sites. The inducible 3-hydroxylation occurs at a type I site, while the noninducible O-demethylation presumably occurs at a type II site.

In summary, the metabolism of BP and its derivatives involves at least three different enzyme activities: (1) a 3-hydroxylase in uninduced microsomes which has some 1-hydroxylase activity, (2) a 3-hydroxylase in 3-MC-induced microsomes which has more 1-hydroxylase activity and which is more sensitive to the structure of the substrate, and (3) an O-dealkylase which is not inducible. This last activity may or may not involve the uninduced 3-hydroxylase. Both have the same positional specificity: the hydroxylase can attack positions 1, 3, and 6, but not 12, while the O-dealkylase can O-dealkylate groups at positions 1, 3, and 6, but not 12. However, the hydroxylation occurs at a type I site and the O-dealkylation at a type II site, and, accordingly, different active sites are involved. The various activities may be due to different forms of cytochrome P-450. Both uninduced and induced microsomes contain a number of forms of these enzyme systems, all of which vary somewhat in substrate specificity,[6,7,44,45] positional specificity,[34,46] and stereospecificity.[46] For example, warfarin[46] can be hydroxylated at five different positions. This is reported to involve at least four different monooxygenases, one of which is not inducible by PB or 3-MC.

Detoxification and elimination of aromatic hydrocarbons generally proceeds through an initial oxidation of the molecule. There has been considerable study of the effects of enzyme induction on the rate of hydrocarbon hydroxylation. However, this study indicates that induction may also affect the position of the initial oxidation. This factor would modify the metabolic pathways, which could conceivably affect the biological activity and disposition of the compound, as well as the change in the rate of oxidation. The biological activity of aromatic hydrocarbons in different tissues and species presumably reflects both the disparate inducibilities and positional specificities of enzymes in different tissues. This important problem warrants further comparison of the products of initial metabolic oxidation of polycyclic aromatic hydrocarbons in uninduced and induced tissues.

Acknowledgment. This research was supported by NIH Grant 1R01CA14826 and by Public Health Service Contract N01 CP33278 from the National Cancer Institute, NIH.

(44) F. P. Guengerich, *J. Biol. Chem.*, **252**, 3970-3979 (1977), and references therein.
(45) J. P. Villeneuve, P. Mavier, and J. G. Joly, *Biochem. Biophys. Res. Commun.*, **70**, 723-728 (1976).
(46) L. R. Pohl, W. R. Porter, W. F. Trager, M. J. Fasco, and J. W. Fenton II, *Biochem. Pharmacol.*, **26**, 109-114 (1977).

Studies on Cardiovascular Agents. 6. Synthesis and Coronary Vasodilating and Antihypertensive Activities of 1,2,4-Triazolo[1,5-*a*]pyrimidines Fused to Heterocyclic Systems

Yasunobu Sato,* Yasuo Shimoji, Hiroshi Fujita, Hiroshi Nishino, Hiroshi Mizuno, Shinsaku Kobayashi, and Seiji Kumakura

Central Research Laboratories, Sankyo Company, Ltd., Shinagawa-ku, Tokyo, Japan. *Received March 8, 1979*

The synthesis and coronary vasodilating and antihypertensive activities of 1,2,4-triazolo[1,5-*a*]pyrimidines fused to pyrrole, thiophene, pyran, pyridine, and pyridazine are described. Among these compounds, 8-*tert*-butyl-7,8-dihydro-5-methyl-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (**23**) was found to be the most promising potential cardiovascular agent, having been shown to be more potent in coronary vasodilating activity than trapidil [7-(diethylamino)-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine] and approximately equipotent to guanethidine sulfate in antihypertensive activity.

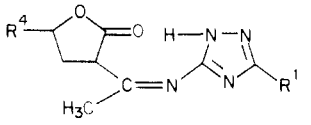
Some 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives are known to possess potent pharmacological activities. For example, trapidil [7-(diethylamino)-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine] is used as a coronary vasodilator[1] and 2-amino-4,5-dihydro-6-methyl-5-oxo-4-propyl-1,2,4-triazolo[1,5-*a*]pyrimidine has shown significant activity against bronchospasm.[2] Therefore, in attempts to prepare new types of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives superior to trapidil, we have synthesized a number of compounds which have a pyrrolotriazolopyrimidine nucleus resulting from the fixation of an ethylamino chain of trapidil to the triazolopyrimidine nucleus in a continuing search for cardiovascular agents.[3] Furthermore, triazolopyrimidines fused to thiophene, pyran, pyridine, and pyridazine were prepared and screened for coronary vasodilating and antihypertensive activities. Among these compounds, 8-*tert*-butyl-7,8-dihydro-5-methyl-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (**23**) was found to be the most promising potential cardiovascular agent. This paper deals with the synthesis and biological activity of the title compounds.

Chemistry. The synthetic routes to the 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines **5-28** and **30-102** are outlined in Scheme I. Condensation of the 3-aminotriazoles (1; R^1 = H, CH_3, C_6H_5, and 4-CH_3O-C_6H_4) with the appropriate α-acetyl-γ-butyrolactones in the presence of boron trifluoride led to the 3-[[1-(tetrahydro-2-oxo-3-furyl)ethylidene]amino]triazoles **2a-f** (Table I), which are

(1) (a) E. Tenor and R. Ludwig, *Pharmazie*, **26**, 534 (1971); (b) H. Fuller, F. Hauschild, D. Modersohn, and E. Thomas, *Pharmazie*, **26**, 554 (1971); (c) "The Merck Index", 9th ed, Merck and Co., Rahway, N.J., 1976, p 1230.
(2) G. E. Davies, *J. Pharm. Pharmacol.*, **25**, 681 (1973).
(3) H. Fujita, Y. Shimoji, S. Kojima, H. Nishino, K. Kamoshita, K. Endo, S. Kobayashi, S. Kumakura, and Y. Sato, *Sankyo Kenkyusho Nempo*, **29**, 75 (1977).

0022-2623/80/1823-0927$01.00/0

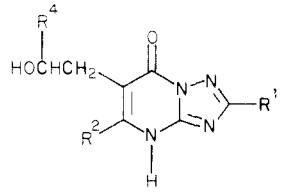
Table I. 3-[[1-(Tetrahydro-2-oxo-3-furyl)ethylidene]amino]-1,2,4-triazoles



no.	R^1	R^4	mp, °C	recrystn solvent	yield, %	formula[a]
2a	H	H	156–158	EtOH	88	$C_8H_{10}N_4O_2$
2b	CH_3	H	179–182	MeOH	50	$C_9H_{12}N_4O_2$
2c	C_6H_5	H	201–202	dioxane	83	$C_{14}H_{14}N_4O_2$
2d	4-CH_3O-C_6H_4	H	192–195	MeOH	63	$C_{15}H_{16}N_4O_3$
2e	H	CH_3	164–166	MeOH	69	$C_9H_{12}N_4O_2$
2f	H	C_2H_5	136–138	MeOH	65	$C_{10}H_{14}N_4O_2$

[a] The compounds were analyzed for C, H, and N. Analytical results are within 0.4% of the theoretical values.

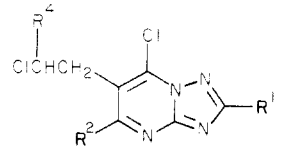
Table II. 6-(Hydroxyalkyl)-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-ones



no.	R^1	R^2	R^4	method[a]	mp, °C	recrystn solvent	yield, %	formula[b]
3a	H	CH_3	H	A	265–266 dec	H_2O	89	$C_8H_{10}N_4O_2$
3b	CH_3	CH_3	H	A	269–270 dec	MeOH	75	$C_9H_{12}N_4O_2$
3c	C_6H_5	CH_3	H	A	278–279	MeOH	88	$C_{14}H_{14}N_4O_2$
3d	4-CH_3O-C_6H_4	CH_3	H	A	293–294 dec	MeOH	57	$C_{15}H_{16}N_4O_3$
3e	H	CH_3	CH_3	A	199–201 dec	*i*-PrOH	57	$C_9H_{12}N_4O_2$
3f	H	CH_3	C_2H_5	A	190–193	*i*-PrOH	80	$C_{10}H_{14}N_4O_2$
3g	4-Cl-C_6H_4	CH_3	H	B	309–310	MeOH	70	$C_{14}H_{13}ClN_4O_2 \cdot 0.5H_2O$
3h	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	H	B	274–275 dec	MeOH	74	$C_{17}H_{20}N_4O_5 \cdot 0.5H_2O$
3i	H	c-C_3H_5	H	B	235–236	dioxane	17	$C_{10}H_{12}N_4O_2$

[a] The letters relate to the procedure given under Experimental Section. [b] The compounds were analyzed for C, H, N, and, where present, Cl. Analytical results were within 0.4% of the theoretical values.

Table III. 7-Chloro-6-(chloroalkyl)-1,2,4-triazolo[1,5-*a*]pyrimidines



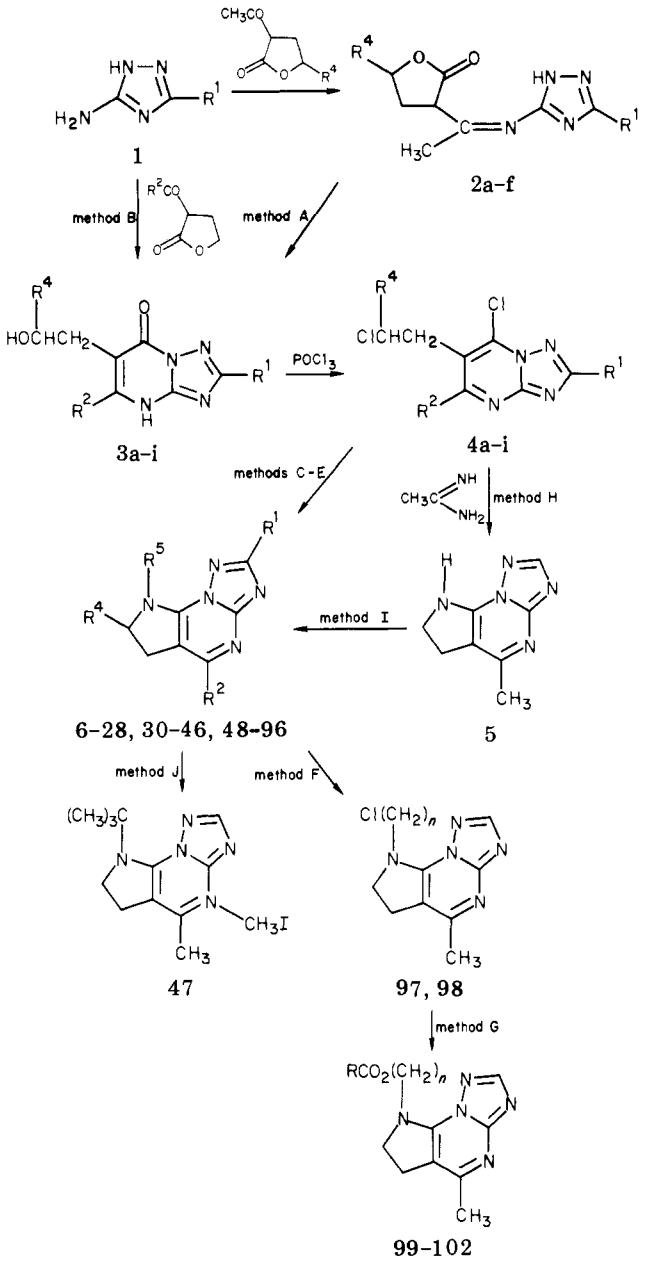
no.	R^1	R^2	R^4	mp, °C	recrystn solvent	yield, %	formula[a]
4a	H	CH_3	H	89–91	THF-*i*-Pr_2O	78	$C_8H_8Cl_2N_4$
4b	CH_3	CH_3	H	153–154	THF-*i*-Pr_2O	87	$C_9H_{10}Cl_2N_4$
4c	C_6H_5	CH_3	H	164–166	THF-*i*-Pr_2O	83	$C_{14}H_{12}Cl_2N_4$
4d	4-CH_3O-C_6H_4	CH_3	H	183–184	THF-*i*-Pr_2O	66	$C_{15}H_{14}Cl_2N_4O$
4e	H	CH_3	CH_3	77–78	THF-*i*-Pr_2O	82	$C_9H_{10}Cl_2N_4$
4f	H	CH_3	C_2H_5	109–110	THF-*i*-Pr_2O	81	$C_{10}H_{12}Cl_2N_4$
4g	4-Cl-C_6H_4	CH_3	H	194–196	THF-*i*-Pr_2O	94	$C_{14}H_{11}Cl_3N_4$
4h	3,4,5-$(CH_3O)_3$-C_6H_2	CH_3	H	239–240	THF	58	$C_{17}H_{18}Cl_2N_4O_3$
4i	H	c-C_3H_5	H	105–107	*i*-Pr_2O	94	$C_{10}H_{10}Cl_2N_4$

[a] See footnote *b* in Table II.

readily cyclized in an aqueous basic solution (method A) to give the 6-(hydroxyalkyl)triazolopyrimidin-7(4*H*)-ones **3a–f** (Table II). Compounds **3g**–i were prepared by heating 1 [R^1 = H, 4-Cl-C_6H_4 and 3,4,5-$(CH_3O)_3$-C_6H_2] with α-acetyl-γ-butyrolactone or α-(2-hydroxyethyl)-β-oxocyclopropanepropionic acid γ-lactone,[4] respectively (method B). The chlorination of **3a**–i with phosphorus oxychloride (Table III), followed by treatment with the appropriate primary amines (methods C, D, and E), afforded the desired compounds **6–28**, **30–46**, and **48–96** (Tables IV, V and VI). Additionally, the chlorination of the 8-(hydroxyalkyl) derivatives **88** and **89** with thionyl chloride (method F), followed by acyloxylation (method G), gave the corresponding acyloxyalkyl compounds **99–102**. Reaction of **4a** with acetamidine (method H) yielded 7,8-dihydro-5-methyl-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]-pyrimidine (**5**). The butylation or benzylation of **5** with butyl or benzyl bromide (method I) proceeded to give **17** and **51**, respectively, but attempts to obtain **23** by alkylation of **5** with *tert*-butyl bromide or iodide were unsuccessful. The reaction of **23** with methyl iodide (method

(4) H. Hart and O. E. Curtis, Jr., *J. Am. Chem. Soc.*, 78, 112 (1956).

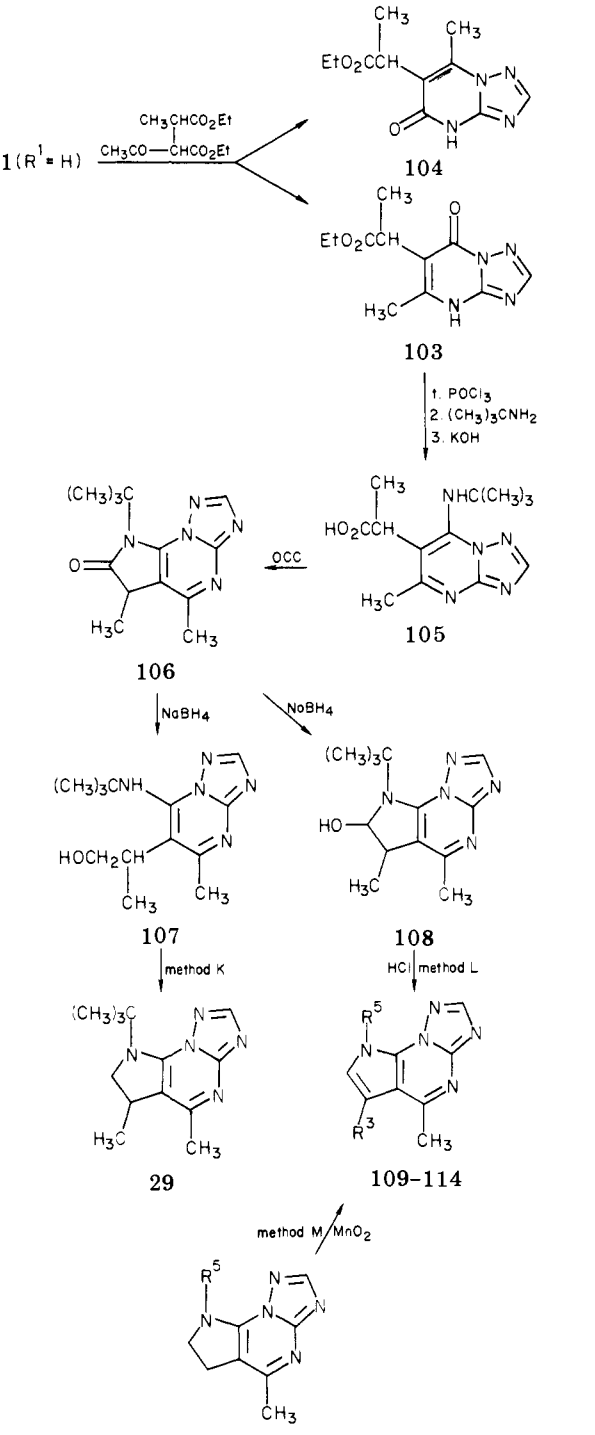
Scheme I



J) afforded its quaternary methiodide **47**.

The 8-*tert*-butyl-7,8-dihydro-5,6-dimethyl-6*H*-pyrrolotriazolopyrimidine **29** was prepared as illustrated in Scheme II. Reaction of 3-aminotriazole (**1**; R^1 = H) with diethyl 2-acetyl-3-methylsuccinate[5] afforded a mixture of the triazolopyrimidin-7-one **103** and the triazolopyrimidin-5-one **104** whose structural assignments were made from their UV spectral data (see Experimental Section). The chlorination of **103** with phosphorus oxychloride, followed by treatment with *tert*-butylamine and successive hydrolysis, gave **105**, which was cyclized to 8-*tert*-butyl-7,8-dihydro-5,6-dimethyl-7-oxo-6*H*-pyrrolo[3,2-*e*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**106**) with dicyclohexylcarbodiimide (DCC) in benzene. Reduction of **106** by means of $NaBH_4$ yielded the 6-(2-hydroxy-1-methylethyl)triazolopyrimidine derivative **107** and the 7-hydroxy-7,8-dihydro-6*H*-pyrrolotriazolopyrimidine **108**. The ring closure of **107** to **29** was accomplished by reaction with thionyl chloride, followed by treatment with sodium hydroxide at

Scheme II



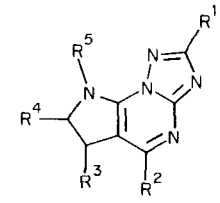
room temperature (method K). The dehydration of **108** with hydrochloric acid (method L) afforded the pyrrolotriazolopyrimidine **109** (Table VII). The other derivatives, **110–114**, were obtained conveniently by dehydrogenation of the corresponding 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines **5**, **22**, **23**, **53**, and **57** with active manganese dioxide (method M).

In order to confirm the new ring system, 6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine, an alternate synthesis of **6** was attempted as shown in Scheme III. Acetylation of 1-methyl-2-(methylthio)-2-pyrroline (**115**)[6] with

(5) P. J. Ashworth, G. H. Whitham, and M. C. Whiting, *J. Chem. Soc.*, 4633 (1957).

(6) R. Gompper and W. Elser, *Justus Liebigs Ann. Chem.*, **725**, 64 (1969).

Table IV. Coronary Vasodilating and Antihypertensive Activities of 7,8-Dihydro-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidines

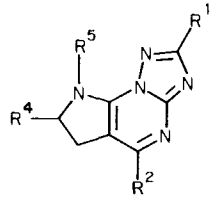


compd	R^1	R^2	R^3	R^4	R^5	method[a]	mp, °C	recrystn solvent	yield, %	formula[b]	mean IVP[c]	mean HI[d]
5	H	CH_3	H	H	H	H	250–252	EtOH	73	$C_8H_9N_5$	6	55
6	H	CH_3	H	H	CH_3	D	215–217	EtOH	64	$C_9H_{11}N_5$	50	10
						N			3			
7	4-CH_3O-C_6H_4	CH_3	H	H	CH_3	C	275–276	EtOH	69	$C_{16}H_{17}N_5O$	0	0
8	H	CH_3	H	H	C_2H_5	D	130–132	H_2O	74	$C_{10}H_{13}N_5$	12	10
9	H	CH_3	H	H	*n*-C_3H_7	D	131–133	THF–*i*-Pr_2O	67	$C_{11}H_{15}N_5$	193	15
10	H	CH_3	H	H	*i*-C_3H_7	D	189–190	THF	59	$C_{11}H_{15}N_5$	24	0
11	C_6H_5	CH_3	H	H	*i*-C_3H_7	C	249–250	benzene–EtOH	52	$C_{17}H_{19}N_5$	*e*	0
12	4-Cl-C_6H_4	CH_3	H	H	*i*-C_3H_7	C	215–217	benzene–EtOH	28	$C_{17}H_{18}ClN_5$	*e*	0
13	4-CH_3O-C_6H_4	CH_3	H	H	*i*-C_3H_7	C	205–207	benzene–EtOH	63	$C_{18}H_{21}N_5O$	*e*	0
14	H	CH_3	H	CH_3	*i*-C_3H_7	C	155–157	EtOH–*i*-Pr_2O	59	$C_{12}H_{17}N_5$	10	0
15	H	CH_3	H	C_2H_5	*i*-C_3H_7	C	142–143	EtOH–*i*-Pr_2O	51	$C_{13}H_{19}N_5$	0	20
16	H	c-C_3H_5	H	H	*i*-C_3H_7	C	198–200 dec	*i*-PrOH	53	$C_{13}H_{17}N_5$·HCl	45	5
17	H	CH_3	H	H	*n*-C_4H_9	C	72–75	*i*-Pr_2O	68	$C_{12}H_{17}N_5$	30	145
						I			36			
18	C_6H_5	CH_3	H	H	*n*-C_4H_9	C	190–192	EtOH	50	$C_{18}H_{21}N_5$	*e*	10
19	H	CH_3	H	CH_3	*n*-C_4H_9	C	95–97	*i*-PrOH–*i*-Pr_2O	50	$C_{13}H_{19}N_5$	50	45
20	H	CH_3	H	C_2H_5	*n*-C_4H_9	C	75–77	hexane–*i*-Pr_2O	36	$C_{14}H_{21}N_5$	120	10
21	H	CH_3	H	H	*s*-C_4H_9	C	148–149	H_2O	26	$C_{12}H_{17}N_5$	5	100
22	H	CH_3	H	H	*i*-C_4H_9	C	143–145	MeOH–H_2O	61	$C_{12}H_{17}N_5$	107	60
23	H	CH_3	H	H	*t*-C_4H_9	C	177–178	*i*-PrOH–H_2O	70	$C_{12}H_{17}N_5$	815	181
24	CH_3	CH_3	H	H	*t*-C_4H_9	C	149–150	THF–*i*-Pr_2O	25	$C_{13}H_{19}N_5$	18	35
25	C_6H_5	CH_3	H	H	*t*-C_4H_9	C	221–223	EtOH	28	$C_{18}H_{21}N_5$	*e*	0
26	4-Cl-C_6H_4	CH_3	H	H	*t*-C_4H_9	C	216–218	benzene–EtOH	14	$C_{18}H_{20}ClN_5$	*e*	10
27	4-CH_3O-C_6H_4	CH_3	H	H	*t*-C_4H_9	C	212–213	EtOH	24	$C_{19}H_{23}N_5O$	*e*	13
28	3,4,5-$(CH_3O)_3$-C_6H_2	CH_3	H	H	*t*-C_4H_9	C	208–210	EtOH	53	$C_{21}H_{27}N_5O_3$	222	50
29	H	CH_3	CH_3	H	*t*-C_4H_9	K	115–116	*i*-Pr_2O	67	$C_{13}H_{19}N_5$	333	20
30	H	CH_3	H	CH_3	*t*-C_4H_9	C	178–180	*i*-PrOH–*i*-Pr_2O	50	$C_{13}H_{19}N_5$·HCl	47	
31	H	CH_3	H	C_2H_5	*t*-C_4H_9	C	170 dec	*i*-PrOH–*i*-Pr_2O	13	$C_{14}H_{21}N_5$·HCl	227	12
32	H	c-C_3H_5	H	H	*t*-C_4H_9	C	201–202 dec	*i*-PrOH–*i*-Pr_2O	59	$C_{14}H_{19}N_5$·HCl	125	20
33	H	CH_3	H	H	*n*-C_5H_{11}	D	77–78	*i*-Pr_2O	31	$C_{13}H_{19}N_5$	15	6
34	H	CH_3	H	H	*i*-C_5H_{11}	D	119–120	*i*-Pr_2O	51	$C_{13}H_{19}N_5$	118	5
35	H	CH_3	H	H	*t*-C_5H_{11}	D	107–108	*i*-Pr_2O	49	$C_{13}H_{19}N_5$	760	40
36	H	c-C_3H_5	H	H	*t*-C_5H_{11}	C	188–190 dec	*i*-PrOH–*i*-Pr_2O	49	$C_{15}H_{21}N_5$·HCl	50	20
37	H	CH_3	H	H	*n*-C_6H_{13}	D	75–78	hexane	46	$C_{14}H_{21}N_5$	14	10
38	H	CH_3	H	H	$CH(CH_3)CH_2CH(CH_3)_2$	D	123–124	*i*-Pr_2O	49	$C_{14}H_{21}N_5$	86	5
39	H	CH_3	H	H	*n*-C_7H_{15}	D	70–71	*i*-Pr_2O	39	$C_{15}H_{23}N_5$	184	30
40	H	CH_3	H	H	$C(CH_3)_2CH_2C(CH_3)_3$	D	82–84	hexane–*i*-Pr_2O	5	$C_{16}H_{25}N_5$	32	
41	H	CH_3	H	H	*n*-$C_{10}H_{21}$	D	78–80	*i*-Pr_2O	55	$C_{18}H_{29}N_5$	*e*	7
42	H	CH_3	H	H	*n*-$C_{12}H_{25}$	D	84–86	*i*-Pr_2O	72	$C_{20}H_{33}N_5$	*e*	10
43	H	CH_3	H	H	$CH_2CH{=}CH_2$	C	137–138	THF	77	$C_{11}H_{13}N_5$	56	70

44	H	CH_3	H	H	c-C_6H_{11}	D	214–216	EtOH	45	$C_{14}H_{19}N_5$	65	12
45	H	CH_3	H	H	c-C_7H_{13}	D	197–198	THF-*i*-Pr_2O	59	$C_{15}H_{21}N_5$	440	45
46	H	CH_3	H	H	c-C_8H_{15}	D	188–190	EtOH	51	$C_{16}H_{23}N_5$	*e*	15
47	H	CH_3	H	H	*t*-C_4H_9-CH_3I	J	204 dec	EtOH-*i*-Pr_2O	16	$C_{12}H_{17}N_5$-CH_3I	9	0
trapidil											142	45
mecamylamine												110
guanethidine sulfate												195

[a,b] See, respectively, footnotes *a* and *b* in Table II. [c] Abbreviation used is integrated vasodilating potency. These values represent the mean products of the compound-induced maximum percent decrease in perfusion pressure and duration of the effect in minutes for 100 μg ia. [d] Abbreviation used is hypotensive index. These values represent the mean area values under the time–hypotension curve for 6 h at 30 mg/kg po. [e] Coronary vasoconstricting action.

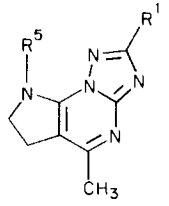
Table V. Coronary Vasodilating and Antihypertensive Activities of 8-Aryl- and 8-Aralkyl-Substituted 7,8-Dihydro-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidines



no.	R^1	R^2	R^4	R^5	method[a]	mp, °C	recrystn solvent	yield, %	formula[b]	mean IVP[c]	mean HI[d]
48	H	CH_3	H	C_6H_5	D	203–205	EtOH	48	$C_{14}H_{13}N_5$	72	15
49	H	CH_3	H	C_6H_3-2,6-Cl_2	E	192–194	THF-*i*-Pr_2O	39	$C_{14}H_{11}Cl_2N_5$	7	0
50	H	CH_3	H	C_6H_4-4-SO_2NH_2	C	283 dec	DMF-H_2O	66	$C_{14}H_{14}N_6O_2S$	14	0
51	H	CH_3	H	$CH_2C_6H_5$	C	170–172	EtOH	61	$C_{15}H_{15}N_5$	46	170
					I			45			
52	H	CH_3	H	$CH_2C_6H_4$-4-CH_3	C	200–202	THF	75	$C_{16}H_{17}N_5$	119	15
53	H	CH_3	H	$CH_2C_6H_4$-4-OCH_3	C	172–174	THF	78	$C_{16}H_{17}N_5O$	55	13
54	H	CH_3	CH_3	$CH_2C_6H_4$-4-OCH_3	C	144–145	EtOH-*i*-Pr_2O	52	$C_{17}H_{19}N_5O$	82	11
55	H	CH_3	H	$CH_2C_6H_3$-3,4-$(OCH_3)_2$	C	179–180	MeOH-*i*-Pr_2O	37	$C_{17}H_{19}N_5O_2$	174	55
56	H	CH_3	H	$CH_2C_6H_2$-3,4,5-$(OCH_3)_3$	C	193–194	EtOH	86	$C_{18}H_{21}N_5O_3$	109	15
57	H	CH_3	H	$CH_2C_6H_4$-2-Cl	C	207–209	EtOH	85	$C_{15}H_{14}ClN_5$	86	30
58	H	CH_3	H	$CH_2C_6H_4$-4-Cl	C	209–211	THF	71	$C_{15}H_{14}ClN_5$	250	145
59	3,4,5-$(CH_3O)_3$-C_6H_2	CH_3	H	$CH_2C_6H_4$-2-Cl	C	234–235	THF	57	$C_{24}H_{24}ClN_5O_3$	*e*	0
60	H	CH_3	CH_3	$CH_2C_6H_4$-2-Cl	C	153–155	EtOH-*i*-Pr_2O	57	$C_{16}H_{16}ClN_5$	80	8
61	H	c-C_3H_5	H	$CH_2C_6H_4$-2-Cl	C	189–191	EtOH	29	$C_{17}H_{16}ClN_5$	5	
62	H	CH_3	H	$CH_2C_6H_4$-2-F	C	186–187	EtOH	39	$C_{15}H_{14}FN_5$	351	5
63	C_6H_5	CH_3	H	$CH_2C_6H_4$-2-F	C	238–240	benzene-EtOH	48	$C_{21}H_{18}FN_5$	*e*	8
64	H	CH_3	CH_3	$CH_2C_6H_4$-2-F	C	149–150	THF-*i*-Pr_2O	69	$C_{16}H_{16}FN_5$	64	5
65	H	CH_3	C_2H_5	$CH_2C_6H_4$-2-F	C	117–118	*i*-PrOH-THF	51	$C_{17}H_{18}FN_5$	67	0
66	H	CH_3	H	$CH(CH_3)C_6H_5$	C	157–159	*i*-Pr_2O	72	$C_{16}H_{17}N_5$	137	5
67	H	CH_3	H	$(CH_2)_2C_6H_5$	C	111–112	THF-*i*-Pr_2O	29	$C_{16}H_{17}N_5$	100	5
68	H	c-C_3H_5	H	$(CH_2)_2C_6H_5$	C	157–159	EtOH	88	$C_{18}H_{19}N_5$	180	12
69	H	CH_3	H	$(CH_2)_2C_6H_3$-3,4-$(OCH_3)_2$	C	141–142	THF	75	$C_{18}H_{21}N_5O_2$	11	15
70	H	CH_3	H	$CH(CH_3)CH(OH)$-C_6H_5	C	232–235	EtOH	71	$C_{17}H_{19}N_5O$	8	0
71	CH_3	CH_3	H	$CH_2C_6H_4$-2-Cl	C	191–193	EtOH-*i*-Pr_2O	52	$C_{16}H_{16}ClN_5$	15	18

[a,b] See, respectively, footnotes *a* and *b* in Table II. [c-e] See, respectively, footnotes *c–e* in Table IV.

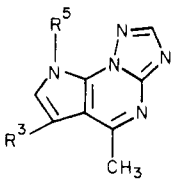
Table VI. Coronary Vasodilating and Antihypertensive Activities of 8-(Substituted-alkyl)-7,8-dihydro-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidines



no.	R^1	R^5	method[a]	mp, °C	recrystn solvent	yield, %	formula[b]	mean IVP[c]	mean HI[d]
72	H	$(CH_2)_2N(C_2H_5)_2$	D	92	*i*-Pr_2O	46	$C_{14}H_{22}N_6$	1	0
73	H	$(CH_2)_2$-c-NC_4H_8	D	89–90	benzene–*i*-Pr_2O	59	$C_{14}H_{20}N_6$	2	0
74	H	$(CH_2)_2$-c-NC_5H_{10}	D	143–144	benzene	27	$C_{15}H_{22}N_6 \cdot 0.5H_2O$	2	10
75	H	$(CH_2)_2$-c-$N(CH_2CH_2)_2O$	D	134–135	benzene	38	$C_{14}H_{20}N_6O$	16	5
76	H	$(CH_2)_2$-c-$N(CH_2CH_2)_2NCH_3$	D	114–116	THF–*i*-Pr_2O	52	$C_{15}H_{23}N_7 \cdot 0.5H_2O$	20	10
77	H	$(CH_2)_3N(CH_3)_2$	D	87–88	benzene–*i*-Pr_2O	42	$C_{13}H_{20}N_6$	0	10
78	H	$(CH_2)_3N(n\text{-}C_4H_9)_2$	D	67–68	*i*-Pr_2O	47	$C_{19}H_{32}N_6$	0	40
79	H	$(CH_2)_3N(CH_2CH_2OH)_2$	D	125–127	MeOH–*i*-Pr_2O	28	$C_{15}H_{24}N_6O_2$	0	45
80	H	$(CH_2)_3$-c-NC_4H_8	D	149–150	benzene–*i*-Pr_2O	70	$C_{15}H_{22}N_6$	0	75
81	CH_3	$(CH_2)_3$-c-NC_4H_8	D	112–113	*i*-Pr_2O	18	$C_{16}H_{24}N_6$	0	10
82	C_6H_5	$(CH_2)_3$-c-NC_4H_8	D	183–185	EtOH–*i*-Pr_2O	22	$C_{21}H_{26}N_6$	105	44
83	4-Cl-C_6H_4	$(CH_2)_3$-c-NC_4H_8	D	210–213	EtOH	51	$C_{21}H_{25}ClN_6$	*e*	0
84	4-CH_3O-C_6H_4	$(CH_2)_3$-c-NC_4H_8	D	178–180	EtOH–*i*-Pr_2O	46	$C_{22}H_{28}N_6O$	0	0
85	H	$(CH_2)_3$-c-NC_5H_{10}	D	137–138	benzene–*i*-Pr_2O	60	$C_{16}H_{24}N_6$	5	45
86	H	$(CH_2)_3$-c-$N(CH_2CH_2)_2O$	D	133–134	benzene–*i*-Pr_2O	66	$C_{15}H_{22}N_6O$	3	40
87	H	$(CH_2)_3$-c-$N(CH_2CH_2)_2N(CH_2)_3$	C	230–232	benzene–*i*-Pr_2O	27	$C_{26}H_{36}N_{12} \cdot 0.5H_2O$	3	0
88	H	$(CH_2)_2OH$	D	207–208	EtOH	71	$C_{10}H_{13}N_5O$	12	0
89	H	$(CH_2)_3OH$	D	158–160	EtOH	74	$C_{11}H_{15}N_5O$	12	105
90	H	$CH_2CH(OH)CH_3$	C	179–180	EtOH–*i*-Pr_2O	80	$C_{11}H_{15}N_5O$	*e*	5
91	H	$C(CH_3)_2CH_2OH$	C	229–231	EtOH	12	$C_{12}H_{17}N_5O$	38	75
92	H	$CH_2CH(OH)CH_2OH$	C	181–183	EtOH	52	$C_{11}H_{15}N_5O_2$	*e*	15
93	H	$(CH_2)_2O(CH_2)_2OH$	C	141–142	EtOH	65	$C_{12}H_{17}N_5O_2$	22	10
94	H	$CH(CH_3)CH_2OC_6H_5$	C	169–170	MeOH–*i*-Pr_2O	45	$C_{17}H_{19}N_5O_2$	63	65
95	H	$(CH_2)_2COC_6H_5$	C	181–182	EtOH	75	$C_{17}H_{17}N_5O$	32	17
96	H	$(CH_2)_2SH$	C	152–154	EtOH–*i*-Pr_2O	50	$C_{10}H_{13}N_5S$	285	10
97	H	$(CH_2)_2Cl$	F	167–168	THF–*i*-Pr_2O	60	$C_{10}H_{12}ClN_5$		
98	H	$(CH_2)_3Cl$	F	137–138	THF	90	$C_{11}H_{14}ClN_5$		
99	H	$(CH_2)_2OCOC_6H_2$-3,4,5-$(OCH_3)_3$	G	197–199	EtOH	63	$C_{20}H_{21}N_5O_5$	21	0
100	H	$(CH_2)_2OCO$-3-C_5H_4N	G	159–160	EtOH	74	$C_{16}H_{16}N_6O_2$	7	30
101	H	$(CH_2)_3OCOC_6H_2$-3,4,5-$(OCH_3)_3$	G	145–146	EtOH–*i*-Pr_2O	65	$C_{21}H_{23}N_5O_5$	26	10
102	H	$(CH_2)_3OCO$-3-C_5H_4N	G	153–154	EtOH	82	$C_{17}H_{18}N_6O_2$	24	30

[a,b] See, respectively, footnotes *a* and *b* in Table II. [c-e] See, respectively, footnotes *c–e* in Table IV.

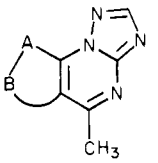
Table VII. Coronary Vasodilating and Antihypertensive Activities of 8*H*-Pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidines



no.	R^3	R^5	method[a]	mp, °C	recrystn solvent	yield, %	formula[b]	mean IVP[c]	mean HI[d]
109	CH_3	t-C_4H_9	L	127–128	i-Pr_2O	35	$C_{13}H_{17}N_5$	330	20
110	H	H	M	300 dec	DMF	41	$C_8H_7N_5$	45	60
111	H	i-C_4H_9	M	121–122	i-PrOH-H_2O	47	$C_{12}H_{15}N_5$	38	15
112	H	t-C_4H_9	M	148–149	i-PrOH-H_2O	73	$C_{12}H_{15}N_5$	246	160
113	H	$CH_2C_6H_4$-4-OCH_3	M	151–152	i-PrOH-H_2O	34	$C_{16}H_{15}N_5O$	55	0
114	H	$CH_2C_6H_4$-2-Cl	M	209–210	EtOH	41	$C_{15}H_{12}ClN_5$	22	12

[a,b] See, respectively, footnotes *a* and *b* in Table II. [c,d] See, respectively, footnotes *c* and *d* in Table IV.

Table VIII. Coronary Vasodilating and Antihypertensive Activities of 1,2,4-Triazolo[1,5-*a*]pyrimidines Fused to Thiophene, Pyran, Pyridine, and Pyridazine



no.	A	B	mp, °C	recrystn solvent	yield, %	formula[a]	mean IVP[b]	mean HI[c]
118	S	$(CH_2)_2$	231–232	EtOH	87	$C_8H_8N_4S$	0	10
119	NCH_3	$NH(CH_2)_2$	224–226	EtOH	51	$C_9H_{12}N_6$	0	5
120	NCH_3	$NCH_3(CH_2)_2$	172–174	THF	53	$C_{10}H_{14}N_6$	45	25
123	O	$(CH_2)_3$	222–223	EtOAc	6	$C_9H_{10}N_4O$	0	
125	$NCH_2C_6H_4$-2-Cl	$(CH_2)_3$	215–217	EtOH	51	$C_{16}H_{16}ClN_5$	*d*	10
126	$NCH_2C_6H_4$-2-F	$(CH_2)_3$	194–196	EtOH	42	$C_{16}H_{16}FN_5$	*d*	0

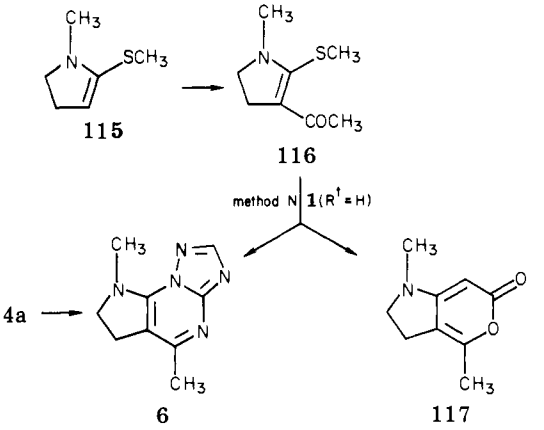
[a] See footnote *b* in Table II. [b-d] See, respectively, footnotes *c–e* in Table IV.

acetyl chloride, followed by condensation with 1 (R^1 = H) (method N), gave a product identical with **6** prepared by method D. In addition, a structural determination of **23** was made by X-ray analysis.[7]

The synthesis of the triazolopyrimidines fused to thiophene, pyran, pyridine, and pyridazine is outlined in Scheme IV. Condensation of **4a** with thiourea and the appropriate hydrazines afforded the thienotriazolopyrimidine **118** and the pyridazinotriazolopyrimidines **119** and **120**, respectively (Table VIII). The dichloro derivative **122** which was obtained from 1 (R^1 = H) and ethyl 2-(3-chloropropyl)acetoacetate[8] was reacted with *tert*-butylamine to afford the pyranotriazolopyrimidine **123** and the 7-(*tert*-butylamino) compound **124** instead of the expected 9-*tert*-butyl-6,7,8,9-tetrahydro-5-methylpyrido[3,2-*e*]-[1,2,4]triazolo[1,5-*a*]pyrimidine. The conversion of **122** to the pyridotriazolopyrimidines **125** and **126** was accomplished by heating with *o*-chloro- or *o*-fluorobenzylamine, respectively.

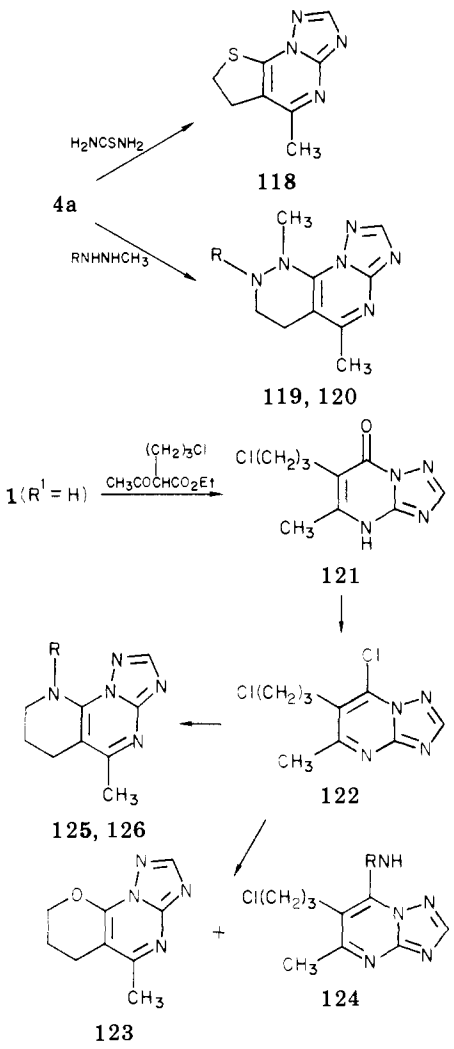
Biological Results and Discussion. Preliminary screening of coronary vasodilating activity was conducted in isolated guinea pig hearts perfused with a constant volume of Tyrode solution by Langendorff's technique. The test compounds were injected intraarterially in a bolus of 100 μg. Coronary vasodilating activity was expressed as a magnitude of integrated vasodilating potency (IVP), the product of the compound-induced maximum percent decrease in the perfusion pressure and the duration of the effect in minutes. For integrated vasodilating potency above 500, coronary vasodilating activity was regarded as excellent, 500–100 as marked, 100–60 as moderate, 60–30 as slight, and below 30 as insignificant. Screening results of the 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines **5–102** are shown in Tables IV–VI. When compared to trapidil, 14 compounds, **9**, **23**, **28**, **29**, **31**, **35**, **39**, **45**, **55**, **58**, **62**, **68**, **94**, and **96**, were found to have integrated vasodilating potency greater than trapidil, with 2 of the 14 (**23** and **35**) possessing excellent activity. Simple manipulation of the 8-alkyl side chain of the 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines indicated that integrated vasodilating potency tended to increase with an increase, up to a maximum of four or five, in the number of carbon atoms (Table IV).

Scheme III



(7) Crystals of **23**·HBr·$(H_2O)_3$ were used for X-ray analysis.
(8) V. P. Gol'mov and V. N. Balakhontseva, *Uch. Zap., Pyatigorsk. Farm. Inst.*, **2**, 322 (1957); *Chem. Abstr.*, **54**, 19475*h* (1960).

Scheme IV



However, a striking specificity of structure was observed in that the 8-*tert*-butyl (**23**) and 8-*tert*-amyl derivatives (**35**) were especially active, but activity markedly diminished when the *tert*-butyl group was replaced with the *n*-butyl, *sec*-butyl, or *n*-amyl group (**17**, **21**, and **33**). A marked decrease in potency found with the 8-ethyl derivative **8**, resulting from the cyclization of an ethylamino chain of trapidil to the triazolopyrimidine nucleus, was of interest. Coronary vasodilating activity changed to coronary vasoconstricting action when the side chain was lengthened to *n*-decyl (**41**) and *n*-dodecyl (**42**). Within the 8-aryl- or 8-aralkyl-substituted 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines, compounds **52**, **55**, **56**, **58**, **62**, and **66–68** showed marked integrated vasodilating potency, but none had levels of activity comparable to **23** and **35** (Table V). The presence of an hydroxy function in the 8-*tert*-butyl group of **23**, as in compound **91**, resulted in a marked decrease of coronary vasodilating activity, similar to that of the 8-(hydroxyalkyl)-substituted 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines **88–89** (Table VI). The 8-(aminoalkyl) or 8-[(acyloxy)alkyl] derivatives **72–87** and **99–102**, with the exception of **82**, were substantially inactive (Table VI).

Therefore, in order to study the influence of the substituent on coronary vasodilating activity, **23**, one of the most active compounds, was selected. The introduction of a methyl or ethyl group at the 2, 6, or 7 position of **23** led to less active compounds (**24**, **29**, **30**, and **31**). The introduction of an aryl group, such as phenyl, *p*-chlorophenyl, *p*-methoxyphenyl, and 3,4,5-trimethoxyphenyl, at the 2 position of **23** (**25–27**) showed coronary vasoconstricting action, with the exception of 3,4,5-trimethoxyphenyl derivative **28**. In general, with the exception of **82**, the other 2-aryl-substituted 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines, **11–13**, **18**, **59**, **63**, and **83**, were also found to be coronary vasoconstrictors. Replacing the methyl group of **23** by the cyclopropyl group to give the compound **32** showed a decrease in coronary vasodilating activity, indicating that, for the activity, the methyl group attached at the 5 position in **23** was preferred. A similar reduction in the activity was observed with **35** and **36** (Table IV). Conversion of **23** to the quaternary methiodide **47** led to a substantially inactive compound. Coronary vasodilating activity was generally reduced by dehydrogenation of the 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines (e.g., **23** vs. **112**). However, compounds **109** and **112** still retained marked activity (Table VII).

Replacing the pyrrole ring of the 7,8-dihydro-6*H*-pyrrolotriazolopyrimidines by thiophene, pyran, and pyridazine led to the slightly active compound **120** and the inactive compounds **118**, **119**, and **123**. The pyridotriazolopyrimidines **125** and **126** showed coronary vasoconstricting activity (Table VIII).

Antihypertensive activity was evaluated in the spontaneously hypertensive rat assay. Genetically hypertensive rats, having a systolic blood pressure of 180 mmHg or greater, were administered the test compounds orally with 0.3% carboxymethylcellulose as the vehicle. Systolic blood pressures were measured in the tail, by the plethysmography method. A predose measurement of blood pressure was made to establish the control level. Compounds were administered at a dose of 30 mg/kg, and blood pressure readings were taken at intervals of 2, 4, and 6 h after dosing. To measure antihypertensive activity, the area under the time–hypotensive response curve for a 6-h period was expressed as a hypotensive index (HI).

The results obtained are shown in Tables IV–VIII. Four compounds, **17**, **51**, **58**, and **112**, were found to be more active than mecamylamine but less active than guanethidine sulfate. The activity of **23** was approximately equal to that of guanethidine sulfate. Since the finding of stronger coronary vasodilating agents than trapidil was one of our synthetic goals, we also evaluated the data in terms of coronary vasodilating activity as described above. Among these five compounds, only **23** showed excellent integrated vasodilating potency (Table IV). Compounds **58** and **112** possessed integrated vasodilating potency greater than trapidil but were less active than **23**. Replacing the *tert*-butyl group of **23** by the *tert*-amyl group, as in compound **35**, resulted in a marked decrease in antihypertensive activity, although coronary vasodilating activity of **35** was nearly equipotent to **23**. These results would appear to indicate that the *tert*-butyl group attached at the 8 position in **23** plays an important role in coronary vasodilating and antihypertensive activities. The dehydrogenation of **23** to give **112** had little influence on antihypertensive activity (Table VII).

The triazolopyrimidines fused to thiophene, pyridine, and pyridazine showed no significant antihypertensive activity, with the exception of **120** which had weak activity (Table VIII).

On the basis of the above observations, **23** was selected to estimate its effect on the coronary blood flow in anesthetized, open-chest dogs. The results obtained are shown in Table IX. When **23** was injected intravenously, it produced a dose-related increase in coronary sinus outflow, even though systemic blood pressure decreased, indicating that the vasodilating action of **23** seemed to be

Table IX. Effects of 23 and Trapidil on Coronary Blood Flow and Blood Pressure in Anesthetized Dogs

compd	dose, mg/kg, iv	no. of dogs	increase in coronary BF,[a] mean ± SE			max % decrease in MBP,[a] mean ± SE
			max %	duration, min	rel potency[b]	
23	0.1	3	34.7 ± 13.5	4.3 ± 0.4	0.7 ± 0.2	−3.3 ± 0.3[c]
	0.3	4	132.3 ± 36.1[c]	9.3 ± 1.9	3.8 ± 0.5[c]	−11.7 ± 2.3[c]
	1.0	7	219.8 ± 49.3[c]	10.6 ± 3.0	8.4 ± 0.6[c]	−32.3 ± 4.4[c]
trapidil	0.3	3	20.3 ± 7.2	2.8 ± 0.7	0.4 ± 0.1	−16.8 ± 7.1
	1.0	12	46.8 ± 6.7[c]	4.7 ± 0.3	1.0	−22.8 ± 2.3[c]
	3.0	5	94.0 ± 16.9[c]	11.4 ± 1.7	4.4 ± 0.3[c]	−37.0 ± 2.8[c]

[a] Abbreviations used are: BF, blood flow; MBP, mean blood pressure. [b] Relative potency is based on the integrated coronary blood flow response to 1 mg/kg, iv, of trapidil. [c] Significantly different from the predose level ($p < 0.05$).

highly selective to the coronary arteries. The coronary vasodilating activity of **23** was approximately eight times as potent as that of trapidil.

Thus, **23** was thought to be the most promising potential coronary vasodilating agent. Further investigation of **23** is now in progress in our laboratories.

Experimental Section

Melting points were determined on a Yamato capillary melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 221. NMR spectra were recorded on a Varian A-60 spectrometer using Me_4Si (δ 0.00) as an internal standard. UV spectra were obtained using Cary 14 and 118-C spectrometers. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within 0.4% of the theoretical values. Typical examples of the various methods are described.

3-[[1-(Tetrahydro-2-oxo-3-furyl)ethylidene]amino]-1,2,4-triazole (2a). To a solution of 1 (R^1 = H; 16.8 g, 0.2 mol) and α-acetyl-γ-butyrolactone (38.4 g, 0.3 mol) in absolute EtOH (60 mL) was added BF_3–MeOH (2 mL). The mixture was allowed to stand at room temperature for 72 h. A colorless precipitate was collected and recrystallized from EtOH to give 34 g (88%) of colorless needles: mp 156–158 °C; UV (EtOH) λ_{max} 306.3 nm (log ϵ 4.31); NMR (Me_2SO-d_6) δ 2.37 (s, 3, CH_3), 2.88 (t, J = 8 Hz, 2, β-CH_2), 4.33 (t, J = 8 Hz, 2, γ-CH_2), 8.4 (s, 1, C_5H), 10.37 (s, 1 NH), 13.58 (s, 1, NH); MS m/e 194 (M^+), 150 (M − CO_2).

Method A. 6-(2-Hydroxyethyl)-5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7(4H)-one (3a). A mixture of **2a** (1.9 g, 9.9 mmol) and triethylamine (1 g, 9.9 mmol) in H_2O (5 mL) was allowed to stand at room temperature for 18 h. The solution was neutralized with AcOH to give a crystalline product. Recrystallization from H_2O afforded 1.7 g (89%) of colorless prisms: mp 265–266 °C dec; UV (EtOH) λ_{max} 210.1 nm (log ϵ 4.35), 240.9 (3.66), 279.0 (4.05).

Method B. 6-(2-Hydroxyethyl)-5-methyl-2-(3,4,5-trimethoxyphenyl)-1,2,4-triazolo[1,5-a]pyrimidin-7(4H)-one (3h). Aminotriazole 1 [R^1 = 3,4,5-$(CH_3O)_3$-C_6H_2] was prepared analogously to 3-amino-5-phenyl-1,2,4-triazole[9] beginning with aminoguanidine hydrogen carbonate and 3,4,5-trimethoxybenzolyl chloride: overall yield 29%; mp 195–196 °C. Anal. ($C_{11}H_{14}N_4O_3$) C, H, N.

A mixture of 1 [R^1 = 3,4,5-$(CH_3O)_3$-C_6H_2; 3 g, 12 mmol) and α-acetyl-γ-butyrolactone (1.5 g, 11.7 mmol) was heated at 155 °C for 1 h under reduced pressure. After the mixture cooled, the solid was recrystallized from MeOH to give 3.2 g (47%) of colorless needles, mp 274–275 °C dec.

7-Chloro-6-(2-chloroethyl)-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine (4a). A mixture of **3a** (85 g, 0.44 mol) and $POCl_3$ (120 mL) was refluxed for 3 h with stirring. After cooling, the mixture was poured into ice–H_2O, and a crystalline solid was collected by filtration. The product was recrystallized from THF–isopropyl ether to give 79 g (78%) of pale yellow crystals, mp 89–91 °C.

Method C. 8-*tert*-Butyl-7,8-dihydro-5-methyl-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine (23). A mixture of **4a** (2.3 g, 9.95 mmol), *tert*-butylamine (1 g, 13.7 mmol), and Na_2CO_3 (1.8 g, 17.0 mmol) in EtOH (20 mL) was refluxed for 2 h, cooled, and filtered. The filtrate was concentrated in vacuo to give a solid, which was recrystallized from *i*-PrOH–H_2O to give 1.6 g (70%) of colorless needles, mp 177–178 °C.

Method D. 7,8-Dihydro-5-methyl-8-(2-morpholinoethyl)-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine (75). A mixture of **4a** (2.3 g, 9.95 mmol), *N*-(2-aminoethyl)morpholine (1.4 g, 10.8 mmol), and triethylamine (3 mL, 21.5 mmol) in EtOH (20 mL) was refluxed for 2 h, cooled, and filtered. The filtrate was concentrated in vacuo and made basic with aqueous NaOH solution to afford crystals, which were recrystallized from benzene to give 1.3 g (38%) of pale yellow needles, mp 134–135 °C.

Method E. 8-(2,6-Dichlorophenyl)-7,8-dihydro-5-methyl-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine (49). A mixture of **4a** (2 g, 8.65 mmol) and 2,6-dichloroaniline (1.45 g, 8.95 mmol) was heated at 190 °C for 0.5 h. After cooling, the mixture was treated with aqueous Na_2CO_3 solution and extracted with $CHCl_3$. The extract was concentrated, and the residue was purified by chromatography on silica gel and recrystallized from THF–isopropyl ether to give 1.08 g (39%) of colorless needles, mp 192–194 °C.

Method F. 8-(2-Chloroethyl)-7,8-dihydro-5-methyl-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine (97). A mixture of **88** (1 g, 4.56 mmol) and $SOCl_2$ (0.8 g, 6.72 mmol) in CH_2Cl_2 (10 mL) was refluxed for 8 h and extracted with H_2O. The extract was made basic with K_2CO_3 to give crystals, which were recrystallized from THF–isopropyl ether to afford 0.65 g (60%) of colorless needles, mp 167–168 °C.

Method G. 7,8-Dihydro-5-methyl-8-[2-[(3,4,5-trimethoxybenzoyl)oxy]ethyl]-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine (99). A mixture of **97** (1 g, 4.21 mmol) and 3,4,5-trimethoxybenzoic acid potassium salt (1.15 g, 4.59 mmol) in DMF (10 mL) was refluxed for 0.5 h. The mixture was concentrated in vacuo. The residue was washed with H_2O and recrystallized from EtOH to give 1.1 g (63%) of colorless needles, mp 197–199 °C.

Method H. 7,8-Dihydro-5-methyl-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine (5). A mixture of **4a** (2 g, 8.65 mmol), acetamidine hydrochloride (0.82 g, 8.67 mmol), and Na_2CO_3 (2.76 g, 26 mmol) in EtOH (40 mL) was refluxed for 4 h, cooled, and filtered. The filtrate was concentrated in vacuo and the residue was recrystallized from EtOH to give 1.1 g (73%) of pale yellow needles, mp 250–252 °C.

Method I. 8-Benzyl-7,8-dihydro-5-methyl-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine (51). To a solution of **5** (175 mg, 0.999 mmol) in DMF (10 mL) was added NaH (52.9% in mineral oil, 54 mg, 1.19 mmol). The mixture was stirred for 0.5 h and then refluxed with benzyl bromide (205 mg, 1.20 mmol) for 1 h with stirring. The mixture was concentrated in vacuo and extracted with $CHCl_3$. The extract was concentrated to give a solid, which was purified by chromatography on silica gel and recrystallized from EtOH to afford 118 mg (45%) of colorless crystals, mp 170–172 °C. These were identical with **51** prepared by method C.

Method J. 8-*tert*-Butyl-7,8-dihydro-5-methyl-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine Methiodide (47). A mixture of **23** (2.31 g, 9.99 mmol) and CH_3I (7.1 g, 50 mmol) in EtOH (20 mL) was refluxed for 16 h. The mixture was concentrated in vacuo and the residue was recrystallized from EtOH–isopropyl ether to give 0.6 g (16%) of pale yellow needles, mp 204 °C dec.

(9) E. Hoggarth, *J. Chem. Soc.*, 612 (1950).

Method K. 8-*tert*-Butyl-7,8-dihydro-5,6-dimethyl-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (29). A mixture of 107 (1.5 g, 5.7 mmol) and $SOCl_2$ (1.36 g, 11.4 mmol) in CH_2Cl_2 (50 mL) was stirred for 1 h and then stirred with 20% aqueous NaOH solution (20 mL) for an additional 2 h at room temperature. The organic layer was separated and concentrated in vacuo. The residue was recrystallized from isopropyl ether to give 0.93 g (67%) of colorless needles, mp 115–116 °C.

Method L. 8-*tert*-Butyl-5,6-dimethyl-8*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (109). A mixture of 108 (102 mg, 0.39 mmol), 0.1 N HCl (10 mL), and $CHCl_3$ (5 mL) was stirred at room temperature for 1 h. The organic layer was separated and concentrated in vacuo. The residue was recrystallized from isopropyl ether to give 33.6 mg (35%) of pale yellow needles: mp 127–128 °C; NMR ($CDCl_3$) δ 1.92 [s, 9, $C(CH_3)_3$], 2.46 (d, J = 1 Hz, 3, C_6CH_3), 2.92 (s, 3, C_5CH_3), 7.00 (m, 1, C_7H), 8.37 (s, 1, C_2H).

Method M. 8-*tert*-Butyl-5-methyl-8*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (112). A mixture of **23** (13.86 g, 0.06 mol) and active MnO_2 (36.51 g, 0.42 mol) in benzene (300 mL) was refluxed with stirring for 50 h. After filtration, the filtrate was concentrated in vacuo to give a crystalline product, which was recrystallized from *i*-PrOH–H_2O to afford 10.1 g (73%) of colorless prismis, mp 148–149 °C. This compound was obtained also by UV irradiation of a solution of **23** in MeOH, yield 25%.

Method N. 7,8-Dihydro-5,8-dimethyl-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (6). To a solution of 115 (2.58 g, 20 mmol) and triethylamine (2.4 g, 24 mmol) in dry DMF (15 mL) was added dropwise a solution of AcCl (1.65 g, 21 mmol) in DMF (8 mL) over a period of 50 min. The mixture was stirred for an additional 1.5 h at 0 °C and filtered. The filtrate was added to a solution of 1 (R^1 = H; 1.68 g, 20 mmol) in DMF (15 mL) and then heated at 80 °C for 10 h. The mixture was concentrated in vacuo and the residue was fractionated by chromatography on silica gel. After concentration of the first eluate, recrystallization from EtOH gave 0.2 g (12%) of colorless needles: mp 164–166 °C; IR (Nujol) 1710, 1670, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.06 (t, J = 2 Hz, 3, C_4CH_3), 2.80 (m, 2, C_3H_2), 2.84 (s, 3, N-CH_3), 3.62 (t, J = 8 Hz, 2, C_2H_2), 4.71 (s, 1, C_7H). This compound was assumed to be 2,3-dihydro-1,4-dimethylpyrano[4,3-*b*]pyrrol-6(1*H*)-one (117). Anal. ($C_9H_{11}NO_2$) C, H, N.

The crystals obtained from the second eluate were recrystallized from EtOH to give 0.1 g (3%) of colorless needles, mp 215–217 °C. These were identical with **6** prepared by method D.

Ethyl 2-[5-Methyl-7(4*H*)-oxo-1,2,4-triazolo[1,5-*a*]pyrimidin-6-yl]propionate (103) and Ethyl 2-[7-Methyl-5(4*H*)-oxo-1,2,4-triazolo[1,5-*a*]pyrimidin-6-yl]propionate (104). A mixture of 1 (R^1 = H; 1.68 g, 20.0 mmol) and diethyl 2-acetyl-3-methylsuccinate[5] (4.6 g, 20 mmol) in AcOH (10 mL) was refluxed with stirring for 10 h. The mixture was poured into ice–H_2O and extracted with $CHCl_3$. The extract was concentrated in vacuo and the residue was fractionated by chromatography on silica gel (5% EtOH–$CHCl_3$). After concentration of the first eluate, recrystallization from EtOH gave 0.56 g (11%) of **104** as colorless needles: mp 139–141 °C; IR (Nujol) 1720, 1700 cm^{-1} (C=O); UV (EtOH) λ_{max} 230.7 nm (log ϵ 4.12), 285.4 (3.59); NMR ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 3, CH_2CH_3), 1.72 (d, J = 7 Hz, 3, $CHCH_3$), 2.31 (d, J = 2 Hz, 3, C_7CH_3), 4.42 (q, J = 7 Hz, 2, CH_2CH_3), 5.08 (dd, J = 7 and 2 Hz, 1, $CHCH_3$), 7.92 (s, 1, C_2H). Anal. ($C_{11}H_{14}N_4O_3$) C, H, N.

The crystals obtained from the second eluate were recrystallized from EtOAc to give 0.57 g (11%) of **103** as colorless needles: mp 139–141 °C; IR (Nujol) 1735, 1670 cm^{-1} (C=O); UV (EtOH) λ_{max} 209.2 nm (log ϵ 4.31), 245.9 (3.70), 277.4 (4.01); NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3, CH_2CH_3), 1.51 (d, J = 7 Hz, 3, $CHCH_3$), 2.57 (s, 3, C_5CH_3), 3.8–4.2 (m, 3), 8.15 (s, 1, C_2H). Anal. ($C_{11}H_{14}N_4O_3$) C, H, N.

2-(7-*tert*-Butyl-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-6-yl)propionic Acid (105). The chloride (10.6 g) prepared by heating **103** (10 g, 0.04 mol) with $POCl_3$ (40 mL, 0.44 mol) was added to a solution of *tert*-butylamine (6.34 g, 0.087 mol) in *i*-PrOH (40 mL), and the mixture was refluxed for 7 h. The mixture was concentrated in vacuo and extracted with $CHCl_3$. The extract was washed with H_2O and concentrated to give an oil (10.8 g, 90%), which was stirred with 5% KOH (80 mL) at room temperature for 1 h. The mixture was made acidic with HCl. The resulting crystals were recrystallized from EtOH to give 6.47 g (66%) of colorless prisms, mp 194.5 °C dec. Anal. ($C_{13}H_{19}N_5O_2$) C, H, N.

8-*tert*-Butyl-7,8-dihydro-5,6-dimethyl-7-oxo-6*H*-pyrrolo-[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (106). A mixture of **105** (1.39 g, 5.01 mmol) and DCC (1.24 g, 6.01 mmol) in benzene (10 mL) was stirred at room temperature for 4 h and allowed to stand overnight. The mixture was filtered and the filtrate was washed with 1 N HCl and concentrated in vacuo. The residue was recrystallized from EtOAc–isopropyl ether to give 0.3 g (23%) of pale yellow needles: mp 128–129 °C; IR (Nujol) 1750 cm^{-1} (C=O). Anal. ($C_{13}H_{17}N_5O$) C, H, N.

7-(*tert*-Butylamino)-6-(2-hydroxy-1-methylethyl)-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (107). To a solution of **106** (259 mg, 0.99 mmol) in MeOH (10 mL) was added $NaBH_4$ (113 mg, 2.9 mmol) under ice cooling, and the mixture was stirred at room temperature for 4 h. Additional $NaBH_4$ (113 mg, 2.9 mmol) was added three times every 1 h. The mixture was allowed to stand overnight and extracted with $CHCl_3$. The extract was evaporated to afford crystals, which were recrystallized from EtOH to give 167 mg (63%) of colorless prisms: mp 224–225 °C dec; NMR (Me_2SO-d_6) δ 1.38 (d, J = 7 Hz, 3, $CHCH_3$), 1.59 [s, 9, $C(CH_3)_3$], 2.52 (s, 3, C_5CH_3), 3.70–3.95 (m, 3, $CHCH_2$-O), 6.03 (t, J = 4 Hz, 1, OH), 8.22 (br, 1, NH), 8.37 (s, 1, C_2H). Anal. ($C_{13}H_{21}N_5O$) C, H, N.

8-*tert*-Butyl-7,8-dihydro-7-hydroxy-5,6-dimethyl-6*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (108). To a solution of **106** (259 mg, 0.99 mmol) in MeOH (10 mL) was added $NaBH_4$ (113 mg, 2.9 mmol) under ice cooling. The mixture was stirred for 0.5 h, decomposed with AcOH (0.2 mL), made basic with 5% $NaHCO_3$, and extracted with $CHCl_3$. The extract was concentrated in vacuo and the residue was recrystallized from MeOH to give 95 mg (36%) of colorless prisims: mp 200–202 °C; NMR (Me_2SO-d_6) δ 1.12 (d, J = 7 Hz, 3, C_6CH_3), 1.75 [s, 9, $C(CH_3)_3$], 2.38 (s, 3, C_5CH_3), 2.98 (q, J = 7 Hz, 1, C_6H), 5.22 (d, J = 8 Hz, 1, C_7H), 6.48 (d, J = 8 Hz, 1, OH), 8.40 (s, 1, C_2H). Anal. ($C_{13}H_{19}N_5O$) C, H, N.

1-Methyl-2-(methylthio)-2-pyrroline (115). This compound was prepared by a modified Gompper's method[6] using 1,5-diazabicyclo[5.4.0]undec-5-ene instead of *t*-BuOK: yield 47%.

5-Methyl-6,7-dihydrothieno[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (118). A mixture of 4a (1 g, 4.33 mmol) and thiourea (0.32 g, 4.20 mmol) in EtOH (10 mL) was refluxed for 2 h and concentrated in vacuo. To the residue was added 3 N K_2CO_3 (10 mL), and the resulting mixture was extracted with $CHCl_3$. The extract was evaporated and the residue was recrystallized from EtOH to give 0.7 g (87%) of pale yellow needles, mp 231–232 °C.

6,7,8,9-Tetrahydro-5,9-dimethylpyridazino[4,3-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (119). A mixture of **4a** (2 g, 8.65 mmol), methylhydrazine (0.4 g, 8.68 mmol), and Na_2CO_3 (3.67 g, 34.6 mmol) in THF (20 mL) was refluxed for 6 h and concentrated in vacuo. The residue was dissolved in H_2O and extracted with $CHCl_3$. The extract was concentrated and the residue was recrystallized from EtOH to give 0.9 g (51%) of colorless needles: mp 224–226 °C; NMR (CF_3CO_2D) δ 2.66 (s, 3, C_5CH_3), 3.05 (t, J = 6 Hz, 2, C_6H_2), 3.65 (t, J = 6 Hz, 2, C_7H_2), 4.29 (s, 3, N_9CH_3), 8.55 (s, 1, C_2H); IR (Nujol) 3220 cm^{-1} (NH); UV (EtOH) λ_{max} 222.2 nm (log ϵ 4.31), 308.9 (4.08).

6,7,8,9-Tetrahydro-5,8,9-trimethylpyridazino[4,3-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (120). The procedure was the same as that used for **119**, except that *N,N'*-dimethylhydrazine was used. Colorless needles resulted: mp 172–174 °C; NMR (CF_3CO_2D) δ 2.69 (s, s, C_5CH_3), 2.94 (s, 3, N_8CH_3), 3.08 (t, J = 6 Hz, 2, C_6H_2), 3.55 (t, J = 6 Hz, 2, C_7H_2), 4.26 (s, 3, N_9CH_3), 8.53 (s, 1, C_2H); UV (EtOH) λ_{max} 224.2 nm (log ϵ 4.29), 310.9 (4.09).

Ethyl 2-(3-Chloropropyl)acetoacetate. This compound was prepared by a modified Gol'mov's method[8] using benzene instead of EtOH as solvent: yield 23%.

6-(3-Chloropropyl)-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one (121). A mixture of 1 (R^1 = H; 1.4 g, 16.7 mmol) and ethyl 2-(3-chloropropyl)acetoacetate (4.57 g, 22.1 mmol) in AcOH (20 mL) was refluxed for 6 h and treated by a procedure similar to that described for **103**. Colorless needles resulted: yield 56%; mp 180–181 °C. Anal. ($C_9H_{11}ClN_4O$) C, H, N, Cl.

7-Chloro-6-(3-chloropropyl)-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (122). This compound was prepared from **121** in a manner similar to that described for **4a**: yield 72%; mp 78–80

°C. Anal. ($C_9H_{10}Cl_2N_4$) C, H, N, Cl.

7,8-Dihydro-5-methyl-6*H*-pyrano[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (123) and 7-(*tert*-Butylamino)-6-(3-chloropropyl)-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (124). A mixture of **122** (0.61 g, 2.49 mmol) and *tert*-butylamine (0.73 g, 9.98 mmol) in EtOH (5 mL) was refluxed for 3 h and concentrated in vacuo. The residue was dissolved in H_2O and extracted with $CHCl_3$. Evaporation of the solvent gave a solid, which was fractionated by chromatography on silica gel (5% EtOH–$CHCl_3$). After concentration of the first eluate, the crystals were recrystallized from isopropyl ether to give 0.05 g (7.1%) of **124**: mp 121–123 °C; MS *m/e* 281 (M^+). Anal. ($C_{13}H_{20}ClN_5$) C, H, N, Cl.

The crystals obtained from the second eluate were recrystallized from EtOAc to give 0.03 g (6.3%) of **123**, mp 222–223 °C; MS *m/e* 190 (M^+). Anal. ($C_9H_{10}N_4O$) C, H, N.

9-(*o*-Chlorobenzyl)-6,7,8,9-tetrahydro-5-methylpyrido[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (125). A mixture of **122** (1.23 g, 5.02 mmol), *o*-chlorobenzylamine (0.78 g, 5.51 mmol), and triethylamine (5 mL) in EtOH (10 mL) was refluxed for 16 h and treated in a manner similar to method D: mp 215–217 °C; UV (EtOH) λ_{max} 215.6 nm (log ϵ 4.41), 268.0 (3.65), 315.1 (4.24).

Pharmacological Method. (1) **Evaluation of Integrated Vasodilating Potency (IVP) in Guinea Pig Hearts.** Guinea pigs of either sex weighing 250 to 500 g were killed by a blow on the head, and their hearts were immediately excised. The isolated hearts were perfused with Tyrode solution aerated with 95% oxygen and 5% CO_2 at 36 °C by Langendorff's technique[10] using a Harvard Model 1203 fixed rate pump. Perfusion pressure close to the aorta was measured with a Nihonkoden Model MPU 0.5 pressure transducer, amplified using a Nihonkoden Model RP-2 amplifier, and recorded continuously on a Nihonkoden Model WI-260 ink-writing oscillograph recorder. The test compounds were dissolved in 0.1 mL of saline or 0.01 N hydrochloric acid and injected intraarterially in 10 s in order to avoid any artifact from the injection itself. Because of constant volume perfusion, a fall in the perfusion pressure indicated coronary vasodilation resulting from the compound being screened. The coronary vasodilating activity for each compound was evaluated by the magnitude of integrated vasodilating potency (IVP) expressed as the product of the compound-induced maximum percent decrease in the perfusion pressure and the time period in minutes required for its return to the predose level. Trapidil, a coronary vasodilator, was used as a standard. Each result represented the mean value of the data obtained from three hearts. The integrated vasodilating potency of trapidil varied from 83 to 179, resulting in a mean value 142, while that of **23** varied from 676 to 1155, yielding a mean value 815.

(2) Effects on Coronary Blood Flow and Blood Pressure in Dogs. Effects of intravenous administration of **23** and trapidil on coronary blood flow were measured in mongrel dogs of either sex weighing 10 to 13 kg, respectively. The dogs were anesthetized with sodium pentobarbital (30 mg/kg iv), and the chest was opened under artificial respiration,[10] using an Aika Model 60-A respirator, with a frequency of 15 strokes/min and a tidal volume of 30 mL/kg. After systemic heparinization (1000 units/kg iv), a cannula was inserted into the coronary sinus through the right atrium and a loop was completed between the cannula and the right jugular vein. Coronary sinus outflow was recorded through a Nihonkoden Model MF-25 electromagnetic flow probe (3 mm in diameter). Blood pressure was measured with a Nihonkoden Model MPU 0.5 pressure transducer and recorded on a Nihonkoden Model WI-380 ink-writing oscillograph recorder. The test compounds were dissolved in 0.1 mL/kg saline containing 0.01 N HCl and injected into the femoral vein at rate of 0.1 mL/s. The results of several experiments were statistically evaluated using student's *t* test for paired samples.

(3) SHR Test for Antihypertensive Activity. Spontaneously hypertensive, male rats, 19 to 23 weeks of age, were used. The systolic blood pressure was determined by the tail plethysmography method using Natsume's apparatus. The tail cuff was inflated to approximately 240 mmHg. The pressure in the cuff was slowly released and, as the pressure fell below the systolic pressure, blood flow in the tail recurred and the volume of the tail increased. The blood pressure of each rat was determined three times, from which a mean value was derived. The animals were prewarmed for 30 min in an incubator set at 30 °C and then placed in a heated cage, set a 45 °C for 3 min, immediately prior to determining the blood pressure. Before any animal was included in the screening program, a 2-week training period was employed to acclimate the animal to the test environment. Groups of five rats, having systolic blood pressure of 180 mmHg or greater, were used per test. The test compounds (30 mg/kg) were administered orally in 0.3% carboxymethylcellulose (2 mL/kg) as a solution or suspension. The systolic blood pressure was determined 1 h before and 2, 4, and 6 h after dosing. The area under the time–hypotensive response curve was expressed as a hypotensive index, calculated from the formula:

$$\text{hypotensive index} = 5X - (2a + 2b + c)$$

where X is the systolic blood pressure 1 h before dosing, and a, b, and c are, respectively, the systolic blood pressure 2, 4, and 6 h after dosing. Each result represents the mean value of the data obtained from five rats. For a hypotensive index below 20, antihypertensive activity was regarded as insignificant.

Acknowledgment. We express our gratitude to Dr. Keisuke Murayama, director of these laboratories, for his encouragement. We are also indebted to K. Endo for his assistance in the pharmacological tests and members of the analytical section of these laboratories for the elemental analyses and spectral measurements.

(10) R. Charlier, *Handb. Exp. Pharmacol.*, (*New Ser.*), 31, 65–70 (1971).