meta isomer **12**: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H, Me_2-*t*-BuSi), 0.92 (s, 9 H, *t*-Bu), 3.57–3.87 (m, 2 H, CH_2), 3.93–4.80 (m, 1 H, CHN), 5.83 (s, 1 H, $CHCl_2$), 5.92 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 4 Hz), 6.63–7.00 (1 H, NH), 7.47–7.80 (m, 2 H, arom), 8.07–8.33 (m, 2 H, arom). For para isomer **13**: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H, Me_2-*t*-BuSi), 0.92 (s, 9 H, *t*-Bu), 3.57–3.87 (m, 2 H, CH_2), 3.93–4.80 (m, 1 H, CHN), 5.83 (s, 1 H, $CHCl_2$), 5.92 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 4 Hz), 6.63–7.00 (1 H, NH), 7.55 and 8.24 (AB q, 4 H, arom, J_{HH} = 9.0 Hz). Next, each separated compound was desilylated back to the desired products **10** and **11** by treatment with tetraethylammonium fluoride in THF and recrystallized from *i*-PrOH–hexane to afford pure samples of **10** (29 mg) and **11** (19 mg), which were characterized as follows. For the meta isomer **10**: mp 144–145 °C; IR ($CHCl_3$) 3405 (NH), 1700 (C=O), 1600 (arom), 1540 and 1350 (NO_2), 1140, 1100 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.50–4.28 (m, 2 H, CH_2), 4.40–4.70 (m, 1 H, CHN), 6.00 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 2.5 Hz), 6.13 (s, 1 H, $CHCl_2$), 7.43–8.40 (m, 4 H, arom); ^{19}F NMR (CD_3OD) δ −35.15 (J = 46, 28 Hz); mass spectrum, m/z 329, 327, and 325 (M^+ + H), 309, 307, and 307 (M^+ − F), 297, 295, and 293 (M^+ − CH_2OH), 241 (M^+ − $CHCl_2$), 174, 172, and 170 (M^+ − $C_6H_4NO_2CHF$), 60 (C_2H_6NO). Anal. Calcd for $C_{11}H_{11}O_4N_2Cl_2F$: C, 40.63; H, 3.41; N, 8.62; F, 5.84. Found: C, 40.77; H, 3.48; N, 8.58; F, 5.53. For the para isomer **11**: mp 139–140 °C; IR ($CHCl_3$) 3400 (NH), 1700 (C=O), 1600 (arom), 1520 and 1350 (NO_2), 1100 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.50–4.28 (m, 2 H, CH_2), 4.40–4.70 (m, 1 H, CHN), 6.00 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 2.5 Hz), 6.13 (s, 1 H, $CHCl_2$), 7.57 and 8.17 (AB q, 4 H, arom, J = 9.0 Hz); ^{19}F NMR (CD_3OD) δ −35.42 (J = 46 Hz, 25 Hz); mass spectrum, m/z 329, 327, and 325 (M^+ + H), 309, 307, and 305 (M^+ − F), 297, 295, and 293 (M^+ − CH_2OH), 241 (M^+ − $CHCl_2$), 174, 172, and 170 (M^+ − $C_6H_4NO_2CHF$), 60 (C_2H_6NO). Anal. Calcd for $C_{11}H_{11}O_4N_2Cl_2F$: C, 40.63; H, 3.41; N, 8.62; F, 5.82. Found: C, 40.75; H, 3.48; N, 8.42; F, 5.70.

Antimicrobial Activity. All fungal and bacterial strains used in this experiment were prepared as reported in our earlier paper.[12] Minimum inhibitory concentrations (MICs) were also determined as reported earlier.

Registry No. DL-1, 80817-88-5; (±)-**2**, 93863-23-1; (±)-**3**, 93863-24-2; DL-**4**, 79617-87-1; DL-4·CF_3SO_3H, 93863-25-3; DL-*o*-NO_2-**4**, 93863-26-4; DL-*m*-NO_2-4, 93863-27-5; DL-*p*-NO_2-**4**, 80817-88-5; DL-**6**, 79617-86-0; DL-**6**·CF_3SO_3H, 93894-94-1; DL-*o*-NO_2-**7**, 93863-28-6; DL-*m*-NO_2-**7**, 93863-29-7; DL-*p*-NO_2-**7**, 93863-30-0; (±)-*o*-NO_2-**8**, 93863-31-1; (±)-*m*-NO_2-**8**, 93863-32-2; (±)-*p*-NO_2-**8**, 93863-33-3; (±)-**9**, 93863-34-4; (±)-**10**, 93863-35-5; (±)-11, 93863-36-6; (±)-**12**, 93863-37-7; (±)-**13**, 93863-38-8; (±)-14, 93863-39-9; (±)-**15**, 93863-40-2; $(Cl_2CHC(O))_2O$, 4124-30-5.

3,4-Diphenyl-1*H*-pyrazole-1-propanamine Antidepressants

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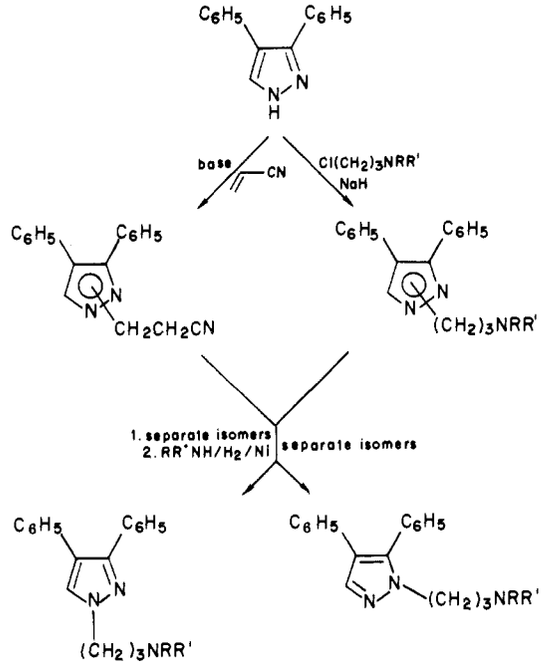
A small series of compounds is described in which a narrow SAR has identified *N,N*-dimethyl-3,4-diphenyl-1*H*-pyrazole-1-propanamine, **3**, as a potential antidepressant with reduced side effects. The isomeric *N,N*-dimethyl-4,5-diphenyl-1*H*-pyrazole-1-propanamine was completely inactive in the primary antidepressant screens. Compounds were synthesized by Michael addition of acrylonitrile to diphenylpyrazole followed by reductive alkylation of the resultant diphenylpyrazolepropionitriles. Compound **3** was equipotent with imipramine in standard antidepressant assays in animals but showed no significant anticholinergic action and did not antagonize the antihypertensive effects of clonidine and guanethidine.

Following on the heels of two decades of intensive research on tricyclic structures as antidepressants, more recent work has brought forth a myriad of compounds of diverse nature. Recent publications describe these "second generation" antidepressants and summarize a vast body of chemistry dedicated to them.[1,2] Major objectives in this new work are drugs with more rapid onset of action and a reduced number and intensity of side effects. Principally, the major targeted adverse effects are sedation and anticholinergic actions which are often encountered in the clinic and which limit outpatient acceptance.

We herein report on a small group of 3,4-diphenylpyrazoles, patterned after the classical tricyclics, whose pharmacological and toxicological profiles in animals suggest they will possess antidepressant activities with marked reductions in side-effect liability. In particular, **3**, fezolamine, was as potent as imipramine in several animal models of depression but, unlike the latter, did not exhibit anticholinergic effects nor induce CNS depression or sedation at oral dosage levels significantly above those required for antidepressant-indicating efficacy in the same animals. Further, **3** was shown to have a significantly reduced potential for producing antihistamine-like and cardiovascular effects as compared to the tricyclics and, unlike imipramine, did not interfere with the antihypertensive effects of guanethidine or clonidine.

Scheme I



Chemistry. The compounds of Table I were prepared

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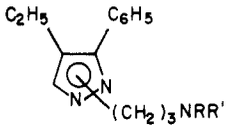
0022-2623/85/1828-0256$01.50/0

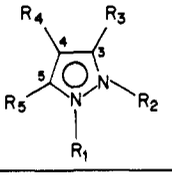
Table I. 3(5),4-Diphenyl-1*H*-pyrazole-1-propanamines



compd	R	R^1	side-chain position	salt	mp, °C	anal.[c]	minimum effective dose,[a,b] mg of base/kg po: mouse tetrabenazine test	minimum effective dose,[a,b] mg of base/kg po: mouse ptosis test
imipramine							4	4
1	H	H	1	$C_4H_4O_4$[d]	176–178	C, H, N	inac[e]	inac[e]
2	H	CH_3	1	HCl	124–132	C, H, N	16	4
3	CH_3	CH_3	1	HCl	171–172	C, H, N	4	8
3a	CH_3	CH_3	2	HCl	182–185	C, H, N	inac[e]	inac[e]
4	C_2H_5	C_2H_5	1	HCl	165–166	C, H, N	inac[e]	inac[e]
4a	C_2H_5	C_2H_5	2	HCl	148–149	C, H, N	inac[e]	inac[e]

[a] Minimum two-factor dose (max 64 mg/kg) that produced scores statistically different ($p \leq 0.05$, two-tailed Mann–Whitney U test) from controls. [b] See Experimental Section for details. [c] All analyses were within ±0.4% of calculated values for the elements shown. [d] (*E*)-2-Butenedioate. [e] At 64 mg of base/kg po, the highest dose tested.

Table II. Chemical Shift of the Three Pyrazole Carbons of Various Pyrazoles[a]



compd	R_1	R_2	R_3	R_4	R_5	pyrazole carbon chemical shift[b]: C3	m	C4	m	C5	m
pyrazole[c]	H		H	H	H	134.3		105.2		134.3	
N-methylpyrazole[c]	CH_3		H	H	H	139.2		105.7		128.7	
3(5),4-diphenyl-1*H*-pyrazole	H		C_6H_5	C_6H_5	H	143.0	s	118.8	s	133.5	d
3	$(CH_2)_3N(CH_3)_2$		C_6H_5	C_6H_5	H	147.0	s	119.2	s	130.4	d
3a		$(CH_2)_3N(CH_3)_2$	C_6H_5	C_6H_5	H	139.2	s	119.9	s	137.0	d

[a] All compounds were converted to the base; Me_2SO-d_6 was the solvent. [b] Chemical shifts in ppm relative to Me_4Si; multiplicity (m) from partial off-resonance decoupling, s = singlet, d = doublet. [c] Reference 4, 5.

as shown in Scheme I. The base-catalyzed Michael addition of acrylonitrile to diphenylpyrazole produced mixtures in which the 3,4-diphenyl isomer predominated to the extent of 85–93%. In practice it was convenient to carry the mixture of isomers through the subsequent steps prior to purification to homogeneity. Direct alkylation of 3,4-diphenylpyrazole with (dialkylamino)propyl halides gave 1:1 mixtures of isomeric products and was not useful for preparative purposes. By careful recrystallization or plate chromatography of acid addition salts or by HPLC separations on the free bases followed by salt preparation, the isomeric pairs **3**, **3a** and 4, 4a of Table I could be isolated.

These materials were examined for their ultraviolet and proton NMR characteristics. For each pair, the minor isomer showed UV absorption maxima at 233 and 249 ± 2 nm, while the major isomers showed absorption maxima at 227 ± 2 and 252 ± 1 nm. In each pair, the extinction coefficients of the 227-nm peaks were higher than those of the corresponding 233-nm peaks.

The NMR spectra of solutions of individual isomers as the free bases in hexamethylphosphoramide (HMPA) showed that, in each pair, the major isomer displayed a downfield shift of the pyrazole ring proton relative to the resonance position of the ring proton in the minor isomer. Thus in, e.g., **3** and **3a** the proton resonances fell at 8.45 and 7.85 ppm, respectively. Elguero and Jacquier[3] have shown that in highly polar solvents such as HMPA, the ring proton adjacent to the substituted nitrogen in a series of 1,4-disubstituted pyrazoles always fell downfield from the ring roton adjacent to the unsubstituted nitrogen. Applying this analogy to our pairs of isomers established **3** and 4 as having the 3,4-disubstituted pattern and **3a** and **4a** as having the 4,5-disubstituted configuration.

A further regular and predictable relationship between members of pairs was evident by examining the chemical shifts of the protons of the side-chain methylene group adjacent to N-1 of the pyrazole ring. The resonances of these methylene protons in the 3,4-isomers were always at lower field than the corresponding resonances in the 4,5-isomers.

Additional confirmation of the identities of the isomers was provided by an examination of the ^{13}C NMR spectra. Levy and Nelson[4] have shown that the rapid tautomerism of pyrazole is disrupted when one of the nitrogens is alkylated. The carbon adjacent to the alkylated nitrogen is shifted upfield by 5.6 ppm and the carbon adjacent to the nonmethylated nitrogen is shifted downfield by 4.9 ppm. The carbon not adjacent to either nitrogen is shifted only 0.5 ppm downfield by alkylation. This same shift has been reported elsewhere.[5]

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(3) Elguero, J.; Jacquier, R. *J. Chem. Phys.* **1966**, *63*, 1242.
(4) Levy, G.; Nelson, G. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972; p 97.

In Table II are compiled the chemical shifts of the ring carbons of pyrazole, *N*-methylpyrazole, and 3(5),4-diphenyl-1*H*-pyrazole (**3** and **3a**). With 3(5),4-diphenyl-1*H*-pyrazole, the expected downfield shifts (relative to pyrazole) occur on the phenyl-substituted carbons 3 and 4, while the shift of the unsubstituted carbon 5 is relatively unchanged and remains a doublet with partial off-resonance decoupling. The structures of **3** and **3a** can be assigned without ambiguity. The expected upfield shift (relative to 3(5),4-diphenyl-1*H*-pyrazole) of 2.9 ppm for the carbon adjacent to the substituted nitrogen, carbon 5, and the downfield shift of 4.0 ppm for the carbon adjacent to the unsubstituted nitrogen, carbon 3, is seen for **3**. For **3a**, the upfield shift for carbon 3 of 4.8 ppm and the downfield shift of 3.5 ppm for carbon 5 confirms the isomeric structure.

Biology. In side-by-side tests in two mouse models of depression, the prevention of tetrabenazine-induced suppression of locomotor activity[6] and the prevention of reserpine-induced ptosis,[7] **3** and imipramine were of comparable potency when given by the oral route up to 4-h pretreatment with the challenge drug. Doses ranged from 4 to 64 mg of base/kg. In separate experiments at 64 mg of base/kg dose, **3** given 18 h pre-tetrabenazine challenge significantly reversed tetrabenazine-induced suppression of locomotor activity, while imipramine had no effect when this time schedule was used. In the less sensitive rat model, **3** at 64 mg of base/kg orally antagonized tetrabenazine-induced suppression of locomotor activity while imipramine was inactive at this dose level.

In order to assess anticholinergic and antihistaminic liabilities, **3** was tested orally side by side with imipramine for its effect on carbachol and histamine-induced bronchoconstriction in the anesthetized guinea pig.[8] At 100 mg of base/kg orally, **3** produced a slight but statistically nonsignificant inhibition of bronchoconstriction induced by carbachol or histamine. Imipramine at an oral dose of 100 mg of base/kg inhibited carbachol and histamine-induced bronchoconstriction by 55% and 96%, respectively. Significant inhibition (54%) against histamine was also observed with imipramine at 10 mg of base/kg orally.

The effect of **3** on locomotor activity measured in photocell cages was examined in the mouse.[9] Spontaneous activity in this species was unaffected by oral doses of **3** as high as 128 mg/kg given 1.5 or 4.5 h prior to observation for two 25-min periods.

The differential effect of **3** and imipramine on the antihypertensive response to guanethidine and clonidine was demonstrated in spontaneously hypertensive rats. Imipramine at an oral dose of 16 mg of base/kg, bid × 4 days inhibited the antihypertensive response to both antihypertensive challenge agents, while **3** at an oral dose of 32 mg of base/kg, bid × 4 days produced no statistically significant reductions of either challenge response.

In a series of in vitro tests reported elsewhere,[10] **3** inhibited [^{3}H]norepinephrine uptake into crude synaptosomes from whole rat brain with an IC_{50} of 3–4 μM. By comparison, the IC_{50} for imipramine was found to be 0.5–3.1 μM, but the concentration–response curves were not parallel. Imipramine (IC_{50} = 0.24 μM) was 50-fold more potent than **3** in blocking [^{3}H]serotonin uptake in this system.

Discussion

Tricyclic antidepressants are still considered the therapy of choice for the treatment of endogenous depression. This is in spite of the fact that their use is frequently accompanied by undesirable side effects, principal among which are sedative and anticholinergic actions. The latter effects include dry mouth, blurred vision, disturbance of accommodation, increased ocular pressure, constipation, paralytic ileus, urinary retention, and dilation of the urinary tract. These effects are particularly troublesome in geriatric populations, a group especially vulnerable to depression. Cardiovascular effects, possibly associated with anticholinergic activity, also represent a serious hazard in antidepressant therapy for the elderly. Further, tricyclic therapy has been reported to interfere with concomitant antihypertensive treatment. Hence, there is a need for new drugs with reduced incidence of side effects.

Compound **3**, a novel structure distinctly different from the fused three-ring system of the prototypical dibenzazepines as exemplified by imipramine, displayed a uniquely different profile of activity in animal testing. Significantly, the positional isomer **3a**, at the maximum doses screened, was completely devoid of activity in the primary antidepressant screens.

While **3** was equipotent with imipramine in the animal models of depression, large multiples of the effective dose of **3** failed to produce sedation or stimulation in the same species, suggesting a separation of this undesirable side effect from clinical efficacy. Similar reduced liability relative to imipramine for the induction of anticholinergic or antihistaminic effect was also demonstrated for **3**. Finally, **3** showed a markedly reduced potential relative to imipramine for drug–drug interaction with clonidine and guanethidine. Since treatment with antihypertensive agents occurs relatively frequently as a cotherapy among depressed patients, this latter demonstration takes on particular significance.

As a result of these and other studies to be reported elsewhere, **3**, fezolamine, has emerged as a promising agent for the treatment of endogenous depression and has been entered into phase 1 tolerance trials in humans.

Experimental Section

Melting points were taken in capillary tubes and are uncorrected. Elemental analyses were performed by Instranal Laboratories, Rensselaer, NY. ^{1}H NMR spectra were recorded with a Varian A-60 spectrometer. ^{13}C NMR spectra were recorded with a JEOL FX60 spectrophotometer.

1-(2-Cyanoethyl)-3,4(and 4,5)-diphenylpyrazole. A solution of 220 g (1 mol) of 3(4),4-diphenyl-1*H*-pyrazole in 900 mL of EtOH containing 2 g of KOH was cooled below 10 °C while 63.6 g (1.2 mol) of acrylonitrile was added over 5 h. The mixture was stirred overnight in the cold and the precipitated solid was isolated by filtration, washed with a small amount of cold EtOH, and dried at 60 °C. The crude product weighed 188 g (69% yield) and melted at 108–111 °C with previous softening. VPC analysis of the product indicated the presence of 92–93% of the 3,4-diphenyl isomer and 7–8% of the 4,5-diphenyl isomer.

3,4-Diphenyl-1*H*-pyrazole-1-propanamine (*E*)-2-Butenedioate (1). A 60-g (0.22 mol) sample of 1-(2-cyanoethyl)-3,4-diphenylpyrazole (92–93% pure) in 1.1 L of EtOH containing 80 g of NH_3 was hydrogenated over 5 g of Raney Ni at ambient temperature and 55 psi. After 16 h, H_2 uptake had ceased and the mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in 100 mL of EtOH and a

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(7) Aceto, M. D.; Harris, L. S. *Toxicol. Appl. Pharmacol.* **1965**, *7*, 329.
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(9) Aceto, M. D.; Harris, L. S.; Lesher, G. Y.; Pearl, J.; Brown, T. G. *J. Pharmacol. Exp. Ther.* **1967**, *158*, 286.
(10) Baizman, E. R.; Pearl, J.; Ferrair, R. A.; Piwonka, R. W. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1981**, *40*, 248.

solution of 27.7 g (0.22 mol) of oxalic acid dihydrate in 400 mL of EtOH was added. After standing for several hours, the mixture was filtered to give 45 g of crude oxalate salt, which was slurried with Et_2O and excess cold 2 N NaOH. The Et_2O solution was dried ($MgSO_4$) and concentrated to give 31 g (50% yield) of oily base. The product was dissolved in 300 mL of *i*-PrOH and 12.5 g (0.11 mol of powdered fumaric acid was added in portions with stirring. After stirring for an additional hour, the precipitated solid was filtered off, pressed dry, and recrystallized from 250 mL of absolute EtOH. The product was isolated by filtration and, after drying at 60 °C in vacuum, consisted of 24 g (28% yield) of white crystalline powder, mp 176–178 °C. Anal. ($C_{18}H_{19}N_3 \cdot C_4H_4O_4$) C, H, N.

***N*-Methyl-3,4-diphenyl-1*H*-pyrazole-1-propanamine Hydrochloride (2).** A mixture of 27.3 g (0.1 mol) of 1-(2-cyanoethyl)-3,4-diphenylpyrazole (92–93% pure) in 200 mL of 5.9 N methanolic CH_3NH_2 and 5 g of Raney Ni was shaken in a Parr apparatus overnight at a H_2 pressure of 50 psi. The catalyst was filtered off and the filtrate was concentrated under vacuum to an oil. Analysis of the crude product by GLC showed a mixture of 1 and 2 in a 2:3 ratio. The oil in 60 mL of EtOH was treated with 40 mL of 5 N HCl in EtOH and the resultant solid (8 g, mostly 1 by GLC) was removed by filtration. The mother liquors were stripped under vacuum to a semisolid mass, which was dissolved in the minimum amount of warm EtOH. To this solution was added EtOAc to cloudiness and the whole was kept at 5 °C for 4 days. The solid which had slowly deposited was a mixture of 2 and the thermally unstable dihydrochloride salt (by Cl analysis). Conversion to 2 was achieved by heating the mixed salts at 70 °C and 0.1 mm over KOH pellets for 3 days. The product consisted of 5.9 g (18% yield) of white solid, mp 124–132 °C. Anal. ($C_{19}H_{21}N_3 \cdot HCl$) C, H, N. In spite of the wide melting range, GLC analysis indicated a purity of >98%.

***N,N*-Dimethyl-3,4-diphenyl-1*H*-pyrazole-1-propanamine Hydrochloride (3).** A 100-g (0.36 mol) sample of 1-(2-cyanoethyl)-3,4-diphenylpyrazole (92–93% pure) in 1 L of absolute EtOH containing 112 g (2.5 mol) of dimethylamine was hydrogenated over 5 g of 10% Pd on C in a Parr apparatus at 50 psi. After 16 h, H_2 uptake had ceased and the mixture was filtered and the filtrate was concentrated under vacuum to a gum. The residue was dissolved in 400 mL of hot *i*-PrOH and a solution of 45.4 g (0.36 mol) of oxalic acid dihydrate in 100 mL of hot *i*-PrOH was added with stirring. After cooling for several hours, the precipitated salt was filtered and dried at 60 °C. The crude product weighed 107 g (75% yield) and had mp 140–143 °C. It was not characterized further but was added with stirring and cooling to a solution of 47 g of KOH in 800 mL of H_2O. Stirring was continued until all of the solids were consumed, and the resulting base was then extracted into isopropyl acetate. The dried solution (K_2CO_3) was filtered and stripped under vacuum and the thick, oily product was dissolved in 675 mL of *i*-PrOH containing 22.4 mL of concentrated HCl. The mixture was evaporated to dryness and the residue was crystallized from 270 mL of dry acetone. The product was filtered, washed with acetone and Et_2O, and dried in vacuum at 60 °C to give 72.9 g (79% yield based on crude oxalate salt) of crystalline solid: mp 171–172 °C; UV (EtOH) $\lambda_{1\text{-max}}$ 227 nm (ϵ 15 300), $\lambda_{2\text{-max}}$ 253 nm (ϵ 12 600); NMR of free base (HMPA), 8.45 (s, 1, pyrazole 5-H), 4.53 ppm (m, 2, CH_2). Anal. ($C_{20}H_{23}N_3 \cdot HCl$) C, H, N.

***N,N*-Dimethyl-4,5-diphenyl-1*H*-pyrazole-1-propanamine Hydrochloride (3a).** Mother liquors from the preparation of 3 were concentrated to a gum under vacuum. A portion basified with 10% NaOH and extracted with Et_2O was shown by GLC to be a 4:1 mixture of 4,5- and 3,4-isomers. A solution of the gum in EtOH was applied to 20 × 40 cm thick-layer (SiO_2) plates, which were then developed with EtOH/NH_4OH (19:1). A wide band near R_f 0.5 was scraped from the dried plate and eluted with MeOH. The solvent was removed in vacuum and the residue was crystallized from acetone–hexane (4:1) to give white crystals: mp 182–185 °C; UV (EtOH) $\lambda_{1\text{-max}}$ 233 nm (ϵ 14 800), $\lambda_{2\text{-max}}$ 247 nm (ϵ 12 800); NMR of free base (HMPA), 7.85 (s, 1, pyrazole 3 H), 4.10 ppm (m, 2 CH_2). Anal. ($C_{20}H_{23}N_3 \cdot HCl$) C, H, N.

***N,N*-Diethyl-3,4-diphenyl-1*H*-pyrazole-1-propanamine Hydrochloride (4) and *N,N*-Diethyl-4,5-diphenyl-1*H*-pyrazole-1-propanamine Hydrochloride (4a).** A mixture of 22.0 g (0.1 mol) of 3(5),4-diphenyl-1*H*-pyrazole and 2.4 g (0.1 mol) of NaH was stirred under reflux for 30 h at which time all of the solids had dissolved. To the solution was added 14.9 g (0.1 mol) of *N*-(3-chloropropyl)-*N,N*-diethylamine and the mixture was stirred and heated for 30 h. The solvent was removed under reduced pressure and the residue was partitioned between 300 mL each of EtOAc and 1 N HCl. The acid solution was neutralized with excess solid K_2CO_3 to free the crude base as a yellow oil, which was shown by GLC to be a 1:1 mixture of the 3,4- and 4,5-diphenyl isomers of *N,N*-diethyl-1*H*-pyrazole-1-propanamine. The mixture of isomers in Et_2O was treated with a slight excess of methanolic HCl to precipitate the crude salts. These were filtered off, washed with Et_2O, and redissolved in H_2O. The free bases were liberated as above and an Et_2O solution of these was again treated with excess methanolic HCl. In this way there was obtained 16.5 g (45% yield) of mixed (1:1 by GLC of freed bases) HCl salts, mp 143–146 °C.

Samples of mixed salts were dissolved in the minimum amount of MeOH and applied to 20 × 40 cm silica gel thin-layer plates at the loading rate of 200 mg/plate. The plates were eluted with 19:1 95% EtOH–NH_4OH, and after drying, the upper one-third of the UV-absorbing band was cut away from the lower two-thirds and each scraping was separately extracted with 1:1 $CHCl_3$–MeOH. The extract from the top one-third was shown by GLC to contain almost pure 4,5-diphenyl isomer. After removal of the solvent from this fraction and crystallization of the residue from acetone–hexane, there was obtained an 18.8% recovery (based on 1:1 composition of loaded sample) of *N,N*-diethyl-4,5-diphenyl-1*H*-pyrazole-1-propanamine hydrochloride (4a): mp 148–149 °C (99.8% pure by GLC); UV (EtOH) $\lambda_{1\text{-max}}$ 233 nm (ϵ 14 200), $\lambda_{2\text{-max}}$ 247 nm (ϵ 12 400); NMR of free base (HMPA), 8.40 (s, 1, pyrazole 3 H), 4.12 ppm (m, 2, CH_2). Anal. ($C_{22}H_{27}N_3 \cdot HCl$) C, H, N.

The extract from the lower two-thirds of the plates was concentrated and the residue was crystallized three times from acetone–hexane to give a 20% recovery of *N,N*-diethyl-3,4-diphenyl-1*H*-pyrazole-1-propanamine hydrochloride (4): mp 165–166 °C (98% pure by GLC); UV (EtOH) $\lambda_{1\text{-max}}$ 227 nm (ϵ 15 000), $\lambda_{2\text{-max}}$ 250 nm (ϵ 12 000); NMR of free base (HMPA), 7.83 (s, 1, pyrazole 5 H), 4.52 ppm (m, 2, CH_2). Anal. ($C_{22}H_{27}N_3 \cdot HCl$) C, H, N.

Effect on Tetrabenazine-Induced Suppression of Locomotor Activity in the Mouse.[6] Male, Swiss-Webster mice (19–24 g) from Taconic Farms were used. The animals, in groups of nine or ten each, were medicated orally with test drug at intervals ranging from 1 to 18 h prior to receiving a 50 mg of base/kg ip injection of tetrabenazine methanesulfonate (dissolved in distilled H_2O). Test drugs were dissolved in distilled H_2O with the exception of imipramine hydrochloride, which was prepared as a suspension in 1% aqueous gum tragacanth. Additional groups of animals received vehicle alone to serve as controls. All medications were given at a constant volume of 0.1 mL/10 g of body weight and all doses were calculated in terms of the base compound. Thirty minutes after administration of tetrabenazine, the mice were placed individually in photocell activity cages, and activity was recorded over two 25-min periods.

Effect on Tetrabenazine-Induced Suppression of Locomotor Activity in the Rat. Male, Charles River rats (90–110 g) were used in this study. The rats, in groups of ten each, were medicated orally with test drug or imipramine hydrochloride at doses of 16 or 64 mg of base/kg, 4 h before receiving a 7 mg of base/kg ip injection of tetrabenazine. All drugs were dissolved in distilled H_2O and were administered at a constant volume of 0.1 mL/100 g of body weight. Thirty minutes after administration of tetrabenazine, the rats were placed individually in photocell cages and tested over a 50-min period.

Prevention of Reserpine-Induced Ptosis in the Mouse.[7] Unfasted male, Swiss-Webster mice (18–24 g) were used in the reserpine ptosis prevention test. The mice, in groups of ten animals each, were medicated orally with test drug 2 h prior to receiving reserpine 2 mg/kg ip. Three hours after the administration of reserpine, the degree of eyelid ptosis was scored. Appropriate vehicle controls were also tested.

Effects on Spontaneous Locomotor Activity in the Mouse.[8] Male, albino Swiss-Webster mice (20–28 g) were housed in animal quarters for at least 1 day prior to testing. On the day of testing, the mice were medicated orally with test drug at doses of 32 or

128 mg of base/kg 1.5 or 4.5 h before being placed into individual photocell activity cages for recording of activity counts over two 25-min periods. The drug was dissolved in distilled H_2O and administered at a constant volume of 0.1 mL/10 g of body weight. Eight to nine mice were used at each dose level for each premedication time period. Appropriate vehicle controls were also run.

Effects on Bronchoconstriction Induced by Carbachol or Histamine in Anesthetized Guinea Pigs. Guinea pigs (300–350 g) were anesthetized with 1.5 g urethane/kg ip. The jugular vein and trachea were cannulated, and the guinea pigs were artificially respired. Bronchoconstriction was induced by serial intravenous injection of 5 μg of histamine base/kg and 6 μg of carbachol base/kg. Bronchoconstriction was measured as peak increases in intratracheal pressure in mmHg.

The guinea pigs, in groups of five animals each, were medicated orally with test drug or imipramine hydrochloride. Control guinea pigs received 0.5% gum tragacanth, the vehicle of the medications. The guinea pigs were anesthetized 0.5 h after medication, and they were injected intravenously with the spasmogens 1 h after the medications.

Antihypertensive Interaction of 3 with Guanethidine and Clonidine in the Spontaneously Hypertensive Rat. Groups of ten male spontaneously hypertensive rats weighing between 300 and 400 g were medicated orally bid (8 a.m. and 4 p.m.) for four consecutive days with the following compounds: **3**, 32 mg of base/kg; imipramine hydrochloride, 16 mg of base/kg; and the vehicle control, gum tragacanth (1%). Doses were given on a volume/weight basis of 1 mL/kg. On day 5 approximately 1 h after the morning final dose, rats randomly selected from each group were anesthetized with sodium pentobarbital (40 mg/kg ip) to induce surgical anesthesia. After tracheotomy, the carotid artery and jugular vein were cannulated with PE 50 and 20 tubing, respectively. Arterial blood pressure was continuously recorded with a Statham P23AC transducer and Model 7 Grass polygraph. A heat lamp maintained body temperature, which was monitored by a rectal tele-thermometer probe. After blood pressure had stabilized, intravenous challenge doses of either guanethidine (1.0 mg/kg) or clonidine (0.02 mg/kg) were injected *stat* to units of five rats in the three premedication groups. Volume of test challenge did not exceed 0.2 mL. A saline wash (0.1 mL) followed. Both challenge compounds were solubilized in 0.09% saline. Blood pressures were monitored until maximum falls occurred as indicated by a period of recovery. A Student's "*t*" test including calculation of group means was utilized to evaluate differences between the groups in antihypertensive responses. Both guanethidine and clonidine groups were compared with their respective vehicle controls.

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