Dialkyl Bicyclic Heterocycles With a Bridgehead Nitrogen as Purine Analogs Possessing Significant Cardiac Inotropic Activity

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A number of 5,7-dialkyl-*s*-triazolo[1,5-*a*]pyrimidines and 5,7-dialkylpyrazolo[1,5-*a*]pyrimidines and related heterocycles containing a bridgehead nitrogen have been prepared and studied as cardiovascular agents in the anesthetized dog. A number of these compounds have exhibited significant inotropic activity with little effect on heart rate. Especially active were 5,7-dialkyl-2-amino or 2-alkylthio-*s*-triazolo[1,5-*a*]pyrimidines. In contrast, highly polar purine analogs in these ring systems compounds such as 5,7-di-*n*-propyl-2-benzylthio-1,3,4-thiadiazolo[3,2-*a*]pyrimidine bromide **45** containing a charge on the bridgehead nitrogen, were inactive. The detailed structure activity relationship of the dialkyl derivatives of related ring systems are discussed. The presence of certain ring nitrogen atoms are vital to potent *in vivo* activity, presumably due to specific enzyme binding at these sites. Several of the compounds studied, showed oral activity and are excellent candiates for further evaluation in man.

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Introduction.

Our interest in derivatives of cAMP and inhibitors of adenosine cyclic 3',5'-monophosphate (cAMP) phosphodiesterase as potential cardiovascular agents has been documented in several of our recent publications (1-4). Ischemic heart disease and its complications are by far the most common cause of death in the United States (5). The rapid decline in heart muscle contractility during ischemia is a major contributing factor to cardiac arrest. A good inotropic agent could be a useful drug to treat chronic or congestive heart failure. We have recently reported (2) that 5,7-di-*n*-propyl-2-benzylthio-1,2,4-triazolo[1,5-*a*]-pyrimidine **19** (Table 1), and the corresponding 2-benzylsulfonyl derivative **18** (Table 1) increase cardiac output 31.5% and 42.3% respectively when given intravenously at 10 mg/kg to anesthetized dogs. These results were achieved with essentially no increase in heart rate. The present study involves the report of various related bicyclic nitrogen heterocycles with a bridgehead nitrogen and the relationship of structure and inotropic acivity in dogs. The original lead came from 3-bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine, (6) **1** (Table 1), which showed an activity as a cAMP phosphodiesterase (PDE) inhibitor against the enzyme isolated from beef heart of 1.7 times that of theophylline in the same system (6). Thus **1** was 70% more effective as a PDE inhibitor aganist this heart enzyme then was theophylline. In anesthetized dogs 3-bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine **1** produced an immediate and moderately prolonged increase in cardiac output, superior to theophylline (8). When 3-bromo-5-methyl-7-*n*-propylpyrazolo[1,5-*a*]pyrimidine **9** was prepared and studied (7) as a PDE inhibitor of the enzyme isolated from bovine heart it showed an activity 6.5 times greater than theophylline as an inhibitor of the same enzyme (7). At 10 mg/kg/hour **9** gave an increase in cardiac output of 36.4% (average of 6 dogs) and increase in stroke volume of 15.5% (Table 1). This result, however, was accompanied by an increase in heart rate of 18.5%. When both alkyl groups were lengthened to *n*-propyl in 3-bromo-5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine (7), **3** (Table 1), in an average of 10 dogs at 10 mg/kg/hour, a cardiac output of 66.7% and a stroke volume of 32.5%, but was accompanied by a heart rate increase of 26.8%. Increasingly the alkyl groups of 5,7-di-*n*-butyl (7), compound **4** showed an increase up to 80.2% in cardiac output at 10 mg/kg/hour, which was accompanied by heart rate increase of 34.3% (Table 1). In an effort to find a related compound which would increase contractility without subsequent increase in heart rate, 3-carbethoxy-5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine **7** was prepared (7) and studied. Although **7** was the most potent PDE inhibitor against cAMP phosphodiesterase from beef heart (7) (9 X potency of theophylline), the maximum cardiac output at 10mg/kg/hour was only a 19.6% increase (Table 1). Introduction of a more polar group at position 3 such as carboxylic acid or sulfonate **8** also resulted in considerable loss of inotropic activity. 5,7-Di-*n*-propylpyrazolo[1,5-*a*]-pyrimidine **5** (7), proved to be an even more potent ino-

tropic agent than 3-bromo-5,7-di-*n*-propylpyrazolo[1,5-*a*]-pyrimidine **3** but still suffered from a substantial increase in heart rate. Introduction of a methyl group at position 2 to give a 2-methyl-5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine **39** gave a compound with greatly reduced *in vivo* inotropic potency as compared with 5,7-di-*n*-propylpyrazolo[1,5-*a*]-pyrimidine **5**. This surprising lessening of potency suggested a critical evaluation of other related bridgehead nitrogen heterocycles in an effort to obtain a better understanding of structure *in vivo* activity relationships of this class of heterocyclic compounds.

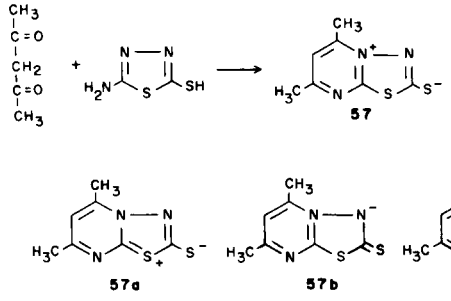
When the position of the dialkyl groups were altered as in 3-*n*-butyryl-4-*n*-propylimidazo[1,2-*c*]-as-triazine (9), all inotropic activity was lost (Table 1).

About this time in our program it became apparent from other studies in our laboratory (10) that the lower alkyl chains, *i.e.* methyl in various 3-halogeno-5,7-dialkyl-pyrazolo[1,5-*a*]pyrimidines gave compounds with strong antianxiety (CNS) effects and the longer alkyl chains, *i.e.* such as in 3-bromo-5,7-di-*n*-propylpyrazolo[1,5-*a*]-pyrimidine **3** (7) and 3-bromo-5,7-di-*n*-butylpyrazolo[1,5-*a*]-pyrimidine **4** (7) provided compounds with potent inotropic activity and lessened central nervous systems effects (10). This appeared to be somewhat general since 5,7-dimethyl-*s*-triazolo[4,3-*a*]pyrimidine **33** has a negative inotropic effect (Table 1).

The present report is an expanded effort to define more precisely the structural requirements for inotropic specificity and represents a major effort to prepare similar heterocycles with greater inotropic potency, low toxicity and with less tendency to increase heart rate.

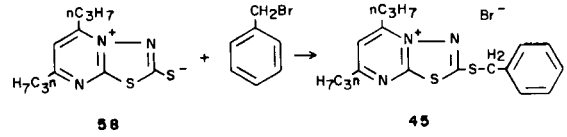
Chemistry.

5-Amino-2-thio-1,3,4-thiadiazole and pentane-2,4-dione were refluxed in the presence of a catalytic amount of piperidine to give 5,7-dimethyl-2-thio-1,3,4-thiadiazolo-[3,2-*a*]pyrimidine **57**.

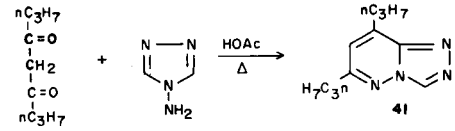


The heterocycle **57** is an interesting polar mesionic compound which could be polarized according to the following structures: **57, 57a, 57b, 57c**. Nonane-4,6-dione and 5-amino-2-thio-1,3,4-thiadiazole gave 5,7-di-*n*-propyl-2-thio-1,3,4-thiadiazolo[3,2-*a*]pyrimidine **58** which was alkylated with benzyl bromide to give 5,7-di-*n*-propyl-2-benzylthio-1,3,4-thiadiazolo[3,2-*a*]pyrimidine bromide **45**.

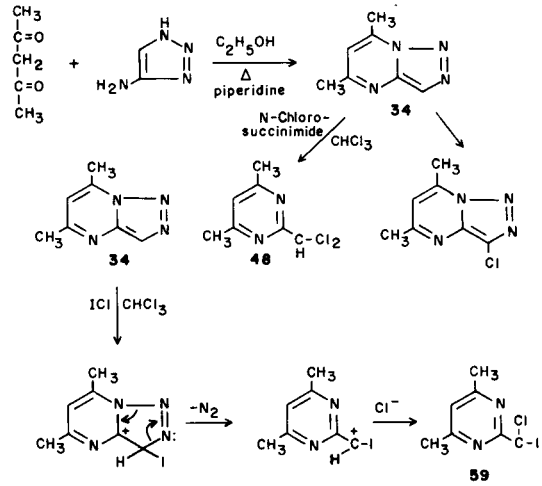
4-amino-1,2,3-triazole (12) was treated with pentane-2,4-dione in refluxing benzene and the water formed was removed azeotropically to give an 81% yield of 5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine **34**. Heptane-3,5-dione, 4-amino-1,2,3-triazole (12) and refluxing ethanol in the presence of a catalytic amount of piperidine gave 5,7-diethyl-1,2,3-triazolo[1,5-*a*]pyrimidine **35** in 51% yield. Similarly, 4-amino-1,2,3-triazole and nonane-4,6-dione provided a 50% yield of 5,7-di-*n*-propyl-1,2,3-triazolo[1,5-*a*]pyrimidine **36**.



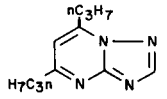
5,7-Di-*n*-propylimidazo[1,2-*a*]pyrimidine **40** was isolated as a hydrochloride salt in 42% yield from ether and dry hydrogen chloride after ring closure of 2-aminoimidazole [prepared from 2-aminoimidazole sulfate (13)] and nonane-4,6-dione in ethanol in the presence of some sodium hydroxide. Similarly, 5-amino tetrazole and nonane-4,6-dione in refluxing ethanol and a few drops of piperidine gave a 42% yield of 5,7-di-*n*-propyltetrazolo[1,5-*a*]-pyrimidine **38**. The synthesis of 5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine **22** was accomplished in 80% yield from 3-amino-1,2,4-triazole, nonane-4,6-dione and refluxing glacial acetic acid. Piperidine catalysis in refluxing ethanol did not give the desired compound. Similarly,



nonane-4,6-dione and 4-amino-1,2,4-triazole (14) in refluxing acetic acid gave 6,8-di-*n*-propyl-1,2,4-triazolo[4,3-*b*]-pyrimidine **41** in 60% yield. 5-Aminotetrazole, heptane-3,5-dione and refluxing glacial acetic acid gave 5,7-diethyltetrazolo[1,5-*a*]pyrimidine **37** in 73.5% yield.



When 5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine **34** was treated with *N*-chlorosuccinimide in an attempt to prepare 3-chloro-5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (analogous in structure to **1**) the desired compound was not obtained but a complex mixture resulted from which was isolated a small amount of 4,6-dimethyl-2-dichloromethylpyrimidine **48**. In an attempt to study this reaction, iodine monochloride was employed. 5,7-Dimethyl-*v*-triazolo[1,5-*a*]pyrimidine **34** and iodine monochloride in chloroform gave a 48.6% yield of 4,6-dimethyl-2-chloroiodomethylpyrimidine **59**. The formation of **59** is viewed to arise from the electrophilic attack of I^+ at carbon 3 which gives a an intermediate that readily loses nitrogen to give a carbo cation which reacts with chloride ion to give **58**. The reported inotropic activity of 5-methyl-7-diethylamino-*s*-triazolo[1,5-*a*]pyrimidine **51**



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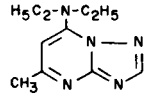

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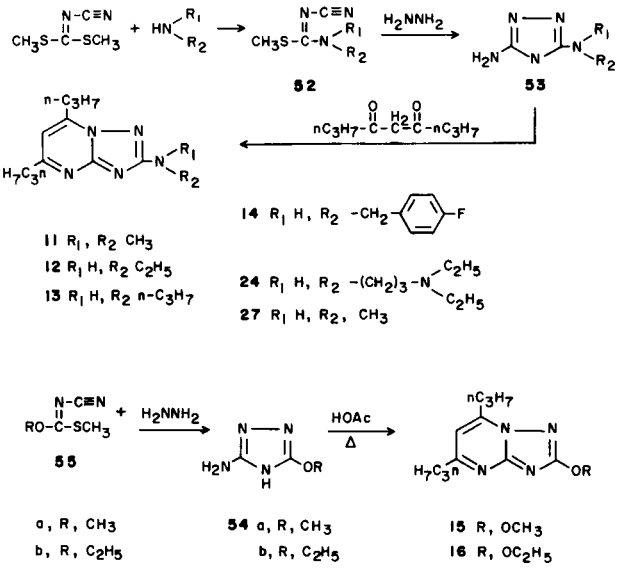
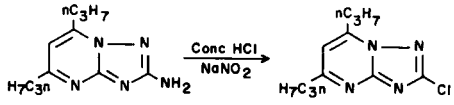
(trapidil or trapymin), (17,18) suggested further study of dialkyl derivatives in the 1,2,4-triazolo[1,5-*a*]pyrimidine ring system (2). The potent inotropic effect of 5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine **22** (Table 1), suggested further studies with varying substituents at position 2. Kreutzberger and Shuecker (19) have reported the synthesis 2-amino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **23** from nonane-4,6-dione and 3,5-diamino-1,2,4-triazole. The authors do not report any biological activity for this compound. In our laboratory on a mg/kg basis, **23** proved to be one of the most potent inotropic agents tested, showing a 45% increase in cardiac output at 1 mg/kg/hour (Table 1). In view of this data the synthesis of a series of 2-substitutedamino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidines was next studied. For the general synthesis of the requisite 3-amino-5-substitutedamino-1,2,4-triazole the procedure of Heitke and McCarty (20) was employed. Dimethylthiocyanoimidocarbonate was treated with the requisite amine to give a substituted-N^1-cyano-*S*-methyl isothiourea **52**. Treatment of **52** with hydrazine gives ring closure to the intermediate 3-amino-5-substitutedamino-1,2,4-triazole **53**. Ring closure of **53** with nonane-4,6-dione in refluxing glacial acetic acid gave the desired products **11-14, 24** and **27** in good yield.

2-Alkoxy-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidines **15** and **16** were prepared by ring closure of the requisite 3-amino-5-alkoxy-1,2,4-triazoles. The synthesis of 3-amino-5-methoxy-1,2,4-triazole **54a** has been reported by Heitke and McCarty (20). Synthesis of 3-amino-5-ethoxy-1,2,4-triazole **54b** was accomplished by a variation of this general procedure which involves treatment of the *O*-alkyl-*s*-methylcyanamide thiocarbonate **55** with hydrazine to give **54**. Ring closure of **54** with nonane-4,6-dione in



refluxing glacial acetic acid gave **15** and **16** respectively in good yield. Treatment of 2-amino-5-phenyl-1,2,4-triazole with nonane-4,6-dione in the presence of glacial acetic gave 2-phenyl-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **26** (Table 1) in good yield. Synthesis of 2-chloro-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **56** was accomplished by diazotization of 2-amino-5,7-di-*n*-proyl-*s*-triazolo[1,5-*a*]-pyrimidine (19) **23** in the presence of hydrochloric acid.



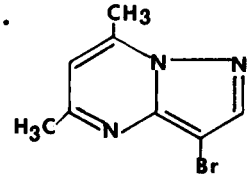
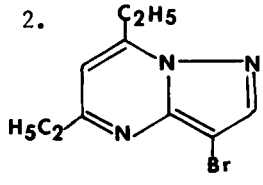
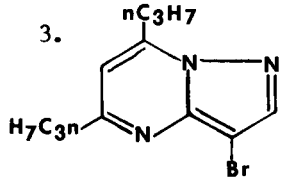
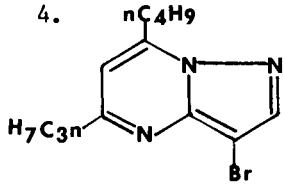
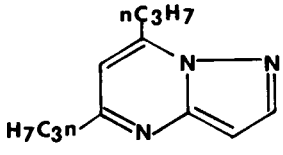
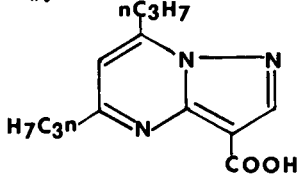
Nonane-4,6-dione and 3-amino-5-γ-hydroxypropyl-1,2,4-triazole (21) in refluxing glacial acetic acid gave a 75% yield of 2-(γ-acetoxy)propyl-5,7-di-*n*-propyl-*s*-triazolo-[1,5-*a*]pyrimidine **20**. It is worthy of note that under these conditions the γ-hydroxy group was acetylated. Methanolic ammonia removed the acetyl group to give 2-(γ-hydroxy)propyl-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **21**. In the ring closure of 3-amino-1,2,4-triazole-5-carboxylic acid (22) with acetylacetone piperidine in water was found to be superior to glacial acetic acid as a catalyst to give a 52% yield of 5,7-dimethyl-1,2,4-triazole[1,5-*a*]-pyrimidine-2-carboxylic acid **25**. Simiarly, 3-amino-1,2,4-triazole-5-carboxylic acid (22) as the sodium salt and nonane-4,6-dione in aqueous solution catalyzed by piperidine gave a 50% yield of 5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]-pyrimidine-2-carboxylic acid **17**. Similarly, 5,7-diethyl-*s*-triazole[1,5-*a*]pyrimidine **32** was preapred in 57% yield from heptane-3,5-dione and 3-amino-1,2,4-triazole.

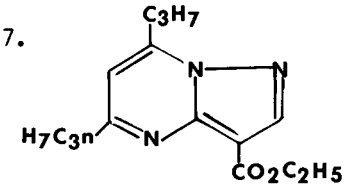
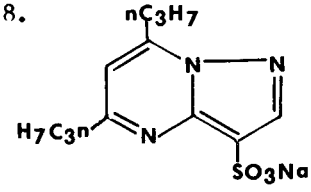
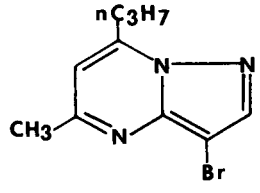
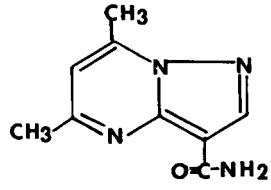
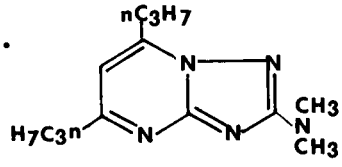
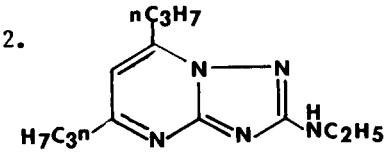
Several new pyrazolo[1,5-*a*]pyrimidines were prepared specifically for the present study. 3-Carbethoxy-5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine **7** (7) was heated in 1*N* potassium hydroxide to yield 5,7-di-*n*-propylpyrazolo-[1,5-*a*]pyrimidine-3-carboxylic acid **6**. In an additional ef-

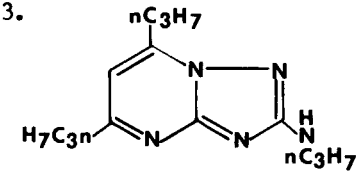
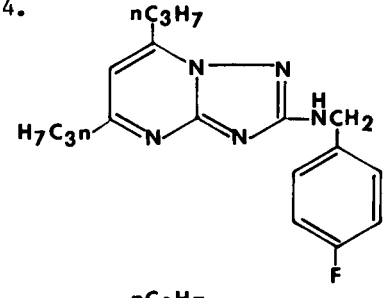
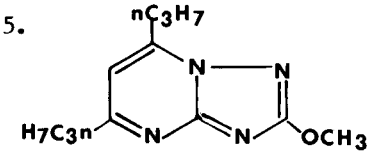
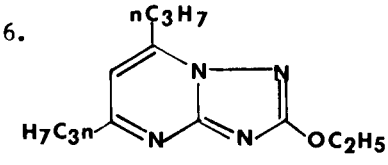
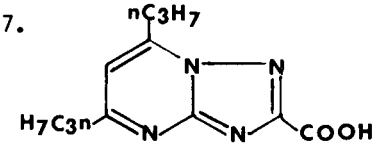
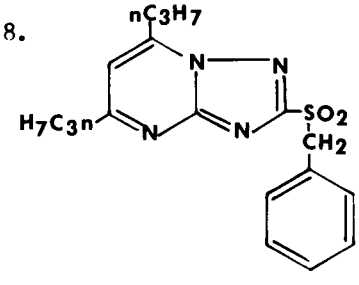
Table 1

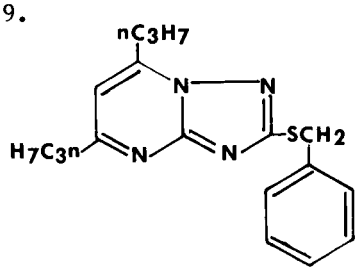
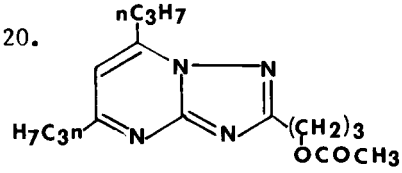
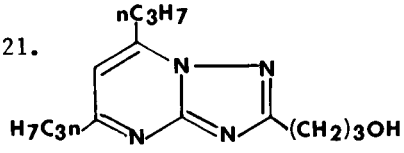
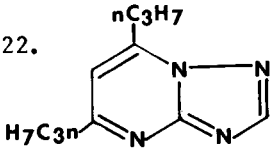
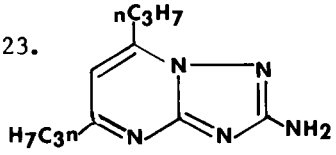
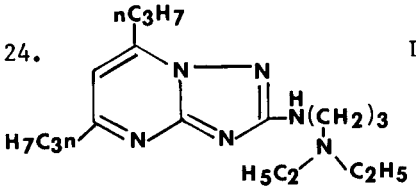
Inotropic Activity of Bridgehead Nitrogen Heterocycles

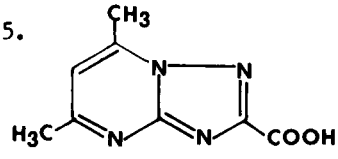
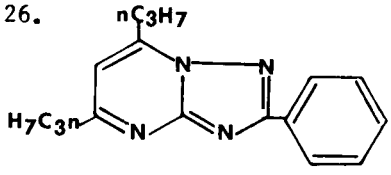
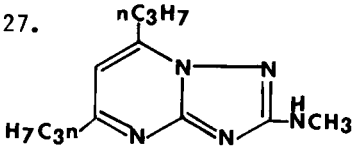
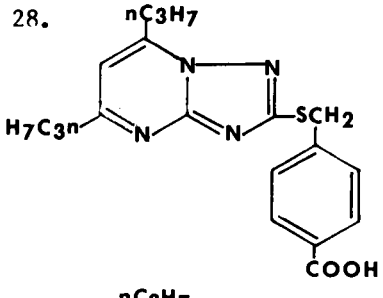
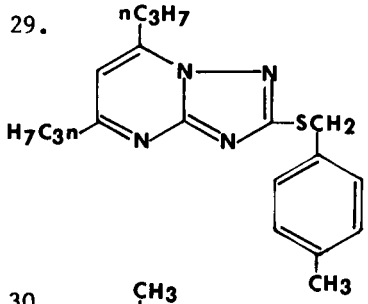
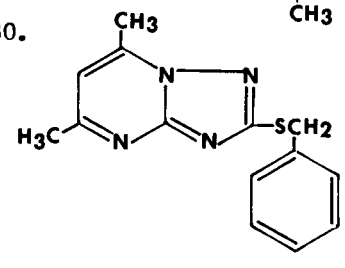
Percentage Change in Cardiac Output, Stroke Volume and Heart Rate in Mongrel Dogs

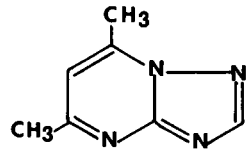
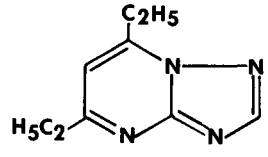
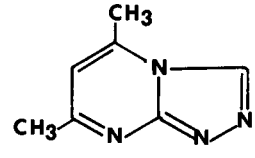
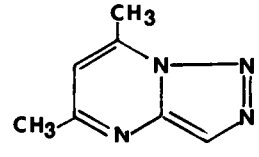
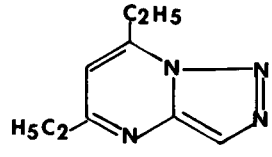
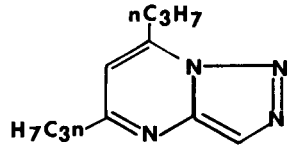
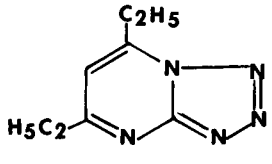
Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change			Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
				Cardiac Output	Heart Rate	Stroke Volume			
1.		DMSO	6	5.1	0.5	5.5	3.1	20	6
2.		DMSO	6	31.8	10.7	19.1	3.1	40	7
			6	37.1	32.2	22.9	10.0	60	
3.		DMSO	10	49.2	18.5	26.6	3.1	40	7
			10	66.7	26.8	32.5	10.0	60	
4.		DMSO	6	54.8	15.6	32.3	3.1	60	7
			6	80.2	34.3	30.5	10.0	60	
5.		DMSO	6	50.4	8.7	38.4	3.1	60	7
			6	71.6	22.0	40.5	10.0	60	
			10	72.8	23.1	41.9	10.0	60	
			1	25.5	16.0	18.0	31.0	60[a]	
6.		Saline 1%	6	24.3	8.0	16.2	10.0	60	
			6	10.6	4.6	6.2	31.0	40	

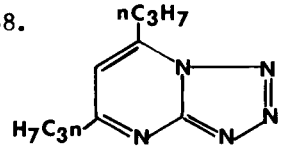
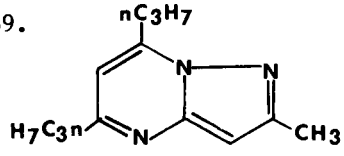
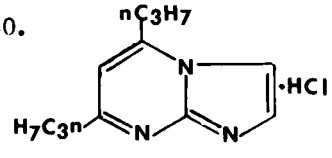
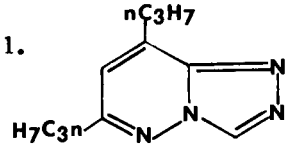
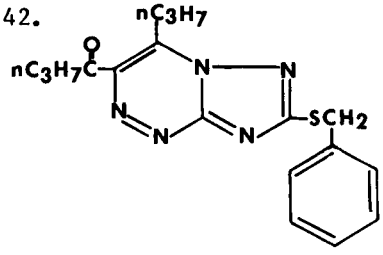
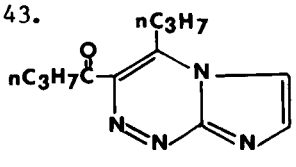
Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change: Cardiac Output	Heart Rate	Stroke Volume	Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
7.		DMSO	6	19.6	2.2	17.0	10.0	40	7
8.		Saline 1%	1	12.9	2.9	9.7	10.0	10	
			1	1.7	3.6	-2.1	10.0	20	
9.		DMSO	1	16.6	10.8	4.0	3.1	60	7
		DMSO	6	36.4	18.5	15.4	10.0	60	
10.		DMSO	6	15.1	13.6	1.1	10.0	40	6
11.		DMSO	10	35.1	14.0	18.6	1.0	60	
			10	66	20	38	3.1	60	
			2	80	38	29	10.0	60	
12.		DMSO	1	207	26	144.9	10.0	40	
			1	75.5	18.8	47.1	10.0	40	

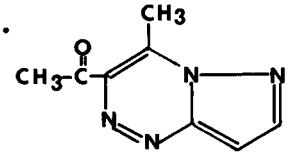
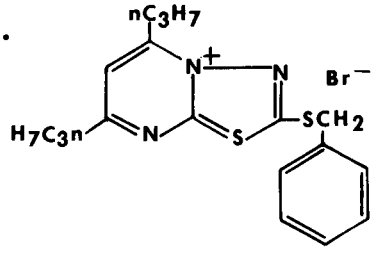
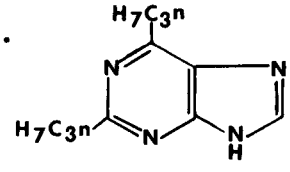
Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change: Cardiac Output	Heart Rate	Stroke Volume	Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
13.		DMSO	1	77.4	-2.4	82.3	10.0	40	
			1	71.5	11.7	56.7	10.0	60	
14.		DMSO	1	21.0	12.1	8.5	10.0	10	
			1	17.4	16.0	1.7	10.0	40	
15.		DMSO	1	21.7	21.6	0.8	10.00	10	
16.		DMSO	1	56.1	20.0	30.7	10.0	60	
17.		Saline 1%	10	25.0	.03	18.0	10.0	40	
			2	48.0	7.2	40.0	31.0	20	
18.		DMSO	6	35.6	0.2	34.7	10.0	40	2

Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change: Cardiac Output	Heart Rate	Stroke Volume	Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
19.		DMSO	5	31.5	0.0	34.4	10.0		2
20.		DMSO	5	55.2	6.5	50.6	10.0	40	
21.		DMSO	3	-15.0	3.0	-13.7	10.0	60	
22.		DMSO	10	47.9	9.4	34.7	3.1	40	
			10	61.7	12.2	44.0	10.0	60	
23.		DMSO	10	45.3	15.7	20.7	1.0	40	
			10	104.3	31.2	58.3	3.1	60	
24.		DMSO	1	-46.6	-35.5	-16.7	10.0	60	
			1	- 8.6	-21.2	16.2	3.1	60	

Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change: Cardiac Output	Heart Rate	Stroke Volume	Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
25.		Saline 1%	1	27.6	16.0	10.0	10.0	20	
26.		DMSO	1	43.6	23.1	10.5	10.0		
27.		DMSO	10	84.1	23.5	48.6	3.1	40	
		DMSO	10	42.7	10.5	28.8	3.1	40	(a)
		DMSO	10	51.8	20.0	26.9	1.0	40	
28.		Saline 1%	6	27.0	-8.1	39.0	10.0	60	25
29.		DMSO	1	34.3	-2.8	38.0	10.0	60	25
30.		DMSO	1	-1.0	7.0	7.0	10.0	-	25

Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change			Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
				Cardiac Output	Heart Rate	Stroke Volume			
31.		DMSO	1	-34.0	-9.7	-26.8	10.0	60	24
32.		DMSO	1	3.4	-3.2	7.6	10.0	10	
33.		DMSO	1	-12.2	-5.8	17.7	10.0	20	11
			1	-18.8	-9.7	-3.5	10.0	60	
34.		DMSO	1	0.02	7.1	-5.5	10.0	10	
35.		DMSO	1	10.6	7.9	2.4	10.0	10	
36.		DMSO	2	54.4	13.6	33.8	10.0	35	
37.		DMSO	1	18.7	2.9	15.8	10.0	60	

Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change Cardiac Output	Heart Rate	Stroke Volume	Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
38.		DMSO	6	28.4	9.4	17.4	3.1	60	
			10	45.8	7.4	35.6	10.0	40	
			1	20.0	5.0	15.0	3.0	20	(a)
39.		DMSO	6	41.0	11.7	27.1	10.0	40	
40.		Saline 1%	6	19.3	5.0	13.2	10.0	60	
41.		DMSO	1	79.1	15.4	50.6	10.0	20	
			1	60.2	19.4	39.1	10.0	60	
42.		DMSO	1	29.5	0.0	30.4	10.0	60	9
43.		DMSO	1	-19.5	6.7	-24.7	10.0	40	9

Compound No.	Nitrogen Heterocycle	Vehicle	No. of Dogs	Maximal % Change Cardiac Output	Heart Rate	Stroke Volume	Dose Mg/Kg/Hr	Time of max C.O.	Ref for Syn
44.		DMSO	1	-4.8	-3.7	-1.5	10.0	20	9
45.		DMSO	1	-36.4	-6.9	-31.6	10.0	60	
46.		DMSO	1	11.6	25.0	-10.7	10.0	20	(b)

(a) Intragastric administration--either by intubation or by direct injection into the stomach.

(b) K. W. Ehler, R. B. Meyer, Jr. and R. K. Robins, synthesis unpublished.

fort to prepare derivatives of greater solubility, 5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine (7) was treated with fuming sulfuric acid at room temperature to give an 80% yield of 5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine-3-sulfonate (sodium salt). Nonane-4,6-dione and 3-amino-5-methylpyrazole (23) was condensed in the presence of piperidine to give a 54% yield of 5,7-di-*n*-propyl-2-methylpyrazolo-[1,5-*a*]pyrimidine **39**.

Heterocyclic Structure and Inotropic Activity in Dogs.

Studies with the 3-bromo-5,7-dialkylpyrazolo[1,5-*a*]-pyrimidines (Table 1) showed that lengthening the alkyl side chains increased cardiac output. However, 3-bromo-5,7-di-*n*-butylpyrazolo[1,5-*a*]pyrimidine **4** also showed significant increase in heart rate. It was therefore decided to study various analogs with di-*n*-propyl side chains. Studies with 5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine **5**, unsubstituted at position 3, showed at 3.1 mg/kg/hour greater than 50% in cardic output with an increase of only 8.7% in heart rate. It appeared that the bromine at carbon 3 might be increasing heart rate (compare **3** *vs* **5**). In an attempt to study a more soluble derivative, 5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine carboxylic acid **6** was prepared and studied. Although **6** was soluble in 1% saline, considerable potency was lost compared to the parent heterocycle **5**. The corresponding ethyl ester **7** was equally less active. The more polar 5,7-di-*n*-propylpyrazolo[1,5-*a*]-pyrimidine-3-sulfonate **8** was almost devoid of inotropic activity. The introduction of a methyl substituent into position 2 (compound **39**) definitely reduced the inotropic potency as compared to the parent heterocycle **5**.

In examining similarly positioned di-*n*-alkyl derivatives

of other ring systems it is noteworthy that 5,7-di-*n*-propylimidazo[1,2-*a*]pyrimidine **40** was considerably less active than **5**. On the other hand, 6,8-di-*n*-propyl-1,2,4-triazolo[4,3-*b*]pyridazine **41** appeared to be more potent than **5** with a significant lowering of heart rate. 5,7-Di-*n*-propyl-1,2,3-triazolo[1,5-*a*]pyrimidine **36** which could be viewed as the exchange of a nitrogen for the C_2 carbon of **5**, retained most of the potency of **5** but was definitely less active. It is interesting to note that the increase in length of the 5,7-dialkyl groups from the dimethyl compound **34**, to diethyl, compound **35**, to di-*n*-propyl in **36**, showed a similar increase in potency as had been observed in the pyrazolo[1,5-*a*]pyrimidine series. The corresponding 5,7-di-*n*-propyltetrazolo[1,5-*a*]pyrimidine **38** would appear to be definitely less active at diminished doses (3.1 mg/kg/hour) than the corresponding pyrazolo[1,5-*a*]pyrimidine, **5**. Most interesting, however, was the activity of 5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine **22** which exhibited potency essentially equivalent to 5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine **5** but at 10 mg/kg/hour showed a definite lowering of the heart rate as compared to **5**. This exciting finding suggested that dialkyl derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine should be investigated in more detail. It is interesting to note that 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine **31** (24) and the corresponding 5,7-diethyl derivative **32** are definitely less active than **22**. The previously reported (19) 2-amino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **23** exhibited a most remarkable inotropic potency even at 1 mg/kg/hour of 45.3% increase in cardiac output with a heart rate increase of 15.7% (Table 1). 2-Methylamino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **27** exhibits a cardiac output increase of 51.8% at 1 mg/kg/hour with an increase of 20% in heart rate. 2-Ethylamino-5,7-di-*n*-propyl-*s*-triazolo-[1,5-*a*]pyrimidine **12** was similarly active. 2-Dimethylamino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **11** was about the same potency as **23**. Other 2-substituted amino derivatives such as **13** and **14** did not appear superior to **23**, **27** and **11**. The 2-(diethylamino-*n*-propylamino)-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine, **24**, showed a decidedly negative effect on cardiac output and heart rate. Other substituents studied at the 2-position were methoxy and ethoxy, compounds **15** and **16** respectively, which resulted in compounds of lesser potency. 5,7-di-*n*-propyl-*s*-triazolo-[1,5-*a*]pyrimidine-2-carboxylic acid **17** was less active than **23** and required approximately 30 times the dosage to exhibit a similar inotropic effect. Substituents such as 2-(γ-acetoxypropyl), compound **20**, and 2-(γ-hydroxypyropyl), compound **21**, were also studied. The polar hydroxyl function eliminated the inotropic effect. Introduction of the benzylthio substituent into the 2-position, 2-benzylthio-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]-pyrimidine **19** (2) provided a compound with 35% increase in cardiac output and no increase in heart rate (2). The corresponding sulfone **18** was even more active, with no increase in heart rate (2). 2-*p*-tolylbenzylthio-5,7-di-*n*-propyl-*s*-triazolo-[1,5-*a*]pyrimidine **29** (25) was similar in activity to **19**. Again, introduction of the carboxylic acid group in place of the methyl group of **29** gave compound **28** which was definitely less active. It is of interest that when the 5,7-dialkyl groups were methyl, as in 5,7-dimethyl-2-benzylthio-*s*-triazolo-[1,5-*a*]pyrimidine **30** (25) the intropic effect had virtually disappeared. Replacement of phenyl in position 2 in place of benzylthio in compound **19** gave compound **26**, 2-phenyl-5,7-di-*n*-propyl-*s*-triazolo-[1,5-*a*]pyrimidine, which showed similar cardiac output but also stimulated heart rate by 23.1%. Most interesting is the exchange of the nitrogen 3 for sulfur in compound **45**, 5,7-di-*n*-propyl-2-benzylthio-1,3,4-thiadiazolo[3,2-*a*]-pyrimidine hydrobromide which showed a definite negative effect on cardiac output. This could be due to the ionic nature of the analog.

The relative change of position of alkyl groups such as in compounds **43** and **44** also resulted in loss of inotropic activity. It is of interest, however, that the presence of the benzylthio substituent in 2-benzylthio-6-*n*-butyryl-7-*n*-propyl-*s*-triazolo[1,5-*c*]-1,2,4-triazine **42** (9) does appear to retain good inotropic activity with no increase in heart rate. The superiority of the dialkylheterocyclic analogs with a bridgehead nitrogen was noteworthy since 2,6-di-*n*-propylpurine **46** was only weakly active with considerable increase in heart rate noted.

Although most of the heterocycles were administered by slow intravenous infusion several compounds were administered by intragastric injection to demonstrate oral activity. It is interesting to note that 5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine **5** did show a significant effect administered by the latter route. Similarly, 5,7-di-*n*-propyltetrazolo[1,5-*a*]pyrimidine **38** showed an inotropic

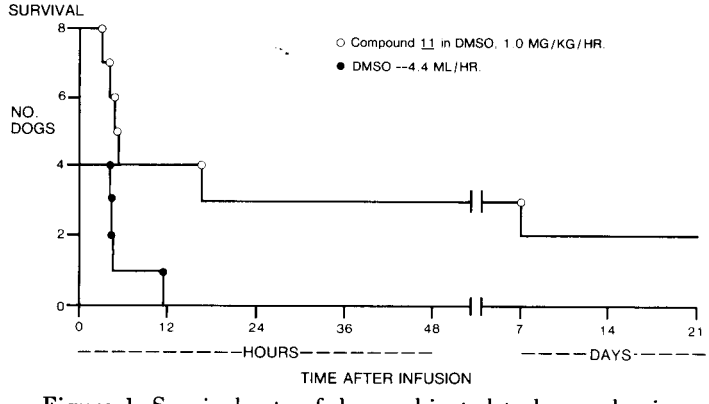


Figure 1. Survival rate of dogs subjected to hemorrhagic shock and treated with dimethylsulfoxide (DMSO, vehicle control) and 2-Dimethylamino-5,7-di-*n*-propyl-*s*-triazolo-[1,5-*a*]pyrimidine **11**. Vehicle or vehicle containing the compound was started 15 minutes following reinfusion of shed blood. Intravenous treatment was continued for 2 hours.

effect when administered intragastrically at 3 mg/kg/hour similar to intravenous infusion at the same level. These data suggest that the more active compounds (Table 1) should exhibit significant oral activity since at least some of these heterocycles are readily absorbed from the stomach. 2-Dimethylamino-5,7-di-*n*-propyl-*s*-triazolo-[1,5-*a*]pyrimidine **11** was also studied in the treatment of hemorrhagic shock in dogs. Although control animals did not survive beyond 12 hours; the intravenous infusion of **11** at 1 mg/kg/hour over a 2-hour period gave a survival of 4 out of 8 dogs for 18 hours, with 3 dogs surviving one weak and 2 animals surviving over 3 weeks (Figure 1).

In this animal model the hemorrhagic shock is similar to that induced in the human by blood loss. Thus an agent for treatment of such shock could prove useful since 15% of patients who suffer a myocardial infraction lapse into shock, of which 80% do not survive (27). Several of the 2-substituted-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidines described in the present study would appear to be excellent candidates for clinical evaluation. Of particular interest is the inotropic potency of 2-dimethylamino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine **11** which shows a 35% increase in cardiac output at 1.0 mg/kg/hour. The corresponding 2-*n*-propylamino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]-pyrimidine **13** at 10 mg/kg/hour showed a 77% increase in cardiac output with no significant increase in heart rate.

Although these heterocycles were originally prepared as inhibitors of cAMP phosphodiesterase (1-4, 10) there is no direct evidence to support the concept that this is indeed the mechanism of the inotropic activity *in vivo*. The active compounds could be binding at an adenosine receptor site, possibly "A_2," which could stimulate the activity of adenylcyclase and raise the level of cAMP in the heart by this mechanism. For further information on adenosine receptors the reader is referred to a number of recent reviews (26-28). Progress in the separation of various physiological effects of theophylline and caffeine *via* certain carbon substituted bridgehead nitrogen heterocycles has recently been reviewed (29). Perhaps such specificity may occur *via* specific binding to different adenosine receptors which may have separate structural requirements depending on the cell or tissue (28). These bridgehead nitrogen heterocycles resembling the purine ring could bind either as agonists or antagonists to adenosine receptors, thus the mechanism of such inotropic activity remains to be elucidated.

EXPERIMENTAL

The pmr spectra in deuteriochloroform and dimethylsulfoxide were obtained on a Hitachi Perkin-Elmer R20A Spectrometer and chemical shifts are reported relative to TMS as internal standard. Ultraviolet spectra in methanol were recorded on a Perkin-Elmer 202 Spectrometer. Infrared spectra in potassium bromide pellets were obtained on a Perkin-Elmer 257 Spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. All melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Woelm silica gel and silica gel plates were used for column chromatography and tlc respectively.

5,7-Di-*n*-propylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid, **6**.

Three ml of 0.05 *M* potassium hydroxide was added to 40 ml of water and the solution added to a suspension of 14.0 g of 5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester (7), **7**, in 200 ml of ethanol. The solution was heated in an open beaker for 2.4 hours. The *p*H gradually changed from *p*H 11 to *p*H 8 and the volume was reduced to 50 ml and cooled. White plates of the potassium salt of **6** separated and were filtered and washed with ethanol. The salt was added to hot water and the boiling solution acidified with 6*N* hydrochloric acid to give 3.3 g of **6**, mp 203-205°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.15; H, 6.88; N, 17.0. Found: C, 63.30; H, 6.91; N, 16.78.

5,7-Di-*n*-propylpyrazolo[1,5-*a*]pyrimidine-3-sulfonate, Sodium Salt, **8**.

5,7-Di-*n*-propylpyrazolo[1,5-*a*]pyrimidine (7) (2.0 g) was added to fuming sulfuric acid (10 ml) and the mixture was stirred at room temperature for one hour. It was poured on ice (~100g) and neutralized with saturated soldium bicarbonate solution. The aqueous solution was evaporated to dryness, and the residue dissolved in methanol and filtered. Evaporation of methanolic solution gave white crystals of the product, 2.3 g (80%) recovered from methanol, dec 183-185°; uv (methanol): λ max 228 nm; nmr (deuterium oxide): δ 1.0 (t, 6H, CH_3), 1.5-2.15 (m, 4H, $-CH_2-$), 2.95 (t, 4H, $-CH_2-$), 6.95 (s, 1H, CH), 8.55 (s, 1H, CH).

Anal. Calcd. for $C_{12}H_{16}N_3O_3S$ Na: C, 47.20; H, 5.28; N, 13.76. Found: C, 47.5; H, 5.42; N, 13.4.

2-Dimethylamino-5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine, **11**.

Nonane-4,6-dione (3.9 g, 25 mmoles) was added to a solution of 3-amino-5-dimethylamino-2,3,4-triazole (20) (3.2 g, 25 mmoles) in glacial acetic acid (80 ml). The mixture was refluxed for 40 hours and acetic acid was removed under reduced pressure. The residue was dissolved in methylene chloride (100 ml), washed with saturated sodium bicarbonate (2 × 50 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in methanol, treated with charcoal (4 g) and crystallized by adding water to give yellowish crystals (2.2 g, mp 64-65°; uv (methanol): λ max 231 and 322 nm; ir (potassium bromide): 3400, 2640, 2870, 1550 (broad s); 1520, 1470, 1430, 1415, 1360, 1305, 1285, 1255, 1185, 925, 815 and 775 cm^{-1}; nmr (deuteriochloroform): δ 0.98 (t, 3H), 1.05 (t, 3H), 1.6-2.1 (m, 4H), 2.6-3.1 (m, 4H), 3.18 (s, 6H), 6.52 (s, 1H).

Anal. Calcd. for $C_{13}H_{21}N_5$: C, 63.12; H, 8.56; N, 28.32. Found: C, 63.19; H, 8.53; N, 28.00.

5,7-Di-*n*-propyl-2-ethylamino-*s*-triazolo[1,5-*a*]pyrimidine, **12**.

Dimethylcyanimidothiocarbonate and ethyl amine gave *N*-ethyl-*N'*-cyano-*s*-methylisothiourea mp 160° according to the general procedure of Heitke and McCarty (20). To 70 ml of acetonitrile was added 14 g of *N*-ethyl-*N'*-cyano-*s*-methylthioisothiourea. Five g of hydrazine (98%) was added dropwise at room temperature and the resulting solution stirred at room temperature for an additional 18 hours after final addition. The reaction mixture was cooled and filtered to give 9.5 g (74%) yield of 3-amino-5-ethylamino-1,2,4-triazole, mp 116-118° which was added to 70 ml of glacial acetic acid to which had been added 11.5 g of nonane-4,6-dione and the mixture refluxed for 7 hours. The excess acetic acid was removed *in vacuo* and the residue dissolved in 500 ml of methylene chloride. The methylene chloride solution was washed with a small amount of dilute aqueous sodium hydroxide and then water (3 × 200 ml). The methylene chloride was then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a dark solid residue. This residue was chromatographed on an alumina column (300 g) and eluted with methylene chloride (500 ml). The eluate was concentrated *in vacuo* and the yellow solid washed with diethyl ether to leave white cubic

crystals, yield 4.7 g of **12**. A small amount was then recrystallized from ethyl acetate to give white plates, mp 126-127°.

Anal. Calcd. for $C_{13}H_{21}N_5$: C, 63.12; H, 8.56; N, 28.32. Found: C, 63.14; H, 8.49; N, 28.27.

5,7-Di-*n*-propyl-2-*n*-propylamino-*s*-triazolo[1,5-*a*]pyrimidine, **13**.

Dimethylcyanamidodithiocarbonate and propylamine gave *N*-*n*-propyl-*N'*-cyano-*s*-methylisothiourea, mp 112-114°, according to the general procedure of Heitke and McCarty (20). To a suspension of 16.0 g of *N*-*n*-propyl-*N'*-cyano-*s*-methylisothiourea in 100 ml of acetonitrile was added 5.0 g of 98% hydrazine dropwise at room temperature and the stirring was continued overnight at room temperature. After cooling the reaction mixture, the resulting precipitate was collected and washed with ether to give 6.6 g of white plates of 3-amino-5-*n*-propylamino-1,2,4-triazole, yield 7.5 g (53%) mp 145-147°; nmr (DMSO-d_6): δ 12.87 (d, 1), 5.65 (d, 1), 5.28 (d, 2) 3.03 (q, 2) 1.5 (m, 2) 0.90 (t, 3). This product (6.6 g) was added to 7.4 g of nonane-4,6-dione dissolved in 70 ml of glacial acetic acid and the solution was refluxed for 10 hours and treated as for the preparation and isolation of **12** to give 9.9 g of **13** as yellow cubic crystals, mp 119-121°. Recrystallization of **13** from ethyl acetate using charcoal gave white needles mp 119-121°C.

Anal. Calcd. for $C_{16}H_{23}N_5$: C, 64.33; H, 8.87; N, 26.80. Found: C, 64.50; H, 8.65; N, 26.78.

5,7-Di-*n*-propyl-2-*p*-fluorobenzylamino-*s*-triazolo[1,5-*a*]pyrimidine, **14**.

To 40 ml of glacial acetic acid was added 1.4 g of 3-amino-5-*p*-fluorobenzylamino-1,2,4-triazole (**53**, R_1 = H, R_2 = *p*-fluorobenzyl) and 2.0 g of nonane-4,6-dione and the solution was heated under reflux for 16 hours. The excess acetic was removed *in vacuo* and the oily residue chromatographed on a silica gel column and eluted with chloroform. The first 300 ml of eluate was collected and evaporated to give 2.1 g of **14** as white needles. Recrystallization from benzene-petroleum ether gave a product, mp 103-104°.

Anal. Calcd. for $C_{18}H_{22}FN_5$: C, 66.03; H, 6.77; N, 21.39. Found: C, 66.15; H, 6.83; N, 21.58.

5,7-Di-*n*-propyl-2-methoxy-*s*-triazolo[1,5-*a*]pyrimidine, **15**.

To 70 ml of glacial acetic acid was added 8.0 g of 3-amino-5-methoxy-1,2,4-triazole (20) and 11.0 g of nonane-4,6-dione and the solution refluxed for 7.5 hours. The excess acetic acid was removed *in vacuo* and the oily residue dissolved in 900 ml ethyl acetate and washed with dilute aqueous sodium hydroxide to remove the unreacted nonane-4,6-dione. The ethyl acetate was then washed twice with 300 ml of water and dried over anhydrous magnesium sulfate. Evaporation of the ethyl acetate *in vacuo* gave an oily residue which was extracted with boiling petroleum ether (60-70°). Concentration of the petroleum ether and cooling gave 5.8 g of **15** as crystals, mp 39-40°.

Anal. Calcd. for $C_{12}H_{18}ON_4$: C, 61.51; H, 7.74; N, 23.91. Found: C, 61.53; H, 7.68; N, 23.88.

5,7-Di-*n*-propyl-2-ethoxy-*s*-triazolo[1,5-*a*]pyrimidine, **16**.

This compound was prepard from 6.5 g of 2-amino-5-ethoxy-1,2,4-triazole (20), (mp 118°) and 7,8 g of nonane-4,6-dione dissolved in refluxing glacial acetic acid as for the preparation and work-up of **15**. The hot petroleum ether extract was cooled in dry ice and acetone to yield crystals which were collected cold and rapidly transferred to another container to give 8.5 g of **16** which gradually melted at room temperature.

Anal. Calcd. for $C_{13}H_{20}ON_4$: C, 62.87; H, 8.11; N, 22.56. Found: C, 62.91; H, 7.96; N, 22.50.

5,7-Di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine-2-carboxylic Acid, **17**.

A suspension of 3-amino-1,2,4-triazolo-5-carboxylic acid (12.8 g, 0.1 mole) in water (100 ml) was neutralized to *p*H 7.2 with 2.5 *N* sodium hydroxide (about 30 ml). Nonane-4,6-dione (15.6 g, 0.1 mole) and piperidine (0.2 ml) was added to the clear solution and the mixture was refluxed for 16 hours. The solution was cooled, filtered, and the *p*H adjusted to 2.0 with 2*N* hydrochloric acid (about 40 ml). The solution was kept in the refrigerator and the crystals which separated were filtered, washed with cold water and dried under vacuum to give **17** as white crystals: 12.5 g (50%), mp 159-160°.

Anal. Calcd. for $C_{12}H_{16}N_4O_2$: C, 58.04; H, 6.49; N, 22.47. Found: C, 58.01; H, 6.76; N, 22.70.

2-γ-Acetoxypropyl-5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine, **20**.

Nonane-4,6-dione (10.9 g) was added to a solution of 3-amino-5-γ-hydroxypropyl-1,2,4-triazole (21) (10.0 g) in glacial acetic acid (100 ml). The mixture was refluxed for 40 hours and the solvent (acetic acid) was then removed under reduced pressure. The residue was distilled under vacuum to give **20** as a colorless liquid, 16.1 g (75%), bp 210-212/1 mm; uv (methanol): γ max 219 and 268 nm; ir (potassium bromide): 2955, 2930, 2870, 1743, 1620, 1550, 1475, 1420, 1388, 1370, 1240 and 1040 cm^{-1}; nmr (deuteriochloroform): 1.0 (t, 3H, CH_3), 1.05 (t, 3H, CH_3), 1.65-2.35 (m, 6H, $-CH_2-$), 2.05 (s, 3H, CH_3CO), 2.7-3.25 (m, 6H, $-CH_2-$), 4.2 (t, 2H, $-CH_2O-$), 6.72 (s, 1H, -CH-), m/e 304. The product slowly solidified and could be recrystallized from ether to give a mp 36-37°.

Anal. Calcd. for $C_{16}H_{24}N_4O_2$: C, 63.16; H, 7.89; N, 18.42. Found: C, 63.20; H, 7.96; N, 18.34.

2(γ-Hydroxypropyl)-5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine, **21**.

Methanol (200 ml) was saturated with ammonia at 0° for 1.5 hours. To this solution was added 13.0 g of 2-(γ-acetoxypropyl)-5,7-di-*n*-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine **20** and the mixture was allowed to come to room temperature (25°) in a pressure bottle for 40 hours. The solvent was then evaporated *in vacuo* and the product was sublimed to remove acetamide, followed by distillation *in vacuo* to yield 8.75 g (78%) of a colorless oil **21**, bp 217-218°/1 mm.

Anal. Calcd. for $C_{14}H_{22}N_4O$: C, 64.09; H, 8.45; N, 21.35. Found: C, 65.19; H, 9.20; N, 21.55.

5,7-Di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine, **22**.

To 50 ml of ethoxyethanol was added 4.2 g of 3-amino-1,2,4-triazole, 7.8 g of nonane-4,6-dione and 2 drops of piperidine. The solution was refluxed 10 hours and the solvent evaporated to yield a yellowish oil. The oil was then distilled at 2 mm to yield 4.5 g of colorless product **22** bp 178-188°/2 mm.

Anal. Calcd. for $C_{11}H_{16}N_4$: C, 64.67; H, 7.89, N, 27.43. Found: C, 64.64; H, 7.73; N, 27.91.

5,7-Di-*n*-propyl-2-(*N,N*-diethylaminopropylamino-*s*-triazolo[1,5-*a*]pyrimidine, **24**.

To 80 ml of glacial acetic acid was added 16.8 g of 3-amino-5-*N,N*-diethylaminopropylamino-1,2,4-triazole and 11 g of nonane-4,6-dione and the solution refluxed for 8 hours. Removal of the excess acetic acid was accomplished *in vacuo* and the residue dissolved in 50 ml of water and the *p*H adjusted to 10 with sodium hydroxide. This solution was extracted with methylene chloride and then poured onto a column of 500 g of Woelm neutral alumina and eluted with 1 liter of methylene chloride. Removal of the solvent gave a white solid which was recrystallized from petroleum ether after cooling in a dry ice-acetone bath to give 916 g of **24**, white crystals, mp 81-82°.

Anal. Calcd. for $C_{18}H_{22}N_6$: C, 65.02; H, 9.70; N, 25.28. Found: C, 64.87; H, 9.84; N, 25.13.

5,7-Dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-2-carboxylic acid, **25**.

To a suspension of 3-amino-1,2,4-triazolo-5-carboxylic acid (22) (1.28 g) in water (20 ml) was added 2.5 normal sodium hydroxide (~3 ml) until the *p*H of the solution was 7.2. Pentane-2,4-dione (1.1 g, 11 mmoles) and piperidine (4 drops) were added and the mixture was refluxed for 16 hours. The solution was cooled and filtered and the *p*H was adjusted to 2 by adding 2*N* hydrochloric acid (~5 ml). The solution was kept in the refrigerator and the crystals which separated were filtered, washed with cold water and dried, 1.0 g (52%), mp 179-180°; (methanol): γ max 217 and 272 nm; ir (potassium bromide): 3500, 1735, 1635, 1555, 1225 and 760 cm^{-1}; nmr (deuteriotrifluoroacetic acid): 82.92 (s, 3H); 3.02 (s, 3H), 7.63 (s, 1H).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.19; N, 29.15. Found: C, 50.1;

H, 4.23; N, 29.4.

5,7-Di-*n*-propyl-2-phenyl-*s*-triazolo[1,5-*a*]pyrimidine, **26**.

To 50 ml of glacial acetic acid was added 5.0 g of 3-amino-5-phenyl-1,2,4-triazole (20) and 5.0 g of nonane-4,6-dione and the solution was refluxed overnight. The excess acetic acid was removed *in vacuo* and the solid residue was triturated with ether and filtered to give 8.8 g of solid. A small amount was recrystallized from ethanol to give colorless crystals of **26**, mp 105-106°.

Anal. Calcd. for $C_{17}H_{19}N_4$: C, 72.82; H, 7.19; N, 19.99. Found: C, 73.10; H, 7.25; N, 19.71.

5,7-Di-*n*-propyl-2-methylpyrazolo[1,5-*a*]pyrimidine, **39**.

Nonane-4,6-dione (4.8 g) was added to a solution of 3-amino-5-methylpyrazole (2.91 g) (23) in ethanol (50 ml). Piperidine (4 drops) was added and the reaction mixture was refluxed for 20 hours. The ethanol was evaporated under reduced pressure and the residue was distilled under vacuum to give a yellowish oil as the product, 3.5 g. This product was further purified by passing it through 200 g of Woelm neutral alumina with methylene chloride as an eluent to give a pure colorless oil (bp 180-183°/1 mm) **39**, 1.2 g; uv (methanol): γ max 231 nm; nmr (deuteriochloroform): δ 1.0 (t, 3H, CH_3), 1.57-2.15 (m, 4H,-CH_2), 2.12 (s, 3H, CH_3), 2.77 (t, 2H, -CH_2-), 3.1 (t, 2H, -CH_2-), 6.36 (s, 1H), 6.46 (s, 1H).

Anal. Calcd. for $C_{13}H_{19}N_3$: C, 71.85; H, 8.81; N, 19.33. Found: C, 71.88; H, 9.14; N, 19.16.

5,7-Di-*n*-propyl-2-methylamino-*s*-triazolo[1,5-*a*]pyrimidine, **27**.

To 100 ml of glacial acetic acid was added 17.0 g of 3-amino-5-methylamino-1,2,4-triazole, (mp 156-157°) prepared by the general method of Heitke and McCarty (20). To this solution was added 23.4 g of nonane-4,6-dione and the solution was refluxed for 8 hours. The excess acetic acid was removed *in vacuo* and the residue dissolved in 500 ml of methylene chloride and the solution washed with dil sodium hydroxide and then with water. The dried methylene chloride solution was then concentrated to 50 ml and poured over a column of 200 g of neutral Woelm alumina and eluted with 500 ml of methylene chloride, Removal of the methylene chloride *in vacuo* gave a yelow solid. The solid was extracted with hot petroleum ether and filtered to give pale pink plates of **27**, 16.0 g, mp 128-129°. Recrystallization of **27** from ethyl acetate raised the mp to 129-130°.

Anal. Calcd. for $C_{12}H_{10}N_5$: C, 61.77; H, 8.20; N, 30.0. Found: C, 61.50; H, 8.50; N, 30.20.

5,7-Di-*n*-propyl-1,2,3-trizolo[1,5-*a*]pyrimidine, **36**

Nonane-4,6-dione (3.12 g) was added to a solution of 4-amino-1,2,3-triazole (12) (1.68 g) in ethanol (40 ml). 4 Drops of peperidine was added and the solution was refluxed for 40 hours. The solvent was evaporated under reduced pressure. Distillation of the residue under vaccum gave **29**, the product, as a colorless oil, 2.05 g (50%), bp 145-146°/3 mm; nmr (deuteriochloroform): δ 1.05 (t, 3H), 1.1 (t, 3H), 1.65-2.2 (m, 4H), 2.9 (s, 2H), 3.3 (s, 2H), 6.73 (s, 1H), 8.17 (s, 1H).

Anal. Calcd. for $C_{11}H_{16}N_4$: C, 64.67; H, 7.89; N, 27.43. Found: C, 64.71; H, 8.02; N, 27.62.

5,7-Diethyltetrazolo[1,5-*a*]pyrimidine, **37**.

A mixture of 5-aminotetrazole (1.05 g) and heptane-3,5-dione (1.28 g) in glacial acetic acid (25 ml) was refluxed for 4 hours. Acetic acid was removed under reduced pressure and the residue recrystallized from ethanol to give white crystals of **37**, 1.3 g (74%), mp 98-99°; uv (methanol): λ max 214 and 266 nm; ir (potassium bromide): 3060, 2980, 1625, 1535, 1455, 1425, 1415, 1395, 1370, 1320, 1292, 1185, 1130, 1113, 1100, 995, 900 and 790 cm^{-1}; nmr (deuteriochloroform): 1.42 (t, 3H, CH_3), 1.54 (t, 3H, CH_3), 3.04 (q, 2H, -CH_2), 3.34 (q, 2H, -CH_2), 7.0 (s, 1H, CH).

Anal. Calcd. for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.38; H, 6.24; N, 39.59.

5,7-Diethyl-1,2,4-triazolo[1,5-*a*]pyrimidine, **32**.

Heptane-3,5-dione (1.3 g) was added to a solution of 3-amino-1,2,4-triazole (0.84 g) in ethanol (25 ml). Piperidine (4 drops) was added and the mixture was refluxed for 20 hours. The reaction mixture was cooled and evaporated to dryness under reduced pressure. Recrystallization of the residue from *n*-heptane gave **32** as white crystals, 1.0 g (57%), mp 83-86°; uv (methanol): λ max 215 and 272 nm; ir (potassium bromide): 2970, 2920, 2880, 1625, 1545, 1460, 1432, 1395, 1298, 1285, 1255, 1200, 905 and 860 cm^{-1}; nmr (deuteriochloroform): δ 1.38 (t, 3H, CH_3), 1.45 (t, 3H, CH_3), 2.67-3.37 (m, 4H, -CH_2), 6.75 (s, 1H, CH), 8.23 (s, 1H, CH).

Anal. Calcd. for $C_9H_{12}N_4$: C, 61.33; H, 6.86; N, 31.79. Found: C, 61.36; H, 6.96; N, 31.69.

5,7-Dimethyl-1,2,3-triazolo[1,5-*a*]pyrimidine, **34**.

4-Amino-1,2,3-triazole (12) (1.68 g) was added to a solution of acetylacetone (2.2 g) in benzene (50 ml). The mixture was refluxed for 24 hours and the water formed was removed azeotropically, using benzene. The solvent was evaporated and the residue recrystallized from benzene/-petroleum ether (bp 40-60°) to give white crystals, of **34**, 2.4 g (81%), mp 87-88°; nmr (DMSO-d_6): δ 2.61 (s, 3H), 2.86 (s, 3H), 7.11 (s, 1H), 8.28 (s, 1H).

Anal. Calcd. for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.32. Found: C, 56.74; H, 5.46; N, 37.80.

5,7-Diethyl-1,2,3-triazolo[1,5-*a*]pyrimidine, **35**.

Heptane-3,5-dione (1,3 g) was added to a solution of 4-amino-1,2,3-triazole (**12**) (0.84 g) in ethanol (25 ml). Piperidine (4 drops) was added and the reaction mixture was refluxed for 20 hours. The reaction mixture was evaporated to dryness under reduced pressure. Recrystallization of the residue from *n*-heptane gave white crystals of **35**, 0.9 g (51%), mp 67-68°; uv (methanol): λ max 221, 275 and 310 (sh); ir (potassium bromide): 3120, 2970, 2940, 2880, 1633, 1532, 1458, 1428, 1400, 1303, 1292, 1208, 1105, 960, 860 and 835 cm^{-1}; nmr (deuteriochloroform): δ 1.37 (t, 3H, CH_3), 1.5 (t, 3H, CH_3), 2.88 (q, 2H, CH_2), 3.26 (q, 2H, CH_2), 6.62 (s, 1H, CH), 7.95 (s, 1H, CH).

Anal. Calcd. for $C_9H_{12}N_4$: C, 61.33; H, 6.86; N, 31.79. Found: C, 61.19; H, 6.93; N, 31.57.

5,7-Di-*n*-propyltetrazolo[1,5-*a*]pyrimidine, **38**.

A mixture of 16.0 g (0.156 mole) of 5-aminotetrazole 25.0 g (0.160 mole) of nonane-4,6-dione and 200 ml ethanol containing 2 drops of piperidine, was refluxed 16 hours. The solvent was evaporated *in vacuo* to yield a syrup which solidified on standing. Recrystallization of this residue from ethanol-water gave 12.5 g (42%) of white crystals, of **38**, mp 57-58°.

Anal. Calcd. for $C_9H_{12}N_4$: C, 42.59; H, 7.22; N, 43.67. Found: C, 42.30; H, 7.50; N, 43.86.

5,7-Di-*n*-propylimidazo[1,2-*a*]pyrimidine hydrochloride, **40**.

To 1.8 g of 2-aminoimidazole sulfate (13) in 50 ml of ethanol was added sufficient (10%) sodium hydroxide (~4 ml) to adjust the *p*H to 7.2. Then 1.6 g of nonane-4,6-dione was added and the solution refluxed for 20 hours. The solution was then evaporated to dryness and the residue dissolved in 25 ml of water and the solution make alkalne with 10% sodium hydroxide and then extracted with chloroform (3 × 10 ml). The chloroform was evaporated and the residue dissolved in dry diethyl ether. Dry hydrogen chloride gas was bubbled through the ethereal solution and the hydrochloride salt precipitated, was filtered and washed with dry ether to yield 1.0 g of **40**, mp 149-150°.

Anal. Calcd. for $C_{12}H_{18}ClN_3$: C, 60.11; H, 7.56; N, 17.52. Found: C, 59.94; H, 7.68; N, 17.48.

6,8-Di-*n*-1,2,4-triazolo[4,3-*b*]pyridazine, **41**.

A mixture of 4-amino-1,2,4-triazole (14) (1.5 g) nonane-4,6-dione (3,0 g) and glacial acetic acid (25 ml) was refluxed for 16 hours. The acetic acid was removed under reduced pressure and the residue distilled under vacuum to give a colorless liquid **41**, 2.2 g (60%), bp 160-165°/3 mm; uv (methanol): λ max 222 and 286 nm; ir (potassium bromide): 2950, 2925, 2865, 1610, 1560, 1495, 1460, 1390, 1330, and 950 cm^{-1}; nmr (deuterio-

chloroform): δ 1.05 (t, 6H, CH_3), 1.6-2.15 (m, 4H, $-CH_2-$), 2.65-3.2 (m, 4H, CH_2), 6.8 (s, 1H, CH), 9.0 (s, 1H, CH).

Anal. Calcd. for $C_{11}H_{16}N_4$: C, 64.67; H, 7.89; N, 27.42. Found: C, 64.81; H, 7.99; N, 27.24.

5,7-Di-*n*-propyl-2-benzylthio-1,3,4-thiadiazole[3,2-*a*]pyrimidine Bromide, **45**.

To 1.5 g of 5,7-di-*n*-propyl-2-thio-1,3,4-thiadiazolo[3,2-*a*]pyrimidine **58** in 30 ml of benzene, was added 1.7 g of benzyl bromide. The reaction mixture was stirred for 2 days at room temperature. The benzene was evaporated under reduced pressure at a temperature below 10° and the residue was suspended in ether. The crystals obtained were filtered, washed with ether and dried to give 2.5 g of **45**, mp 120-122° dec. A small sample was recrystallized from a methanol-diethyl ether mixture.

Anal. Calcd. for $C_{18}H_{22}BrN_3S_2$: C, 50.93; H, 5.22; S, 15.1. Found: C, 50.80; H, 5.23; S, 14.98.

4,6-Dimethyl-2-dichloromethylpyrimidine, **48**.

To 70 ml of chloroform was added 1.5 g of **33**, 2.0 g of *N*-chlorosuccinimide was added slowly over a 5-minute period while the reaction was cooled in a dry ice bath. The temperature was gradually allowed to reach room temperature and the solution stirred for 20 hours. The solution was then washed with aqueous saturated sodium bicarbonate and then with water and dried over anhydrous magnesium sulfate. Evaporation of the chloroform gave an oily residue which was chromatographed on a 280 g column of Woelm neutral alumina and eluted with chloroform. The first 50 ml of chloroform eluate was discarded. The next 60 ml eluate was concentrated *in vacuo* and the residue crystallized from petroleum ether (bp 30-60°) to give 100 mg of white needles of **48**, mp 77-78°.

Anal. Calcd. for $C_7H_8Cl_2H_2$: C, 44.01; H, 4.22; N, 14.66. Found: C, 43.96; H, 4.08; N, 14.56.

5,7-Dimethyl-2-thio-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, **57**.

A mixture of 5-amino-1,3,4-thiadiazole-2-thiol (2.66 g, 20 mmoles), pentane-2,4-dione (2.2 g, 22 mmoles) ethanol (25 ml) and piperidine (4 drops) was refluxed for 4 hours, filtered hot and cooled. The crystals which separated were filtered hot and cooled. The crystals which separated were filtered and recrystallized from ethanol to give yellow crystals of the product **57**, 1.2 g (31%), mp 220-221°; (methanol): λ max 214, 258 and 346 nm; ir (potassium bromide): 1610, 1525, 1380, 1340, 1188, 1058, 1000 and 960 nm; nmr (deuteriochloroform): δ 2.66 (s, 3H), 2.86 (s, 3H), 7.26 (s, 1H).

Anal. Calcd. for $C_7H_7N_3S_2$: C, 42.64; H, 3.57; N, 21.31. Found: C, 42.71; H, 3.84; N, 21.19.

3-Amino-5-*p*-fluorobenzylamino-1,2,4-triazole (**53**, R_1, H, R_2, *p*-fluorobenzyl).

To 2.0 g of *N*-*p*-fluorobenzylamino-*N'*-cyano-S-methylisothiourea prepared by the procedure of Heitke and McCarty (20) was added 20 ml of acetonitrile and 0.5 g of 95% hydrazine and the solution was stirred for 2 days at room temperature and the reaction mixture was cooled and filtered to yield 850 mg of long needles of 3-amino-5-*p*-fluorobenzylamino-1,2,4-triazole. The product was recrystallized from methanol to give 650 mg mp 165-166°.

Anal. Calcd. for $C_8H_8FN_5$: C, 49.73; H, 4.17; N, 36.25. Found: C, 49.27; H, 4.91; N, 36.54.

2-Chloro-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]pyrimidine, **56**.

To a suspension of 4,7 g of 2-amino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]-pyrimidine (19) **23**, in 20 ml of concentrated hydrochloric acid and 30 ml of ice and water, was slowly added dropwise a solution of 1.5 g of sodium nitrite in 15 ml of water. The addition was maintained at 0° and was completed in 7 minutes. The solution was stirred at 0° for an additional 1 ½ hours. The resulting precipitate was filtered and washed repeatedly with ice water to yield 4.4 g of crude product. This material was further purified by dissolving in methylene chloride and adding it to a 200 g column of Woeln neutral alumina. The column was eluted with 500 ml of methylene chloride and the eluate discarded. Then a gradient of methanol and methylene chloride was employed as the eluate and 500 ml of this eluate was concentrated *in vacuo* and the dark oily residue was extracted with hot petroleum ether (bp 40-50°). The hot extract was treated with charcoal and filtered and concentrated to 20 ml and cooled. The resulting white needles were filtered to yield 1.9 g of **56**, mp 47.5-48.5°.

Anal. Calcd. for $C_{21}H_{15}ClN_4$: C, 55.35; H, 6.33; N, 23.47. Found: C, 55.36; H, 6.27; N, 23.56.

5,7-Di-*n*-propyl-2-thio-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, **58**.

To 40 ml of ethanol was added 2.67 g of 5-amino-1,3,4-thiadiazole-2-thiol, 3.15 g of nonane-4,6-dione and 6 drops of piperidine. The reaction mixture was refluxed for 24 hours and the solvent removed. The residue was dissolved in benzene and filtered. Upon concentration of the benzene solution sufficient petroleum ether was added to cause crystallization of the product **58**, 2.7 g.

Anal. Calcd. for $C_{11}H_{15}N_3S_2$: C, 52.14; H, 5.96; N, 16.58. Found: C, 52.30; H, 6.00; N, 16.45.

4,6-Dimethyl-2-Chloroiodomethylpyrimidine, **59**.

To 50 ml of chloroform was added 1.0 g of 5,7-dimethyl-*v*-triazolo-[1,5-*a*]pyrimidine **30** and 1.1 g of iodine monochloride. Vigorous bubbling occurred and the dark solution set in the refrigerator overnight. The solution was poured over a 200 g of Woelm neutral alumina column and the column was then eluted with methylene chloride. The methylene chloride eluate was concentrated *in vacuo* to give a yellow oily residue which crystallized upon cooling. Recrystallization from petroleum ether (bp 60°) gave 1.2 g (49%) of **59** as pale yellow cubes, mp 73-75°.

Anal. Calcd. for C_7H_8ClIN: C, 29.76; H, 2.85; N, 9.92. Found: C, 29.72; H, 2.88; N, 9.60.

Inotropic Studies in Dogs. Methods.

Adult mongrel dogs of either sex were anesthetized by intravenous administration of sodium pentobarbital, 15 mg/kg plus sodium barbital 220 mg/kg. Animals were artificially respired using a Harvard Respirator, Model 614. A Beckman type RM polygraph was used to record the following parameters: (1) arterial pressure, (2) central venous pressure, (3) electrocardiogram, (4) blood dye concentration, and (5) cardiac contractility. Arterial blood pressure was determined by cannulation of the right carotid artery using a Statham Model P23AA pressure transducer. The left jugular vein was cannulated centrally with the tip of the cannula advanced to the level of the right atrium. This cannula was used to inject dye for cardiac output determination and to monitor central venous pressure using s Statham Model P23BB pressure transducer. Lead II electrocardiograms were recorded and served to determine heart rate.

Cardiac output was determined by dye dilution using a Lyons Densitometer/Cardiac Output Computer. (Physio-Tronics, Inc., Burbank, CA) and indocyanine green (Cardio-Green) as the dye. Blood was withdrawn using a Sage infusion pump from a cannula inserted into the left femoral artery for determination of dye concentrations. The dye concentration curve was recorded by coupling the densitometer with a Beckman type RM polygraph. A digital read-out of cardiac output was presented by the Lyons Densitometer/Cardiac Output Computer. Cardiac contractility was recorded by attaching a Walton-Brodie encased strain gauge arch to the left ventricle. A left thoracotomy at the interspace between the fourth and fifth ribs was performed in attaching the strain gauge.

Dimethyl sulfoxide was used as a vehicle for most test compounds. Certain test compounds with adequate aqueous solubility were solubilized in 1% saline vehicle. Solutions of test compounds were administered by infusion through a cannula inserted into right femoral vein. Test compound solutions were infused at a rate of 4.4 ml/hour using a Unita I infusion pump. Compounds were administered in doses of either 3.1 mg/kg/hour or 10.0 mg/kg/hour for a period of one hour. Cardiovascular parameters were recorded during a 20 minutes pre-infusion period, during a 60-minute infusion period and during a 60-minute pos-infusion period.

The data (Table 1) are presented as the mean values of maximal percent change of caridac output, heart rate and stroke volume from that of the same animal prior to administration of the test compound.

In order to demonstrate oral activity, selected test compounds were utilized as described, with the exception that the compounds were administered intragastrically to the test animals. The compounds wer injected by fast injection after establishing base line data for each test animal. The 120-minute time period of of the test was started as per time of injection.

Treatment of Hemorrhagic Shock. (Figure 1).

One compound, 2-Dimethylamino-5,7-di-*n*-propyl-*s*-triazolo[1,5-*a*]-pyrimidine **11** was used to determine its effect on servival of dogs subjected to hemorrhagic shock. The hemorrhagic shock model in dogs was that described by Crowell, Jones and Smith (30). Hemorrhagic shock was induced by bleeding to a mean arterial pressure of 30 mm of mercury. Arterial pressure was maintained at 30 mm of mercury until 20% of the shed blood volume had returned to the animal at which time the remainder of the shed blood was re infused. Treatment with the compound was started within 15 minutes following reinfusion of the shed blood. The compound was administered intravenously at a rate of 10 mg/kg/hour for two hours. Vehicle (dimethyl sulfoxide) treated control dogs did not survive beyond 12 hours whereas three out of eigh compound-treated dogs survived for seven days. In this model allopurinol gave 25% survival at 12 hours and no survivors at 24 hours (30).

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