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Registry No. (\pm)-2a, 27719-97-7; (\pm)-3a, 78701-31-2; (\pm)-3b, 78701-23-2; (\pm)-3c, 78701-43-6; (\pm)-4a, 16851-56-2; (+)-(S)-4a, 79815-20-6; (\pm)-5a, 78701-32-3; (R)-5a, 84171-38-0; (S)-5a, 84171-40-4; (\pm)-5b, 78701-24-3; (\pm)-5b-DCHA, 78701-41-4; (+)-(R)-5b, 78701-37-8; (-)-(S)-5b, 78701-38-9; (+)-(R)-5b-DHAA, 78701-39-0; (R)-5c, 84171-33-5; (S)-5c, 84171-39-1; (\pm)-6a, 78701-33-4; (R)-6a, 84171-36-8; (S)-6a, 84171-41-5; (\pm)-(R*,R*)-6b, 78701-25-4; (\pm)-(R*,S*)-6b, 78701-28-7; (-)-(S,S)-6b, 78779-25-6; (-)-(S,S)-6b-DCHA, 78821-38-2; (+)-(S,R)-6b, 78779-26-7; (+)-

(S,R)-6b-DCHA, 78821-39-3; (+)-(R,S)-6b, 78779-28-9; (+)-(R,S)-6b-DCHA, 78821-41-7; (-)-(R,R)-6b, 78779-27-8; (-)-(R,R)-6b-DCHA, 78821-40-6; (\pm)-(R*,R*)-6c, 84171-34-6; (\pm)-(R*,R*)-6c-DCHA, 84171-35-7; (S,S)-6c-DCHA, 84117-83-9; (S,S)-6d, 84117-84-0; (S,S)-6d-DCHA, 84117-85-1; (\pm)-(R*,R*)-6e, 78701-40-3; (\pm)-(R*,R*)-6e-DCHA, 78739-20-5; (\pm)-(R*,S*)-6e, 78701-54-9; (\pm)-(R*,S*)-6e-DCHA, 78701-55-0; (R)-7a, 84171-32-4; (S)-7a, 84171-37-9; (\pm)-(R*,S*)-7b, 78701-29-8; (\pm)-(R*,R*)-7b-DCHA, 78701-27-6; (-)-(S,S)-7b, 78779-29-0; (+)-(R,S)-7b, 83212-49-1; (-)-(S)-8, 72679-02-8; (R)-9, 74654-91-4; (S,S)-10, 78779-31-4; (4S,11aR)-11, 78701-50-5; (S)-12, 84117-80-6; 13-H₃CCO₂H, 84130-23-4; 14, 84117-81-7; ACE, 9015-82-1; methacryloyl chloride, 920-46-7; thiobenzoic acid, 98-91-9; *tert*-butyl indole-2-carboxylate, 84117-86-2; *tert*-butyl 1-(2-methyl-1-oxo-2-propenyl)indole-2-carboxylate, 84130-24-5; *tert*-butyl 1-[3-(benzoylthio)-2-methyl-1-oxopropyl]indole-2-carboxylate, 84117-87-3.

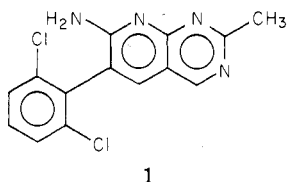
Antihypertensive Activity of 6-Arylpyrido[2,3-*d*]pyrimidin-7-amine Derivatives. 2. 7-Acyl Amide Analogues

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The effect of acylation with a variety of acids on the antihypertensive activity of 6-(2,6-dichlorophenyl)pyrido[2,3-*d*]pyrimidin-7-amine (1) is reported, and structure-activity relationships are discussed. Although several of the compounds show good oral antihypertensive activity in the conscious, spontaneously hypertensive rat (SHR), their activity profile appears to differ from 1 in that the onset of action is shortened at comparable blood pressure lowering doses, and the magnitude of effect is considerably greater at higher doses. A variety of urea, thiourea, guanidine, and amidine analogues also were prepared. Although many of these derivatives showed some antihypertensive effects when dosed orally to SHR, this activity was weaker and of shorter duration than that obtained with 1. Aqueous solubilities and hydrolytic stabilities for four of the more active compounds were measured and suggest that these do not function as prodrugs of 1.

In a recent paper,¹ we reported the antihypertensive activity of a novel series of 6-arylpyrido[2,3-*d*]pyrimidin-7-amine derivatives. Compound 1 emerged from that



study as the most promising candidate for further evaluation. Although 1 met our initial objectives of oral activity and long duration, the requirements for activity of the substituent in the 7-position of the pyridopyrimidine ring had not been explored. One transformation that seemed particularly appealing in this connection was acylation. If activity could be maintained, a variety of new polar and/or nonpolar moieties could easily be introduced into the molecule. However, if inherent activity was lost on acylation, the known relative lability of this type of heterocyclic amide might provide a prodrug form of 1 with altered absorption characteristics or modified onset or duration effects. Finally, from a purely chemical standpoint, acylation of the 7-amino group could provide activation for further transformations at this position, e.g., reduction or alkylation to alkylamino analogues. We thus explored

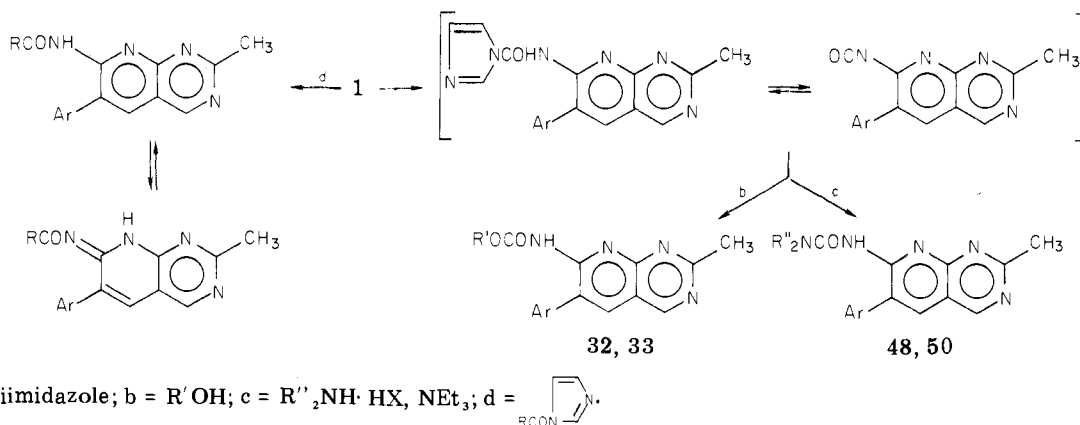
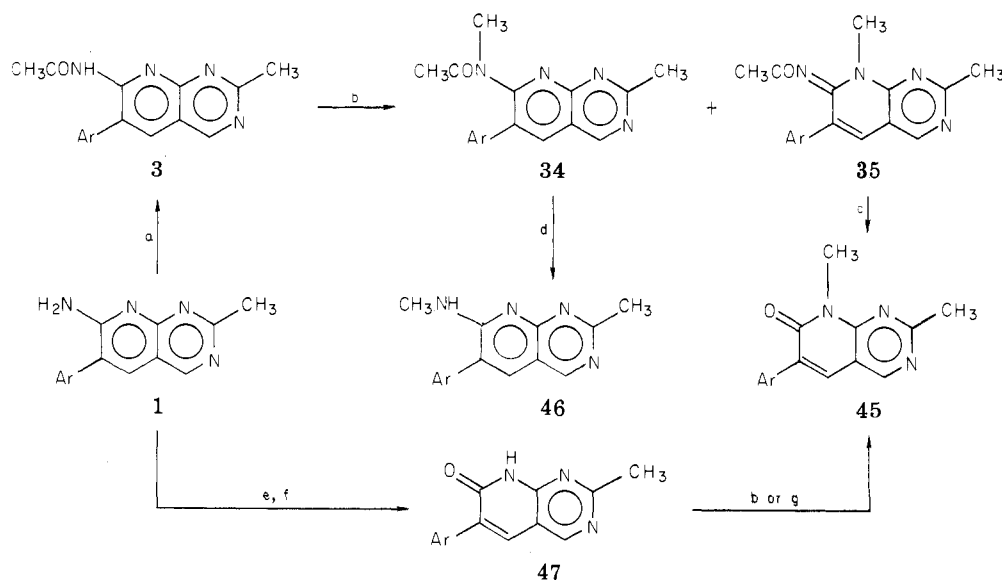
these possibilities and report in this paper the synthesis and biological activity of a series of 7-(acylamino)-6-arylpyrido[2,3-*d*]pyrimidines related to 1.

Chemistry. When 1 was heated in the presence of acetic anhydride, a modest yield of 3 was obtained. The yield and purity of 3 were substantially improved when the reaction was run with a slight excess of acetic anhydride in refluxing ethyl acetate. In this case, 3 crystallized from the mixture on cooling. When 3 was found to have antihypertensive effects similar to 1 in the spontaneously hypertensive rat (SHR) at the screening dose of 50 mg/kg, we moved to prepare a larger series of analogues. Readily available acid anhydrides were employed initially (method A) for the preparation of several of the analogues in Table I, including the extremely labile trifluoroacetamide, 10, which was cleaved immediately to 1 on dissolution in MeOH. We found that the standard acylating method with acid chloride/tertiary amine systems was generally unsuitable for acylating 1, although methanesulfonamide 31 was later obtained by this procedure. Considering other acylating methods that might have application in this situation, we elected to try acylimidazolides.² Indeed,

- (1) (a) This paper has been presented in part; see "Abstracts of Papers", Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 24-29, 1980; American Chemical Society: Washington, DC, 1980; Abstr MEDI 52. (b) Bennett, L. R.; Blankley, C. J.; Fleming, R. W.; Smith, R. D.; Tessman, D. K. *J. Med. Chem.* 1981, 24, 382 (paper 1 of the series).

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Scheme I^aScheme II^a

benzamide 18 was formed cleanly from benzoylimidazole, formed in situ from benzoic acid and 1,1'-carbonyldiimidazole (CDI), and 1, and this was identical with 18 prepared from 1 and benzoic anhydride following method A.

Most of the compounds of Table I were subsequently prepared by this procedure (method C). The reaction proceeded equally well for aliphatic, aromatic, or heterocyclic acids. No difficulty was encountered with the bulky pivalic acid, but 2,6-dimethylbenzoic acid failed to condense. Even the rather sensitive chloroacetamide 8 could be obtained by this method if the reaction was run for a short time at room temperature and the desired product was isolated immediately by chromatography.

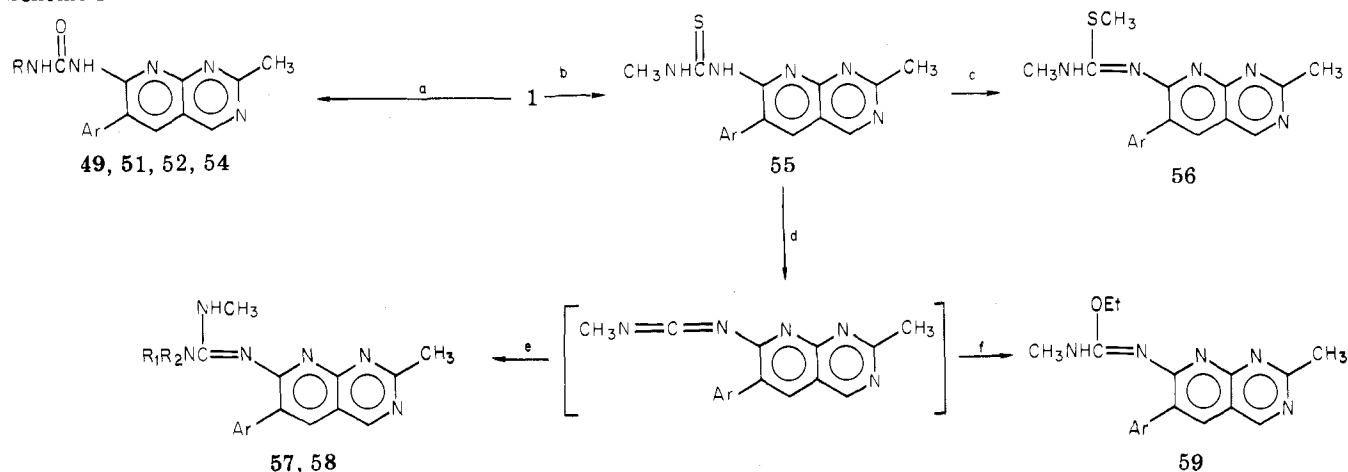
When CDI was heated in solution with 1 alone for several hours and then MeOH was added to the mixture, urethane 32 was obtained. Examination of the IR spectrum of a portion of the reaction mixture before addition of the alcohol revealed a strong absorption at 2345 cm⁻¹ in addition to carbonyl absorptions at 1760 and 1735 cm⁻¹. Most probably, an equilibrium mixture of isocyanate and imidazolurea is present; either intermediate can react with MeOH to give the observed product (Scheme I). More

strongly basic amines than 1 normally react with CDI to give symmetrical ureas.² We did not observe the latter in the case of 1, due no doubt to the combination of weak basicity and steric hindrance. Ammonia and simple amines, however, did react with the reaction complex of CDI and 1 to give unsymmetrical urea analogues 48–50.

Refluxing dimethylformamide dimethyl acetal converted 3 to an approximately equal mixture of 34 and 35. The latter isomers were separated by column chromatography. Although DMF acetals have been used to alkylate various acidic compounds,³ including pyridone-type structures,⁴

- (3) Gloede, J.; Costisella, B. *J. Prakt. Chem.* 1971, 313, 277.
- (4) For leading references, see Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron*, 1979, 1675.
- (5) Blankley, C. J.; Bennett, L. R. In ref 1, Abstr ORGN 174.
- (6) Blankley, C. J.; Bennett, L. R., unpublished results, manuscript in preparation.
- (7) The pK_a values of 2-amino-, 2-acetamido-, 2-benzamido-, 2-(N-methylacetamido)pyridine are 6.86, 4.09, 3.33, and 2.01, respectively.⁸ Although the solvent used for the titrations in this paper is aqueous DMF and not water as in ref 8, the near equivalence of the basic pK_a' values of 3, 18 (pK_a' = 4.1), and 34, on the one hand, and the fact that all of these are greater than that of 1, on the other hand, cannot be explained by a solvent effect alone. Covalent hydration⁹ is probably occurring to an appreciable extent during protonation of many of the compounds reported in this paper.⁵

(2) Staab, H. A.; Rohr, W. In "Newer Methods of Preparative Organic Chemistry"; Foerst, W., Ed.; Academic Press: New York, 1968; Vol. 5.

Scheme III^a

^a Ar = 2,6-dichlorophenyl; a = RNCO; b = RNCS; c = CH₃I, base; d = HgO; e = R₁R₂NH; f = EtOH.

we are not aware of their previous use in this context. This may turn out to be a generally useful reaction for systems of this type. Suffice it to note that the attempted alkylation of 3 under a variety of conditions with either organic (triethylamine, DBN) or inorganic (NaH) bases and methyl iodide gave only intractable mixtures.

The structures of 34 and 35 were verified by their hydrolytic behavior (Scheme II). Thus, 34, on treatment with base, was converted to 46, the 7-methylamino analogue of 1, with analytical and spectroscopic characteristics to confirm this. On the other hand, 35, on treatment with either acid or base, was converted to 45, which was obtained in an alternate manner by diazotization-hydrolysis of 1, followed by methylation of the oxo derivative 47 thus obtained.

Monosubstituted ureas 49 and 51-54 were prepared from 1 and the appropriately substituted isocyanate (Scheme III). In a similar manner, 1 and methyl isothiocyanate gave 55. Methylation of the latter gave 56. The method of Roy and Guha¹⁰ allowed us to prepare guanidines 57 and 58 directly from 55 by using mercuric oxide and the desired amine. When this latter reaction was run with cyanamide in place of an amine, none of the expected cyanoguanidine was found. The only isolated product proved to be 59, which arose from the competitive addition of solvent EtOH to an intermediate carbodiimide. Amidines 60 and 61 were prepared by heating 1 in DMF or DMA dimethyl acetals, respectively, at reflux.¹¹

The amide derivatives of Table I, in addition to being weak bases, as is 1, are also titratable as weak acids with pK_a' values (67% DMF) in the range of 10-13 for those measured. Several members of the series exhibit tautomeric equilibria between acylamino and acylimino forms, which are variously influenced by electronic, H-bonding, and medium effects.⁵ This will be discussed elsewhere in more detail.⁶ As might be expected, the compounds possess varying degrees of hydrolytic lability. The results of a hydrolytic stability study on compounds 3, 25, 28, and 32 are given in Table II, along with certain other physical properties for the purpose of assessing the possible connection of these properties with activity. Similar data for

1, 34, and 35 are included for comparison.

Biological Results and Discussion

The compounds were screened orally for antihypertensive activity in conscious SHR, in the manner described previously.¹ Usually, an initial screening dose of 50 mg/kg was used, but in several cases the compounds were tested at 10 mg/kg. Those compounds showing good effects at the initial screening dose were retested at 10 mg/kg and dosed once a day orally over a 3-day period. The results are summarized in Table I.

Several of the compounds lowered blood pressure in a dose range comparable to 1. However, acylation by no means automatically preserved activity. For example, acetamides 36, 37, and 41-44 were less active than their previously reported¹ parent amines (cf. also 34 vs. 46). In contrast, amides 3 and 40 show comparable efficacy and duration to their parents. The most consistent effect observed among the active amides of 1 was that the time required to achieve the maximum effect was substantially shorter than with 1. Moreover, this time period to maximum effect was fairly constant, namely, 3 to 6 h. The magnitude and duration of the effect achieved, however, were quite variable. One reasonable possibility might be that the amides are absorbed somewhat more efficiently than 1. The improved aqueous solubilities over 1 listed in Table II for four of the most active amides would likely contribute to such an improvement. The stability studies in neutral or acidic media indicate that these amides possess a stability sufficient to survive nonenzymatic hydrolysis by stomach or gut contents if absorption is rapid.

None of the amides of 1 is significantly more potent than 1 itself. For example, the doses (mg/kg) required to attain a 30% drop in mean blood pressure at 5 h postdose for 1 and the four amides of Table II were as follows: 1, 17; 3, 12; 25, 25; 28, 18; 32, 9. The apparent differences in milligram potency are largely accounted for by differences in the time to peak effect and nonparallel dose-response curves. However, at doses in excess of 100 (mg/kg)/day, the amides lowered blood pressure to severe hypotensive levels, eventually resulting in the death of the rats. This latter effect was not observed for 1, and thus a lower therapeutic index is suggested for the amides compared to 1.

Higher activity seems to be associated with smaller acyl groups or those containing electron-withdrawing substituents. The aryl amides, however, do not fit this pattern (i.e., good activity for 18, 26, and 28, but none for 27). Furthermore, the studies summarized in Table II estab-

(8) Jones, R. A.; Katritzky, A. R. *J. Chem. Soc.* 1959, 1317.

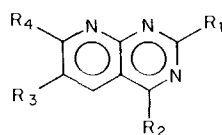
(9) Albert, A.; Armarego, W. L. F. *Adv. Heterocycl. Chem.*, 1965, 4, 1. Perrin, D. D. *Ibid.* 1965, 4, 43. Albert, A. *Ibid.* 1976, 20, 117.

(10) Roy, A. C.; Guha, P. C. *J. Sci. Ind. Res.* 1950, 9B, 262; *Chem. Abstr.* 1951, 45, 6636b.

(11) Richter, R.; Ulrich, H. *Chem. Ber.* 1970, 103, 3525.

Table I. *N*-(6-Arylprido[2,3-*d*]pyrimidin-7-yl)acyl Amides

no.	R ₁	R ₂	R ₃	R ₄	mp, °C	recrystn solv ^a	react cond ^b		formula	anal. ^c	po dose, mg/kg	act. rating in SHR ^d			max % decr, h
							method	yield				hour postdose			
												2	10	24	
1	CH ₃	H	2,6-Cl ₂ Ph	NH ₂	288-290	A			C ₁₄ H ₁₀ Cl ₂ N ₄		50	1	3	3	32 (10)
2	CH ₃	H	2,6-Cl ₂ Ph	NHCHO	257-259	A	B	27	C ₁₅ H ₁₀ Cl ₂ N ₄ O	C, H, N	50	2	3	3 ^f	33 (18)
3	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₃	202-203	B	A	33	C ₁₆ H ₁₂ Cl ₂ N ₄ O	C, H, Cl, N	50	3	3	3 ^f	45 (6)
4	CH ₃	H	2,6-Cl ₂ Ph	NHCOC ₂ H ₅	192-193	B	A	14	C ₁₇ H ₁₄ Cl ₂ N ₄ O	C, H, N	50	3	3	3 ^f	35 (5)
5	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH(CH ₃) ₂	231-232.5	A	A	60	C ₁₈ H ₁₆ Cl ₂ N ₄ O	C, H, N	10	1	0	0	15 (4)
6	CH ₃	H	2,6-Cl ₂ Ph	NHCO- <i>c</i> -C ₃ H ₅	211-213	C	C	34	C ₁₈ H ₁₄ Cl ₂ N ₄ O	H, Cl, N; C ^h	50	0	0	0	
7	CH ₃	H	2,6-Cl ₂ Ph	NHCOC(CH ₃) ₃	226-228	B	C	74	C ₁₉ H ₁₈ Cl ₂ N ₄ O	C, H, Cl, N	10	0	0	0	
8	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ Cl	170 dec	D	C	26	C ₁₆ H ₁₁ Cl ₃ N ₄ O	C, H, Cl, N	10	1	2	0	24 (10)
9	CH ₃	H	2,6-Cl ₂ Ph	NHCOCHCl ₂	199 dec	D	C	19	C ₁₆ H ₁₀ Cl ₃ N ₄ O	C, H, Cl, N	10	1	1	0	16 (4)
10	CH ₃	H	2,6-Cl ₂ Ph	NHCOCF ₃	195 dec	C	A	17	C ₁₆ H ₉ Cl ₂ F ₃ N ₄ O	C, H, F, N	50	2	2	2 ^f	23 (5)
11	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ OCH ₃	185-189	D	C	39	C ₁₇ H ₁₄ Cl ₂ N ₄ O ₂	C, H, Cl, N	50	2	2	2	29 (6)
12	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ SC ₂ H ₅	147-149	B	C	16	C ₁₈ H ₁₆ Cl ₂ N ₄ OS	C, H, N, S	10	1	0	0	19 (3)
13	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ N(CH ₃) ₂	180 dec	C	C	18	C ₁₈ H ₁₇ Cl ₂ N ₅ O	C, H, Cl, N	10	1	1	0	18 (6)
14	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ NHCO ₂ CH ₂ Ph	113-120	C	C	48	C ₂₄ H ₁₉ Cl ₂ N ₅ O ₃	C, H, Cl, N	50	1	2	1	29 (5)
15	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ Ph	158-161	B	C	51	C ₂₂ H ₁₆ Cl ₂ N ₄ O	C, H, Cl, N	50	1	1	1	17 (6)
16	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ (2,6-Cl ₂ Ph)	160 dec	E	C	49	C ₂₂ H ₁₄ Cl ₄ N ₄ O	C, H, Cl, N	10	0	0	0	
17	CH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₂ [3,4-(OCH ₃) ₂ Ph]	128-130	B	C	37	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₃ · 0.4CH ₃ CN 0.5H ₂ O	C, H, N, H ₂ O	10	0	0	0	
18	CH ₃	H	2,6-Cl ₂ Ph	NHCOPh	185-187	B	A	19	C ₂₁ H ₁₄ Cl ₂ N ₄ O	C, H, N	50	2	2	2	30 (5)
19	CH ₃	H	2,6-Cl ₂ Ph	NHCO(2-FPh)	115-125	C	C	14	C ₂₁ H ₁₃ Cl ₂ FN ₄ O· 0.25H ₂ O	C, H, N, H ₂ O	10	0	0	0	
20	CH ₃	H	2,6-Cl ₂ Ph	NHCO(2-CH ₃ Ph)	199-200	C	C	34	C ₂₂ H ₁₆ Cl ₂ N ₄ O	C, H, Cl, N	50	0	1	1	23 (5)
21	CH ₃	H	2,6-Cl ₂ Ph	NHCO(2-OCH ₃ Ph)	219-225	E	C	42	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂	C, H, Cl, N	10	0	0	0	
22	CH ₃	H	2,6-Cl ₂ Ph	NHCO(4-NO ₂ Ph)	227-229	C	C	52	C ₂₁ H ₁₃ Cl ₂ N ₅ O ₃	C, H, Cl, N	10	0	0		
23	CH ₃	H	2,6-Cl ₂ Ph	NHCO[3-N(CH ₃) ₂ Ph]	207-208.5	C	C	11	C ₂₃ H ₁₉ Cl ₂ N ₅ O	C, H, Cl, N	50	0	1	1	15 (5)
24	CH ₃	H	2,6-Cl ₂ Ph	NHCO[3,4-(OCH ₃) ₂ Ph]	175-177	C	C	57	C ₂₃ H ₁₈ Cl ₂ N ₄ O ₃	C, H, Cl, N	10	1	1	0	16 (6)
25	CH ₃	H	2,6-Cl ₂ Ph	NHCO(2-furyl)	228-230.5	D	C	50	C ₁₉ H ₁₂ Cl ₂ N ₄ O ₂	C, H, Cl, N	50	1	2	2	27 (4)
26	CH ₃	H	2,6-Cl ₂ Ph	NHCO(3-furyl)	219-221	B	C	39	C ₁₉ H ₁₂ Cl ₂ N ₄ O ₂	C, H, Cl, N	10	2	2	1	28 (3)
27	CH ₃	H	2,6-Cl ₂ Ph	NHCO(2-pyridyl)	260-262	D	C	71	C ₂₀ H ₁₃ Cl ₂ N ₅ O	H, N; C ⁱ	50	1	2	2	29 (8)
28	CH ₃	H	2,6-Cl ₂ Ph	NHCO(3-pyridyl)	174.5-176	B	C	57	C ₂₀ H ₁₃ Cl ₂ N ₅ O	C, H, Cl, N	50	1	2	1	26 (4)
29	CH ₃	H	2,6-Cl ₂ Ph	NHCO(4-pyridyl)	201-204	C	C	34	C ₂₀ H ₁₃ Cl ₂ N ₅ O	C, H, Cl, N	10	1	1	1	18 (4)
30	CH ₃	H	2,6-Cl ₂ Ph	NHCO(2-pyrazinyl)	258-260.5	D	C	55	C ₁₉ H ₁₂ Cl ₂ N ₆ O	C, H, N	10	0	0		11 (5)



31	CH ₃	H	2,6-Cl ₂ Ph	NHSO ₂ CH ₃	212-213	C	D	8	C ₁₅ H ₁₂ Cl ₂ N ₄ O ₂ S	C, H, N, S	50	1	1	2	22 (24)
32	CH ₃	H	2,6-Cl ₂ Ph	NHCO ₂ CH ₃	136-139	B	E	22	C ₁₆ H ₁₂ Cl ₂ N ₄ O ₂ · 0.25H ₂ O	C, H, Cl, N	50	1	1	1	29 (5)
33	CH ₃	H	2,6-Cl ₂ Ph	NHCO ₂ CH(CH ₃) ₂	170 dec	B	E	36	C ₁₈ H ₁₆ Cl ₂ N ₄ O ₂	C, H, Cl, N	10	0	1	0	15 (3)
34	CH ₃	H	2,6-Cl ₂ Ph	N(CH ₃)COCH ₃	196-199	A	F	11	C ₁₇ H ₁₄ Cl ₂ N ₄ O	C, H, N	50	0	0	0	
35	CH ₃	H	2,6-Cl ₂ Ph	=NCOCH ₃ , 8-CH ₃	194-199	A	F	9	C ₁₇ H ₁₄ Cl ₂ N ₄ O	C, H, N	50	1	0	1	17 (3)
36	CH ₃	CH ₃	2,6-Cl ₂ Ph	NHCOCH ₃	201-203	C	A	46	C ₁₇ H ₁₄ Cl ₂ N ₄ O	C, H, N	50	2	0	0	20 (2)
37	CH ₃	CH ₃	2-CH ₃ Ph	NHCOCH ₃	138-140	F	A	17	C ₁₈ H ₁₈ N ₄ O	C, H, N	50	0	0	0	
38	CH ₃	NHCOCH ₃	2,6-Cl ₂ Ph	NHCOCH ₃	308 dec	G	A	28	C ₁₈ H ₁₅ Cl ₂ N ₅ O ₂	C, H, N	50	0	0	0	
39	NHCOCH ₃	H	2,6-Cl ₂ Ph	NHCOCH ₃	223-225	B	A	9	C ₁₇ H ₁₃ Cl ₂ N ₅ O ₂	C, H, N	50	0	2	3 ^f	32 (18)
40	c-C ₃ H ₅	H	2,6-Cl ₂ Ph	NHCOCH ₃	189-191	B	A	62	C ₁₈ H ₁₄ Cl ₂ N ₄ O	C, H, N	50	1	1	0	24 (3)
41	H	H	2,6-Cl ₂ Ph	NHCOCH ₃	215-217	B	A	34	C ₁₅ H ₁₀ Cl ₂ N ₄ O	C, H, N	50	1	1	0	16 (6)
42	H	H	2-BrPh	NHCOCH ₃	181-182	B	A	19	C ₁₅ H ₁₁ BrN ₄ O	C, H, N	50	1	1	0	19 (3)
43	H	H	2-CH ₃ Ph	NHCOCH ₃	152-154	C	C	39	C ₁₆ H ₁₄ N ₄ O	C, H, N	50	0	0	0	
44	CH ₃	H	2-CH ₃ Ph	NHCOCH ₃	145-148.5	C	C	36	C ₁₇ H ₁₆ N ₄ O	C, H, N	50	0	0	0	
45	CH ₃	H	2,6-Cl ₂ Ph	=O, 8-CH ₃	219-220	A	j		C ₁₅ H ₁₁ Cl ₂ N ₃ O	C, H, N	50	0	0	0	
46	CH ₃	H	2,6-Cl ₂ Ph	NHCH ₃	230-231	C	j		C ₁₅ H ₁₂ Cl ₂ N ₄	C, H; N ^k	50	1	1	2 ^f	21 (5)
47	CH ₃	H	2,6-Cl ₂ Ph	=O, 8-H	265-267.5	H	j		C ₁₄ H ₉ Cl ₂ N ₃ O	C, H, Cl, N	50	0	1	1 ^f	10 (6)
48	CH ₃	H	2,6-Cl ₂ Ph	NHCONH ₂	196-198	A	G	37	C ₁₅ H ₁₁ Cl ₂ N ₅ O	C, H, N, Cl	50	0	0	0	16 (4)
49	CH ₃	H	2,6-Cl ₂ Ph	NHCONHCH ₃	168-171	B	H	64	C ₁₆ H ₁₃ Cl ₂ N ₅ O· 0.5H ₂ O	C, H, N, H ₂ O ^l	50	2	1	0	26 (4)
50	CH ₃	H	2,6-Cl ₂ Ph	NHCON(CH ₃) ₂	177-181	B	G	36	C ₁₇ H ₁₅ Cl ₂ N ₅ O	C, H, N, Cl	50	1	1	2	26 (4)
51	CH ₃	H	2,6-Cl ₂ Ph	NHCONHC ₂ H ₅	189-191	A	H	66	C ₁₇ H ₁₅ Cl ₂ N ₅ O· 0.5H ₂ O	C, H, N, H ₂ O	50	0	0	0	
52	CH ₃	H	2,6-Cl ₂ Ph	NHCONHC(CH ₃) ₃	204-207	A	J	68	C ₁₉ H ₁₉ Cl ₂ N ₅ O	C, H, N	50	0	0	0 ^f	
53	CH ₃	H	2,6-Cl ₂ Ph	NHCONHPh	211-215	A	H ^m	36	C ₂₁ H ₁₅ Cl ₂ N ₅ O	C, H, N	50	0	0	0	
54	CH ₃	H	2,6-Cl ₂ Ph	NHCONHCH ₂ CH=CH ₂	169-172	A	H	38	C ₁₈ H ₁₅ Cl ₂ N ₅ O· 0.5H ₂ O	C, H, N, H ₂ O	50	0	1	0	13 (6)
55	CH ₃	H	2,6-Cl ₂ Ph	NHCSNHCH ₃	207-208	I	J	57	C ₁₆ H ₁₃ Cl ₂ N ₅ S	C, H, N	50	0	1	0	12 (6)
56	CH ₃	H	2,6-Cl ₂ Ph	N=C(SCH ₃)NHCH ₃	163-165	F	J	48	C ₁₇ H ₁₅ Cl ₂ N ₅ S	C, H, N	50	0	0	0	
57	CH ₃	H	2,6-Cl ₂ Ph	N=C(NH ₂)NHCH ₃	250-251	J	I	61	C ₁₆ H ₁₄ Cl ₂ N ₆	C, H, N	50	2	1	0	24 (4)
58	CH ₃	H	2,6-Cl ₂ Ph	N=C(NHCH ₃)NHCH ₃	279-283	J	I	29	C ₁₇ H ₁₆ Cl ₂ N ₆	C, H, N	50	2	1	0	24 (3)
59	CH ₃	H	2,6-Cl ₂ Ph	N=C(OC ₂ H ₅)NHCH ₃	110-112	F	J	9	C ₁₈ H ₁₇ Cl ₂ N ₅ O	C, H, N	50	0	0	0	10 (8)
60	CH ₃	H	2,6-Cl ₂ Ph	N=CHN(CH ₃) ₂	236-238	E	J	64	C ₁₇ H ₁₅ Cl ₂ N ₅	C, H, N	50	0	1	1	17 (6)
61	CH ₃	H	2,6-Cl ₂ Ph	N=C(CH ₃)N(CH ₃) ₂	219-221	I	J	55	C ₁₈ H ₁₇ Cl ₂ N ₅	C, H, N	50	1	0	1	18 (2)
hydralazine											10	3	2	1	51 (4)
											3	2	2	1	27 (1)

^a Solvents: A, EtOH; B, EtOAc; C, toluene; D, CHCl₃/Et₂O; E, CH₃CN; F, isopropyl ether; G, DMF; H, cellosolve; I, 2-propanol; J, EtOH/H₂O. ^b Methods as described under Experimental Section; yields reported are for purified first crop only. ^c Analyses within ±0.4% for indicated elements, except as noted. ^d Activity ratings: all results were analyzed for statistically significant differences from predose control values by using Student's *t* test. Compounds producing a significant (*p* < 0.05) blood pressure reduction of > 30% = 3, of 20-30% = 2, of 10-20% = 1, and those producing no significant reduction were rated 0. The individual treatment group mean aortic blood pressures were from 151 ± 5 to 178 ± 12 mmHg. The maximum percent decrease observed and the hour postdose at which it was first attained is also given. ^e This level of effect maintained for up to 72 h with once daily oral dosing. ^f 18 h. ^g Maximum effect observed at 3-5 h postdose. ^h C: calcd, 57.92; found, 57.42. ⁱ C: calcd, 58.55; found, 58.00. ^j See Experimental Section. ^k N: calcd, 17.55; found, 17.03. ^l H₂O: calcd, 2.43; found, 2.02. ^m Column chromatography required to isolate product (SiO₂, CHCl₃/MeOH, 99:1).

Table II. Physicochemical Properties

no.	pK_a^a		solubility, mg/mL		stability (half-life, $t_{1/2}$)			tautomer ratio in $CDCl_3$, A/B ^c
			0.1 N HCl	pH 7 ^b	0.1 N HCl	1:1 MeOH/pH 7 PB ^b	1:1 MeOH/0.1 N NaOH	
1	3.0		4.85	0.007	stable ^d	stable	^e	
3	4.1	12.8	34.2	6.05	12.5 h	60 h	<5 min	100% A
25	4.3	10.7	6.6	0.22	stable	15-17 d	4 h	55:45
28	4.1	9.8	26.6	2.63	stable	54 h	4 h	100% B
32	4.2	11.3	14.6	0.28	stable	stable	6 h	80:20
34	4.2		ND ^e		stable	stable	1.6 h	100% A
35	~2.5		ND ^e		3.4 h	stable	8.8 h	100% B

^a Measured in 67% DMF/H₂O. ^b Phosphate buffer. ^c A = acylamino, B = acylimino tautomers, assessed by NMR. ^d <5% change after 14 days at 25 °C. ^e Not determined.

lished the following: (a) The only hydrolysis product of the amides 3, 25, 28, and 32 that was found was 1. (b) The electronic properties of the pyridopyrimidine ring portion of 1 (or 46) and the amides are different. This is reflected in the fact that the apparent pK_a' of the amides is higher than the amines, contrary to what would be expected if protonation were taking place in the same manner for the two types.⁷ Among the amides themselves, tautomeric preference varies greatly, depending on structure and solvent.⁵

Optimal activity for the ureas occurs with mono- or disubstituted methylureas (49 and 50). Bulkier substitution, such as ethyl (51), *tert*-butyl (52), or phenyl (53) is unfavorable, although the allylurea (54) retained some activity. The unsubstituted urea (48) had a very low level of activity. Replacement of oxygen (49) with sulfur (55) also led to a decrease in activity. As a class, the guanidines (57 and 58) were comparable to the methyl-substituted ureas (49 and 50). The amidines (60 and 61) showed minimal activity.

Taken together, the above results on amides of 1 suggest that they possess antihypertensive activity per se without requiring prior hydrolysis to 1. The irregular effect of acetylation on active 7-amino derivatives other than 1, the activity of 31, 32, and 50, compounds expectedly more stable to hydrolytic or enzymatic cleavage, and the different physical properties of the acyl amides all are in accord with this conclusion. Preliminary experiments to determine the mechanism of action of 1 or its acyl derivatives have given no clear indication of a specific effect. Cardiovascular and autonomic evaluation of 1 demonstrated a reduction in the pressor responses to epinephrine, norepinephrine, tyramine, and angiotensin II, suggesting a nonspecific effect on vascular activity. Further studies on the pharmacology of these compounds will be reported separately.

In summary, we have reported here the preparation of a series of amides of antihypertensive pyrido[2,3-*d*]pyrimidin-7-amines. Several of these, e.g., 3, 25, 28, and 32 show similar antihypertensive effects to 1 in the SHR at low doses, but all have shown a lower therapeutic ratio.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ¹H NMR 90-MHz spectra were obtained with a Varian Associates EM-390 or Bruker B-N-C-12 instrument. Chemical shifts are recorded in parts per million (δ) relative to (CH₃)₄Si as internal standard. NMR spectra of all compounds and intermediates were consistent with the assigned structures. IR spectra were determined on Digilab DP-1-5 and Beckman IR-9 spectrophotometers. UV spectra were measured on a Cary 118 spectrophotometer. MgSO₄ was used as a drying agent unless otherwise noted.

N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-7-yl]-2-methylpropanamide (5). Method A. A mixture of 5.0 g (0.013 mol) of 1 and 25 mL of isobutyric anhydride was

heated on a steam bath for 30 min. The resulting slurry was cooled and filtered, and the solid was washed with Et₂O. Recrystallization from EtOH (charcoal treatment) gave 5 as a white solid: yield 3.7 g (60%); mp 231-232.5 °C. Anal. (C₁₈H₁₆Cl₂N₄O) C, H, N.

N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-7-yl]acetamide (3). An improved method for the preparation of 3, which is probably more generally useful, was the following: A suspension of 20.0 g (0.066 mol) of 1 in 400 mL of EtOAc was treated with 20 g (0.20 mol) of Ac₂O and heated at reflux for 4 h. The hot solution was treated with charcoal and filtered. Cooling led to a first crop of 9.7 g of pale yellow 3. Concentration of the filtrate led to additional crops of 7.6 g: total yield 17.3 g (76%). One recrystallization from EtOAc gave an analytical sample: mp 201-203 °C; IR (KBr) 1690 (C=O) cm⁻¹; UV λ_{max} (MeOH) 213 nm (ϵ 41 460), 320 (13 100); UV λ_{max} (MeOH, 1 N HCl) 224 nm (30 800), 267 (8730), 299 (13 100); NMR (Me₂SO-*d*₆) δ 2.10 (s, 3 H), 2.85 (s, 3 H), 7.60 (m, 3 H), 8.55 (s, 1 H), 9.55 (s, 1 H), 10.40 (s, 1 H). Anal. (C₁₆H₁₂Cl₂N₄O) C, H, Cl, N.

N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-7-yl]formamide (2). Method B. Formic acid (98%) (6.2 g, 0.13 mol) was added to 13.4 g (0.13 mol) of cold (0 °C) Ac₂O. The solution was warmed at 45-60 °C for 15 min and then cooled to 0 °C, and 10 g (0.03 mol) of 1 was added. A solid formed. Addition of 15 mL of Et₂O gave a slurry, which after 2 h of stirring at 25 °C had formed a yellow solution. Concentration of the reaction mixture at reduced pressure gave a solid, which was slurried with Et₂O and filtered. This solid was recrystallized from EtOH to give 2.9 g (27%) of 2, mp 257-259 °C dec. Anal. (C₁₅H₁₀Cl₂N₄O) C, H, N.

N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-7-yl]-2,2-dimethylpropanamide (7). Method C. A suspension of 3.0 g (0.01 mol) of 1 and 1.6 g (0.016 mol) of pivalic acid in 50 mL of 1,2-dichloroethane was distilled to azeotropically remove any solvated H₂O (vapor temperature 82 °C). The mixture was allowed to cool, and 2.6 g (0.016 mol) of 1,1'-carbonyldiimidazole was added. After gas evolution had moderated, the solution was heated at reflux for 16 h. The cooled reaction mixture was added directly to a column of 150 g of SiO₂, and elution was carried out first with CHCl₃ and then with 1% MeOH/CHCl₃ to elute the product. Trituration of the oily product from the combined product fractions with ether gave 3.1 g (79%) of 7, mp 226-228 °C. Recrystallization of this from EtOAc gave an analytical sample, mp 226-228 °C, as white crystals. Anal. (C₁₉H₁₈Cl₂N₄O) C, H, N, Cl.

N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-7-yl]methanesulfonamide (31). Method D. An azeotropically dried suspension of 3.0 g (0.01 mol) of 1 in 100 mL of 1,2-dichloroethane was cooled to 0 °C and treated with 1.2 g (0.01 mol) of methanesulfonyl chloride, followed dropwise by 1.0 g (0.01 mol) of triethylamine. Stirring was continued while the mixture was allowed to warm to room temperature during 4 h. Since TLC examination at this point revealed unconsumed 1, the mixture was cooled again to 0 °C, and an additional 1.2 g (0.01 mol) of methanesulfonyl chloride and 1.0 g (0.01 mol) of triethylamine were added. After stirring overnight at room temperature, the dark mixture was filtered through Celite, and the filtrate was chromatographed directly over SiO₂. The product was eluted with 1% MeOH/CHCl₃. Trituration with ether gave 0.7 g (18%) of crude 31, mp 210-213 °C. Recrystallization from toluene gave an analytical sample, mp 212-213 °C; as pale yellow crystals: UV

λ_{\max} (MeOH) 217 nm (ϵ 43 800), 322 (15 600), 335 (16 600), 349 (11 250); UV λ_{\max} (MeOH, 5 N HCl) 216 nm (ϵ 39 800), 261 (6150), 303 (13 700); UV λ_{\max} (MeOH, 6 N KOH) 279 nm (ϵ 7350), 345 (17 200); NMR (CDCl₃) δ 2.80 (s, 3 H), 3.00 (s, 3 H), 7.35 (m, 3 H), 7.70 (s, 1 H), 8.85 (s, 1 H), 11.90 (br s, 1 H). Anal. (C₁₅H₁₂Cl₂N₄O₂S) C, H, N, Cl, S.

Methyl *N*-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]carbamate (32). Method E. An azeotropically dried suspension of 20.0 g (0.066 mol) of 1 in 450 mL of 1,2-dichloroethane was treated with 15.0 g (0.093 mol) of 1,1'-carbonyldiimidazole and heated at reflux for 24 h. The mixture was cooled and decanted through Celite from a brown gummy precipitate and then treated with an additional 3.0 g (0.018 mol) of 1,1'-carbonyldiimidazole and heated at reflux for an additional 24 h. (The yield is not much affected if this second stage is omitted.) The cooled mixture was again filtered and then treated with 20 mL of MeOH and stirred at room temperature overnight. The product was isolated as described above in method C by chromatography over 400 g of SiO₂. The product-containing fractions were triturated with ether to yield a total of 16.6 g (69%) of 32, mp 145–160 °C dec. Recrystallization from EtOAc gave an analytical sample, mp 155–162 °C dec, as white prisms. Anal. (C₁₆H₁₂Cl₂N₄O₂) C, H, Cl; N: calcd, 15.42; found, 15.92. This compound has an affinity for water, and occasionally a partial hydrate is obtained with mp 133–136 °C dec: IR (KBr) 1740 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 223 nm (ϵ 47 500), 324 (13 400); NMR (Me₂SO-*d*₆) δ 2.80 (s, 3 H), 3.60 (s, 3 H), 7.6 (m, 3 H), 8.50 (s, 1 H), 9.50 (s, 1 H), 10.15 (s, 1 H).

***N*-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-*N*-methylacetamide (34) and *N*-[6-(2,6-Dichlorophenyl)-2,8-dimethylpyrido[2,3-d]pyrimidin-7(8*H*)-ylidene]acetamide (35).** Method F. A mixture of 11.9 g (0.034 mol) of 3 and 40 mL of *N,N*-dimethylformamide dimethyl acetal was heated at reflux for 1 h. The cooled solution was treated with water and extracted with CH₂Cl₂. The organic layer was washed with saturated NaCl solution, dried, and concentrated at reduced pressure. The products were separated from each other and unreacted 3 by column chromatography over SiO₂, eluting with CHCl₃/MeOH or EtOAc/MeOH mixtures. After 2.9 g (25%) of unreacted 3 was recovered in early fractions, 34 eluted and was recrystallized from EtOH to give 1.2 g of white solid: mp 196–199 °C; IR (KBr) 1690 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 318 nm (ϵ 10 300); NMR (CDCl₃) δ 2.20 (s, 3 H), 3.00 (s, 3 H), 3.10 (s, 3 H), 7.40 (m, 3 H), 8.20 (s, 1 H), 9.35 (s, 1 H). Anal. (C₁₇H₁₄Cl₂N₄O) C, H, N.

Following this, 35 was eluted and recrystallized from EtOH to give 1.3 g of pale yellow solid: mp 194–199 °C; IR (KBr) 1580 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 221 nm (ϵ 42 200); NMR (CDCl₃) δ (s, 3 H), 3.80 (s, 3 H), 7.30 (m, 3 H), 7.35 (s, 1 H), 8.60 (s, 1 H). Anal. (C₁₇H₁₄Cl₂N₄O) C, H, N.

6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (47). A solution of 10.0 g (0.033 mol) of 1 in 50 mL of concentrated H₂SO₄ was cooled to 0 °C and treated with 6.0 mL (4.5 g, 0.036 mol) of commercial 40% NOHSO₄. After 2 h at 5 °C, the solution was poured onto ice, at which time gas evolution was observed. After stirring for 1.5 h, the cold solution was made strongly basic with 50% NaOH (ice was added to control the temperature). The initial precipitate redissolved as the solution became strongly basic. Filtration removed some insoluble material, and the pH was then adjusted to 5–6 with glacial HOAc. After 1 h, the white precipitate was collected by filtration to give, after drying, 11.1 g of 47. Recrystallization from hot ethyl Cellosolve (charcoal) gave pure 47, 8.0 g (80%), in two crops. An analytical sample had mp 265–267.5 °C; IR (KBr) 1675 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 304 nm (ϵ 14 750), 314 (16 550), 326 (sh); UV λ_{\max} (MeOH, 5 N HCl) 218 nm (ϵ 4900), 308 (15 500), 300 (sh); UV λ_{\max} (MeOH, 6 N KOH) 270 nm (inf), 330 (ϵ 14 900); NMR (CDCl₃) δ 2.90 (s, 3 H), 7.35 (m, 3 H), 7.65 (s, 1 H), 8.85 (s, 1 H), 10.80 (br s, 1 H). Anal. (C₁₄H₈Cl₂N₃O) C, H, N, Cl.

6-(2,6-Dichlorophenyl)-2,8-dimethylpyrido[2,3-d]pyrimidin-7(8*H*)-one (45). (a) A mixture of 4.0 g (0.013 mol) of 47 and 12 mL of dimethylformamide dimethyl acetal was heated at reflux for 4 h. The solution was cooled, treated with water, and extracted with CH₂Cl₂. The organic layer was washed with saturated NaCl solution, dried, and concentrated at reduced pressure to give a residue, which solidified on trituration with Et₂O. Recrystallization

from EtOH gave a 2.9 g of 45: mp 219–220 °C; IR (KBr) 1650 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 315 nm (ϵ 15 800), 306, 326 (sh); UV λ_{\max} (MeOH, 5 N HCl) 221 nm (ϵ 18 000), 310 (14 900), 301, 320 (inf); NMR (CDCl₃) δ 2.82 (s, 3 H), 3.85 (s, 3 H), 7.35 (m, 3 H), 7.6 (s, 1 H), 8.75 (s, 1 H). Anal. (C₁₅H₁₁Cl₂N₃O) C, H, N.

(b) To a solution of 0.3 g (0.05 mol) of NaOMe in 50 mL of EtOH was added 2.0 g (0.06 mol) of 47 and 1.2 g (0.08 mol) of methyl iodide. The mixture was heated at reflux for 16 h and then cooled and concentrated at reduced pressure. The residue was slurried with 2 N NaOH and filtered to give 1.7 g of crude 45. Recrystallization of this from CH₃CN gave 0.7 g of light brown crystals, mp 212–216 °C, identical with material obtained under method a above by spectroscopic comparison.

(c) A mixture of 1.0 g (2.8 mmol) of 35 and 10 mL of 1 N HCl was stirred overnight at room temperature. The white precipitate was collected by filtration to give 0.8 g (89%) of 45, mp 218–220 °C, identical with independently synthesized 45 by IR comparison.

(d) Similarly, 1.9 g (5.3 mmol) of 35 was stirred with 50 mL of 1 N NaOH at room temperature for 2.5 days. The slurry was cooled and filtered to separate 1.6 g (94%) of 45, mp 214–216 °C identical by IR comparison with material obtained under method a above.

6-(2,6-Dichlorophenyl)-*N*,2-dimethylpyrido[2,3-d]pyrimidin-7-amine (46). A mixture of 1.0 g (2.8 mmol) of 34, 10 mL of 2 N NaOH, and 1 mL of EtOH was heated at reflux for 30 min. The resulting slurry was cooled and filtered, and the solid was washed with H₂O. The product was isolated by chromatography on SiO₂, eluting with a MeOH/CHCl₃ (1:49) mixture. Several recrystallizations of the major fraction from toluene gave 0.1 g of 46: mp 230–231 °C; UV λ_{\max} (MeOH) 225 nm (ϵ 38 500), 274 (6450), 337 (14 300); UV λ_{\max} (MeOH, 5 N HCl) 355 nm (ϵ 15 000); NMR (Me₂SO-*d*₆) δ 2.65 (s, 3 H), 2.90 (d, 3 H), 6.95 (br d, 1 H), 7.60 (m, 3 H), 7.80 (s, 1 H), 8.95 (s, 1 H). Anal. (C₁₅H₁₂Cl₂N₄) C, H; N: calcd, 17.55; found, 17.03.

***N*-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]urea (48).** Method G. A suspension of 3.0 g (0.01 mol) of 1 in 50 mL of 1,2-dichloroethane was heated at reflux until all water of crystallization was removed as the azeotrope (vapor temperature 82 °C). To this was then added 2.0 g (0.012 mol) of 1,1'-carbonyldiimidazole, and the mixture was heated at reflux for 24 h. After cooling to room temperature, the mixture was treated with 1.5 g (0.020 mol) of ammonium acetate, followed by two drops of triethylamine. This was stirred overnight at room temperature, ether was added to the resulting slurry, and the mixture was filtered. Recrystallization of the solid from EtOH (charcoal treatment) gave pure 48: mp 196–198 °C dec; NMR (CDCl₃) δ 3.0 (s, 3 H), 6.2 (br s, 1 H), 7.5 (m, 3 H), 8.0 (s, 1 H), 9.2 (s, 1 H), 9.8 (br s, 1 H); IR (KBr) 1710 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 226 nm (ϵ 52 000), 319 (15 700), 328 (15 500). Anal. (C₁₅H₁₁Cl₂N₅O) C, H, N, Cl.

***N*-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-*N'*-ethylurea Hemihydrate (51).** Method H. A mixture of 3.05 g (0.01 mol) of 1 and 15 mL of ethyl isocyanate was heated at reflux for 1 h, cooled, and diluted with 20 mL of Et₂O. The solvent was evaporated, and the residue was recrystallized from EtOH (charcoal treatment) to give 2.5 g of pure 51: mp 189–191 °C dec; IR (KBr) 1685 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 224 nm (ϵ 50 500), 320 (15 600), 330 (15 500). Anal. (C₁₇H₁₅Cl₂N₅O·0.5H₂O) C, H, N, H₂O.

***N*-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-*N'*-(1,1-dimethylethyl)urea (52).** A solution of 3.0 g (0.01 mol) of 1 in 45 mL of DMF was treated with 0.48 g (0.01 mol) of NaH (50% oil dispersion). Gas was evolved, and an orange-red precipitate formed. After stirring for 1 h at room temperature, this mixture was treated with 1.0 g (0.01 mol) of *tert*-butyl isocyanate and stirred 16 h longer. The mixture was then added carefully to 500 mL of H₂O, and the resulting solid was collected by filtration. Recrystallization from EtOH (charcoal treatment) gave 2.7 g of 52: mp 204–207 °C dec; IR (KBr) 1700 (C=O) cm⁻¹; UV λ_{\max} (MeOH) 224 nm (ϵ 55 800), 319 (17 300), 330 (1720). Anal. (C₁₉H₁₉Cl₂N₅O) C, H, N. In the absence of NaH, no significant amount of 52 was formed.

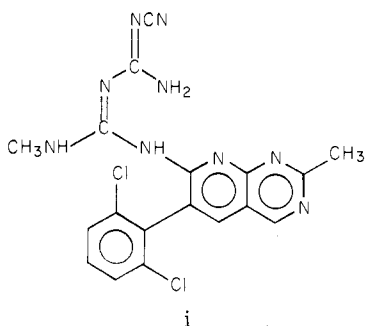
***N*-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-*N'*-methylthiourea (55).** A mixture of 3.05 g (0.01 mol) of 1 and 2.2 g (0.03 mol) of methyl isothiocyanate in 15 mL of toluene was heated at reflux for 30 h. On cooling, a yellow solid

separated, which was filtered, washed with Et₂O, and recrystallized from 2-PrOH (charcoal treatment) to give 1.5 g of **55**: mp 207–208 °C; UV λ_{max} (MeOH) 340 nm (ε 20 700). Anal. (C₁₆H₁₃Cl₂N₅S) C, H, N.

Methyl N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-N'-methylcarbamimidothioate (56). To a solution of 0.8 g (0.015 mol) of NaOMe in 45 mL of EtOH was added 5.0 g (0.013 mol) of **55**. The resulting orange-red solution was heated to reflux and then treated dropwise with a solution of 2.1 g (0.015 mol) of methyl iodide in 5 mL of EtOH. After heating for 1 h, the mixture was cooled and concentrated at reduced pressure. The residue was dissolved in CHCl₃, and the solution was washed with H₂O. After drying, the organic layer was concentrated to dryness, and the residue was recrystallized from diisopropyl ether (charcoal treatment) to give 2.5 g of **56**: mp 163–165 °C; NMR (CDCl₃) δ 1.9 (s, 3 H), 2.9 (s, 3 H), 3.1 (d, 3 H), 7.3 (m, 3 H), 7.8 (s, 1 H), 9.0 (s, 1 H), 11.5 (br s, 1 H); UV λ_{max} (MeOH) 289 nm (ε 9800), 360 (31 500), 374 (32 700). Anal. (C₁₇H₁₅Cl₂N₅S) C, H, N.

Ethyl N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-N'-methylcarbamimidate (59). A mixture of 3.1 g (8.2 mmol) of **55**, 1.8 g (8.2 mmol) of HgO, and 0.34 g (8.1 mmol) of cyanamide in 40 mL of EtOH was heated at reflux for 30 min. A further 0.18 g (4.3 mmol) of cyanamide was added, and heating was continued for 15 min. The mixture was filtered from HgS and concentrated to give an oily solid residue. This was chromatographed on SiO₂, eluting with CHCl₃ to obtain the major product as an oil, which slowly crystallized. Recrystallization from diisopropyl ether gave 0.3 g of a compound, mp 110–112 °C, whose analytical and spectroscopic data led to the assignment of structure **59**: NMR (CDCl₃) δ 1.0 (t, 3 H), 2.9 (s, 3 H), 3.0 (d, 3 H), 3.9 (q, 2 H), 7.3 (m, 3 H), 7.8 (s, 1 H), 9.0 (s, 1 H), 10.4 (br s, 1 H); UV λ_{max} (MeOH) 219 nm (ε 37 800), 282 (6600), 348 (19 000), 363 (18 600). Anal. (C₁₈H₁₇Cl₂N₅O) C, H, N.

When the reaction was run in toluene instead of EtOH, the desired cyanoguanidine was not obtained either. Rather, the major product was a different compound for which the structure **i** seems most likely from spectral and analytical data.



N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-N'-methylguanidine (57). **Method I**. A mixture of 3.8 g (0.01 mol) of **55**, 2.2 g (0.01 mol) of HgO, and 4 mL of concentrated NH₄OH in 40 mL of EtOH was heated at reflux until the black precipitate of HgS had formed (20 min). The hot mixture was filtered, and the filtrate was concentrated to give a yellow solid. Recrystallization of this from aqueous EtOH (charcoal treatment) gave 2.2 g of **57**: mp 250–251 °C; NMR (CDCl₃) δ 2.5 (br d, 3 H), 2.8 (s, 3 H), 6.7 (br s, 1 H), 7.4 (m, 3 H), 7.7 (s, 1 H), 8.1 (br s, 1 H), 8.9 (s, 1 H); UV (MeOH) λ_{max} 293 nm (ε 9670), 360 (23 800). Anal. (C₁₆H₁₄Cl₂N₆) C, H, N.

N-[6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-d]pyrimidin-7-yl]-N,N-dimethylmethanimidamide (60). **Method J**. A mixture of 2.1 g (7.0 mmol) of **1** and 10 mL of dimethylformamide dimethyl acetal was warmed on a steam bath. Solution occurred initially, followed by exothermic reaction and precipitation of a yellow solid. After 24 h at room temperature, the mixture was diluted with ether and filtered. Recrystallization from CH₃CN gave 1.6 g of **60**: mp 236–238 °C; NMR (Me₂SO-d₆) δ 2.65 (s, 3 H), 2.80 (s, 3 H), 3.14 (s, 3 H), 7.50 (m, 3 H), 8.15 (s, 1 H), 8.80 (s, 1 H), 9.20 (s, 1 H); UV λ_{max} (MeOH) 289 nm (9150), 365 (27 500), 240, 260 (inf). Anal. (C₁₇H₁₅N₅Cl₂) C, H, N.

Physicochemical Measurements. The aqueous solubilities

were determined by preparing saturated solutions of the compounds in 0.1 N HCl, under which conditions all of the compounds exist in the protonated form, and measuring the ultraviolet absorption at the long-wavelength (320–330 nm) maximum. The pH was then adjusted to 7 to form the unprotonated bases, and after removal of the precipitate, the supernatant solution was again assayed by ultraviolet absorption.

The results are listed in Table II, along with the dissociation constants, which were determined by potentiometric titration in 67% N,N-dimethylformamide/water.

Stabilities were determined under acidic, neutral, and basic conditions. It was ascertained that in all cases of decomposition of the acylated derivatives, **1** was the only identifiable product. The ultraviolet spectrum of **1** differs sufficiently from its acylated analogues to allow this method to be used to obtain reasonable estimates of the rates of transformation of the latter to **1**.

Solutions of the compounds, ca. 0.001–0.002%, were prepared at room temperature in 0.1 N HCl (pH ~1.5), 50% MeOH/pH 7 phosphate buffer (pH ~8.0), and 50% MeOH/0.05 N aqueous NaOH (pH ~12.2), and any changes in the ultraviolet spectra were monitored over a 2-week period. Results were then plotted on graph paper to obtain estimates of the half-life, *t*_{1/2}, for decomposition with two different wavelengths for analysis when possible. The results are also given in Table II.

Spectral Data for Compounds of Table II. **1**: UV λ_{max} (0.1 N HCl) 331 nm (ε 15 555); UV λ_{max} (1:1 MeOH/pH 7 buffer) 225 nm (ε 52 460), 329 (14 880); NMR (CDCl₃) δ 2.8 (s, 3 H), 6.5 (br s, 2 H), 7.4 (m, 3 H), 7.7 (s, 1 H), 8.9 (s, 1 H). **3**: UV λ_{max} (0.1 N HCl) (initial) 266 nm (ε 8830), 297 (12 460); UV λ_{max} (1:1 MeOH/pH 7 buffer) 320 nm (ε 12 390); UV λ_{max} (1:1 MeOH/0.05 N NaOH) too unstable to measure; NMR (CDCl₃) δ 2.8 (s, 3 H), 2.9 (s, 3 H), 7.4 (m, 3 H), 8.0 (s, 1 H), 9.2 (s, 1 H). **25**: UV λ_{max} (0.1 N HCl) (initial) 259 nm (ε 23 300), 299 (20 910); UV λ_{max} (1:1 MeOH/pH 7 buffer) 242 nm (27 340), 323 (18 950), 368 (1230), 385 (985); UV λ_{max} (1:1 MeOH/0.1 N NaOH) 360 nm (ε 17 440); NMR (CDCl₃) δ 2.8 and 2.95 (2 s, 3 H), 6.35 and 6.45 (2 m, 1 H), 6.75 and 7.15 (2 m, 1 H), 7.4 (m, 4 H), 7.8 and 8.2 (2 s, 1 H), 8.9 and 9.3 (2 s, 1 H), 8.6 and 14.3 (2 br s, 1 H), 55:45 mixture of tautomers. **28**: UV λ_{max} (0.1 N HCl) (initial) 256 nm (ε 14 760), 297 (15 870); UV λ_{max} (1:1 MeOH/pH 7 buffer) 222 nm (ε 52 890), 240 sh (32 060), 322 (13 610), 360 (3200), 380 (2400); UV λ_{max} (1:1 MeOH/0.1 N NaOH) 348 nm (ε 15 990); NMR (CDCl₃) δ 2.85 (s, 3 H), 7.2–7.6 (m, 4 H), 7.9 (s, 1 H), 8.2 (d of m, 1 H), 8.7 (d of m, 1 H), 8.95 (s, 1 H), 9.1 (s, 1 H), 14.8 (br s, 1 H). **32**: UV λ_{max} (0.1 N HCl) 218 nm (ε 36 180), 265 (7580), 301 (13 240); UV λ_{max} (1:1 MeOH/pH 7 buffer) 225 nm (ε 48 170), 318 (12 870), 324 (13 600), 350 (inf) (960); UV λ_{max} (1:1 MeOH/0.1 N NaOH) 290 nm (ε 6880), 358 (16 660); NMR (CDCl₃) δ 2.85 and 2.90 (2 s, 3 H), 7.4 (m, 3 H), 7.75 and 8.0 (2 s, 1 H), 8.9 and 9.2 (2 s, 1 H), 13.7 and 7.0 (2 br s, 1 H), 80:20 mixture of tautomers. **34**: UV λ_{max} (0.1 N HCl) 295 nm (ε 13 220); UV λ_{max} (1:2 MeOH/pH 7 buffer) 214 nm (ε 48 720), 320 (10 980); UV λ_{max} (1:2 MeOH/0.05 N NaOH) 320 nm (ε 10 940); NMR (CDCl₃), see above. **35**: UV λ_{max} (0.1 N HCl) (initial) 283 nm (ε 7360), 347 (18 370); UV λ_{max} (1:2 MeOH/pH 7 buffer) 221 nm (ε 42 840), 284 (5780), 341 (16 830), 284 (5550), 341 (16 690), 350 (16 420); NMR (CDCl₃), see above.

Pharmacological Method. New compounds were evaluated for their effect on the blood pressure and heart rate in 22–24 week old conscious male SHR of Kyoto-Wistar origin weighing from 250 to 350 g. The continuous direct monitoring of aortic blood pressure and heart rate in the freely moving unanesthetized rat was carried out as previously described.^{1,12} All drugs were prepared for oral administration by suspension in a 4% gum acacia vehicle by homogenization and ultrasonification. Each dose was administered by gavage in a 2 mL/kg volume. All doses are expressed as free base. Each drug was administered to groups of three to four rats. Only SHR with mean blood pressure greater than 150 mmHg and with a pulse pressure of greater than 25 mmHg during the predose period were selected for dosing. The mean of individual 30-min values was calculated and compared

(12) (a) Smith, R. D., et al. *DHEW Publ. (NIH) (U.S.) 1977, NIH 78-1473*, 41. Williams, D. B.; Blouin, L. T.; Olszewski, B. J.; Currier, G. A. *Pharmacologist* 1973, 15, 538.

to pretreatment values for each group as described (footnote d, Table I).

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Registry No. 1, 76574-80-6; 2, 77206-70-3; 3, 77206-69-0; 4, 77206-81-6; 5, 84279-04-9; 6, 84279-05-0; 7, 84279-06-1; 8,

77206-73-6; 9, 84279-07-2; 10, 77206-71-4; 11, 77206-84-9; 12, 84279-08-3; 13, 84279-09-4; 14, 84279-10-7; 15, 84279-11-8; 16, 84279-12-9; 17, 84279-13-0; 18, 77206-86-1; 19, 84279-14-1; 20, 84279-15-2; 21, 84279-16-3; 22, 84279-17-4; 23, 84279-18-5; 24, 84279-19-6; 25, 77206-72-5; 26, 84279-20-9; 27, 77206-82-7; 28, 77206-83-8; 29, 84279-21-0; 30, 84279-22-1; 31, 77206-76-9; 32, 77206-85-0; 33, 84279-23-2; 34, 84279-24-3; 35, 84279-25-4; 36, 84279-26-5; 37, 84279-27-6; 38, 84279-28-7; 39, 84279-29-8; 40, 84279-30-1; 41, 77206-80-5; 42, 84279-31-2; 43, 84279-32-3; 44, 84279-33-4; 45, 84279-34-5; 46, 84279-35-6; 47, 84279-36-7; 48, 84279-37-8; 49, 77206-74-7; 50, 77206-75-8; 51, 84279-38-9; 52, 84279-39-0; 53, 84279-40-3; 54, 84279-41-4; 55, 77206-77-0; 56, 84279-42-5; 57, 84279-43-6; 58, 77206-79-2; 59, 84279-44-7; 60, 77206-78-1; 61, 84279-45-8; i, 84279-46-9; cyanamide, 420-04-2.

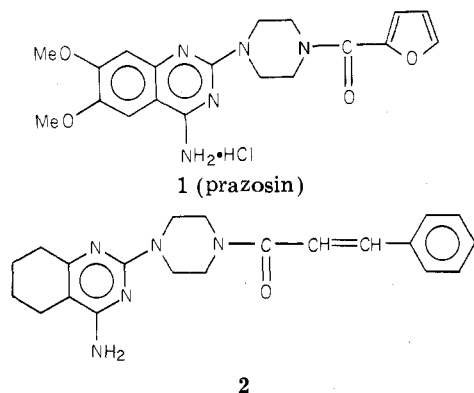
Pyrimidine Derivatives. 4.¹ Synthesis and Antihypertensive Activity of 4-Amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazoline Derivatives¹

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A series of 30 4-amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazoline derivatives was prepared and tested for their ability to reduce blood pressure in conscious, spontaneously hypertensive rats (SHR). A number of these compounds, notably 4-amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazolines **3a** ($R^1 = H$; $R^2 = Ph$), **3j** ($R^1 = H$; $R^2 = 4-EtOPh$), and **5a** ($R^1 = H$; $R^2 = 2-furyl$), showed activity at oral doses of 0.3–10 mg/kg. The effects of the 4-substituents of the piperazino group on activity are discussed. Compounds **3a**, **3j**, and **5a** were effective in renal hypertensive rats at oral doses of 3 and 10 mg/kg and showed α -adrenoceptor blocking effects in isolated aortas of rats. A 5-day consecutive oral administration of **3a** and **3j** in SHR did not lead to development of tolerance.

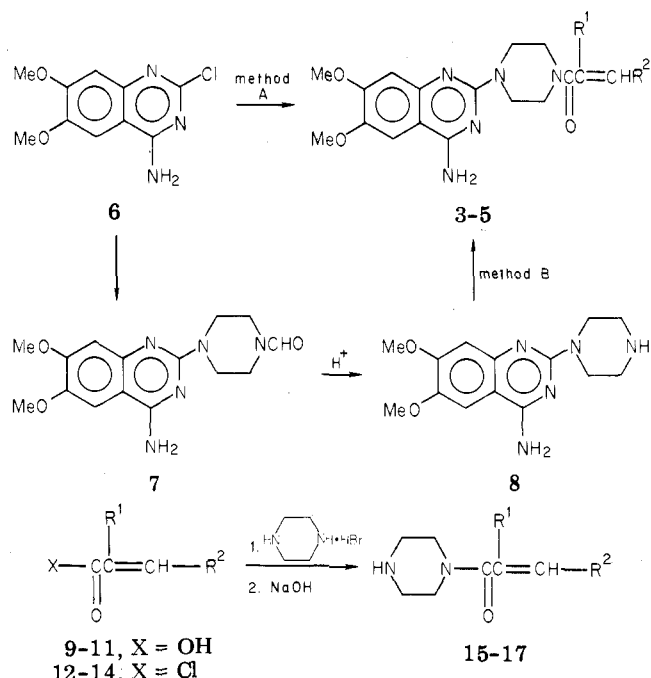
Prazosin (**1**), 4-amino-6,7-dimethoxy-2-[4-(2-furoyl)-



piperazino]quinazoline, is known to have an excellent antihypertensive effect resulting from its postsynaptic α -adrenergic blockade;² therefore, it is often used in the treatment of hypertension. Compounds structurally related to prazosin, such as trimazosin,³ E-643,⁴ tiadazosin,⁵ and terazosin,⁶ have also been reported to show hypotensive activity.

In the course of an ongoing program in the development of novel agents for the treatment of hypertension, certain compounds in a series of 4-amino-2-piperazino-5,6-poly(methylene)pyrimidine derivatives previously reported as hypoglycemic agents⁷ were examined for antihypertensive activity. Of these derivatives, 4-amino-2-(4-cinnamoyl-

Scheme I^a



^a $R^1 = H$ or Me. $R^2 =$ phenyl (**3**, **9**, **12**, and **15**), thienyl (**4**, **10**, **13**, and **16**), or furyl (**5**, **11**, **14**, and **17**); see Table I. For methods A and B, see Experimental Section.

piperazino)-5,6,7,8-tetrahydroquinazoline (**2**) showed an antihypertensive effect when examined in spontaneously

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(1) Part III: T. Sekiya, H. Hiranuma, T. Kanayama, S. Hata, and S. Yamada, *Eur. J. Med. Chem.*, 17, 75 (1982).