# Synthesis and Anorectic Activity of Some 1-Benzylcyclopropylamines

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1-Benzylcyclopropylamine (1) reduces food consumption in several animal species. A series of 55 benzene ring substituted, N-alkylated, -aralkylated, and -acylated derivatives of 1 was prepared in order to investigate the influence of structure on anorectic activity. 1-Benzylcyclopropanecarboxylic esters, employed as intermediates for 1 and related compounds, were synthesized most conveniently and in excellent yield by the abnormal Hofmann elimination reaction of diethyl benzyl(dimethylaminoethyl)malonate methoethoxides. Similar reaction of a dimethylaminopropylmalonate was studied as a potential route to 1-substituted cyclobutanecarboxylates; however, in this case, normal Hofmann elimination products were identified. The anorectic activity of this series of 1-benzylcyclopropylamines was evaluated in rats and dogs. Some substitutions on the benzene ring increased anorectic potency slightly; others decreased it. N-Substitution generally decreased anorectic potency.

As part of a study of the monoamine oxidase (MAO)-inhibiting activity of cyclopropylamines, we prepared 1-benzylcyclopropylamine (**1**) and its *N*-methyl derivative (**17**).[1] Although these compounds only weakly inhibited MAO, as measured *in vivo* by potentiation of tryptamine-induced convulsions in rats,[2] they exhibited potent anorectic activity in several animal species. In a test employing rats trained to eat their daily food rations in 6 hr,[3] 1-benzylcyclopropylamine (**1**) was approximately one-third as potent as dextroamphetamine. In order to investigate the influence of structure on anorectic activity, a series of benzene ring substituted, N-alkylated, -aralkylated, and -acylated derivatives was prepared and studied for anorectic activity in rats and dogs. The synthesis and anorectic evaluation of these compounds are described in this paper.

**Chemistry.**—1-Benzylcyclopropylamines were prepared from 1-benzylcyclopropanecarboxylic acids *via* the Curtius reaction. In our earlier study,[1] 1-benzylcyclopropanecarboxylic acid was prepared from cyclopropyl phenyl ketone by way of benzylation, $NaNH_2$ cleavage of the intermediate 1-benzylcyclopropyl phenyl ketone and hydrolysis of the resulting cyclopropanecarboxamide.[4,5] The yield of 1-benzylcyclopropanecarboxylic acid from this sequence is low because benzylation is incomplete. In addition, a mixture of amides is formed during $NaNH_2$ cleavage[6] which can occur on either side of the ketone carbonyl.[4]

Higher yields of the acid (IV, R = Ph) were obtained from the route outlined in Chart I. This method was also employed to prepare a series of related 1-substituted cyclopropanecarboxylic acids (IV).

α-Substituted malonates I were alkylated with 2-dimethylaminoethyl chloride to give the diethyl benzyl(dimethylaminoethyl)malonates II listed in Table I. Thermal decomposition of quaternary methoethoxides derived from II resulted in decarbethoxylation and abnormal Hofmann elimination[7,8] to give ethyl 1-substituted cyclopropanecarboxylates III. These esters (III), which could also be obtained in lower yield by thermal decomposition of corresponding methiodides, were hydrolyzed to the acids IV indicated in Table II. 1-Substituted cyclopropanecarboxylic acids IV were converted, *via* acid chlorides and azides, into the corresponding isocyanates V by the Curtius procedure. HCl hydrolysis of V gave primary amines VI listed in Table III. Reduction of V with LAH gave the methylamine derivatives VII which are tabulated in Table IV.

The success of the abnormal Hofmann elimination reaction for synthesis of ethyl 1-benzylcyclopropanecarboxylate and related compounds led us to investigate a similar reaction of homologous diethyl benzyl(3-dimethylaminopropyl)malonate (VIII) as a potential source of ethyl 1-benzylcyclobutanecarboxylates. As shown in Chart II, VIII was prepared by aminopropylation of diethyl benzylmalonate. In this case, however, thermal decomposition of the quaternary ethoxide derived from VIII did not give the cyclic product, ethyl 1-benzylcyclobutanecarboxylate. Instead, decarbethoxylation and normal Hofmann elimination gave IX (R = Et) plus an approximately equal amount of the tertiary amine (X, R = Et). In addition, minor amounts of corresponding Me esters (IX, X, R = Me) were detected as products. These compounds, which apparently arose from facile ester interchange with MeOH denaturant in the EtOH solvent, were obtained as the major products when the reaction was carried out in MeOH.

A series of N-alkylated, -aralkylated, and -acylated derivatives of 1-benzylcyclopropylamine, its *o*-Cl, *m*-$F_3C$, and *p*-Me congeners was prepared from corresponding primary amines and isocyanates by conventional methods which are described in the Experimental Section. N-Substituted 1-benzylcyclopropylamines are tabulated in Table IV.

Upon reduction of *N*-(1-benzylcyclopropyl)acetamide (XI) with excess LAH in refluxing $Et_2O$ for 6 hr the product obtained was not the *N*-Et derivative of 1-benzylcyclopropylamine. As indicated in Chart III, cleavage of the cyclopropane ring occurred and α,*N*-diethylphenethylamine (XII), whose structure was

(1) 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).

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

(3) G. C. Heil, C. A. Leonard, and D. H. Tedeschi, *Pharmacologist*, **7**, 155 (1965).

(4) F. J. Piehl and W. G. Brown, *J. Amer. Chem. Soc.*, **75**, 5023 (1953).

(5) A. Haller and E. Bropist, *Ann. Chim. (Paris)*, **17**, 25 (1923); *C. R. Acad. Sci.*, **154**, 1570 (1912).

(6) For a review of the cleavage of nonenolizable ketones with $NaNH_2$ see: K. E. Hamlin and A. W. Weston, *Org. React.*, **9**, 1 (1957).

(7) J. Weinstock, *J. Org. Chem.*, **21**, 540 (1956).

(8) M. A. T. Rogers, *ibid.*, **22**, 350 (1957).

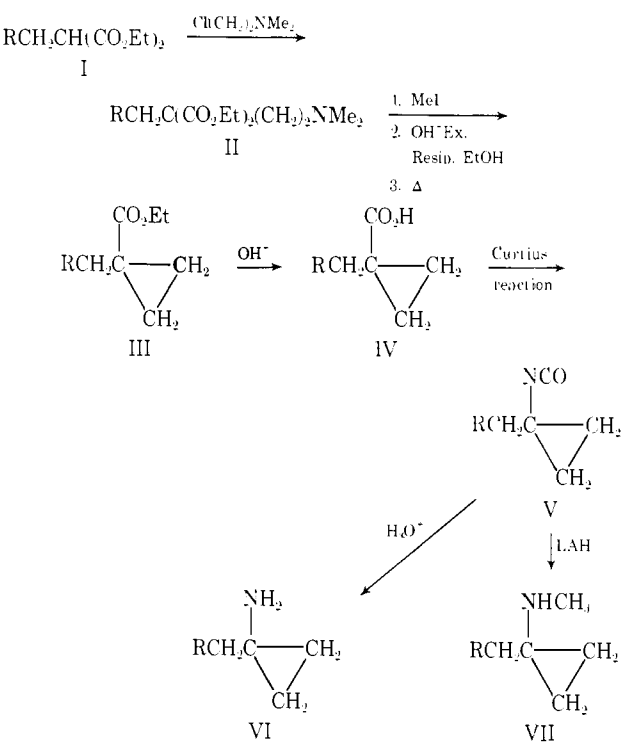
TABLE I
DIETHYL BENZYLMALONATES AND DIETHYL BENZYL-(2-DIMETHYLAMINOETHYL)MALONATES

| | $RCH_2CH(CO_2Et)_2$ | | $RCH_2C(CO_2Et)_2(CH_2)_2NMe_2$ | | | | |
|---|---|---|---|---|---|---|---|
| R | Bp, °C (mm) | Yield, % | Methiodide,[a] mp, °C | Yield,[b] % | Salt, mp, °C | Recrystn solvent | Formula[c] |
| $C_6H_5$ | *d* | | *e*, *f* | 88 | | | |
| 2-$ClC_6H_4$ | 158-164[g] (1.2) | 68 | 106–109 | 70 | | | |
| 2-$MeC_6H_4$ | 137–143[h] (1.2) | 79 | 145-147 | 78 | 98-100[i] | *i*-PrOH-$Et_2O$ | $C_{19}H_{29}NO_4 \cdot C_6H_{13}NO_3S$[j,k] |
| 2-$CF_3C_6H_4$ | 134-141 (1.0) | 70 | *f* | 88 | | | |
| 3-$ClC_6H_4$ | 152–158[l] (0.8) | 55 | 166-169 | 70 | | | |
| 3-$MeC_6H_4$ | 139–148 (0.7) | 54 | 119-121 | 71 | | | |
| 3-$CF_3C_6H_4$ | 141-147 (0.7) | 54 | 183–185 | 66 | | | |
| 4-$BrC_6H_4$ | 164–172[n] (0.4) | 59 | 210–212 | 71 | 178-179 | $Me_2CO$ | $C_{18}H_{26}BrNO_4 \cdot HCl$ |
| 4-$ClC_6H_4$ | 141–147[o] (0.6) | 59 | 206-207 dec | 82 | 190–191 | EtOH-$Et_2O$ | $C_{18}H_{26}NO_4 \cdot HCl$ |
| 4-$MeC_6H_4$ | 136–140[p] (0.4) | 63 | 197-199 | 77 | 152–153 | $Me_2CO$-$Et_2O$ | $C_{19}H_{29}NO_4 \cdot HCl$ |
| 4-$MeOC_6H_4$ | 149–165[q] (0.8) | 69 | 209-211 | 70 | 159-160 | EtOH-$Et_2O$ | $C_{19}H_{29}NO_5 \cdot HCl$ |
| 4-$CF_3C_6H_4$ | 124-131 (0.4) | 57 | 154-156[r] | 80 | 124-125 | $Me_2CO$ | $C_{19}H_{26}F_3NO_4 \cdot 0.5C_4H_4O_4$[s] |
| 4-$CF_3OC_6H_4$ | 136–142 (0.3) | 58 | 188-190 | 74 | 130–131 | EtOAc-$Et_2O$ | $C_{19}H_{26}F_3NO_5 \cdot C_4H_4O_4$[t] |
| 4-$CF_3SC_6H_4$ | 145–151 (0.6) | 51 | 165–167 | 69 | 115–117 | EtOAc-$Et_2O$ | $C_{19}H_{26}F_3NO_4S \cdot C_4H_4O_4$[t] |
| 2,6-$Cl_2C_6H_4$ | 164-172 (0.4) | 98 | 168-170 | 68 | 124-126 | EtOAc-$Et_2O$ | $C_{18}H_{25}Cl_2NO_4 \cdot C_4H_4O_4$[t] |
| *cyclo*-$C_6H_{11}$ | 111-122[u] (0.5) | 71 | 186–188 dec | 73 | 144-145 | *i*-PrOH | $C_{18}H_{33}NO_4 \cdot C_4H_4O_4$[t] |

[a] All methiodides were prepared in $Me_2CO$, unless indicated otherwise. [b] The yield of methiodide. [c] All compounds which were converted into a salt, but not methiodides, were analyzed for C, H, N and the analytical values were within ±0.4 of the calculated figures, unless indicated otherwise. [d] Diethyl benzylmalonate was obtained from a commercial source. [e] Reference 16. [f] The methiodide was prepared in $Et_2O$; it was a viscous liquid which was used for further reaction without purification. [g] R. A. Barnes and L. Gordon [*J. Amer. Chem. Soc.* **71**, 2644 (1949)] reported bp 155–160° (4 mm). [h] B. B. Elsner and K. J. Parker [*J. Chem. Soc.*, 592 (1957)] reported bp 133° (0.2 mm). [i] The free base had bp 156–162° (1.3 mm). [j] Cyclohexylsulfamate. [k] C: calcd., 58.34; found, 57.83. [l] J. Kenner and E. Witham [*J. Chem. Soc.*, **119**, 1452 (1921)] reported bp 213–214° (40 mm). [m] J. P. Trivedi and J. J. Trivedi, [*J. Indian Chem. Soc.*, **35**, 687 (1958)] reported bp 180° (30 mm). [n] J. von Braun and J. Nelles [*Ber.*, **66**, 1464 (1933)] reported bp 193–198° (14 mm). [o] J. von Braun and J. Nelles [*ibid.*, **66**, 1464 (1933)] reported bp 190–192° (14 mm). [p] G. Darzens and A. Heinz [*C. R. Acad. Sci.*, **184**, 33 (1927)] reported bp 179–180°. [q] G. Darzens and A. Lévy [*ibid.*, **200**, 469 (1935)] reported bp 178–180° (3 mm). [r] The methiodide was recrystallized from EtOH-$Et_2O$. [s] Hemimaleate. [t] Maleate. [u] G. S. Hiers and R. Adams [*J. Amer. Chem. Soc.*, **48**, 2385 (1926)] reported bp 135–136° (3 mm).

established by comparison with an unambiguously synthesized sample, was obtained. Hydrogenolysis of this cyclopropane derivative is another example of reductive ring-opening of an NH-substituted cyclopropane by LAH, possibly by a mechanism[9] resembling one postulated by Hochstein and Brown[10] for LAH reduction of cinnamyl alcohol. Necessity for initial formation of a N anion, as suggested by this mechanism,[9,10] is supported by the observation that LAH reduction of several tertiary *N*-(1-benzylcyclopropyl)amides to amines occurred without cleavage of the cyclopropane ring. Additionally, in analogy with LAH reduction of the double bond of allyl alcohol, which proceeds relatively more slowly than that of cinnamyl alcohol,[10] hydrogenolysis of the cyclopropane ring might be anticipated to occur less readily with XI than with 2-arylcyclopropylamine derivatives in which the anion can achieve benzylic stabilization.[9] Hydrogenolysis was not observed upon LAH reduction of 1-benzylcyclopropyl isocyanates at 25°. Also, reductive cleavage of XI could be avoided by a shorter reduction time (30 min) which gives 1-benzyl-*N*-ethylcyclopropylamine (XIV, R = Ph) in low yield. *N*-Ethyl 1-substituted cyclopropylamines XIV were obtained in higher yield from corresponding formamides XIII *via* ethylation and subsequent acid hydrolysis of the formyl group, as indicated in Chart III.

CHART I



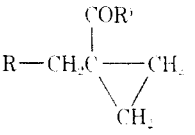

**Structure–Activity Relationships.**—Anorectic activity of 1-benzylcyclopropylamines was determined in the rat and dog anorexia tests described in the Experimental Section. The parent compound of the series, 1-benzylcyclopropylamine (**1**), is a potent anorectic agent which reduces food consumption of rats, dogs, and cats. The main side effects of **1** are those of mild CNS stimulation as indicated by slight restlessness and occasional increased motor activity observed in dogs. Cardiovascular effects in dogs treated with **1** are comparable to those noted with equivalent anorectic doses of dextroamphetamine.

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

(10) F. A. Hochstein and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3484 (1948).

TABLE II

ETHYL 1-BENZYLCYCLOPROPANECARBOXYLATES, 1-BENZYLCYCLOPROPANECARBOXYLIC ACIDS, AND 1-BENZYLCYCLOPROPANECARBONYL CHLORIDES[a]

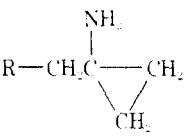


| | R¹ = OEt | | | R¹ = OH | | | R¹ = Cl | |
|---|---|---|---|---|---|---|---|---|
| R | Bp, °C (mm) | Yield, % | Mp, °C | Recrystn solvent | Yield, % | Formula[a] | Bp, °C (mm) | Yield, % |
| $C_6H_5$ | 109–120[b] (2) | 65 | 105–107[c] | Hexane | 95 | | *d* | 99 |
| 2-$ClC_6H_5$ | 152–156 (12) | 63 | 143–144 | EtOH | 97 | $C_{10}H_9ClO_2$ | 160–164 (12) | 94 |
| 2-$MeC_6H_4$ | 140–144 (13) | 63 | 125–127 | EtOH | 77 | $C_{12}H_{14}O_2$ | 146–148 (14) | 87 |
| 2-$CF_3C_6H_4$ | 140–146 (18) | 31 | 135–137 | EtOAc | 97 | $C_{12}H_9F_4O_2$ | 127–131 (11) | 85 |
| 3-$ClC_6H_4$ | 146–151 (11) | 67 | 62–64 | Hexane | 98 | $C_{10}H_9ClO_2$ | 142–152 (2.7) | 95 |
| 3-$MeC_6H_4$ | 147–151 (14) | 55 | 69–71 | Hexane | 98 | $C_{12}H_{14}O_2$ | 146–152 (14) | 95 |
| 3-$CF_3C_6H_4$ | 132–136 (13) | 70 | *f* | | 97 | $C_{12}H_9F_3O_2$ | 142–145 (15) | 86 |
| 4-$BrC_6H_4$ | 152–158 (0.4) | 76 | 148–149 | EtOH | 79 | $C_{10}H_9BrO_2$ | 141–149 (0.7) | 91 |
| 4-$ClC_6H_4$ | 152–157 (12) | 76 | 138–140 | EtOH | 98 | $C_{10}H_9ClO_2$ | 156–158 (9) | 94 |
| 4-$MeC_6H_4$ | 141–144 (12) | 71 | 118–120 | EtOH | 98 | $C_{12}H_{14}O_2$ | 141–144 (10) | 95 |
| 4-$MeOC_6H_4$ | 147–155 (0.9) | 69 | 110–112 | EtOH | 89 | $C_{12}H_{14}O_3$ | 128–137 (0.4) | 91 |
| 4-$CF_3C_6H_4$ | 151–154 (27) | 63 | 90–91 | Hexane | 96 | $C_{12}H_9F_3O_2$ | 158–161 (26) | 90 |
| 4-$CF_3OC_6H_4$ | 124–127 (10) | 69 | 80–82 | Hexane | 98 | $C_{12}H_9F_3O_3$ | 130–135 (10) | 84 |
| 4-$CF_3SC_6H_4$ | 147–150 (9) | 58 | 77–79 | Hexane | 99 | $C_{12}H_9F_3O_2S$ | *g* | 98 |
| 2,6-$Cl_2C_6H_3$ | 124–132 (0.4) | 56 | 167–169 | EtOH | 99 | $C_{10}H_8Cl_2O_2$ | 132–141 (0.5) | 92 |
| *cyclo*-$C_6H_{11}$ | 115–118 (12) | 62 | 95–97 | EtOAc | 98 | $C_{10}H_{14}O_2$[h] | 118–120 (12) | 87 |

[a] All carboxylic acids were analyzed for C, H and the analytical values were within ±0.4% of the calculated figures, unless indicated otherwise. [b] Reference 16; see also ref 7 and 8. [c] Reference 4, mp 106.5–108°. [d] This acid chloride was not distilled. [e] C: calcd, 62.72; found, 63.39. [f] Bp 130–135° (1 mm). [g] This acid chloride decomposed on attempted distillation; therefore, it was used for further reaction without purification. [h] C: calcd, 72.49; found, 72.02.

TABLE III

1-BENZYLCYCLOPROPYLAMINE HYDROCHLORIDES



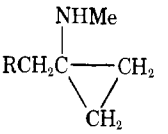
| No. | R | Mp, °C | Recrystn solvent | Yield, %[a] | Formula[b] | Anorectic activity $ED_{50}$ (po) mg/kg (fiducial limits)[c,d] Rat[e] | Dog[f] |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | 157.5–159[g,h] | | | | 4.3 (3.2–6.1) | 2.6 (1.7–3.9) |
| 2 | 2-$ClC_6H_4$ | 201–203 | *i*-PrOH | 92 | $C_{10}H_{12}ClN \cdot HCl$ | 20 = −57% | |
| 3 | 2-$MeC_6H_4$ | 209–210 | *i*-PrOH | 86 | $C_{11}H_{15}N \cdot HCl$ | 7.4 (4.5–10.9) | 8.2 = *i* |
| 4 | 2-$CF_3C_6H_4$ | 198–200 | *i*-PrOH–$Et_2O$ | 75 | $C_{10}H_{12}F_3N \cdot HCl$ | 21.4 = −12% | |
| 5 | 3-$ClC_6H_4$ | 148–151 | MeCN | 83 | $C_{10}H_{12}ClN \cdot HCl$ | 20.6 = −98% | |
| 6 | 3-$MeC_6H_4$ | 154–155 | *i*-PrOH–$Et_2O$ | 82 | $C_{11}H_{15}N \cdot HCl$ | 12.0 = −69% | |
| 7 | 3-$CF_3C_6H_4$ | 180–181 | MeCN | 89 | $C_{10}H_{12}F_3N \cdot HCl$ | 8.6 = −44% | |
| 8 | 4-$BrC_6H_4$ | 205–206 | EtOH–$Et_2O$ | 93 | $C_{10}H_{12}BrN \cdot HCl$ | 4.9 (4.3–5.6)[c] | 4.3 = *i*, 8.6 = *j* |
| 9 | 4-$ClC_6H_4$ | 203–205 | *i*-PrOH | 98 | $C_{10}H_{12}ClN \cdot HCl$ | 2.9 (2.4–3.4) | 1.6 (1.1–2.3) |
| 10 | 4-$MeC_6H_4$ | 184–186 | *i*-PrOH–$Et_2O$ | 99 | $C_{11}H_{15}N \cdot HCl$ | 3.6 (2.6–4.8) | 4.8 (2.1–10.5) |
| 11 | 4-$MeOC_6H_4$ | 164–166 | EtOH–$Et_2O$ | 89 | $C_{11}H_{15}NO \cdot HCl$ | 6.5 (4.6–10.2) | 8.3 = *i* |
| 12 | 4-$CF_3C_6H_4$ | 168–169 | $Me_2CO$ | 93 | $C_{10}H_{12}F_3N \cdot HCl$ | 10.3 (7.8–13.9) | |
| 13 | 4-$CF_3OC_6H_4$ | 143–145 | EtOAc–$Et_2O$ | 71 | $C_{11}H_{12}F_3NO \cdot HCl$ | 13.8 (8.3–23.2) | 13 = *i* |
| 14 | 4-$CF_3SC_6H_4$ | 167–168 | $Me_2CO$–$Et_2O$ | 78 | $C_{11}H_{12}F_3NS \cdot HCl$ | 16.3 (7.2–73.3) | |
| 15 | 2,6-$Cl_2C_6H_3$ | 209–211 | *i*-PrOH–$Et_2O$ | 78 | $C_{10}H_{11}Cl_2N \cdot HCl$ | 26.9 (21.1–36.4) | 8.6 = *i*, 21.6 = *j* |
| 16 | *cyclo*-$C_6H_{11}$ | 161–162 | *i*-PrOH–$Et_2O$ | 79 | $C_{10}H_{19}N \cdot HCl$ | 20 = −37%, 40 = −35% | |

[a] Yield from corresponding 1-benzylcyclopropanecarbonyl chloride. [b] All hydrochlorides were analyzed for C, H, N and the analytical values were within ±0.4% of the calculated values. [c] See Experimental Section, Pharmacological Methods for description of activity of compounds whose $ED_{50}$ was not determined. [d] Compounds were administered orally as free base or salt as indicated. $ED_{50}$'s calculated as free base. [e] In the rat anorexia test dextroamphetamine $ED_{50}$ = 1.3 mg/kg, lit.[3] [f] In the dog anorexia test, dextroamphetamine $ED_{50}$ = 0.6 mg/kg, lit.[3] [g] Lit.[1] [h] Sulfate, mp 234–235° (from *i*-PrOH–$H_2O$). *Anal.* ($C_{20}H_{32}N_2O_4S$) C, H, N. [i] *Anal.* calcd for $0.25H_2O$.

In the rat anorexia test, 1-benzylcyclopropylamine was about one-third as potent as dextroamphetamine, whereas in the dog it was approximately one-fourth as potent (see Table III). The cyclopropane **1** was slightly more potent than the related α,α-dimethylphenethylamine (phentermine) which has $ED_{50}$ (po) 5.1 (3.4–8.2) mg/kg in the rat anorexia test.[3]

Certain substitutions of the benzene ring of 1-benzyl-

TABLE IV
*N*-METHYL 1-BENZYLCYCLOPROPYLAMINES



| No. | R | Salt, Mp, °C | Recrystn solvent | Yield, %[a] | Formula[b] | Anorectic activity[c,d] —$ED_{50}$ (po) mg/kg (fiducial limits)— Rat[e] | Dog[f] |
|---|---|---|---|---|---|---|---|
| 17 | $C_6H_5$ | 160-162[f] | EtOH-$Et_2O$ | 38 | $C_{11}H_{15}N \cdot HCl$ | 6.5 = 35%, 8.2 = −86% | 4.1 = 1/4 |
| 18 | 2-$ClC_6H_4$ | 150-152 | *i*-PrOH | 75 | $C_{11}H_{14}ClN \cdot C_4H_4O_4$ | 10 = −36% | |
| 19 | 2-$MeC_6H_4$ | 174-176 | *i*-PrOH-$Et_2O$ | 64 | $C_{12}H_{17}N \cdot HCl$ | 16.7 (9.9-28.4) | 16.6 = 1/4 |
| 20 | 2-$CF_3C_6H_4$ | 178-180 | *i*-PrOH-$Et_2O$ | 83 | $C_{12}H_{14}F_3N \cdot HCl$ | 21.6 = −38% | |
| 21 | 3-$ClC_6H_4$ | 132-134 | *i*-PrOH | 77 | $C_{11}H_{14}ClN \cdot C_4H_4O_4$[g] | 12.6 = −80% | |
| 22 | 3-$MeC_6H_4$ | 98-100 | EtOAc-$Et_2O$ | 86 | $C_{12}H_{17}N \cdot C_4H_4O_4$[g] | 15.1 = −24% | |
| 23 | 3-$CF_3C_6H_4$ | 82-85 | EtOAc-$Et_2O$ | 83 | $C_{12}H_{16}F_3N \cdot C_4H_4O_4$[g] | 8.8 (5.9-11.6) | 6.6 = 2/4 |
| 24 | 4-$BrC_6H_4$ | 147-149 | EtOH-$Et_2O$ | 79 | $C_{11}H_{14}BrN \cdot HCl$ | 8.7 = −56%, 21.7 = −98% | |
| 25 | 4-$ClC_6H_4$ | 152-154 | *i*-PrOH | 76 | $C_{11}H_{14}ClN \cdot C_4H_4O_4$[g] | 6.4 = −78%, 17 = −99% | 6.4 = 3/4 |
| 26 | 4-$MeC_6H_4$ | 152-154 | *i*-PrOH-$Et_2O$ | 78 | $C_{12}H_{17}N \cdot HCl$ | 5.2 (2.7-17.6) | 8.3 = 2/4 |
| 27 | 4-$MeOC_6H_4$ | 136-138 | *i*-PrOH-$Et_2O$ | 60 | $C_{12}H_{13}NO \cdot HCl$ | 21 = −85% | 8.4 = 3/4 |
| 28 | 4-$CF_3C_6H_4$ | 144-146 | $Me_2CO$ | 74 | $C_{12}H_{13}F_3N \cdot C_4H_4O_4$[g] | 16.6 = −55% | |
| 29 | 4-$CF_3OC_6H_4$ | 117-118.5 | $Me_2CO$-$Et_2O$ | 76 | $C_{12}H_{14}F_3NO \cdot C_4H_4O_4$[g] | 10.7 (6.0-15.8) | 6.8 = 0/4 |
| 30 | 4-$CF_3SC_6H_4$ | 123-125 | $Me_2CO$-$Et_2O$ | 47 | $C_{12}H_{13}F_3NS \cdot C_4H_4O_4$[g] | 11 = +1% | |
| 31 | 2,6-$Cl_2C_6H_3$ | 160-162 | *i*-PrOH | 87 | $C_{11}H_{13}Cl_2N \cdot C_4H_4O_4$[g] | 16.6 = −17% | |
| 32 | *cyclo*-$C_6H_{11}$ | 137-139 | *i*-PrOH-$Et_2O$ | 97 | $C_{11}H_{21}N \cdot C_4H_4O_4$[g] | 15 = +16% | |

[a] Overall yield from appropriate 1-benzylcyclopropanecarbonyl chloride. [b] All *N*-methylamine salts were analyzed for C, H, N and the analytical values were within ±0.4% of the calculated figures. [c] See footnote *c*, Table III. [d] See footnote *d*, Table III. [e] See footnote *e*, Table III. [f] Reference 1. [g] Maleate.

cyclopropylamine increased anorectic potency slightly whereas others decreased it. Results of anorectic testing of a series of substituted 1-benzylcyclopropylamines and their N-methylated derivatives in rats and dogs are tabulated in Tables III and IV. Substitution of the *ortho* position of 1-benzylcyclopropylamine with Me (**3**) reduced anorectic potency in the rat by 0.5, whereas similar substitution with Cl (**2**) or $CF_3$ (**4**) resulted in an even greater decrease of potency. Substitution of the *meta* position with Cl (**5**), Me (**6**), or $CF_3$ (**7**) also decreased anorectic potency; however, the decrease was less than with the *ortho* isomers. Introduction of substituents into the *para* position of 1-benzylcyclopropylamine had a variable influence on anorexia. A *p*-Cl derivative (**9**) was somewhat more potent than the parent **1** in both rats and dogs. Likewise, the *p*-Me congener **10** was more potent than **1** in producing anorexia in rats, but it was less potent in dogs. A *p*-Br (**8**) derivative was approximately equipotent with **1** in rats, but it was less potent in dogs. The *p*-MeO (**11**) analog was only slightly less potent than the parent, whereas *p*-$CF_3$ (**12**), $CF_3O$ (**13**), and $CF_3S$ (**14**) derivatives were less than one-half as potent in rats. Only one disubstituted compound, a 2,6-dichloro derivative **15**, was studied; it was about one-sixth as potent as **1** in the rat anorexia test.

A cyclohexyl congener **16** was less than 0.1 as effective as 1-benzylcyclopropylamine in producing anorexia in rats.

Although the N-methylated derivatives (**17–32**) were generally less potent than the corresponding primary amines, in several instances, *e.g.*, *m*-$CF_3$ (**7**, **23**) and *p*-$CF_3O$ (**13**, **29**), the substituted derivatives and their unsubstituted analogs were approximately equipotent as anorectics in rats and dogs.

CHART II

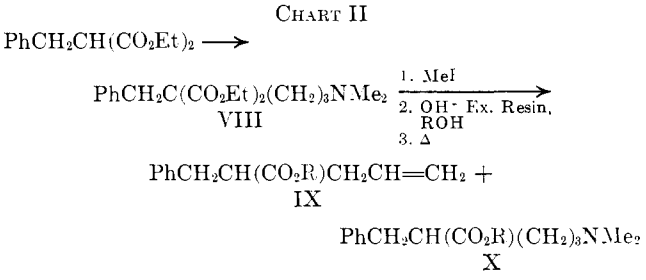
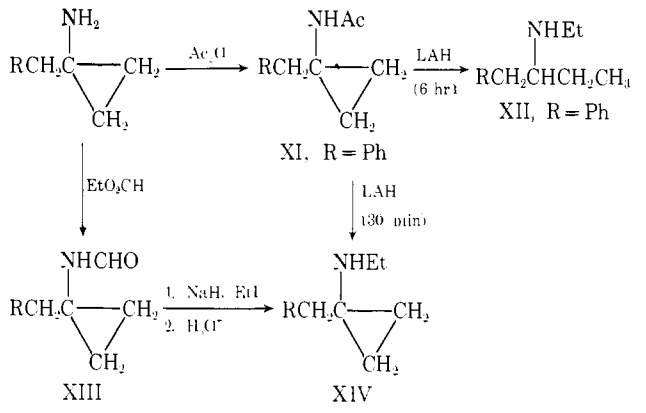
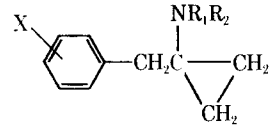



CHART III




Results of anorectic examination of various other N-substituted 1-benzylcyclopropylamines in rats and dogs are tabulated in Table V. *N*-Ethyl-1-benzylcyclopropylamine (**33**) and its *o*-Cl (**42**), *p*-Cl (**45**), *m*-Me (**44**), and *p*-Me (**51**) derivatives were slightly less potent than the corresponding primary amines or their *N*-Me counterparts; however, in the *m*-$CF_3$ series an *N*-Et derivative **43** was somewhat more potent than either the primary amine or its *N*-Me homolog. The only other sec-

## Table V
### N-Substituted 1-Benzylcyclopropylamines




| No. | X | $R_1$ | $R_2$ | Mp, °C | Method[a] | Yield, %[b] | Recrystn solvent | Formula[c] | Anorectic activity $ED_{50}$ (po), mg/kg (fiducial limits[d,e]) Rat[f] | Dog[g] |
|---|---|---|---|---|---|---|---|---|---|---|
| 33 | H | H | Et | 194–195 | I | 73 | EtOH–$Et_2O$ | $C_{12}H_{17}H \cdot HCl$ | 9.9 (7.1–12.9) | *ca.* 4.1–8.3 |
| 34 | H | H | $(CH_2)_2OH$ | 116–117 | *h* | 30 | MeCN | $C_{12}H_{17}NO \cdot HCl$ | 10.1 = −41%, 21 = −71% | 2.1 = 1/4, 4.2 = 1/2 |
| 35 | H | Me | Me | 199–201 | K | 71 | *i*-PrOH–$Et_2O$ | $C_{12}H_{17}N \cdot HCl$ | 12.4 = −64% | |
| 36 | H | Me | Et | 190–192 | K | 80 | MeCN–$Et_2O$ | $C_{13}H_{19}N \cdot HCl$ | 12.6 = −67% | |
| 37 | H | Et | Et | 181–182 | K | 35.5 | EtOH–$Et_2O$ | $C_{14}H_{21}N \cdot HCl$ | 10.4 (4.8–24.8) | 4.3 = 1/4, 8.5 = 1/8 |
| 38 | H | Me | $CH_2Ph$ | 133–135 | K | 87 | EtOAc–$Et_2O$ | $C_{18}H_{21}N \cdot C_4H_4O_4$ | 17.1 = −3% | |
| 39 | H | Me | $(CH_2)_2Ph$ | 158–160 | *j* | 92 | $Me_2CO$–$Et_2O$ | $C_{19}H_{23}N \cdot HCl$ | 44 = −26% | |
| 40 | H | H | $CO_2Et$ | 55–57 | *k* | 98 | Hexane | $C_{13}H_{17}NO_2$ | 12.2 (8.2–19.5) | 10 = 1/4, 20 = 1/2 |
| 41 | H | H | $CO_2CH_2Ph$ | 90–91.5 | *l* | 87 | Hexane | $C_{18}H_{19}NO_2$ | 50 = −10% | |
| 42 | 2-Cl | H | Et | 200–202 | I | 70 | EtOH–$Et_2O$ | $C_{12}H_{16}N \cdot HCl$ | 17 = −55% | |
| 43 | 3-$CF_3$ | H | Et | 187–189 | I | 63 | EtOH–$Et_2O$ | $C_{13}H_{16}F_3N \cdot HCl$ | 6.6 (3.0–11.5) | 17.4 = 1/2 |
| 44 | 3-Me | H | Et | 187–189 | I | 63 | EtOH–$Et_2O$ | $C_{13}H_{19}N \cdot HCl$ | 16.8 = −57% | |
| 45 | 4-Cl | H | Et | 206–208 | I | 74 | EtOH–$Et_2O$ | $C_{12}H_{16}ClN \cdot HCl$ | 6.6 (4.9–8.2) | 4.3 = 1/2, 6.4 = 1/1 |
| 46 | 4-Cl | Me | Me | 214–216 | K | 63 | EtOH–$Et_2O$ | $C_{12}H_{16}ClN \cdot HCl$ | 21.2 = −98% | 8.5 = 1/4 |
| 47 | 4-Cl | Et | Et | 191–193 | K | 84 | EtOH–$Et_2O$ | $C_{14}H_{20}ClN \cdot HCl$ | 21.7 = −79% | 8.7 = 1/4 |
| 48 | 4-Cl | H | CHO | 85–86 | Ia | 79 | EtOAc–hexane | $C_{11}H_{12}ClNO$ | 25 = −97% | 10.0 = 1/2 |
| 49 | 4-Cl | H | COMe | 116–118 | J | 92 | EtOAc–hexane | $C_{12}H_{14}ClNO$ | 25 = −2% | |
| 50 | 4-Cl | H | $CO_2Et$ | 69–70 | *m* | 43 | Hexane | $C_{13}H_{16}ClNO_2$ | 12.2 (8.0–27.7) | 10.0 = 1/4 |
| 51 | 4-Me | H | Et | 205–206 | I | 64 | EtOH–$Et_2O$ | $C_{13}H_{19}N \cdot HCl$ | 21 = −70%, 16.8 = −52% | 8.4 = 1/4 |
| 52 | 4-Me | Me | Me | 209–211 | K | 69 | EtOH–$Et_2O$ | $C_{13}H_{19}N \cdot HCl$ | 20.4 (15.4–28.7) | 16.8 = 1/2 |
| 53 | 4-Me | Et | Et | 170–172 | K | 36 | EtOH–$Et_2O$ | $C_{15}H_{23}N \cdot HCl$ | 21 = −18% | |
| 54 | 4-Me | H | COMe | 108–110 | J | 70 | EtOAc–hexane | $C_{13}H_{17}NO$ | 25 = −14% | |
| 55 | 4-Me | H | $CO_2Et$ | 52–54 | *m* | 82 | Hexane | $C_{14}H_{19}NO_2$ | 50 = −3% | |

[a] See Experimental Section, General Methods, for description of method. [b] Yield from primary amine or appropriate benzylcyclopropyl isocyanate. [c] All compounds were analyzed for C, H, N and the analytical values were within ±0.4% of the calculated figures. [d] See footnote *c*, Table III. [e] See footnote *d*, Table III. [f] See footnote *e*, Table III. [g] See footnote *f*, Table III. [h] From equimolar amounts of **1** and ethylene oxide in MeOH (4-hr reflux); bp 104–115° (0.3 mm). [i] Maleate. [j] From amide, obtained from 2 moles of **17** base and 1 mole of phenylacetyl chloride in PhH at 25° for 1 hr, by LAH reduction. [k] From 1-benzylcyclopropyl isocyanate in refluxing EtOH (4 hr). [l] From equimolar 1-benzylcyclopropyl isocyanate and $PhCH_2OH$ in refluxing PhH (12 hr). [m] From 2 moles of appropriate primary amine and 1 mole of ethyl chloroformate by 30-min reflux in PhH.

ondary amine studied was *N*-(2-hydroxyethyl)-1-benzylcyclopropylamine (**34**); it was approximately equipotent to the corresponding *N*-Et congener **33**.

N,N-Disubstitution of 1-benzylcyclopropylamine and substituted analogs with Me or Et, *e.g.*, **35–36**, **46**, **47**, **52**, generally afforded compounds with anorectic potency approximately equivalent to the corresponding *N*-monoethyl derivatives. An exception is *N*,*N*-diethyl-1-(4-methylbenzyl)cyclopropylamine (**53**); it is much less potent than either its *N*-Et (**51**) or *N*,*N*-$Me_2$ (**52**) counterpart. Two *N*-aralkyl-*N*-methyl-1-benzylcyclopropylamines (**38**, **39**) exhibited markedly reduced potency in the rat.

Several N-acylated 1-benzylcyclopropylamines were also examined for anorectic activity in rats and dogs. An *N*-carbethoxy derivative (**40**) of 1-benzylcyclopropylamine was less than half as potent as the primary amine in the rat anorexia test whereas the corresponding benzyl carbamate **41** was only weakly active at 50 mg/kg. *N*-Formyl (**48**) and *N*-carbethoxy (**50**) derivatives of 1-(4-chlorobenzyl)cyclopropylamine, although less potent than the primary amine, retained significant anorectic activity; however, an N-acetylated congener **49** failed to produce significant anorexia in rats at 25 mg/kg. Similarly, *N*-Ac (**54**) and *N*-carbethoxy (**55**) derivatives of 1-(4-methylbenzyl)cyclopropylamine had only weak anorectic activity at the doses studied.

## Experimental Section

**Pharmacology. Methods. A. Rat Anorexia Test.**[3]—Anorectic activity in the rat was determined by measuring changes in food consumption of male, albino rats (Wistar strain) specially trained to consume their normal 24-hr food intake in only 6 hr. Compounds were administered orally by gastric intubation (8 rats per treatment group). Food (powdered Purina Laboratory Chow) was presented in tared cups at the predetermined time of peak effect. After 1 hr the cups were weighed and the mean food consumption of each drug-treated group was compared to controls. A dose–response curve was obtained by plotting mean food consumption against the log of the dose. The $ED_{50}$ is the dose that produces a 50% reduction in food consumption of drug-treated rats relative to controls. Fieller's Theorem[11] was used to calculate 95% fiducial limits. In cases where $ED_{50}$'s were not determined, the results (Tables III–V) are expressed as per cent reduction of food consumption of rats treated with the indicated dose, relative to controls.

**B. Dog Anorexia Test.**—Anoretic activity was determined in groups of dogs fasted for 18 hr prior to oral administration of various doses of test compounds. About 0.1 of the daily food ration (a commercial canned meat preparation) was offered to the dogs at 0.5-hr intervals following administration of the drug. Anorexia is defined as failure to eat for two successive feedings. The dose of drug effective in causing anorexia in 50% of the dogs ($ED_{50}$) and 95% fiducial limits were calculated by the method of Litchfield and Wilcoxon.[12] For compounds whose $ED_{50}$'s were not determined, results are presented (Tables III–V) as the number of dogs displaying anorexia/the total number tested at the indicated dose.

**Chemistry.**[13] **Benzyl Halides.**—Both benzyl chlorides and bromides were employed for alkylation of diethyl malonate. With the exception of 2- and 4-$CF_3$-, 4-$CF_3O$-, and 4-$CF_3S$-benzyl chlorides, the required benzyl halides were obtained from commercial sources and were distilled prior to reaction. 4-Trifluoromethylbenzyl chloride was prepared according to literature directions.[14] The same method was employed for synthesis of 2-$CF_3$-, 4-$CF_3O$-, and 4-$CF_3S$-benzyl chlorides. Requisite substituted benzoic acids were reduced with LAH and the resulting alcohols were treated with $SOCl_2$ to afford 2-$CF_3C_6H_4CH_2Cl$ (76.5% yield), bp 103–110° (25 mm), 4-$CF_3OC_6H_4CH_2Cl$ (86%), bp 86–90° (25 mm), and 4-$CF_3SC_6H_4CH_2Cl$ (55%), bp 86–92° (9 mm).

**General Methods. A. Diethyl Benzylmalonates.**—Diethyl malonate (80.1 g, 0.5 mole) was added dropwise at 20–25° to a stirred suspension of 20.5 g (0.5 mole) of a 58.5% dispersion of NaH in mineral oil in 200 ml of DMSO. The mixture was stirred at this temperature until $H_2$ evolution was completed, then 0.5 mole of the appropriate benzyl chloride or bromide in 100 ml of DMSO was added slowly. After the mixture was heated for 30 min on the steam bath, it was poured into 1-l. of ice–$H_2O$. The precipitated oil was extracted into $Et_2O$. The $Et_2O$ extracts were dried ($MgSO_4$) and concentrated. Distillation of the residual liquids gave the diethyl benzylmalonates listed in Table I.

**B. Diethyl Benzyl(dimethylaminoethyl)malonates.**—Alkylation of diethyl benzylmalonates with 2-dimethylaminoethyl chloride was carried out with NaH in DMSO by method A. In most instances, diethyl benzyl(dimethylaminoethyl)malonates were converted into quaternary methiodides by treatment with an excess of MeI in $Me_2CO$–$Et_2O$. Several of the esters were characterized as salts (see Table I).

**C. Ethyl 1-Benzylcyclopropanecarboxylates.**—An approximately threefold excess of anion-exchange resin ($OH^-$ form)[15] was washed several times with EtOH. The resin (*ca.* 0.6 mole) was suspended in 500 ml of EtOH, and 0.2 mole of the appropriate diethyl benzyl(dimethylaminoethyl)malonate methiodide was added. The mixture was stirred at 25° for 1 hr; then it was filtered and the filtrate was concentrated *in vacuo*. The residue was gradually heated to 150–200° at water aspirator pressure (10–25 mm). After decomposition, as evidenced by gas evolution, was completed the residual liquid was distilled to give the ethyl 1-benzylcyclopropanecarboxylates tabulated in Table II. Ethyl 1-benzylcyclopropanecarboxylate was also prepared (25% yield) by thermal decomposition of diethyl benzyl(2-dimethylaminoethyl)malonate methiodide[16] at 200° (10 mm.).

**D. 1-Benzylcyclopropanecarboxylic Acids.**—Ethyl 1-benzylcyclopropanecarboxylates were hydrolyzed with a 20% excess of KOH in EtOH–$H_2O$. After distillation of the EtOH, the crystalline acids (Table II) were precipitated by acidification of the aq solution with 3 *N* HCl.

The structure of each of the 1-benzylcyclopropanecarboxylic acids was confirmed by their nmr spectra. Typically, the nmr ($CDCl_3$) had peaks at $\delta$ 0.7–1.1 (m, cyclopropyl $CH_2$), 1.25–1.55 (m, cyclopropyl $CH_2$), 2.9–3.1 (s, benzyl $CH_2$), 7–7.4 (aromatic **H**'s), and 12.0–12.2 (s, COO**H**). 1-Cyclohexylmethylcyclopropanecarboxylic acid gave an nmr ($CDCl_3$) in which the peaks for the cyclopropyl H's ($A_2B_2$ pattern at $\delta$ 0.78 and 1.25) were superimposed with the cyclohexylmethyl H peaks (m, 1.0–2.0); it also showed a peak at $\delta$ 12.0 (s, COO**H**).

**E. 1-Benzylcyclopropanecarbonyl Chlorides.**—A mixture of 1 mole of 1-benzylcyclopropanecarboxylic acid and 2 moles of $SOCl_2$ was allowed to stand at 25° for 24 hr (or until gas evolution was completed). After excess $SOCl_2$ was removed *in vacuo*, the acid chlorides were distilled. For boiling points and yields of 1-benzylcyclopropanecarbonyl chlorides see Table II.

**F. 1-Benzylcyclopropyl Isocyanates.**—1-Benzylcyclopropanecarbonyl chlorides were converted into 1-benzylcyclopropyl isocyanates by the "wet $NaN_3$ procedure" as described previously.[1] The isocyanates were obtained in nearly quantitative yield by this procedure. They were employed for further reaction without additional purification.

**G. Acid Hydrolysis of Isocyanates.**—1-Benzylcyclopropyl isocyanates were hydrolyzed to primary amines by the same procedure described for "2-Substituted Cyclopropylamines. Acid

(11) D. J. Finney, "Probit Analysis," 2nd ed, Cambridge University Press, London, 1952.

(12) J. T. Litchfield, Jr. and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

(13) All melting points were determined with a capillary melting point apparatus and are uncorrected. Boiling points are also uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Elemental analyses were performed by Miss Margaret Carroll and coworkers of the Analytical and Physical Chemistry Section, Research and Development Division, Smith Kline and French Laboratories. Ir spectra were as anticipated for all compounds. They were determined as Nujol mulls or natural films and were recorded on a Perkin-Elmer Infracord spectrophotometer. Nmr analyses were carried out on a Varian T60 nmr spectrometer and are reported in $\delta$ (ppm) calibrated against TMS.

(14) J. R. Owen and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **88**, 5809 (1966).

(15) A strongly basic polystyrene alkyl quaternary amine (hydroxide form) of medium porosity was employed. Research grade Rexyn 201 (OH), purchased from the Fisher Scientific Co., and Amberlite IRA, purchased from Mallinckrodt Chemical Works, were found equally satisfactory.

(16) C. K. Ingold and M. A. T. Rogers, *J. Chem. Soc.*, 722 (1935).

Hydrolysis of Isocyanates."[1] The amines were purified *via* their acid salts (Table III).

**H. Reduction of Isocyanates to Methylamines.**—To a stirred suspension of 3.8 g (0.1 mole) of LAH in 200 ml of $Et_2O$ was added dropwise a solution of 0.05 mole of the appropriate 1-benzylcyclopropyl isocyanate in 50 ml of $Et_2O$. After the mixture was stirred and refluxed for 1 hr, it was cooled, and while stirring 4 ml of $H_2O$, followed by 4 ml of 2 *N* NaOH, and 12 ml of $H_2O$, was added dropwise. The precipitated solid was filtered and the filtrate was concentrated to leave the oily methylamine derivatives, which were purified by recrystallization of the acid salts indicated in Table IV.

1. ***N*-Ethyl-1-benzylcyclopropylamines. (a) N-Formylation.** A mixture of 0.1 mole of the appropriate primary amine and 100 ml of ethyl formate was stirred and refluxed for 16 hr. The solution was concentrated *in vacuo* to give crude *N*-substituted formamides, which could be purified by recrystallization from EtOAc; however, they were used for further reaction without purification.

**(b) N-Ethylation of *N*-Formyl Derivatives.**—Appropriate *N*-substituted formamides were alkylated with EtI by method A. In some instances it was necessary to heat the formamides with NaH in DMSO (50–60°) in order to form the Na derivative (as evidenced by $H_2$ evolution).

**(c) Hydrolysis of *N*-Ethyl-*N*-(1-benzylcyclopropane)formamides.**—A mixture of 0.5 mole of the appropriate *N*-ethylformamide and 125 ml of 6 *N* HCl was stirred and refluxed for 3 hr. The solution was concentrated, and the residue was dissolved in $H_2O$. After the aq solution was extracted with $Et_2O$ it was made alkaline. The mixture was extracted with $Et_2O$, and the extracts were dried and concentrated to leave oily amines which were converted into hydrochlorides (Table V, **33**, **42**–**45**, **51**).

**J. *N*-(1-Benzylcyclopropyl)acetamides.**—A mixture of 0.1 mole of primary amine and 30 ml of $Ac_2O$ was stirred at 100° for 1 hr, then it was cooled and stirred with $H_2O$ for 2 hr. Crystalline *N*-Ac derivatives (Table V, **49**, **54**) were filtered.

**K. *N*,*N*-Dialkyl-1-benzylcyclopropylamines.**—*N*-(1-Benzylcyclopropyl)formamides (Method Ia) and -acetamides (method J) were alkylated with MeI, EtI, or $PhCH_2Cl$ (Method Ib). Resulting tertiary amides were reduced with LAH in the same manner described for isocyanates (method H) to give **35**–**38**, **46**, **47**, **52**, **53** (Table V).

**Diethyl Benzyl(3-dimethylaminopropyl)malonate (VIII).**—Alkylation of diethyl malonate with 3-dimethylaminopropyl chloride (method A) gave 94% of VIII. A **methiodide** was prepared in $Me_2CO$–$Et_2O$, mp 201–202°. A **hydrochloride** was also prepared in $Me_2CO$–$Et_2O$, mp 139–141°. *Anal.* ($C_{19}H_{29}NO_4 \cdot HCl$) C,H,N.

**Hofmann Elimination of VIII.**—The **methiodide** derived from VIII (14.2 g, 0.03 mole), was subjected to Hofmann elimination conditions (method C) to give 5.1 g of a colorless liquid, bp *ca.* 100–168° (10 mm). An $Et_2O$ solution of the distillate was separated into neutral and basic fractions by extraction with 1 *N* HCl. The neutral fraction was distilled to give 2.5 g of a colorless liquid, bp 123–132° (10 mm); glpc (175°)[17] showed 4 peaks, 1.2 min (5.5%), 1.4 min (78.3%), 1.6 min (9.6%), 3.2 min (6.6%). The structure of the major component (IX, R = Et) is based on the nmr ($CDCl_3$): $\delta$ 1.1 (t, 3, $J$ = 7.5, $OCH_2CH_3$), *ca.* 1.6 (m, 1, $CHCOOEt$), *ca.* 2.2 (m, 2, $CH_2CH{=}CH_2$), 2.83 (d, 2, $J$ = 2, $PhCH_2$), 4.05 (q, 2, $J$ = 7.5, $OCH_2CH_3$), 4.97 (m, 1, *cis*-$CH{=}CH_2$), 5.15 (m, 1, *trans*-$CH{=}CH_2$), 5.7 (broad m, 1, $-CH{=}CH_2$), 7.25 (s, 5, Ph). The nmr also showed a small peak at $\delta$ 3.6 for $COOCH_3$ impurity.

The basic fraction, 2.4 g, bp 164–168° (10 mm), showed 3 peaks in glpc (175°),[17] 2.1 min (8%), 2.6 min (75%), 3.6 min (17%). The major component was isolated *via* a cyclohexylsulfamate, mp 92–95° (EtOH–$Et_2O$). *Anal.* ($C_{36}H_{56}N_2O_2 \cdot C_6H_{13}NO_3S \cdot 0.5H_2O$) C,H,N. The base (X, R = Et) had nmr ($CDCl_3$): $\delta$ 1.1 (t, 3, $J$ = 7.5, $OCH_2CH_3$), 1.52 (m, 4, $CH(CH_2)_2CH_2N$), 2.1 (s, 6, $N(CH_3)_2$), 2.13 (m, 2, $CH_2N$), 2.8 (m, 3, $PCH_2CH$–), 4.05 (q, 2, $OCH_2CH_3$), 7.25 (s, 5, Ph); glpc (175°)[17] 2.6 min, M⁺ 263).

Similar Hofmann elimination of VIII methiodide in MeOH gave 2.5 g of a neutral fraction and 2.6 g of a basic fraction. The neutral fraction was a colorless liquid: glpc (175°),[17] 3 peaks, 1.2 min (64.2%), 1.4 min (22.7%), 3.0 min (13.1%). The structure of the major component (IX, R = Me) is based on the nmr ($CDCl_3$): $\delta$ 3.6 (s, 3, $OCH_3$), and only small peaks at $\delta$ 1.1 (t) and $\delta$ 4.05 (q) for COOEt. The basic fraction, glpc (175°),[17] 2 peaks, 2.1 min (74.5%), 2.6 min (24.5%) was purified by recrystallization of a HCl salt from $Me_2CO$–$Et_2O$, to give X (R = Me), mp 108–109°. *Anal.* ($C_{15}H_{24}NO_2 \cdot HCl$) C,H,N. The base (X, R = Me) had nmr ($CDCl_3$), $\delta$ 1.5 (m, 4, $CH(CH_2)_2CH_2N$), 2.1 (s, 6, $N(CH_3)_2$), 2.2 (m, 2 $-CH_2N$), 2.84 (m, 2, $PhCH_2$–), 2.9 (m, 1, $PhCH_2CH$), 3.6 (s, 3, $OCH_3$), 7.25 (s, 5, Ph); glpc (175°)[17] 2.1 min, M⁺ 218.

**Reduction of XI with LAH.**—*N*-(1-Benzylcyclopropyl)acetamide (mp 93–95° from EtOAc–hexane), prepared by acetylation of 1 (method J), was reduced with 3 moles of LAH in refluxing $Et_2O$ for 6 hr (method H) to give 56% of a colorless liquid; **hydrochloride**, mp 143–145° (from $Me_2CO$–$Et_2O$). *Anal.* ($C_{12}H_{19}N \cdot HCl$) C,H,N. A mixture melting point with unambiguously obtained XII·HCl was undepressed. The nmr ($CDCl_3$) and ir spectra of this material were also identical with those of α,*N*-diethylphenethylamine.

Reduction of XI using the same conditions, but with a 30-min reflux period, gave approximately 20% of **33** [identical (nmr, ir) with an authentic sample prepared by method H] and 80% of recovered amide.

**α,*N*-Diethylphenethylamine (XII).**—Reduction of *N*-acetyl-α-ethylphenethylamine[18] with 3 moles of LAH in refluxing $Et_2O$ for 7 hr (method H) gave 72% of XI; hydrochloride, mp 143–145° (EtOH–$Et_2O$).

(17) Glpc were obtained isothermally at a flow rate of 50 ml/min on silicone rubber SE30, 10% Gas Chrom Z, in a copper column 1460 × 6.4 mm with thermal detection.

(18) M. Metayer, *Ann. Chim. (Paris)*, **4**, 196 (1949); *Chem. Abstr.*, **44**, 3922 (1950).