Synthesis and Pharmacological Evaluation of Some New Tetrahydroisoquinoline Derivatives Inhibiting Dopamine Uptake and/or Possessing a Dopaminomimetic Property

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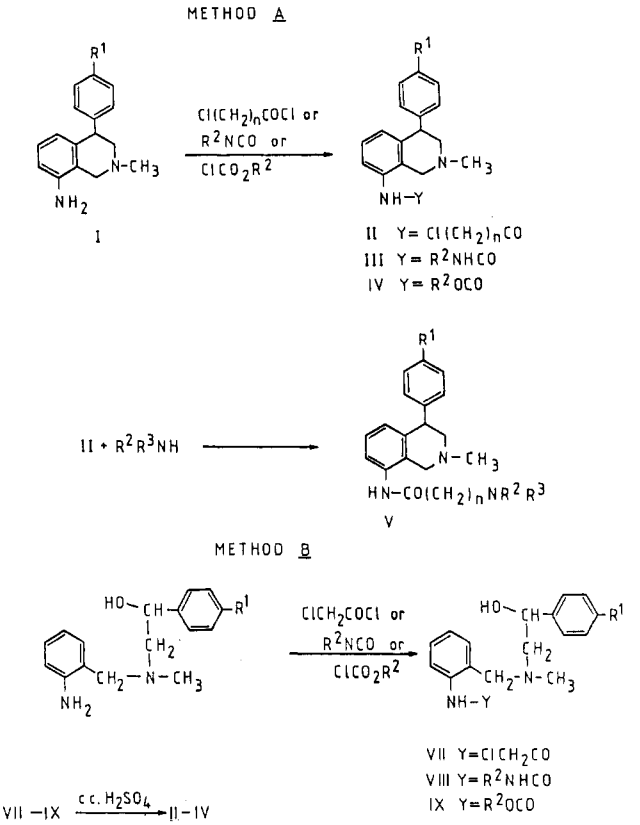
As shown by structure–activity relationship studies in 8-(substituted-amino)-4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines, the most important structural requirement for a marked antidepressant action is the presence of an ureido, (alkoxycarbonyl)amino, or [(alkylamino)acyl]amino group attached to the isoquinoline skeleton in position 8. In one of the biological tests a significant difference was found between 8-amino-4-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (nomifensine) and the new compounds synthesized. Nearly all compounds substituted in the amino group either decrease the spontaneous motility in mice or exert no effect on it. Two syntheses have been elaborated for the preparation of the compounds represented by the general formulas II–V where R^1 = hydrogen, halogen, or methyl; Y = CONHR, OCOR, or $CO(CH_2)_nNHR$, in which R = alkyl or aralkyl or NHR = cyclic amine and n = 1–2. The syntheses start either from the corresponding 8-amino-4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines or from the corresponding noncyclized amino alcohols. Of the compounds, 4-(*p*-chlorophenyl)-8-[(ethoxycarbonyl)amino]-2-methyl-1,2,3,4-tetrahydroisoquinoline was found to possess the highest activity.

Several natural alkaloids (e.g., salsolinol, salsolidine, bulbocapnine, emetine) contain the 1,2,3,4-tetrahydroisoquinoline skeleton. Some derivatives of tetrahydropapaveroline stimulate the dopamine-sensitive adenylate cyclase,[1] inducing circling behavior and stereotypy.[2] Nomifensine[3] is the 8-amino-2-methyl-4-phenyl derivative of 1,2,3,4-tetrahydroisoquinoline. It inhibits the neuronal uptake of dopamine and other catecholamines[4] and has dopaminomimetic activity, inducing stereotypy and circling behavior.[5]

One of the metabolites of nomifensine (I, R^1 = H), the 4′-hydroxy derivative (I, R^1 = OH), is also biologically active and has dopamine-like activity.[6] The 3′,4′-dihydroxy derivative activates the dopamine-sensitive adenylate cyclase,[7] dilates the canine renal vessels,[8] and is 6 times more potent at postsynaptic DA receptors than is the parent drug (measured by the displacement of ligand binding in vitro[9]). The clinical utility of nomifensine as an antidepressant has also been described.[10,11]

On the basis of these results, we assumed that the 4-aryl substituent and the 8-amino group have an important role in the central nervous activity. It was surprising that, although 8-amino-4-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline and its derivatives carrying hydroxyl groups in the C-4 phenyl group have been extensively investigated,

Scheme I



there are relatively few data available regarding other derivatives of the parent compound. Therefore, it was decided to investigate structure–activity relationships, and the effects of the following factors on the biological activity of these compounds have been studied: (a) substituents in the phenyl group at site 4; (b) acylation of the amino group with fatty acids and nonconventional acids, to obtain ω-chloroacyl, carbamoyl, and alkoxycarbonyl derivatives; and (c) formation of a more basic center by introducing the amino group into the side chain, preparing the (alkylamino)acyl derivatives.

Chemistry. The 8-(alkylcarbamoyl)amino, 8-(alkoxycarbonyl)amino, and 8-[(alkylamino)acyl]amino derivatives (III–V) were synthesized by two general methods shown in Scheme I. Method A started from the corresponding 8-amino-4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinoline (I, Table I), which was made to react with chloroacyl chloride,

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(9) Gianutsos, G.; Morrow, G.; Light, S.; Sweeney, M. J. *Pharmacol. Biochem. Behav.* **1982**, *17*, 951.
(10) Goldstein, B. J.; Brauzer, B.; Kentsmith, D.; Rosenthal, S.; Charalapous, K. D. *J. Clin. Psychiatry* **1984**, *45*(2), 52.
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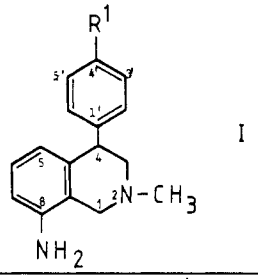
Table I. 8-Amino-4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines (I)

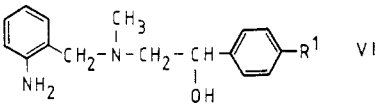


I

no.	R^1	mp,[a] °C	crystn solvent[b]	yield,[c] %	formula[d]
1	H	201[e]	MeOH	74	$C_{16}H_{18}N_2 \cdot C_4H_4O_4$[f]
2	Cl	130	B–PE	34	$C_{16}H_{17}ClN_2$
		212 dec[g]	EtOH	66	$C_{16}H_{17}ClN_2 \cdot C_4H_4O_4$[f]
3	F	183 dec	EtOH	62	$C_{16}H_{17}FN_2 \cdot C_4H_4O_4$[f]
4	Me	86–88	PE[h]	21	$C_{17}H_{20}N_2$
		212 dec	MeOH	30	$C_{17}H_{20}N_2 \cdot C_4H_4O_4$[f]
5	*i*-Pr	194 dec	EtOH	52	$C_{19}H_{24}N_2 \cdot C_4H_4O_4$

[a] Uncorrected melting points, capillary tube method. [b] B, benzene; PE, petroleum ether. [c] Yield of analytically pure material; yields were not optimized. [d] Analyses were obtained for C, H, N, and, when present, for Cl and F. Analytical results were within ±0.4 of the theoretical values. All compounds exhibited IR spectra consistent with the assigned structure. [e] Literature mp 199–201 °C (EtOH) (ref 3a); 194–196 °C (ref 12). [g] Literature mp 209–211 °C (EtOH) (ref 12). [f] Maleate salt. [h] Treated with PE.

Table II. *N*-(2-Aminobenzyl)-1-aryl-2-(methylamino)-1-ethanol Derivatives (VI)

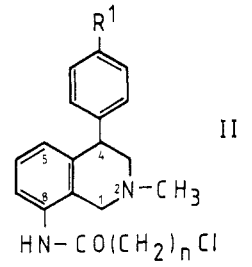


VI

no.	R^1	mp,[a] °C	crystn solvent[b]	yield,[c] %	formula[d]
6	H	72[e]	EtOH–H_2O	87	$C_{16}H_{20}N_2O$
7	Cl	78	B–PE	80	$C_{16}H_{19}ClN_2O$
8	F	62	P	70	$C_{16}H_{19}FN_2O$
9	Me	85	B–PE	73	$C_{17}H_{22}N_2O$
10	*i*-Pr	58	PE[f]	38	$C_{19}H_{26}N_2O$

[a,c,d] See footnotes a, c, and d, respectively, in Table I. [b] P, petrol, and see footnote in Table I. [e] Literature mp 67–69 °C (ref 3a). [f] Treated with PE.

Table III. 4-Aryl-8-[(chloroacyl)amino]-2-methyl-1,2,3,4-tetrahydroisoquinolines (II)



II

compd. no.	R^1	*n*	mp,[a] °C	crystn solvent	yield,[b] %	formula[c]	method
11	H	1	240 dec		42	$C_{18}H_{19}ClN_2O$	
			222 dec	EtOH	81	$C_{18}H_{19}ClN_2O \cdot HCl$	A
			222 dec	EtOH	38	$C_{18}H_{19}ClN_2O \cdot HCl$	B
12	H	2	220 dec	EtOH–Et_2O	60	$C_{19}H_{21}ClN_2O \cdot HCl$	A
13	Cl	1	220 dec		91	$C_{18}H_{18}Cl_2N_2O \cdot HCl$	A
14	Me	1	228 dec		92	$C_{19}H_{21}ClN_2O \cdot HCl$	A

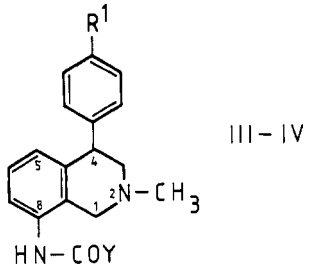
[a] See footnote *a* in Table I. [b] See footnote *c* in Table I. [c] See footnote *d* in Table I.

alkyl isocyanate, or alkyl chloroformate. The resulting chloroacyl derivatives reacted with an amine in the subsequent step to furnish the N-substituted derivatives desired. According to Method B, the amino alcohols VI (Table II) underwent reaction with chloroacetyl chloride, alkyl isocyanate, or ethyl chloroformate at the amino group, and the crude derivatives VII–IX obtained in this way were subjected to cyclization catalyzed by sulfuric acid to yield compounds II–IV.

The starting materials in method A, 8-amino-4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines (I), were synthesized according to literature descriptions or analogies[3a] starting from substituted 2-bromoacetophenones (X) and *N*-methyl-2-nitrobenzylamine (Scheme II). The carbonyl group of the ketone XI obtained in the first step was reduced with $NaBH_4$ to a hydroxyl group; then the nitro group was reduced to an amino group in the presence of Raney nickel catalyst to give the amino alcohols VI (Table II). Intramolecular alkylation of VI, catalyzed by sulfuric acid, furnished the compounds with tetrahydroisoquinoline ring. Data of the derivatives II–IV are summarized in Tables III–V.

Structure–Activity Relationships. Table VI (parts 1 and 2) shows the biological activities of compounds 1–38.

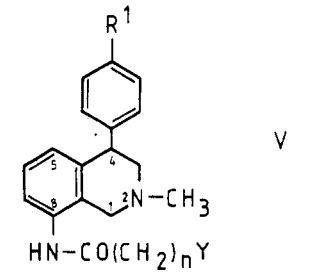
Table IV. 4-Aryl-8-(ureido)-2-methyl-1,2,3,4-tetrahydroisoquinolines (III) and 8-[(Alkoxycarbonyl)amino]-4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines (IV)



					III–IV		
no.	R^1	Y	mp,[a] °C	crystn solvent	yield,[b] %	formula[c]	method
15	H	EtNH	140 dec	EtOH	77	$C_{19}H_{23}N_3O \cdot C_4H_4O_4$[d]	A
16	H	PrNH	149–150	EtOH–Et_2O	53	$C_{20}H_{25}N_3O \cdot C_4H_4O_4$[d]	A
17	H	BuNH	145	EtOH–Et_2O	42	$C_{21}H_{27}N_3O \cdot C_4H_4O_4$[d]	A
			145	EtOH–Et_2O	61	$C_{21}H_{27}N_3O \cdot C_4H_4O_4$[d]	B
18	Cl	BuNH	165		60	$C_{21}H_{26}ClN_3O$	A
			134	EtOH–Et_2O	32	$C_{21}H_{26}ClN_3O \cdot C_4H_4O_4$[d]	
19	Me	BuNH	169 dec	EtOH–Et_2O	42	$C_{22}H_{29}N_3O \cdot C_4H_4O_4$[d]	A
20	H	EtO	178	EtOH	55	$C_{19}H_{22}N_2O_2$	A
			174	EtOH	65	$C_{19}H_{22}N_2O_2$	B
21	Cl	EtO	155	EtOH	46	$C_{19}H_{21}ClN_2O_2$	A
			145–150 dec	EtOH–Et_2O	45	$C_{19}H_{21}ClN_2O_2 \cdot HCl$	
22	F	EtO	163	EtOH	72	$C_{19}H_{21}FN_2O_2$	B
23	H	BuO	106	EtOH	53	$C_{21}H_{26}N_2O_2$	A
24	H	$PhCH_2O$	147–148	EtOH	49	$C_{24}H_{24}N_2O_2$	A
			166–167	EtOH	40	$C_{24}H_{24}N_2O_2 \cdot C_4H_4O_4$[d]	
25	H	$Cl(CH_2)_2O$	154	EtOH	52	$C_{19}H_{21}ClN_2O_2$	A

[a] See footnote *a* in Table I. [b] See footnote *c* in Table I. [c] See footnote *d* in Table I. [d] Maleate salt.

Table V. 8-[[(Alkylamino)acyl]amino]-4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines (V)



no.	R^1	Y	*n*	mp,[a] °C	crystn solvent[b]	yield,[c] %	formula[d]
26	H	NHEt	1	111	B–PE	80	$C_{25}H_{25}N_3O$
				170	Et–H	71	$C_{25}H_{25}N_3O \cdot C_4H_4O_4$[e]
27	H	NH-*i*-Pr	1	91	B–PE	76	$C_{21}H_{27}N_3O$
				134	EtOH	63	$C_{21}H_{27}N_3O \cdot C_4H_4O_4$[e]
28	H	NHBu	1	174	EtOH	49	$C_{22}H_{29}N_3O \cdot C_4H_4O_4$[e]
29	H	NHEt	2	162	EtOH	47	$C_{21}H_{27}N_3O \cdot C_4H_4O_4$[e]
30	H	NH-*i*-Pr	2	158	EtOH	77	$C_{22}H_{29}N_3O \cdot C_4H_4O_4$[e]
31	H	NHBu	2	147	EtOH	72	$C_{23}H_{31}N_3O \cdot C_4H_4O_4$[e]
32	H	C_4H_8N[f]	1	130	Et_2O–PE	77	$C_{22}H_{27}N_3O$
				120	EtOH–Et_2O	63	$C_{22}H_{27}N_3O \cdot 2C_4H_4O_4$[e]
33	H	$C_5H_{10}N$[g]	1	150–165	EtOH–Et_2O	61	$C_{23}H_{29}N_3O \cdot 2C_4H_4O_4$[e]
34	H	C_4H_8NO[h]	1	120	Et_2O–PE	70	$C_{22}H_{27}N_3O_2$
				176	EtOH	58	$C_{22}H_{27}N_3O_2 \cdot 2C_4H_4O_4$[e]
35	Cl	NHEt	1	189	EtOH	65	$C_{20}H_{24}ClN_3O \cdot C_4H_4O_4$[e]
36	Cl	NHBu	1	152	EtOH	57	$C_{22}H_{28}ClN_3O \cdot C_4H_4O_4$[e]
37	Me	NHEt	1	176 (dec)	EtOH–Et_2O	66	$C_{21}H_{27}N_3O \cdot C_4H_4O_4$[e]
38	Me	NHBu	1	172 (dec)	EtOH–Et_2O	92	$C_{23}H_{31}N_3O \cdot C_4H_4O_4$[e]

[a,b,c,d] See footnotes *a*, *b*, *c*, and *d*, respectively, in Table I. [e] Maleate salt. [f] C_4H_8N, 1-pyrrolidinyl. [g] $C_5H_{10}N$, piperidino. [h] C_4H_8NO, morpholino.

Three methods were used for the evaluation of the potential dopaminomimetic activity (antihaloperidol activity, stereotypy, circling behavior), five methods to obtain knowledge on the antidepressant-like activities (anti-tetrabenazine, antireserpine, dopamine-potentiating and amine-uptake inhibitory activities), and two methods for the examination of side effects (spontaneous motility and amphetamine-induced motility).

Substitution of the 4′-hydrogen in the phenyl ring by chloro or fluoro atoms or by a methyl group (**2–4**) enhances the activity of most compounds as compared with the parent compound **1**; the isopropyl substituent (**5**) has an opposite effect.

Substitution of the 8-amino group by (butylcarbamoyl)amino- (**17**), (ethylamino)acetyl- (**26**), or (butylamino)acetyl- (**28**) group results in a reduced efficacy.

Table VI. Comparison of the Pharmacological Activities

Part 1

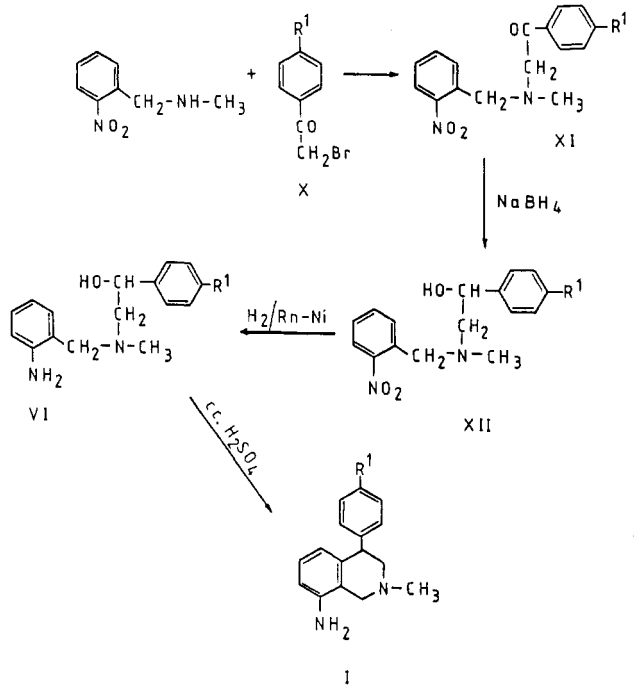
no.	lethal[a] dose (LD_{50}) in mice	inhibitory doses in mice, mg/kg, sc[a] haloperidol catalepsy (ED_{50})	tetrabenazine catalepsy (ED_{50})	tetrabenazine ptosis (ED_{50})
1	336 (263–430)	17 (11–25)	13 (9–18)	1.6 (1.2–2.2)
2	240 (201–287)	1.5 (0.8–2.8)	1.6 (0.95–2.5)	1.1 (0.8–1.4)
3	222 (208–237)	7.5 (4.3–13)	~3.6	0.25 (0.16–0.39)
4	800 (541–1182)	~22	1.6 (1.2–2.2)	~1.2
5	1100 (886–1366)	~65	>80	68 (47–98)
11	94 (80–110)	~10	10 (7–14)	3 (1.7–5.4)
12	89 (78–101)	19 (13–27)	>30	8.8 (6.2–12)
15	290 (260–323)	>80	80	54 (32–90)
16	455 (418–496)	>120	>80	>80
17	430 (333–555)	69 (49–96)	~40	23 (15–35)
18	>1000	~120	44 (26–74)	15 (7.5–30)
19	>1200	>100	40 (29–56)	~15
20	71 (59–85)	2.5 (1.8–3.5)	3.2 (1.9–5.5)	~4
21	830 (696–990)	21 (15–29)	4.8 (3.7–6.3)	0.6 (0.3–1.1)
22	255 (229–283)	4.6 (2.8–7.5)	3.5 (1.9–6.5)	3.3 (2.1–5.1)
23	180 (145–223)	12 (7.8–18)	4 (2.9–5.5)	2.6 (1.6–4.3)
24	>1000	25 (18–35)	~15	16 (8.3–31)
25	160 (140–183)	11 (7.7–15.7)	9 (7.3–11)	2.5 (1.5–4.2)
26	320 (262–390)	~60	47 (33–67)	
27	300 (241–374)	~30	14 (8–25)	
28	240 (195–295)	25 (13–48)	32 (19–55)	
29	720 (666–778)	190 (127–284)	>200	>160
30	900 (755–1072)	~200	150 (96–234)	~125
31	292 (258–330)	>60	~46	74 (54–102)
32	380 (320–451)	45 (30–68)	39 (29–52)	~25
33	520 (430–629)	~60	~65	
34	295 (270–322)	>60	39 (26–59)	
35	325 (251–421)	~25	24 (14–41)	6.4 (5.0–8.1)
36	320 (246–417)	22 (13–39)	13.5 (8.8–21)	3.9 (2.5–6.0)
37	320 (256–400)	~15	~45	5.6 (3.1–10.1)
38	320 (262–390)	14 (8.1–24)	34 (18–63)	~2.5

Part 2

no.	inhibitory doses in mice, reserpine hypothermia (ED_{min}), mg/kg, sc	doses inducing stereotypy in rats (ED_{min}), mg/kg, sc	doses influencing (+ or −) the motility in mice (ED_{min}), mg/kg, ip: spontaneous	doses influencing (+ or −) the motility in mice (ED_{min}), mg/kg, ip: amphetamine induced	doses potentiating the dopamine-induced hypotension in cats (ED_{min}), mg/kg, iv	concentrations inhibiting the uptake of dopamine noradrenaline on synaptosome preparations: M/L	concentrations inhibiting the uptake of dopamine noradrenaline on synaptosome preparations: M/L
1	10	7.4	10+	>5	0.5	2.6×10^{-8}	1.2×10^{-8}
2	2	5	10+	5−	0.2	8.0×10^{-7}	
3	2	8	5−	10−	0.2	9.0×10^{-8}	1.0×10^{-8}
4	2	12.8	15+	10−	0.2		
5	50	8	80−	80−	2.0	1.0×10^{-5}	2.4×10^{-6}
11	>30	8	20+	10−	1.0		
12	>30	20.5	>30	>15	1.0		
15	40	>83	80−	40+	6.0		
16	>60	>83	>80	80−	10.0		
17	>40	>83	80−	80−	2.0		
18	>100	134	15−	>30	3.0		
19	20	83	20−	20+	>5.0		
20	2	>12.8	>8	4−		5.1×10^{-6}	5.5×10^{-8}
21	10	5.2	3−	20−	0.5	6.7×10^{-7}	0.9×10^{-8}
22	10	8.0	20−	5−	2.0	3.2×10^{-6}	5.3×10^{-8}
23	20	20.5	5−	>5	2.0		
24	20	12	100−	100−	>5.0		
25	20	>20.5	>20	5−	2.0		
26	60	52.4	>60	>30	2.0		
27	20	>52.4	30+	>30	1.0		
28	>40	32.8	15+	>30	2.0		
29	200	134	160−	>160	4.0		
30	200	>83	160−	160−	2.0		
31	>40	>83	>80	>80	>5.0		
32	50	52.4	120−	>120	3.0		
33	20	>83	>100	>60	3.5		
34	20	83	60−	60+	3.0		
35	5	32.8	20−	>20	0.5		
36	5	32.8	>20	>20	0.5		
37	20	>83	10−	>10	1.5		
38	10	52.4	5−	>10	1.0		

[a] Numbers in parentheses are 95% confidence limits.

Scheme II



When, however, a halogen atom or a methyl group is attached to the para position of the 4-phenyl group (**18**, **19**, **35–38**), the activity of the compounds is increased with some exceptions (**18**, **19**), but still does not reach that of the parent compound (**1**).

Substitution of the 8-amino group by (ethoxycarbonyl)amino (**20**) results in increased efficacy of the compound; however, the toxicity is also higher. When this molecule contains a *p*-chloro substituent in the 4-phenyl group (**21**), toxicity decreased to one-tenth of that of compound **20** and the pharmacological activity remained very strong. The activities of compound **20** in mice appear at 2.4–5.6% of the sc lethal dose; these values of **21** vary between 0.07% and 2.5%.

In one test, a significant difference was found between nomifensine and the analogues that we synthesized. While nomifensine increases spontaneous motility in mice, most compounds substituted in the amino group—except for the compounds **2**, **4**, **11**, **27**, and **28**—either decrease or exert no effect on spontaneous motility.

Their activity, low toxicity, and the lack of the hypermotility-inducing effect (characteristic of psychostimulants) make these compounds—or at least compound **21**—promising potential antidepressant drugs.

A clear differentiation of the effects of substituents upon antidepressant and dopaminomimetic activity was not established. A correlation between these activities was observed.

Experimental Section

Biological Methods. The experiments were performed in randomly treated CFLP (Swiss) male mice (Laboratory Animals Institute—Chinoin, Gödöllö, Hungary), weighing 18–22 g. Catalepsy was tested on a vertical grid; haloperidol (5 mg/kg, 60 min) or tetrabenazine (25 mg/kg, 30 min before testing) were administered intraperitoneally. Ptosis was evaluated by a person having no knowledge of the treatment. Tetrabenazine (35 mg/kg, −20 min) was administered ip. Rectal temperature was measured by a thermistor probe, and reserpine (1 mg/kg, 3 h before testing) was given ip. Motility was measured in an apparatus that works by closing an electric circuit when the animal passes between certain points,[13] and (±)-amphetamine (7.5 mg/kg, 5 min before placing the mice into the apparatus) was administered subcutaneously. The new compounds were administered 15 or 30 min before testing; the number of animals was 10/group.

Stereotypy was observed in CFY (Sprague–Dawley) male rats (from the same source as the mice). The animals showing the phenomenon were put in a Varimex activity meter (Columbus Instruments), and the doses inducing a 5 times higher motility than the control were determined. The dopamine-induced hypotension was examined in chloralose–urethane anesthetized cats; the threshold iv doses of the compounds were determined, which increased the dopamine-induced hypotension (15–20 mmHg) at least 50%.

Uptake of noradrenaline was estimated by using a crude synaptosomal fraction from rat brain hypothalami, as described by Komiskey et al.[14]

The accumulation of dopamine in rat striatal synaptosomes was measured according to the method described by Hyttel.[15]

Most compounds were dissolved in physiological saline, several of them (**3**, **20**, **22**, **25**) in the presence of an equimolar amount of hydrochloric acid. Compounds **5** and **25** could be dissolved only in Tween-80; in the case of the derivatives **2**, **4**, **18**, **19**, **26**, **28**, **36**, and **38** Tween-80 was needed for the lethal-dose determinations only. For dissolving compound **23** maleic acid and Tween-80 were added. The different solvents were administered to the control animals.

Chemistry. 8-Amino-2-methyl-4-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline (4). *N*-(2-Aminobenzyl)-2-(methylamino)-1-(4′-tolyl)-1-ethanol (**9**) (18.3 g, 0.067 mol) was dissolved in dichloromethane (150 mL). Concentrated H_2SO_4 (100 mL) was added over 15 min under cooling in ice to 6–8 °C and with vigorous stirring. The reaction mixture was then stirred further at 6–8 °C for 30 min. It was then poured into ice–water (450 g) and made alkaline with 30% NaOH solution (500 mL) while cooling in ice and stirring. The oil that separated was extracted repeatedly with ether (1000 mL); the ethereal solution was dried and evaporated to dryness in vacuum to leave a viscous brown foam (18 g). This was dissolved in ethanol (300 mL) and treated with a solution of maleic acid (10 g, 0.086 mol) in ethanol (20 mL). After cooling, the salt which separated was collected by filtration and washed with ethanol, acetone, and ether (20–20 mL) to obtain an orange powder (14.4 g): mp 207 °C dec. Two recrystallizations from 50-fold amounts of methanol gave yellow crystals (7.7 g, 30%): mp 212 °C dec. Compounds **1–5** were prepared similarly.

***N*-(2-Aminobenzyl)-2-(methylamino)-1-(4′-tolyl)-1-ethanol (9).** *N*-(2-Nitrobenzyl)-2-(methylamino)-1-(4′-tolyl)-1-ethanol (XII, $R^1 = CH_3$; 55.6 g, 0.185 mol) was dissolved in ethanol (400 mL). In the presence of Raney nickel catalyst (10 g), prehydrated in ethanol (80 mL), the mixture was hydrogenated under atmospheric pressure until absorption of the calculated amount of hydrogen occurred (12 h). The reaction mixture was filtered on an activated carbon bed, evaporated to dryness, and rubbed with petroleum ether (5 × 100 mL), whereby it solidified to a white fluffy substance (36.1 g, 73%): mp 83 °C. Recrystallization from benzene–petroleum ether gave white crystals: mp 85 °C. Compounds **6–10** were prepared similarly.

***N*-(2-Nitrobenzyl)-2-(methylamino)-1-(4′-tolyl)-1-ethanol (XII).** 2-[*N*-Methyl-*N*-(2-nitrobenzyl)]-amino-*p*-methylacetophenone (XI, $R^1 = CH_3$; 126 g, 0.42 mol) was dissolved in methanol (1200 mL). A solution of $NaBH_4$ (18 g, 0.47 mol) in water (100 mL) was added dropwise at 25–30 °C, with stirring and cooling, and the mixture was then stirred further at room temperature for 4 h. The solvent was evaporated and the residual crystalline mass rapidly heated to boiling in water (350 mL) and refluxed for 3 min. It was quickly cooled and extracted with ether (5 × 200 mL). The extract was dried and the solvent evaporated. The residual orange solid (120 g) was dissolved in benzene (300 mL) and subjected to chromatographic separation on a silica gel 40 column (100 g). The benzene eluate (1500 mL) was evaporated to leave a yellowish oil (113 g, 89.7%). Yellow crystals were

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obtained from ethanol: mp 73 °C. Anal. ($C_{17}H_{20}N_2O_3$) C, H, N.

The following compounds were synthesized in a similar manner: *N*-(2-nitrobenzyl)-2-(methylamino)-1-phenyl-1-ethanol. (88%, oil). Anal. ($C_{16}H_{18}N_2O_3$) C, H, N; *N*-(2-nitrobenzyl)-2-(methylamino)-1-(4′-chlorophenyl)-1-ethanol (70%); mp 80 °C (EtOH and benzene–petroleum ether). Anal. ($C_{16}H_{17}ClN_2O_3$) C, H, N, Cl; *N*-(2-nitrobenzyl)-2-(methylamino)-1-(4′-cumyl)-1-ethanol (65%, oil). Anal. ($C_{19}H_{24}N_2O_3$) C, H, N; *N*-(2-nitrobenzyl)-2-(methylamino)-1-(4′-fluorophenyl)-1-ethanol (74%): mp 74 °C (benzene–petroleum ether). Anal. ($C_{16}H_{17}FN_2O_3$) C, H, N, F.

2-[*N*-Methyl-*N*-(2-nitrobenzyl)amino]-4′-methylacetophenone (XI, $R^1 = CH_3$). *N*-(2-Nitrobenzyl)methylamine (73 g, 0.44 mol) was dissolved in anhydrous ether (1000 mL). Anhydrous triethylamine (60 mL) and then 2-bromo-*p*-methylacetophenone (94 g, 0.44 mol) were added to the solution at 15–18 °C, with stirring and cooling. The reaction mixture was stirred for 4 h at 18–25 °C and allowed to stand at room temperature overnight, and the separated salt was collected by filtration and washed with ether (4 × 200 mL). The washing liquor and the filtrate were combined and evaporated to dryness. The residual brown oil (135.3 g) was dissolved in benzene (130 mL) and subjected to chromatographic separation. After evaporation of the solvent from the eluate obtained with benzene (1000 mL), yellow oil remained (118 g, 97%). Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

The following compounds were synthesized in a similar manner: 2-[*N*-methyl-*N*-(2-nitrobenzyl)amino]acetophenone (93%, oil). Anal. ($C_{16}H_{16}N_2O_3$) C, H, N. Hydrochloride: $C_{16}H_{16}N_2O_3$·HCl, mp 173 °C (lit[12] mp 165–167 °C). 2-[*N*-Methyl-*N*-(2-nitrobenzyl)amino]-(4′-chloroacetophenone) (94%, oil). Anal. ($C_{16}H_{15}ClN_2O_3$) C, H, N, Cl. The hydrochloride was crystallized from acetone: mp 169 °C. Anal. ($C_{16}H_{15}ClN_2O_3$·HCl) C, H, N, Cl. 2-[*N*-Methyl-*N*-(2-nitrobenzyl)amino]-4′-isopropylacetophenone (86%, oil). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N. 2-[*N*-Methyl-*N*-(2-nitrobenzyl)amino]-4′-fluoroacetophenone (63%, oil). Anal. ($C_{16}H_{15}FN_2O_3$) C, H, N, F.

4-Phenyl-8-[(chloroacetyl)amino]-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11). Method A. 8-Amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline maleate (**1**) (31.9 g, 0.09 mol) was dissolved in water (200 mL). Ether was added (500 mL) to the mixture, and it was made alkaline with 30% NaOH solution (150 mL) under vigorous stirring and cooling in ice. The ethereal phase was separated and the aqueous phase extracted with ether (3 × 300 mL). The combined ethereal solutions were dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuum (25 °C/2.7 kPa). The residual yellowish oil (22.5 g) was dissolved in anhydrous benzene (600 mL), and a solution of chloroacetyl chloride (7.6 mL, 11.4 g, 0.101 mol) in anhydrous benzene (40 mL) was added dropwise, with stirring. The reaction mixture was then stirred for 2 h. After cooling, the substance which separated was collected and washed with anhydrous benzene (3 × 60 mL) and with anhydrous ether (3 × 70 mL) to yield a white powder (32 g): mp 217 °C dec. Recrystallization from ethanol (230 mL) gave a white powderlike substance (25.5 g, 81%): mp 222 °C dec.

Method B. *N*-(2-Aminobenzyl)-2-(methylamino)-1-phenyl-1-ethanol (**6**) (3.12 g, 0.012 mol) was dissolved in anhydrous ether (70 mL). Anhydrous pyridine (0.95 g, 0.012 mol) and then chloroacetyl chloride (1.62 g, 0.0144 mol) were added at 3–6 °C, with cooling in ice and vigorous stirring. The yellowish white precipitate-containing reaction mixture was stirred at room temperature for 30 min. It was then poured into ice water (100 mL) and extracted with ether (3 × 100 mL). The ethereal solution was dried over anhydrous Na_2SO_4 for 30 min. It was then evaporated to dryness in vacuum, without heating, to leave an orange oil (4.2 g). The crude *N*-chloroacetyl derivative obtained in this way was directly subjected to cyclization. The oil was dissolved in dichloromethane (30 mL), filtered, added dropwise to concentrated H_2SO_4 (20 mL) with cooling and stirring at 0–3 °C over 15 min, and then stirred further at the given temperature for 20 min. The reaction mixture was poured onto ice (100 g) and extracted with chloroform (4 × 200 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuum to obtain an orange powder (3.0 g), which, after washing with ether (3 × 30 mL), gave a beige powder (2.3 g). After recrystallization from ethanol, a white powder was obtained (1.6 g, 46.4%): mp 240 °C dec.

The base (1.5 g, 0.0047 mol) was suspended in ethanol (25 mL) and mixed with ether saturated with hydrogen chloride (5 mL) while cooling, and the solution was then made opaque by the addition of ether (50 mL). The substance separated and was collected after cooling to obtain a white powder (1.5 g): mp 222 °C dec. Total yield was 38.2%.

Compounds **12–14** (Table III) were prepared in a similar manner by use of the corresponding chloroacyl chlorides.

8-[(Butylcarbamoyl)amino]-4-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline Maleate (17). Method A. 8-Amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**) (2.38 g, 0.01 mol) was refluxed with butyl isocyanate (1.10 g, 0.011 mol) in anhydrous benzene (24 mL) for 2 h. The reaction mixture was then evaporated to dryness in vacuum. The residual yellow oil (3.5 g) was dissolved in chloroform (35 mL), transferred onto a column packed with silica gel 40 (60 g) in carbon tetrachloride, and eluted with a 1:9 mixture of ethanol and chloroform (300 mL). The eluate was evaporated to dryness in vacuum to obtain a yellow oil (3.2 g). This was dissolved in ethanol (30 mL), treated with a solution of maleic acid (2 g, 0.017 mol) in ethanol (20 mL), and diluted with ether (800 mL). The substance separated on cooling and was collected. The yellow powder (2.6 g) was recrystallized from a mixture of ethanol (40 mL) and ether (200 mL) to yield a white powder (1.9 g, 42%): mp 145 °C (dec).

Method B. *N*-(2-Aminobenzyl)-1-phenyl-2-(methylamino)-1-ethanol (**6**) (5.2 g, 0.02 mol) was refluxed with butyl isocyanate (2.2 g, 0.022 mol) in anhydrous benzene (100 mL) for 2 h. The reaction mixture was then evaporated to dryness in vacuum to yield a grayish oil (7.2 g), which solidified on standing. The crude *N*-carbamoyl derivative obtained in this way was directly subjected to cyclization. The solidified substance (7.2 g) was dissolved in dichloromethane (100 mL) and added dropwise to concentrated H_2SO_4 (4.4 mL) at 2–6 °C with cooling and stirring over 45 min, and the reaction mixture was stirred further at 6 °C for 30 min. It was then poured onto ice (100 g), made alkaline with 30% NaOH solution, and extracted with chloroform (4 × 100 mL). The chloroform solution was dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuum to leave a yellowish white solid (5.4 g). This was dissolved in ethanol (30 mL), treated with maleic acid (2.75 g, 0.0235 mol), and mixed with ether (300 mL) gradually. The substance that separated after cooling was collected to afford a yellowish white substance (6.8 g), which upon recrystallization from ethanol–ether gave a white powder (6.0 g, 61.6%): mp 145 °C.

Compounds **15–19** were prepared similarly by employing the corresponding isocyanates.

8-[(Ethoxycarbonyl)amino]-4-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (20). Method A. 8-Amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (5.5 g, 0.023 mol) in anhydrous benzene (55 mL) was refluxed for 3 h with a solution of ethyl chloroformate (3.4 g, 0.031 mol) in anhydrous benzene (30 mL). The solvent was evaporated in vacuum and the residue dissolved in water (5 mL). The solution was made alkaline with 30% NaOH with cooling and extracted with chloroform (3 × 50 mL). The chloroform solution was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was washed with cold ethanol then recrystallized from ethanol to furnish white crystals (4.4 g): mp 178 °C.

Method B. A solution of *N*-(2-aminobenzyl)-2-(methylamino)-1-phenyl-1-ethanol (**6**) (2.6 g, 0.01 mol) and anhydrous pyridine (0.79 g, 0.01 mol) in ether (30 mL) was treated with ethyl chloroformate (1.0 g, 0.012 mol) at 15 °C with cooling in ice and vigorous stirring. The reaction mixture (white precipitate) was stirred at room temperature for 30 min. It was then poured into ice–water (30 mL). The aqueous phase was extracted with ether (3 × 100 mL) and dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuum to leave a yellowish white oil (2.8 g). The resulting crude *N*-acyl derivative was directly subjected to cyclization. The oily residue (2.8 g) in dichloromethane (40 mL) was added dropwise to concentrated H_2SO_4 (15.4 mL) at 5–6 °C with cooling and stirring over 30 min, and stirring was continued at the given temperature for 20 min more. The mixture was then poured onto ice (60 g) and made alkaline with 30% NaOH solution, while being cooled and stirred. It was extracted with chloroform (6 × 80 mL), and the organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuum to give

a yellowish white solid (2.3 g). This was recrystallized from ethanol to yield white crystals (2.0 g): mp 174 °C.

Compounds **21–24** were prepared as given for **20**. During the preparation of compound **24**, the reaction mixture was stirred for 2 h at room temperature.

4-Phenyl-8-[[(β-chloroethoxy)carbonyl]amino]-2-methyl-1,2,3,4-tetrahydroisoquinoline (25). Method A. 8-Amino-4-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (3.5 g, 0.015 mol) was dissolved in anhydrous benzene (100 mL) and mixed with anhydrous pyridine (1.28 g, 0.016 mol), and then a solution of β-chloroethyl chloroformate (2.14 g, 0.015 mol) in anhydrous benzene (10 mL) was added dropwise at room temperature, with stirring and cooling. The reaction mixture was stirred at room temperature for 1 h. It was then poured into ice–water (50 mL), and the organic phase was separated and the aqueous phase extracted with benzene (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 then evaporated to dryness in vacuum to obtain a yellowish white substance (4.5 g). Two recrystallizations from ethanol gave white crystals (2.7 g, 52%): mp 154 °C.

8-[[(Ethylamino)acetyl]amino]-4-phenyl-1,2,3,4-tetrahydroisoquinoline Maleate (26). A mixture of 4-phenyl-8-[(chloroacetyl)amino]-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**11**) (5.3 g, 0.015 mol) and ethylamine (15 mL, 10.4 g, 0.23 mol) in ethanol (50 mL) was heated in a bomb tube at 60 °C for 5 h. The reaction mixture was evaporated to dryness, and the residual yellow oil (7.1 g) was rubbed with water (50 mL), made alkaline with 30% NaOH solution (30 mL) with stirring and cooling, then extracted with ether (10 × 100 mL). The ethereal solution was dried over anhydrous Na_2SO_4 and evaporated to dryness, and the remaining oil was rubbed with petroleum ether. The product was a yellowish white powder (4.3 g, 0.0133 mol). This crude base was dissolved in ethanol (30 mL); a solution of maleic acid (1.6 g, 0.0138 mol) in alcohol (15 mL) was added, and the separated substance was collected after cooling to obtain a yellowish white powder (5.2 g): mp 169 °C. Recrystallization from ethanol (50 mL) gave a white powderlike substance (4.7 g, 71.2%): mp 170 °C.

Compounds **27–38** were prepared similarly, starting from the corresponding chloroacyl derivatives and using the appropriate amine. In cases involving reagents other than ethylamine, the reaction mixture was refluxed. In the case of compounds **32–34**, the crude base was purified via the dimaleate salt.

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Synthesis and Gastric Antisecretory Properties of α Chain Diene Derivatives of Misoprostol[1]

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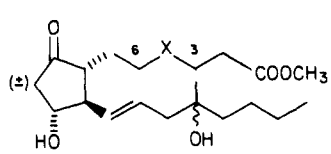
The synthesis and gastric antisecretory activity in dogs of seven α chain diene derivatives of misoprostol are described. The key intermediates in the preparation of these compounds were C-9 *tert*-butyldimethylsilyl enol ethers that were obtained by in situ silylation of cuprate enolates derived from α chain unsaturated cyclopentenones. Selenylation chemistry on these intermediates provided the C_2–C_3 trans dienes that, where possible, were also deconjugated to produce the corresponding C_3–C_4 dienes. The most interesting structure in this series is the C_5–C_6 cis, C_3–C_4 cis/trans (1:1) diene that could not be readily separated chromatographically into its individual geometric isomers. The gastric antisecretory activity of the mixture of isomers was approximately 3 times greater than that of misoprostol by intragastric administration. The separation of undesired diarrheogenic effects from antisecretory activity was significantly improved relative to misoprostol.

Insertion of a cis double bond between carbons 4 and 5 of misoprostol (**1a**; 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 methyl ester)[2] imparts favorable changes in the pharmacological profile of the resulting compound **1b**.[3] This unsaturated derivative was more potent as a gastric antisecretory agent, longer acting, and more selective with respect to diarrheogenic activity than the parent compound **1a**.



1a, X = CH_2CH_2
b, X = CH=CH (cis)

On the basis of these findings, we decided to examine the effects that two double bonds in the α chain might have on the intensity and duration of the gastric antisecretory activity of **1a**. Of particular interest was the $\Delta^{3,5}$ conjugated diene system because these olefinic bonds flank carbons 4 and 5 and thus mimic the electronic environment at this position in **1b**. In addition, a conjugated diene moiety at this position has been reported to dramatically improve antinidatory effects in a series of $PGF_{2\alpha}$ compounds.[4]

Chemistry

The synthesis of the C_2–C_3 trans,C_5–C_6 dienes is outlined in Scheme I. The C_5–C_6 cis hydroxy cyclopentenone **2a**[2] was protected as its triethylsilyl ether **3a** by treatment with triethylchlorosilane in dimethylformamide and imidazole at room temperature[5] and then subjected to the well-documented[3] conjugate addition reaction with the cuprate species **4**[3] at −60 °C. Instead of the usual acidic quenching, the enolate was converted in situ to the silyl enol ether **5a** by treatment of the reaction mixture with excess *tert*-bu-

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