Amidines.† 2.[1] A New Class of Antihypertensive Agents. 1,2,3,5-Tetrahydroimidazo[2,1-*b*]quinazolines

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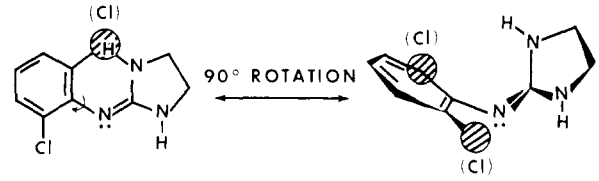
Synthesis of a series of tetrahydroimidazo[2,1-*b*]quinazolines for evaluation of antihypertensive activity is described. The assignment of tautomeric structures based on nmr spectral data is discussed. 1,2,3,5-Tetrahydroimidazo[2,1-*b*]quinazoline (3a) was found to be the most effective compound in this series in lowering blood pressure of the metacorticoid hypertensive rat and the unanesthetized neurogenic hypertensive dog by oral administration. Modification of 3a generally gave less active analogs. Some pharmacological properties of 3a are described and a comparison of structural features and pharmacological properties with 2-(2,6-dichlorophenylamino)imidazoline, a new antihypertensive agent, is made. The structure-activity relationships of 3a and its analogs are discussed.

As part of a broad investigation of structures containing an "amidine" moiety† as potential antihypertensive agents, we synthesized a series of imidazoquinazolines **3** (see Scheme I). One of these was found to be particularly effective in lowering the blood pressure of experimental animals.[1]

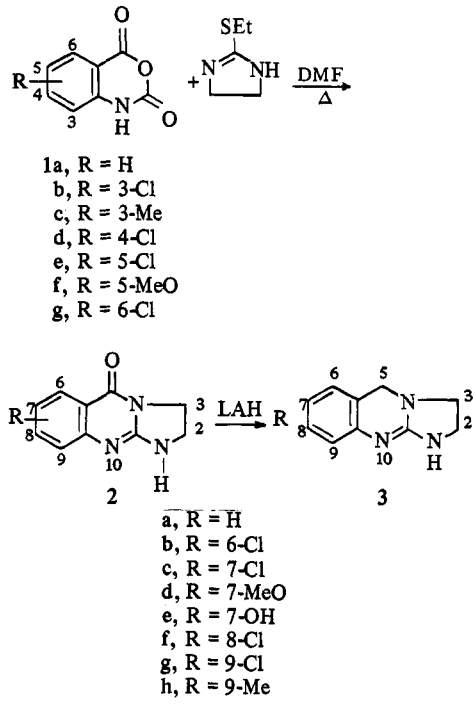
2-(2,6-Dichlorophenylamino)imidazoline‡[2] (I) is a potent centrally acting new antihypertensive agent. One of the unique features of this molecule is the steric influence of ortho substituents in the phenyl ring. Spectral studies[3] have shown that the imino form is the predominant tautomer; in this form, geometrical isomerization of the phenyl ring is possible, but this would give rise to two identical species. From a structure-activity point of view, we only considered the probable conformations resulting from rotation of the phenyl ring about the imino bond. Nmr studies[3] and examination of molecular models indicate that the perpendicular conformation Ib is preferred over the other extreme conformation Ia where the phenyl ring is coplanar with the heterocyclic ring. If the two rings were to be connected by a methylene bridge, a rigid tricyclic system such as **3** (see Scheme I) would be obtained, which, at the basic center, should possess a spatial arrangement and electronic distribution similar to Ia.



Ia — PLANAR CONFORMATION

Ib — PERPENDICULAR CONFORMATION

Scheme I



1a, R = H
b, R = 3-Cl
c, R = 3-Me
d, R = 4-Cl
e, R = 5-Cl
f, R = 5-MeO
g, R = 6-Cl

2

a, R = H
b, R = 6-Cl
c, R = 7-Cl
d, R = 7-MeO
e, R = 7-OH
f, R = 8-Cl
g, R = 9-Cl
h, R = 9-Me

3

It was of interest to determine whether such a tricyclic system might indicate which conformation was biologically preferred for producing the antihypertensive activity. Since the perpendicular conformation (Ib) is sterically preferred, the new modification would be expected either to abolish the antihypertensive activity or to give rise to an antihypertensive agent with a mechanism of action unrelated to that of I. The work described in this paper confirms the latter possibility.

Synthesis. Although imidazo[2,1-*b*]quinazolinones have been described,[4a-c] the oxygen-free parent system (*i.e.*, **3**) is not known. A high yield, one-step synthesis of the potential precursor **2a** was recently developed by Ziegler, *et al.*[4b] (see Scheme I), involving condensation of isatoic anhydride with 2-ethylmercapto-2-imidazoline, and leads directly to the lactam **2a**. Reduction of the lactam **2a** with LAH affords the desired **3a**. Analogs **3b** and **3e-3h** with substituents on the aromatic ring were similarly prepared from the corresponding isatoic anhydrides. Demethylation of **3d** with HBr gave **3e**.

With the exception of the unknown If,§ the substituted isatoic anhydrides were prepared by chromic acid oxidation[6] of the corresponding substituted isatins.# This procedure was found to be more convenient than the one which requires conversion of the isatins to the anthranilic acids followed by $COCl_2$ treatment.[5]

The heterocyclic system **3** containing a cyclic guanidine

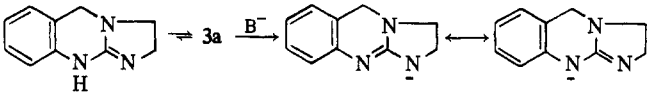
†We include in the term "amidines," those compounds containing the moiety N–C(=N)–X (X = C, N, O, or S).

‡Catapres.

§Oxidation of 5-methoxyisatin to 1f was unsuccessful. It was prepared by $COCl_2$ treatment of 5-methoxyanthranilic acid (precedure of ref 5).

#The isatins for 1b, 1c, and 1e were supplied by Research Organic Co. For preparation of the isatins for 1d and 1g see ref 7.

moiety, unexpectedly proved to be rather resistant to alkylation and acylation. The reaction failed to proceed with MeI in boiling MeOH, and when **3a** was treated with MeI under forcing conditions, a mixture of **4a** and **5a** (9:1 ratio) was obtained. Treatment of **3a** with NaH-DMSO and MeI gave a mixture of 3 components which were separated and identified as **4a**, **5a**, and **6**, with **5a** being the major product. Reaction in liq NH_3 with $NaNH_2$ and MeI according to the procedure of North and Day[8] also afforded **4a** (minor) and **5a**. The formation of **5a** as a minor product under neutral conditions is probably due to alkylation of the imino nitrogen in the tautomer II, the population of which might become significant at elevated reaction temperature. The unexpected product distribution in the alkylation of **3a** under basic conditions can be partly explained on the grounds of the resonance contribution derived from the major anion contributors III and IV. Although the kinetic factor cannot



II III IV

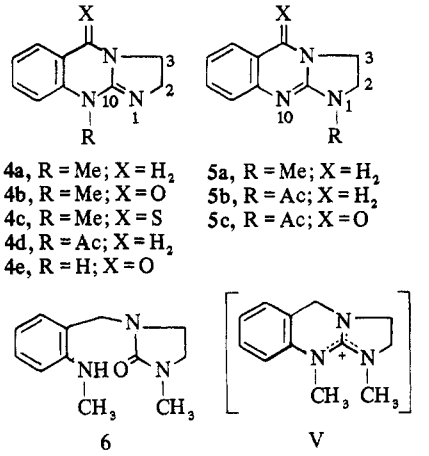
be ignored in this reaction, the resonance contribution of IV is reasonably assumed to be quite significant. The mechanistic pathway for the formation of **6** is not clearly understood. One possibility involves cleavage of an unstable dimethylated intermediate V by hydroxide ion in the isolation process.

In an attempt to obtain **4a** unambiguously by an alternative route, the lactam **4b** was prepared by condensation of *N*-methyl isatoic anhydride with the ethylmercaptoimidazoline in the usual manner. Attempted reduction of **4b** to **4a** by LAH gave unidentifiable material. **4b** was converted to the corresponding thiolactam **4c** by P_2S_5 in refluxing pyridine. Attempted desulfurization with Raney Nickel catalyst apparently gave only cleavage products.

Compounds **3a** did not react with Ac_2O at 25°, but gave the N-1 acetylation product **5b** on heating. Acetylations carried out with Ac_2O-pyridine or AcCl-pyridine gave similar results.

The benzylic carbon atom in **5b** underwent autoxidation readily. The lactam **5c** was rapidly formed when a solution of **5b** in chloroform was exposed to air. The autoxidation product **5c** was characterized by comparison of its nmr and

Chart I



4a, R = Me; X = H_2
4b, R = Me; X = O
4c, R = Me; X = S
4d, R = Ac; X = H_2
4e, R = H; X = O

5a, R = Me; X = H_2
5b, R = Ac; X = H_2
5c, R = Ac; X = O

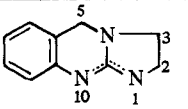
6 V

mass spectra and gas chromatogram with those of an authentic sample prepared by acetylation of **2a**. Compound **3a** was much less susceptible to autoxidation, but could be slowly oxidized to **2a** by bubbling air into a boiling solution in pyridine.

Structure Assignments. The nmr and uv spectral data of compounds relevant to the following discussion are summarized in Table I. Structures **2** and **3** are potentially tautomeric. Although studies of the prototropic tautomerism of lactams related to **2a** by uv spectroscopy have been described,[9] **2a** was never unequivocally established as the predominant tautomer. The location of the double bond in **2a** has now been established by nmr and uv analyses. The nmr spectrum of **2a** displays a symmetrical pair of multiplets corresponding to the C-2 and C-3 methylene protons, respectively. The C-2 proton signal of the potential tautomer **4e** would be expected to appear downfield (as in **4b**) due to the anisotropy of the imino bond. In fact, the C-2 and C-3 methylene protons of **4b** appeared as one unresolved multiplet at lower field. A distinct difference of uv absorption maxima between **2a** and **4b** further supports the assignment.

The predominant tautomer **3a** was similarly determined. A four-proton singlet was observed in the nmr spectrum corresponding to four equivalent protons (C-2 and C-3 methylenes). Protons in similar positions in the alternative tautomer II would be expected to give rise to multiplets due to the pronounced anisotropic effect of the imino bond on

Table I. Spectral Data of Tetrahydroimidazo[2,1-*b*]quinazolines



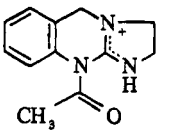
Compound	Solvent[b]	Nmr,[a] δ, ppm 2-H	3-H	5-H	CH_3	uv,[c] λ_{max}^{EtOH}, mμ (log ε)
2a base	DMSO-*d*	3.73 m	4.19 m			230 (4.58), 263 (4.09), 270 (4.12)
3a base	DMSO-*d*	3.34 s	(3.34 s)	4.20 s		278 (4.09)
3a base	TFA-*d*	3.98 s	(3.98 s)			
4a fumarate	$CDCl_3$-KOD	3.78 m	3.40 m	4.11 s	3.45 s	256 (4.34)
4a fumarate	TFA-*d*	3.98 s	(3.98 s)	4.60 s	3.52 s	
4b base	DMSO-*d*	3.94 m	(3.94 m)		3.48 s	231 (4.55), 240 (4.48), 246 (4.40)
5a fumarate	$CDCl_3$-KOD	3.30 s	(3.30 s)	4.25 s	2.95 s	279 (4.21)
5b base	$CDCl_3$	3.97 m	3.32 m	4.47 s	2.74 s	279 (3.96)
5b base	Concd HCl[d]	4.15 m	4.60 m	4.97 s	2.65 s	
5b base	TFA	4.05 m	4.50 m	4.93 s	2.55 s	
5c base	$CDCl_3$	4.18 s	(4.18 s)		2.82 s	230 (4.48), 263 (4.05), 270 (4.04)

[a] s = singlet, m = multiplet; the chemical shift of a multiplet is a measure of the midpoint of the signal at base line. [b] Spectra obtained in acidic solvents and $CDCl_3$-KOD systems represent the protonated ions and free bases of samples, respectively. [c] The uv absorptions of only the free bases are indicated; aqueous NaOH was added to the solns. [d] External Me_4Si reference.

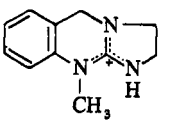
the C-2 protons (as in **4a**). There is good agreement between the spectra of **3a** and **5a**. The structure of **5a** can be readily distinguished from **4a** by comparing the nmr signals of the C-2, C-3, and *N*-methyl protons; a pair of symmetrical multiplets corresponding to the C-3 and C-2 protons was observed for **4a** in contrast to a four-proton singlet found in **5a**; the downfield shift ($\Delta\delta$ 0.50) of the *N*-methyl proton signal of **4a** from that of **5a** is consistent with structure **4a** where long range deshielding due to the adjacent aromatic ring current is possible. The uv absorption of **3a** supports the structure assigned as **5a** rather than **4a**.

The structure of **6** was deduced from the following evidence: the molecular ion peak at *m/e* 219 and the elemental analysis correspond to the assigned formula. The ir spectrum shows absorption bands at 5.90 and 2.90 μ corresponding to a carbonyl group and NH stretching. The nmr spectrum displays a pair of three-proton singlets at δ 2.80 and 2.85 corresponding to two methyl groups in different chemical environments. A four-proton singlet at δ 3.24 was assigned to the equivalent methylene protons in the imidazoline ring. One exchangeable proton was found at δ 5.30 corresponding to one NH proton. A pair of multiplets centered at δ 6.61 and 7.17 constitutes a typical pattern of an ortho-substituted aniline. After addition of deuteriotrifluoroacetic acid to the nmr sample solution, one of the *N*-methyl singlets shifted downfield from the other ($\Delta\delta$ 0.43) and the aromatic proton signals merged to one multiplet centered at δ 7.51. This suggests that one of the methyl groups is connected to the anilino nitrogen as formulated in **6**.

The assignment of structure **5b** (rather than **4d**) for the product obtained by acetylation of **3a** was based on the following. The C-2 and C-3 methylene proton signals of the free base appeared as a pair of symmetrical multiplets in the nmr spectrum. Protonation of **5b** or **4d** should take place at the imino nitrogen N-10 or N-1, respectively, for maximum resonance stabilization of the resulting cation. In strong acid solution, the two multiplets corresponding to C-2 and C-3 methylene protons are expected to retain their symmetry for protonated **5b** but lose their symmetry for protonated **4d** due to additional coupling of the C-2 protons with the NH proton. The observed retention of symmetry of the multiplets shifted downfield when measured in concentrated HCl and trifluoroacetic acid indicates that the NH proton (singlet at δ 10.30 in concd HCl) does not couple with the C-2 protons and is therefore located at the N-10 position. The positive charge of protonated **4d** would be expected to be delocalized in the N-1 and N-4 amidine moiety, with less contribution from the lone pair of electrons of the N-10 nitrogen atom which is a part of the amide system. It follows that the C-2 and C-3 protons in protonated **4d** would give rise to a four-proton *singlet* analogous to protonated **4a** (or protonated **3a**) due to the similar chemical environ-



protonated **4d**



protonated **4a**

ment for these protons. The observed *multiplicity* eliminates structure **4d**. The similarity of uv absorptions of this material and **5a** is also in agreement with the assignment.

The assignment of the position of the acetyl group in **5c** was also done by nmr. Both N-1 or N-10 acetylation of **2a** is possible. The observed sharp four-proton singlet is due to the C-2 and C-3 protons which are accidentally equivalent. The further downfield shift of the C-2 proton signal of **5c**

Table II. Chemical and Pharmacological Testing Data

No.	Method[a]	Salt	Recrystn solvent: Salt	Recrystn solvent: Base	Mp, °C: Salt	Mp, °C: Base	Formula[b]	pK_a[c]	Antihypertensive act.[d]: Rat[e]	Antihypertensive act.[d]: Dog[f]
1f	Ref 5			EtOH		244-246	C_9H_7NO			
2a	Ref 4b			EtOH		264-266	$C_{10}H_9N_3O$			
2b	A			MeOH		285-287	$C_{10}H_8ClN_3O$[g]			
2c	a	HCl	MeOH	EtOH	343-345	303-308	$C_{10}H_8ClN_3O$		NA/80	
2d	A			EtOH		300-302	$C_{11}H_{11}N_3O_2$[h]			
2f	A			DMF		295-298	$C_{10}H_8ClN_3O$[g]			
2g	A			MeOH		335-339	$C_{10}H_8ClN_3O$[i]			
2h	A			MeOH		295-298	$C_{11}H_{11}N_3O$			
3a	a	HCl	EtOH	EtOH	251-253	255[j]	$C_{10}H_{11}N_3$	8.29	++++	++++
3b	B	HCl	EtOH	EtOH	292-294	216-219	$C_{10}H_{10}ClN_3$	7.60	++	++
3c	B	$HCl \cdot 0.5H_2O$	$CHCl_3$	MeOH	253-255	315-318	$C_{10}H_{10}ClN_3$	7.60	+++	+
3d	B	HCl	MeOH-Et_2O	THF	281-283	252-254	$C_{11}H_{13}N_3O$	8.93		++
3e	a	HCl	EtOH-H_2O		286-288		$C_{10}H_{11}N_3O$[g]			NA/10
3f	B	HCl	EtOH	EtOH	287-289	300-304	$C_{10}H_{10}ClN_3$	7.61	++	+++
3g	B	HCl	EtOH	MeOH	273-276	340	$C_{10}H_{10}ClN_3$	7.62	NA/20	NA/3
3h	B	HCl	$CHCl_3$-hexane	MeOH	258-260	183-194	$C_{11}H_{13}N_3$	9.07		NA/10
4a	a	Fumarate	EtOH-iPr_2O		188-189		$C_{11}H_{13}N_3$			NA/10
4b	A			EtOH		213-215	$C_{11}H_{11}N_3O$			
4c	a			EtOH		225-227	$C_{11}H_{11}N_3S$			
5a	a	Fumarate	EtOH		216-217		$C_{11}H_{13}N_3$	7.53		+
5b	a			Me_2CO		189-191	$C_{12}H_{13}N_3O$		++	+
5c	a			$CHCl_3$-hexane		241-243	$C_{12}H_{11}N_3O_2$			NA/10
6	a	Picrate	EtOH	Cyclohexane-hexane	158-160	73-74	$C_{12}H_{17}N_3O$			

[a] See Experimental Section. [b] All compds were analyzed for C, H, N and analytical values were within ±0.4% of calcd values unless otherwise noted. [c] pK_a values were determined by potentiometric titration of the compds in Methyl Cellosolve-H_2O (4:1) soln. [d] See Pharmacology in text. Threshold effective doses for lowering the blood pressure of rats and dogs are arbitrarily converted to activity scores to relate the potency of compds tested in both species. NA denotes "not active at the dose indicated in mg/kg." [e] Rat activity score: + 80 mg/kg, ++ 20 mg/kg, +++ 5-20 mg/kg, ++++ 5 or <5 mg/kg. [f] Dog activity score: + 10 mg/kg, ++ 5 mg/kg, +++ 2.5 mg/kg, ++++ 1 or <1 mg/kg. [g] Analyzed for C, H. [h] C: calcd, 60.82; found, 59.96; M^+ 217 found in the mass spectrum. [i] No analysis; M^+ 221 found in the mass spectrum. [j] Free base analyzed for C, H, N.

from that of **4a** ($\Delta\delta$ 0.40) is due to the anisotropic effect of the N-10 acetyl carbonyl group, whereas the C-2 proton signal of the alternative structure **4d** (N-10 acetylation) would be expected to be in similar position as **4a**.

Pharmacology. The test compounds were evaluated for antihypertensive activity in metacorticoid hypertensive rats[10] and unanesthetized neurogenic hypertensive dogs[11] by oral administration. Blood pressure was determined 5 and 24 hr after each dose in the rat; 3 and 24 hr after each dose in the dog. The results are summarized in Table II.

In the present study, **3a** was found to be the most potent and consistent agent in lowering blood pressure in rats and dogs. It is also active in anesthetized cats and rabbits. A chronic study in unanesthetized normotensive dog showed that the onset of the hypotensive activity occurred at 60–90 min following an oral dose (2.5 mg/kg) of **3a**. The effect peaked at about 3 hr and continued for 24 hr. In a crossover experiment, phenoxybenzamine (15 mg/kg po) produced little effect on blood pressure. Repeated administration of **3a** to dogs over a period of 3 weeks produced no tolerance.

Renal blood flow in dogs was slightly increased at the hypotensive dose of **3a**. In a series of tests in rats at high doses (50–100 mg/kg po), no significant CNS or neurological influence was apparent. In a toxicology study, the oral LD_{50} of **3a** (·HCl) was found to be higher in rats (900 mg/kg) than in mice (265 mg/kg).

The pressor effects of injected epinephrine were blocked or reversed by **3a** in cats and dogs indicating α-adrenergic blockade. However, unlike phenoxybenzamine, **3a** does not block compensatory reflex responses in the rabbit tilt test.[12] Mechanisms involving direct vascular dilation or ganglion blockade were excluded by studies in the isolated rabbit aortic strip and the cat nictitating membrane. **3a** does not manifest the direct vasoconstrictor effect which has been observed with I.[13] Electrical activity recorded from the cat renal sympathetic nerve in the presence of a reduced blood pressure produced by **3a** was augmented rather than reduced. The hypotensive activity of **3a** does not appear to depend on central sympathetic inhibition as does I.[2b]

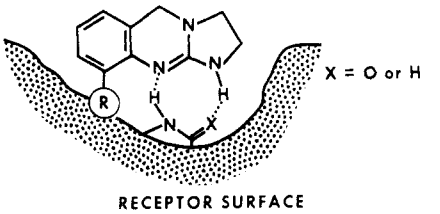
Other experiments suggest that the hypotensive action is not entirely due to α blockade. In some experiments **3a** produced an initial rise in blood pressure which appeared to be dose related. This is attributed to the release of catecholamines. A moderate depletion of catecholamines in the rat brain cortex and heart was found at higher doses.

Structure–Activity Relationships (SAR). Examination of molecular models of the free base **3a** suggests that the molecule assumes a nearly planar conformation.** Although the mechanism of action of **3a** is not fully understood, it is clear that it is different from that of I. This suggests that I does *not* interact with the receptor site in the *planar* conformation Ia.

Modification of the parent ring system **3a** generally gave compounds less potent as antihypertensives than the parent. The effect of aromatic substitution was typified by four monochloro analogs. The activities found in the rat (**3c** > **3b** ≃ **3f** ≫ **3g**) are not consistent with those in the dog (**3f** > **3b** > **3c** > **3g**). From a SAR point of view, compound **3g** is of particular interest because the 9-chloro substituent is in an ortho position and capable of exerting greater electronic influence on the guanidine moiety as well as providing steric hindrance to the interaction of the basic center with the receptor site. The results with the 9-chloro (**3g**) and the 9-methyl (**3h**) analogs suggest that steric factors play a large role in this interaction. The fact that the 7-methoxy analog (**3d**), which is of approximately the same basicity as **3h**, showed good activity seems to support this view.

Substitution on the nitrogen atom (*i.e.*, **4a**, **5a**, **5b**) generally diminishes the activity. This suggests that an NH hydrogen on the basic center may be essential for binding with the receptor, if the free base is the active species. An interesting speculation on the nature of interaction of this series of compounds with the receptor site through hydrogen bonding as illustrated is consistent with the fact that an R substituent diminishes the activity by steric hindrance.

There was no correlation of antihypertensive activity with the ionization constants (see Table II) of the compounds. Major structural modifications of **3a** were carried out and will be described in future publications.



Experimental Section††

Experimental methods A and B are representative procedures for compounds **2** and **3**.

Method A.‡‡ 7-Chloro-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-5-one (2c). A soln of 2.0 g (0.01 mole) of **1e** and 1.45 g (0.011 mole) of 2-ethylmercapto-2-imidazoline[14] in 20 ml of DMF was heated at 100° for 2 hr with a stream of N_2 bubbling into the soln. On cooling, a ppt formed and was filtered and washed with Et_2O. After digesting this material in boiling EtOH, 1.25 g (56%) of **2c** was collected by hot filtration.

Method B. 1,2,3,5-Tetrahydroimidazo[2,1-*b*]quinazoline (3a). To a stirred suspension of 2.09 g (0.054 mole) of LAH in 35 ml of THF under N_2 was slowly added a slurry of 5 g (0.027 mole) of **2a** in 85 ml of THF, and the mixt was refluxed for 30 min. The excess LAH was decomposed by dropwise addn of 2.1 ml of H_2O, 2.1 ml of 15% NaOH soln, and 6.3 ml of H_2O. The ppt was filtered and extd with 200 ml of hot $CHCl_3$.§§ The combined filtrates were evapd to dryness giving 3.98 g (85%) of **3a**; mass spectrum *m/e* 173 (M^+), 172, 145, 129, 117, 102, 77, 57, 43.

The HCl salt was prepd by treating a stirred suspension of the free base in warm MeOH with ethereal HCl soln and evapn of the MeOH soln.

7-Hydroxy-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (3e). A mixt of 1.91 g (0.01 mole) of **3d** in 100 ml of 48% HBr soln was refluxed for 18 hr. On cooling, 2.04 g of pptd **3e** (HBr salt) was filtered. An addnl 0.36 g of the crude product was recovered by evapn of the filtrate. Recrystn of the combined crude product from EtOH–H_2O gave 1.94 g of **3e**·HBr, mp 303–306°; **3e**·HCl, mass spectrum *m/e* 189 (M^+), 187, 172, 161, 145, 133, 80.

Methylation of 3a. 10-Methyl-2,3,5,10-tetrahydroimidazo[2,1-*b*]quinazoline (4a), 1-Methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (5a), and 1-(2-Methylaminobenzyl)-3-methylimidazolidin-2-one (6). A. Neutral Condition. A suspension of 8.0 g of **3a** and 8 ml of MeI in 150 ml of MeOH was heated in a bomb at 150° for 18

**Although the planarity of a guanidinium *ion* is well documented, the geometry of the free *base* is less certain. The assumed planar conformation of the guanidine base would be expected to permit maximum overlap of p electrons to the π electron system for greater stability.

††Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline and French Laboratories. Uv spectra were obtained on a Cary II instrument. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMM-6E mass spectrometer. pK_a determinations were performed by Mr. W. Hamill of our laboratories on a Sargent Titrimeter Model D. Nmr spectra were obtained on a Varian T-60 instrument (Me_4Si).

‡‡A modification of Ziegler's procedure (see ref 4b) was employed using DMF as the solvent.

§§In some of the other prepns, hot THF was preferred.

hr. The solvent was evapd, and the solid residue stirred with 10% NaOH soln and extd with $CHCl_3$. Following the usual work-up, a dark brown oil (7.2 g) was obtained. A sample of this oil was shown by gc analysis## to be a mixt of **4a** and **5a** (9:1 ratio). The main portion was chromatographed on neutral alumina (Woelm act. I) packed in C_6H_6. Elution with Et_2O gave an oil which was converted to 0.35 g of the fumarate salt of **5b**. Similarly, elution with Me_2CO–Et_2O and Me_2CO gave 3.5 g of **4a**·fumarate.

B. Basic Condition. (a) A soln of 0.058 mole of NaH (dispersed in oil) in 80 ml of anhyd DMSO under N_2 was stirred for 30 min. After 1.5 hr following the introduction 8.0 g (0.046 mole) of **3a**, a soln of 9.15 g (0.064 mole) of MeI in 20 ml of DMSO was slowly added with external cooling keeping the temp below 20°. After standing at 25° for 18 hr, the mixt was poured into crushed ice and extd with $CHCl_3$. The $CHCl_3$ soln was washed with H_2O to remove the DMSO and evapd to dryness leaving an oil. A sample was shown by gc analysis## to be a mixt of **4a** (24%), **5a** (56%), **6** (17%, retention time, 10.8 min) and an unidentified material (3%, retention time, 14.8 min). The oily mixt was chromatographed as described in the previous expt. From the C_6H_6 fractions, there was isolated 0.2 g of **6**. Compounds **4a** (3.6 g) and **5a** (0.8 g) were isolated as fumarates identical with that previously obtained.

(b) A suspension of 2.0 g (0.0116 mole) of **3a** and 0.5 g (0.0127 mole) of $NaNH_2$ in 60 ml of liq NH_3 was stirred for 30 min until dissolution occurred. A soln of 8.2 g (0.057 mole) of MeI in 20 ml of anhyd THF was added dropwise. After 5 hr, external cooling was discontinued, and the liq NH_3 evapd. The THF layer was decanted and the residue washed with H_2O, filtered, and dried to give 2.5 g of a solid. Recrystn from EtOH gave 0.6 g of **5a** (HI), mp 274–283° dec; nmr ($CDCl_3$–KOD) identical with that of **5a** (base) previously prepd. *Anal.* ($C_{11}H_{13}N_3O$·HI) C, H, N. The mother liquor was concd to give a ppt (mp 230–234°) which was suspended in MeOH and basified with 10% NaOH soln. On evapn of the MeOH and addn of H_2O to the residue, an oily material was pptd. Extn with Et_2O and evapn of Et_2O gave an oil, nmr spectrum ($CDCl_3$) identical with that of **4a** (base) previously prepd; mp of the fumarate also identical with that of **4a**·fumarate.

10-Methyl-2,3,5,10-tetrahydroimidazo[2,1-*b*]quinazoline-5-thione (4c). To a stirred soln of 1.0 g (0.005 mole) of **4b** in 40 ml of pyridine was added 4.2 g (0.0189 mole) of P_2S_5 and the mixt was refluxed for 5 hr. After evapg the solvent, the residue was triturated with hot H_2O to give **4c** (0.8 g after recrystn).

1-Acetyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (5b). A soln of 0.9 g (0.0052 mole) of **3a** in 25 ml of Ac_2O was heated on a steam bath for 15 min. It was concd, and the cryst ppt was filtered giving 0.93 g of **5b**.

1-Acetyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-5-one (5c). A soln of 1.5 g (0.008 mole) of **2a** in 25 ml of Ac_2O was warmed on a steam bath for 30 min. On cooling, the cryst product was filtered and washed with Et_2O giving 1.65 g of **5c**.

##Gas chromatography was performed on a Hewlett-Packard 5750 instrument with a 8 ft × 0.125 in. column, 3% OV-17 on 80–100 chromosorb W (HP), He 30 ml/min; initial column temp 150°, programmed 5°/min. Peaks were integrated automatically by an Infotronics CRS-100 instrument. Found retention time (min): **4a**, 8.3; **5a**, 10.1.

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Synthetic Antibacterials. 4.[1] Nitrofurylvinylpyrido[2,3-*d*]pyrimidine Derivatives

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The synthesis of several 5-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylic acid derivatives and related compounds are discussed. Some members of the series display broad *in vitro* antibacterial activities against Gram-positive and Gram-negative organisms.

The attachment of a heterocyclic ring to the 2 position of the 5-nitrofuran ring frequently gives antimicrobial agents[2] and the introduction of a conjugated double bond between these rings often results in enhancing the *in vitro* activities.[3,4] In view of these facts we have synthesized several nitrofurylvinyl heterocycles[1,5,6] in an effort to obtain useful antibacterial agents and found that certain nitrofurylvinyl-1,8-naphthyridines (I)[6] possess outstanding activity against *Pseudomonas aeruginosa* as well as a variety of organisms. This paper is concerned with the synthesis and biological evaluation of 5-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido-[2,3-*d*]pyrimidine-6-carboxylic acid derivatives (II), which correspond to the analogous system of I mentioned above.

Chemistry. Treatment of ethyl 4-substituted-2-methyl-5-hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylates (III)[7] with 5-nitrofurfural led to the formation of the respective nitrofurylvinylpyrido[2,3-*d*]pyrimidines (**1–6**) when the substituent in the 4 position was H, OH, OR, or PhO. The reaction was generally performed by heating the reactants in AcOH or Ac_2O. The free carboxylic acids of III do not condense with 5-nitrofurfural. Catalysts, such as concd H_2SO_4, which saponify III are therefore unsuited for the condensation reaction. Nitrofurylvinylpyrido[2,3-*d*]pyrimidines bearing amino substituents in the 4 position were prepared by heating the corresponding 4-alkoxy derivatives with amines such as $MeNH_2$, pyrrolidine, piperidine, or morpholine in DMF. This amination offers a convenient synthetic method of 4-aminonitrofurylvinylpyrido[2,3-*d*]pyrimidines (**7–10**), which could not be obtained by direct condensation from the corresponding 4-amino-5-hydroxy-2-methyl-