Anal. Calcd. for $C_{13}H_{13}ClN_2OS_2$: C, 48.78; H, 4.19; N, 8.96. Found: C, 48.84; H, 4.03; N, 8.78.

Fungistatic and bacteriostatic assays were performed by a serial dilution method which has been described previously.[1]

Acknowledgment.—The authors are indebted to Priscilla Griffin and Georgia Lundquist who performed the microbiological tests. The work described in this paper was supported by grant E695(C) from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service.

2-Substituted Cyclopropylamines. I. Derivatives and Analogs of 2-Phenylcyclopropylamine

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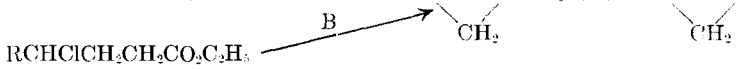
A series of analogs and derivatives of 2-phenylcyclopropylamine has been prepared in order to study relationships between chemical structure and monoamine oxidase inhibiting activity.

trans-2-Phenylcyclopropylamine[4,5] is a potent monoamine oxidase (MAO) inhibitor[6] and a clinically useful antidepressant agent. To investigate the effect of structure upon MAO inhibitory activity we have studied numerous analogs, homologs, isomers, and derivatives of this drug. Their preparation is reported in this paper; their biological activity is presented in the following article.

(1) Smith Kline and French Laboratories Postdoctoral Fellow, 1960.
(2) Smith Kline and French Laboratories Postdoctoral Fellow, 1961-1962.
(3) Smith Kline and French Laboratories Postdoctoral Fellow, 1958-1960.
(4) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).
(5) Tranylcypromine, Parnate®.
(6) R. E. Tedeschi, D. H. Tedeschi, P. L. Ames, L. Cook, P. A. Mattis, and E. J. Fellows, *Proc. Soc. Exptl. Biol. Med.*, **102**, 380 (1959); D. H. Tedeschi, R. E. Tedeschi, and E. J. Fellows, *J. Pharmacol. Exptl. Therap.*, **126**, 223 (1959); H. Green and R. W. Erickson, *ibid.*, **129**, 237 (1960).

Analogs of 2-phenylcyclopropylamine (Tables I and II) were prepared according to the scheme.



The intermediate ethyl cyclopropanecarboxylates were obtained by two general methods: condensation of ethyl diazoacetate with an olefin (Method A)[4] or cyclization of alkyl 4-aryl-4-chlorobutyrates (Method B).[7] Method A gave mixtures of *cis* and *trans* esters, in which the thermodynamically more stable *trans* isomer probably predominated,[8] whereas in Method B only *trans* esters were isolated. The esters were hydrolyzed to the corresponding acids with aqueous-ethanolic potassium hydroxide. Geometrical isomers of 2-(4-chlorophenyl)-[9,10] and 2-(3,4-methylenedioxyphenyl)-[10] cyclopropanecarboxylic acids were separated. Proof of the configuration of these acids was accomplished by ozonolysis to *cis*- and *trans*-1,2-cyclopropanedicarboxylic acids.[11] *cis* and *trans*[12] isomers of 1-methyl-2-phenylcyclopropanecarboxylic acid were obtained by selective hydrolysis[13] of the mixture of isomeric methyl esters.[14] In most instances, however, separation of isomeric acids was not performed, but the isomeric mixtures were used for further reaction.

2-Substituted cyclopropanecarboxylic acids were converted, *via* their azides, to corresponding amines by the Curtius procedure.[15] Several of the azides were obtained from the reaction of acid chlorides with sodium azide in anhydrous[16] or aqueous[17] media. In cases where decomposition or isomerization occurred in the preparation of acid chlorides, mixed carboxylic-carbonic anhydrides[18] were used in forming the azides. The azide of *trans*-2-(3,4-methylenedioxy-

(7) M. Julia, S. Julia, and B. Bémont, *Bull. soc. chim. France*, 304 (1960).

(8) For example, see (a) J. Farkaš, P. Kovářm, and F. Šorm, *Collection Czechoslov. Chem. Commun.*, **24**, 2460 (1959); (b) J. H. Looker and L. L. Braun, *J. Org. Chem.*, **23**, 930 (1958); (c) P. S. Skell and R. M. Etter, *Proc. Chem. Soc.*, 443 (1961).

(9) E. N. Trachtenberg and G. Odian, *J. Am. Chem. Soc.*, **80**, 4015 (1958).

(10) R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, *J. Org. Chem.*, **27**, 733 (1962).

(11) H. L. deWaal and G. W. Perold, *Chem. Ber.*, **85**, 574 (1952).

(12) G. W. Perold, *J. S. African Chem. Inst.*, **8**, 1 (1955).

(13) H. M. Walborsky and L. Plonsker, *J. Am. Chem. Soc.*, **83**, 2138 (1961). In the present series, selective hydrolysis of mixtures of isomeric esters was attempted only for the separation of *cis* and *trans* 2-phenylcyclopropanecarboxylic acids and *cis*- and *trans*-1-methyl-2-phenylcyclopropanecarboxylic acids. In both cases, excellent results were obtained.

(14) A. Burger, C. S. Davis, H. Green, D. H. Tedeschi, and C. L. Zirkle, *J. Med. Pharm. Chem.*, **4**, 571 (1961).

(15) P. A. S. Smith, *Org. Reactions*, **III**, 337 (1946).

(16) C. Naegeli and G. Stefanovitsch, *Helv. Chim. Acta*, **11**, 609 (1928).

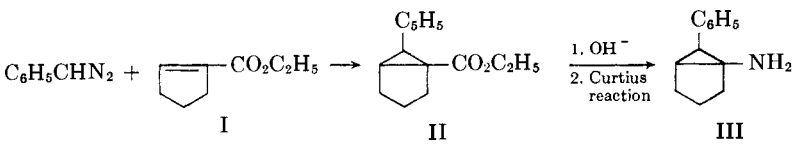
(17) H. Lindemann, *ibid.*, **11**, 1027 (1928).

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

phenyl)cyclopropanecarboxylic acid was prepared by treatment of the hydrazide of the latter with nitrous acid. Some of the azides were not isolated, but were rearranged directly to isocyanates. In those instances where the azides were isolated, rearrangement was achieved by carefully heating a solution of the azide in toluene.

A variety of conditions[15] was employed for hydrolysis of isocyanates, or carbamates derived from them, to amines. Hydrochloric acid hydrolysis was the most generally successful procedure, but in several cases a decided improvement was brought about by alkaline hydrolysis of trifluoroethyl carbamates obtained from the azide and 2,2,2-trifluoroethanol. Substituted cyclopropylamines (Tables I and II) were purified by recrystallization of their salts. Distillation of the amines generally was not attempted because of the relative instability of compounds of this type.[19]

In addition to the amines listed in Tables I and II, 1-amino-6-phenyl[3.1.0]bicyclohexane (III) was prepared by addition of phenyldiazomethane to ethyl 1-cyclopentenecarboxylate (I), hydrolysis of the ester (II), and Curtius degradation of the resulting acid *via* the mixed carboxylic–carbonic anhydride.[18]



I II III

1-Methyl-2-phenylcyclopropylamine had been synthesized earlier[14] from a mixture of *trans*- and *cis*-1-methyl-2-phenylcyclopropanecarboxylic acids. The sulfate salt obtained from this amine appeared to be homogeneous but its configuration was not determined. In the present work pure samples of the *trans* and *cis* amines and their hydrochlorides (Table II) were prepared from the isolated isomeric carboxylic acids. Chromatographically, the base obtained from the *trans* hydrochloride was identical with the amine liberated from the previously reported[14] sulfate.

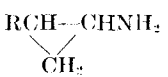
Resolution of *trans*-2-phenylcyclopropylamine was accomplished by recrystallization of its D- and L-tartrates from aqueous 2-propanol.

Several N-substituted derivatives of 2-phenylcyclopropylamine have been reported previously.[4,19] In Table III are listed descriptive and analytical data for additional compounds of this type. Synthetic details for these derivatives are given in the Experimental Part. Similar data for 2-arylcyclopropanecarboxhydrazides, -carboxamides

(19) C. Kaiser, A. Burger, L. Zirngibl, C. S. Davis, and C. L. Zirkle, *J. Org. Chem.*, **27**, 768 (1962).

TABLE I

2-SUBSTITUTED CYCLOPROPYLAMINES

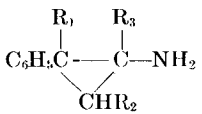


Cpd.	R	Config.[a]	M.p. of salt, °C.	Solvent of crystallization	Yield, %[b]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	4-ClC_6H_4	*trans*	195–198 dec	EtOH–Et_2O	64.5	$C_9H_{10}ClN.HCl$	52.95	52.73	5.43	5.44
2	4-$CF_3C_6H_4$		203–205	EtOH–Et_2O	33	$C_{10}H_{10}F_3N.HCl$	50.54	50.39	4.67	5.02
3	4-$CH_3C_6H_4$		158–162.5	EtOH–Et_2O	32	$C_{10}H_{13}N.HCl$	65.39	65.53	7.68	7.89
4	4-$CH_3OC_6H_4$		178.5–180.5	EtOH–Et_2O	30	$C_{10}H_{13}NO.HCl$	60.15	60.03	7.07	7.00
5	3-$CF_3C_6H_4$[c]		182–183	Me_2CO–Et_2O	54	$C_{10}C_{10}F_3N.HCl$	50.54	50.46	4.67	4.74
6	3-ClC_6H_4		177–179	EtOH–Et_2O	60	$C_9H_{10}ClN.HCl$	52.96	52.74	5.43	5.69
7	3,4-$(CH_3O)_2C_6H_3$[d]	*trans*	139.5–141.5	EtOH–EtOAc	63	$C_{11}H_{15}NO_2.C_6H_{13}NO_3S$[e]	54.82	54.72	7.58	7.67
8	3,4-$OCH_2OC_6H_3$	*trans*	206–208	EtOH–Et_2O	48	$C_{10}H_{11}NO_2.HCl$	56.21	56.23	5.66	5.71
9	3,4-$Cl_2C_6H_3$		196–198	EtOH–Et_2O	57	$C_9H_9Cl_2N.HCl$	45.31	45.46	4.23	4.53
10	2,5-$Cl_2C_6H_3$		203–205	EtOH–Et_2O	47	$C_9H_9Cl_2N.HCl$	45.31	45.38	4.23	4.34
11	2-ClC_6H_4		174.5–176.5	EtOH–Et_2O	61	$C_9H_{10}ClN.HCl$	52.96	52.93	5.43	5.69
12	$CH_3(CH_2)_4$		128.5–130	EtOH–Et_2O	31	$C_8H_{17}N.C_6H_{13}NO_3S$[e]	54.87	54.56	9.87	9.82
13	Cyclohexyl		120–122	EtOAc–Et_2O	31	$C_9H_{17}N.C_4H_4O_4$[f]	61.15	61.05	8.29	8.36
14	1-Naphthyl		213–214.5	*i*-PrOH–Et_2O	60	$C_{13}H_{13}N.HCl$	71.06	70.82	6.42	6.37
15	2-Naphthyl	*trans*	215–217	EtOH–Et_2O	17	$C_{13}H_{13}N.HCl$	71.06	71.22	6.42	6.56
16	2-Thianaphthenyl		199–204	EtOH–Et_2O	27.5	$C_{11}H_{11}NS.HCl$	58.52	58.29	5.36	5.15
17	3-Thianaphthenyl	*trans*	230–231	EtOH–Et_2O	18	$C_{11}H_{11}NS.HCl$	58.52	58.87	5.36	5.58
18	C_6H_5O[g]	*cis*	188–190 dec	*i*-PrOH	57	$C_9H_{11}NO.HCl$	58.22	58.50	6.52	6.86
19	C_6H_5O[g]	*trans*	206–208 dec	EtOH–Et_2O	66	$C_9H_{11}NO.HCl$	58.22	58.27	6.52	6.71
20	$C_6H_5CH_2$		104.5–106.5	EtOH–Et_2O	32	$C_{10}H_{13}N.HCl$	65.39	65.32	7.68	7.91
21	$C_6H_5CH_2CH_2$		149–150	EtOH–EtOAc	73	$C_{11}H_{15}N.HCl$[g]	66.83	67.62	8.16	7.97
22	C_6H_5S		186.5–188.5	EtOH–Et_2O	41	$C_9H_{11}NS.HCl$	53.58	53.86	6.00	6.21
23	2-Thienyl		139–140	MeOH–Et_2O	13	$C_7H_9NS.HCl$	47.86	47.32	5.74	5.36

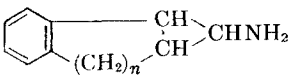
[a] Unless otherwise noted, configuration is not known; however, the products probably are mainly the *trans* isomer, see ref. 8. [b] Yield from corresponding carboxylic acid. [c] The free base was a colorless liquid, b.p. 53–55° (0.35 mm.). [d] A. Burger and G. T. Fitchett, *J. Am. Chem. Soc.*, **74,** 3415 (1952). [e] Cyclohexylsulfamate. [f] Maleate. [g] N, Calcd.: 7.08. Found: 6.89. [h] From *cis*-2-phenoxycyclopropanecarboxylic acid.[8b] [i] From *trans*-2-phenoxycyclopropanecarboxylic acid.[8b]

TABLE II

CYCLOPROPANE-RING SUBSTITUTED DERIVATIVES



Cpd.	R_1	R_2	R_3	B.p., °C. (mm.)	M.p. of salt °C.	Solvent of crystallization	Yield, %[a]	Formula	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
24[b]	CH_3	H	H	69–72 (1.1)	181–184	HCO_2Et	63	$C_{10}H_{13}N.HCl$	65.39	65.33	7.68	7.64
25[c]	H	CH_3	H	53–55 (0.3)			46	$C_{10}H_{13}N$	81.58	81.34	8.90	8.62
26[d]	C_6H_5	H	H	130–140 (0.45)	188–189 dec.	Me_2CO–MeOH	31	$C_{15}H_{15}N.HCl$	73.31	72.88	6.56	6.40
27[e]	H	C_6H_5	H	140–145 (0.5)[f]	185–187 dec.	Cyclohexane-Me_2CO	40	$C_{15}H_{15}N.HCl$	73.31	73.13	6.56	6.27
28[g]	H	H	CH_3	55–57 (0.5)[h]	198–199	EtOH–Et_2O	65	$C_{10}H_{13}N.HCl$	65.39	65.58	7.68	7.79
29[i]	H	H	CH_3	48-49 (0.25)[j]	193–194	EtOH–Et_2O	62	$C_{10}H_{13}N.HCl$	65.39	65.49	7.68	7.70
30	—$(CH_2)_3$—		H	93 (0.5)	183–186	EtOH–EtOAc	50	$C_{12}H_{15}N.HCl$	68.72	68.50	7.69	7.60
31	—$(CH_2)_4$—		H	154(24)	157–161 dec.	EtOH–EtOAc	38	$C_{13}H_{17}N_2.0.5H_2SO_4$	66.07	66.09	7.68	7.77



	n	M.p. of Salt °C.	Solvent of crystallization	Yield, %[a]	Formula	Analyses — Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
32	1	183–184	EtOH–Et_2O	82	$C_{10}H_{11}N.HCl$	66.11	65.98	6.66	6.77
33[k]	2	211–212	EtOH–Et_2O	76	$C_{11}H_{13}N.HCl$	67.51	67.61	7.21	7.18

[a] Yield from corresponding carboxylic acid. [b] From 2-methyl-2-phenylcyclopropanecarboxylic acid [V. Biro, W. Voegtli and P. Läuger, *Helv. Chim. Acta*, **37**, 2230 (1954)]. [c] From an isomeric mixture of 2-methyl-3-phenylcyclopropanecarboxylic acids, predominantly the *trans* (phenyl to carboxyl) isomer.[8a] [d] From 2,2-diphenylcyclopropanecarboxylic acid, m.p. 165–167°; reported, m.p. 171° [H. Wieland and O. Probst., *Ann.*, **530**, 274 (1937)]. [e] From *trans*-2,3-diphenylcyclopropanecarboxylic acid, m.p. 156.5–157.5° [W. M. Jones, *J. Am. Chem. Soc.*, **81**, 3776 (1959)]. [f] Crystallized from hexane as colorless crystals, m.p. 52–55°. [g] From *trans*-1-methyl-2-phenylcyclopropanecarboxylic acid, m.p. 81–83°; reported,[12] m.p. 79–80°. [h] Chromatographed on thin layer of alumina using $CHCl_3$, EtOAc, Et_2NH (95:4:1) solvent; R_f = 0.60. [i] *cis* isomer. [j] Chromatographed on thin layer of alumina using $CHCl_3$, EtOAc, Et_2NH (95:4:1) solvent; R_f = 0.85. [k] From 1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene-1-carboxylic acid [M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958)].

TABLE III

N-SUBSTITUTED DERIVATIVES OF 2-ARYLCYCLOPROPYLAMINES

Cpd.	Ar	R_1	R_2	Config.[a]	M.p. °C.	Solvent of crystln.	Yield, %	Formula	Analyses, % — Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
34	C_6H_5	$CH_2C_6H_5$	H	*trans*	168–169	EtOH–Et_2O	95	$C_{16}H_{17}N.HCl$	73.97	73.86	6.98	7.25
35	C_6H_5	$CH_2C_6H_5$	CH_3	*trans*	149–150	EtOH–Et_2O	25	$C_{17}H_{19}N.HCl$	74.57	74.64	7.36	8.09
36	C_6H_5	$CH(CH_3)CH_2$-C_6H_5	H	*trans*	112–113	*i*PrOH–Et_2O	98	$C_{18}H_{21}N.C_4H_4O_4$[b]	71.91	71.64	6.86	6.90

37	C_6H_5	$CH(CH_3)CH_2C_6H_5$	H	*cis*	121-122	$CHCl_3$–EtOAc	67	$C_{18}H_{21}N.C_4H_4O_4$[b]	71.91	71.78	6.86	7.15
38	C_6H_5	$(CH_2)_3N(CH_3)_2$	H	*trans*	134-135	EtOH–Et_2O	91	$C_{14}H_{22}N_2.2C_4H_4O_4$[c]	58.65	58.61	6.71	6.90
39	C_6H_5	CO-4-Py	H	*trans*	139-140	EtOAc	75	$C_{15}H_{14}N_2O$	75.60	75.64	5.92	5.95
40	C_6H_5	$SO_2C_6H_4$-4-CH_3	H	*trans*	78.5-79.5	Cyclohexane–H_2O	76	$C_{16}H_{17}NO_2S$	66.87	66.64	5.96	6.03
41	C_6H_5	$CO_2C_2H_5$	H	*trans*	47.5-49.5	EtOAc–hexane	96	$C_{12}H_{15}NO_2$	70.22	70.16	7.37	7.49
42	C_6H_5	$CO_2CH_2C_6H_5$	H	*trans*	75-76	EtOAc–hexane	70	$C_{17}H_{17}NO_2$	76.38	76.20	6.41	6.45
43	C_6H_5	$CO_2C(CH_3)_3$	H	*trans*	80–82	EtOAc–hexane	65	$C_{14}H_{19}NO_2$	72.07	71.63	8.21	8.36
44	C_6H_5	$CONH_2$	H	*trans*	157-158.5	EtOH–H_2O	82	$C_{10}H_{12}N_2O$	68.16	67.95	6.86	7.10
45	C_6H_5	$CON(CH_3)_2$	H	*trans*	94–96	EtOAc–hexane	80	$C_{12}H_{16}N_2O$	70.56	70.94	7.90	8.39
46	C_6H_5	$CONHNH_2$	H	*trans*	200–201.5	EtOH–Et_2O	42	$C_{10}H_{13}N_3O$. HCl	52.75	52.90	6.20	6.05
47	3-ClC_6H_4	CH_3	CH_3		173-174	EtOH–Et_2O	77	$C_{11}H_{14}ClN$. HCl	56.91	56.80	6.51	6.36
48	3,4-$Cl_2C_6H_3$	CH_3	CH_3		176.5-177.5	EtOH-Et_2O	81	$C_{11}H_{13}Cl_2N$. HCl	49.56	49.78	5.29	5.45
49	3,4-$Cl_2C_6H_3$	$CH(CH_3)_2$	H		135-136.5	Me_2CO-Et_2O	92	$C_{12}H_{15}Cl_2N.C_4H_4O_4$[b]	53.35	53.28	5.32	5.32
50	3,4-$Cl_2C_6H_3$	$CONH_2$	H		161–162.5	EtOAc	56	$C_{10}H_{10}Cl_2N_2O$	49.00	48.97	4.11	4.23
51	$C_6H_5CH_2$[d]	CH_3	CH_3		157.5–159.5	EtOH-Et_2O	57	$C_{12}H_{17}N$. HCl	68.07	67.87	8.57	8.97
52	2-ClC_6H_4	$CONH_2$	H		90–94	EtOAc–hexane	89	$C_{10}H_{11}ClN_2O$	57.01	57.29	5.29	5.35
53	C_6H_5	(→0)CH_3	CH_3	*trans*	111-113	*i*-PrOH-Et_2O	85	$C_{11}H_{15}NO$. HCl	61.82	61.80	7.55	7.53
54	3,4-$OCH_2OC_6H_3$	CO_2CH_3	H	*trans*	86-88	EtOH–H_2O	61	$C_{12}H_{13}NO_4$	61.26	60.99	5.57	5.62
55	3,4-$OCH_2OC_6H_3$	CO_2CH_3	H	*cis*	97-99	EtOH–H_2O	34	$C_{12}H_{13}NO_4$	61.26	61.04	5.57	5.25
56	2-Thienyl	$CO_2C_2H_5$	H		53.2-53.7	C_6H_6–hexane	87	$C_{10}H_{13}NO_2S$	56.85	56.81	6.20	6.16

[a] Unless otherwise noted configuration is not known but is probably mainly *trans*.[8] [b] Maleate. [c] Dimaleate. [d] The free base was a colorless liquid, b.p. 58–61° (1.0 mm.).

and -methylamines are presented in Table IV, and in the Experimental Part.

A homologous series of 2-phenylcycloalkylamines[20] was also needed for pharmacological comparison with 2-phenylcyclopropylamine. 2-Phenylcyclopentylamine[21] and 2-phenylcycloheptylamine[22] had been prepared previously from the corresponding ketones *via* the Leuckart procedure. Conversion of similar ketones to amines by the Leuckart method gives predominantly the *cis* isomer,[23] whereas reduction with sodium and ethanol of related oximes usually affords the *trans* isomer.[23,24] Reduction of 2-phenylcyclopentanone and 2-phenylcycloheptanone oximes with sodium and ethanol gave amines differing from those reported previously.[21,22] Ultraviolet absorption data were in agreement with assignment of the *cis* configuration to the previously reported 2-phenylcyclopentylamine (λ_{max} = 267, $\epsilon = 1.12 \times 10^2$) and the *trans* configuration to the amine (λ_{max} = 267, $\epsilon = 1.19 \times 10^2$) obtained by reduction with sodium and ethanol of the corresponding oxime. Ultraviolet spectra for the two 2-phenylcycloheptylamines were almost identical.

A series of 1-substituted cyclopropylamines (Table V) was also required for comparison with 2-phenylcyclopropylamine. The preparation of compounds 67–69 (Table V) from 1-phenylcyclopropanecarbonitrile[25] and compounds 70–72 (Table V) from 1-benzylcyclopropanecarbonitrile[26] is described in the Experimental Part and Table V.

In the course of synthesis of aryl modified analogs of 2-phenylcyclopropylamine two stereoisomers of 2-(2-pyridyl)cyclopropanecarboxylic acid were prepared, but attempts to degrade them to amines were unsuccessful. The ethyl esters[27] were obtained from 2-vinylpyridine and ethyl diazoacetate. Chromatography on neutral alumina furnished 74% of an ester which was hydrolyzed to 2-(2-pyridyl)cyclopropanecarboxylic acid, m.p. 109–110° (previously reported,[27,28] m.p. 97–99°, 98–100°). Further elution of the chroma-

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TABLE IV

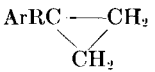
2-ARYLCYCLOPROPANECARBOXHYDRAZIDES, -CARBOXAMIDES AND -METHYLAMINES

Cpd.	Ar	R	Configuration	M.p., °C.	Solvent of crystln.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
57[a]	4-ClC$_6$H$_4$	CONHNH$_2$	*trans*	162-163.5	EtOH–H$_2$O	76	C$_{10}$H$_{11}$ClN$_2$O	57.01	56.59	5.27	5.14
58	3,4-OCH$_2$OC$_6$H$_3$	CONHNH$_2$	*trans*	142–144	EtOH	86	C$_{11}$H$_{12}$N$_2$O$_3$	59.99	59.93	5.49	5.28
59	3,4-OCH$_2$OC$_6$H$_3$	CONHN=C(CH$_3$)$_2$	*cis*	129-130	EtOH-H$_2$O	80	C$_{14}$H$_{16}$N$_2$O$_3$	64.62	64.49	6.19	6.41
60[b]	2-Pyridyl	CONHNH$_2$	*trans*	118-118.5	Toluene	88	C$_9$H$_{11}$N$_3$O	61.00	61.31	6.26	6.63
61[c]	2-Pyridyl	CONHNH$_2$	*cis*	151-152.5	Toluene	76	C$_9$H$_{11}$N$_3$O	61.00	60.94	6.26	6.51
62[d]	C$_6$H$_5$	CONH$_2$	*cis*	87-89	Hexane	10	C$_{10}$H$_{11}$NO	74.51	74.32	6.88	6.73
63[e]	4-ClC$_6$H$_4$	CONH$_2$	*trans*	183-184.5	MeOH	49	C$_{10}$H$_{10}$ClNO	61.39	61.33	5.15	5.28
64	C$_6$H$_5$	CH$_2$NH$_2$	*trans*	187–188	*i*-PrOH-Et$_2$O	59	C$_{10}$H$_{13}$N.HCl[f]	65.39	64.62	7.68	7.76
65[g]	C$_6$H$_5$	CH$_2$N(CH$_3$)$_2$	*trans*	146–147	*i*-PrOH-Et$_2$O	79	C$_{12}$H$_{17}$N.HCl[h]	68.07	67.86	8.57	8.57
66	C$_6$H$_5$			217.5–219.5	*i*-PrOH-Et$_2$O	18	C$_{12}$H$_{14}$N$_2$.HCl[i]	64.71	63.75	6.79	7.01
67[j]	3-CF$_3$C$_6$H$_4$	CONHNH$_2$		94.5-95.5	Toluene	95	C$_{11}$H$_{11}$F$_3$N$_2$O	54.10	53.38	4.54	4.54

[a] From *trans*-2-(4-chlorophenyl)cyclopropanecarboxylic acid with ethereal diazomethane (methyl ester, b.p.140-142° (2 mm.), 70% yield) and refluxing with equimolar amount of hydrazine in ethanol for 24 hr. [b] From ethyl *trans*-2-(2-pyridyl)cyclopropanecarboxylate with 1.5 equivs. of hydrazine in ethanol, 7 hr. reflux, and removal of solvent. [c] From *cis*-2-(2-pyridyl)cyclopropanecarboxylic acid *via* the methyl ester [b.p. 90–95° (0.05 mm.)] as in [a]. [d] A mixture of *cis* and *trans*-2-phenylcyclopropanecarboxylic acids was treated with thionyl chloride in benzene[4] and then with ammonia. The *trans*-amide precipitated and was filtered; the *cis*-amide was obtained by concentration of the mother liquors. [e] From *trans*-2-(4-chlorophenyl)cyclopropanecarbonyl chloride with ammonia. [f] Caled.: N, 7.63; equiv. wt., 183.7. Found: N, 7.51; equiv. wt., 183.2. [g] From *trans*-2-aminomethyl-1-phenylcyclopropane as described for N,N-dimethyl-2-substituted cyclopropylamines. The oily colorless base had b.p. 70–85° (0.7 mm.): n^{25}D 1.5182. [h] Caled.: N, 6.62. Found: N, 6.52. [i] Equiv. wt.: Caled.: 222.7. Found: 221.4. [j] From the ethyl ester with hydrazine hydrate in boiling ethanol for 5 hr.

TABLE V

1-SUBSTITUTED CYCLOPROPYLAMINES



Cpd.	Ar	R	M.p. of salt, °C.	Solvent of crystln.	Yield, %	Formula	Carbon: Calcd.	Carbon: Found	Hydrogen: Calcd.	Hydrogen: Found
68	C_6H_5	CH_2NH_2	176.5–177.5	*i*-PrOH	86	$C_{10}H_{13}N\cdot HCl$	65.39	64.97	7.68	8.07
69	C_6H_5	$NHCH_3$	145–146.5	EtOH–Et_2O	40	$C_{10}H_{13}N\cdot C_6H_{13}NO_3S$[a]	58.86	58.85	8.03	8.29
70	C_6H_5		202–203	*i*-PrOH–Et_2O	18	$C_{14}H_{19}N\cdot HCl$	70.72	70.62	8.48	8.48
71[b]	$C_6H_5CH_2$	CH_2NH_2	185–186.5	*i*-PrOH	61	$C_{11}H_{15}N\cdot HCl$	66.82	66.74	8.16	8.14
72[c]	$C_6H_5CH_2$	NH	157.5–159	*i*-PrOH–Et_2O	55	$C_{10}H_{14}N\cdot HCl$	65.39	65.41	7.68	7.73
73[d]	$C_6H_5CH_2$	$NHCH_3$	160–162	EtOH–Et_2O	38	$C_{11}H_{15}N\cdot HCl$	67.17	67.04	8.20	8.39

[a] Cyclohexylsulfamate. [b] From 1-benzylcyclopropanecarbonitrile[26] with lithium aluminum hydride as described for compound 68. [c] Prepared by acid hydrolysis of 1-benzylcyclopropyl isocyanate (see method for 2-substituted cyclopropylamines). The isocyanate was obtained from 1-benzylcyclopropanecarboxylic acid[26] by the mixed carboxylic–carbonic anhydride procedure. [d] From 1-benzylcyclopropyl isocyanate (see[c]) with lithium aluminum hydride as described for compound 69. The colorless oily base boiled at 57–59° (0.5 mm.).

TABLE VI

2-SUBSTITUTED CYCLOPROPANECARBOXYLIC ESTERS, ACIDS AND CHLORIDES[a]

	$R_3 = OC_2H_5$[b]				$R_3 = OH$			$R_3 = Cl$[c]	
R	R_1	R_2	B.p., °C. (mm.)	Yield, %	M.p., °C.	Yield, %	Solvent of crystln.	B.p., °C. (mm.)	Yield, %
2-ClC_6H_4	H	H	92–119 (0.3)	29	[d]			103–108 (0.4)	71
3-ClC_6H_4	H	H	91–100 (0.3)	53	[d]			126–130 (0.6)	77
4-ClC_6H_4	H	H	126–146 (1–2)	60				101–103 (0.35)	91
			146–165 (1–2)	11					
4-$CF_3C_6H_4$	H	H	74–96 (0.5)	55	[e]			101–103 (0.3)	88

3-$CF_3C_6H_4$	H	H	87–89 (0.4)	63	63–81	30	Cyclohexane	80–85 (0.45)	90
4-$CH_3C_6H_4$	H	H	88–105 (0.5)	52	[d]			109–112 (0.4)	91
4-$CH_3OC_6H_4$	H	H	121–131 (0.8)	69	[d]				
3,4-$Cl_2C_6H_3$	H	H	104–125 (0.4)	36	[d]			143–148 (0.5)	83
2,5-$Cl_2C_6H_3$	H	H	130–138 (0.8)	30	73.5–76	91	EtOH–H_2O	103–108 (0.5)	71
3,4-$(OCH_2O)C_6H_3$	H	H	141–192 (0.6)	65					
3,4-$(CH_3O)_2C_6H_3$[f]	H	H			102–104[g]	58			
$C_6H_5CH_2$	H	H	103–108 (0.4)	50	[d]			107–118 (0.9)	78
$C_6H_5(CH_2)_2$[h]	H	H	103–116 (0.3)	34	[di]				
C_6H_5S	H	H	111–138 (0.4)	76	[d]				
n-C_5H_{11}	H	H	104–120 (8)	67	[d]			104–105 (8)	98
cyclo-C_6H_{11}	H	H	93–120 (0.7)	31	[d]			85–89 (0.5)	86
1-Naphthyl	H	H	150–184 (2)	47	[d]				
2-Naphthyl[f]	H	H			150–152.5[j]	73	EtOH–H_2O		
2-Thianaphthenyl	H	H	149–164 (0.5)	71	166–168	91	$C_6H_5CH_3$	[k]	
3-Thianaphthenyl[f]	H	H			104–114[l]	80	$C_6H_5CH_3$	[k]	
C_6H_5	CH_3	H	82–110 (0.25)	86	[d]				
C_6H_5	H	CH_3	89–113 (0.3)	17	[d]				
C_6H_5[h]	—$(CH_2)_3$—		161–165 (24)	36	139–140[m]	31	EtOH–H_2O		
C_6H_5[h]	—$(CH_2)_4$—		171–174 (21)	17	183–184[n]	69	EtOH–H_2O		

[a] Most of these derivatives were not purified further and were not analyzed but were used directly in subsequent steps. [b] Ethyl 1,1a,2,-6b-tetrahydrocyclopropa[a]indene-1-carboxylate, b.p. 95–120° (0.5 mm.), yield, 55%, was prepared by the same procedure. [c] 1,1a,2,6b-Tetrahydrocyclopropa[a]idene-1-carbonyl chloride was prepared by the same procedure, b.p. 120–131° (1.5 mm.), yield, 52%. [d] Obtained in 65–95% yield by the same procedure but not isolated. [e] Two fractions of this ester were collected. [f] *trans* isomer. [g] A. Burger and G. T. Fitchett, *J. Am. Chem. Soc.*, **74,** 3415 (1952), reported m.p. 105–105.5°. [h] Catalytic amount of copper sulfate used in preparation of ester. [i] *S*-Benzylisothiouronium salt, colorless crystals, m.p. 162–163°. *Anal.* Calcd. for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.79. Found: C, 67.55; H, 6.69. [j] *Anal.* Calcd. for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.26; H, 4.65. [k] Obtained by the same procedure but not distilled. [l] *Anal.* Calcd. for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 65.55; H, 4.55. [m] *Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.89. Found: C, 77.33; H, 6.89. [n] *Anal.* Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.87; H, 7.18.

togram with ether gave an ester (15.5% yield) which was hydrolyzed to an isomeric acid, m.p. 164.5–165.5°.

Experimental determination of effective chromatographic conditions was tedious, involving evaporation of a large number of fractions. In order to shorten this time consuming effort, the eluate was allowed to run through a cell of an infrared spectrophotometer which had been set at the carbonyl frequency of the ester mixture, and rapid evaluation of combinations of solvent and adsorbent could be monitored in this manner (see Experimental). This method constitutes a considerable simplification of earlier procedures for continuous spectrophotometric recordings of chromatographic eluates.[29]

X-Ray diffraction studies[30] showed that the acid, m.p. 110°, was isomorphic with *trans*-2-phenylcyclopropanecarboxylic acid, whereas the acid, m.p. 165.5°, and *cis*-2-phenylcyclopropanecarboxylic acid were isomorphic. On the basis of these studies, the *trans* configuration has been assigned to 2-(2-pyridyl)cyclopropanecarboxylic acid, m.p. 110°, and the *cis* configuration to the isomer melting at 165.5°. Ultraviolet absorption spectra were consistent with these assignments.[31] The *trans* acid showed an absorption maximum at 269 mμ ($\epsilon = 4.94 \times 10^3$) and the *cis* isomer at 265 mμ ($\epsilon = 4.07 \times 10^3$).

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Experimental[32]

trans-**2-Phenylcyclopropylamine.**—In addition to the physical properties reported previously,[4] these data are now available for this amine: m.p. 44–45°; b.p. 74–76° (1.6 mm.), 125–129° (32 mm.); $n^{27.5}D$ 1.5560.

Anal. Calcd. for $C_9H_{11}N$: C, 81.16; H, 8.33. Found: C, 80.31; H, 8.32.

Resolution of *trans*-2-Phenylcyclopropylamine.—To a solution of 79 g. (0.525 mole) of D-tartaric acid in 400 ml. of ethanol was added a solution of 70 g. (0.525 mole) of *trans*-2-phenylcyclopropylamine in 50 ml. of ethanol. The mixture was cooled to 0° and the crystals, m.p. 157–168°, were filtered. After five recrystallizations from 75% aqueous 2-propanol, 45.0 g. of (−)-*trans*-2-phenylcyclo-

(29) A. Deutsch, R. Zuckerman, and M. S. Dunn, *Anal. Chem.*, **24**, 1763 (1952); W. C. Kenyon, J. E. McCarley, E. G. Boucher, A. E. Robinson, and A. K. Wiebe, *ibid.*, **27**, 1888 (1955).

(30) These studies were performed by Dr. Walter E. Thompson and Mr. Richard J. Warren, Analytical and Physical Chemistry Section, Smith Kline and French Laboratories, to whom we are indebted.

(31) R. J. Mohrbacher and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 401 (1957).

(32) Melting points are corrected; boiling points are uncorrected. Microanalyses by Mrs. Doris Rolston and co-workers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories, and Mrs. Dolores Ellis of the University of Virginia.

propylamine D-tartrate, m.p. 188–190°; $[\alpha]^{25}D$ – 30.5° (1% in water), was obtained. This salt was converted, via the free base, into a **hydrochloride**, m.p. 180–181°; $[\alpha]^{25}D$ −75.5° (1% in water), after recrystallization from 2-propanol-ether.

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.71; H, 7.13. Found: C, 63.86; H, 7.43.

Mother liquors from recrystallization of the above D-tartrate were combined and the amine was liberated. This amine (45 g., 0.338 mole) was treated with 51 g. (0.338 mole) of L-tartaric acid in the same manner described for the D-tartrate and 96 g. of crystalline salt, m.p. 171–177°, was obtained. Three recrystallizations from 75% aqueous 2-propanol gave 58.0 g. of (+)-*trans*-2-phenylcyclopropylamine L-tartrate, m.p. 189–191°; $[\alpha]^{25}D$ + 31.0° (1% in water) which was converted into a **hydrochloride,** m.p. 181–182°; $[\alpha]^{25}D$ + 75.7°.

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.71; H, 7.13. Found: C, 63.94; H, 7.35.

trans-**2-Phenylcyclopentylamine Hydrochloride.**—Sodium (26.5 g., 1.15 g.-at.) was added to a warm solution of 20 g. (0.114 mole) of 2-phenylcyclopentanone oxime[33] in 250 ml. of ethanol at a rate sufficient to maintain reflux. After reaction of sodium was completed, the solution was diluted with water and the mixture was extracted with ether. The ether extracts were dried and concentrated to give 13.2 g. of a colorless liquid, b.p. 70–83° (0.8 mm.), which was converted into a hydrochloride, m.p. 143.5–145°, after recrystallization from methanol–ethyl acetate.

Anal. Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16. Found: C, 66.96; H, 8.29.

2-Phenylcycloheptanone Oxime.—This compound was obtained in 68% yield from 2-phenylcycloheptanone in the usual manner.[33] The colorless crystals were recrystallized from aqueous ethanol; m.p. 77.5–79.5°

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.88; H, 8.66.

trans(?)-**2-Phenylcycloheptylamine Hydrochloride.**—This compound was obtained from 2-phenylcyclopentanone oxime in 63% yield using conditions identical with those described above for the synthesis of *trans*-2-phenylcyclopentylamine hydrochloride. The colorless crystalline hydrochloride was recrystallized from ethanol–ether, m.p. 227–229°.

Anal. Calcd. for $C_{13}H_{20}ClN$: C, 69.16; H, 8.93. Found: C, 69.16; H, 9.09.

2-Vinylthianaphthene.—A solution of 148 g. (0.83 mole) of α-methyl-2-thianaphthenylmethanol[34] in 750 ml. of acetic anhydride was refluxed for 1 hr. Excess acetic anhydride was removed *in vacuo*, the residue was diluted with water and the mixture was extracted with ether. The ether extracts were dried and concentrated to give 164 g. of **α-methyl-2-thianaphthenylmethyl acetate,** b.p. 123–129° (0.3 mm.); $n^{26}D$ 1.5690. A vertical column (2.5 × 30 cm.) filled with glass helices (0.6 × 10 mm.) was heated to 470° and the acetate was added dropwise in a nitrogen atmosphere. The product was collected in a cooled receiver at the bottom of the column; it was distilled to give 67.9 g. (63%) of a colorless liquid, b.p. 78° (0.3 mm.), which solidified on cooling. Recrystallization from aqueous ethanol gave colorless crystals, m.p. 61–64°.

Anal. Calcd. for $C_{10}H_8S$: C, 74.95; H, 5.03. Found: C, 74.98; H, 5.31.

Ethyl 2-Substituted-cyclopropanecarboxylates. Method A (Reaction of Ethyl Diazoacetate with Substituted Olefins).[4]—Ethyl diazoacetate (1 mole) and a substituted olefin (1.1 moles) were mixed at 0°. A small portion of the solution (5–10 ml.) was gradually heated to 100–170° until rapid evolution of

(33) R. T. Arnold, J. S. Buckley, Jr., and R. M. Dodson, *J. Am. Chem. Soc.*, **72**, 3153 (1950).
(34) D. A. Shirley and M. D. Cameron, *ibid.*, **74**, 664 (1952).

nitrogen was noted. In some cases (see Table VI) 5–10 g. of anhydrous copper sulfate was added. The remainder of the solution was added to the stirred reaction mixture at a rate sufficient to maintain the reaction temperature. After addition was completed, the temperature was increased 20° and the mixture was held at this temperature until nitrogen evolution stopped (2–6 hr.) See Table VI for boiling points and yields of ethyl cyclopropanecarboxylates prepared by this procedure.

Reaction of ethyl diazoacetate with 2-chlorostyrene, 3,4-dichlorostyrene and 2-vinylpyridine[27] was also performed by dropwise addition of the ester-olefin mixture to refluxing xylene (5 ml. per g. of mixture). In each instance temperature control was easier and improved yields (63%, 75% and 90%, respectively) were obtained.

Method B (Cyclization of Alkyl 4-Aryl-4-chlorobutyrates).—To a solution of 1 mole of 4-aryl-4-oxobutyric acid [4-oxo-4-(3-thianaphthenyl)butyric acid,[35] 3-veratroylpropionic acid,[36] or 3-(2-naphthoyl)propionic acid[37]] in 1.3 l. of 0.5 *N* sodium hydroxide was added slowly sodium borohydride (1 mole) so that the temperature remained at 40° or below. The mixture was stirred at room temperature for 4 hr., diluted with water, acidified with hydrochloric acid and extracted with ether. The ether extracts were dried and concentrated to afford crude 4-aryl-4-hydroxybutyric acids. These crude acids were heated at 140° (20 mm.) for 2.5 hr. to give the corresponding lactones. To a suspension of lactone in 1.4 l. of benzene was added 1 mole of thionyl chloride. After the mixture was refluxed for 4 hr., it was concentrated, the residual oil was cooled to 0° and 200 ml. of the required alcohol saturated with hydrogen chloride was added slowly. Excess alcohol was removed *in vacuo*, the residue was dissolved in ether and the solution was washed with aqueous sodium bicarbonate solution. Boiling points, °C. (mm.), and yields for chloro esters were: ethyl 4-chloro-4-(3-thianaphthenyl)butyrate, 150° (0.007) (63%); methyl-4-chloro-4-veratrylbutyrate, 170–180° (1–2) (59%); and ethyl 4-chloro-4-(2-naphthyl)butyrate, 140° (0.001) (75%).

To a refluxing solution of 1.1 moles of potassium *tert*-butoxide in 500 ml. of *tert*-butanol and 2 l. of benzene, 1 mole of chloro ester was added dropwise. The mixture was refluxed and stirred for 5 hr. After cooling, water (1 l.) was added and the layers were separated. The benzene layer was dried and concentrated. A solution of the residue in 600 ml. of acetone was shaken for 1 min. with 30 ml. of 1% aqueous potassium permanganate, diluted with water and extracted with ether. The ether extracts were dried, concentrated, and the residue was distilled *in vacuo*. Boiling points, °C. (mm.), and yields of *trans* esters were: ethyl 2-(3-thianaphthenyl)cyclopropanecarboxylate, 170–176° (0.7), $n^{24}D$ 1.5697 (55%); methyl 2-(3,4-dimethoxyphenyl)cyclopropanecarboxylate, 160–165° (1) (37%); ethyl 2-(2-naphthyl)cyclopropanecarboxylate, 164–168° (0.5) (85%). The latter ester crystallized at room temperature.

Hydrolysis of Alkyl 2-Substituted Cyclopropanecarboxylates.—A mixture of alkyl 2-substituted cyclopropanecarboxylate (1 mole) and excess potassium hydroxide (2–4 moles) in 85% aqueous ethanol (5 ml. per g. of ester) was stirred and refluxed for 4–8 hr. The mixture was concentrated and the residue dissolved in water. After washing with ether, the aqueous solution was acidified with

(35) N. P. Buu-Hoï and P. Cagniant, *Ber.*, **76**, 1269 (1943).

(36) M. A. Haq, M. L. Kapur, and J. N. Ray, *J. Chem. Soc.*, 1087 (1933).

(37) M. S. Newman, R. B. Taylor, T. Hodgson, and A. B. Garrett, *J. Am. Chem. Soc.*, **69**, 1784 (1947).

hydrochloric acid. Crystalline acids were filtered and recrystallized. Melting points, solvent of crystallization and yields (%) of isolated 2-arylcyclopropanecarboxylic acids are listed in Table VI.

trans-**2-(4-Chlorophenyl)cyclopropanecarboxylic Acid.**[9,10]—The two fractions obtained by distillation of ethyl 2-(4-chlorophenyl)cyclopropanecarboxylate (Table VI) were hydrolyzed separately. The lower boiling fraction gave a 63% yield of acid, m.p. 96.5–98°, after recrystallization from methylcyclohexane.

Anal. Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.16; H, 4.34.

Ozonization of this acid in acetic acid solution[11] produced a 1,2-cyclopropanedicarboxylic acid consisting of a mixture of the *cis* and *trans* isomers (m.p. 110–143°; mixture melting point of equal parts of *cis*- and *trans*-1,2-cyclopropanedicarboxylic acids, 115–145°), from which a little *trans* isomer (m.p. 173–176°) could be elaborated only by repeated fractional crystallization from water.

A mixture of 54 g. (0.27 mole) of 2-(4-chlorophenyl)cyclopropanecarboxylic acid (m.p. 96–98°) and 75 ml. of redistilled thionyl chloride was allowed to stand at 26° for 24 hr., excess thionyl chloride was removed *in vacuo* and the oily residue was distilled to give 52.4 g. (88%) of colorless oil, b.p. 131–133° (1.4 mm.). Hydrolysis of this 2-(4-chlorophenyl)cyclopropanecarbonyl chloride with 5 vols. of water at 25° for 48 hr. gave a colorless solid, m.p. 96–98°, but one recrystallization from water raised the melting point to 115–117°, undepressed by admixture of a sample of *trans*-2-(4-chlorophenyl)cyclopropanecarboxylic acid below. Apparently, chlorination and hydrolysis had isomerized some of the *cis* isomer.

Hydrolysis of the higher boiling ester yielded 48% of an acid which was recrystallized from 340 parts of boiling water, m.p. 114–116°.

Anal. Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 60.97; H, 4.83.

Ozonolysis of this acid gave a 77% yield of a product, m.p. 176–178° (after recrystallization from water) which was identical (mixture m.p.) with 1,2-cyclopropanedicarboxylic acid. Thus, this acid is *trans*-2-(4-chlorophenyl)cyclopropanecarboxylic acid.

2-(3,4-Methylenedioxyphenyl)cyclopropanecarboxylic Acids.—Hydrolysis of ethyl 2-(3,4-methylenedioxyphenyl)cyclopropanecarboxylate gave 83% of an acid, m.p. 90–100°. The product (8.6 g.) was dissolved in 1 l. of hot water; the solution was cleared with charcoal, and allowed to cool to 35° to give 5.6 g. (65%) of feathery colorless needles, m.p. 124.5–125°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.87. Found: C, 64.33; H, 5.08.

The configuration of this substance as *trans*-2-(3,4-methylenedioxyphenyl)-cyclopropanecarboxylic acid was proved by ozonolysis.[11] A yield of 85% of *trans*-1,2-cyclopropanedicarboxylic acid, m.p. 176–178°, was obtained after recrystallization from ether–petroleum ether. A mixture melting point with authentic *trans*-1,2-cyclopropanedicarboxylic acid gave no depression.

Concentration of the aqueous mother liquors of *trans*-2-(3,4-methylenedioxyphenyl)cyclopropanecarboxylic acid produced 0.85 g. (8%) of colorless prisms, m.p. 145–147° after recrystallization from 70 ml. of water.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.87. Found: C, 64.08; H, 5.24.

The configuration of this acid as *cis*-2-(3,4-methylenedioxyphenyl)-cyclopropanecarboxylic acid follows from its ozonolysis in acetic acid solution. A 79% yield of colorless crystals (from ether-petroleum ether), m.p. 134–137°, was obtained. A mixture melting point with authentic *cis*-1,2-cyclopropanedicarboxylic acid (m.p. 139–140°) was 136–138°.

cis **and** *trans*-**1-Methyl-2-phenylcyclopropanecarboxylic Acids.**—A cold solution

of 49.3 g. (0.26 mole) of methyl 1-methyl-2-phenylcyclopropanecarboxylate[14] and 9.75 g. (0.17 mole) of potassium hydroxide in 150 ml. of ethanol and 25 ml. of water was stirred at room temperature for 3 hr., then it was refluxed for 1 hr. Solvent was removed *in vacuo*, the residue was suspended in water, and the mixture extracted with ether. Acidification of the aqueous fraction gave 27.5 g. (60%) of *trans* acid which melted at 81–83° (reported,[12] m.p. 79–80°) after one recrystallization from aqueous ethanol. The acid was converted to *trans*-1-methyl-2-phenylcyclopropanecarboxamide, m.p. 200–202°; reported,[12] m.p. 200.5°. Mixture melting points of the acid and amide with authentic samples, generously supplied by Professor G. W. Perold, Pretoria, South Africa, were not depressed. The ether extracts were dried and concentrated. Residual ester (19.0 g.) was hydrolyzed by refluxing with an excess of potassium hydroxide in aqueous ethanol to give 17.6 g. of crude acid, m.p. 67–85°. Recrystallization from hexane gave 10.3 g. (23%) of *cis* acid, m.p. 104–105°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.74; H, 6.74.

The near infrared spectrum of this acid showed cyclopropane absorption (1.65 μ).

***cis*-1-Methyl-2-phenylcyclopropanecarboxamide.**—*cis*-1-Methyl-2-phenylcyclopropanecarboxylic acid (1.76 g., 0.01 mole) was converted to an acid chloride as described for 2-substituted cyclopropanecarbonyl chlorides. The acid chloride was added slowly to 20 ml. of cold 15 *N* ammonium hydroxide to give 1.6 g. (91%) of colorless crystals, m.p. 102–103°, after recrystallization from ether-petroleum ether.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.14; H, 7.50; N, 7.75.

2-Substituted Cyclopropanecarbonyl Chlorides.—A mixture of 1 mole of 2-substituted cyclopropanecarboxylic acid and 2 moles of thionyl chloride was allowed to stand at 26° for 24 hr. (or until gas evolution was completed). Excess thionyl chloride was removed *in vacuo*. For boiling points and yields of 2-substituted cyclopropanecarbonyl chlorides see Table VI.

2-Substituted Cyclopropyl Isocyanates. (1) **Dry Sodium Azide Procedure.**[15]—A stirred suspension of 2 moles of sodium azide in 1.2 l. of anhydrous toluene was gradually heated to reflux and a solution of 1 mole of the appropriate acid chloride in 250 ml. of dry toluene was added dropwise. The mixture was stirred and refluxed until nitrogen evolution was completed (2–48 hr.), then cooled and filtered. Concentration of the filtrate *in vacuo* gave the crude isocyanate (λ = 4.4 μ). These isocyanates were obtained by this procedure in nearly quantitative yield: *trans*-2-(4-chlorophenyl)-, 2-(4-methylphenyl)-, 2-(2,5-dichlorophenyl)-, and 2-(*n*-amyl)-cyclopropyl isocyanate. The latter compound boiled at 37–43° (0.5 mm.).

(2) **Wet Sodium Azide Procedure.**[17]—To a stirred solution of 0.1 mole of 2-substituted cyclopropanecarbonyl chloride in 300 ml. of acetone at 0° a solution of 0.2 mole of sodium azide in 45 ml. of water was added dropwise. After stirring the mixture at 0° for 30 min., it was poured into 1 l. of ice-water. The mixture was extracted with toluene, the extracts were dried in the cold and then heated *cautiously* on a steam-bath until nitrogen evolution was completed. Concentration of the solution gave the isocyanate. These isocyanates, obtained in nearly quantitative yield, were employed without additional purification: 2-(3-chlorophenyl)-, 2-cyclohexyl-, 2-(2 thianaphthenyl)-, *trans* 2-(3-thianaphthenyl)- and 1,1a,2,6b-tetrahydrocyclopropa[a]indene-1-isocyanate. Boiling points, °C.

(mm.), and yields of other 2-substituted cyclopropyl isocyanates obtained by this procedure are: 2-(4-trifluoromethylphenyl)-, 84–88° (0.5) (87%); 2-(3,4-dichlorophenyl)-, 119–124° (0.4) (87%); 2-(2-chlorophenyl)-, 86–89° (0.3) (72%); and 2-benzyl-, 96–99° (0.7) (55%).

(3) **Mixed Carboxylic-carbonic Anhydride Procedure.**[18]—To a solution of 0.1 mole of acid in 140 ml. of acetone and 27 ml. of water at 0° was added slowly 0.15 mole of triethylamine in 50 ml. of acetone, and then 0.15 mole of ethyl chlorocarbonate in 50 ml. of acetone. After stirring the mixture at 0° for 30 min., 0.2 mole of sodium azide in 45 ml. of water was added dropwise. The mixture was stirred for 30 min. and then poured into an excess of ice-water. The precipitated carboxazide was extracted with ether, the ether extracts were dried and concentrated below 30°. A solution of the residual carboxazide in 400 ml. of toluene was heated *cautiously* until nitrogen evolution was completed. Concentration of the solution gave the crude isocyanate. These isocyanates were utilized without purification: 2-(4-methoxyphenyl)-, 2-(3-trifluoromethylphenyl)-, *trans*-2-(2-naphthyl)-, 2-phenethyl-, *cis*- and *trans*-2-phenoxy-, 2-methyl-2-phenyl-, and 2-methyl-3-phenyl-, *cis*- and *trans*-1-methyl-2-phenyl-[14] cyclopropyl isocyanates, 1-phenylbicyclo[3.1.0]hexane-6-isocyanate, and 1-phenyl[4.1.0]heptane-7-isocyanate. Boiling points, °C. (mm.), and yields for distilled isocyanates were: 2-(3,4-dimethoxyphenyl)-, 133–139° (0.8) (70%); 2-(1-naphthyl)-, 140–143° (0.7) (60%); 2-phenylthio-, 134–158° (15) (32%); and 1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthyl isocyanate, 84–90° (0.2) (72%). 2,2- and 2,3-diphenylcyclopropanecarboxazides and 2-(2-thienyl)cyclopropanecarboxazide also were prepared by this procedure; however, they were converted directly to trifluoroethyl carbamates without isolation of the isocyanates.

2-Substituted Cyclopropylamines. (1) **Acid Hydrolysis of Isocyanates.**—Amines listed in Tables I and II, with the exception of compounds 8, 16, 17, 23, 26 and 27, were prepared by this procedure. The appropriate isocyanate (0.1 mole) was stirred and refluxed with 7 *N* hydrochloric acid until gas evolution had ceased (1–15 hr.). The mixture was concentrated *in vacuo* and the residue dissolved in water. After extracting the aqueous solution with ether, it was made alkaline with 2 *N* sodium hydroxide, extracted with ether, and the ether extracts were dried and concentrated to give an oily amine. In most instances, the amines were purified *via* an acid salt; however, several of the amines were distilled (Table I and II).

(2) **Alkaline Hydrolysis of Isocyanates.**—To a solution of 0.1 mole of isocyanate in 400 ml. of benzene was added 40 ml. of 10 *N* potassium hydroxide. After the mixture was refluxed and stirred for 1 hr., it was cooled and the layers were separated. The organic layer was extracted with 2 *N* hydrochloric acid. The acid extracts were made basic and the mixture was extracted with ether. The ether solution was dried and concentrated. Treatment of an alcoholic solution of the residual amine with ethereal hydrogen chloride gave compounds 16 and 17.

(3) **Alkaline Hydrolysis of Trifluoroethyl Carbamates.**—2,2- and 2,3-diphenylcyclopropanecarboxazides (0.08 mole), obtained by the mixed anhydride procedure, were refluxed with 0.13 mole of 2,2,2-trifluorethanol in 50 ml. of dry benzene for 4 hr. After evaporation of solvent and excess reagent, viscous red oils were obtained. These oils were subjected to hydrolysis, as described above for alkaline hydrolysis of isocyanates, to afford compounds 26 and 27 (Table II).

trans-**2-(3,4-Methylenedioxyphenyl)cyclopropanecarboxhydrazide (Compound 58).**—*trans*-2-(3,4-Methylenedioxyphenyl)cyclopropanecarboxylic acid (15.1 g.,

0.073 mole) was methylated with diazomethane in ether, and the oily methyl ester was refluxed with 200 ml. of 100% hydrazine hydrate in 35 ml. of absolute ethanol for 5 hr. and worked up.

Methyl *trans*-2-(3,4-Methylenedioxyphenyl)cyclopropanecarbamate (Compound 54).—To a stirred suspension of 13.6 g. (0.062 mole) of *trans*-2-(3,4-methylenedioxyphenyl)cyclopropanecarboxhydrazide in 300 ml. of 5% hydrochloric acid cooled to 0° was added, dropwise, a solution of 4.3 g. (0.062 mole) of sodium nitrite in 50 ml. of water at such a rate that the temperature did not exceed 0°. The cooled solution was extracted with toluene, the extracts were filtered, dried and concentrated to 500 ml. under reduced pressure. Methanol (300 ml.) was added, the mixture was refluxed for 5 hr., the solvents were removed under vacuum, and the brown oily residue was induced to crystallize by addition of a few drops of methanol at 0°.

***trans*-2-(3,4-Methylenedioxyphenyl)cyclopropylamine Hydrochloride (Compound 8).**—A mixture of 6.0 g. of methyl *trans*-2-(3,4-methylenedioxyphenyl)-cyclopropanecarbamate and 300 ml. of a saturated methanolic solution of barium hydroxide was refluxed for 36 hr., cooled to 0°, filtered, and the filtrate was concentrated. The residue was extracted with anhydrous ether, the ether solution was dried, concentrated to 100 ml., filtered, and treated with hydrogen chloride.

Ethyl 2-(2-Thienyl)cyclopropanecarbamate (Compound 55).—A solution of 6.1 g. (0.03 mole) of 2-(2-thienyl)cyclopropanecarboxazide, obtained by the mixed anhydride method (see above), was refluxed for 1.5 hr. with 30 ml. of ethanol. The dark carbamate was decolorized by filtering its ether solution through a short alumina column, and solidified when a concentrated methanolic solution was cooled to −17°.

2-(2-Thienyl)cyclopropylamine Hydrochloride (Compound 23).—A solution of 5.8 g. (0.027 mole) of ethyl 2-(2-thienyl)cyclopropanecarbamate in 500 ml. of saturated methanolic barium hydroxide solution was refluxed with stirring for 45 hr., the mixture was filtered, and the filtrate evaporated under reduced pressure. The residue was made alkaline and the mixture was extracted with ether. The resulting amine boiled at 55–60° (0.25 mm.); it was converted to a hydrochloride in ether.

1-Amino-6-phenyl[3.1.0]bicyclohexane Sulfate (III).—To a stirred solution of phenyldiazomethane (5.5 g., 0.048 mole) in 175 ml. of ether was added 11.5 g. (0.08) mole) of ethyl 1-cyclopentenecarboxylate.[38] After standing at 25° for 24 hr. ether was removed and the residual oil was heated at 120° (15 mm.) for 30 min. The resulting ester was distilled, b.p. 102–108° (0.3 mm.); it was hydrolyzed to an acid as described for alkyl 2-substituted cyclopropanecarboxylates. The crude oily acid was converted to an isocyanate as described for 2-substituted cyclopropyl isocyanates, mixed carboxylic-carbonic anhydride procedure.[18] Acid hydrolysis of the isocyanate was carried out as described for 2-substituted cyclopropylamines to give 0.21 g. (2.5%) of a colorless oil, b.p. 90° (0.5 mm.). The sulfate crystallized from 2-propanol–ethyl acetate as colorless needles, m.p. 144–145°.

Anal. Calcd. for $C_{24}H_{32}N_2O_4S$: C, 64.84; H, 6.80. Found: C, 64.90; H, 6.66.

N-Alkyl- and aralkyl 2-arylcyclopropylamines (Compounds 34, 36, 37 and 49).—A solution of 0.15 mole of 2-arylcyclopropylamine and 0.16 mole of the appropriate aldehyde or ketone in 200 ml. of benzene was refluxed azeotropically until

(38) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934).

removal of water was completed (1–2 hr.). After removing the solvent *in vacuo*, the residual oil was dissolved in 100 ml. of ethanol and 0.3 g. of platinum oxide was added. The mixture was hydrogenated at 3.5 kg./cm.^{2} and 26° for 2 hr., filtered and the filtrate was concentrated *in vacuo*. Compounds 34, 36, 37 and 49 (Table III) were purified by recrystallization of their acid salts.

trans-**N-(3-Dimethylaminopropyl)-2-phenylcyclopropylamine Dimaleate (Compound 38)**.—A suspension of 12.7 g. (0.075 mole of *trans*-N-(2-phenylcyclopropyl)-formamide[19] and 3.2 g. (0.08 mole) of sodium amide in 100 ml. of anhydrous toluene was stirred and refluxed under nitrogen for 2 hr., and then a solution of 12.1 g. (0.1 mole) of 3-dimethylaminopropyl chloride in 45 ml. of toluene was added dropwise. The mixture was stirred and refluxed for 12 hr., 100 ml. of water was added, and the layers were separated. The organic layer was dried and concentrated to give a dark brown oil. A mixture of 15 g. (0.06 mole) of this oil and 150 ml. of 12 *N* hydrochloric acid was stirred and refluxed for 20 hr., cooled and extracted with ether. The aqueous layer was made alkaline, the mixture was extracted with ether and the ether extracts were concentrated *in vacuo* to leave an amber oil, which was treated with maleic acid in ethanol.

trans-**N-Isonicotinoyl-2-phenylcyclopropylamine (Compound 39)**.—A solution of 28 g. (0.21 mole) of *trans*-2-phenylcyclopropylamine and 14.8 g. (0.11 mole) of isonicotinoyl chloride in 100 ml. of benzene was stirred and refluxed for 30 min. The mixture was cooled, filtered, and the filter cake was dissolved in water. The aqueous solution was made alkaline and the mixture was extracted with methylene chloride; the extracts were dried and concentrated.

trans-**N-(2-Phenylcyclopropyl)-*p*-toluenesulfonamide (Compound 40)**.—A solution of 17.0 g. (0.1 mole) of *trans*-2-phenylcyclopropylamine hydrochloride and 19.1 g. (0.1 mole) of *p*-toluenesulfonyl chloride in 80 ml. of pyridine was heated at 100° for 2.5 hr., and then poured into water. The precipitated oil was decanted, dissolved in ethanol, and the solution was chilled to give dense rosettes.

Ethyl *trans*-2-Phenylcyclopropanecarbamate (Compound 41).—Ethyl chlorocarbonate (29.6 g., 0.27 mole) was added gradually to a stirred mixture of *trans*-2-phenylcyclopropylamine (35.6 g., 0.27 mole) in 70 ml. of 4 *N* sodium hydroxide at 10°. After stirring the mixture for 30 min., it was extracted with ether. The ether extracts were washed with 2 *N* hydrochloric acid, dried and concentrated. The residual oil distilled at 131–136° (0.1 mm.) and crystallized on standing.

Benzyl *trans*-2-Phenylcyclopropanecarbamate (Compound 42).—This compound was obtained from *trans*-2-phenylcyclopropylamine and benzyl chlorocarbonate as colorless crystals by the same procedure employed for ethyl *trans*-2-phenylcyclopropanecarbamate.

tert-**Butyl *trans*-2-Phenylcyclopropanecarbamate (Compound 43)**.—*trans*-2-Phenylcyclopropyl isocyanate[39] (15.9 g., 0.1 mole) was added dropwise to 100 ml. of *tert*-butanol to which *ca.* 0.1 g. of lithium[40] had been added. The solution was refluxed for 1 hr., then concentrated to give an oil, which soon crystallized.

Reaction of 2-Arylcyclopropyl Isocyanates with Amines (Compounds 44, 45, 46, 50 and 52).—To a stirred solution of 1 mole of the appropriate amine (ammonia, dimethylamine, or hydrazine) in 25 ml. of benzene at 10° was added slowly a solution of 0.1 mole of 2-arylcyclopropyl isocyanate in 100 ml. of benzene.

(39) This compound was obtained from *trans*-2-phenylcyclopropanecarboxylic acid via the mixed anhydride method[18]; b.p. 53–55° (0.5 mm.).

(40) W. J. Bailey and J. R. Griffith, Abstracts of Papers, p. 12–O, 137th Meeting American Chemical Society, Cleveland, Ohio, April 5–14, 1960.

The resulting mixture was stirred for 15 min. Compounds 39, 34 and 47 were obtained by filtration of the mixture. For compounds 40 and 41, the benzene solution was concentrated *in vacuo* to give viscous liquids, which solidified on standing.

N,N-Dimethyl-2-Substituted Cyclopropylamines (Compounds 47, 48 and 51).—The appropriate 2-substituted cyclopropylamine hydrochloride (compound 6, 9 or 20) (0.05 mole) was added in portions and with stirring to 18.4 g. (0.4 mole) of 98% formic acid at 0°. A 37% formaldehyde solution (10.5 g., 0.13 mole) was added and the mixture was stirred and refluxed for 5 hr. The mixture was cooled, 5 ml. of 12 *N* hydrochloric acid was added and it was concentrated *in vacuo*. The residue was made alkaline with 10 *N* sodium hydroxide and the mixture extracted with ether. The ether extracts were washed with water, dried and concentrated. The residual tertiary amines were purified by recrystallization of their hydrochlorides.

trans-N-Benzyl-N-methyl-2-phenylcyclopropylamine hydrochloride (Compound 35) was obtained from *trans*-N-benzyl-2-phenylcyclopropylamine hydrochloride (Compound 34) by the same procedure.

***trans*-N,N-Dimethyl-2-phenylcyclopropylamine-N-oxide Hydrochloride (Compound 52).**—A mixture of 7.7 g. (0.48 mole) of *trans*-N,N-dimethyl-2-phenylcyclopropylamine[4] and 8.15 g. (0.072 mole) of 30% hydrogen peroxide was stirred at 26° for 20 hr. The solution was treated with charcoal (0.2 g.) and 10% platinum on carbon (0.2 g.) to decompose excess hydrogen peroxide. The mixture was filtered and the filtrate concentrated *in vacuo* to give a colorless syrup, an ethanolic solution of which was converted to a hydrochloride.

***cis*-2-(3,4-Methylenedioxyphenyl)cyclopropanecarboxhydrazide (Compound 59).**—This was obtained by the same procedure described for the *trans*-isomer (Compound 58). As the hydrazide could not be crystallized, a small portion was identified as the *isopropylidene* derivative.

Methyl *cis*-2-(3,4-Methyldioxyphenyl)cyclopropanecarbamate (Compound 55).—This was obtained by diazotization of the *cis*-hydrazide, followed by methanolysis as described for the *trans*-isomer (Compound 54).

***cis*- and *trans*-2-(2-Pyridyl)cyclopropanecarboxylic Acids.**—A mixture of ethyl 2-(2-pyridyl)cyclopropanecarboxylates was obtained by the reaction of ethyl diazoacetate with 2-vinylpyridine.[27] Chromatography through 65 parts of Fisher adsorption alumina using benzene as an eluent furnished 20% of the ester which had been applied to the column. Saponification of 14.5 g. (0.076 mole) of this ester with 30 ml. of an 80% ethanolic solution of 4 g. (0.1 mole) of sodium hydroxide, removal of the solvent, acidification to pH 6.5 and continuous extraction with ether gave an acid which after recrystallization from benzene or toluene appeared as rosettes, m.p. 109–109.5°. This acid was shown by X-ray diffraction studies[30] to be isomorphic with *trans*-2-phenylcyclopropanecarboxylic acid: it is therefore assigned the *trans*-configuration.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56. Found: C, 66.73; H, 5.47.

Further elution of the column with dry ether furnished another 13% of an isomeric ester which after saponification gave an acid crystallizing from benzene as tiny clusters, m.p. 164.5–165.5°. X-Ray diffraction studies[30] have shown this acid isomorphic with *cis*-2-phenylcyclopropylamine; it is therefore assigned the *cis*-configuration.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56. Found: C, 66.29; H, 5.71.

Slightly higher yields were obtained in larger runs, but the evaporation of up to

80 eluate fractions was time consuming and recovery was incomplete.

Therefore, another method for the separation of the isomeric ester was developed. The eluate was passed through the solute cell of a Perkin–Elmer infrared spectrophotometer, Model 21. The wave length was set at the carbonyl band which was the highest absorbancy for both esters. The connection between recording drum drive and wave length scanning was disengaged so that the pen recorded the concentration of carbonyl compound in the eluate, as a function of time. In preliminary experiments, the sensitivity of the instrument setting was determined. At 5.785 μ in an 0.06 mm. cell without solvent compensation and base line at 100 ± 1% transmission, values for transmission ran from 11% of a 10.3 vol. % solution of the ester in carbon tetrachloride to 94% of an 0.5 vol. % solution of the ester. That means that concentrations of 0.2 vol. % of ester could be detected readily in an eluate.

The chromatographic column was clamped directly to the solute cell by means of a short capillary tubing and a syringe-glass joint. The eluate was drained from the cell through another tube into a measuring cylinder. Seven experiments were performed, each with 0.4 ml. of ester being applied to a 1.8 × 9 cm. column of 20 g. of neutral adsorption alumina (Woelm). The data are listed in Table VII.

Table VII

Development of the Chromatographic Separation of the Geometrically Isomeric Ethyl 2-(2-Pyridyl)cyclopropanecarboxylates (0.4 ml.)

Experiment	Eluent	Total eluate(s), ml.	Remarks
1	CCl_4	100	1 sharp peak (no separation)
2	Ether	290	1 flat peak (no separation)
3	CCl_4 with 10 vol. % of ether	200	2 superimposed peaks (poor separation)
4	CCl_4 with 5 vol. % of ether	60	2 close but separate peaks (satisfactory separation)
5	CCl_4 with 2.5 vol. % of ether	200	2 well separated peaks (ideal separation)
6	(a) CCl_4	130	1 sharp peak, followed by
	(b) Ether	190	a second sharp peak (ideal separation)

Experiment 6 provided ideal separation by elution first with carbon tetrachloride and then with ether. Another experiment (no. 7) using 5 times the amount of ester but only the same amount of adsorbent was carried out with the same favorable results. Thus, a large-scale separation could now be undertaken without continuous infrared analysis of the eluate, but patterned on experiments No. 6 and 7.

A 6.9 × 45 cm. column was filled with 1.4 kg. of carbon tetrachloride-slurried neutral adsorption alumina (Woelm), and 154.3 g. of the stereoisomeric ester mixture was applied. Elution with 14.2 l. of carbon tetrachloride produced, after evaporation, 114 g. of pale yellow oil, b.p. 86–93° (0.1 mm.), with 1.8 g. of tarry distillation residue. Further elution with 28.1 l. of ether gave the second isomer, 23.6 g. of a yellow oil, b.p. 82–95° (0.1 mm.), with a tarry distillation residue weigh-

ing 2.6 g. The more abundant ester eluted with carbon tetrachloride gave on hydrolysis the acid of m.p. 109–109.5°, while the ether-eluted ester gave acid melting at 164.5–165.5° only.

Attempts to interconvert the two stereoisomeric acids *via* the acyl chloride were unsuccessful, the unchanged starting acids being recovered from the hydrolysis of the acid chlorides (hydrochloride) for the most part.

trans-**2-Aminomethyl-1-phenylcyclopropane Hydrochloride (Compound 64).**—*trans*-2-Phenylcyclopropanecarboxamde (84 g., 0.52 mole) was added during 24 hr. to a suspension of lithium aluminum hydride (65 g., 1.71 mole) in 1200 ml. of tetrahydrofuran by means of a continuous return extractor.[41] The mixture was cooled and decomposed with a 10% excess of water, diluted with tetrahydrofuran, then filtered, and the filter cake was washed with tetrahydrofuran. The filtrate was concentrated *in vacuo* to give a colorless liquid, b.p. 76–84° (0.4 mm.); $n^{25}D$ 1.5472. The amine was converted to a hydrochloride in the usual way.

2-(2-Phenylcyclopropyl)imidazoline Hydrochloride (Compound 66).—A mixture of 61.7 g. (0.32 mole) of ethyl 2-phenylcyclopropanecarboxylate,[4] 47.9 g. (0.36 mole) of ethylenediamine dihydrochloride and 90 g. (1.5 moles) of ethylenediamine was heated at 250° for 2 hr., allowing excess ethylenediamine and water to distill. The mixture was suspended in 350 ml. of 4 *N* hydrochloric acid, and extracted with ether. The acidic layer was made alkaline and extracted with methylene chloride. The organic extracts were dried and concentrated to give 18.7 g. of a viscous oil, b.p. 180–210° (8 mm.). A mixture of this oil and 28.5 g. (0.51 mole) of calcium oxide was heated for 15 hr. at 230° in a nitrogen atmosphere. The mixture was extracted with ethanol and the ethanolic extracts were concentrated *in vacuo*. The tarry residue was dissolved in 2 *N* hydrochloric acid. After the acidic solution was washed with ether, it was made alkaline and extracted with ether. The ether extracts were dried and concentrated to give a pale yellow liquid, b.p. 125–135° (0.4 mm.), which was converted to a hydrochloride.

1-Aminomethyl-1-phenylcyclopropane Hydrochloride (Compound 68).—A solution of 20.8 g. (0.15 mole) of 1-phenylcyclopropanecarbonitrile[15] in 100 ml. of ether was added dropwise to a stirred suspension of 5.7 g. (0.15 mole) of lithium aluminum hydride in 200 ml. of ether. The mixture was stirred and refluxed for 12 hr., then treated with 6 ml. of water, 6 ml. of 2 *N* sodium hydroxide and 18 ml. of water. It was filtered, the filtrate concentrated and the residue converted to a hydrochloride.

N-Methyl-1-phenylcyclopropylamine Cyclohexylsulfamate (Compound 69).—A solution of 5.0 g. (0.03 mole) of 1-phenylcyclopropyl isocyanate (prepared from 1-phenylcyclopropanecarboxylic acid[25] by the mixed carboxylic-carbonic anhydride method) in 50 ml. of ether was added slowly to a suspension of 1.2 g. (0.3 mole) of lithium aluminum hydride in 50 ml. of ether. The mixture was stirred and refluxed for 4 hr., decomposed (1 ml. of water, 1 ml. of 2 *N* sodium hydroxide and 3 ml. of water), filtered, and the filtrate concentrated to give a colorless liquid, b.p. 44–47° (0.3 mm.). A solution of this liquid in ethanol was treated with an ethanolic solution of cyclohexylsulfamic acid.

1-(N-Piperidinyl)-1-phenylcyclopropane Hydrochloride (Compound 70).—A solution of 26.6 g. (0.2 mole) of 1-phenylcyclopropylamine[42] (prepared by hydrolysis of 1-phenylcyclopropyl isocyanate with hydrochloric acid), 23 g. (0.1 mole) of 1,5-dibromopentane and 100 ml. of benzene was stirred and refluxed for

(41) W. G. Brown, *Org. Reactions*, **IV**, 469 (1951).
(42) S. C. Bunce and J. B. Cloke, *J. Am. Chem. Soc.*, **76**, 2244 (1954).

20 hr. The mixture was cooled and filtered and the filtrate was concentrated *in vacuo*. The residue was refluxed with 50 ml. of acetic anhydride for 1 hr., the solution was concentrated *in vacuo* and the residue dissolved in water. After extraction with ether, the solution was made alkaline and the mixture was extracted with ether. The ether extracts were dried and concentrated to give a colorless liquid, b.p. 75–83° (0.3 mm.), which was converted to a hydrochloride.

2-Substituted Cyclopropylamines. II. Effect of Structure upon Monoamine Oxidase-Inhibitory Activity as Measured *in Vivo* by Potentiation of Tryptamine Convulsions

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The monoamine oxidase (MAO)-inhibitory activity of numerous analogs and ring-homologs of 2-phenylcyclopropylamine, and related compounds, as measured *in vivo* by potentiation of tryptamine convulsions, has been determined. The results indicated that the structural requirements for potent *in vivo* MAO-inhibitory activity in this class of compounds are: (1) a cyclopropane ring, (2) an amino group attached directly to the cyclopropane ring, and (3) a 2-substituent containing an aromatic moiety. On the basis of an examination of molecular models of cyclopropylamine derivatives and other types of MAO-inhibitors, possible modes of interaction of these compounds with MAO have been considered.

An earlier paper[1] in this series reported the monoamine oxidase (MAO)-inhibitory activities of *trans*- and *cis*-2-phenylcyclopropylamine and various other types of compounds as measured by potentiation of tryptamine convulsions in rats.[2,3] By this and other test

(1) D. H. Tedeschi, R. E. Tedeschi, and E. J. Fellows, *Proc. Soc. Exp. Biol. Med.*, **103**, 680 (1960).

(2) D. H. Tedeschi, R. E. Tedeschi, and E. J. Fellows, *J. Pharmacol. Exptl. Therap.*, **126**, 223 (1959).

(3) D. R. Maxwell, W. R. Gray, and E. M. Taylor, *Brit. J. Pharmacol.*, **17**, 310 (1961), recently have reported on a similar test procedure in the mouse wherein tryptamine potentiation was used as a measure of MAO inhibition.