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Polyaza Cavity Shaped Molecules. 4. Annelated Derivatives of 2,2′:6′,2″-Terpyridine

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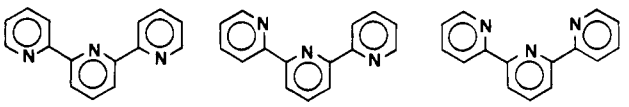
A two-step method is presented for oxidation of the two α-methylene positions of 2,3:5,6-dicycloalkenopyridines **5a–d**. The resulting diketones may be condensed with β-aminoacrolein to afford 3,3′:5′,3″-bis-annelated tripyridines **2b** and **2d**. Similar condensation of these diketones with *o*-aminobenzaldehyde afforded bis-annelated derivatives of 2,6-di(2′-quinolyl)pyridine **13b–d** while condensation with 2-aminonicotinaldehyde afforded bis-annelated derivatives of 2,6-di(1′,8′-naphthyrid-2′-yl)pyridine **14b–d**. An alternative enamine approach is presented for the preparation of the bis-annelated tripyridines **2b** and **2c**. Analyses by NMR indicated that in systems where the annelating bridges contain four methylene units the molecule is conformationally rigid at room temperature, providing diastereomeric meso and *d,l* forms. Examination of the UV spectra indicated that absorption maxima and intensity varied as a function of the dihedral angle between adjacent aromatic rings.

The 2,2′:6′,2″-terpyridine molecule is the second of a homologous series of polypyridines of which 2,2′-bipyridine is by far the best known member. There has been only limited work done on higher homologues,[1] with a most notable example being the recently reported syntheses of "cyclosexipyridine"[2] and a disubstituted derivative.[3]

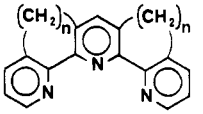
If one assumes that the three rings of tripyridine prefer a planar geometry for maximum conjugative interaction, three conformations are possible: anti-anti (**1a**), syn-anti (**1b**), and syn-syn (**1c**). Although definitive structural data



1a **1b** **1c**

is lacking, studies on the NMR[4] and ultraviolet[5] spectra of 2,2′:6′,2″-terpyridine as well as analogy to the well-studied 2,2′-bipyridine system argue for conformation **1a** where nitrogen lone pair repulsions are minimized. It is the syn-syn conformation (**1c**), however, which is responsible for the most important chemical feature of this molecule, its ability to act as a tridentate ligand in coordinating with various metals.

We have recently become interested in the consequences of bridging various azabiaryl systems such that the dihedral angle between the two adjacent aromatic rings can be varied in a regular fashion as a function of the bridge length.[6] This concept has now been extended to 2,2′:6′,2″-terpyridine by the preparation of bis-annelated derivatives such as **2a–d** where the relative orientation of



2 a n = 1
b n = 2
c n = 3
d n = 4

the three connected pyridine rings is controlled by methylene bridges between the 3,3′ and 5′,3″ positions. Furthermore this bridged ligand is now forced to adopt a conformation more closely approximating **1c** causing nitrogen lone pair interactions to become important. In this work we describe the synthesis and conformational features of **2b–d** and some related benzo- and pyrido-fused analogues. Later reports will deal with the chemistry and coordination properties of these systems.

Synthesis

The general approach that we have used for the preparation of annelated derivatives of diazabiaryl-type compounds has been the Friedlander condensation of a cyclic ketone or diketone with an appropriate β-amino-α,β-un-

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(2) Newkome, G. R.; Lee, H.-W. *J. Am. Chem. Soc.* **1983**, *105*, 5956.
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(6) (a) Thummel, R. P.; Lefoulon, F.; Cantu, D.; Mahadevan, R. *J. Org. Chem.* **1984**, *49*, 2208. (b) Thummel, R. P.; Lefoulon, F. *Ibid.* **1985**, *50*, 666.

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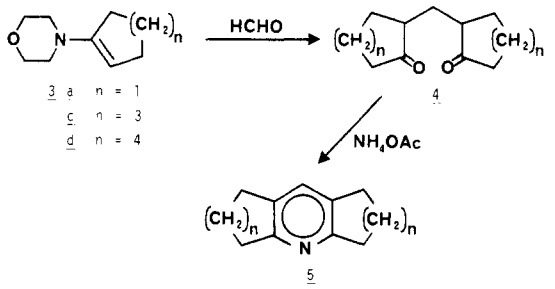
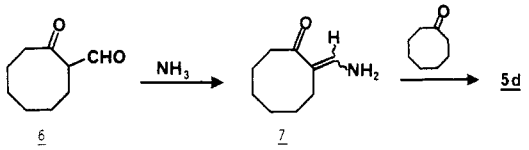
saturated aldehyde. Thus the starting material of choice for the synthesis of our target annelated tripyridines would be the diketones **9a–d**. We have previously reported an efficient two-step method for the introduction of a keto function at the 2-methylene position of a 2,3-cycloalkenopyridine.[6a] We reasoned that 2,3:5,6-dicycloalkenopyridines (**5**) could undergo the same two-step conversion and thus we set out to obtain the prerequisite pyridines **5a–d**.

When the morpholine enamine of a cyclic ketone is reacted with formaldehyde in refluxing dioxane, a bis(2-oxocycloalkyl)methane (**4**) is formed.[7] If this diketone is then treated with ammonium acetate, the 2,3:5,6-dicycloalkenopyridines **5a–d** may be prepared.[8] System **5b**,



1,2,3,4,5,6,7,8-octahydroacridine, is commercially available.[9]

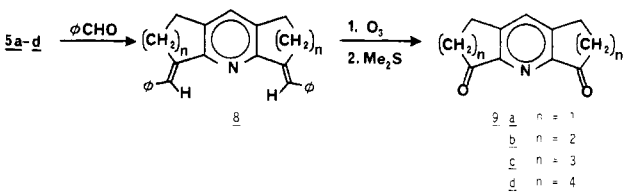
We also developed an alternate synthesis of **5d** which proceeded in approximately the same overall yield of 25%. In this approach a chloroform solution of 2-formylcyclooctanone was treated with ammonia gas to provide 2-(aminomethylene)cyclooctanone (**7**) in 92% yield. When this material is combined with 1 equiv of cyclooctanone, the dicyclooctenopyridine **5d** was obtained. Normal



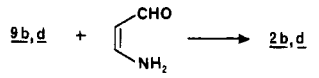
Friedlander condensation would not be expected to provide this linearly fused isomer but instead the 2,3:4,5 angularly fused one. We have observed this same rearrangement in condensations of the cyclopentanone and cyclohexanone analogues of **7**.[10] Similar behavior has also been noted by Curran for condensations with 1,3-cyclohexanedione and dimedone. He proposes an explanation which invokes a prior equilibration of the two reactants to provide the enamine of the carbonyl component and the 1,3-dicarbonyl precursor of the aminomethylene species which then combine in a normal fashion to give the observed product.[11]

The dicycloalkenopyridines **5** were reacted with benzaldehyde in acetic anhydride to provide the dibenzylidene derivatives **8a–d** in yields of 66–100%. For the five- and six-membered ring cases, **8a** and **8b**, the reaction occurred readily and was complete after several hours at reflux. For the seven- and eight-membered rings, **8c** and **8d**, the reaction was much slower requiring 6 days at reflux to complete. Ozonolysis was carried out in dichloromethane at −70 °C and the intermediate ozonide was reduced in situ with methyl sulfide to provide the diketones **9**.

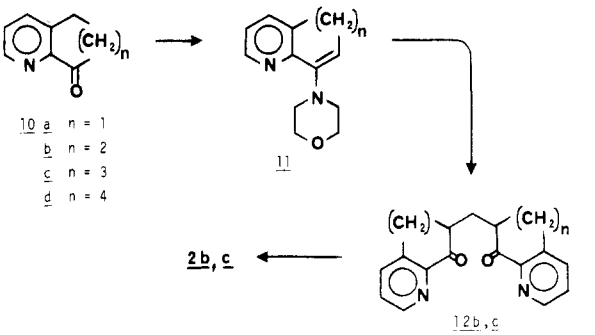
The reaction of β-aminoacrolein with the diketones **9b** and **9d** according to the procedure of Breitmaier and Bayer[12] led to only 3% and 2% yields respectively of the



annelated tripyridines **2b** and **2d**. The reaction of β-am-

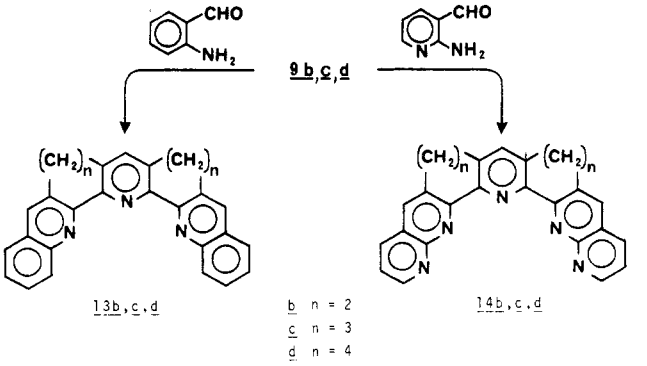


inoacrolein with diketone **9a** did not yield any identifiable product and in all three cases no unreacted diketone was recovered. Clearly, a higher yield, more easily controlled preparation of the tripyridine **2** was required. Such a synthesis was realized by preparing the pyrido-fused analogues of the diketones **4**. Thus we first treated the previously described pyridyl ketones **10a–c**[6a] with morpholine in refluxing toluene to afford the corresponding enamines **11** in moderate yields. When these enamines were combined with paraformaldehyde as described above for **3**, the diketones **12** could be prepared. These diketones



were not purified but rather reacted directly with ammonium acetate to provide the annelated tripyridines. The overall yields from enamine were 31% and 21% for **2b** and **2c**, respectively, which represented a 10-fold increase over the β-aminoacrolein approach. Nevertheless, this route was also unsuccessful for the preparation of the mono(methylene)-bridged tripyridine **2a**. Ketone **10d** is available in only very limited amounts at this time and thus it was not utilized in this sequence.

For Friedlander condensations it has been determined that aromatic fused-ring derivatives of β-aminoacrolein give much higher product yields than the parent unfused system. Thus we discovered that the reaction of **9b–d** with *o*-aminobenzaldehyde proceeded smoothly to afford the bis-annelated 2,6-di(2′-quinolyl)pyridines **13b–d** in yields



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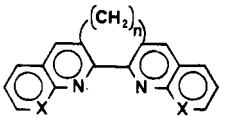
of 87%, 76%, and 77%, respectively. The parent unbridged system had been prepared earlier from a similar reaction with 2,6-diacetylpyridine.[13] Similarly reaction of these same three diketones with 2-aminonicotinaldehyde led to the bis-annelated 2,6-di(1′,8′-naphthyrid-2′-yl)pyridines **14b–d** in yields of 70%, 58%, and 64%, respectively. When either of these two amino aldehydes was treated with the five-membered ring diketone **9a**, a rapid reaction occurred but no identifiable product could be obtained.

Conformational Properties

In earlier studies we have carefully analyzed the conformations of 3,3′-bridged derivatives of 2,2′-biquinoline **15** and 2,2′-bi-1,8-naphthyridine **16**. We have found that



15 X = CH
16 X = N

a n = 1
b n = 2
c n = 3
d n = 4

for the dimethylene- and trimethylene-bridged systems, rapid conformational inversion was occurring at room temperature on the NMR time scale. The tetramethylene-bridged system, however, showed four well-resolved upfield signals indicating that a four-carbon bridge could impose conformational rigidity. Thus these molecules exist as racemic mixtures and efforts are currently under way to effect an optical resolution.

If such bridged biaryl systems may be considered to have one "chiral center" by virtue of twisting about the 2,2′-bond, then the tripyridines **2**, **13**, and **14** might be considered to have two such "chiral centers" controlled by twisting around the 2,2′ and 6′,2″ bonds. Thus these bridged tripyridines ($n \gtrsim 2$) can potentially exist as a pair of diastereomers, one of which would be a *d,l* form having C_2 symmetry and capable of optical activity and the other being a meso form having C_s symmetry.

In the decoupled ^{13}C NMR spectrum of **13b** and **13c**, the upfield region shows two and three lines respectively, indicating that on the NMR time scale at room temperature conformational inversion of the bridges is sufficiently rapid that diastereomeric differentiation is not possible. For **13d**, however, this same region shows eight lines, all of about equal intensity. Each diastereomer of **13d** accounts for four separate carbon lines since within each molecule the two bridges may be made equivalent by a C_2 or C_s symmetry operation.

There are two nonequivalent benzylic methylene groups in **2**, **13**, and **14**. In principle, therefore, the methylene proton resonances should be more complex than for **15** and **16** where the benzylic positions are equivalent. In fact, however, these positions are so nearly equivalent in the annelated tripyridines that they are unresolved at 300 MHz. Thus a broad singlet is observed in the upfield region where $n = 2$ and a downfield triplet and upfield quintet where $n = 3$. For the tetramethylene system, however, the upfield region becomes so complex that simple analysis is not possible. This is not surprising in view of the fact that both diastereomers would give rise to 16 nonequivalent hydrogens.

For the annelated 2,2′-biquinolines **15**, we have noted an interesting relationship between the chemical shift of H-8 and H-8′ and the dihedral angle between the two quinoline rings. As this angle becomes greater, H-8 and

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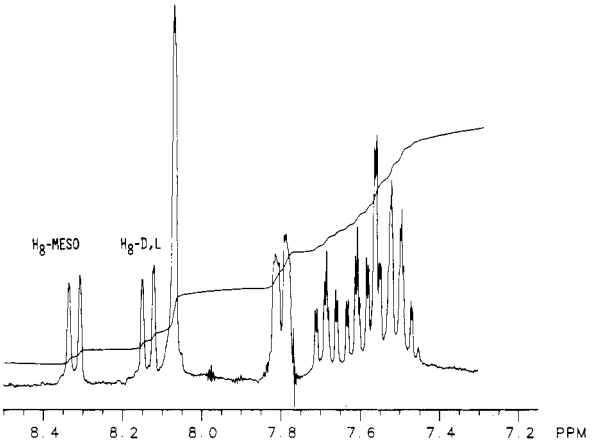
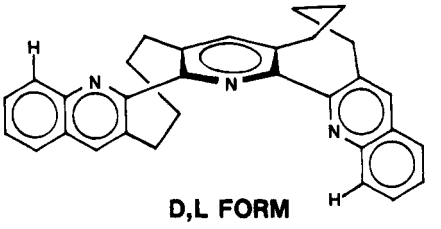
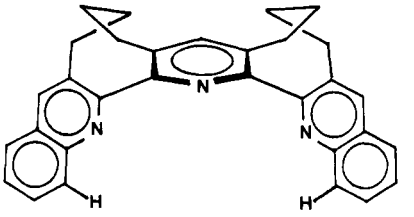


Figure 1. Downfield region of the 300-MHz ^1H NMR spectrum of **13d**.

H-8′ are held less in the deshielding region of the other quinoline ring and hence they resonate at higher field. Careful analysis of the downfield region of the 300-MHz NMR spectrum of **13d** (Figure 1) reveals two doublets of about equal intensity at 8.32 and 8.14 ppm, integrating for a total of two protons. These two resonances are assigned to H-8′ (and H-8″) in the meso and *d,l* forms of the



D,L FORM



MESO FORM

molecule which we already know to be present in approximately equal amounts. The more dishielded proton at 8.32 ppm is assigned to the meso form of **13d** where the two quinoline rings are held facing one another although somewhat out of coplanarity. In the *d,l* form the two quinoline rings are turned away from one another such that H-8′ (or H-8″) of one ring is unaffected by the other ring.

Although the above discussion has dealt with the hydrogens and carbons of conformationally rigid systems like **2d**, **13d**, and **14d**, it should be pointed out that the nitrogen lone pair orientations should be very different in the two diastereomeric forms of these molecules. We are currently studying the metal complex chemistry of these systems particularly with a view toward selective metal chelation as a means of separating meso and *d,l* forms.

Figure 2 shows the ultraviolet absorption spectra for **1** and **2b–d** in 95% ethanol and Table I summarizes the absorption maxima and extinction coefficients. Two significant trends are apparent and may again be correlated to the dihedral angles between adjacent pyridine rings. With increasing length of the polymethylene bridges

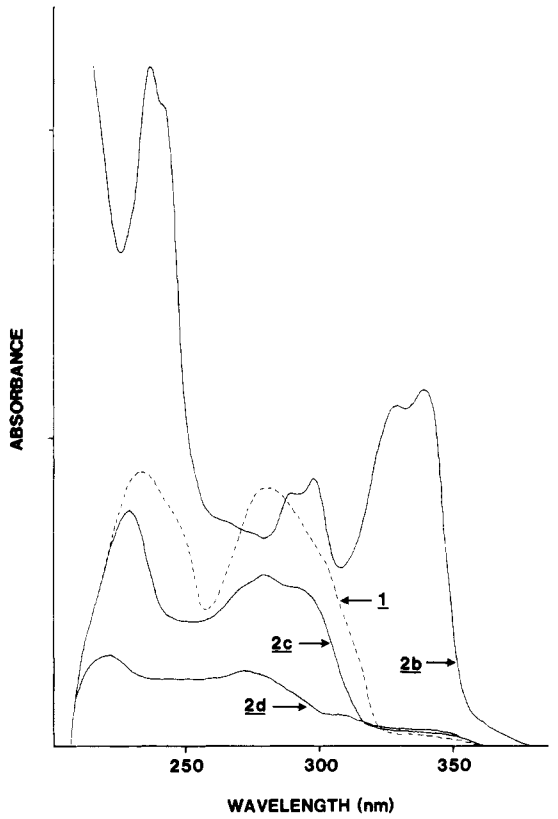


Figure 2. Ultraviolet absorption spectra (95% EtOH) of 2,2′:6′,2″-terpyridine and bis-annelated derivatives.

Table I. Ultraviolet Absorption Data for Bis-Annelated Tripyridines

system	λ_{max} (95% EtOH)	ϵ
1	232	22 300
	280	20 900
2b	238	60 100
	243	54 000
	288	20 500
	298	21 600
	328	27 500
	340	24 000
2c	228	19 100
	278	14 000
	290	13 000
2d	209	7 300
	275	6 200

connecting the pyridine rings, the maxima for both of the major tripyridine absorption bands shift to shorter wavelength indicating a higher energy transition. At the same time the intensity of these absorptions is found to decrease with lengthening of the bridges. Both observations are consistant with a decrease in the conjugative interaction between adjacent aromatic rings as the dihedral angle between them becomes larger. System **2b**, which is the most planar, shows a bathochromic shift of 50 nm over **2c** for its long-wavelength band and also shows significant splitting of this band. The absorption bands for the parent unbridged tripyridine (**1**) appear intermediate between the dimethylene and trimethylene bridged molecules, **2b** and **2c**. This suggests that the average conformation of this molecule is not planar as in **1a** but rather the pyridine rings lie somewhere between 20–50° out of plane with respect to each other.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ on a Varian Associates T-60 or FT-80 spectrometer or a Nicollet NT-300 WB spectrometer and chemical shifts are reported in parts per million downfield from Me_4Si. Infrared spectra (IR) were obtained on a Perkin-Elmer 330 spectrophotometer in KBr, except where noted. Ultraviolet spectra were obtained on a Cary 14 spectrometer. Mass spectra (MS) were obtained by direct sample introduction into a Hewlett-Packard 5933A GC-mass spectrometer and are reported herein as m/e (relative intensity). High-resolution mass spectral analyses were performed by Dr. David Hachey of the Baylor College of Medicine on a Finnigan MAT-212 at 90 eV. Benzaldehyde and acetic anhydride (Ac_2O) were freshly distilled reagent grade. Ozone was generated on a Welsbach T-23 ozonator. The β-aminoacrolein,[10] *o*-aminobenzaldehyde,[14] and 2-aminonicotinaldehyde[15] were prepared according to literature procedures. The 1,2,3,4,5,6,7,8-octahydroacridine (**5b**) was obtained from Aldrich Chemical Co. and the 2,3:5,6-bis(trimethylene)pyridine (**5a**) was prepared according to the method of Colonge et al.[8] All melting points are uncorrected.

Bis(2-oxocycloheptyl)methane (4c). A solution of 44.75 g (.25 mol) of *N*-1-cycloheptenylmorpholine, 3.78 g of paraformaldehyde, and 6 mL of dioxane was heated at 150 °C overnight under nitrogen. The reaction mixture was cooled and acidified with 5 N HCl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent and distillation of the residue gave 16.41 g (56%) of **4c** as an oil: bp 145 °C (0.05 mm), lit.[16] bp 202–203 °C (11 mm); IR (thin film) 2930, 2860, 1700, 1450, 935 cm^{-1}.

Bis(2-oxocyclooctyl)methane (4d). A solution of 9.63 g (0.05 mol) of *N*-1-cyclooctenylpyrrolidine,[17] 1.00 g of paraformaldehyde, and 2 mL of dioxane was treated in the manner described above for **4c** to give 7.54 g (52%) of diketone **4d**: bp 145 °C (0.05 mm); ^1H NMR (60 MHz) δ 2.40 (br s, 6 H), 1.57 (br s, 22 H); IR (thin film) 2930, 2860, 1705, 1695, 1460, 1445 cm^{-1}; MS, m/e 265 (M + 1, 6), 264 (M, 24), 126 (78), 98 (95), 86 (62), 84 (100).

2,3:5,6-Bis(pentamethylene)pyridine (5c). A mixture 16.41 g (0.07 mol) of **4c** and 11.5 g of NH_4OAc in 30 mL of glacial AcOH was refluxed for 2 h. The solution was cooled, made basic with 50% NaOH, and extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 6.33 g of a precipitate. Chromatography of the filtrate on 20 g of silica eluting with hexane gave an additional 2.53 g for a total of 8.86 g (60%): mp 110–112 °C, lit.[8] mp 112 °C; IR 2920, 2850, 1564, 1435, 1100, 904 cm^{-1}; ^1H NMR (80 MHz), δ 7.04 (s, 1 H, Ar H), 2.96 (m, 4 H, Ar CH_2), 2.68 (m, 4 H, Ar CH_2), 1.74 (br m, 12 H, CH_2); ^{13}C NMR (20 MHz) 158.8, 137.3, 134.6, 38.5, 34.4, 32.3, 27.8, 26.4 ppm.

2-(Aminomethylene)cyclooctanone[18] (7). Into a solution of 16.76 g (0.1 mol) of 2-(hydroxymethylene)cyclooctanone[19] in 50 mL of $CHCl_3$ was passed a slow stream of ammonia gas for 20 min such that the temperature of the solution did not rise appreciably. The mixture was allowed to stand overnight, dried over anhydrous $MgSO_4$, and filtered. Evaporation of the solvent gave 13.5 g (92%) of **7**: mp 95–97 °C; ^1H NMR (80 MHz) δ 6.72 (t, =CH, J = 10.6 Hz), 4.9 (br s, NH_2), 2.5 (m, 4 H), 1.5 (m, 8 H), upon addition of D_2O, the signal at 6.72 collapsed to a singlet and the one at 4.9 disappeared; IR 3370, 2930, 2860, 1635, 1485, 1295, 1234, 1100, 900 cm^{-1}.

2,3:5,6-Bis(hexamethylene)pyridine (5d). Method A. A mixture of 10 g (0.065 mol) of **7**, 8.25 g (0.065 mol) of freshly distilled cyclooctanone, and 50 mg of NH_4OAc in 60 mL of ethylene glycol was heated at 120 °C under N_2 for 20 h. The mixture was cooled in the refrigerator and the precipitate was collected to give 4.25 g (27%) of **5d**: mp 147–147.5 °C; ^1H NMR (80 MHz) δ 7.04 (s, Ar H), 2.92 (dd, 4 H, Ar CH_2, J = 5.3, 6.6 Hz), 2.70 (dd, 4 H, Ar CH_2, J = 5.1, 6.6 Hz), 1.71 (m, 8 H), 1.47 (m,

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8 H); ^{13}C NMR (20 MHz) 157.5 (C-2), 136.8 (C-4), 133.2 (C-3), 33.7, 32.0, 31.1, 30.5, 25.7, and 25.6; IR 2970, 2860, 1570, 1468, 1453, 1108, 910 cm^{-1}.

Method B. A mixture of 2.86 g (10.8 mmol) of diketone **4d** and 1.80 g of NH_4OAc in 10 mL of glacial AcOH was heated at 150 °C for 2 h. After cooling, the solution was made basic with 50% NaOH and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the residue from 95% EtOH gave 1.20 g (50%) of **5d**, mp 144–145 °C; other spectral features were identical with those described in method A.

α,α′-Dibenzylidene-2,3:5,6-bis(trimethylene)pyridine (8a). A mixture of 1 g (6 mmol) of 2,3:5,6-bis(trimethylene)pyridine (**5a**), 6 g of benzaldehyde, and 5 g of Ac_2O was refluxed under N_2 for 8 h. The mixture was then cooled and the precipitate collected and washed with cold 95% EtOH to give 1.75 g (87%) of **8a**: mp 299–300 °C; ^{1}H NMR (80 MHz) δ 7.7–7.2 (m, Ar H), 7.29 (s, Pyr H), 2.16 (m, CH_2); IR 2940, 1500, 1458, 1406, 1265, 1108, 910, 770, 698 cm^{-1}; MS, *m/e* 336 (12, M + 1), 335 (63, M), 334 (100), 91 (16).

1,8-Dibenzylidene-1,2,3,4,5,6,7,8-octahydroacridine (8b). A mixture of 23.5 g (0.13 mol) of **5b**, 119 g of benzaldehyde, and 102 g of Ac_2O was treated as described above for **8a** to afford 43.3 g (92%) of **8b**, mp 184–185 °C (lit.[20] mp 184–186 °C).

α,α′-Dibenzylidene-2,3:5,6-bis(pentamethylene)pyridine (8c). A mixture of 1.35 g (6 mmol) of **5c**, 6 g of benzaldehyde, and 5 g of Ac_2O was heated to reflux for 6 days. The solvents were removed by vacuum distillation and 20 mL of water was added to the residue which was made alkaline with 50% NaOH and then extracted with CH_2Cl_2. The extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to give a sticky material which was chromatographed on 30 g of silica gel eluting with hexane and hexane–CH_2Cl_2 (8:2). Early fractions of the mixed eluent gave 1.53 g (66%) of **8c**: mp 156–157 °C; ^{1}H NMR (80 MHz) δ 7.54–7.15 (overlapping m, 13 H, Ar H and C=CH), 2.73 (m, 8 H), 1.86 (m, 8 H); IR 2930, 2855, 1492, 1446, 1100, 904, 757, 695 cm^{-1}.

α,α′-Dibenzylidene-2,3:5,6-bis(hexamethylene)pyridine (8d). A mixture of 4 g (16.5 mmol) of **5d**, 15 g of benzaldehyde, and 13 g of Ac_2O was refluxed under N_2 for 6 days. The solvents were removed by vacuum distillation and the dark residue was chromatographed on 20 g of silica gel eluting with CH_2Cl_2 to give **8d** quantitatively: mp 53–55 °C; ^{1}H NMR (80 MHz) δ 7.4–7.0 (m, Ar H), 6.5 (m, =CH), 2.69 (m, 8 H), 1.56 (m, 12 H); IR 2940, 2860, 1440, 1240, 920, 757, 700 cm^{-1}.

α,α′-Dioxo-2,3:5,6-bis(trimethylene)pyridine (9a). A solution of 1 g (3 mmol) of **8a** in 300 mL of CH_2Cl_2 was cooled to −70 °C and ozone/oxygen bubbled through it until a blue color persisted. The dissolved ozone was purged by bubbling oxygen (blue color disappears), 1 mL of Me_2S was added, and the mixture was allowed to warm to room temperature and stirred overnight. The solution was concentrated by heating on the steam bath. The residue was washed with hot hexane (2 × 20 mL) and diluted with 50 mL of CH_2Cl_2. This solution was washed with water (2 × 20 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent and drying under vacuum gave a dark solid which was chromatographed on 30 g of silica gel, eluting with CH_2Cl_2–EtOAc (1:1). Early fractions of the mixed eluent gave 0.23 g (41%) of **9a**: mp 212 °C dec; ^{1}H NMR (80 MHz) δ 8.06 (s, Ar H), 3.27 (dd, CH_2), 2.85 (dd, CH_2); ^{13}C NMR (20 MHz) δ 203.6 (C=O), 152.4 (C-2), 134.3 (C-3), 128.3 (C-4), 35.4, 23.6; IR 2940, 1730, 1595, 1406, 1390, 1321, 1152, 905 cm^{-1}; MS, *m/e* 188 (18, M + 1), 187 (100, M), 130 (74).

1,8-Dioxo-1,2,3,4,5,6,7,8-octahydroacridine (9b). A solution of 5.46 g (15 mmol) of **8b** in 200 mL of CH_2Cl_2 was ozonized and worked up as described above for **9a**. The crude product was chromatographed on 75 g of silica gel, eluting with CH_2Cl_2 followed by CH_2Cl_2–EtOAc (4:1). Early fractions of the mixed eluent gave 2.23 g (69%) of **9b**: mp 150–151 °C; ^{1}H NMR (80 MHz) δ 7.68 (s, Ar H), 3.09 (t, 4 H, *J* = 5.8 Hz), 2.80 (t, 4 H, *J* = 5.9 Hz), 2.19 (quintet, 4 H, *J* = 5.8 Hz); ^{13}C NMR (20 MHz) δ 195.5 (C=O), 146.9, 143.6, 138.7, 39.3, 28.8, 21.8; IR 2940, 1700, 1588, 1420, 1318, 1255, 1210, 1165, 972, 710 cm^{-1}; MS, *m/e* 215 (66, M), 187 (30), 186 (100), 161 (43), 159 (44), 130 (50).

α,α′-Dioxo-2,3:5,6-bis(pentamethylene)pyridine (9c). A solution of 1.53 g (4 mmol) of **8c** in 200 mL of CH_2Cl_2 was ozonized and worked up as described above for **9a**. The crude product was chromatographed on 15 g of silica gel, eluting with CH_2Cl_2 followed by CH_2Cl_2–MeOH (9:1). Early fractions of the mixed eluent gave 0.51 g (54%) of **9c**: mp 135.5–137 °C; ^{1}H NMR (80 MHz) δ 7.50 (s, 1, Ar H), 2.92–2.68 (overlapping t, 8 H), 1.88 (m, 8 H); ^{13}C NMR (20 MHz) δ 203.4 (C=O), 153.1, 139.0, 137.4, 39.7, 29.9, 24.2, 20.6; IR 2930, 2865, 1693, 1585, 1465, 1238, 1147, 1100, 900 cm^{-1}; MS, *m/e* 244 (32, M + 1), 243 (100, M), 229 (13), 215 (33), 214 (91), 200 (35), 187 (47), 186 (86).

α,α′-Dioxo-2,3:5,6-bis(hexamethylene)pyridine (9d). A solution of 6.88 g (16.5 mmol) of **8d** in 500 mL of CH_2Cl_2 was ozonized and worked up as described above for **9a**. The crude product was chromatographed on 20 g of silica gel, eluting with CH_2Cl_2–hexane followed by EtOAc-hexane (3:7). Early fractions of the latter eluent gave 1.56 g (35%) of **9d**: mp 105–106 °C; ^{1}H NMR (60 MHz) δ 7.40 (s, Ar H), 2.85 (m, 8 H), and 1.75 (m, 12 H); ^{13}C NMR (20 MHz) δ 208.5 (C=O), 154.6, 139.0, 134.2, 44.7, 30.8, 28.1, 26.8, 23.0; IR 2940, 2875, 1700, 1440, 1315, 1285, 1215, 1185, 1120, 905 cm^{-1}; MS, *m/e* 272 (9, M + 1), 271 (24, M), 243 (56), 242 (51), 228 (100).

7-Morpholino-5*H*-1-pyrindene (11a). A solution of 5.46 g (0.04 mol) of 5,6-dihydro-7*H*-1-pyrinden-7-one,[6a] 6.00 g (0.1 mol) of morpholine, and 100 mg of *p*-toluenesulfonic acid in 120 mL of toluene was refluxed for 5 h under a Dean Stark trap. Excess morpholine and toluene were removed by distillation and the residue was distilled to afford 3.10 g (37%) of an orange oil: bp 128–130 °C (0.15 mm); ^{1}H NMR (80 MHz) δ 8.34 (dd, H_2, $J_{2,3}$ = 5.0 Hz), 7.63 (dd, H_4, $J_{3,4}$ = 7.5 Hz), 7.05 (dd, H_3), 5.67 (t, =CH, *J* = 2.5 Hz), 3.92 (AB quartet, 4 H), 3.40 (AB quartet, 4 H), 3.26 (d, CH_2); IR (thin film) 2970, 2860, 1602, 1568, 1455, 1390, 1273, 1245, 1195, 1127, 1037, 901 cm^{-1}.

8-Morpholino-5,6-dihydroquinoline (11b). A solution of 3.0 g (0.02 mol) of 5,6,7,8-tetrahydro-8-quinolone[6a] in 150 mL of toluene was treated with 3.36 g (0.04 mol) of morpholine for 26 h as described above for **11a**. The crude product was sublimed at 55 °C (0.05 mm) to give 3.30 g (75%) of **11b**: mp 84–85 °C; ^{1}H NMR (80 MHz) δ 8.44 (dd, H_2, $J_{2,3}$ = 4.8 Hz), 7.42 (dd, H_4, $J_{3,4}$ = 7.3 Hz), 7.01 (dd, H_3), 5.44 (t, H_7, *J* = 4.7 Hz), 3.91 (m, 4 H), 2.96 (m, 4 H), 2.73 (t, 2 H, *J* = 7.4 Hz), 2.32 (m, 2 H); IR 2970, 2840, 1612, 1562, 1441, 1385, 1272, 1151, 1120, 1026, 933, 920, 902 cm^{-1}; MS, *m/e* 216 (18, M), 198 (21), 185 (16), 171 (29), 170 (23), 158 (30), 157 (34), 131 (72), 130 (100).

3,3′:5′,3″-Bis(dimethylene)-2,2′:6′,2″-terpyridine (2b). Method A. To a solution of 1.08 g (5 mmol) of **9b** and 0.71 g (10 mmol) of β-aminoacrolein in 30 mL of ethylene glycol was added 30 mg of NH_4OAc. The mixture was heated at 140 °C overnight under N_2, cooled, poured into 100 mL of water, and extracted with CH_2Cl_2. The organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated to give 0.9 g of residue which was chromatographed on 60 g of alumina, eluting with EtOAc and EtOAc–MeOH (7:3). Early fractions of the mixed eluent gave material which was chromatographed again on 40 g of alumina, eluting with MeOH–acetone (1:9) to give 20 mg (3%) of **2b** as a semisolid: IR 2960, 1432, 1410, 1225, 1095, 900 cm^{-1}; ^{1}H NMR (300 MHz) δ 8.72 (dd, H_6, $J_{5,6}$ = 4.8, $J_{4,6}$ = 2.2 Hz), 7.56 (dd, H_4, $J_{4,5}$ = 7.6 Hz), 7.44 (s, $H_{4'}$), 7.23 (dd, H_5), 5.07 (s, H_2O), 3.01 (s, CH_2); MS, *m/e* 286 (22, M + 1), 285 (100, M), 284 (52), 161 (61), 149 (54).

Method B. A solution of 2.16 g (0.01 mol) of 8-morpholino-5,6-dihydroquinoline (**11b**) and 0.16 g (0.005 mol) of paraformaldehyde in 15 mL of dioxane was heated at 150 °C for 8 h under nitrogen. The mixture was cooled and made acidic with 5 N HCl and the organic layer separated. The aqueous layer was made basic with 50% NaOH and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to give 1.50 g of material which was combined with 1.0 g of NH_4OAc in 15 mL of AcOH and refluxed for 2 h. After cooling, the solution was made basic with 50% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on 40 g of alumina eluting with hexane–CH_2Cl_2 (1:1) followed by CH_2Cl_2. The early

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CH_2Cl_2 fractions gave 0.45 g (31%) of **2b**: mp 237–238 °C; spectral properties were identical with those described in method A.

3,3′:5′,3″-Bis(trimethylene)-2,2′:6′2″-terpyridine (2c). An enamine was prepared by treating a solution of 5.00 g (0.03 mol) of cyclohepta[b]pyridin-9-one[6a] in 150 mL of toluene with 6.70 g (0.08 mol) of morpholine as described above for **11a**. Removal of excess morpholine and toluene by distillation gave 6.38 g (89%) of an orange oil which showed no C=O band in the IR. This material was combined with 0.42 g (0.015 mol) of paraformaldehyde in 30 mL of dioxane and treated as described above for **2b** method B. The crude product was recrystallized from $CHCl_3$ to give 0.60 g of product. The $CHCl_3$ filtrate was evaporated and the residue chromatographed on silica gel, eluting with EtOAc followed by EtOAc–CH_3OH (9:1). The early fractions of the mixed solvent gave an additional 0.30 g of **2c** (overall yield 21%): mp >310 °C; ^1H NMR (300 MHz) δ 8.71 (dd, H_6, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.5 Hz), 7.57 (dd, H_4, $J_{4,5}$ = 7.7 Hz), 7.48 (s, $H_{4'}$), 7.24 (dd, H_5), 2.59 (t, Ar CH_2, J = 7 Hz), 2.28 (quintet, $CH_2CH_2CH_2$); IR 2940, 2861, 1565, 1454, 1418, 1100, 919, 900, 808 cm^{-1}; MS, m/e 314 (M + 1, 27), 313 (M, 100), 312 (52), 298 (18), 285 (31), 284 (17), m/e calcd for $C_{21}H_{19}N_3$ 313.1581, found 313.1581.

3,3′:5′,3″-Bis(tetramethylene)-2,2′:6′,2‴-terpyridine (2d). A mixture of 0.4 g (1.5 mmol) of **9d** and 0.21 g (3 mmol) of β-aminoacrolein was treated as described above for **2b** method A. The crude product (0.48 g) was chromatographed on alumina, eluting with acetone, to give 10 mg (2%) of **2d**: mp >310 °C; IR 2930, 2850, 1563, 1451, 1422, 1152, 1137, 1100, 932, 901, 790 cm^{-1}; ^1H NMR (300 MHz) δ 8.62 (dd, H_6 (meso), $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.5 Hz), 8.59 (dd, H_6 (*d,l*), $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.5 Hz), 7.58 (overlapping d, H_4, $J_{4,5}$ = 7.8 Hz), 7.52 (s, $H_{4'}$ (*d,l*), 7.50 (s, $H_{4'}$ (meso)), 7.28 and 7.26 (overlapping dd, H_5), 2.85–2.71 (m, 4 H), 2.43–2.12 (overlapping m, 8 H), 1.67–1.53 (m, 4 H); MS, m/e 342 (8, M + 1), 341 (31, M), 340 (9), 313 (36), 312 (100).

3,3′:5,3″-Bis(dimethylene)-2,6-di(2′-quinolyl)pyridine (13b). To a mixture of 0.65 g (3 mmol) of **9b** and 0.73 g (6 mmol) of *o*-aminobenzaldehyde in 25 mL of absolute EtOH was added a solution of 0.05 g of KOH in 2 mL of absolute EtOH. The mixture was refluxed for 4 h under N_2, cooled, diluted with 20 mL of H_2O, and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$ and evaporated to give 1.87 g of a solid which was chromatographed on 30 g of alumina. Elution with acetone gave 0.87 g (87%) of **13b**: mp 245–247 °C dec; IR 2950, 2850, 1628, 1600 1550, 1500, 1440, 1416, 1224, 1105, 915 cm^{-1}; ^1H NMR (300 MHz) δ 8.50 (d, $H_{8'}$, $J_{7',8'}$ = 8.4 Hz), 7.89 (s, $H_{4'}$), 7.70 (t, $H_{7'}$, J = 7 Hz), 7.68 (d, $H_{5'}$, $J_{5',6'}$ = 7.4 Hz), 7.43 (t, $H_{6'}$, J = 7 Hz), 7.32 (s, H_4), 3.08 (t, CH_2CH_2, J = 7.0 Hz), 2.95 (t, CH_2CH_2, J = 7.0 Hz); MS, m/e 386 (29, M + 1), 385 (100, M), 384 (48), 192 (46).

3,3′:5,3″-Bis(trimethylene)-2,6-di(2′-quinolyl)pyridine (13c). A mixture of 0.24 g (1 mmol) of **9c** and 0.24 g (2 mmol) of *o*-aminobenzaldehyde was treated as described above for **13b**. After 1 h of reflux, a precipitate formed which was collected to provide 0.31 g (76%) of **13c**: mp >300 °C; IR 3050, 2940, 2860, 1624, 1604, 1548, 1493, 1411, 1158, 1100, 913, 757 cm^{-1}; ^1H NMR (300 MHz) δ 8.40 (d, $H_{8'}$, $J_{7',8'}$ = 8.5 Hz), 8.04 (s, $H_{4'}$), 7.82 (d, $H_{5'}$, $J_{5',6'}$ = 7.7 Hz), 7.70 (t, $H_{7'}$, J = 7.7 Hz), 7.55 (t, $H_{6'}$, J = 7.7 Hz), 7.53 (s, H_4), 2.84 (t, Ar CH_2, J = 7 Hz), 2.67 (t, Ar CH_2, J = 7 Hz), 2.32 (quintet, CH_2, J = 7 Hz); ^{13}C NMR (20 MHz) δ 157.8, 154.4, 147.0, 137.3, 135.3, 135.1, 132.6, 129.4, 128.9, 126.6, 126.5, 30.9, 29.8, 29.2; MS, m/e 414 (31, M + 1), 413 (100, M), 412 (41), 385 (10), m/e calcd for $C_{29}H_{23}N_3$ 413.1847, found 413.1892.

3,3′:5,3″-Bis(tetramethylene)-2,6-di(2′-quinolyl)pyridine (13d). A mixture of 0.27 g (1 mmol) of **9d** and 0.24 g (2 mmol) of *o*-aminobenzaldehyde was treated as described above for **13b**. After cooling, 0.21 g of precipitate was collected. The filtrate was concentrated and chromatographed on 15 g of alumina, eluting with CH_2Cl_2, CH_2Cl_2–EtOAc (9:1), and CH_2Cl_2–EtOAc (1:1). From the latter fractions was obtained an additional 0.13 g of material (combined yield 77%): mp >310 °C; IR 2940, 2865, 1600, 1495, 1455, 1420, 1103, 904, 758 cm^{-1}; ^1H NMR (300 MHz) δ 8.32 (d, $H_{8'}$ (meso), $J_{7'8'}$ = 8.3 Hz), 8.14 (d, $H_{8'}$ (*d,l*), $J_{7'8'}$ = 8.3 Hz), 8.07 (s, $H_{4'}$), 7.80 (d, $H_{5'}$), 7.7–7.45 (overlapping m, $H_{6'}$, $H_{7'}$), 7.56 (s, H_4), 3.0 (m, 2), 2.84 (m, 2), 2.6 (overlapping m, 2), 2.25 (m, 6), 1.7 (m, 4); ^{13}C NMR (20 MHz) δ (upfield only) 33.4, 33.1, 32.9, 32.6, 32.3, 32.2, 31.2, 30.9; MS, m/e 442 (12, M + 1), 441 (31, M), 413 (36), 412 (100), 384 (6).

3,3′:5,3″-Bis(dimethylene)-2,6-di(1′,8′-naphthyrid-2′-yl)pyridine (14b). A mixture of 0.88 g (4.1 mmol) of **9b** and 1.0 g (8.2 mmol) of 2-aminonicotinaldehyde was treated as described above for **13b**. After reaction the solvent was evaporated, 80 mL of MeOH was added and the undissolved material was filtered. Evaporation of the filtrate gave 1.62 g of crude material which was chromatographed on 60 g of alumina, eluting with EtOAc, EtOAc–MeOH (9:1), and EtOAc–MeOH (1:1). Early fractions of the last eluent gave 1.1 g (70%) of **14b**: mp 197–199 °C dec; IR 1600, 1550, 1435, 1385, 1150, 1100, 904, 790 cm^{-1}: ^1H NMR (80 MHz) δ 8.85 (dd, $H_{7'}$, $J_{6',7'}$ = 4.2, $J_{5',7'}$ = 2.0 Hz), 8.04 (dd, $H_{5'}$, $J_{5',6'}$ = 8.1 Hz), 7.94 (s, $H_{4'}$), 7.53 (s, H_4), 7.33 (dd, $H_{6'}$), 3.45 (s, 4 H); MS, m/e 388 (66, M + 1), 387 (100, M), 385 (43).

3,3′:5,3″-Bis(trimethylene)-2,6-di(1′,8′-naphthyrid-2′-yl)pyridine (14c). A mixture of 0.12 g (0.5 mmol) of **9c** and 0.12 g (1 mmol) of 2-aminonicotinaldehyde was treated as described above for **13b**. After cooling, 50 mL of H_2O was added to the reaction mixture which was then extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent evaporated to give 0.17 g of solid which was chromatographed on 15 g of alumina, eluting with CH_2Cl_2 and CH_2Cl_2–MeOH (9:1). The latter eluent gave 0.12 g (58%) of material which was recrystallized from $CHCl_3$: mp >300 °C dec; IR 2940, 2860, 1615, 1550, 1455, 1103, 905 cm^{-1}; ^1H NMR (80 MHz) δ 9.15 (dd, $H_{7'}$, $J_{6',7'}$ = 4.0, $J_{5',7'}$ = 2.0 Hz), 8.21 (dd, $H_{5'}$, $J_{5',6'}$ = 8.1 Hz), 8.07 (s, $H_{4'}$), 7.53 (s, H_4), 7.50 (dd, $H_{6'}$), 2.77 (overlapping t), 2.35 (br m); MS, m/e 416 (30, M + 1), 415 (100, M), 400 (18), 387 (24), 386 (24); MS, m/e calcd for $C_{27}H_{21}N_5$ 415.1832, found 415.1797.

3,3′:5,3″-Bis(tetramethylene)-2,6-di(1′,8′-naphthyrid-2′-yl)pyridine (14d). A mixture of 0.43 g (1.6 mmol) of **9d** and 0.44 g (3.6 mmol) of 2-aminonicotinaldehyde was treated as described above for **13b**. After 1 h of reflux, the solution was cooled and 0.45 g (64%) of precipitate was collected: mp >310 °C; IR 2930, 2860, 1608, 1550, 1450, 1240, 1100, 905 cm^{-1}; ^1H NMR (300 MHz) δ 9.18 (d, $H_{7'}$ (meso), $J_{6',7'}$ = 4.6 Hz), 9.06 (d, $H_{7'}$ (*d,l*), $J_{6',7'}$ = 4.6 Hz), 8.20 (dd, $H_{5'}$, $J_{5',6'}$ = 8.4, $J_{5',7'}$ = 2.0 Hz), 8.11 (s, $H_{4'}$), 7.62 (s, H_4 (meso)), 7.58 (s, H_4 (*d,l*)), 7.50 (dd, $H_{6'}$ (meso)), 7.46 (dd, $H_{6'}$ (*d,l*)), 3.04 (dd), 2.85 (dd), 2.69 (t), 2.31 (m), 2.11 (m), 1.65 (m); MS, m/e 444 (4.6, M + 1), 443 (13, M), 442 (4), 415 (35), 414 (100).

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Registry No. **2b**, 96413-21-7; **2c**, 96413-22-8; *dl*-**2d**, 96413-23-9; *meso*-**2d**, 96479-49-1; **3c**, 7182-08-3; **3d**, 17344-01-3; **4c**, 92860-29-2; **4d**, 96413-24-0; **5a**, 34421-99-3; **5b**, 1658-08-8; **5c**, 6574-73-8; **5d**, 72148-49-3; **6**, 1459-36-5; **7**, 42997-64-8; **8a**, 96413-25-1; **8b**, 32462-10-5; **8c**, 96413-26-2; **8d**, 96413-27-3; **9a**, 96413-28-4; **9b**, 63371-62-0; **9c**, 96413-29-5; **9d**, 96413-30-8; **10a**, 31170-78-2; **10b**, 56826-69-8; **10c**, 41043-13-4; **11a**, 96413-31-9; **11b**, 96413-32-0; **11c**, 96413-33-1; **12b**, 96413-34-2; **13b**, 96413-35-3; **13c**, 96413-36-4; *dl*-**13d**, 96413-37-5; *meso*-**13d**, 96479-50-4; **14b**, 96427-33-7; **14c**, 96413-38-6; *dl*-**14d**, 96413-39-7; *meso*-**14d**, 96479-51-5; NH_4OAc, 631-61-8; paraformaldehyde, 30525-89-4; cyclooctanone, 502-49-8; benzaldehyde, 100-52-7; morpholine, 110-91-8; β-aminoacrolein, 25186-34-9; *o*-aminobenzaldehyde, 529-23-7; 2-aminonicotinaldehyde, 7521-41-7.