dose) units of virus: HSV 1 (63), VV (200), Para 3 (56), VSV (3), and concentrations of each compound in one-half log dilutions ranging from 1000 to 1 μg/mL were added within 15–30 min. The degree of CPE inhibition was observed microscopically after 72 h of incubation at 37 °C in 5% CO_2 and scored numerically in order to calculate a virus rating (VR) as previously reported.[36] Significance of antiviral activity in terms of VRs has been assigned as follows: 0.5, slight or no activity; 0.5–0.9, moderate activity; ≥1.0, marked activity.

Antitumor Evaluation. L1210 leukemia and P388 lymphoid neoplasm were maintained in RPMI-1640 medium supplemented with 10% heat-inactivated fetal calf serum. For determination of cell growth inhibition, L1210 and P388 cells were seeded in 13 × 100 tubes at 5 × 10^4 cells/mL (2 mL/tube). Cells were grown in the presence of the compound of interest, at 4–5 log doses, for 48 h at 37 °C. Cell growth was assessed by cell count, using a Coulter cell counter. Cell growth at each dose level was expressed as a percentage of growth in control tubes and dose resulting in 50% inhibition of growth was determined.

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Registry No. 1, 41729-52-6; 2, 56039-11-3; 3, 56039-13-5; 4, 56039-06-6; 5, 91713-21-2; 6, 58931-20-7; 8, 91713-22-3; 12, 91713-23-4; 13, 62190-71-0; 14 (isomer 1), 58459-35-1; 14 (isomer 2), 56596-91-9; 15, 4330-34-1; 16, 91713-28-9; 17, 4330-21-6; 18, 91713-24-5; 19, 91713-25-6; 20, 91713-26-7; 21, 91713-27-8; 22, 91713-29-0; 26, 83587-64-8; 27, 83587-63-7; 24, 91741-79-6; 25, 83587-61-5; 28, 83587-62-6; 29, 87202-41-3; hydrazine hydrate, 7803-57-8; 5-(cyanomethyl)-1-β-D-ribofuranosylimidazole-4-carboxamide, 91796-78-0.

(1,3-Dialkyl-5-amino-1*H*-pyrazol-4-yl)arylmethanones. A Series of Novel Central Nervous System Depressants

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A series of novel (1,3-dialkyl-5-amino-1*H*-pyrazol-4-yl)arylmethanones was synthesized. Pharmacological evaluation of these compounds demonstrated central nervous sytem depressant activity, potential anticonvulsant properties, and a low order of acute toxicity. In addition, selected compounds showed potential antipsychotic effects. This report focuses on the synthesis and structure–activity relationships of these compounds. (5-Amino-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)(2-chlorophenyl)methanone (**21**) was the most active compound against pentylenetetrazole-induced convulsions. (5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(3-chlorophenyl)methanone (**4**) also has a favorable anticonvulsant depression ratio. (5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(3-trifluoromethylphenyl)methanone (**8**), (5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(3-thienyl)methanone (**13**), and (5-amino-3-ethyl-1-methyl-1*H*-pyrazol-4-yl)phenylmethanone (**14**) are very potent depressants. (5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-thienyl)methanone (**12**) possessed marked central depressant activity without anticonvulsant activity and without impairment of motor functioning. (5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-fluorophenyl)methanone (**2**) has a behavioral profile suggestive of antipsychotic activity and gave a positive Ames test result.

Epilepsy is a continuing medical problem despite the discovery and successful marketing of a number of drugs for its treatment;[1-3] thus the search continues for useful anticonvulsant agents.

A short series of novel (1,3-dialkyl-5-amino-1*H*-pyrazol-4-yl)arylmethanones had been prepared as intermediates in the synthesis of a series of compounds with antianxiety activity.[4,5] When these were submitted for pharmacological evaluation, some were found to possess interesting central nervous system depressant activity, potential anticonvulsant properties, plus a low order of acute toxicity. The series was expanded to attempt to maximize the level of activity and to study the structure–activity relationships. Encouraging activity was also observed in selected compounds when evaluated for potential antipsychotic activity.

Chemistry. Three general methods were developed for the synthesis of the title compounds. These are summarized in Chart I.

Route A. Many of the (1,3-dialkyl-5-amino-1*H*-pyrazol-4-yl)methanones were prepared by reaction of the (1,3-dialkyl-5-chloro-1*H*-pyrazol-4-yl)methanones[6] with concentrated ammonium hydroxide under heat and pressure.

Route B. A series of 1,3-dialkyl-5-amino-1*H*-pyrazoles were prepared by a variation of the method of Taylor and Hartke[7] in which 3-amino-2-butenenitrile was condensed with methylhydrazine. Larger alkylhydrazines do not ring close under neutral or basic conditions, the reaction stopping at the open alkylhydrazone stage. However, Koike et al.[8] used hydrogen chloride to effect this type of ring closure with phenylhydrazine. In our case, the addition of more than 1 equiv of concentrated hydrochloric acid to the larger alkylhydrazones resulted in high yields

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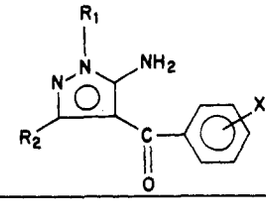
Table I



no.	R_1	R_2	X	CNS dep[a]	anticonvulsant 4+ dose[a]	synth route	% yield	formula	mp or bp (mmHg), °C	recrystn solvent[b]	anal.
1	CH_3	CH_3	H	63	500	C	55	$C_{12}H_{13}N_3O$	147–150	A	C, H, N
2	CH_3	CH_3	2-F	32	250	B	81	$C_{12}H_{12}FN_3O$	108–109	B	C, H, N
3	CH_3	CH_3	2-Cl	63	125	A	80	$C_{12}H_{12}ClN_3O$	113–115	A	C, H
4	CH_3	CH_3	3-Cl	125	63	A	80	$C_{12}H_{12}ClN_3O$·HCl	175–177	D	C, H, N
5	CH_3	CH_3	4-Cl	125	125	A	78	$C_{12}H_{12}ClN_3O$	157–159	J	C, H, N
6	CH_3	CH_3	2-Br	63	125	A	30	$C_{12}H_{12}BrN_3O$·HBr	243–245	C	C, H, N
7	CH_3	CH_3	2-CF_3	125	250	A	75	$C_{13}H_{12}F_3N_3O$·HBr	231–233	D	C, H, N
8	CH_3	CH_3	3-CF_3	4	125	A	90	$C_{13}H_{12}F_3N_3O$·HBr	199–200	D	C, H, N
9	CH_3	CH_3	2-CH_3O	32	125	A	60	$C_{13}H_{15}N_3O_2$·HBr	224–226	C	C, H, N
10	CH_3	CH_3	2-CH_3	32	125	A	90	$C_{13}H_{15}N_3O$	154–155 (0.15)		C, H, N
11	CH_3	CH_3	2-Cl, 3-CH_3O	32	250	A	21	$C_{13}H_{14}ClN_3O_2$·HBr	212–214	D	C, H
12	CH_3	CH_3	2-thiophene	8	Neg	A	90	$C_{10}H_{11}N_3OS$·HBr	185–187	G	C, H, N
13	CH_3	CH_3	3-thiophene	16	Neg	A	80	$C_{10}H_{11}N_3OS$	136–138	B	C, H, N
14	CH_3	C_2H_5	H	16	250	B	72	$C_{13}H_{15}N_3O$	101–103	B	C, H, N
15	CH_3	C_2H_5	2-F	32	250	B	61	$C_{13}H_{14}FN_3O$	103–105	B	C, H, N
16	CH_3	C_2H_5	3-F	63	500	B	85	$C_{13}H_{14}FN_3O$	91–93	B	C, H, N
17	CH_3	C_2H_5	2-Cl	63	500	A	84	$C_{13}H_{14}ClN_3O$·HCl	170–172	D	C, H, N
18	CH_3	n-C_3H_7	2-Cl	32	125	A	80	$C_{14}H_{16}ClN_3O$	108–110	E	C, H, N
19	CH_3	i-C_3H_7	2-Cl	63	Neg	A	50	$C_{14}H_{16}ClN_3O$	163–165 (0.1)		C, H, N
20	CH_3	n-C_4H_9	2-Cl		125	A	69	$C_{15}H_{18}ClN_3O$	110–112	F	C, H
21	C_2H_5	CH_3	2-Cl	32	16	A	90	$C_{13}H_{14}ClN_3O$·HCl	166–168	D	C, H
22	n-C_3H_7	CH_3	2-Cl	8	32	B	85	$C_{14}H_{16}ClN_3O$	150–151 (0.15)		C, H
23	n-C_3H_7	CH_3	2-CH_3	16	63	B	41	$C_{15}H_{19}N_3O$·HBr	201–203	G	C, H, N
24	n-C_3H_7	CH_3	2-Br	8	32	B	51	$C_{14}H_{16}BrN_3O$·HBr	193–195	G	C, H, N
25	n-C_3H_7	CH_3	2-CF_3	8	63	A	85	$C_{15}H_{16}F_3N_3O$·HBr	206–208	H	C, H
26	n-C_3H_7	CH_3	4-Cl	16	32	B	24	$C_{14}H_{16}ClN_3O$·HBr	208–210	G	C, H, N
27	n-C_3H_7	CH_3	2-CH_3O	16	125	A	48	$C_{15}H_{19}N_3O_2$·HBr	180–182	D	C, H
28	i-C_3H_7	CH_3	2-Cl	63	500	B	25	$C_{14}H_{16}ClN_3O$·HBr	183–185	G	C, H, N
29	n-C_4H_9	CH_3	2-Cl	8	125	B		$C_{15}H_{18}ClN_3O$·HCl	145–147	D	C, H
30	n-C_4H_9	CH_3	3-Cl	32	500	B	26	$C_{15}H_{18}ClN_3O$	128–130	F	C, H
31	C_6H_{11}	CH_3	2-Cl	c	Neg	A	95	$C_{17}H_{20}ClN_3O$	168–169	I	C, H, N
32	n-C_3H_7	CH_3	2-Cl, 3-CH_3O	16	63	A	15	$C_{15}H_{18}ClN_3O_2$	198–200 (0.1)		C, H, N
33	Ph	CH_3	2-Cl	250	Neg	A	69	$C_{17}H_{14}ClN_3O$	138–140	H	C, H, N
34	CH_3	Ph	2-Cl	250	Neg	A	89	$C_{17}H_{14}ClN_3O$	185–187	J	C, H, N
35	n-C_3H_7	CH_3	2-thiophene	250	125	A	72	$C_{12}H_{15}N_3OS$	155–158 (0.1)		C, H, N

[a] This is the mg/kg dose expressed as base of the agent tested. [b] The following code gives recrystallization solvents: A = benzene, B = ethyl acetate–petroleum ether (bp 39–60 °C), C = water, D = 2-propanol–diethyl ether, E = toluene, F = toluene–petroleum ether (bp 39–60 °C), G = ethanol–diethyl ether, H = methanol–diethyl ether, I = diethyl ether–heptane, J = diethyl ether. [c] Quiet at 250 mg/kg.

of the desired ring-closed products. The 1,3-dialkyl-5-amino-1*H*-pyrazoles where the 3-alkyl group was larger than methyl were prepared from the corresponding 3-oxoalkanenitriles. Finally, aroylation of the intermediate 1,3-dialkyl-5-amino-1*H*-pyrazoles under Friedel–Crafts conditions produced [1,3-dialkyl-5-(aroylamino)-1*H*-pyrazol-4-yl]arylmethanones and acid hydrolysis gave the title compounds.

Route C. The starting 1,3-dialkyl-5-amino-1*H*-pyrazole-4-carbonitriles were prepared by the method of Cheng and Robins.[9] These nitriles were in turn treated with a large excess of an aryllithium or aryl-Grignard reagent to yield the (1,3-dialkyl-5-amino-1*H*-pyrazol-4-yl)aroylmethanone imines. Acid hydrolysis produced the title compounds.

Structure–Activity Relationships

Table I summarizes the central depressant activity[10] (the lowest dose at which depression was observed; the animals were usually rated as quiet one to two dose levels lower). Depression was characterized by reduced spontaneous motor activity and reduced responsiveness to external stimuli as compared to that of the control group. The anti-pentylenetetrazole activity (the lowest dose giving a 4+ (all four animals protected) rating is listed).[11] The majority of the target compounds protected mice from a convulsant dose (93 mg/kg administered subcutaneously) of pentylenetetrazole and demonstrated central nervous system depressant activity in otherwise untreated mice. The most active compound in the anticonvulsant test was (5-amino-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)(2-chlorophenyl)methanone (21) with an anticonvulsant active dose that was one-half of the central depressant dose. An ortho substituent on the aryl ring, particularly a chloro or bromo group, enhanced anticonvulsant and central depressant activity. Central depressant activity was also enhanced when the 1-alkyl group was lengthened (compare 3 with 21). Longer alkyl groups at the 3-position of the pyrazole ring or branching of the 1-alkyl group resulted in lowered activity. Replacement of either of the alkyl groups with

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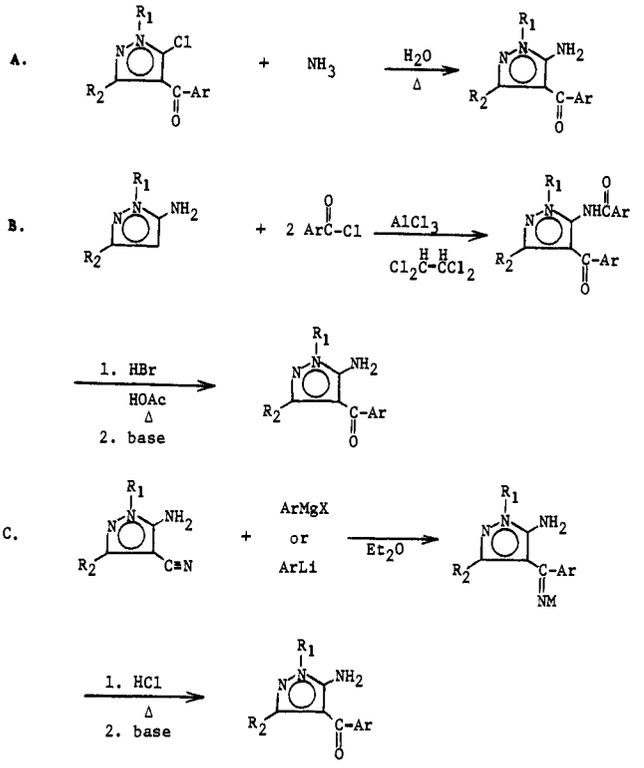
Chart I



a phenyl group (**33**, **34**) gave inactive compounds. 1,3-Dimethyl-4-(phenylmethyl)-1*H*-pyrazol-5-amine,[10] which represents replacement of the methanone moiety with a methylene group, was completely inactive. Compound **12** with a 2-thienyl group replacing the phenyl substituent was exceptional in producing marked central depressant activity while being devoid of anticonvulsant activity.

Selected compounds from this series were also evaluated behaviorally for potential antipsychotic activity. Our model consisted of a two-part test in mice, dosed by the intraperitoneal route (IP), designed to measure inhibition of spontaneous locomotor activity and impairment of motor function (falling off an inverted screen).[12] This test was based on the observation that antipsychotic agents, e.g., pimozide and thioridazine, inhibit spontaneous locomotion in mice at doses that do not produce severe depression, impaired motor function, or CNS toxicity. As reported in Table II, compound **1** showed modest activity, having a rating of C at 30 mg/kg and an A at 100 mg/kg. However, addition of an ortho fluorine to the phenyl ring (compound **2**) resulted in greatly enhanced activity. the fluorine substitution was very specific since replacement with other ortho substituents resulted in compounds with little activity. Replacement of the 3-methyl substituent on the pyrazole ring with the larger ethyl group (compound **15**) resulted in increased depressant activity and thus a loss of separation in the test model. Interestingly, the 2-thienyl analogue **12** was also quite active in this model. Compound **2** gave a positive Ames test result.

Summary

A series of (1,3-dialkyl-5-amino-1*H*-pyrazol-4-yl)arylmethanones with interesting central nervous system depressant activity has been developed. The compounds demonstrate potential anticonvulsant properties with a low order of acute toxicity. In addition, selected compounds show activity in behavioral tests indicative of potential antipsychotic effects.

Compounds **4** and **21** have favorable anticonvulsant/depression ratios. Compounds **8**, **13**, and **14** are very potent depressants. Compound **12** shows depressant activity without loss of the animal's ability to remain on an inverted screen. Compound **2** of this series has a behavioral profile most suggestive of antipsychotic activity. A more detailed discussion of the biological profiles of **2** and **12** will be presented elsewhere.[13]

Table II. Activity of Selected Compounds in Inhibition of Locomotion-Screen Falloff Test

	LA screen test[a] rating		
	dose,[b] mg/kg		
compd	10	30	100
1	N	C	A
2[c]	A	A	
3	N	N	A
4	N	N	C
5	N	N	A
6	C	N	C
7	N	C	A
8	N	N	C
9	N	C	C
10	C	N	A
12[d]	N	A	A
14	C	A	C
15	N	N	C
pimozide	A[e]		
thioridazine	A[f]		

[a] Data obtained from the screen test was expressed as percent of mice falling off the screen. Data derived from the locomotor activity of drug-treated mice were compared to the activity of vehicle-treated animals and were expressed as percent inhibition of spontaneous locomotion. All percentages for inhibition of locomotion were based upon data accumulated for 1 h. Both phases of testing were graded: A = 60-100%; C = 31-59%; N = 0-30%. An overall rating of A resulted from an A rating in inhibition of locomotion and either a C or N rating in screen falloff. A C rating resulted from an A rating in both or a C rating in locomotion and a C or N rating in the screen portion. All other combinations resulted in an N rating. [b] Administered by the intraperitoneal route. [c] Estimated ED_{50} = 9.4 mg/kg ± 0.3. [d] Estimated ED_{50} = 34.2 mg/kg ± 1.4. [e] ED_{50} = 5.9 mg/kg ± 2.2. [f] ED_{50} = 2.9 mg/kg ± 0.05.

Experimental Section

Chemistry. The melting points were determined in open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined with a Beckman IR-9 spectrophotometer. NMR spectra were recorded with a Varian A-60 instrument with Me_4Si as the internal standard. Concentration was carried out under reduced pressure. IR and NMR spectra were obtained for all compounds and were consistent with the assigned structures. C, H, and N analyses were performed on all compounds prepared and, unless otherwise noted, checked within ±0.4%. The (1,3-dialkyl-5-chloro-1*H*-pyrazol-4-yl)arylmethanones were prepared as described by Butler and DeWald.[6] The aroyl chlorides were either commercially available or were prepared by the use of thionyl chloride on the commercially available aromatic carboxylic acids and were used without purification. With the ortho-substituted acids, a drop of pyridine catalyst was particularly important to ensure completion of this reaction. The 3-amino-2-butenenitrile (85%) was purchased (Aldrich Chemical Co.) and was used without further purification.

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Methylhydrazine was purchased (Olin Matheson Chemical Corp.). *n*-Propylhydrazine[13] and *n*-butylhydrazine[14] were synthesized by alkylation of a large excess of 85% hydrazine hydrate followed by continuous extraction with diethyl ether and distillation at atmospheric pressure under nitrogen. The 2-propylhydrazine was prepared by hydrogenation of a mixture of acetone and hydrazine hydrochloride.[15] The following compounds were prepared by the cited literature references: 1,3-Dimethyl-1*H*-pyrazol-5-amine,[7] 4-bromo-5-chloro-1-methyl-3-phenyl-1*H*-pyrazole,[16] 4-bromo-5-chloro-3-methyl-1-phenyl-1*H*-pyrazole,[17] 4-bromo-5-chloro-3-methyl-1-propyl-1*H*-pyrazole.[6]

Route A. Typical Amination of a (1,3-Dialkyl-5-chloro-1*H*-pyrazol-4-yl)arylmethanone Using Aqueous Ammonium Hydroxide. Synthesis of (5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-chlorophenyl)methanone (3). A mixture of (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-chlorophenyl)-methanone[6] (40 g, 0.15 mol) and 120 mL of 30% ammonium hydroxide were heated at 155–160 °C for 18 h in a sealed pressure vessel. After cooling, the mixture was concentrated at reduced pressure, and the solids were partitioned between diethyl ether and dilute NaOH. The ethereal extracts were dried ($MgSO_4$), filtered, and concentrated. Recrystallization of the residue from benzene–cyclohexane gave **3**, mp 113–115 °C. The hydrochloride of **3** was prepared from 2-propanolic hydrogen chloride, mp 194–196 °C.

In a few cases, an effort was made to maximize the yield in this procedure. The best yields were obtained at the lowest reaction temperature at which the conversion rate was appreciable. The reaction time was simply increased. When the 1-alkyl group was methyl and the aryl group was not ortho substituted, 18 h was sufficient.

Route B. Typical Friedel–Crafts Reaction on a 1,3-Dialkyl-1*H*-pyrazol-5-amine. Synthesis of (5-Amino-3-methyl-1-propyl-1*H*-pyrazol-4-yl)(2-bromophenyl)-methanone (24). A suspension of aluminum chloride (67 g, 0.5 mol) in 1,1,2,2-tetrachloroethane (400 mL) was cooled to 5–10 °C and 2-bromobenzoyl chloride (140 g, 0.7 mol) was added dropwise. 3-Methyl-1-propyl-1*H*-pyrazol-5-amine hydrochloride (**24a**) (34 g, 0.2 mol) was added through a powder funnel. The mixture was stirred and refluxed overnight. After cooling, the mixture was poured into 1.17 N hydrochloric acid (1 L), and the two-phase system was stirred 1 h. The layers were separated, and the organic layer was washed with dilute ammonium hydroxide and water. The intermediate 5-benzamide was readily isolated at this point. The organic layer containing *N*-[3-methyl-1-propyl-1*H*-pyrazol-5-yl]-2-bromobenzamide (**24b**) was concentrated at reduced pressure and dissolved in 48% HBr (454 mL) and glacial acetic acid (150 mL). The mixture was refluxed 16 h, concentrated under reduced pressure, made basic with excess dilute NaOH, and extracted with diethyl ether. The extracts were dried ($MgSO_4$), filtered, and concentrated, and the product was distilled under pressure. See Table I for physical characteristics and yields.

Route C. Typical Aryl-Grignard Reaction with 1,3-Dialkyl-5-amino-1*H*-pyrazole-4-carbonitrile. Synthesis of (5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-chlorophenyl)-methanone (3). A solution of (2-chlorophenyl)magnesium bromide was prepared from Mg (9.6 g, 0.4 mol) and 2-bromo-1-chlorobenzene (76 g, 0.4 mol) in 150 mL of diethyl ether. Under nitrogen a solution of 1,3-dimethyl-5-amino-1*H*-pyrazole-4-carbonitrile[9] (24 g, 0.175 mol) was added. The mixture was stirred at reflux 16 h, cooled, and treated with saturated aqueous ammonium chloride (150 mL). The organic layer containing 4-[(2-chlorophenyl)iminomethyl]-1,3-dimethyl-1*H*-pyrazol-5-amine was separated, washed with saturated aqueous NaCl, and extracted with 1 N HCl (400 mL). Concentrated HCl (30 mL) was added and the aqueous layer was heated at steam bath temperatures for 10 min. The solution was made strongly basic with 50% NaOH and extracted with chloroform. The extracts were combined, washed with water, dried ($MgSO_4$), filtered, and concentrated, giving the crystalline product compound **3**. The **3**·HCl was identical with that synthesized by route A. See Table I for physical characteristics and yields.

Route C. Typical Aryllithium Reaction with a 1,3-Dialkyl-5-amino-1*H*-pyrazole-4-carbonitrile. Synthesis of (5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)phenylmethanone (1). Powdered 1,3-dimethyl-5-amino-1*H*-pyrazole-4-carbonitrile[9] (25 g, 0.184 mol) was added portionwise to a solution of phenyllithium prepared from lithium (9.6 g, 0.8 mol) and bromobenzene (62.8 g, 0.4 mol) in 400 mL of diethyl ether, and the mixture was stirred and refluxed 18 h. The mixture was treated with 150 mL of saturated ammonium chloride solution; the organic layer was separated and extracted with 400 mL of 1 N HCl. The aqueous acid extract was treated with 20 mL of concentrated HCl and heated on a steam bath for 10 min. The solution was cooled, made strongly basic with concentrated sodium hydroxide, and extracted with chloroform. The product **1** crystallized upon removal of the solvent at reduced pressure. See Table I for physical characteristics and yield.

Synthesis of Required New Intermediates. Typical Synthesis of a 1,3-Dialkyl-1*H*-pyrazol-5-amine. 3-Methyl-1-propyl-1*H*-pyrazol-5-amine (24a). A solution of 3-aminobutenenitrile (289 g, 3.0 mol based on 85% purity) in anhydrous ethanol (1 L) was stirred and *n*-propylhydrazine (222 g, 3.0 mol) was added dropwise. The mixture was stirred, refluxed 18 h, and cooled. Concentrated hydrochloric acid (300 mL) was added and the mixture was refluxed 18 h. The mixture was concentrated at reduced pressure. The 3-methyl-1-propyl-1*H*-pyrazol-5-amine hydrochloride crystallized and was isolated by filtration, 420 g (80%), mp 133–150 °C. The hydrochloride was dissolved in water and made strongly basic with 50% sodium hydroxide solution and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), filtered, and concentrated at reduced pressure to yield 3-methyl-1-propyl-1*H*-pyrazol-5-amine as an oil. The hydrochloride of this oil was prepared from 2-propanolic HCl, mp 158–160 °C (from 2-propanol–diethyl ether). Anal. ($C_7H_{13}N_3$·HCl) C, H: C, 47.88. Found: C, 48.64.

1-Butyl-3-methyl-1*H*-pyrazol-5-amine (**29a**) prepared in the same manner from 1.865 mol of *n*-butylhydrazine yielded 280 g (79%) of free base **29a**, mp 177–179 °C (HCl). Anal. ($C_8H_{15}N_3$·HCl) C, H.

Synthesis of (5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(2-chlorophenyl)methanone (33a). A solution of 21 g (0.063 mol) of 5-chloro-α-(2-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-methanol (**33b**) in dry acetone (1.5 L) was treated with 25 mL (0.1 equiv) of Jones reagent with stirring. After the mixture was stirred 5 min, 2-propanol (50 mL) was added to destroy excess oxidant. Powdered sodium bicarbonate (16.8 g, 0.2 mol) was added followed by anhydrous diethyl ether (1.5 L). The reaction mixture was filtered through filter aid and concentrated at reduced pressure to yield **33a** as a crystalline solid. The crystalline **33a** was triturated with petroleum ether, bp 39–60 °C, and dried in vacuo to yield **33a**, 16 g (77%), mp 78–81 °C. Anal. ($C_{17}H_{12}Cl_2N_2O$) C, H, N.

(5-Chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)(2-chlorophenyl)methanone (34a). Compound **34a** was synthesized by Jones oxidation of 5-chloro-α-(2-chlorophenyl)-1-methyl-3-phenyl-1*H*-pyrazole-4-methanol (**34b**) in 85% yield, bp 183–185 °C (0.15 mm). Anal. ($C_{17}H_{12}Cl_2N_2O$) C, H, N.

(5-Chloro-3-methyl-1-propyl-1*H*-pyrazol-4-yl)(2-thienyl)methanone (35a). Compound **35a** was synthesized by Jones oxidation of crude 5-chloro-3-methyl-1-propyl-α-(2-thienyl)-1*H*-pyrazole-4-methanol (**35b**) prepared in turn by reaction of 4-bromo-5-chloro-3-methyl-1-propyl-1*H*-pyrazole with *n*-BuLi followed by thiophene-2-aldehyde in 80% overall yield, bp 128–130 °C (0.15 mm). Anal. ($C_{12}H_{13}ClN_2OS$) C, H, N.

5-Chloro-α-(2-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-methanol (33b). A solution of 4-bromo-5-chloro-3-methyl-1-phenyl-1*H*-pyrazole (30 g, 0.11 mol) in anhydrous diethyl ether (1 L) under N_2 was treated with *n*-butyllithium solution in heptane (90 mL, 0.11 mol) followed by 2-chlorobenzaldehyde (21 g, 0.15 mol). The mixture was stirred 15 min and treated with H_2O (100 mL). The layers were separated. The organic layer was washed with H_2O (500 mL), dried ($MgSO_4$), filtered, and

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concentrated at reduced pressure. Trituration of the residue with anhydrous diethyl ether and drying in vacuo yielded **33b**, 5-chloro-α-(2-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-methanol, 23.5 g, (70%), mp 132–134 °C. Anal. ($C_{17}H_{14}Cl_2N_2O$) C, H, N.

5-Chloro-α-(2-chlorophenyl)-1-methyl-3-phenyl-1*H*-pyrazole-4-methanol (34b). Compound **34b** was synthesized from 4-bromo-5-chloro-1-methyl-3-phenyl-1*H*-pyrazole by lithium exchange and reaction with 2-chlorobenzaldehyde, mp 118–121 °C (from Et_2O–petroleum ether, bp 39–60 °C), 73% yield. Anal. ($C_{17}H_{14}Cl_2N_2O$) C, H, N.

Pharmacology. CNS Depression Test.[10] Compounds were subjected to a general test for drug-induced neurological, autonomic, and behavioral effects in male albino mice (Webster strains, 20–26-g body weight). Groups of five mice were injected intraperitoneally with mg/kg (based upon calculated active component in the case of salts) doses of 250, 125, 63, ..., until no drug effect was observed. The test compounds were dissolved in 0.9% saline or 100% propylene glycol. During the 15–60-min period after dosing, observations were made by highly trained observers on the reactions of the animals to noise, touch, restraint, and transfer. The following signs and symptoms, among others, were checked: motor activity, ataxia, depression, hypersensitivity, grasping, and righting reflexes, corneal and pineal reflexes, body posture, muscle tone, lacrimation, and ocular manifestations. Surviving animals were held for 24 h to establish a provisional acute toxicity level.

Anticonvulsant Screening Test.[11] A convulsive dose of pentylenetetrazole (93 mg/kg) was administered subcutaneously 30 min after the test drug had been administered orally. Water-insoluble compounds were suspended in methocel. Four animals (rats) were studied at each dose level. Antagonism of pentylenetetrazole convulsant activity is judged by (1) the time of onset and severity of clonic convulsant seizures and (2) the number of animals completely protected from convulsions. Compounds are rated as follows: 4+, all rats protected; 3+, three or four rats protected; 2+, one or two rats protected; 1+, delay in onset of convulsions; 0, no effect. In this test known compounds are rated as follows: tridione, 4+ at 500 mg/kg and 3+ at 250 mg/kg; phensuximide, 3–4+ at 125 mg/kg; methaqualone, 4+ at 63 mg/kg, 3+ at 32 mg/kg, and depression at 125.

Inhibition of Locomotion–Screen Falloff Test.[12] Nine unfasted Swiss–Webster male mice (Buckberg Laboratories) weighing 20–30 g were equally divided into three groups of three mice for each dose level (9 at each dose level). Three dose levels (10, 30, and 100 mg/kg) were tested for each compound. Treatments were administered intraperitoneally 1 h prior to testing. All dosages were calculated as parent compound and given in volumes of 10 mL/kg. Compounds were dissolved or suspended in 0.2% methocel. Control animals were injected with methocel. First the screen test was performed. This test consisted of placing mice on individual wire screens that were rotated 180° at the start of a 60-s observation period. The number of mice falling off the inverted screen was recorded. Immediately following the screen test, the animals were tested for inhibition of locomotion. Each group of mice was placed in an actophotometer. The actophotometer consisted of a cylindrical chamber whose center contained the illumination for six photocells located on the perimeter of the chamber. Six light-beam interruptions equalled one count. Locomotor activity was recorded by computer at 10-min intervals for 1 h. Data obtained from the screen test was expressed as percent of mice falling off the screen. Data derived from the locomotor activity of drug-treated mice were compared to the activity of vehicle-treated animals and were expressed as percent inhibition of spontaneous locomotion. All percentages for inhibition of locomotion were based upon data accumulated for 1 h. Both phases of testing were graded: A = 60–100%; C = 31–59%; N = 0–30%. An overall rating of A resulted from an A rating in inhibition of locomotion and either a C or N rating in screen falloff. A C rating resulted from an A rating in both or a C rating in locomotion and a C or N rating in the screen portion. All other combinations resulted in an N rating.

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Registry No. 1, 31272-19-2; **2**, 31272-21-6; **3**, 31272-20-5; **3**·HCl, 91411-58-4; **3** (chloride), 29938-74-7; **4**, 54454-13-6; **4**·HCl, 91411-20-0; 4 (chloride), 29938-75-8; **5**, 38009-49-3; **5** (chloride), 30093-77-7; **6**, 91411-21-1; **6**·HBr, 91411-22-2; **6** (chloride), 29938-76-9; **7**, 91411-23-3; **7**·HBr, 91411-24-4; **7** (chloride), 30093-78-8; **8**, 91411-25-5; **8**·HBr, 91411-26-6; **8** (chloride), 29938-77-0; **9**, 91411-27-7; **9**·HBr, 91411-28-8; **9** (chloride), 29938-78-1; **10**, 91411-29-9; **10** (chloride), 29938-80-5; 11, 91411-30-2; **11**·HBr, 91411-31-3; **11** (chloride), 29938-82-7; **12**, 85723-70-2; **12**·HBr, 91411-32-4; **12** (chloride), 29938-85-0; **13**, 85723-68-8; **13** (chloride), 29938-86-1; **14**, 63960-57-6; **15**, 31272-30-7; **16**, 91411-33-5; **17**, 31272-22-7; **17**·HCl, 91411-34-6; **17** (chloride), 29938-91-8; **18**, 91411-35-7; **18** (chloride), 30093-80-2; **19**, 31272-24-9; **19** (chloride), 30093-81-3; **20**, 91411-36-8; **20** (chloride), 29938-92-9; **21**, 68221-35-2; **21**·HCl, 91424-02-1; **21** (chloride), 29938-93-0; **22**, 91411-37-9; **23**, 91411-38-0; **23**·HBr, 91411-39-1; **24**, 91411-40-4; **24**·HBr, 91411-41-5; **24a**, 3524-34-3; **24a**·HCl, 91411-63-1; **24b**, 91411-64-2; **25**, 91411-42-6; **25**·HBr, 91411-43-7; **25** (chloride), 29938-95-2; **26**, 91411-44-8; **26**·HBr, 91411-45-9; **27**, 91411-46-0; **27**·HBr, 91411-47-1; **27** (chloride), 29938-94-1; **28**, 91411-48-2; **28**·HBr, 91411-49-3; **29**, 91411-50-6; **29**·HCl, 91411-51-7; **29a**, 3524-35-4; **30**, 91411-52-8; **31**, 91411-53-9; **31** (chloride), 29938-97-4; **32**, 91411-54-0; **32** (chloride), 91411-59-5; **33**, 91411-55-1; **33a**, 91411-60-8; **33b**, 91411-66-4; **34**, 91411-56-2; **34a**, 91411-61-9; **34b**, 91411-67-5; **35**, 91411-57-3; **35a**, 91411-62-0; **35b**, 91411-68-6; 2-FC_6H_4COCl, 393-52-2; PhCOCl, 98-88-4; 2-ClC_6H_4COCl, 609-65-4; 2-$CH_3C_6H_4COCl$, 933-88-0; 2-BrC_6H_4COCl, 7154-66-7; 4-ClC_6H_4COCl, 122-01-0; 3-ClC_6H_4COCl, 618-46-2; 2-BrC_6H_4Cl, 694-80-4; *n*-$C_3H_7NHNH_2$, 5039-61-2; 2-ClC_6H_4CHO, 89-98-5; 1,3-dimethyl-1*H*-pyrazol-5-amine, 3524-32-1; 3-ethyl-1-methyl-1*H*-pyrazol-5-amine, 3524-46-7; 1-isopropyl-3-methyl-1*H*-pyrazol-5-amine, 1124-16-9; 1,3-dimethyl-5-amino-1*H*-pyrazole-4-carbonitrile, 54820-92-7; 4-[(2-chlorophenyl)iminomethyl]-1,3-dimethyl-1*H*-pyrazol-5-amine, 91411-65-3; 3-aminobutenenitrile, 1118-61-2; 4-bromo-5-chloro-3-methyl-1-propyl-1*H*-pyrazole, 29939-07-9; thiophene-2-aldehyde, 98-03-3; 4-bromo-5-chloro-3-methyl-1-phenyl-1*H*-pyrazole, 91411-69-7; 4-bromo-5-chloro-1-methyl-3-phenyl-1*H*-pyrazole, 91411-70-0.