Chelation-Controlled Regioselectivity in the Synthesis of Substituted Pyrazolylpyridine Ligands. 2. Tridentates

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A new, more reliable synthesis of tetraketone **4** was found. With ^{t}BuNHNH$_2$, PhNHNH$_2$, and 4-hydrazinobenzoic acid, it condensed to give mostly *in,in*-disubstituted derivatives (**7***ii*–**9***ii*) of the parent, *C*-linked 2,6-bis(pyrazol-3-yl)pyridine **5**, along with some *in,out* materials. MeNHNH$_2$ also provided some *out,out* isomer (**6***oo*). This same derivative was also produced by NaH-mediated methylation of **5** with CH$_3$I, presumably *via* a Na$^+$ chelate that disallowed access to the *inner* pyrazole nitrogens, and was able, as a tridentate, to solubilize solid sodium picrate (NaPic) into CDCl$_3$, with ^{1}H-NMR detection of the complex. In contrast, the bidentate *in,out* isomer did not solubilize NaPic. Similarly, ethyl bromoacetate produced **10***oo* and it also solubilized NaPic. Previously reported alkylations of **5** had also given *out,out* products that bound alkali metal ions. **10***oo* was hydrolyzed to the disalt **13***oo*. In the presence of ZnCl$_2$, **1** reacted with PhNHNH$_2$ to give the *out,out* derivative **8***oo*, presumably through a metal-mediated activation of the *inner* carbonyls of **1**. Though **8***oo* also solubilized NaPic, a better NMR spectrum was obtained by treatment with CF$_3$COOD, which indicated multidentate binding of D$^+$. The same phenomenon was also observed with the *out,out* diester **11***oo*, which was obtained by the nucleophilic aromatic substitution by **5** of ethyl 4-fluorobenzoate, presumably *via* a K$^+$ chelate that also disallowed *in* substitution. A mono-*out*-substituted product **12** was also isolated from this reaction. Apart from mechanistic arguments and the ability or inability to dissolve NaPic, the aromatic ^{1}H-NMR regions were diagnostic of the regiochemistries: In all cases, the pyridine H-3/5 doublet lay upfield of the H-4 triplet for *in,in* isomers and downfield for *out,out* isomers, while *in,out* isomers showed one doublet on either side of the triplet. The binding of Na$^+$ or D$^+$ by the *out,out* isomers resulted in shifts of the H-3/5 doublets to upfield positions. The deuteration of *in,in* isomers did not. This situation was analogous to that of the bidentates reported in the accompanying paper and was similarly interpreted in conformational terms, with support from MM2 calculations: Like terpyridine, the imino nitrogens of the *out,out* materials prefer *anti* orientations due to electronic and steric repulsions (calculated $\Delta G_{\text{syn-anti}} > 2.7$ kcal/mol between rotamers about each pyridine–pyrazole bond in **6***oo* and **7***oo* and about the *out*-substituted pyrazole–pyridine bonds of **6***io* and **7***io*), but they are forced into *syn* orientations upon binding Na$^+$ or D$^+$. This induces a shielding interaction between the pyridine H-3/5 and neighboring CH$_2$ groups. This same shielding is present in any conformation of the *in,in* products and of the *in*-substituted side of *in,out* isomers, which are much closer in energy ($|\Delta G_{\text{syn-anti}}| \leq 0.4$ kcal/mol for any ring–ring bond in **6***ii* and **7***ii* and for the *in*-substituted pyrazole–pyridine bonds of **6***io* and **7***io*).

Introduction

In the previous paper were reported the short syntheses of bidentate, *C*-linked pyrazolylpyridines which we sought as lipophilic and ionizable ligands for Ru^{II} and Ru^{III}, as well as the methods by which their regiochemistries could be assigned. We also sought tridentates which, in contrast to previously known *N*-linked 2,6-bis(pyrazol-1-yl)pyridines[1,2] and *C*-linked 2,6-bis(pyrazol-3-yl)pyridines,[3] would also be lipophilic and ionizable. In the past, we have succeeded in preparing the parent **5** from the bis-(β-diketone) precursor **4**, and used straightforward *N*-alkylation reactions to transform **5** into pentadentate and macrocyclic ligands for alkali metal ions.[4] In addition to describing routes to substituted derivatives of **5** analogous to those used in the previous paper, this paper reports how the binding of H$^+$ or Na$^+$ by such tridentates can be used to supplement the NMR evidence for the determination of the product regiochemistries.

Results and Discussion

The preparation of "tetraketone" **4** (actually a mixture of tautomers) has already been described,[4] using 2,6-pyridinedicarbonyl dichloride (**1**) and the morpholine-derived enamine of cyclohexanone, but there have been difficulties in reproducing the reported yield, partly because of the difficult workup and purification. A similar tetraketone has been prepared using a Claisen condensation of acetone with the diethyl ester **2**,[3] but an analogous reaction with cyclohexanone failed in our hands. With the more active diphenyl ester **3**,[5] **4** was reliably prepared in acceptable yield (41% after recrystallization). The quantitative conversion of **4** to **5** has already been reported,[4] as was the evidence for H-bonding in **5**, whether as drawn or as equilibrating, singly H-bonded structures.

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(2) For chiral examples, see Watson, A. A.; House, D. A.; Steel, P. J. *J. Org. Chem.* **1991**, *56*, 4072. Lecloux, D. D.; Tolman, W. B. *J. Am. Chem. Soc.* **1993**, *115*, 1153. *N*-Linked 6-(pyrazol-1-yl)-2,2′-bipyridines are also known: Downard, A. J.; Honey, G. E.; Steel, P. J. *Inorg. Chem.* **1991**, *30*, 3733. A *C*- and *N*-linked 1,3-bis(pyridin-2-yl)pyrazole is reported in the previous paper.

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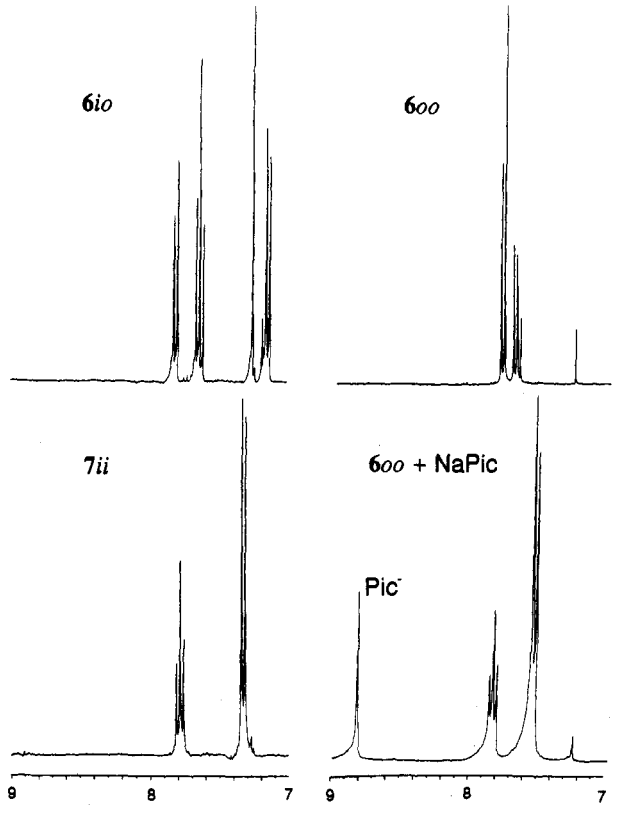

Figure 1. Representative patterns in the ^{1}H-NMR aromatic regions.

The criteria by which the regiochemistries of substituted derivatives can be assigned were established with the isomeric *N,N'*-dimethyl derivatives **6**. The condensation of **4** with CH_3NHNH_2 proceeded readily but produced all three possible disubstituted products, only the least polar of which was obtainable in pure state by chromatography (45% isolated yield). The rest (32% yield) consisted of a *ca.* 3:1 mixture of the other two regiomers. The NMR spectra of the major product showed a set of asymmetric signals and it was immediately assignable as the *in,out* isomer, designated **6***io*. (*In* and *out* refer to the pyrazole 2- and 1-positions, respectively.)

Another isomer, the most polar of the three (by TLC) and the least abundant component of the condensation product mixture, was obtained pure by methylation of the parent **5** (NaH/CH_3I/THF/60% isolated). In analogy with previous alkylations of **5**,[4] the tridentate *out,out* isomer, **6***oo*, was expected because its exclusive formation could be attributed to the intermediacy of a Na^+ chelate that disallows alkylation at the inner pyrazole nitrogens. Indeed, its NMR spectrum showed symmetry, and it was able to entrain solid sodium picrate (NaPic) into $CDCl_3$, producing a bright yellow solution, while the potentially bidentate **6***io* was not.

The ^{1}H-NMR spectra were diagnostic (Figure 1), especially in the aromatic region. That of **6***oo* included a single pyridine H-3/5 doublet at low field (7.80 ppm) which shifted to higher field (7.60 ppm) in the presence of NaPic, in spite of the overall deshielding effect of the metal, which caused, for instance, the downfield migration of the pyridine H-4 triplet (to 7.79 from 7.69 ppm). The spectrum of **6***io* included two pyridine H-3/5 doublets, one at a low field position similar to that with **6***oo* (7.81 ppm), *i.e.* downfield of the H-4 signal, and the other at high field (7.14 ppm). By subtraction of the signals due to **6***oo* from the spectrum of the aforementioned 3:1 mixture, the third isomer, **6***ii*, was deduced to give rise to a similar upfield doublet. The ^{t}Bu analogue (*vide infra*) illustrates the pattern in Figure 1. Our interpretation of these patterns is entirely analogous to the bidentate case in the previous paper: It appears that **6***oo*, like terpyridine,[6] prefers *anti* orientations of the pyridine and pyrazole nitrogens for electronic reasons, as drawn, but is forced into the *syn,syn* conformation upon binding Na^+, whence the pyridine H-3/5 and the nearby cyclohexenyl CH_2 groups become mutually shielding. Similarly, the *out*-substituted side of **6***io* prefers the same *anti* orientation and gives rise to the same downfield doublet, but the *in*-substituted side, like **6***ii*, suffers the same kind of shielding in both conformations and gives rise to an upfield doublet. (This implies rapid interconversion between conformers on the NMR timescale.)

Using similar arguments and NaPic complexation experiments, it was found that the condensations of **4** with ^{t}BuNHNH$_2$, PhNHNH$_2$, or 4-hydrazinobenzoic acid produced mostly *in,in* products (47–48% isolated yields) and some *in,out* materials (0–18% isolated yields) but no detectable *out,out* isomers, while the alkylation of **5** with $BrCH_2COOEt$ (NaH/THF) produced only *out,out* product **10***oo* (71% yield). In the case of PhNHNH$_2$, this was confirmed by the NMR and complexation behavior of *out,out* material (**8***oo*) obtained by a different reaction (*vide infra*).

This analysis of the NMR patterns was supported by the results of molecular mechanics calculations for *syn/anti* conformers of analogous bidentate regiomers, as described in the previous paper. The conformational picture in the tridentate cases here was complicated by the local conformations of the two cyclohexene moieties and by longer-range steric interactions. Nevertheless, with all regiomers of **6** and **7**, similar calculations revealed significant energy differences ($\Delta G_{syn\text{-}anti} > 2.7$ kcal/mol) between rotamers about each pyridine–pyrazole bond when the pyrazole ring was *out*-substituted. This difference favored the *anti* forms, as is true with terpyridine,[6] and ensures that *anti* forms dominate the conformational equilibria. In contrast, there were only small energy differences ($|\Delta G_{syn\text{-}anti}| \leq 0.4$ kcal/mol) between rotamers involving *in*-substituted pyrazole moieties, suggesting similar levels of steric congestion for both conformers.

In mechanistic terms, the results of the condensation reactions implied that the outer carbonyls in **4** were the preferred sites of the initial attack by the more reactive NH_2 ends of the hydrazines, although the more hindered but more nucleophilic $NHCH_3$ end of methylhydrazine appeared able to compete with the NH_2 end. In order to influence the regiochemistry of these condensations, we attempted to transiently block the outer carbonyls (as imine or enamine groups) before reaction with PhNHNH$_2$, but this failed to significantly alter the isomer distribution.

We instead succeeded in producing **8***oo* from **4** in the presence of $ZnCl_2$. Several solvents, several ratios of $ZnCl_2$ to **4**, and three different preparations of $ZnCl_2$ were explored, with NMR analysis of each crude product mixture after demetalation with NH_4OH. Using 10 equiv of commercially available THF solutions of $ZnCl_2$ and 2 equiv of PhNHNH$_2$ in $CHCl_3$ solvent, the crude product mixture was found to consist of *ca.* 50% **8***oo*, *ca.* 40% **8***io*

(6) Thummel, R. P.; Jahng, Y. *J. Org. Chem.* **1985**, *50*, 2407.

and the rest was *in,in* isomer. Thus, the $ZnCl_2$ directed *ca.* 70% of the β-diketone sites to produce *out* substitution. The reaction produced an insoluble deposit that was found to consist of Zn complexes of both 8*oo* and 8*io*, while the supernatant contained mostly 8*ii*. After workup with NH_4OH, chromatography, and recrystallization, pure 8*oo* was isolated in 27% yield. With commercial Et_2O solutions of $ZnCl_2$, the isolated yield dropped to 9%. A much better product distribution, containing *ca.* 70% 8*oo*, was obtained by using a homemade THF solution of $ZnCl_2$, prepared by refluxing commercial anhydrous $ZnCl_2$ in dry THF and filtering off the residue from the cloudy, yellowish supernatant. However, the concentration and purity of this reagent were too uncertain to ensure reproducible results.

In analogy with the $ZnCl_2$-mediated syntheses of the bidentates reported in the accompanying paper, where *N,O* chelation was evident, the $ZnCl_2$ in these reactions can serve as a template to deliver the hydrazine or to enhance the electrophilicity of the inner carbonyls of 4 *via* chelation centered at the pyridine (as drawn), as opposed to ionization of the β-diketone groupings. Since the mixtures of $ZnCl_2$ and 4 were homogeneous in this case, the weak complexation was presumably enhanced by the excess $ZnCl_2$. Given the significant amounts of *in,out* material produced, the chelation may not have been tripodal. Other roles for the metal cannot be excluded.

The regiochemistry of 8*oo* could be established by a solubilization of NaPic in $CDCl_3$ to give a yellow solution, as before, but pronounced broadening of the crowded aromatic region precluded its detailed analysis. Instead, a drop of CF_3COOD to a $CDCl_3$ solution of 8*oo* produced a similar shielding effect, presumably by virtue of a stabilization of the *in*-protonated *syn,syn* form through H-bonding: all the signals were shifted downfield except the pyridine H-3/5 doublet, which remained at roughly the same position and found itself upfield of the H-4 triplet. A control experiment with the *in,in* isomer produced downfield shifts for all signals, with the H-3 doublet remaining downfield of the H-4 triplet. It was noteworthy that 8*oo*, like 6*oo*, was the least mobile of the three isomers on silica gel, presumably because of a higher basicity resulting from the same stabilization of the protonated form.

Unfortunately, the similar use of $ZnCl_2$ in condensations with the other hydrazines was less satisfactory: No improvement in the proportion of 6*oo* was obtained for reasons that remain unclear. From $^tBuNHNH_2$, no 7*oo* was formed, but pure 7*io* could be isolated from its uncharacterized but insoluble Zn complex, while the mother liquor contained mostly *in,in* product. The mixture of isomers of 9 formed from 4-hydrazinobenzoic acid under these conditions, after workup with disodium EDTA, could not be properly analyzed by NMR owing to severe signal overlap, nor could the mixture be chromatographically separated nor recrystallized.

The benzoic acid derivative 11*oo* was obtained from 5 by nucleophilic aromatic substitution at high temperature with ethyl 4-fluorobenzoate[7] (4 equiv/Na_2CO_3/DMSO/150 °C/48 h) in 31% isolated yield, and this was accompanied by traces of unsubstituted material and some *mono-out*-substituted material 12 (20% isolated yield), which is an interesting tridentate ligand in its own right. The configuration of 11*oo* was indicated by the ^1H-NMR spectrum and was demonstrated by treatment with CF_3COOD, as before. The spectrum of the asymmetric 12 included two pyridine doublets, one at a downfield position, as with 11*oo*, and one at an upfield position, as with 5. The latter signal was attributed to a *syn* conformation of the bond from the pyridine to the unsubstituted pyrazole, enforced by hydrogen bonding between the pyridine N and the *in*-positioned pyrazole N–H, as drawn, a situation entirely analogous to that previously found with 5.[4]

In this reaction, the second step appeared to be much slower than the first. Using only 3 equiv of the electrophile produced the same yields in a slower reaction, while the use of NaH in refluxing THF or of metallic K in hot diglyme[1] produced no detectable disubstitution. Some decomposition of the 4-fluorobenzoate accompanied these reactions, as did ester hydrolyses, but there was no sign of *in* substitution. Again, a transient chelation of Na^+ was probably responsible. The more soluble Li_2CO_3 could also be used but without much improvement in yield. To test whether chelation was important in directing the regiochemistry in this reaction, we attempted the same reactions with Et_3N and DBU as bases. Both cases produced many side-products and it was unclear whether any substitution had occured, let alone with what regiochemistry.

Thus, the ^1H-NMR patterns in the pyridine region and the results of a treatment with NaPic or CF_3COOD served as reliable indicators of regiochemisty. An exception to this pattern was the bis(tetramethylammonium) disalt 13*oo*, obtained by hydrolysis of 10*oo* with Me_4NOH. In this case, the pyridine H-3/5 doublet lay upfield of the H-4 triplet, normally indicative of *in* substitution. Possible explanations include the presence of new shielding effects or the enforcement of a *syn,syn* conformation through ionic interactions.

The hydrolyses of the 11*oo* and 12 and their use in forming Ru^{II} complexes will be reported elsewhere.

Experimental Section

All the solvents used were reagent grade and used without drying or purification, except for THF, which was distilled over K and benzophenone, and DMSO, which was distilled over molecular sieves (5 Å). Phenylhydrazine was distilled prior to use. The petroleum ether (PE) used was the light fraction (bp 30–60 °C). The diphenyl ester 3 was prepared in 89% isolated yield using a slight modification of the procedure described by Rasshofer *et al.*[5] with Et_3N in CH_2Cl_2 replacing pyridine as solvent: mp 175 °C (lit.[5] 175 °C); ^1H-NMR: 7.30 (m, 6H), 7.45 (m, 4H), 8.15 (t, 1H, J = 7.8 Hz), 8.50 (d, 2H, J = 7.9 Hz) ppm; ^{13}C-NMR: 121.60, 126.25, 128.91, 129.53, 138.57, 148.20, 150.84, 163.16 ppm. The melting points are not corrected. NMR spectra were obtained on a 300-MHz instrument in $CDCl_3$, unless otherwise indicated. For detailed listings with assignments and spectra in the presence of NaPic or CF_3COOD, see the supplementary material. Mass spectrometry was carried out by Dr. B. Khouw. The microanalyses were performed by Canadian Microanalytical Services, Burnaby, B.C., Guelph Chemical Laboratories Ltd., Guelph, Ont., or Galbraith Laboratories, Knoxville, TN. Molecular modeling was performed using PC-MODEL version 4 (Serena Software, Bloomington, IN).

2,6-Bis[(2-oxocyclohexanyl)carbonyl]pyridine (4). A mixture of cyclohexanone (24.8 mL, 240 mmol), NaH (10.5 g, 438 mmol), and diester 3 (34.8 g, 109 mmol) in dry THF (500 mL) was refluxed for 18 h under Ar. The reaction mixture was allowed to cool to room temperature and the yellow/grey disalt was filtered off. This was then added to a stirring solution of ice cold 1.0 M HOAc (300 mL). After 1 h the crude product was extracted into CH_2Cl_2. Some highly polar side-products were removed from

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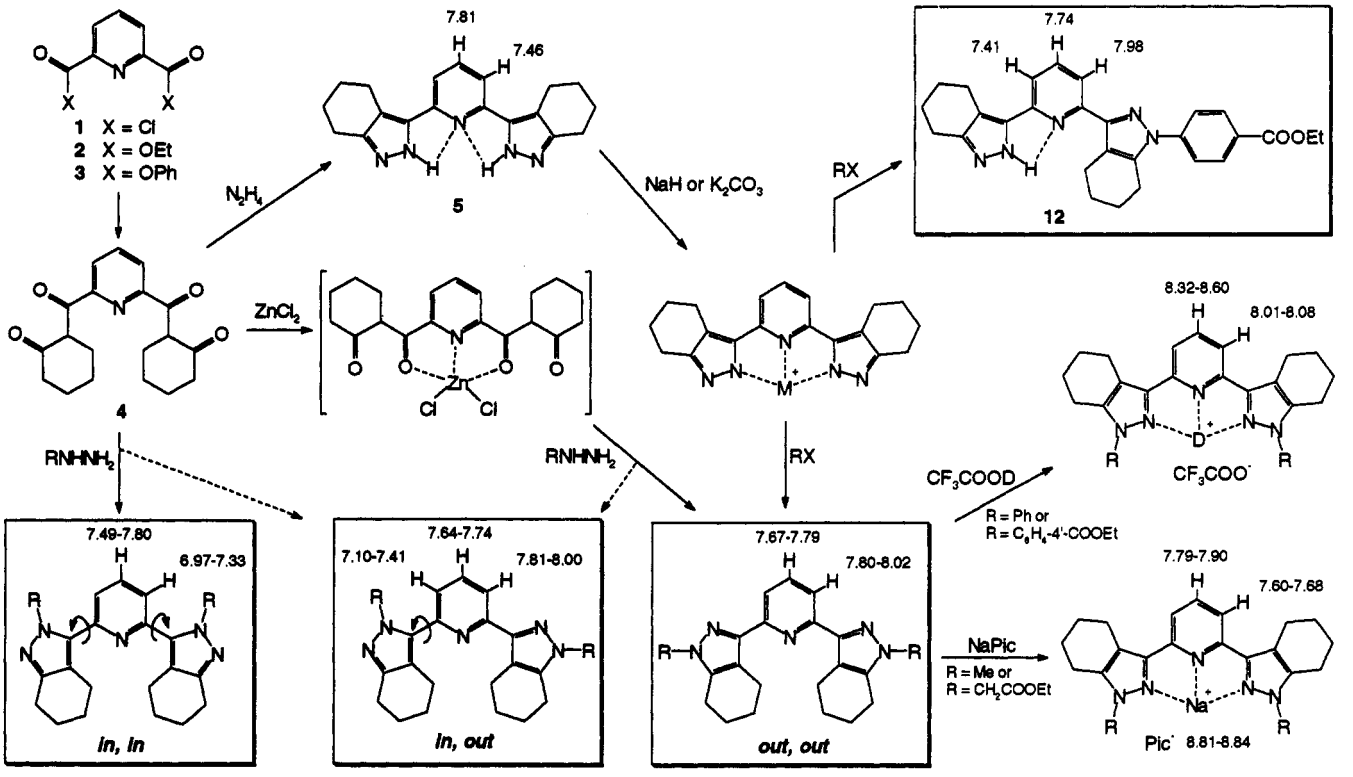
Scheme 1



6 R = Me 7 R = t-Bu 8 R = Ph 9 R = C_6H_4-4'-COOH 10 R = CH_2COOEt 11 R = C_6H_4-4'-COOEt 13 R = $CH_2COO^- Me_4N^+$

the extract using a short silica gel column and 30:70 EtOAc:PE as eluent. Recrystallization from Et_2O afforded 14.6 g (41%) of the tetraketone **4**. The spectra and melting point were identical to those already reported.[4]

2,6-Bis(1-methyl-4,5,6,7-tetrahydrobenzopyrazol-3-yl)pyridine (6*oo*). To a stirred suspension of NaH (0.038 g, 1.6 mmol) in dry THF (15 mL) was added 2,6-bis(1*H*-4,5,6,7-tetrahydrobenzopyrazol-3-yl)pyridine **5**[4] (0.210 g, 0.66 mmol) slowly. H_2 gas was immediately released and a white precipitate (the Na^+ disalt) formed. The mixture was kept under Ar and stirred for 2 h at room temperature and then treated with CH_3I (93 μL, 1.49 mmol). After stirring overnight, the solution was washed with H_2O and extracted with $CHCl_3$. The solvent was removed from the organic phase, and the remaining oil was purified by column chromatography on alumina using 30:70 EtOAc:PE as eluent. This afforded 0.138 g of 6*oo* (60%): mp 213 °C; ^{1}H-NMR δ 1.75 (m, 4H), 1.87 (m, 4H), 2.61 (m, 4H), 2.95 (m, 4H), 3.80 (s, 6H), 7.69 (t, A portion of AB_2 system, 1H, J_{AB} = 7.9 Hz), 7.80 (d, B portion of AB_2 system, 2H), ppm; ^{13}C-NMR δ 21.69, 22.50, 22.90, 23.25, 35.72, 115.71, 118.94, 136.52, 139.78, 147.16, 153.19 ppm; MS: *m/z* (%) 347 ($M^{\cdot+}$, 100), 332 (8, $M^{\cdot+} - CH_3$), 174 (10), 149 (13), 135 (10), 109 (12), 83 (30). Anal. Calcd for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.19; H, 7.04; N, 19.95.

2-(1-Methyl-4,5,6,7-tetrahydrobenzopyrazol-3-yl)-6-(2-methyl-4,5,6,7-tetrahydrobenzopyrazol-3-yl)pyridine (6*io*). To a solution of tetraketone **4** (0.436 g, 1.33 mmol) in $CHCl_3$ (30 mL) was added methylhydrazine (156 μL, 2.96 mmol), and the reaction was left stirring overnight under Ar. After removal of the solvent, the desired regioisomer was obtained by column chromatography on alumina using 30:70 benzene:$CHCl_3$ as eluent. The early fractions were collected and stripped of solvent. Crystallization of the yellow oil over 3 weeks from Et_2O gave 0.208 g (45%) of white crystals of 6*io*, mp 125–128 °C. Later fractions contained an inseparable mixture of *in,in* and *out,out* isomers: ^{1}H-NMR for 6*io* δ 1.64 (m, 4H), 1.75 (m, 4H), 2.59 (m, 4H), 2.64 (m, 2H), 2.82 (m, 2H), 3.70 (s, 3H), 4.00 (s, 3H), 7.14 (d, 1H, *J* = 7.6 Hz), 7.64 (t, 1H, *J* = 7.8 Hz), 7.81 (d, 1H, *J* = 7.9 Hz) ppm; ^{13}C-NMR δ 21.60, 22.08, 22.35, 22.87, 23.07, 23.26, 23.32, 23.60, 35.72, 38.26, 115.40, 115.88, 118.91, 121.49, 136.44, 138.16, 140.04, 146.36, 147.73, 149.02, 154.03 ppm; MS *m/z* (%) 347 (100, $M^{\cdot+}$), 332 (79, $M^{\cdot+} - CH_3$), 318 (76, $M^{\cdot+} - H - C_2H_4$), 304 (63, $M^{\cdot+} - H - C_3H_6$), 279 (50, $M^{\cdot+} - C_3H_6CN$), 174 (80), 153 (67), 135 (55), 84 (55), 51 (65). Anal. Calcd for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N,20.16. Found: C, 72.14; H, 7.16; N, 20.31.

2-[1-(1,1-Dimethylethyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl]-6-[2-(1,1-dimethylethyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl)pyridine (7*io*) and 2,6-Bis[2-(1,1-dimethylethyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl]pyridine (7*ii*). A mixture of *tert*-butylhydrazine hydrochloride (0.268 g, 2.15 mmol), Et_3N (0.300 mL, 2.15 mmol), and tetraketone **4** (0.320 g, 0.98 mmol) in $CHCl_3$ (50 mL) was allowed to stir overnight at room temperature. The solution was washed with H_2O to remove the $Et_3NH^+Cl^-$. Further purification was carried out by column chromatography on silica gel using 80:20 EtOAc:PE as eluent. The first fractions contained 7*io* which, after recrystallization from MeOH, afforded 0.046 g of white crystals (11%): mp 186–189 °C; ^{1}H-NMR δ 1.50 (s, 9H), 1.66 (s, 9H), 1.69 (m, 4H), 1.81 (m, 4H), 2.23 (m, 2H), 2.74 (m, 2H), 2.87 (m, 4H), 7.10 (d, 1H, J = 7.8 Hz), 7.68 (t, 1H, *J* = 7.8 Hz), 8.00 (d, 1H, *J* = 7.8 Hz) ppm; ^{13}C-NMR δ 20.54, 22.81, 23.18, 23.26, 23.39, 23.47, 23.55, 25.54, 29.92, 31.00, 59.84, 60.49, 116.88, 117.49, 119.69, 123.03, 135.94, 138.88, 139.01, 144.40, 145.74, 152.35, 154.50 ppm; MS *m/z* (%) 431 (37, $M^{\cdot+}$), 374 (58, $M^{\cdot+} - {}^t$Bu), 318 (100, $M^{\cdot+} + H - 2^t$Bu), 173 (17), 56 (19, ^{t}Bu). Anal. Calcd for $C_{27}H_{37}N_5$: C, 75.13; H, 8.64; N, 16.23. Found: C, 75.33; H, 8.45; N, 16.27.

Later fractions contained 7*ii*. Recrystallization from PE/EtOAc afforded 0.203 g of white crystals (48%): mp 215–219 °C; ^{1}H-NMR δ 1.45 (s, 18 H), 1.69 (m, 4H), 1.80 (m, 4H), 2.23 (m, 4H), 2.23 (m, 4H), 7.33 (d, 2H, *J* = 7.8 Hz), 7.79 (t, 1H, *J* = 7.8 Hz) ppm; ^{13}C-NMR δ 20.44, 23.32, 23.38, 23.48, 31.07, 60.48, 117.25, 124.76, 136.15, 137.62, 145.95, 153.70 ppm; MS *m/z* (%) 431 ($M^{\cdot+}$, 16), 374 (36, $M^{\cdot+} - {}^t$Bu), 318 (100, $M^{\cdot+} + H - 2^t$Bu). Anal. Calcd for $C_{27}H_{37}N_5$: C, 75.13; H, 8.64; N, 16.23. Found: C, 75.50; H, 9.00; N, 16.59.

2-(1-Phenyl-4,5,6,7-tetrahydrobenzopyrazol-3-yl)-6-(2-phenyl-4,5,6,7-tetrahydrobenzopyrazol-3-yl)pyridine (8*io*) and 2,6-Bis(2-phenyl-4,5,6,7-tetrahydrobenzopyrazol-3-yl)-pyridine (8*ii*). Following the procedure described above for *in,out* **6**, tetraketone **4** (0.270 g, 0.825 mmol) was treated with phenylhydrazine (178 μL, 1.82 mmol). Chromatography was carried out on silica gel using 40:60 EtOAc:PE as eluent. The first fractions contained 8*io* which, after recrystallization from Et_2O, afforded 0.070 g (18%) of yellow/white crystals: mp 229–232 °C; ^{1}H-NMR δ 1.57 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 1.91

(m, 2H), 2.69 (m, 4H), 2.83 (m, 2H), 7.25 (m, 7H), 7.48 (m, 4H), 7.69 (t, 1H, J = 7.7 Hz), 8.01 (d, 1H, J = 7.4 Hz) ppm; ^{13}C-NMR δ 21.76, 22.76, 22.81, 23.26, 23.45, 23.54, 23.93, 118.14, 118.26, 119.50, 122.25, 123.37, 124.59, 126.28, 126.89, 128.62, 129.04, 136.37, 138.00, 139.88, 139.95, 141.02, 148.08, 149.17, 150.26, 154.06 ppm; MS m/z (%) 471 (100, M·$^+$), 470 (20), 442 (20), 403 (17), 236 (18), 77 (19). Anal. Calcd for $C_{31}H_{29}N_5$: C, 78.95; H, 6.20; N, 14.85. Found: C, 78.36; H, 6.26; N, 14.71.

Subsequent fractions contained 8*ii*. Recrystallization from Et_2O afforded 0.187 g (48%) of pale orange crystals: mp 166–169 °C; ^{1}H-NMR δ 1.67 (m, 4H), 1.83 (m, 4H), 2.29 (m, 4H), 2.77 (m, 4H), 6.97 (d, 2H, J = 7.9 Hz), 7.27 (m, 10H), 7.49 (t, 1H, J = 7.9 Hz) ppm; ^{13}C-NMR δ 20.89, 23.14, 23.25, 23.48, 118.95, 122.71, 124.89, 126.82, 128.90, 136.02, 137.24, 140.70, 150.44, 150.50 ppm; MS m/z (%) 471 (M·$^+$, 100), 442 (19), 403 (17), 236 (18), 77 (37). Anal. Calcd for $C_{31}H_{29}N_5$: C, 78.95; H, 6.20; N, 14.85. Found: C, 79.22; H, 6.39; N, 14.79.

2,6-Bis(1-phenyl-4,5,6,7-tetrahydrobenzopyrazol-3-yl)pyridine (8*oo*). To a mixture of the tetraketone 4 (0.729 g, 2.23 mmol) and $ZnCl_2$ (44.5 mL, 0.5 M in THF) in $CHCl_3$ (100 mL) was added phenylhydrazine (0.482 mL, 4.90 mmol) and the resulting mixture was stirred overnight. After removal of the solvent under reduced pressure, H_2O was added followed by a 20-fold excess of concentrated NH_4OH and the metal-free mixture was extracted with CH_2Cl_2. Purification was carried out by column chromatography using alumina and CH_3CN as eluent. A 1:6 mixture of the *in,in* and *in,out* isomers of 8 eluted first (0.515 g, 49% yield). The desired 8*oo* subsequently eluted using 99:1 CH_3CN:NH_4OH as eluent. The appropriate fractions were combined, washed with H_2O, and extracted into CH_2Cl_2. Recrystallization from EtOAc/PE afforded 0.284 g (27%) of white crystals: mp 191 °C; ^{1}H-NMR δ 1.86 (m, 8H), 2.79 (m, 4H), 3.09 (m, 4H), 7.34 (t, 2H, J = 7.3 Hz), 7.47 (t, 4H, J = 7.5 Hz), 7.59 (d, 4H, J = 7.7 Hz), 7.75 (t, 1H, J = 7.8 Hz), 8.00 (d, 2H, J = 7.8 Hz) ppm; ^{13}C-NMR δ 22.88, 23.10, 24.00, 117.47, 120.00, 123.49, 126.87, 129.06, 136.78, 139.88, 140.08, 152.96 ppm; MS m/z (%) 471 (M·$^+$, 60), 236 (33), 212 (87), 184 (61), 111 (36), 97 (70), 83 (76), 69 (85), 55 (91), 43 (100). Anal. Calcd for $C_{31}H_{29}N_5$: C, 78.95; H, 6.20; N, 14.85. Found: C, 78.68; H, 6.17; N, 14.80.

2,6-Bis[2-(4-carboxyphenyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl]pyridine (9*ii*). A mixture of tetraketone 4 (0.097 g, 0.30 mmol) and 4-hydrazinobenzoic acid (0.099 g, 0.65 mmol) in dry THF (10 mL) was allowed to reflux for 7 days under Ar. The white precipitate that formed during the reaction was filtered off to afford 0.082 g (47%) of 9*ii*: mp 216 °C; ^{1}H-NMR (DMSO-d_6) δ 1.55 (m, 4H), 1.72 (m, 4H), 2.15 (m, 4H), 2.63 (m, 4H), 7.22 (m, 6H), 7.80 (t, 1H, J = 7.8 Hz), 7.89 (d, 4H, J = 8.1 Hz) ppm.; ^{13}C-NMR (DMSO-d_6) δ 20.18, 22.53, 22.88, 118.86, 123.27, 123.87, 128.61, 130.15, 137.05, 137.39, 143.58, 149.41, 150.18, 166.56 ppm; MS m/z (%) 559 (M·$^+$, 6), 378 (4), 167 (29), 89 (51), 71 (40), 45 (100). Anal. Calcd for $C_{33}H_{29}N_5O_4 \cdot H_2O$: C, 68.62; H, 5.41; N, 12.12. Found: C, 68.48; H, 5.54; N, 11.91.

Recrystallization from EtOH produced the THF-insoluble hemisolvate (confirmed by NMR): mp > 300 °C. Anal. Calcd for $C_{33}H_{29}N_5O_4 \cdot {}^1/_2$EtOH: C, 70.09; H, 5.53; N, 12.02. Found: C, 69.90; H, 5.78; N, 11.79.

2,6-Bis[1-(carboxymethyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl]pyridine Diethyl Ester (10*oo*). Following the procedure for 6*oo*, bis-pyrazole 5 (0.187 g, 0.59 mmol) was treated with NaH (0.032 g, 1.33 mmol) and ethyl bromoacetate (148 μL, 1.30 mmol) and this was worked up as before. Recrystallization from MeOH yielded 0.206 g (71%) of white crystals: mp 135 °C; ^{1}H-NMR δ 1.29 (t, 6H), 1.77 (m, 4H), 1.88 (m, 4H), 2.57 (m, 4H), 2.97 (m, 4H), 4.23 (q, 4H), 4.85 (s, 4H), 7.67 (t, 1H, J = 7.8 Hz), 7.81 (d, 2H, J = 7.8 Hz) ppm; ^{13}C-NMR δ 14.12, 21.47, 22.32, 22.81, 23.10, 50.54, 61.66, 116.31, 119.47, 136.37, 140.47, 148.33, 152.98, 167.93 ppm; MS m/z (%) 492 (M·$^+$, 70), 418 (14, M·$^+$ – H – COOEt), 252 (53), 235 (30), 140 (92), 123 (100).

2,6-Bis[1-(4-carboxyphenyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl]pyridine Diethyl Ester (11*oo*) and 2-(1*H*-4,5,6,7-tetrahydrobenzopyrazol-3-yl)-6-[1-(4-carboxyphenyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl]pyridine Ethyl Ester (12). A mixture of 5 (212 mg, 0.67 mmol), ethyl 4-fluorobenzoate (0.448 g, 2.66 mmol), and Na_2CO_3 (0.282 g, 2.66 mmol) in dry DMSO was stirred for 48 h at 150 °C. After removal of the solvent, the crude product was taken up in $CHCl_3$ and washed with H_2O. Further purification was carried out by column chromatography on alumina using $CHCl_3$ as eluent. The first fractions contained the desired diester 11*oo*. Recrystallization from EtOAc yielded 0.127 g of a white powder (31%): mp 223–227 °C; ^{1}H-NMR δ 1.42 (t, 6H), 1.88 (m, 8H), 2.86 (m, 4H), 3.07 (m, 4H), 4.41 (q, 4H), 7.71 (d, 4H, J = 8.7 Hz), 7.79 (t, 1H, J = 7.7 Hz), 8.02 (d, 2H, J = 7.8 Hz), 8.15 (d, 4H, J = 8.7 Hz) ppm; ^{13}C-NMR δ 14.33, 22.94, 23.07, 24.55, 61.08, 118.52, 120.33, 122.22, 128.34, 130.64, 136.60, 140.03, 143.70, 149.96, 152.94, 165.99 ppm; MS m/z (%) 615 (M·$^+$, 100), 570 (10), 495 (14), 308 (15), 269 (18), 97 (33), 83 (38), 55 (54). Anal. Calcd for $C_{37}H_{37}N_5O_4$: C, 72.18; H, 6.06; N, 11.37. Found: C, 72.00; H, 6.11; N, 11.07.

Later fractions contained the monoester 12 (63 mg, 20%): mp 195–197 °C; ^{1}H-NMR δ 1.38 (t, 3H), 1.83 (m, 8H), 2.58 (m, 2H), 2.77 (m, 4H), 3.05 (m, 2H), 4.36 (q, 4H), 7.41 (d, 1H, J = 7.8 Hz), 7.67 (d, 4H, J = 8.7 Hz), 7.74 (t, 1H, J = 7.8 Hz), 7.98 (d, 1H, J = 7.8 Hz), 8.11 (d, 4H, J = 8.7 Hz) ppm; ^{13}C-NMR δ 14.32, 22.40, 22.92, 23.06, 23.48, 24.52, 61.08, 118.25, 118.48, 120.30, 122.20, 122.32, 130.62, 136.53, 137.09, 140.01, 140.49, 143.67, 152.94, 165.99 ppm; MS m/z (%) 467 (M·$^+$, 96), 347 (100), 318 (82), 197 (32), 97 (75), 69 (80), 55 (85).

2,6-Bis[1-(carboxymethyl)-4,5,6,7-tetrahydrobenzopyrazol-3-yl]pyridine Bis(tetramethylammonium) Salt (13*oo*). A mixture of 10*oo* (0.271 g, 0.552 mmol) and $Me_4NOH \cdot 5H_2O$ (0.220 g, 1.15 mmol) in EtOH (20 mL) was refluxed for 3 h. Removal of the solvent under reduced pressure and subsequent recrystallization of the remaining oil from $CHCl_3$ yielded 0.240 g of white, hygroscopic, needle-like crystals (66%): mp 192–196 °C; ^{1}H-NMR δ 1.74 (m, 4H), 1.82 (m, 4H), 2.65 (m, 4H), 2.72 (m, 4H), 3.24 (s, 24H), 4.67 (s, 4H), 7.48 (d, 2H, J = 7.8 Hz), 7.70 (t, 1H, J = 7.8 Hz) ppm; ^{13}C-NMR δ 21.16, 22.09, 22.48, 22.94, 52.79, 55.12, 114.87, 119.26, 136.47, 140.69, 146.35, 153.00, 172.43 ppm; MS: m/z (%) 463 (dimethyl ester, 75), 404 (42, dimethyl ester – $COOCH_3$), 386 (78), 236 (47), 43 (100). Anal. Calcd for $C_{31}H_{47}N_7O_4 \cdot 4H_2O$: C, 56.95; H, 8.48; N, 15.00, Found: C, 57.31; H, 8.54; N, 15.04.

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Supplementary Material Available: NMR peak listings with assignments for all new compounds, including spectra in the presence of NaPic or CF_3COOD (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.