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Central Stimulants. Chemistry and Structure-Activity Relationships of Aralkyl Hydrazines

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RECEIVED OCTOBER 31, 1958

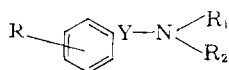
The replacement of an amino or alkylamino group by a hydrazino or alkyl hydrazino moiety in a variety of aralkylamines has yielded a group of potent central stimulants which produce their effect by a dual mechanism: (1) direct stimulation of the central nervous system (analeptic action), and (2) powerful inhibition of the enzyme monoamine oxidase (MAO) which is responsible for the metabolic destruction of endogenous central excitatory hormones. Definite structure-activity relationships have been established and will be discussed. One of the compounds, N-aminoamphetamine, displayed forty times the MAO inhibitory potency of iproniazid (Marsilid). The synthesis of the aralkyl hydrazines was accomplished *via* the reductive hydrazinolysis of phenyl-alkanones or reaction of hydrazine with a phenylalkyl halide. The nature of the products obtained was dependent on the reaction conditions. It is demonstrated also that the Raney nickel cleavage of substituted hydrazines constitutes a convenient means of obtaining pure primary and secondary amines.

The sympathomimetic amines have yielded valuable therapeutic agents in the fields of bronchodilators, central stimulants and cardiovascular agents. However, their clinical usefulness has been severely limited because of their great susceptibility toward enzymatic degradation in the body and the multiplicity of their pharmacologic effects.

In an effort to arrive at substances having more desirable therapeutic properties, we replaced the amino group with a hydrazino moiety in a large variety of sympathomimetic amines.

We turned to hydrazine analogs for a number of reasons: (1) We hoped that the hydrazines would have a greater affinity for the cell receptor sites and would not be subject to the same type of enzymatic degradation. In this way a more intense and prolonged action could be expected. (2) Certain hydrazine derivatives such as hydrazinophthalazine (Apresoline) had been shown to be useful blood pressure lowering agents¹⁻³ and the incorporation of a hydrazine group into a skeleton with an already high affinity for the blood pressure regulating centers appeared to be a logical approach to the development of agents for the "manual" control of blood pressure disturbances. (3) Lastly, we were interested in testing the isosteric effect of replacing a methyl or methylene by an NH₂ or NH grouping on biological activity.

The type of series chosen for synthesis resembled closely that of Barger and Dale for the sympathomimetic amines. In their classical work they showed that the nature of the physiological response elicited by the phenylalkyl amines was dependent on: (1) the nature of the nuclear substituent "R", (2) the nature and length of the side chain "Y" and (3) the type of substituent on the amino nitrogen (R₁ and R₂)⁴



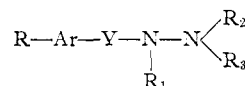
Our series of compounds may be represented by the general formula

(1) B. N. Craver, W. Barrett, A. Cameron and F. F. Yonkman, *J. Am. Pharm. Assoc., Sci. Ed.*, **XI**, 559 (1951).

(2) H. A. Schroeder, *Circulation*, **5**, 28 (1952).

(3) R. L. Johnson, E. D. Freis and H. W. Schnaper, *ibid.*, **5**, 833 (1952).

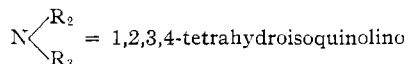
(4) G. Barger and H. H. Dale, *J. Physiol.*, **41**, 19 (1910).



R = H, alkyl, alkoxy, hydroxy, dimethoxy, methylenedioxy, trimethoxy, chloro

Y = straight or branched alkylene chain, hydroxyethyl

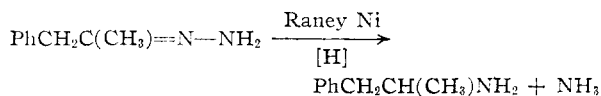
R₁ = H, methyl; R₂ = H or alkyl; R₃ = H, alkyl, aralkyl, acyl



Ar = phenyl, pyridyl, thienyl, furyl, benzodioxanyl

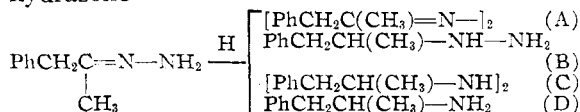
β -Phenethylhydrazine, β -phenyl- β -hydroxyethylhydrazine and N-(β -phenyl- β -hydroxyethyl)-N',N'-dimethylhydrazine had previously been prepared by Bovet and found to have pressor properties very similar to those of the parent amines.⁵ Several difficulties presented themselves in the synthesis of the mono-(aralkyl)-hydrazines. They were due primarily to the fact that the hydrazine molecule has three reactive centers. Reaction with carbonyl compounds results in the formation of both hydrazones and azines.

In the case of reactive aldehydes (R'' = H) it was very difficult to control the reaction at the monosubstituted hydrazone state.⁶ Treatment of hydrazine with phenylalkyl halides results in polyalkylation products unless a large excess of hydrazine is employed.⁷ The N-N bond is quite sensitive to reductive cleavage and the choice of



catalyst, solvent and proper reaction conditions is of paramount importance to the successful reduction of the hydrazones.

Our major synthetic difficulties may be summarized for the reduction of 1-phenyl-2-propyl hydrazone



(5) G. Benoit and D. Bovet, *Compt. rend. soc. biol.*, **136**, 356 (1942).

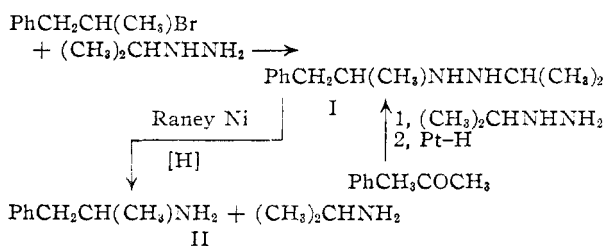
(6) C. C. Clark, "Hydrazine," first edition, Mathieson Chemical Corp., Baltimore, Md., 1953, p. 39.

(7) *Ibid.*, p. 36.

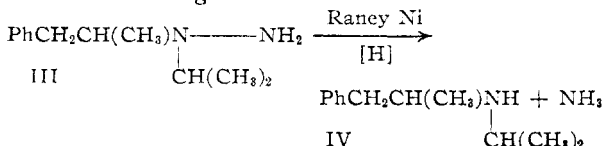
Formation of large amounts of (A) occurred when reduction proceeded slowly and incompletely with such catalyst as palladium-on-charcoal, rhodium, ruthenium, platinum oxide, and solvents such as alcohol, water, ethyl acetate, tetrahydrofuran and dioxane. Product C was obtained when the hydrogenation proceeded slowly to completion as with platinum oxide in aqueous acetic acid. Products A and D were formed almost exclusively during the Raney nickel reduction of the hydrazone in ethyl alcohol. The use of platinum oxide or platinum-on-a-carrier in alcoholic acetic acid at a pressure of 2,000 pounds represented the optimum conditions for obtaining the desired compound (B) in acceptable yields of 55-70%. The major by-product of this reaction was compound C accompanied by small amounts of (A). The chemical reduction of 1-phenyl-2-propyl hydrazone with sodium borohydride and aluminum chloride in the dimethyl ether of diethylene glycol⁹ produced the N,N'-bis-(1-phenyl-2-propyl)-hydrazine (C) in 89% yield.

The aralkylation of hydrazine with primary aralkyl halides afforded the mono-(aralkyl)-hydrazines in satisfactory yields (60-75%) provided a three to five molar excess of hydrazine hydrate was used. With secondary aralkyl halides, yields dropped to 35-45% because of dehydrohalogenation to the phenylalkene.

When 1-phenyl-2-propyl bromide was treated with isopropylhydrazine, the major reaction product isolated was N-(1-phenyl-2-propyl)-N'-isopropylhydrazine rather than the expected⁷ unsymmetrically substituted hydrazine. The structure of the reaction product I was established by reductive cleavage to 1-phenyl-2-propylamine (II) and unequivocal synthesis *via* the reductive hydrazinolysis of phenylacetone with isopropyl hydrazine



The unsymmetrically substituted compound III would have yielded the secondary amine IV on reductive cleavage

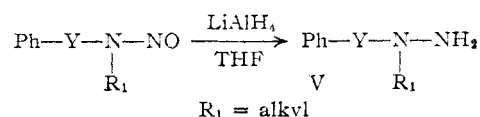


The preparation of the mono-(aralkyl)-hydrazones was accomplished in excellent yields (80-100%) by treating the ketone or a moderately reactive aldehyde (e.g., hydratropaldehyde) with a three molar excess of hydrazine hydrate, the carbonyl compound being added slowly to the refluxing methanolic hydrazine hydrate solution.

(8) H. C. Brown and B. C. SubbaRao, *THIS JOURNAL*, **78**, 2582 (1956)

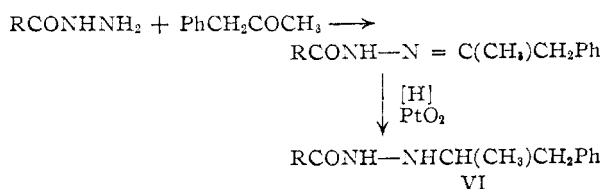
In many instances these hydrazones were reduced in their crude form, *i.e.*, without distilling them first.

3,4,5-Trimethoxybenzaldehyde formed a hydrazone with difficulty and in very low yield. Hence, the aldehyde was reduced to the alcohol with lithium aluminum hydride in tetrahydrofuran (a sodium borohydride reduction in methanol was unsuccessful). 3,4,5-Trimethoxybenzyl alcohol was then converted to the chloride with thionyl chloride in chloroform and the latter reacted with a methanolic solution of hydrazine hydrate to form the desired hydrazine in 62% yield. The synthesis of the N,N'-di- or N,N',N'-trisubstituted hydrazines was quite readily accomplished by the reductive hydrazinolysis of the respective ketone or aldehyde with the unsymmetrically substituted hydrazine in the presence of platinum oxide and alcoholic acetic acid. The *unsym*-aralkyl hydrazines V were obtained by the nitrosation of the secondary amine followed by the lithium aluminum hydride reduction of the nitrosamine⁹



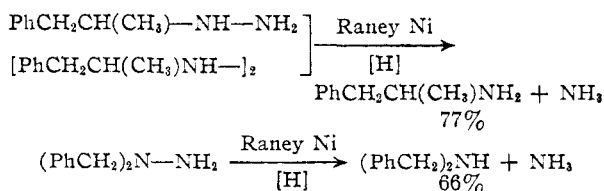
In order to study the effect of a reduced phenyl ring on physiologic activity, we attempted to prepare 1-cyclohexyl-2-propylhydrazine *via* the nuclear hydrogenation of the phenyl derivative with platinum oxide in glacial acetic acid. However, the only product obtained was 1-cyclohexyl-2-propylamine. The compound was finally produced by the reduction of phenylacetone to 1-cyclohexyl-2-propanol, oxidation to the propanone followed by reductive hydrazinolysis of 1-cyclohexyl-2-propanone.

In the preparation of the aralkyl hydrazides VI we were not successful in producing them directly from the mono-(aralkyl)-hydrazines and the respective esters. We did obtain the desired compounds, however, by the reductive aralkylation of the hydrazides following the method of Fox and Gibas¹⁰



The Raney nickel cleavage of the nitrogen-nitrogen bond first reported by Ainsworth^{11,12} and extended by Hinman¹³⁻¹⁵ proved in our hands a convenient means of producing pure primary and secondary amines starting with either a mono-aralkyl hydrazine, a *sym*-N,N'-disubstituted aralkyl hydrazine or an *unsym*-N,N-disubstituted hydrazine

- (9) C. Hanna and F. W. Schueler, *ibid.*, **74**, 3693 (1952).
 (10) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **17**, 1653 (1952).
 (11) C. Ainsworth, *THIS JOURNAL*, **78**, 1635 (1956).
 (12) C. Ainsworth, *ibid.*, **78**, 1636 (1956).
 (13) R. L. Hinman and J. Rosene, *J. Org. Chem.*, **21**, 1539 (1956).
 (14) R. L. Hinman, *ibid.*, **22**, 148 (1957).
 (15) R. L. Hinman, *THIS JOURNAL*, **79**, 414 (1957).



That this represents a fairly general preparative method for producing primary and secondary amines has been demonstrated by us for a variety of hydroxyalkylhydrazines, aminoalkylhydrazines and heterocyclic hydrazines.¹⁶

Structure-Activity Relationships

It had previously been demonstrated by Zeller that certain hydrazine derivatives such as methyl- and ethylhydrazine, as well as N-isopropyl-N'-isonicotinoylhydrazine (iproniazid) are potent inhibitors of monoamine oxidase (MAO),^{17,18} the enzyme responsible for the metabolic degradation of such central excitatory hormones as epinephrine, nor-epinephrine and dihydroxyphenylethylamine (dopamine) in animals¹⁹⁻²³ and man.²⁴ Hence, the compounds were screened by us (P.A.N., A.C.C., A.H.) for both their *in vitro* and *in vivo* MAO inhibitory effects and their analeptic properties.

The tests were based on the ability of MAO inhibitors to prevent the metabolic destruction of such endogenous monoamines as serotonin, epinephrine, nor-epinephrine and dihydroxyphenylethylamine (dopamine) as shown by Pletscher, Shore and Brodie^{25,26} as well as Carlsson and Chessin.^{27,28} Analeptic potency was measured by the ability of the test drug to arouse the animal from its reserpine stupor. This type of action would be comparable to that of amphetamine or Ritalin.^{28,29} The structure-activity data are summarized in Tables VIII and IX.

The length and character of the alkylene side chain was of paramount importance to MAO inhibitory and analeptic properties of the compounds. While phenylhydrazine (no. 1) was devoid of any activity, benzylhydrazine (no. 2) was a potent MAO inhibitor. Lengthening the straight alkylene chain (nos. 3 and 3a) resulted in a sharp

drop of the *in vivo* activity. However, the addition of a methyl group to the side chain afforded very powerful MAO inhibitors (nos. 7, 8 and 9), of which only the N-aminoamphetamine compound (no. 7) displayed also potent analeptic activity. This compound was the most active member of the entire series both as an MAO inhibitor and analeptic agent. Its potent properties have been confirmed in other animal tests³⁰⁻³² and in man.^{33,34} It is interesting to note that the structural prerequisite for optimum central stimulant properties appears to be 1-phenyl-2-propyl side chain which parallels the structural relationships in the sympathomimetic series where only the 1-phenyl-2-propylamine (amphetamine) displays potent CNS stimulating activities:



Barger and Dale³⁵ demonstrated similar structure-activity relationships for the sympathomimetic activities of the aralkylamines. Maximum pressor activity was associated with a β -phenethyl or an α -methyl- β -phenethyl side chain.

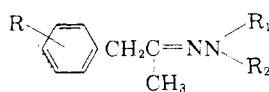
Replacement of the phenyl with a heterocyclic ring (nos. 12-16) brought about a sharp drop in the MAO inhibitory action. The thienyl group which is usually considered isosteric with the phenyl ring afforded also the most potent of the heterocyclic derivatives synthesized.

Similar findings have been reported for some heterocyclic sympathomimetic amines of the pyridine and thiophene series.³⁶⁻³⁹ Nuclear substitution, N-alkylation and N-acylation (Table IX) generally reduced MAO inhibitory activity and reduced or abolished the analeptic properties of the unsubstituted derivatives. The 3,4-methylenedioxy and 3-chloro derivatives (nos. 20 and 23) were among the more potent of the nuclear-substituted compounds.

Nuclear substitution in the amphetamine series likewise abolished or sharply decreased the central stimulatory action of the parent compound.⁴⁰⁻⁴⁴

- (16) J. H. Biel, W. K. Hoya and H. A. Leiser, *THIS JOURNAL*, **81**, 2527 (1959).
- (17) E. A. Zeller and J. Barsky, *Proc. Soc. Exptl. Biol. Med.*, **81**, 459 (1952).
- (18) E. A. Zeller, J. Barsky, J. R. Fouts, F. A. Kirchner and L. S. Van Orden, *Experientia*, **8**, 349 (1952).
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- (20) K. H. Beyer and H. S. Morrison, *Ind. Eng. Chem.*, **37**, 143 (1945).
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- (24) O. Resnick, J. M. Wolfe, H. Freeman and F. Elmadjian, *ibid.*, **127**, 1116 (1958).
- (25) A. Pletscher, P. A. Shore and B. B. Brodie, *ibid.*, **122**, 374 (1955).
- (26) P. A. Shore, A. Pletscher and B. B. Brodie, *J. Pharmacol. Exptl. Therap.*, **116**, 51 (1956).
- (27) A. Carlsson and N. Hillarp, *Kungl. Fysiogr. Sallsk. Lund. Forh.*, **26**, 1 (1956).
- (28) M. Chessin, E. R. Kramer and C. C. Scott, *J. Pharmacol. Exptl. Therap.*, **119**, 453 (1957).
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- (30) S. Spector, D. Prockop, P. A. Shore and B. B. Brodie, *Science*, **127**, 704 (1958).
- (31) A. Horita, *J. Pharmacol. Exptl. Therap.*, **122**, 176 (1958).
- (32) J. H. Biel, A. E. Drukker, P. A. Shore, S. Spector and B. B. Brodie, *THIS JOURNAL*, **80**, 1519 (1958).
- (33) (a) H. V. Agin, Am. Psychiatric Assoc. Meeting, San Francisco, Calif., May 13, 1958; (b) *Ann. N. Y. Acad. Sci.*, **68**, in press.
- (34) N. S. Kline and J. C. Saunders, Society of Biol. Psychiatry Meeting, San Francisco, Calif., May 10, 1958.
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- (36) L. A. Walter, W. H. Hunt and R. J. Fosbinder, *THIS JOURNAL*, **63**, 2771 (1941).
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- (38) G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2110 (1938).
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- (42) T. M. Patrick, E. T. McBee and H. B. Hass, *THIS JOURNAL*, **68**, 1009 (1946).
- (43) W. Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).
- (44) L. S. Goodman and A. Gilman, "The Pharmacologic Basis of Therapeutics," 2nd edition, The Macmillan Co., New York, N. Y., 1955, pp. 505-527.

TABLE I



R	N(R ₁)(R ₂)	B.p.		Formula	Nitrogen, %	
		°C.	mm.		Calcd.	Found
H	NH ₂	81	0.17	C ₉ H ₁₂ N ₂ ^a	18.90	19.00
4-MeO	NH ₂	124	.015	C ₁₀ H ₁₄ N ₂ O	15.72	15.62
3,4-(MeO) ₂	NH ₂	147	.04	C ₁₁ H ₁₆ N ₂ O ₂	13.46	13.22
3,4,5-(MeO) ₃	NH ₂	156	.05	C ₁₂ H ₁₈ N ₂ O ₃ ^b	11.76	11.44
3,4-O ₂ CH ₂	NH ₂	135	.03	C ₁₀ H ₁₂ O ₂ N ₂	14.56	14.46
2-Me	NH ₂	93	.04	C ₁₀ H ₁₄ N ₂	17.38	17.00
4-Isopropyl	NH ₂	117	.12	C ₁₂ H ₁₈ N ₂	14.72	14.70
H	NHCH ₃	83	1.0	C ₁₀ H ₁₄ N ₂	17.26	16.98
H	N(CH ₃) ₂	67	0.15	C ₁₁ H ₁₆ N ₂	15.90	15.86
H	1,2,3,4-THIQ ^c	162	0.35	C ₁₃ H ₂₀ N ₂	10.60	10.76

^a Anal. Calcd.: C, 72.92; H, 8.18. Found: C, 72.98; H, 8.22. ^b M.p. 65°. ^c Tetrahydroisquinoline.

TABLE II

R	R ₁	B.p.		Formula	Nitrogen, %	
		°C.	mm.		Calcd.	Found
H	C ₂ H ₅	82	0.4	C ₉ H ₁₂ N ₂	18.90	18.70
H	CH ₃	93	.8	C ₈ H ₁₀ N ₂	20.88	20.50
4-MeO	H	127	.3	C ₈ H ₁₀ N ₂ O	18.66	18.58
H	H	96	0.07	C ₁₀ H ₁₄ N ₂	17.22	16.96
4-MeO	H	134	0.1	C ₁₁ H ₁₆ N ₂ O	14.56	14.3
		147	0.06	C ₁₅ H ₂₀ N ₂	10.44	10.5

Alkylation of the nitrogen bearing the aralkyl group (no. 32) was particularly detrimental to both types of activity. Curiously enough, this compound which is a true nitrogen isostere of amphetamine was entirely devoid of any analeptic properties.

It was shown by Tainter⁴⁵ that N,N-bis-dialkylation of amphetamine practically abolishes the analeptic properties of the free or mono-alkylated amines.

Although the N-isopropyl compound (no. 27) appeared only moderately active in the initial screening test, Spector⁴⁶ found that on repeated administration this compound appeared to be as effective as compound no. 7 in raising serotonin and nor-epinephrine brain levels in the rabbit. It is possible that this compound is converted metabolically to a more active derivative. Of the N-acyl derivatives the 5-pyrrolidone-2-carboxyl (no. 36) group afforded by far the most potent MAO inhibitor.

Conclusions.—The replacement of an amino by a hydrazino radical in a series of sympathomimetic

(45) A. Novelli and M. L. Tainter, *J. Pharm. Exptl. Therap.*, **77**, 324 (1943).

(46) S. Spector, P. A. Shore and B. B. Brodie, Fall Meeting of the Am. Soc. for Pharmacol. Exptl. Therap., Ann Arbor, Mich., Aug. 22-28, 1958.

amines has yielded a number of potent central stimulants and monoamine oxidase inhibitors. The structural requirement for optimum CNS stimulating properties appeared to be a 1-phenyl-2-propyl skeleton. Nuclear substitution or hydrogenation of the phenyl ring, alkylation or acylation of either nitrogen atom, and replacement of the phenyl by a heterocyclic ring abolished or sharply reduced the analeptic properties and decreased MAO inhibitory potency. Similar parallelisms in the structure-activity relationships are to be found among the sympathomimetic amines. The sympathomimetic hydrazines differ, however, from the parent amines in several important respects: (1) they are much more powerful MAO inhibitors, (2) they are not metabolized as rapidly by the body's enzyme systems and thus afford a prolonged duration of action, (3) they decrease blood pressure instead of increasing it,⁴⁷ (4) they do not cause tachyphylaxis on repeated administration and (5) they tend to increase appetite rather than decrease it.

Several of the compounds are now undergoing intensive clinical trial for the treatment of the mentally depressed state and as possible therapeutic agents in the field of cardiovascular diseases.

Acknowledgment.—We are indebted to Mr. E. Kluchesky for the analytical data. We also wish to thank Dr. H. L. Friedman for his helpful suggestions and Dr. H. L. Daiell for his continued interest and encouragement throughout the course of this project.

Experimental

Phenyl Alkanones.—The general method of Hass⁴⁸ was followed, consisting of reductive hydrolysis of nitro-alkenes. Ketones not earlier mentioned in the literature are:

1-(3',4'-Methylenedioxy)-phenyl-2-propanone, b.p. 80° (0.08 mm.), *n*_D²⁰ 1.5420. Anal. Calcd. for C₁₀H₁₁O₃: CO, 15.74. Found: CO, 15.19.

1-(3',4',5'-Trimethoxy)-phenyl-2-propanone, b.p. 130° (0.03 mm.), m.p. 67-68°, *n*_D²⁰ 1.5319. Anal. Calcd. for C₁₂H₁₅O₄: CO, 12.49. Found: CO, 12.27.

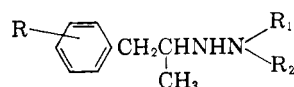
1-(3'-Chloro)-phenyl-2-propanone, b.p. 75° (0.06 mm.), *n*_D²⁰ 1.5350. Anal. Calcd. for C₈H₉ClO: Cl, 21.03. Found: Cl, 20.73.

Mono-aralkyl Hydrazones. Benzylacetone Hydrazone.—A solution of 49.3 g. (0.33 mole) of benzylacetone in 100 cc. of methanol was added to a refluxing solution of 59 g. (1.0

(47) A. Sjoerdsma and L. Gillespie, private communication.

(48) H. Hass, A. Susie and R. Heider, *J. Org. Chem.*, **15**, 8 (1950).

TABLE III



R	N $\begin{matrix} \text{R}_1 \\ \text{R}_2 \end{matrix}$	Bases						Salts				M.p., °C.
		°C.	B.p. Mm.	Formula	Nitrogen, %		Salt	Nitrogen, %		Anion, %		
					Calcd.	Found		Calcd.	Found	Calcd.	Found	
H	NH ₂	82-84	0.6	C ₉ H ₁₄ N ₂	18.65	18.71	HCl	15.02	15.04	18.99	18.97	123
4-MeO	NH ₂	107	.2	C ₁₀ H ₁₆ N ₂ O	15.56	15.28	HCl	12.92	13.45	16.36	16.45	126
3,4-(MeO) ₂	NH ₂	132	.04	C ₁₁ H ₁₈ N ₂ O ₂	13.32	11.71 ^d	H ₃ PO ₄	9.08	9.23	30.82	30.94	^a
3,4,5-(MeO) ₃	NH ₂	142	.03	C ₁₂ H ₂₀ N ₂ O ₃	11.66	11.91	HCl	10.12	10.35	12.81	12.87	150
3,4-O ₂ CH ₂	NH ₂	124	.45	C ₁₀ H ₁₄ N ₂ O ₂	14.42	14.02	HCl	12.14	12.40	15.37	15.49	118
4-HO	NH ₂	180	.05 ^b	C ₉ H ₁₄ N ₂ O	16.86	16.98						
2-Me	NH ₂	85	.04	C ₁₀ H ₁₆ N ₂	17.06	16.67	HCl	13.96	13.82	17.66	17.97	127
4-Isopropyl	NH ₂	90	.1	C ₁₂ H ₂₀ N ₂	14.56	14.32	H ₃ PO ₄	9.65	9.88	32.93	33.10	^c
3-Cl	NH ₂	86	.1	C ₉ H ₁₄ ClN ₂	15.09	12.66 ^d	H ₃ PO ₄	9.88	9.92	33.49	33.55	^e
H	NHCH ₃	78	1.0	C ₁₀ H ₁₆ N ₂	17.06	16.86	HCl			17.66	17.99	115-117
H	N(CH ₃) ₂	60	0.35	C ₁₁ H ₁₈ N ₂	15.72	15.78	HCl			16.51	16.52	128
H	THIQ ^f	140	0.15	C ₁₈ H ₂₂ N ₂	10.52	10.62	HCl	9.26	9.16	11.71	11.65	221

^a No definite m.p.; shrinks at *ca.* 150-160°. ^b M.p. 124-126°. ^c No definite m.p.; compound shrinks at *ca.* 158°. ^d Base evolves nitrogen on standing. ^e Compound decomposes at *ca.* 265°. ^f 1,2,3,4-Tetrahydroisoquinoline.

TABLE IV

R	R ₁	R ₂	Bases						Salts				
			°C.	B.p. Mm.	Formula	Nitrogen, %		Salt	Nitrogen, %		Anion, %		M.p., °C.
						Calcd.	Found		Calcd.	Found	Calcd.	Found	
H	H	H	107	8.0	C ₇ H ₁₀ N ₂	22.92	22.70	HCl	17.66	17.74	22.35	22.44	112-113
H	CH ₃	H	69	0.65	C ₈ H ₁₂ N ₂	20.56	20.24	H ₃ PO ₄	11.96	11.88	40.56	40.74	150
H	C ₂ H ₅	H	70	0.55	C ₉ H ₁₄ N ₂	18.65	18.77	HCl	15.00	14.98	18.99	19.05	108-111
H	H	CH ₃	80	8.0	C ₈ H ₁₂ N ₂	20.56	20.48	H ₃ PO ₄	11.96	11.92	40.56	40.92	111-112
4-MeO	H	H	106	0.45	C ₈ H ₁₂ N ₂ O	18.40	17.78 ^d	HCl	14.85	14.88	18.79	18.67	205
3,4,5-(MeO) ₃	H	H	140	0.1	C ₁₀ H ₁₆ N ₂ O ₃		^a	HCl	11.26	11.18	14.25	14.26	176

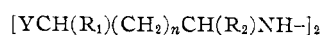
R	R ₁	R ₂	Bases						Salts				
			°C.	B.p. Mm.	Formula	Nitrogen, %		Salt	Nitrogen, %		Anion, %		M.p., °C.
						Calcd.	Found		Calcd.	Found	Calcd.	Found	
H	H	H	74	0.1	C ₉ H ₁₃ N ₂	20.57	20.85	HCl ^b	16.23	16.47	20.53	20.54	174
H	CH ₃	H	70	.1	C ₉ H ₁₄ N ₂	18.65	17.57 ^d	H ₃ PO ₄	11.28	11.01	38.26	38.00	^c
H	OH	H	133	.06	C ₉ H ₁₂ N ₂ O	18.41	18.50	HCl	14.85	14.73	18.79	81.85	158

R	R ₁	R ₂	Bases						Salts				
			°C.	B.p. Mm.	Formula	Nitrogen, %		Salt	Nitrogen, %		Anion, %		M.p., °C.
						Calcd.	Found		Calcd.	Found	Calcd.	Found	
H	H	H	82	.025	C ₁₀ H ₁₆ N ₂	17.06	16.36 ^a	H ₂ SO ₄	10.86	11.01	36.60	37.04	96
4-MeO	H	H	115	.15	C ₁₁ H ₁₈ N ₂ O	14.42	14.43	H ₂ SO ₄	9.58	9.54	32.86	33.09	104-105

R	Bases						Salts				
	°C.	B.p. Mm.	Formula	Nitrogen, %		Salt	Nitrogen, %		Anion, %		M.p., °C.
				Calcd.	Found		Calcd.	Found	Calcd.	Found	
	112	0.6	C ₉ H ₁₂ N ₂	18.90	18.46	HCl	15.17	15.23	19.20	19.25	124-126

^a Compound decomposes on distillation. ^b Calcd.: C, 55.39; H, 7.48. Found: C, 55.58; H, 7.59. ^c No definite m.p. ^d Base evolves nitrogen on standing.

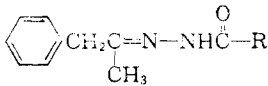
TABLE V



Y	R ₁	R ₂	n	Bases			Nitrogen, %	
				°C.	B.p. Mm.	Formula	Calcd.	Found
Ph	H	CH ₃	0	127	0.02	C ₁₈ H ₂₄ N ₂ ^c	10.44	10.42
3,4-(MeO) ₂ Ph	H	CH ₃	0	220	.06	C ₂₂ H ₃₂ N ₂ O ₄	7.86	7.93
4-Isopropyl-Ph	H	CH ₃	0	175	.07	C ₂₄ H ₃₆ N ₂	7.95	7.94
Ph	CH ₃	H	0	130-140 ^a	.08	C ₁₈ H ₂₄ N ₂	10.44	9.81 ^b
Ph	H	CH ₃	1	150	.02	C ₂₀ H ₂₈ N ₂	9.46	9.26
C ₆ H ₁₁	H	CH ₃	0	126	.25	C ₁₈ H ₃₆ N ₂	9.98	9.98

^a Compound decomposed slightly during distillation. ^b Base evolves nitrogen on standing. ^c M.p. of hydrochloride, 174-175°. *Anal.* Calcd. for C₁₉H₂₅ClN₂: Cl, 11.63; N, 9.18. Found: Cl, 11.71; N, 9.15.

TABLE VI



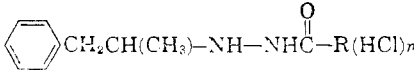
R	Formula	Nitrogen, %		M.p., °C.	Yield, %
		Calcd.	Found		
Ph ₂ C(OH)	C ₂₃ H ₂₂ N ₂ O ₂	16.59	16.53	134-135	83
4-Pyridyl	C ₁₅ H ₁₅ N ₂ O ₂	16.59			
3-Pyridyl	C ₁₅ H ₁₅ N ₂ O ₂	16.59	16.53	134-135	83
2-Pyridyl	C ₁₅ H ₁₅ N ₂ O ₂	16.59	16.20	145-146	90
5-1-Glutamyl	C ₁₄ H ₁₉ N ₃ O ₃	15.15	14.80	173-174	72
5-Keto-2-pyrrolidinyl	C ₁₄ H ₁₇ N ₃ O ₂	16.20	16.35	153-154	92

ethereal solution was dried with potassium carbonate, filtered and fractionated; b.p. 82° (0.025 mm.), 36.4 g. (69%), n_D^{20} 1.5333. *Anal.* Calcd. for C₁₀H₁₆N₂: N, 17.06. Found: N, 17.36.

N-Aralkyl-N',N'-Disubstituted Hydrazines. 1. **N-(1-Phenyl-2-propylidene)-N',N'-dimethylhydrazine.**—To a solution of 54 g. (0.9 mole) of N,N-dimethylhydrazine in 500 cc. of methanol was added with stirring 120.8 g. (0.90 mole) of phenylacetone. After stirring for 3 hr. at room temperature, the methanol was removed by distillation and the residue was subjected to vacuum distillation. The compound was collected at 67° (0.15 mm.), yield 144 g. (91%), n_D^{20} 1.5185. *Anal.* Calcd. for C₁₁H₁₆N₂: N, 15.90. Found: N, 15.86.

2. **N-(1-Phenyl-2-propyl)-N',N'-dimethylhydrazine.**—To a solution of 59.0 g. (0.33 mole) of the above hydrazine

TABLE VII



R	n	Formula	Nitrogen, %		Chlorine, %		M.p., °C.	Yield, %
			Calcd.	Found	Calcd.	Found		
NC-CH ₂	0	C ₁₂ H ₁₃ N ₃ O	19.35	19.16	
Ph ₂ C(OH)	1	C ₂₃ H ₂₅ ClN ₂ O ₂	10.59	10.50	8.93	8.80	200-202	66
4-Pyridyl	2	C ₁₈ H ₁₉ Cl ₂ N ₃ O	12.80	13.03	21.60	21.71	239-240	85
3-Pyridyl	2	C ₁₈ H ₁₉ Cl ₂ N ₃ O	12.80	12.69	21.60	21.43	237-238	55
2-Pyridyl	2	C ₁₈ H ₁₉ Cl ₂ N ₃ O	12.80	12.60	21.60	21.35	189-190	32
5-1-Glutamyl	0	C ₁₄ H ₂₁ N ₃ O ₃	15.05	15.25	174-175	85
5-Keto-2-pyrrolidinyl	0	C ₁₄ H ₁₉ N ₃ O ₂	16.08	15.95	160-161	60

TABLE VIII

No.	Ar	Y	Ar-Y-NH-NH ₂		<i>In vivo</i> ^a potency (Iproniazid = 1)	<i>In vitro</i> potency % inhibition 10 ⁻⁵ M	10 ⁻⁴ M	Analeptic ^b activity (Amphet- amine = 1.0)
1	Ph	..			Inactive			0
2	Ph	CH ₂ -			40	100	21	?
3	Ph	C ₂ H ₄ -			4	50	30	0
3a	Ph	C ₃ H ₅ -			<1			0
4	Ph	CH(CH ₃)-			20			0
5	Ph	CH(OH)CH ₂ -			8	0		0
6	Ph	CH(C ₂ H ₅)-			2	65	5	0
7	Ph	CH ₂ CH(CH ₂)-			40	100	60	1.0
8	Ph	CH(CH ₃)CH ₂ -			16	80	25	0
9	Ph	CH ₂ CH ₂ CH(CH ₃)-			20	100	80	0
10	Ph	CH=CH-CH ₂ -			2			0
11	Iproniazid					25	0	0
12	2-Pyridyl	CH ₂				15		0
13	3-Pyridyl	CH ₂			4	73		0
14	2-Thienyl	CH ₂			8	57		0
15	2-Furyl	CH ₂						0
16	2-Benzodioxane	CH ₂			5			0

^a Drug was admin. to mice (i.p.) 2 hr. prior to 5.0 mg./kg. (i.p.) of reserpine. ^b 5.0 mg./kg. (i.p.) of reserpine admin. to mice 3-4 hr. prior to admin. of drug. ^c Convulsions at 60 mg./kg.; Amphetamine is active at 1.0 mg./kg.

mole) of hydrazine hydrate 85% in 175 cc. of methanol. The solution was refluxed for 2 hr. and the methanol removed by distillation. The residue was extracted with ether and the ethereal solution was dried over potassium carbonate, filtered and fractionated. Benzylacetone hydrazone was collected at 96° (0.07 mm.), yield 46.5 g. (86%), n_D^{20} 1.5521.

Anal. Calcd. for C₁₆H₁₄N₂: N, 17.26. Found: N, 16.86.

Mono-aralkyl Hydrazines. 1-Phenyl-3-hydrazinebutane. —To a solution of 52.2 g. (0.32 mole) of benzylacetone hydrazone in 250 cc. of alcohol was added 19.3 g. (0.32 mole) of acetic acid and the resulting solution was subjected to hydrogenation in the presence of 0.5 g. of platinum oxide catalyst at 60 p.s.i. of hydrogen. The catalyst was removed by filtration and the alcohol was removed by distillation. Water was added to the residue and the mixture was made alkaline by the addition of potassium hydroxide. The resulting mixture was extracted with ether and the

in 150 cc. of ethanol was added 20 g. of glacial acetic acid (0.33 mole) and the resulting solution was hydrogenated in the presence of 500 mg. of platinum oxide catalyst at 60 p.s.i. of hydrogen. The catalyst was removed by filtration and the alcohol was removed by distillation. Water was added to the residue and the mixture was made strongly alkaline by the addition of potassium hydroxide. The resulting mixture was extracted with ether, the ethereal solution was dried with potassium carbonate, filtered and fractionated. The product was collected at 60° (0.35 mm.), n_D^{20} 1.4993, yield 43 g. (73%). *Anal.* Calcd. for C₁₁H₁₈N₂: N, 15.72. Found: N, 15.78.

N-Amino-1,2,3,4-tetrahydroisoquinoline.—To a mixture of 26.6 g. (0.20 mole) of 1,2,3,4-tetrahydroisoquinoline and 170 cc. of water was added 51 g. of 30% sulfuric acid. The solution was then cooled and, while stirring, a solution of 34 g. (0.49 mole) of sodium nitrite in 60 cc. of water was added in 25 minutes at 5-10°. Stirring was continued for another 2 hr. at room temperature. The solution was then

TABLE IX

No.	R ₁	R ₂	R ₃	<i>In vivo</i> ^a potency (Iproni- azid = 1)	<i>In vitro</i> potency % inhibition 10 ⁻⁴ M	10 ⁻⁶ M	Analeptic ^b activity (Amphet- amine = 1)
17	4-OCH ₃	H	H	8	100	10	0.10
18	3,4-(OCH ₃) ₂	H	H	4	65	15	
19	3,4,5-(OCH ₃) ₃	H	H	2	50	5	
20	3,4-(CH ₂ O) ₂	H	H	20	100	55	.07
21	2-Methyl	H	H	20	100	45	.08
22	4-Isopropyl	H	H	4	95	25	
23	3-Chloro	H	H	20	100	49	.33
24	Hexahydro Iproni-azid	H	H	4	86	0	.13
				1	25		0
25	H	H	CH ₃	3			
26	H	CH ₃	CH ₃	8			0.10
27	H	H	CH(CH ₃) ₂	2			.07
28	H	(CH ₂ SO ₃ Na) ₂		16	100		.02
29	H	H	SO ₃ H	20			
30	H	1,2,3,4-THIQ ^c		2			0
31	H	H	CH(CH ₃)CH ₂ Ph	2	12	0	
32	PhCH ₂ N(CH ₃)NH ₂			2	6	0	0
33	H	H	COCH ₂ CN	2			0
34	H	H	Isonicotinyl	4	50	0	0
35	H	H	Benzyl	2			0
36	H	H	5-Pyrrolidone-2-carboxyl	8	90	30	0

^a Drug admin. to mice (i.p.) 2 hr. prior to the admin. of 5.0 mg./kg. (i.p.) of reserpine. ^b 5.0 mg./kg. (i.p.) of reserpine admin. to mice 3-4 hr. prior to admin. of drug. ^c Tetrahydroisoquinoline.

extracted with ether and the ethereal extracts washed with 50 cc. of 40% potassium hydroxide solution. The ethereal extracts were dried over potassium carbonate, filtered, and the ether was removed by distillation. The residue, consisting of 29 g. of crude 2-nitroso-1,2,3,4-tetrahydroisoquinoline, was dissolved in 400 cc. of ether and the ethereal solution was added in a dropwise fashion to a suspension of 8.8 g. (0.23 mole) of lithium aluminum hydride in 400 cc. of refluxing dry ether. Stirring was continued for 4 hr. after which the hydride complex was decomposed by addition of 40% potassium hydroxide. The reaction mixture was extracted with ether. The ethereal extracts were dried with potassium carbonate, filtered and fractionated. The product was collected at 85° (0.5 mm.), yield 21.7 g. (73%), *n*_D²⁰ 1.5793. *Anal.* Calcd. for C₉H₁₂N₂: N, 18.90. Found: N, 18.70.

N-Aralkylhydrazines in which N' is Part of a Ring System.
N'-[N''-(1-Phenyl-2-propylidene)]-amino-1,2,3,4-tetrahydroisoquinoline.—A solution of 37.1 g. (0.25 mole) of N-amino-1,2,3,4-tetrahydroisoquinoline in 150 cc. of alcohol was added to a solution of 33.5 g. (0.25 mole) of phenylacetone in 150 cc. of alcohol. The solution was refluxed for 3 hr. and the alcohol was removed by distillation. The residue was extracted with ether and dried with potassium carbonate. The carbonate was filtered off and the compound was isolated by fractionation; 55.6 g. (84%) was collected at 152° (0.35 mm.), *n*_D²⁰ 1.5858. *Anal.* Calcd. for C₁₈H₂₀N₂: N, 10.60. Found: N, 10.76.

N'-[N''-(1-Phenyl-2-propyl)]-amino-1,2,3,4-tetrahydroisoquinoline.—A solution of 26.4 g. (0.10 mole) of N-[N''-(1-phenyl-2-propylidene)]-amino-1,2,3,4-tetrahydroisoquinoline in 175 cc. of dry ether was added in a dropwise fashion to a suspension of 3.4 g. (0.09 mole) of lithium aluminum hydride in 200 cc. of dry ether. The reaction mixture was refluxed and stirred for 5 hr. after which the hydride complex was decomposed by addition of potassium hydroxide solution. The mixture was extracted with ether, the ethereal solution was dried with potassium carbonate, filtered and fractionated. The product was collected at 135° (0.15 mm.), yield 22.5 g. (84%), *n*_D²⁰ 1.5674. *Anal.* Calcd. for C₁₈H₂₂N₂: N, 10.52. Found: N, 10.62.

N,N'-sym-Bis-(aralkyl)-hydrazines. **N,N'-Bis-(1-phenyl-2-propylidene)-hydrazine.**—A solution of 11.75 g. (0.20 mole) of hydrazine hydrate 85% in 50 cc. of methanol was added to a solution of 53.6 g. (0.40 mole) of phenylacetone in 500 cc. of methanol. The solution was stirred for 3 hr.

at room temperature. The methanol was removed by distillation and the residue was extracted with ether. The ethereal extracts were dried with potassium carbonate, filtered and fractionated. The azine was collected at 147° (0.06 mm.), yield 47.3 g. (90%), *n*_D²⁰ 1.5731. *Anal.* Calcd. for C₁₈H₂₀N₂: N, 10.61. Found: N, 10.52.

N,N'-Bis-(1-phenyl-2-propyl)-hydrazine.—To a solution of 33.8 g. (0.125 mole) of N,N'-bis-(1-phenyl-2-propylidene)-hydrazine in 150 cc. of ethanol were added 15 g. (0.25 mole) of glacial acetic acid and the resulting solution was subjected to hydrogenation in the presence of 500 mg. of platinum oxide catalyst at a pressure of 60 lb. The catalyst was removed by filtration and the alcohol by distillation. The residue was taken up in water and made alkaline with potassium hydroxide. The reaction mixture was then extracted with ether, the ethereal extract was dried over potassium carbonate, filtered and fractionated. The product was collected at 127° (0.02 mm.), yield 27.6 g. (80.5%), *n*_D²⁰ 1.5468. *Anal.* Calcd. for C₁₈H₂₂N₂: N, 10.44. Found: N, 10.42.

3,4,5-Trimethoxybenzyl Alcohol.—To 6.5 g. (0.17 mole) of lithium aluminum hydride (LAH) in 300 cc. of tetrahydrofuran (THF) was added with stirring 45.7 g. (0.23 mole) of crude 3,4,5-trimethoxybenzaldehyde in 200 cc. of THF. After the exothermic reaction had subsided, the mixture was stirred and refluxed for an additional 5 hr. The complex was then decomposed with 40% aqueous potassium hydroxide, the organic phase decanted and dried with potassium carbonate. The product was collected at 124° (0.06 mm.), *n*_D²⁰ 1.5432. *Anal.* Calcd. for C₁₀H₁₄O₄: OH, 8.58. Found: OH, 8.30.

3,4,5-Trimethoxybenzyl Chloride.—To a solution of 25.5 g. (0.13 mole) of 3,4,5-trimethoxybenzyl alcohol in 150 cc. of chloroform was added 29.8 g. (0.25 mole) of thionyl chloride. After the mixture was refluxed for 2.5 hr., the chloroform and excess of thionyl chloride were removed by distillation. The residue was subjected to vacuum distillation through a 4'' column; yield 21.1 g. (76%), b.p. 126° (0.7 mm.). *Anal.* Calcd. for C₁₀H₁₃ClO₃: Cl, 16.36. Found: Cl, 16.02.

Hydrazinolysis of Aralkyl Halides. **3,4,5-Trimethoxybenzylhydrazine.**—A solution of 21.0 g. (0.098 mole) of 3,4,5-trimethoxybenzyl chloride in 100 ml. of ethanol was added over a period of 1 hr. to a refluxing solution of 30 g. (0.51 mole) of 85% hydrazine hydrate in 200 ml. of ethanol. After a reflux period of 6 hr., the alcohol was removed by

distillation. The residue was extracted with ether, the ethereal extracts dried with potassium carbonate, filtered and fractionated. The compound decomposed during distillation; approx. b.p. 140° (0.1 mm.), yield 13.2 g. (62%). The crude base was then converted to the hydrochloride: 2.12 g. of base was dissolved in a mixture of 20 cc. of ethanol and 15 cc. of ether and ethereal hydrochloric acid was added to pH 5. A white crystalline product was isolated by filtration, yield 2.1 g. The hydrochloride was recrystallized from ethanol; m.p. 175°. *Anal.* Calcd. for $C_{10}H_{17}ClN_2O_3$: N, 11.26; Cl, 14.25. Found: N, 11.11; Cl, 14.16.

N-Aralkyl-N-alkylhydrazines. N-Methyl-N-benzylhydrazine.—A solution of 40.8 g. (0.27 mole) of N-nitroso-N-methylbenzylfuran in 150 cc. of tetrahydrofuran was added dropwise with stirring in 20 minutes to a refluxing solution of 15.2 g. (0.40 mole) of lithium aluminum hydride in 450 cc. of tetrahydrofuran. Refluxing was continued for 5 hr. after which the hydride complex was decomposed by addition of aqueous potassium hydroxide. The tetrahydrofuran solution was decanted, dried over potassium carbonate, filtered and fractionated. The product was collected at 80° (8.0 mm.), yield 21.9 g. (59%), n_D^{20} 1.5352. *Anal.* Calcd. for $C_8H_{12}N_2$: N, 20.56. Found: N, 20.48.

N-Benzyl- and unsym-N,N-Dibenzylhydrazine.—Benzyl chloride was treated with 85% hydrazine hydrate in the manner described above. From 126.5 g. (1.0 mole) of benzyl chloride and 295 g. (5.0 moles) of the hydrazine hydrate (85%) there was obtained 90 g. (74%) of N-benzylhydrazine, b.p. 107° (8.0 mm.), n_D^{20} 1.5601 (*Anal.* Calcd. for $C_7H_{10}N_2$: N, 11.46. Found: N, 11.35) and 21 g. of N,N-dibenzylhydrazine, m.p. 55°¹⁹ after recrystallization from n-heptane.

Reductive Cleavage of Aralkylhydrazines. (a) Cleavage of N,N-Dibenzylhydrazine.—To a solution of 6.3 g. (0.50 mole) of N,N-dibenzylhydrazine in 100 ml. of ethanol was added 1.5 tablespoons of alcohol-washed Raney nickel and the mixture was subjected to reductive cleavage at 50° and 60 lb. pressure for 4 hr. The catalyst was removed by filtration and the alcohol by distillation. The residue was fractionated through a short column. No low boiling fraction (benzylamine) was obtained and our yield consisted exclusively of 3.9 g. (66%) of dibenzylamine, b.p. 111° (0.08 mm.), n_D^{20} 1.5718. *Anal.* Calcd. for $C_{14}H_{18}N_2$: N, 7.10. Found: N, 7.01.

The amine was converted to the hydrochloride salt in a 90% yield, m.p. 265–266°. *Anal.* Calcd. for $C_{14}H_{18}ClN$: N, 5.99; Cl, 15.17. Found: N, 5.98; Cl, 14.93.

Cleavage of N,N'-Bis-(1-phenyl-2-propyl)-hydrazine.—Three teaspoonsful of alcohol-washed Raney nickel was added to a solution of 13.4 g. of N,N'-bis-(1-phenyl-2-propyl)-hydrazine in 250 cc. of alcohol and the mixture was subjected to reductive cleavage at 60° and 400 lb. hydrogen pressure for 12 hr. The catalyst was removed by filtration and the solvent by distillation. The residue was fractionated through a 12' column; 10.4 g. (77%) of phenylisopropylamine was collected at 80° (12 mm.), n_D^{20} 1.5175. *Anal.* Calcd. for $C_9H_{13}N$: N, 10.36. Found: N, 10.24. The amine was converted to the hydrochloride in 97% yield, m.p. 147°, which was raised to 151° after recrystallization from a mixture of isopropyl alcohol and ether. *Anal.* Calcd. for $C_9H_{13}ClN$: N, 8.16; Cl, 20.65. Found: N, 8.15; Cl, 20.47.

N-(1-Phenyl-2-propyl)-N',N'-bis-(methylene Sodium Sulfonate)-hydrazine.—To a solution of 15.7 g. (0.15 mole) of sodium bisulfite and 10.3 cc. (0.14 mole) of 37% formalin in 25 cc. of water was added dropwise 20.3 g. (0.135 mole) 1-phenyl-2-propylhydrazine. The mixture was refluxed for 2 hrs. and then concentrated *in vacuo*. The gummy residue was crystallized from 450 cc. of isopropyl alcohol and collected by filtration; yield 27.2 g. (95%). *Anal.* Calcd. for $C_{11}H_{18}Na_2O_6S_2$: N, 7.33; Na, 12.03. Found: N, 7.61; Na, 12.03.

N-(1-Phenyl-2-propyl)-hydrazino-N'-methylenesulfonic Acid.—To 5.73 g. (0.015 mole) of the bis-methylene sodium sulfonate compound in 50 cc. of water was added 7.3 g. (0.075 mole) of concd. hydrochloric acid. On standing for several days, the solution yielded a white precipitate, which was collected by filtration and washed repeatedly with water; yield 3.11 g. (85%), m.p. 133–135°. *Anal.* Calcd. for $C_{10}H_{14}N_2SO_3$: N, 11.47; S, 13.13. Found: N, 11.26; S, 13.31.

(49) T. Curtius, *Ber.*, **34**, 552 (1901).

Alkylation of Sterically-hindered Hydrazines. The Reaction of 1-Phenyl-2-bromopropane with Isopropylhydrazine.—To a solution containing 71.6 g. (0.97 mole) of isopropylhydrazine in 250 cc. of n-butyl alcohol was added dropwise 203 g. (0.97 mole) of 1-phenyl-2-bromopropane. The solution was refluxed with stirring for 56 hr. The solvent was removed by distillation and the residue suspended in 360 cc. of 0.33 mole aqueous hydrochloric acid. The acid mixture was extracted repeatedly with di-isopropyl ether and the aqueous phase made strongly alkaline with solid potassium hydroxide. The alkaline mixture was extracted repeatedly with ether and the ether extracts dried with potassium carbonate. After removal of the solvent and some unreacted isopropylhydrazine, the residue was subjected to a vacuum distillation and the distillate collected at 123–126° (15 mm.), yield 54 g., n_D^{20} 1.5065. *Anal.* Calcd. for $C_{12}H_{20}N_2$: N, 14.57. Found: N, 14.20.

Hydrochloride Salts.—To 51.8 g. (0.27 mole) of the above distillate dissolved in 250 cc. of ether was added ethereal hydrochloric acid to pH 1. The white solid was collected by filtration, yield 58.2 g. (94%), m.p. 110–118°. After two recrystallizations from isopropyl alcohol and acetonitrile 25.2 g. (41%) of a solid was collected, m.p. 146–147°. A mixed m.p. with an authentic sample of N-(1-phenyl-2-propyl)-N'-isopropylhydrazine hydrochloride showed no depression. A Raney nickel cleavage of the above base (obtained by the neutralization of the pure hydrochloride salt) yielded 1-phenyl-2-propylamine, m.p. of the hydrochloride salt 153–154°; a mixed m.p. with amphetamine hydrochloride showed no depression.

The mother liquors from the recrystallization of the crude hydrochloride salts were concentrated. However, only a gummy mass remained which could not be purified further. The residue was therefore converted to the free bases with aqueous potassium hydroxide solution and alkaline mixture extracted with ether. The ether was removed by distillation and the residual bases subjected to a Raney nickel cleavage. No separation could be effected by fractional distillation. The Hinsberg reagent (benzenesulfonyl chloride) yielded an oily sulfonamide in alkaline solution which indicated that at least 50% of the cleavage product was a secondary amine. The hydrolysis of the oily sulfonamide with 48% hydrobromic acid and phenol proceeded in low yield, but we were able to isolate a small amount of a base which formed a hydrochloride salt, m.p. 156–157°; a mixed m.p. with an authentic sample of N-(1-phenyl-2-propyl)-N-isopropylamine.HCl showed no depression. Hence, we conclude that the reaction of isopropylhydrazine with 1-phenyl-2-bromopropane yielded the symmetrically substituted hydrazine to the extent of 60–80%, but that the unsymmetrically substituted hydrazine is formed as one of the by-products.

N-(1-Phenyl-2-propyl)-N-isopropylamine was prepared by heating 0.30 mole of 1-phenyl-2-bromopropane and 1.5 moles of isopropylamine in 100 cc. of isopropyl alcohol in a pressure bottle at 100° for 18 hr. The product was worked up in the usual manner and collected at 96–97° (12 mm.), yield 7.0 g., n_D^{20} 1.4902. *Anal.* Calcd. for $C_{12}H_{19}N$: N, 7.90. Found: N, 7.82. The hydrochloride salt melted at 156–158°; mixed m.p. with 1-phenyl-2-propylamine hydrochloride 118–122°.

The Reduction of Phenylacetone Hydrazone. A. Catalytic Reductions. (1) Raney Nickel.—A solution of 39.3 g. (0.27 mole) of phenylacetone hydrazone in 160 cc. of absolute alcohol was subjected to hydrogenation at 60 lb. pressure and 50° in the presence of 6 g. of Raney nickel catalyst. The catalyst was removed by filtration and the filtrate was fractionated. 1-Phenyl-2-propylamine was collected at 96° (20 mm.), yield 17.5 g. (48.5%), n_D^{20} 1.5183. *Anal.* Calcd. for $C_9H_{13}N$: N, 10.36. Found: N, 10.04, hydrochloride salt, m.p. 150–152°. A mixed m.p. with amphetamine hydrochloride showed no depression. The distillation residue was unreacted N,N'-bis-(1-phenyl-2-propyl)-hydrazine.

(2) **Platinum Oxide.**—a. A solution of 37.0 g. (0.25 mole) of phenylacetone hydrazone in 425 cc. of absolute alcohol was subjected to hydrogenation at 500 lb. pressure in the presence of 1.0 g. of platinum oxide catalyst. The catalyst was removed by filtration and the filtrate was fractionated; 18.6 g. (49.5%) of 1-phenyl-2-hydrazinopropane was collected at 82° (0.04 mm.), n_D^{20} 1.5338; hydrochloride salt, m.p. 122°; and 14.2 g. (43%) of a mixture of N,N'-bis-(1-phenyl-2-propylidene)-hydrazine and N,N'-

bis-(1-phenyl-2-propyl)-hydrazine was collected at 138° (0.02 mm.).

b. A solution of 37.0 g. (0.25 mole) of phenylacetone hydrazone in 425 cc. of absolute alcohol was subjected to hydrogenation at 80° and 500 lb. pressure in the presence of 1.0 g. of platinum oxide catalyst. The catalyst was removed by filtration and the filtrate was fractionated; 15.6 g. (46%) of 1-phenyl-2-propylamine was collected at 50° (0.3 mm.); hydrochloride salt, m.p. 153°; and 10.5 g. (38%) of 1-phenyl-2-hydrazino propane, b.p. 80° (0.25 mm.); hydrochloride salt, m.p. 122°.

c. Alcoholic hydrochloric acid (0.50 mole) was added to a solution of 74.1 g. (0.50 mole) of phenylacetone hydrazone in 100 cc. of absolute alcohol and the resulting solution was subjected to hydrogenation at 60 lb. pressure in the presence of 900 mg. of platinum oxide catalyst. The catalyst was removed by filtration and the alcohol by distillation. Dilute hydrochloric acid was then added to the residue to pH 1 and the solution was extracted with ether. The aqueous phase was made strongly alkaline with potassium hydroxide and was repeatedly extracted with ether. The combined ethereal extracts were dried with potassium carbonate and fractionated *in vacuo*; 23.3 g. of amphetamine collected (34.5%) at 95° (18 mm.), n_D^{20} 1.5171 (*Anal.* Calcd. for $C_9H_{13}N$: N, 10.36. Found: N, 10.10); hydrochloride salt, m.p. 149–151°; 18.2 g. (24.2%) of 1-phenyl-2-hydrazinopropane was collected at 75° (0.3 mm.), n_D^{20} 1.5369 (*Anal.* Calcd. for $C_9H_{14}N_2$: N, 18.66. Found: N, 18.02); and 9.3 g. (14%) of a mixture of N,N'-bis-(1-phenyl-2-propylidényl)-hydrazine and N,N'-bis-(1-phenyl-2-propyl)-hydrazine was collected at 140° (0.5 mm.), n_D^{20} 1.554.

d. To a solution of 741 g. (5.0 moles) of phenylacetone hydrazone in 900 cc. of absolute ethanol were added 300 g. (5.0 moles) of glacial acetic acid and the resulting solution was subjected to hydrogenation at 1875 lb. pressure in the presence of 10.0 g. of platinum oxide catalyst. The catalyst was removed by filtration and washed with alcohol. The alcohol was removed from the filtrate by distillation. Dilute hydrochloric acid was added to the residue to pH 1 and the solution extracted with ether. The aqueous solution was then made strongly alkaline with potassium hydroxide and the alkaline mixture extracted several times with ether. The combined ethereal extracts were dried with potassium carbonate and fractionated; 512 g. (68%) of 1-phenyl-2-propylhydrazine was collected at 85° (0.3 mm.), n_D^{20} 1.5375 (*Anal.* Calcd. for $C_9H_{14}N_2$: N, 18.66. Found: N, 18.74); and 160 g. (23.5%) of a mixture of N,N'-bis-(1-phenyl-2-propyl)-hydrazine and N,N'-bis-(1-phenyl-2-propylidényl)-hydrazine was collected at 135° (0.25 mm.), n_D^{20} 1.557. This mixture was dissolved in absolute ethanol, 72 g. (1.2 moles) of glacial acetic acid was added and the resulting solution was hydrogenated in the presence of 2.5 g. of platinum oxide catalyst at 60 lb. pressure. The uptake of hydrogen indicated that 36% of the above mixture had been N,N'-bis-(1-phenyl-2-propylidényl)-hydrazine. After the usual work-up there was collected 150.8 g. of N,N'-bis-(1-phenyl-2-propyl)-hydrazine at 127° (0.1 mm.), n_D^{20} 1.5458. *Anal.* Calcd. for $C_{15}H_{24}N_2$: N, 10.44. Found: N, 10.40.

1-Phenyl-2-propylhydrazine Hydrochloride.—Into a solution of 52.1 g. (0.35 mole) of the base dissolved in 50 cc.

of isopropyl alcohol and 520 cc. of diisopropyl ether was passed gaseous hydrochloric acid to pH 1. The resulting precipitate was collected by filtration and was recrystallized several times from 500-cc. portions of acetonitrile; yield 56.2 g. (86.6%), obtained, m.p. 124–125°. *Anal.* Calcd. for $C_9H_{13}N_2Cl$: Cl, 18.99; N, 15.01. Found: Cl, 19.00; N, 15.16.

Chemical Reduction.—A solution of 26.7 g. (0.20 mole) of aluminum chloride was prepared in 200 cc. of diglyme. To this solution was added 14.8 g. (0.10 mole) of phenylacetone hydrazone. While stirring at room temperature, a solution of 22.8 g. (0.60 mole) of sodium borohydride in 550 cc. of diglyme was added and stirring was continued for 2 hr. The borohydride was destroyed by addition of 100 cc. of concd. hydrochloric acid after which the reaction mixture was made strongly alkaline with potassium hydroxide. The solution was repeatedly extracted with ether and the combined extracts were dried with potassium carbonate, filtered and fractionated; 11.9 g. (89%) of N,N'-bis-(1-phenyl-2-propyl)-hydrazine was collected at 135° (0.03 mm.), n_D^{20} 1.5469. *Anal.* Calcd. for $C_{18}H_{24}N_2$: N, 10.44. Found: N, 10.06. Hydrochloride salt, m.p. 175–176°. *Anal.* Calcd. for $C_{18}H_{26}ClN_2$: Cl, 11.63. Found: Cl, 11.75.

Cleavage of 1-Phenyl-2-hydrazinopropane.—To a solution of 12.3 g. (0.082 mole) of 1-phenyl-2-hydrazinopropane in 200 cc. of alcohol was added 3 teaspoonfuls of alcohol-washed Raney nickel and the mixture was hydrogenated at 45° and a pressure of 60 p.s.i. till no more hydrogen was taken up. The catalyst was then filtered off and the alcohol was removed by distillation. The residue was fractionated through a 3'' column and 11.0 g. (99%) of 1-phenyl-2-propylamine was collected at 74° (8 mm.), n_D^{20} 1.5179. *Anal.* Calcd. for $C_9H_{13}N$: N, 10.36. Found: N, 10.15.

Hydrochloride.—Ethereal hydrochloric acid was added to a solution of 6.75 g. (0.05 mole) of the base in 175 cc. of dry ether. The white precipitate was filtered off, rinsed with dry ether and dried in a vacuum desiccator; yield 7.2 g. (84%), m.p. 152–154°. *Anal.* Calcd. for $C_9H_{14}ClN$: N, 8.16; Cl, 20.66. Found: N, 8.10; Cl, 20.79. A mixed m.p. with amphetamine hydrochloride showed no depression.

The Preparation of Aralkyl Hydrazides. (a) **N-(5-L-Glutamyl)-N'-(1-phenyl-2-propylidényl)-hydrazine.**—To 16.1 g. (0.10 mole) of 5-L-glutamic acid hydrazide dissolved in 200 cc. of water at 35° was added 13.4 g. (0.10 mole) of phenylacetone and the mixture stirred 3 hr. The white precipitate was collected by filtration, yield 20 g. (72%), m.p. 173°. *Anal.* Calcd. for $C_{14}H_{19}N_3O_2$: N, 15.15. Found: N, 14.90.

(b) **N-(5-L-Glutamyl)-N'-(1-phenyl-2-propyl)-hydrazine.**—An aqueous methanol solution containing 5.54 g. (0.020 mole) of the above hydrazone was subjected to hydrogenation at 60 lb. of hydrogen and in the presence of 750 mg. of platinum oxide. The catalyst was removed by filtration and the solvent by distillation. The residue was crystallized from ether; yield 4.75 g. (85%), m.p. 174–175°. *Anal.* Calcd. for $C_{14}H_{21}N_3O_2$: N, 15.05. Found: N, 15.35.

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