Synthesis and Enzymic Activity of Various Substituted Pyrazolo[1,5-a]-1,3,5-triazines as Adenosine Cyclic 3',5'-Phosphate Phosphodiesterase Inhibitors

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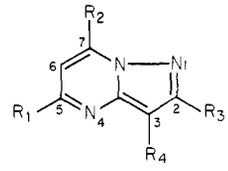
A series of various pyrazolo[1,5-a]-1,3,5-triazines have been prepared and studied as inhibitors of cAMP phosphodiesterase isolated from bovine brain, bovine heart, and rabbit lung. A number of compounds were found to be superior to theophylline. 2-Ethyl-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (**35**) was found to be 97 times more potent than theophylline as an inhibitor of bovine brain PDE. 8-Bromo-2,4-dimethyl-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (**52**) showed $\alpha_{lung} = 40$ compared to $\alpha_{heart} = 3.0$. Thus, various substituents could increase or decrease the inhibition relative to the type and source of tissue from which the PDE was isolated. The most active compound was 8-bromo-4-(diethylamino)-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (**25**), which was 185 times more potent than theophylline as an inhibitor of PDE isolated from rabbit lung. The stepwise synthesis via ring-closure procedures of requisite pyrazole intermediates, followed by electrophilic substitution in the pyrazole ring and/or nucleophilic substitution in the 1,3,5-triazine moiety, resulted in the various pyrazolo[1,5-a]-1,3,5-triazines listed in Tables I and II. Structure–activity relationships are reviewed.

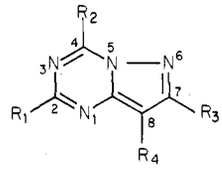
Our interest in the synthesis of cAMP phosphodiesterase inhibitors as an approach to new medicinal agents has been discussed in several of our previous publications.[1-4] Amer and Kreighbarum[5] have reviewed the concepts of phosphodiesterase (PDE) inhibition as an approach to selectively regulate the level of cAMP in various tissues. These authors conclude there is a correlation between the in vitro PDE inhibition of a number of drugs and their in vivo effects. A review of the various compounds known to be inhibitors of cAMP PDE has recently appeared.[6] Weiss and Hait[7] have recently pointed out that cyclic nucleotide phosphodiesterases exist in several molecular forms which are unequally distributed in tissue. These authors point out that specific inhibitors of PDE found in discrete cell types should provide effective and specific therapeutic agents.[7] Weiss and Fertel[8a] have recently reviewed the data on the existence of multiple forms of phosphodiesterase from a variety of tissues. The pattern and ratio of the different molecular forms of PDE are unique to each tissue and cell type.[8a] Harris and co-workers[8b] have recently listed eight diseases where inhibitors of cAMP phosphodiesterase could be potential therapeutic agents. These are (1) asthma, (2) diabetes mellitus, (3) female fertility control, (4) male infertility, (5) psoriasis, (6) thrombosis, anxiety, and (7) hypertension. The data in support of these conclusions have also been summarized by these authors.[8b]

Our interest in various substituted pyrazolo[1,5-a]pyrimidines as unique phosphodiesterase inhibitors has been the subject of several publications from our laboratories.[1-4] The success in obtaining derivatives with in vitro potency 5 to 15 times that of theophylline as inhibitors of cAMP phosphodiesterase suggested that the structure–activity relationships of the pyrazolo[1,5-a]pyrimidines, **1**, might carry over to the pyrazolo[1,5-a]-1,3,5-triazines, **2**, with even greater potency. This, indeed, proved to be the case and is the subject of the present report.

As noted in Scheme I, treatment of 7-phenyl-4-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine[9] (**3**) with various primary and secondary amines in alcohol heated on the steam bath gave the 7-phenyl-4-(alkylamino)pyrazolo[1,5-a]-1,3,5-triazines **5–8** listed in Table I. Synthesis of 2-methyl-4-(*n*-butylamino)-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (**16**) was achieved by treatment of 2-methyl-4-(methylthio)-7-phenylpyrazolo[1,5-a]-1,3,5-triazine[11,14] with *n*-butylamine in refluxing ethanol. 4-(Diethylamino)-7-phenyl-8-bromopyrazolo[1,5-a]-1,3,5-triazine (**25**) was prepared from 4-(diethylamino)-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (**7**) and *N*-bromosuccinimide in refluxing chloroform (Scheme I). Treatment of 2-(methylthio)-4-chloropyrazolo[1,5-a]-1,3,5-triazine[10] with various primary and secondary amines gave the 2-(methylthio)-4-(alkylamino)pyrazolo[1,5-a]-1,3,5-triazines **10** and **11** in Table I. Treatment of 2-(methylthio)-4-chloro-8-bromo-



1, pyrazolo[1,5-a]-pyrimidine



2, pyrazolo[1,5-a]-1,3,5-triazine

(1) T. Novinson, R. Hanson, M. K. Dimmitt, L. N. Simon, R. K. Robins, and D. E. O'Brien, *J. Med. Chem.*, **17**, 645 (1974).
(2) T. Novinson, J. P. Miller, M. Scholten, R. K. Robins, L. N. Simon, D. E. O'Brien, and R. B. Meyer, Jr., *J. Med. Chem.*, **18**, 460 (1975).
(3) W. E. Kirkpatrick, T. Okabe, I. W. Hillyard, R. K. Robins, A. T. Dren, and T. Novinson, *J. Med. Chem.*, **20**, 386 (1977).
(4) R. H. Springer, M. B. Scholten, D. E. O'Brien, T. Novinson, J. P. Miller, and R. K. Robins, *J. Med. Chem.*, preceding paper in this issue.
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(6) M. Chasin and D. N. Harris, *Adv. Cyclic Nucleotide Res.*, **7**, 225 (1976).
(7) B. Weiss and W. N. Hait, *Annu. Rev. Toxicol.*, **17**, 441 (1977).
(8) (a) B. Weiss and R. Fertel, *Adv. Pharmacol. Chemother.*, **14**, 189 (1977). (b) D. N. Harris, M. B. Phillips, H. J. Goldenberg, and M. M. Asaad, in "Enzyme Inhibitors As Drugs", M. Sandler, Ed., University Park Press, Baltimore, 1980, p 127.
(9) J. Kobe, D. E. O'Brien, R. K. Robins, and T. Novinson, *J. Heterocycl. Chem.*, **11**, 991 (1974).
(10) J. Kobe, R. K. Robins, and D. E. O'Brien, *J. Heterocycl. Chem.*, **11**, 199 (1974).
(11) T. Novinson, K. Senga, J. Kobe, R. K. Robins, D. E. O'Brien, and A. A. Albert, *J. Heterocycl. Chem.*, **11**, 691 (1974).

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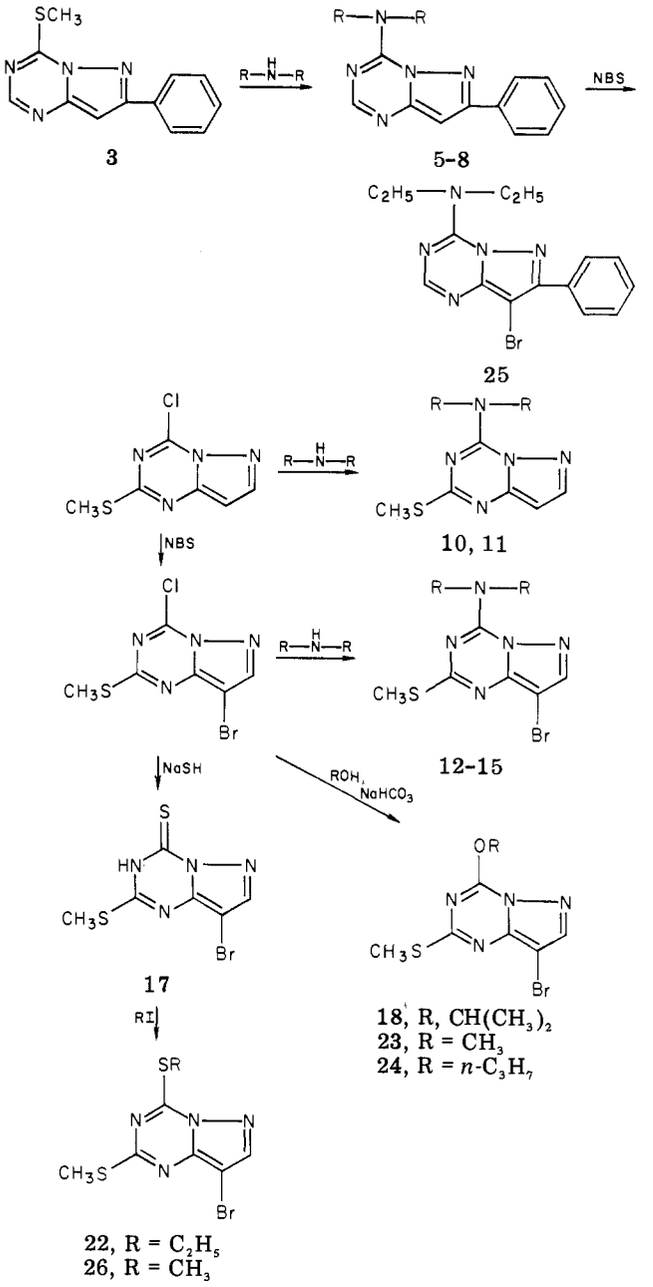
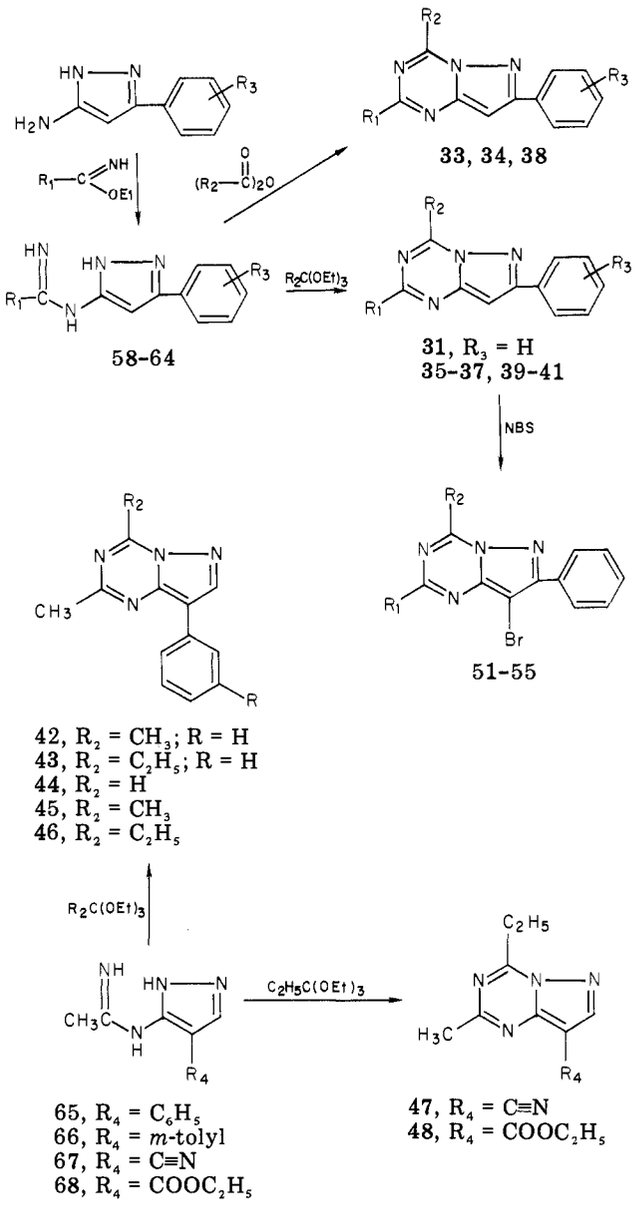
Scheme I



pyrazolo[1,5-*a*]-1,3,5-triazine[10] with the requisite amines (Scheme I) provided the 2-(methylthio)-4-(alkylamino)-8-bromopyrazolo[1,5-*a*]-1,3,5-triazines **12–15** listed in Table I. Treatment of 2-(methylthio)-4-chloro-8-bromopyrazolo[1,5-*a*]-1,3,5-triazine[10] with sodium hydrosulfide in aqueous ethanol gave 8-bromo-4-thio-2-(methylthio)-pyrazolo[1,5-*a*]-1,3,5-triazine (**17**). Treatment of **17** with methyl iodide gave 2,4-bis(methylthio)-8-bromopyrazolo-[1,5-*a*]-1,3,5-triazine (**26**). Ethyl iodide and **17** gave 4-(ethylthio)-2-(methylthio)-8-bromopyrazolo[1,5-*a*]-1,3,5-triazine (**22**). Sodium bicarbonate in the requisite alcohol at reflux provided **18**, **23**, and **24** (Table I).

The synthesis of 2,4-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine (**27**) was first reported[12] from our laboratory in 1973 by ring closure of *N*-(pyrazol-3-yl)acetamidine with triethyl orthoacetate. The synthesis of various 2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazines from 3-aminopyrazoles has been developed in our laboratories[11,12,19] so that alkyl

Scheme II



groups different from those in position 4 may be introduced in position 2. Compounds **28–30** and **32** (Table II) have previously been reported[11] by these ring-closure procedures.

3-Amino-5-phenylpyrazole,[13] or 3-amino-5-(substituted-phenyl)pyrazole[13] was treated with the corresponding alkyl ethylimidate in acetonitrile in the presence of acetic acid and treated as per method A, B, or C (see Table I) to give the corresponding *N*-(pyrazol-3-ylalkyl)amidines **58–64** listed in Table III (see reaction Scheme II). Ring closure of **58-64** with the requisite alkyl triethyl orthoester gave the corresponding 2,4-dialkyl-7-phenyl- or -substituted-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**31**, **35–37**, and **39–41**) listed in Table II. Ring closure could also be accomplished by the appropriate anhydride (see Scheme II) to give **33** (R_2 = *n*-C_3H_7) and **34** and **38** (R_2 = C_6H_5) (see Table II). The treatment of 3-amino-4-phenylpyrazole[15] or 3-

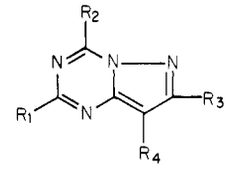
(12) A. H. Albert, Roland K. Robins, and D. E. O'Brien, *J. Heterocycl. Chem.*, 10, 885 (1973).

(13) H. Beyer, T. Pyl, and K. H. Wunsh, *Chem. Ber.*, **93**, 2209 (1960).

(14) T. Novinson, B. Bhooshan, T. Okabe, G. R. Revankar, R. K. Robins, K. Senga, and H. R. Wilson, *J. Med. Chem.*, **19**, 512 (1976).

(15) C. Alberti, *Gazz. Chim. Ital.*, **89**, 1017 (1959).

Table I. Pyrazolo[1,5-*a*]-1,3,5-triazines as Inhibitors of cAMP Phosphodiesterase



compd	R_1	R_2	R_3	R_4	ref	α_{lung}	α_{heart}	α_{brain}
3	H	SCH_3	C_6H_5	H	9	11.0	7.3	
4	CH_3	SCH_3	C_6H_5	H	11, 14			
5	H	$NHCH_2CH_2CH_3$	C_6H_5	H		26.0	3.8	
6	H	NH-*n*-C_4H_9	C_6H_5	H		13.5	2.5	
7	H	$N(C_2H_5)_2$	C_6H_5	H		143	57	146
8	H	piperidyl	C_6H_5	H		29	11	
9	CH_3	OH	C_6H_5	H	11	1.9	0.5	4.7
10	SCH_3	NH-*n*-C_3H_7	H	H		12.0	5.8	
11	SCH_3	$N(C_2H_5)_2$	H	H		19.0	12.2	12.0
12	SCH_3	NH-C_2H_5	H	Br		40.0	8.0	17.0
13	SCH_3	NH-*n*-C_3H_7	H	Br		67.0	6.9	
14	SCH_3	$N(C_2H_5)_2$	H	Br		26.0	6.2	
15	SCH_3	NH-*n*-C_4H_9	H	Br		160	12.5	18.0
16	CH_3	NH-*n*-C_4H_9	C_6H_5	H		11.0	1.7	
17	SCH_3	SH	H	Br		1.0	0.68	
18	SCH_3	$OCH(CH_3)_2$	H	Br		1.5	4.0	
19	SCH_3	CH_3	H	H	10	1.6	0.0	
20	SCH_3	SC_2H_5	H	H		8.0	3.2	
21	SCH_3	OCH_3	H	H	10	0.6	0.5	
22	SCH_3	SC_2H_5	H	Br		13.0	2.6	
23	SCH_3	OCH_3	H	Br	10	9.0	3.2	
24	SCH_3	O-*n*-C_3H_7	H	Br		2.7	0.7	
25	H	$N(C_2H_5)_2$	C_6H_5	Br		185	40	
26	SCH_3	SCH_3	H	Br		5.0	1.5	

amino-4-*m*-tolylpyrazole[16] with ethylacetimidate gave the corresponding *N*-(pyrazol-3-yl)acetamidine **65** or **66**, respectively, in good yield (see Table III). Ring closure with the requisite alkyl triethyl orthoester gave the corresponding 2,4-dialkyl-8-phenyl- or -substituted-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**42–46**) listed in Table II. Treatment of 3-amino-4-pyrazolecarbonitrile[17] or ethyl 3-aminopyrazole-4-carboxylate[18] with ethyl acetimidate gave **67** or **68**, respectively (Table III). Ring closure with triethyl orthopropionate gave 8-cyano-4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**47**) and 8-carbethoxy-4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**48**) (Scheme II).

Treatment of various 2,4-dialkyl-7-phenylpyrazolo[1,5-*a*]pyrimidines with *N*-bromosuccinimide in refluxing chloroform (Scheme II) gave the corresponding 2,5-dialkyl-7-phenyl-8-bromopyrazolo[1,5-*a*]-1,3,5-triazine (**51–55**; Table II). The site of bromination was readily determined by the disappearance of the C_8 proton in the ^1H NMR (sharp singlet[11] at δ 6.75–6.85) upon bromination. Similarly, 2-methyl-4-ethyl-8-chloropyrazolo[1,5-*a*]-1,3,5-triazine (**49**) was prepared by treatment of 2-methyl-4-ethylpyrazolo[1,5-*a*]-1,3,5-triazine (**28**) with *N*-chlorosuccinimide in refluxing chloroform. 2-Methyl-4-ethyl-8-bromopyrazolo[1,5-*a*]-1,3,5-triazine (**50**) was prepared by treatment of **28** with *N*-bromosuccinimide in a similar manner. 8-Bromo-4-(diethylamino)-2-(methylthio)-pyrazolo[1,5-*a*]-1,3,5-triazine (**14**) was prepared by bromination of 4-(diethylamino)-2-(methylthio)pyrazolo[1,5-*a*]-1,3,5-triazine (**11**) with *N*-bromosuccinimide in refluxing chloroform.

(16) E. L. Anderson, J. E. Casey, L. C. Greene, J. J. Lafferty, and H. E. Reiff, *J. Med. Chem.*, **7**, 259 (1964).
(17) R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).
(18) P. Schmidt and J. Druey, *Helv. Chim. Acta.*, **39**, 986 (1956).
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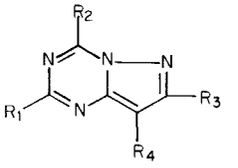
Discussion

PDE Inhibition and Biological Activity. Inspection of Tables I and II reveal a considerable number of compounds superior to theophylline as phosphodiesterase (PDE) inhibitors against PDE isolated from rabbit lung, rabbit heart, and bovine brain. Comparison of the α values for the pyrazolo[1,5-*a*]-1,3,5-triazines, **2**, with the corresponding pyrazolo[1,5-*a*]pyrimidines,[4] **1**, reveals that, in general, the pyrazolo[1,5-*a*]-1,3,5-triazines are more active as PDE inhibitors. It is interesting to note that 2,4-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine (**27**) is essentially equivalent to theophylline in lung and heart (Table II). Changing the alkyl at C_2 to ethyl increases the activity to $\alpha = 2.4$ in lung and decreases the potency in heart. The addition of a phenyl group at position 7 greatly enhances the activity, with compound **31** exhibiting an α_{lung} of 22 and α_{brain} of 19. It is interesting that α_{heart} was increased only to 3.5. The specificity is quite remarkable when the deletion of a single methyl group at C_4 increases α_{brain} to 49.0 (see compound **30**). The change in activity is even more striking with 2-ethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**35**), which is 97 times more potent than theophylline as an inhibitor of brain PDE, while the α_{lung} dropped from 25 to 14 with an increase of one methylene group at C_2. A shift of the phenyl group from position 7 to position 8, which gives rise to 2,4-dimethyl-8-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**42**) made little difference in the α_{lung} (22 vs. 25) but resulted in an increase from 19 to 40 with α_{brain}; once again the α_{heart} remained about the same. Increasing the length of the alkyl groups at positions 2 and 4, in general, appears to increase the PDE inhibition of the enzyme from the heart (see **33** and **39**, Table II). A significant difference in activity between α_{lung} and α_{heart} can be seen with 8-bromo-2,4-dimethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**52**), with $\alpha_{lung} = 40$ compared to $\alpha_{heart} = 3.0$. The presence of the 8-bromo group raised the α_{lung} from 22 to 40 (compare **31** vs. **52**). Changing the methyl groups to ethyl groups in the comparison of **52** with

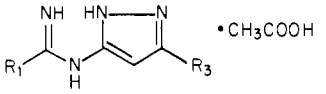
Table II. Pyrazolo[1,5-*a*]-1,3,5-triazines as Inhibitors of cAMP Phosphodiesterase



compd	R_1	R_2	R_3	R_4	ref	method	crystn solvent[a]	mp, °C	yield, %	formula	PDE inhibn α_{lung}	PDE inhibn α_{heart}	PDE inhibn α_{brain}
27	CH_3	CH_3	H	H	12	A	PE	49.5–50.5	74	$C_7H_8N_4$	1.0	0.9	
28	CH_3	C_2H_5	H	H	11	A	PE	78–79	53	$C_8H_{10}N_4$	1.1	0.7	
29	C_2H_5	CH_3	H	H	11	A	PE	58–59	69	$C_8H_{10}N_4$	2.4	0.5	
30	CH_3	H	C_6H_5	H	11	A	benzene	214–215	68	$C_{12}H_{10}N_4$	25.0	3.0	49.0
31	CH_3	CH_3	C_6H_5	H		A, B	benzene	164.5–165	83, 45	$C_{13}H_{12}N_4$	22.0	3.5	19.0
32	CH_3	C_2H_5	C_6H_5	H	11	A	benzene	137–138.5	65	$C_{14}H_{14}N_4$	21.0	4.0	
33	CH_3	*n*-C_3H_7	C_6H_5	H		C	*n*-hexane	112–113	73	$C_{15}H_{16}N_4$	10.0	11.0	
34	CH_3	C_6H_5	C_6H_5	H		C	DMF–EtOH	160–162	53	$C_{18}H_{14}N_4$	10		
35	C_2H_5	H	C_6H_5	H		B	*n*-hexane–$CHCl_3$	155–156	54	$C_{13}H_{12}N_4$	14.0	0.5	97.0
36	C_2H_5	CH_3	C_6H_5	H		B	*n*-heptane	93–95	71	$C_{14}H_{14}N_4$	12.0	2.7	
37	C_2H_5	C_2H_5	C_6H_5	H		B	*n*-heptane	83–85	72	$C_{15}H_{16}N_4$	20.0	7.0	12.0
38	C_2H_5	C_6H_5	C_6H_5	H		C	EtOH	135–137	5	$C_{19}H_{16}N_4$			
39	C_2H_5	C_2H_5	C_6H_4-*o*-CH_3	H		D	PE	177–178	15	$C_{16}H_{18}N_4$	15.0	16.0	42.0
40	CH_3	C_2H_5	C_6H_4-*p*-OCH_3	H		D	PE	148–150	72	$C_{15}H_{16}N_4O$	16.0	3.0	
41	C_2H_5	C_2H_5	C_6H_4-*p*-OCH_3	H		D	PE	115–116	59	$C_{16}H_{18}N_4O$	14.0	8.0	
42	CH_3	CH_3	H	C_6H_5		A	benzene–PE	143–144.5	64	$C_{13}H_{12}N_4$	25.0	3.0	49.0
43	CH_3	C_2H_5	H	C_6H_5		A	*n*-hexane	83–84	64	$C_{14}H_{14}N_4$	27.0	10.0	39.0
44	CH_3	H	H	C_6H_4-*m*-CH_3		A	EtOH	100–101	74	$C_{13}H_{12}N_4$	1.5	0.4	
45	CH_3	CH_3	H	C_6H_4-*m*-CH_3		A	benzene–PE	152–153	75	$C_{14}H_{14}N_4$	14.0	2.0	
46	CH_3	C_2H_5	H	C_6H_4-*m*-CH_3		A	*n*-heptane	106–108	68	$C_{15}H_{16}N_4$		5.0	
47	CH_3	C_2H_5	H	C≡N		A	acetone–*n*-hexane	100–103	43	$C_9H_9N_5$	1.2	1.7	
48	CH_3	C_2H_5	H	$COOC_2H_5$		A	EtOH	178–180	56	$C_{11}H_{14}N_4O_2$	0.7	1.2	
49	CH_3	C_2H_5	H	Cl			Et_2O–*n*-hexane	62–63	33	$C_8H_9N_4Cl$	1.8	0.8	
50	CH_3	C_2H_5	H	Br			Et_2O–*n*-hexane	87–88	41	$C_8H_9N_4Br$	2.5	1.0	
51	CH_3	H	C_6H_5	Br			benzene–PE	155–157	84	$C_{12}H_9N_4Br$	1.8	0.9	
52	CH_3	CH_3	C_6H_5	Br			*n*-heptane	136–138	98	$C_{13}H_{11}N_4Br$	40.0	3.0	
53	CH_3	C_2H_5	C_6H_5	Br			*n*-hexane	123–125	88	$C_{14}H_{13}N_4Br$	14.0	7.0	
54	CH_3	*n*-C_3H_7	C_6H_5	Br			*n*-hexane	110–112	35	$C_{15}H_{15}N_4Br$	8.0	2.0	
55	C_2H_5	C_2H_5	C_6H_5	Br			*n*-heptane	85–87	93	$C_{15}H_{15}N_4Br$	9.0	2.0	

[a] PE = petroleum ether.

Table III. *N*-(Pyrazol-3-yl)alkylamidine Acetates



compd	R_1	R_3	R_4	method	mp, °C	yield, %	ref	formula
56	CH_3	H	H	A	159-160	70	19	$C_7H_{12}N_4O_2$
57	C_2H_5	H	H	A	115-116	96	11	$C_8H_{14}N_4O_2$
58	CH_3	C_6H_5	H	A	188-189	90	11	$C_{13}H_{16}N_4O_2$
59	CH_3 [b]	C_6H_5	H	B	236-237	68[c]		$C_{11}H_{12}N_4$
60	C_2H_5 [b]	C_6H_5	H	B	154-156	55		$C_{12}H_{14}N_4$
61	CH_3 [a]	C_6H_4-*o*-CH_3	H	C	oil			$C_{14}H_{18}N_4O_2$
62	C_2H_5 [a]	C_6H_4-*o*-CH_3	H	C	oil			$C_{15}H_{20}N_4O_2$
63	CH_3 [a]	C_6H_4-*p*-CH_3O	H	C	oil			$C_{14}H_{18}N_4O_3$
64	C_2H_5 [a]	C_6H_4-*p*-OCH_3	H	C	oil			$C_{15}H_{20}N_4O_3$
65	CH_3	H	C_6H_5	A	186-187	90		$C_{13}H_{16}N_4O_2$
66	CH_3	H	C_6H_4-*m*-CH_3	A	150-151	80		$C_{14}H_{18}N_4O_2$
67	CH_3	H	C≡N	A	345 dec	77[c]		$C_8H_{11}N_5O_2$
68	CH_3	H	$COOC_2H_5$	A	>340 dec	32[d]		$C_{10}H_{16}N_4O_4$

[a] These compounds were obtained as oil. [b] These compounds were obtained as free amidines. [c] Recrystallized from EtOH. [d] Recrystallized from acetone-Et_2O.

55 shows a decrease in α_{lung} from 40 to 9 (Table II). An amazing increase in activity to α_{lung} of 185 was obtained by combining the 7-phenyl-8-bromo function with a diethylamino group at C_4 in 4-(diethylamino)-8-bromo-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**25**; Table I). A study of Table I reveals that the combination of a 7-phenyl and a 4-diethylamino function gives an α_{lung} 143 times that of theophylline (see compound **7**). The introduction of a bromo group at C_8 increases the α_{lung} to 185 (see compound **25**). The dialkylamino substituent is preferred over an alkylamino group (compare α_{lung} for **5**, **6**, and **7**, Table I). This can also be seen by comparing **10** and **11**. It is of interest that in the presence of a methylthio substituent at C_2 the superiority of the C_4 diethylamino group is still evident (compare the α_{lung} of **10** vs. **11**). However, the introduction of a bromo group at C_8 reverses this effect, since 8-bromo-2-(methylthio)-4-(*n*-propylamino)pyrazolo-[1,5-*a*]-1,3,5-triazine (**13**) exhibits an α_{lung} of 67 vs. 26 for the corresponding 4-diethylamino derivative **14**. In fact, increasing the chain to *n*-butylamino with an 8-bromo substituent (see compound **15**) raises the α_{lung} to 160. A most interesting observation with 8-bromo-2-(methylthio)-4-(*n*-butylamino)pyrazolo[1,5-*a*]-1,3,5-triazine (**15**) is that althouth the α_{lung} is 160, the α_{brain} value is only 18. This is a strong indication that PDE inhibitors can be found which will have considerable tissue specificity. In contrast, compound **7**, which exhibits an α_{lung} of 143, also shows high activity against the heart enzyme (α_{heart} = 57) and is very active against the PDE of brain (α_{brain} = 146). The highest activity obtained in this series was an α_{brain} value of 250 for compound **25** (Table I). These data are very encouraging and provide a clear-cut example of the differing sensitivities to inhibition of PDE enzymes isolated from different sources. Although most active compounds have not been tested in a general pharmacological evaluation, the following in vitro and in vivo results are available. 2-(Methylthio)-4-(diethylamino)pyrazolo[1,5-*a*]-1,3,5-triazine (**11**) at 10 μg/mL showed a positive response as a uterine relaxant with about the same activity as isoxsuprine. 4-(Diethylamino)-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**7**) was essentially as active as meprobamate at similar dose levels as an anticonvulsant when tested against the induction of convulsions by electric shock according to the procedure of Chen.[20] 8-Bromo-2-(methylthio)-4-(*n*-propylamino)pyrazolo[1,5-*a*]-1,3,5-triazine (**13**) at 10 mg/kg protects guinea pigs from histamine-induced bronchospasm as determined by the procedure of Levine and Vaz.[21] The LD_{50} of **13** is 550 mg/kg (single dose) injected ip in mice. This compound should be investigated further for its antiasthmatic potential.

(20) G. Chen, *Proc. Soc. Exp. Biol. Med.*, **87**, 334 (1954).

Experimental Section

The compounds prepared are listed in Tables I–III. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed on all compounds by the Heterocyclic Chemical Co., Harrisonville, MO, and were analyzed for C, H, and N within ±0.4% of theoretical values.

Enzyme Assays. The details of the preparation and assay of the beef heart, rabbit lung, and bovine brain phosphodiesterases have been described previously.[22] The specific activities of the enzyme preparations were 14, 70, and 9.3 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 in 1 min under the standard assay conditions described below (except that a saturating concentration, 50 μM, of cAMP is used).

The K_m values (average of six determinations) for cAMP were 0.63 (±0.22), 0.56 (±0.24), and 1.3 (±0.37) μM for the beef heart, rabbit lung, and bovine brain enzymes, respectively. The K_i values (average of three determinations) for theophylline were 77 (±14), 180 (±42), and 150 (±29) μM for the beef heart, rabbit lung, and bovine brain 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 detd. 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 μmol 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*]-1,3,5-triazine 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 inhibition 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

(21) B. B. Levine and N. Vaz, *Int. Arch. Allergy Appl. Immunol.*, **39**, 156 (1970).

(22) J. P. Miller, D. A. Shuman, M. B. Scholten, M. K. Dimmitt, C. M. Stewart, T. A. Khwaja, R. K. Robins, and L. N. Simon, *Biochemistry*, **12**, 1010 (1973).

above conditions are 90 (±38), 210 (±84), and 190 (±60) μM for the beef heart, rabbit lung, and bovine brain enzymes, respectively. The data on the new PDE inhibitors are expressed relative to theophylline as α values,[2,23] where $\alpha = I_{50}$ for theophylline/I_{50} for the test compound. All α values represent the results of triplicate determinations which were reproducible within 20% of the value reported.

***N*-[4(5)-Substituted-pyrazol-3-ylalkyl]amidine Acetates (Table III, 56–58 and 65–68). Method A.** To a mixture of the appropriate 3-aminopyrazole (0.01 mol) and ethyl imidate (0.02 mol) in dry CH_3CN (50 mL) was added dropwise acetic acid (0.01 mol) with stirring. A mild exothermic reaction took place. After the mixture was stirred overnight at room temperature, the precipitate was filtered, washed with acetonitrile, and dried to give the product.

Method B. *N*-(5-Phenylpyrazol-3-yl)acetamidine (59) and *N*-(5-Phenylpyrazol-3-yl)propionamidine (60) (Free Amidines, Table III). A mixture of 3-amino-5-phenylpyrazole (13; 0.03 mol) and the appropriate ethyl imidate (0.035 mol) in dry CH_3CN (50 mL) was stirred at room temperature for 48 h. The reaction mixture was concentrated to 20 mL volume in vacuo at below 40 °C. The precipitate was filtered and washed with Et_2O to yield the product. When a mixture of **59** (0.005 mol) and acetic acid (0.005 mol) in dry CH_3CN (10 mL) was stirred for 16 h at room temperature, **58** was obtained in 60% yield.

Method C. A mixture of 3-amino-5-(substituted-phenyl)-pyrazole (14; 0.01 mol), ethyl imidate (0.03 mol), and acetic acid (0.01 mol) in dry CH_3CN (50 mL) was stirred at room temperature for 3 h. The reaction mixture was evaporated in vacuo at below 40 °C to give the product. The oil was used directly in the next step without further purification.

2,4-Dialkyl- and 2-Alkyl-4-phenylpyrazolo[1,5-*a*]-1,3,5-triazines (Table II). Method A. A mixture of *N*-(pyrazol-3-ylalkyl)amidine acetate (0.01 mol) and the appropriate triethyl orthoester (10 mL) was heated at reflux for 24 h. After the mixture was cooled, the precipitate was filtered, washed with Et_2O, and recrystallized from the solvent listed in Table II to give the pure product.

Method B. A mixture of *N*-[(5-phenylpyrazol-3-yl)alkyl]-amidine (**59** or **60**; 0.01 mol) and the appropriate triethyl orthoester (10 mL) was heated at reflux for 24 h. The reaction mixture was treated as described in method A to give the product listed in Table II.

Method C. A mixture of *N*-[(5-phenylpyrazol-3-yl)alkyl]-amidine (**59** or **60**; 0.01 mol) and the appropriate carboxylic acid anhydride (10 mL) was refluxed for 3 h. The reaction mixture was allowed to stand at room temperature, and the precipitate was collected and washed with Et_2O. Recrystallization from the indicated solvent in Table II gave a pure product.

Method D. A mixture of an oil of *N*-[(5-substituted-pyrazol-3-yl)alkyl]amidine (**62–64**; ~0.01 mol) and the proper triethyl orthoester (15 mL) was heated at reflux for 16 h. The reaction mixture was evaporated in vacuo, and the resulting residue was diluted with 30–60 °C petroleum ether. The separated solid was filtered and recrystallized from the solvent listed in Table II to give a pure product.

2,4-Dimethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (31). Method A. A mixture of 3.5 g (13.5 mmol) of **58** and 10 g of triethyl orthoacetate was heated under refluxing for 24 h. After the reaction mixture was cooled, precipitated crystals were collected by filtration, washed with ether, and dried to give 2.5 g (83%) of product. Recrystallization from benzene gave analytically pure **31**, mp 164.5–165 °C. Anal. ($C_{13}H_{12}N_4$) C, H, N.

Method B. A mixture of 1 g (5 mmol) of **58** and 20 mL of acetic anhydride was refluxed for 3 h. After the mixture stood at room temperature overnight, the precipitated crystals were collected by filtration, washed with ether, and dried to give 0.5 g (45%) of **31**, which is identical in all respects with the product prepared by method A.

2-Methyl-4-*n*-propyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (33). Method C. A mixture of 3.0 g (15 mmol) of **58** and 10 mL of *n*-butyric anhydride was refluxed for 3 h. After the mixture stood overnight at room temperature, separated crystals were collected by filtration, washed with ethanol, and dried to give 2.75 g (73%) of crystals. Recrystallization from *n*-hexane gave analytically pure **33**, mp 112–113 °C. Anal. ($C_{15}H_{16}N_4$) C, H, N.

2-Methyl-4,7-diphenylpyrazolo[1,5-*a*]-1,3,5-triazine (34). Method A. A mixture of 3 g (15 mmol) of **58** and 4.48 g (20 mmol) of triethyl orthobenzoate in 20 mL of dimethylformamide was refluxed for 16 h. The reaction mixture was evaporated to dryness in vacuo. Ether was added to the resulting residue, and the insoluble crystals were collected by filtration, washed with ether, and dried to give 1.95 g (46%) of analytically pure **34**, mp 160–162 °C. Anal. ($C_{18}H_{14}N_4$) C, H, N.

Method B. A mixture of 1 g (5 mmol) of **59** and 2.26 g (10 mmol) of benzoic anhydride in 20 mL of dimethylformamide was refluxed for 5 h. The reaction mixture was evaporated in vacuo. Ether was added to the resulting residue, and the insoluble crystals were collected by filtration, washed with ether, and dried to give 0.6 g (53%) of **34**, which is identical in all respects with the product prepared by method A.

2-Ethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (35). Method A. A mixture of 2.14 g (10 mmol) of **60** and 10 mL of triethyl orthoformate was refluxed for 5 h. The reaction mixture was evaporated to dryness in vacuo, and 1.2 g (54%) of crystals was obtained. Recrystallization from a mixture of *n*-hexane and chloroform gave analytically pure **35**, mp 155–156 °C. Anal. ($C_{13}H_{12}N_4$) C, H, N.

2-Ethyl-4,6-diphenylpyrazolo[1,2-*a*]-1,3,5-triazine (38). A mixture of 4.28 g (20 mmol) of **60** and 4.52 g (20 mmol) of benzoic anhydride in 20 mL of dimethylformamide was refluxed for 16 h. The reaction mixture was evaporated to dryness in vacuo. Ether was added to the resulting residue, and the insoluble crystals were collected by filtration, washed with ether, and dried to afford 0.3 g of yellow crystals as an analytically pure **38**, mp, 133–137 °C. Anal. ($C_{19}H_{16}N_4$) C, H, N.

Preparation of 2,4-Dialkyl-7-phenyl-8-bromopyrazolo-[1,5-*a*]-1,3,5-triazines (51–55). (Table II). A mixture of 6 mmol of the requisite 2,4-dialkyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**30–33** and **37**) and the equivalent molar amount of *N*-bromosuccinimide in 30 mL of chloroform was refluxed for 10–20 min. The resulting solution was stirred at room temperature for 30 min. The reaction mixture was washed with saturated aqueous sodium carbonate solution (25 mL × 2) and water (25 mL × 1). The chloroform solution was dried over sodium sulfate and then evaporated to dryness in vacuo to afford the product. Recrystallization from an appropriate solvent gave the analytically pure product. See Table II for recrystallization solvent, yield, and melting point.

8-Bromo-4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (50). A mixture of 4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**28**; 2.0 g, 0.0123 mol) and *N*-bromosuccinimide (2.6 g, 0.015 mol) in 50 mL of chloroform was refluxed for 15 min and then poured onto 20 g of ice, and the chloroform solution was separated (separatory funnel) and washed with 2 × 50 mL portions of 10% sodium carbonate solution. The organic phase was dried (Na_2SO_4) and upon evaporation the solid obtained was recrystallized from ether–hexane to afford 1.2 g (41%) of ivory white needles: mp 87–88 °C; NMR ($CDCl_3$) δ 1.48 (t, C-ethyl), 2.73 (s, C_5 methyl), 3.30 (q, C-ethyl), 8.10 (s, C_2 H). Anal. ($C_8H_9N_4Br$) C, H, N.

8-Chloro-4-ethyl-3-methylpyrazolo[1,5-*a*]-1,3,5-triazine (49). A mixture of 4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**28**; 2.0 g, 0.0123 mol), *N*-chlorosuccinimide (1.8 g), and chloroform (50 mL) was refluxed for 15 min. The cooled solution was washed with 2 × 50 mL portions of cold 10% sodium carbonate solution, and the organic phase was dried (Na_2SO_4) and evaporated to give a solid. Recrystallization of this solid from ether–hexane yielded 800 mg (33%) of yellowish needles: mp 62–63 °C; NMR ($CDCl_3$) δ 1.50 (t, C-ethyl), 2.70 (s, C_5 methyl), 3.33 (q, C-ethyl), 8.10 (s, C_2 H). Anal. ($C_8H_9N_4Cl$) C, H, N.

4-(Diethylamino)-2-(methylthio)pyrazolo[1,5-*a*]-1,3,5-triazine (11). A solution of 2-(methylthio)-4-chloropyrazolo-[1,5-*a*]-1,3,5-triazine[10] (3.0 g) and diethylamine (2.24 g) in 15 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 solid residue was washed with cold water and dried. Recrystallization from *n*-hexane afforded 3.0 g (88%) of pure **11**, mp 61–63 °C. Anal. ($C_9H_{15}N_5S$) C, H, N.

(23) J. P. Miller, K. H. Boswell, R. B. Meyer, Jr., L. F. Christensen, and R. K. Robins, *J. Med. Chem.*, **23**, 242 (1980).

4-(n-Propylamino)-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (10). A solution of 15 g of 2-(methylthio)-4-chloropyrazolo[1,5-a]-1,3,5-triazine[10] and 8.85 g of *n*-propylamine in 200 mL of absolute ethanol was stirred at room temperature for 1 h and then evaporated to dryness in vacuo. The residue was triturated with water and then recrystallized from aqueous ethanol to give 15 g (90%) of pure **10**, mp 73–75 °C. Anal. ($C_9H_{13}N_5S$) C, H, N.

4-(Ethylthio)-2-(methylthio)-8-bromopyrazolo[1,5-a]-1,3,5-triazine (22). A solution of 8-bromo-2-(methylthio)-4-thiopyrazolo[1,5-a]-1,3,5-triazine (17; 2.77 g, 10 mmol), ethyl iodide (10 mmol), and concentrated aqueous ammonia (3 mL) in 200 mL of methanol was refluxed for 1 h, and the solution was evaporated to dryness. Recrystallization of the residue from *n*-heptane gave a 48% yield of **22**, mp 119–212 °C. Anal. ($C_8H_9BrN_4S_2$) C, H, N.

2,4-Bis(methylthio)-8-bromopyrazolo[1,5-a]-1,3,5-triazine (**26**) was similarly prepared, in 45% yield, mp 148–149, recrystallized from *n*-heptane.

8-Bromo-4-thio-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (17). 8-Bromo-2-(methylthio)-4-chloropyrazolo[1,5-a]-1,3,5-triazine[10] (15 g) and sodium hydrosulfide (20 g) in 400 mL of 50% ethanol was stirred at room temperature for 16 h. The solution was then warmed to 60 °C and acidified to pH of 1 with 6 N hydrochloric acid. The precipitated solid was filtered, washed, and recrystallized from aqueous ethanol to afford 13.9 g (94%) of pure **17**, mp 203–205 °C dec. Anal. ($C_6H_5BrN_4S_2$) C, H, N.

4-(n-Butylamino)-2-methyl-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (16). A mixture of 0.89 g (3.5 mmol) of 2-methyl-4-(methylthio)-7-phenylpyrazolo[1,5-a]-1,3,5-triazine,[11] 0.26 g (3.5 mmol) of *n*-butylamine, and absolute ethanol (20 mL) was refluxed for 4 h. The reaction mixture was evaporated to dryness in vacuo, and the resulting residue was recrystallized from *n*-hexane to afford 0.75 g (76%) of pure 4-(*n*-butylamino)-2-methyl-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (**16**), mp 115–116 °C. Anal. ($C_{16}H_{19}N_5$) C, H, N.

7-Phenyl-4-(n-propylamino)pyrazolo[1,5-a]-1,3,5-triazine (5). A solution of 7-(methylthio)-2-phenylpyrazolo[1,5-a]-1,3,5-triazine[9] (1.21 g, 5 mmol) and *n*-propylamine (0.30 g, 5 mmol) in 50 mL of anhydrous methanol was stirred at room temperature for 2 days (or refluxed for 4 h). At the end of this time, the solution was evaporated to dryness. The residue was recrystallized from a mixture of ethanol and water to afford 1.2 g (96%) of pure **5**, mp 140–141 °C. Anal. ($C_{14}H_{15}N_5$) C, H, N.

7-(Methylamino)-2-phenylpyrazolo[1,5-a]-1,3,5-triazine (7). A mixture of 7-(methylthio)-2-phenylpyrazolo[1,5-a]-1,3,5-triazine[9] (0.8 g, 3.3 mmol) and diethylamine (0.24 g, 3.3 mmol) in 25 mL of absolute ethanol was heated at reflux for 36 h. At the end of this time a solvent was removed at reduced pressure and the dark oil residue was covered with 10 mL of water. The white solid residue that precipitated was separated by filtration and washed with an additional 10 mL of water. Recrystallization from *n*-heptane afforded 0.6 g (71%) of analytically pure **7**, mp 87–88 °C. Anal. ($C_{15}H_{17}N_5$) C, H, N.

2-Phenyl-7-piperidinopyrazolo[1,5-a]-1,3,5-triazine (8). A solution of 7-(methylthio)-2-phenylpyrazolo[1,5-a]-1,3,5-triazine[9] (1.5 g, 6.9 mmol) and piperidine (0.59 g, 6.8 mmol) in 50 mL of anhydrous methanol was heated at reflux for 8 h. At the end of this time, a solvent was removed at reduced pressure, and the residue was titurated with 10 mL of water. The residue was recrystallized from a mixture of methanol and water to afford 0.97 g (5.0 mmol) of pure **8**, mp 82–84 °C. Anal. ($C_{16}H_{17}N_5$) C, H, N.

7-(n-Butylamino)-2-phenylpyrazolo[1,5-a]-1,3,5-triazine (6). A solution of 7-(methylthio)-2-phenylpyrazolo[1,5-a]-1,3,5-triazine[9] (1.5 g, 6.9 mmol) and *n*-butylamine (0.51 g, 6.9 mmol) in 50 mL of anhydrous methanol was refluxed for 4 h. At the end of this time, the solvent was removed at reduced pressure, and the residue was titurated with 10 mL of water. The crystalline residue was recrystallized from a mixture of ethanol and water to afford 1.6 g (94%) of analytically pure product, mp 120–122 °C. Anal. ($C_{15}H_{17}N_5$) C, H, N.

8-Bromo-4-(diethylamino)-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (14). A mixture of 4-(diethylamino)-3-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (11; 1.80 g, 8 mmol) and *N*-bromosuccinimide (1.44 g, 8.1 mmol) in 15 mL of chloroform was heated at reflux for 15 min and then allowed to stir at room temperature for 2 h. The mixture was filtered, and the filtrate was washed with saturated sodium carbonate solution. The chloroform layer was then evaporated to afford a yellow oil, which slowly crystallized. Recrystallization from *n*-hexane afforded 1.9 g (75%) of pure 8-bromo-4-(diethylamino)-2-(methylthio)-pyrazolo[1,5-a]-1,3,5-triazine (**14**), mp 63–65 °C. Anal. ($C_{10}H_{14}N_5SBr$) C, H, N.

8-Bromo-4-(ethylamino)-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (12). A solution of 8-bromo-4-chloro-2-(methylthio)pyrazolo[1,5-a]pyrimidine[10] (2.79 g, 10 mmol) and ethylamine (20 mmol) in 30 mL of ethanol was stirred at room temperature for 1 h and evaporated to dryness in vacuo. The residue was triturated with cold water and recrystallized from aqueous ethanol to give a 90% yield of product, mp 93–95 °C. Anal. ($C_8H_{10}BrN_5S$) C, H, N.

8-Bromo-4-(n-propylamino)-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (13). Compound **13** was prepared similarly to **12**, using *n*-propylamine to give **13** in 85% yield, mp 88–90 °C. Recrystallization was accomplished from ethyl acetate–hexane. Anal. ($C_9H_{12}BrN_5S$) C, H, N.

8-Bromo-4-(n-butylamino)-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (15). The synthesis of **15** was accomplished from 8-bromo-4-chloro-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine[10] and *n*-butylamine in a similar manner to **12**. The product was obtained in 63% yield and was purified by recrystallization from aqueous ethanol, mp 87–89 °C. Anal. ($C_{19}H_{14}BrN_5S$) C, H, N.

8-Bromo-4-n-propoxy-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (24). A solution of 2.79 g of 8-bromo-4-chloro-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine,[10] 84 mg of sodium bicarbonate, and 200 mL of 1-propanol was refluxed for 1 h. The mixture was cooled and filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from *n*-heptane to give a 73% yield of **24**, mp 100–102 °C. Anal. ($C_9H_{11}BrN_4OS$) C, H, N.

Compound **18** was similarly prepared from 2-propanol in 70% yield; recrystallized from *n*-heptane to give mp 93–95 °C.

4-(Ethylthio)-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (20). A solution of sodium methoxide in methanol was prepared by dissolving sodium (0.29 g, 0.0126 formula weights) in 20 mL of methanol. With good stirring, ethanethiol (0.45 g, 13.8 mmol) was added to the sodium methoxide solution. The resulting solution of sodium ethylmercaptide was stirred at room temperature for 30 min and then treated with 4-chloro-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine[9] (2.5 g, 12.5 mmol). This solution was stirred at room temperature for 30 min and then evaporated to dryness at reduced pressure. The resulting residue was purified by column chromatography on silica gel (50 g) using a solvent system of petroleum ether (60–90 °C)–ethyl acetate (8:2). Evaporation of the eluate and recrystallization of the residue from *n*-heptane afforded 1.10 g (49%) of pure 4-(ethylthio)-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (**20**), mp 73–75 °C. Anal. ($C_8H_{10}N_4S_2$) C, H, N.