A solution of 7.6 g of NaNO₂ in 20 ml of water was added dropwise and stirred 15 min, and the separated ether layer was dried. The filtered azide solution was added to 350 ml of dry toluene, heated on a steam bath to distil the ether, and the resultant solution was refluxed for 6 hr. The toluene was evaporated *in vacuo* (nitrogen). The liquid residue was redissolved in dry toluene, added to 30 ml of concentrated HCl, and warmed. After the gas evolution which took place at about 50° was complete, the solution, and extracted with ether. The liquid remaining after evaporating the ether was distilled, bp 75–79° (1 mm). It was converted into its hydrochloride and recrystallized from ethanol-ethyl acetate mixture; mp 181–183°, yield 4 g (19%).

Anal. Calcd for $C_{10}H_{13}NO \cdot HC1$: C, 60.30; H, 7.03; N, 7.03. Found: C, 60.53; H, 7.05; N, 7.04.

Biological Results.—In comparison with several active compounds, 2-methyl-3-phenoxycyclopropylamine demonstrated no *in vitro* activity and very little *in vivo* activity against brain monoamine oxidase (rats) (Table I).

TABLE]	Ĺ
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	MAO in vitro	Brain in vivo ED50 (rats)
$4-(NC_5H_4)CONHNHCH(CH_3)_2^b$	50% mmb, M 5.3×10^{-6}	mg/kg 25.0
$C_6H_5OCHCHNH_2$	$>1 \times 10^{-3}$	50.0
CHCH_3		
trans-C ₆ H ₅ OCHCHNH ₂ ^c	1.6×10^{-7}	0.37
	1 9 10 -7	0.95
CH2	1.8 X 10 '	0.55
trans-C6H5CHCHNH2e	8×10^{-6}	0.25
$\widetilde{\mathrm{CH}}_2$		

^a The pharmacological data were obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories. The methods are described in detail by L. O. Randall and R. E. Bagdon, Ann. N. Y. Acad. Sci., **80**, 626 (1959). ^b Iproniazid, Hoffmann-La Roche, Inc. ^c Reference 1. ^d J. Finkelstein, E. Chiang, F. M. Vane, and J. Lee, in press. ^e Tranyleypromine, Smith Kline and French Laboratories, Inc.

Similarly, Zirkle and co-workers^{1b} observed that although 2phenylcyclopropylamine has potent MAO inhibitory activity, 2methyl-3-phenylcyclopropylamine has relatively little activity.

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Agents Affecting Lipid Metabolism. XXI. Miscellaneous Compounds Related to *trans*-1,4-Bis(2-chlorobenzylaminomethyl)cyclohexane¹

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We have recently reported the synthesis²⁻⁴ of many symmetrical compounds derived structurally from the potent cholesterol-lowering agent *trans*-1,4-bis(2-chloro-

(2) L. G. Humber, *ibid.* 7, 826 (1964).

benzylaminomethyl)cyclohexane.⁵ This report describes the synthesis of some miscellaneous related compounds. The biological activities of these and other compounds of this series²⁻⁴ are reported separately.¹

The first group of compounds consists of the unsymmetrically N,N'-disubstituted cyclohexanebis(methylamine) derivatives (IV-VI, Chart I). They were prepared from cyclohexane-trans-1,4-bis(methylamine) (I) by reducing the Schiff's base formed with 1 equiv of a carbonyl component, to yield the monosubstituted derivatives II and III, and then condensing these with a second carbonyl component to yield, after reduction, the unsymmetrical disubstituted compounds IV-VI. The properties of the final products and intermediates as their hydrochloride salts are presented in Table I.



A second group of compounds, represented by the series shown in Chart II, are analogs of a 1,4-bis(benzylaminomethyl)cyclohexane in which one of the nitrogens is replaced by oxygen, sulfur, the sulfoxide, or the sulfonyl group. They were prepared from 1-hydroxymethyl-4-cyclohexanemethylamine (VII) as indicated in Chart II. The physical properties and analytical data are given in Table II.



The primary amino group of VII was substituted by either the benzyl or 2-chlorobenzyl group, by reducing the Schiff base formed with the appropriate aldehydes, to give VIII and IX, respectively, which were con-

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⁽¹⁾ Part XX: L. G. Humber, C. I. Chappel, A. V. Marton, M. Kraml, and J. Dubuc, J. Med. Chem., 9, 329 (1966).

TABLE I

UNSYMMETRICALLY SUBSTITUTED CYCLOHEXANE-*lrans*-1,4-Bis(METHYLAMINES) AND INTERMEDIATES

No.	Carbonyl components	Primary amine component	Mp, °C	Recrystn solvent	Formula	Caled	Cl	Caled	- N Found
$\Pi^{b,c}$	2-Chlorobenzaldehyde	I	>310	EtOП	$C_{15}H_{23}ClN_2 \cdot HCl$	23.38	22,90	9.23	9.03
$III^{b,d}$	Cyclohexanone	T	>325	EtOH	$C_{14}H_{28}N_2 \cdot 2HCl$	23.85	23.44	9.42	9.32
IV^b	Cyclohexane- carboxaldehyde	п	>310	MeOH	$\mathrm{C}_{22}\mathrm{H}_{35}\mathrm{ClN}_2\!\cdot\!2\mathrm{H}\mathrm{Cl}$	24.40	24.44	6.43	6.49
\mathcal{V}^{b}	Cyclohexanone	11	>310	MeOH– ether	$\mathrm{C}_{21}\mathrm{H}_{33}\mathrm{ClN}_2\!\cdot\!2\mathrm{H}\mathrm{Cl}$	25.21	25.36	6,64	6.53
$V1^{b}$	Cyclohexane- carboxaldehyde	III	>320	MeOH	$C_{21}H_{40}N_2\!\cdot\! 2HCl$	18.04	17.86	7.12	7.18

^a These components were condensed to the corresponding Schiff base which was then reduced with sodium borohydride to yield the final products (see Experimental Section for typical procedure). ^b See Chart I for structures. ^c This compound was prepared from the corresponding Schiff base by reduction with hydrogen in the presence of platinum oxide. The free base had bp $165-167^{\circ}$ (0.1 mm). We thank Dr. T. Massiah of our pilot plant for the preparation of this compound. ^d The free base had bp 110° (0.6 mm).

TABLE II

Physical Properties of the Compounds of Chart II

	ma-										
	terials										
	and	Yield,		Recrystn		~~~%	Cl	- ~~ ··· •~~!{{	. N 	· · · · · · · · · · · · · · · · · · ·	8
No.	methods	%	$Mp_{e} \circ C$	solvent	Formula	Caled	Found	Caled	Found	Caled	Found
VIII+HCl	a	92	160 - 161	2-Propanol-ether	$C_{15}H_{24}CINO$	13.14	13.40	5.19	5.44		
IX · HBr	b	85	146 - 148	Methanol-ether	$C_{15}H_{23}BrClNO$	<i>!</i>				·• ···-	
X · HCl	d	86	230 - 230.5	2-Propanol	$C_{15}H_{23}Cl_2N$	24.60	24.70	4.86	4.71		
XI HCl	e	47	$209 - 210^{f}$	2-Propanol	$\mathrm{C_{15}H_{22}Cl_{3}N}$	32.96	32.25	· •• •			
XII · HCl	a	91	188 - 190	Methanol-ether	$\mathrm{C}_{22}\mathrm{H}_{30}\mathrm{ClNS}$	9.45	9.55	3.75	3.64	• •	
XIII · HBr	g	74	114 - 116	2-Propanol-ether	$C_{22}H_{29}BrClNS$	7.79	8.04	·		7.05	7.02
XIV ·HCl	h	89	218 - 220	2-Propanol	$C_{22}H_{30}ClNOS$	9.04	8.94			8.18	8.94
XV·HCl	i	83	251 - 253	Methanol-ether	$\mathrm{C}_{22}\mathrm{H}_{30}\mathrm{ClNO}_2\mathrm{S}$	8.69	8.77		· · · · •	7.86	7.24
XVI · HCl	a	55	175.5 - 176	Methanol-ether	$C_{22}H_{29}ClNO$	9.89	9.74	<i>I</i>			

^a See Experimental Section. ^b From 2-chlorobenzaldehyde and VII. See Experimental Section for typical procedure. ^c. Anal. Calcd: C, 51.50; H, 6.92; Br, 22.85. Found: C, 51.86; H, 7.00; Br, 22.95. ^d From VIII and thionyl chloride in refluxing CHCl₃ for 14 hr. ^e From IX, as described in footnote d. ^f The free base has bp 168° (0.75 mm). ^g From XI·HCl and benzyl mercaptan. See Experimental Section for typical procedure. ^b From XII·HCl by oxidation with sodium metaperiodate using the conditions of N. J. Leonard and C. R. Johnson, J. Org. Chem., 27, 282 (1962). ⁱ From XII·HCl by oxidation with 30% hydrogen peroxide in glacial acetic acid. ⁱ Anal. Calcd: C, 73.68; H, 8.15. Found: C, 73.88; H, 8.34.

verted to the chloromethyl derivatives X and XI with thionyl chloride. Reaction of these with benzyl mercaptan yielded the thio analogs XII and XIII. Compound XII was oxidized with hydrogen peroxide to give the sulfone (XV) or with sodium metaperiodate to give the sulfoxide (XIV). The oxygen analog (XVI) was obtained from intermediate VIII by condensation with benzyl chloride. A number of other miscellaneous compounds were prepared for testing.

 $\begin{array}{c} & I^{\bigoplus} \\ & \oplus \\ X VII, R = cyclohexylmethyl \\ X VIII, R = 2 - ClC_6H_4CH_2 \end{array} \qquad \begin{array}{c} & I^{\bigoplus} \\ & \oplus \\ CH_2NCH_2-2-ClC_6H_4 \\ & \oplus \\ CH_3 \\ & CH_3 \\ CH_3 \\ & CH_3 \\ CH$

They are the 3-azabicyclo[3.2.2]nonane derivatives XVII and XVIII, the mono and bisquaternary methoiodides XIX and XX of *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane and N,N'-di(2-chlorobenzyl)cyclohexane-*trans*-1,4-bis(carboxamide) (XXI). The synthesis of these compounds is described in the Experimental Section. Table III contains compounds XXII-XXVII, obtained by the reduction of the appropriate Schiff base.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are corrected. Analyses were done by Mr. W. Turnbull and staff of our laboratories.

N-Benzyl-1-hydroxymethyl-4-cyclohexanemethylamine (VIII). —1-Hydroxymethyl-4-cyclohexanemethylamine (a mixture of cis and trans 1,4-isomers, VII) (42.9 g) and benzaldehyde (31.8 g) were refluxed in benzene (400 ml) until the theoretical quantity of water had been removed azeotropically. The resulting Schiff base, λ_{max}^{EtOH} 247 m μ (ϵ 17,800), was dissolved in methanol (300 ml) and refluxed for 3 hr with sodium borohydride (11.4 g). The conventional work-up procedure gave VIII, λ_{max}^{EtOH} 259 m μ (ϵ 267), as an oil in 92% yield. The hydrochloride melted at 160–161° (2-propanol-ether).

Anal. Calcd for C15H24CINO: Cl, 13.14; N, 5.19. Found: Cl, 13.40; N, 5.44.

N-Benzyl-1-benzylthiomethyl-4-cyclohexanemethylamine (XII).—Benzyl mercaptan (9.3 g) was dissolved in 70%ethanol (100 ml) containing NaOH (6.3 g). Hydrochloride of X (22.0 g) in 150 ml of 1:1 ethanol-water was added over 15 min and the mixture refluxed for 30 min. The ethanol was removed

Starting

TABLE III Miscellaneous Compounds Prepared by Reduction of Schiff Bases

No.	Compd	Start- ing ^a ma- terial	Mp, °C	Recrystn solvent	Formula	Calcd	Cl Found	Calcd	N Found
XXII	2-ClC ₆ H ₄ CH ₂ NHCH ₂ C ₆ H ₁₁ ^b	С	96-98	MeOH-ether	$\mathrm{C}_{14}\mathrm{H}_{20}\mathbf{N}\cdot\mathbf{H}\mathrm{Cl}$	12,93	12.93	5.11	4.95
XXIII	$2\text{-ClC}_{6}H_{4}CH_{2}NH - CH_{2}C_{5}H_{5}$	d	284-290	MeOH-EtOAc	$\mathrm{C_{19}H_{23}ClN_2\cdot 2HCl}$	27.42	27.80	7.22	7.07
XXIV	$C_{\phi}H_{s}CH_{2}NHCH_{2}-CH_{2}C_{e}H_{5}$	e	307-308	EtOH	$\mathrm{C_{20}H_{26}N_2\cdot 2HCl}$	19.40	19.60	7.67	7.24
XXV	$[2-ClC_6H_4CH_2NHCH(CH_4)CH_2CH_2-]_2$	ſ	238-242	MeOH	$\mathrm{C}_{22}\mathrm{H}_{30}\mathrm{N}_{2}\cdot 2\mathrm{HCl}$	30.41	30.20		
XXVI	HNCH(CH ₃)CH ₂ CH ₂ -	g	h	_	$\mathrm{C}_{28}\mathrm{H}_{64}\mathrm{N}_{2}{}^{i}$	_		6.72	6.74
XXVII	NHCH(CH _a)CH ₂ CH ₂ -	j	215	MeOH	$C_{28}H_{60}N_2\cdot 2 HCl$	14.25	14.46	5.63	5.73

^a These starting materials were condensed to the corresponding Schiff base which was then reduced with sodium borohydride to yield the desired compounds. See Experimental Section for typical procedure. ^b C₆H₁₁ = cyclohexyl. ^c Cyclohexanecarboxaldehyde and 2-chlorobenzylamine. ^d 2-Chlorobenzaldehyde and 1-benzyl-4-aminopiperidine. ^e 1-Benzyl-4-aminomethylpiperidine (see Experimental Section) and benzaldehyde. ^f 2,7-Octanediamine [J. Wiemann and J. Kossanyi, *Compt. Rend.*, **247**, 649 (1958)] and 2-chlorobenzaldehyde. ^g 2,7-Octanediamine and citral. ^h Boiling point of free base, 163–168° (0.01–0.02 mm), $n^{\infty}D$ 1.4848. ⁱ Anal. Calcd: C, 80.69; H, 12.58. Found: C, 80.61; H, 12.42. ⁱ Obtained by reduction of XXVI with hydrogen and platinum oxide catalyst at 22° and atmospheric pressure.

in vacuo and the aqueous solution was extracted with benzene to give XII as an oil (91%), $\lambda_{\text{max}}^{\text{EtOH}}$ 250 m μ (ϵ 805); hydrochloride, mp 188-190° (methanol-ether).

Anal. Caled for C₂₂H₂₉ClNS: Cl, 9.45; N, 3.75. Found: Cl, 9.55; N, 3.64.

N-Benzyl-1-benzyloxymethyl-4-cyclohexanemethylamine (XVI).—Compound VIII (7.5 g) was dissolved in toluene (50 ml) and sodium (796 mg) was added. When all the sodium had dissolved, benzyl chloride (4.36 g) in toluene was added and the mixture refluxed for 3 hr. Sodium chloride was removed by filtration, and XVI was obtained by fractional distillation of the filtrate; bp 194–196° (0.12 mm), 5.5 g. The hydrochloride salt had mp 175.5–176° (methanol-ether).

Anal. Calcd for $C_{22}H_{29}CINO$: C, 73.68; H, 8.15; Cl, 9.89. Found: C, 73.88; H, 8.34; Cl, 9.74..

N-Cyclohexanecarbonyl-3-azabicyclo[3.2.2] nonane.—3-Azabicyclo[3.2.2] nonane (18.8 g) was dissolved in aqueous 1 NNaOH (150 ml), and cyclohexanecarbonyl chloride (14.6 g) in acetone (50 ml) was added dropwise with stirring. The mixture was refluxed for 2 hr then the acetone was distilled. On cooling, the title compound crystallized. It was washed well with water, dried, and recrystallized from an ether-hexane mixture; mp 81-82.5°.

Anal. Caled for C₁₆H₂₅NO: C, 76.53; H, 10.70. Found: C, 76.79; H, 10.86.

N-(2-Chlorobenzoyl)-3-azabicyclo[3.2.2]nonane.—Working in the same manner as above, but using 2-chlorobenzoyl chloride (26.2 g) instead of cyclohexanecarbonyl chloride, the title product was obtained; mp 101-102° (benzene-hexane).

Anal. Calcd for C₁₅H₁₈ClNO: C, 68.30; H, 6.88. Found: C, 68.58; H, 7.00.

N-Cyclohexylmethyl-3-azabicyclo[3.2.2] nonane (XVII).—N-Cyclohexanecarbonyl-3-azabicyclo[3.2.2] nonane (24.1 g) was dissolved in ether (150 ml) containing lithium aluminum hydride (3.8 g), and the mixture was refluxed for 20 hr. The title compound was obtained as an oil, bp 92° (0.08 mm); hydrochloride, mp 291-292° (2-propanol-ether).

Anal. Calcd for C_{1b}H₂₈ClN: Cl, 13.73; N, 5.43. Found: Cl, 13.71; N, 5.39.

N-(2-Chlorobenzyl)-3-azabicyclo[3.2.2]nonane (XVIII).--N-(2-Chlorobenzoyl)-3-azabicyclo[3.2.2]nonane (24.8 g) was reduced as described above using tetrahydrofuran as solvent. The title compound had bp 134° (0.15 mm); hydrochloride, mp 229-230° (2-propanol).

Anal. Caled for C15H22Cl2N: Cl, 24.68. Found: Cl, 24.65.

Mono- and Bisquaternary Methiodides of N,N'-Di(2-chlorobenzyl)cyclohexane-trans-1,4-bis(methylamine) (XIX and XX). --N,N'-[Di(2-chlorobenzyl)cyclohexane-trans-1,4-bis(methylamine)² (7.8 g) was dissolved in methanol (80 ml). Sodium bicarbonate (8.0 g) and methyl iodide (28.6 g) were added, and the mixture was heated on the steam bath for 48 hr. The methanol was removed *in vacuo* and the residue was boiled with CHCl₃. The CHCl₃-soluble fraction yielded the monoquaternary methiodide (XIX) as an oil (12.9 g) which was obtained crystalline from a methanol-ether mixture; mp 166-169°.

Anal. Calcd for C24H33Cl2IN2: I, 23.0. Found: I, 23.05.

The CHCl₃-insoluble fraction was triturated in warm water, and the residue was crystallized from ethanol to yield XX (750 mg), mp $252-255^{\circ}$.

Anal. Calcd for C₂₆H₃₈Cl₂I₂N₂: I, 36.08. Found: I, 36.12. N,N'-Di(2-chlorobenzyl)cyclohexane-trans-1,4-bis(carbox-amide) (XXI).—Cyclohexane-trans-1,4-dicarbonyl chloride⁶ (10.0 g) in benzene (50 ml) was added slowly to a solution of 2-chlorobenzylamine (30 g) in benzene (200 ml). The mixture was refluxed for 4 hr, then the benzene was removed *in vacuo*, and the residue was triturated in hot water. The insoluble portion was crystallized from dimethylformamide to yield XXI (15.0 g), mp 325-326°.

Anal. Calcd for C₂₂H₂₄Cl₂N₂O₂: C, 63.16; H, 5.78; Cl, 16.95. Found: C, 62.80; H, 6.00; Cl, 16.59.

N-Benzyl-4-aminomethylpiperidine.⁷—4-Aminomethylpiperidine (11.3 g) in tertahydrofuran (60 ml) was added to a suspension of lithium aluminum hydride (9.5 g) in tetrahydrofuran. The mixture was brought to reflux, and ethyl benzoate (45 g) in tetrahydrofuran (90 ml) was added over a period of 80 min. Refluxing was continued for 18 hr, water was added, and the mixture was worked up in the usual manner to yield the title compound (11.5 g, 57%), bp 185° (0.25 mm); **dihydrochloride**, mp 263–266° (2-propanol).

Anal. Calcd for $C_{13}H_{22}Cl_2N_2$: Cl, 25.58; N, 10.10. Found: Cl, 25.24; N, 9.70.

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