D[i]
H	H	COC_5H_4N[g]	118–119[e]	D

Recrystallization solvent: [a] aqueous ethanol. [b] ethyl acetate–ligroin. [c] ethyl acetate. [i] Reported by Chessin *et al.*[17] [j] Reported in Swiss Patent 309,771 (1955). [k] Reported in analysis (ionizable). [n] Bromine analysis. [o] Sulfur analysis. [p] P.o. mice ALD_{50} mg./kg.

TABLE II

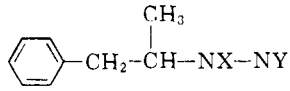
α-METHYLPHENETHYL HYDRAZINES

X	Y	M.p. (b.p.), °C.	Method of prepn.	Empirical formula
H	H	116–118[d]	B[k]	$C_9H_{14}N_2 \cdot HCl$
H	$COCH_3$	75–77[b]	C	$C_{11}H_{16}N_2O$
H	$COOC_2H_5$	(130–131 (0.7 mm.))	D	$C_{12}H_{18}N_2O_2$
$COOC_2H_5$	$COOC_2H_5$	93–95[a]	F	$C_{18}H_{22}N_2O_4$
H	$COOCH_3$	47–50[b]	D	$C_{11}H_{16}N_2O_2$

(*Continued*)

Empirical formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Acute toxicity[p]	Reserpine-challenge test[q]
$C_9H_{14}N_2 \cdot C_2H_2O_4$	54.99	54.85	6.71	6.95	11.66	11.79	230	5
$C_{11}H_{16}N_2O$	68.72	69.11	8.39	8.75	14.57	14.79	200	28
$C_{12}H_{18}N_2O_2$	64.84	64.65	8.16	8.32	12.60	12.91	575	15
$C_9H_{13}ClN_2 \cdot HCl$	48.88	48.66	6.38	6.51	16.03	15.90[m]	400	30
$C_{11}H_{16}N_2O_2$	63.44	63.46	7.74	7.80	13.45	13.63	>1000	>150
$C_{10}H_{16}N_2 \cdot HCl$	68.56	68.33	7.29	7.54	10.66	10.76	540	5
$C_8H_{12}N_2 \cdot HCl$	55.65	55.96	7.59	7.82	20.55	20.48[m]	125	10
$C_{10}H_{14}N_2O$	67.38	67.38	7.92	7.87	...	...	180	20
$C_{15}H_{16}N_2O$	74.97	74.73	6.71	6.67	11.65	11.81	390	50
$C_{15}H_{17}N_3O$	70.56	70.49	6.71	6.89	16.46	16.62	...	...
$C_{14}H_{18}N_2O \cdot 2HCl$	22.25[m]	22.15	...	...	13.37	13.36	150	30
$C_{11}H_{18}N_2 \cdot HCl$	16.51[m]	16.63	...	...	...	...	212	10
$C_{10}H_{14}N_2O_2$	61.83	61.96	7.26	7.27	14.42	12.58	125	10
$C_{11}H_{16}N_2O_2$	63.44	63.37	7.74	7.76	13.45	13.38	215	20
$C_{11}H_{16}N_2O_3$	58.91	58.99	7.19	7.19	12.49	12.35	460	20
$C_{11}H_{15}ClN_2O_2 \cdot HCl$	47.32	47.30	5.78	5.87	10.04	10.13	375	25
$C_9H_{14}N_2O \cdot H_2SO_4$	40.90	40.80	6.10	6.21	10.60	10.33	225	20
$C_8H_{11}ClN_2 \cdot H_2SO_4$	35.72	35.82	4.89	5.41	11.93	12.02[o]	175	20
$C_{14}H_{16}N_2 \cdot HCl$	67.59	67.86	6.89	7.02	11.26	11.31	200	10
$C_9H_{14}H_2 \cdot H_2SO_4$	43.53	43.22	6.50	6.83	11.28	10.94	166	26
$C_{11}H_{16}N_2O$	68.72	68.75	8.39	8.60	14.57	14.35	345	>50
$C_{15}H_{17}N_3O$	70.56	70.68	6.71	7.03	16.46	16.44	600	55

[d] isopropyl alcohol. [e] benzene. [f] Nicotinoyl. [g] Isonicotinoyl. [h] Reported by Biel *et al.*[10] British Patent 864,108 (1961). [l] Reported in U. S. Patent 3,000,903 (1961). [m] Chlorine [q] 3 hr. Med mg./kg. i.p.



Footnotes same as in Table I.

Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Acute toxicity[p]	Reserpine-challenge test[q]
57.90	57.75	8.10	8.34	15.01	14.89	85	5
68.72	68.77	8.39	8.59	14.57	14.86	75	30
64.84	64.45	8.16	8.15	12.60	12.38	180	10
61.20	61.40	7.53	7.51	9.52	9.57	1000	100
63.44	63.59	7.74	7.74	13.45	13.70	93	10

Method B.—Direct reaction of a carbonyl compound with excess hydrazine hydrate, isolation of the resulting hydrazone and catalytic reduction (using platinum oxide and palladium on charcoal) gave five compounds in 40–75% yield.

***p*-Methoxy-α-methylbenzylhydrazine Monooxalate.**—A solution of 75.1 g. (0.5 mole) of *p*-methoxyacetophenone in 200 ml. of 95% ethanol was added dropwise, with stirring, over 1 hr., to a refluxing solution of 100 g. (2.0 moles) of hydrazine hydrate in 100 ml. of 95% ethanol. The mixture was refluxed for 4 hr., cooled, filtered and dried to yield 64.3 g. (78%) of *p*-methoxy-α-methylbenzylidenehydrazine, as a yellow solid, m.p. 114–116°. The hydrazone was mixed with 0.5 g. of PtO_2, 2 g. of 5% Pd on charcoal and 300 ml. of absolute ethanol, and hydrogenated, with heating, in a Parr shaker until the calculated amount of hydrogen was absorbed (approx. 24 hr.). The mixture was filtered and the filtrate distilled to yield 38.2 g. of *p*-methoxy-α-methylbenzylhydrazine, as a colorless oil, b.p. 93–95° (0.09 mm.). The oxalate salt, m.p. 155–156°, was prepared in absolute ethanol and recrystallized from aqueous ethanol.

Method C.—Reaction of an alkyl carbazate (methyl, ethyl or *t*-butyl) with a carbonyl compound and catalytic reduction of the intermediate gave 21 substituted alkyl carbazates in 45–94% yield. Hydrolysis, with simultaneous decarboxylation, using ethanolic alkali (Claisen's method) yielded five monosubstituted hydrazines in 50–85% yield.

***p*-Butoxybenzylhydrazine Monooxalate.**—A mixture of 25 g. (0.14 mole) of *p*-butoxybenzaldehyde, 14.6 g. (0.14 mole) of ethyl carbazate and 150 ml. of isopropyl alcohol was refluxed for 4 hr. The solvent was removed under vacuum and the residue recrystallized twice from ethyl acetate–petroleum ether to yield 36.4 g. (98%) of ethyl 3-(*p*-butoxybenzylidene)carbazate as colorless crystals, m.p. 111–112°.

A mixture of 200 ml. of isopropyl alcohol, 36 g. (0.136 mole) of ethyl 3-(*p*-butoxybenzylidene)carbazate and 0.5 g. of PtO_2 was hydrogenated, with heating, in a Parr shaker until the theoretical amount of hydrogen was absorbed (7 hr. initial pressure, 3.5 kg./cm.^{2}). The mixture was filtered, the solvent removed under vacuum and the residue recrystallized from 50% aqueous methanol to yield 34.7 g. (96%) of ethyl 3-(*p*-butoxybenzyl)carbazate, as colorless crystals, m.p. 58–60°.

A mixture of 13.3 g. (0.05 mole) ethyl 3-(*p*-butoxybenzyl)carbazate, 5.7 g. (0.1 mole) of potassium hydroxide and 150 ml. of absolute ethanol was refluxed for 8 hr. The solvent was removed and the residue extracted with two 100-ml. portions of ether. The combined ether extract was filtered and a solution of 9 g. (0.1 mole) of anhydrous oxalic acid in ether added. The precipitate was recrystallized from aqueous methanol to yield 7.2 g. (51%) of *p*-butoxybenzylhydrazine monooxalate, as colorless crystals, m.p. 176–177°.

Method D.—Analogous to Method C using an acylhydrazine instead of an alkyl carbazate: nineteen compounds were prepared by the reduction of the intermediate hydrazones in 60–95% yield. Subsequent hydrolysis gave an additional seven substituted hydrazines in 30–65% yield.

***p*-Chloro-α-methylbenzylhydrazine Hydrochloride.**—A mixture of 22.2 g. (0.3 mole) of acetylhydrazine, 46.4 g. (0.3 moles) of *p*-chloroacetophenone and 250

ml. of ethanol was refluxed for 8 hr. and cooled to yield 63.2 g. (77%) of 1-acetyl-2-(*p*-chloro-α-methylbenzylidene)hydrazine, as colorless crystals, m.p. 161–161.5°. Recrystallization from isopropyl alcohol raised the m.p. to 169°.

A mixture of 39 g. (0.185 mole) of 1-acetyl-2-(*p*-chloro-α-methylbenzylidene)-hydrazine, 250 mg. of PtO_2 and 275 ml. of methanol was hydrogenated until the calculated amount of hydrogen was adsorbed (7 hr.; initial pressure, 3.5 kg./cm.^{2}). The mixture was filtered, freed of solvent and the residue recrystallized several times from ethyl acetate–ligroin to yield 37 g. (94%) of 1-acetyl-2-(*p*-chloro-α-methylbenzyl)hydrazine, as colorless crystals, m.p. 119–121°. A solution of 21.2 g. (0.1 mole) of this product in 75 ml. of 10% ethanolic potassium hydroxide was refluxed for 8 hr. The solvent was removed and the residue extracted with ether. The organic layer was distilled to yield 6.4 g. (38%) of *p*-chloro-α-methylbenzylhydrazine, b.p. 90–95° (0.8 mm.). The base (4.0 g.) was dissolved in 250 ml. of dry ether and the solution saturated with dry hydrogen chloride. The salt was recrystallized from chloroform–petroleum ether to yield 3.2 g. of colorless crystals, m.p. 146–148°.

Method E.—Reaction of monoacetylated aralkyl hydrazines with excess acetic anhydride to yield diacetylated compounds. Three compounds prepared by this method are reported in Table I in 40–55% yields.

1,2-Diacetyl-2-*p*-*n*-butoxybenzylhydrazine.—A mixture of 17 g. (0.072 mole) of 1-acetyl-2-*p*-*n*-butoxybenzylhydrazine, 50 ml. of acetic anhydride and 1 drop of concd. sulfuric acid was heated for 0.5 hr. on a steam bath. After standing overnight, the acetic anhydride was removed under vacuum, the residue washed with water and recrystallized several times from ethyl acetate–petroleum ether to yield 8.4 g. (41.5%) of colorless, fluffy needles, m.p. 89–91°.

Method F.—Analogous to Method E, using an alkyl chloroformate in place of acetic anhydride with yields of 75–80%.

1-Carbethoxy-2-carbomethoxy-1-(α-methylbenzyl)hydrazine.—A mixture of 19.4 g. (0.1 mole) of methyl 3-(α-methylbenzyl)carbazate, 11.9 g. (0.11 mole) of ethyl chloroformate, 12.6 g. (0.15 mole) of sodium bicarbonate and 200 ml. of absolute ethanol was refluxed for 1 hr. and filtered hot. Removal of the solvent and distillation of the residue yielded 21.3 g. (80%) of colorless, viscous oil, b.p. 160–162° (0.7 mm.); $n^{22}D$ 1.5091.

Method G.—Reaction of an aralkyl hydrazine with a cyclic carbonate (*i.e.*, ethylene carbonate) to yield an ω-hydroxyalkyl carbazate. Subsequent treatment with thionyl chloride yields the ω-chloroalkyl carbazate. This is essentially the method described by Delaby *et al.*[21]

β-Chloroethyl 3-Phenethylcarbazate Hydrochloride.—A mixture of 44 g. (0.5 mole) of ethylene carbonate and 68 g. (0.5 mole) of phenethylhydrazine was heated on a steam bath for 1 hr. The reaction mixture was extracted with 500 ml. of boiling benzene. Cooling the benzene layer yielded 85 g. (64%) of β-hydroxyethyl 3-phenethylcarbazate as colorless crystals, m.p. 90°. Recrystallization from benzene and drying for analysis raised the m.p. to 98–99°.

A mixture of 58 g. (0.26 mole) of β-hydroxyethyl 3-phenethylcarbazate, 40 g. (0.33 mole) of thionyl chloride and 1000 ml. of benzene was allowed to stand for

(21) R. Delaby, R. Damiens, and M. L. Capmau, *Compt. rend.*, **246**, 3353 (1958).

24 hr. The benzene and excess thionyl chloride were removed and the residue (33 g.) was recrystallized several times from ethyl acetate–petroleum ether to yield 21 g. (29%) of β-chloroethyl 3-phenethylcarbazate hydrochloride, m.p. 163.5–164°.

Structure-Activity Relationships.—The compounds reported in this paper were put through our general screening program, with results that were interesting and in some cases surprising. In general, comparing monosubstituted hydrazines with their acyl derivatives, the monosubstituted hydrazines were found to be the most active and the most toxic. The carbazates were slightly less active and less toxic. The acetyl derivatives were the least active and least toxic. However, acute toxicity and activity were not directly related from one homologous series to the next. For example, *p*-phenoxy-α-methylbenzylhydrazine is one of the most active and least toxic of the compounds.

The relative activity of the acetylated and carboalkoxylated aralkyl hydrazines apparently is dependent upon the relative rates of hydrolysis of these blocking groups, yielding the free aralkyl hydrazines. Observations in the course of preparing the free hydrazines from the acylated compounds suggest that the *in vivo* activity of the compound is proportional to the rate of chemical hydrolysis of the blocking group. In addition, studies with ethyl 3-(α-methylbenzyl)-carbazate show that although it is among the more potent inhibitors *in vivo* (reserpine challenge and elevation of brain serotonin), it is only a weak inhibitor of MAO *in vitro*.

Compounds containing bulky *para* substituents (such as butoxy, phenyl, phenoxy, etc.) appear to be the most potent and least toxic on the basis of this preliminary work.