105727-90-0; **32**, 69-78-3; **33**, 105728-34-5; **34a**, 105728-35-6; **34b**, 105762-12-7; **35**, 105728-36-7; **36**, 105728-37-8; **3m**, 105728-38-9; **38**, 105728-39-0; **39**, 105695-41-8; **40**, 105695-42-9; **41**, 105695-43-0; **42**, 105728-40-3; **43**, 105728-41-4; **44**, 105728-59-4; **45**, 105728-42-5; **46**, 105695-44-1; **47**, 105728-43-6; **48**, 105728-44-7; **51**, 105762-36-5; **52**, 105728-45-8; **53**, 105695-45-2; **54**, 94192-98-0; **55**, 94219-48-4; **56**, 105728-46-9; **57**, 105727-91-1; **58**, 105728-48-1; **59**, 105728-47-0; **60**, 105728-50-5; **61**, 105728-49-2; **62**, 105695-46-3; **63**, 105695-47-4; **64**, 94193-38-1; **66**, 105695-48-5; **67**, 105728-51-6; **68**, 105728-52-7; **69**, 105728-53-8; **71**, 105695-49-6; **72a**, 94192-86-6; **72b**, 94192-87-7; **73a**, 94192-89-9; **73b**, 94192-88-8; **74a**, 94192-93-5; **74b**, 94192-92-4; **75a**, 94192-85-5; **75b**, 94192-84-4; **76a**, 105727-92-2; **76b**, 105727-93-3; **77a**, 94192-97-9; **77b**, 94192-96-8; **78a**, 94192-95-7; **78b**, 94192-94-6; **82**, 105727-94-4; **83**, 105727-95-5; **84**, 105727-96-6; **85**, 105727-97-7; (±)-**88**, 105728-54-9; **89**, 105728-55-0; (±)-**90**, 105728-56-1; (±)-**91**, 105728-57-2; (±)-**92**, 105727-98-8; **93**, 105727-60-7; **94**, 105728-58-3; **95**, 105727-99-9; **96**, 105728-00-5; **97**, 105728-01-6; **98**, 86798-59-6; **99**, 77671-31-9; **100**, 81840-15-5; **101**, 78415-72-2; $(t\text{-BuOCO})_2CHBr$, 15960-79-9; $PhCH_2O_2CCl$, 501-53-1; GlyOEt·HCl, 623-33-6; $BrCH_2CO_2Et$, 105-36-2; $Br(CH_2)_4CO_2Me$, 5454-83-1; $Br(CH_2)_5CO_2Et$, 25542-62-5; $Br(CH_2)_6CO_2)Et$, 29823-18-5; $EtO_2C(CH_2)_3Br$, 2969-81-5; $MeO_2C(CH_2)_2C{\equiv}CH$, 21565-82-2; $Br(CH_2)_2OAc$, 927-68-4; $Cl(CH_2)_2NCO$, 1943-83-5; $HO(CH_2)_2NH_2{\cdot}HCl$, 2002-24-6; $NH_2(CH_2)_2CO_2Me$, 4138-35-6; $pClCO_2C_6H_4NO_2$, 7693-46-1; *N*-cyclohexyl-6-hydroxyhexanamide, 105728-28-7; *N*-cyclohexyl-4-hydroxybutyramide, 20388-04-9; cAMP PDE, 9036-21-9; *trans*-4-aminocyclohexanol hydrochloride, 50910-54-8; *trans*-4-[(benzyloxycarbonyl)amino]cyclohexanol, 27489-63-0; 4-(2-aminoethyl)morpholine, 2038-03-1; cyclohexanone, 108-94-1; *N*-(2-chloroethyl)cyclohexylamine hydrochloride, 50597-62-1; *N*-carbobenzoxy-*N*-(2-*Chloroethyl*)cyclohexylamine, 101269-83-4; imidazole, 288-322-4; *N*-carbobenzoxy-*N*-(2-(*N*-imidazolyl)ethyl)cyclohexylamine, 105762-37-6; 6-hydroxy-2-nitrobenzaldehyde, 16855-08-6; 4-hydroxy-2-nitrobenzaldehyde, 90151-04-5; 3-hydroxy-2-nitrobenzaldehyde, 42123-33-1; *N*-methylcyclohexylamine, 100-60-7; 5-(3-chloropropyl)-1-cyclohexyltetrazole, 73963-29-8; 1,1′-thiocarbonyldiimidazole, 6160-65-2; 2-(methylthio)hydantoin, 90567-37-6; 2-(ethylthio)imidazoline, 7320-60-7; 2-chloro-3-hydroxy-6-nitrobenzaldehyde, 19183-03-0; L-dimethyl aspartate, 6384-18-5; methyl carbazate, 6294-89-9; L-methyl asparaginate, 6384-09-4.

1-Aryl-2-(aminomethyl)cyclopropanecarboxylic Acid Derivatives. A New Series of Potential Antidepressants

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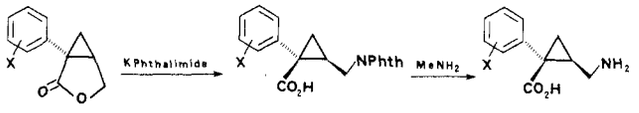
A series of 1-aryl-2-(aminomethyl)cyclopropanecarboxylic acid derivatives were synthesized and evaluated as potential antidepressants. Compounds with the *Z* configuration were synthesized from 1-aryl-2-oxo-3-oxabicyclo[3.1.0]hexane and those with the *E* configuration from (*E*)-1-phenyl-2-(hydroxymethyl)cyclopropanecarboxylic acid. The compounds were evaluated in animal tests designed to reveal potential antidepressant activity and the existence of undesirable side effects. Several derivatives were more active than imipramine and desipramine. On the basis of its activity in pharmacological animal tests of antidepressant activity and its potential lack of side effects, 1-phenyl-1-[(diethylamino)carbonyl]-2-(aminomethyl)cyclopropane hydrochloride, midalcipran (INN), was selected for further development. This compound is currently in phase III clinical evaluation.

Antidepressant drugs suffer from two main disadvantages in addition to their eventual side effects and toxicity. No antidepressant studied so far has been shown to be active in more than 60–70% of the cases of major depressive disorders and all antidepressants require 10–20 days administration (depending on the criteria used) before any therapeutic benefit is seen.[1] Thus even if the more recent second and third generation antidepressants, such as mianserin[2] and fluoxetine,[3] have less side effects than the tricyclic antidepressants, they still suffer from these drawbacks. In an attempt to find a new structural prototype for antidepressant therapy, we have studied a series of bifunctional cyclopropane derivatives,[4,5] some of which have interesting potential antidepressant profiles.

Scheme I. Synthesis of (*Z*)-γ-Amino Acids



I II III

We describe here the structure–activity relationship of this series of compounds, based on variations in the phenyl ring and substitution on the amine and carboxylic acid functions.

Chemistry

(*Z*)-γ-Amino Carboxylic Acids and Esters (Schemes I and II). Amino acid III was obtained by reaction of lactone I with potassium phthalimide in di-

(1) Jenner, F. A. *Br. J. Clin. Pharmacol.* **1977**, *4*, 1995.
(2) Pinder, R. M.; Fink, M. In *Non-Tricyclic and Non-Monoamine Oxidase Inhibitors*; Lehmann, H. E., Ed.; Karger: Basel, 1982; pp 70–101.
(3) Lemberger, L.; Fuller, R.; Wong, D.; Stark, P. In *Frontiers in Neuropsychiatric Research*; Usdin, E., Goldstein, M. Friedhafl, A. S., Goergotas, A., Eds.; Macmillan: London, 1983; pp 233–240.
(4) Mouzin, G.; Cousse, H.; Bonnaud, B.; Morre, M.; Stenger, A. Eur. Pat. Appl. EP 68699, 1983.
(5) Moret, C.; Charveron, M.; Finberg, J. P. M.; Couzinier, J. P.; Briley, M. *Neuropharmacology* **1985**, *24*, 1211.
(6) Briley, M. *Drugs Future* **1986**, *11*, 21.
(7) Serre, C.; Clerc, G.; Escande, M.; Feline, A.; Gineste, D.; Tignol, J.; Van Amerongen, P. *Curr. Ther. Res.* **1986**, *39*, 156.
(8) Bondinell, W. E.; Kaiser, C. *Annual Reports in Medicinal Chemistry*; Hess, Hans-Jüngen, Ed.; Academic: New York, 1982; pp 41–50.

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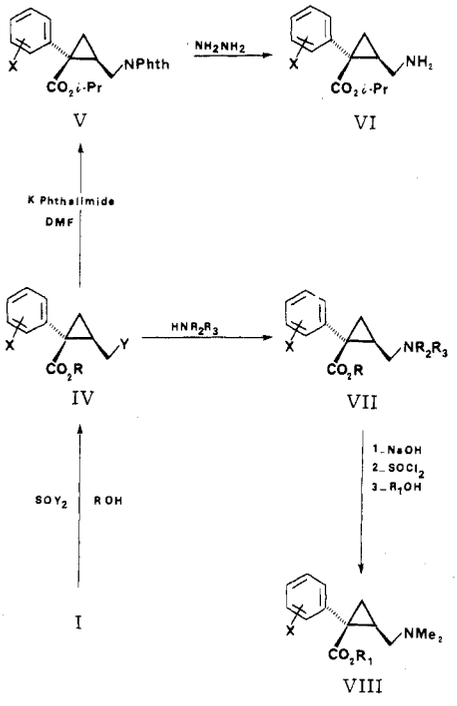
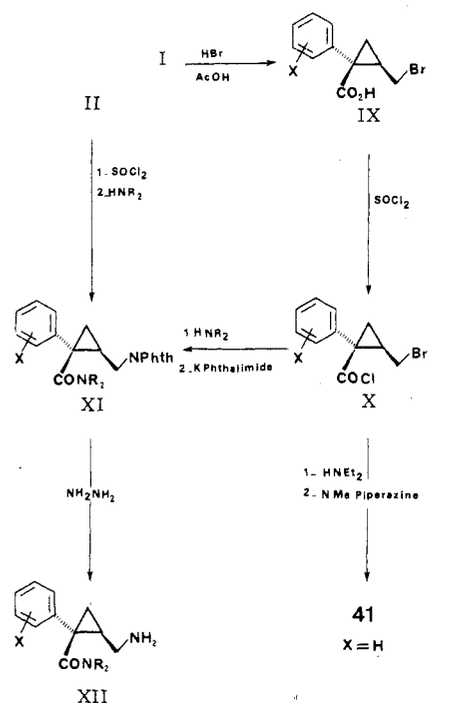
Scheme II. Synthesis of (*Z*)-γ-Amino Esters

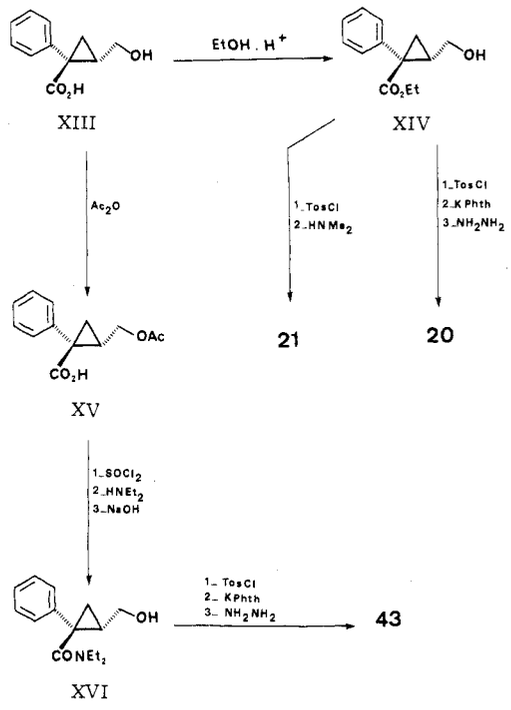


Scheme III. Synthesis of (*Z*)-γ-Amino Amides



methylformamide,[9] followed by treatment with an aqueous methylamine solution.[10] The reaction of lactone I with thionyl halide in the presence of an alcohol of low molecular weight gave good yields of the halogenated esters IV. Esters VI, bearing a primary amine function in the γ position, were obtained by the classical Gabriel synthesis starting from halogenated esters IV. The reaction of secondary amines or hindered primary amines with halogenated esters IV gave the γ-amino esters VII. For less

Scheme IV. Synthesis of (*E*)-γ-Amino Esters and Amides



hindered primary amine derivatives, condensation of the corresponding N-benzylated amine with halogenated esters IV and subsequent hydrogenolysis proved to be the method of choice.

(*Z*)-γ-Amino Carboxamides (Scheme III). Brominated acids IX were obtained by heating lactones I at 80 °C with 48% hydrobromic acid in acetic acid.[11] A reaction temperature higher than 80 °C gave poor results with opening of the cyclopropane ring and decrease of the expected yield. Treatment of the acid chlorides X obtained from acids IX, with 2 equiv of a dialkylamine with cooling, followed without isolation by condensation with potassium phthalimide in dimethylformamide at 110 °C, gave the corresponding amides XI. Several amides XI were obtained by treatment of γ-phthalimidomethyl carboxylic acid II with $SOCl_2$ followed by condensation of the unpurified product with dialkylamines. Hydrazinolysis of the phthalimido group gave the corresponding γ-amino carboxamides XII.

Carboxylic esters and carboxamides with the *E* configuration were obtained by the classical Gabriel synthesis starting from the corresponding tosyl esters of (*E*)-1-phenyl-2-(hydroxymethyl)cyclopropanecarboxylic ester XIV and amide XVI (Scheme IV).

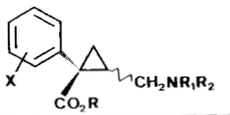
Results and Discussion

The potential antidepressant activity of the amino acids and esters synthesized (Table I) were low with the exception of the primary γ-amino ester **3** and the γ-dimethylamino ester **8**, both *p*-chlorophenyl substituted.

In the series of γ-amino amides (Table II), modifications were made at three points: substitution at the level of the carboxamide function, alkylation and acylation of the primary γ-amine function, and substitution on the aromatic ring. When the carboxamide function of the inactive primary amine **22** was substituted by progressively larger aliphatic carbon chains (**23–25**, **32–35**), we found that potency was maximized for the tertiary amide **25** (diethyl

(9) Bornstein, S.; Bedell, F.; Drummond, P. E.; Kosloski, C. L. *J. Am. Chem. Soc.* **1956**, *78*, 83.
(10) Wolfe, S.; Hasan, S. K. *Can. J. Chem.* **1979**, *48* 3572.
(11) Lemaire, C. H.; Luxen, A.; Christiaens, L.; Guillaume, M. *J. Heterocycl. Chem.* **1983**, *20*, 811.

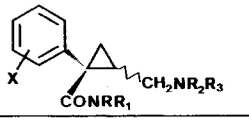
Table I. Physical Properties and Biological Activity of 1-Aryl-2-(aminomethyl)cyclopropanecarboxylic Acid and Esters



no.	conf	X	R	R_1	R_2	mp, °C	recryst solvent[a] (% yield)	formula[b]	LD_{50} (95% CL), mg/kg po	yohimbine toxicity: ED_{50} (95% CL), mg/kg po	tetrabenazine ptosis: ED_{50} (95% CL), mg/kg po	% mydriasis	pot. 5-HTP head twitch: ED_{50} (95% CL), mg/kg po
1	*Z*	H	H	H	H	289–291	IX (61)	$C_{11}H_{13}NO_2$·HCl	>1000	>100	>30	NS[e]	>100
2	*Z*	H	*i*-C_3H_7	H	H	131–133	IV (45)	$C_{14}H_{19}NO_2$·HCl	100 (26–378)	18 (2.4–130)		20	54 (6–1000)
3	*Z*	*p*-Cl	*i*-C_3H_7	H	H	205–207	I (55)	$C_{14}H_{18}ClNO_2$·HCl	255 (110–600)	2 (0.2–19)	8 (0.07–899)	23	50 (7–230)
4	*Z*	*p*-CH_3	*i*-C_3H_7	H	H	151–154	IV (38)	$C_{15}H_{21}NO_2$·HCl	1000 (514–1940)	30 (2.5–370)	17 (1.6–199)	NS	100 (15–700)
5	*Z*	H	C_2H_5	H	CH_3	132–134	I (49)	$C_{14}H_{19}NO_2$·HCl	562 (337–938)	30 (3.1–270)		62	
6	*Z*	H	C_2H_5	H	$CH_2C_6H_5$	179–181	II (78)	$C_{20}H_{23}NO_2$·HCl	316 (163–614)	>30		16	
7	*Z*	H	CH_3	CH_3	CH_3	149–151	I (57)	$C_{14}H_{19}NO_2$·HCl	750 (422–1330)	29 (11–80)	30 (0.4–22)	60	
8	*Z*	*p*-Cl	C_2H_5	CH_3	CH_3	131–133	I (85)	$C_{15}H_{20}ClNO_2$·HCl	422 (175–1020)	2 (0.1–28)	6 (1–35)	24	35 (3.5–350)
9	*Z*	*p*-OCH_3	C_2H_5	CH_3	CH_3	169–171	I (65)	$C_{16}H_{23}NO_3$·HCl	562 (220–1440)	>30		38	
10	*Z*	*p*-F	C_2H_5	CH_3	CH_3	164–166	I (65)	$C_{15}H_{20}FNO_2$·HCl	562 (249–1270)	12 (3–50)	8 (1.8–36)	76	
11	*Z*	H	*n*-C_3H_7	CH_3	CH_3	113–115	I (57)	$C_{20}H_{27}NO_6$[d]	562 (737–938)	25 (11–58)	30 (11–70)	55	>100
12	*Z*	H	*i*-C_3H_7	CH_3	CH_3	157–159	I (72)	$C_{16}H_{23}NO_2$·HCl	422 (237–750)	18 (3.1–94)	7 (1.2–36)	73	
13	*Z*	H	$CH_2CH{=}CH_2$	CH_3	CH_3	91–93	I (50)	$C_{20}H_{25}NO_6$[d]	1000 (514–1940)	16 (2.1–120)		44	
14	*Z*	H	C_2H_5	CH_2CH_2OH	CH_2CH_2OH	101–103	VII (69)	$C_{21}H_{29}NO_8$[c]	>1000	>100		NS	
15	*Z*	H	C_2H_5	*i*-C_3H_7	*i*-C_3H_7	107–109	VII (45)	$C_{23}H_{33}NO_6$[c]	750 (422–1330)	70 (24–200)		49	
16	*Z*	H	C_2H_5		$(CH_2)_4$	139–141	IV (70)	$C_{17}H_{23}NO_2$·HCl	562 (249–1270)	>100		53	
17	*Z*	H	C_2H_5	CH_3	CH_2CH_2OH	138–140	VI (34)	$C_{20}H_{27}NO_7$[d]	>1000	56 (33–93)		23	
18	*Z*	H	C_2H_5	CH_3	*n*-C_4H_9	131–133	VII (42)	$C_{18}H_{27}NO_2$·HCl	255 (110–600)	27 (2–240)		61	
19	*Z*	H	C_2H_5	CH_3	$CH_2CH_2C_6H_5$	111–113	I (54)	$C_{22}H_{27}NO_2$·HCl	1000 (514–1940)	15 (1.4–130)	>30	30	>30
20	*E*	H	C_2H_5	H	H	180–182	IV (55)	$C_{13}H_{17}NO_2$·HCl	316 (163–614)	100 (10–520)	30 (10–93)	33	73 (9–600)
21	*E*	H	C_2H_5	CH_3	CH_3	152–154	I (75)	$C_{15}H_{21}NO_2$·HCl	>1000	10 (5.1–19.4)	1.4 (0.7–3)	40	
desimipramine									572 (300–1300)	2 (0.1–15)	3 (0.25–24.5)	46	>100
clomipramine									556 (280–1300)	5 (0.7–42)	9 (3.7–21)	38	37 (16–85)
imipramine									400 (180–900)	7 (0.9–47)	5 (0.18–146)	61	60 (12–280)

[a] I, EtOH–Et_2O; II, EtOH–*i*-Pr_2O; III, acetone; IV, EtOAc–Et_2O; V, EtOAc; VI, EtOH; VII, *i*-PrOH–Et_2O; VIII, *i*-PrOH; IX, H_2O–EtOH. [b] The analyses of all compounds were within 0.4% of the theoretical value for C, H, N, Cl, and F. The ^1H NMR were consistent with the assigned structure. [c] Maleate. [d] Fumarate. [e] NS, not significant.

Table II. Physical Properties and Biological Activity of 1-Aryl-2-(aminomethyl)cyclopropanecarboxamides



no.	conf	X	R	R_1	R_2	R_3	mp, °C	recryst solvent[a] (% yield)	formula[b]	LD_{50} (95% CL), mg/kg po	yohimbine toxicity: ED_{50} (95% CL), mg/kg po	tetrabenazine ptosis ED_{50} (95% CL), mg/kg po	% mydriasis	pot. 5-HTP head twitch: ED_{50} (95% CL), mg/kg po
22	Z	H	H	H	H	H	244–246	II (15)	$C_{11}H_{14}N_2O$·HCl	>300	>100	>30		>100
23	Z	H	H	C_2H_5	H	H	149–151	IX (35)	$C_{15}H_{20}N_2O_5$[c]	316 (163–164)	19 (1.7–230)	>30	NS[f]	>100
24	Z	H	CH_3	CH_3	H	H	204–206	II (28)	$C_{13}H_{18}N_2O$·HCl	316 (163–164)	20 (8.1–47.9)	14 (6.5–28.5)	10	
25	Z	H	C_2H_5	C_2H_5	H	H	179–181	I (82)	$C_{15}H_{22}N_2O$·HCl	237 (98–571)	0.5 (0.06–4.7)	0.5 (0.05–4.76)	NS	>100
26	Z	*o*-Cl	C_2H_5	C_2H_5	H	H	174–176	I (59)	$C_{15}H_{21}ClN_2O$·HCl	422 (175–1020)	48 (15–150)	>30	NS	>30
27	Z	*m*-Cl	C_2H_5	C_2H_5	H	H	209–211	III (65)	$C_{15}H_{21}ClN_2O$·HCl	100 (51–194)	3 (0.2–30)	0.9 (0.04–233)	NS	>10
28	Z	*p*-Cl	C_2H_5	C_2H_5	H	H	184–186	II (61)	$C_{15}H_{21}ClN_2O$·HCl	422 (140–1540)	3 (0.5–32)	9 (0.3–266)	11	>100
29	Z	*p*-F	C_2H_5	C_2H_5	H	H	189–191	III (39)	$C_{15}H_{21}FN_2O$·HCl	422 (140–1540)	5 (0.6–45)	10 (1.2–80)	NS	50 (1–250)
30	Z	*p*-CH_3	C_2H_5	C_2H_5	H	H	171–173	I (74)	$C_{16}H_{24}N_2O$·HCl	750 (311–1810)	14 (1–220)	2 (0.14–33)	11	>100
31	Z	H	C_2H_5	CH_2CH_2OH	H	H	189–191	IX (45)	$C_{34}H_{48}N_4O_8$[d]		34 (11.5–86)	20 (7.5–56)	19	100 (10–1000)
32	Z	H	*n*-C_3H_7	*n*-C_3H_7	H	H	177–179	I (75)	$C_{19}H_{28}N_2O_5$[c]	100 (12–818)	9 (4.5–18.1)	5.5 (2.4–12.7)	27	
33	Z	H	*i*-C_3H_7	*i*-C_3H_7	H	H	251–253	IV (76)	$C_{17}H_{26}N_2O$·HCl	100 (51–194)	15 (3.4–62)	30 (6–100)	NS	>30
34	Z	H	*n*-C_4H_9	*n*-C_4H_9	H	H	79–81	VII (88)	$C_{21}H_{32}N_2O_5$[c]	562 (220–1440)	>100	>30	NS	>100
35	Z	H	*n*-C_6H_{13}	*n*-C_6H_{13}	H	H	74–76	VII (64)	$C_{25}H_{40}N_2O_5$[c]	>1000	>100	>30	NS	>1000
36	Z	H	$(CH_2)_4$		H	H	134–136	IX (35)	$C_{17}H_{22}N_2O_5 \cdot {}^1/_2H_2O$[c]	562 (220–1440)	48 (10–230)	20 (4.5–90)	12	>100
37	Z	H	$CH(Me)(CH_2)_2CH(Me)$[e]		H	H	179–181	I (57)	$C_{21}H_{28}N_2O_5$[d]	100 (44.3–226)	3 (0.8–7.5)	>30	NS	>30
38	Z	H	$CH(Me)(CH_2)_3CH(Me)$[e]		H	H	184–186	I (75)	$C_{22}H_{30}N_2O_5$[d]	133 (55.4–321)	9 (1.7–48)	30 (6.5–130)	NS	>100
39	Z	H	C_2H_5	C_2H_5	H	CH_3	143–145	I (70)	$C_{18}H_{26}N_2O_5$[c]	316 (140–714)	4 (0.2–42)	13 (0.9–180)	NS	>100
40	Z	H	C_2H_5	C_2H_5	H	$COCH_3$	142–144	V (80)	$C_{17}H_{24}N_2O_2$	>1000	30 (10–93)	30 (10–93)	NS	>100
41	Z	H	C_2H_5	C_2H_5	H	$COCH_2NH_2$	91–93	VI (62)	$C_{17}H_{25}N_3O_2$	237 (98–571)	1 (0.1–10)	10 (1–100)	19	
42	Z	H	C_2H_5	C_2H_5	$(CH_2CH_2)_2NCH_3$		219–221	I (74)	$C_{20}H_{31}N_3O$·2HCl	>1000	82 (18–400)	>30	NS	>100
43	E	H	C_2H_5	C_2H_5	H	H	214–216	I (65)	$C_{15}H_{22}N_2O$·HCl	562 (220–1440)	>100	>30	NS	>100

[a] I, EtOH–Et_2O; II, EtOAc; III, *i*-PrOH–Et_2O; IV, MeOH–H_2O; V, EtOAc–*i*-Pr_2O; VI, $CHCl_3$–*i*-Pr_2O; VII, EtOH–*i*-Pr_2O; VIII, DMF–H_2O; IX, MeOH–EtOAc; X, *i*-Pr_2O. [b] The analyses of all compounds were within 0.4% of the theoretical value for C, H, N, Cl, and F. The ^1H NMR spectra were consistent with the assigned structures. [c] Oxalate. [d] Fumarate. [e] Cis–trans mixture of 2,5- and 2,6-dimethyl substituants. [f] NS, not significant.

carboxamide) and decreased with further lengthening of the carbon chain. The immediate inferior (**24**) and superior (**32**) homologues of the clinically active compound **25** were at least 10-fold less active in the yohimbine test.

Certain cyclic carboxamides were synthesized to see whether the steric hinderance had any effect on the potency. The activity of these derivatives (**36–38**) was low as compared to that of compound **25** and was not correlated with the size of the cyclic substituents.

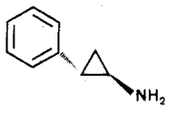
Alkylation (**39**, **42**) or acylation (**40**) of the primary γ-amine function induced a decrease or a complete loss of activity, with the exception of the glycinamide derivative (**41**), which maintained a high potency in particular on the yohimbine test. This may be due to the maintenance of a free terminal amine group.

In all cases, substitution of the aromatic ring appeared unfavorable, especially in the ortho position (**26**).

Anticholinergic activity as shown by mydriasis was present in all esters active in the antidepressant tests (Table I). In the amide series (Table II), however, anticholinergic activity was low or absent and unrelated to antidepressant activity.

It is obvious from the results of this present series of cyclopropanic compounds that several conditions have to be satisfied to maintain a high level of activity. A tertiary carboxamide function and a primary γ-amine in the *Z* position with preferably an unsubstituted phenyl group in the α position of the carboxamide are all necessary.

Clinically proven antidepressant activity has been found in a wide variety of chemical structures.[8] No clear structure–activity relationships have yet emerged between the different chemical families or even between compounds with similar pharmacological profiles.[8] The compounds discussed here have little, if anything, in common with the tricyclic antidepressants or any other known antidepressant drugs, with the possible exception of tranylcypromine (XVII).



XVII

There is, however, no similarity between the pharmacological profiles of tranylcypromine, a monoamine oxidase inhibitor, and compounds of the present series that are totally devoid of this activity.[5] Thus the 1-aryl-2-(aminomethyl)cyclopropanecarboxylic acid derivatives represent and original molecular prototype in the medicinal chemistry of antidepressant drugs.

Derivative **25** [1-phenyl-1-[(diethylamino)carbonyl]-2-(aminomethyl)cyclopropane hydrochloride, midalcipran (INN)], which shows a higher potential antidepressant activity than imipramine in several classical animal tests and which demonstrated no anticholinergic side effects, has been selected for further development[6] and is currently in phase III clinical evaluation.[7]

Experimental Section

Chemistry. Melting points were taken on a Kofler stage and were not corrected. Elemental analyses are within ±0.4% of theory. Infrared spectra were determined with Perkin-Elmer Model 177 infrared spectrophotometer. ^{1}H NMR spectra were determined with Hitachi Perkin-Elmer Model R 24B spectrometer, and chemical shifts are reported in δ downfield from tetramethylsilane as the internal standard. Ascending thin-layer chromatography was performed on precoated plates of silica gel 60 F_{254} (Merck), and the spots were made visible by an UV lamp or iodine vapor. The preparation of 1-aryl-2-oxo-3-oxabicyclo[3.1.0]hexane I and (*E*)-1-aryl-2-(hydroxymethyl)cyclopropanecarboxylic acids XIII, the starting materials for the synthesis of the differents derivatives, was described in previous publications.[12,13]

(*Z*)-1-Phenyl-2-(phthalimidomethyl)cyclopropanecarboxylic Acid. A mixture of 34.8 g (0.2 mol) of 1-phenyl-2-oxo-3-oxabicyclo[3.1.0]hexane, 40.7 g (0.22 mol) of potassium phthalimide, and 180 mL of dimethylformamide was refluxed with stirring for 15 h. The solution, combined with ice water, was extracted with EtOAc and then acidified with AcOH. Crystalline product was collected by filtration, washed with H_2O, and dried to give 36.5 g (57%) of (*Z*)-1-phenyl-2-(phthalimidomethyl)-cyclopropanecarboxylic acid: mp 185–187 °C; IR (KBr) 1760, 1705, 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.1–2 (m, 3, cyclopropyl H), 3.9 (d, 2, CH_2N), 7.1 (s, 5, aromatic H), 7.7 (s, 4, aromatic H).

(*Z*)-1-Phenyl-2-(aminomethyl)cyclopropanecarboxylic Acid (1). A mixture of 16.1 g (0.05 mol) of (*Z*)-1-phenyl-2-(phthalimidomethyl)cyclopropanecarboxylic acid and 200 mL of 40% aqueous methylamine solution was allowed to stand at room temperature for 6 days. The resulting solution was concentrated in vacuo and diluted with EtOH. The precipitate was filtered, dissolved in 60 mL of 1 N HCl, concentrated in vacuo, and crystallized by addition of ethyl alcohol to give 6.95 g (61%) of **1**: mp 289–291 °C dec; IR (KBr) 1690 cm^{-1} (C=O); ^{1}H NMR (D_2O) δ 0.95–1.9 (m, 3, cyclopropyl H), 3.1 (d, 2, CH_2N), 7.15 (s, 5, aromatic H).

(*Z*)-Ethyl 1-Phenyl-2-(bromomethyl)cyclopropanecarboxylate. To 750 mL of ethyl alcohol was added dropwise with stirring and cooling at −15 °C 93 mL of $SOBr_2$ (1.2 mol). To this solution was added 69.7 g (0.4 mol) of 1-phenyl-2-oxo-3-oxabicyclo[3.1.0]hexane, and the solution was stirred overnight at room temperature. The solvent was removed in vacuo to give an oil, which was distilled to give 102.4 g (90%) of (*Z*)-ethyl 1-phenyl-2-(bromomethyl)cyclopropanecarboxylate: bp 105–110 °C (0.1 mmHg); IR (film) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3, CH_3), 1.4–2.3 (m, 3, cyclopropyl H), 3.7 (m, 2, CH_2Br), 4.05 and 4.1 (2 q, 2, CH_2), 7.3 (m, 5, aromatic H).

(*Z*)-Isopropyl 1-Phenyl-2-(phthalimidomethyl)cyclopropanecarboxylate. A mixture of 40 g (0.158 mol) of (*Z*)-isopropyl 1-phenyl-2-(chloromethyl)cyclopropanecarboxylate, 30 g (0.16 mol) of potassium phthalimide, and 100 mL of dimethylformamide was stirred at 110–120 °C for 3 h. The cooled solution was combined with water, and the crystalline product collected by filtration was recrystallized from diisopropyl ether to give 43.6 g (76%) of (*Z*)-isopropyl 1-phenyl-2-(phthalimidomethyl)cyclopropanecarboxylate: mp 93–95 °C; IR (KBr) 1780, 1720, 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6, CH_3), 1.3–2.1 (m, 3, cyclopropyl H), 5.05 (dd, 2, CH_2N), 5.0 (m, 1, CH), 7.1 (s, 5, aromatic H), 7.65 (m, 4, aromatic H).

(*Z*)-Isopropyl 1-Phenyl-2-(aminomethyl)cyclopropanecarboxylate (2). To a stirred solution of 10.9 g (0.03 mol) of (*Z*)-isopropyl 1-phenyl-2-(phthalimidomethyl)cyclopropanecarboxylate in 80 mL ethyl alcohol was added 1.6 mL (0.033 mol) of hydrazine hydrate. The solution was stirred and heated under reflux for 1 h. The reaction mixture was concentrated to remove the solvent and treated with 160 mL of 1 N HCl, and the insoluble material was filtered. To the cooled filtrate was added excess K_2CO_3, and the mixture was extracted twice with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo to give an oil, which was acidified with cooling with an ethanolic HCl solution. After addition of Et_2O, the crystalline product was collected by filtration and recrystallized from EtOAc–Et_2O to give 3.64 g (45 %) of **2**: mp 131–133 °C; IR (KBr) 1705 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6, CH_3), 1.2–2.2 (m, 3, cyclopropyl H), 3.3 (dd, 2, CH_2N), 4.85 (m, 1, CH), 7.1 (m, 5, aromatic H).

(*Z*)-Isopropyl 1-Phenyl-2-[(dimethylamino)methyl]-cyclopropanecarboxylate (12). A mixture of 7.5 g (0.03 mol) of (*Z*)-isopropyl 1-phenyl-2-(chloromethyl)cyclopropanecarboxylate, 22 mL of 33% dimethylamine in benzene, 30 mL of toluene, and a catalytic amount of KI was allowed to stand ov-

(12) Casadio, S.; Bonnaud, B.; Mouzin, G.; Cousse, H. *Boll. Chim. Farm.* **1978**, *117*, 331.
(13) Mouzin, G.; Cousse, H.; Bonnaud, B. *Synthesis* **1978**, *4*, 304.

ernight in a closed vessel at 100 °C. The solvent was removed under vacuc, and the residual material was taken up in aqueous 5% $NaHCO_3$. This aqueous suspension was extracted twice with EtOAc, and the combined organic phases were washed with water, dried over Na_2SO_4, and concentrated to remove the solvent. The residual oil was acidified with an ethanolic HCl solution, and the resulting solid was recrystallized from EtOH–Et_2O to give 6.43 g (72%) of **12**: mp 157–159 °C; IR (KBr) 1705 cm^{-1} (C=O); ^1H NMR (D_2O) δ 1.15 and 1.25 (2 d, 6, CH_3), 1.4–2.3 (m, 3, cyclopropyl H), 3.1 (s, 6, NCH_3), 3.65 (m, 2, CH_2N), 5.05 (m, 1, CH), 7.35 (m, 5, aromatic H).

(*Z*)-Ethyl 1-Phenyl-2-[[(2-phenylethyl)methylamino]-methyl]cyclopropanecarboxylate (19). To a solution of (*Z*)-ethyl 1-phenyl-2-(bromomethyl)cyclopropanecarboxylate and 14.17 g (0.105 mol) of *N*-methyl-2-phenylethylamine in 250 mL of methyl ethyl ketone were added 15.2 g (0.11 mol) of K_2CO_3 and a catalytic amount of KI. The suspension was stirred and heated under reflux for 8 h. The cooled suspension was filtered and the solvent was removed in vacuo. The residual material was taken up in 5% aqueous $NaHCO_3$ and extracted twice with EtOAC. The organic phases were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was acidified with an ethanolic HCl solution, and the isolated product was recrystallized from EtOH–Et_2O to give 20.2 g (54%) of **19**: mp 111–113 °C; IR (KBr) 1710 cm^{-1} (C=O); ^1H NMR (D_2O) δ 1.05 (t, 3, CH_3), 1.3–1.8 (m, 2, cyclopropyl H), 2.1–2.6 (m, 1, cyclopropyl H), 2.9 (s, 3, NCH_3), 3.25 (s, 4, CH_2CH_2), 3.5 (d, 2, CH_2N), 4 (q, 2, CH_2O), 7.2 (m, 10 H, aromatic H).

(*Z*)-Allyl 1-Phenyl-2-[(dimethylamino)methyl]cyclopropanecarboxylate (13). To 2.56 g (0.01 mol) of (*Z*)-1-phenyl-2-[(dimethylamino)methyl]cyclopropanecarboxylic acid obtained by saponification of ester **7** was added 6 mL of $SOCl_2$ at room temperature, and the reaction mixture was stirred overnight. Et_2O (40 mL) was added dropwise, and the precipitated solid was collected by filtration. This crude chloride in 10 mL of CH_2Cl_2 was added dropwise to a solution of 0.58 g (0.01 mol) of allyl alcohol and 3.48 mL (0.025 mol) of triethylamine in 25 mL of CH_2Cl_2. After stirring overnight at room temperature, the mixture was washed with 2 N NaOH and water and then dried over Na_2SO_4 and filtered. The solvent was removed in vacuo, and the residual oil was treated with an ethanolic solution of fumaric acid. The resulting solid was recrystallized from EtOH–diisopropyl ether to give 1.87 g (50%) of **13**: mp 91–93 °C; IR (KBr) 1715 cm^{-1} (C=O); ^1H NMR (D_2O) δ 1.5–2.2 (m, 3, cyclopropyl H), 2.95 (s, 6, NCH_3), 3.55 (dd, 2, CH_2N), 4.55 (m, 2, CH_2O), 5.0 (m, 1, HC=), 5.25 (m, 1, HC=), 5.75 (m, 1, HC=), 7.35 (s, 5, aromatic H).

(*Z*)-1-Phenyl-2-(bromomethyl)cyclopropanecarboxylic Acid. To a stirred solution of 70 mL of 33% HBr solution in acetic acid (w/w) at room temperature was added portionwise 17.41 g (0.1 mol) of 1-phenyl-2-oxo-3-oxabicyclo[3.1.0]hexane, and the solution was heated to 80 °C in an oil bath for 2 h. The solution obtained was cooled to room temperature and stirred with 300 g of crushed ice. The crystalline product was collected by filtration and dried in vacuo to give 24.6 g (96%) of (*Z*)-1-phenyl-2-(bromomethyl)cyclopropanecarboxylic acid: mp 147–149 °C; IR (KBr) 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.3–2.2 (m, 3, cyclopropyl H), 3.8 (d, 2, CH_2Br), 7.2 (m, 5, aromatic H), 11.5 (s, 1, COOH, exchangeable with D_2O).

(*Z*)-1-Phenyl-2-(bromomethyl)cyclopropanecarbonyl Chloride. To 75 mL of $SOCl_2$ was added portionwise 25.5 g (0.1 mol) of (*Z*)-1-phenyl-2-(bromomethyl)cyclopropanecarboxylic acid, and the resulting solution was refluxed with stirring for 2 h. Excess $SOCl_2$ was removed in vacuo, and the residual oil was distilled to give 24.6 g (90%) of (*Z*)-1-phenyl-2-(bromomethyl)cyclopropanecarbonyl chloride: bp 120–125 °C (0.5 mmHg); IR (film) 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.6–2.7 (m, 3, cyclopropyl H), 3.6 (m, 2, CH_2Br), 7.3 (m, 5, aromatic H).

(*Z*)-1-Phenyl-2-[(4-methylpiperazinyl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide (42). To 10.9 g (0.04 mol) of (*Z*)-1-phenyl-2-(bromomethyl)cyclopropanecarbonyl chloride in 120 mL of Et_2O was added dropwise a solution of 8.3 mL (0.08 mol) of diethylamine in 25 mL of Et_2O with stirring and cooling in an ice bath. The mixture was then stirred overnight at room temperature. The precipitate was filtered off and the solvent was removed in vacuo at 25 °C. This crude halogenated amide in 50 mL of methyl ethyl ketone was added to 4 mL (0.04 mol) of *N*-methylpiperazine, 5.52 g (0.04 mol) of K_2CO_3, and a catalytic amount of KI. The mixture was stirred under reflux for 2 h. After the mixture was cooled to room temperature, the inorganic material was filtered and the solvent was removed in vacuo. The residual material was dissolved in EtOAc, washed with water, dried over Na_2SO_4, and filtered, and the solvent was removed under vacuo. The residual oil was acidified with an ethanolic HCl solution and the solid obtained was recrystallized from EtOH–Et_2O to give 11.9 g (74%) of **42**: mp 219–221 °C; IR (KBr) 1710 cm^{-1} (C=O); ^1H NMR (D_2O) δ 0.85 (t, 3, CH_3), 1.15 (t, 3, CH_3), 1.55–2.1 (m, 3, cyclopropyl H), 2.95 (s, 3, NCH_3), 3.0–3.85 (m, 14, CH_2N), 7.3 (s, 5, aromatic H).

(*Z*)-1-Phenyl-2-(phthalimidomethyl)-*N*,*N*-diethylcyclopropanecarboxamide. To 12.4 g (0.04 mol) of crude (*Z*)-1-phenyl-2-(bromomethyl)-*N*,*N*-diethylcyclopropanecarboxamide obtained by treatment of (*Z*)-1-phenyl-2-(bromomethyl)cyclopropanecarbonyl chloride with diethylamine as described above were added 8.35 g (0.045 mol) of potassium phthalimide and 30 mL of dimethylformamide. The mixture was stirred at 110 °C for 2.5 h. After the mixture was cooled to room temperature, water was added and the crystalline product was filtered and dried to give 13.8 g (94%) of (*Z*)-1-phenyl-2-(phthalimidomethyl)-*N*,*N*-diethylcyclopropanecarboxamide: mp 130–132 °C; IR (KBr) 1775, 1710, 1635 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.8 (t, 3, CH_3), 1.2 (t, 3, CH_3), 1.5–2.4 (m, 3, cyclopropyl H), 3–3.7 (m, 5, CH_2N and CHN), 4.2 (dd, 1, CHN), 7.1 (s, 5, aromatic H), 7.65 (m, 4, aromatic H).

(*Z*)-1-Phenyl-1-(pyrrolidinocarbonyl)-2-(phthalimidomethyl)cyclopropane. To 60 mL of $SOCl_2$ was added 16 g (0.05 mol) of (*Z*)-1-phenyl-2-(phthalimidomethyl)cyclopropanecarboxylic acid, and the solution was stirred under reflux for 4 h. Excess $SOCl_2$ was removed in vacuo. The residual crude chloride in 40 mL of dichloromethane was added dropwise to the solution of 10 mL (0.12 mol) of pyrrolidine and 100 mL of dichloromethane with stirring and cooling in an ice bath. After stirring 15 h at room temperature, the mixture was washed successively with 0.5 N HCl, water, aqueous $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and filtered and the solvent removed in vacuo. The residual product was crystallized twice from ethyl acetate–diisopropyl ether to give 10.3 g (55%) of (*Z*)-1-phenyl-1-(pyrrolidinocarbonyl)-2-(phthalimidomethyl)-cyclopropane: mp 104–106 °C; IR (KBr) 1765, 1710, 1625 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 3, cyclopropyl H), 1.8–2.2 (m, 4, CH_2CH_2), 2.9–4.1 (m, 6, CH_2N), 7.05 (m, 5, aromatic H), 7.85 (m, 4, aromatic H).

(*E*)-Ethyl 1-Phenyl-2-(phthalimidomethyl)cyclopropanecarboxylate. To a stirred solution of 10 g (0.045 mol) of (*E*)-ethyl 1-phenyl-2-(hydroxymethyl)cyclopropanecarboxylate and 25 mL of dried pyridine was added portionwise 9.1 g (0.048 mol) of *p*-toluenesulfonyl chloride with stirring and cooling in an ice bath. After 15 h at 5 °C, the mixture was combined with ice and extracted with Et_2O. The organic layer was washed twice with ice–water, dried over Na_2SO_4, and filtered. The solvent was removed under vacuo to give an oil. To this crude tosyl ester in 100 mL of dimethylformamide was added 9.25 g (0.05 mol) of potassium phthalimide, and the mixture was stirred under reflux for 1 h. After the mixture was cooled to room temperature, water was added and the crystalline product was filtered and dried to give 11 g (70%) of the title compound: mp 112–114 °C; IR (KBr) 1760, 1715, 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.1 (t, 3, CH_3), 1.6 (m, 2, cyclopropyl H), 2.15 (m, 1, cyclopropyl H), 2.6 (dd, 1, CHN), 3.8 (dd, 1, CHN), 4.0 (q, 2, CH_2), 7.25 (s, 5, aromatic H), 7.55 (m, 4, aromatic H).

(*E*)-Ethyl 1-Phenyl-2-[(dimethylamino)methyl]cyclopropanecarboxylate (21). To the crude tosyl ester obtained above from (*E*)-ethyl 1-pheny-2-(hydroxymethyl)cyclopropanecarboxylate was added 120 mL of 33% dimethylamine ethanolic solution and the mixture was kept at room temperature in a closed vessel overnight. After addition of ice and excess 2 N NaOH, the mixture was extracted with Et_2O, washed twice with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residual oil was acidified with an ethanolic HCl solution. The solid obtained was recrystallized from EtOH–Et_2O to give 8.8 g (75%) of **21**: mp 152–154 °C; IR (KBr) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.15 (t, 3, CH_3), 1.5–2.5 (m, 3, cyclopropyl H), 2.8 (s,

6, NCH_3), 3.3 (d, 2, CH_2N), 4.05 (q, 2, CH_2O), 7.25 (s, 5, aromatic H).

(Z)-Ethyl 1-Phenyl-2-[(methylamino)methyl]cyclopropanecarboxylate (5). The solution of 3.6 g (0.01 mol) of (Z-ethyl 1-phenyl-2-[(methylbenzylamino)methyl]cyclopropanecarboxylate in 40 mL of glacial acetic acid was stirred under hydrogen atmosphere at 80 °C for 1 h in a closed vessel in presence of 0.3 g of 10% palladium on charcoal. The cooled suspension was filtered and acetic acid was removed in vacuo. After addition of 5% aqueous $NaHCO_3$, the product was extracted with Et_2O, washed with water, dried over Na_2SO_4, and filtered. The residual oil was acidified with an ethanolic HCl solution. The solid obtained was recrystallized from EtOH–Et_2O to give 1.32 g (49%) of **5**: mp 132–134 °C; IR (KBr) 1710 cm^{-1} (C=O); ^1H NMR (D_2O) δ 1.2 (t, 3, CH_3), 1.5–2.2 (m, 3, cyclopropyl H), 2.9 (s, 3, NCH_3), 3.5 (dd, 2, CH_2N), 4.15 (q, 2, CH_2O), 7.4 (s, 5, aromatic H).

(Z)-1-Phenyl-2-[(acetylamino)methyl]-*N*,*N*-diethylcyclopropanecarboxamide (40). This compound was obtained in a 80% yield by acetylation of **25** with Ac_2O in pyridine at room temperature: IR (KBr) 1600, 1665 (C=O); ^1H NMR ($CDCl_3$) δ 0.8 (t, 3, CH_3), 1.15 (t, 3, CH_3), 1.5 (m, 3, cyclopropyl H), 1.95 (s, 3, CH_3CO), 2.6 (m, 1, CHN), 3.25 (m, 4, CH_2N), 3.8 (m, 1, CHN), 7.1 (m, 5, aromatic H).

(Z)-1-Phenyl-2-[(glycylamino)methyl]-*N*,*N*-diethylcyclopropanecarboxamide (41). To the solution of 2.46 g (0.01 mol) of **25** and 1.4 mL (0.01 mol) of triethylamine in 30 mL of dioxane was added dropwise with stirring in an ice bath 2.33 g (0.01 mol) of phthalimidoacetyl chloride in 5 mL of dioxane, and the suspension was kept at room temperature for 15 h. The solvent was removed in vacuo, and the residual material was poured into 0.5 N NaOH. The product was extracted with dichloromethane and washed successively with 0.5 N HCl and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. This crude product was treated without purification with 1 mL of hydrazine hydrate in 50 mL of ethyl alcohol under reflux for 2 h. The reaction mixture was concentrated to remove the solvent and treated with 80 mL 1 N HCl, and the insoluble material was filtered. To the cooled filtrate was added excess 6 N NaOH, and the product was extracted with EtOAc, washed with water, and dried over Na_2SO_4 and the solvent was removed in vacuo. The residual oil was crystallized twice in dichloromethane–isopropyl alcohol to give 1.88 g (62%) of **41**: mp 91–93 °C; IR (KBr) 1620, 1655 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.85 (t, 3, CH_3), 1.15 (t, 3, CH_3), 1.5 (m, 3, cyclopropyl H), 2.6–3.9 (m, 6, CH_2N), 3.25 (s, 2, CH_2CO), 7.1 (s, 5, aromatic H).

Pharmacology. Acute Toxicity. Groups of 10 mice (male, 20–26 g, Swiss strain, St. Denis, France) were administered the test compounds orally at various doses. LD_{50} (with 95% confidence limits) was defined as the dose that killed 50% of the animals 24 h after drug administration.

Antidepressant Activity. Potentiation of the yohimbine-induced mortality in mice was determined by the method of Quinton[14] as recently reevaluated by Malick.[15] The ED_{50} values, defined as the dose of test drug that killed 50% of the animals given a sublethal dose of yohimbine (25 mg/kg sc), were estimated (with 95% confidence limits) by probit analysis.[16]

Antagonism of tetrabenazine-induced ptosis in mice[17] was measured in mice pretreated orally at various doses of a test compound 30 min before the administration of tetrabenazine 40 mg/kg ip. The highest dose of test compound was 30 mg/kg. Thirty minutes after tetrabenazine, each mouse was scored for blepharoptosis and the degree of ptosis estimated on a scale from 0 to 2. The sum of these scores for each group of mice was expressed as a percentage and the ED_{50} (with 95% confidence limits) estimated by probit analysis.[16]

The potentiation of 5-hydroxytryptophan-induced behavior in mice was evaluated in mice according to Christensen.[18] The ED_{50} values (with 95% confidence limits), defined as the dose that induced half-maximal score of the 5HTP syndrome, were calculated by probit analysis.[16]

Mydriatic Properties. One drop (0.1 mL) of a 1% aqueous solution of test compound was instilled into the left eye of 10 mice, the right eye serving as a control. The pupillary diameters of both eyes were measured with a ocular micrometer. The average mydriasis was expressed as the percent increase of the diameter of the test pupil in comparison with that of the control pupil. One drop of a 0.01% solution of atropine produced 75% mydriasis.

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Registry No. 1, 69160-57-2; 1·HCl, 105310-28-9; 2, 105309-91-9; 2·HCl, 105310-29-0; 3, 105309-92-0; 3·HCl, 105310-30-3; 4, 105309-93-1; 4·HCl, 105310-31-4; 5, 105309-94-2; 5 (benzyl deriv.), 105310-94-9; 5·HCl, 85467-19-2; 6, 105309-95-3; 6·HCl, 85467-32-9; 7, 105309-96-4; 7 (acid), 105310-88-1; 7 (acid chloride), 105310-89-2; 7·HCl, 85467-58-9; 8, 105309-97-5; 8·HCl, 85467-68-1; 9, 105309-98-6; 9·HCl, 85467-77-2; 10, 105309-99-7; 10·HCl, 85467-80-7; 11, 85467-59-0; 11·fumarate, 85467-60-3; 12, 105310-00-7; 12·HCl, 85467-61-4; 13, 85467-64-7; 13·fumarate, 85467-65-8; 14, 85467-23-8; 14·maleate, 85467-24-9; 15, 85467-34-1; 15·maleate, 85467-35-2; 16, 105310-01-8; 16·HCl, 85467-17-0; 17, 85467-27-2; 17·fumarate, 85467-28-3; 18, 105310-02-9; 18·HCl, 85467-56-7; 19, 105310-03-0; 19·HCl, 85467-54-5; 20, 105310-04-1; 20·HCl, 105310-32-5; 21, 105310-05-2; 21·HCl, 105310-33-6; 22, 105310-06-3; 22·HCl, 105310-34-7; 23, 105310-07-4; 23·oxalate, 105310-35-8; 24, 105310-08-5; 24·HCl, 105335-53-3; 25, 105310-09-6; 25 (phthalimidoacetyl deriv.), 105310-95-0; 25·HCl, 86181-08-0; 26, 105310-10-9; 26·HCl, 105310-36-9; 27, 105310-11-0; 27·HCl, 105310-37-0; 28, 105310-12-1; 28·HCl, 105310-38-1; 29, 105310-13-2; 29·HCl, 105335-54-4; 30, 105310-14-3; 30·HCl, 105310-39-2; 31, 105310-15-4; 31·$^1/_2$ fumarate, 105310-40-5; 32, 105310-16-5; 32·oxalate, 105310-41-6; 33, 105310-17-6; 33·HCl, 105310-42-7; 34, 105310-18-7; 34·oxalate, 105310-43-8; 35, 105310-19-8; 35·oxalate, 105310-96-1; 36, 105310-20-1; 36·oxalate, 105310-44-9; 37 (isomer 1), 105310-21-2; 37 (isomer 2), 105370-66-9; 37·fumarate (isomer 1), 105370-64-7; 37·fumarate (isomer 2), 105452-26-4; 38 (isomer 1), 105310-22-3; 38 (isomer 2), 105370-65-8; 38·fumarate (isomer 1), 105370-61-4; 38·fumarate (isomer 2), 105370-67-0; 39, 105310-23-4; 39·oxalate, 105310-45-0; 40, 105310-24-5; 41, 105310-25-6; 42, 105310-26-7; 42 (bromoamide), 105310-90-5; 42·2HCl, 105310-46-1; 43, 105310-27-8; 43·HCl, 105310-47-2; I (X = H), 63106-93-4; I (X = *p*-Cl), 85467-85-2; I (X = *p*-F), 85467-93-2; I (X = *p*-OCh_3), 85467-91-0; I (X = *p*-CH_3), 85467-92-1; I (X = *o*-Cl), 105310-65-4; I (X = *m*-Cl), 85467-87-4; IV (X = H, R = CH_3, Y = Br), 105310-48-3; IV (X = H, R = C_2H_5, Y = Br), 105310-49-4; IV (X = H, R = C_3H_7, Y = Cl), 105310-50-7; IV (X = H, R = C_3H_7-*i*, Y = Cl), 105310-51-8; IV (X = *p*-Cl, R = C_2H_5, Y = Br), 105310-52-9; IV (X = *p*-Cl, R = C_3H_7-*i*, Y = Cl), 105310-53-0; IV (X = *p*-F, R = C_2H_5, Y = Cl), 105310-54-1; IV (X = *p*-OCH_3, R = C_2H_58 Y = Cl), 105310-55-2; IV (X = *p*-CH_3, R = C_3H_7-*i*, X = Br), 105310-56-3; V (X = H), 105310-57-4; V (X = H, acid), 69160-56-1; V (X = *p*-Cl), 105310-58-5; V (X = *p*-CH_3), 105310-59-6; IX (X = H), 69160-63-0; IX (X = *o*-Cl), 105310-60-9; IX (X = *m*-Cl), 105310-61-0; IX (X = *p*-Cl), 105310-62-1; IV (X = *p*-F), 105310-63-2; IX (X = *p*-CH_3), 105310-64-3; X (X = H), 105310-66-5; X (X = *o*-Cl), 105310-67-6; X (X = *m*-Cl), 105310-68-7; X (X = *p*-Cl), 105310-69-8; X (X = *p*-F), 105310-70-1; X (X = *p*-CH_3), 105310-71-2; XI (X = R_1 = R_2 = H), 105310-72-3; XI (X = H, acid chloride), 105310-91-6; XI (X = R_1 = H, R_2 = C_2H_5), 105310-73-4; XI (X = H, R_1 = R_2 = CH_3), 105310-74-5; XI (X = H, R_1 = R_2 = C_2H_5), 105310-75-6; XI (X = *o*-Cl, R_1 = R_2 = C_2H_5), 105310-76-7; XI (X = *m*-Cl, R_1 = R_2 = C_2H_5), 105310-77-8; XI (X = *p*-Cl, R_1 = R_2 = C_2H_5),

(14) Quinton, R. M. *Br. J. Pharmacol.* **1963**, *21*, 56.
(15) Malick, J. B. In *Antidepressants: Neurochemical, Behavioral and Clinical Perspectives* Enna, S. J; Malick, J. B., Richelson, E.; Raven: New York, 1981; pp 141–155.
(16) Carmines, E. L.; Carchman, R. A.; Borzelleca, J. F. *J. Environ. Pathol. Toxicol.* **1980**, *4*, 23.
(17) Howard, J. L.; Soroko, F. E.; Cooper, B. R. In *Antidepressants: Neurochemical, Behavioral and Clinical Perspectives*; Enna, S. J., Malick, J. B., Richelson, E., Eds.; Raven: New York, 1981; pp 107–120.
(18) Christensen, A. V.; Fjalland, B.; Pedersen, V.; Samsoe, P. D.; Svendsen, O. *Eur. J. Pharmacol.* **1977**, *41*, 153.

105310-78-9; **XI** (X = *p*-F, $R_1 = R_2 = C_2H_5$), 105310-79-0; **XI** (X = *p*-CH_3, $R_1 = R_2 = C_2H_5$), 105310-80-3; **XI** (X = H, $R_1 = R_2 = C_6H_7$), 105335-55-5; **XI** (X = H, $R_1 = R_2 = C_4H_9$), 105310-81-4; **XI** (X = H, $R_1 = R_2 = C_6H_{13}$), 105310-82-5; **XI** (X = H, $R_1 = C_2H_5$, $R_2 = (CH_2)_2OH$), 105310-83-6; **XI** (X = H, $R_1 = R_2 = C_6H_7$-*i*), 105310-84-7; **XI** (X = H, $R_1 = R_2 = (CH_2)_4$), 105310-85-8; *cis*-**XI** (X = H, $R_1 = R_2 = CH(CH_3)(CH_2)_2CH(CH_3)$), 105310-86-9; *trans*-**XI** (X = H, $R_1 = R_2 = CH(CH_3)(CH_2)_2CH(CH_3)$), 105370-62-5; *trans*-**XI** (X = H, $R_1 = R_2 = CH(CH_3)(CH_2)_3CH(CH_3)$), 105310-87-0; *cis*-**XI** (X = H, $R_1 = R_2 = CH(CH_3)(CH_2)_3CH(CH_3)$), 105370-63-6; **XIV**, 22613-97-4; **XIV** (tosyl ether), 105310-92-7; **VIV** (phthalimide deriv.), 105310-93-8; $H_3CNH(CH_2)_2C_6H_5$, 589-08-2; *N*-methylpiperazine, 109-01-3; phthalimidoacetyl chloride, 6780-38-7.

Supplementary Material Available: Tables containing physical properties of synthetic intermediates: (*Z*)-1-aryl-2-(halomethyl)cyclopropanecarboxylic acids esters (IV), (*Z*)-1-aryl-2-(phthalimidomethyl)cyclopropanecarboxylic acids esters (V), (*Z*)-1-aryl-2-(bromomethyl)cyclopropanecarboxylic acids (IX), (*Z*)-1-aryl-2-(bromomethyl)cyclopropanecarbonyl chlorides (X), (*Z*)-1-aryl-2-(phthalimidomethyl)cyclopropanecarboxamides (XI) (5 pages). Ordering information is given on any current masthead page.

Structure–Activity Relationships of Sparsomycin and Its Analogues. Inhibition of Peptide Bond Formation in Cell-Free Systems and of L1210 and Bacterial Cell Growth⊥

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The biological activity of 14 analogues of sparsomycin (**1**) was studied in cell-free systems of *Escherichia coli*, *Saccharomyces cerevisiae*, and *Sulfolobus solfataricus* by measuring the inhibition of protein synthesis. The inhibition of L1210 colony formation in soft agar and bacterial cell growth in solid as well as in liquid medium was also examined. Each analogue possesses not more than two structural modifications of the sparsomycin molecule. This enabled us to determine unambiguously several structural and stereochemical features that are required for an optimal biological activity in these assays. Sparsomycin, having the S_CR_S chirality, is the most potent of the four possible stereoisomers. The results obtained with compounds **5–7** indicate that the presence of an oxygen atom on the S(α) atom is essential. Substitution of the bivalent sulfur atom by a CH_2 group (**10**) or of the SCH_3 moiety by a Cl atom (**12**) affects the activity of the molecule partially. Compound **12** is surprisingly active against intact cells. Substitution of the C(6)-CH_3 group by a H (**14**) reduces the activity of the molecule. Isomerization of the trans double bond into the cis double bond yields *cis*-sparsomycin (**15**), which is inactive. The hydrophobic derivatives **8**, **9**, and **11** are considerably more active than sparsomycin; thus the ribosomal binding site for sparsomycin may have a hydrophobic character.

Sparsomycin (**1**)[1] is a potent inhibitor of protein synthesis, and there is ample evidence that its site of interaction is the larger ribosomal subunit, where it prevents peptide transfer by interfering with the peptidyl transferase center.[2–6] Sparsomycin has been shown to inhibit the interaction of substrates with the peptidyl transferase A site, while stimulating at the same time the binding of substrates at the P site. This mutual interaction might be due to an allosteric effect.[7] It was shown recently that the sulfoxide moiety of sparsomycin is important for its activity.[8,9] It was observed, moreover, that the proper oxidation state of the sulfur atom of sparsomycin is important for the enhanced inhibition of peptidyl transferase that is observed when *Escherichia coli* polysomes are preincubated with the drug; this effect was called the "preincubation effect".[8,10] It was proposed that a peptidyl transferase mediated Pummerer rearrangement of the sulfoxide moiety of sparsomycin is responsible for this preincubation effect.[8] This mechanistic rationale of the mode of action of sparsomycin was corroborated recently by studying the four possible stereoisomers of sparsomycin as inhibitors of peptide bond formation in *E. coli* polysomes.[11] It was found that only the S_CR_S stereoisomer (**1**) places the sulfoxide moiety in the same orientation as the nitrogen–carbon bond of the natural substrate, i.e., L-aminoacyl-tRNA, thus inducing the Pummerer rearrangement. This stresses the structural similarity of the drug and the natural substrate of peptidyl transferase.

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(1) Sparsomycin is a metabolite of *Streptomyces sparsogenes* (Argoudelis, A. D.; Herr, R. R. *Antimicrob. Agents Chemother.* **1962**, 780) and of *Streptomyces cuspidosporus* (Higashide, E.; Hasegawa, T.; Shibata, M.; Mizuno, K.; Akaide, H. *Takeda Kenkyusho Nempo* **1966**, *25*, 1; *Chem. Abstr.* **1967**, 66, 54238).
(2) Pestka, S. *Ann. Rev. Microbiol.* **1971**, *25*, 488.
(3) Vázquez, D. *FEBS Lett.* **1974**, *40*, S63.
(4) Vázquez, D. *Mol. Biol. Biochem. Biophys.* **1979**, 30.
(5) Pestka, S. In *Molecular Mechanisms of Protein Synthesis*; Weisbach, H., Pestka, S., Eds.; Academic: New York, 1977; pp 467–553.
(6) Goldberg, I. H. In *Antibiotics*; Hahn, F. E., Ed.; Springer-Verlag: Berlin, 1979; pp 264–271.
(7) Ottenheijm, H. C. J.; v.d. Broek, L. A. G. M.; Ballesta, J. P. G.; Zylicz, Z. In *Progress in Medicinal Chemistry*, Ellis, G. P., West, G. B., Eds.; Elsevier: Amsterdam, 1986; Vol. 23, pp 219–268.
(8) Flynn, G. A.; Ash, R. J. *Biochem. Biophys. Res. Commun.* **1983**, *114*, 1.
(9) Liskamp, R. M. J.; Colstee, J. H.; Ottenheijm, H. C. J.; Lelieveld, P.; Akkerman, W. *J. Med. Chem.* **1984**, *27*, 301.
(10) See also: Coutsogeorgopoulos, C.; Miller, J. T.; Hann, D. M. *Nucleic Acid Res.* **1975**, *2*, 1053, and ref 37.
(11) Ash, R. J.; Flynn, G. A.; Liskamp, R. M. J.; Ottenheijm, H. C. J. *Biochem. Biophys. Res. Commun.* **1984**, *125*, 784.

0022-2623/87/1830-0325$01.50/0