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.

(17) Tedeschi, D. H.; Tedeschi, R. E.; Fellows, E. J. *J. Pharmacol. Exp. Ther.* **1959**, *126*, 223.

Acknowledgment. The authors express their appreciation to Marc N. Agnew for spectral data and to Laurence R. Meyerson, Jeffrey C. Wilker, Mark Szewczak, James Kiley, Susan C. Nicolacopulos, and Dan Salomone for contributions to the biological evaluation. We also gratefully acknowledge June D. Baird-Strupczewski and Ann Van Dine for library research and Rose Marie Boysen for assistance in preparation of the manuscript.

(±)-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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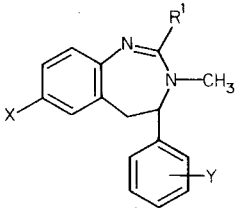
(1) This paper has been presented in part; see "Abstracts of Papers", 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 20–Apr 3, 1981, American Chemical Society: Washington, DC, Abstr MEDI 8.
(2) Geyer III, H. M.; Martin, L. L.; Crichlow, C. A.; Dekow, F. W.; Ellis, D. B.; Kruse, H.; Setescak, L. L.; Worm, M. *J. Med. Chem.*, preceding paper in this issue.
(3) Garcia, E. E.; Fryer, R. K. *J. Heterocycl. Chem.* **1974**, *11*, 219.

0022-2623/82/1825-0346$01.25/0

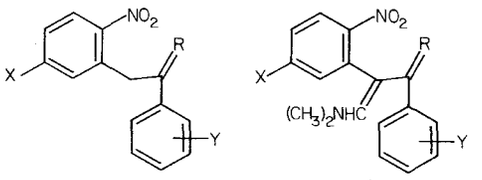
Table I. (±)-4-Aryl-4,5-dihydro-3*H*-1,3-benzodiazepines[a,g]



no.	R^1	X	Y	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]	pharmacol:[f] TBZ ED_{50}, mg/kg po
9a	CH_3	H	4-CH_3	8a	L	285–288	45	B-D	$C_{18}H_{20}N_2 \cdot HCl$	C, H, N	5.2 (4.9–5.5)
9b	CH_3	H	4-OCH_3	8b	L	130–132	54	A	$C_{18}H_{20}N_2O$	C, H, N	19.8 (17.6–22.7)
9c	CH_3	H	4-Cl	8c	L	290–291	42	B-D	$C_{17}H_{17}ClN_2 \cdot HCl$	C, H, N	0.52 (0.48–0.57)
9d	CH_3	H	4-F	8d	L	253–255	55	B-D	$C_{17}H_{17}FN_2 \cdot HCl$	C, H, N	3.6 (3.4–3.8)
9e	CH_3	H	3,4-$(OCH_3)_2$	8e	L	222–226	41	B-D	$C_{19}H_{22}N_2O_2 \cdot HCl$	C, H, N	5.0 (4.0–6.5)
9f	CH_3	H	2-F	8f	L	250–252	41	B-D	$C_{17}H_{17}FN_2 \cdot HCl$	C, H, N	7.6 (6.3–9.4)
9g	CH_3	H	2-Cl	8g	L	245–250	67	D-E	$C_{17}H_{17}ClN_2 \cdot HCl$	C, H, N	>5[h]
9h	CH_3	Cl	H	8h	L	288–292	74	D-E	$C_{17}H_{17}ClN_2 \cdot HCl$	C, H, N	≥20[h]
9i	CH_3	H	2-CH_3	8i	L	239–248	86	D-E	$C_{18}H_{20}N_2 \cdot HCl$	C, H, N	5.5 (5.1–6.0)
9j	CH_3	Cl	2-F	8j	L	285–290	69	G	$C_{17}H_{16}ClFN_2 \cdot HCl$	C, H, N	>20[h]
9k	CH_3	H	H								2.1 (1.8–2.4)
10a	C_2H_5	H	4-CH_3	8a	L	267–268	44	B-D	$C_{19}H_{22}N_2 \cdot HCl$	C, H, N	6.1 (5.0–7.8)
10b	C_2H_5	H	4-OCH_3	8b	L	240–242	68	F	$C_{19}H_{22}N_2O \cdot HCl$	C, H, N	2.8 (2.5–3.1)
10c	C_2H_5	H	4-Cl	8c	L	288–293	50	B-D	$C_{18}H_{19}ClN_2 \cdot HCl$	C, H, N	<5[h,i]
10d	C_2H_5	H	4-F	8d	L	145–150	39	D-E	$C_{18}H_{19}FN_2 \cdot HCl$[j]	C, H	8.4 (5.0–11.6)
10e	C_2H_5	H	3,4-$(OCH_3)_2$	8e	L	214–216	52	B-D	$C_{20}H_{24}N_2O_2 \cdot HCl$	C, H, N	8.2[h] (7.1–9.6)
10f	C_2H_5	H	2-F	8f	L	242–248	63	B-D	$C_{18}H_{19}FN_2 \cdot HCl$	C, H, N	7.0 (6.0–8.4)
10g	C_2H_5	H	2-Cl	8g	L	243–244	56	B-D	$C_{18}H_{19}ClN_2 \cdot HCl$	C, H, N	4.1 (3.8–4.5)
10h	C_2H_5	Cl	H	8h	L	265–269	84	D-E	$C_{18}H_{19}ClN_2 \cdot HCl$	C, H, N	~20[h]
10i	C_2H_5	H	2-CH_3	8i	L	213–218	81	D-E	$C_{19}H_{22}N_2 \cdot HCl$	C, H, N	3.1 (2.9–3.3)
10j	C_2H_5	Cl	2-F	8j	L	274–275	57	B-D	$C_{18}H_{18}ClFN_2 \cdot HCl$	C, H, N	>20[h]
10k	C_2H_5	H	H								1.6 (1.4–1.9)
amitriptyline											1.9 (1.4–2.5)

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material unless otherwise noted. [d] A = acetonitrile; B = absolute ethanol; C = 95% ethanol; D = ether; E = ethereal hydrogen chloride; F = 2-propanol; G = methanol; H = methyl formate; I = water; J = ethyl acetate. [e] Analytical results within ±0.4% of theoretical values unless otherwise noted. [f] Pharmacological properties were assessed in a battery of assays which included prevention of tetrabenazine-induced ptosis in mice (TBZ), potentiation of the 5-hydroxytryptophan-induced behavorial 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 5HTP, ED_{50} > 10 mg/kg, ip, 9a,c,d,f,k and 10a,g,k; PTZ, ED_{50} > 40 mg/kg, po, 9a–k and 10a,b,e–k; AAT, ED_{50} > 20 mg/kg, po, 9a–k and 10a–c,e–f,i–k. [g] The syntheses of 9k and 10k were described in the preceding paper.[2] [h] Administered ip. [i] Motor stimulation noted. [j] Monohydrate.

Table II. 1-Aryl-2-(2-nitrophenyl)ethanone Derivatives[a]

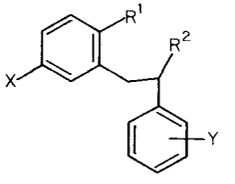


2-4 12

no.	R	X	Y	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]
2a	O	H	4-CH_3	1, 12a	A, B	67–70[f]	64, 86	C	$C_{15}H_{13}NO_3$	
2b	O	H	4-OCH_3	1	A	112–115[g]	36	C	$C_{13}H_{13}NO_4$	C, H
2c	O	H	4-Cl	12b	B	70–72	88	B	$C_{14}H_{10}ClNO_3$	C, H, N
2d	O	H	4-F	1, 12c	A, B	80–81	26, 93	C	$C_{14}H_{10}FNO_3$	C, H, N
2e	O	H	3,4-$(OCH_3)_2$	1	A	146–147[h]	25	C	$C_{16}H_{15}NO_5$	
2f	O	H	2-F	12d	B	77–79[i]	19[j]	C	$C_{14}H_{10}FNO_3$	
2g	O	H	2-Cl	12e	B	64–66	37	C	$C_{14}H_{10}ClNO_3$	C, H, N
2h	O	Cl	H	12f	B	111–116	16[k]	C	$C_{14}H_{10}ClNO_3$	C, H, N
2i	O	H	2-CH_3	12g	B	60–64	37	C	$C_{15}H_{13}NO_3$	C, H, N
2j	O	Cl	2-F	12h	B	105–107	26	C	$C_{14}H_9ClFNO_3$	C, H, N
3a	NOH	H	4-CH_3	2a	C	129–132	94	C	$C_{15}H_{14}N_2O_3$	C, H, N
3b	NOH	H	4-OCH_3	2b	C	106–110	86	C	$C_{15}H_{14}N_2O_4$	C, H
3c	NOH	H	4-Cl	2c	C	131–139	96	C	$C_{14}H_{11}ClN_2O_3$	C, H, N
3d	NOH	H	4-F	2d	C	139–142	72	C	$C_{14}H_{11}FN_2O_3$	C, H, N
3e	NOH	H	3,4-$(OCH_3)_2$	2e	C	129–130	96	C	$C_{16}H_{16}N_2O_5$	C, H, N
3f	NOH	H	2-F	2f	C	105–109	83	C	$C_{14}H_{11}FN_2O_3$	C, H, N
3g	NOH	H	2-Cl	2g	C	159–165	86	C	$C_{14}H_{11}ClN_2O_3$	C, H, N
3h	NOH	Cl	H	2h	C	124–126	96	C–I	$C_{14}H_{11}ClN_2O_3$	C, H, N
4a	NOC(=O)CH_3	H	4-CH_3	3a	D	95–98	96	C	$C_{17}H_{16}N_2O_4$	C, H, N
4b	NOC(=O)CH_3	H	4-OCH_3	3b	D	65–69	58	C	$C_{17}H_{16}N_2O_5$	C, H
4c	NOC(=O)CH_3	H	4-Cl	3c	E	85–88	98	C	$C_{16}H_{13}ClN_2O_4$	C, H, N
4d	NOC(=O)CH_3	H	4-F	3d	D	74–75	88	C	$C_{16}H_{13}FN_2O_4$	C, H, N
4e	NOC(=O)CH_3	H	3,4-$(OCH_3)_2$	3e	E	118–120	75	C	$C_{18}H_{18}N_2O_6$	C, H, N
4f	NOC(=O)CH_3	H	2-F	3f	D	133–135[l]	95	oil	$C_{16}H_{13}FN_2O_4$	C, H, N
4g	NOC(=O)CH_3	H	2-Cl	3g	E	65–71	97	C	$C_{16}H_{13}ClN_2O_4$	C, H, N
4h	NOC(=O)CH_3	Cl	H	3h	E	110–114	78	C	$C_{16}H_{13}ClN_2O_4$	C, H, N
12a	O	H	4-CH_3	11a	M	136–138	30	A	$C_{18}H_{18}N_2O_3$	C, H, N
12b	O	H	4-Cl	11a	M	142–148	72	C	$C_{17}H_{15}ClN_2O_3$	C, H, N
12c	O	H	4-F	11a	M	129–132	17	J	$C_{17}H_{15}FN_2O_3$	C, H, N
12d	O	H	2-F	11a	M			oil	$C_{17}H_{15}FN_2O_3$	
12e	O	H	2-Cl	11a	M		98	oil	$C_{17}H_{15}ClN_2O_3$	C, H, N
12f	O	Cl	H	11b	M			oil	$C_{17}H_{15}ClN_2O_3$	
12g	O	H	2-CH_3	11a	M	114–116	81	D	$C_{18}H_{18}N_2O_3$	C, H, N
12h	O	Cl	2-F	11b	M		100[m]	oil	$C_{17}H_{14}ClFN_2O_3$	

[a-e] See corresponding footnotes to Table I. [f] Literature[4] mp 77–78 °C (ether). [g] Literature[4] mp 116–117 °C (methanol). [h] Literature[5] mp 134 °C. [i] Literature[3] mp 85–86 °C (CCl_4). [j] Yield from 2-nitrotoluene. [k] Yield from 4-chloronitrobenzene. [l] Boiling point, 5 mmHg. [m] Yield of crude material.

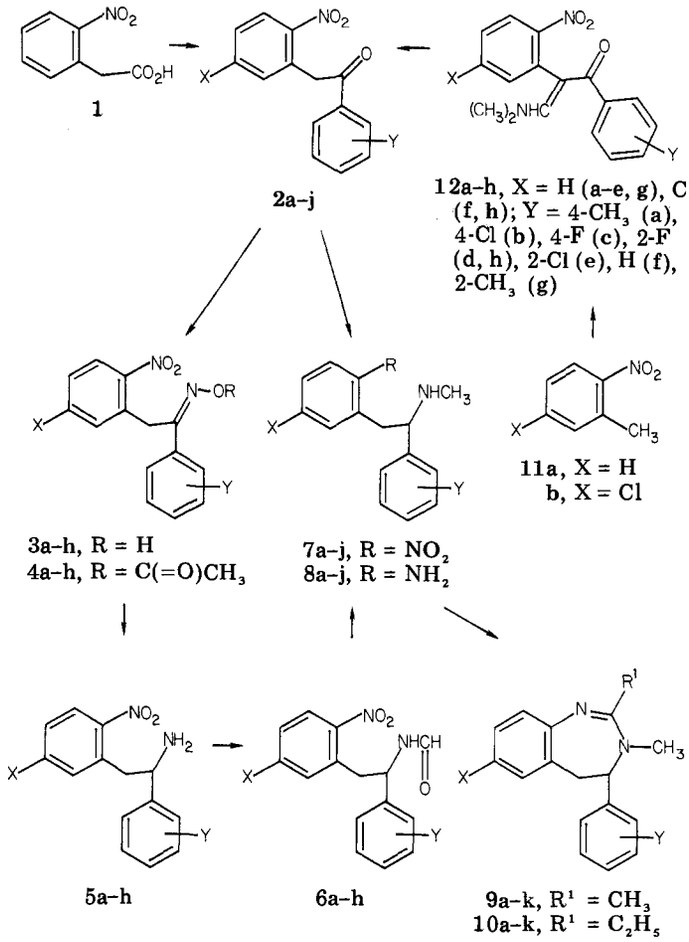
Table III. (±)-α-Arylbenzeneethanamine Derivatives[a]



no.	R^1	R^2	X	Y	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]
5a	NO_2	NH_2	H	4-CH_3	4a	F	265–269	60	B	$C_{15}H_{16}N_2O_2 \cdot HCl$	C, H, N
5b	NO_2	NH_2	H	4-OCH_3	4b	F	240–242	62	C	$C_{15}H_{16}N_2O_3 \cdot HCl$	C, H
5c	NO_2	NH_2	H	4-Cl	4c	F	246–251	86	B–G	$C_{14}H_{13}ClN_2O_2 \cdot HCl$	C, H, N
5d	NO_2	NH_2	H	4-F	4d	F	239–243	73	B	$C_{14}H_{13}FN_2O_2 \cdot HCl$	C, H, N
5e	NO_2	NH_2	H	3,4-$(OCH_3)_2$	4e	F	229–231	53	B–G	$C_{16}H_{18}N_2O_4 \cdot HCl$	C, H, N
5f	NO_2	NH_2	H	2-F	4f	F	225–227	39	B	$C_{14}H_{13}FN_2O_2 \cdot HCl$	C, H, N
5g	NO_2	NH_2	H	2-Cl	4g	F	205–208	12	D–E	$C_{14}H_{13}ClN_2O_2 \cdot HCl$	C, H, N
5h	NO_2	NH_2	Cl	H	4h	F	220–224	78	D–E	$C_{14}H_{13}ClN_2O_2 \cdot HCl$	C, H, N
6a	NO_2	NHC(=O)H	H	4-CH_3	5a	G	130–132	82	C	$C_{16}H_{16}N_2O_3$	C, H, N
6b	NO_2	NHC(=O)H	H	4-OCH_3	5b	G	151–153	74	H	$C_{16}H_{16}N_2O_4$	C, H, N
6c	NO_2	NHC(=O)H	H	4-Cl	5c	G	149–150	73	C	$C_{15}H_{13}ClN_2O_3$	C, H, N
6d	NO_2	NHC(=O)H	H	4-F	5d	G	142–145	86	C	$C_{15}H_{13}FN_2O_3$	C, H, N
6e	NO_2	NHC(=O)H	H	3,4-$(OCH_3)_2$	5e	G	135–139	77	C	$C_{17}H_{18}N_2O_5$	C, H, N
6f	NO_2	NHC(=O)H	H	2-F	5f	G	118–120	94	C	$C_{15}H_{13}FN_2O_3$	C, H, N
6g	NO_2	NHC(=O)H	H	2-Cl	5g	G		100[f]	oil	$C_{15}H_{13}ClN_2O_3$	
6h	NO_2	NHC(=O)H	Cl	H	5h	G	127–128	100[f]	C	$C_{15}H_{13}ClN_2O_3$	C, H, N
7a	NO_2	$NHCH_3$	H	4-CH_3	6a	H	235–238	70	B	$C_{16}H_{18}N_2O_2 \cdot HCl$	C, H, N
7b	NO_2	$NHCH_3$	H	4-OCH_3	6b	H	181–185	93	F	$C_{16}H_{18}N_2O_3 \cdot HCl$	C, H, N
7c	NO_2	$NHCH_3$	H	4-Cl	6c	H	148–151	56	B–D	$C_{15}H_{15}ClN_2O_2 \cdot HCl$	C, H, N
7d	NO_2	$NHCH_3$	H	4-F	6d	H	241–243	67	B	$C_{15}H_{15}FN_2O_2 \cdot HCl$	C, H, N
7e	NO_2	$NHCH_3$	H	3,4-$(OCH_3)_2$	6e	H	185–188	88	B	$C_{17}H_{20}N_2O_4 \cdot HCl$	C, H, N
7f	NO_2	$NHCH_3$	H	2-F	6f	H	201–206	51	B–D	$C_{15}H_{15}FN_2O_2 \cdot HCl$	C, H, N
7g	NO_2	$NHCH_3$	H	2-Cl	6g	H	175–177	73	B–D	$C_{15}H_{15}ClN_2O_2 \cdot HCl$	C, H, N
7h	NO_2	$NHCH_3$	Cl	H	6h	H	255–256	94	D–E	$C_{15}H_{15}ClN_2O_2 \cdot HCl$	C, H, N
7i	NO_2	$NHCH_3$	H	2-CH_3	2i	I	184–187	91	D–E	$C_{16}H_{18}N_2O_2 \cdot HCl$	C, H, N
7j	NO_2	$NHCH_3$	Cl	2-F	2j	I	225–227	91	D–E	$C_{15}H_{14}ClFN_2O_2 \cdot HCl$	C, H, N
8a	NH_2	$NHCH_3$	H	4-CH_3	7a	J	225–228	68	B–D	$C_{16}H_{20}N_2 \cdot 2HCl$	C, H, N
8b	NH_2	$NHCH_3$	H	4-OCH_3	7b	J	223–226[g]	85	F	$C_{16}H_{20}N_2O \cdot 2HCl$	C, H, N
8c	NH_2	$NHCH_3$	H	4-Cl	7c	J	120–130	96	D–E	$C_{15}H_{17}ClN_2 \cdot 2HCl$	C, H, N
8d	NH_2	$NHCH_3$	H	4-F	7d	K		88	oil	$C_{15}H_{17}FN_2$	C, H, N
8e	NH_2	$NHCH_3$	H	3,4-$(OCH_3)_2$	7e	J		99[f]	oil	$C_{17}H_{22}N_2O_2$	
8f	NH_2	$NHCH_3$	H	2-F	7f	J	155–158[h]	92	oil	$C_{15}H_{17}FN_2$	C, H, N
8g	NH_2	$NHCH_3$	H	2-Cl	7g	K	245–247	89	D–E	$C_{15}H_{17}ClN_2 \cdot 2HCl$	C, H, N
8h	NH_2	$NHCH_3$	Cl	H	7h	K		99[f]	oil	$C_{15}H_{17}ClN_2$	
8i	NH_2	$NHCH_3$	H	2-CH_3	7i	K	249–259	66	D–E	$C_{16}H_{20}N_2 \cdot 2HCl$	C, H, N
8j	NH_2	$NHCH_3$	Cl	2-F	7j	K	214–216	77	D–E	$C_{15}H_{16}ClFN_2 \cdot HCl$[i]	C, H, N

[a-e] See corresponding footnotes to Table I. [f] Yield of crude material. [g] Decomposition. [h] Boiling point, 0.5 mmHg. [i] Hemihydrate.

Scheme I[a]



[a] For 2–10: X = H (a–g, i, k), Cl (h, j); Y = 4-CH_3 (a), 4-OCH_3 (b), 4-Cl (c), 4-F (d), 3,4-$(OCH_3)_2$ (e), 2-F (f, j), 2-Cl (g), H (h, k), 2-CH_3 (i).

intermediate enamino ketone **12d**, the ketone **2f**. With this method as a model, ketones **2a,c,d,f–j** were readily synthesized, and both limitations of the Friedel–Crafts synthesis were thus largely negated. Five of the intermediate enamino ketones (**12a–c,e,g**) were isolated and characterized (Table II). Ketones **2a–h** were converted to oxime acetates **4a–h** (Table II) by standard methods, and borane reduction of **4a–h** afforded primary amines **5a–h** (Table III). Acylation of **5a–h** with methyl formate afforded formamides **6a–h**, which were reduced with borane to give secondary methylamines **7a–h** (Table III). Alternatively, secondary amines **7i,j** were prepared by reductive amination of ketones **2i,j** with methylamine and sodium cyanoborohydride. This modification significantly shortened the synthetic sequence and afforded the secondary amines in high yield. Catalytic (Pd/C) or chemical (Fe/HCl) reduction of **7a–j** gave diamines **8a–j**, which were cyclized with the appropriate ortho esters under acidic conditions to afford nuclear-substituted 1,3-benzodiazepines **9a–j** and **10a–j** (Table I).

Results and Discussion

Potential antidepressant activity for all 1,3-benzodiazepines included in Table I was assessed by their prevention of tetrabenazine-induced ptosis in mice (TBZ). An adjunct test for antidepressant-like activity was the potentiation of 5-hydroxytryptophan-induced behavioral 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 access neuroleptic-like activity.

The results suggest that marked anti-TBZ activity is the most prominent pharmacological property of these nuclear-substituted 1,3-benzodiazepines (Table I). Significant enhancement of anti-TBZ activity with respect to unsubstituted analogues **9k** and **10k** was not observed, with the exception of **9c** which was slightly more active than **9k**. With respect to 5HTP, PTZ, and AAT, only slight activity at best was observed at the screening doses (Table I, footnote *f*). Compound **9k** was selected for in-depth evaluation, and results of those studies are reported in the preceding paper.[2]

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (JEOL C60HL; tetramethylsilane) spectra. 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.

1-(4-Methylphenyl)-2-(2-nitrophenyl)ethanone (2a). Method A. A stirred mixture of 2-nitrophenylacetic acid (1; 23.8 g, 0.13 mol) and 1,2-dichloroethane (50 mL) was treated dropwise at ambient temperature with thionyl chloride (23.8 g, 0.2 mol), followed by heating at 65–70 °C for 0.75 h. To the cooled mixture was added a solution of toluene (17.9 g, 0.195 mol) and 1,2-dichloroethane (50 mL). Aluminum chloride (18.66 g, 0.14 mol) was then added in portions, followed by heating at 42 °C for 0.75 h. The mixture was poured onto ice and concentrated hydrochloric acid (50 mL) and extracted with dichloromethane. The organic phase was washed with 5% sodium hydroxide solution and water, dried (Na_2SO_4), and concentrated to an oil, which crystallized. Recrystallization from 95% ethanol gave 21 g (64%) of **2a**, mp 67–70 °C [lit.[4] mp 77–78 °C (Et_2O)]. Properties of **2a**, and of **2b**,[4]**d**,**e**[5] prepared in similar manner, are included in Table II.

Method B. A stirred mixture of **12a** (56.0 g, 0.18 mol), dioxane (150 mL), and water (50 mL) was refluxed overnight and concentrated, and the residue was partitioned between water and dichloromethane. The dried (Na_2SO_4) organic phase was concentrated to an oil, which crystallized on trituration with 95% ethanol to afford **2a** (39.5 g, 86%). Properties of **2a**, and of **2c,d,f**[3]**–j** prepared in similar manner, are included in Table II.

1-(4-Methylphenyl)-2-(2-nitrophenyl)ethanone Oxime (3a). Method C. This compound was prepared from **2a** (50 g, 0.2 mol), hydroxylamine hydrochloride (27.8 g, 0.4 mol), sodium acetate (36.1 g, 0.44 mol), water (100 mL), and 95% ethanol (200 mL) to afford **3a** (50.8 g, 94%) in a manner analogous to that previously described for 2-(2-nitrophenyl)-1-phenylethanone oxime.[2] Properties of **3a**, and of **3b–h** prepared in similar manner, are included in Table II.

1-(4-Methylphenyl)-2-(2-nitrophenyl)ethanone Oxime Acetate (4a). Method D. This compound was prepared from **3a** (42.3 g, 0.17 mol), pyridine (100 mL), and acetic anhydride to afford **4a** (50.8 g, 96%) in a manner analogous to that previously described for 2-(2-nitrophenyl)-1-phenylethanone oxime acetate.[2] Properties of **4a**, and of **4b,d,f** prepared in similar manner, are included in Table II.

1-(4-Chlorophenyl)-2-(2-nitrophenyl)ethanone Oxime Acetate (4c). Method E. A stirred mixture of **3c** (84 g, 0.29 mol) and acetic anhydride (44 g, 0.44 mol) was heated for 0.5 h at 60 °C. The cooled mixture was triturated with water and filtered to give **4c** (91 g, 98%) as an isomeric mixture. Properties of **4c**,

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and of **4e,g,h** prepared in similar manner, are included in Table II.

(±)-α-(4-Methylphenyl)-2-nitrobenzeneethanamine Hydrochloride (5a). Method F. This compound was prepared from **4a** (48 g, 0.1 mol) and tetrahydrofuran (350 mL) by treatment with 1.01 M borane in tetrahydrofuran (594 mL) to afford **5a** (26.0 g, 60%) in a manner analogous to that previously described for (±)-2-nitro-α-phenylbenzeneethanamine.[2] Properties of **5a**, and of **5b–h** prepared in similar manner, are included in Table III.

(±)-*N*-Formyl-α-(4-methylphenyl)-2-nitrobenzeneethanamine (6a). Method G. This compound was prepared from **5a** free base (19.6 g, 0.076 mol) and methyl formate (230 mL) to afford **6a** (17.7 g, 82%) in a manner analogous to that previously described for (±)-*N*-formyl-2-nitro-α-phenylbenzeneethanamine.[2] Properties of **6a**, and of **6b–h** prepared in similar manner, are included in Table III.

(±)-*N*-Methyl-α-(4-methylphenyl)-2-nitrobenzeneethanamine Hydrochloride (7a). Method H. This compound was prepared by treatment of **6a** (17.0 g, 0.06 mol) and tetrahydrofuran (200 mL) with 0.98 M borane in tetrahydrofuran (122 mL) to afford **7a** (12.8 g, 70%) in a manner analogous to that previously described for (±)-*N*-methyl-α-phenyl-2-nitrobenzeneethanamine.[2] Properties of **7a**, and of **7b–h** prepared in similar manner, are included in Table III.

(±)-*N*-Methyl-α-(2-methylphenyl)-2-nitrobenzeneethanamine Hydrochloride (7i). Method I. A cold (−40 °C), stirred solution of **2i** (10.2 g, 0.04 mol) and toluene (150 mL) was treated with methylamine (40 mL). After 15 min, a solution of titanium tetrachloride (2.4 mL, 0.02 mol) and toluene (40 mL) was added dropwise. The reaction mixture was warmed over 0.5 h to ambient temperature and then heated for 5 h at 80 °C (internal temperature). After stirring overnight at ambient temperature, the mixture was filtered, and the filtrate was concentrated to afford a red oil (10.7 g). A solution of the oil and anhydrous methanol (150 mL) was treated dropwise with ethereal hydrogen chloride to pH 3–5 (red color discharged). A solution of sodium cyanoborohydride (2.5 g, 0.04 mol) and methanol (60 mL) was added, followed by stirring for 0.5 h (acidic pH maintained with ethereal hydrogen chloride). The mixture was concentrated, and the residue was treated with 5% sodium hydroxide and extracted with ether. The organic phase was washed with water, dried (Na_2SO_4) and treated with ethereal hydrogen chloride to afford **7i** (11.1 g, 91%). Properties of **7i**, and of **7j** prepared in similar manner, are included in Table III.

(±)-2-Amino-*N*-methyl-α-(4-methylphenyl)benzeneethanamine Dihydrochloride (8a). Method J. A mixture of **7a** free base (8.81 g, 0.0325 mol), potassium hydroxide (1.8 g), 10% Pd/C catalyst (0.5 g), and absolute ethanol was hydrogenated on a Paar apparatus (2 h, 50 psi, ambient temperature). Filtration, treatment of the filtrate with ethereal hydrogen chloride, and recrystallization afforded **8a** (7.0 g, 68%). Properties of **8a**, and of **8b,c,e,f** prepared in similar manner, are included in Table III.

(±)-2-Amino-α-(2-chlorophenyl)-*N*-methylbenzeneethanamine Dihydrochloride (8g). Method K. This compound was prepared from **7g** free base (20.8 g, 0.07 mol), iron powder (39 g, 0.7 g-atom, reduced electrolytic, Mallinckrodt), 95% ethanol (300 mL), water (75 mL) and concentrated hydrochloric acid (2 mL) to afford **8g** in a manner analogous to that previously described for (±)-2-amino-*N*-methyl-α-phenylbenzeneethanamine.[2] Properties of **8g**, and of **8d,h–j** prepared in similar manner, are included in Table III.

(±)-4,5-Dihydro-2,3-dimethyl-4-(4-methylphenyl)-3*H*-1,3-benzodiazepine Hydrochloride (9a). Method L. This compound was prepared from **8a** (3.0 g, 0.001 mol), triethyl orthoacetate (3.42 g, 0.057 mol), and acetic acid (3.3 mL) to afford **9a** in a manner analogous to that previously described for (±)-4,5-dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine.[2] Properties of **9a**, and of **9b–j** and **10a–j** prepared in similar manner from the corresponding free bases, are included in Table I.

β-(Dimethylamino)-α-(4-methylbenzoyl)-2-nitrostyrene (12a). Method M. A stirred mixture of *trans*-β-(dimethylamino)-2-nitrostyrene [124 g, 0.65 mol, prepared from 2-nitrotoluene (**11a**) and *N,N*-dimethylformamide diethyl acetal as described by Garcia and Fryer[3]], triethylamine (65 g, 0.65 mol), and toluene (800 mL) was treated dropwise with *p*-toluoyl chloride (100 g, 0.65 mol) at ambient temperature. The mixture was refluxed for 15 h, cooled, and treated with water to dissolve the precipitated salts. An orange solid remained and was collected by filtration. The organic phase was dried (Na_2SO_4) and concentrated to give a red oil, which crystallized on trituration with ether. The combined crops of solid were recrystallized from acetonitrile to afford **12a** (61 g, 30%). Properties of **12a**, and of **12b–h** prepared in similar manner, are included in Table II. For **12e,g**, the crude oils were chromotographed (**12e**: silica gel, EM reagents, 5% ethyl acetate in dichloromethane; **12g**: alumina, EM reagents, neutral, activity I, ethyl acetate). For **12d,f,h**, the crude products were hydrolyzed (method B) to the corresponding ketones. For the synthesis of **12f,h**, 5-chloro-2-nitrotoluene (**11b**) was prepared from 4-chloronitrobenzene as described by Traynelis and McSweeney.[6] The crude **11b** was partially purified by chromatography (alumina, ether) to afford a mixture of **11b** (60% by HPLC analysis) and 4-chloronitrobenzene, which was used without further purification for condensation with *N,N*-dimethylformamide dimethyl acetal.

Pharmacological Methods. Procedural details for the prevention of tetrabenazine-induced ptosis,[7] potentiation of 5-hydroxytryptophan-induced behavioral syndrome,[7] inhibition of pentylenetetrazol-induced lethality,[8] and prevention of amphetamine aggregation toxicity[8] were previously reported.

Acknowledgment. The authors express their appreciation to Marc N. Agnew and Anastasia Rizwaniuk for spectral data and to Mark Szewczak, James Kiley, Daniel Salomone, and Susan C. Nicolacopulos for performing pharmacological assays. We also gratefully acknowledge June D. Baird-Strupczewski and Ann Van Dine for library research and Rose Marie Boysen for assistance in preparation of the manuscript.

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