Pyrazolodiazepines. 3. 4-Aryl-1,6,7,8-tetrahydro-1,3-dialkylpyrazolo[3,4-e][1,4]diazepines as Antidepressant Agents

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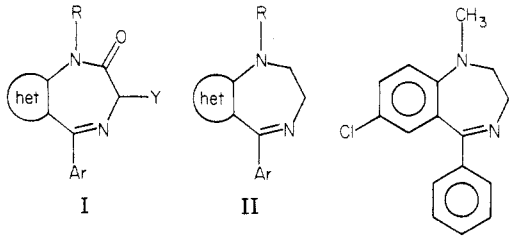
A series of 4-aryl-1,6,7,8-tetrahydro-1,3-dialkylpyrazolo[3,4-e][1,4]diazepines was prepared. The principal pharmacological property of these diazepines is the potentiation of certain behavior responses to methamphetamine in several animal models. One compound (3, zometapine) is being studied in the clinic as an antidepressant.

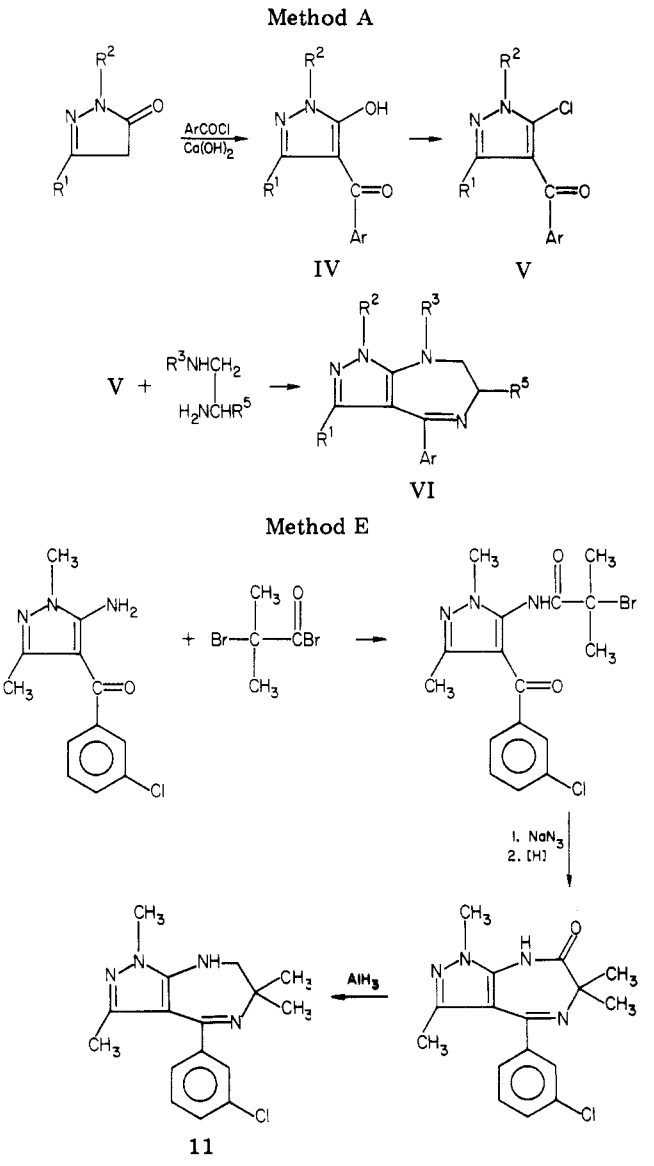
Previous publications[1] from this laboratory have described compounds (I), related to the benzodiazepines, in



I II III

which the fused benzo ring has been replaced by pyrazolo and thieno. It was found that some of these compounds were potential tranquilizing agents comparable to Valium and Librium. These series showed the same general SAR pattern that had been seen with the benzodiazepinones. In summary, *N*-oxides and hydroxyl derivatives (I, Y = OH) were active; activity was retained when R was a small alkyl group, and activity was particularly sensitive to position substitution when Ar was phenyl. Thus, activity was markedly enhanced when Ar was *o*-chlorophenyl or *o*-fluorophenyl and greatly diminished when Ar was substituted in the para position. In view of this overall SAR identity with the benzodiazepinones, it was somewhat surprising to discover early in our work that the pyrazolodiazepines and thienodiazepines (II) were inactive as antianxiety or anticonvulsant agents, surprising since the corresponding benzodiazepines, exemplified by the marketed agent medazepam (III), exhibit all of the characteristic depressant, anxiolytic, and anticonvulsant properties of the benzodiazepinones. Although the inactivity of these heterodiazepines (II) discouraged extensive investigation of this type as antianxiety agents, it was observed at that time that these pyrazolodiazepines had a much different CNS profile from the pyrazolo (and thieno) diazepinones in mice. Whereas the heterodiazepinones were typical depressants as seen by a reduction of spontaneous motor activity, loss of righting and grasping reflexes, ataxia, and ptosis, with minimal acute toxicity, the CNS pattern of the heterodiazepines was characterized by increased toxicity, tremors, preconvulsiveness, and convulsions, a profile resembling that of antidepressants. At this time a number of new behavioral screens for potential antidepressant activity that were not necessarily reflections of biogenic amine uptake were being explored in these laboratories. Drug potentiation of the anorectic effects of methamphetamine in milk drinking (rats) became a standard primary screen (ME) for antidepressant activity in this laboratory, and the series VI was developed chemically as shown in Scheme I. A significant number of these new pyrazolodiazepines showed stronger effects than imipramine in this screen.

Scheme I



IV V VI 11

Chemistry. These diazepines were obtained readily in moderate to good yield from the reaction of (1,3-dialkyl-5-chloro-1*H*-pyrazol-4-yl)arylmethanones (V) with 1,2-diamines. Nucleophilic displacement of chlorine in V with NH_4OH and alkylamines has been reported earlier.[2] The reaction of V with alkylenediamines proceeds with greater facility by merely refluxing with excess diamine. In ad-

(1) (a) H. A. DeWald, I. C. Nordin, Y. J. L'Italien, and R. F. Parcell, *J. Med. Chem.*, **16**, 1346 (1973); (b) F. J. Tinney, J. P. Sanchez, and J. A. Nogas, *ibid.*, **17**, 624 (1974); (c) H. A. DeWald, S. Lobbestael, and D. E. Butler, *ibid.*, **20**, 1562 (1977).

(2) H. A. DeWald and D. E. Butler, U.S. Patent 3 660 425 (1972).

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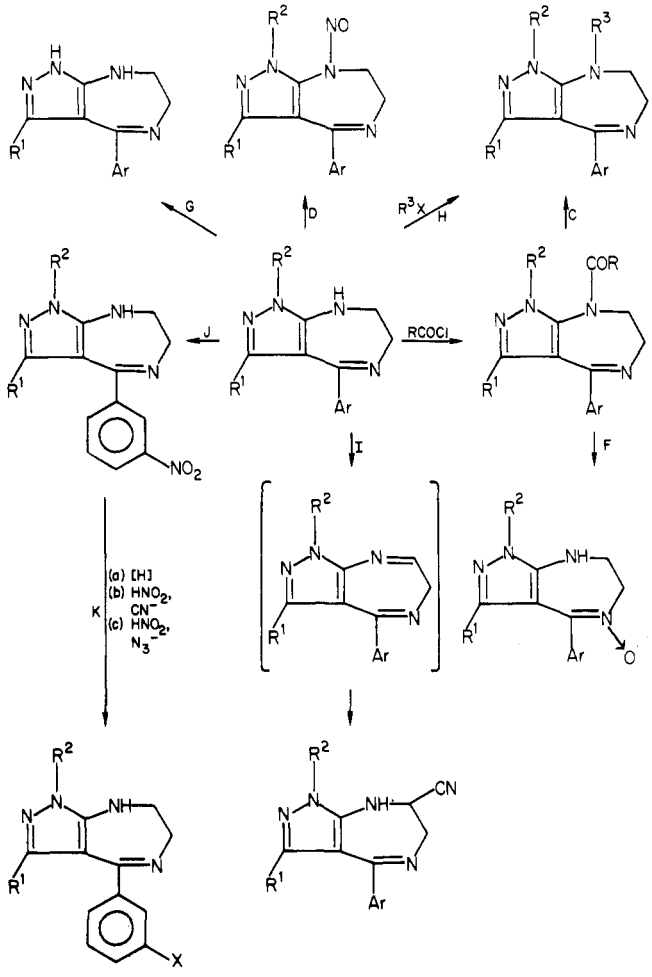
Scheme II



a, X = NH_2
b, X = CN
c, X = N_3

dition to the methods described previously[3] for the preparation of chloro ketones V, these versatile intermediates were obtained also by C-acylation of 1,3-dialkylpyrazolones with aroyl chlorides in the presence of $Ca(OH)_2$ to yield (1,3-dialkyl-5-hydroxy-1*H*-pyrazol-4-yl)arylmethanones IV.[4] Treatment of IV with phosphorus oxychloride or phenylphosphonic dichloride gave V. The reaction of chloro ketone V with unsymmetrical diamines proceeded as shown in reaction A. A similar preference, where the sterically less hindered amine becomes attached to the aromatic nucleus, was observed[5] in the reaction of 2-chlorobenzophenones with diamines. The unequivocal synthesis of one compound, **11** (method E), and NMR supported this mode of reaction with chloropyrazoles. In these substituted compounds (VI, R^5 = alkyl), the NH appeared as a triplet split by the adjacent methylene group when spectra were obtained in Me_2SO.

The pyrazolodiazepines VI were alkylated, acylated, nitrosated, nitrated, oxidized, and dealkylated (methods B–D and F–K) as illustrated in Scheme II.

Pharmacology. In mice, the CNS profile of the pyrazolodiazepines differed markedly from the typical depressant profile of the pyrazolodiazepinones. The predominant CNS indications of the pyrazolodiazepines were those of tremors, convulsions, and an increased acute toxicity. Novel behavioral screens were employed to measure potential antidepressant activity. Contrary to the prevailing opinion in the early 1970s, we adopted an earlier concept of Sigg[6] and attempted to devise a behavioral screen that might reflect the concept of adrenergic sensitization, rather than amine uptake, as an important feature of antidepressant drug action. The screen (ME) was based on these observations: small doses of methamphetamine slightly reduced milk drinking in fasted rats, standard antidepressant drugs potentiated this effect, and the effect could be measured easily by employing graduated drinking tubes. Finally, this potentiating effect by an antidepressant was increased if a longer period for drug absorption was permitted. This differential potentiation, with time, was the basis for describing antidepressant activity. Potentiation by antidepressants of the anorectic effect of methamphetamine on milk drinking had been described earlier,[7] but this test described only acute effects. By the present test method, imipramine has an MED of 2.5 mg/kg (Table I).

Table I. Milliliters of Milk Ingested (per 100 g of Body Weight) under Various Doses of Antidepressant Drugs after the 15- and 120-min Methamphetamine Challenges[a] (ME)

compd	dose, mg/kg	amount of milk ingested, mL: 15-min methamphetamine challenge	amount of milk ingested, mL: 120-min methamphetamine challenge	rating
zometapine	10	0.0	0.1	A
	5	0.1	0.1	A
	2.5	0.0	0.2	A
	1.25	1.7	0.2	A
	0.625	1.1	0.5	A
	0.312	4.2	3.6	N
imipramine	10	0.0	0.0	A
	5	0.5	0.1	A
	2.5	3.3	2.2	A
	1.25	2.7	4.8	N
	0.625	4.0	3.3	N

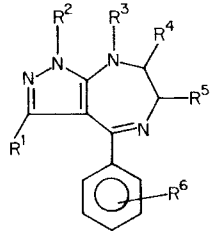
[a] The corresponding mean milk ingestion values under the two control conditions were as follows: placebo–placebo = 5.4 mL; placebo–methamphetamine = 4.2 mL.

A variety of the pyrazolodiazepines showed activity at 2.5 mg/kg (Table II). The diazepines with a meta substituent in the phenyl ring (compounds **3**, **4**, **6**, **7**, **10**, and **25–27**) represent compounds superior to imipramine. Small alkyl groups on the diazepine ring nitrogen (R^3, position 8) gave active compounds (**12**, **17**, **19**, **22**, and **49**). However, when R^3 was dialkylaminoalkyl (**8**, **9**, **15**, **20**, **30**, **32**, **34**, and **47**) or acyl (**5**), the compounds were at best weakly active. Alkyl substitution at position 6 (R^5) led to compounds with moderate to good activity (**10**, **11**, and **16**). One example of a 5-*N*-oxide (compound **13**) was inactive.

Selected compounds were tested for their potentiation of methamphetamine effects on intracranial self-stimulation in the rat.[8] This test is based on the method of Stein and Seifter[9] who reported that imipramine augmented and prolonged methamphetamine-induced increases in rate of self-stimulation of rats working for rewarding intracranial stimulation. This test method was modified so that the

(3) D. E. Butler and H. A. DeWald, *J. Org. Chem.*, **36**, 2545 (1971).
(4) (a) H. A. DeWald and Y. J. L'Italien, U.S. Patent 3 873 565 (1975); (b) T. Konotsune, U.S. Patent, 4 063 925 (1977).
(5) L. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, **28**, 3013 (1963).
(6) E. B. Sigg, *Can. Psychiatr. Assoc. J.*, **4**, 78 (1959).
(7) M. I. Gluckman, *Psychopharmacology*, **15**, 169 (1969).
(8) B. P. H. Poschel and F. Ninteman, *Life Sci.*, **7**, 317 (1968).
(9) L. Stein and J. Seifter, *Science*, **134**, 286 (1961).

Table II



no.	R^1	R^2	R^3	R^4	R^5	R^6	method	mp, °C	recrystn solvent[a]	yield, %	formula[b]	potentiation of methamphetamine MED,[m] mg/kg	potentiation of methamphetamine SS,[n] mg/kg
1	CH_3	CH_3	H	H	H	H	A	300	I	40	$C_{14}H_{16}N_4 \cdot HCl$	2.5	
2	CH_3	CH_3	CH_3	H	H	H	A	260	I	42	$C_{15}H_{18}N_4 \cdot HCl$	2.5	>10
3	CH_3	CH_3	H	H	H	3-Cl	A	186–188	II	50–70	$C_{14}H_{15}ClN_4$	0.63	1.25
4	CH_3	CH_3	CH_3	H	H	3-Cl	A	170–172	I	30	$C_{15}H_{17}ClN_4 \cdot 2HCl$	0.63	
5	CH_3	CH_3	$COCH_3$	H	H	3-Cl	B	267–268	I	85	$C_{16}H_{17}ClN_4O \cdot HCl$[c]	>10	
6	CH_3	CH_3	C_2H_5	H	H	3-Cl	C	175	I	12	$C_{16}H_{19}ClN_4 \cdot 2HCl$[d]	0.63	
7	CH_3	CH_3	NO	H	H	3-Cl	D	118–120	III	28	$C_{14}H_{14}ClN_5O$	1.25	
8	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	H	H	3-Cl	H	75–77	IV	20	$C_{19}H_{26}ClN_5$	>10	
9	CH_3	CH_3		H	H	3-Cl	H	265	I	69	$C_{20}H_{26}ClN_5 \cdot 2HCl$	>10	
10	CH_3	CH_3	H	H	CH_3	3-Cl	A	96–98	III	37	$C_{15}H_{17}ClN_4$[e]	0.63	
11	CH_3	CH_3	H	H	$(CH_3)_2$	3-Cl	E	155–157	III	57	$C_{16}H_{19}ClN_4$	2.5	10
12	CH_3	CH_3	$(CH_2)_2(CH_2)_2$		H	3-Cl	A	183 (0.15 mm)		25	$C_{18}H_{21}ClN_4$	2.5	
13	CH_3	CH_3	H	H	H	3-Cl(NO)	F	225–228	I	65	$C_{14}H_{15}ClN_4O$[g]	>10	
14	CH_3	H	H	H	H	3-Cl	G	200–203	II	40	$C_{13}H_{13}ClN_4$	2.5	
15	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	H	H	H	H	79–81	III	35	$C_{19}H_{27}N_5$	>10	
16	CH_3	CH_3	H	CH_3	CH_3	H	A	101–102	V	35	$C_{16}H_{20}N_4 \cdot 0.5\ H_2O$	10	
17	CH_3	CH_3	$(CH_2)_2(CH_2)_2$		H	H	A	148–150 (0.15 mm)		45	$C_{18}H_{22}N_4$	5	
18	CH_3	CH_3	H	H	H	2-Cl	A	209–212	VI	40	$C_{14}H_{15}ClN_4$	2.5	
19	CH_3	CH_3	CH_3	H	H	2-Cl	A	255	I	35	$C_{15}H_{17}ClN_4 \cdot 2HCl$[h]	2.5	
20	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	H	H	2-Cl	H	50–53	IV	44	$C_{19}H_{26}ClN_5$	>10	
21	CH_3	CH_3	H	CN	H	2-Cl	I	140–142	II	72	$C_{15}H_{14}ClN_5 \cdot H_2O$	>10	
22	CH_3	C_2H_5	CH_3	H	H	2-Cl	A	274–275	I	30	$C_{16}H_{19}ClN_4 \cdot HCl$	5	>10
23	CH_3	CH_3	H	H	H	$2\text{-}CH_3$, 3-Cl	A	204–206	V	64	$C_{15}H_{17}ClN_4$	1.25	5
24	CH_3	CH_3	H	H	H	$3,4\text{-}Cl_2$	A	150	I	52	$C_{14}H_{14}Cl_{12}N_4 \cdot HCl \cdot 0.5H_2O$	2.5	
25	CH_3	CH_3	H	H	H	$3\text{-}CF_3$	A	95–98	III	22	$C_{14}H_{14}Cl_2N_4 \cdot HCl$	0.63	1.25
26	CH_3	C_2H_5	H	H	H	$3\text{-}CF_3$	A	184–185	II	40	$C_{16}H_{17}F_3N_4$	0.63	
27	CH_3	CH_3	H	H	H	3-Br	A	153–155	V	62	$C_{14}H_{15}BrN_4$	0.63	5
28	C_2H_5	CH_3	H	H	H	3-Br	A	289–291	I	50	$C_{15}H_{17}BrN_4 \cdot HCl$	1.25	5
29	CH_3	CH_3	H	H	H	3-F	A	114–116	V	37	$C_{14}H_{15}FN_4 \cdot H_2O$	2.5	2.5
30	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	H	H	3-F	H	80–82	IV	30	$C_{19}H_{26}FN_5$[i]	>10	
31	C_2H_5	CH_3	H	H	H	3-F	A	143–145	III	52	$C_{15}H_{17}FN_4$[i]	2.5	
32	C_2H_5	CH_3	$(CH_2)_3N(CH_3)_2$	H	H	3-F	H	73–75	IV	55	$C_{20}H_{28}FN_5 \cdot 0.5H_2O$	>10	
33	CH_3	CH_3	H	H	H	$3\text{-}CH_3$	A	244–246	I	78	$C_{15}H_{18}N_4 \cdot HCl$	2.5	10
34	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	H	H	$3\text{-}CH_3$	H	120–124	IV	65	$C_{20}H_{29}N_5$[j]	>10	

35	C_2H_5	CH_3	H	H	H	3-CH_3	A	177–180	II	41	$C_{16}H_{20}N_4$·oxalate	5	
36	CH_3	CH_3	H	H	$(CH_3)_2$	3-CH_3	A	128–130	III	20	$C_{17}H_{22}N_4$·0.5 H_2O	>10	
37	CH_3	CH_3	H	H	H	3,5-$(CH_3)_2$	A	221–223	III	35	$C_{16}H_{20}N_4$	>10	
38	CH_3	CH_3	H	H	H	2,5-$(CH_3)_2$	A	197–200	I	17	$C_{16}H_{20}N_4$·HCl[k]	>10	
39	CH_3	CH_3	H	H	H	3-OH	A	115–118	I	26	$C_{15}H_{18}N_4O$·2HCl·$(CH_3)_2CHOH$	2.5	10
40	CH_3	CH_3	H	H	H	3,5-$(OCH_3)_2$	A	145–147	III	11	$C_{16}H_{20}N_4O_2$	2.5	10
41	CH_3	CH_3	H	H	H	3-NO_2	J	242–245	I	41	$C_{14}H_{15}N_5O_2$·HCl	5	
42	CH_3	CH_3	H	H	H	3-NH_2	K	296	I	89	$C_{14}H_{17}N_5$·2HCl	2.5	
43	CH_3	CH_3	H	H	H	3-CN	L	183–185	V	25	$C_{15}H_{15}N_5$[l]	1.25	
44	CH_3	CH_3	H	H	H	3-N_3	L	129–131	V	38	$C_{14}H_{15}N_7$[l]	2.5	
45	CH_3	CH_3	H	H	H	4-Cl	A	184–186	III	53	$C_{14}H_{15}ClN_4$	2.5	
46	CH_3	CH_3	H	H	H	4-CH_3	A	227–229	III	51	$C_{15}H_{18}N_4$	2.5	
47	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	H	H	4-CH_3	H	99–101	IV	35	$C_{20}H_{29}N_5$	>10	
48	CH_3	CH_3	H	H	H	4-OCH_3	A	198–200	III	57	$C_{15}H_{18}N_4O$	>10	
49	CH_3	CH_3	CH_3	H	H	4-OH	A	195–197	I	36	$C_{15}H_{18}N_4O$·2HCl·H_2O	2.5	5–10
imipramine												2.5	1.25

[a] Recrystallization solvents: I, 2-PrOH·HCl; II, CH_3CN; III, EtOAc–petroleum ether; IV, petroleum ether, V, acetone; VI, toluene. [b] Analytical results within ±0.4%, except where indicated. [c] N: calcd, 15.86; found, 15.24. [d] C: calcd, 51.14; found, 50.46. [e] N: calcd, 19.39; found 18.42. [f] The requisite diamine, 2-(aminomethyl)piperidine was prepared by hydrogenating 2-picolylamine. [g] C: calcd, 57.82; found, 56.75. [h] N: calcd, 15.49; found, 16.05. [i] N: calcd, 20.57; found, 19.91. [j] C: calcd, 70.75; found, 69.47. [k] N: calcd, 18.38; found, 19.09. [l] N: calcd, 35.10; found, 34.45. [m] MED = the lowest active dose which met these criteria. The mean amount of milk ingested after the 15-min challenge had to be less than 3.5 mL, and a greater anorectic effect had to be evidenced after the 120 min challenge; unless the milk ingestion was 1.0 mL or less after both 15 and 120 min, then the dose was automatically rated "active". Milk ingestion was the mean from a minimum of eight animals at a minimum of three dose levels, with a control group of eight animals. [n] Lowest dose tested and found to be active; that is, chronic administration of the drug produced a greater potentiation of the rate of self-stimulation than the acute test. Activity had to be shown in three out of five animals.

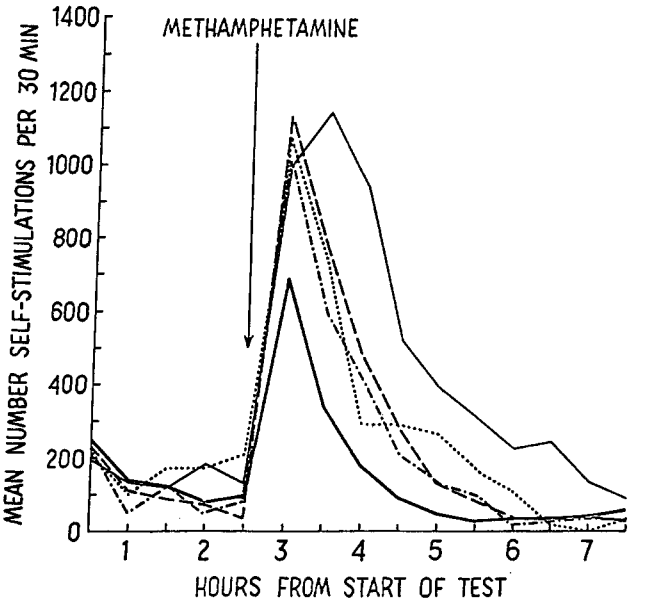


Figure 1. Self-stimulation–methamphetamine potentiation. Effects of a 0.25 mg/kg intraperitoneal dose of methamphetamine on self-stimulation responses made per hour by rats receiving a 1.25 mg/kg oral dose of zometapine or imipramine on an acute or subacute basis. The control condition shows the effect of the methamphetamine treatment acting alone, i.e., after placebo. Zometapine: acute (···), subacute (—). Imipramine: acute (-•-), subacute (---). Control (—).

self-stimulation electrodes were stereotaxically aimed at the medial forebrain bundle, and testing was directed at the effects of prolonged administration. Figure 1 shows the results obtained at 1.25 mg/kg of compound **3** and 1.25 mg/kg of imipramine. Compound **3** shows the stronger potentiating action of the two drugs, especially under the chronic dosing conditions.

Compound **3** was chosen for additional pharmacological studies. A detailed report of these pharmacological studies is in press.[10] Compound **3** is presently in phase II clinical studies.[11]

Experimental Section

Melting points taken in a capillary tube are uncorrected. The structures of the compounds were supported by IR, UV, and NMR spectra determined by the Parke-Davis physical chemistry staff. The analytical results (Parke-Davis staff) were within ±0.4% of the theoretical values if not otherwise stated. Compounds **12**, **17**, and **22** were prepared by Dr. D. Butler, and compounds **1**, **16**, **25**, and **26** were prepared by Y. L'Italien.

Method A. 4-(3-Chlorophenyl)-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine (3). A mixture of 195 g (0.78 mol) of (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)(3-chlorophenyl)methanone[3] and 450 mL of 1,2-ethanediamine was stirred and heated under reflux (~120 °C) for 20 h. The condenser was set for downward distillation, and 280 mL of diamine was distilled from the mixture. The residue was poured into 3 L of 0.35 N NaOH to precipitate a viscous oil. The oil was separated by decantation, dissolved in 1 L of CH_2Cl_2, washed twice with brine, dried, and evaporated. The oil was partitioned in excess 3 N HCl and 400 mL of ethyl acetate. The separated aqueous phase was made strongly basic with concentrated NaOH and extracted into CH_2Cl_2. The extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was crystallized from 350 mL of acetonitrile to give 105 g (50%) of **3**, mp 180–185 °C.

(10) B. P. H. Poschel, F. Ninteman, and M. Smith, *Drugs Exp. Clin. Res.*, in press.
(11) (a) V. Teason, M. Garvey, L. Goodman, and L. Borgen, *Curr. Ther. Res.*, **27**, 94 (1980); (b) N. James, J. Searle, L. Goodman, and L. Borgen, *ibid.*, 100 (1980).

A solution of 5.4 g (0.01 mol) of **3** in 12 mL of 2-propanol was treated with 5 mL of 20% 2-propanolic HCl and then 90 mL of tetrahydrofuran to give 6 g (mp 279–281 °C) of the hydrochloride salt.

Alternate Preparation of IV via (1,3-Dimethyl-5-hydroxy-1*H*-pyrazol-4-yl)(3-chlorophenyl)methanone. A suspension of 112 g (1.0 mol) of 1,3-dimethyl-1*H*-pyrazol-5-one and 148 g (2.0 mol) of $Ca(OH)_2$ powder in 700 mL of dioxane was stirred vigorously and treated with 175 g (1.0 mol) of 3-chlorobenzoyl chloride. The addition in a slow stream required ~15 min as the reaction temperature rose to 78 °C. The mixture was stirred and heated under reflux for another 1.5 h and then poured into 2.5 L of ice-cold 1.2 N HCl. A transient solution resulted and then a new solid precipitated. The mixture was filtered after 1 h, and the product was washed with water. The crude product was recrystallized from methanol: yield 170 g (68%); mp 165–167 °C.

A mixture of 115 g (0.46 mol) of this compound (VI, $R^1 = R^2 = CH_3$; Ar = 3-ClC_6H_4) and 153 g (1.0 mol) of $POCl_3$ was stirred under reflux for 6 h and then added slowly with stirring and cooling at 10–20 °C to a mixture of 500 mL of CH_2Cl_2, 400 g of ice, and 350 mL of concentrated NH_4OH. The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated. The oil was crystallized from hexane to give 100 g (81%), mp 83–85 °C, of compound IV ($R^1 = R^2 = CH_3$; Ar = 3-ClC_6H_4).

Method A. 4-(3-Chlorophenyl)-1,6,7,8-tetrahydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepine Dihydrochloride (4). A mixture of 7 g (0.026 mol) of (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)(3-chlorophenyl)methanone and 15 mL of *N*-methylethanediamine was stirred under reflux for 16 h and evaporated in vacuo. The residue was partitioned in 100 mL of 1 N HCl and 100 mL of ethyl acetate. The aqueous portion was made strongly basic with concentrated NaOH and extracted with CH_2Cl_2 to give 5 g of red oil. The oil was dissolved in 50 mL of acetone and treated with 2-propanolic HCl to give 2.7 g (30%) of **4** as the dihydrochloride salt, mp 170 °C dec.

Method B. 8-Acetyl-4-(3-chlorophenyl)-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine (5). A solution of 10 g (0.04 mol) of compound **3** in 100 mL of CH_2Cl_2 was treated with 5 mL of acetic anhydride and allowed to stand at 20 °C for 16 h. The solution was evaporated, and the residue was redissolved in CH_2Cl_2, washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The oil was dissolved in acetone and treated with 2-propanolic HCl to yield the hydrochloride salt: yield 12 g (85%); mp 248–255 °C. The analytical sample from 2-propanol melted at 267–268 °C.

Method C. 4-(3-Chlorophenyl)-8-ethyl-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine (6). Aluminum hydride was generated in situ by the addition of a solution of 3.9 g (0.03 mol) of aluminum chloride in 80 mL of ether to a stirred suspension of 3.6 g (0.09 mol) lithium aluminum hydride in 150 mL of tetrahydrofuran and 75 mL of ether at 10 °C. The resulting suspension was stirred at 10 °C for 15 min, and a solution of 11 g (0.035 mol) of compound **5** as the free base in 40 mL of tetrahydrofuran was added dropwise. After the mixture was stirred at 15–25 °C for 1.5 h, it was decomposed by the slow addition of 9 mL of H_2O, 9 mL of 20% NaOH, and then 14 mL of water. The aluminum salts were removed by filtration. Evaporation of the filtrate left 10 g of colorless oil. The oil was dissolved in 2-propanolic HCl and diluted slowly with ethyl acetate to yield 8.5 g (mp 170 °C) of slightly crude 4-(3-chlorophenyl)-8-ethyl-1,4,5,6,7,8-hexahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine dihydrochloride. Anal. ($C_{16}H_{21}ClN_4 \cdot 2HCl \cdot 0.5H_2O$) C, H, Cl, N. NMR spectra in D_2O showed a single benzylic H.

This hexahydro compound (4.5 g, 0.011 mol) as the free base was added to a mixture of 19 g of manganese dioxide in 150 mL of benzene and stirred under reflux for 16 h. The mixture was filtered and evaporated in vacuo. The product **6** was isolated in low yield (12%) as the dihydrochloride salt from 2-propanolic HCl and tetrahydrofuran, mp 175 °C dec.

Method D. 4-(3-Chlorophenyl)-1,6,7,8-tetrahydro-1,3-dimethyl-8-nitrosopyrazolo[3,4-*e*][1,4]diazepine (7). A solution of 5.5 g (0.02 mol) of compound **3** in 50 mL of glacial acetic acid was treated in portions with 2 g of sodium nitrite. After stirring at room temperature for 1 h, the solution was evaporated in vacuo. The residual oil was dissolved in CH_2Cl_2 and stirred with excess $NaHCO_3$ solution. The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was crystallized from ethyl acetate–petroleum ether (bp 35–60 °C) to give 1.7 g (28%) of **7**, mp 118–120 °C.

Method E. 4-(3-Chlorophenyl)-1,6,7,8-tetrahydro-1,3,6,6-tetramethylpyrazolo[3,4-*e*][1,4]diazepine (11). Aluminum hydride was prepared in situ by the addition of 1.3 g (0.01 mol) of aluminum chloride in 30 mL of ether to a stirred suspension of 1.2 g (0.03 mol) of lithium aluminum hydride in 75 mL of tetrahydrofuran and 30 mL of ether at 10–15 °C.

4-(3-Chlorophenyl)-1,3,6,6-tetramethyl-6,8-dihydropyrazolo-[3,4-*e*][1,4]diazepin-7(1*H*)-one (3.3 g, 0.01 mol) was added, and the mixture was stirred under reflux for 2.5 h. The mixture was cooled and decomposed by the addition of 3 mL of H_2O, 3 mL of 20% NaOH, and 5 mL of H_2O. The mixture was filtered and the filtrate was evaporated to give an oil, which was crystallized from ether–petroleum ether (bp 35–60 °C): yield 2 g (57%); mp 152–155 °C. This product was identical with that product from the reaction of chloro ketone IV ($R^1 = R^2 = CH_3$) with 2-methyl-1,2-propanediamine. The N*H* appeared as a triplet at δ 7 in Me_2SO with reference to $(CH_3)_4Si$.

4-(3-Chlorophenyl)-1,3,6,6-tetramethyl-6,8-dihydropyrazolo-[3,4-*e*][1,4]diazepin-7(1*H*)-one was prepared by method E (Scheme I) previously described.[1c] Ammonolysis of (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)(3-chlorophenyl)methanone[2] gave (5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(3-chlorophenyl)methanone (mp 101–103 °C) from ether. Acylation with 2-bromo-2-methylpropanoyl bromide in dichloroethane at reflux temperature afforded 2-bromo-*N*-[4-(3-chlorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]-2-methylpropanamide, mp 104–106 °C, from ether. Nucleophilic displacement with NaN_3 in DMF at 40 °C gave 2-azido-*N*-[4-(3-chlorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]-2-methylpropanamide, mp 133-135 °C, from ether. Hydrogenation of the azide in glacial acetic acid in the presence of 5% Pd/C catalyst led to the cyclized diazepinone, mp 210 °C, from acetone. Anal. ($C_{16}H_{17}ClN_4O$) C, H, N.

Method F. 4-(3-Chlorophenyl)-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine 5-Oxide (13). A solution of 6.5 g (0.024 mol) of compound **3** in 75 mL of CH_2Cl_2 was treated at room temperature with 5 mL of trifluoroacetic anhydride. After 5 h, the solution was stirred with excess saturated $NaHCO_3$ solution. The organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The oil was crystallized from petroleum ether (bp 35–60 °C) to give 4-(3-chlorophenyl)-8-(trifluoroacetyl)-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*]-[1,4]diazepine, mp 183–185 °C. Anal. ($C_{16}H_{14}F_3ClN_4O$) C, H, N.

A solution of the 8-(trifluoroacetyl) derivative (8.4 g, 0.022 mol) in 250 mL of $CHCl_3$ was cooled to 10 °C and 5 g (0.03 mol) of 3-chloroperbenzoic acid was added. After standing overnight, the solution was washed with excess $NaHCO_3$ solution and dried over $MgSO_4$, and the solvent was evaporated. The oil was dissolved in acetone and treated with 2.2 g of oxalic acid dihydrate. Dilution with ethyl acetate gave 5.5 g of oxalate salt. The salt (3.5 g) was dissolved in 20 mL of water and the solution was made basic with concentrated NH_4OH to precipitate 2.75 g (mp 225–228 °C) of compound **13** after recrystallization from 2-propanol–ether.

Method G. 4-(3-Chlorophenyl)-1,6,7,8-tetrahydro-3-methylpyrazolo[3,4-*e*][1,4]diazepine (14). Compound **3** (17 g, 0.062 mol) was added to pyridine hydrochloride (prepared by mixing 85 g of pyridine and 100 mL of concentrated HCl and distilling to a pot temperature of 220 °C). The reaction mixture was stirred under reflux for 6 h and poured into 800 mL of water. The mixture was made basic with concentrated NH_4OH and extracted with CH_2Cl_2. The organic extract was dried and evaporated. The residue was crystallized from 250 mL of acetonitrile to give 6 g (40%), mp 200–203 °C.

Method H. 1,3-Dimethyl-8-[(dimethylamino)propyl]-1,6,7,8-tetrahydro-4-phenylpyrazolo[3,4-*e*][1,4]diazepine (15). A solution of 17 g (0.07 mol) of compound **1** and 24 g (0.2 mol) 3-chloro-*N*,*N*-dimethyl-1-propanamine in 150 mL of DMF was stirred under N_2 and treated portionwise with 4 g (0.08 mol) of NaH (50% dispersion in oil). The mixture was stirred at 60 °C for 16 h and evaporated in vacuo. The residue was partitioned in 300 mL of 2 N HCl and 150 mL of ethyl acetate. The aqueous

layer was made strongly basic with 50% NaOH solution and extracted with CH_2Cl_2. The organic extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was crystallized from ether–petroleum ether (bp 35–60 °C) to give 7.7 g (35%), mp 79–81 °C.

Method I. 4-(2-Chlorophenyl)-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine-7-carbonitrile (21). Manganese dioxide (General Metallic Oxides) (100 g) was dried by refluxing for 1 h in 1 L of benzene in a flask fitted with a water separator. Compound 18 (10 g) was added, the mixture was stirred under reflux 5 h and then filtered using filter cel, and the filtrate was evaporated. The yellow oil was crystallized from ether to give 6.3 g (mp 105–107 °C) of 4-(2-chlorophenyl)-1,6-dihydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine. A similar oxidation of benzodiazepines was described by Coffen et al.[12]

A solution of 10 g (0.037 mol) of the above diazepine in 50 mL of tetrahydrofuran was cooled in an ice bath and treated simultaneously with a solution of 8 g of KCN in 18 mL of water and 10 mL of acetic acid in 30 mL of methanol. The mixture was stirred for 1 h and concentrated in vacuo. The residue was diluted with CH_2Cl_2 and stirred with excess dilute NH_4OH. The organic layer was separated, washed with saturated $NaHCO_3$ solution, dried ($MgSo_4$), and evaporated. The oil was crystallized from ether to give 8 g of **21** (mp 130–135 °C) and recrystallized from acetonitrile–ether, mp 139–142 °C.

Method J. 4-(3-Nitrophenyl)-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine (41). A solution of 6 g of potassium nitrate in 25 mL of concentrated H_2SO_4 was added dropwise at 10 °C to a solution of 12 g (0.05 mol) of compound 1 in 50 mL of concentrated H_2SO_4. The solution was stirred at 10 °C for 1 h and at room temperature for 3 h and then poured onto 500 g of ice. The mixture was made basic at 10 °C with concentrated NH_4OH and filtered. The wet filter cake was dissolved in ethyl acetate, dried ($MgSO_4$), and evaporated to give 8 g (59%). The solid, dissolved in tetrahydrofuran, was treated with 2-propanolic HCl to give 6.8 g of **41** as the hydrochloride salt, mp 292–295 °C.

Method K. 3-(1,6,7,8-Tetrahydro-1,3-dimethylpyrazolo-[3,4-*e*][1,4]diazepin-4-yl)benzenamine Dihydrochloride (42). Compound 41 (5.5 g) was dissolved in water, treated with excess NH_4OH, and extracted with CH_2Cl_2 to yield 4.7 g (0.017 mol) of the free base. This was hydrogenated in 100 mL of methanol in the presence of 0.5 g of Raney Ni catalyst at 50 psi at room temperature. The mixture was filtered from the catalyst and the solvent was evaporated. The residue was dissolved in 40 mL of tetrahydrofuran and treated with 2-propanolic HCl and ether to give 5 g of 4 as the dihydrochloride salt, mp 296 °C dec.

Method L. 3-(1,6,7,8-Tetrahydro-1,3-dimethylpyrazolo-[3,4-*e*][1,4]diazepin-4-yl)benzonitrile (43). A solution of 5 g (0.015 mol) of compound **42** in 60 mL of 0.3 N HCl was cooled to 0 °C and a solution of 1.1 g (0.016 mol) of sodium nitrite in 4 mL of water was added dropwise. After the mixture was stirred at 10 °C for 10 min, a cyanide solution (prepared by adding 5 g of potassium cyanide to a suspension of 4.5 g of cuprous cyanide in 15 mL of water containing 2.5 g of potassium carbonate) was added. The mixture was stirred at room temperature for 1 h and extracted with CH_2Cl_2. The extracts were evaporated and the residue was crystallized from acetone to yield 1.1 g (25%), mp 183–185 °C.

Method M. 4-(3-Azidophenyl)-1,6,7,8-tetrahydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]diazepine (44). A solution of 5 g (0.015 mol) of compound **42** in 120 mL of 0.2 N HCl was cooled to 0 °C and a solution of 1.1 g (0.016 mol) of sodium nitrite in 3 mL of water was added dropwise. After the mixture stirred for another 10 min at 10 °C, a solution of 1.1 g (0.016 mol) of sodium azide in 3 mL of water was added. The mixture was stirred for 1.5 h at 5–10 °C, made alkaline with sodium hydroxide, and extracted with CH_2Cl_2. The solvent was evaporated and the residue was crystallized from acetone–ether to yield 1.6 g (38%), mp 129–131 °C.

Pharmacology Methods. Time-Related Potentiation of Methamphetamine-Induced Anorexia (ME). Male Holtzman rats were deprived of food and water for 20 h prior to the test. At the test time they were dosed intraperitoneally with the test compound, with separate groups of eight rats each receiving a dose of 10, 5, or 2.5 mg/kg (base). Immediately following dosing, the rats were placed into individual metabolism cages without food or water for a waiting period; for half of the rats at each dose level the waiting period was 15 min, and for the other half it was 2 h. After the waiting period, all the rats were given an intraperitoneal injection of 0.75 mg/kg of methamphetamine (base) and then, 20 min later, were allowed access to a milk preparation in a graduated and calibrated tube. The preparation consisted of one part sweetened condensed milk and two parts deionized water. Total milk ingestion of each animal after 30 min, 1 h, 90 min, and 2 h was recorded and compared with that of control animals that were dosed only with methamphetamine. The total amount ingested after 2 h was considered the critical amount and was the one used to assess activity.

Rats dosed only with methamphetamine normally consumed an average of 4.2 mL of milk (per 100 g of body weight). A test compound was considered to be active if (a) at a dose of 10 mg/kg (base) or less it lead to ingestion of 3.5 mL or less in those rats dosed with methamphetamine 15 min after injection of the compound and (b) if at the same dosage it lead to an even lower injestion of milk in those animals dosed with methamphetamine after a waiting period of 2 h. One exception is granted; if milk ingestion is 1.0 mL or less after both the 15- and 120-min waiting period, the test dose is automatically rated active (Table I). By these criteria, only CNS antidepressants have shown the appropriate response.

Potentiation of Methamphetamine Effects on Intracranial Electrical Self-stimulation (SS). Five male albino rats of the Holtzman strain, weighing about 290 g, were implanted with permanent electrodes aimed at the medial forebrain bundle about 0.5 mm rostral to the mamillary bodies. A 30-gauge platinum wire with about 0.5 mm of insulation scraped off at the tip served as the monopolar stimulating electrode. A stainless-steel screw secured to the skull served as the indifferent electrode.

About 4 weeks after surgery, the animals were trained to press a lever to stimulate their brains electrically. The lever was housed in a box with an open top and metal grid floor. Each lever press delivered 60-Hz sine wave stimulation, 40 μA in intensity, and 0.4 s in duration.

After the preliminary training, the stimulating current was reduced individually for each rat to a level moderately above the self-stimulation threshold so that relatively low, but stable, rates of self-stimulation were generated. How the rats' self-stimulation rates were affected by a small intraperitoneal dose of methamphetamine hydrochloride was then determined under three conditions: (A) after placebo, (B) after a single oral dose (1.25–10 mg/kg) of test drug injected 90 min before the methamphetamine treatment, and (C) after four consecutive daily oral doses [1.25–10 (mg/kg)/day] of test drug, the last dose of test drug occurring 22 h before the methamphetamine treatment. In sum, tests were run for the base-line effect of methamphetamine (condition A), for the effect of methamphetamine after *acute* dosing with test drug (condition B), and for the effect of methamphetamine after *chronic* dosing with test drug (condition C).

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