Synthesis and Enzymic Activity of 6-Carbethoxy- and 6-Ethoxy-3,7-disubstituted-pyrazolo[1,5-*a*]pyrimidines and Related Derivatives as Adenosine Cyclic 3′,5′-Phosphate Phosphodiesterase Inhibitors

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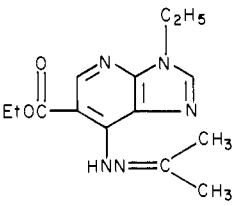
A number of 3,7-disubstituted 6-carbethoxypyrazolo[1,5-*a*]pyrimidines and 3,7-disubstituted 6-ethoxypyrazolo-[1,5-*a*]pyrimidines have been prepared and evaluated as adenosine cyclic 3′,5′-phosphate (cAMP) phosphodiesterase (PDE) inhibitors vs. the low K_m enzyme isolated from beef heart, rabbit lung, and kidney preparations. The results were found to be between 0.5 to 13 times as potent as theophylline as inhibitors of PDE, depending on the tissue source. A number of these PDE inhibitors exhibited significant physiological effects in different animal systems, suggesting it should be possible to obtain selective PDE inhibition in various tissues. Several of these heterocycles were found superior to adenosine in inhibiting ADP-induced platelet aggregation in vitro.

Inhibitors of adenosine cyclic 3′,5′-phosphate phosphodiesterase as potentially useful medicinal agents has been reviewed by Amer and McKinney.[1] The selection of pyrazolo[1,5-*a*]pyrimidine derivatives for study as PDE inhibitors has been outlined in two of our publications.[2,3] The search for selectivity of phosphodiesterase (PDE) inhibition in certain organs or tissues could lead to an agent of high potency with fewer side effects than known PDE inhibitors, such as theophylline.

In certain diseases, lower cAMP levels have been associated with decreased activity of adenylate cyclase. A correlation of cAMP deficiency to disease state has been observed in hypertension[4] and asthma.[5] Decreased intracellular concentrations of cAMP have been reported in the depressed immune response,[6] inflammation[7] anaphylaxis,[8] and neurotransmitter release.[9]

There is increasing evidence that cyclic nucleotide phosphodiesterases exist in several molecular forms and that these isozymes have characteristic differences from tissue to tissue.[10] Thus, the finding of selective inhibitors of these different isozymes should allow one to selectively increase the level of cAMP in certain organs or cell types. Indeed, Lowe and Henderson[11] have shown that caffeine exhibits antitumor activity against lymphoma L-5178 cells. Mouse B16 melanoma cells cultured in the presence of theophylline are arrested in the late G_1 or early G_2 phase of the cell cycle,[12] and the cells are returned to a normal fibroblast-type morphology.[12] Tisdale[13] has recently suggested that it may be possible to design PDE inhibitors which would specifically increase cAMP only in cancer cells as a hormonal approach to the cancer problem. Recently, methylisobutylxanthine has been shown to be active against the metastases of Lewis lung carcinoma in mice.[14] Certain derivatives of pyrazolo[1,5-*a*]pyrimidine prepared in our laboratory[2,3] have been shown to be inhibitors of PDE isolated from beef heart and rabbit lung. The report of 5-carbethoxy-1-ethyl-4-(isopropylidenehydrazino)-pyrazolo[3,4-*b*]pyridine[15] (1) as a potent inhibitor of PDE from rat brain prompted us to extend our studies of the pyrazolo[1,5-*a*]pyrimidines to include certain 6-carbethoxy-3,7-disubstituted-pyrazolo[1,5-*a*]pyrimidines, **2**, which is the subject of the present report.

The synthesis of 6-carbethoxy-7-hydroxypyrazolo[1,5-*a*]pyrimidine (4) was accomplished from 3-aminopyrazole and diethyl ethoxymethylenemalonate according to the procedure of Makisumi (Scheme I).[16] Similarly, 3-amino-4-carbethoxypyrazole,[17] 3-amino-4-bromopyrazole,[18] and 3-amino-4-ethylpyrazole were treated with diethyl ethoxymethylenemalonate to give 3,6-dicarbethoxy-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**5**), 3-bromo-6-carbethoxy-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**6**), and 3-ethyl-6-carbethoxy-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**7**), respectively. The required 3-amino-4-ethylpyrazole (**3**) was prepared by treatment of *n*-butyronitrile with ethyl formate in the presence of sodium to give α-formyl-*n*-butyronitrile, which was treated directly with hydrazine hydrate in ethanol to give 3-amino-4-ethylpyrazole (**3**) in 21% yield. Treatment of 3-amino-4-carbethoxypyrazole,[17]



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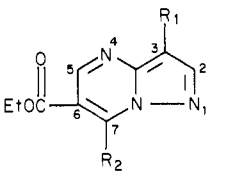

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§ SRI International.
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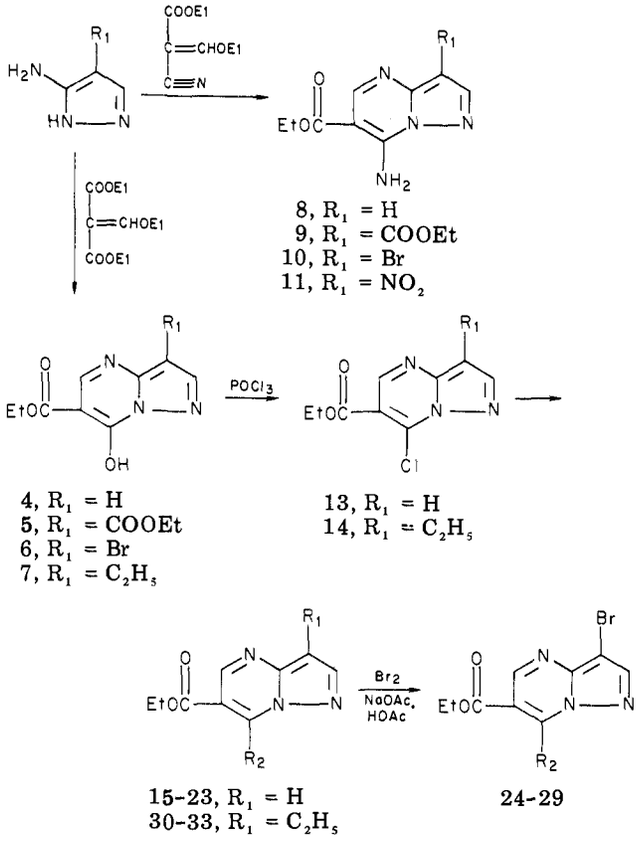
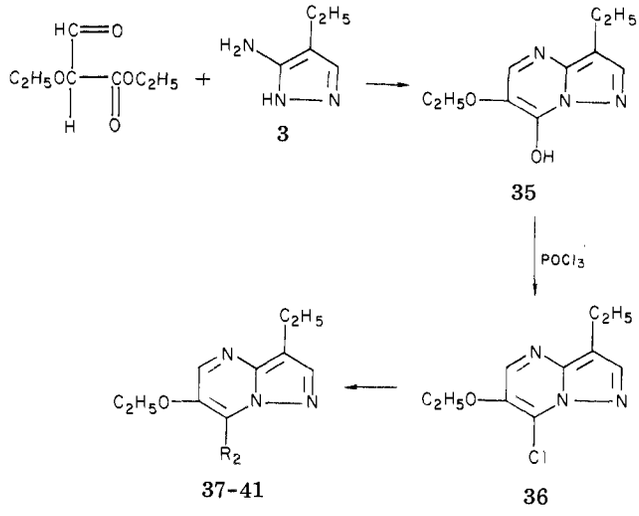
Scheme I



3-amino-4-bromopyrazole,[18] and 3-amino-4-nitropyrazole[18] with ethyl ethoxymethylenecyanoacetate in glacial acetic according to Makisumi[16] for the synthesis of **8** gave 3,6-dicarbethoxy-7-aminopyrazolo[1,5-*a*]pyrimidine (**9**), 3-bromo-6-carbethoxy-7-aminopyrazolo[1,5-*a*]pyrimidine (**10**), and 3-nitro-6-carbethoxy-7-aminopyrazolo[1,5-*a*]pyrimidine (**11**), respectively. The yields of **9** and **10** were good, but **11** was obtained in only 6% yield by this procedure.

Treatment of 6-carbethoxy-7-hydroxypyrazolo[1,5-*a*]-pyrimidine[16] (**4**) with phosphorus oxychloride in the presence *N,N*-diethylaniline gave 6-carbethoxy-7-chloropyrazolo[1,5-*a*]pyrimidine (**13**) in 63% yield. Treatment of **13** with various nucleophilic reagents provided the various 6-carbethoxy-7-substituted-pyrazolo[1,5-*a*]pyrimidines in Table I (compounds **15–23**). The chlorine is quite reactive toward nucleophilic displacement reactions. For example, a solution of sodium *n*-propoxide in 1-propanol at 35 °C converts compound **13** into 6-carbethoxy-7-*n*-propoxypyrazolo[1,5-*a*]pyrimidine (**15**). Similarly, treatment of compound **13** with primary and secondary amines in ethanol at 25–50 °C affords the 6-carbethoxy-7-substituted-aminopyrazolo[1,5-*a*]pyrimidines **17–21**. The treatment of compound **13** with an ethanolic solution of thiourea affords 6-carbethoxy-7-mercaptopyrazolo[1,5-*a*]pyrimidine (**22**), and a solution of sodium ethylmercaptide in methanol readily converted **13** to 6-carbethoxy-7-ethylthiopyrazolo[1,5-a]pyrimidine (**23**). Direct bromination of certain of these 6-carbethoxy-7-substituted-pyrazolo[1,5-*a*]pyrimidines with bromine in the presence of sodium acetate in glacial acetic resulted in the introduction of bromine at position 3 to give 3-bromo-6-carbethoxy-7-substituted-pyrazolo[1,5-*a*]pyrimidines (see Table I, compounds **24–29**). The site of bromination is expected as position 3 from prior studies[2] of bromination of pyrazolo[1,5-*a*]pyrimidines and was corroborated by ring closure of 3-amino-4-bromopyrazole to give **6**. The dis-

Scheme II



appearance of the upfield proton at C_3 in the region δ 6.6 in the brominated derivatives[2] established the site of bromination as C_3.

When 3-ethyl-6-carbethoxy-7-hydroxypyrazolo[1,5-*a*]-pyrimidine (**7**) was treated with phosphorus oxychloride and *N,N*-dimethylaniline, 6-carbethoxy-7-chloro-3-ethylpyrazolo[1,5-*a*]pyrimidine (**14**) was isolated in 98% yield. Treatment of **14** with various nucleophilic reagents at room temperature similarly gave replacement of the chlorine to yield compounds **30–33** (Table I).

When ethyl α-ethoxy-α-formyl acetate and 3-amino-4-ethylpyrazole (**3**) were reacted together, followed by refluxing in glacial acetic acid, ring closure occurred to give a 59% yield of 3-ethyl-6-ethoxy-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**35**; Scheme II). Treatment of **35** with phosphorus oxychloride and *N,N*-dimethylaniline gave an 81% yield of 3-ethyl-6-ethoxy-7-chloropyrazolo[1,5-*a*]pyrimidine (**36**). Nucleophilic substitution gave compounds **37–41** (Table II). The good inhibition of cAMP phosphodiesterase by the 3-ethyl derivatives (Table I) suggested the synthesis of various 3-ethyl-5-methyl-6-substituted-pyrazolo[1,5-*a*]pyrimidines (Scheme III, Table III). These were prepared by treatment of 3-amino-4-ethylpyrazole (**3**) with acetoacetic acid ester to give 3-ethyl-7-hydroxy-5-methylpyrazo[1,5-*a*]pyrimidine (**51**). Treatment of **51** with phosphorus oxychloride gave 7-chloro-3-ethyl-5-methylpyrazolo[1,5-*a*]pyrimidine (**52**) in 90% yield. Treatment of **52** with various nucleophilic reagents gave the compounds **42–44** listed in Table III. For comparison, several 7-substituted amino derivatives with hydrogen at position 3 were similarly prepared from 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[19,20] (see Table III). Several of these were brominated directly to give the 3-bromo-5-methyl-7-(alkylamino)pyrazolo[1,5-*a*]pyrimidines **45** and **46** (Table III). 3-Amino-4-carbethoxypyrazole[17] and ethoxymethylenemalononitrile in refluxing acetic acid gave a 17% yield of 7-amino-6-cyano-3-carbethoxypyrazolo-[1,5-*a*]pyrimidine (**53**).

Discussion

Phosphodiesterase Inhibition and Biological Activity. Inspection of Table I shows that 7-substitution of

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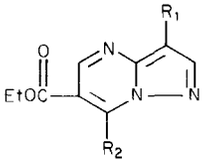
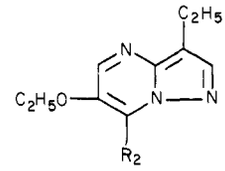
Table I. Phosphodiesterase Inhibition and Inhibition of ADP-Induced Platelet Aggregation by 6-Carbethoxy-3,7-disubstituted-pyrazolo[1,5-*a*]pyrimidines



compd	R_1	R_2	yield, %	mp, °C	formula[a]	PDE inhibn[b,c] α_{lung}	PDE inhibn[b,c] α_{kidney}	PDE inhibn[b,c] α_{heart}[d]	inhibn of ADP-induced platelet aggregation[e] concn, mcg/mL	inhibn of ADP-induced platelet aggregation[e] % inhibn
5	CO_2Et	OH	57	302–303 dec	$C_{12}H_{13}N_3O_5$	0.6	0.4		100	68
									50	23
6	Br	OH	62	273–275 dec	$C_9H_8N_3O_3Br$	0.5	1.0		100	88
									50	34
7	C_2H_3	OH	54	299–301	$C_{11}H_{13}N_3O_3$					
8	H	NH_2	71	132–134	$C_9H_{10}N_4O_2$	0.9	1.0		100	94
									50	50
9	CO_2Et	NH_2	43	229–233	$C_{12}H_{14}N_4O_2$	1.5	2.0	0.7	100	96
									50	47
10	Br	NH_2	62	264–266 dec	$C_9H_9N_4O_2Br$	insol[f]			100	68
									25	67
11	NO_2	NH_2	13	335–336 dec	$C_9H_9N_5O_4$	insol[f]				
13	H	Cl	63	85–87	$C_9H_9N_3O_2Cl$	0.6	0.6			
15	H	O-*n*-C_3H_7	48	127–129	$C_{12}H_{15}N_3O_3$	0.6	0.6			
16	H	NHC_2H_5	98	78–80	$C_{11}H_{14}N_4O_2$	4.3	5.2		100	86
									50	42
17	H	NH-*n*-C_3H_7	71	60–62	$C_{12}H_{16}N_4O_2$	5.9	13.0			
18	H	$N(C_2H_5)_2$	63	46–48	$C_{13}H_{18}N_4O$	1.8	2.0	2.3		
19	H	$NH(CH_2)_2OH$	84	178–179	$C_{11}H_{14}N_4O_3$	1.5	0.3		100	92
									50	47
20	H	$NHCH_2CO_2H$	76	279–281 dec	$C_{11}H_{12}N_4O_4$	1.7	1.2		100	76
									50	67
21	H	$NHN(CH_3)_2$	87	129–130	$C_{11}H_{15}N_5O_2$	2.0	1.1			
22	H	SH	97	208–210	$C_9H_9N_3O_2S$	2.0	1.0	1.2		
23	H	SC_2H_5	37	40–41	$C_{11}H_{13}N_3O_2S$	4.3	0.8			
24	Br	OC_3H_7	59	127–129	$C_{12}H_{14}N_3O_3Br$	2.7	1.8			
25	Br	NHC_2H_5	60	108–110	$C_{11}H_{13}N_4O_2Br$	4.0	8.0		100	77
26	Br	NHC_3H_7	95	77–79	$C_{12}H_{15}N_4O_2Br$	6.0	7.2		100	50
27	Br	$N(C_2H_5)_2$	81	58–60	$C_{13}H_{17}N_4O_2Br$	6.0	6.0	3.5		
28	Br	$NH(CH_2)_2OH$	96	171–173	$C_{11}H_{13}N_4O_3Br$	1.3	3.1		100	72
29	Br	$NHCH_2CO_2H$	77	262–264	$C_{11}H_{11}N_4O_4Br$	2.4	1.5	2.6		
adenosine[g]									100	64
30	C_2H_5	$NHN(CH_3)_2$	91	74–76	$C_{13}H_{19}N_5O_2$	3.7	1.4			
31	C_2H_5	NH-*n*-C_3H_7	91	62–64	$C_{14}H_{20}N_4O_2$	3.6	3.2			
32	C_2H_5	O-*n*-C_3H_7	48	37–38	$C_{14}H_{19}N_3O_3$	2.4	2.4			
33	C_2H_5	SC_2H_5	75	41–42	$C_{13}H_{17}N_3O_2S$	13.0	5.5			

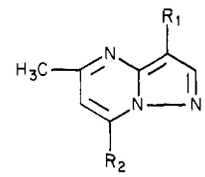
[a] Analyses within ±0.4% for C, H, and N. [b] Phosphodiesterases isolated from rabbit lung, beef heart, and kidney. [c] $\alpha = I_{50}$ of compound/I_{50} of theophylline. [d] α_{heart} determined only for certain compounds with α_{lung} and α_{kidney} values >1.0. [e] Determined via method of ref 22. [f] Enzyme data was determined for compounds with solubility $>10^{-4}$ N in H_2O. [g] Adenosine used as a standard in ADP-induced platelet aggregation inhibition evaluation; see ref 23. Values of 100 mcg/mL or less producing >50% inhibition are considered significant.

Table II. 3-Ethyl-6-ethoxy-7-substituted-pyrazolo[1,5-*a*]pyrimidines



compd	R_2	yield, %	mp, °C	formula	PDE inhibn α_{lung}	PDE inhibn α_{kidney}
35	OH	59	261–263	$C_{10}H_{13}N_3O$		
36	Cl	81	60–61	$C_{10}H_{12}N_3OCl$		
37	SCH_2CH_3	66	oil	$C_{12}H_{17}N_3OS$		
38	NH-*n*-C_3H_7	65	56–58	$C_{13}H_{20}N_4O$	3.7	3.4
39	O-*n*-C_3H_7	78	24–25	$C_{13}H_{19}N_3O_2$	1.6	1.3
40	$NHCH_2COOH$	81	213–215	$C_{12}H_{16}N_4O_3$	0.7	0.4
41	$NHCH_2CH_2COOH$	60	164–166	$C_{13}H_{18}N_4O_3$	1.0	0.6

Table III. 5-Methyl-3,7-disubstituted-pyrazolo[1,5-*a*]pyrimidines

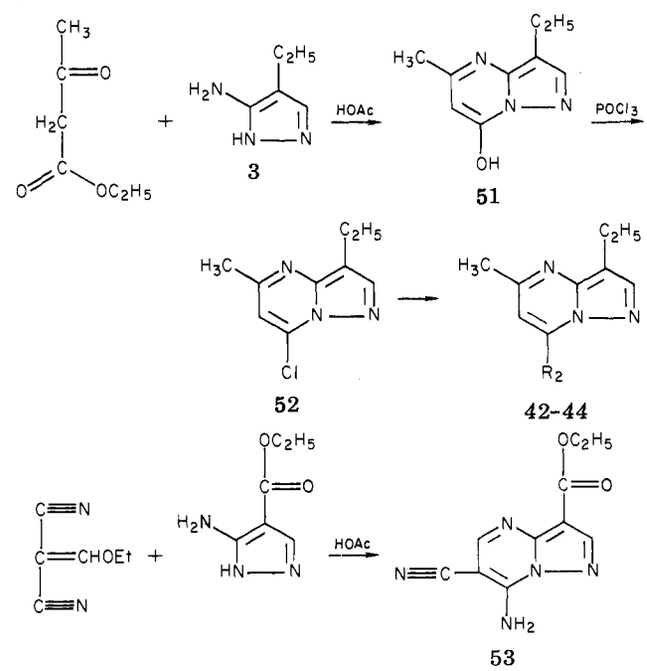


compd	R_1	R_2	yield, %	mp, °C	formula	PDE inhibn α_{lung}	PDE inhibn α_{heart}
42	C_2H_5	NH-*n*-C_3H_7	64	46–48	$C_{12}H_{18}N_4$	9.4	
43	C_2H_5	O-*n*-C_3H_7	77	92–94	$C_{12}H_{17}N_3O$	5.4	
44	C_2H_5	SC_2H_3		oil	$C_{11}H_{15}N_3S$	8.9	
45	Br	NH-*n*-C_4H_9	50	99–100	$C_{11}H_{14}N_4Br$	1.5	6.0
46	Br	$NHCH_2CH_2(OCH_3)_2$	79	134–135	$C_{11}H_{15}N_4O_2Br$	6.8	4.5
47	H	c-NC_5H_{10}	78	78–79	$C_{12}H_{16}N_4$	2.4	1.5
48	H	$NHCH_2CH_2OH$	51	162–163	$C_9H_2N_4O$	0.5	3.7
49	H	OC_2H_5	67	146–148	$C_9H_{11}N_3O$	1.4	1.0
50	H	$NHNH_2$	36	228–230	$C_7H_9N_5$	1.5	0.5

alkylamino and alkoxy or alkylthio groups provided better PDE inhibition than 7-hydroxy, -amino, or -chloro substituents. The presence of an alkyl group, such as ethyl, or a bromo substituent at position 3 also appeared to increase PDE inhibition. For example, compare **15** with **24** or **32** (Table I). Ethyl at the 3 position seemed to be superior to bromo in most cases. Compare **42** vs. **45**.

It has previously been noted in our laboratory[3] that a substituent at position 3, such as bromo or carbethoxy, greatly increased the inhibitory effect of various 5,7-dialkylpyrazolo[1,5-*a*]pyrimidines, especially with regard to lung PDE. Inspection of Tables I–III reveals that there is often a quite substantial difference in the α values, depending on the tissue studied. The highest α value obtained in this study was 13 for compound **33** as an inhibitor of lung PDE. The question as to whether such an in vitro assay as employed here is a useful indication of in vivo physiological response is of primary importance. A number of selected compounds were studied for physiological responses in various systems. 7-Amino-3,6-dicarbethoxypyrazolo[1,5-*a*]pyrimidine (**9**) demonstrated coronary dilation and a positive inotropic effect at a concentration of 10 mcg/mL in the isolated guinea pig heart preparation determined according to the procedure of Anderson and Craver.[24] 6-Carbethoxy-7-[(β-hydroxyethyl)amino]pyrazolo[1,5-*a*]pyrimidine (**19**) prevented anaphylactic death when administered orally to mice at 100 mg/kg with the absence of antihistaminic or antiserotonin properties, as determined according to the method of Kind.[25]

Scheme III



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6-Carbethoxy-7-(ethylamino)pyrazolo[1,5-*a*]pyrimidine (**16**) (α_{kidney} = 5.2) and 6-carbethoxy-7-(*n*-propylamino)-pyrazolo[1,5-*a*]pyrimidine (**31**) (α_{kidney} = 3.2) produced significant coronary dilation in the isolated guinea pig heart preparation at 5 μg/mL. This dilation was observed in the absence of chronotropic and inotropic effects. 5-Ethyl-5-methyl-7-(*n*-propylamino)pyrazolo[1,5-*a*]pyrimidine (**42**) (α_{lung} = 9.4) when administered orally to rats at 100 mg/kg according to the protocol of Winter[26] exhibited significant antiinflammatory activity as judged by a 40% decrease in foot volume 4 h after dosing. Following the procedure of D. A. Brodie,[27] 6-ethoxy-3-ethyl-7-(ethylthio)pyrazolo-[1,5-*a*]pyrimidine (**37**) administered orally to rats at 25 mg/kg inhibited stress-induced ulcers by 70% 6 h after dosing. 6-Carbethoxy-3-ethyl-7-(*N*,*N*-dimethylhydrazino)pyrazolo[1,5-*a*]pyrimidine (**21**) (α_{lung} = 2.0) significantly inhibited systemic anaphylaxis in mice at an oral dose of 50 mg/kg following the procedure of Levine and Vaz.[28] 3-Bromo-6-carbethoxy-7-aminopyrazolo[1,5-*a*]pyrimidine (**10**) in the Langendorf heart preparation[29] was found to be a potent coronary dilator over a range of 0.5 to 10 μg/mL with the absence of inotropic or chronotropic response. *N*-(6-Carbethoxy-3-ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*,*N*-dimethylhydrazine (**30**) (α_{lung} = 3.7) and 3-ethyl-5-methyl-7-(*n*-propylamino)pyrazolo[1,5-*a*]-pyrimidine (**42**) (α_{lung} = 9.4) both bring about smooth-muscle relaxation at 2 μg/mL as judged by the relaxation of isolated guinea pig uteri according to the protocol of Levy and Tazzi.[23b]

A number of the 3,7-disubstituted pyrazolo[1,5-*a*]pyrimidines in Table I were evaluated for their ability to inhibit ADP-induced platelet aggregation. 3-Bromo-6-carbethoxy-7-aminopyrazolo[1,5-*a*]pyrimidine (**10**) was more active than adenosine at one-fourth the concentration of adenosine. Harris and co-workers[30] have recently studied the inhibition of platelet aggregation by cAMP phosphodiesterase inhibitors and provided additional evidence that the inhibition of platelet aggregation is mediated by cAMP. These workers point out that such PDE inhibitors have the potential to be used in the treatment of atherosclerosis and myocardial ischemia.[30]

It is quite clear that subtle changes in the structure of this group of PDE inhibitors can cause profound changes in the inhibition of various phosphodiesterases isolated from various tissues. Studies in animal systems provide substantial difference in various physiological responses. It would seem that the present work supports the suggestion[10] that specific PDE inhibitors may allow the selective increase of cAMP in certain organs, resulting in rather specific physiological responses. This approach would appear to provide a fruitful field for the search for new and useful medicinal agents.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a Hitachi Perkin-Elmer R-20A high-resolution nuclear magnetic resonance spectrophotometer. All analytical samples displayed a single spot on thin-layer chromatography in at least two systems and were analyzed for carbon, hydrogen, and nitrogen by the Heterocyclic Chemical Corp., Harrisonville, MO. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

cAMP Phosphodiesterase Assays. The details of the preparation and assay of the beef heart, rabbit lung, and rabbit kidney phosphodiesterases were described previously.[31] The specific activities of the enzyme preparations were 14, 70, and 913 units/mg for the beef heart, rabbit lung, and rabbit kidney enzymes, respectively; where 1 unit is that amount of enzyme that converts 1 pmol of cAMP of 5′-AMP in 1 min under the standard assay conditions described below (except that a saturating concentration of cAMP, 50 μM, is used).

The K_m values (average of six determinations) for cAMP were 0163 (±0.22), 0.56 (±0.24), and 0.79 (±0.20) μM for the beef heart, rabbit lung, and rabbit kidney enzymes, respectively. The K_i values (average of three determinations) for theophylline were 77 (±14), 180 (±42), and 110 (±19) μM for the beef heart, rabbit lung, and rabbit kidney enzymes, respectively. The K_m values were determined from Lineweaver–Burk plots using rates of cAMP hydrolysis measured at cAMP concentrations of 0.08, 0.13, 0.20, 0.53, 0.81, and 1.4 μM. The K_i values were determined from Dixon plots using rates of cAMP hydrolysis measured at the above cAMP concentrations in the presence of theophylline concentrations of 50, 75, 100, 150, 250, and 350 μM.

The assay for the inhibition studies contained the following components in 0.5 mL: 25 μmol of Tris-HCl, pH 7.5; 5 μmool of $MgCl_2$; 10–75 μg of phosphodiesterase protein; 350 pmol of [8-^{3}H]cAMP (850 cpm/pmol); and at least seven different concentrations (0.5 μM to 5 mM) of the pyrazolo[1,5-*a*]pyrimidine being tested as an inhibitor. The amount of 5′-AMP formed was determined at several (at least three) time points (3–12 min) to ensure that linear reaction rates were being measured.

The concentration producing 50% inhibition (I_{50}) was determined graphically from a plot of percent inhibtion vs. the log concentration of inhibitor. The I_{50} for theophylline was determined in each experiment as an internal standard. The I_{50} values (average of 14 determinations) for theophylline under the above conditions are 90 (±38), 210 (±84), and 85 (±47) μM for the beef heart, rabbit lung, and rabbit kidney enzyme, respectively. The data on the new PDE inhibitors are expressed relative to theophylline as α values,[3,32] where $\alpha = I_{50}$ for theophylline/I_{50} for the test compound. All α values represent the result of triplicate determinations, which were reproducible within 20% of the value reported.

ADP-Induced Platelet Aggregation (Table I). Pig blood was obtained from a slaughter house and mixed with 19% aqueous sodium citrate to give a final concentration in the blood of 0.3 g/100 mL. The blood was centrifuged at 500*g* for 20 min at room temperature (20 °C), and the upper layer (about 17 mL per tube of plasma rich in platelets) was transferred with a Pasteur pipet into a graduated cylinder. The concentration of platelets in the plasma was determined by counting in duplicate.[21] Each milliliter contained about 2.0 to 8.0 × 10^8 platelets. Optical density changes were employed to determine platelet aggregation, using the method of Born and Cross.[22] The platelet-plasma mixture was stirred via a Teflon magnetic bar, and measurements were recorded at 600 nm. All additions were made by pipetting into the plasma while it was stirred. The adenosine diphosphate induced aggregation has been described by Gaarder and co-workers,[23a] and the turbidimetric method in citrate media, as described by Born,[22] sufficed. The values obtained are listed in Table I. A significant value was considered a 50% inhibition of platelet aggregation by the addition of 100 mcg/mL of test compound or less, as compared with the standard inhibitor adenosine.

Preparation of 3-Amino-4-ethylpyrazole (3). A suspension of sodium metal (53.0 g, 2.31 mol) in 1500 mL of anhydrous ether was stirred at 20 °C while a mixture of ethyl formate (180.0 g, 2.43 mol) and *n*-butyronitrile (158.0 g, 2.31 mol) was added

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dropwise over a period of 2 h. After the addition was complete, the mixture was stirred at 20–25 °C for 2 days, at which time the sodium metal was completely reacted. The reaction mixture was cooled to 10 °C and neutralized by the dropwise addition of glacial acetic acid (138.0 g, 2.31 mol). The temperature of the mixture during neutralization was maintained at 10–15 °C. The solid was separated by filtration, and the filtrate was evaporated to dryness at reduced pressure, keeping the temperature below 20 °C. The resulting crude α-formyl-*n*-butyronitrile was utilized directly for the formation of 3-amino-4-ethylpyrazole (**3**) without further purification. The crude α-formyl-*n*-butyronitrile was dissolved in 200 mL of ethanol and treated with 85% hydrazine hydrate (118 g, 2.0 mol and 36 mL of glacial acetic acid. The resulting solution was heated at reflux for two hours and then evaporated to dryness. The residual oil was purified by distillation at 0.2 mmHg. The fraction that had a boiling point of 120–124 °C was collected. This fraction weighed 55.2 g (21%) and was found to be analytically pure 3-amino-4-ethylpyrazole (**3**). Anal. ($C_5H_9N_3$) C, H, N.

Preparation of 7-Amino-6-carbethoxypyrazolo[1,5-*a*]pyrimidines (8–11). A solution of ethyl ethoxymethylenecyanoacetate (3.15 g, 18.5 mmol) and 3-amino-4-substituted-pyrazoles (18.5 mmol) in 25 mL of glacial acetic acid was heated at reflux with stirring for 2 h. At the end of this time, the acetic acid solution was evaporated to dryness at reduced pressure, and the residue was washed with water. Recrystallization of **10** from aqueous ethanol (in the case of **9** and **11**, from DMF and water) afforded the analytically pure products in the yield and with the melting point recorded in Table I.

Preparation of 6-Carbethoxy-7-hydroxy-3-substituted-pyrazolo[1,5-*a*]pyrimidines (5–7). A solution of diethyl ethoxymethylenemalonate (4.01 g, 18.5 mmol) and 3-amino-4-substituted-pyrazolo (18.5 mmol) in 25 mL of glacial acetic acid was heated at reflux with stirring for 2 h. At the end of this time, the acetic acid solution was evaporated to dryness at reduced pressure. The residue was washed well with water and then purified by recrystallization from aqueous ethanol to afford the analytically pure products **5–7** characterized in Table I.

6-Carbethoxy-7-chloropyrazolo[1,5-*a*]pyrimidine (13). A mixture of 6-carbethoxy-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**4**; 42 g, 0.203 mol), *N*,*N*-diethylaniline (55 mL), and phosphorus oxychloride (500 mL) was stirred and heated to reflux. After the mixture was refluxed for 3 h, the excess phosphorus oxychloride was removed by distillation at reduced pressure. The syrup residue was added to 1 kg of crushed ice with good stirring. The resulting cold aqueous solution was extracted with ether (3 × 250 mL), and the combined ethereal extracts were washed with the saturated sodium bicarbonate solution (2 × 100 mL) and then with water (2 × 100 mL) and dried over anhydrous sodium sulfate. Evaporation of the ether solution afforded 29 g (63%) of 6-carbethoxy-7-chloropyrazolo[1,5-*a*]pyrimidine (compound **13**), which had a melting point of 83–85 °C. Recrystallization of this product from *n*-heptane afforded an analytical sample of this product, mp 85–87 °C. Anal. ($C_9H_8ClN_3O_2$) C, H, N.

6-Carbethoxy-7-chloro-3-ethylpyrazolo[1,5-*a*]pyrimidine (14). A suspension of 6-carbethoxy-3-ethyl-7-hydroxypyrazolo-[1,5-*a*]pyrimidine (**7**; 11.75 g, 50 mmol) and 10 mL of *N*,*N*-dimethylaniline in 100 mL of phosphorus oxychloride was removed in vacuo, utilizing the steam bath as the source of heat. The residual syrup was added slowly with good stirring to 200 g of crushed ice. The resulting solution was extracted with absolute ether (3 × 150 mL), and the combined ethereal extracts were washed with sodium bicarbonate solution (3 × 100 mL) and then with 100 mL of water. The ethereal extract was dried over anhydrous sodium sulfate and then evaporated to dryness. The resulting crude chloro derivative was purified by recrystallization from *n*-heptane and then by vacuum sublimation at 120–140 °C (0.1 mm) to afford 11.8 g (89%) of analytically pure product, mp 38–39 °C. Anal. ($C_{11}H_{12}N_3O_2Cl$) C, H, N.

6-Carbethoxy-7-*n*-propoxypyrazolo[1,5-*a*]pyrimidine (15). A solution of sodium *n*-propoxide in 1-propanol was prepared by dissolving sodium metal (1.02 g, 0.044 mol) in 200 mL of 1-propanol. With good stirring, 6-carbethoxy-7-chloropyrazolo-[1,5-*a*]pyrimidine (**13**; 10.0 g, 44.4 mmol) was added to the sodium *n*-propoxide solution. The resulting solution was warmed at 35 °C for 2 h and then evaporated to dryness at 35 °C under reduced pressure. The residue was washed with water and then recrystallized from aqueous ethanol to afford a 48% yield of analytically pure product, mp 127–129 °C. Anal. ($C_{12}H_{14}BrN_3O_3$) C, H, N.

6-Carbethoxy-7-(substituted-amino)pyrazolo[1,5-*a*]pyrimidines (16–21). A solution of 6-carbethoxy-7-chloropyrazolo-[1,5-*a*]pyrimidine (**13**; 4.0 g, 17.5 mmol) and the requisite amine as per Table I (35.0 mmol) in 40 mL of absolute ethanol was stirred for 2 h and then diluted with 100 mL of water. The resulting solution was chilled overnight, and the crude 6-carbethoxy-7-(substituted-amino)pyrazolo[1,5-*a*]pyrimidines were separated by filtration. These products were purified by recrystallization from aqueous ethanol to afford the analytically pure products **16–21** listed in Table I.

***N*-(6-Carbethoxypyrazolo[1,5-*a*]pyrimidin-7-yl)glycine (20).** A mixture of 6-carbethoxy-7-chloropyrazolo[1,5-*a*]pyrimidine (**13**; 2.25 g, 10 mmol), glycine (1.5 g, 20 mmol), and sodium carbonate (1.06 g) in 50 mL of water was stirred and heated at reflux for 2 h. At the end of this time, the solution was cooled and acidified with formic acid. The crude product was separated by filtration, washed with water, and purified by recrystallizing from a mixture of DMF and water to afford a 76% yield of analytically pure product, mp 279–281 °C dec. Anal. ($C_{11}H_{12}N_4O_4$) C, H, N.

6-Carbethoxy-7-mercaptopyrazolo[1,5-*a*]pyrimidine (22). A mixture of 6-carbethoxy-7-chloropyrazolo[1,5-*a*]pyrimidine (**13**; 5.50 g, 20 mmol) and thiourea (1.67 g) in 75 mL of absolute ethanol was stirred and heated at reflux for 2 h. At the end of this time, the mixture was cooled and the solid was separated by filtration. The solid was dissolved in a minimum amount of diluted sodium hydroxide solution (0.1 N), treated with decolorizing carbon, and filtered. The pH of the filtrate was adjusted to pH 1 by the addition of 6 N hydrochloric acid. The precipitated product was separated by filtration, washed with water, and then recrystallized from water to afford the analytically pure product: yield 5.4 g (97%); mp 208–210 °C. Anal. ($C_9H_9N_3O_2S$) C, H, N.

6-Carbethoxy-7-(ethylthio)pyrazolo[1,5-*a*]pyrimidine (23). A solution of sodium methoxide in methanol was prepared by dissolving sodium (0.23 g) in 20 mL of absolute methanol. Ethanethiol (0.7 g) was added to the sodium methylate solution with good stirring. The resultant solution was stirred at room temperature for 15 min, and then 6-carbethoxy-7-chloropyrazolo-[1,5-*a*]pyrimidine (**13**; 2.25 g) was added to the solution. This solution was stirred at room temperature for 15 min, heated at 45 °C for 15 min, and then evaporated to dryness. The residue was recrystallized from *n*-heptane to yield 925 mg (37%) of analytically pure product, mp 40–41 °C. Anal. ($C_{11}H_{13}N_3O_2S$) C, H, N.

***N*-(6-Carbethoxy-3-ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*,*N*-dimethylhydrazine (30).** A solution of 6-carbethoxy-7-chloro-3-ethylpyrazolo[1,5-*a*]pyrimidine (**14**; 0.78 g) and unsymmetrical dimethylhydrazine (0.2 g) in 20 mL of absolute ethanol was stirred at room temperature for 1 h. At the end of this time, the solution was evaporated to dryness and the residue was titurated with 30 mL of water. Recrystallization of the residue from aqueous ethanol afforded 0.781 g (91%) of analytically pure product, mp 74–76 °C. Anal. ($C_{13}H_{19}N_5O_2$) C, H, N.

6-Carbethoxy-3-ethyl-7-(*n*-propylamino)pyrazolo[1,5-*a*]-pyrimidine (31). A solution of 7-chloro-3-ethyl-6-carbethoxypyrazolo[1,5-*a*]pyrimidine (**14**; 3 mmol) and *n*-propylamine (0.35 g, 6 mmol) in 20 mL of absolute ethanol was stirred at room temperature for 2 h. At the end of this time, the solution was evaporated to dryness and the residue was titurated with 30 mL of water. Recrystallization of the residue from aqueous ethanol afforded a 91% yield of analytically pure product, mp 62–64 °C. Anal. ($C_{14}H_{20}N_4O_2$) C, H, N.

6-Carbethoxy-3-ethyl-7-*n*-propoxypyrazolo[1,5-*a*]pyrimidine (32). A solution of sodium *n*-propoxide was prepared by dissolving sodium metal, (0.165 g) in 40 mL of 1-propanol. This solution was stirred at room temperature, and 6-carbethoxy-7-chloro-3-ethylpyrazolo[1,5-*a*]pyrimidine (**14**; 6.6 mmol) was added. The resultant solution was stirred at room temperature for 1 h and then evaporated to dryness in vacuo at room temperature. The residue was extracted with boiling 60–90 °C petroleum ether (3 × 15 mL), and the combined extracts were evaporated to dryness to yield crude 6-carbethoxy-3-ethyl-7-propoxypyrazolo-[1,5-*a*]pyrimidine (**32**). The product was purified by column chromatography on silica gel (100 g), using a solvent system of

60–90 °C petroleum ether–ethyl acetate (8:2) to afford an analytically pure product: mp 37–38 °C; 48% yield. Anal. ($C_{14}H_{19}N_3O_3$) C, H, N.

6-Carbethoxy-3-ethyl-7-(ethylthio)pyrazolo[1,5-*a*]pyrimidine (33). Ethanethiol (0.5 g, 8.06 mmol) was added to a solution of sodium metal (0.165 g) in 15 mL of anhydrous methanol. The resulting solution was stirred at room temperature for 20 min, and then 6-carbethoxy-7-chloro-3-ethylpyrazolo[1,5-*a*]pyrimidine (14; 6.6 mmol) was added. The resulting solution was stirred at room temperature and then evaporated to dryness in vacuo at 25 °C. The residue was extracted with boiling 60–90 °C petroleum ether (3 × 10 mL), and the combined extracts were evaporated to yield crude 6-carbethoxy-3-ethyl-7-(ethylthio)-pyrazolo[1,5-*a*]pyrimidine (33). The product was purified by column chromatography on silica gel (100 g), utilizing a solvent system of 60–90 °C petroleum ether–ethyl acetate (9:1) to afford a 75% yield of analytically pure product, mp 41–42 °C. Anal. ($C_{13}H_{17}N_3O_2S$) C, H, N.

Preparation of 3-Bromo-6-carbethoxy-7-substituted-pyrazolo[1,5-*a*]pyrimidines (24-29). A solution of the requisite 6-carbethoxy-7-substituted-pyrazolo[1,5-*a*]pyrimidine (10 mmol) and sodium acetate (2.47 g) in 25 mL of glacial acetic acid was stirred at room temperature while a solution of 1.6 g of bromine in 10 mL of glacial acetic acid was added dropwise. After the addition was complete, the solution was stirred at room temperature for 1 h and then added to 150 mL of water. The resultant mixture was chilled overnight, and the crude 3-bromo derivative was separated by filtration, washed with water, and recrystallized from aqueous ethanol to afford the analytically pure products **24–29** listed in Table I.

6-Ethoxy-3-ethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (35). A mixture of ethyl α-ethoxy-α-formylacetate (0.112 mol) and 3-amino-4-ethylpyrazole (3; 12.0 g, 0.108 mol) was stirred at room temperature for 10 min and then diluted by adding 100 mL of glacial acetic acid. The resulting mixture was stirred and heated at reflux for 3 h and then allowed to cool to room temperature. The mixture was added to 200 mL of ethyl acetate, and the products were separated by filtration. The solid product was separated by filtration and purified by recrystallization from aqueous ethanol to afford 13.2 g (59%) of analytically pure product, mp 261–263 °C. Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

7-Chloro-6-ethoxy-3-ethylpyrazolo[1,5-*a*]pyrimidine (36). A suspension of 6-ethoxy-3-ethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (35; 50 mmol) and 10 mL of *N*,*N*-dimethylaniline in 100 mL of phosphorus oxychloride was stirred and heated at reflux for 1 h. At the end of this time, the excess phosphorus oxychloride was removed in vacuo, utilizing the steam bath as the source of heat. The residual syrup was added slowly with good stirring to 200 g of crushed ice. The resulting solution was extracted with absolute ether (3 × 150 mL), and the combined ethereal extracts were washed with sodium bicarbonate solution (3 × 100 mL) and then with water (100 mL). The ethereal extract was dried over anhydrous sodium sulfate and then evaporated to dryness. The resulting crude chloro derivative was purified by recrystallization from *n*-heptane and then by vacuum sublimation at 120–140 °C (0.1 mm) to afford 9.11 g (81%) of analytically pure product, mp 60–61 °C. Anal. ($C_{10}H_{12}N_3OCl$) C, H, N.

6-Ethoxy-3-ethyl-7-(ethylthio)pyrazolo[1,5-*a*]pyrimidine (37). Ethanethiol (0.5 g, 8.06 mmol) was added to a solution of sodium metal (0.165 g) in 15 mL of anhydrous methanol. The resulting solution was stirred at room temperature for 20 min, and then the 7-chloro-6-ethoxy-3-ethylpyrazolo[1,5-*a*]pyrimidine (36; 1.48 g, 6.6 mmol) was added. The resulting solution was stirred at room temperature and then evaporated to dryness in vacuo at 25 °C. The residue was extracted with boiling 60–90 °C petroleum ether (3 × 10 mL), and the combined extracts were evaporated to yield crude 6-ethoxy-3-ethyl-7-(ethylthio)-pyrazolo[1,5-*a*]pyrimidine (37). The product was purified by column chromatography on silica gel (100 g), utilizing a solvent system of 60–90 °C petroleum ether–ethyl acetate (9:1), to afford a 66% yield of analytically pure product that was isolated as a pure oil, which did not crystallize. Anal. ($C_{12}H_{17}N_3OS$) C, H, N.

6-Ethoxy-3-ethyl-7-(*n*-propylamino)pyrazolo[1,5-*a*]pyrimidine (38). A solution of 6-chloro-6-ethoxy-3-ethylpyrazolo-[1,5-*a*]pyrimdine (36; 675 mg) and *n*-propylamine (0.35 g) in 20 mL of absolute ethanol was stirred at room temperature for 2 h. At the end of this time, the solution was evaporated to dryness, and the residue was titurated with 30 mL of water. Recrystallization of the residue from aqueous ethanol afforded 503 mg (65%) of analytically pure product, mp 56–58 °C. Anal. ($C_{13}H_{20}N_4O$) C, H, N.

6-Ethoxy-3-ethyl-7-*n*-propoxypyrazolo[1,5-*a*]pyrimidine (39). A solution of sodium *n*-propoxide was prepared by dissolving sodium metal (0.165 g) in 40 mL of 1-propanol. This solution was stirred at room temperature, and 1.4 g of 1-chloro-6-ethoxy-3-ethylpyrazolo[1,5-*a*]pyrimidine (36) was added. The resultant solution was stirred at room temperature for 1 h and then evaporated to dryness in vacuo at room temperature. The residue was extracted with boiling 60–90 °C petroleum ether (3 × 15 mL), and the combined extracts were evaporated to dryness to yield crude 6-ethoxy-3-ethyl-7-*n*-propoxypyrazolo[1,5-*a*]pyrimidine (39). The product was purified by column chromatography on silica gel (100 g), utilizing a solvent system of 60–90 °C petroleum ether–ethyl acetate (8:2) to afford a 78% yield of analytically pure product, mp 24–25 °C. Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

Preparation of *N*-(7-Ethoxy-3-ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)glycine (40) and *N*-(6-Ethoxy-3-ethylpyrazolo-[1,5-*a*]pyrimidin-7-yl)-β-alanine (41). A solution of the amino acid (9.3 mmol), sodium carbonate (4.9 mmol), and 7-chloro-6-ethoxy-3-ethylpyrazolo[1,5-*a*]pyrimidine (36) in 50 mL of water was stirred and heated at reflux for 2 h. At the end of this time, the solution was cooled and acidified by the addition of formic acid. The precipitated solid was collected by filtration, washed with water, and recrystallized from aqueous ethanol to afford the analytically pure products **40** and **41** listed in Table II.

7-Amino-6-cyano-3-carbethoxypyrazolo[1,5-*a*]pyrimidine (53). A solution of 3-amino-4-carbethoxypyrazole (3 g, 19.3 mmol)[17] and ethoxymethylenemalononitrile (3 g, 24.6 mmol) in 40 mL of glacial acetic acid was refluxed for 3 h. The solution was then cooled and filtered, and the product was recrystallized from DMF and water: yield 0.7 g (17%); mp 300–301 °C dec. Anal. ($C_{10}H_9N_5O_2$) C, H, N.

7-Piperidino-5-methylpyrazolo[1,5-*a*]pyrimidine (47). A solutioin of 840 mg of 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[19] and 800 mg of piperidine was heated in ethanol on the steam bath for 2 h. Excess ethanol was removed, and the residue was recrystallized from ethanol–water to give 900 mg of ivory-colored platelets, mp 78–79 °C. Anal. ($C_{12}H_{16}N_4$) C, H, H.

7-[(β-Hydroxyethyl)amino]-5-methylpyrazolo[1,5-*a*]pyrimidine (48). This compound was prepared from 300 mg of 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[19] which was added to 10 mL of ethanol containing 100 mg of 2-aminoethanol, and the solution was refluxed for 3 h. Evaporation of the solution and recrystallization of the solid residue from methanol–ether afforded 175 mg of yellow-white cubes, mp 162–163 °C. Anal. ($C_9H_{12}N_4O$) C, H, N.

7-Ethoxy-5-methylpyrazolo[1,5-*a*]pyrimidine (49). To a solution of 300 mg of sodium in 50 mL of anhydrous ethanol, cooled to 25 °C, was added 1.68 g (0.01 mol) of 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[19] with stirring. Stirring was continued at 25–30 °C for 24 h, then the ethanolic solution was evaporated to dryness under reduced pressure, and the residue was dissolved in 20 mL of water and adjusted to pH 7 with a few drops of 2 N hydrochloric acid. The solution was extracted three times with 20-mL portions of chloroform. The chloroform solution was dried (Na_2SO_4) and evaporated to yield the product as white crystals (67% yield), mp 146–148 °C, recrystallized from benzene. Anal. ($C_9H_{11}N_3O$) C, H, N.

7-Hydrazino-5-methylpyrazolo[1,5-*a*]pyrimidine (50). This compound was prepared from 1.0 g of 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[19,20] which was added to 30 mL of ethanol containing 6 mL of 85% hydrazine hydrate. After 2 h of reflux, the solution was concentrated to 10 mL, whereupon the product separated as crystals. The material was recrystallized from ethanol to yield 420 mg of white plates, mp 228–230 °C dec. Anal. ($C_7H_9N_5$) C, H, N.

3-Ethyl-7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine (51). A solution of ethyl acetoacetate (14.6 g) and 3-amino-4-ethylpyrazole (12.0 g) was stirred at room temperature for 10 min and then diluted by adding 100 mL of glacial acetic acid. The resulting mixture was stirred and heated at reflux for 3 h and then

allowed to cool to room temperature. The mixture was added to 200 mL of ethyl acetate. The solid product was separated by filtration and purified by recrystallization from aqueous ethanol to afford 14.7 g (77%); the analytically pure product had a melting point of 290–292 °C. Anal. ($C_9H_{11}N_3O_2$) C, H, N.

3-Bromo-7-(*n*-butylamino)-5-methylpyrazolo[1,5-*a*]pyrimidine (45). The 7-(*n*-butylamino)-5-methylpyrazolo[1,5-*a*]pyrimidine was prepared from 1.68 g (0.01 mol) of the corresponding 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[19] and 1.46 g (0.02 mol) of *n*-butylamine in the usual manner, and the oil obtained on workup was utilized for the bromination without further purification. Bromination was achieved in chloroform with *n*-bromosuccinimide as for compound **46**. Recrystallization from ether–petroleum ether gave a product that was obtained as white platelets: mp 99–100 °C; yield 1.41 g (50%). Anal. ($C_{11}H_{14}N_4Br$) C, H, N, Br.

3-Bromo-7-[(2,2-dimethoxyethyl)amino]-5-methylpyrazolo[1,5-*a*]pyrimidine (46). Treatment of 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[19] (1.68 g) with aminoacetaldehyde dimethyl acetal (2.3 g, 0.021 mol) in ethanol, followed by refluxing for 1 h, gave the corresponding 7-[(2,2-dimethoxyethyl)amino] derivative, which was brominated with *N*-bromosuccinimide (1.78 g) in 50 mL of chloroform. After refluxing the chloroform solution for 1 h, the succinimide was filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on basic alumina (Merck), and the product was recrystallized from petroleum ether to give pale ivory-colored cubettes: yield 2.5 g (79%); mp 134–135 °C. Anal. ($C_{11}H_{15}N_4O_2Br$) C, H, N, Br.

7-Chloro-3-ethyl-5-methylpyrazolo[1,5-*a*]pyrimidine (52). A suspension of 3-ethyl-7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine (**51**; 8.85 g) and 10 mL of *N,N*-dimethylaniline in 100 mL of phosphorus oxychloride was stirred and heated at reflux for 1 h. At the end of this time, the excess phosphorus oxychloride was removed in vacuo, utilizing the steam bath as the source of heat. The residual syrup was added slowly with good stirring to 200 g of crushed ice. The resulting solution was extracted with absolute ether (3 × 150 mL), and the combined ethereal extracts were washed with sodium bicarbonate solution (3 × 100 mL) and then with water (100 mL). The ethereal extract was dried over anhydrous sodium sulfate and then evaporated to dryness. The resulting crude chloro derivative was purified by recrystallization from *n*-heptane to afford 8.6 g (90%) of pure product, mp 61–62 °C. Anal. ($C_9H_{10}N_3Cl$) N.

3-Ethyl-5-methyl-7-(*n*-propylamino)pyrazolo[1,5-*a*]pyrimidine (42). A solution of 7-chloro-3-ethyl-5-methylpyrazolo[1,5-*a*]pyrimidine (**52**; 0.585 g) and *n*-propylamine (0.35 g) in 20 mL of absolute ethanol was stirred at room temperature for 2 h. At the end of this time, the solution was evaporated to dryness and the residue was triturated with 30 mL of water. Recrystallization of the residue from aqueous ethanol afforded 0.425 g (64%) the pure product, mp 46–48 °C. Anal. ($C_{12}H_{18}N_4$) C, H, N.

3-Ethyl-5-methyl-7-*n*-propoxypyrazolo[1,5-*a*]pyrimidine (43). A solution of sodium *n*-propoxide was prepared by dissolving sodium metal (0.165 g) in 40 mL of 1-propanol. This solution was stirred at room temperature, and 7-chloro-3-ethyl-5-methylpyrazolo[1,5-*a*]pyrimidine (**52**; 1.29 g) was added. The resultant solution was stirred at room temperature for 1 h and then evaporated to dryness in vacuo at room temperature. The residue was extracted with boiling 60–90 °C petroleum ether (3 × 15 mL), and the combined extracts were evaporated to dryness to yield crude 3-ethyl-7-*n*-propoxy-5-methylpyrazolo[1,5-*a*]pyrimidine (**43**). The product was purified by column chromatography on silica gel (100 g), utilizing a solvent system of 60–90 °C petroleum ether–ethyl acetate (8:2), to afford 1.11 g (77%) of analytically pure product, mp 92–94 °C. Anal. ($C_{12}H_{17}N_3O$) C, H, N.

3-Ethyl-7-(ethylthio)-5-methylpyrazolo[1,5-*a*]pyrimidines (44). Ethanethiol (0.5 g) was added to a solution of sodium metal (0.16 g) in 15 mL of anhydrous methanol. The resulting solution was stirred at room temperature for 20 min, and then 7-chloro-3-ethyl-5-methylpyrazolo[1,5-*a*]pyrimidine (**52** 1.29 g) was added. The resulting solution was stirred at room temperature and then evaporated to dryness in vacuo at 25 °C. The residue was extracted with boiling 60–90 °C petroleum ether (3 × 10 mL), and the combined extracts were evaporated to yield crude 3-ethyl-7-(ethylthio)-5-methylpyrazolo[1,5-*a*]pyrimidine (**44**). The product was purified by column chromatography on silica gel (100 g), utilizing a solvent system of 60–90 °C petroleum ether–ethyl acetate (9:1), to yield the analytically pure product, which was isolated as an oil. Anal. ($C_{11}H_{15}N_3S$) C, H, N.