lization from isopropyl ether gave 4.5 g (31.4%) of colorless needles, mp 83–85°; **hydrochloride** from ethanol, mp 207–212° dec.

Method B.—A solution of 3 g (0.017 mole) of **1** and 3.67 g (0.017 mole) of 1,4-dibromobutane in 70 ml of absolute toluene was refluxed with stirring for 4 hr. To the mixture was added 2.9 g of $NaHCO_3$ and stirring under refluxing was continued further for 10 hr. After cooling, the basic mixture was extracted with 10% HCl, and the acid solution was made alkaline (K_2CO_3) and extracted ($CHCl_3$). The extract was dried (K_2CO_3) and evaporated under reduced pressure. Distillation of the residue gave 1.75 g of a colorless oil, bp 140–160° (0.3 mm), which crystallized on standing. Recrystallization from isopropyl ether gave 1.6 g (41%) of white needles, mp 82–84°. The infrared spectrum of this product was identical with that of the product from method A.

3-Dimethyl-1-(*p*-tolyl)-2-pyrrolidinone (14).—A mixture of 1 g (0.0052 mole) of 3-amino-5-(*p*-tolyl)-2-pyrrolidinone (XIVa), 5 ml of 97% formic acid, and 5 ml of 35% formaldehyde was heated on a water bath for 8 hr. Evaporation of excess formic acid and formaldehyde left a viscous oil, which was distilled at 0.08 mm (bath temperature, 150–170°) to give 0.7 g (61%) of a colorless oil. The **hydrochloride** crystallized as white needles from ethanol, mp 185–187°; **picrate,** yellow needles from aqueous ethanol, mp 209–211° dec.

4-Carbobenzoxyamino-1-phenyl-2-pyrrolidine (XXII).—A mixture of 19.5 g (0.0945 mole) of 5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (XIX), 23 g of $SOCl_2$, 1 drop of pyridine, and 95 ml of chloroform was refluxed for 3 hr. Solvent and excess $SOCl_2$ were evaporated *in vacuo* to leave the crude chloride (XX). The chloride, dissolved in 40 ml of dioxane, was added to a mixture of 8.4 g (0.13 mole) of NaN_3, 43 ml of water, and 19 ml of dioxane at 0° with stirring. Further stirring at the same temperature gave a crystalline precipitate. Filtration and drying afforded 20 g of the crude azide (XXI), mp 87–89° dec. The azide was refluxed with 9.5 g of benzyl alcohol in 300 ml of benzene for 2 hr. After removal of the solvent, the residue was recrystallized from ethanol to give 16.0 g (55%) of XXII, mp 149–151°.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.62; H, 5.47; N, 9.16.

4-Amino-1-phenyl-2-pyrrolidinone (29). Method A. Catalytic Reduction of XXII.—To 60 ml of a dioxane–acetone (1:1) solution containing 1.0 g (0.0032 mole) of XXII was added 0.4 g of 15% Pd–C catalyst and 1.5 ml of 10% NaOH. The mixture was subjected to hydrogen at room temperature under atmospheric pressure. After the theoretical amount of hydrogen was consumed, the reaction mixture was neutralized with dilute HCl. Removal of the catalyst and solvent left a colorless oil, which was dissolved in 10% HCl. After neutralization of the acid solution, a basic product was extracted ($CHCl_3$). The extract was dried (K_2CO_3) and concentrated. Distillation of the residue yielded 0.4 g (78%) of **29,** bp 135–140° (0.06 mm). The **hydrochloride** crystallized as colorless needles from ethanol, mp 178–180°.

Anal. Calcd for $C_{10}H_{12}N_2O \cdot HCl$: C, 56.47; H. 6.12; N, 13.18. Found: C, 56.36; H, 6.24; N, 13.10.

The **picrate** crystallized as yellow needles from the aqueous ethanol, mp 232–235° dec.

Method B. Hydrolysis of Crude XXI.—A solution of 1.0 g (0.00435 mole) of XXI in 20 ml of dioxane was heated at 90–95° for 30 min. After cooling, 5 ml of concentrated HCl was added and the mixture was stirred at 60° for 20 min. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was recrystallized from ethanol to give 0.44 g (47%) of the **hydrochloride** of **29,** mp 180–183°, which was identified by the comparison of its infrared spectrum with that of the sample prepared by method A.

4-Dimethylamino-1-phenyl-2-pyrrolidinone (30).—To a mixture of 0.8 g (0.0045 mole) of **29,** 1.36 g (0.016 mole) of $NaHCO_3$ and 10 ml of water was added 2.35 g (0.0152 mole) of diethyl sulfate at room temperature, and the mixture was stirred at 50–60° for 2 hr. The oily product was extracted ($CHCl_3$) and dried (K_2CO_3), and the solvent was evaporated. After removal of the starting material and secondary amine in the usual way, the residue was distilled at 0.1 mm (bath temperature, 200–210°) to give 0.3 g (29%) of XXVIc. The **hydrochloride** crystallized as prisms from isopropyl alcohol, mp 187–187.5°.

Anal. Calcd for $C_{14}H_{20}N_2O \cdot HCl$: C, 62.56; H, 7.82; N, 10.42. Found: C, 62.77; H, 7.42; N, 10.68.

4-Phenethylamino-1-phenyl-2-pyrrolidinone (32).—To a solution of 0.1 g (0.0057 mole) of XXIII and 0.82 g (0.0068 mole) of phenylacetaldehyde in 40 ml of absolute ethanol was added 0.1 g of prereduced PtO_2, and the mixture was shaken in an atmosphere of hydrogen until the uptake of hydrogen stopped. Removal of the catalyst and solvent left a colorless oil, which crystallized on standing. Recrystallization from benzene–ether gave 0.65 g (40.5%) of XXIV, mp 89–90°.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.35; H, 6.95; N, 9.83.

The hydrochloride was obtained as colorless needles from ethanol, mp 216–218°.

Synthesis of *trans*-2-Cyclohexyloxycyclopropylamine and Derivatives

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In continuing the study of the relationship between chemical constitution and monoamine oxidase inhibition, *trans*-2-cyclohexyloxycyclopropylamine was synthesized. The compound was discovered to be 20–50 times as active as iproniazid in the six biological tests employed. Comparative data were also obtained for the clinically active tranylcypromine and isocarboxazid.

In our further investigation of 2-substituted cyclopropylamines as monoamine oxidase inhibitors (MAO),[1] we synthesized 2-cyclohexyloxycyclopropylamine and discovered it to be a potent compound. After the completion of this work, Kaiser and co-workers,[2] in an extensive study, synthesized the closely related compound, 2-cyclohexylcyclopropylamine, and Zirkle and co-workers[3] reported that it was almost completely devoid of MAO inhibition, as determined by *in vivo* potentiation of tryptamine convulsions in rats. As a result of this and other findings, they concluded that the structural requirements for a potent *in vivo* MAO inhibitor in this class of compounds are (a) a cyclopropyl ring, (b) an amino group attached directly to the cyclopropyl ring, and (c) a 2-substituent containing an aromatic moiety. Since 2-cyclohexyloxycyclopropylamine (**9**) is a potent inhibitor, requirement c must be modified.

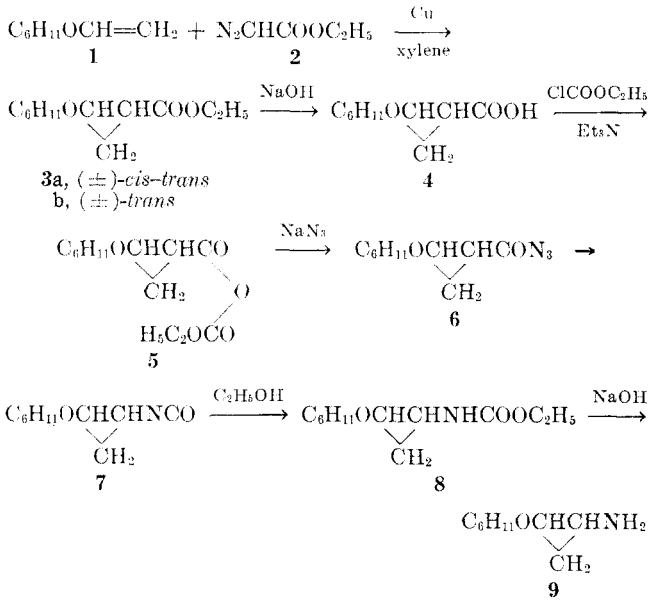
The synthesis of 2-cyclohexyloxycyclopropylamine (**9**) was accomplished by the series of reactions shown in

(1) J. Finkelstein, E. Chiang, and J. Lee, *J. Med. Chem.*, **8**, 432 (1965).

(2) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *ibid.*, **5**, 1243 (1962).

(3) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *ibid.*, **5**, 1265 (1962).

SCHEME I



Scheme I. The cyclohexylvinyl ether[4] (**1**) was treated with ethyl diazoacetate[5] (**2**) in a modification of the method of Julia[6] for the preparation of cyclopropanecarboxylic esters. The *cis–trans* ester **3a,** was obtained in 85% yield, and vpc analysis indicated that the composition was approximately 78% *trans* and 17% *cis*. These results are essentially in agreement with our earlier observation that the thermodynamically more stable *trans* form of ethyl 2-phenoxycyclopropanecarboxylate is produced preferentially. This is also confirmed by a study of the Dreiding molecular models. It is noted that cyclohexyloxy vinyl ether and carbethoxycarbene develop a considerably crowded condition in an attempt to form the *cis* isomer. However, for the formation of the *trans* isomer, the two bulky groups did not interfere with each other. Because our previous findings showed that, within the limits of biological variations, there were no consistent differences in MAO inhibition between the *cis*- and *trans*-2-phenoxycyclopropylamines, we did not investigate the *cis* series of the 2-cyclohexyloxycyclopropane compounds, and epimerized the isolated esters **3a,** to the ethyl *trans*-2-cyclohexyloxycyclopropanecarboxylate (**3b**).

By refluxing the *cis–trans* ester mixture **3a,** in absolute ethanol containing sodium ethoxide for 16 hr, the vpc analysis showed the (±)-*trans* ester **3b** was present to the extent of 87% and the *cis* isomer was reduced to 10% with some tailing. These results were not altered appreciably when the reaction time was extended to 42 hr which indicated that, in ethanol, an equilibrium ratio of 87% *trans* to 10% *cis* was established. When the absolute ethanol was replaced with 1,2-dimethoxyethane and the solution was refluxed for 24 hr, the conversion was practically complete; the vpc showed a single peak, accounting for 97% (±)-*trans* isomer.

The ethyl (±)-*trans*-2-cyclohexyloxycyclopropane carboxylate (**3b**) was hydrolyzed by aqueous sodium hydroxide to the corresponding (±)-*trans* acid **4** isolated as a crystalline product which, by vpc proved to be a single substance.

In our synthesis of 2-phenoxycyclopropylamine,[1] we showed that the Curtius rearrangement,[7] starting with the corresponding ester and proceeding through the hydrazide intermediate, was preferred to the Hofmann degradation[8] and the Lossen rearrangement.[9] In the synthesis developed herein for **9,** we also employed the Curtius rearrangement, but used the improved method of Weinstock[10] to prepare the intermediate azide **6**. Thus, we treated the (±)-*trans* acid **4** with ethyl chloroformate in the presence of triethylamine according to Vaughan's[11] procedure to obtain the mixed anhydride **5**. Without isolation, this was treated with sodium azide to form the azide **6** which was rearranged immediately *in situ* to the isocyanate **7,** which in turn was treated with ethanol to give the urethan **8**. This compound was then hydrolyzed to the desired (±)-*trans*-2-cyclohexyloxycyclopropylamine (**9**), isolated as a stable, distillable liquid (vpc, single peak) in 47% over-all yield from the acid. The designation of the amine **9** as *trans* is based upon the reported evidence that the Curtius rearrangement occurs with retention of optical and geometric configuration.[12] The base readily formed a hydrochloride **10** and diastereoisomeric D-tartrates **11**. The latter salts, by repeated recrystallization, were resolved successfully into (+)-*trans*-2-cyclohexyloxycyclopropylamine-D-tartrate (**12**) and (−)-*trans*-2-cyclohexyloxycyclopropylamine-D-tartrate (**13**). These resolved salts were then decomposed into their respective (+)-*trans* free base **14** and (−)-*trans* free base **15,** and each was further characterized as its (+)-*trans* amine hydrochloride **16** and (−)-*trans* amine hydrochloride **17**. These isomers were also tested to determine their pharmacological activities.

To investigate the biological potential of the 2-cyclohexyloxycyclopropyl group, we prepared a number of derivatives for screening. Starting with the ester **3b,** we prepared the corresponding hydrazide **18** which in turn was reduced by the method of Ainsworth[13] to the amide **19**. When the ester **3b** was reduced with lithium aluminum hydride, the (±)-*trans*-2-cyclohexyloxycyclopropylmethanol (**20**) was obtained. From the (±)-*trans* amine **9,** the following derivatives were made: N-benzylamino (**21**), the N-benzyl-N-methylamino **22,** mono-N-methylamino **23,** N,N-dimethylamino **24,** and guanidino **25**.

The nmr spectrum of 2-cyclohexyloxycyclopropylamine was obtained in a deuteriochloroform solution. The cyclopropyl hydrogens appeared in three multiplets centered at $\delta \approx 3.17$ (>CHO–), 2.45 (>CHN<), and 0.67 ppm ($>CH_2$). The methylene protons of the

(4) This compound was purchased from Maybridge Chemical Co., Lansing, Sussex, England. When the material assayed 94% by vpc and the infrared showed the absence of hydroxyl and carbonyl groups, it was suitable for synthetic use. One shipment which contained approximately 20% cyclohexanone (confirmed by infrared and dinitrophenylhydrazone) was purified by repeated washings with a saturated solution of sodium bisulfite followed by distillation.

(5) F. B. La Forge, W. A. Gersdorff, N. Green, and M. S. Schechter, *J. Org. Chem.*, **17**, 381 (1952).

(6) M. Julia, *Bull. Soc. Chim. France*, 181 (1956).

(7) P. A. S. Smith, *Org. Reactions*, **3**, 337 (1946).

(8) E. S. Wallis and J. F. Lane, *ibid.*, **3**, 267 (1946).

(9) J. B. Dickey, J. M. Straley, and T. E. Stanin, U. S. Patent 2,394,597 (1946); *Chem. Abstr.*, **40**, 2848[3] (1946).

(10) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

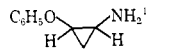
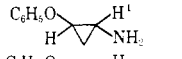
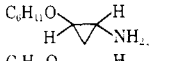
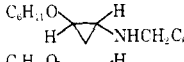
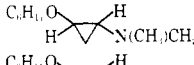
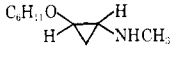
(11) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951).

(12) P. A. S. Smith in "Molecular Rearrangements," Part I, P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 530.

(13) C. Ainsworth, *J. Am. Chem. Soc.*, **76**, 5774 (1954).

TABLE I

SELECTED NMR DATA

Compd	ΣJ, cps >CHO–	ΣJ, cps >CHN<
	16	19.2
	11.6	14.5
	12.0	14.5
	13.0	14.5
	12.0	*a*
	12.5	14.5

[a] Overlap with cyclohexyl protons prevented the determination of the ΣJ value.

cyclohexyl group and the amine protons formed a broad multiplet between 1.20 and 2.10 ppm. The broad band for cyclohexylmethine (>CHO–) was centered at 3.33 ppm.

A comparison (see Table I) of the sum of the coupling constants (ΣJ values) of the two low-field cyclopropyl protons with those of *cis*- and *trans*-2-phenoxycyclopropylamine supports the *trans* stereochemistry of **9** and its N-benzyl, N-methyl-N-benzyl, and N-methyl derivatives.

The complexity of the multiplets of the cyclopropyl hydrogens prevented the determination of the individual coupling constants. The difference in the ΣJ values for the *cis* and *trans* isomers should be primarily due to the difference in coupling constants between the cyclopropyl hydrogens on the substituted carbons. It is well known that J_{cis} is larger than J_{trans} in three-membered rings.[14]

Biological Results.—Table II shows the *in vivo* and *in vitro* MAO inhibitory activities of the (±)-*trans*-, (+)-*trans*-, and (−)-*trans*-2-cyclohexyloxycyclopropylamines, and (±)-*trans*-methylamino-2-cyclohexyloxycyclopropane (**23**). They are compared with other active MAO inhibitors. The compounds that were prepared but not listed in the table were inactive.

In the six tests reported for (±)-*trans*-2-cyclohexyloxycyclopropylamine (**9**), the compound showed a consistently good degree of activity against monoamine oxidase when compared with (±)-*trans*-2-phenoxycyclopropylamine[1] and isocarboxazid. When compared with tranylcypromine, it was more effective in two of the tests. Among the stereoisomers of **9**, there were observed variations but no striking differences.

The acute toxicity of (±)-*trans*-2-cyclohexyloxycyclopropylamine (LD_{50}, 72 hr) in mice is 159 mg/kg ip, 199 mg/kg *po*, and 199 mg/kg sc. This highest dose is approximately 400 times greater than the ED_{50} for inhibition of brain amine oxidase in rats.

Experimental Section[15]

Ethyl *cis*-*trans*-2-Cyclohexyloxycyclopropanecarboxylate (3a).—To 100 g of cyclohexyl vinyl ether[4] (**1**) in 110 ml of dry xylene and 2 g of copper bronze warmed at 110° with stirring, a solution of 133 g of ethyl diazoacetate (**2**)[5] in 130 ml of dry xylene was added dropwise at such a rate a sto maintain the reaction temperature between 110–120° and avoid too vigorous a reaction. After the addition, the reaction was continued until no more nitrogen was evolved and then for 3 additional hr. The solvent and volatile products were removed *in vacuo* (nitrogen) at 50°. The residual oil was fractionated and the colorless ester was collected at 106–108° (2 mm); yield 145 g (85%). Vpc showed two peaks representing 78 and 17% and four minor peaks; ν^{CHCl_3} 2976, 1706, 1024 cm^{-1} as well as bands in the ether regions.

Anal. Calcd for $C_{12}H_{20}O_3$: C,67. 92; H, 9.43. Found: C, 67.73; H, 9.23.

Ethyl (±)-*trans*-2-Cyclohexyloxycyclopropanecarboxylate (3b).—One liter of dry xylene was added to a solution of 23 g of sodium dissolved in 500 ml of absolute ethanol. The ethanol and much of the xylene were distilled under nitrogen. The solution was permitted to cool and sodium ethoxide crystallized. Then 1 l. of dry 1,2-dimethoxyethane was added followed by 212 g of *cis*-*trans* **3a** and the mixture was refluxed with stirring for 16 hr. The solution was cooled to 0° and neutralized with 6 *N* HCl. It was then concentrated *in vacuo* (nitrogen), the residue was treated with water, adjusted to pH 3 with acid, and extracted with ether. The dried ethereal solution was concentrated, and the residual oil was distilled to give the colorless ester, bp 86–89° (1 mm), yield 161 g. Vpc showed a single peak amounting to at least 97%; the infrared spectrum ($CHCl_3$) is superimposable on the spectrum of **3a** and the nmr spectrum is compatible with the proposed structure.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 68.12; H, 9.46.

(±)-*trans*-2-Cyclohexyloxycyclopropanecarboxylic Acid (4).—A solution of 161 g of *trans* ester **3b** in 370 ml of ethanol was added to a solution of 60 g of NaOH in 75 ml of water and refluxed 5 hr. After distilling most of the ethanol *in vacuo* (nitrogen), the residue was dissolved in water and adjusted to pH 3 by the addition of 6 *N* HCl. The resulting oil crystallized upon scratching. After standing at 0° for 16 hr, the product was filtered, washed with a small amount of water, and recrystallized from 40% ethanol. The hot solution was clarified by rapid filtration, and the filtrate was cooled and scratched to induce crystallization of the compound in the form of fine crystals. If permitted to crystallize slowly, the acid is obtained as a lump and, in this form, is of inferior quality; yield 106 g (76%). It was dried in a vacuum desiccator at room temperature; mp 77–79°. Vpc showed one peak; ν^{CHCl_3} 3500, 3000, 2600 region, 1685, 1098, and 1025 cm^{-1}.

(±)-*trans*-2-Cyclohexyloxycyclopropylamine (9).—To a stirred solution of 60 g of acid **4** in 150 ml of acetone and 75 ml of water at −5°, a solution of 40.5 g of triethylamine in 300 ml of acetone was added. After stirring for a short time, a solution of 43.5 g of ethyl chloroformate in 100 ml of acetone was added, and stirring at −5° was continued for 30 min longer. Then, a solution of 32.5 g of NaN_3 in 200 ml of water was added, and stirring was continued for an additional 2 hr between −5 and 0°. The reaction mixture was poured into an ice-cold saturated solution of NaCl and extracted several times with ether. The combined ethereal extracts were dried ($MgSO_4$) and filtered, and the filtrate was added to 1 l. of absolute ethanol. This solution was heated gently on the steam bath to distil the ether slowly, and the resultant solution was refluxed for 6 hr. The ethanol was then removed *in vacuo* from a water bath to yield 65 g of crude urethan. This product was treated with 300 ml of 40% aqueous NaOH solution and refluxed for 36 hr. The solution was cooled and exhaustively extracted with ether, the extract was washed with water, dried, filtered, and concentrated. The residual oil was distilled *in vacuo* and the amine was collected at 50–60° (1 mm), yield 22 g (47%) over-all from the acid. Vpc showed a single peak; ν^{CHCl_3} 3330, 1600 broad, 1151, 1088, and 1024 cm^{-1}.

(±)-*trans*-2-Cyclohexyloxycyclopropylamine Hydrochloride (10).—The base **9** was dissolved in anhydrous ether and saturated

(14) J. D. Graham and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962); H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **40**, 875 (1964); T. Shono, T. Morikawa, A. Oku, and R. Oda, *Tetrahedron Letters*, 791 (1964).

(15) The infrared spectra were determined on a Beckman IR 5 double-beam spectrophotometer with NaCl optics (with references to L. J. Bellemy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958). Gas chromatography analyses were carried out on a Beckman GC 2A gas chromatograph, Thermotra C temperature programmer, and Sargent recorder Model SR. The nmr spectra were obtained with Varian A-60 spectrophotometer on 10–15% (w/v) solutions of samples in $CDCl_3$ with Me_4Si as the internal standard. Accuracy limits are about $\tau \pm 0.02$ ppm for chemical shifts and ±0.2 cps for coupling constants. The melting points were determined on a Uni-Melt Thomas–Hoover capillary melting point apparatus and are corrected.

TABLE II

PHARMACOLOGICAL DATA[a]

Compd	5-HTP[b] potentiation ED50, mg/kg ip	× M[c]	DOPA[d] potentiation ED50, mg/kg ip	× M[c]	MAO *in vitro* inhib. 50% inhib, *M*	× M[c]	Amine oxidase (rats) Brain ED50, mg/kg	× M[c]	Liver ED50, mg/kg	× M[c]	Heart ED50, mg/kg	× M[c]
(±)-*trans*-$C_6H_{11}OCHCHNH_2$ (CH$_2$ bridge)	3	20	2	25	1.85×10^{-7}	29	0.5	50	0.03	20	0.76	26
(+)-*trans*-$C_6H_{11}OCHCHNH_2$ (CH$_2$ bridge)					2×10^{-7}	26	0.29	86	0.10	7	0.25	80
(−)-*trans*-$C_6H_{11}OCHCHNH_2$ (CH$_2$ bridge)					3.5×10^{-7}	15	0.25	100	0.12	6	0.68	30
(±)-*trans*-$C_6H_{11}OCHCHNHCH_3$ (CH$_2$ bridge)	6	10	3	18	1.3×10^{-7}	4	1.5	17	3	0.2	1.5	13
(±)-*trans*-$C_6H_5OCHCHNH_2$[e] (CH$_2$ bridge)	5	12	2.5	20	1.6×10^{-7}	33	0.37	70	0.27	3	2.5	8
(±)-*trans*-$C_6H_5CHCHNH_2$[f] (CH$_2$ bridge)	1.5	40	1	75	8.6×10^{-6}	0.6	0.25	100	0.26	3	0.38	53
CH_3—C(=N)—O—C(=CH)—CONHNHCH$_2$$C_6H_5$[g]	2	30	6.7	22	8×10^{-7}	6.6	0.75	33	0.4	1.8	2.5	8

[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] 5-Hydroxytryptophan. [c] Activity in terms of iproniazid (Marsilid®) as standard. [d] 3,4-Dihydroxyphenylalanine. [e] Reference 1. [f] Parnate®, tranylcypromine, Smith Kline and French Laboratories, Inc.; A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70,** 2198 (1948). [g] Isocarboxazid (Marplan®).

with dry HCl to precipitate the salt. It was then recrystallized from a mixture of ethanol–ethyl acetate and obtained as a white crystalline compound: mp 174–176°; ν^{CHCl_3} 2800–2600 region, 1605, 1174, 1092, and 1025 cm^{-1}.

Anal. Calcd for $C_9H_{17}NO \cdot HCl$: C, 56.54; H, 9.42; N, 7.33. Found: C, 56.25; H, 9.37; N, 7.37.

Resolution of (±)-*trans*-2-Cyclohexyloxycyclopropylamine.—To a hot solution of 15 g of D-tartaric acid dissolved in 80 ml of ethanol, a solution of 15.5 g of (±)-*trans*-2-cyclohexyloxycyclopropylamine (**9**) in 20 ml of ethanol was added. Upon cooling, a crystalline product was obtained; mp 167–169°, yield 27 g, $[\alpha]^{25}D$ +15° (H_2O). Twenty grams of this product (**11**) was recrystallized once from 90% 2-propanol and then seven times from 90% ethanol to give 4 g of salt **12,** mp 171–172°, $[\alpha]^{25}D$ +31.16 (0.227 g in 25 ml of H_2O).

Anal. Calcd for $C_9H_{17}NO \cdot C_4H_6O_6$: C, 51.14; H, 7.54; N, 4.59. Found: C, 51.25; H, 7.60; N, 4.69.

The tartrate was decomposed in the usual manner to liberate the free base, (+)-*trans*-2-cyclohexyloxycyclopropylamine (**14**); the infrared spectrum ($CHCl_3$) was superimposable on previous amine spectrum. Its hydrochloride (**16**) was prepared and recrystallized from ethanol–ethyl acetate; mp 179.5–180.5°, $[\alpha]^{25}D$ +24.67 (0.2290 g in 25.0 ml of water).

Anal. Calcd for $C_9H_{17}NO \cdot HCl$: C, 56.54; H, 9.42; N, 7.33. Found: C, 56.59; H, 9.58; N, 7.30.

All the mother liquors from the above resolution recrystallizations were combined and concentrated *in vacuo* to one-third volume to obtain a crystalline tartrate precipitate; 5 g, mp 163–164.5°. The filtrate from this product was further concentrated *in vacuo* to yield 10 g of tartrate. This latter product was recrystallized five times from 2-propanol and the compound **13** thus obtained had mp 164–164.5°, $[\alpha]^{25}D$ +9.1° (0.2290 in 25.0 ml of H_2O).

Anal. Calcd for $C_9H_{17}NO \cdot C_4H_6O_6$: C, 51.14; H, 7.54; N, 4.59. Found: C, 50.80; H, 7.50; N, 4.47.

This tartrate was also decomposed in the usual manner to liberate the free base, (−)-*trans*-2-cyclohexyloxycyclopropylamine (**15**); infrared spectrum ($CHCl_3$) superimposable on previous amine spectra. Its hydrochloride (**17**) was prepared and recrystallized from an ethanol–ethyl acetate mixture; mp 176–177.5°, $[\alpha]^{25}D$ −23.90° (0.2290 g in 25.0 ml of H_2O).

Anal. Calcd for $C_9H_{17}NO \cdot HCl$: C, 56.54; H, 9.42; N, 7.33. Found: C, 56.83; H, 9.49; N, 7.29.

(±)-*trans*-2-Cyclohexyloxycyclopropanecarboxhydrazide (18).—A solution of 66 g of ethyl (±)-*trans*-2-cyclohexyloxycyclopropanecarboxylate in 150 ml of ethanol and 157 ml of 85% hydrazine hydrate was refluxed for 24 hr and concentrated *in vacuo* from a warm water bath to a yellowish syrup. After the addition of water, the product was extracted with ether which was washed with water, dried, and concentrated. The residual viscous liquid was distilled, bp 150–153° (1 mm), and the product was obtained as a very syrupy liquid; yield 38.3 g; ν^{CHCl_3} 3472, 3333, 1684, 1431, and 1025 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.60; H, 9.09; N, 14.14. Found: C, 60.93; H, 9.41; N, 14.22.

(±)-*trans*-2-Cyclohexyloxycyclopropanecarboxamide (19).—A solution of 10 g of the hydrazide **18** in 500 ml of 97% ethanol was stirred and refluxed with 80 g of Raney nickel for 3 hr.[13] The solution was filtered and concentrated *in vacuo* to obtain an oily residue. The oil was converted into a solid by drying by azeotropic distillation of benzene. It was washed with ether and recrystallized from CCl_4; yield 5 g; ν^{CHCl_3} showed bands at 3490, 3385, 1675, 1590, 1087, and 1026 cm^{-1}.

(±)-*trans*-2-Cyclohexyloxy-1-cyclopropylmethanol (20).—To a solution of 9.5 g of $LiAlH_4$ in 150 ml of anhydrous ether, 42.5 g of **3b** dissolved in 150 ml of anhydrous ether was added at a rate to maintain gentle refluxing. After completion of the addition, the reaction mixture was refluxed for an additional 3 hr. While stirring in an ice bath, the excess $LiAlH_4$ was decomposed carefully by adding 20 ml of ethanol, followed by 150 ml of water, and finally by acidification with dilute H_2SO_4. The ethereal layer was separated, washed, dried, and concentrated. The residual oil was distilled *in vacuo;* bp 85–88° (1 mm); yield 25 g; ν^{CHCl_3} 3580, 1450, 1196, 1166, and 1025 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.58; H, 10.58. Found: C, 70.81; H, 10.42.

(±)-*trans*-N-Benzyl(2-cyclohexyloxycyclopropyl)amine (21).—A solution of 20 g of amine **9** and 14.8 g of benzaldehyde in 80 ml of absolute ethanol was refluxed for 20 hr. The ethanol was removed by evaporation *in vacuo* and the resultant oil was dissolved in methanol, mixed with Raney nickel, and reduced under 3.5 kg/cm^2 pressure of hydrogen until the theoretical

amount was absorbed. The free base, bp 130–145° (1 mm), was isolated and converted into its hydrochloride which was recrystallized from ethanol; mp 163–165°; yield 17 g; ν^{CHCl_3} 3280, 1445, 1170, 1090, 1024, and 675 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO \cdot HCl$: C, 68.32; H, 8.54; N, 4.98. Found: C, 68.37; H, 8.36; N, 4.92.

(±)-*trans*-N-Benzyl-N-methyl-2-(cyclohexyloxy)cyclopropylamine (22).—A solution of 15 g of **21** and 6 g of formalin in 250 ml of methanol containing Raney nickel was reduced under 3.5 kg/cm^2 of hydrogen pressure. The theoretical amount of hydrogen was absorbed. After the catalyst was filtered and the filtrate was concentrated, the residual oil was distilled *in vacuo;* bp 115–124° (1 mm); yield 17 g; ν^{CHCl_3} 1445, 1165, 1096, 1026, and 698 cm^{-1}.

The base was converted into its hydrochloride and purified by recrystallization from 2-propanol; mp 158–159°.

Anal. Calcd for $C_{17}H_{24}NO \cdot HCl$: C, 69.15; H, 8.81; N, 4.74. Found: C, 68.93; H, 8.78; N, 4.77.

(±)-*trans*-1-Methylamino-2-cyclohexyloxycyclopropane (23).—A solution of 2.6 g of the tertiary amine **22** in 100 ml of absolute methanol containing 3 ml of 20% 2-propanolic HCl and 2 g of 10% Pd–C was shaken under 3 kg/cm^2 pressure of hydrogen until reduction was complete. The filtered solution was concentrated *in vacuo,* diluted with water, and made alkaline (NaOH), and the base was extracted with ether. The ethereal extracts were washed with water, dried, and evaporated, ν^{CHCl_3} was compatible: 3333, 1455, 1165, 1100, and 1023 cm^{-1}. The base was converted into its hydrochloride and recrystallized from ethyl acetate; mp 112–113°, yield 1.5 g.

Anal. Calcd for $C_{10}H_{19}NO \cdot HCl$: C, 58.53; H, 9.75; N, 6.82. Found: C, 58.20; H, 9.59; N, 6.82.

(±)-*trans*-1-Dimethylamino-2-cyclohexyloxycyclopropane (24).—A solution of 7.8 g of amine **9** and 9 g of formalin in 250 ml of methanol was reduced in the presence of Raney nickel and the hydrogen uptake ceased at theory. The solution was filtered, concentrated, and distilled, bp 48–53° (1 mm), yield 6.6 g. The base was converted into its hydrochloride and recrystallized from a mixture of ethanol–ethyl acetate; mp 187–189°; ν^{CHCl_3} 2500–2000 region, 1450, 1170, 1098, and 1024 cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO \cdot HCl$: C, 60.27; H, 10.04; N, 6.39. Found: C, 60.47; H, 10.26; N, 6.25.

(±)-*trans*-(2-Cyclohexyloxycyclopropyl)guanidine Nitrate (25).—A mixture of 4 g of 1-guanyl-3,5-dimethylpyrazole nitrate[16] and 3.1 g of amine **9** in 40 ml of ethanol was refluxed for 6 hr under nitrogen. The solution was evaporated to dryness *in vacuo,* and the oily residue was triturated with eight 30-ml portions of anhydrous ether to remove 3,5-dimethylpyrazole. The residual oil crystallized on standing and was recrystallized from ethyl acetate; mp 110–111°; yield 3.1 g; ν^{CHCl_3} 3420–3140 region, 1667, 1610, 1390, 1340, 1023, and 823 cm^{-1}.

Anal. Calcd for $C_{10}H_{19}N_3O \cdot HNO_3$: C, 46.15; H, 7.69; N, 21.53. Found: C, 46.10; H, 7.37; N, 21.47.

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Hypocholesterolemic Agents. VI.[1] A- and B-Ring-Modified Azacholesterols

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The potent hypocholesterolemic activity of certain diazacholesterol analogs prompted the synthesis of a series of diaza derivatives having the A and B rings modified from that of cholesterol. The comparative hypocholesterolemic activity of these compounds was examined and certain tentative suggestions regarding their structure–activity relationship were presented.

One successful approach to the development of hypocholesterolemic agents has been the preparation of compounds which will in some manner interfere with the synthesis of endogenous cholesterol. Several groups[2,3] have reported finding a significant suppression of hepatic cholesterol when cholesterol was fed to certain laboratory animals. This inhibitory effect has become known as a negative feedback control[4] mechanism involving the first irreversible step in the biosynthesis of cholesterol, that is, the conversion of hydroxymethylglutaryl-CoA to mevalonic acid.[5]

Previous publications[6,7] from these laboratories described a variety of synthetic diazacholesterol analogs which were prepared in an effort to simulate cholesterol in this feedback mechanism. Biological studies[8] demonstrated that a number of compounds were extremely potent inhibitors of cholesterol biosynthesis in animals. Subsequent clinical studies demonstrated that 22,25-diazacholestanol[9] and 20,25-diazacholesterol[10] (IIIa) caused a significant reduction in serum cholesterol levels in subjects with hypercholesterolemia and coronary atherosclerosis.

Structure–activity relationship studies with the azacholesterols suggested that a receptor site with dimensions specific for cholesterol was involved[6,7] and that adsorption of the inhibitor at the receptor site occurred *via* the less hindered α face of the steroid molecule.[1] Moreover, variation of the position of the nitrogen atom in the monoaza side-chain analogs resulted in dramatic changes in the hypocholesterolemic activity.[1] This paper represents a continuation in part of our structure–activity relationship studies and describes the synthesis and hypocholesterolemic activ-

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