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3-Halo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidines, a Nonbenzodiazepinoid Class of Antianxiety Agents Devoid of Potentiation of Central Nervous System Depressant Effects of Ethanol or Barbiturates

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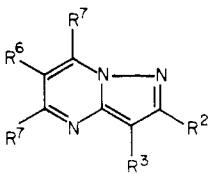
Forty derivatives (1–40) of pyrazolo[1,5-*a*]pyrimidine were synthesized and evaluated for antianxiety properties via gross behavioral observations in rats. Five of these compounds, including 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**6**) and the 3-fluoro (**7**), 3-chloro (**8**), 3-bromo (**9**), and 3-iodo (**10**) derivatives, were selected for advanced evaluation. Although **6** and **7** had marginal activity, **8–10** had an anxiolytic effect in animals comparable to the clinically useful benzodiazepines, diazepam, and chlorodiazepoxide. Comparison with chlorpromazine indicated that **6–10** are probably not antipsychotic agents. These compounds also lacked activity in anticonvulsant and analgesic tests. Acute toxicity data (mouse, ip and po) indicated that **8–10** had excellent therapeutic ratios, although **10** was more poorly absorbed than **8** and **9**. Further demonstration of anxiolytic efficacy was obtained by comparing the effects of **8** and **9** with the benzodiazepines in modifying provoked aggression in monkeys, rats (muricide), and fighting mice. The most remarkable observation, however, was that **8** and **9** had no effect, at the anxiolytic threshold, in potentiating the CNS depressant effects of ethanol or sodium barbital (po) in treated mice. In contrast, diazepam and chlorodiazepoxide potentiated this drug interaction effect at minimal anxiolytic doses.

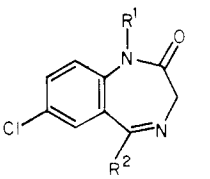
In two earlier publications,[2] we reported that certain 3-substituted 5,7-dialkylpyrazolo[1,5-*a*]pyrimidines I were selective inhibitors of cyclic 3′,5′-adenosine monophosphate (cAMP) phosphodiesterases in vitro. The control of these enzymes at the molecular level has been proposed as an approach to drug design in those areas of pharmacology associated with effects attributed to cAMP activity. Beer[3a] and Horovitz,[3b] and their co-workers, have demonstrated that the reduction of anxiety in rats by certain drugs was closely correlated with decreased cAMP phosphodiesterase activity in rat brain. This information prompted the present study in which the derivatives of I were screened for possible antianxiety properties.

We now report that several of these compounds do indeed possess anxiolytic properties comparable to the benzodiazepines II and III. The methods of evaluating these compounds are presently described. A total of 40 compounds were synthesized in order to explore possible structure–activity relationships (**1–40**, Table I).

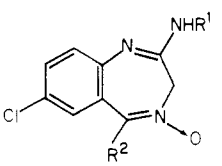
Compounds **1–40** (Table I) were initially screened for antianxiety employing standard gross behavioral observations described elsewhere.[4] From this screen, several of the more potent compounds (in comparison to the benzodiazepines) were selected for advanced evaluation. Passive avoidance (punished responding, Table II) data were obtained to provide a quantitative estimation of the anxiolytic effect of these compounds in comparison with diazepam (II) and chlorodiazepoxide (III). Active avoidance (avoidance response, Table II) data were also obtained to determine if these compounds had antipsychotic properties (major tranquilizer) comparable to chlorpromazine.



I (1–40)



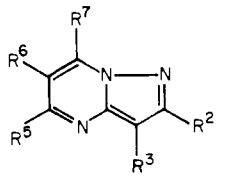
II (diazepam, $R^1 = CH_3$; $R^2 = C_6H_5$)



III (chlorodiazepoxide, $R^1 = CH_3$; $R^2 = C_6H_5$)

One of the potential hazards encountered in the use of the benzodiazepines[5] in humans is the potentiation of CNS

Table I. Physical and Pharmacological Properties of Substituted Pyrazolo[1,5-a]pyrimidines



No.	R^2	R^3	R^5	R^6	R^7	Mp, °C	Formula (mol wt)[a]	Anti-anxiety[b] act. in mouse, 50 and 100 mg/kg ip
1	H	H	H	H	H	105-106[c]	$C_6H_5N_3$ (119)	+
2	H	H	CH_3	H	H	124-125[d]	$C_7H_7N_3$ (133)	+
3	H	H	CH_3	CH_3	H	86-87	$C_8H_9N_3$ (147)	0
4	H	H	H	H	CH_3	59-60[d]	$C_7H_7N_3$ (133)	0
5	H	H	H	CH_3	H	110-112	$C_7H_7N_3$ (133)	0
6	H	H	CH_3	H	CH_3	39-40[e]	$C_8H_9N_3$ (147)	+
7	H	F	CH_3	H	CH_3	70-71[f]	$C_8H_8N_3F$ (165)	+
8	H	Cl	CH_3	H	CH_3	89-90[g]	$C_8H_8N_3Cl$ (181.6)	++
9	H	Br	CH_3	H	CH_3	121-122[g]	$C_8H_8N_3Br$ (226)	++
10	H	I	CH_3	H	CH_3	137-138[g]	$C_8H_8N_3I$ (273)	++[h]
11	H	CN	CH_3	H	CH_3	172-173[g]	$C_9H_8N_4$ (172)	0
12	H	SCN	CH_3	H	CH_3	123-124	$C_9H_8N_4S$ (204)	0[i]
13	H	CO_2Et	CH_3	H	CH_3	107-107.5[g]	$C_{11}H_{13}N_3O_2$ (219.2)	0
14	H	$CONH_2$	CH_3	H	CH_3	247-248[g]	$C_9H_{10}N_4O$ (190.2)	+
15	H	SH	CH_3	H	CH_3	235-236	$C_8H_9N_3S$ (179)	0
16	H	NO	CH_3	H	CH_3	166-167	$C_8H_8N_4O$ (176.2)	0
17	H	NO_2	CH_3	H	CH_3	156-157.5[g]	$C_8H_8N_4O_2$ (192.2)	0
18	H	NH_2	CH_3	H	CH_3	234.5-235.5[j]	$C_8H_{10}N_4 \cdot H_2SO_4$ (260)	0
19	H	$C(=NOH)NH_2$	CH_3	H	CH_3	217-218	$C_9H_{11}N_5O$ (205.2)	0
20	H	SO_2Cl	CH_3	H	CH_3	157-158	$C_8H_8N_3O_2SCl$ (245.7)	0
21	H	SO_2NH_2	CH_3	H	CH_3	211-212	$C_8H_{10}N_4O_2S_2$ (226)	0
22	H	SO_2-c-$N(CH_2CH_2)_2N$-Me	CH_3	H	CH_3	173-174.5	$C_{13}H_{19}N_5O_2S$ (309.3)	0
23	H	CH_3	CH_3	H	CH_3	35-37	$C_9H_{11}N_3$ (161)	+
24	H	$COCF_3$	CH_3	H	CH_3	168-169[f]	$C_8H_8N_3OF_3$ (243)	0[k]
25	H	$C(=S)NH_2$	CH_3	H	CH_3	219-220	$C_9H_{10}N_4S$ (206.2)	0
26	H	Br	H	H	H	145-146	$C_6H_4N_3Br$ (198)	0
27	H	Br	H	H	CH_3	83-84	$C_7H_6N_3Br$ (212)	0
28	H	Br	CH_3	CH_3	H	115-117	$C_8H_8N_3Br$ (226)	0
29	H	Br	C_2H_5	H	C_2H_5	64-65[l]	$C_{10}H_{12}N_3Br$ (254)	+
30	H	Br	CH_3	H	C_2H_5	75-76[l]	$C_9H_{10}N_3Br$ (240)	+
31	H	Br	CH_3	H	n-C_3H_7	74-75[l]	$C_{10}H_{12}N_3Br$ (254)	+
32	H	Br	i-C_3H_7	H	i-C_3H_7	Bp 85-87 (0.1)[l]	$C_{12}H_{16}N_3Br$ (282)	0
33	H	Br	n-C_4H_9	H	n-C_4H_9	47-48[l]	$C_{14}H_{20}N_3Br$ (310.3)	0
34	H	H	CF_3	H	CF_3	105-106	$C_8H_5N_3F_6$ (255)	0
35	OH	H	CH_3	H	CH_3	235-236[m]	$C_8H_9N_3O$ (139)	0
36	OH	Br	CH_3	H	CH_3	212-213[m,n]	$C_8H_8N_3OBr \cdot HBr$ (323)	0
37	Br	H	CH_3	H	CH_3	98-99[m]	$C_7H_6N_3Br$ (214)	+
38	Cl	H	CH_3	H	CH_3	67-69[m]	$C_7H_6N_3Cl$ (181.5)	+
39	H	H	CH_3	H	CH_2COCH_3	84-85	$C_{10}H_{11}N_3O$ (189)	+
40	H	C_6H_5	CH_3	H	CH_3	81-82	$C_{14}H_{13}N_3$ (223)	0

[a] Analyzed for C, H, and N. [b] ++ = active; + = slightly active; 0 = inactive (see text for criteria of activity). [c] Reference 8. [d] Reference 10. [e] Reference 9. [f] Reference 14. [g] Reference 2a. [h] Poorly absorbed orally. [i] Convulsive. [j] Sulfate. [k] Tremorogenic. [l] Reference 2b. [m] Reference 16. [n] Hydrobromide.

depressant effects in the presence of alcohol or barbiturates. Therefore, an animal model was devised which reasonably predicts the drug interaction between antianxiety agents and other CNS depressants at the clinical level (Table II).

Since physical tension is a prominent symptom of anxiety states, the more promising derivatives (e.g., as anxiolytic agents) were tested for muscle relaxant activity, using a variation of the rotating rod test[6] (forced motor activity, Table II). The pyrazolo[1,5-a]pyrimidines evaluated in the advanced tests were also examined for anticonvulsant activity, since this property is associated with most antianxiety agents. Additionally, the compounds were explored for possible analgesic activity.

The modification of unusual animal behavior patterns, such as aggression, constitutes another method of evaluating antianxiety potential. Thus, the most promising anxiolytic agents of this series were studied in fighting mice, the rat–mouse muricide test, and in provoked aggression of monkeys (Table III). Finally, acute toxicity data (Table II) were obtained in order to evaluate the therapeutic potential of the agents under study.

Chemistry. The parent pyrazolo[1,5-a]pyrimidine (**1**) was synthesized from 3-aminopyrazole[7] and 1,1,3,3-tetraethoxypropane according to a recent literature method.[8] The condensation of acetylacetone with 3-aminopyrazole afforded the 5,7-dimethyl compound **6** first described by Makisumi.[9] The 5-methyl analogue **2** was prepared by reduction of the 7-chloro-5-methyl derivative with palladium on charcoal, as reported in the literature.[10] The 7-methyl isomer **4** was prepared via hydrolysis and decarboxylation of the 5-ethoxycarbonyl-7-methyl derivative.[10] The 5,6-dimethyl analogue **3** was prepared via the reduction of the 7-chloro-5,6-dimethyl compound, which we recently reported.[11] The 6-methylpyrazolo-[1,5-a]pyrimidine (**5**) was prepared by reducing the 5,7-

Table II. CNS and Toxicology Profile of 3-Halo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidines

Compd	X	Punished[a,b] responding (rat), mg/kg po	ip	Avoidance[a] response, ip (rat), ED_{50}, mg/kg	Ethanol[a,c,d] potentiation, po (mouse), HD_{50}, mg/kg	Sodium[a,c,e] barbital, ip (mouse), potentiation, HD_{50}, mg/kg	Forced[a,f] motor act., ip (rat), ED_{50}, mg/kg	Spontaneous[a,f] motor act., ip (rat), ED_{50}, mg/kg	Acute toxicity, LD_{50}, mg/kg[a] (mouse) po	ip
6	H	60	40	60.3 ± 4.7	228.6 ± 15.7	118.8 ± 15.7	65.0 ± 6.0	79.0 ± 17.0	927.8 ± 42.0	537.3 ± 36.5
7	F	80	40	40.2 ± 2.0	*g*	*g*	*g*	*g*	*g*	*g*
8	Cl	10	10	31.8 ± 2.3	391.7 ± 33.5	60.9 ± 20.8	32.7 ± 7.5	38.6 ± 9.5	599.4 ± 55.0	369.2 ± 28.5
9	Br	20	10	29.5 ± 12.0	236.8 ± 9.4	61.9 ± 12.1	18.4 ± 2.7	27.1 ± 3.9	1346.5 ± 141.5	457.8 ± 45.0
10	I	120	20	39.1 ± 8.7	296.1 ± 20.5	142.8 ± 10.1	19.8 ± 7.7	24.9 ± 6.4	>3000.0	612.0 ± 38.0
Diazepam		20	20	11.3 ± 2.9	1.5 ± 0.3	0.5 ± 0.8	5.6 ± 0.4	9.2 ± 7.6	1314.7 ± 316.0	992.7 ± 155.5
Chlorodiazepoxide		60	20	14.3 ± 4.3	12.6 ± 0.9	6.4 ± 0.4			938.8 ± 82.0	183.3 ± 52.5
Chlorpromazine				3.7 ± 2.5						

[a] 95% confidence interval. [b] Minimal effective doses. [c] Dose causing loss of righting reflex in 50% of mice. [d] 5 g/kg of ethanol. [e] 100 mg/kg of sodium barbital. [f] Dose causing 50% reduction in forced or spontaneous motor activity. [g] Insufficient quantities of compound available for advanced evaluation.

dichloro-6-methyl analogue (also recently reported[11]) with palladium on charcoal and hydrogen.

The treatment of **6** with various electrophilic reagents gave the 3-chloro- (**8**), 3-bromo- (**9**), 3-iodo- (**10**), and 3-nitro- (**17**) 5,7-dimethylpyrazolo[1,5-*a*]pyrimidines, as we reported earlier.[2a] The condensation of acetylacetone with the 4-cyano, 4-ethoxycarbonyl, or 4-carboxamido derivatives of 3-aminopyrazole afforded the corresponding 3-cyano (**11**), 3-ethoxycarbonyl (**13**), and 3-carboxamido (**14**) derivatives of **6**, as we have also reported.[2a]

The treatment of **11** with hydroxylamine gave the 3-carboxamidrazonyl derivative **19**. Chlorosulfonic acid treatment of **6** gave the 3-chlorosulfonyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**20**). The reaction of **20** with ammonia gave the 3-sulfonamide (**21**) and the analogous reaction with *N*-methylpiperazine gave the 3-(*N*-methyl)piperazinylsulfonamide (**22**). The 3,5,7-trimethyl derivative **23** was prepared by using a procedure similar to that reported by Ried and Kocher[12] for 5,7-dimethyl-3-ethylpyrazolo[1,5-*a*]pyrimidine. Ethyl 2-bromopropionate was converted to ethyl 2-cyanopropionate, which was then treated with hydrazine, followed by cyclization of the resultant pyrazole with acetylacetone to afford 2-hydroxy-3,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine. Chlorination with $POCl_3$ gave the 2-chloro-3,5,7-trimethyl derivative, which was reduced with palladium on charcoal and hydrogen to yield **23** as the product.

The reaction of **6** with bromine and potassium thiocyanate in methanol gave 5,7-dimethyl-3-thiocyanatopyrazolo[1,5-*a*]pyrimidine (**12**). Saponification of **12** gave the 3-mercapto analogue **15**.

Nitrosation of **6** at 0 °C gave the 3-nitroso derivative **16**. Reduction of the 3-nitro analogue **17** with palladium on charcoal and hydrogen gave the 3-amino derivative[2a] **18** which was isolated as a sulfate salt. Diazotization of **18** in fluoroboric acid and photolysis of the resultant 3-diazonium fluoroborate employing a recently developed modification[13] of the Schiemann reaction gave a good yield of the 3-fluoro[14] derivative **7**. A modification of the Friedel–Crafts acylation using trifluoroacetic anhydride as both the acylating agent and Lewis acid gave the 3-trifluoroacetyl[14] derivative **24** from **6**. The reaction of 3-amino-4-cyanopyrazole with hydrogen sulfide gave 3-amino-4-thiocarbamoylpyrazole, which was then condensed with acetylacetone to afford 5,7-dimethyl-3-thiocarbamoylpyrazolo[1,5-*a*]pyrimidine (**25**).

Since bromination of pyrazolo[1,5-*a*]pyrimidine (**1**) resulted in dibromination at the 3 and 6 positions, according to Lynch[8] et al., we prepared the 3-bromo derivative (**26**) of **1** by condensing 3-amino-4-bromopyrazole[15] with 1,1,3,3-tetraethoxypropane. Similarly, the 3-bromo-7-methyl derivative **27** was prepared from the condensation of 3-amino-4-bromopyrazole with 1,1-dimethoxybutan-2-one. The 3-bromo-5,6-dimethyl derivative **28** was prepared via the treatment of **3** with *N*-bromosuccinimide, employing identical conditions for the previously reported[2b] 3-bromo-5,7-diethyl (**29**), 3-bromo-7-ethyl-5-methyl (**30**), 3-bromo-5-methyl-7-*n*-propyl (**31**), 3-bromo-5,7-diisopropyl (**32**), and 3-bromo-5,7-di-*n*-butyl (**33**) derivatives.

The condensation of 3-aminopyrazole with 1,1,1,5,5,5-hexafluoroacetylacetone or heptane-2,4,6-trione gave the corresponding 5,7-bis(trifluoromethyl)- (**34**) or 5-methyl-7-(propan-2-oyl)pyrazolo[1,5-*a*]pyrimidines (**39**), respectively.

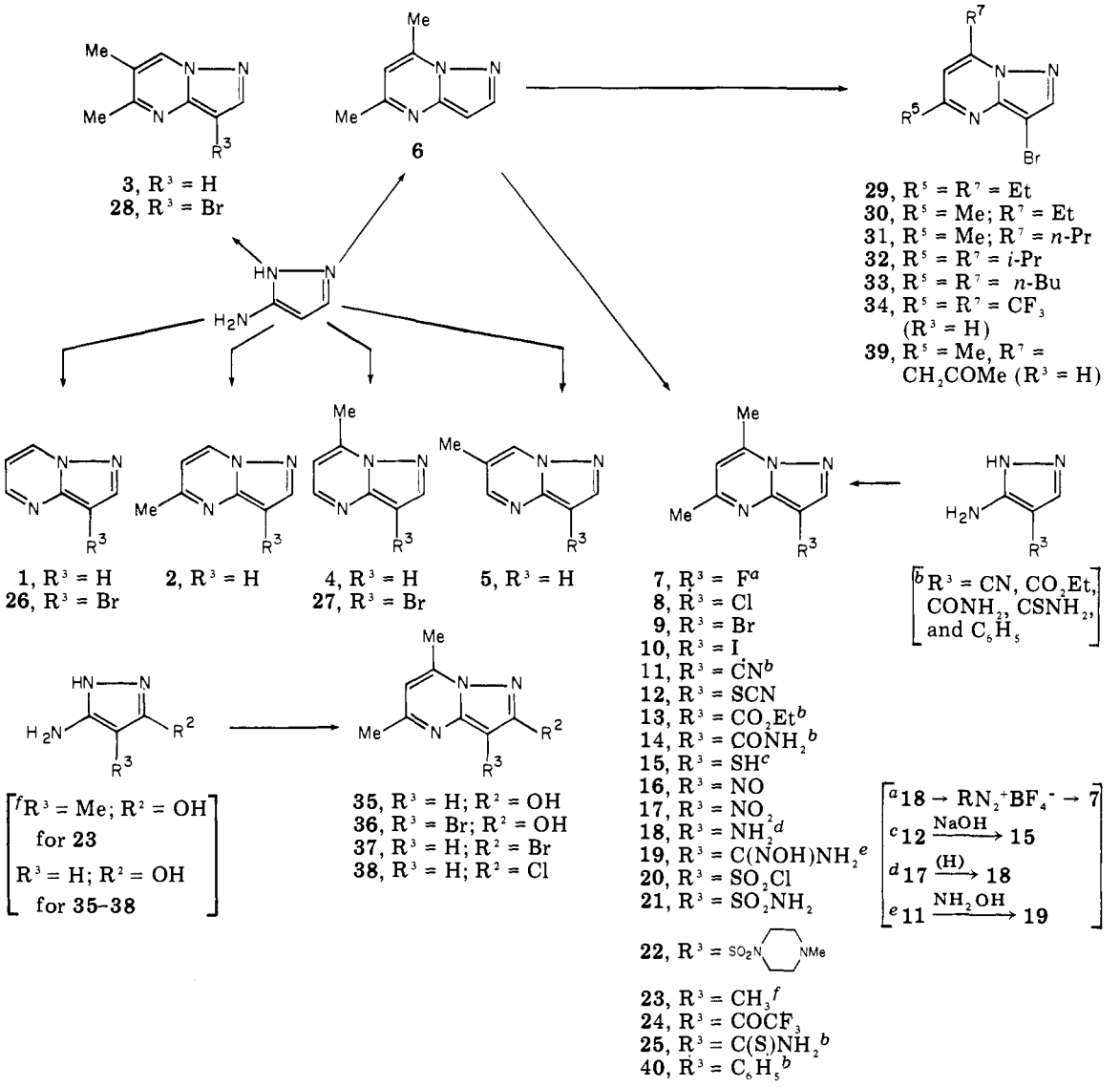
The condensation of acetylacetone with 3-aminopyrazol-5-one gave 2-hydroxy-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine[16] (**35**). Sealed tube reactions of **35** with

Table III. Antiaggressive Activity of Pyrazolo[1,5-a]pyrimidines

	Footshock-induced fighting behavior in mice			Muricide behavior in rats		Provoked aggression in monkeys	
		Percent change in fighting behavior[a]					
Compd	Dose, mg/kg po	30 min	90 min	Dose, mg/kg po	% suppression	Dose, mg/kg po	Effects
8	20	−3	+22[b]	20	0	25–100	Slight to moderate decrease, 0–6 h
	80	−89[b]	−57[b]	80	80		
9	20	+30	+13	20	0–20	25–100	Slight to moderate decrease, 0–6 h
	80	−46[b]	−8	80	60–100		
Diazepam	5	−73[b]	−86[b]	20	0	2.5–10	Moderate decrease, 0–6 h
				80	20		

[a] "+" indicates increase; "−" indicates decrease. [b] $p < 0.05$.

Scheme I



phosphorus oxybromide or phosphorus oxychloride gave the 2-bromo (**37**) and 2-chloro (**38**) isomers of **9** and **8**, respectively.[16] Bromination of **35** with molecular bromine gave the hydrobromide salt of 3-bromo-5,7-dimethyl-2-hydroxypyrazolo[1,5-a]pyrimidine[16] (**36**) (see Scheme I).

The structures of all of the new compounds were confirmed by ^{1}H NMR, IR, and UV spectra, as well as being established by analyses. The site of electrophilic halogenation has been discussed in our earlier work.[2,11,14] The reactions of the cyano group with hydroxylamine (cf. **19**) and hydrogen sulfide (cf. **25**) employed conditions similar to those reported on certain cyanotriazoles.[17] The electrophilic introduction of the thiocyanato group (**12**) was similar to that reported[18] for pyrazolo[1,5-a]pyridine, a related heterocycle.

Pharmacology. Compounds **1**–**40** were evaluated for

CNS depressant activity in a preliminary screen based on observation of gross behavior of rats injected intraperitoneally (ip) with 50 and 100 mg/kg. Animals were observed for ataxia, catatonia, and alterations in motor activity and also startle reflex, 30, 60, and 120 min after injection. Compounds were classified as equiactive, slightly active, or not active (Table I) in comparison with diazepam and chlorodiazepoxide. The active analogues were found to have a nonhypnotic CNS depressant profile somewhat similar to the benzodiazepines but with the important distinctions of lacking pronounced anticonvulsant potency and failing to potentiate ethanol and sodium barbital. Compounds **6**, **8**, **9**, and **10** were studied in the following pharmacological tests: avoidance behavior in rats, drug interaction in mice, motor activity in rats, analgesic and anticonvulsant profile in mice, and acute toxicity in mice. Compounds **8** and **9**, the most potent analogues of the series, were evaluated for antiaggressive activity in mice, rats, and monkeys.

Avoidance Behavior. Passive Avoidance. An approach–avoidance model was used to study antianxiety activity. Rats were motivated to emit a behavior for which they were shocked (punished responding). The influence of compounds in punished responding was determined in the conditioned lick suppression behavioral model described by Vogel.[19] Table II shows the lowest dose of drug (ip and po) producing a statistically significant difference in the number of shocks accepted by treated and control animals. Compounds **8** and **9** influenced avoidance behavior in the rat at a slightly lower threshold dose than diazepam. Both the benzodiazepines and the pyrazolo[1,5-*a*]pyrimidines caused an increase in punished responding at doses not producing overt behavioral depression.

Active Avoidance. Antipsychotic activity was studied in rats using a nondiscriminated Sidman avoidance procedure similar to that described by Niemegeers.[20] Table II lists doses (ip) causing 50% reduction (ED_{50}) in avoidance responding. This test is sensitive to the phenothiazines. For example, chlorpromazine was the most active compound while the benzodiazepines had intermediate activity and the pyrazolo[1,5-*a*]pyrimidines were least active of the compounds tested. The ED_{50} for **6–10** in the Sidman avoidance test equaled or exceeded those ip doses which increased punished responding in the lick suppression test, indicating a lack of antipsychotic specificity for these compounds.

Drug Interaction. Ethanol Potentiation. Interaction between **6–10** given orally (po) and subhypnotic doses of ethanol (5 g/kg po) was studied in mice. Table II shows the oral dose of compound which, in combination with ethanol, produced loss of righting reflex in 50% of treated animals (HD_{50}). Unlike the benzodiazepines, large doses of the pyrazolo[1,5-*a*]pyrimidines were required to potentiate the CNS depressant effects of ethanol.

Barbiturate Potentiation. Interaction between a subhypnotic dose of sodium barbital (100 mg/kg ip) and **6–10** (ip) was studied in mice. Table II shows the HD_{50} for potentiation of sodium barbital using loss of righting reflex as an indicator of CNS depression. In contrast to the benzodiazepines large doses of test compounds were required to potentiate the CNS depressant activity of sodium barbital.

Motor Activity. Forced Motor Activity. The effect of compounds in forced motor activity was studied in rats trained to maintain themselves on a rotating rod. Doses (ip) causing 50% impairment of motor performance are listed in Table II. The separation between doses required to disrupt motor coordination and produce anxiolytic activity was most favorable for compound **8**. In contrast to diazepam the pyrazolo[1,5-*a*]pyrimidines produced motor impairment at doses exceeding those increasing punished responding in rats.

Spontaneous Motor Activity. The influence of compounds in spontaneous motor activity in rats was studied by placing individual animals in an activity sensing cage for 15 min. The dose of compound (ip) causing 50% reduction in activity score is shown in Table II. With the pyrazolo[1,5-*a*]pyrimidines overt behavioral depression characterized by reduction in spontaneous motor activity occurred at doses exceeding those which were anxiolytic in rats.

Analgesic and Anticonvulsant Profile. Analgesic Profile. Compounds **6**, **8**, **9**, and **10** showed no analgesic specificity in the mouse hot-plate or phenylquinine writhing models. Inhibition of response to noxious stimuli occurred at doses (ip) which produced marked CNS depression.

Anticonvulsant Profile. Compounds **6**, **8**, **9**, and **10** injected ip did not protect mice against pentylenetetrazole, strychnine, or electroshock induced convulsions.

LD_{50} Determinations. The acute, single dose, toxicity of compounds **6**, **8**, **9**, and **10** in mice following ip and po administration is shown in Table II in terms of quantitative lethal potency. These data indicate a relatively similar lethality with compounds administered ip and an approximate safety margin ratio of at least 10. A more variable lethality is observed with oral dosing, presumably as a result of a more variable absorption from this route.

Antiaggressive Activity. Fighting Mice. The effect of compounds **8** and **9** on aggressive behavior in mice was studied using the foot-shock induced fighting model described by Tedeschi.[21] Aggressive behavior of pairs of mice was quantitated before and after drug (po) and activity was expressed as percent change in fighting behavior. Table III shows that, compared with diazepam, higher doses of the pyrazolo[1,5-*a*]pyrimidines were required to reduce fighting behavior. Compound **8** was more active than compound **9**. Low doses of **8** and **9** increased aggressive behavior while higher doses reduced fighting, suggesting a dose-dependent biphasic effect on behavior.

Muricide Test. Male Long–Evans black-hooded rats, weighing between 300 and 500 g, were housed in individual isolation cages and were tested for their tendency to kill mice introduced into their home cages. Only animals which killed mice were selected for the experiment. At various time intervals following drug administration, mice were introduced into the cages. A 2-min period was allowed for the kill and at the end of this period the mouse was removed. If the mouse was alive, the killing response was considered suppressed. Muricidal behavior was evaluated before and 1, 2, 4, and 6 h after drug administration (po). Animals served as their own controls and results were expressed as percent suppression of muricidal behavior. Table III shows the range of suppression occurring at each dose level. Compounds **8** and **9** were more active than diazepam in causing inhibition of killing behavior.

Provoked Aggression. Rhesus monkeys were preselected for display of aggressive reactions to pole prodding. The aggressive monkey responds by biting, pushing, or attacking the pole and by vocalizing. Reduction of any of these responses was regarded as a measure of the tranquilizing properties of test compounds. Compounds **8** and **9** were given orally to one male and one female monkey at each dose level. As shown in Table III, compared with

diazepam, higher doses of compounds 8 and 9 were needed to reduce aggression in the monkey.

Results and Discussion

Examination of the data in Table I indicates that optimal activity was obtained with the 3-halo-5,7-dimethylpyrazolo[1,5-a]pyrimidines (7–10), although the 3-fluoro derivative 7 was similar in properties to the nonhalogenated 5,7-dimethyl compound 6. Apparently the position and number of methyl groups on the heterocyclic nucleus were important for activity. A reduction in the number of methyl groups, or substitution at carbons other than C_5 or C_7, or extension of the alkyl group to ethyl, propyl, or butyl, substantially decreased the anxiolytic potential in the primary screen, relative to 6–10 (Table I).

The hydrophobic and electronic properties of the halogen substituents were apparently important for activity, as other electron-withdrawing groups (compounds 11–25) or an electron-donating group (3-methyl, 23) contributed little or nothing to the anxiolytic properties of 5,7-dimethylpyrazolo[1,5-a]pyrimidine.

The substitution of halogens in the C_2 position rather than the C_3 position of this heterocycle (e.g., 6) was less effective in eliciting an anxiolytic effect, as can be seen (Table I) in the comparison of the qualitative activities of the 3-chloro and 3-bromo derivatives 8 and 9 with those of the 2-chloro and 2-bromo isomers 37 and 38. An investigation of the electronic properties of both the substituents and rings systems of related nitrogen bridgehead heterocycles is now underway in our laboratories. The hydrophobic properties are being studied via partition coefficients.

It may be of interest to mention that related pharmacological activity has been observed elsewhere for both pyrazoles and pyrazolo[1,5-a]pyrimidines. Some years ago, researchers in the Soviet Union identified significant antianxiety (minor tranquilizer) properties common to certain 5-aminopyrazoles.[22] Japanese investigators reported that antipyretic, analgesic, and antiinflammatory activity was associated with 7-amino-3-bromopyrazolo-[1,5-a]pyrimidines.[23] We did not observe these properties in 6–10, however.

The pharmacological profile and favorable toxicity data of 6–10 (Table II) illustrate that these compounds do possess an interesting nonhypnotic CNS depressant (anxiolytic) effect in animals. The data from the passive avoidance (punished responding) test indicated that 6–10 had activity in the same range as the clinically useful antianxiety agents, chlorodiazepoxide and diazepam. The active avoidance (avoidance response, Table II) test characterized 6–10 as being closer to anxiolytic (minor tranquilizer) than antipsychotic (major tranquilizer) in character, in comparison with chlorpromazine.

The "3-halo" compounds 8–10 appear to be fairly specific in anxiolytic activity, being devoid of analgesic, anticonvulsant, or muscle-relaxant properties common to the benzodiazepines. The impairment of motor coordination and reduction of spontaneous motor activity in rats (Table II) occurred at relatively high doses of 8–10 compared to diazepam. More importantly, these doses were at a higher range than those necessary to produce a minimal anxiolytic effect (punished responding, Table II) by these compounds.

From the group of 6–10, 8 and 9 were selected for further evaluation on the basis of potency and favorable toxicity data (Table II). As an alternate method of estimating antianxiety potential, 8 and 9 were compared with diazepam in decreasing animal aggression in monkeys, rats, and mice (Table III). In mice, 8 and 9 possessed a dose-dependent stimulant-depressant profile. These compounds were more potent than diazepam in suppressing aggressive behavior in the rat, but less potent than diazepam in reducing aggression in monkeys.

The most prominent feature of these 3-halo-5,7-dimethylpyrazolo[1,5-a]pyrimidines is that, unlike the benzodiazepines, they do not potentiate the CNS depressant effects of alcohol or sodium barbital at psychoactive doses. Table II illustrates that diazepam and chlorodiazepoxide potentiated such drug effects at $^1/_{10}$–$^1/_{20}$th the dose required to elicit minimal anxiolytic effects. In contrast (comparing loss of righting reflex to punished responding), 8 and 9 potentiated these effects only at 6–40 times and 3–10 times, respectively, the minimal dose at which anxiolytic effects were observed. Such a remarkable difference in mechanism between the pyrazolo[1,5-a]pyrimidines and the benzodiazepines makes 8 and 9 worthy of further investigation as possible therapeutic agents. Such studies are presently underway in these and other laboratories.

Experimental Section

Analyses for all compounds were performed by Galbraith Labs, Knoxville, Tenn., and were within ±0.4% of the calculated values for C, H, and N (and other elements, where noted). Spectral determinations were performed with the Perkin-Elmer 257 (IR, KBr pellets for solids and NaCl cells for liquids), Perkin-Elmer 202 (UV, MeOH or H_2O as solvents, as noted) and Hitachi Perkin-Elmer R20A (high-resolution ^1H NMR, in $CDCl_3$ or Me_2SO with Me_4Si as internal standards, or D_2O with sodium 2,2-dimethylsilapentane-5-sulfonate as internal standard for compounds with aqueous solubility) instruments. All structures were consistent with spectra and elemental analyses. Melting point determinations were taken in capillary tubes (Hoover-Thomas apparatus) and were recorded uncorrected. Column chromatography was performed with ICN Woelm alumina (basic or neutral, as noted), activity grade I. Thin-layer chromatography (TLC) was performed with ICN Woelm silica gel plates (with indicator) eluted with methylene chloride, ethyl acetate, or methylene chloride–methanol (5:1).

5,6-Dimethylpyrazolo[1,5-a]pyrimidine (3). A mixture of 1.85 g (0.01 mol) of 7-chloro-5,6-dimethylpyrazolo[1,5-a]pyrimidine,[11] 900 mg of anhydrous sodium acetate, 300 mg of 10% palladium on charcoal, and 30 ml of ethanol was hydrogenated in a Parr apparatus at 13 psi of hydrogen. As soon as the theoretical amount of hydrogen was absorbed (60 min), the mixture was purged with nitrogen and filtered through Celite. The filtrate was evaporated in vacuo [40 °C (10 mm)] and the residue was extracted with ether. The ether was washed with saturated aqueous sodium bicarbonate and then water. The ether was evaporated in vacuo [20 °C (10 mm)] and the residue was extracted with boiling petroleum ether (bp 60–80 °C). The solution, upon cooling, deposited white needles: yield, 800 mg (60%); mp 86–87 °C. Anal. ($C_8H_9N_3$) C, H, N.

5,7-Dimethylpyrazolo[1,5-a]pyrimidine (6) was prepared, as reported by Makisumi,[9] by condensing 3-aminopyrazole with acetylacetone in refluxing ethanol with a catalytic amount of piperidine added. The 5,7-dialkylpyrazolo[1,5-a]pyrimidines employed as precursors for 29–33 have all been described in our earlier publication,[2b] employing this method.

In a similar manner, **5,7-bis(trifluoromethyl)pyrazolo-[1,5-a]pyrimidine (34)** was prepared from 3-aminopyrazole and 1,1,1,5,5,5-hexafluoroacetylacetone in 67% yield, mp 105–106 °C, and recrystallized from ligroine as white needles. Anal. ($C_8H_3N_3F_6$) C, H, N.

Also in a similar fashion, **5-methyl-7-(propan-2-oyl)-pyrazolo[1,5-a]pyrimidine (39)** was prepared from 3-aminopyrazole and heptane-2,4,6-trione (Willowbrook Labs, Wis.) in 62% yield, mp 79–81 °C, and recrystallized from ligroine as bright yellow needles. Anal. ($C_{10}H_{11}N_3O$) C, H, N.

5,7-Dimethyl-3-thiocyanatopyrazolo[1,5-a]pyrimidine (12). A solution of 1.47 g (10 mmol) of 5,7-dimethylpyrazolo[1,5-a]-pyrimidine[9] (6) and 1.5 g (15.5 mmol) of potassium thiocyanate in 25 ml of methanol was treated with 2.4 g (15 mmol) of bromine

in 20 ml of methanol over a 5-min period at room temperature. The potassium bromide was filtered off and the filtrate was evaporated in vacuo [40 °C (10 mm)] to give a solid residue. The residue was recrystallized from ligroine to give 750 mg (37.5%) of product, mp 123–124 °C, as colorless needles: IR (KBr) 2158 cm^{-1} (SCN). Anal. ($C_9H_8N_4S$) C, H, N.

5,7-Dimethyl-3-mercaptopyrazolo[1,5-*a*]pyrimidine (15). A mixture of 1.0 g (5 mmol) of **12**, 5 ml of 4% aqueous potassium hydroxide, and 30 ml of methanol was stirred at room temperature for 1 h. A yellow precipitate formed which was collected by filtration and washed with methanol. Recrystallization from methanol gave 650 mg (71.4%) of the product as white needles, mp 234–235 °C. Anal. ($C_8H_9N_3S$) C, H, N.

5,7-Dimethyl-3-nitrosopyrazolo[1,5-*a*]pyrimidine (16). A solution of 1.47 g (10 mmol) of 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine[9] (**6**) in 12 ml of 1.5 N hydrochloric acid (0–5 °C) was treated with portions of 800 mg (14 mmol) of sodium nitrite over a 10-min period. The solution developed a deep green color and a dark blue precipitate separated. The blue precipitate was filtered and washed with cold water. Recrystallization of this material from methanol gave 850 mg (50.0%) of product as cerulean blue needles, mp 166–167 °C. Anal. ($C_8H_8N_4O$) C, H, N.

3-*N*-Hydroxyamidino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (19). To 6.4 g (4 mmol) of 3-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine[2a] (**11**) in 200 ml of ethanol was added 2.3 g (10 mmol) of hydroxylamine and the mixture was heated at reflux for 8 h. The solution was allowed to cool to room temperature and crystals deposited on the walls of the flask. Recrystallization of the crude product from methanol afforded 6.0 g (77.8%) of the product as yellowish needles: mp 220.5–221.5 °C; IR (KBr) no absorption at 2250 cm^{-1} (absence of C≡N). Anal. ($C_9H_{11}N_5O$) C, H, N.

3-Amino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine Sulfate (18). A mixture of 8.0 g (40 mmol) of 3-nitro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine[2a] (**17**) and 0.5 g of 10% palladium-on-charcoal catalyst in 150 ml ethanol was reduced at 57 psi of hydrogen. The reaction mixture was filtered through a Celite pad and the catalyst was washed with 10 ml of ethanol. The filtrate and washings were combined and cooled to 0 °C, with stirring, as 4 ml of concentrated sulfuric acid (18 M) was added dropwise. A thick white precipitate formed. The mixture was chilled in the freezer for 3 h and then filtered on a glass Buchner funnel and washed with anhydrous ether. The white solid was recrystallized from methanol to give 9.1 g (84%) of the product as a white powder, mp 234.5–235.5 °C dec. Anal. ($C_8H_{10}N_4 \cdot H_2SO_4$) C, H, N.

3-Fluoro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (7). A solution of 3.1 g (44.3 mmol) of sodium nitrite in 10 ml of water was added to a stirred solution of 11.4 g (43.8 mmol) of **18** in 100 ml of 48% fluoroboric acid maintained at about −20 °C (dry ice–methanol bath). The addition was carried out over a 10-min period and then the cold solution was placed in the well of 450-W Ace-Hanovia ultraviolet apparatus. The solution was allowed to warm to room temperature and was then irradiated (2300 Å) for 45 h (with stirring, Teflon bar). The resulting dark mixture was poured into 600 ml of ice water and was extracted with four 100-ml portions of chloroform. The organic extract was washed with four 100-ml portions of water and was then dried ($MgSO_4$). Evaporation of the solvent [30 °C (10 mm)] gave a black oil. Chromatography of the oil on neutral alumina (200 g, Woelm grade I) with methylene chloride gave a yellow oil which eventually solidified. Recrystallization from petroleum ether (bp 30–60 °C) at −40 °C (dry ice–acetone) gave 2.35 g (32.5%) of white needles, mp 70–71 °C (lit.[14] mp 69–70 °C).

3-Chlorosulfonyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (20). Chlorosulfonic acid (40 ml) was cautiously added to 6.0 g (40 mmol) of 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine[9] (**6**) at 15–20 °C over a 10–15-min period. Upon completion of the addition, the mixture was carefully heated at 80–85 °C and was maintained at this temperature for 4 h. The resultant brown solution was allowed to cool to room temperature and was then carefully poured over 100 g of crushed ice, with manual stirring, over a 10–15-min period. The suspension which resulted was filtered and the white precipitate was washed well with water. The precipitate was dissolved in 100 ml of methylene chloride, and the solvent was washed with water and dried ($MgSO_4$). The solution was evaporated at 30 °C (15 mm) to afford a white solid which, upon recrystallization from benzene–ligroine, gave 2.8 g (28%) of the product in the form of white cubettes: mp 157–158 °C; IR (KBr) 843 and 1130 cm^{-1} (SO_2 bands). Anal. ($C_8H_8N_3O_2SCl$) C, H, N.

5,7-Dimethyl-3-sulfonamidopyrazolo[1,5-*a*]pyrimidine (21). A solution of 20 ml of 17 N ammonium hydroxide in 30 ml of methanol was cooled to 15 °C and 1.0 g (5 mmol) of **20** was added in portions over a 10-min period. The mixture was stirred for 24 h at ambient temperature. The solvent was removed in vacuo [40 °C (10 mm)] and the residue was recrystallized from methanol to afford 700 mg (76%) of the product, mp 210–212 °C, as white needles. Anal. ($C_8H_{10}N_4O_2S$) C, H, N.

In a similar manner, **5,7-dimethyl-3-(*N*-methylpiperazinyl)sulfonylpyrazolo[1,5-*a*]pyrimidine (22)** was prepared in 71% yield from **20**, *N*-methylpiperazine, and methanol. Recrystallization from ethyl acetate afforded the product as white cubettes, mp 173–174.5 °C. Anal. ($C_{13}H_{19}N_5O_2S$) C, H, N.

3,5,7-Trimethylpyrazolo[1,5-*a*]pyrimidine (23). A mixture of 18.1 g of ethyl 2-bromopropionate, 5.0 g of sodium cyanide, and 50 ml of methanol was refluxed for 3.5 h with stirring. The dark solution was evaporated (Rotovac) and extracted with four 100-ml portions of ether. The combined ether extract was distilled, giving **ethyl 2-cyanopropionate** as a yellow oil (5.2 g), bp 90–110 °C (1.5 mm). In an analogous method to that used by Ried and Kocher,[12] 5.2 g of the cyanopropionate ester was dissolved in 30 ml of ethanol and 2.4 g of 85% hydrazine hydrate was cautiously added. The solution was refluxed 10 h and then was concentrated to an oil (Rotovac), dissolved in 70 ml of ethanol, and mixed with 4.0 g of acetylacetone and 1.5 ml of acetic acid. The mixture was refluxed for 1 h and then cooled to room temperature as 50 ml of 2 N NaOH was added, followed by a reflux period of another 1 h. The solution was cooled to room temperature and neutralized with 12 N HCl, and a white precipitate of **2-hydroxy-3,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine** was obtained. Recrystallization of this material from MeOH gave 3.4 g of white needles (49%), mp 248–250 °C. Chlorination of this compound (3.0 g) with 13.0 ml of phosphorus oxychloride at 200–205 °C (sealed tube or metal bomb) for 6 h gave a dark mixture which was concentrated in vacuo, poured over 100 g of ice, made alkaline with 6 N NaOH (pH 9–10), and extracted with ether (4 × 50 ml). The ether extract was evaporated to give a pale yellow solid which was recrystallized from petroleum ether (bp 30–60 °C) to afford 250 mg of **2-chloro-3,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine**, mp 108–110 °C (somewhat unstable but homogeneous on thin-layer chromatography with ethyl acetate). A mixture of 1.3 g (6.5 mmol) of this material was reduced in ethanol with hydrogen (48 psi) in the presence of 0.5 g of 10% palladium on charcoal and 0.6 g of sodium acetate (Parr bomb). The reduction was complete in 7 h, at which time the mixture was filtered through Celite, the ethanol evaporated (Rotovac), and the residue extracted with methylene chloride (3 × 50 ml). The dried ($MgSO_4$) extract was evaporated (Rotovac) to yield an oil which solidified upon standing. Preparative thin-layer chromatography (basic alumina, grade II) with ethyl acetate afforded 250 mg (30%) of the title product **23** as white needles. Recrystallization from petroleum ether gave analytically pure material, mp 35–37 °C (structure confirmed by ^1H NMR in $CDCl_3$ and UV in MeOH). Anal. ($C_9H_{11}N_3$) C, H, N.

5,7-Dimethyl-3-trifluoroacetylpyrazolo[1,5-*a*]pyrimidine (24). A mixture of 3.0 g (20 mmol) of 5,7-dimethylpyrazolo-[1,5-*a*]pyrimidine[9] (**6**), 4 ml of trifluoroacetic anhydride, and 50 ml chloroform was refluxed for 10–12 h. The solution was allowed to cool to room temperature and was poured over 100 g of crushed ice. The mixture was made alkaline (pH 8) with 6 N sodium hydroxide and the organic material was extracted with three 50-ml portions of methylene chloride. The solvent was dried (Na_2SO_4) and chromatographed on neutral alumina, eluting the products with more methylene chloride. Evaporation of the fractions gave 700 mg of starting material and 1.2 g (24.7%) of the product as yellowish needles, mp 168–169 °C (lit.[14] mp 165–167 °C).

5,7-Dimethyl-3-thiocarbamoylpyrazolo[1,5-*a*]pyrimidine (25). Ammonia was passed into a stirred solution of 4.0 g of 3-amino-4-cyanopyrazole in 60 ml of ethanol at 0 °C for 1 h. Then hydrogen sulfide was passed into the mixture for another 1 h. The black solution was heated at 90–100 °C (steel bomb) for 3.5 h and was then allowed to cool to room temperature overnight. The

contents were concentrated in vacuo (Rotovac) to yield a dark solid. Recrystallization from water gave 4.0 g (80%) of **3-amino-4-thiocarbamoylpyrazole**, mp 229–231 °C in the form of yellowish white platelets. Condensation of 2.60 g of this material with 2.0 g of acetylacetone in 70 ml of ethanol (with 1 ml of piperidine) gave 1.75 g (45.7%) of the title compound as yellowish needles, mp 219–220 °C, from methanol. Anal. ($C_9H_{10}N_4S$) C, H, N.

3-Bromopyrazolo[1,5-a]pyrimidine (26). A solution of 3.24 g (20 mmol) of 5(3)-amino-4-bromopyrazole[15] in 25 ml of ethanol was treated with 1.7 ml of concentrated hydrochloric acid (12 N) and 3.3 g (21 mmol) of 1,1,3,3-tetramethoxypropane. The clear solution was warmed at 50–60 °C for 80 min. The solution acquired a dark green color and crystals separated. The mixture was cooled and filtered and the crystals which separated were recrystallized from ethanol to give 3.0 g (64%) of white needles, mp 145–146 °C. Anal. ($C_6H_5N_3Br$) C, H, N.

3-Bromo-7-methylpyrazolo[1,5-a]pyrimidine (27) was synthesized in a similar manner from 5(3)-amino-4-bromopyrazole (5.0 g, 30 mmol) and 1,1-dimethoxybutan-2-one (4.2 g, 30 mmol) in 50 ml of ethanol containing 2.5 ml concentrated hydrochloric acid. In this case, however, the product did not separate from the dark reaction mixture, so the solvent was evaporated [40 °C (10 mm)] and the residue obtained was dissolved in water (30 ml) and neutralized with solid sodium bicarbonate. The solution was extracted with ethyl acetate, and the organic solvent was washed with water (100 ml), dried (Na_2SO_4), and evaporated [40 °C (10 mm)]. The residual oil was chromatographed on neutral alumina (Woelm, grade I) with methylene chloride (300 ml). Evaporation of the eluent gave 1.1 g (18%) of the product, recrystallized from petroleum ether (bp 30–60 °C) as pale yellow needles, mp 83–84 °C. Anal. ($C_7H_6N_3Br$) C, H, N.

3-Bromo-5,6-dimethylpyrazolo[1,5-a]pyrimidine (28). A solution of 1.47 g (10 mmol) of 5,6-dimethylpyrazolo[1,5-a]pyrimidine (3) and 1.0 g of *N*-bromosuccinimide in 50 ml of methylene chloride was refluxed for 20 min. The yellowish solution was evaporated [30 °C (10 mm)] and the residual oil obtained was chromatographed on neutral alumina (Woelm, grade I). The pale yellow solid obtained upon evaporation of the eluent was recrystallized from petroleum ether (bp 30–60 °C) to afford 1.5 g (66.4%) of the product, mp 115–117 °C, as white cubettes with a faint pink tinge. Anal. ($C_8H_8N_3Br$) C, H, N.

5,7-Dimethyl-3-phenylpyrazolo[1,5-a]pyrimidine (40). A mixture of 2.5 g (17 mmol) of 3-amino-4-phenylpyrazole, 1.8 g (18 mmol) of acetylacetone, and 30 ml of glacial acetic acid was refluxed for 6 h. The solution was evaporated in vacuo to afford a yellow solid. Recrystallization of this material from petroleum ether gave 2.4 g (63%) of white needles, mp 81–82 °C. Anal. ($C_{14}H_{13}N_3$) C, H, N.

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