and 1-methoxy-2-propanol (2.3 ml) in liquid NH_3 (2 l.) gave **15** as an oil (3.6 g) which was stirred overnight at room temperature in 5.5 *N* HCl–MeOH (60:60 ml). The ketonic product was decomposed with hydrazine sulfate as before to give the base **7** as a yellow oil (2.08 g) giving a hydrochloride and hydriodide identical with those obtained as in A.

2-Acetyl-1′,2′-secoemetine (8).—2-Acetylemetine (11 g) was refluxed for 30 hr under N_2 with **20** (11 g) in MeCN (40 ml), and the cooled mixture was added to ether to give the salt **5** as a yellow powder (7 g). The salt (6.2 g) was reduced with Li (129 mg) and 1-methoxy-2-propanol (0.92 ml) in liquid NH_3 (2 l.). The oily ketal **16** was hydrolyzed with methanolic HCl and the resulting ketone decomposed with aqueous methanolic hydrazine sulfate as before. The product was chromatographed on Al_2O_3, elution with $CHCl_3$ giving the secoemetine **8** (8 g), mp 140–142°. The analytical sample had mp 140–141.5° (from ether).

Anal. Calcd for $C_{31}H_{44}N_2O_5$: C, 70.96; H, 8.45; N, 5.34. Found: C, 71.23; H, 8.69; N, 5.49.

The base formed an amorphous **hydrochloride**, mp 146–152°.

Anal. Calcd for $C_{31}H_{45}ClN_2O_5 \cdot 1.5H_2O$: C, 63.02; H, 8.21; N, 4.76. Found: C, 63.27; H, 8.02; N, 4.92.

2-Ethyl-2′-methyl-1′,2′-secoemetine (17).—Compound **6** (5 g) was refluxed with $LiAlH_4$ (5 g) in THF (350 ml) for 3 hr, and the cooled mixture was added to crushed ice. Recrystallization of the product from hexane gave **17** (2.8 g), mp 95–99°. The analytical sample had mp 99–100.5° (from hexane).

Anal. Calcd for $C_{32}H_{48}N_2O_4$: C, 73.24; H, 9.22; N, 5.34. Found: C, 73.27; H, 9.59; N, 5.66.

The base formed an amorphous **dihydrochloride**.

Anal. Calcd for $C_{32}H_{50}Cl_2N_2O_4 \cdot 1.5H_2O$: C, 61.50; H, 8.56; Cl, 11.40; N, 4.50. Found: C, 61.54; H, 8.76; Cl, 12.1; N, 4.61.

2-Ethyl-1′,2′-secoemetine (18). A.—Compound **6** (2 g) was kept with BrCN (2.4 g) in ether–benzene (120:40 ml) for 18 hr. The product was worked up and purified as for the analogous reaction with **9** to give a neutral oil (1.8 g) which with $LiAlH_4$ (2 g) was refluxed for 16 hr in THF–ether (50:50 ml). Recrystallization of the product from ether–hexane gave **18** (0.7 g), mp 146–148°.

Anal. Calcd for $C_{31}H_{46}N_2O_4$: C, 72.90; H, 9.08; N, 5.49. Found: C, 72.59; H, 9.01; N, 5.33.

The base formed an amorphous **dihydrochloride**.

Anal. Calcd for $C_{31}H_{48}Cl_2N_2O_4 \cdot H_2O$: C, 61.89; H, 8.38; Cl, 11.79; N, 4.66. Found: C, 61.93; H, 8.55; Cl, 11.65; N, 4.66.

B.—Reduction of **8** (2.8 g) with $LiAlH_4$ (4 g) in ether–THF (1:1, 400 ml) gave **18** (1.4 g), mp 153–154° (from hexane), undepressed by material prepared as in A.

Chemical and Biological Properties of Some Aminomethyl-2-phenylcyclopropane Derivatives. Pharmacological Comparison with Tranylcypromine

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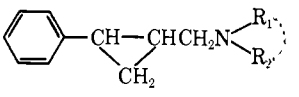
The synthesis of a series of aminomethyl-2-phenylcyclopropane derivatives is described. Unlike tranylcypromine in which the nitrogen atom is attached directly to the cyclopropane ring, none of the amino derivatives tested inhibited the activity of monoamine oxidase (MAO). However, the compounds appeared to retain marked antidepressant activity and interesting sympathomimetic properties. The intermediate amido derivatives were also examined.

One of the early studies about the biological properties of molecules containing small rings was by Burger and Yost[1] on cyclopropane compounds. Following the suggestion that "alicyclic residues might confer desirable pharmacological properties if introduced into compounds containing an auxopharm group"[2] Burger chose the cyclopropane ring as an alicyclic residue for incorporation in the phenethyl group. The compound, 2-phenylcyclopropylamine, originally examined as a sympathomimetic agent, later proved to be an interesting psychotherapeutic drug and a potent MAO inhibitor. Nevertheless, there is no evidence that the clinical antidepressant activity is related to the MAO-inhibitory action. In approaching this interesting question we found that a compound related to tranylcypromine, *i.e.*, *trans*-2-phenylcyclopropylmethylenamine, exhibited actions similar to those of tyramine (motor excitatory effects, hypertensive and anorexic activities). This compound had been shown to exhibit no MAO-inhibitory action,[3] but it serves indeed as substrate of the enzyme.

Therefore we wished to study whether in such a structure retaining sympathomimetic action but lacking MAO-inhibitory activity one would encounter tranylcypromine-like antidepressant action. For this purpose we prepared a series of phenylcyclopropane derivatives having the structural formula I where R_1 and R_2 represent hydrogen, alkyl, alkylene, cycloalkyl, or arylalkyl radicals as specified in Tables III and IV.

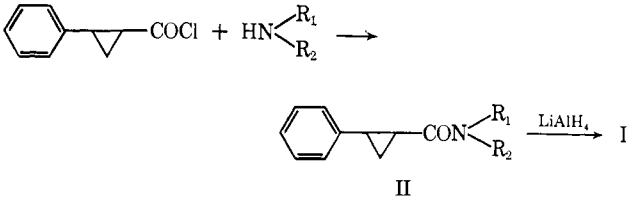


I

Such compounds exist as *cis* or *trans* isomers; most of the substances prepared by us are the *trans* isomers, but some *cis* compounds have been synthesized in order to examine whether any difference of biological activity is detectable for the two different configurations. We generally synthesized the products I according to Scheme I.

The amide derivatives II (Tables I and II) were obtained from the reaction of the acid chloride or by treating ethyl 2-phenylcyclopropanecarboxylate with

SCHEME I

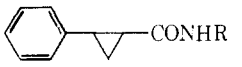


II

(1) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).
(2) W. Braker, E. J. Pribyl, and W. A. Lott, *ibid.*, **69**, 866 (1947).
(3) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *J. Med. Pharm. Chem.*, **5**, 1265 (1962).

TABLE I

N-(MONOSUBSTITUTED) 2-PHENYLCYCLOPROPANECARBOXAMIDES

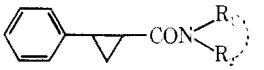


Compd	R	Config	Procedure[a]	Yield, %	Recrystn solvent	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1[b]	H	*trans*	A	78.5	THF	190–191	$C_{10}H_{11}NO$	74.50	6.82	8.68			
2	CH_3	*trans*	A	95	EtOAc	98–99	$C_{11}H_{13}NO$	75.40	7.48	7.99	75.60	7.52	8.04
3	C_2H_5	*trans*	A	92.5	EtOAc	105–106	$C_{12}H_{15}NO$	76.15	7.99	7.40	75.96	7.99	7.40
4	C_2H_5	*cis*	C	30	(*i*-Pr)$_2$O	61–62	$C_{12}H_{15}NO$	76.15	7.99	7.40	76.33	7.94	7.44
5	*n*-C_3H_7	*trans*	B	27	EtOAc	123–124	$C_{13}H_{17}NO$	76.81	8.43	6.89	77.09	8.38	6.89
6	*i*-C_3H_7	*trans*	A	87	EtOAc	151–152	$C_{13}H_{17}NO$	76.81	8.43	6.89	76.28	8.48	6.94
7	*n*-C_4H_9	*trans*	A	83.5	EtOAc	108–109	$C_{14}H_{19}NO$	77.38	8.81	6.45	76.98	8.80	6.40
8	*i*-C_4H_9	*trans*	A	87	EtOH–H_2O	112–113	$C_{14}H_{19}NO$	77.38	8.81	6.45	77.83	8.89	6.50
9	*sec*-C_4H_9	*trans*	A	85	C_6H_6	133–134	$C_{14}H_{19}NO$	77.38	8.81	6.45	77.58	8.60	6.53
10	*t*-C_4H_9	*trans*	A	78	(*i*-Pr)$_2$O	136–138	$C_{14}H_{19}NO$	77.38	8.81	6.45	77.93	8.57	6.51
11	*n*-C_5H_{11}	*trans*	A	91	EtOAc	95–96	$C_{15}H_{21}NO$	77.88	9.15	6.05	77.60	9.26	6.01
12	Cyclohexyl	*trans*	A	92	*i*-PrOH	173–174	$C_{16}H_{21}NO$	78.97	8.70	5.76	79.32	8.74	5.80

[a] See Experimental Section. [b] See ref 1 and 6.

TABLE II

N-(DISUBSTITUTED) 2-PHENYLCYCLOPROPANECARBOXAMIDES

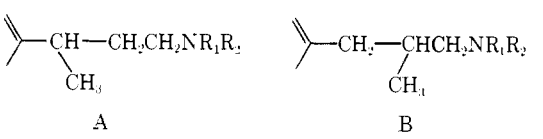


Compd	R_1	R_2	Config	Procedure[a]	Yield, %	Recrystn solvent	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
13[b]	CH_3	CH_3	*trans*	A	78.5	Ligroin	63–64	$C_{12}H_{15}NO$	76.15	7.99	7.40	75.95	7.85	7.48
14	C_2H_5	C_2H_5	*trans*	A	75		129–131 (0.5)	$C_{14}H_{19}NO$	77.38	8.81	6.45	77.34	8.82	6.44
15	C_2H_5	C_2H_5	*cis*	C	78	(*i*-Pr)$_2$O	58–59	$C_{14}H_{19}NO$	77.38	8.81	6.45	77.48	8.86	6.60
16	*n*-C_3H_7	*n*-C_3H_7	*trans*	A	86		137–139 (0.5)	$C_{16}H_{23}NO$	78.32	9.45	5.71	78.46	9.39	5.66
17	*i*-C_3H_7	*i*-C_3H_7	*trans*	A	90		115–118 (0.2)	$C_{16}H_{23}NO$	78.32	9.45	5.71	77.88	9.44	5.66
18	*n*-C_4H_9	*n*-C_4H_9	*trans*	A	92.5		137–140 (0.4)	$C_{18}H_{27}NO$	79.07	9.95	5.12	79.06	9.96	5.10
19	*i*-C_4H_9	*i*-C_4H_9	*trans*	A	91	(*i*-Pr)$_2$O	54–55	$C_{18}H_{27}NO$	79.07	9.95	5.12	79.12	9.78	5.16
20	*sec*-C_4H_9	*sec*-C_4H_9	*trans*	A	98		134–136 (0.5)	$C_{18}H_{27}NO$	79.07	9.95	5.12	79.65	9.93	5.10
21	*n*-C_5H_{11}	*n*-C_5H_{11}	*trans*	A	92		155–160 (0.5)	$C_{20}H_{31}NO$	79.68	10.36	4.65	79.20	10.26	4.52
22	C_2H_5	Benzyl	*trans*	A	86		155–160 (0.2)	$C_{19}H_{21}NO$	81.68	7.58	5.01	81.35	7.60	5.01
23	Pyrrolidine		*trans*	A	92	EtOAc	102.5–103	$C_{14}H_{17}NO$	78.11	7.96	6.51	78.30	7.90	6.49
24	Piperidine		*trans*	A	84	EtOAc	90–91	$C_{15}H_{19}NO$	78.56	8.35	6.11	78.51	8.34	6.10
25	Morpholine		*trans*	A	81	(*i*-Pr)$_2$O	72–73	$C_{14}H_{17}NO_2$	72.70	7.41	6.06	72.63	7.49	6.19

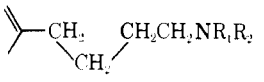
[a] See Experimental Section. [b] J. Šmejkal and J. Farkaš, *Collection Czech. Chem. Commun.*, **28,** 404 (1963).

the amines. The amines I (Tables III and IV) were prepared by reducing the corresponding amides with $LiAlH_4$.

Cleavage of the cyclopropane ring had to be considered upon treatment with a metal hydride: an example of cyclopropyl ring opening by $LiAlH_4$ is given by Kaiser, *et al.*,[4] for *trans*-2-phenylcyclopropylamine. In order to exclude this possibility we synthesized for comparison with our derivatives the three



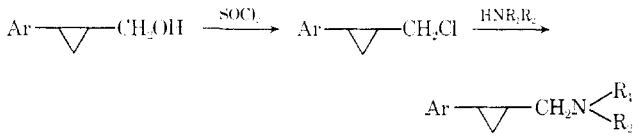
A B



C

compounds, A, B, C, which could be formed from amides by reduction with $LiAlH_4$. For R_1 = hydrogen and R_2 = ethyl, they were prepared following conventional procedures; synthetic details for these derivatives are given in the Experimental Section. It was found that the phenylbutylamines A–C were all different from I where R_1 = H and R_2 = C_2H_5. Some amines I were also synthesized by another route as illustrated in Scheme II, but these steps often gave poor yields, because of rearrangement of intermediate cyclopropylcarbinyl ions.

SCHEME II



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

Experimental Section

All melting points are uncorrected.

Chemical Study. Procedure A. ***trans*-N-Ethyl-2-phenylcyclopropanecarboxamide.** *trans*-2-Phenylcyclopropanecarbonyl chloride[1] (30 g, 0.166 mole) was added dropwise, with stirring, to 54 g (0.838 mole) of 70% aqueous ethylamine at below 10°. After the addition was complete, the mixture was stirred for 1 hr and allowed to warm up to room temperature. It was then poured into 200 ml of water. The precipitate was collected by filtration, washed with water until free from Cl^-, and dried at 50° *in vacuo*.

Procedure B. ***trans*-N-(*n*-Propyl)-2-phenylcyclopropanecarboxamide.**—A mixture of 19.1 g (0.1 mole) of ethyl *trans*-2-phenylcyclopropanecarboxylate,[4] 12 g (about 0.2 mole) of *n*-propylamine, and 200 ml of ethanol was heated at 150° in a sealed tube. After about 10 hr, solvent was removed under reduced pressure. The residue was dried at 50° *in vacuo* and crystallized from ligroin. Most of the unreacted ester has been recovered from the mother liquors.

Procedure C. ***cis*-N-Ethyl-2-phenylcyclopropanecarboxamide.**—$SOCl_2$ (59.4 g, 0.499 mole) in 160 ml of petroleum ether (bp 40–60°) was added dropwise, with stirring, to a suspension of 40 g (0.246 mole) of *cis*-2-phenylcyclopropanecarboxylic acid in 160 ml of petroleum ether below 15°. After the addition was complete, the mixture was stirred for 1 hr and allowed to warm to room temperature. Removal of the petroleum ether under reduced pressure left orange oily *cis*-2-phenylcyclopropanecarbonyl chloride. A nearly similar procedure has been disclosed by Šmejkal and Farkaš.[5] The *cis*-2-phenylcyclopropanecarbonyl chloride was dissolved in 100 ml of anhydrous ether and dropped, with stirring, into a solution of 28 g (0.610 mole) of ethylamine in 250 ml anhydrous ether at below 10°. After the addition was complete, the mixture was stirred for 1 hr and allowed to warm to room temperature. After standing overnight, the precipitate was removed by filtration and washed with ether. The combined filtrate and ethereal washings were treated with 100 ml of 0.1 *N* NaOH and water until free from Cl^-, dried (Drierite), filtered, and decolorized with carbon black. Evaporation of the solvent left a solid product.

Procedure D. ***trans*-1-Ethylaminomethyl-2-phenylcyclopropane.**—A solution of 20 g (0.105 mole) of *trans*-N-ethyl-2-phenylcyclopropanecarboxamide in 50 ml of anhydrous THF was added dropwise, with stirring, to a suspension of 8.5 g of $LiAlH_4$ in 100 ml of anhydrous THF. After the addition was complete, the suspension was refluxed for 5 hr, allowed to cool to room temperature, and treated with a mixture of 40 ml of water and 100 ml of THF. The precipitate was filtered off and washed with THF. The combined filtrate and washings were acidified with 5% H_2SO_4. The solvent was evaporated and the residue was diluted to 160 ml with water. The aqueous solution was washed with benzene and rendered alkaline with 20 g of KOH. The oily layer was extracted with ether, dried, and evaporated under reduced pressure. The residue was dissolved with benzene. The benzene was removed by distillation and the oil was distilled.

Procedure E. ***trans*-1-(N-Methyl-N-*n*-butyl)aminomethyl-2-phenylcyclopropane.**—*trans*-Methylaminomethyl-2-phenylcyclopropane[6] (9.8 g, 0.06 mole), 9.1 g (0.066 mole) of *n*-butyl bromide, and 4.4 g of 85% KOH were heated at about 150° in a sealed tube. After 8 hr the reaction mixture was washed twice with 20-ml portions of ether and the residual inorganic salt was dissolved in 30 ml of water. The aqueous layer was washed with 30 ml of ether. The ether extracts were combined and dried (K_2CO_3). Thereafter the solvent was removed by distillation. The oily residue was dissolved in 20 ml of benzene. After removing the benzene, the residue was fractionated.

Procedure F. ***trans*-1-Chloromethyl-2-phenylcyclopropane.**—A solution of 14.8 g (0.1 mole) of *trans*-1-hydroxymethyl-2-phenylcyclopropane in $CHCl_3$ (50 ml) was dropped, with stirring, into a solution of 23.8 g (0.2 mole) of $SOCl_2$ in 50 ml of $CHCl_3$. After the addition was complete, the reaction mixture was refluxed for 90 min. The solvent and the unreacted $SOCl_2$ were removed by distillation. The residue was fractionated, bp 62–63° (0.2 mm).

Anal. Calcd for $C_{10}H_{11}Cl$: C, 72.07; H, 6.65; Cl, 21.28. Found: C, 71.49; H, 6.64; Cl, 21.53.

***trans*-1-(N,N-Di-*n*-butyl)aminomethyl-2-phenylcyclopropane.**—*trans*-1-Chloromethyl-2-phenylcyclopropane (4 g, 0.024 mole) and 6.84 g (0.0528 mole) of di-*n*-butylamine in 50 ml of xylene were refluxed for 35–40 hr. The reaction mixture was cooled and the precipitate was removed by filtration. The solution was washed with 1 *N* NaOH. The solvent was evaporated, and the oily residue was fractionated; yield 1 g.

δ-Phenyl-N-ethylaminobutane hydrochloride was prepared following the procedure of Külz and Rosenmund.[7]

α-Benzyl-N-ethylpropionamide.—α-Benzylpropionyl chloride[8] (19.7 g, 0.108 mole) at 5–10° was added dropwise to 48 g (0.743 mole) of a stirred aqueous solution of 70% ethylamine. After the addition was complete, the solution was stirred for 1 hr and the temperature was maintained at 10°. The mixture was then allowed to warm up to room temperature and poured into 100 ml of water. The product which separated was extracted with ether, and the ether extracts were washed (dilute acid, $NaHCO_3$, H_2O) and dried (Na_2SO_4). The solvent was evaporated. The oily product (19.15 g) solidified after standing 48 hr at 4° and was purified by crystallization from ligroin; mp 59–60°.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.37; H, 8.43; N, 7.36. Found: C, 75.72; H, 8.55; N, 7.41.

β-Methyl-γ-phenyl-N-ethylaminopropane Hydrochloride.—A solution of 13.0 g (0.068 mole) of α-benzyl-N-ethylpropionamide in 65 ml of dry THF was added dropwise to a stirred suspension of 3.9 g of $LiAlH_4$ in 45 ml of dry THF. After the addition, the mixture was refluxed for 20 hr and then cooled to room temperature. A solution of 20 ml of water and 50 ml of THF was added cautiously. The insoluble material was filtered off and the filtrate was concentrated. The residue was distilled under reduced pressure yielding 10.10 g (84%) of the base, bp 65.5–66.5° (0.10 mm). The hydrochloride was prepared in dry ether solution and crystallized from 2-propanol as colorless crystals, mp 144–146°.

Anal. Calcd for $C_{12}H_{19}N \cdot HCl$: C, 67.43; H, 9.43; N, 6.55; Cl, 16.59. Found: C, 67.39; H, 9.38; N, 6.49; Cl, 16.67.

γ-Phenyl-N-ethylaminobutane Hydrochloride.—β-Phenylbutyryl chloride[8] (14 g, 0.0765 mole) was added dropwise to 80 g (1.23 mole) of a stirred 70% aqueous solution of ethylamine at 5–10°. After stirring for another 60 min the mixture was allowed to warm to room temperature and poured into H_2O (150 ml). The oily product which separated was extracted with ether. The ether extracts were washed (dilute acid, $NaHCO_3$, H_2O), dried (Na_2SO_4), filtered, and evaporated. The solid residue was dissolved into 65 ml of dry THF; the solution was dropped, under stirring, into a suspension of 3.9 g of $LiAlH_4$ in 45 ml of anhydrous THF. After refluxing for 20 hr, the suspension was allowed to cool to room temperature, treated with a mixture of 20 ml of H_2O and 50 ml of THF, and filtered. The filtrate was evaporated *in vacuo* and the oily residue was distilled. The fraction boiling at 110–115° (0.6 mm) was collected; yield 10 g (73.5% based on β-phenylbutyryl chloride). The compound was dissolved in 200 ml of anhydrous ether and made neutral to congo red with ethereal HCl. After standing overnight at 4° the precipitate was filtered off; yield 11.10 g, mp 116–118° (from ethyl acetate).

Anal. Calcd for $C_{12}H_{19}N \cdot HCl$: C, 67.43; H, 9.43; N, 6.55; Cl, 16.59. Found: C, 67.65; H, 9.51; N, 6.54; Cl, 16.60.

Pharmacological Study. Effects on Central Nervous System.—Experimental conditions and criteria adopted for the quantitative evaluation of the activity of individual derivatives are listed below. The results are summarized in Table V.

(1) **Influence on Spontaneous Motility.**—The test by Dews[9] was used. The derivatives under examination were administered intraperitoneally as a water solution or 2% arabic gum aqueous suspension at two dosage levels, 25 and 50 mg/kg, respectively, to groups of five mice each. Treatment was given 30 min before starting the observation of spontaneous motility, which lasted for 15 min. Only the compounds increasing or reducing the number of counts at the higher dose by at least 30% were considered active.

(2) **Anorexic Effect.**—Rats were fasted for 16 hr and the reduction of food intake for a 5-hr period was evaluated starting 15 min after subcutaneous injection of the compounds under study at the dose of 25 mg/kg. The compounds able to reduce the food intake by at least one-half of that obtained in the same experimental conditions with 2.5 mg of amphetamine/kg sc were considered active.

(3) **Change in Body Temperature.**—Normal rats were pretreated with 200 mg/kg of subcutaneous iproniazid 24 hr before evaluation at 22°. Temperature readings were performed by a rectal thermocouple each hour for the 3 hr following oral administration 30 min previously of the compounds, given at the dose of 50 mg/kg. Compounds which increased body temperature by not less than 1.5° were considered active.

(5) J. Šmejkal and J. Farkaš, *Collection Czech. Chem. Commun.*, **28**, 481 (1963).

(6) 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).

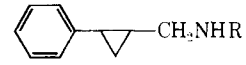
(7) F. Külz and K. W. Rosenmund, *Chem. Ber.*, **72B**, 2161 (1939).

(8) H. Rupe, *Ann. Chem.*, **369**, 315 (1909).

(9) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).

TABLE III

1-(MONOSUBSTITUTED) AMINOMETHYL-2-PHENYLCYCLOPROPANE

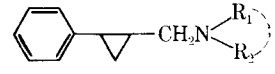


Compd	R	Config	Procedure[a]	Yield, %	Salt	Bp (mm) or mp, °C	Recrystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % X	Found, % C	Found, % H	Found, % N	Found, % X
26[b]	H	*trans*	D	59	Hydrochloride	187–188	*i*-PrOH–Et_2O	$C_{10}H_{13}N \cdot HCl$	65.39	7.68			64.62	7.76		
27	CH_3	*trans*	D	92		74–75 (0.6)										
					Hydrochloride	124–126	Me_2CO–Et_2O	$C_{11}H_{15}N \cdot HCl$			7.08	17.93			7.04	17.84
28	C_2H_5	*trans*	D	80		90–92 (0.9)										
					Hydrochloride	146–148	Et_2O–EtOH	$C_{12}H_{17}N \cdot HCl$	68.07	8.57	6.61	16.75			6.63	16.87
29	C_2H_5	*cis*	D	55		75–80 (0.5)										
					Hydrochloride	133–134	Et_2O–EtOH	$C_{12}H_{17}N \cdot HCl$	68.07	8.57	6.61	16.75			6.71	16.57
30	*n*-C_3H_7	*trans*	D	85		92–93 (0.6)										
					Hydrochloride	156–158	Me_2CO	$C_{13}H_{19}N \cdot HCl$	69.16	8.93	6.20	15.71			6.24	15.78
31	*i*-C_3H_7	*trans*	D	79		89–90 (0.8)										
					Hydrochloride	154–155	Et_2O–EtOH	$C_{13}H_{19}N \cdot HCl$	69.16	8.93	6.20	15.71			6.27	15.74
32	*n*-C_4H_9	*trans*	D	85.2		100–103 (0.4)										
					Hydrochloride	183–185	Me_2CO–Et_2O	$C_{14}H_{21}N \cdot HCl$	70.12	9.27	5.84	14.79			5.83	15.00
33	*i*-C_4H_9	*trans*	D	91.3		89–91 (0.3)										
					Hydrochloride	163–164	Et_2O–EtOH	$C_{14}H_{21}N \cdot HCl$	70.12	9.27	5.84	14.79			5.86	14.85
34	*sec*-C_4H_9	*trans*	D	99		95–96 (0.5)										
					Hydrochloride	120–122	Et_2O–EtOH	$C_{14}H_{21}N \cdot HCl$	70.12	9.27	5.84	14.79	70.67	9.31	5.71	14.51
35	*t*-C_4H_9	*trans*	D	60		93–95 (0.7)										
					Hydrochloride	187–188	Me_2CO–Et_2O–EtOH	$C_{14}H_{21}N \cdot HCl$	70.12	9.27	5.84	14.79			5.99	15.02
36	*n*-C_5H_{11}	*trans*	D	85		110–115 (0.3)										
					Hydrochloride	176–177	Et_2O–EtOH	$C_{15}H_{23}N \cdot HCl$	70.98	9.53	5.52	13.97			5.47	14.09
37	Cyclohexyl	*trans*	D	65		125–128 (0.2)										
					Hydrochloride	204–206	Et_2O–EtOH	$C_{16}H_{23}N \cdot HCl$	72.29	9.10	5.27	13.34			5.32	13.19

[a] See Experimental Section. [b] See ref 6.

TABLE IV

1-(DISUBSTITUTED) AMINOMETHYL-2-PHENYLCYCLOPROPANE



Compd	R_1	R_2	Config	Procedure[a]	Yield, %	Salts	Bp (mm) or mp, °C	Recrystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % X	Found, % C	Found, % H	Found, % N	Found, % X
38[b]	CH_3	CH_3	*trans*	D	88		78–80 (0.6)										
						Hydrochloride	146–147	Me_2CO–Et_2O	$C_{12}H_{17}N \cdot HCl$	68.07	8.57	6.62	16.75			6.64	16.58
39	CH_3	*n*-C_4H_9	*trans*	E	85.3		108–110 (0.6)		$C_{15}H_{23}N$	82.89	10.67	6.44		81.98	10.53	6.51	
40	C_2H_5	C_2H_5	*trans*	D	70		86–89 (0.6)										
						Picrate	82–83	EtOH	$C_{20}H_{24}N_4O_7$	55.55	5.59	12.96		55.98	5.68	13.15	
41	C_2H_5	C_2H_5	*cis*	D	84		77–79 (0.5)										
						Picrate	89–90	EtOH	$C_{20}H_{24}N_4O_7$	55.55	5.59	12.96		55.53	5.67	12.96	

42	C_2H_5	$CH_2C_6H_5$	*trans*	D	65		129–131 (0.3)	$C_{19}H_{23}N$	85.99	8.74	5.28		86.05	8.84	5.32			
43	C_2H_4OH	C_2H_4OH	*trans*	D	84		170–180 (0.6)	$C_{14}H_{21}NO_2$	71.46	8.99	5.95		71.14	9.05	6.06			
44	*n*-C_3H_7	*n*-C_3H_7	*trans*	D	88.8		94–96 (0.2)	$C_{16}H_{25}N$	83.05	10.89	6.05		83.21	10.81	5.99			
						Picrolonate	107–108	$C_{26}H_{33}N_5O_5$	63.01	6.71	14.16		63.17	6.60	14.26			
						Methiodide	105–107	$C_{17}H_{28}NI$	54.69	7.56	3.75	33.99			3.75	34.23		
45	*i*-C_3H_7	*i*-C_3H_7	*trans*	D	90		95–96 (0.4)	$C_{18}H_{29}N \cdot HCl$	73.07	10.22	4.73	11.98						
46	*n*-C_4H_9	*n*-C_4H_9	*trans*	F	16		120–124 (0.7)											
						Hydrochloride	56–58	$C_{28}H_{37}N_3O_4$	64.38	7.12	13.40		64.66	7.19	13.39			
						Picrolonate	107–108	$C_{19}H_{29}NI$	56.86	8.04	3.49	31.62			3.49	31.46		
						Methiodide	99–100	$C_{18}H_{29}N$	83.33	11.27	5.40							
47	*i*-C_4H_9	*i*-C_4H_9	*trans*	D	87		101–102 (0.4)	$C_{18}H_{29}N$	83.33	11.27	5.40							
48	*sec*-C_4H_9	*sec*-C_4H_9	*trans*	D	88.3		102–104 (0.4)	$C_{20}H_{33}N$	83.56	11.57	4.87							
49	*n*-C_5H_{11}	*n*-C_5H_{11}	*trans*	D	91.7		133–135 (0.4)											
50	Pyrrolidine		*trans*	D	89		100–101 (0.5)											
						Hydrochloride	147–148	$C_{14}H_{18}N \cdot HCl$	70.72	8.48	5.89	14.91	70.89	8.60	6.05	14.80		
						Methyl bromide	99–101	$C_{15}H_{22}NBr$	60.81	7.49	4.73	26.97			4.75	26.96		
51	Piperidine		*trans*	D	87		107–110 (0.6)											
						Hydrochloride	166–167	$C_{15}H_{21}N \cdot HCl$	71.55	8.81	5.56	14.08			5.63	14.27		
52	Morpholine		*trans*	D	89		111–114 (0.4)											
						Hydrochloride	192–193	$C_{14}H_{19}NO \cdot HCl$	66.27	7.94	5.52	13.97			5.60	14.01		
						Methiodide		$C_{15}H_{22}NOI$	50.15	6.17	3.90	35.32			3.93	34.51		

42	C_2H_5	$CH_2C_6H_5$	*trans*	D	65		129–131 (0.3)	$C_{19}H_{23}N$	85.99	8.74	5.28		86.05	8.84	5.32			
43	C_2H_4OH	C_2H_4OH	*trans*	D	84		170–180 (0.6)	$C_{14}H_{21}NO_2$	71.46	8.99	5.95		71.14	9.05	6.06			
44	*n*-C_3H_7	*n*-C_3H_7	*trans*	D	88.8		94–96 (0.2)	$C_{16}H_{25}N$	83.05	10.89	6.05		83.21	10.81	5.99			
						Picrolonate	107–108	$C_{26}H_{33}N_5O_5$	63.01	6.71	14.16		63.17	6.60	14.26			
						Methiodide	105–107	$C_{17}H_{28}NI$	54.69	7.56	3.75	33.99			3.75	34.23		
45	*i*-C_3H_7	*i*-C_3H_7	*trans*	D	90		95–96 (0.4)	$C_{18}H_{29}N \cdot HCl$	73.07	10.22	4.73	11.98						
46	*n*-C_4H_9	*n*-C_4H_9	*trans*	F	16		120–124 (0.7)											
						Hydrochloride	56–58	$C_{28}H_{37}N_3O_4$	64.38	7.12	13.40		64.66	7.19	13.39			
						Picrolonate	107–108	$C_{19}H_{29}NI$	56.86	8.04	3.49	31.62			3.49	31.46		
						Methiodide	99–100	$C_{18}H_{29}N$	83.33	11.27	5.40							
47	*i*-C_4H_9	*i*-C_4H_9	*trans*	D	87		101–102 (0.4)	$C_{18}H_{29}N$	83.33	11.27	5.40							
48	*sec*-C_4H_9	*sec*-C_4H_9	*trans*	D	88.3		102–104 (0.4)	$C_{20}H_{33}N$	83.56	11.57	4.87							
49	*n*-C_5H_{11}	*n*-C_5H_{11}	*trans*	D	91.7		133–135 (0.4)											
50	Pyrrolidine		*trans*	D	89		100–101 (0.5)											
						Hydrochloride	147–148	$C_{14}H_{18}N \cdot HCl$	70.72	8.48	5.89	14.91	70.89	8.60	6.05	14.80		
						Methyl bromide	99–101	$C_{15}H_{22}NBr$	60.81	7.49	4.73	26.97			4.75	26.96		
51	Piperidine		*trans*	D	87		107–110 (0.6)											
						Hydrochloride	166–167	$C_{15}H_{21}N \cdot HCl$	71.55	8.81	5.56	14.08			5.63	14.27		
52	Morpholine		*trans*	D	89		111–114 (0.4)											
						Hydrochloride	192–193	$C_{14}H_{19}NO \cdot HCl$	66.27	7.94	5.52	13.97			5.60	14.01		
						Methiodide		$C_{15}H_{22}NOI$	50.15	6.17	3.90	35.32			3.93	34.51		

[a] See Experimental Section. [b] See ref 6.

TABLE V

Test	Substituted amides Mono	Substituted amides Di	Substituted amines Mono	Substituted amines Di
Motility				
enhancement			26,27,28	40,50,52
depression	2,10	13,14,19,21	6,7,8,12	46,47
Anorexia			26,27,28,[a]37	50,51
Hyperthermia (after MAO inhib)			27,28,37	38,40,50
Barbiturates (enhancement)	1,2,3,10	13,14,19,23	26,27,28	38,40,46,47
Pentylenetetrazole (protection)	1,2			
Reserpine (reversal)			26,27,28	40,50

[a] The *cis* isomer is inactive.

(4) **Enhancement of Barbiturate-Induced Hypnosis.**—Groups of six male rats received 75 mg of isoamylethylbarbituric acid/kg intraperitoneally 30 min after oral administration of 50 mg/kg of the compounds. Only the compounds increasing the hypnosis by not less than 50% as compared to the controls were considered active.

(5) **Protection from Pentylenetetrazole Convulsions.**—The derivatives were given subcutaneously at 50 mg/kg to groups of five rats, which were later administered with an LD_{99} of pentylenetetrazole (100 mg/kg ip under our conditions). The compounds proving able to abolish convulsions in three out of five animals were considered active.

(6) **Reversal of Reserpine-Induced Depressant Effects.**—Rabbits previously treated with 5 mg/kg of intravenous reserpine, according to the method proposed by Maxwell,[10] were used. The compounds were perfused at the constant speed of 1 mg/kg/min. The derivatives which 15 min after the beginning of perfusion were seen to cause the disappearance of ptosis and to bring responsiveness to stimuli to normal were considered active.

(7) **Influence on Brain and Liver MAO Activity in the Rat. Indirect *in vitro* Evaluation.**—Groups of four rats each were given the compound orally at 100 mg/kg. Controls were given iproniazid (100 mg/kg) and tranylcypromine (5 mg/kg). MAO activity of brain and liver was assayed 60 min later by the Warburg manometric technique according to Creasey,[11] by determining the oxygen consumption in the presence of tyramine as a substrate. The amines assayed were **26**–**29**, **38**, **40**, **41**, and **50** and the amides **1**, **2**, **13**. No significant variation of MAO activity was found for either brain or liver. Parallel experiments carried out *in vitro*, by using the above amines as a substrate instead of tyramine, showed in the presence of amine **26** an increase in oxygen consumption; the hypothesis seems, therefore, justified that such a compound may be considered as a substrate of liver MAO activity. By contrast, no variation was demonstrated for the brain MAO activity.

Effects on Peripheral Nervous System. *In Vivo* **Effects.**—The compounds were injected intravenously through a cannula inserted into the jugular vein in the cat under chloralose anesthesia (80 mg/kg iv), and arterial pressure was recorded with a mercury manometer connected to the carotid. (a) Direct effects on pressure, (b) influence on hypotensive responses to electrical stimulation of the peripheral right vagus, and (c) the effects on the responses of the nictitating membrane to sympathetic electrical stimulation at preganglionic level were recorded.

In vitro effects recorded were (a) on the rat seminal vesicle, isolated and perfused with Ringer-Locke solution and directly stimulated with norepinephrine; (b) on the rat uterus, isolated and perfused with Dale solution after previous castration and treatment with estradiol for 5 days; (c) on the guinea pig ileum, isolated and perfused with Ringer solution and directly stimulated with histamine, ACh, and $BaCl_2$.

In vivo the monoalkylamino derivatives **26**–**28** had some indirect sympathomimetic properties: they induced hypertension at doses of 400–800 μg/kg and enhanced significantly contraction of the nictitating membrane. The hypertensive effect was still observed in the adrenalectomized animal and its occurence is prevented by a pretreatment with 5 mg of cocaine/kg sc.

Lengthening of the alkyl radical, as in **30**–**35** and **37**, abolished the hypertensive properties and brought about a reduction of the

(10) D. R. Maxwell, Proceedings of the 3rd International Congress of Neuro-Psychopharmacology, Munich, Sept 1962, Elsevier Publishing Co., Amsterdam, 1964, p 501.

(11) N. H. Creasey, *Biochem. J.*, **64**, 178 (1956).

responses to vagal stimulation; no effect was observed on the responses to direct injection of ACh, nor on the nictitating membrane.

The dialkyl-substituted amines displayed quite different properties: **38** and to a lower extent **40** appeared to be slightly hypotensive and to slow down the heart rate. *In vitro* **38** proved to be a competitive antagonist of norepinephrine. Lengthening of the alkyl chain causes the appearance of oxytocic activity: *in vitro* marked oxytocic activity, already evident for the lower homologs **44** and **45**, was exerted also by **46**, **48**, **49**, and **51**.

Some of quaternary derivatives, particularly **38** and **46**-methiodide, showed strong nicotinic properties. If given intravenously at 0.5–1 mg/kg, they caused a biphasic pressor response, characterized by a mild hypotension immediately followed by hypertension, which may be abolished by a pretreatment with hexamethonium (5 mg/kg sc). Previous adrenalectomy reduced this response considerably. The amides at 10 mg/kg ip in aqueous suspension, in the cat, appeared to have no appreciable effect on autonomic responses.

Of some interest is the spasmolytic activity of the disubstituted amides **16-21**, **23**, **24**, observed *in vitro* on the guinea pig ileum stimulated with histamine, ACh, and $BaCl_2$.

Antiexudative Property.—The dialkylamines **38** and **40** and the compounds **50–52**, given orally at the dose of 50 mg/kg, provided marked protection toward the foot edema produced by egg albumin in the rat.

Fungistatic Activity.—Unlike monoalkyl amino derivatives, quaternary compounds, and amido compounds, almost all tertiary amine derivatives have shown *in vitro* a mild activity toward *Candida albicans*, *Aspergillus niger*, and *Epidermophyton floccosam*. No appreciable effect toward gram-positive and gram-negative organisms was observed.

Discussion

The pharmacological study of the compounds examined has shown the following. (1) Few of the amides are effective on the central nervous system and exert a somehow depressant activity, synergistic with that of barbiturates; the lower homologs, such as the nonsubstituted amide and its N-monomethyl derivative exerted some protection toward pentylenetetrazole convulsant activity (see Table V). The N,N-disubstituted amides showed an interesting peripheral spasmolytic papaverine-like activity on smooth muscles. (2) In the series of amines lower monoalkyl-substituted members exert antidepressant and sympathomimetic effects qualitatively comparable to those of tranylcypromine and amphetamine, without modifying the brain and liver MAO activity (see Table V). In accordance with earlier observations by Zirkle, *et al.*,[3] we observed the importance of the *cis* and *trans* configuration for the appearance of the specific activity in the compounds studied: compound **29**, the *cis* analog of **28**, is devoid of any excitatory, anorexic, hyperthermic activities in the animal with a monoamine oxidase block, nor does it antagonize reserpine. Like the *cis*-phenethylamine derivatives,[12] our dialkylamino compounds appear endowed with antiepinephrine and oxytocic activity, the oxytocic properties being the more evident the longer the alkyl moiety. (3) The quaternary compounds are completely ineffective at the CNS level, but show significant nicotine-like properties.

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(12) P. Zamboni, *Arch. Sci. Biol.* (Bologna), **38**, 575 (1954).

The Effects of Bile Acid Derivatives[1,2] on Bacterial Permeability and Enzyme Induction

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A series of twenty derivatives of cholanic acid has been tested for their abilities to accelerate cell swelling and to inhibit enzyme induction of a strain of *Pseudomonas aeruginosa*. The series included conjugated as well as unconjugated natural bile acids all of which bear a negative charge at physiological pH. These anionic substances may increase the rate of cell swelling but have no effect on enzyme induction. Evidence is presented that they increase bacterial permeability. Other anionic derivatives, not found naturally, behave similarly. Bile acids conjugated with N^1-trimethylethylenediamine, cholamine, are more potent in accelerating bacterial swelling. In addition, the cationic substances inhibit protein synthesis as evidenced by their inhibition of the induction of the enzymes which catabolize benzoic acid. Chenodeoxycholylcholamine, the more potent analog, approaches in effectiveness benzalkonium chloride (which is shown to have the same properties). The two effects on swelling and on enzyme induction are apparently not causally related. By altering the conditions of incubation, one can affect either cell swelling or enzyme induction.

When surface active agents are incubated with microorganisms, they apparently react with the cell membrane. Cell constituents such as potassium,[3] amino acids,[4] purines, and pyrimidines[5] diffuse into the medium, and protoplasts are rapidly lysed.[6] Anionic compounds are more active in acid solution probably because under these conditions the nitrogen groups in the proteins are more positively charged and thus facilitate ionic bonding.[7] In addition to ionic binding, other forces, possibly hydrophobic binding, must be involved in the interactions between anionic detergents and proteins. Thus, detergent may be associated

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(2) Parts of this paper were presented at the Fall Meetings (1966) of the American Society for Pharmacology and Experimental Therapeutics in Mexico City, and the National Academy of Sciences at Durham.

(3) (a) R. D. Hotchkiss, *Ann. N. Y. Acad. Sci.*, **46**, 479 (1946); (b) T. G. Sclarff and W. C. Maupin, *Biochem. Pharmacol.*, **5**, 79 (1960).

(4) E. F. Gale and E. S. Taylor, *J. Gen. Microbiol.*, **1**, 77 (1947).

(5) M. R. J. Salton, *ibid.*, **5**, 391 (1951).

(6) J. Tomasic, *Proc. Soc. Exptl. Biol. Med.*, **89**, 459 (1955).

(7) H. N. Glassman, *Ann. N. Y. Acad. Sci.*, **53**, 91 (1950).