Acknowledgments.—The authors express their appreciation to Dr. L. M. Long for encouragement in this investigation, to Dr. A. J. Glazko and Mr. W. A. Dill for the biochemical studies, to Mr. W. Pearlman for carrying out the hydrogenations, and to Miss J. D. Multhaup, Mr. F. H. Tendick, and Miss E. A. Weinstein for synthesizing several of the compounds described herein. We also thank Dr. J. M. Vandenbelt and associates for the determination of the infrared and ultraviolet absorption spectra and Mr. C. E. Childs and associates for the microanalyses.

Synthesis and Biological Properties of Aminoalkylhydrazines. A Unique Nitrogen–Nitrogen Scission of 1-(2-Diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine

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Received January 8, 1964

Several 2-(3-aminopropyl)-1,1-dialkylhydrazines (IIIa–d, Table I) were prepared by reduction of the appropriate 3-(2,2-dialkylhydrazino)propionitriles (IIa–d) with lithium aluminum hydride. Treatment of various dialkylaminoalkyl chlorides with excess hydrazine gave the corresponding (dialkylaminoalkyl)hydrazines (IV, Table II) as the preponderant products; small amounts of the 1,1-bis(dialkylaminoalkyl)hydrazines (V, Table III) were isolated from high boiling fractions of the larger-scale runs. Condensation of IV, V, and 1,4-diaminopiperazine with various aldehydes and ketones gave the corresponding dialkylaminoalkylhydrazones (VI, VII, Tables IV, V), which were reduced with lithium aluminum hydride to the appropriate 1-(dialkylaminoalkyl)-2-(1-phenyl-2-propyl)hydrazines (VII, Table VI), 1-substituted-2-(2-diethylaminoethyl)hydrazines (Table VII), and 1,4-bis(phenylalkylamino)piperazines (IX, Table VIII). Upon acid treatment, 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine (X) undergoes a unique scission of the nitrogen–nitrogen bond to give amphetamine (XII) in good yield. Details of this novel reaction are discussed. A summary of the biological properties of the aminoalkylhydrazines is presented.

Interest in the synthesis of aminoalkylhydrazines was evidenced as early as 1925 when Sommer and coworkers[1] reported the synthesis of 1-hydrazino-2-aminoethane from ethylenediamine and hydroxylamine-O-sulfonic acid. In recent years research on related compounds has skyrocketed,[2–20] sparked in part by reports of the usefulness of isoniazid, nitrofurantoin, iproniazid, phenelzine, (1-phenyl-2-propyl)-hydrazine, and analogous materials in medicine. During the past decade we have prepared a variety of novel aminoalkylhydrazines for biological evaluation and for use as synthetic intermediates, many of which are the subject of this report.

The addition of acrylonitrile to 1,1-dimethylhydrazine (Ia) utilizing the procedure of Hinman and Rosene[21] gave 3-(2,2-dimethylhydrazino)propionitrile (IIa) as a colorless liquid, b.p. 54–55° (0.6 mm.), $n^{25}D$ 1.4387 (lit.[21] b.p. 80–90° (3 mm.), $n^{25}D$ 1.441), in yields from 53 to 56% in three runs. The addition of acrylonitrile to 1,1-diethylhydrazine (Ib), 1-amino-

$$\underset{\text{I}}{R_1R_2NNH_2} + CH_2{=}CHCN \longrightarrow \underset{\text{II}}{R_1R_2NNHCH_2CH_2CN} \xrightarrow{LiAlH_4} \underset{\text{III}}{R_1R_2NNH(CH_2)_3NH_2}$$

R_1R_2N = (a) $N(CH_3)_2$ (b) $N(C_2H_5)_2$ (c) $N(CH_2)_5$ (d) $N[(CH_2)_2]_2NCH_3$

piperidine (Ic), and 1-amino-4-methylpiperazine (Id) afforded 3-(2,2-diethylhydrazino)propionitrile (IIb), 3-(1-piperidinoamino)propionitrile (IIc), and 3-(4-methyl-1-piperazinylamino)propionitrile (IId), respectively. The hygroscopic nitriles were difficult to analyze and in most instances were not completely characterized, but following distillation were reduced to the corresponding amines III (**1–4**, Table I) with lithium aluminum hydride in anhydrous ether. Compound IId was characterized by formation of 3-(*p*-butoxyphenyl)-1-(2-cyanoethyl)-1-(4-methyl-1-piperazinyl)-2-thiourea upon heating with *p*-butoxyphenylisothiocyanate.

The condensation of hydrazine with alkyl halides usually gives a mixture of monoalkyl and asymmetric dialkylhydrazines.[22] With long chain alkyl chlorides,

(1) F. Sommer, O. F. Schulz, and M. Nassau, *Z. Anorg. Allgem. Chem.*, **147**, 142 (1925).
(2) J. G. Michels and G. Gever, *J. Am. Chem. Soc.*, **78**, 5349 (1956).
(3) L. H. Werner, D. C. Schroeder, and S. Ricca, Jr., *ibid.*, **79**, 1675 (1957).
(4) M. Carissimi, *Farmaco* (Pavia) *Ed. Sci.*, **13**, 817 (1958); *Chem. Abstr.*, **53**, 8154c (1959).
(5) J. H. Biel, W. K. Hoya, and H. A. Leiser, *J. Am. Chem. Soc.*, **81**, 2527 (1959).
(6) A. Ebnöther, E. Jucker, A. Lindenmann, E. Rissi, R. Steiner, R. Süess, and A. Vogel, *Helv. Chim. Acta*, **42**, 533 (1959).
(7) E. Jucker, *Angew. Chem.*, **71**, 321 (1959).
(8) A. Ebnöther, E. Jucker, E. Rissi, J. Rutschmann, E. Schreier, R. Steiner, R. Süess, and A. Vogel, *Helv. Chim. Acta*, **42**, 918 (1959).
(9) A. Ebnöther, E. Jucker, and A. Lindenmann, *ibid.*, **42**, 1201 (1959).
(10) W. Schuler and E. Wyss, *Arch. Intern. Pharmacodyn.*, **128**, 431 (1960).
(11) J. H. Biel, A. E. Drukker, and T. F. Mitchell, Jr., *J. Am. Chem. Soc.*, **82**, 2204 (1960).
(12) V. R. Gaertner, U. S. Patent 2,965,536 (Dec. 20, 1960).
(13) H. Klös and H. A. Offe, German Patent 1,095,841 (Dec. 29, 1960).
(14) D. B. McCormick and E. E. Snell, *J. Biol. Chem.*, **236**, 2085 (1961).
(15) G. N. Walker, M. A. Moore, and B. N. Weaver, *J. Org. Chem.*, **26**, 2740 (1961).
(16) K. Eiter and E. Truscheit, German Patent 1,108,233 (June 8, 1961).
(17) J. H. Biel, P. A. Nuhfer, A. E. Drukker, T. F. Mitchell, A. C. Conway, and A. Horita, *J. Org. Chem.*, **26**, 3338 (1961).
(18) D. J. Drain, J. G. B. Howes, R. Lazare, A. M. Salaman, R. Shadbolt, and H. W. R. Williams, *J. Med. Chem.*, **6**, 63 (1963).
(19) J. Finkelstein, J. A. Romano, E. Chiang, and J. Lee, *ibid.*, **6**, 153 (1963).
(20) J. E. Robertson, J. H. Biel, and F. DiPierro, *ibid.*, **6**, 381 (1963).
(21) R. L. Hinman and J. Rosene, *J. Org. Chem.*, **21**, 1539 (1956).
(22) C. C. Clark, "Hydrazine," Mathieson Chemical Corp., Baltimore, Md., 1953, p. 30.

Table I

2-(3-Aminopropyl)-1,1-dialkylhydrazines (III)[a] $R_1R_2NNH(CH_2)_3NH_2$

Compd. no.	NR_1R_2	B.p., °C. (mm.)	$n^{25}D$	Yield purified, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$N(CH_3)_2$	159–160 (737)	1.4448	59	$C_5H_{15}N_3$	51.24	51.01	12.90	13.15	35.86	35.50
2	$N(C_2H_5)_2$	60–61 (2.3)	1.4549	60	$C_7H_{19}N_3$	57.88	57.09	13.18	13.15	28.93	28.25
3	$N(CH_2)_5$	61–62 (0.6)	1.4845	48	$C_8H_{19}N_3$	61.10	60.71	12.18	11.93	26.72	26.26
4	$N[(CH_2)_2]_2NCH_3$	73–74 (0.5)	1.4908	64	$C_8H_{20}N_4$	55.77	55.82	11.70	11.71	32.52	32.47

[a] Compounds are hygroscopic colorless liquids.

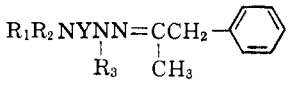
a large excess (5 moles) of hydrazine and comparatively low temperatures (100–120°) favor the formation of monoalkylhydrazines, while a smaller excess of hydrazine (2 moles) and higher temperatures (160–170°) give more of the unsymmetrical dialkylhydrazine.[22] The ready availability of a variety of dialkylaminoalkyl halides prompted us to investigate the preparation of (dialkylaminoalkyl)hydrazines from these halides and hydrazine or methylhydrazine.

Heating various dialkylaminoalkyl chlorides with a 3–4 mole excess of aqueous hydrazine in the presence of potassium carbonate at 100° gave the corresponding (dialkylaminoalkyl)hydrazines (IV, Table II) as the preponderant product. Yields ranged from 24 to 59%. Small amounts (6–21%) of the 1,1-bis(dialkylamino-

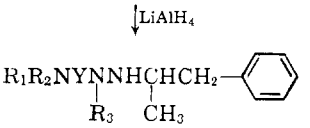
$$R_1R_2NYCl\cdot HCl \xrightarrow{H_2NNH_2} \underset{IV}{R_1R_2NYNHNH_2} + \underset{V}{(R_1R_2NY)_2NNH_2}$$

alkyl)hydrazines (V, Table III) were isolated from high boiling fractions of the larger scale runs. The condensation of 2-chlorotriethylamine with methylhydrazine gave 1-(2-diethylaminoethyl)-1-methylhydrazine in 74% yield. Subsequent to the initiation of our work, the synthesis of (2-dimethylaminoethyl)hydrazine, (2-diethylaminoethyl)hydrazine, and 1,1-bis(2-diethylaminoethyl)hydrazine by similar procedures has been reported independently.[5,6,13]

The (dialkylaminoalkyl)hydrazines (IV) and 1,1-bis(dialkylaminoalkyl)hydrazines (V) were allowed to react with phenylacetone in benzene or toluene to give the corresponding phenyl-2-propanone dialkylaminoalkylhydrazones (VI, Table IV). Similarly, various 1,4-bis(phenylalkylideneamino)piperazines (VII) were



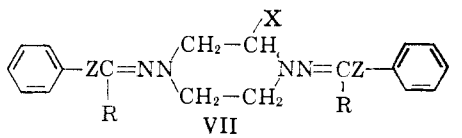
VI



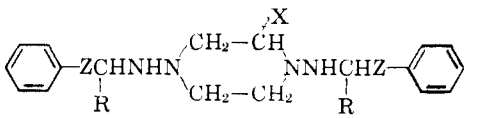
VIII

R_1R_2 = alkyl; Y = alkylene
R_3 = H, CH_3, or YNR_1R_2

prepared by the condensation of benzaldehyde, phenylacetaldehyde, or phenylacetone with 1,4-diaminopiperazine and 1,4-diamino-2-methylpiperazine, and a group of (2-diethylaminoethyl)hydrazones (Table V) was prepared from 2-diethylaminoethylhydrazine and cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, cyclopropyl ketone, benzophenone, 3,4-



VII



IX

Z = — or —CH_2—;
R, X = H or CH_3

dihydro-1(2H)naphthalenone, 3,4-dihydro-2(1H)naphthalenone, 1-methyl-4-piperidone, and 4-pyridinecaldehyde. Quaternization of 1-methyl-4-(1-phenyl-2-propylideneamino)piperazine (**20**) with methyl iodide gave the corresponding methiodide.

Reduction of the phenyl-2-propanone dialkylamino-alkylhydrazones (VI, Table IV), 1,4-bis(phenylalkylidene amino)piperazines (VII), and (2-diethylaminoethyl)-hydrazones (Table V) with lithium aluminum hydride in ether proceeded normally in most instances to give the corresponding 1-(dialkylaminoalkyl)-2-(1-phenyl-2-propyl)hydrazines (VIII, Table VI), 1,4-bis-(phenylalkylamino)piperazines (IX, Table VIII), and 1-substituted 2-(2-diethylaminoethyl)hydrazines (Table VII), respectively. However, attempts to reduce 3,4-dihydro-2(1H)naphthalenone (2-diethylaminoethyl)hydrazone (**36**) and benzophenone (2-diethylaminoethyl)hydrazone (**37**) under similar conditions failed to give products of analytical purity. Although asymmetric carbon atoms were present in several of the aminoalkylhydrazines, no attempt was made to separate the stereoisomers.

A majority of the aminoalkylhydrazines were isolated as colorless or pale yellow liquids and were purified by vacuum distillation. Attempts to demonstrate the homogeneity of several of them utilizing vapor phase chromatography techniques were thwarted by the thermal lability of the compounds. For example, the chromatogram of 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine (X, **41**)[23] exhibited three major and four minor peaks. Further evidence of decomposition was obtained in independent runs.[24,25] In order to demonstrate conclusively that

(23) Compound was run on a Barber Coleman Model 20 instrument using a 185 cm. column packed with 5% SE-30; temperature: injection port 300°, column 150° isothermal.

(24) Compound was run on a Research Specialties Inc. Model 600 G. C. instrument using a 185 cm. glass column packed with 80–100 mesh Gaschrom P coated with ECNSS-M (silanized); temperature: injection port 120°, column 108° isothermal.

(25) Compound was run on an F and M Model 500 instrument using a 123 cm. stainless steel column packed with a mixture of 20% Apiezon L and 2% SE-30 on 60–80 mesh Chromosorb P; temperature: injection port 300°, column 175° isothermal.

TABLE II

(DIALKYLAMINOALKYL)HYDRAZINES (IV)[a] $R_1R_2NYNNH_2$ (with R_3 on N)

Compd. no.	NR_1R_2	Y	R_3	B.p., °C. (mm.)	$n^{25}D$	Yield purified, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
5	$N(CH_3)_2$	$-(CH_2)_2-$	H	71–72 (18)	1.4559	44	$C_4H_{13}N_3$[b]	46.57	46.81	12.70	12.88	40.73	40.47
6	$N(CH_3)_2$	$-(CH_2)_3-$	H	88–89 (15)	1.4590	58	$C_5H_{15}N_3$	51.24	51.39	12.90	13.03	35.86	35.60
7	$N(CH_3)_2$	$-CH_2CH(CH_3)CH_2-$	H	77–78 (16)	1.4554	40	$C_6H_{17}N_3$	54.92	54.81	13.06	13.02	32.02	31.71
8	$N(CH_3)CH(CH_3)_2$	$-(CH_2)_2-$	H	92–93 (17)	1.4582	47	$C_6H_{17}N_3$	54.92	55.24	13.06	13.38		
9	$N(C_2H_5)_2$	$-(CH_2)_2-$	H	76–77 (7)	1.4574	59	$C_6H_{17}N_3$[c]	54.92	55.02	13.06	12.99	32.02	32.81
10	$N(CH_2)_4$	$-(CH_2)_3-$	H	127–128 (21)	1.4877	44	$C_7H_{17}N_3$	58.70	59.10	11.97	12.23		
11	$N(C_2H_5)_2$	$-(CH_2)_2-$	CH_3	77–78 (15)	1.4495	74	$C_7H_{19}N_3$	57.88	57.43	13.18	13.42	28.93	28.95
12	$N(C_2H_5)_2$	$-(CH_2)_3-$	H	106–107 (18)	1.4606	48	$C_7H_{19}N_3$	57.88	58.12	13.18	13.33	28.93	28.47
13	$N(CH_3)(CH_2)_3CH_3$	$-(CH_2)_2-$	H	105–107 (18)	1.4515	24	$C_7H_{19}N_3$	57.88	57.90	13.18	13.24		
14	$N(CH_2)_5$	$-(CH_2)_3-$	H	133–135 (20)	1.4899	47	$C_8H_{19}N_3$	61.10	61.17	12.18	12.30	26.72	26.32

[a] Compounds are hygroscopic colorless liquids. [b] Reported previously by J. H. Biel, W. K. Hoya, and H. A. Leiser, *J. Am. Chem. Soc.*, **81**, 2527 (1959). [c] Reported previously by A. Ebnöther, E. Jucker, A. Lindenmann, E. Rissi, R. Steiner, R. Süess, and A. Vogel, *Helv. Chim. Acta*, **42**, 533 (1959).

TABLE III

1,1-BIS(DIALKYLAMINOALKYL)HYDRAZINES (V)[a] $(R_1R_2NY)_2NNH_2$

Compd. no.	NR_1R_2	Y	B.p., °C. (mm.)	$n^{25}D$	Yield purified, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
15	$N(CH_3)_2$	$-(CH_2)_3-$	78–79 (0.3)	1.4596	20	$C_{10}H_{26}N_4$	59.36	59.40	12.95	12.91	27.69	27.92
16	$N(CH_3)_2$	$-CH_2CH(CH_3)CH_2-$	58–59 (0.05)	1.4526	10	$C_{12}H_{30}N_4$	62.55	62.56	13.13	13.04	24.32	23.55
17	$N(C_2H_5)_2$	$-(CH_2)_2-$	69–70 (0.1)	1.4597	6	$C_{12}H_{30}N_4$[b]	62.55	62.74	13.13	13.15	24.32	24.58
18	$N(CH_3)(CH_2)_3CH_3$	$-(CH_2)_2-$	82–84 (0.05)	1.4581	21	$C_{14}H_{34}N_4$	65.06	65.20	13.26	13.29	21.68	21.70
19	$N(CH_2)_5$	$-(CH_2)_3-$	143–144 (0.1)	1.4952	13	$C_{16}H_{34}N_4$	68.03	68.48	12.13	12.08	19.84	19.48

[a] Compounds are hygroscopic colorless liquids. [b] Reported previously by H. Klös and H. A. Offe, German Patent 1,095,841 (Dec. 29, 1960).

TABLE IV

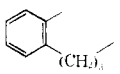
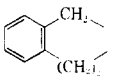
PHENYL-2-PROPANONE DIALKYLAMINOALKYLHYDRAZONES $R_1R_2N—Y—NN=CCH_2—C_6H_5$ (R$_3$, CH$_3$)

Compd. no.	$R_1R_2N—Y—NR_3—$	B.p., °C. (mm.)	$n^{25}D$	Yield purified, %	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
20	$CH_3N[(CH_2)_2]_2N—$	96–97 (0.1)	1.5340	78	$C_{14}H_{24}N_2$	72.68	72.39	9.15	9.11	18.16	18.25
21	$(CH_3)_2N(CH_2)_3NH—$	103–106 (0.05)	1.5220	93	$C_{14}H_{26}N_2$	72.05	71.87	9.93	9.97	18.01	18.20
22	$(CH_3)_2NCH_2CHCH_3CH_2NH—$	104–105 (0.1)	1.5160	56	$C_{15}H_{28}N_2$	72.83	72.75	10.19	10.58	16.99	16.84
23	$(C_2H_5)_2N(CH_2)_2NH—$	95–97 (0.05)	1.5140	93	$C_{15}H_{28}N_2$	72.83	72.90	10.19	10.41	16.99	16.79
24	$(C_2H_5)_2N(CH_2)_3NH—$	131–133 (1.0)	1.5161	95	$C_{16}H_{27}N_2$	73.51	73.82	10.41	10.78	16.07	16.46
25	$[(C_2H_5)_2N(CH_2)_2NCH_3—$	90–91 (0.05)	1.5042	69	$C_{16}H_{27}N_2$	73.51	73.47	10.41	10.41	16.07	16.38
26	$(CH_2)_5N(CH_2)_3NH—$	129–130 (0.5)	1.5346	85	$C_{17}H_{27}N_2$	74.67	73.93	9.96	9.94	15.37	15.38
27	$[(CH_3)_2N(CH_2)_3]_2N—$	149–150 (0.7)	1.5070	33	$C_{19}H_{34}N_4$	71.65	71.30	10.76	10.32	17.59	17.78
28	$[(C_2H_5)_2N(CH_2)_2]_2N—$	129–131 (0.7)	1.5032	55	$C_{21}H_{38}N_4$	72.78	73.12	11.05	10.82	16.17	16.14

[a] Compounds are yellow liquids.

TABLE V

MISCELLANEOUS KETONE (2-DIETHYLAMINOETHYL)HYDRAZONES[a] $XYC=NNH(CH_2)_2N(C_2H_5)_2$

Compd. no.	X, Y	B.p., °C. (mm.)	$n^{25}D$	Yield purified, %	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
29	—$(CH_2)_4$—	66–67 (0.15)	1.4810	79	$C_{11}H_{23}N_3$	66.96	67.15	11.75	12.02	21.30	21.58
30	—$(CH_2)_5$—	69–70 (0.03)	1.4860	86	$C_{12}H_{25}N_3$	68.19	68.25	11.92	11.52	19.88	19.51
31	—$(CH_2)_2NCH_3(CH_2)_2$—	83–84 (0.3)	1.4897	81	$C_{12}H_{26}N_4$	63.67	63.75	11.58	11.74	24.75	24.71
32	$\left(\begin{array}{c}—CH—CH_2\\ \diagdown\ \diagup\\ CH_2\end{array}\right)_2$	76–77 (0.05)	1.4873	43	$C_{13}H_{25}N_3$	69.90	69.54	11.28	11.40	18.81	18.51
33	—$(CH_2)_6$—	78–79 (0.05)	1.4880	70	$C_{13}H_{27}N_3$	69.28	69.09	12.08	12.19	18.64	18.50
34	—$(CH_2)_5$—[b]	98–100 (0.1)	1.4912	72	$C_{14}H_{29}N_3$	70.24	70.44	12.21	12.22	17.55	17.69
35		128–129 (0.03)	1.5614	70	$C_{16}H_{25}N_3$	74.08	73.80	9.72	9.91	16.20	15.98
36		142–143 (0.1)	1.5455	65	$C_{18}H_{25}N_3$	74.08	73.69	9.72	9.53	16.20	16.05
37	$(—C_6H_5)_2$[b]	162–163 (0.8)	1.5786	86	$C_{15}H_{25}N_3$	77.24	77.14	8.53	8.53	14.22	14.22

[a] Compounds are yellow liquids. [b] *p*-Toluenesulfonic acid (1 g.) was added to the reaction mixture.

TABLE VI

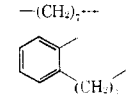
1-(DIALKYLAMINOALKYL)-2-(1-PHENYL-2-PROPYL)HYDRAZINES VIII[a] $R_1R_2N—Y—NNHCHCH_2—C_6H_5$ (R_3, CH_3)

Compd. no.	$R_1R_2N—Y—NR_3—$	B.p., °C. (mm.)	$n^{25}D$	Yield purified, %	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
38	$CH_3N[(CH_2)_2]_2N—$	87–88 (0.1)	1.5158	93	$C_{14}H_{24}N_2$[b]	72.06	71.33	9.93	9.90	18.01	17.90
39	$(CH_3)_2N(CH_2)_3NH—$	101–103 (0.1)	1.5073	48	$C_{14}H_{26}N_2$	71.44	71.55	10.71	10.60	17.85	17.71
40	$(CH_3)_2NCH_2CHCH_3CH_2NH—$	98–99 (0.1)	1.4995	50	$C_{15}H_{28}N_2$	72.24	71.50	10.91	10.46	16.85	16.86
41	$(C_2H_5)_2N(CH_2)_2NH—$	92–93 (0.05)	1.5017	53	$C_{15}H_{28}N_2$	72.24	72.05	10.91	11.29	16.85	16.99
42	$(C_2H_5)_2N(CH_2)_3NH—$	110–111 (0.1)	1.5043	72	$C_{16}H_{29}N_3$	72.95	73.16	11.10	11.01	15.95	15.65
43	$(C_2H_5)_2N(CH_2)_2NCH_3—$	105–106 (0.8)	1.4940	59	$C_{16}H_{29}N_3$	72.95	72.41	11.10	10.70	15.95	15.92
44	$(CH_2)_5N(CH_2)_3NH—$	153–155 (1.0)	1.5207	70	$C_{17}H_{29}N_3$	74.13	74.28	10.61	10.61	15.26	15.33
45	$[(C_2H_5)_2N(CH_2)_2]_2N—$	121–124 (0.2)	1.5012	21	$C_{24}H_{46}N_4$	72.36	73.09	11.57	11.62	16.07	15.67

[a] Compounds are colorless or pale yellow. [b] Dihydrochloride, colorless crystals from ethanol–2-propanol, m.p. 252–254° dec.; *Anal.* Calcd. for $C_{14}H_{24}N_2 \cdot 2HCl$: C, 54.90; H, 8.23; N, 13.72; Cl, 23.15. Found: C, 55.11; H, 8.29; N, 13.61; Cl, 23.13.

TABLE VII

MISCELLANEOUS 1-SUBSTITUTED 2-(2-DIETHYLAMINOETHYL)HYDRAZINES[a] $XYCHNHNH(CH_2)_2N(C_2H_5)_2$

Compd. no.	X, Y	B.p., °C. (mm.)	$n^{25}D$	Yield purified, %	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
46	—$(CH_2)_4$—	57–58 (0.03)	1.4686	95	$C_{11}H_{25}N_3$	66.28	66.22	12.64	12.79	21.08	21.13
47	—$(CH_2)_5$—	64–65 (0.03)	1.4700	73	$C_{12}H_{27}N_3$	67.55	67.74	12.76	12.67	19.69	19.59
48	—$(CH_2)_2NCH_3(CH_2)_2$—	79–81 (0.05)	1.4761	97	$C_{12}H_{28}N_4$	63.11	63.00	12.36	12.31	24.53	24.81
49	$\left[\begin{array}{c}—CH—CH_2\\ \diagdown\ \diagup\\ CH_2\end{array}\right]_2$	79–80 (0.1)	1.4717	62	$C_{13}H_{27}N_3$	69.28	68.99	12.08	12.10	18.64	18.43
50	—$(CH_2)_6$—	82–83 (0.03)	1.4762	82	$C_{13}H_{29}N_3$	68.67	69.01	12.86	12.83	18.48	18.69
51	—$(CH_2)_7$—	93–94 (0.05)	1.4810	39	$C_{14}H_{31}N_3$	69.65	69.20	12.94	12.62	17.41	17.44
52		129–132 (0.03)	1.5370	38	$C_{16}H_{27}N_3$	73.51	73.53	10.41	10.08	16.07	15.90

[a] Compounds are colorless or pale yellow.

decomposition had occurred, the main peak was trapped[25] and rechromatographed.[25] The infrared spectrum of the trapped material proved to be identical with the spectrum of the starting material, and a gas chromatogram of the trapped material exhibited a similar complex pattern. When lower temperatures were used, less but significant decomposition occurred. Gas chromatograms of 2-diethylaminoethylhydrazine (**9**) and 1-(3-diethylaminopropyl)-2-(1-phenyl-2-propyl)hydrazine (**42**) also exhibited complex patterns indicative of extensive decomposition.[26]

In most instances pharmacological studies were carried out with the aminoalkylhydrazine free bases. Following preliminary reports that 1,4-bis[1-phenyl-2-propylamino]piperazine (**55**) and 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine (X) exhibited interesting pharmacological properties, efforts were made to prepare solid, water-soluble salts of these bases. Although 1,4-bis[1-phenyl-2-propylamino]piperazine formed stable, solid acid addition salts, numerous attempts to prepare salts of X with a variety of organic and inorganic acids gave only sticky semisolids. However, when hot acetone solutions containing hydrazine X and succinic acid were combined, a colorless crystalline solid, m.p. 155–157°, separated in low yield. Successive crystallizations from acetone and acetonitrile raised the melting point to 162–163°. Surprisingly, the salt did not analyze correctly for a succinate salt of 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine (X), but microanalytical results were in excellent agreement with calculated values for amphetamine succinate. Indeed, the salt was shown to be identical with an authentic sample of *dl*-amphetamine succinate by comparison of their infrared absorption spectra, melting points, and mixture melting points. Obviously, a unique scission of the nitrogen–nitrogen bond had occurred.

Subsequently, X was converted to *dl*-amphetamine (XII) in 78% yield upon heating with 1 *N* hydrochloric

$$\underset{\text{X}}{(C_2H_5)_2N(CH_2)_2NHNHCH(CH_3)CH_2C_6H_5} \longrightarrow \underset{\text{XI}}{(C_2H_5)_2N(CH_2)_2NH_2} + \underset{\text{XII}}{H_2NCH(CH_3)CH_2C_6H_5}$$

acid for 15 hr. 2-Diethylaminoethylamine (XI) was also isolated from the reaction mixture, although the recovery was poor. In contrast, 1-alkyl- or 1-aralkyl-2-(1-phenyl-2-propyl)hydrazine salts,[27,28] 1-methyl-4-(1-phenyl-2-propylamino)piperazine (**38**), and 1,4-bis-[1-phenyl-2-propylamino]piperazine (**55**) are stable in an acid environment. These findings, together with the observation that X is stable when boiled with sodium hydroxide in aqueous methanol (see Experimental section), suggest that the cleavage reaction is dependent on the proximity of the protonated tertiary amine to the hydrazine function, and possibly is associated with the formation of a cyclic intermediate. To our knowledge, this is the first published report of an acid-induced scission of the nitrogen–nitrogen bond of a symmetrical dialkylhydrazine compound,

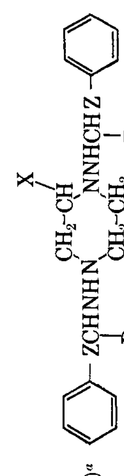
(26) Same conditions as footnote 23, except column was packed with 5% XE-60.

(27) J. Biel, U. S. Patent 3,000,903 (Sept. 19, 1961).

(28) Lakeside Laboratories, British Patent 863,158 (March 15, 1961).

TABLE VIII

1,4-BIS(PHENYLALKYLAMINO)PIPERAZINES (IX)[a]



Compd. no.	Z	R	X	M.p. or b.p. (mm.), °C.	Procedure	Yield purified, %	Purification[b] solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
53	...	H	H	113–115	I	60[c]	A	$C_{18}H_{24}N_4$	72.94	73.27	8.16	8.16	18.90	19.17
54	—CH_2—	H	H	116–120	II	18[d]	B	$C_{20}H_{28}N_4$	74.03	74.14	8.70	8.64	17.27	17.46
55	—CH_2—	CH_3	H	186–188 (0.5[e])	I	83[c]		$C_{22}H_{32}N_4$	74.95	75.06	9.15	9.05	15.89	15.92
56	—CH_2—	CH_3	H	255 dec.	I	83[j]	C	$C_{22}H_{32}N_4 \cdot H_2SO_4 \cdot 1.25H_2O$[f]	55.85	55.80	7.78	7.66		
57	—CH_2—	CH_3	H	197–201	I	88[j]	D	$C_{22}H_{32}N_4 \cdot 1.9H_3PO_4 \cdot 0.7H_2O$[g]	47.93	48.10	7.15	7.03	10.16	10.00
58	—CH_2—	CH_3	CH_3	176–178 (0.1[h])	II	25[d]		$C_{23}H_{34}N_4$[i]	75.36	75.68	9.35	9.25	15.29	15.16

[a] Compounds are colorless or pale yellow. [b] A, ethanol; B, 2-propanol; C, dimethyl sulfoxide-water; D, not recrystallized. [c] Yield based on alkylidene intermediate. [d] Yield over-all. [e] $n^{25}D$ 1.5432. [f] *Anal.* Calcd.: S, 6.78. Found: S, 6.76. [g] *Anal.* Calcd.: P, 10.67. Found: P, 10.70. [h] $n^{25}D$ 1.5403. [i] Dihydrochloride from 2-propanol–water, m.p. 230–234° dec. *Anal.* Calcd. for $C_{23}H_{34}N_4 \cdot 2HCl$: C, 62.86; H, 8.26; N, 12.75; Cl, 16.14. Found: C, 62.28; H, 8.35; N, 12.96; Cl, 15.94. [j] Yield starting from free base.

although disproportionation[29] and hydrolytic cleavage[30] reactions of several arylhydrazines have been reported. Extensive investigations are currently in progress in these laboratories to define further the scope, structural requirements, experimental conditions, and mechanism of this scission reaction. Results of these studies will be the subject of future communications.

Summary of Biological Properties.—The aminoalkylhydrazines were evaluated in a variety of biological systems. Their ability to inhibit monoamine oxidase *in vitro* was measured[31] by the manometric method of Davison[32] using guinea pig brain homogenate as an enzyme source. Tyramine was used as a substrate at a concentration of 5×10^{-3} *M*. Potential inhibitors were preincubated with the enzyme for 10 min. before the addition of the substrate. Although none of the aminoalkylhydrazines is a highly potent inhibitor of monoamine oxidase *in vitro*, compounds **7**, **25**, **35**, **40**, and **41** gave 50% inhibition at the following concentrations: 4.9×10^{-4} *M*, 3.0×10^{-4} *M*, 4.4×10^{-4} *M*, 6.0×10^{-4} *M*, and 4.0×10^{-4} *M*. Under comparable conditions iproniazid afforded 50% inhibition at a concentration of 1.9×10^{-4} *M*.

Representative compounds were tested for their antidepressant effect in mice receiving reserpine according to the procedure described earlier by Chen and Bohner.[33,34] Briefly, the degree of antagonism against reserpine-induced ptosis (closure of eyelids) was utilized as an index of the antidepressant activity of a compound. The aminoalkylhydrazines were given by intraperitoneal injection 1 hr. before reserpine and the observation of ptosis was made 3 hr. after reserpine administration. Compounds **32**, **39**, **40**, **41**, **42**, and **55**, which represent the most promising members of the series, induced complete antagonism of reserpine-induced ptosis in mice at doses ranging from 63–125 mg./kg.

The direct cerebral stimulating effect of 1,4-bis[1-phenyl-2-propylamino]piperazine (**55**) was measured by observing the increase in motor activity of rats in "jiggle cages" following subcutaneous administration of the drug.[35,36] This compound exhibited a strong direct stimulating action of long duration at a dose of 12.5 mg./kg.

In a study of the inhibitory potencies of certain carbonyl reagents, and their condensation products with pyridoxal, for pyridoxal kinases of beef brain,[14] compounds **7**, **9**, **14**, or **17** were added at 5 μM to an assay mixture containing 0.5 m*M* pyridoxal and ATP, 0.01 m*M* Zn^{++}, 70 m*M* potassium phosphate, and 0.40 mg. of brain kinase. Each hydrazine formed a potent inhibitor with pyridoxal. The results reflect both the ability of the hydrazine to form a hydrazone with pyridoxal under the assay conditions, and the inhibitory effect of the hydrazone formed.

Many of the aminoalkylhydrazines were also tested against various parasites, bacteria, and viruses including *Entamoeba histolytica*, *Trichomonas vaginalis*, *Trypanosoma cruzi*, *Schistosoma mansoni*, *Syphacia obvelata*, *Aspiculuris tetraptera*, *Nematospiroides dubius*, *Hymenolepis nana*, *Streptococcus pyogenes* (C-203), *Staphylococcus aureus* (UC-76), *Klebsiella pneumoniae* (AD), *Proteus vulgaris* (MGH-1), *Pseudomonas aeruginosa* (No. 28), *Salmonella typhimurium* (V-31), *Mycobacterium tuberculosis* (H37Rv), herpes simplex, polio, measles, and adenovirus.[37–39] Only four compounds exhibited noteworthy activity. 1,1-Bis(3-dimethylaminopropyl)hydrazine (**15**) was active against *Syphacia obvelata* at high dose levels[37]; 2-(3-aminopropyl)-1,1-diethylhydrazine (**2**), 1-(3-aminopropylamino)-4-methylpiperazine (**4**), and 4-[2-(2-diethylaminoethyl)hydrazinomethyl]pyridine were lethal to *Mycobacterium tuberculosis* (H37Rv) *in vitro* at concentrations of 10 to 20 γ/ml., but none was promising in mice.[38]

Experimental[40]

Preparation of 3-(2,2-Dialkylhydrazino)propionitriles (II).—Acrylonitrile (278 g., 5.2 moles) was added dropwise with stirring over a period of 45 min. to a hot solution of 403 g. (3.5 moles) of 1-amino-4-methylpiperazine in 158 ml. of water. Subsequently, the mixture was stirred and heated on a steam bath for 20 hr. and the volatile materials were removed *in vacuo* on a water aspirator. The residue was distilled twice *in vacuo* through a 25-cm. Vigreux column to give 3-(4-methyl-1-piperazinylamino)-propionitrile (IId) as a colorless liquid, b.p. 74–75° (0.2 mm.), $n^{25}D$ 1.4820, 432 g. (73% yield). The hygroscopic base was difficult to analyze. Therefore, a small sample of the base was dissolved in anhydrous ether and treated with anhydrous hydrogen chloride. The off-white dihydrochloride salt was crystallized from ethanol and dried *in vacuo* at 45°; m.p., 202–204° dec.

Anal. Calcd. for $C_8H_{16}N_4 \cdot 2HCl$: N, 23.20; Cl, 29.40. Found: N, 22.69; Cl, 29.80.

3-(*p*-Butoxyphenyl)-1-(2-cyanoethyl)-1-(4-methyl-1-piperazinyl)-2-thiourea.—A mixture of 8.4 g. (0.05 mole) of 3-(4-methyl-1-piperazinylamino)propionitrile and 10.4 g. (0.05 mole) of *p*-butoxyphenylisothiocyanate was heated on a steam bath for 0.5 hr. Upon cooling, the material solidified and was crystallized from ethanol to give 18.0 g. (96%) of off-white crystals, m.p. 114–116°.

Anal. Calcd. for $C_{19}H_{29}N_5OS$: C, 60.77; H, 7.78; N, 18.65. Found: C, 60.79; H, 7.69; N, 18.70.

Preparation of 2-(3-Aminopropyl)-1,1-dialkylhydrazines (III) (Table I).—To a suspension of 135 g. (3.5 moles) of lithium aluminum hydride in 5 l. of anhydrous ether was added dropwise with stirring a solution of 292 g. (1.74 moles) of 3-(4-methyl-1-piperazinylamino)propionitrile in 3 l. of anhydrous ether. The mixture was stirred at room temperature for 24 hr., then refluxed on a steam bath for 6 hr. The hydride mixture was cautiously decomposed,[41] filtered, and the ether filtrate dried over anhydrous sodium sulfate. The drying agent was collected, the ether was removed, and the residue distilled *in vacuo* through a 25 cm. Vigreux column. The desired 1-(3-aminopropylamino)-4-methylpiperazine was obtained as a colorless hygroscopic liquid, b.p. 73–74° (0.5 mm.), $n^{25}D$ 1.4908, 193 g. (64%).

Preparation of (Dialkylaminoalkyl)hydrazines (IV) and 1,1-Bis(dialkylaminoalkyl)hydrazines (V) (Tables II and III).—To a mixture of 800 g. (13.5 moles) of 85% technical hydrazine

(29) F. D. Chattaway and M. Aldridge, *J. Chem. Soc.*, **99**, 404 (1911).
(30) H. Wieland and C. Müller, *Ber.*, **46**, 3304 (1913).
(31) J. R. McLean, unpublished results, Parke, Davis and Co., Ann Arbor, Mich.
(32) A. N. Davison, *Biochem. J.*, **67**, 316 (1959).
(33) G. Chen and B. Bohner, *J. Pharmacol. Exptl. Therap.*, **131**, 179 (1961).
(34) G. Chen, unpublished results, Parke, Davis and Co., Ann Arbor, Mich.
(35) For a description of test method, see J. W. Schulte, E. C. Reif, J. A. Bocher, W. S. Lawrence, and M. L. Tainter, *J. Pharmacol. Exptl. Therap.*, **71**, 62 (1941).
(36) G. Chen and C. Ensor, unpublished results, Parke, Davis and Co., Ann Arbor, Mich.
(37) P. E. Thompson, A. Bayles, P. McClay, and J. E. Meisenhelder, unpublished results, Parke, Davis and Co., Ann Arbor, Mich.
(38) M. W. Fisher and A. L. Erlandson, unpublished results, Parke, Davis and Co., Detroit, Mich.
(39) G. J. Dixon and F. Schabel, unpublished results, Southern Research Institute, Birmingham, Ala.
(40) Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus.
(41) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

monohydrate[42] and 800 ml. of water was slowly added at room temperature over a period of 2 hr. with vigorous mechanical stirring 688 g. (4.0 moles) of 2-chlorotriethylamine hydrochloride.[43] Initially, the reaction was very exothermic. After the addition was complete, 280 g. of anhydrous potassium carbonate was added and the mixture was stirred and boiled under reflux for 7 hr. Upon cooling, the reaction mixture was made strongly alkaline by the cautious portionwise addition of 1500 g. of solid sodium hydroxide. The mixture was extracted with two 2-l. portions of ether and the combined ether extracts were dried over solid potassium hydroxide. The ether was removed on a steam bath and the residue distilled (water aspirator) through a 30 cm. Vigreux column. The desired (2-diethylaminoethyl)-hydrazine was obtained as a colorless liquid, b.p. 76–77° (7 mm.), $n^{25}D$ 1.4574; yield, 308 g. (59%). Distillation of the residue under high vacuum gave 28 g. (6%) of 1,1-bis(2-diethylaminoethyl)hydrazine as a colorless liquid, b.p. 69–70° (0.1 mm.), $n^{25}D$ 1.4597.

Preparation of Phenyl-2-propanone Dialkylaminoalkylhydrazones (VI, Table IV) and Miscellaneous Ketone (2-Diethylaminoethyl)hydrazones (Table V).—A mixture of 201 g. (1.5 moles) of phenylacetone, 196 g. (1.5 moles) of (2-diethylaminoethyl)hydrazine, and 1.5 l. of anhydrous benzene was boiled under reflux for 4 hr. The water formed was removed through a Dean–Stark water separator. The benzene was removed and the residue distilled *in vacuo* through a 22 cm. Vigreux column. Phenyl-2-propanone 2-diethylaminoethylhydrazone was obtained as a yellow liquid, b.p. 95–97° (0.05 mm.), $n^{25}D$ 1.5140; yield, 345 g. (93%).

Preparation of 1-(Dialkylaminoalkyl)-2-(1-phenyl-2-propyl)-hydrazines (VIII, Table VI) and Miscellaneous 1-Substituted 2-(2-Diethylaminoethyl)hydrazines (Table VII).—A solution of 124 g. (0.50 mole) of phenyl-2-propanone 2-diethylaminoethylhydrazone in 2 l. of anhydrous ether was added dropwise over a period of 2 hr. to a slurry of 38 g. (1.0 mole) of lithium aluminum hydride in 1.5 l. of anhydrous ether. The mixture was boiled under reflux with vigorous stirring for 8 hr., cooled, and decomposed by the cautious addition of 40 ml. of water followed by 30 ml. of 20% aqueous sodium hydroxide and 140 ml. of water.[41] The precipitate was removed by filtration and discarded; the ether filtrate was concentrated to an oil. The crude 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine was distilled twice through a 22 cm. Vigreux column under high vacuum giving a colorless liquid, b.p. 92–93° (0.05 mm.), $n^{25}D$ 1.5017, 66 g. (53% yield).

1-Methyl-4-(1-phenyl-2-propylideneamino)piperazine Methiodide.—Methyl iodide (28.4 g., 0.2 mole) was added at 0° to a solution of 11.6 g. (0.05 mole) of 1-methyl-4-(1-phenyl-2-propylideneamino)piperazine in 25 ml. of acetone. The reaction mixture was allowed to stand at room temperature for 18 hr. and the colorless solid that separated was collected by filtration and crystallized from methanol–ether; yield, 8.0 g. (43%), m.p. 159–163°.

Anal. Calcd. for $C_{15}H_{24}IN_3$: C, 48.26; H, 6.48; N, 11.26; I, 34.00. Found: C, 48.26; H, 6.80; N, 11.29; I, 33.83.

4-[2-(2-Diethylaminoethyl)hydrazinomethyl]pyridine.—A mixture of 66 g. (0.5 mole) of (2-diethylaminoethyl)hydrazine, 54 g. (0.5 mole) of 4-pyridinealdehyde, and 250 ml. of dry benzene was boiled under reflux for 3 hr. and the water that formed was removed by a Dean–Stark water separator. The benzene was removed *in vacuo* and the residue was diluted with 500 ml. of anhydrous ether. The ether solution was added dropwise to a stirred suspension of 27 g. (0.75 mole) of lithium aluminum hydride in 1 l. of anhydrous ether. The mixture was boiled under reflux with stirring for 6 hr. and decomposed cautiously with water.[41] The inorganic solids were collected by filtration and washed thoroughly with anhydrous ether. The combined ether filtrates were dried over anhydrous sodium sulfate, the drying agent was collected by filtration, and the ether was removed *in vacuo*. The residue was distilled *in vacuo* through a 22 cm. Vigreux column giving a pale yellow liquid, b.p. 144–146° (0.6 mm.), $n^{25}D$ 1.5745; yield, 57 g. (51%).

Anal. Calcd. for $C_{12}H_{22}N_4$: C, 64.82; H, 9.98; N, 25.20. Found: C, 64.74; H, 9.21; N, 25.25.

1,4-Bis(1-phenyl-2-propylideneamino)piperazine.—A mixture of 333 g. (2.48 moles) of phenylacetone, 144 g. (1.24 moles) of 1,4-diaminopiperazine, and 2 l. of toluene was boiled under reflux for 4 hr. and the water that formed was removed through a Dean–Stark water separator. Volatile materials were removed *in vacuo* and the solid residue was washed thoroughly with petroleum ether (b.p. 30–60°); yield, 401 g. (80%), m.p. 106–110°. A small sample was crystallized from 2-propanol to give pale yellow crystals, m.p. 108–113°.

Anal. Calcd. for $C_{22}H_{28}N_4$. C, 75.84; H, 8.10; N, 16.08. Found: C, 75.62; H, 7.99; N, 16.20.

1,4-Bis(benzylideneamino)piperazine.—Utilizing the procedure described above for the preparation of 1,4-bis(1-phenyl-2-propylideneamino)piperazine, 106 g. (1.0 mole) of benzaldehyde, and 76 g. (0.05 mole) of 1,4-diaminopiperazine dihydrate afforded 106 g. (73%) of 1,4-bis(benzylideneamino)piperazine, yellow crystals from chloroform, m.p. 211–213°.

Anal. Calcd. for $C_{18}H_{20}N_4$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.93; H, 6.80; N, 19.63.

Preparation of 1,4-Bis(phenylalkylamino)piperazines (IX) (Table VIII). Method I.—A solution of 222 g. (0.64 mole) of 1,4-bis(1-phenyl-2-propylideneamino)piperazine in 2 l. of anhydrous ether was slowly added to a slurry of 97 g. (2.56 moles) of lithium aluminum hydride in 1.5 l. of anhydrous ether and the mixture was allowed to stir at room temperature for 18 hr. Subsequently, the mixture was heated under reflux with stirring for 16 hr. and cautiously decomposed with 100 ml. of water, 77 ml. of 20% aqueous sodium hydroxide, and 360 ml. of water.[41] The inorganic precipitate was removed by filtration and washed with ether. The combined ether filtrates were concentrated to an oil which was distilled *in vacuo* through a 20 cm. Vigreux column. The product was thus obtained as a pale yellow liquid, b.p. 186–188° (0.5 mm.), $n^{25}D$ 1.5432, 189 g. (83% yield).

A portion of the oily liquid was dissolved in warm petroleum ether (b.p. 30–60°) and crystallization was induced by scratching. Colorless crystals, m.p. 84–90°, were thus obtained (33% recovery); recrystallization from petroleum ether and ethanol raised the melting point to 92–94°. The initial petroleum ether filtrate was concentrated to a viscous oil which resisted attempts to induce crystallization. Both the solid and oily fractions analyzed correctly for the desired product, indicating that isomer separation was occurring. A portion of the latter oily residue was dissolved in anhydrous ether and the solution was treated with a solution of sulfuric acid in ether. The crude sulfate salt that precipitated was collected, dried and crystallized from dimethyl sulfoxide–water.

The original oil obtained by distillation was converted to the phosphate salt as follows: to a solution of 125 g. (0.356 mole) of the base in 2 l. of warm methanol was added slowly with stirring 82.0 g. (0.712 mole) of 85% phosphoric acid. The solution thus obtained was filtered and the filtrate concentrated to dryness *in vacuo*. Trituration with anhydrous ether gave 173 g. (88%), m.p. 197–201°.

Method II.—A mixture of 13.7 g. (0.118 mole) of 1,4-diaminopiperazine, 25.3 g. (0.236 mole) of phenylacetaldehyde and 500 ml. of benzene was boiled under reflux for 4 hr. and water was removed through a Dean–Stark water separator. Volatile materials were removed *in vacuo* and the residue was dissolved in 500 ml. of anhydrous ether. The ether solution of the crude hydrazone was added dropwise with stirring to a slurry of 18 g. (0.47 mole) of lithium aluminum hydride in 1 l. of anhydrous ether and the mixture was boiled under reflux with stirring for 16 hr. The mixture was decomposed cautiously with 18 ml. of water, 14 ml. of 20% aqueous sodium hydroxide, and 66 ml. of water, and filtered.[41] The filtrate was evaporated to dryness and the crude product was crystallized from 2-propanol giving 6.7 g. (18%) of pale yellow crystals, m.p. 116–120°.

Attempted Preparation of 1-(2-Diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine Succinate.—Hot acetone solutions of 2.8 g. (0.011 mole) of 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine (X) and 1.2 g. (0.01 mole) of succinic acid were mixed, heated for a short time, and the mixture was cooled. The crystalline precipitate that separated was collected and dried *in vacuo;* it weighed 0.35 g., m.p. 155–157°. Recrystallization from acetone and then acetonitrile raised the melting point to 162–163°, which was not depressed on admixture with an authentic sample of the succinic acid salt prepared from *dl*-amphetamine.

Anal. Calcd. for $C_9H_{13}N \cdot C_4H_6O_4$: C, 61.64; H, 7.56; N, 5.55. Found: C, 61.66; H, 7.63; N, 5.62.

Treatment of 1-(2-Diethylaminoethyl)-2-(1-phenyl-2-propyl)-hydrazine (X) with Hydrochloric Acid.—A solution of 24.9 g.

(42) Minimum hydrazine content 54.4%, purchased from the Olin Mathieson Chemical Corp., Baltimore, Md.

(43) Purchased from the Michigan Chemical Corp., St. Louis, Mich.

(0.10 mole) of 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)-hydrazine (X) in 500 ml. of 1 *N* hydrochloric acid was boiled under reflux for 15 hr. After cooling to room temperature, the orange-brown reaction mixture was extracted twice with 250 ml. portions of ether (extract A). The aqueous layer was then treated with 50 ml. of 50% sodium hydroxide solution and the alkaline mixture was again extracted twice with 250-ml. portions of ether (extract B). Subsequent addition of 200 g. of solid sodium hydroxide (cooling) and extraction gave a third ether solution (extract C). Each of the ether extracts was dried over anhydrous potassium carbonate, and the ether removed through a short Vigreux column to give residues A, B, and C.

Residue A weighed 0.5 g.; vapor phase chromatography[23] indicated that phenylacetone was the major component.

Residue B weighed 15.4 g.; vapor phase chromatography[23] indicated that amphetamine was the major constituent. A portion (14.9 g.) was distilled *in vacuo* through a short Vigreux column to give 10.3 g. (78%) of a colorless liquid, b.p. 82–87° (13 mm.). This material was shown to be identical with an authentic sample of *dl*-amphetamine by comparison of their infrared absorption spectra and their succinate salts, m.p. and mixture m.p. 161–163°.

Residue C weighed 3.3 g.; vapor phase chromatography[23] indicated that 2-diethylaminoethylamine was probably the major component. Distillation at atmospheric pressure gave 0.74 g. of a colorless liquid which was shown to be identical with an authentic sample of 2-diethylaminoethylamine by comparison of their infrared absorption spectra and their picrate salts, m.p. and mixture m.p. 209–211°.

Anal. Calcd. for $C_6H_{16}N_2 \cdot 2C_6H_3N_3O_7$: C, 37.63; H, 3.86; N, 19.51. Found: C, 37.92; H, 3.93; N, 19.51.

Treatment of 1-(2-Diethylaminoethyl)-2-(1-phenyl-2-propyl)-hydrazine (X) with Sodium Hydroxide.—A solution of 24.9 g. (0.10 mole) of 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)-hydrazine (X) in a mixture of 250 ml. of 1 *N* sodium hydroxide solution and 250 ml. of methanol was boiled under reflux for 16 hr. During the last 2 hr. of heating, 275 ml. of solvent was removed at atmospheric pressure. The orange-brown reaction mixture was cooled and extracted with two 250-ml. portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate, the drying agent was collected, and the ether was removed through a short Vigreux column. The residue (25.2 g.) was distilled *in vacuo* to give 17.4 g. (70%) of a pale yellow liquid, b.p. 78–83° (0.08 mm.) which was identical with the starting material.

Acknowledgments.—The authors wish to express their appreciation to Dr. L. M. Long for his interest in and encouragement of this work. Further, we take this opportunity to thank Dr. G. M. Chen, Mr. C. Ensor, Dr. M. W. Fisher, Dr. J. R. McLean, Dr. P. E. Thompson, and Dr. E. E. Snell for the biological studies, and Dr. M. L. Black, Mr. C. E. Childs, Dr. F. S. Hom, Dr. D. H. Szulczewski, and Dr. J. M. Vandenbelt for microanalytical, spectral, and gas chromatography studies. We also wish to acknowledge the helpful discussions with Professor P. A. S. Smith and Professor C. L. Stevens regarding the hydrazine scission reaction.

Agents Affecting Lipid Metabolism. VIII. N,N′-Dibenzylethylenediamine, the Key to a Novel Class of Cholesterol Biosynthesis Inhibitors[1]

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Received February 4, 1964

A number of mevalonic acid analogs and their N,N′-dibenzylethylenediamine (DBED) salts have been tested for their effect on the incorporation of mevalonate-2-C^{14} into cholesterol by rat liver homogenates. In contrast to the mevalonic acid analogs, their DBED salts exhibited an inhibitory property which was found to reside in DBED itself. The site of action of DBED is at the level of the conversion of 7-dehydrocholesterol to cholesterol. DBED was moderately effective in lowering serum sterols in hypercholesterolemic rats. Molecular modifications of DBED have resulted in compounds of increased potency, showing activity, *in vitro*, at a concentration of 1×10^{-6} *M*.

In a previous publication[2] we reported the synthesis of a series of mevalonic acid analogs. Most of these analogs were oils and it was found convenient to characterize them as solid derivatives. For the purification and characterization of synthetic mevalonic acid itself,[3] the salt with N,N′-dibenzylethylenediamine (DBED) was employed and, consequently, this diamine was also our choice for the preparation of crystalline salts of our mevalonic acid analogs.

In due course, it was discovered that, in contrast to the mevalonic acid analogs, their salts with DBED inhibited the incorporation of mevalonate-2-C^{14} into cholesterol by rat liver homogenates and, quite unexpectedly, we found that the inhibitory activity resided in DBED itself. These results led us to investigate various analogs, homologs, and derivatives of DBED for their ability to inhibit cholesterol biosynthesis. DBED itself has also been studied *in vivo* with respect to its effects on rat serum sterol levels.

The discovery of the inhibitory effect of DBED on hepatic cholesterogenesis has eventually led to the synthesis of *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane dihydrochloride,[4] a representative of a novel class of cholesterol biosynthesis inhibitors[5] which acts by interfering with the conversion of 7-dehydrocholesterol to cholesterol.[6] Thus, we have also studied the effect *in vitro* of DBED on the metabolism of 7-dehydrocholesterol. These results form the basis of this report.

(1) (a) Presented before the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 6–10, 1964; (b) part VII: D. Dvornik, M. Kraml, and J. Dubuc, *Proc. Soc. Exptl. Biol. Med.*, **113** (1964), in press; for part VI, see ref. 5.

(2) L. G. Humber, M. Kraml, J. Dubuc, and R. Gaudry, *J. Med. Chem.*, **6**, 210 (1963).

(3) C. H. Hoffman, A. F. Wagner, A. N. Wilson, E. Walton, C. Shunk, D. E. Wolf, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, **79**, 2316 (1957).

(4) L. G. Humber, Belgian Patent 627,610 (1963); Derwent Belgian Patent Report 30 (1963).

(5) C. Chappel, J. Dubuc, D. Dvornik, M. Givner, L. Humber, M. Kraml, K. Voith, and R. Gaudry, *Nature*, **201**, 497 (1964).

(6) D. Dvornik, M. Kraml, J. Dubuc, M. Givner, and R. Gaudry, *J. Am. Chem. Soc.*, **85**, 3309 (1963).