heated under reflux under an atmosphere of nitrogen for 15 h and concentrated to dryness in vacuo. The residue was triturated with $Me_2CO$ to give 0.25 g (46%) of 17.

**2,3,6,7,8,9-Hexahydro[1]benzothieno[2,3-*d*]imidazo[1,2-*a*]pyrimidin-2-one Hydrochloride** (18). To a solution of 5.0 g (17.5 mmol) of 9m in 1.5 L of MeOH was introduced air at 50–55 °C for 24 h. The solution was treated with charcoal and concentrated in vacuo to give 2.4 g (49%) of 18: mp 263–265 °C dec (MeOH); IR (KBr) 1785, 1650, 1545, 1360 $cm^{-1}$; NMR ($CF_3CO_2H$) $\delta$ 1.85–2.4 (m, 4 H, $C_7$- and $C_8$-$CH_2$), 2.4–3.2 (m, 4 H, $C_6$- and $C_9$-$CH_2$), 5.64 (s, 2 H, $C_3$-$CH_2$), 9.15 (s. 1 H, $C_5$-CH). Anal. ($C_{12}H_{12}ClN_3OS$) C, H, N.

**Biological Method. Test Animals.** Male Wistar-Imamichi rats weighing 250 g (8 weeks old) were used as routine test animals in our laboratory.

**Preparation of Platelet-Rich Plasma.** Blood was taken from the carotid artery of rats into a plastic syringe containing 0.1 volume of 3.13% sodium citrate dihydrate solution under pentobarbital anesthesia (Nembutal, Abbott Laboratories, 40 mg/kg, ip). The citrated blood was centrifuged at 230*g* for 7 min at room temperature to obtain platelet-rich plasma (PRP). The sediment was further centrifuged at 1500*g* for 10 min to obtain platelet-poor plasma (PPP). The platelet count of PRP was adjusted to approximately $5 \times 10^5/\mu L$ by adding PPP.

**Platelet Aggregation Test in Vitro.** Platelet aggregation was measured by a Bryston Aggregometer at 30 °C under stirring at 1100 rpm. Aggregation was initiated by adding 50 $\mu$L of an aggregating agent to 0.45 mL of PRP. The agents used were 10 $\mu$M ADP (Sigma Chemical Co.) in 25 mM Tris-HCl, 0.13 M NaCl buffer solution, pH 7.4, containing 10 mM $CaCl_2$ and a collagen suspension, which was prepared by homogenizing collagen (bovine achilles tendon, Sigma Chemical Co.) in the Tris buffer, centrifuging the homogenate at 200*g* for 5 min, and diluting supernatant with the Tris buffer to give 0.270 of absorbancy at 420 nm.[13] The fine collagen suspension of this strength induced aggregation after a lag period of 2–3 min. The compound to be tested for antiaggregatory action was added as a saline or MeOH solution in a volume of 5 $\mu$L to PRP before addition of the aggregating agent.

Platelet aggregation was expressed by the maximum decrease in absorbancy of PRP (extent, $\Delta A$) for ADP-induced aggregation and by the maximum rate of decrease in absorbancy at the initial aggregation phase (rate, $\Delta A$/min) for collagen-induced aggregation.[13]

**Platelet Aggregation Test ex Vivo.** The compounds to be tested were dissolved or suspended in 0.5% Tween 80 solution and given to rats fasted overnight at a dose of (50 mg/10 mL)/kg of body weight. Control rats received vehicle alone (0.5% Tween 80, 10 mL/kg). At the time indicated, blood samples were taken to prepare PRP under pentobarbital anesthesia as described above. Platelet aggregation was tested as in the in vitro test, and the antiaggregatory action of the test compounds was expressed as inhibition percent, calculated from comparison of the platelet aggregation between the test and control rats.[13]

**Measurement of Blood Pressure and Heart Rate.** The compounds to be tested were suspended in 0.5% CMC solution, except for **9m** which was suspended in 0.5% Tween 80 solution. They were orally given to rats at a dose of (50 mg/7.5 mL)/kg of body weight. Systolic blood pressure and heart rate were measured by the tail-cuff method[14] with a blood pressure recorder 8002 (W+W Electronic Inc.) after prewarming the rats at 55–60 °C for 3 min prior to and at specified time intervals after the administration of a test compound.

(13) S. Ashida and Y. Abiko, *Thromb. Haemostasis*, **40**, 542 (1978).
(14) M. Gerold and H. Tschirky, *Arzneim.-Forsch.*, **18**, 1285 (1968).

# Antihypertensive Activity of 6-Arylpyrido[2,3-*d*]pyrimidin-7-amine Derivatives

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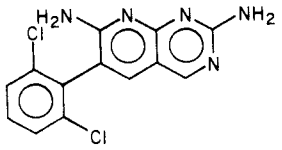
A series of 51 6-arylpyrido[2,3-*d*]pyrimidin-7-amine derivatives was prepared and evaluated for antihypertensive activity in the conscious spontaneously hypertensive rat. A number of these compounds, notably 6-(2,6-dichlorophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-7-amine (**36**), lowered blood pressure in these rats in a gradual and sustained manner to normotensive levels at oral doses of 10–50 mg/kg. Normalized blood pressure levels could then be maintained by single daily oral doses. The effect of structural variation in the 6-aryl group and in the 2 and 4 positions of the pyridopyrimidine ring on activity is reported and discussed.

In the course of an ongoing program to develop novel agents for the treatment of hypertension, we had occasion to reexamine certain compounds in a series of pyrido[2,3-*d*]pyrimidine-2,7-diamines, disclosed previously from these laboratories as potent potassium-sparing diuretics.[1] One compound in particular, 6-(2,6-dichlorophenyl)-pyrido[2,3-*d*]pyrimidine-2,7-diamine (1), showed promising



1

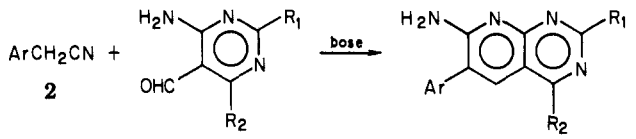
antihypertensive effects when tested in the spontaneously hypertensive rat (SHR). The magnitude of this effect was clearly greater than that previously observed with known diuretic substances, suggesting that 1 might be working through a mechanism other than diuresis and the associated blood volume reduction. Examination of other potent diuretics of this series supported this possibility, since none possessed comparable antihypertensive effects in this model.[2]

The present study was undertaken to prepare analogues of 1 to explore further the relationship between the diuretic and antihypertensive effects in this series of compounds. The combination of effects might well be desirable, considering the effectiveness and popularity of antihypertensive regimens which combine a diuretic agent with another hypotensive agent operating by a different mechanism of action.[3] However, it was recognized that

(1) J. Davoll, U.S. Patent 3 534 039 (1970).
(2) Unpublished results.

0022-2623/81/1824-0382$01.25/0 

Scheme I



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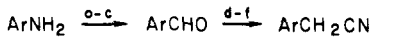
Scheme II[a]



[a] a = HONO; b = $CH_2$=NOH, NaOAc; c = $H_3O^+$; d = $NaBH_4$; e = $SOCl_2$; f = KCN.

if two separate mechanisms were operative in 1, a divergence of these activities might be expected upon structural modification. Further aims were to improve the "quality" of antihypertensive action of 1, e.g., by increasing potency, onset or duration of action or by decreasing tachycardia, and by increasing solubility in order to facilitate pharmacological evaluation and pharmaceutical formulation.

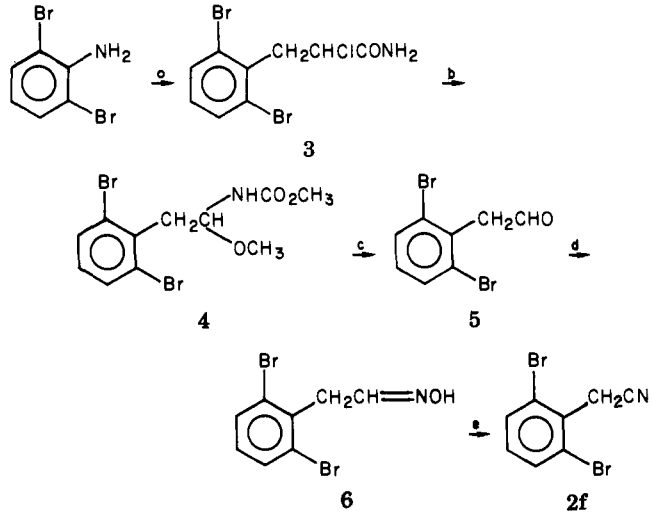
In this paper, we report the effect of varying the substitution in the 6-aryl ring and in the 2 and 4 positions of the pyrido[2,3-*d*]pyrimidine ring on antihypertensive activity in the SHR. Subsequent papers will discuss the effect of other structural variations.

**Chemistry.** Most of the target compounds reported here were made by the same general route used earlier[1] for the diaminopyridopyrimidines. This consisted of condensing a substituted phenylacetonitrile with a suitable 2,6-disubstituted 4-amino-5-pyrimidinecarboxaldehyde in a basic medium (Scheme I).

The phenylacetonitriles employed were mostly commercial samples. Table I lists those which were prepared. Compounds **2a**, **2c**, **2j**, **2k**, and **2l** were obtained from available benzyl alcohol or benzyl halide precursors by reaction of the latter with KCN. The benzyl bromide intermediates for **2e**, **2h**, and **2i** were obtained by NBS bromination of the corresponding toluenes. The mixture of **2h** and **2i** which resulted when 1-bromo-2,3-dimethylbenzene was used as the starting material was found by GLC and NMR analysis to contain about equal amounts of the two isomers. These were not separated but reacted directly with 4-amino-2-methyl-5-pyrimidinecarboxaldehyde to yield a mixture of the pyridopyrimidines **40** and **41**. Pure samples of each isomer were then obtained by column chromatography over silica gel. The first eluting isomer showed the NMR signal for the aryl methyl group at slightly lower field than the more slowly eluting isomer. In addition, the resolvable downfield aryl proton signal was at lower field in the more rapidly eluting isomer. These observations, interpreted in the light of known effects of substituents on aryl proton chemical shifts,[4] allow a reasonably certain assignment of the rapidly eluting isomer as the 2-bromo-6-methyl analogue **41** and the slower moving isomer as the 3-bromo-2-methyl analogue **40**. The observed antihypertensive effects of the two isomers are also consistent with this assignment.

Substituted anilines provided precursors for **2b**, **2d**, and **2g** via the intermediacy of benzaldehyde derivatives obtained by the reaction of the diazonium salts with formaldoxime followed by hydrolysis[5] (Scheme II). Two compounds for which this method was not useful were 2,6-dimethylaniline (complex product mixture) and 2,6-dibromoaniline (inefficient diazonium salt formation).

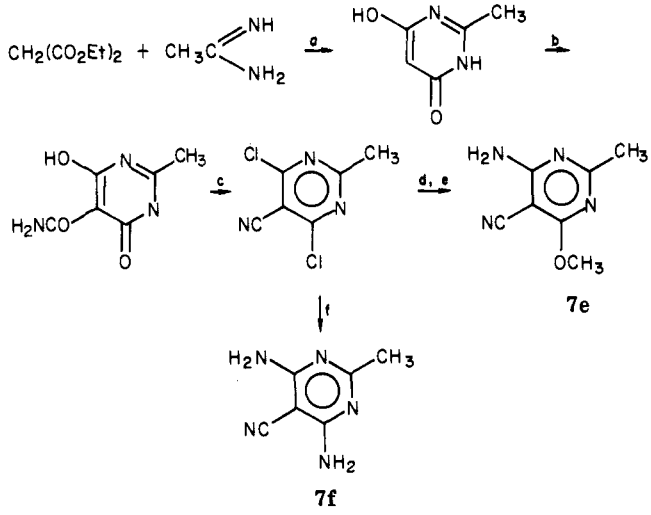
Scheme III[a]



[a] a = AmONO, $CuCl_2$, $CH_2$=$CHCONH_2$; b = $Br_2$, $NaOCH_3$; c = $H_3O^+$; d = $NH_2OH$; e =



Scheme IV[a]

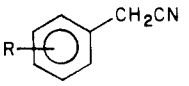


[a] a = NaOEt; b = KOCN, urea; c = $POCl_3$, $PhNMe_2$; d = $NH_3$/EtOH; e = NaOMe; f = $NH_3$ (liq).

While this work was in progress, Doyle et al.[6] reported an improved variation of the Meerwein reaction of diazonium salts with olefins. This looked particularly attractive to us, since the best yields were obtained with highly electron-deficient anilines. Scheme III outlines our subsequent preparation of **2f**. The weak step in this otherwise convenient sequence was the hydrolysis of urethane **4** to the phenylacetaldehyde **5**. The great tendency to self-condensation of the latter, combined with the fairly vigorous acid hydrolysis conditions required to form it from **4**, led to a very low yield. Although we did no further work to improve this step, it seems likely that milder, neutral hydrolysis procedures, such as the recently developed iodotrimethylsilane method,[7] might well be used to advan-

(3) See M. Wilhelm and G. de Stevens, *Prog. Drug Res.*, **20**, 197 ff (1976).
(4) See J. L. Gove, *J. Org. Chem.*, **38**, 3517 (1973) and references cited therein.
(5) (a) S. D. Jolad and S. Rajagopal, *Org. Synth.*, **46**, 13 (1966); (b) L. G. Humber, *J. Med. Chem.*, **7**, 826 (1964).
(6) M. P. Doyle, B. Siegfried, R. C. Elliott, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2431 (1977).
(7) See G. A. Olah, S. C. Narang, B. G. Balaram Gupta, and R. Malhotra, *J. Org. Chem.*, **44**, 1247 (1979) for leading references.

Table I. Prepared Phenylacetonitriles

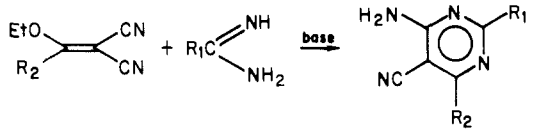


2a–l

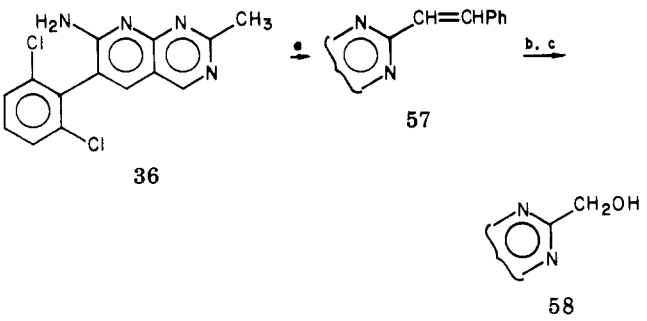
| no. | R | mp or bp (mmHg), °C | lit. mp or bp (mmHg), °C | recrystn solv | method[a] | formula[b] |
|---|---|---|---|---|---|---|
| 2a | 2-I | 160–164 (14) | 119–121 (1)[c] | | A | $C_8H_6IN$ |
| b | 2-$C_2H_5$ | 125–126 (9) | 138–140 (20)[d] | | C | $C_{10}H_{11}N$ |
| c | 2-$CF_3$ | 113–116 (23) | 92 (11)[e] | | A | $C_9H_6F_3N$ |
| d | 2,3-$Cl_2$ | 65–68 | 72–74[f] | hexane | C | $C_8H_5Cl_2N$ |
| e | 2-Cl, 6-Br | 82–84 | | EtOH–$H_2O$ | B | $C_8H_5BrClN$ |
| f | 2,6-$Br_2$ | 94–96.5 | 97–97.5[g] | EtOH | D | $C_8H_5Br_2N$ |
| g | 2-Cl, 6-$CH_3$ | 49–51 | | EtOH | C | $C_9H_8ClN$ |
| h | 2-Br, 6-$CH_3$ | 170–175 (18) | | | B | $C_9H_8BrN$ |
| i | 3-Br, 2-$CH_3$ | | | | | |
| j | 2,3-$(CH_3)_2$ | 50.5–53 | 52–53[h] | petr ether (30–60 °C) | A | $C_{10}H_{11}N$ |
| k | 2,6-$(CH_3)_2$ | 142–143 (19) | 129–130 (12)[i] | | A | $C_{10}H_{11}N$ |
| l | 2,4,6-$(CH_3)_3$ | 78–80 | 79–80[j] | hexane | A | $C_{11}H_{13}N$ |

[a] See Experimental Section. [b] C, H, and N analyses of new compounds were within ±0.4% of calculated values. Known compounds were verified by spectral data and properties. [c] J. A. Faust, L. S. Yee, and M. Sahyun, *J. Org. Chem.*, 26, 4044 (1961). [d] B. vanZanten and W. Th. Nauta, *Recl. Trav. Chim. Pays-Bas*, 79, 1211 (1960). [e] C. van der Stelt et al., *Arzneim.-Forsch.*, 15, 1251 (1965). [f] R. W. Fuller, B. B. Malloy, W. A. Day, B. W. Roush, and M. M. Marsh, *J. Med. Chem.*, 16, 101 (1973). [g] A. Areschka and A. Bruylants, *Bull. Soc. Chim. Fr.*, 496 (1958). [h] G. S. Skinner, T. F. Sanderson, E. R. Bieber, and H. Ewadh, *J. Org. Chem.*, 24, 403 (1959). [i] N. Lofgren, U. Ragnarsson, and K. Sjoberg, *Acta Chem. Scand.*, 17, 1252 (1963). [j] R. C. Fuson and N. Rabjohn, "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 557.

Scheme V



Scheme VI[a]



[a] a = PhCHO, piperidine; b = $O_3$; c = $NaBH_4$.

tage here. One attempt to convert **4** directly to oxime **6** with hydroxylamine was unsuccessful.

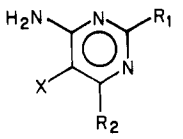
The 4-amino-5-pyrimidinecarboxaldehydes, **8**, were prepared by the reduction of the corresponding 4-amino-5-pyrimidinecarbonitriles, **7**. The latter were mostly known compounds. Compound **7a** was prepared by the method of Baddiley et al.[8] by condensing 2 equiv of formamidine with malononitrile. Compounds **7e** and **7f** were obtained by the method outlined in Scheme IV[9] and the remainder resulted from the condensation of amidines with ethoxymethylenemalononitriles (Scheme V).

The reduction of heterocyclic nitriles to aldehydes has been accomplished under a variety of conditions by others.[10] We chose to use primarily a method developed by W. Pearlman of these laboratories using Raney nickel catalyzed hydrogenation in aqueous formic acid.[11] Yields generally were in the 30–50% range in the successful cases. Compound **8c** was also prepared by what is probably a better method, namely, hydrogenation over 10% Pd/C in dilute sulfuric acid. If conditions were properly controlled, this latter method gave a 60–70% yield of **8c** uncontaminated with **7c**. Some amount of unreduced nitrile invariably remained when the Raney nickel procedure was used and, although its presence was easily detected and quantitated by NMR, it proved very difficult to remove from the aldehyde. In many cases the subsequent condensation reaction with **2** to form the pyridopyrimidine was carried out with **8** containing up to 15% of **7**. The latter impurity did not react effectively with **2** under the conditions employed and was lost in the subsequent workup. Compound **8f** could only be obtained by the palladium-catalyzed reduction, while **7e** failed to react under these conditions and gave **8e** only using the Raney nickel method. Table II lists the 4-amino-5-pyrimidinecarbonitriles **7** and -carboxaldehydes **8** prepared in this work.

The condensation reaction of **2** with **8** to give the target pyrido[2,3-*d*]pyrimidin-7-amines was routinely carried out in ethanol using a catalytic amount of sodium ethoxide. This contrasted with the experience of Davoll[1] in the diuretic series of compounds related to **1** where refluxing ethoxyethanol was required to obtain useful yields. It was our general impression, even though the yields and conditions reported in Table III do not always reflect this, that the ease of the reaction was dependent on a combination of electronic and steric effects in the phenylacetonitrile and also to a degree on electronic effects in the pyrimidinecarboxaldehyde. Facilitation of the reaction by electron withdrawal was most clearly seen in the rapid condensation of 3-pyridinylacetonitrile and 4-nitrophenylacetonitrile, while **2k** and **2l** showed the retarding effect of steric hindrance. The electron-attracting properties of 2-chloro or

(8) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 386 (1943).
(9) Z. Budesinsky and J. Kopecky, *Coll. Czech. Chem. Commun.*, **20**, 52 (1955).
(10) (a) O. G. Backeberg and B. Staskun, *J. Chem. Soc.*, 3961 (1962); (b) E. Reimann, *Justus Liebigs Ann. Chem.*, 1963 (1978); (c) L. T. Weinstock, D. E. O'Brien, and C. C. Cheng, *J. Med. Chem.*, 11, 1238 (1968); (d) A. Taurins and V. T. Khouw, *Can. J. Chem.*, 1741 (1973).
(11) W. Pearlman, unpublished results, personal communication.

Table II. 4-Amino-5-pyrimidinecarbonitriles and -Carboxaldehydes



7a–j, X = CN
8a–j, X = CHO

| | | | X = CN | | X = CHO | | | |
|---|---|---|---|---|---|---|---|---|
| no. | $R_1$ | $R_2$ | mp, (lit.), °C | method[a] | mp, °C | method[a] | purifn[b] | formula[c] |
| a | H | H | 248–250 (250)[d] | E | 179–182[e] | H | | $C_5H_5N_3O$ |
| b | H | $CH_3$ | 216–219 (217–219)[f] | F | 158–160 | H | 1 | $C_6H_7N_3O$ |
| c | $CH_3$ | H | 250–252 (249)[g] | F | 193–195[h] | H, I | | $C_6H_7N_3O$ |
| d | $CH_3$ | $CH_3$ | 225–226 (220.5)[i] | F | 147–148 | H | 1 | $C_7H_9N_3O$[j] |
| e | $CH_3$ | $OCH_3$ | 244–245 | G | 195–196 | H | 2 | $C_7H_9N_3O_2$ |
| f | $CH_3$ | $NH_2$ | >400 (>360)[k] | G | >300 dec | I | 3 | $C_6H_8N_4O$[l] |
| g | $CF_3$ | H | 246–248 (245–246)[m] | F | 230–231 | H | 4 | $C_6H_4F_3N_3O$ |
| h | $C_2H_5$ | H | 201–202 (198)[i] | F | 150–152 | H | 1 | $C_7H_9N_3O$ |
| i | c-$C_3H_5$ | H | 189–191 (185–188)[n] | F | 184–185 | H | 5 | $C_8H_9N_3O$ |
| j | $CH_2OCH_3$ | H | 160–162 | F | 127–129 | H | 6 | $C_7H_9N_3O_2$ |

[a] See Experimental Section. [b] Analytical samples were purified by the following methods: (1) HPLC, $SiO_2$/EtOAc; (2) column chromatography, $SiO_2$/$CHCl_3$–MeOH–HCOOH (98:2:0.2); (3) recrystallized $H_2O$; (4) HPLC, $SiO_2$/$CHCl_3$; (5) recrystallized EtOH; (6) column chromatography, $SiO_2$/EtOAc–MeOH (95:5). [c] C, H, and N analyses were within ±0.4% of the calculated values unless noted otherwise. [d] Reference 8. [e] H. Bredereck, G. Simchen, and H. Traut, *Chem. Ber.*, 100, 3664 (1967). [f] E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Am. Chem. Soc.*, 82, 5711 (1960). [g] R. Grewe, *Z. Physiol. Chem.*, 242, 89 (1936). [h] D. Price, E. L. May, and F. D. Pickel, *J. Am. Chem. Soc.*, 62, 2818 (1940). [i] W. Huber and H. A. Holscher, *Chem. Ber.*, 71, 87 (1938). [j] N: calcd, 27.80; found, 27.37. [k] Reference 9. [l] C, H, and N analyses not performed. [m] J. A. Barone, E. Peters, and H. Tieckelman, *J. Org. Chem.*, 24, 198 (1959). [n] R. H. Mizzoni, R. A. Lucas, R. Smith, J. Boxer, J. E. Brown, F. Goble, E. Konopka, J. Gelzer, J. Szanto, D. C. Maplesden, and G. DeStevens, *J. Med. Chem.*, 13, 878 (1970).

2-bromo substituents appeared to overbalance their steric properties.

Compounds **57** and **58** were prepared by further transformation of **36** as shown in Scheme VI.[12] Compound **50** was obtained when 2,6-dichlorophenylacetonitrile was reacted with **8e** in ethanol. This facile exchange of alkoxy groups is perhaps not surprising in retrospect, considering the high reactivity toward nucleophiles of the analogous position in other related heterocyclic ring systems.[13]

## Biological Results and Discussion

Compounds **9–60** were screened orally at 50 mg/kg in conscious SHR with indwelling catheters for the continuous monitoring of blood pressure and heart rate. We have recorded in Table III blood pressure ratings at three different time periods to give some idea of the onset and duration of action, as well as the maximum effect observed. The most obvious structural correlate of high activity and good duration of action is the presence of at least one and, preferably, two ortho substituents of moderate size on the 6-aryl group. When this latter group was held constant as 2,6-dichlorophenyl, the activity of analogues variously substituted in the 2 position of the pyridopyrimidine ring seemed to show a size dependence with a maximum at methyl (**36**). At the 4 position, H is preferred for best activity, although methyl is tolerated. A larger neutral substituent (-OEt) leads to a less active compound (**50**), while a polar amino group (**49**) destroys activity.

Returning to the 6-aryl substituents, we found that two such substituents, especially Cl or Br, gave the best compounds (**36**, **37**, and **39**). The determinants of activity in the 6-aryl group appear not to be electronic, as shown by the inactivity of **26**, **29**, or **46** compared to slightly active **25** or highly active **36** or by the roughly equivalent activity of **31** and **25**. Neither does the lipophilicity of this group appear decisive if the four dichlorophenyl analogues **33–36** are compared or if **30** and **32** are compared with **36**. The size of the aryl 2-substituent was the factor most consistently associated with high potency, with an optimum at Cl, Br, or $CH_3$. Even here, the halogens were somewhat better than methyl.

Several of the more active compounds were retested at lower doses as shown in Table III. The activity of **36** was clearly superior to anything else in the series, with an approximate $ED_{30}$ of 17 mg/kg (defined as the dose required to lower blood pressure by 30 mmHg 5-h posttreatment). The compound is well tolerated, having an acute $LD_{50}$ in rats greater than 7000 mg/kg. It displayed no diuretic effects in conscious dogs at doses of 10 and 30 mg/kg po, and, hence, the 2-amino function appears to be required for diuretic activity.[15]

The mode of action of **36** is presently being investigated. In contrast to clonidine or other antihypertensive agents which contain a 2,6-dihalo-substituted aryl ring, **36** shows no evidence of CNS effects. Also, unlike clonidine which produces an immediate heart rate increase followed by a longer lasting bradycardia **36** produces only a gradual and moderate tachycardia.

In summary, we have discovered a new class of antihypertensive compounds, of which **36** is the most interesting

(12) (a) D. C. Baker and S. R. Putt, personal communication; (b) C. C. Overberger and J. K. Weise, *J. Am. Chem. Soc.*, **90**, 3525 (1968).
(13) For a review, see G. Illuminati, *Adv. Heterocycl. Chem.*, **3**, 285 ff (1964).
(14) W. L. Lipschitz, A. Hadidian, and A. Kerpesar, *J. Pharmacol. Exp. Ther.*, **79**, 97 (1943).
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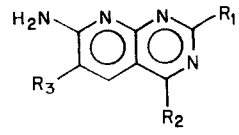
Table III. 6-Arylpyrido[2,3-*d*]pyrimidin-7-amines




| no. | $R_1$ | $R_2$ | $R_3$ | mp, °C | recrystn solv[a] | reactn conditions: solv | reactn conditions: time, h | reactn conditions: % yield | formula | anal.[c] | po dose, mg/kg | act. rating in SHR[d]: hour post dose 2 | 10 | 24 | max % decrease h |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $NH_2$ | H | 2,6-$Cl_2$Ph[e] | 338–341 | A–D | C | 4 | 26 | $C_{13}H_9Cl_2N_5$ | C, H, N | 50 | 0 | 1 | 2 | 18 (24) |
| | | | | | | | | | | | 10 | 0 | 0 | 1[f] | |
| 9 | H | H | Ph[e] | 289–290 | B–D | C | 2 | 79 | $C_{13}H_{10}N_4$ | C, H, N | 50 | 0 | 0 | 0 | |
| 10 | H | H | 2-ClPh | 269–270 | A–D | B | 3 | 67 | $C_{13}H_9ClN_4$ | C, H, N, Cl | 50 | 0 | 0 | 0 | |
| 11 | H | H | 2-BrPh | 265–267 | A–D | B | 3 | 60 | $C_{13}H_9BrN_4$ | C, H, N | 50 | 0 | 1 | 1[g] | 16 (5) |
| | | | | | | | | | | | 10[h] | 0 | 0 | 0[i] | |
| 12 | H | H | 2-IPh | 262–264 | C | B | 4 | 62 | $C_{13}H_9IN_4$ | C, H, N | 50 | 0 | 0 | 1 | 11 (8) |
| 13 | H | H | 2-MePh | 253–255 | B | B | 3 | 68 | $C_{14}H_{12}N_4$ | C, H, N | 50 | 1 | 1 | 0 | 18 (2) |
| | | | | | | | | | | | 10 | 0 | 0 | 0 | |
| 14 | H | H | 2-EtPh | 235–236 | B | B | 6 | 35 | $C_{15}H_{14}N_4$ | C, H, N | 50 | 3 | 0 | 0 | 33 (2) |
| 15 | H | H | 2-$CF_3$Ph | 291–292 | B | B | 1 | 58 | $C_{14}H_9F_3N_4$ | C, H, N | 50 | 0 | 0 | 0 | |
| 16 | H | H | 2,6-$Cl_2$Ph | 328–330 | A–D | B | 3 | 77 | $C_{13}H_8Cl_2N_4$ | C, H, N, Cl | 50 | 0 | 0 | 2 | 22 (24) |
| | | | | | | | | | | | 10[h] | 0 | 0 | 0[i] | |
| | | | | | | | | | | | 3[h] | 0 | 0 | 0[i] | |
| 17 | H | H | 2-Cl-6-BrPh | 326–330 | C | B | 6 | 83 | $C_{13}H_8BrClN_4$ | C, H, N, Br | 50 | 1 | 2 | 1[g] | 28 (6) |
| | | | | | | | | | | | 10 | 1 | 1 | 1 | |
| 18 | H | H | 2-Cl-6-MePh | 300–302 | H | B | 6 | 29 | $C_{14}H_{11}ClN_4$ | C, H, N, Cl | 50 | 1 | 2 | 1[g] | 21 (10) |
| 19 | H | H | 2,3-$Me_2$Ph | 317–319 | B | B | 3 | 73 | $C_{15}H_{14}N_4$ | C, H, N | 50 | 0 | 0 | 0 | |
| 20 | H | H | 2,6-$Me_2$Ph | 285–287 | B | B | 3 | 19 | $C_{15}H_{14}N_4$ | C, H, N | 50 | 1 | 0 | | 12 (3) |
| 21 | H | H | 3-pyridyl | 295–297 | A | B | 16[j] | 73 | $C_{12}H_9N_5$ | C, H, N | 50 | 0 | 0 | 0 | |
| 22 | H | $CH_3$ | 2,6-$Cl_2$Ph | 280–282 | B | B | 0.5 | 19[k] | $C_{14}H_{10}Cl_2N_4$ | C, H, N | 50 | 2 | 2 | | 26 (6) |
| | | | | | | | | | | | 10 | 0 | 0 | 0 | |
| 23 | $CH_3$ | H | Ph | 229–230 | B | B | 7 | 81 | $C_{14}H_{12}N_4 \cdot 0.4H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |
| 24 | $CH_3$ | H | 2-FPh | 278–279 | B | B | 1 | 73 | $C_{14}H_{11}FN_4 \cdot 0.5H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |
| 25 | $CH_3$ | H | 2-ClPh | 259–260 | A–D | C | 3 | 48 | $C_{14}H_{11}ClN_4 \cdot 0.67H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 1 | 1 | 16 (8) |
| 26 | $CH_3$ | H | 4-ClPh | 262–264 | A–D | C | 3 | 53 | $C_{14}H_{11}ClN_4$ | C, H, N, Cl | 50 | 0 | 0 | 0 | |
| 27 | $CH_3$ | H | 2-BrPh | 228–230 | B | B | 3 | 63 | $C_{14}H_{11}BrN_4 \cdot 0.75H_2O$ | C, H, N, $H_2O$ | 50 | 1 | 1 | 0 | 19 (4) |
| | | | | | | | | | | | 10[h] | 0 | 0 | 0 | |
| 28 | $CH_3$ | H | 2-IPh | 255–258 | E | B | 4 | 41 | $C_{14}H_{11}IN_4$ | C, H, N, I | 50 | 0 | 0 | 0 | |
| 29 | $CH_3$ | H | 4-$NO_2$Ph | 299–301 | B | B | 1 | 33[k] | $C_{14}H_{11}N_5O_2 \cdot 0.5H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |
| 30 | $CH_3$ | H | 2-$CF_3$Ph | 244–245 | F | B | 4 | 45 | $C_{15}H_{11}F_3N_4 \cdot 0.1H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |
| 31 | $CH_3$ | H | 2-MePh | 234–235 | B | C | 2 | 42 | $C_{15}H_{14}N_4 \cdot 0.5H_2O$ | C, H, N, $H_2O$ | 50 | 1 | 1 | 1 | 22 (4) |
| 32 | $CH_3$ | H | 2-EtPh | 211–213 | E | B | 6 | 45[k] | $C_{16}H_{16}N_4$ | C, H, N | 50 | 0 | 0 | 0 | |
| 33 | $CH_3$ | H | 2,3-$Cl_2$Ph | 270–272 | A–D | C | 3 | 73 | $C_{14}H_{10}Cl_2N_4 \cdot H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **34** | $CH_3$ | H | 2,4-$Cl_2$Ph | 259–261 | A–D | B | 1.5 | 63 | $C_{14}H_{10}Cl_2N_4 \cdot 0.5H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 1 | 1 | 13 (8) |
| **35** | $CH_3$ | H | 3,4-$Cl_2$Ph | 267–268 | A–D | B | 1.5 | 70 | $C_{14}H_{10}Cl_2N_4$ | C, H, N | 50 | 0 | 0 | | |
| **36** | $CH_3$ | H | 2,6-$Cl_2$Ph | 288–290 | B | B | 3 | 61 | $C_{14}H_{10}Cl_2N_4$ | C, H, N | 50 | 1 | 3 | 3 | 32 (10) |
| | | | | | | | | | | | 10 | 1 | 1 | 1[f] | |
| | | | | | | | | | | | 3 | 1 | 1 | 1[f] | |
| **37** | $CH_3$ | H | 2-Cl-6-BrPh | 272–274 | E | B | 24 | 49 | $C_{14}H_{10}BrClN_4$ | C, H, N, Br | 50 | 2 | 2 | 2 | 26 (5) |
| | | | | | | | | | | | 10[h] | 1 | 1 | 0[g] | |
| **38** | $CH_3$ | H | 2-Cl-6-MePh | 267–271 | F | B | 24 | 43 | $C_{15}H_{13}ClN_4$ | C, H, N, Cl | 50 | 1 | 2 | 2[g] | 30 (5) |
| **39** | $CH_3$ | H | 2,6-$Br_2$Ph | 260–264 | B | C | 24 | 32 | $C_{14}H_{10}Br_2N_4$ | C, H, N, Br | 50 | 2 | 2 | 2 | 28 (6) |
| | | | | | | | | | | | 10 | 1 | 2 | 1[g] | |
| **40** | $CH_3$ | H | 2-Me-3-BrPh | 253–257 | E | B | 6 | 6 | $C_{15}H_{13}BrN_4$ | C, H, N; Br[l] | 50 | 0 | 0 | 0 | |
| **41** | $CH_3$ | H | 2-Me-6-BrPh | 257–259 | E | B | 6 | 7 | $C_{15}H_{13}BrN_4$ | C, H, N, Br | 50 | 0 | 1 | 0 | 18 (5) |
| **42** | $CH_3$ | H | 2,3-$Me_2$Ph | 259–261 | B | C | 5 | 33 | $C_{16}H_{16}N_4 \cdot H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |
| **43** | $CH_3$ | H | 2,6-$Me_2$Ph | 273–275 | B | B | 3 | 5 | $C_{16}H_{16}N_4 \cdot H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |
| **44** | $CH_3$ | H | 2,4,6-$Me_3$Ph | 254–255 | B | B | 26 | 15 | $C_{17}H_{18}N_4$ | H, N; C[m] | 50 | 1 | 0 | 0 | 18 (2) |
| **45** | $CH_3$ | H | 2-furyl | 232–233 | B | B | 1 | 54 | $C_{12}H_{10}N_4O \cdot 0.5H_2O$ | C, H, N; $H_2O$[n] | 50 | 0 | 0 | 0 | |
| **46** | $CH_3$ | H | 3-pyridyl | 296–298 | A | B | 4[j] | 36 | $C_{13}H_{11}N_5$ | C, H, N | 50 | 0 | 0 | 0 | |
| **47** | $CH_3$ | $CH_3$ | 2-MePh | 234–236 | G | B | 0.5 | 29 | $C_{16}H_{16}N_4$ | C, H, N | 50 | 0 | 0 | 0 | 11 (8) |
| **48** | $CH_3$ | $CH_3$ | 2,6-$Cl_2$Ph | 239–240 | G | B | 0.7 | 28 | $C_{15}H_{12}Cl_2N_4$ | C, H, N | 50 | 2 | 3 | 2[g] | 32 (6) |
| | | | | | | | | | | | 10[h] | 1 | 0 | 0 | |
| **49** | $CH_3$ | $NH_2$ | 2,6-$Cl_2$Ph | 389–391 | B | B | 5 | 14 | $C_{14}H_{11}Cl_2N_5$ | C, H, N | 50 | 0 | 0 | 0 | |
| **50** | $CH_3$ | OEt | 2,6-$Cl_2$Ph | 237–239 | B | B | 3 | 24 | $C_{16}H_{14}Cl_2N_4O$ | C, H; N[o] | 50 | 0 | 0 | 0 | |
| **51** | $C_2H_5$ | H | 2-ClPh | 186–188 | B | B | 3.5 | 50 | $C_{15}H_{13}ClN_4 \cdot H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 0 | 0 | |
| **52** | $C_2H_5$ | H | 2-MePh | 192–193 | B | B | 3.5 | 31 | $C_{16}H_{16}N_4$ | C, H, N | 50 | 0 | 0 | 0 | |
| **53** | $C_2H_5$ | H | 2,6-$Cl_2$Ph | 269–270 | B | B | 3 | 27 | $C_{15}H_{12}Cl_2N_4 \cdot H_2O$ | C, H, N, $H_2O$ | 50 | 0 | 1 | 0 | 15 (6) |
| **54** | *c*-$C_3H_5$ | H | 2-BrPh | 227–229 | B | B | 3.5 | 52 | $C_{16}H_{13}BrN_4$ | C, H, N | 50 | 0 | 0 | 0 | |
| **55** | *c*-$C_3H_5$ | H | 2-MePh | 211–212 | B | B | 3 | 43 | $C_{17}H_{16}N_4$ | H, N; C[p] | 50 | 0 | 0 | 0 | |
| **56** | *c*-$C_3H_5$ | H | 2,6-$Cl_2$Ph | 261–262 | B | B | 3.5 | 49 | $C_{16}H_{12}Cl_2N_4$ | H, N; C[q] | 50 | 0 | 0 | 0 | |
| **57** | CH=CHPh | H | 2,6-$Cl_2$Ph | 269–271 | B | | *r* | 35 | $C_{21}H_{14}Cl_2N_4$ | C, H, N | 50 | 0 | 1 | 0 | 13 (6) |
| **58** | $CH_2OH$ | H | 2,6-$Cl_2$Ph | 244–246 | B | | *r* | 28 | $C_{14}H_{10}Cl_2N_4O$ | C, H, N | 50 | 0 | 1 | 1 | 17 (10) |
| **59** | $CH_2OCH_3$ | H | 2,6-$Cl_2$Ph | 208–209 | G | B | 1 | 13 | $C_{15}H_{12}Cl_2N_4O$ | C, H, N | 50 | 1 | 1 | 1 | 14 (3) |
| **60** | $CF_3$ | H | 2,6-$Cl_2$Ph | 288–289 | B | B | 0.5[j] | 29 | $C_{14}H_7Cl_2F_3N_4$ | C, H, N, F | 50 | 0 | 0 | 0 | |
| hydralazine | | | | | | | | | | | 10 | 3 | 2 | 1 | 51 (4) |
| | | | | | | | | | | | 3 | 2 | 2 | 1 | 27 (1) |
| | | | | | | | | | | | 1 | 0 | 0 | 0 | |
| clonidine | | | | | | | | | | | 3 | 0 | 2 | 2 | 25 (10) |
| | | | | | | | | | | | 1 | 1 | 1 | 1 | 21 (6) |
| | | | | | | | | | | | 0.3 | 1 | 1 | 0 | 20 (6) |

[a] Solvents: A, DMF; B, EtOH; C, ethoxyethanol; D, $H_2O$; E, $CH_3CN$; F, *i*-PrOH; G, EtOAc. [b] Reactions run in refluxing solvent (as in footnote *a*) for indicated time; yields reported are for purified first crop only. [c] Analyses within ±0.4% for indicated elements. [d] Activity ratings: all results were analyzed for statistically significant differences from predose control values 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] Prepared by Dr. J. Davoll. [f] This level of effect maintained for up to 72 h with once daily oral dosing. [g] 18 h. [h] Maximum effect at 3–5 h postdose. [i] Significant decrease observed on 2nd and 3rd day. [j] 25 °C. [k] Chromatographic purification required. [l] Br: calcd, 24.28; found, 24.73. [m] C: calcd, 73.35; found, 72.90. [n] $H_2O$: calcd, 3.83; found, 4.30. [o] N: calcd, 16.04; found, 15.54. [p] C: calcd, 73.89; found, 73.42. [q] C: calcd, 58.02; found, 57.50. [r] See Experimental Section.

member. Doses of 10–50 mg/kg po bring about a gradual lowering of blood pressure in the SHR to nearly normotensive levels, which are then maintainable by once daily oral doses. Side effects are minimal and the compound is tolerated well at doses greater than 300 mg/kg. Further studies are now in progress to determine the mechanism of action of **36** and its suitability for clinical studies.

## Experimental Section

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. $^1$H NMR 90-MHz spectra were obtained using a Varian Associates EM-390 or Bruker B-NC-12 instrument. Chemical shifts are recorded in parts per million ($\delta$) relative to $(CH_3)_4Si$ 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. $MgSO_4$ was used as a drying agent unless otherwise noted.

**Preparation of Phenylacetonitriles (2). Method A.** The benzyl alcohol was treated in benzene solution with 1.5 equiv of $SOCl_2$ at reflux for 2–3 h to afford the benzyl chlorides, which were isolated by distillation. After their structures had been confirmed by NMR, they were converted directly to the phenylacetonitriles by reaction with KCN in aqueous EtOH at reflux for 4–6 h. Isolation by filtration or extraction and purification by recrystallization or distillation gave the desired products whose properties are listed in Table I. The benzyl alcohol precursor for **2k** was prepared by reduction of the available benzaldehyde with $NaBH_4$ in MeOH.

**Method B.** Available anilines were converted by the method of ref 5 to the substituted benzaldehydes. These were isolated via $NaHSO_3$ addition products and then reduced to the benzyl alcohols with $NaBH_4$ in MeOH and then to the phenylacetonitriles following method A.

**2-Bromo-6-chlorophenylacetonitrile (2e). Method C.** A mixture of 20.0 g (0.10 mol) of 1-bromo-3-chloro-2-methylbenzene,[17] bp 98–105 °C (18 mmHg), and 18.0 g (0.10 mol) of NBS in 200 mL of $CCl_4$ was treated with ca. 10 mg of benzoyl peroxide and heated to reflux. After 24 h, the NBS had been consumed, and the mixture was cooled and filtered. Concentration of the filtrate to dryness gave 31.0 g of a lachrymatory oil which solidified on standing: mp 56–60 °C; NMR ($CDCl_3$) showed clean conversion to the desired 1-bromo-2-(bromomethyl)-3-chlorobenzene [$\delta$ 4.7 (s, 2 H, $CH_2Br$)] and this was then converted to **2e** by reaction with KCN following method A without further purification.

**2,6-Dibromophenylacetonitrile (2f). Method D.** Following a general method,[6] a solution (warming was necessary) of 50 g (0.20 mol) of 2,6-dibromoaniline in 150 mL of $CH_3CN$ was dropped into a suspension of 30 g (0.22 mol) of anhydrous $CuCl_2$ and $CuCl$, 100 g (1.42 mol) of acrylamide in 250 mL of $CH_3CN$, and 30 g (0.25 mol) of isoamyl nitrite, keeping the temperature below 30 °C. After stirring for 1 h at room temperature, the reaction mixture was poured into 400 mL of cold 6 N HCl. The slurry was diluted with $H_2O$ and filtered, washing the solids with 2 N HCl and finally $H_2O$, to yield, after air drying, 53.8 g of solid, mp 120–130 °C, containing a mixture of the desired amide, **3**, and unreacted aniline. Recrystallization from EtOH gave a first crop of 28.7 g of pure **3**: mp 142–144.5 °C; NMR ($CDCl_3$) $\delta$ 3.5–4.0 (m, 2 H, $CH_2CH$), 4.9 (dd, 1 H, $CHCl$), 6.0–6.6 (br s, 2 H, $NH_2$), 7.0 (t, 1 H), 7.6 (d, 2 H). Anal. ($C_9H_8Br_2ClNO$) C, H, Br, Cl, N. A second crop of 6.8 g, mp 140–142 °C, was also obtained (total yield 36.5 g, 54%).

A solution of 6.1 g (0.26 g-atom) of Na in 500 mL of MeOH was prepared and cooled to 0 °C, **3** (30.0 g, 0.088 mol) was added, and then 14.0 g (0.088 mol) of $Br_2$ was dropped in while the temperature was maintained somewhat below 0 °C. The solution was stirred for 2 h at 0 °C, warmed to room temperature during 1 h, and then heated at reflux for 1 h. The residue obtained after cooling and concentrating the mixture under reduced pressure was triturated with water and filtered. The wet filter cake was slurried with $CH_3CN$. Filtration gave a first crop of 7.6 g of a white solid, mp 119–122 °C dec. A second crop of 4.5 g was also obtained from the filtrate. The structure **4** was assigned to this material on the basis of the following data: IR (KBr) 3320 (NH), 1700, 1530 cm$^{-1}$ (NHCOO); NMR ($Me_2SO$-$d_6$) $\delta$ 3.1 (s, 3 H, $OCH_3$), 3.0–3.5 (m, 2 H, $CH_2$), 3.5 (s, 3 H, $OCH_3$), 7.1 (t, 1 H), 7.6 (d, 2 H), 7.6–7.9 (br, 1 H, NH). This was used without further purification.

A 12.0-g (0.03 mol) sample of **4** was combined with 100 mL of 1% aqueous $H_2SO_4$ and heated in a steam distillation apparatus. Only 1.4 g (15%) of the desired **5** distilled as a white solid, mp 93–94 °C. This was combined with material from another run and recrystallized from cyclohexane to give an analytical sample: mp 93.5–95.5 °C; NMR ($CDCl_3$) $\delta$ 4.2 (s, 2 H), 7.0 (t, 1 H), 7.6 (d, 2 H), 9.7 (s, 1 H); IR (KBr) 1720 cm$^{-1}$ (CHO). Anal. ($C_8H_6Br_2O$) C, H, Br.

Conversion of this to **2f** was accomplished via the oxime **6** (from $NH_2OH$·HCl and NaOAc in aqueous EtOH), mp 173–175 °C. Anal. ($C_8H_7Br_2NO$) C, H, Br, N. Dehydration was carried out by treatment of a $CH_2Cl_2$ solution of **6** with 1,1′-carbonyldiimidazole[18] to give a nearly quantitative yield of **2f**.

**Preparation of 4-Amino-5-pyrimidinecarbonitriles (7).** These were all obtained by literature procedures.

**Method E.** Compound **7a** was prepared by condensing malononitrile with 2 equiv of formamidine following the procedure of ref 8.

**4-Amino-2-(methoxymethyl)-5-pyrimidinecarbonitrile (7j). Method F.** A solution of 7.3 g (0.32 g-atom) of Na in 300 mL of EtOH was prepared, and this was cooled and treated with 39.7 g (0.32 mol) of 2-methoxyacetamidine hydrochloride.[19] After 1 h, the mixture was filtered to remove NaCl, and then, with rapid stirring, the filtrate was added to a solution of 39.4 g (0.32 mol) of ethoxymethylenemalononitrile in 300 mL of EtOH. After the initial exothermic reaction, the mixture was allowed to return to room temperature over 2 h and then it was concentrated at reduced pressure. The white solid which separated on cooling was filtered and washed with $Et_2O$, giving 35.5 (68%) of crude **7j**), mp 159–163 °C. Recrystallization from EtOH gave an analytical sample: mp 160–162 °C; IR (KBr) 3370, 3340, 2240, 1670 cm$^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 3.3 (s, 3 H), 4.3 (s, 2 H), 7.9 (br s, 2 H), 8.6 (s, 1 H); UV (MeOH) $\lambda_{max}$ 298 nm ($\epsilon$ 4650), 243 (11 900). Anal. ($C_7H_8N_4O$) C, H, N.

**4-Amino-6-methoxy-2-methyl-5-pyrimidinecarbonitrile (7e). Method G.** The common intermediate for **7e** and **7f**, 4,6-dichloro-2-methyl-5-pyrimidinecarbonitrile, mp 113–116 °C, was prepared and converted with $NH_3$/EtOH to 4-amino-6-chloro-2-methyl-5-pyrimidinecarbonitrile, mp 252–254 °C, following the procedure of ref 9. A modification of the procedure described for the 6-ethoxy analogue was used to prepare **7e**. Thus, 3.0 g (0.018 mol) of 4-amino-6-chloro-2-methyl-5-pyrimidinecarbonitrile was added to a solution of 0.45 g (0.018 g-atom) of Na in 90 mL of MeOH at room temperature and stirred overnight. Filtration of the mixture gave the crude product, which was purified by recrystallization from EtOH to give 2.6 g (90%) of white flocculent solid **7e**: mp 244–245 °C; IR(KBr) 3390, 3350, 2230, 1680 cm$^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 2.3 (s, 3 H), 3.9 (s, 3 H), 7.6 (br s, 2 H); UV (MeOH) $\lambda_{max}$ 280 nm ($\epsilon$ 3980), 244 (5850). Anal. ($C_7H_9N_3O_2$) H, N; C: calcd, 51.22; found, 50.60.

Liquid $NH_3$ treatment of 4,6-dichloro-2-methyl-5-pyrimidinecarbonitrile gave **7f** directly.

**4-Amino-2-cyclopropyl-5-pyrimidinecarboxaldehyde (8i). Method H.** A mixture of 37.5 g (0.23 mol) of **7i** and 4 g of commercial Raney nickel catalyst in 400 mL of 60% aqueous $HCO_2H$ was hydrogenated in a Parr apparatus at room temperature and an initial pressure of 50 psi until the calculated amount of $H_2$ was absorbed (3 h). The filtrate, after removal of the catalyst, was concentrated at reduced pressure, and the residue was dissolved in $H_2O$. The pH was adjusted to 8 with concentrated $NH_4OH$, and the solid which precipitated was filtered and washed with $H_2O$. Recrystallization from EtOH gave 18.8 g (49%) of **8i**: mp 180–182 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 1.02 (m, 2 H), 1.06 (s, 2 H), 2.02 (m, 1 H), 7.97 (br s, 2 H), 8.58 (s, 1 H), 9.78 (s, 1 H, CHO). Small additional signals at $\delta$ 8.43 (s) and 7.67 (br s) indicated the

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presence of ca. 5% of unreacted 7i.

**4-Amino-2-methyl-5-pyrimidinecarboxaldehyde (8c). Method I.** To a solution of 7.5 mL of concentrated $H_2SO_4$ in 50 mL of $H_2O$ was added at room temperature 6.7 g (0.05 mol) of 7c and 0.5 g of 10% Pd/C and hydrogenation was carried out in a Parr apparatus at an initial pressure of 54 psi until the calculated uptake of $H_2$ was complete (1 h). The filtrate obtained after removal of the catalyst was adjusted to pH 8 with concentrated $NH_4OH$, and the resulting thick precipitate was filtered and washed with $H_2O$ to yield 4.2 g of 8c: mp 188–192 °C; NMR indicated that the desired product was free of 7c.

**6-(2,6-Dichlorophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-7-amine (36).** To a solution of 5.4 g (0.24 g-atom) of Na in 800 mL of EtOH were added 80.0 g (0.58 mol) of 8c and 119.4 g (0.64 mol) of 2,6-dichlorophenylacetonitrile. The resulting slurry was heated at reflux for 3 h, during which time a homogeneous solution slowly was formed. Toward the end of the period a yellow precipitate began to separate. The mixture was cooled, and the precipitate of crude 36 was filtered and washed with $Et_2O$. After this had been recrystallized from 95% EtOH, 109.8 g (61%) of 36, mp 288–290 °C, was obtained. This material tenaciously retains varying amounts of $H_2O$, which may be removed by recrystallization from anhydrous EtOH or, better, by azeotropic removal with a solvent, such as toluene. Spectral data for the anhydrous material follows: NMR ($CDCl_3$) $\delta$ 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); UV (MeOH) $\lambda_{max}$ 224 nm ($\epsilon$ 49 600), 331 (14 100).

**Preparation of 40 and 41.** Method C was used to convert 1-bromo-2,3-dimethylbenzene to a mixture of bromomethyl compounds, which was immediately converted to a mixture of 2h and 2i with KCN in EtOH. Distillation separated a 45% yield of a 60:40 mixture of two compounds, bp 170–175 °C (18 mmHg), as judged by GLC (3% OV-17) and NMR: $\delta$ 2.4 (3 H, $CH_3$, 2 s with 2-Hz separation), 3.65 and 3.8 (2 H, $CH_2CN$). This liquid gave the correct analysis for $C_9H_8BrN$ and was, thus, a mixture of the desired nitriles 2h and 2i. This mixture was condensed with 8c following the procedure described above for the preparation of 36. The reaction mixture was concentrated to dryness and then taken up in $CHCl_3$ and chromatographed on a column of $SiO_2$, eluting first with $CHCl_3$ and then with increasing percentages of EtOAc. Unreacted nitrile and some amide were eluted. A solvent mixture of MeOH–EtOAc (2:98) eluted first one isomer of the product, followed by a mixture, and finally by pure fractions of the second isomer. The more rapidly eluting isomer was recrystallized from $CH_3CN$ to give 41: mp 257–259 °C; NMR ($CF_3COOD$) $\delta$ 2.30 (s, 3 H, $ArCH_3$), 3.15 (s, 3 H, $HetCH_3$), 7.4 (m, 2 H, Ar*H*) 7.7 (m, 1 H), 8.4 (s, 1 H), 9.7 (s, 1 H). Anal. ($C_{15}H_{13}BrN_4$) C, H, N, Br.

The later eluting isomer was recrystallized from $CH_3CN$/MeOH to give yellow crystals of 40: mp 253–257 °C; NMR ($CF_3COOD$) $\delta$ 2.35 (s, 3 H, $ArCH_3$), 3.15 (s, 3 H, $HetCH_3$), 7.3 (m, 2 H, Ar*H*), 7.85 (m, 1 H), 8.35 (s, 1 H), 9.65 (s, 1 H). A small amount of MeOH was tenaciously retained by this isomer (spurious signal at $\delta$ 3.65). Anal. ($C_{15}H_{13}BrN_4$) C, H, N; Br: calcd, 24.28; found, 24.73.

**6-(2,6-Dichlorophenyl)-2-(2-phenylethenyl)pyrido[2,3-*d*]pyrimidin-7-amine (57).** A mixture of 42.4 g (0.40 mol) of benzaldehyde and 30.5 g (0.10 mol) of 36 with 6.1 g of piperidine was heated at 155–160 °C for 22 h. The solid obtained after the mixture was cooled was filtered and washed with $Et_2O$. Crude 57, mp 244–268 °C, was obtained after recrystallization from EtOH (charcoal treatment). Subsequent recrystallization from $CH_3CN$ afforded pure 57 as yellow crystals yield: 13.7 g (35%); mp 269–271 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 7.1 (br s, 2 H), 7.3 (d, 1 H), 7.4–7.9 (m, 8 H), 8.0 (s, 1 H), 8.1 (d, 1 H), 9.1 (s, 1 H).

**7-Amino-6-(2,6-dichlorophenyl)pyrido[2,3-*d*]pyrimidine-2-methanol (58).** A slurry of 3.5 g (8.9 mmol) of 57 in 35 mL of $CH_2Cl_2$ and 20 mL of MeOH was cooled to −55 °C and ozone was bubbled in until a green solution formed. The solution was purged with $O_2$ until it became yellow. The temperature was allowed to rise to −30 °C, and then a solution of 0.37 g (9.8 mmol) of $NaBH_4$ in 15 mL of MeOH was added at this temperature. The solution was stirred for 2 h while warming to room temperature. After HOAc was added to destroy excess $NaBH_4$, the mixture was concentrated at reduced pressure, and the residue was taken up in $CHCl_3$ and washed with $H_2O$. The organic layer was dried, concentrated at reduced pressure, and then chromatographed on $SiO_2$. The major fraction eluting with MeOH–$CHCl_3$ (2:98) was crystallized from EtOH to give 0.8 g of 58: mp 244–246 °C dec; NMR ($Me_2SO$-$d_6$) $\delta$ 4.67 (d, 2 H), 5.1 (t, 1 H), 7.1 (br s, 2 H), 7.7 (m, 3 H), 7.97 (s, 1 H), 9.08 (s, 1 H).

**Pharmacological Method.** New drugs were evaluated for their effect on blood pressure and heart rate in 22–24 week old, conscious male, spontaneously hypertensive rats (SHR) of Kyoto–Wistar origin weighing from 250 to 350 g from the W-L/P-D colony or from a commercial supplier (Charles-River, Wilmington, MA). The continuous direct monitoring of aortic blood pressure and heart rate in the freely moving unanesthetized rat was carried out as previously described.[20,21] Each rat was housed in an individual cage and allowed to recover 24–48 h following the surgical implantation of the aortic blood pressure monitoring cannula before being tested. Each rat received approximately 0.8 mL of heparinized saline/day (approximately 160 units of heparin/day). The blood pressure of each rat was sampled for 3 min out of each 30 min and recorded on strip chart recorders (Model 220; Gould-Brush, Cleveland, OH),[20] or on in-lab printers,[21] and on magnetic tape for later computer analysis. An integrated mean blood pressure and heart rate were derived from the pulsatile pressure signal. All drugs were prepared for oral administration by suspension in a 4% gum acacia vehicle by homogenization and ultrasonication. Each dose was administered by gavage in a 2 mL/kg volume. All doses are expressed as the 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 were used. The mean of individual 30-min values was calculated and compared to pretreatment values for each group as described (footnote *d*, Table III).

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