11-oxo steroid a greater hypnotic activity than the 11-unsubstituted steroid. Some of these compounds have just been described as exceptional in other respects, **26** having no substituent on C-3, **4** being previously reported as a hypnotic,[3] and **33** being an ester whose free alcohol is inactive.

In two of the pairs (**72**, **104** and **73**, **105**) which were 16α-methyl steroids, the hypnotic activities were equal and in twelve (**13**, **48**; **24**, **54**; **64**, **88**; **65**, **89**; **66**, **90**; **67**, **91**; **75**, **114**; **76**, **116**; **78**, **130**; **81**, **132**; **82**, **133**; and **83**, **134**) the 11-unsubstituted steroid was the more active; indeed, five of the 11-oxo steroids (**48**, **54**, **114**, **132**, and **133**) were inactive. Induction times tended to be shorter with the 11-oxo steroids.

In all but one (**23**, **53**) of the twelve pairs for which LD_{50} values were recorded, the toxicity of the 11-oxo steroid was lower, often much lower, than that of the corresponding 11-unsubstituted compound. The therapeutic indices (LD_{50}/25-min. sleep dose) of 11-oxo steroids tended to be higher, as they were for three of the four directly comparable pairs.

11-Hydroxyl or -acetoxyl and 9,11- or 11,12-epoxide substitution diminished or abolished any hypnotic activity of the parent steroids. Water-soluble 11-hydroxy steroids were less toxic than their 11-deoxy counterparts.

Further Studies.—3α-Hydroxy-5β-pregnane-11,20-dione 3-phosphate disodium (**91**) was considered promising as an intravenous anesthetic. It formed stable aqueous solutions, had a high therapeutic index, and did not produce thrombophlebitis in experimental animals as hydroxydione did.

Two *Cynomolgus* monkeys injected intravenously with 145 and 165 mg. of **91**/kg. of body weight slept for about 130 min. (induction time 4 to 5 min.). After a dose of 385 mg./kg. another monkey slept for 5 hr.; recovery was rapid. A fourth monkey received a dose of 540 mg./kg.; it slept for more than 8 hr., and the next day it had fully recovered. Two cats injected intraperitoneally with 150 mg./kg. became surgically anesthetized in 20 or 30 min.; after a further 60 min. the sleeping cats were given intravenous doses repeatedly over a period of 105 min. The cats survived total doses of 800 or 900 mg./kg.

This steroid was tried clinically by Dr. A. H. Galley, who has kindly allowed us to describe his results. Intravenous doses of 1.0 to 1.5 g. produced sleep in adult patients. In all of them, shortly after a first injection of as little as 50 mg., an extremely unpleasant paresthesia developed. "Prickling" or "pins and needles" began in the head and extended to the trunk and legs; it was worst in the buttocks. The paresthesia ceased spontaneously after a few minutes and did not recur with subsequent doses. This symptom, also found by Robertson,[4] was considered sufficiently serious to preclude further use of the steroid. Its cause is unknown, but it may be related to the ability of the steroid to release erythrocyte potassium into the plasma,[11] or to the pyrogenicity of its parent steroid (though **81** is also pyrogenic and hydroxydione, its succinate, is not).[6,12]

Other Steroids.—The 26 other steroids we tested are listed in Table II. Some produced convulsions, but none had hypnotic activity. Selye found that one of them, 3β-hydroxyandrost-5-en-17-one 3-hemisuccinate sodium (dehydroepiandrosterone succinate) was hypnotic in the partially hepatectomized rat.[1]

(11) R. M. Atkinson, J. G. MacGregor, M. A. Pratt, and E. G. Tomich, *Biochem. Pharmacol.*, **12**, 931 (1963).

(12)(a) A. Kappas, W. Soybel, D. K. Fukushima, and T. F. Gallagher, *Trans. Assoc. Am. Physicians*, **72**, 54 (1959); (b) A. Kappas, W. Soybel, P. Ghekman, and D. K. Fukushima, *A.M.A. Arch. Internal Med.*, **105**, 701 (1960).

Synthesis of *cis*- and *trans*-2-Phenoxycyclopropylamines and Related Compounds

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In continuing the study of MAO inhibitors in these laboratories, the two 2-phenoxycyclopropylamines were synthesized and found to be potent compounds. From the various intermediates, derivatives were prepared to explore their biological potentials. Also, several substituted aryloxycyclopropylamines were synthesized to determine the relationship between chemical constitution and pharmacological activity.

In 1959, Tedeschi and co-workers[1] announced the discovery of a potent nonhydrazine monoamine oxidase inhibitor, SKF (*trans*) 385. This compound, 2-phenylcyclopropylamine hydrochloride,[2a] had been synthesized some years earlier by Burger and Yost[2b] in connection with a study of cyclized sympathomimetic amines. A preliminary report[3] indicated that the compound is more rapid in its action, of shorter duration, effective at smaller doses, and relatively free of the side effects exhibited by the hydrazine monoamine oxidase inhibitors used for the treatment of depression. However, since its clinical evaluation is complicated by its strong amphetamine-like action,[4] we decided to synthesize some related compounds which might retain the desired pharmacological activity of the new drug without this side effect. For this purpose, we synthesized *cis*- and *trans*-2-phenoxycyclopropylamine and some of its derivatives,[5] as well as several substituted aryloxycyclopropylamines. In the interim, this compound was

(1) R. E. Tedeschi, D. H. Tedeschi, L. Cook, P. A. Mattis, and E. J. Fellows, presented at the 43rd Federation Meeting, April 13-17, 1959, Atlantic City, N. J.

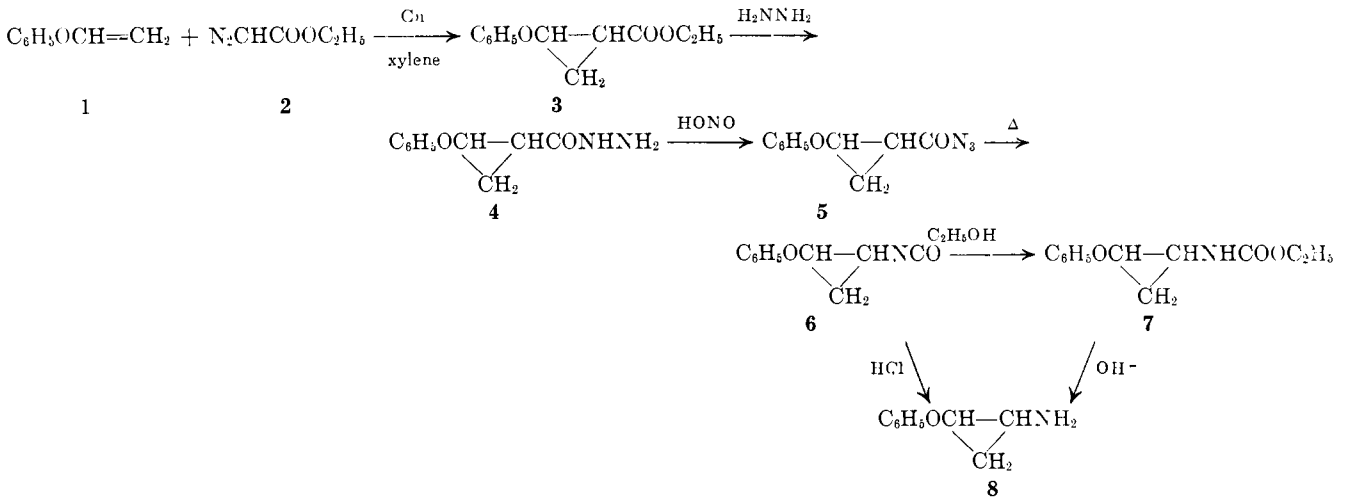
(2) (a) Parnate®, tranylcypromine, Smith Kline and French Laboratories, Inc.; (b) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).

(3) F. Lemaire, *Am. J. Psychiat.*, **117**, 249 (1960).

(4) V. J. Kinross-Wright, *Ann. N. Y. Acad. Sci.*, **80**, 840 (1959).

(5) J. Finkelstein, F. A. Smith, and J. Lee, Belgian Patent 613,910 (Feb. 21, 1961).

SCHEME I



included in an exhaustive study by Kaiser and co-workers[6a] and by Zirkle and co-workers[6b] on the effect of chemical structure upon MAO inhibition. Nevertheless, we wish to describe our chemical work and pharmacological findings in this field.

The synthesis of 2-phenoxycyclopropylamine was accomplished by the series of reactions shown in Scheme I.

The reaction between phenyl vinyl ether (1) and ethyl diazoacetate (**2**) in the presence of copper was employed by Julia[7] to obtain ethyl 2-phenoxycyclopropanecarboxylate (**3**); he hydrolyzed the ester to the corresponding acid, m.p. 112°. Since he described the one acid rather than the two possible diastereomeric acids, one might assume that the synthesis produced only one ester. Later, Looker and Braun[8] employed the same reactants but without copper and under slightly different experimental conditions, to prepare the ester **3**. They stated that no attempt was made to obtain the pure diastereomeric ethyl esters. However, upon hydrolysis they were able to demonstrate the presence of the two acids, *i.e.*, *trans*-2-phenoxycyclopropanecarboxylic acid, m.p. 113–113.7°, and the *cis* isomer, m.p. 135–137°. They therefore concluded that the latter acid was not obtained by Julia, and that the *trans* acid was his sole reaction product. In our hands, the reaction between **1** and **2** in the presence of copper produced the ester **3**, which proved to be a mixture of the *cis* and *trans* esters of **3**. The isomers were separated by redistillation through a spinning-band column and characterized. Thus, we were able to obtain a fraction which contained 87.3% of one ester and 99.4% of the other, based upon v.p.c. analyses. The interrelationship of the two ester forms was established when it was found that the 99.4% ester, which had a longer retention time could be epimerized by refluxing with sodium ethoxide in absolute ethanol into 95.1% of the other ester with the shorter retention time. We designated the ester with the shorter retention time as *trans* and the ester with the longer retention time as *cis*.

Additional evidence to confirm these designations was obtained by hydrolyzing each ester separately to its corresponding acid. Thus, the *cis* ester yielded the *cis* acid **9**, m.p. 136–138°. The *trans* ester gave the *trans* acid **10**, m.p. 111–113°. These respective melting points are in good agreement with those previously reported.[8]

It will be noted that the synthesis favored the formation of the thermodynamically more stable *trans* form by a ratio of approximately 3:1 over the *cis* form. A study of the Dreiding models indicated that phenyl vinyl ether and carbethoxycarbene, during reaction, develop a considerable crowding effect in an attempt to form the *cis* isomer. In the formation of the *trans* product, the two bulky groups do not interfere with each other. In retrospect, this relationship in yield of the *cis* and *trans* isomers, can be detected by careful comparison of the infrared spectrum of the mixture, as obtained, with the spectra of the pure *cis* and *trans* esters.

Having prepared the ester **3** in *cis* and *trans* forms, each was then treated separately by the same series of reactions. Thus, the *cis* and *trans* hydrazides **4** were prepared by refluxing the esters with 85% hydrazine hydrate in ethanol. The hydrazides were then subjected to the Curtius degradation.[9] Proceeding through the azides **5**, isocyanates **6**, and urethans **7**, we encountered no unexpected difficulties. However, the urethan was extremely resistant to hydrolysis and poor yields of the amines **8** were obtained. Then, it was found that the isocyanates **6** could be isolated and when these were hydrolyzed with concentrated HCl, high yields of the amines **8**, *cis* and *trans*, were obtained as readily distillable colorless liquids which formed pure salts, such as oxalates, maleates, and nonhygroscopic hydrochlorides. The designations of the amines as *cis* and *trans*, since they were obtained from their respective *cis* and *trans* esters, is based upon related and direct evidence. There is overwhelming evidence that the Curtius rearrangement occurs with retention of optical and geometric configuration.[10] Our own n.m.r. studies, presently to be discussed in detail, revealed that the coupling constant for the *trans* amine, obtained from the *trans* ester, is also smaller than that for the *cis* amine, obtained from the *cis* ester. Had there been any

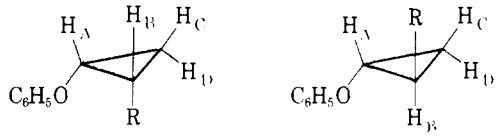
(6) (a) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *J. Med. Pharm. Chem.*, **5**, 1243 (1962); (b) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *ibid.*, **5**, 1265 (1962).

(7) M. Julia, *Bull. soc. chim. France*, 181 (1956).

(8) J. H. Looker and L. L. Braun, *J. Org. Chem.*, **23**, 933 (1958).

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

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



cis
Ia, R = COOH
b, R = $COOC_2H_5$
c, R = NH_2

trans
IIa, R = COOH
b, R = $COOC_2H_5$
c, R = NH_2

Figure 1.

change in configuration, these values would have been reversed.

The n.m.r. studies of the *cis* and *trans* esters, acids, and amines supplied invaluable evidence to support the structural configurations and relationships. Table I contains the pertinent n.m.r. data and Figure 1 illustrates the proton designations. Information about the stereochemistry of the disubstituted cyclopropanes can be obtained from H_A which appears at a lower field than the other cyclopropyl hydrogens due to the deshielding effect of the phenoxide group. In the *trans* series, the eight-line pattern of H_A is sufficiently distorted so that a first-order analysis is not possible. In Ia, H_A appears as two overlapping triplets with $J_{AD} = 5.0$ c.p.s. and $^1/_2(J_{AB} + J_{AC}) = 6.7$ c.p.s. (the appearance of a triplet does not necessitate that $J_{AB} = J_{AC}$). H_A is also two triplets in Ib with $J_{AD} = 4.8$ c.p.s. and $^1/_2(J_{AB} + J_{AC}) = 6.7$ c.p.s. The first-order estimates for the coupling constants for Ic are: $J_{AB} = 5.3$ c.p.s. and $J_{AD} = 3.6$ c.p.s.

TABLE I

CHEMICAL SHIFTS AND SUM OF COUPLING CONSTANTS FOR H_A

Comod.	Chemical Shift for H_A, τ	$J_{AB} + J_{AC} + J_{AD}$, c.p.s.
Ia	5.95	18.2
IIa	5.87	13.2
Ib	6.05	18.2
IIb	5.95	13.0
Ic	6.42	16.0
IIc	6.43	11.7

Even though a first-order comparison of J_{AB} in the *cis* and *trans* structures is not possible, the sums of J_{AB}, J_{AC}, and J_{AD} can be obtained from the width of the multiplets. $(J_{AC} + J_{AD})$ should be approximately the same in the *cis*- and *trans*-substituted cyclopropanes. Therefore, the sum should reflect the difference in J_{AB}. Table I gives the sum of J_{AB}, J_{AC}, J_{AD} as being largest for the *cis* structures which agrees with *cis* coupling constants being larger than *trans* for cyclopropyl compounds. This agrees with recent published data.[11]

In testing the *cis*- and *trans*-2-phenoxycyclopropylamines (**8**), it was found that within the limits of biological variations, there are no consistent differences in activity as MAO inhibitors. This result agrees with that of Belleau, *et al.*,[12] who discovered that the monoamine oxidase lacks optical specificity, substrate specificity, and does not distinguish between geometric isomers. These facts simplified matters and all further work was carried out with the *trans* amine. Also, in repeated preparations, the *cis-trans* mixture of the esters **3**, as obtained, was subjected to epimerization to produce the essentially pure *trans* ester which eliminated the separation procedure.

The possibility of synthesizing the 2-phenoxycyclopropylamine (**8**) by other routes was investigated. Two such methods studied were the Hofmann degradation and the Lossen rearrangement.

The compound required for the Hofmann degradation, 2-phenoxycyclopropanecarboxamide (**11**) could not be obtained by treating the ester **3** with ammonia. However, it was readily obtained from the hydrazide (**4**) by the Ainsworth[13] method of hydrogenolysis with Raney nickel. The amide **11** was then treated with bromine in NaOH solution[14] to form the N-bromoamide which rearranged to the azide and this was hydrolyzed to the amine **8**. The 2-phenoxycyclopropanecarbohydroxamic acid (**12**) required for the Lossen rearrangement was prepared from the ester **3** and hydroxylamine. This was then treated with thionyl chloride[15] to produce the isocyanate which was hydrolyzed in the established manner to 2-phenoxycyclopropylamine (**8**). Both of these procedures were inferior to the Curtius reaction.

To investigate further the biological potential of the 2-phenoxycyclopropyl group, we prepared a variety of derivatives for screening. By reducing ethyl 2-phenoxycyclopropanecarboxylate (**3**) with lithium aluminum hydride, 2-phenoxy-1-cyclopropylmethanol (**13**) was obtained. Also, from the ester **3**, the β-diethylaminoethyl ester (**14**), the β-diethylaminoethylamide (**15**), and the benzylhydrazide (**16**) were prepared. From 2-phenoxycyclopropylisocyanate we prepared the toluenesulfonylurea (**17**), the *p*-trifluorophenylsulfonylurea (**18**), *p*-chlorophenylsulfonylurea (**19**), and the *m*-nitrophenylsulfonylurea (**20**). Starting with 2-phenoxycyclopropylamine (**8**), the following amino derivatives were made: propynyl (**21**), dimethylamino (**22**) and its methiodide (**23**), the chloroacetamide (**24**) which was converted into the diethylaminoacetamide (**25**), the guanide (**26**), and the 3,4,5-trimethoxybenzamide (**27**). A higher homolog, 1-aminomethyl-2-phenoxycyclopropane (**28**), was prepared by reducing 2-phenoxycyclopropanecarboxamide (**11**) with lithium aluminum hydride.

We also expanded the program to include substituted aryloxycyclopropylamines in order to study the relationship between chemical constitution and MAO inhibition. These compounds were synthesized from their esters[5] by a series of reactions similar to those employed for the preparation of 2-phenoxycyclopropylamine (**8**). Based on previous information, these esters were not separated into their *cis* and *trans* forms. The corresponding hydrazides are listed in Table II. Their respective substituted aryloxycyclopropylamines are listed in Table III.

Biological Results.—Table IV reveals the *in vivo* and *in vitro* MAO-inhibitory activities of the various aryloxycyclopropylamines synthesized and their comparison with other active compounds. How-

(11) J. D. Graham and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962); H. M. Hutton and T. Schaeffer, *Can. J. Chem.*, **40**, 875 (1962); for a discussion on the analyses of triplet structures for ABX systems, see John D. Roberts, "An Introduction to Spin-Spin Splitting in High Resolution Nuclear Magnetic Resonance Spectra," W. A. Benjamin and Co., New York, N. Y., 1961, pp. 76–77.

(12) B. Belleau, M. Frang, J. Burba, and J. Moran, *J. Am. Chem. Soc.*, **82**, 5752 (1960).

(13) C. Ainsworth, *Science*, **76**, 5774 (1954).

(14) E. S. Wallis and J. F. Lane, *Org. Reactions*, **3**, 267 (1946).

(15) J. B. Dickey, J. M. Staley, and T. E. Stanin, U. S. Patent 2,394,567 (1946); *Chem. Abstr.*, **40**, 2848[8] (1946).

TABLE II

2-SUBSTITUTED CYCLOPROPYLCARBOXHYDRAZIDES

RCH—CHCONHNH$_2$
\ /
CH$_2$

No.	R	M.p., °C.[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
29	*p*-$(CH_3)_2NC_6H_4O$	151–153	$C_{12}H_{17}N_3O_2$	61.27	7.23	17.87	61.22	7.54	17.97
30	*p*-$CH_3OC_6H_4O$	140–141	$C_{11}H_{14}N_2O_3$	59.43	6.32	12.64	59.38	6.56	12.85
31	*p*-FC_6H_4O	138–140	$C_{10}H_{11}FN_2O_2$	57.14	5.24	13.33	57.04	5.55	12.65
32	*o*-$CH_3C_6H_4O$	137–139	$C_{11}H_{14}N_2O_2$	64.05	6.84	13.58	63.76	6.73	13.66
33	*p*-$CH_3C_6H_4O$	163–165	$C_{11}H_{14}N_2O_2$	64.05	6.84	13.58	64.30	6.88	13.52
34	*p*-ClC_6H_4O	148–149	$C_{10}H_{11}ClN_2O_2$	52.93	4.86	12.36	52.90	4.60	12.82

[a] Water was used as the solvent.

TABLE III

2-SUBSTITUTED CYCLOPROPYLAMINES

RCH—CHNH$_2$
\ /
CH$_2$

No.	R	Base b.p., °C. (mm.)	Salt	M.p., °C. (solvent)	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
35	*p*-$(CH_3)_2NC_6H_4O$	125–135 (2.5)	$C_{11}H_{16}N_2O\cdot 2HCl$	211–213 (CH_3OH)	49.81	6.79	10.56	49.70	7.07	10.01
36	*p*-$CH_3OC_6H_4O$	110–115 (2)	$C_{10}H_{13}NO_2\cdot HCl$	184–186 (*i*-PrOH)	55.81	6.51	6.51	56.16	6.60	6.74
37	*p*-FC_6H_4O	70–72 (1)	$C_9H_{10}FNO\cdot HCl$	177–179 (CH_3CN)	53.20	5.41	6.89	52.92	5.43	6.80
38	*o*-$CH_3C_6H_4O$	88–92 (2)	$C_{10}H_{13}NO\cdot HCl$	212–214 (*i*-PrOH)	60.17	7.06	7.01	60.08	7.36	6.98
39	*p*-$CH_3C_6H_4O$	74–76 (1)	$C_{10}H_{13}NO\cdot HCl$	168–170 (*i*-PrOH)	60.17	7.06	7.01	60.18	6.97	6.89
40	*p*-ClC_6H_4O	94–97 (1.5)	$C_9H_9NO\cdot 2HCl$	193–195 (*i*-PrOH)	49.11	5.04	6.36	48.86	4.97	6.26

ever, our findings for the *cis*- and *trans*-2-phenoxycyclopropylamines are not in agreement with those published,[6b] where it was demonstrated that the *cis* compound is ten times as active as the *trans*. These variations may be due to the different testing methods employed.

In our laboratories, the *in vivo* tests were conducted in mice, and the *cis* isomer was found to be slightly more active than the *trans* in the potentiation of 5-HTP and DOPA. This qualitatively agrees with the reported findings where the tryptamine convulsant test in rats was used.[6b] Furthermore, in our *in vivo* rat tests, it was discovered that the *cis* isomer is less active on the brain, equally as active on the liver, and more active on the heart than the *trans* form. Our *in vitro* tests were performed on the rat liver mitochondria in contrast to their[6b] using the normal rat brain homogenate, and here we found the *cis* less active. Therefore, our conclusion is that there is no consistent difference between the *cis*- and *trans*-2-phenoxycyclopropylamines when measured in the six tests for MAO inhibition used in these laboratories.

The duration of action for the *trans*-2-phenoxycyclopropylamine (8) is between 5 and 9 days, while that for tranylcypromine[2a] is 2 to 5 days and for isocarboxazid it is approximately 30 days. It possesses moderate appetite depressant effects in rats and stimulates the locomotor activity in rats.

The acute toxicity (LD_{50}, 72 hr.) in mice was 43 ± 6 mg./kg. i.p. and 71 ± 6 mg./kg. *p.o.* The result of subacute toxicity studies of *trans*-2-phenoxycyclopropylamine conducted in rats and dogs revealed this nonhydrazine amine oxidase inhibitor to be a well-tolerated drug. Administration of 100 mg./kg. produced a marked retardation of growth in rats but lower doses (10 and 1 mg./kg.) were without effect. This highest dose of 100 mg./kg. is approximately 75 times greater than the ED_{50} for inhibition of brain amine oxidase in this species. Food consumption, hematological, gross, and microscopic findings did not indicate drug-induced pathology. Administration of 20 mg. of *trans*-2-phenoxycyclopropylamine to dogs produced signs of sympathomimetic stimulation resembling the effects produced by amphetamine, whereas 5 mg./kg. did not elicit signs of drug activity. These doses exerted no unusual toxic manifestations following repeated administrations to dogs and rats.

Compounds **13–28** were also tested for MAO inhibition (*in vivo* and *in vitro*), HTP potentiation, and DOPA potentiation, and found to be inactive.

Experimental[16]

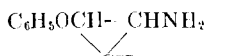
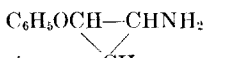
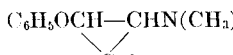
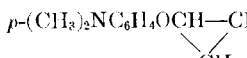
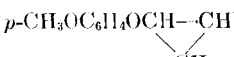
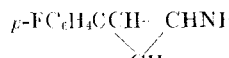
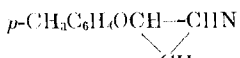
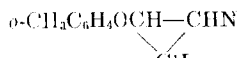
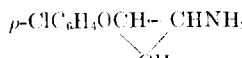
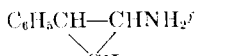
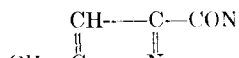
Ethyl *cis–trans*-2-Phenoxycyclopropanecarboxylate (3).—A solution of 695.5 g. of phenyl vinyl ether[17] (1) in 700 ml. of dry

(16) The infrared spectra were determined on a Beckman IR 5 double-beam spectrophotometer with NaCl optics (with references to L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954). Gas chromatographic analyses were carried out on a Beckman GC 2A gas chromatography, Thermotra C temperature programmer, and Sargent recorder Model SR. The preparative g.c. runs were made on 50–65-μl. samples using a Perkin-Elmer Model 154C vapor fractometer on a 2.5 m. × 12.5 mm. i.d. glass column, packed with 15% DC 710-85% Celite 545 at 200° with a He rate about 350 cc./min. The n.m.r. spectra were obtained with a Varian A-60 spectrometer on 10–15% (w./v.) solutions of samples in deuterated chloroform with tetramethylsilane as the internal standard. Accuracy limits are about τ ±0.02 for chemical shifts and ±0.2 c.p.s. for coupling constants. The melting points were obtained on a Uni-Melt Thomas–Hoover capillary melting point apparatus and are corrected.

(17) S. M. McElvain and B. Fajardo-Pinzon, *J. Am. Chem. Soc.*, **67**, 650 (1945).

TABLE IV

PHARMACOLOGICAL DATA[a]

Compd.	5-HTP[b] potentiation ED_{50}, mg./kg. i.p.	× M[d]	DOPA[c] potentiation ED_{50}, mg./kg. i.p.	× M[d]	MAO *in vitro* inhib. 50% inhib., *M*	× M[d]	Amine oxidase (rats) Brain ID_{50}, mg./kg.	× M[d]	Liver ID_{50}, mg./kg.	× M[d]	Heart ID_{50}, mg./kg	× M[d]
 *trans*	5	12	2.5	20	1.6×10^{-7}	33	0.37	70	0.27	3	2.5	8
 *cis*	3	20	1.7	26	4.0×10^{-7}	13	0.75	33	0.25	3	0.98	20
	13	4	15	3	2.1×10^{-6}	2.5	3	8	2.5	0.3	5.8	3.4
	3.0	20	15	3	7.7×10^{-6}	0.7	7.0	3.6	1.5	0.5	10	2
	15	4	10	5	10^{-6}	5.3	0.4	60	0.38	2	6	3.3
	5	12	3	25	4×10^{-7}	13	1.0	25	0.7	1	1.0	20
	10	6	10	5	4.8×10^{-7}	11	1	25	0.2	3.5	6	3.3
	4	15	5	10	1.85×10^{-7}	29	0.6	42	0.2	2.3	0.7	29
	25	2	40	1	7.9×10^{-7}	7	4.4	5.7	3.0	0.2	8	2.5
 *trans*	1.5	40	1	75	8.6×10^{-6}	0.6	0.25	100	0.26	3	0.33	53
	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] 3,4-Dihydroxyphenylalanine. [d] Activity in terms of iproniazid (Marsilid®) as standard. [e] Prepared from *cis-trans* mixture of isters. [f] Ref. 2a. [g] Isocarboxazid (Marplan®).

xylene plus 2 g. of copper powder was stirred and heated to 120°. Then a solution of 935 g. of ethyl diazoacetate[18] (**2**) in 1 l. of dry xylene was added dropwise and at such a rate as to maintain the reaction temperature and avoid too vigorous a reaction. When all had been added and the evolution of nitrogen had ceased, the reaction mixture was refluxed for 1 hr. The solvent and volatile products were removed *in vacuo* (nitrogen) at water bath temperature. The residual oil was fractionated through a 30-cm. Vigreux column, and the colorless ester was collected at 113–115° (1 mm.); yield 1001.5 g. (84%).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 70.83; H, 6.96.

V.p.c. showed 66.1% at 7.6 min., 27.5% at 9.4 min., with 4 minor impurities to account for 100%. By applying v.p.c. preparative methods, pure samples of the 7.6-min. ester (*trans*) and the 9.4-min. ester (*cis*) were obtained. Essentially, the infrared spectra of these compounds contained common characteristic bands. However, upon superimposition, the finger print region clearly revealed bands that were present only in the individual spectrum and not common to both. These respective bands may be considered to be characteristic for identifying the pure *trans* and *cis* forms. Infrared bands common to pure *cis* and pure *trans* ester are 2611, 1730, 1248, 1038, 1026, and 968 cm.$^{-1}$; infrared bands found only in pure *trans* ester are 1350, 1164, 1149, 1091, 1074, 1035, 1004, and 966 cm.$^{-1}$; infrared bands found only in pure *cis* ester are 1325, 1163, 1147, 1124, 1087, 1074, 1053, 1026, and 1005 cm.$^{-1}$.

Separation of *cis* and *trans* Esters (3).—A 500-ml. portion of the above *cis-trans* ester mixture was slowly redistilled at 1.5 mm. through a 1.65-m. spinning-band column. The following fractions were separated: fraction I, b.p. 68–102° (30 ml.), $n^{25}D$ 1.4810, v.p.c. analysis, 68.3% from 1–4 min., 29.5% at 7 min. 23 sec. (*trans*), 2.2% at 9 min. 4 sec (*cis*); fraction II, b.p. 102–109° (350 ml.), $n^{25}D$ 1.5065, v.p.c. analysis, 87.3% at 7 min. 34 sec. (*trans*), 9.3% at 9 min. 14 sec. (*cis*), infrared spectrum similar to infrared spectrum of v.p.c. preparative *trans* sample (*Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.79. Found: C, 69.79; H, 6.91.); fraction III, b.p. 110–113° (41 ml.), $n^{25}D$ 1.5100, v.p.c. analysis, 33.5% at 7 min. 23 sec. (*trans*), 66.4% at 9 min. 44 sec. (*cis*); fraction IV, still residue (60 ml.), $n^{25}D$ 1.5090, v.p.c. analysis, 6.4% at 7 min. 3 sec. (*trans*), 90.2% at 9 min. 48 sec. (*cis*). When this fraction was redistilled, the *cis* ester was obtained 99.4% v.p.c. pure and its infrared spectrum was superimposable on the spectrum of the *cis* v.p.c. preparative sample.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.79. Found: C, 70.02; H, 7.06.

Epimerization of Ethyl *cis*-2-Phenoxycyclopropanecarboxylate to the *trans* Ester (3). Sodium Ethoxide Method.—A solution of 1.84 g. of sodium in 100 ml. of absolute ethanol and 11 g. of *cis* ester (99.4%) was refluxed for 20 hr., and then the solvent was distilled *in vacuo*. The residue was diluted with 50 ml. of water and acidified with 3 *N* HCl. No acid crystallized. The solution was extracted with ether, washed free of alkali, dried, and distilled. The *trans* ester boiled at 97–98° (1 mm.). By v.p.c. analysis, it was shown to contain 95.1% of *trans* ester and 4.9% of the starting *cis* ester.

Potassium *t*-Butoxide–Ethanol Method.—A solution of 31 g. of ester **3** (86.6% *cis* and 13.4% *trans*) in 250 ml. of absolute ethanol containing 8.4 g. of potassium *t*-butoxide was refluxed for 20 hr. The excess solvent was distilled *in vacuo*, and the residue was worked up as above. By v.p.c. analysis, it was shown to contain 95.0% of *trans* ester and 5.0% of *cis* ester. The infrared spectrum was indistinguishable from the authentic v.p.c. *trans* preparative sample.

When the epimerization with potassium *t*-butoxide was conducted in *t*-butyl alcohol, 72.2% of *trans* ethyl ester was obtained and ester interchange to the extent of 21.8% took place.

Epimerization of Ethyl *cis-trans*-2-Phenoxycyclopropanecarboxylate to the *trans* Isomer.—(The *cis-trans* ester mixture as obtained from the reaction contained, by v.p.c. analysis, 7.0% of volatile impurities, 67.0% of *trans*, and 26.0% of *cis* ester.) A solution of 93 g. of this product in 375 ml. of absolute ethanol containing 25.2 g. of potassium *t*-butoxide was refluxed for 20 hr. Worked up as above, the product obtained showed a correct analysis for 92.8% of *trans* and 3.2% of *cis* esters along with 4% of combined more volatile products. The infrared spectrum agreed very well over the entire range with the pure sample.

***cis*-2-Phenoxycyclopropanecarboxylic Acid (9).**—A solution of 41.2 g. of ethyl *cis*-2-phenoxycyclopropanecarboxylate in 100 ml. of ethanol containing 12 g. of NaOH and 15 ml. of water was refluxed for 3 hr. The white sodium salt of the acid precipitated from the solution. Most of the solvent was removed *in vacuo*. The residue was diluted with 50 ml. of water and acidified with dilute HCl. The crystalline product was filtered and washed free of acid; yield 33.5 g. (94.4%), m.p. 136–138°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.62. Found: C, 67.46; H, 5.59.

***trans*-2-Phenoxycyclopropanecarboxylic Acid (10).**—A solution of 41.2 g. of ethyl *trans*-2-phenoxycyclopropanecarboxylate in 100 ml. of ethanol containing 12 g. of NaOH in 15 ml. of water was refluxed for 3 hr. A very small amount of the sodium salt precipitated from solution. After distilling most of the solvent *in vacuo*, water was added, and the solution was acidified with dilute HCl to produce a crystalline product. It was filtered, washed free of acid, and dried; yield 32 g. (90.1%). After recrystallization from water and drying in high vacuum at 80°, it melted at 111–113°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.62. Found: C, 67.78; H, 5.60.

The infrared spectra of the pure *cis* and the pure *trans* acids possessed characteristic bands in common for the functional groups. However, bands that appeared in each exclusively that may be considered to be indigenous are: *cis* acid, 800, 880, 1080, 1087, 1108, 1227, and 1340 cm.$^{-1}$; *trans* acid, 820, 870, 893, 900, 1092, and 1299 cm.$^{-1}$.

***cis*-2-Phenoxycyclopropanecarboxhydrazide (4).**—A solution of 61 g. of *cis* ester **3** in 65 ml. of absolute ethanol and 220 ml. of 85% hydrazine hydrate was refluxed for 24 hr. Most of the ethanol was removed by distillation, and refluxing was continued for an additional 10 hr. The mixture was cooled and held at 0° until crystallization was complete. The product was then filtered, washed with cold water, and dried; yield 47 g. (82.5%), m.p. 143–144.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.46; H, 6.25; N, 14.60. Found: C, 62.31; H, 6.25; N, 14.61.

***trans*-2-Phenoxycyclopropanecarboxhydrazide (4).**—As above, 363 g. of *trans* ester **3** was allowed to react with hydrazine hydrate to yield 254 g. (75%) of this product, m.p. 132–134°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.46; H, 6.25; N, 14.60. Found: C, 62.63; H, 6.48; N, 14.63.

The infrared spectra of the *cis* hydrazide and the *trans* hydrazide contained the expected characteristic group bands. However, bands which appeared in each exclusively and which may be considered to be indigenous are: *cis* hydrazide, 804, 847, 980, 1025, 1107, and 1370 cm.$^{-1}$; *trans* hydrazide, 714, 836, 935, 970, 1036, 1091, 1250, 1333, and 1390 cm.$^{-1}$.

***trans*-2-Phenoxycyclopropylisocyanate (6).**—A solution of 120 g. of *trans*-hydrazide **4** in 960 ml. of water and 108 ml. of 6 *N* HCl was diazotized at 0° with 48 g. of sodium nitrite dissolved in 110 ml. of water. After completion of the reaction, the oily product was extracted with ether and dried. The dried solution was added to 900 ml. of dry toluene and warmed on the steam bath. As soon as the ether was removed by distillation, evolution of nitrogen commenced and continued at a vigorous rate. After all the nitrogen had been eliminated, the solution was refluxed for 5 hr. and then it was evaporated *in vacuo* under nitrogen. The brown residual liquid was fractionated and the product, b.p. 95–96° (1.5 mm.), was collected as a clear, colorless liquid, yield 78 g. (74%).

Anal. Calcd. for $C_{10}H_9NO_2$: N, 7.99. Found: N, 8.05.

Ethyl *trans*-(2-Phenoxycyclopropyl)carbamate (7).—A solution of 20 g. of isocyanate (**6**) in 100 ml. of ethanol was refluxed for 3 hr. and then was concentrated *in vacuo* under nitrogen. The residual oil was distilled at 1.5 mm. and the product boiled at 146–148°, yield 24 g. (96%); infrared ($CHCl_3$), 3448, 1736, 1238, 1033, and 693 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.26; H, 6.88; N, 6.00.

***trans*-2-Phenoxycyclopropylamine (8). A. From Carbamate.**—A solution of 20 g. of carbamate **7** in 30 ml. of acetic acid and 60 ml. of concentrated HCl was refluxed for 24 hr. and then was concentrated *in vacuo* under nitrogen from a water bath. The residue was dissolved in 100 ml. of water, and the solution was made alkaline with 10% NaOH. The base was extracted with ether, dried, filtered, and added to a solution of 10 g. of maleic

(18) F. B. LaForge, W. A. Gersdorff, N. Green, and M. S. Schecter, *J. Am. Chem. Soc.*, **17**, 381 (1952).

acid in dry ether. A yellowish precipitate formed which was recrystallized from 2-propanol; yield 5 g., m.p. 122–124°.

Anal. Calcd. for $C_9H_{11}NO \cdot C_4H_4O_4$: C, 58.88; H, 5.66; N, 5.28. Found: C, 59.10; H, 5.91; N, 5.43.

The base formed an oxalate, m.p. 162–163°, from 2-propanol.

Anal. Calcd. for $(C_9H_{11}NO)_2 \cdot C_2H_2O_4$: C, 61.84; H, 6.18; N, 7.21. Found: C, 61.84; H, 6.00; N, 7.11.

Other reagents investigated for hydrolysis of the carbamate were $Ba(OH)_2$, concentrated HCl, dilute HCl with and without acetic acid, and refluxing with NaOH. None of these methods was better than the one described above.

B. From Isocyanate 6.—A mixture of 26 g. of *trans* isocyanate **6**, 60 ml. of concentrated HCl, and 30 ml. of toluene was warmed to about 80° at which temperature the evolution of nitrogen began. It was kept at 80–90° for 12 hr., and the excess acid and solvent were removed by distillation *in vacuo*. The solid residue was dissolved in 100 ml. of water, and the solution was made alkaline with 20% NaOH solution. The oily base was extracted with ether, dried, concentrated, and distilled *in vacuo*; b.p. 87–89° (1.5 mm.); yield 18.5 g. (83%) of clear colorless liquid; maleate, m.p. 122–124° from 2-propanol.

Anal. Calcd. for $C_9H_{11}NO \cdot C_4H_4O_4$: C, 58.88; H, 5.66; N, 5.28. Found: C, 58.86; H, 5.74; N, 5.18.

The **hydrochloride**, prepared in dry ether with dry HCl, was recrystallized from a small amount of ethanol; m.p. 210–212°.

Anal. Calcd. for $C_9H_{11}NO \cdot HCl$: C, 58.20; H, 6.47; N, 7.55. Found: C, 58.55; H, 6.70; N, 7.79.

***cis*-2-Phenoxycyclopropylamine (8).**—Starting with *cis*-2-phenoxycyclopropanecarboxhydrazide (**4**), the above procedure for the preparation of azide, isocyanate, and amine was repeated without isolating any intermediates. The *cis* amine was thus obtained as a colorless liquid, b.p. 64–67° (1 mm.). Reaction with maleic acid in 2-propanol gave the *cis* **maleate salt**, m.p. 145–146°.

Anal. Calcd. for $C_9H_{11}NO \cdot C_4H_4O_4$: C, 58.88; H, 5.66; N, 5.28. Found: C, 58.66; H, 5.38; N, 5.33.

Hydrochloride had m.p. 189–191° (ethanol).

Anal. Calcd. for $C_9H_{11}NO \cdot HCl$: C, 58.20; H, 6.47; N, 7.55. Found: C, 58.04; H, 6.46; N, 7.47.

The infrared spectra of the pure *cis* amine and the pure *trans* amine possessed characteristic bands in common for the functional groups. However, bands which appeared in each spectrum exclusively and which may be considered to be indigenous are: *cis* amine, 800, 827, 862, 1003, 1027, 1048, 1107, 1170, 1292, and 1344 cm.$^{-1}$; *trans* amine, 812, 845, 850, 908, 972, 1020, 1167, 1282, and 1384 cm.$^{-1}$.

***cis*-2-Phenoxycyclopropanecarboxamide (11).**—A suspension of 30 g. of hydrazide **4** in 3 l. of 95% ethanol and approximately 240 g. of moist Raney nickel was refluxed for 3 hr. The initial evolution of ammonia, which was vigorous at first, subsided after 2 hr. The reaction mixture was cooled and filtered from the nickel, and the filtrate was evaporated *in vacuo* until crystallization caused excessive bumping. The mixture was then heated to obtain complete solution, filtered hot, and the colorless filtrate was cooled to produce a colorless crystalline product; yield 10 g. (37%); m.p. 165–167°; infrared ($CHCl_3$), 3534, 3413, 3175, 3003, 1675, 1592, 1502, 1232, 1044, 1028, 1010, and 689 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.25; N, 7.90. Found: C, 67.66; H, 5.99; N, 7.78.

***cis*-2-Phenoxycyclopropylamine *via* the Hofmann Degradation.**—Sixteen grams of bromine was added dropwise to a stirred solution of 17 g. of NaOH in 130 ml. of water at 0°, and immediately followed by 11 g. of 2-phenoxycyclopropanecarboxamide (**11**). The reaction mixture was stirred as the amide slowly dissolved and then for 1 additional hr. The solution was slowly warmed up to 70°, then kept at 70–80° for 2 hr. and cooled to 0°. The insoluble matter was filtered off and the filtrate was extracted with several portions of ether. The combined ether extracts were washed with water and dried. The filtered etheral solution was treated with excess maleic acid dissolved in anhydrous ether, and the crystalline maleate was obtained; yield 1.5 g. It was recrystallized three times from 2-propanol and then melted at 149–150°. A mixture melting point with the previously prepared *cis*-2-phenoxycyclopropylamine maleate showed no depression.

Anal. Calcd. for $C_9H_{11}NO \cdot C_4H_4O_4$: C, 58.88; H, 5.66; N, 5.28. Found: C, 58.58; H, 5.39; N, 5.17.

***trans*-2-Phenoxycyclopropanehydroxamic Acid (12).**—A solution of 2.5 g. of sodium dissolved in 80 ml. of absolute methanol was added to a solution of 3.5 g. of hydroxylamine hydrochloride in 50 ml. of absolute ethanol. After swirling the mixture, NaCl was filtered, the filtrate was refluxed with 11 g. of ethyl *trans*-2-phenoxycyclopropanecarboxylate for 2 hr., and the solvent was removed *in vacuo* under nitrogen. The residue was diluted with 70 ml. of water, acidified with 3 *N* HCl to pH 3–4, and extracted with ether. Upon evaporation of the ether, a solid was obtained which was first recrystallized from water–ethanol mixture and then from benzene to obtain the pure white crystalline product; m.p. 144–146°; infrared (KBr pellet), 3300, 3150, 1613, 1258, 1228, 1027, 1013, and 692 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.69; N, 7.25. Found: C, 62.36; H, 5.91; N, 7.46.

***trans*-2-Phenoxycyclopropylamine *via* Lossen Rearrangement.**—A mixture of 7 g. of the hydroxamic acid (**12**) and 9 g. of thionyl chloride in 250 ml. of anhydrous toluene was refluxed for 3 hr. and then concentrated under reduced pressure to an oily residue. Upon distillation, 1.7 g. of the corresponding isocyanate, b.p. 95–100° (2 mm.), was collected. The distilled isocyanate was dissolved in 10 ml. of toluene, added to 10 ml. of concentrated HCl, and refluxed for 12 hr. The excess acid and solvent were removed by concentration under reduced pressure to yield a dark oily residue which was treated with 50 ml. of water. The aqueous phase was decanted from the insoluble oil, made alkaline with 20% aqueous NaOH, and extracted with several portions of ether. The combined ether extracts were washed with water and dried. The filtered ethereal solution was added to a solution of 4 g. of maleic acid in 25 ml. of dry ether. A white crystalline maleate was obtained and recrystallized from 2-propanol, m.p. 124–126°, yield 200 mg. A mixture melting point with the product obtained previously showed no depression.

Anal. Calcd. for $C_9H_{11}NO \cdot C_4H_4O_4$: C, 58.88; H, 5.66; N, 5.28. Found: C, 59.00; H, 5.79; N, 5.06.

***trans*-2-Phenoxy-1-cyclopropylmethanol (13).**—A solution of 40 g. of ethyl *trans*-2-phenoxycyclopropanecarboxylate in 120 ml. of dry ether was added dropwise to a stirred suspension of 8.6 g. of $LiAlH_4$ in 125 ml. of dry ether, and the mixture was refluxed for 2 hr. While cooling, 20 ml. of absolute ethanol was added followed by 100 ml. of cold water. The solution was then acidified with 10% H_2SO_4 and extracted with ether. After evaporation of the ether, the oil was fractionally distilled and redistilled to give a pure product; yield 25.6 g.; b.p. 105–109° (1 mm.); infrared ($CHCl_3$), 3600, 3060, 3000, 1601, 1486, 1240, 1040, 1027, and 692 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32. Found: C, 73.84; H, 7.60.

β-Diethylaminoethyl *cis*-*trans*-2-Phenoxycyclopropanecarboxylate (14).—A mixture of 12 g. of dry β-diethylaminoethanol in 50 ml. of dry toluene and 0.15 g. of clean sodium was heated to reflux in a flask with a short fractionating column. Slowly, 15 g. of ester **3** in 50 ml. of dry toluene was added and the vapor temperature dropped from 110 to 83°. After the addition, the reaction mixture was refluxed for 1 hr. and heated until the vapor temperature of the distillate reached 110°. After cooling the residue, it was extracted with 3 *N* HCl. The acid extracts were made alkaline with 4 *N* NaOH and the liberated oily base was extracted with ether. After washing, drying, and evaporating the solvent, the oil was distilled *in vacuo*, and the base was obtained as a colorless liquid, b.p. 149–151° (2 mm.).

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.35; N, 5.05. Found: C, 69.41; H, 8.08; N, 4.98.

The hydrochloride, prepared in ether with dry HCl, was obtained as a white crystalline compound. It was recrystallized from a mixture of dioxane–cyclohexane; m.p. 124–126°.

Anal. Calcd. for $C_{16}H_{23}NO_3 \cdot HCl$: C, 61.23; H, 7.71; N, 4.46. Found: C, 61.01; H, 7.97; N, 4.39.

N-(β-Diethylaminoethyl) *cis*-*trans*-2-Phenoxy-1-cyclopropanecarboxamide (15).—A mixture of 22 g. of ester **3** and 12 g. of β-diethylaminoethylamine was refluxed for 24 hr. The solution was acidified with 3 *N* HCl, and the oil which separated was removed. The acid solution was then made alkaline with dilute NaOH, the product was extracted with ether, and this solution was dried and concentrated. The residual oil was distilled *in vacuo*; b.p. 200–203° (2 mm.). The compound was a yellowish viscous material.

Anal. Calcd. for $C_{16}H_{24}N_2O_3$: C, 69.60; H, 8.75; N, 10.15. Found: C, 69.69; H, 9.04; N, 10.32.

***cis*-*trans*-2-Phenoxycyclopropanecarboxylic Acid Benzyl Hydrazide (16).**—A mixture of 31 g. of ester **3** and 18.3 g. of benzylhydrazine was heated at 150° for 3 days in an apparatus designed to permit the ethanol to distil. After cooling, the residual solid

was recrystallized from 2-propanol; m.p. 160–161°; infrared ($CHCl_3$), 3448, 1667, 1235, 1028, and 692 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.44; N, 9.92. Found: C, 72.26; H, 6.40; N, 9.68.

***cis–trans*-N-(2-Phenoxycyclopropyl)-N'-(*p*-toluenesulfonamido)urea (17).**—To a mixture of 30 ml. of triethylamine and 15 ml. of dimethylformamide, 10.9 g. of *p*-toluenesulfonamide and 11.2 g. of *cis–trans* isocyanate **6** were added. The mixture was stirred for 20 hr. at room temperature, and then heated on the steam bath for 1 hr. After cooling, 100 ml. of water was added, and the mixture was extracted with 100 ml. of ether which was discarded. The aqueous layer was made acid with dilute HCl forming a yellow oil which was extracted with ethyl acetate. After drying and evaporating the solvent, the oil was set at 0° for several days to crystallize. The product was recrystallized from methanol 4 times to give a white substance, m.p. 168–170°.

Anal. Calcd. for $C_{17}H_{18}N_2O_4S$: C, 58.96; H, 5.20; N, 8.09. Found: C, 59.32; H, 5.10; N, 7.83.

***trans*-N-(2-Phenoxycyclopropyl)-N'-(*p*-trifluoromethylbenzenesulfonyl)urea (18).**—To a mixture of 15 ml. of triethylamine and 8 ml. of dimethylformamide, 7 g. of *p*-trifluoromethylbenzenesulfonamide[19] and 5.6 g. of *cis–trans* isocyanate **6** were added, stirred at room temperature for 20 hr., and then heated on the steam bath for 1 hr. After cooling, 50 ml. of cold water was added, and the mixture was extracted with ether which was discarded. The aqueous solution was acidified with dilute HCl to produce an oil which crystallized while standing overnight. The product was filtered and recrystallized from 80% ethanol; m.p. 147–149°.

Anal. Calcd. for $C_{17}H_{15}N_2O_4$: C, 51.00; H, 3.75; N, 7.00. Found: C, 51.02; H, 3.73; N, 7.24.

***cis–trans*-N-(2-Phenoxycyclopropyl)-N'-(*p*-chlorobenzenesulfonyl)urea (19).**—Treating 30 ml. of triethylamine, 15 ml. of dimethylformamide, 12.2 g. of *p*-chlorobenzenesulfonamide,[20] and 11.2 g. of the isocyanate **6** as above, the product was obtained as a yellow crystalline compound from 95% ethanol; m.p. 161–163°.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_4S$: C, 52.46; H, 4.10; N, 7.65. Found: C, 52.70; H, 4.17; N, 7.66.

***cis–trans*-N-(2-Phenoxycyclopropyl)-N'-(*m*-nitrobenzenesulfonyl)urea (20).**—As above (**19**), the isocyanate **6** was allowed to react with *m*-nitrobenzenesulfonamide, extracted with ethyl acetate, and recrystallized from 2-propanol to obtain the yellow compound; m.p. 159–160°.

Anal. Calcd. for $C_{16}H_{15}N_3O_6S$: C, 50.92; H, 4.00; N, 11.14. Found: C, 51.87; H, 3.95; N, 11.29.

***cis–trans*-2-Phenoxy-N-(2-propynyl)cyclopropylamine (21).**—To a mixture of 14.9 g. of 2-phenoxycyclopropylamine (**8**) and 10 g. of powdered anhydrous Na_2CO_3 in 150 ml. of absolute ethanol, 12 g. of propargyl bromide was added slowly while stirring at ambient temperature, and then it was refluxed for 20 hr. It was cooled and filtered, and the filtrate was evaporated under reduced pressure to yield a solid residue which was diluted with 200 ml. of water and extracted with ether. The dried extract was concentrated and the residual oil was fractionated *in vacuo*. The product was collected at 107–111° (1 mm.), yield 10 g. The crystalline maleate melted at 106–107°.

Anal. Calcd. for $C_{12}H_{13}NO \cdot C_4H_4O_4$: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.29; H, 5.85; N, 4.63.

***cis–trans*-1-Dimethylamino-2-phenoxycyclopropane (22).**—A mixture of 7.5 g. of amine **8**, 8.5 g. of 37% formalin in 250 ml. of methanol and Raney nickel was reduced under 3 atm. of hydrogen until the theoretical amount of hydrogen was absorbed. The catalyst was filtered, and the filtrate was concentrated under reduced pressure. The oil was mixed with 50 ml. of water and extracted with ether. The dried solution was added to a dilute solution of 6 g. of maleic acid in dry ether and the crystalline salt was recrystallized from 2-propanol; m.p. 111–113°. When mixed with 2-phenoxycyclopropylamine maleate, the melting point was depressed.

Anal. Calcd. for $C_{11}H_{15}NO \cdot C_4H_4O_4$: C, 61.43; H, 6.48; N, 4.77. Found: C, 61.72; H, 6.70; N, 4.91.

***cis–trans*-1-(2-Phenoxycyclopropyl)trimethylammonium Iodide (23).**—A dried ether solution of the dimethylamino compound **22** and excess methyl iodide was kept at room temperature for 24 hr. The white crystalline product was recrystallized from 2-propanol; m.p. 171–173°.

Anal. Calcd. for $C_{12}H_{18}INO$: C, 45.14; H, 5.64; N, 4.39. Found: C, 45.34; H, 5.82; N, 4.39.

***trans*-2-Chloro-N-(2-phenoxycyclopropyl)acetamide (24).**—A mixture of 14.9 g. of amine **8** in 150 ml. of acetone and 15 g. of powdered anhydrous K_2CO_3 was cooled in an ice bath and stirred while 11.2 g. of chloroacetyl chloride was added dropwise. After the addition, the reaction was permitted to reach room temperature and then it was refluxed for 3 hr. After filtration and distillation of the solvent, the residue was suspended in 50 ml. of water. Adjustment to pH 9 with aqueous Na_2CO_3 caused the product to precipitate. It was recrystallized from ligroin (60–90°); m.p. 107–108°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.66; H, 5.33; N, 6.22. Found: C, 58.96; H, 4.95; N, 6.24.

***trans*-2-Diethylamino-N-(2-phenoxycyclopropyl)acetamide (25).**—A solution of 18 g. of **24** and 11.7 g. of diethylamine in 450 ml. of benzene was heated in an autoclave at 120° under 70.3 kg. of nitrogen pressure for 8 hr. The solution was filtered, the solvent was evaporated, and the residue was diluted with water. The pH was adjusted to 9 with Na_2CO_3 solution, and the product was extracted with ether. After evaporation of the solvent, the residual oil was distilled; b.p. 158–159° (1 mm.).

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.39; N, 10.68. Found: C, 68.55; H, 8.42; N, 10.48.

***trans*-(2-Phenoxycyclopropyl)guanidine Nitrate (26).**—A solution of 4 g. of 1-guanyl-3,5-dimethylpyrazole nitrate[21] and 3 g. of amine **8** in 40 ml. of absolute ethanol was stirred and refluxed for 6 hr. under nitrogen. The solution was evaporated *in vacuo* to a thick oil which was triturated with several portions of ether. The resulting semisolid was recrystallized from 2-propanol and then ethanol; m.p. 162–163°. Mixed with the guanyl reagent, the melting point was depressed.

Anal. Calcd. for $C_{10}H_{14}N_4O_4$: C, 47.24; H, 5.51. Found: C, 47.59; H, 5.90.

***cis–trans*-N-(2-Phenoxycyclopropyl)-3,4,5-trimethoxybenzamide (27).**—A solution of 4.6 g. of 3,4,5-trimethoxybenzoyl chloride in 12 ml. of dry benzene was added to a stirred solution of 3 g. of amine **8** in 10 ml. of dry benzene containing 3 g. of dry powdered Na_2CO_3 in suspension, and stirring was maintained for 1 hr. Cold water was added, and the solid was filtered. It was triturated with petroleum ether and recrystallized from benzene to yield colorless needles, m.p. 143–145°.

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 66.45; H, 6.12; N, 4.08. Found: C, 66.61; H, 6.42; N, 3.93.

***cis–trans*-1-Aminomethyl-2-phenoxycyclopropane (28).**—A solution of 17.5 g. of 2-phenoxycyclopropanecarboxamide (**11**) in 200 ml. of THF was added to a stirred refluxing mixture of 5 g. of $LiAlH_4$, and then refluxing was continued for an additional hour. While cooling with an ice bath, 20 ml. of methanol was added followed by 200 ml. of water. The solution was acidified with dilute HCl and then alkalized with 30% NaOH. The THF was separated with the aid of ether, and the combined extracts were evaporated on the steam bath. The residue was extracted with ether, dried, and concentrated. After two fractional distillations, 5 g. of product, b.p. 90–95° (2 mm.), was obtained as a colorless liquid. The base was converted into the hydrochloride which was recrystallized from 2-propanol and dried *in vacuo* at 100°; m.p. 190–192°.

Anal. Calcd. for $C_{10}H_{14}ClNO$: C, 60.30; H, 7.03; N, 7.03. Found: C, 59.69; H, 7.16; N, 6.83.

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