2-(Alkylthio)-1,2,4-triazolo[1,5-*a*]pyrimidines as Adenosine Cyclic 3′,5′-Monophosphate Phosphodiesterase Inhibitors with Potential as New Cardiovascular Agents

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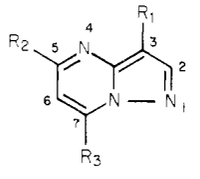
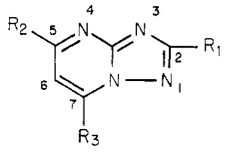
Novitex Laboratories, Inc., Ventura, California 93003, Viratek, Inc., Covina, California 91722, Life Sciences Division, SRI International, Menlo Park, California 94025, and Cancer Research Center, Department of Chemistry, Brigham Young University, Provo, Utah 84602. *Received April 30, 1981*

A series of new 2-(alkylthio)-5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines have been prepared as inhibitors of cAMP phosphodiesterase from various tissues. These derivatives were prepared via ring closure of various requisite 3-amino-1,2,4-triazole intermediates. 2-(Benzylthio)-5-methyl-7-(dimethylamino)-1,2,4-triazolo[1,5-*a*]pyrimidine (**15a**) is 6.3 times as potent as theophylline in inhibiting cAMP PDE isolated from rabbit heart. Treatment of dogs intravenously with 5 (mg/kg)/h of **15a** gave a cardiac output increase of 69%, which was largely sustained for a 2-h period after administration of drug had ceased. There was no significant increase in heart rate upon administration of **15a**. Related studies with 5,7-di-*n*-propyl-2-(benzylthio)-1,2,4-triazolo[1,5-*a*]pyrimidine (**22a**) in five dogs showed a 31.5% increase in cardiac output with an increase in stroke volume of 34.4% with no increase in heart rate. The specificity of action of these PDE inhibitors could be due to selective binding at a certain cAMP PDE site in the cardiovascular system. Several of these compounds are candidates for further studies with a view to clinical evaluation.

In previous reports we have described the preparation of a number of pyrazolo[1,5-*a*]pyrimidines (**1**) and have reported their ability to inhibit cAMP phosphodiesterase (PDE) isolated from various tissues.[1-3] The activity of several derivatives as potent PDE inhibitors suggested the extension of these structure–activity relationships to a study of the 1,2,4-triazolo[1,5-*a*]pyrimidine (**2**) ring system.

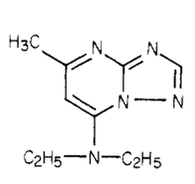


1, pyrazolo-[1,5-*a*]pyrimidine



2, *s*-triazolo-[1,5-*a*]pyrimidine

It is interesting to note that 5-methyl-7-(diethylamino)-*s*-triazolo[1,5-*a*]pyrimidine (**3**, trapidil or trapymin)



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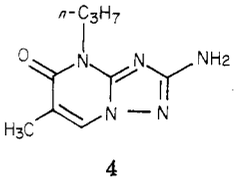

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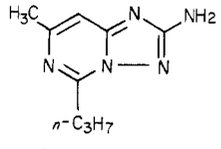

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has been introduced into clinical medicine as a coronary dilator.[4] Ogura, Taira, and Hashimoto[5] have shown that **3** is not only a coronary vasodilator but also a potent cardiotonic drug. 2-Amino-6-methyl-4-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (**4**) has shown significant activity against histamine-induced bronchospasm.[6] The closely related 2-amino-5-methyl-7-*n*-propyl-1,2,4-triazolo[2,3-*c*]pyrimidine (**5**) has been prepared by Rose and co-workers[7] and shown to be a good inhibitor of cAMP PDE and to be 100 times more effective than theophylline in protecting laboratory animals from histamine-induced bronchospasms.[8,9] The synthesis of various 2-(alkylthio)-*s*-triazolo[1,5-*a*]pyrimidines as potential inotropic agents was prompted by the observation that 8-(methylthio)- and 8-(benzylthio)-cAMP were found in our laboratory to be good inhibitors of cAMP phosphodiesterase.[10] More recently, it has been noted that 2-methyl-8-(benzylthio)-cAMP (**6**),[11] and 2-methyl-N^6,N^6-diethyl-8-(benzylthio)cAMP (**7**) exhibited, respectively, PDE inhibition of 23 and 18 times that of theophylline when evaluated against PDE isolated from cat heart.[12]

Burlow and Haas[13] first reported the condensation of 3-amino-1,2,4-triazole with acetylacetone to yield 5,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine. Kano and Makisumi[14] obtained 7-hydroxy-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine by the condensation of 3-amino-1,2,4-triazole and ethyl acetoacetate. Reynolds and co-workers[15] have established

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(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. K. Scholten, R. K. Robins, L. N. Simon, D. E. O'Brien, and R. B. Meyer, Jr., *J. Med. Chem.*, 18, 460 (1975).
(3) R. H. Springer, D. E. O'Brien, M. K. Scholten, T. Novinson, J. P. Miller, and R. K. Robins, *J. Med. Chem.*, in press.
(4) E. Tenor and R. Ludwig, *Pharmazie*, 26, 534 (1971); see also H. Füller, F. Hauschild, D. Modersohn, and E. Thomas, *ibid.*, 26, 554 (1971).
(5) K. Oguro, N. Taira, and K. Hashimoto, *Arzneim.-Forsch*, 24, 911 (1974).
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(7) G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 3357 (1965).
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(10) K. Muneyama, R. J. Bauer, D. A. Shuman, R. K. Robins, and L. N. Simon, *Biochemistry*, 10, 2390 (1971).
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(13) C. Bulow and K. Haas, *Ber. Dtsch. Chem. Ges.*, 42, 4638 (1909).
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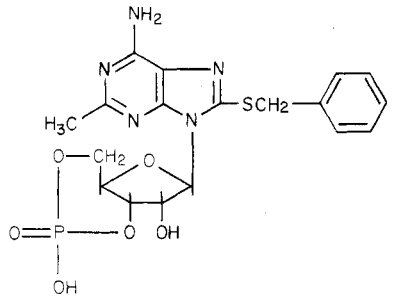

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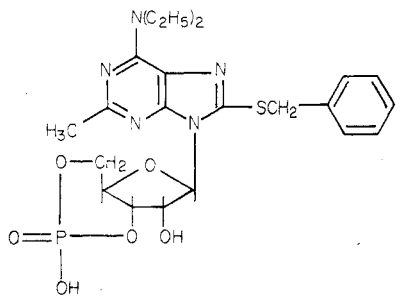

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the structure of these products as triazolo[1,5-a]pyrimidines rather than the alternate triazolo[4,3-a]pyrimidine structure. Okabe and co-workers[16] have condensed 3-amino-5-thio-1,2,4-triazole (8) with acetylacetone and claimed the product to be 3-thio-5,7-dimethyl-s-triazolo-[4,3-a]pyrimidine. A recent communication from our laboratory,[17] however, has established this product as 5,7-dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (9) (Scheme I). It is well known that under acidic conditions the s-triazolo[4,3-a]pyrimidines rearrange to the thermodynamically more stable s-triazolo[1,5-a]pyrimidines.[17,18]

The condensation of 3-amino-5-(benzylthio)-s-triazole (**11a**)[19] or 3-amino-5-[(p-chlorobenzyl)thio]-s-triazole (**11b**) with acetylacetone gave 2-(benzylthio)-5,7-dimethyl-s-triazolo[1,5-a]pyrimidine (**12a**) and 2-[(p-chlorobenzyl)-thio]-5,7-dimethyl-s-triazolo[1,5-a]pyrimidine (**12b**), respectively. The structure of **12a** was established as follows. According to the general procedure of Williams,[20] we have condensed 3-amino-5-thio-s-triazole (**8**) with acetylacetone in acetic acid to obtain 5,7-dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (**9**), whose structure has been conclusively established. The treatment of **9** with benzyl chloride in alkaline solution afforded **12a**, which is identical in all respects with the product obtained from **11a** by ring closure.[17] Due to the PDE activity of **12b**, Table I (5.4 times that of theophylline against the enzyme isolated from bovine heart), a number of substituted benzylthio derivatives were prepared for study by treatment of 5,7-dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (**9**) with various phenyl-substituted benzyl chlorides. These compounds, **12c–i**, are listed in Table I. Treatment of 5,7-dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (**9**) with various alkyl halides gave the corresponding 2-(alkylthio)-5,7-dimethyl-s-triazolo[1,5-a]pyrimidines (**10a–e**) (Table I).

The condensation of 3-amino-5-(benzylthio)-s-triazole (**11a**) with acetoacetic ester in acetic acid gave 2-(benzylthio)-7-hydroxy-5-methyl-s-triazolo[1,5-a]pyrimidine (**13**). The structural assignment of this product follows from the previous work of Williams,[20] who similarly prepared 7-hydroxy-5-methyl-2-(methylthio)-s-triazolo[1,5-a]pyrimidine. The treatment of 2-(benzylthio)-7-hydroxy-5-methyl-s-triazolo[1,5-a]pyrimidine (**13**) with refluxing phosphorus oxychloride yielded 2-(benzylthio)-7-chloro-5-methyl-s-triazolo[1,5-a]pyrimidine (**14**). The nucleophilic displacement of the chloro moiety of **14** with various primary and secondary amines in warm ethanol afforded compounds **15a–h** (Table II). The reaction of **14** with hydrazine or *unsym*-dimethylhydrazine afforded 2-(benzylthio)-7-hydrazino-5-methyl-s-triazolo[1,5-a]pyrimidine (**15d**) and the corresponding 7-(dimethylhydrazino) analogue **15e**, respectively. The action of sodium hydrosulfide on **14** gave 2-(benzylthio)-7-thio-5-methyl-s-triazolo[1,5-a]pyrimidine (**19**).

Condensation of 3-amino-5-(benzylthio)-s-triazole (**11a**) with diethyl ethoxymethylenemalonate gave 2-(benzylthio)-6-carbethoxy-7-hydroxy-s-triazolo[1,5-a]pyrimidine (**16**). The structural assignment of **16** follows from the work of Williams,[21] who condensed diethyl ethoxymethylenemalonate with 3-amino-5-(methylthio)-s-triazole to obtain 6-carbethoxy-7-hydroxy-2-(methylthio)-s-triazolo[1,5-a]pyrimidine. The action of refluxing phosphorus oxychloride on **16** afforded a good yield of 2-(benzylthio)-6-carbethoxy-7-chloro-s-triazolo[1,5-a]pyrimidine (**17**). The chloro group of **17** was smoothyl replaced by various primary amines to yield compounds **18a–c** (Table IV). Morpholine and **17** gave **26** in 70% yield. The action of sodium hydrosulfide on **17** afforded 2-(benzylthio)-6-carbethoxy-7-thio-s-triazolo[1,5-a]pyrimidine (**20**).

3-Amino-5-thio-s-triazole (**8**) and nonane-4,6-dione in acetic acid gave 5,7-di-n-propyl-2-thio-s-triazolo[1,5-a]-pyrimidine (**21**) (Scheme II). Treatment of **21** with p-tolylbenzyl chloride in sodium hydroxide gave **22b** in good yield. Oxidation of **22a** and **22b** with m-chloroperbenzoic acid in chloroform gave the corresponding sulfone **23a** and **23b**, respectively (Table III). Treatment of **21** with β- or γ-picolyl chloride hydrochloride gave 5,7-di-n-propyl-2-(β- or γ-picolylthio)-s-triazolo[1,5-a]pyrimidine, **24** and **25**, respectively (Table III).

Discussion

PDE Inhibition and Pharmacological Activity. Inspection of the data on the inhibition of PDE from various sources by the 2-(alkylthio)-s-triazolo[1,5-a]pyrimidines (Table I, II, and IV) reveals some interesting structure–activity relationships. With the 5,7-dimethyl-2-(alkylthio)-s-triazolo[1,5-a]pyrimidines (Table I) it can be noted that with the aliphatic side chains on the 2-thio function, 2-n-propylthio (**10b**) is about equal to theophylline in inhibiting the enzymes from rabbit kidney or rabbit heart. Branching of the alkyl group (**10c,d**) diminished the inhibitory activity to one-tenth the value in heart and lung but increased the α value 1.3 in kidney. The introduction of a benzylthio group at position 2 increased the α value from 2.1 to 2.5 in compound **12a**. 5,7-Dimethyl-2-[(p-chlorobenzyl)thio]-s-triazolo[1,5-a]pyrimidine (**12b**) showed an inhibitory activity of 5.4 times that of theophylline with PDE isolated from rabbit heart. This activity increased to α_{heart} = 9.40 with the corresponding p-methylbenzylthio derivative **12g**. It is of

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(18) K. Shirakawa, *Yakugaku Zasshi*, **78**, 1396 (1958).
(19) L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.*, 3437 (1970).
(20) L. A. Williams, *J. Chem. Soc.*, 1829 (1960).
(21) L. A. Williams, *J. Chem. Soc.*, 2222 (1962).
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Scheme I

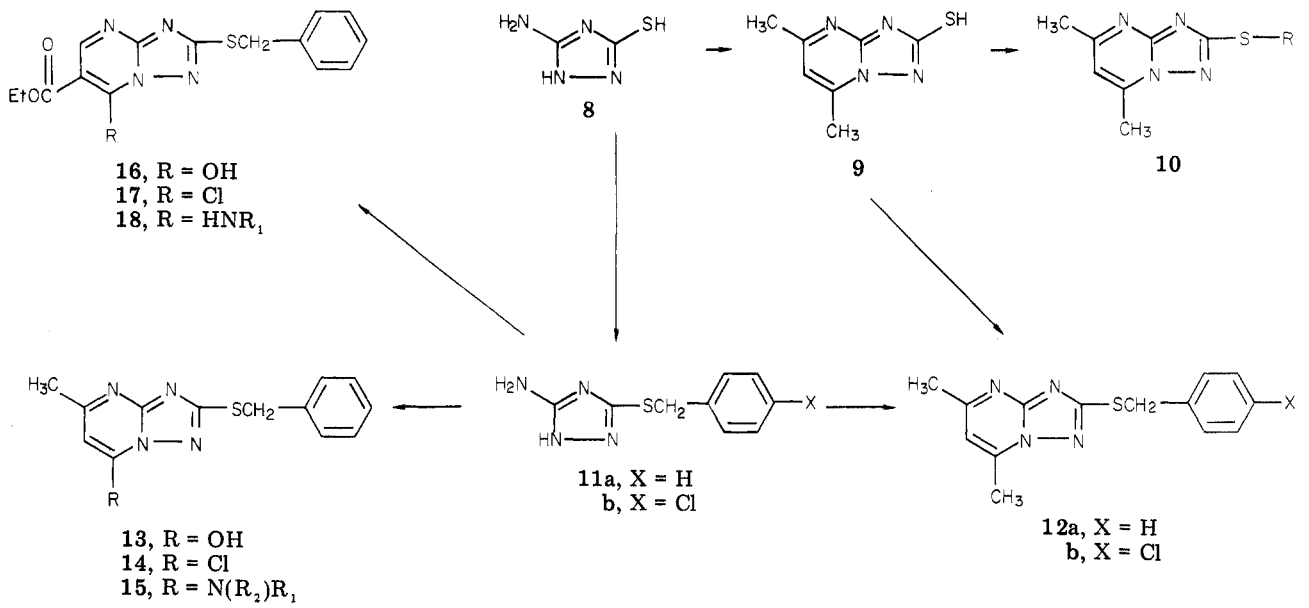
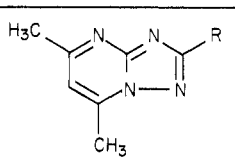


Table I. 5,7-Dimethyl-2-(alkylthio)-*s*-triazolo[1,5-*a*]pyrimidines and PDE Inhibitory Activity



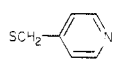
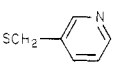
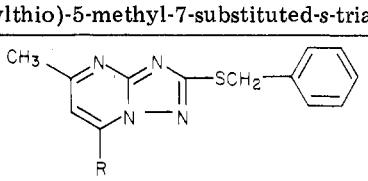
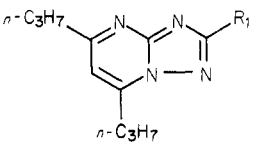
no.	R	recrystn solvent	yield, %	mp, °C	formula	α_{kidney}	α_{heart}	α_{lung}
10a	SCH_3	methanol-water	76	154-155	$C_8H_{10}N_4S$	0.25	0.30	0.50
10b	$S(CH_2)_2CH_3$	methanol-water	82	97-98	$C_{10}H_{14}N_4S$	1.0	0.90	0.90
10c	$SCH_2CH(CH_3)_2$	ethanol-water	72	119-121 dec	$C_{11}H_{16}N_4S$	0.5	0.10	0.10
10d	$SCH(CH_3)_2$	ethanol-water	60	95-96	$C_{10}H_{14}N_4S$	1.30	0.10	0.10
12a	$SCH_2C_6H_5$	ethanol	89	132-134	$C_{14}H_{14}N_4S$	2.1	2.50	2.50
12b	SCH_2-C_6H_4-Cl-*p*	ethanol-water	76	136-137	$C_{14}H_{13}N_4ClS$	4.0	5.40	4.0
12c	SCH_2-C_6H_4-COOH-*p*	ethanol	93	190-193	$C_{15}H_{14}N_4O_2S$	0.7	0.66	1.20
12d	SCH_2-C_6H_4-CH_3-*o*	DMF-methanol	75	110-111	$C_{15}H_{16}N_4S$	4.0	6.90	1.80
12f	SCH_2-C_6H_4-CH_3-*m*	DMF-methanol	94	120-121	$C_{15}H_{16}N_4S$	0.70	6.60	2.00
12g	SCH_2-C_6H_4-CH_3-*p*	ethanol	95	124-125	$C_{15}H_{16}N_4S$	1.0	9.40	<0.10
12h		ethanol	75	143-145	$C_{13}H_{13}N_5S$	0.70	6.30	0.80
12i		ethanol	75	164-165	$C_{13}H_{13}N_5S$	0.0	4.20	1.17
12j	SCH_2CH_2-C_6H_5	ethanol	62	91-92	$C_{15}H_{16}N_4S$	2.50	2.50	2.50

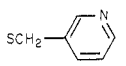
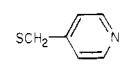
Table II. PDE Inhibition of Certain 2-(Benzylthio)-5-methyl-7-substituted-*s*-triazolo[1,5-*a*]pyrimidines



no.	R	yield, %	mp, °C	formula	α_{kidney}	α_{heart}	α_{lung}
13	OH	50	252-253	$C_{13}H_{12}N_4OS$	0.75	0.4	0.75
14	Cl	70	95-96	$C_{13}H_{11}N_4ClS$	1.40	0.5	4.00
19	SH	72	224-225	$C_{13}H_{12}N_4S_2$		1.60	1.37
15a	$N(CH_3)_2$	92	140-142	$C_{15}H_{17}N_5S$	3.40	6.30	1.6
15b	$N(CH_2)_2CH_3 \cdot HCl$	65	250-252	$C_{16}H_{19}N_5S \cdot HCl$	0.90	2.00	2.00
15c	$N(CH_2CH_2OH)_2$	72	174-175	$C_{17}H_{21}N_5O_2S$	2.30	2.50	2.10
15d	$NHNH_2 \cdot 2HCl$	85	260-261	$C_{13}H_{14}N_6S \cdot 2HCl$		3.10	6.70
15e	$NHN(CH_3)_2$	71	181-183	$C_{15}H_{17}N_6S$	8.0	5.30	5.30
15f	c-NC_5H_{10}	62	89-90	$C_{18}H_{21}N_5S$	3.2	11.00	10.00
15g	c-$N(CH_2CH_2)_2O$	64	118-120	$C_{17}H_{19}N_5OS$	4.80		7.70
15h	$N(C_2H_5)_2$	83	249-250	$C_{17}H_{21}N_5S$	2.30	8.0	4.2

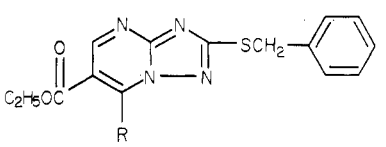
Table III. Percentage Change in Cardiac Output, Stroke Volume, and Heart Rate at a Dosage of 10 (mg/kg)/h iv, in Mongrel Dogs



no.	R_1	yield, %	mp, °C	formula	% change[a] cardiac output	stroke volume	heart rate	no. of dogs
22a	SCH_2-C_6H_4	77	59-61	$C_{18}H_{22}N_4S$	+31.5	+34.4	0	5
22b	SCH_2-C_6H_4-CH_3-*p*	77	67-68	$C_{19}H_{24}N_4S$	+34.3	+38	−2.8	4
23a	SO_2CH_2-C_6H_5	47	109-111	$C_{18}H_{22}N_4O_2S$	+42.3	+46.6	+0.2	3
23b	SO_2CH_2-C_6H_4-CH_3-*p*	80	106-107	$C_{19}H_{24}O_2S$	+16.4	+36.1	14.3	2
24		30	128-129	$C_{17}H_2N_5SO_2S\cdot H_2SO_4$	+20	+35	−10.9	3
25		27	151-152	$C_{17}H_2N_3O_2S\cdot H_2SO_4$	+27	+39	−8.1	3

[a] Data compiled as an average of the number of dogs studied.

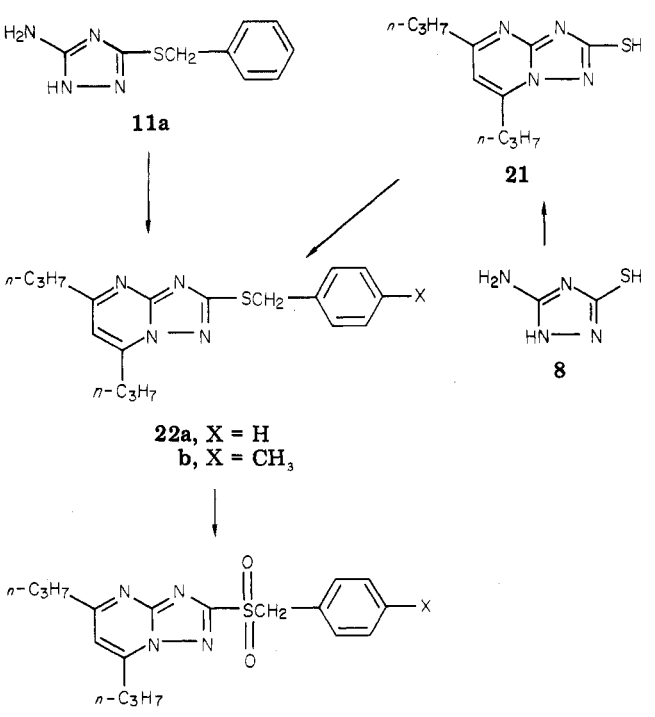
Table IV. 2-(Benzylthio)-6-carbethoxy-7-substituted-*s*-triazolo[1,5-*a*]pyrimidines and PDE Inhibition



no.	R	yield, %	recrystn solvent	mp, °C	formula	PDE inhibn[a] α_{lung}	α_{kidney}
16	OH	63	ethanol-water	246-247	$C_{15}H_{14}N_4O_3S$	0.00	0.00
17	Cl	73	heptane	127-129	$C_{15}H_{13}ClN_4O_2S$	Ins	Ins
18a	$NHCH_2$-C_6H_5	75	ethanol	114-116	$C_{22}H_{21}N_5O_2S$	Ins	Ins
18b	$NHCH_2CH_2OH$	65	methanol	168-170	$C_{18}H_{21}N_5O_3S$	Ins	Ins
18c	NH-*n*-C_3H_7	85	ethanol-water	94-96	$C_{18}H_{21}N_5O_2S$	21.0	7.0
20	SH	80	ethanol-water	133-136	$C_{15}H_{14}N_4O_2S_2$	Ins	Ins
26	c-$N(CH_2CH_2)_2O$	70	methanol	92-94	$C_{19}H_{21}N_5O_3S$	6.90	2.90

[a] Ins, too insoluble to determine.

Scheme II



considerable interest to note that this activity is quite specific for heart PDE with almost no inhibitory activity with PDE from lung and activity about equal to theophylline against PDE isolated from rabbit kidney. 5,7-Dimethyl-4-[(pyridylmethyl)thio]-*s*-triazolo[1,5-*a*]pyrimidine (**12h**) retained most of the PDE inhibition against the heart enzyme, $\alpha_{heart} = 6.30$, with relatively little potency against the enzymes from kidney or lung. The highest α_{lung} was found with 2-(benzylthio)-6-carbethoxy-7-(*n*-propylamino)-*s*-triazolo[1,5-*a*]pyrimidine (**18c**) with an α value of 21.0.

Preliminary pharmacological evaluation has revealed that 2-(benzylthio)-7-(diethylamino)-5-methyl-*s*-triazolo-[1,5-*a*]pyrimidine (**15b**) and 2-(benzylthio)-6-carbethoxy-7-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine (**18c**) possess the ability to bring about coronary dilation at a concentration of 10 μg/mL in an isolated guinea pig heart preparation. Compounds **15h** and **18c** are significant smooth-muscle relaxants as determined by their ability to relax isolated guinea pig uteri at concentrations of 2 μg/mL.

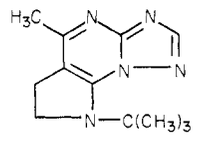
2-(Benzylthio)-7-hydrazino-5-methyl-*s*-triazolo[1,5-*a*]-pyrimidine (**15d**) has been found to possess significant antihypertensive activity as determined by the method of Weeks and Jones.[23] At an oral dose of 50 mg/kg in rats, there was a decrease in mean blood pressure at 1, 3, and

(23) J. R. Weeks and J. A. Jones, *J. Pharmacol. Exp. Ther.*, **104**, 646 (1960).

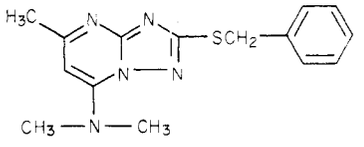
6 h of 11, 13, and 24%, respectively. This same compound had significant hypotensive activity at an oral dose of 25 mg/kg in the rat. This effect was maintained for at least a 6-h period. An oral dose of 300 mg/kg of **15d** showed no toxicity in the mouse. The encouraging increase in PDE inhibition especially, α_{heart}, due to the presence of the 2-benzylthio substituent suggested in vivo evaluation in the dog. The compound first chosen for further evaluation was 2-(benzylthio)-5-methyl-7-(dimethylamino)-*s*-triazolo[1,5-*a*]pyrimidine (**15a**) due to its structural relationship to trapymin (**3**). It should be noted that $\alpha_{bovine\ heart}$ for trapymin (**3**) is 1.3 as compared to $\alpha_{rabbit\ heart}$ of 6.30 for **15a**. The compound **15a** was administered in saline intravenously at 5 (mg/kg)/h to an anesthetized, mongrel, open-chested dog over a 2-h period. The cardiac output rose 69% at the end of the 2-h period and maintained a 64% increase up to 2 h after administration of **15a** had ceased. A second dog showed a similar increase in cardiac output of 44%, which dropped to 35% 2 h after administration of the drug. The heart rate dropped about 5% during drug administration.

In comparison, trapymin (trapidil, **3**) appears to be more potent in causing a greater increase in coronary blood flow,[24] but the duration is very limited and the increase of coronary flow is accompanied by a marked tachycardia.[5] The interest generated by these experiments led to further studies in which it was found that 5,7-di-*n*-propyl substituents seemed to be superior in promoting the desirable properties of an inotropic agent. Due to the increase in α_{heart} with a 2-benzylthio substituent (**12a**) or a 2-*p*-methylbenzylthio group (**12g**), it was decided to prepare a series of 5,7-di-*n*-propyl-2-(benzylthio)- and -2-(β- and γ-2-picolylthio)-*s*-triazolo[1,5-*a*]pyrimidines, **22a,b**, **24**, and **25** (Table III), for evaluation. This group of compounds was especially active as inotropic agents anesthetized in open-chested dogs. Inspection of Table III reveals that compounds **22a** and **22b** gave an increased cardiac output of 31.5 and 34.3%, respectively. In each case, the heart rate was decreased or remained essentially the same as control animals. The corresponding β- and γ-2-picolylthio derivatives, **24** and **25**, also gave a good inotropic response. The most active compound of this series was 5,7-di-*n*-propyl-2-[(benzylsulfonyl)thio]-*s*-triazolo[1,5-*a*]pyrimidine (**23a**), which gave an average increase in cardiac output of 42.3%, with an increase of 46.6% in stroke volume with a less than 1% increase in heart rate.

In the treatment of congestive heart failure and cardiovascular shock it is highly desirable to have increased cardiac output and increased stroke volume accompanied by a decrease or no change in heart rate. In this regard, a number of the 2-(benzylthio)-5-alkyl-7-substituted-*s*-triazolo[1,5-*a*]pyrimidines reported here would appear to be superior to trapymin (**3**) and 8-*tert*-butyl-7,8-dihydro-5-methyl-6-pyrrolo[3,2-*e*]-*s*-triazolo[1,5-*a*]pyrimidine (**27**),



27



15a

which has recently been reported[24] to be more potent in coronary vasodilating activity than trapymin but of rather short duration. The similarity of **15a** to **27** and trapymin (**3**) is quite apparent. Inspection of Table II reveals that the PDE inhibition of **15a** is indeed quite specific. The increase in heart rate observed with trapymin (**3**) has been shown[24] to be dose dependent. This marked tachycardia[5,24] would appear to be absent in the 2-benzylthio derivative **15a** and the potent compounds **22a,b** and **23a**. It is of considerable interest to note that N^6-*n*-butyl-8-(benzylthio)-cAMP[25] has recently been shown to be a potent inotropic agent in the anesthetized dog.

Our present results are to be contrasted with those of Mushlin and co-workers,[26] who recently studied various alkylated xanthines in rabbits and concluded that PDE inhibition was the mechanism by which these compounds increased heart rate but questioned the importance of PDE inhibition as being involved in contraction. The present studies would indicate that it may indeed be possible to separate the various effects of cyclic nucleotide PDE inhibition with specific PDE inhibitors which act at only one site. Wells and co-workers[27] have recently shown that there is more than one form of cyclic nucleotide phosphodiesterase isolated from pig coronary arteries. In our present studies it would appear that with compounds such as **22a,b** and **23a** (Table III) significant increase in contractility as measured by cardiac output and stroke volume was achieved with virtually no increase in heart rate. It is quite clear that ring systems which are structurally related to purine may offer distinct advantages in giving rise to cyclic nucleotide PDE inhibitors with greater potency and specificity.

Several of the *s*-triazolo[1,5-*a*]pyrimidines described here would appear to be excellent candidates for a full pharmacological workup with a view to clinical evaluation as useful inotropic agents.

Experimental Section

The compounds prepared are listed in Tables I–IV. Melting points were determined 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, N, and S within ±0.4% of the theoretical values.

Enzymic Assays of PDE Inhibition. The details of the preparation and assay of the beef heart, rabbit lung, and rabbit kidney phosphodiesterase were described previously.[2,22,28] 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 picomol of cAMP to 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 0.63 (±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, 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 μmol of $MgCl_2$; 10–75 μg of phosphodiesterase protein; 350 pmol of [8-^{3}H]cAMP (850 cpm/pmol); and at least

(24) Y. Sato, Y. Shimoji, H. Fujita, H. Nishino, H. Mizuno, S. Kobayashi, and S. Kumakura, *J. Med. Chem.*, **23**, 927 (1980).
(25) J. P. Miller, K. H. Boswell, R. B. Meyer, Jr., L. F. Christensen, and R. K. Robins, *J. Med. Chem.*, **23**, 242 (1980).
(26) P. Mushlin, R. C. Boerth, and J. N. Wells, *Mol. Pharmacol.*, **20**, 179 (1981).
(27) J. N. Wells, J. E. Garst, and G. L. Kramer, *J. Med. Chem.*, **24**, 954 (1981).
(28) 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).

seven different concentrations (0.5 μM–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 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 above conditions are 90 (±38), 210 (±84), and 85 (±47) μM for the beef heart, rabbit lung, and rabbit kidney enzymes, respectively. The data on the new PDE inhibitors are expressed relative to theophylline as α values,[2,28] 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.

Inotropic Studies in Dogs. Adult mongrel dogs of either sex were anesthetized with sodium methohexital and permitted to breathe spontaneously. The chest was opened, and cardiac output in liters per minute was obtained using the dye-dilution procedure and computer analysis. The stroke volume was also determined along with the monitoring of heart rate. Changes in each parameter were expressed as a percentage of the preinfusion values. Each drug was dissolved in Me_2SO and infused at the rate of 10 (mg/kg)/h. These data are recorded in Table III.

5,7-Dimethyl-2-(benzylthio)-1,2,4-triazolo[1,5-a]pyrimidine (12a). A mixture of 750 mg of 3-amino-5-(benzylthio)-s-triazole[17] (**11a**; 3.6 mmol), 400 mg of acetylacetone (4.0 mmol), 25 mL of ethanol, and 6–10 drops of piperidine was refluxed for 45 h. The solution was cooled, and the crystals were filtered, washed with ice-cold ethanol, and air-dried to yield 500 mg, mp 120–121 °C. Anal. ($C_{14}H_{12}N_4S$) (M_r 268.34) C, H, N.

5,7-Dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (9). To 910 g (0.056 mol) of 3-amino-5-thio-s-triazole in 5.6 g of acetylacetone (0.056 mol) was added 200 mL of acetic acid and 0.5 mL of piperidine. The solution was refluxed for 10 h and then cooled. The product rapidly separated as needles. The product was filtered, washed with water, and dried to yield 9.5 g, mp 263–264 °C dec. Recrystallization of this product from acetic acid raised the melting point to 270–271 °C dec. Another 1.0–1.5 g could be recovered from the acetic acid filtrate by dilution with water: UV, λ_{max} (MeOH), at pH 7, 210, 250, 350 nm at pH 11, 245, 330 nm. Anal. ($C_7H_8N_4S$) (M_r 180.23) C, H, N, S.

3-[(p-Chlorobenzyl)thio]-5-amino-1,2,4-triazole (11b). In a 250-mL Erlenmeyer flask, 4.64 g (0.04 mol) of 3-amino-5-thio-1,2,4-triazole was mixed with 40 mL of 1 N NaOH solution (0.04 mol). Then, 7.55 g (0.048 mol) of p-chlorobenzyl chloride dissolved in 80 mL of absolute ethanol was added, and the olive-green mixture was warmed on the steam bath at 70–75 °C for 15–20 min. The turbidity disappeared, the solution became clear, and the color changed to amber. Then the solution was evaporated under reduced pressure to about 50 mL, diluted with water, and refrigerated. The next day the solid that precipitated was filtered, mixed with benzene, and heated, and then the water was azeotroped with the benzene on the rotovac. The crude residue was recrystallized from hot chloroform to yield 4.3 g: mp 107–108 °C; NMR ($CDCl_3$) δ 4.27 (s, CH_2S), 6.1 (s, NH_2), 7.45 (s, phenyl). Anal. ($C_9H_9N_4SCl$) (M_r 240.72) C, H, N.

2-(Arylthio)-5,7-dimethyl-s-triazolo[1,5-a]pyrimidines. General Procedure. The appropriate amount of 2-thio-5,7-dimethyltriazolo[1,5-a]pyrimidine (**9**) was suspended in water and dissolved by the addition of 20% sodium hydroxide dropwise, with stirring at 25 °C. The appropriate arylmethyl halide dissolved in methanol was then added, and the solution was stirred until a precipitate formed. The precipitate was filtered, washed with water, dried, and recrystallized from an appropriate solvent, as noted. Several examples are described in detail.

5,7-Dimethyl-2-(methylthio)-s-triazolo[1,5-a]pyrimidine (10a). A solution of 900 mg (5 mmol) of 5,7-dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (**9**) and 500 mg of potassium hydroxide, dissolved in 10 mL of H_2O, was stirred as 750 mg of methyl iodide was added. Within 10–15 min of stirring, a voluminous precipitate of white crystals formed. The mixture was stirred for another hour, and then the crystals were filtered, washed with distilled water, air-dried, and recrystallized from methanol–water to yield 500 mg of white needles, mp 154–155 °C. Anal. ($C_8H_{10}N_4S$) (M_r 194.28) C, H, N, S.

5,7-Dimethyl-2-[(p-chlorobenzyl)thio]-s-triazolo[1,5-a]pyrimidine (12b). To 100 mL of acetic acid was added 2.4 g (0.01 mol) of 3-[(p-chlorobenzyl)thio]-5-amino-1,2,4-triazole (**11b**). One gram of acetylacetone was added, and the solution was heated on a steam bath at 80–90 °C for 3 h and then allowed to stand overnight. The solution was colorless at first, then turned yellow, and finally became red and cloudy (greenish fluorescence). The acetic acid solution was then poured into water to give a milky emulsion, and the acetic acid was azeotroped off under reduced pressure at 70 °C (15 mm). The aqueous solution was evaporated to one-third the volume (75–80 mL), and the white precipitate was filtered. This material was washed well with water and recrystallized from ethanol–water (9:1) to yield 2.0 g of product. Two more recrystallizations gave an analytical sample: mp 136–137 °C; NMR (Me_2SO-d_6) δ 2.58 (s, CH_3), 2.72 (s, CH_3), 4.53 (s, CH_2S), 7.12 (s, C_6 H), 7.50 (s, phenyl protons), integrated 3:3:2:1:4. Anal. ($C_{14}H_{13}N_4ClS$) C, H, N.

5,7-Dimethyl-2-[(p-carboxybenzyl)thio]-s-triazolo[1,5-a]pyrimidine (12c). In a small flask, 1.8 g of 5,7-dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (**9**; 9.01 mol) was dissolved in a solution of 0.18 g of potassium hydroxide in 20 mL of water. Then, 1.8 g of p-(chloromethyl)benzoic acid was added, and the solution was stirred and heated on the steam bath at 60–70 °C for 10 min. The heat was removed, and stirring was continued for 45 min, at which time the temperature fell to 35 °C. Then 10–15 mL of glacial acetic acid was added dropwise, with stirring, until pH 7 was obtained, and a gummy precipitate formed. Chloroform was added, and with some heating on the steam bath, the gum eventually went into the organic layer. The heterogeneous solution was placed in a separatory funnel, and the organic layer was withdrawn, dried over Na_2SO_4, and evaporated (Na_2SO_4) to a viscous foam, which crystallized after 0.5-h trituration with ethanol, followed by cooling. Filtration and recrystallization from ethanol gave 1.80 g: mp 190–193 °C; NMR (Me_2SO-d_6) δ 2.6 and 2.7 (2 s, CH_3), 4.6 (s, CH_2S), 7.11 (s, C_6 H), 7.8 (s, phenyl protons), 11.6 (br s, COOH). Anal. Calcd. for $C_{15}H_{14}N_4O_2S$ (M_r 316.39): C, 56.94; H, 5.09; N, 17.70. Found: C, 56.91; H, 4.98; N, 17.63.

5,7-Dimethyl-2-[(4-pyridylmethyl)thio]-s-triazolo[1,5-a]pyrimidine (12h). In a small flask, 0.9 g of 5,7-dimethyl-2-thio-s-triazolo[1,5-a]pyrimidine (**9**; 0.005 mol) was dissolved in 10 mL of 20% NaOH solution. To this solution was added 0.7 g of 4-picolyl chloride hydrochloride (0.007 mol), and the solution turned deep red in color. Stirring was continued for 10 min at 25 °C, then 50 mL of $CHCl_3$ was added, and stirring was continued for another 30 min. The $CHCl_3$ layer was removed with a separatory funnel, dried over anhydrous sodium sulfate, and evaporated to yield 500 mg of **12h**.

The product was recrystallized from ethanol twice to give a pure sample: mp 143–145 °C; NMR (Me_2SO-d_6) δ 2.57 and 2.60 (2 s, CH_3 groups), 4.54 (s, CH_2S), 7.13 (s, C_6 H), 7.54 and 8.54 with coupling (2 s, J = 0.5 Hz, pyridine protons). Anal. Calcd for $C_{13}H_{13}N_5S$ (M_r 271.35): C, 57.54; H, 4.82; N, 25.81; S, 11.81. Found: C, 57.55; H, 4.75; N, 25.83; S, 11.69.

2-(Benzylthio)-5-methyl-7-hydroxy-s-triazolo[1,5-a]pyrimidine (13). A mixture of 10 g of 3-amino-5-(benzylthio)-1,2,4-triazole (**11a**), 6 g of ethyl acetoacetate 20 mL of ethanol, and 100 mL of glacial acetic acid was refluxed for 12 h. While the solution was cooling, the product precipitated as a white solid. After filtering, washing with cold ethanol and then with ether, and air-drying, 5.6 g of analytically pure product was obtained, mp 252–253 °C. Anal. ($C_{13}H_{10}H_4SO$) (M_r 270) C, H, N, S.

2-(Benzylthio)-5-methyl-7-chloro-s-triazolo[1,5-a]pyrimidine (14). Five grams of **13** was added to 250 mL of phosphorus oxychloride, and the solution was heated at reflux for 45 min, with stirring. The excess phosphorus oxychloride was then distilled off at 15 mm pressure, and the residual dark liquid, approximately 10 mL, was poured onto 250 g of crushed ice, with vigorous stirring. A thick, gummy precipitate was obtained, which was dissolved in methylene chloride. The organic solvent was washed with five successive portions of saturated sodium carbonate solution, and dried over sodium sulfate for 10 h. The methylene chloride solution was filtered through 50 g of basic alumina, and the alumina was washed with more methylene chloride. The combined solvent was evaporated to leave 3.5 g of a yellowish oil, which

solidified to yellow crystals upon the addition of petroleum ether. Recrystallization from chloroform–pentane gave white needles, mp 95–96 °C. Anal. ($C_{13}H_9N_4SCl$) C, H, N.

2-(Benzylthio)-5-methyl-7-thio-*s*-triazolo[1,5-*a*]pyrimidine (19). In a flask was placed 2.9 g of **14**, 3.2 g of sodium hydrosulfide hydrate, and 100 mL of ethylene glycol. The mixture was heated at 70–80 °C for 1 h, whereupon a solution occurred. This solution was poured into 250 mL of ice–water, and concentrated hydrochloric acid was added to adjust the pH to 1. A precipitate formed, which was filtered and washed with water, then resuspended in boiling water, and filtered hot, and the filtrate was cooled. The yellow crystals obtained were recrystallized from ethanol to give 2.7 g, mp 224–225 °C. Anal. ($C_{13}H_{12}N_4S$) C, H, N, S.

2-(Benzylthio)-5-methyl-7-(dimethylamino)-*s*-triazolo[1,5-*a*]pyrimidine (15a). In a small flask, a mixture of 3.0 g of **14** in 20 mL of ethanol was mixed with 7 mL of 40% dimethylamine. The reaction was exothermic. An immediate crystalline mass formed, but when the mixture was heated on a steam bath for 20 min, all the solid redissolved. After the mixture cooled to room temperature, the solid was filtered and washed with water and then suspended in boiling water, and ethanol was added to the point of clarity. The filtered solution gave 2.8 g of product. Recrystallization from ethanol–water gave a product, mp 140–142 °C. Anal. ($C_{15}H_{17}N_5S$) C, H, N, S.

General Procedure for the Preparation of 2-(Benzylthio)-5-methyl-7-(substituted-amino)-*s*-triazolo[1,5-*a*]pyrimidines (15b–g). A solution of 2-(benzylthio)-7-chloro-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (**14**; 2.88 g, 10 mmol) and the substituted amine (12.5 mmol) in 30 mL of absolute ethanol was heated at reflux for 3 h and then evaporated to dryness. The residue was washed with water and then recrystallized from aqueous ethanol to afford the pure products listed in Table II.

A solution of 2-(benzylthio)-7-hydrazino-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (**14**) was dissolved in warm dilute hydrochloric acid, and the solution was allowed to cool, which provided the dihydrochloride salt **15d** listed in Table II.

2-(Benzylthio)-6-carbethoxy-7-hydroxy-*s*-triazolo[1,5-*a*]pyrimidine (16). A mixture of 25 g (0.121 mol) of 3-amino-5-(benzylthio)-*sym*-triazole (**11a**) and 28.1 g (0.13 mol) of diethyl ethoxymethylenemalonate was added to a solution of 3 g of sodium metal previously dissolved in 250 mL of absolute ethanol. The solution was refluxed overnight, and then the ethanol was removed in vacuo. About 200 mL of 2 N HCl and 75 mL of methanol was added to the residue, and after chilling for 1 h, the product was filtered, washed with 50 mL of water, and dried. Recrystallization from ethanol–water gave 22.3 g of colorless crystals: mp 246–247 °C; NMR (Me_2SO-d_6) δ 1.28 (t, ethyl CH_3), 4.27 (q, ethyl CH_2), 4.48 (s, SCH_2), 7.4 (m, phenyl), 8.6 (s, C_5 H). Anal. ($C_{15}H_{14}N_4O_3S$) C, H, N.

2-(Benzylthio)-6-carbethoxy-7-chloro-*s*-triazolo[1,5-*a*]-pyrimidine (17). Approximately 20 g (0.605 mol) of **16** was added to 250 mL of phosphorus oxychloride. The mixture was refluxed for 2 h, then the excess phosphorus oxychloride was distilled off under vacuo, and the residual liquid was decomposed by pouring onto ice with good stirring. The aqueous solution was extracted with three 200-mL portions of ether, and the ether extract was washed with 300 mL of saturated sodium bicarbonate and then dried over anhydrous sodium sulfate. Evaporation of the ether gave 15.3 g (74%) of crude product. Recrystallization of **17** from heptane gave white crystals: mp 127–129 °C; NMR ($CDCl_3$) δ 1.43 (t, ethyl CH_3), 4.46 (q, ethyl CH_2), 4.51 (s, SCH_2), 7.35 (m, phenyl), 9.23 (s, C_5 H). Anal. ($C_{15}H_{13}N_4O_2SCl$) C, H, N.

2-(Benzylthio)-6-carbethoxy-7-thio-*s*-triazolo[1,5-*a*]pyrimidine (20). In a small flask was placed 1 g of sodium sulfide hydrate, 1 g (2.88 mol) of **17**, and 20 mL of ethanol. The mixture was heated at 55 °C with stirring, for 10 min, and then stirred for an additional 2 h at room temperature. To this mixture was added 70 mL of water and enough acetic acid to pH 5. The solution was chilled, and the precipitate was filtered and recrystallized from water–ethanol to yield 0.8 g (80%) of crystals: mp 133–136 °C dec; NMR ($CDCl_3$) δ 1.42 (t, ethyl CH_3), 4.5 (q, ethyl CH_2), 7.4 (m, phenyl), 9.2 (s, C_5 H). Anal. ($C_{15}H_{14}N_4O_2S_2$) C, H, N.

2-(Benzylthio)-6-carbethoxy-7-(*N*-morpholino)-*s*-triazolo[1,5-*a*]pyrimidine (26). A mixture of 1 g (2.88 mmol) of the corresponding chloro compound, 0.5 g (5.76 mmol) of morpholine, and 30 mL of absolute ethanol was heated at 55 °C for 10 min and then stirred at room temperature for 2 h. Then, 80 mL of water was added to the mixture, and the solution was chilled (refrigerator) overnight. The water was decanted the next day, and the gummy residue was recrystallized from methanol to give 0.8 g (70%) of white crystalline product: mp 92–94 °C; NMR (Me_2SO-d_6) δ 1.34 (t, ethyl CH_3), 3.61 (m, morpholine protons), 4.34 (q, ethyl CH_2), 4.48 (s, CH_2S), 7.38 (m, phenyl), 9.2 (s, C_5 H). Anal. ($C_{19}H_{21}N_5O_3S$) C, H, N.

2-(Benzylthio)-6-carbethoxy-7-(substituted-amino)-*s*-triazolo[1,5-*a*]pyrimidines (18a–c). The following general method was used to prepare compounds **18a–c** (Table IV). The precursor, **17**, was dissolved in ethanol and the amine or hydrazine was added. The solution was heated at 55 °C for 10 min, then stirred at room temperature for 1 h, and diluted with 70 mL of water, and the solid obtained was triturated, filtered, and recrystallized from the solvent indicated in Table IV.

2-(Benzylthio)-5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine (22a). A mixture of 8.24 g (0.04 mol) of 3-amino-5-(benzylthio)-1,2,4-triazole (**11a**),[19] 6.24 g (0.04 mol) of nonane-4,6-dione, and 50 mL of acetic acid was refluxed for 4 h. The solvent was distilled in vacuo, and the residue was then distilled to afford 10.5 g (77%) of the product, bp 295–297 °C (5 mm), which was recrystallized from heptane–acetone to give colorless needles, mp 59–61 °C. Anal. ($C_{18}H_{22}N_4S$) C, H, N.

5,7-Di-*n*-propyl-2-mercapto-1,2,4-triazolo[1,5-*a*]pyrimidine (21). A mixture of 4.68 g (0.03 mol) of nonane-4,6-dione, 3.48 g (0.03 mol) of 3-amino-5-thio-1,2,4-triazole (**8**), and 50 mL of glacial acetic acid was refluxed for 20 h. The reaction mixture was evaporated in vacuo, the residue was partly dissolved in ethanol, and an insoluble substance was filtered. The filtrate was evaporated in vacuo, and the residue was recrystallized from ethyl acetate–heptane to yield 4.3 g (57%) of **21** as light yellow crystals, mp 147–148 °C. Anal. ($C_{11}H_{16}N_4S$) C, H, N.

Preparation of the 2-(Aralkylthio)-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidines in Table III (22a,b, 24, and 25). A mixture of 2.36 g (0.01 mol) of 5,7-di-*n*-propyl-2-thio-1,2,4-triazolo[1,5-*a*]pyrimidine (**21**), 0.01 mol of the araalkyl halide, and a solution of 1 g of sodium hydroxide dissolved in 50 mL of water was stirred at room temperature for 20 h. The mixture was extracted with $CHCl_3$, and the organic layer was dried (Na_2SO_4) and evaporated in vacuo to yield a residue. Recrystallization of the residue from ethyl acetate afforded the pure product, **22a,b**, **24**, and **25**, listed in Table III.

Preparation of the 2-(Aralkylsulfonyl)-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidines in Table III (23a,b). A solution of 0.01 mol of 2-(aralkylthio)-5,7-di-*n*-propyl-1,2,4-triazole[1,5-*a*]pyrimidine (**22a** or **22b**) in 70 mL of $CHCl_3$ was cooled to 0–5 °C, and 4.0 g (0.02 mol) of 85% *m*-chloroperbenzoic acid was added in portions. The mixture was allowed to stand for 24 h at room temperature, and then the $CHCl_3$ was extracted with 3 × 50 mL of saturated sodium bicarbonate solution to remove unreacted *m*-chlorobenzoic acid. The $CHCl_3$ solution was washed with H_2O (separatory funnel), dried (Na_2SO_4), and evaporated in vacuo to yield an oil. The oil was chilled to 0 °C for 2 h, whereupon it solidified. The solid was recrystallized from *n*-heptane–acetone to afford the analytically pure products **23a** and **23b** listed in Table III.