Articles

(±)-4-Aryl-4,5-dihydro-3*H*-1,3-benzodiazepines. 1. Synthesis and Evaluation of (±)-4,5-Dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine and Analogues as Potential Antidepressant Agents[1]

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A series of (±)-4,5-dihydro-4-phenyl-3*H*-1,3-benzodiazepines and (±)-4,5-dihydro-4-phenyl-1*H*-1,3-benzodiazepines was synthesized as part of a program to develop novel psychotropics. Of these compounds, (±)-4,5-dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine (**10a**, HRP 543) emerged as a potential antidepressant. In in vivo mouse tests (inhibition of tetrabenazine-induced ptosis and potentiation of yohimbine toxicity) which are predictive of antidepressant-like activity, **10a** is comparable to amitriptyline. The similarity is also maintained in vitro, as both **10a** and amitriptyline inhibit norepinephrine and serotonin uptake into rat brain synaptosomes. No significant inhibition of rat brain monoamine oxidase A or B was found with **10a**, nor did the compound potentiate tryptamine-induced seizures. On chronic administration, the number of cortical β-adrenergic receptor sites was similarly reduced by **10a** and desipramine. The anticholinergic activity of clinically useful antidepressants, such as amitriptyline, is a proposed cause of side effects which reduce patient compliance. In contrast to the tricyclics, **10a** apparently lacks anticholinergic activity, as evidenced in vitro by negligible displacement of [^{3}H]quinuclidinyl benzylate from rat brain muscarinic receptors and in vivo by insignificant antagonism of the cholinergic stimulation produced by physostigmine or oxotremorine. These data suggest that **10a** may be clinically useful as a novel nontricyclic antidepressant which is devoid of anticholinergic side-effect liability. Further evaluation of **10a** in nonrodent species is in progress.

Many structurally diverse compounds display clinically efficacious antidepressant activity and/or antidepressant-like activity in preclinical studies. Although the benzodiazepines as a class have provided many psychotherapeutic agents, clinically useful antidepressant activity is infrequently associated with these compounds. Recently a number of 1,4-benzodiazepines, including zometapine,[2] alprazolam,[3] and a series of 1-(aminoalkyl)-6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines,[4] were reported to display significant antidepressant-like properties; however, similar activity would not appear to have been previously associated with 1,3-benzodiazepine derivatives. As part of a program to develop novel psychotropic agents, a series of (±)-4,5-dihydro-4-phenyl-3*H*-1,3-benzodiazepines and (±)-4,5-dihydro-4-phenyl-1*H*-1,3-benzodiazepines was synthesized in our laboratories. Broad CNS screening revealed that marked antidepressant-like activity is associated with some of these 1,3-benzodiazepines, and a profile more favorable than that of the classic tricyclic antidepressants, such as amitriptyline, was established for the lead compound (**10a**). The synthesis and evaluation of (±)-4,5-dihydro-4-phenyl-1,3-benzodiazepines where substituents at N_1, C_2, and N_3 were varied are reported in this paper.

Chemistry. The synthesis of (±)-4,5-dihydro-4-phenyl-3*H*-1,3-benzodiazepines **10a–o** is outlined in Scheme I, and their properties are summarized in Table I. Properties of intermediates **2–5** are included with the experimental section, and all other intermediates are listed in Table II. Ketone **2** was prepared by Friedel–Crafts synthesis and converted to oxime acetate **4** by standard methods. Borane reduction of **4** gave primary amine **5**, which was acylated to afford secondary amides **6a–f**. Borane reduction of **6a–e** gave secondary amines **7a–e**. Catalytic (Pd/C) or chemical (Fe/HCl) reduction of the nitro group of **5**, **6b,e,f**, and **7a–d** afforded **8a–e** and **9a–c**. Cyclization of diamines **8a–e** with a variety of ortho esters under acid catalysis gave 1,3-benzodiazepines **10a–m**. Cyclic dehydration of amide **9c** with thionyl chloride gave 2-cyclopropyl-1,3-benzodiazepine **10n**, which was alkylated to afford **10o**. The alkylation of **10n** and assignment of **10o** as the N_3-CH_3 derivative will be subsequently described.

The synthesis of isomeric (±)-4,5-dihydro-4-phenyl-1*H*-1,3-benzodiazepines **13a,b** is outlined in Scheme II, and their properties are listed in Table I. Kadin[5] reported monomethylation of primary aromatic amines by conversion of the amines to *N*-arylaminomethylsuccinimide derivatives and subsequent solvent-specific borohydride reduction. With this method as a model, aromatic amines **9a,b** were smoothly converted to succinimide derivatives **11a,b**, which were reduced ($NaBH_4$/Me_2SO) to methylamines **12a,b**. Cyclic dehydration of **12a** with phosphorous pentachloride and **12b** with thionyl chloride afforded **13a** and **13b**, respectively.

Rodriguez et al.[6] have reported that N_3 of 2-aryl- and

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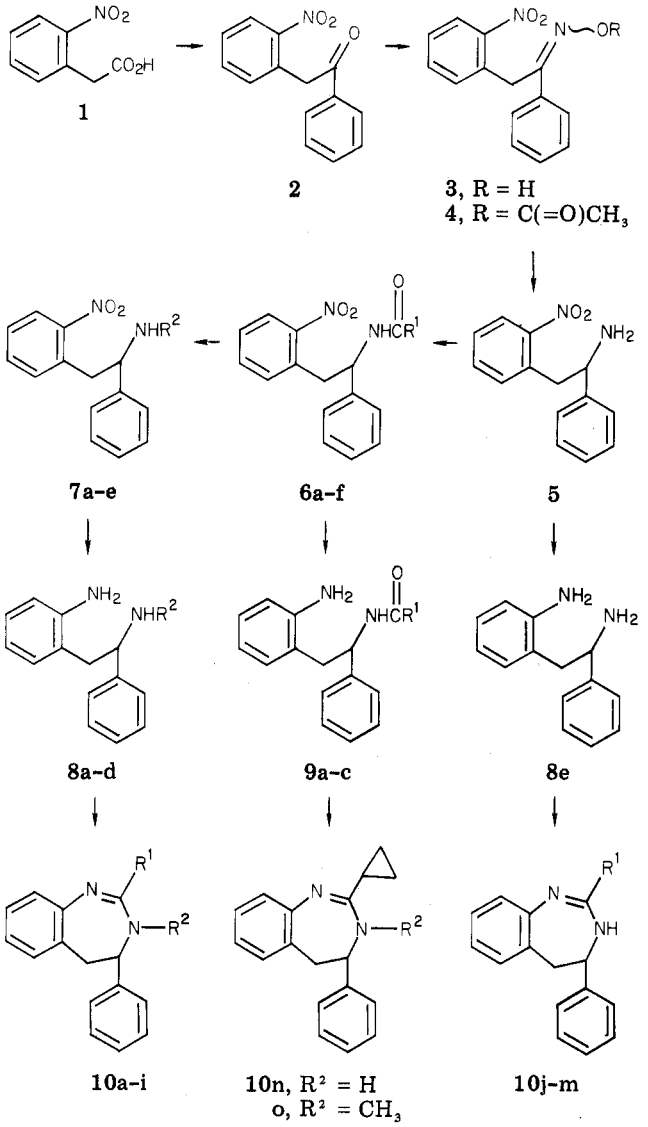
(1) This paper has been presented in part; see "Abstracts of Papers", VII International Symposium on Medicinal Chemistry, Costa del Sol, Torremolinos (Malaga), Spain, Sept 2–5, 1980; Cotswold Press Ltd.: Oxford; Abstr P178.
(2) Tuason, V. B.; Garvey, M.; Goodman, L. J.; Borgen, L. A. *Curr. Ther. Res.* **1980**, *27*, 94.
(3) Fabre, L. F.; McLendon, D. M. *Curr. Ther. Res.* **1980**, *27*, 474.
(4) Hester, J. B. *J. Org. Chem.* **1979**, *44*, 4165.
(5) Kadin, S. B. *J. Org. Chem.* **1973**, *38*, 1348.
(6) Rodriguez, H. R.; Zitko, B.; DeStevens, G. *J. Org. Chem.* **1968**, *33*, 670.

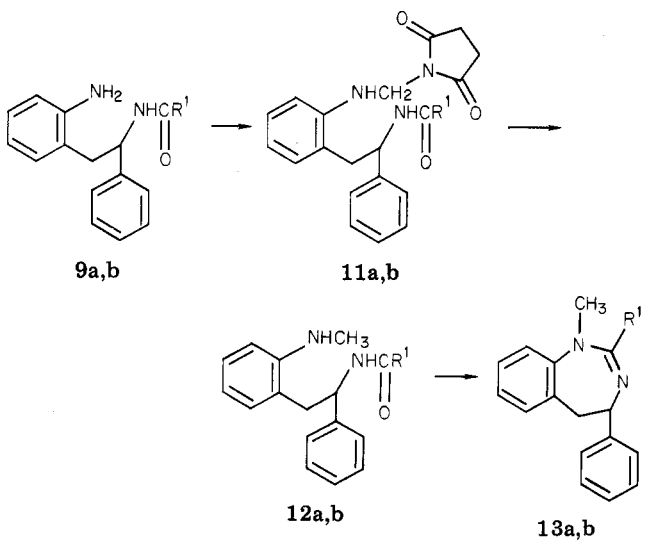
0022-2623/82/1825-0340$01.25/0

Scheme I[a]



[a] R^1 = H, alkyl, cyclopropyl, phenyl. R^2 = alkyl, cycloalkylmethyl, phenylmethyl.

Scheme II[a]



[a] R^1 = CH_3 (a), C_6H_5 (b).

2-alkyl-4,5-dihydro-7,8-dimethoxy-3*H*-1,3-benzodiazepines is the site of initial attack by alkylation with *n*-butyllithium and methyl *p*-toluenesulfonate. Similar alkylation of **10n** and conversion to the hydrochloride salt afforded a 2.5:1 mixture (^{1}H NMR, N-CH_3 ratio) of isomeric 1,3-benzodiazepines. Recrystallization from acetonitrile gave the major isomer **10o**, which was tentatively assigned as the N_3-CH_3 derivative in analogy with the observation of Rodriguez et al.[6] ^{1}H NMR studies of 1,3-benzodiazepines **10a,c,k** and **13a** permitted assignment of the singlet N_1, C_2, and N_3 methyl groups.[7] The downfield position of the N_1-CH_3 of **13a** relative to the N_3-CH_3 of **10a** would be expected due to diamagnetic anisotropic deshielding by the fused aromatic ring. Similar studies with major isomer **10o** and the mixture from which **10o** was isolated indicated that the N-CH_3 (δ 3.99) of the minor isomer in the mixture is deshielded relative to the N-CH_3 (δ 3.38) of **10o**. These data support the tentative assignment of **10o** as the N_3-CH_3 derivative.

Results and Discussion

Potential antidepressant activity for all benzodiazepine derivatives (**10a–o** and **13a,b**; Table I) and selected intermediates (**9a** and **11a**; Table II, footnote *h*) was assessed by their prevention of tetrabenazine-induced ptosis in mice (TBZ). An adjunct test for antidepressant-like activity was the potentiation of the 5-hydroxytryptophan-induced behavorial syndrome in pargyline-pretreated rats (5HTP), which detects compounds, including certain antidepressants, that enhance serotonergic mechanisms. Since the 1,4-benzodiazepines showing anxiolytic activity also inhibit pentylenetetrazol lethality (PTZ) as part of their overall profile, our compounds were also tested for protection from PTZ. The prevention of amphetamine aggregation toxicity (AAT) was used to assess neuroleptic-like activity.

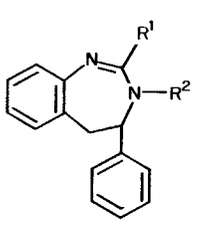
As noted in Table I, anti-TBZ activity was the most significant pharmacological property of these 1,3-benzodiazepines, and optimal activity is associated with (±)-4,5-dihydro-3-methyl-4-phenyl-3*H*-1,3-benzodiazepines **10a,b**. Anti-TBZ activity is significantly reduced when R^2 is H (**10j–n**), R^1 is H and R^2 is CH_3 (**10c**), R^1 is CH_3 and R^2 is larger than CH_3 (**10f–i**), and when R^2 is CH_3 and R^1 is larger than C_2H_5 (**10d,e,o**). Isomeric (±)-4,5-dihydro-1-methyl-4-phenyl-1*H*-1,3-benzodiazepines **13a,b** were devoid of significant anti-TBZ activity. In 5HTP, PTZ, and AAT tests, no significant activity was observed for any compound at the doses investigated (Tables I and II, footnote *f*). Compound **10a** was also tested for anxiolytic activity in the Geller conflict test with rats and was inactive from 4 to 32 mg/kg ip.

Lead compound **10a** was selected for further investigation as a potential antidepressant, and the results of these studies are summarized in Table III. In addition to anti-TBZ activity, potentiation of yohimbine-induced toxicity and inhibition of muricidal behavior are also properties of most antidepressants.[8] Compound **10a** is approximately equipotent to amitriptyline with respect to anti-TBZ activity and potentiation of yohimbine-induced toxicity, and it produced only marginal inhibition of muricidal behavior. With respect to 5HTP potentiation, **10a** is less potent than amitriptyline. The anticholinergic activity of clinically useful antidepressants, such as amitriptyline, is a proposed cause of side effects which reduce patient compliance. Anticholinergic properties of **10a** were

(7) ^{1}H NMR (HCl salts, $CDCl_3$, Me_4Si) for **10a**, δ 3.25 (2-CH_3), 3.52 (3-CH_3); for **10c**, δ 3.55 (3-CH_3); for **10k**, δ 2.83 (2-CH_3); for **13a**, δ 3.73 (1-CH_3), 2.95 (2-CH_3).

(8) Smith, D. H.; Vernier, V. G., *Drugs Pharm. Sci.* **1978**, *5*, 231–233. In "New Drugs, Discovery and Development"; Rubin, A. A., Ed.; Marcel Dekker: New York, 1978.

Table I. (±)-4,5-Dihydro-4-phenyl-3*H*-1,3-benzodiazepines (10a–o) and (±)-4,5-Dihydro-1-methyl-4-phenyl-1*H*-1,3-benzodiazepines (13a,b)[a]



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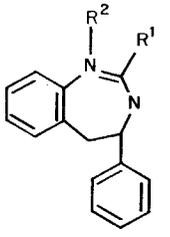

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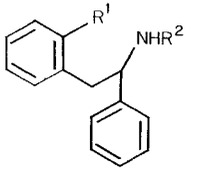
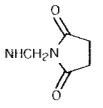
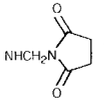
no.	R^1	R^2	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]	pharmacol:[f] TBZ ED_{50}, mg/kg ip (mouse)
10a	CH_3	CH_3	8a	F	240–243	40	E-G	$C_{17}H_{18}N_2$·HCl	C, H, N	1.5 (1.3–1.8)
10b	C_2H_5	CH_3	8a	F	242–244	17	B	$C_{18}H_{20}N_2$·HCl	C, H, N	0.6 (0.5–0.7)
10c	H	CH_3	8a	F	251–254	28	K-G	$C_{16}H_{16}N_2$·HCl	C, H, N	9.7 (7.9–12.5)
10d	n-C_3H_7	CH_3	8a	F	258–262	80	G[g]	$C_{19}H_{22}N_2$·HCl	C, H, N	>20
10e	C_6H_5	CH_3	8a	F	258–259	29	B	$C_{22}H_{20}N_2$·HCl[i]	C, H, N	>20
10f	CH_3	C_2H_5	8b	F	249–252	67	A	$C_{18}H_{20}N_2$·HCl	C, H, N	~20
10g	CH_3	n-C_3H_7	8c	F	272–275	41	E-G	$C_{19}H_{22}N_2$·HCl	C, H, N	>5
10h	CH_3	CH_2-c-C_6H_{11}	8d	F	256–258	52	H-I	$C_{23}H_{28}N_2$·HCl	C, H, N	~20
10i	CH_3	$CH_2C_6H_5$	7e	O, F	245–247	40[j]	A	$C_{23}H_{22}N_2$·HCl	H, N; C[k]	>20
10j	H	H	8e	F	184–186	58	K-G	$C_{15}H_{14}N_2$·HCl	C, H, N	~20
10k	CH_3	H	8e	F	194–198	19	E-G	$C_{16}H_{16}N_2$·HCl	C, H, N	>20
10l	C_2H_5	H	8e	F	242–245	64	J	$C_{17}H_{18}N_2$·HCl	C, H, N	>5
10m	C_6H_5	H	8e	F	244–247	40	B	$C_{21}H_{18}N_2$·HCl	C, H, N	>20
10n	c-C_3H_5	H	9c	G	231–232	24	J	$C_{18}H_{18}N_2$·HCl	C, H, N	>20
10o	c-C_3H_5	CH_3	10n	H	195–196	24	B	$C_{19}H_{20}N_2$·HCl	C, H, N	>20
13a	CH_3	CH_3	12a	K	103–110	43	J	$C_{17}H_{18}N_2$·HCl[l]	C, H, N	>20
13b	C_6H_5	CH_3	12b	L	98–101	47	F	$C_{22}H_{20}N_2$	C, H	>20
amitriptyline										1.5 (1.4–1.6)

[a] All compounds exhibited IR and ^{1}H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material; yields were not optimized. [d] A = acetone; B = acetonitrile; C = carbon tetrachloride; D = cyclohexane; E = absolute ethanol; F = 95% ethanol; G = ether; H = ethyl acetate; I = hexane; J = 2-propanol; K = methanol; L = tetrahydrofuran; M = toluene; N = water. [e] Analytical results within ±0.4% of theoretical values unless otherwise noted. [f] Pharmacological properties of 10a–o and 13a,b were assessed in a battery of assays, which included prevention of tetrabenazine-induced ptosis in mice (TBZ), potentiation of 5-hydroxytryptophan-induced behaviorial syndrome in pargyline pretreated rats (5HTP), inhibition of pentylenetetrazol lethality in mice (PTZ), and prevention of amphetamine aggregation toxicity in mice (AAT). For TBZ, ED_{50} values were determined by linear regression analysis, and 95% confidence limits are presented in parentheses. For 10a–o and 13a,b: 5HTP, $ED_{50} \gtrsim 10$ mg/kg ip; PTZ, $ED_{50} > 40$ mg/kg po; AAT, $ED_{50} > 20$ mg/kg po. [g] Precipitated with ethereal HCl. [h] Decomposition. [i] Hemihydrate. [j] Calculated from 7e. [k] C: calcd, 76.03; found, 75.59. [l] Hemihydrate and hemisolvate with 2-propanol. Drying resulted in loss of crystal structure and formation of a glass.

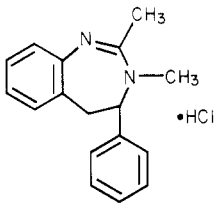
Table II. (±)-α-Phenylbenzeneethanamine Intermediates[a]



no.	R^1	R^2	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]
6a	NO_2	C(=O)H	5	A, B	151-153	45, 68	E	$C_{15}H_{14}N_2O_3$	C, H, N
6b	NO_2	$C(=O)CH_3$	5	A	171-172	73	E	$C_{16}H_{16}N_2O_3$	C, H, N
6c	NO_2	$C(=O)C_2H_5$	5	A	149-151	74	E-N	$C_{17}H_{18}N_2O_3$	C, H, N
6d	NO_2	C(=O)-c-C_6H_{11}	5	A	210-212	58	K	$C_{21}H_{24}N_2O_3$	C, H, N
6e	NO_2	$C(=O)C_6H_5$	5	A	188-190	84	M	$C_{21}H_{18}N_2O_3$	C, H, N
6f	NO_2	C(=O)-c-C_3H_5	5	A	181-183	73	E	$C_{18}H_{18}N_2O_3$	C, H, N
7a[f]	NO_2	CH_3	6a	C	192-196	71	J	$C_{15}H_{16}N_2O_2 \cdot HCl$	C, H, N
7b	NO_2	C_2H_5	6b	C	216-225[g]	72	E	$C_{16}H_{18}N_2O_2 \cdot HCl$	C, H, N
7c	NO_2	n-C_3H_7	6c	C	189-192	84	J	$C_{17}H_{20}N_2O_2 \cdot HCl$	C, H, N
7d	NO_2	CH_2-c-C_6H_{11}	6d	C	225-228	80	E	$C_{21}H_{26}N_2O_2 \cdot HCl$	C, H, N
7e	NO_2	$CH_2C_6H_5$	6e	C	215-218	50	E	$C_{21}H_{20}N_2O_2 \cdot HCl$	C, H, N
8a	NH_2	CH_3	7a	D, E	243-250	80, 89	K-G	$C_{15}H_{18}N_2 \cdot 2HCl$	C, H, N
8b	NH_2	C_2H_5	7b	D	249-256	68	J	$C_{16}H_{20}N_2 \cdot 2HCl$	C, H, N
8c	NH_2	n-C_3H_7	7c	D	243[g]	70	K-H	$C_{17}H_{22}N_2 \cdot 2HCl$	C, H, N
8d	NH_2	CH_2-c-C_6H_{11}	7d	D	205[g]	73	K-H	$C_{21}H_{28}N_2 \cdot 2HCl$	C, H, N
8e	NH_2	H	5	D	43-45	57	D	$C_{14}H_{16}N_2$	C, H
9a[f,h]	NH_2	$C(=O)CH_3$	6b	D	119-122	75	C	$C_{16}H_{18}N_2O$	C, H
9b	NH_2	$C(=O)C_6H_5$	6e	D	189-192	77	F	$C_{21}H_{20}N_2O$	C, H, N
9c	NH_2	C(=O)-c-C_3H_5	6f	E	136-138	52	C	$C_{18}H_{20}N_2O$	C, H
11a[f,h]		$C(=O)CH_3$	9a	I	157-161	80	F	$C_{21}H_{23}N_3O_3$	C, H, N
11b		$C(=O)C_6H_5$	9b	I	181-182	97	B	$C_{26}H_{25}N_3O_3$	C, H, N
12a	$NHCH_3$	$C(=O)CH_3$	11a	J	93	74	L	$C_{17}H_{20}N_2O \cdot HCl \cdot C_4H_8O$	C, H, N
12b	$NHCH_3$	$C(=O)C_6H_5$	11b	J	164-165	60	F	$C_{22}H_{22}N_2O$	C, H, N

[a-e] See corresponding footnotes to Table I. [f] Potentiation of 5-hydroxytryptophan-induced behavorial syndrome in pargyline-pretreated rats, ED_{50} > 10 mg/kg ip; inhibition of pentylenetetrazol lethality in mice, ED_{50} > 40 mg/kg po; prevention of amphetamine aggregation toxicity in mice, ED_{50} > 20 mg/kg po. [g] Decomposition. [h] Prevention of tetrabenazine-induced ptosis in mice, ED_{50} > 20 mg/kg ip.

Table III. Profile of 10a as a Potential Antidepressant



screening method[a]	10a	standard[b]
	In Vivo (ED_{50},[c] mg/kg ip)	
TBZ ptosis prevention[d]	1.5 (1.3-1.8) 2.1 (1.8-2.4)[f]	1.5 (1.4-1.6) 1.9 (1.4-2.5)[f]
yohimbine toxicity potentiation[d]	5.9 (3.2-10.7)[f]	8.0 (4.1-15.6)[f]
muricide[e]	>20	8.2 (5.7-12)[g]
5HTP potentiation[e]	>10	7.1 (3.0-9.1)
physostigmine lethality[d]	>25	9.6 (6.6-13.9)
oxotremorine antagonism[d]	>25[h] >25[i]	1.3 (0.8-2.1)[h] >5[i]
tryptamine seizure potentiation[e]	>25	>25[g]
	In Vitro	
inhibn of neuronal uptake (IC_{50}, μM)[j]		
NE (WB)	1.7	4.7
(H)	0.9	
dopamine (ST)	5.3	14
serotonin (WB)	8.4	2.0
inhibn of MAO (IC_{50}, M)[k]		
type A	$>1 \times 10^{-3}$	
type B	$>1 \times 10^{-3}$	
QNB (IC_{50}, M)[l]	$>1 \times 10^{-5}$	3.0×10^{-7}
β-adrenergic sensitivity[m]	−44%	−50%[g]

[a] TBZ = tetrabenazine; 5HTP = 5-hydroxytryptophan; NE = norepinephrine. [b] Data are for amitriptyline unless otherwise noted. [c] 95% confidence limits are included in parentheses. [d] Mouse. [e] Rat. [f] Administered po. [g] Desipramine. [h] Tremors. [i] Salivation. [j] Rat brain synaptosomes; WB = whole brain; H = hypothalamus; ST = striatum. Values listed are the mean for three separate experiments. [k] Rat whole brain mitochondria. [l] Rat whole brain membrane preparation. [m] Compounds administered to rats at 10 mg/kg, po, twice daily for 10 days.

assessed in vivo by prevention of physostigmine-induced lethality and antagonism of oxotremorine-induced tremors and salivation and in vitro by displacement of [^{3}H]-quinuclidine benzylate (QNB) from muscarinic receptor sites on brain membranes. The insignificant activity of **10a** in these assays suggests that the compound is devoid of anticholinergic properties.

A predominant biochemical property of almost all antidepressants is their inhibition of the monoaminergic neuronal reuptake mechanisms and/or inhibition of monoamine oxidase (MAO). Compound **10a** displayed weak to modest activity with respect to in vitro inhibition of synaptosomal biogenic amine uptake and was inactive with respect to inhibition of rat brain mitochondrial MAO, type A and B.[9] In tryptamine seizure potentiation, an in vivo test which is indicative of MAO inhibition, **10a** was inactive, as was desipramine. Recently, chronic, but not acute, antidepressant administration has been shown to be accompanied by development of a subsensitivity (decreased density) of cortical β-adrenergic receptor sites labeled by [^{3}H]dihydroalprenolol.[10] Administration of **10a** to rats (10 mg/kg, po, twice daily for 10 days) was shown to significantly decrease the maximal number of cortical binding sites by 44%.[9] Desipramine produced a comparable decrease in the maximal number of cortical binding sites.[9] The profile thus derived from Table III suggests that **10a** may be clinically useful as a novel nontricyclic antidepressant which is devoid of anticholinergic side-effect liability. Further evaluation of **10a** in rodents and other species is in progress. Studies with nuclear substituted analogues are reported in the following paper in this issue.[11]

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^{1}H NMR (JEOL C60HL; tetramethylsilane) spectra. All chemical shifts are given in parts per million (δ) relative to tetramethylsilane as an internal standard. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro Tech Laboratories, Skokie, IL. Results are within ±0.4% of theoretical values unless otherwise noted in the tables. Reactions with moisture-sensitive reagents were maintained under a dry nitrogen atmosphere. Solvents dried over molecular sieves were employed for reactions requiring anhydrous solvents.

2-(2-Nitrophenyl)-1-phenylethanone (2) was prepared by Friedel–Crafts acylation of benzene with 2-nitrophenylacetyl chloride, which was generated in situ as previously described.[12] An attempted synthesis of the acid chloride by warming 2-nitrophenylacetic acid with a slight excess of thionyl chloride resulted in a vigorous decomposition with tar formation and liberation of a brown gas. Such decomposition was never observed during numerous in situ preparations of the acid chloride.

2-(2-Nitrophenyl)-1-phenylethanone Oxime (3). A stirred mixture of **2** (43.0 g, 0.18 mol), sodium acetate (31.2 g, 0.38 mol), hydroxylamine hydrochloride (24.3 g, 0.35 mol), 95% ethanol (200 mL), and water (100 mL) was heated for 1 h under reflux. After the mixture was cooled, the crystalline oxime was collected, washed with 60% aqueous ethanol and water, and recrystallized from 95% ethanol to afford **3** (32.1 g, 72%) as colorless crystals, mp 119–122 °C (lit.[13] mp 118 °C). Anal. ($C_{14}H_{12}N_2O_3$) C, H, N.

2-(2-Nitrophenyl)-1-phenylethanone Oxime Acetate (4). A stirred solution of **3** (5.0 g, 0.02 mol) and pyridine (10 mL) was treated in portions with acetic anhydride (5.0 mL). After heating (steam bath, 0.75 h), the solution was decanted into ice–water, and the oil that separated gradually solidified. The solid was collected, washed with water, and recrystallized from 95% ethanol to afford **4** (4.3 g, 74%) as colorless crystals, mp 63–66 °C. Anal. ($C_{16}H_{14}N_2O_4$) C, H, N.

(±)-2-Nitro-α-phenylbenzeneethanamine Hydrochloride (5). A stirred, cooled (5 °C) solution of **4** (36.7 g, 0.12 mol) and tetrahydrofuran (250 mL) was treated over 40 min with 1.0 M borane in tetrahydrofuran (485 mL). The solution was stirred for 30 min at 5 °C and then allowed to stand for 48 h at ambient temperature. The solution was chilled and treated dropwise with 5% hydrochloric acid (200 mL) and glacial acetic acid (20 mL). After stirring for 1.5 h, the solution was made alkaline, diluted with water, and concentrated to remove the tetrahydrofuran. The residue was extracted with methylene chloride (3 × 300 mL), and the combined, dried (Na_2SO_4) organic phase was concentrated

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to an oil, which was converted to the hydrochloride salt. Recrystallization from methanol afforded **5** (16.9 g, 49%) as pale yellow crystals, mp 262–264 °C dec. Anal. ($C_{14}H_{14}N_2O_2$·HCl) C, H, N.

(±)-*N*-Formyl-2-nitro-α-phenylbenzeneethanamine (6a). Method A. A solution of **5** (free base; 31.7 g, 0.13 mol) and benzene (100 mL) was added dropwise at 10–15 °C to formic-acetic anhydride, prepared from acetic anhydride (27.6 g, 0.26 mol) and formic acid (13.8 g, 0.30 mol). After the stirred suspension was heated for 2 h at 50 °C, the product was collected and the filtrate was evaporated to dryness. A methylene chloride solution of the combined residue and filter cake was washed with 5% hydrochloric acid, dried (Na_2SO_4), and evaporated to dryness. Recrystallization from absolute ethanol gave **6a** (15.7 g, 45%) as pale yellow crystals. Properties of **6a**, and of **6b,c,e** prepared in similar manner from acetic, propionic, and benzoic anhydrides, respectively, are included in Table II. Properties of amides **6d,f** which were prepared from **5**, the corresponding acid chlorides in toluene and chloroform, respectively, and in the presence of pyridine and triethylamine, respectively, are included in Table II.

Method B. A solution of **5** (free base; 8.7 g, 0.036 mol) and methyl formate (200 mL) was heated for 48 h at 80 °C in a Parr bomb. After the solution was cooled, the methyl formate was evaporated to afford the crude amide. Recrystallization from absolute ethanol afforded **6a** (6.6 g, 68%).

(±)-*N*-Methyl-α-phenyl-2-nitrobenzeneethanamine Hydrochloride (7a). Method C. A chilled (5 °C) suspension of **6a** (35.0 g, 0.013 mol) and tetrahydrofuran was treated over 0.5 h with 1.0 M borane in tetrahydrofuran (259 mL). The mixture was stirred for 4 h at ambient temperature and quenched with 5% hydrochloric acid (100 mL) and glacial acetic acid (20 mL). After stirring for 0.5 h at ambient temperature, the mixture was basified with 50% sodium hydroxide and concentrated to remove the organic solvents. The residue was diluted with water and extracted with methylene chloride (2 × 200 mL). The dried ($MgSO_4$) organic phase was concentrated to an oil, which was converted to the hydrochloride salt. Recrystallization from 2-propanol afforded **7a** (32.5 g, 71%) as colorless crystals. Properties of **7a**, and of **7b–e** prepared in similar manner, are included in Table II.

(±)-2-Amino-*N*-methyl-α-phenylbenzeneethanamine Dihydrochloride (8a). Method D. A suspension of **7a** (free base; 22.6 g, 0.10 mol), 95% ethanol (200 mL), potassium hydroxide (1.0 g), and 10% Pd/C (1.5 g) was hydrogenated on a Paar apparatus (3 h, 50 psi, ambient temperature). The resultant filtrate was concentrated, diluted with water, and extracted with methylene chloride (2 × 300 mL). The dried ($MgSO_4$) organic phase was concentrated, and the residual oil was converted to the dihydrochloride salt. Recrystallization from methanol–ether afforded **8a** (24.7 g, 80%) as colorless crystals. Properties of **8a**, and of **8b–e** and **9a,b** prepared in similar manner, are included in Table II.

Method E. A stirred suspension of **7a** (free base; 17.4 g, 0.068 mol), iron powder (37.9 g, 0.68 g-atom, reduced electrolytic, Mallinckrodt), 95% ethanol (240 mL), and water (60 mL) was treated with concentrated hydrochloric acid (1.6 mL). After the solution was refluxed for 0.5 h, Celite was added and the mixture was filtered. The filtrate was concentrated, basified, and extracted with ether. The dried (Na_2SO_4) organic phase was treated with ethereal hydrogen chloride to afford **8a** (16.0 g, 89%) as colorless crystals. Properties of **8a**, and of **9c** prepared in similar manner, are included in Table II.

(±)-4,5-Dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine Hydrochloride (10a). Method F. A stirred mixture of **8a** (free base; 15.7 g, 0.07 mol), triethyl orthoacetate (68.0 g, 0.42 mol), and glacial acetic acid (26.0 mL) was heated for 2 h under reflux, concentrated, and partitioned between 5% sodium hydroxide and ether. The dried (Na_2SO_4) organic phase was treated with ethereal hydrogen chloride, and the crude material was recrystallized from absolute ethanol–ether to afford **10a** (8.0 g, 40%) as colorless crystals. Properties of **10a**, and of **10b–m** prepared in similar manner, are included in Table I.

(±)-2-Cyclopropyl-4,5-dihydro-4-phenyl-3*H*-1,3-benzodiazepine Hydrochloride (10n). Method G. A stirred solution of **9c** (11.2 g, 0.04 mol) and alcohol-free chloroform (250 mL) was treated with thionyl chloride (19.0 g, 0.16 mol). After refluxing for 3 h, the cooled solution was diluted with ether (500 mL) and allowed to stand overnight at ambient temperature. The precipitate was collected and converted to the free base by partitioning between 10% sodium hydroxide and methylene chloride. Concentration of the dried (Na_2SO_4) organic phase afforded on oil, which was converted to the hydrochloride salt. Recrystallization from 2-propanol afforded **10n** (2.82 g, 24%) as colorless crystals. Properties of **10n** are included in Table I.

(±)-2-Cyclopropyl-4,5-dihydro-3-methyl-4-phenyl-3*H*-1,3-benzodiazepine Hydrochloride (10o). Method H. A stirred chilled (−40 °C) solution of **10n** (4.99 g, 0.019 mol) and tetrahydrofuran (130 mL) was treated with 2.2 M *n*-butyllithium in hexane (10.3 mL). After stirring several minutes, the solution was treated at −48 °C with a solution of methyl *p*-toluenesulfonate (3.85 g, 0.021 mol) and tetrahydrofuran (10 mL). The solution was stirred for 4 h at ambient temperature, quenched with water (300 mL), and extracted with methylene chloride (2 × 250 mL). The organic phase was washed with water, dried (Na_2SO_4), and concentrated to an oil, which was dissolved in anhydrous ether. Treatment with ethereal hydrogen chloride afforded 5.4 g of a 2.5:1 mixture (^1H NMR, N-CH_3 ratio) of **10o** and the isomeric 1-methyl derivative. Fractional recrystallization from acetonitrile afforded **10o** (1.42 g, 24%) as colorless crystals. Properties of **10o** are included in Table I.

(±)-*N*-Acetyl-2-[[(2,5-dioxo-1-pyrrolidinyl)methyl]-amino]-α-phenylbenzeneethanamine (11a). Method I. This compound was prepared from **9a** (6.35 g, 0.025 mol) in a similar manner as described by Kadin.[5] On cooling, the product crystallized from the reaction solution to afford **11a** (7.36 g, 80%) as colorless crystals. Properties of **11a**, and of **11b** prepared in similar manner, are included in Table II.

(±)-*N*-Acetyl-2-(methylamino)-α-phenylbenzeneethanamine Hydrochloride (12a). Method J. This compound was prepared by $NaBH_4$ reduction of **11a** (3.65 g, 0.01 mol) in a similar manner as described by Kadin.[5] The crude product was converted to the hydrochloride salt and recrystallized from tetrahydrofuran to afford **12a** (2.77 g, 74%) as faintly pink crystals (1:1 solvate with tetrahydrofuran). Properties of **12a**, and of **12b** prepared in similar manner, are included in Table II.

(±)-4,5-Dihydro-1,2-dimethyl-4-phenyl-1*H*-1,3-benzodiazepine Hydrochloride (13a). Method K. A stirred mixture of **12a** (5.55 g, 0.015 mol), alcohol-free chloroform (42 mL), and phosphorous pentachloride (3.75 g, 0.018 mol) was heated for 3.5 h under reflux, cooled to ambient temperature, and washed with 10% sodium hydroxide solution. The dried (Na_2SO_4) organic phase was concentrated to an oil which was converted to the hydrochloride salt. Recrystallization from 2-propanol afforded **13a** (2.04 g, 43%) as beige crystals (hemihydrate and hemisolvate with 2-propanol). Properties of **13a** are included in Table I.

(±)-4,5-Dihydro-2,4-diphenyl-1-methyl-1*H*-1,3-benzodiazepine (13b). Method L. A stirred solution of **12b** (2.64 g, 0.008 mol), pyridine (7.56 g, 0.096 mol), and alcohol-free chloroform (43 mL) was treated over 0.5 min with thionyl chloride (11.52 g, 0.096 mol). The solution was stirred for 24 h at ambient temperature, decanted into 500 mL of 4% sodium hydroxide solution, and extracted with ether. The organic phase was washed with water, dried (Na_2SO_4), and concentrated to an oil, which crystallized. The material was triturated with hexane, filtered, and recrystallized from 95% ethanol to afford **13b** (1.17 g, 47%) as colorless crystals. Properties of **13b** are included in Table I.

Biological Methods. Procedural details for the inhibition of synaptosomal biogenic amine uptake,[9] inhibition of monoamine oxidase,[9] induction of β-adrenergic subsensitivity,[9] prevention of tetrabenazine-induced ptosis,[14] potentation of 5-hydroxytryptophan-induced behavorial syndrome,[14] potentiation of physostigmine lethality,[14] prevention of pentylenetetrazol-induced lethality,[15] prevention of amphetamine aggregation toxicity,[15] Geller conflict,[15] [^3H]quinuclidinyl benzylate binding,[16] and

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tryptamine seizure potentiation[17] were previously reported.

Yohimbine Toxicity Potentiation. Groups of ten male CD-1 mice (Charles Rivers, 20–30 g) were utilized. The test compound was prepared in distilled water with one drop of surfactant and administered at 0.2, 0.6, 2.0, 6.0, and 20.0 mg/kg po (10 mL/kg). The control group received vehicle. Yohimbine hydrochloride was prepared in distilled water and administered at 22.3 mg/kg, sc, 60 min after the test compound or vehicle. The groups of ten mice were then placed in cages with food and water. Mortality rate was assessed 18 h after dosing. The ED_{50} of potentiated yohimbine toxicity was calculated by probit analysis.

Oxotremorine Antagonism. Groups of six male CD-1 mice (Charles Rivers, 18–21 g) were utilized. Food and water were available ad libitum. The test compound was prepared in distilled water with one drop of surfactant and administered at 25 mg/kg ip (10 mL/kg). At 30, 60, and 120 min after administration of the test compound, oxotremorine was administered at 2.5 mg/kg ip to each pretreatment group and the vehicle control group. The animals were evaluated 15 min later for protection from central (tremors) and peripheral (salivation) effects of oxotremorine. ED_{50} values were calculated by probit analysis.

Muricide Prevention. Male Sprague–Dawley rats which consistently killed mice within 5 min of presentation were used. The rats were individually housed and a male albino mouse was placed in the home cage of the rats at 30, 60, and 120 min after the rats had been injected intraperitoneally with the test compound or saline. Failure to kill the mice within 5 min was considered as inhibition of murcidal behavior. Seven to eight muricidal rats were used at each dose of the test compound. Probit analysis was used to calculate ED_{50} for prevention of muricide.

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(±)-4-Aryl-4,5-dihydro-3*H*-1,3-benzodiazepines. 2. Nuclear-Substituted Analogues of (±)-4,5-Dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine and (±)-4,5-Dihydro-2-ethyl-3-methyl-4-phenyl-3*H*-1,3-benzodiazepine as Potential Antidepressant Agents[1]

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Antidepressant-like activity, as evidenced by marked inhibition of tetrabenazine-induced ptosis, was previously reported for (±)-4,5-dihydro-4-phenyl-3*H*-1,3-benzodiazepine derivatives. Since optimal antitetrabenazine activity was associated with (±)-4,5-dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine (**9k**, HRP 543) and the 2-ethyl-3-methyl analogue (**10k**), the synthesis and evaluation of nuclear-substituted derivatives of these two compounds was also investigated. The initial synthesis involved Friedel–Crafts acylation of substituted benzenes with 2-nitrophenylacetyl chloride to afford 1-aryl-2-(2-nitrophenyl)ethanones **2**, which were converted in five steps to (±)-α-aryl-*N*-methyl-2-nitrobenzeneethanamines **7**. Greater flexibility with respect to the introduction of nuclear substituents was achieved by conversion of 2-nitrotoluene derivatives to **2** via acylation of intermediate β-(dimethylamino)-2-nitrostyrenes with various aroyl chlorides and hydrolysis. Reductive amination of **2** with methylamine and sodium cyanoborohydride afforded **7** directly and significantly reduced the number of synthetic steps. Reduction of **7a–j** to diamines **8a–j** and cyclization with appropriate ortho esters gave nuclear-substituted analogues of **9k** and **10k**. Marked antitetrabenazine activity was associated with many of these compounds. Significant enhancement of activity with respect to the unsubstituted analogues **9k** and **10k** was not observed, with the exception of **9c** which appeared to be slightly more potent than **9k**.

Antidepressant-like activity, as evidenced by marked inhibition of tetrabenazine-induced ptosis, was reported for (±)-4,5-dihydro-4-phenyl-3*H*-1,3-benzodiazepine derivatives in the first paper of this series.[2] Since optimal activity was associated with (±)-4,5-dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine (**9k**) and the 2-ethyl-3-methyl analogue (**10k**) (Table I), the synthesis and evaluation of nuclear-substituted analogues of these compounds were also investigated and constitute the subject of this paper.

Chemistry. The synthesis of 1,3-benzodiazepines **9a–j** and **10a–j** is outlined in Scheme I, and their properties are summarized in Table I. Properties of the various intermediates are summarized in Tables II and III. Ketones **2a,b,d,e** were prepared by Friedel–Crafts synthesis with 2-nitrophenylacetyl chloride. Although of good utility, this synthesis was limited by the availability of nuclear-substituted 2-nitrophenylacetic acids and by the pattern of substitution possible for the acylated ring.

Garcia and Fryer[3] condensed 2-nitrotoluene (**11a**) with *N,N*-dimethylformamide diethyl acetal to give a β-(dimethylamino)-2-nitrostyrene, which was acylated with 2-fluorobenzoyl chloride to afford, after hydrolysis of the

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