1-Benzhydryl-3-(pivaloyloxy)-1,4-dihydro-1,2-diazete (11a): mp 112–113 °C (from dichloromethane/hexane), 78% yield; IR (Nujol) 1760, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5–7.2 (m, 10 H, 10 Ar H), 4.57 (br s, 3 H, NCH_2CO + Ph_2CHN), 1.25 (s, 9 H, 3 CH_3).

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.74; H, 6.99; N, 8.84.

1-Benzhydryl-3-(pivaloyloxy)-4-methyl-1,4-dihydro-1,2-diazete (11b): mp 86–87 °C (from pentane), 57% yield; IR (Nujol) 1756, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.7–7.2 (m, 10 H, 10 Ar H), 4.60 (s, 1 H, Ph_2CH), 4.50 (q, 1 H, J = 7 Hz, NCHCO), 1.28 (s, 9 H, 3 CH_3), 1.28 (d, 3 H, J = 7 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.7, 168.3, 141.2, 141.0, 128.4, 128.2, 127.7, 127.1, 75.9, 74.3, 39.0, 26.5, 14.5.

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.32. Found: C, 74.68; H, 7.08; N, 8.59.

1-(1,1-Diphenyl-1-ethyl)-3-(pivaloyloxy)-1,4-dihydro-1,2-diazete (11c): mp 55–58 °C (from pentane), 60% yield; IR (Nujol) 1758, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–7.2 (m, 10 H, 10 Ar H), 4.48 (s, 2 H, NCH_2CO), 1.84 (s, 3 H, CH_3), 1.25 (s, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$) δ 173.5, 163.4, 143.8, 128.0, 127.7, 126.8, 67.3, 61.4, 39.1, 26.5, 22.8.

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.32. Found: C, 74.64; H, 7.51; N, 8.48.

Synthesis of 4,5-Dihydro-1,3,4-oxadiazin-6-ones (12). General Procedure. A solution of the N-2-acylated 1,2-diazetidin-3-one (2 mmol) in ethyl chloroformate (30 mL) was stirred overnight at 25 °C. Evaporation in vacuo followed by trituration with hexane afforded the product, which was then recrystallized.

2-Phenyl-4-benzhydryl-5-methyl-4,5-dihydro-1,3,4-oxadiazin-6-one (12a): mp 158–159 °C (from ethyl acetate), 80% yield; IR (Nujol) 1790, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75–7.18 (m, 15 H), 5.45 (s, 1 H), 3.75 (q 1 H, J = 7 Hz), 1.37 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.52; H, 5.66; N, 7.86. Found: C, 77.28; H, 5.60; N, 7.77.

X-ray Data. The compound crystallizes as colorless prisms from ethyl acetate: space group *Pn*, two molecules per unit cell, a = 9.353 ± 0.003 Å, b = 8.861 ± 0.002 Å, c = 11.638 ± 0.002 Å, β = 101.03 ± 0.02°, calculated density 1.25 g cm^{-3}. With use of monochromatic copper Kα radiation, 1492 reflections were measured on a four-angle automated diffractometer. The structure was solved by direct methods (SHELXTL) and refined by the least-squares method to R = 0.041 for 1352 observed reflections. See supplementary material for ORTEP drawing of molecule (Figure 2), atom coordinates, bond distances and bond angles (Tables VIII–XII).

2-Phenyl-4-benzhydryl-4,5-dihydro-1,3,4-oxadiazin-6-one (12b): mp 126.5–128.5 °C (from ethyl acetate/hexane), 80% yield; IR (KBr) 1800, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79–7.24 (m, 15 H), 5.31 (s, 1 H), 3.45 (s, 2 H).

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.14; H, 5.05; N, 7.91.

2-(4-Nitrophenyl)-4-benzhydryl-5-methyl-4,5-dihydro-1,3,4-oxadiazin-6-one (12c): mp 167 °C dec, 95% yield; IR (Nujol) 1800, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 and 7.81 (d, 2 H, J = 9 Hz), 7.4–7.2 (m, 10 H), 5.50 (s, 1 H), 3.80 (q, 1 H, J = 7 Hz), 1.44 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{23}H_{19}N_3O_4$: C, 68.81; H, 4.77; N, 10.47. Found: C, 68.61; H, 4.55; N, 10.46.

Acknowledgment. We are deeply indebted to Eli Lilly and Co., Indianapolis, IN, for financial support of this work.

Registry No. 1, 79289-49-9; **2a**, 80351-11-7; **2b**, 80351-13-9; **2c**, 80351-12-8; **2d**, 89773-55-7; **3a**, 89773-56-8; **3b**, 89773-57-9; **3c**, 89773-58-0; **3e**, 89773-59-1; **8a**, 89773-80-8; **8b**, 79559-06-1; **8c**, 80351-05-9; **8d**, 89773-81-9; **8e**, 79289-53-5; **8f**, 21083-14-7; **8g**, 80351-18-4; **9a**, 89773-60-4; **9b**, 89773-61-5; **9c**, 89773-62-6; **9d**, 89773-63-7; **9e**, 89773-64-8; **9f**, 89773-65-9; **9g**, 89773-66-0; **9h**, 89773-67-1; **9i**, 89773-68-2; **9j**, 89773-69-3; **9k**, 89773-70-6; **9l**, 89773-71-7; **10a**, 89773-72-8; **10b**, 89773-73-9; **10c**, 89773-74-0; **11a**, 89773-75-1; **11b**, 89773-76-2; **11c**, 89773-77-3; **12a**, 89773-78-4; **12b**, 80351-23-1; **12c**, 89773-79-5; C_6H_5COCl, 98-88-4; 4-$CH_3OC_6H_4COCl$, 100-07-2; 4-$O_2NC_6H_4COCl$, 122-04-3; $(CH_3)_3CCOCl$, 3282-30-2; $C_6H_5CH_2OCOCl$, 501-53-1; 4-$CH_3C_6H_4NCO$, 622-58-2; cyclohexanecarbonyl chloride, 2719-27-9; $(CH_3CO)_2O$, 108-24-7.

Supplementary Material Available: Tables of the final atomic parameters, bond lengths, and bond angles and structures for compounds **3b** and **12a** (13 pages). Ordering information is given on any current masthead page.

Polyaza Cavity-Shaped Molecules. Annelated Derivatives of 2-(2′-Pyridyl)-1,8-naphthyridine and 2,2′-Bi-1,8-naphthyridine

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A two-step method is presented for the oxidation of the 2-methylene position of 2,3-cycloalkenopyridines. The pyridyl ketones thus obtained may be reacted with 2-aminonicotinaldehyde to yield 3,3′-annelated derivatives of 2-(2′-pyridyl)-1,8-naphthyridine. Treatment of cyclic α-diketones in a similar manner provided 3,3′-annelated derivatives of 2,2′-bi-1,8-naphthyridine. Analyses by NMR indicate that when the 3,3′ bridge contains four methylene units the molecule is conformationally rigid at room temperature. UV and pK_a data indicate interactions between the two heteroaromatic rings which vary as a function of the dihedral angle between the rings.

The effectiveness of 2,2′-bipyridine as a coordinating ligand stems from its having two pyridine rings joined such that their nitrogen lone pair orbitals bear a 1,4 relationship to one another, thus enabling the system to function in a bidentate fashion. Similarly 1,8-naphthyridine, although less basic than 2,2′-bipyridine, can also function as a bidentate ligand where the nitrogen lone pairs are now fixed nearly parallel and coplanar in a 1,3 relationship. By joining a pyridine and 1,8-naphthyridine ring at their 2-positions as in **1** or two 1,8-naphthyridine rings at their 2-positions as in **2**, one is able to create a molecule capable of functioning either as a 1,3 or 1,4 diaza ligand.

The effectiveness of coordination is a function of both the availability of the nitrogen lone pair electrons (basicity) as well as the spatial orientation of these lone pairs with respect to one another. It was of interest to us, therefore, to prepare and study the annelated derivatives of 2-(2′-pyridyl)-1,8-naphthyridine (**3a–c**) and 2,2′-bi-1,8-

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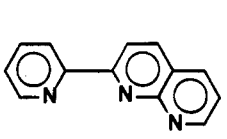

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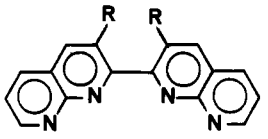
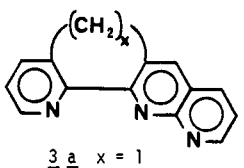
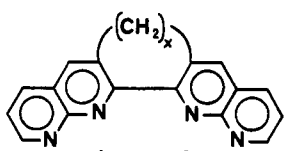


2 a R = H
b R = CH_3

naphthyridine (**4a–d**), where the length of a polymethylene



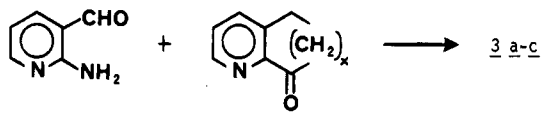
3 a x = 1
b x = 2
c x = 3



4 a x = 2
b x = 3
c x = 4
d x = 8

bridge connecting the 3- and 3′-positions will control the dihedral angle between the aromatic ring systems. These pyrido-fused derivatives of 3,3′-annelated-2,2′-bipyridines are cavity-shaped molecules with sp^2-hybridized nitrogen atoms at every nonbridgehead position in the "bay region".

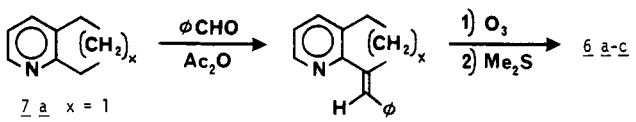
Synthesis. Caluwe has reported on the use of *o*-amino aldehydes to carry out heteroannelation reactions where the strategic choice of reaction partners can lead to a variety of fused pyridine and fused 1,8-naphthyridine systems.[1] Our target molecules are annelated derivatives of 1,8-naphthyridine and thus can be formulated to arise from the reaction of 2-aminonicotinaldehyde (**5**) with an appropriate ketone. In this fashion system **1** may be readily prepared by the reaction of **5** with 2-acetylpyridine. To obtain the 3,3′-annelated 2-(2′-pyridyl)-1,8-naphthyridines **3a–c**, compound **5** was treated with the annelated pyridyl ketones **6a–c**.



5

6 a x = 1
b x = 2
c x = 3

The prerequisite ketones were prepared in two steps from the commercially available 2,3-cycloalkenopyridines **7**. Treatment of the pyridines **7** with benzaldehyde in

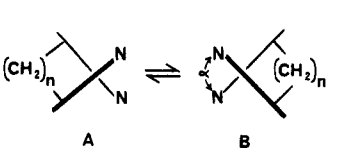


7 a x = 1
b x = 2
c x = 3

8

acetic anhydride led to formation of the α-benzylidene derivatives **8a–c** in purified yields of 70–94%. Ozonolysis of **8** was carried out in methanol at −35 °C, and methyl sulfide was employed to reduce the intermediate ozonides, thus affording the ketones **6**. When catalytic hydrogenation was employed to reduce the ozonide, overreduction often occurred and the product was contaminated with substantial amounts of the corresponding pyridyl alcohols.

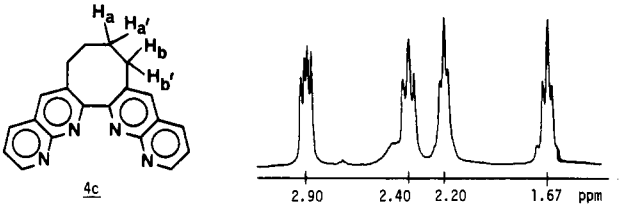
It has been demonstrated that 2 equiv of 2-aminonicotinaldehyde (**5**) will react with 1,2-diketones to afford compounds of the type **2**.[2] In this fashion we obtained



n	α	Estimated Barrier
1	0°	0 Kcal/mole
2	20	4
3	50	13
4	65	
8	180	

A B

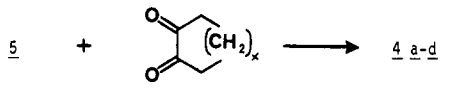
Figure 1.



4c

Figure 2.

2a from the reaction of **5** with 2,3-butanedione and **2b** from reaction with 3,4-hexanedione. Caluwe and Majewicz have prepared the 3,3′-dimethylene-bridged system **4a** by



9 a x = 2
b x = 3
c x = 4
d x = 8

treatment of **5** with 1,2-cyclohexanedione. We found this reaction to be general for the higher homologues of **9a**, and the yields were substantially better than those for **9a**. In the case of 1,2-cyclopentanedione, none of the corresponding monomethylene-bridged bi-1,8-naphthyridine was obtained.

Properties. The estimated dihedral angles between the phenyl rings in 2,2′-bridged biphenyls have been summarized by Calder et al.[3] and are not expected to differ greatly from the corresponding angles of the bridged biaryl systems **3** and **4**. These angles are summarized in Figure 1, which also points out that the nonplanar systems are capable of conformational enantiomerism via twisting about the 2,2′-bond. For the biphenyl systems (n = 2, 3) Mislow has calculated inversion barriers[4] that should represent upper limits for **3** and **4** since the steric interaction of two nitrogen lone pairs has been shown to be less than that for two benzene C–H bonds in studies on [2,2]metacyclophane and its pyridine analogue.[5] If the barrier to inversion is sufficiently high it should be possible to isolate a pure enantiomer (A or B) at room temperature.

In the high-resolution (400 MHz) NMR spectra of **4b**, the aliphatic region shows a four-proton triplet at 2.57 ppm and a two-proton quintet at 2.06 ppm. This observation is consistent with a 3,3′-trimethylene bridge which is undergoing rapid inversion of the A ⇄ B type shown in Figure 1. The aliphatic region of **4c** is shown in Figure 2. The appearance of four distinct resonances for H_a, $H_{a'}$, H_b, and $H_{b'}$ indicates that this molecules is conformationally rigid at room temperature. The low-field peak at 2.90 ppm is assigned to the benzylic proton H_b, which lies most nearly in the deshielded plane of the adjacent aromatic ring. The high-field peak at 1.67 ppm is assigned to the

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Table I. Basicity[a] and Ultraviolet Absorption Data

	$\lambda_{max}^{95\% EtOH}$ (ϵ)	pK_1 (HNP, mV)	pK_2 (HNP, mV)
3a	347 (36 640)	4.14 (349)	0.64 (576)
3b	349 (21 350)	5.65 (258)	1.31 (536)
3c	325 (13 050)	5.40 (272)	1.76 (504)
4a	236 (42 500), 365 (29 500)		
4b	239 (33 000), 329 (16 500)		
4c	215 (83 000), 323 (22 000)		

[a] Determined as half-neutralization potential (HNP) by titration with 0.1 N $HClO_4$/HOAc in acetic anhydride.

nonbenzylic proton H_a, which is directed toward the shielding region of the further removed aromatic ring. Spin orbital coupling suggests that the peaks at 2.40 and 2.70 pm can be assigned to $H_{b'}$ and $H_{a'}$; respectively.

In the case of bridged derivatives of biphenyl, ultraviolet spectroscopy has been used extensively to evaluate the relationship between the deviation from planarity of two covalently bonded aromatic rings and the degree of conjugative interaction between them. Absorption maxima are found to shift toward shorter wavelength or higher energy as the two rings become less coplanar. Homer and Tomlinson have demonstrated this same effect for 1,1'-bridged diquaternary derivatives of 2,2'-bipyridine.[6] Table I summarizes the ultraviolet absorption data for **3a–c** and **4a–c**. For both series of compounds the expected shift of absorption maxima is observed where the least coplanar systems **3c** and **4c** absorb at shortest wavelength.

In a study involving annelated derivatives of 2,2'-biimidazole, Deady has examined the effect of dihedral angle on lone-pair cooperativity.[7] In the alkylation (or protonation) of azabiaryl systems similar to **1** and **2**, several effects will govern the ease of reaction. The electronic effect of a 2-substituted-azaaryl group will generally be deactivating, especially when the two rings are coplanar. The steric effect of quaternizing a nitrogen atom will also be deactivating for a coplanar system. Lone-pair cooperativity, however, will function better as the nitrogen lone pairs are held closer. The basicities of **3a–c** were determined by nonaqueous titration. Values for **4a–c** could not be measured due to poor solubility. As expected, the pyridine ring is significantly more basic than the 1,8-naphthyridine ring, and two clear equivalence points could be observed. Fore pK_2 there is a trend toward increased basicity with increasing dihedral angle. For this second protonation there can be no variation in lone-pair cooperativity since the pyridine ring is already protonated. Steric and resonance effects both become more favorable as the length of the 3,3' bridge increases. The pK_1 of **3b** appears to be greater than would be predicted on the grounds of only steric and resonance effects. This increased basicity can be attributed to favorable cooperativity effects from the 1,8-naphthyridine N-1 lone-pair electrons.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 or FT-80 spectrometer or a Bruker WH-400 spectrometer (University of South Carolina Magnetic Resonance Laboratory) and chemical shifts are reported in parts per million downfield from Me_4Si. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Ultraviolet spectra were obtained on a Cary 14 spectrometer. Mass spectra were obtained by direct sample introduction into a Hewlett-Packard 5933A GC–mass spectrometer. Elemental analyses were performed by Canadian Microanalytical Service, Ltd., Vancouver, BC.[8] Benzaldehyde and acetic anhydride (Ac_2O) were freshly distilled reagent grade. 2-Aminonicotinaldehyde was prepared according to a literature procedure.[9] All cycloalkenopyridines were distilled prior to use. All melting points are uncorrected.

7-Benzylidene-6,7-dihydro-5*H*-1-pyrindene (8a). A mixture of 30 g (0.25 mol) of 2,3-cyclopentenopyridine, 40.1 g (0.38 mol) of benzaldehyde, and 49 g of Ac_2O was heated to reflux at 170 °C with stirring under N_2 for 17 h. Benzaldehyde, Ac_2O, and acetic acid were then removed by distillation under reduced pressure. Water (250 mL) was added to the residue, and the mixture was made distinctly alkaline by the addition of aqueous NaOH and then extracted with CH_2Cl_2 (4 × 200 mL). The organic extracts were washed well with water, dried over anhydrous $MgSO_4$, and concentrated to a viscous liquid, which was fractionally distilled to give 41 g (78%) of 7-benzylidene-6,7-dihydro-5*H*-[1]-pyrindene: bp 140–145 °C (0.15 mm), mp 74–75 °C (lit.[10] mp 74.5–75.5 °C).

5,6-Dihydro-7*H*-1-pyrinden-7-one (6a). A solution of 10 g (48 mmol) of **1** in 200 mL of MeOH was treated with mixture of ozone and oxygen at −35 °C until the solution became blue, indicating that it was saturated with ozone. The dissolved ozone was purged by bubbling N_2 through the solution, 6 mL of methyl sulfide was added, and the mixture was stirred for 0.5 h at −35 °C. After being warmed to room temperature and stirred overnight, the solution was concentrated by heating on a steam bath. The residue was distilled to give a buff colored solid, bp 130–150 °C (0.1 mm). Trituration of this material with ether followed by filtration gave 4.5 g (70%) of 5,6-dihydro-7*H*-1-pyrinden-7-one: mp 118–120 °C (lit.[11] mp 118–120 °C); IR (KBr) 1680 cm^{-1}.

8-Benzylidene-5,6,7,8-tetrahydroquinoline (8b). A mixture of 50 g (0.38 mol) of 2,3-cyclohexenopyridine, 59 g (0.56 mol) of benzaldehyde, and 74 g of Ac_2O was heated to reflux at 170 °C with stirring under N_2 for 17 h. Workup as described above for **1** followed by fractional distillation gave 78.1 g (94%) of 8-benzylidene-5,6,7,8-tetrahydroquinoline, bp 115–160 °C (0.15 mm), as a yellow solid; mp 62–64 °C (lit.[12] mp 66–67 °C).

5,6,7,8-Tetrahydro-8-quinolone (6b). A solution of 10 g (45 mmol) of **3** in 175 mL of MeOH was ozonized and worked up as described above for **2**. Fractional distillation of the crude product gave an orange-yellow solid, bp 115–122 °C (.03 mm), which was triturated with ether and then pentane to give 4.72 g (71%) of 5,6,7,8-tetrahydro-8-quinolone; mp 102–103 °C (lit.[13] mp 98–100 °C); IR (KBr) 1685 cm^{-1}.

9-Benzylidenecyclohepta[*b*]pyridine (8c). A mixture of 13.1 g (89 mmol) of 2,3-cycloheptenopyridine, 14.13 g (.133 mol) of benzaldehyde, and 17.7 g of Ac_2O was heated to reflux at 170 °C with stirring under N_2 for 136 h. Workup as described above for **1** followed by fractional distillation gave 14.6 g (70%) of 9-benzylidenecyclohepta[*b*]pyridine as a viscous yellow liquid: bp 110–148 °C (0.3 mm); ^1H NMR ($CDCl_3$) δ 8.5 (d of d, 1 H, J = 1.8 Hz, J = 4.8 Hz), 7.6–7.0 (overlapping m, 7 H) 6.65 (s, 1 H), 2.75 (m, 4 H), 1.85 (m, 4 H); IR (thin film) 2940, 1450, 1430, 780, 700 cm^{-1}.

Cyclohepta[*b*]pyridin-9-one (6c). A solution of 6.58 g (28 mmol) of **5** in 200 mL of MeOH was ozonized and worked up as described above for **2**. Fractional distillation of the crude product gave 3.1 g (69%) of cyclohepta[*b*]pyridin-9-one: bp 110–115 °C (0.1 mm) (lit.[14] bp 125 °C (0.3 mm)); IR (thin film) 1700 cm^{-1}.

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3,3′-Methylene-2-[2′-pyridyl]-1,8-naphthyridine (3a). To a mixture of 0.51 g (4.2 mmol) of 2-aminonicotinaldehyde and 0.5 g (3.4 mmol) of 5,6-dihydro-7*H*-1-pyrinden-7-one was added 20 mL of glacial acetic acid and 4 drops of concentrated sulfuric acid. The mixture was refluxed for 14 h, cooled, and poured into 40 mL of NH_4OH and 20 g of ice. A dark green precipitate appeared. The mixture was extracted with CH_2Cl_2 (5 × 50 mL). The organic extracts were combined, washed with water, dried over anhyd Na_2CO_3, and evaporated to give 0.51 g of crude product, which was purified by chromatography on 40 g of silica gel. Elution with 1:1 EtOAc–MeOH gave 0.336 g (41%) of **3a** as a green solid: mp 265–268 °C dec; ^1H NMR[15] (80 MHz, $CDCl_3$) δ 9.14 (d of d, H_9, $J_{8,9}$ = 4.2 $J_{7,9}$ = 1.9 Hz), 8.82 (d of d of t, poorly resolved, H_2, $J_{2,3}$ = 4.6 Hz), 8.23 (s, H_6), 8.16 (d of d, $J_{7,8}$ = 8.4, $J_{7,9}$ = 2 Hz), 7.89 (d of m, H_4, $J_{3,4}$ = 8 Hz), 7.44 (d of d, H_8, $J_{7,8}$ = 8.4, $J_{8,9}$ = 4.2 Hz), 7.33 (d of d, H_3, $J_{2,3}$ = 4.6, $J_{3,4}$ = 8 Hz), 4.02 (s, $-CH_2-$); IR (KBr) 1610, 1565, 1494, 1410, and 803 cm^{-1}; UV λ_{max} (95% C_2H_5OH) 208 (35 940), 240 (21 940), 331 (25 080), 337 (23 120), 347 nm (36 640).

3,3′-Dimethylene-2-[2′-pyridyl]-1,8-naphthyridine (3b). The same procedure as described above for **3a** was followed, using 0.50 g (4.1 mmol) of 2-aminonicotinaldehyde and 0.50 g (3.4 mmol) of 5,6,7,8-tetrahydro-8-quinolone, to give 0.87 g of crude product. Purification by chromatography gave 0.76 g (96%) of **8** as a pale yellow solid: mp 186–187 °C; ^1H NMR[15] (80 MHz, $CDCl_3$) δ 9.08 (d to d, H_{10}, $J_{9,10}$ = 4, $J_{8,10}$ = 2 Hz), 8.80 (d of d, H_2, $J_{2,3}$ = 4.5, $J_{2,4}$ = 1.6 Hz), 8.12 (d of d, H_8, $J_{8,9}$ = 8.2, $J_{8,10}$ = 2 Hz), 8.00 (s, H_7), 7.61 (d of d, H_4, $J_{3,4}$ = 7.5, $J_{2,4}$ = 1.6 Hz), 7.42 (d of d, H_9, $J_{8,9}$ = 8.2, $J_{9,10}$ = 4 Hz), 7.28 (d of d, H_3, $J_{2,3}$ = 4.5, $J_{3,4}$ = 7.5 Hz), 3.12 (br s, $-CH_2-$); IR (KBr) 1105, 900, 790 cm^{-1}; UV λ_{max} (95% C_2H_5OH) 218 (ϵ 31 910), 335 (20 030), 349 nm (21 350).

3,3′-Trimethylene-2-[2′-pyridyl]-1,8-naphthyridine (3c). The same procedure as described above for **3a** was followed, using 0.99 g (8.13 mmol) of 2-aminonicotinaldehyde and 1.19 g (7.39 mmol) of cyclohepta[*b*]pyridin-9-one, to give 1.8 g of crude product. Purification by chromatography gave 0.61 g (33%) of **3c** as a yellow solid: mp 198–199 °C; ^1H NMR[15] (80 MHz, $CDCl_3$) δ 9.13 (d of d, H_{11}, $J_{10,11}$ = 4, $J_{9,11}$ = 2 Hz), 8.77 (d of d, H_2, $J_{2,3}$ = 4.8, $J_{2,4}$ = 1.5 Hz), 8.18 (d of d, H_9, $J_{9,10}$ = 8.2, $J_{9,11}$ = 2 Hz) 8.03 (s, H_8), 7.64 (d of d, H_4, $J_{3,4}$ = 8, $J_{2,4}$ = 1.5 Hz), 7.41 (d of d, H_{10}, $J_{9,10}$ = 8.2, $J_{10,11}$ = 4 Hz), 7.31 (d of d, H_3, $J_{2,3}$ = 4.8, $J_{3,4}$ = 8 Hz), 2.75 (t, H_7, J = 6.5 Hz), 2.58 (t, H_5, J = 6.5 Hz), 2.28 (d of d, H_6, J = 13, J = 6.5 Hz); IR (KBr) 2948, 1545, 1449, 790 cm^{-1}; UV λ_{max} (95% C_2H_5OH) 218 (ϵ 38 560), 315 (13 050), 325 nm (13 050).

3,3′-Dimethylene-2,2′-bi-1,8-naphthyridine (4a). To a solution of 0.5 g (4.5 mmol) of 1,2-cyclohexanedione[16] and 1.25 g (10.2 mmol) of 2-aminonicotinaldehyde in 40 mL of absolute ethanol was added 0.08 g of KOH dissolved in 2 mL of absolute ethanol. The solution was refluxed under N_2 for 1 h. After cooling, a white precipitate was collected and dried to afford 0.6 g (47%) of **4a**, which was recrystallized from water: mp 320 °C (lit.[17] mp 315 °C); ^1H NMR (80 MHz, $CDCl_3$) δ 9.23 (dd, H_7 and $H_{7'}$, $J_{6,7}$ = 4.2, $J_{5,7}$ = 1.9 Hz), 8.18 (dd, H_5 and $H_{5'}$, $J_{5,6}$ = 8.2 Hz), 8.12 (s, H_4 and $H_{4'}$), 7.50 (dd, H_6 and $H_{6'}$), 3.31 (s, 4, $-CH_2-$); IR (Nujol) 1605, 1480, 1460, 1130, 1030, 900, 810, 780, 770, 715 cm^{-1}; mass spectrum, *m/e* (relative intensity) 284 (100, parent ion).

3,3′-Trimethylene-2,2′-bi-1,8-naphthyridine (4b). To a solution of 1.14 g (9.0 mmol) of 1,2-cycloheptanedione[18] and 2.5 g (20.4 mmol) of 2-aminonicotinaldehyde in 80 mL of absolute ethanol was added 0.16 g of KOH dissolved in 2 mL of absolute ethanol. The solution was refluxed under N_2 for 4 h. The solvent was then evaporated, and the unreacted 2-aminonicotinaldehyde was removed by extraction with EtOAc. The residue was chromatographed on silica gel, eluting with EtOAc–MeOH (1:1) to afford 1.8 g (67%) of a light brown solid. Recrystallization from EtOAc gave pure **4b**: mp 305 °C; ^1H NMR (80 MHz, $CDCl_3$) δ 9.08 (dd, H_7 and $H_{7'}$, $J_{5,7}$ = 1.2, $J_{6,7}$ = 4.1 Hz), 8.22 (dd, H_5 and $H_{5'}$, $J_{5,6}$ = 7.9 Hz), 8.06 (s, H_4 and $H_{4'}$), 7.44 (dd, H_6 and $H_{6'}$), 2.57 (t, 4, α-CH_2-), 2.06 (quintet, 2, β-CH_2-); IR (KBr) 1620, 1605, 1555, 1480, 1460, 1135, 1125, 1115, 1110, 915, 910 cm^{-1}; mass spectrum, *m/e* (relative intensity) 298 (100, parent). Anal. Calcd for $C_{19}H_{14}N_4$: C, 76.49; H, 4.73; N, 18.78. Found: C, 76.49; H, 4.73; N, 18.66.

3,3′-Tetramethylene-2,2′-bi-1,8-naphthyridine (4c). The procedure described for **4a** was followed by using 0.65 g (4.5 mmol) of 1,2-cyclooctanedione[19] and 1.25 g (10.2 mmol) of 2-aminonicotinaldehyde. After 4 h at reflux, a white precipitate was collected, 1.15 g (82%), and recrystallized from MeOH to afford **4c** as colorless crystals: mp 346–348 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (dd, 2, H_7 and $H_{7'}$, $J_{5,7}$ = 1.7, $J_{6,7}$ = 4.2 Hz), 8.21 (dd, H_5 and $H_{5'}$, $J_{5,6}$ = 8.1 Hz), 8.09 (s, H_4 and $H_{4'}$), 7.48 (dd, H_6 and $H_{6'}$), 2.90 (quartet, 2), 2.40 (t, 2), 2.20 (t, 2), 1.67 (quintet, 2); IR (KBr) 2940, 1610, 1550, 1480, 1450, 1130, 1100, 1040, 930, 900, 790 cm^{-1}. Anal. Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.73; H, 5.21; N, 18.00.

3,3′-Octamethylene-2,2′-bi-1,8-naphthyridine (4d). The procedure described for **4a** was followed by using 0.34 g (1.73 mmol) of 1,2-cyclododecanedione[20] and 0.45 g (3.7 mmol) of 2-aminonicotinaldehyde. After 10 h at reflux, a brown precipitate was collected, 0.44 g (70%), and recrystallized from EtOAc to afford **4d**: mp 340 °C dec; ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (dd, H_7, and $H_{7'}$, $J_{5,7}$ = 2.0, $J_{6,7}$ = 4.2 Hz), 8.18 (dd, H_5 and $H_{5'}$, $J_{5,6}$ = 8.1 Hz), 8.15 (s, H_4 and $H_{4'}$), 7.47 (dd, H_6 and $H_{6'}$), 3.37 (m, 2), 2.85 (m, 4), 1.61 (m, 2), 1.25 (m, 4), 0.92 (m, 2), 0.70 (m, 2); IR (KBr) 2940, 1605, 1560, 1440, 1410, 1125, 910, 790 cm^{-1}.

2,2′-Bi-1,8-naphthyridine (2a). The procedure described for **4a** was followed by using 0.76 g (9 mmol) of 2,3-butanedione and 2.5 g (20.4 mmol) of 2-aminonicotinaldehyde. After 1 h at reflux, a precipitate was collected and recrystallized from water to give 0.6 g (26%) of colorless needles: mp 250 °C (lit.[21] mp 226–227 °C); ^1H NMR (80 MHz, CD_3OD/HMDS) δ 9.00 (dd, H_7 and $H_{7'}$, $J_{5,7}$ = 2.0, $J_{6,7}$ = 4.0 Hz), 8.42 (d, H_4 and $H_{4'}$, $J_{3,4}$ = 8.5 Hz), 8.42 (dd, H_5 and $H_{5'}$, $J_{5,6}$ = 8.5 Hz), 8.16 (d, H_3 and $H_{3'}$), 7.58 (dd, H_6 and $H_{6'}$); IR (KBr) 1600, 1540, 1495, 1440, 1420, 1300, 1240, 1140, 1130, 1080, 1040, 945, 860, 850, 815, 800, 770 cm^{-1}; mass spectrum, *m/e* (relative intensity) 258 (100, parent), 259 (18), 257 (48), 102 (15).

3,3′-Dimethyl-2,2′-bi-1,8-naphthyridine (2b). The procedure described for **4b** was followed by using 0.53 g (4.5 mmol) of 3,4-hexanedione[22] and 1.25 g (10.2 mmol) of 2-aminonicotinaldehyde. After 12 h at reflux and removal of unreacted 2-aminonicotinaldehyde, the residue was extracted with MeOH. The MeOH was evaporated and the residue recrystallized from EtOAc to afford 0.7 g (55%) of a colorless solid: mp 178 °C; ^1H NMR (80 MHz, $CDCl_3$) δ 9.09 (dd, H_7 and $H_{7'}$, $J_{5,7}$ = 1.5, $J_{6,7}$ = 3.7 Hz), 8.22 (dd, H_5 and $H_{5'}$, $J_{5,6}$ = 7.4 Hz), 8.15 (s, H_4 and $H_{4'}$), 7.50 (dd, H_6 and $H_{6'}$), 2.50 (s, 6, CH_3); IR (KBr) 1610, 1550, 1480, 1445, 1240, 1130, 1010, 905, 800 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.09; H, 4.90; N, 19.43.

Basicity Measurements. Basicities were determined according to the method of Markgraf and Katt[23] by potentiometric titration with a Radiometer RTS622 recording titration system fitted with a glass indicator electrode and a saturated calomel reference electrode, previously equilibrated with Ac_2O for 48 h. Titrations were carried out at 25.00 ± 0.05 °C under an N_2 atmosphere in a water-jacketed cell connected to a constant-temperature bath and fitted with a neoprene cover drilled to accommodate two electrodes, a buret, a therometer, and an N_2 inlet tube. In a typical run, an accurately weighed amount of the naphthyridine derivative (ca. 5 × 10^{-2} mol) was dissolved in Ac_2O in a N_2-swept, 25-mL volumetric flask; a 10-mL aliquot was transferred to the titration cell, diluted with 60 mL of Ac_2O, and with magnetic stirring titrated with 0.10 N perchloric acid in acetic acid (Fisher No. SO-P-399, ca. 3.5 mL). The end point and half-neutralization potential were determined graphically. All

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runs were carried out in duplicate, with a precision of ±2 mV.

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Registry No. **2a**, 69110-33-4; **2b**, 89691-16-7; **3a**, 89709-52-4; **3b**, 89691-11-2; **3c**, 89691-12-3; **4a**, 56488-13-2; **4b**, 89691-13-4; **4c**, 89691-14-5; **4d**, 89691-15-6; **5**, 7521-41-7; **6a**, 31170-78-2; **6b**, 56826-69-8; **6c**, 41043-13-4; **7a**, 533-37-9; **7b**, 10500-57-9; **7c**, 7197-96-8; **8a**, 74701-35-2; **8b**, 28707-60-0; **8c**, 89691-10-1; **9a**, 765-87-7; **9b**, 3008-39-7; **9c**, 3008-37-5; **9d**, 3008-41-1; benzaldehyde, 100-52-7; 2,3-butanedione, 431-03-8; 3,4-hexanedione, 4437-51-8.

5-Aryl-4-hydroxy-3(2*H*)-isothiazolone 1,1-Dioxide Derivatives. Synthesis and ^{13}C NMR Characterization

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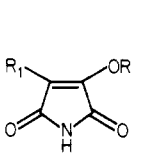
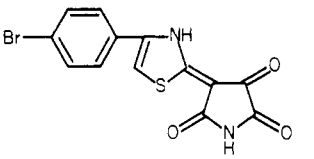
5-Phenyl- and 5-thiazolyl-4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide derivatives have been prepared by base-catalyzed cyclocondensation of diethyl oxalate with an arylmethanesulfonamide, as well as by reaction of an arylmethanesulfonamide with methyl or ethyl oxalyl chloride followed by base-catalyzed intramolecular cyclization. To verify that the preferred tautomeric structure of this until recently unexplored type of derivative was as indicated in the title, ^{13}C NMR spectral data were determined for four members of the isothiazolone 1,1-dioxide class, as well as for seven derivatives in the closely related 4-substituted-3-hydroxy-1*H*-pyrrole-2,5-dione series. The ^{13}C NMR evidence served to confirm the correctness of the structural assignments in both series for all compounds except those in which either acidic five-membered ring system was attached to the 2-position of a thiazole ring. In these instances the favored tautomer is the diketo form in which a proton resides on the thiazole ring nitrogen, with a double bond connecting the two rings.

In a search for novel inhibitors of glycolic acid oxidase (glycolate:O_2 oxidoreductase, EC 1.1.3.1) (GAO),[1] we have investigated a number of diacidic systems containing lipophilic moieties.[2,3] A key series consisted of 4-substituted-3-hydroxy-1*H*-pyrrole-2,5-dione derivatives[2] including **1a–f** and **4** (Scheme I). Examples of the closely analogous 5-substituted-4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide ring system (e.g., **2a–c**) were then prepared to determine if members of this system would exhibit comparable enzyme inhibitory activities. Although examples of the 3(2*H*)-isothiazolone 1,1-dioxide ring system have been described,[4] derivatives with a 4-hydroxyl substituent appear to have been prepared for the first time in these laboratories.[5] We report two synthetic methods to compounds of this class, where the 5-position substituent is a phenyl or substituted thiazole moiety. The ^{13}C chemical shifts and C–H couplings presented and assigned in this work for **1a–f**, **2a–c**, **3**, and **4** are the first reported for either of these two heterocyclic ring systems. Analysis of this data showed that when either of the five-membered, diacidic heterocyclic ring systems is attached to the 2-position of a thiazole nucleus (as in **3** and **4**), the keto tautomer, with a proton residing on the thiazole nitrogen and a double bond connecting the two rings, is preferred over the hydroxy tautomer. The latter is the tautomeric form which we observed for all remaining members of both heterocyclic series investigated.

Scheme I. 4-Substituted-3-hydroxy-1*H*-pyrrole-2,5-dione Derivatives for which ^{13}C NMR Spectral Data are Reported



1a–f



4

	R	R_1
1a	H	*n*-dodecyl
1b	H	[1,1′-biphenyl]-4-yl
1c	H	4′-bromo-[1,1′-biphenyl]-4-yl
1d	CH_3	[1,1′-biphenyl]-4-yl
1e	H	2-(3,4-dichlorophenyl)thiazol-4-yl
1f	H	2-(4-pyridyl)thiazol-4-yl

Results

A standard synthetic route to compounds of structure 1, where the 4-position substituent is aryl or heteroaryl, involves reaction of an arylacetamide with dialkyl oxalate and 2 mol of strong base in either protic or aprotic sol-

(1) This flavoenzyme catalyzes the oxidation of glycolic acid to glyoxylic acid, and glyoxylic acid to oxalic acid. The name in parentheses is that recommended by the Nomenclature Committee of the International Union of Biochemistry (see: "Enzyme Nomenclature 1978"; Academic Press: New York, 1979; p 55). Inhibitors of this enzyme are of interest for study in diseases, such as the primary hyperoxalurias and calcium oxalate renal lithiasis, as an approach to preventing calcium oxalate crystallization in the kidney (see ref 2).

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