Tröger's Base. An Alternate Synthesis and a Structural Analog with Thromboxane A_2 Synthetase Inhibitory Activity

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The synthesis of 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (Tröger's base) from *p*-toluidine and of two Tröger's base analogs from other anilines by reaction with hexamethylenetetramine in trifluoroacetic acid is described. 2,3,6,7-Tetrahydro-9-methyl-2,6-di-*p*-tolyl-1*H*,5*H*-pyrimido[5,6,1-*ij*]quinazoline is formed as a secondary product in the reaction of *p*-toluidine and hexamethylenetetramine. One of the Tröger's base analogs, 2,8-bis(3'-pyridylmethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**5**), is an effective inhibitor of the enzyme, thromboxane A_2 (TxA_2) synthase, with an ED_{50} of 30 ng/mL in a specified *in vitro* assay. Three analogs having substituents on the bridging methylene group of the bicyclic nucleus of the Tröger's base structure were prepared, but all were considerably less active than the aforementioned compound in the inhibition assay. The structures of these inhibitors of TxA_2 synthase fall outside the classical structure–activity relationship that has been established for this class of enzyme inhibitors.

Introduction

Tröger's base (**1**) was first isolated in 1887[1] and was structurally characterized in 1935[2] as the product of reaction between *p*-toluidine (**2**) and formaldehyde in an acidic aqueous solution. During our work aimed at the development of a thromboxane A_2 (TxA_2) synthetase inhibitor,[3,4] we performed an experiment in which hexamethylenetetramine **3** and the substituted aniline **4** were allowed to react in a trifluoroacetic acid solution. The reaction produced a new crystalline compound **5** (67% yield) which, upon interpretation of the analytical data, was identified as an analog of Tröger's base. Two reasons lead us to present a brief account of our results in this paper. First, we wish to bring broader attention to this alternate method for the synthesis of Tröger's base structures[5] and, second, we wish to report the TxA_2 synthetase inhibitory activity of **5**, a compound whose structural features fall outside the structure–activity correlations found for most TxA_2 synthetase inhibitors.

Results and Discussion

Chemistry. In our synthesis of the TxA_2 synthetase inhibitor, sodium furegrelate,[3,4] the formylation of a phenol in the ortho position was achieved[4] with the use of hexamethylenetetramine in trifluoroacetic acid—a modification[6] of the Duff reaction.[7] Having the aniline **4** readily available, we naively submitted it to the same conditions used to formylate the aforementioned phenol and were pleased to obtain a new crystalline compound in 67% yield. The high-resolution mass spectrum of the new compound indicated an empirical formula of $C_{27}H_{24}N_4$, which is the sum of two molecules of **4** ($C_{12}H_{12}N_2$ each) and three carbon atoms. The ^1H NMR spectrum of the compound indicated the presence of two new methylene groups in addition to the benzylic methylene groups derived from **4**. The bicyclic structure **5** fulfilled the requirements of this analytical data and, with reference to the chemical literature, is an analog of Tröger's base (**1**). The conditions under which we had obtained **5** bear resemblence to those of the classical Tröger's base synthesis since hexamethylenetetramine (**3**) is known to be a convenient source of methylenamine (CH_2=NH) under acid catalysis,[8] provided in our case by the trifluoroacetic acid, and therefore can be envisioned as playing a role similar to that of formaldehyde as a source of the new methylene groups in **5**.

Of further interest was the fact that compound **5** was a potent inhibitor of the enzyme TxA_2 synthetase (see the following section). We therefore sought to obtain additional analogs of this structural type. When the closely related aniline **6** was allowed to react with hexamethylenetetramine in trifluoroacetic acid, the Tröger's base analog **7** was obtained but in much lower yield (26%) than for **5**. The formation of **7** was accompanied by a second crystalline substance of undetermined structure.

Another route which we used to obtain analogs of **5** was based on literature precedent and is illustrated in Scheme I by structures **8**–**12**. Reaction of **5** with nitrous acid produces the bis-*N*-nitrosoamine **8** which, in turn, is reduced to the bisamine **9** with cuprous chloride in a mixture of aqueous HCl and acetic acid.[9] Bisamine **9** is converted into analogs **10**–**12** by condensation with the appropriate ketone or aldehyde. As described in the following section, the four analogs (**7**, **10**–**12**) of **5**, as well as intermediate **9**, showed either reduced or no ability to inhibit the TxA_2 synthetase assay. For this reason and because of other intervening activities, we did not pursue further this potential class of TxA_2 synthetase inhibitors.

However, we have examined one additional question of chemistry and that is whether, and to what extent, Tröger's base (**1**) itself will be produced by our alternate reaction conditions, *i.e.*, hexamethylenetetramine in trifluoroacetic acid. When *p*-toluidine (**2**) and hexamethylenetetramine (**3**) were allowed to react in essentially the same 1:1 molar ratio of reactants used for the preparation of **5**, two major products and several minor products were detected by thin-layer chromatography of the reaction mixture. One of the major products crystallized directly from the crude reaction mixture but was more efficiently isolated by column chromatography. Chromatography of the reaction mixture gave the two major components in 26% and 41% yield which, after recrystallization, exhibited melting points of 145–147 °C and 137–138 °C, respectively. The melting point of the second of these two products together with its spectral properties (see the Experimental Section)

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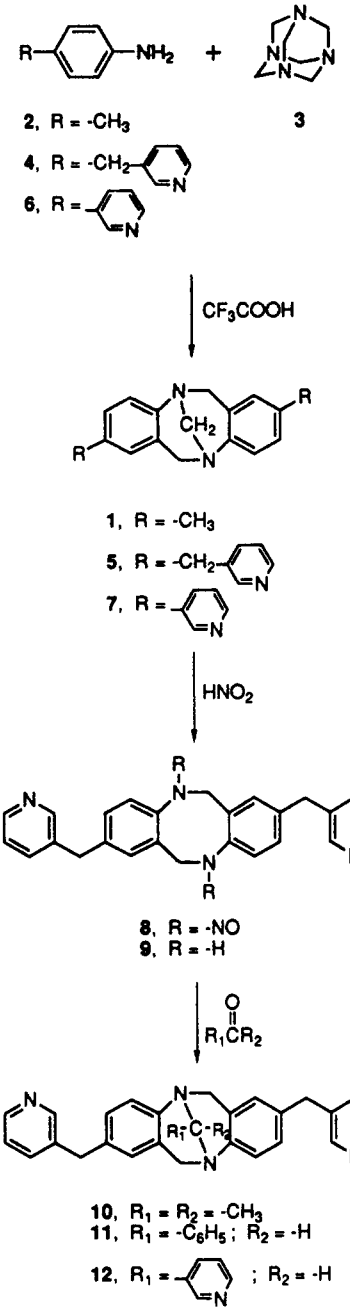
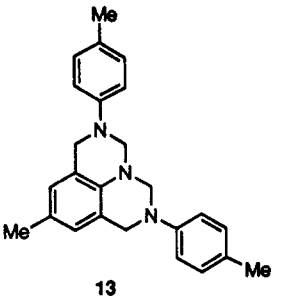
Scheme I



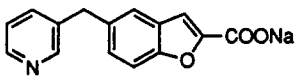
characterize it as Tröger's base, **1**. The empirical formula of the compound, mp 145–147 °C, was found from the mass spectrum and elemental analysis to be $C_{25}H_{27}N_3$. The ratio of signals in the ^1H NMR spectrum of this compound was as follows: aromatic, 4:4:2; $-CH_2-$, 4:4; and $-CH_3$, 6:3 (the two methylene signals coincidently fall at the same chemical shift in $CDCl_3$ but have different chemical shifts when the spectrum is run in C_6D_6). From this data, we postulated structure **13** for this compound. A search of the *Chemical Abstracts* formula indices revealed that a compound isolated in low yield (3%) from a large-scale classical Tröger's base synthesis has been assigned this structure and is reported to have mp 148 °C.[10] We conclude that our compound, mp 145–147 °C, has structure **13**. Although we have not carried out an extensive study of the effect that changing reaction conditions may have upon the ratio of **1** and **13**, we have observed that by changing the molar ratio of reactants **2** and **3** to 4:1 and keeping the reaction mixture cooled during



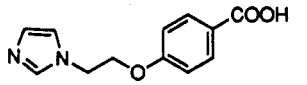
13

the initial phase, the ratio and yield of **1** and **13** is improved to 73% vs 13%. We also have found that compound **13** is stable when stirred at room temperature in a solution of trifluoroacetic acid containing hexamethylenetetramine.

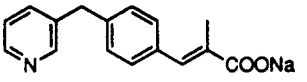
Pharmacology. The rationale for studying the inhibition of TxA_2 synthetase and the experimental details of our *in vitro* screen used to evaluate potential inhibitors of this enzyme have been described in our previous reports.[3,4] Briefly, microsomal enzyme from human platelets was incubated with the potential inhibitor for 5 min before adding the enzyme substrate, prostaglandin H_2 (PGH_2). Thirty seconds after addition of PGH_2, the incubation mixture was passed over rabbit aorta strips and the response of the strip taken as a measure of TxA_2 concentration. In this way, the ED_{50} values summarized in Table I were obtained for the compounds described in this paper. For comparison, the ED_{50} values for sodium furegrelate[4], dazoxiben,[11] and OKY-1581[12] are included in Table I. These three compounds are among a number of TxA_2 synthase inhibitors that have been extensively studied. The results in Table I show that the Tröger's base analog **5** is as potent an inhibitor of this assay system as are several of these benchmark inhibitors. The results also show that all of the structural analogs of **5** that we examined exhibited a considerable loss of potency.



sodium furegrelate



dazoxiben



OKY-1581

The majority of TxA_2 synthetase inhibitors are found to have the characteristics of the following structure–activity relationship:[13] (a) a pyridine or imidazole ring which interacts with a cytochrome P-450 of the enzyme, (b) substitution in the 3-position of the pyridine or the 1-position of the imidazole with a side chain terminating in a carboxylic acid, and (c) an optimum distance of 8.5–10 Å between the heterocyclic nitrogen atom and the carboxyl group. Compound **5** clearly falls outside of this SAR pattern since it does not have a carboxylic acid function. We note that the moderately basic bridgehead nitrogen atoms of the central bicyclic ring system in **5**, in fact, are found at about the same distance from the pyridine

Table I. TxA_2 Synthetase Inhibition in Human Platelet Microsomes

compd	ED_{50},[a] ng/mL
5	30
7	>10000
9	3000
10	300
11	>10000
12	3000
Na furegrelate	10
dazoxiben	30
OKY-1581	30

[a] ED_{50} is the concentration causing a 50% reduction in the generation of TxA_2 as assayed on the rabbit aortic strip (see ref 3). Test accuracy for inhibition of TxA_2 synthesis will reflect statistically significant ($p < 0.05$) differences in potency when compounds differ in potency by $^1/_2$ log unit or more, ie. 10 ng/mL is different from 30 ng/mL; 30 ng/mL is different from 10 or 100 ng/mL. ED_{50} estimates are rounded to the nearest $^1/_2$ log dose in increment, e.g., 10, 30, 100, 300, 1000, and 3000 ng/mL. Therefore, small differences in potency (less than $^1/_2$ log unit), which may exist, will not be detected in this screen for activity.

nitrogen as is optimum for the carboxylic acid groups in the standard SAR. We wish to add compound **5** to the small list of structures which fall outside the normal SAR pattern.[13b,14]

Experimental Section

General Methods. Reactions were monitored by thin-layer chromatography (TLC) using plates purchased from Analtech, Inc. (silica gel GF, 250 μm in thickness, 1 in. × 4 in.) with solvent systems made up of mixtures of common laboratory solvents. The compounds were visualized on the plates with UV light and/or by spraying with a mixture of 5% HNO_3 in 1:1 H_2SO_4/H_2O followed by charring on a hot plate. Melting points were determined on a Fisher-Johns melting point apparatus. The ^1H NMR spectra were obtained with either a Bruker AM 300 (compounds 1, 13) or a Varian EM 390 (all other compounds) spectrometer.

2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (1, Tröger's Base) and 2,3,6,7-Tetrahydro-9-methyl-2,6-di-*p*-tolyl-1*H*,5*H*-pyrimido[5,6,1-*ij*]quinazoline (13). A. Conditions Similar to Those Used for Synthesis of 5. Trifluoroacetic acid (10 mL) was added to hexamethylenamine (2.80 g, 20 mmol) and *p*-toluidine (2.14 g, 20 mmol) in a 100-mL flask. The mixture became very warm and was partially cooled in an ice bath. The resulting red-orange solution was stirred for 30 min, and a sample was quenched in EtOAc–10% aqueous Na_2CO_3. The EtOAc solution was examined by TLC (silica gel, 30% EtOAc–hexane) which showed that the *p*-toluidine had completely reacted. The viscous solution was stirred at room temperature overnight, after which TLC revealed no qualitative change in the reaction mixture. The reaction mixture was diluted with EtOAc (50 mL), 10% aqueous Na_2CO_3 (100 mL) was added, and the two layers were thoroughly mixed. The organic layer was separated (the aqueous layer tested weakly alkaline to pH paper), and the aqueous layer was extracted with a second portion of EtOAc (25 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed over silica gel (gravity, 210 g) packed in 7.5% EtOAc in hexane. The residue was dissolved in a small volume of this solvent with the aid of a little CH_2Cl_2 and applied to the column, and the column was eluted (50-mL fractions) with 7.5% EtOAc–hexane (1.5 L), 10% EtOAc–hexane (1 L), 25% EtOAc–hexane (1 L), and 50% EtOAc–hexane. Fractions 31–45 were pooled to give a crystalline solid (0.644 g, 1.74 mmol, 26%). Recrystallization from EtOAc–hexane gave 0.582 g of yellow crystals, mp 140–145 °C. A second recrystallization gave very pale yellow crystals of **13**: mp 145–147 °C (lit.[10] mp 148 °C); ^1H NMR ($CDCl_3$, TMS) δ 6.98 (d, 4H, J = 8.3 Hz), 6.83 (d, 4H, J = 8.5 Hz), 6.68 (s, 2H), 4.46 (s, 8H), 2.25 (s, 6H), 2.20 (s, 3H), (C_6D_6, TMS) 6.93 (d, 4H, J = 8.7 Hz), 6.82 (d, 4H, J = 8.7 Hz), 6.42 (s, 2H), 4.27 (s, 4H), 4.09 (s, 4H), 2.16 (s, 6H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, TMS) δ 146.9, 129.3, 124.8, 119.9, 117.3, 64.7, 51.1, 20.3, 20.2; IR (mull) 1612, 1513, 1353, 1294, 1278, 1202, 1170, 1157, 1062, 1035, 860, 822 cm^{-1}; mass spectrum, 369 (45%), 354, 249 (100) *m/e*. Anal. ($C_{25}H_{27}N_3$) C, N, N.

Fractions 71–85 were pooled and gave **1** as a crystalline solid (1.023 g, 4.1 mmol, 41%). Recrystallization from EtOAc–hexane was inefficient (compare below where EtOH–H_2O was used), giving 0.445 g of **1**, ^1H NMR spectrum identical to that of the sample obtained below.

B. Modified Conditions. Hexamethylenetetramine (0.700 g, 5.0 mmol) and *p*-toluidine (2.14 g, 20 mmol) were placed with a stirring bar in a 100-mL flask, and the flask was immersed in an ice–water bath. Trifluoroacetic acid (10 mL) was added to the flask, and the mixture was stirred. (For larger scale reactions precooling of the CF_3COOH before addition to the reactants may be advisable.) The mixture was left stirring overnight as the bath slowly warmed to room temperature. TLC (30% EtOAc–hexane) suggested a trace of *p*-toluidine remained; additional hexamethylenetetramine (0.100 g) was added and stirring continued for 48 h; however this was unnecessary as there was no change in the TLC picture after this time. The reaction was worked up as described in part A, above, and the crude product mixture (3.15 g) was chromatographed in the same way. Fractions 28–50 were pooled and gave 0.330 g (0.89 mmol, 13%) of **13**. Recrystallization from EtOAc–hexane gave light yellow crystals (0.296 g) of **13**, mp 138–141 °C.

Fractions 71–87 were pooled and gave 1.83 g (7.32 mmol, 73%) of **1**. Recrystallization from EtOH–H_2O gave a first crop (1.475 g) and a second crop (0.132 g) of **1**. The first crop had a mp of 137–138 °C (lit.[2] mp 135–136 °C); ^1H NMR ($CDCl_3$, TMS) δ 7.02 (d, 2H, J = 8.1 Hz), 6.96 (d, 2H, J = 9.7 Hz), 6.70 (s, 2H), 4.64 (d, 2H, J = 16.6 Hz), 4.30 (d, 2H, J = 1.1 Hz), 4.10 (d, 2H, J = 16.7 Hz), 2.21 (s, 6H).

2,8-Bis(3′-pyridylmethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (5). A solution of 3-(4′-aminobenzyl)pyridine (1.84 g, 10 mmol) and hexamethylenetetramine (1.40 g, 10 mmol) in trifluoroacetic acid (30 mL) was stirred at room temperature for 1 h. The solution was warmed to 70 °C for 30 min, and after cooling, excess CF_3COOH was removed under reduced pressure, water was added, and the solution was made alkaline by the addition of solid Na_2CO_3. The alkaline mixture was extracted thoroughly with EtOAc, and the extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was crystalline, and a first crop of **5** (1.143 g of yellow crystals) was obtained by recrystallization from acetone–hexane. The filtrate was concentrated, and the residue was chromatographed over one Merck size B Lobar column (40–63-μm silica gel) using acetone for elution of the column and collecting fractions of 25-mL volume. Additional **5** (0.200 g, total 1.343 g, 3.33 mmol, 67%) was obtained as a yellow solid in fractions 38–52. Recrystallization from acetone preceded by decolorization of the solution with activated charcoal gave **5** as colorless crystals, mp 170–171 °C. A second crystallization from acetone gave colorless crystals: mp 171–172 °C; ^1H NMR ($CDCl_3$, TMS) δ 8.44 (m, 4H, pyridine C_2H and C_6H), 7.43 (m, 2H), 7.18 (m 2H), 7.05 (m, 2H), 6.96 (m, 2H), 6.69 (s, 2H), 4.63 (d, 2H, J_{gem} = 15.7 Hz), 4.27 (s, 2H, NCH_2N), 4.09 (d, 2H, J_{gem} = 16.8 Hz), 3.84 (s, 4H, $PyCH_2Ar$); ^{13}C NMR ($CDCl_3$, TMS) 150.17, 147.67, 146.47, 136.32, 135.47, 127.98, 127.83, 127.06, 125.31, 123.41, 66.82, 58.53, 38.52; mass spectrum, 404.1994 ($C_{27}H_{24}N_4$ requires 404.2001), no other major fragmentation peaks. Anal. ($C_{27}H_{24}N_4$): C, calcd 80.17; found, 79.75; H, N.

2,8-Di(3-pyridyl)-6*H*,12*H*-5,11-methanodibenzo)[*b*,*f*][1,5]diazocine (7). A solution of 3-(4-aminophenyl)pyridine (0.980 g, 5.75 mmol) and hexamethylenetetramine (0.807 g, 5.75 mmole) in trifluoroacetic acid (18 mL) was stirred at room temperature. TLC (acetone) analyses after 20 and 92 h were similar and indicated formation of two new, more polar materials. The excess CF_3COOH was removed, water (25 mL) was added, and the solution was made alkaline with solid Na_2CO_3 and was extracted with EtOAc (2x) and with CH_2Cl_2 (2x). The two separate extracts were dried ($MgSO_4$), filtered, and concentrated to give oils (0.810 g from EtOAc and 0.301 g from CH_2Cl_2) which when treated with acetone gave crystals. The crystals were collected together (0.160 g, R_f on TLC is the same as that of the more polar of the two new products), mp 175–225 °C, and the combined filtrates were chromatographed over silica gel (one Merck size B Lobar column,

acetone, 25-mL fractions). The less polar of the two new products was eluted in fractions 32–42 and after crystallization from acetone–hexane gave a first crop (0.245 g), mp 188–190 °C, and a second crop (0.028 g, total 0.273 g, 0.75 mmol, 26%) of **7**. Two recrystallizations from acetone–hexane gave colorless crystals of **7**: mp 188–190 °C; IR (mull) 1609, 1590, 1574, 1500, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ 8.75 (d, 2H, J = 2.2 Hz), 8.54 (m, 2H), 7.77 (dt, 2H, J = 2.0, 8.0 Hz), 7.41 (dd, 2H, J = 2.0, 8.3 Hz), 7.33–7.26 (m, 4H), 7.16 (d, 2H, J = 2.0 Hz), 4.82 (d, 2H, J_{gem} = 16.7 Hz), 4.40 (s, 2H), 4.31 (d, 2H, J_{gem} = 16.7 Hz); ^{13}C NMR ($CDCl_3$, TMS) 210.91, 148.26, 148.06, 136.06, 133.97, 133.67, 128.47, 126.29, 125.81, 125.66, 123.48, 66.95, 58.83; mass spectrum, 376.1688 ($C_{25}H_{30}N_4$ requires 376.1679), 375 m/e. Anal. ($C_{25}H_{30}N_4$) C, calcd: 79.76; found: 78.98; H, N.

2,8-Bis(3-pyridylmethyl)-5,11-dinitroso-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocine (8). A solution of $NaNO_2$ (8.8 g, 127 mmol) in H_2O (50 mL) was added dropwise over a period of 1 h to a stirred, cold (ice bath) solution of **5** (4.042 g, 10 mmol) in concentrated HCl (60 mL). The solution became orange in color, and a crystalline solid precipitated. The mixture was poured into ice and made alkaline by the careful addition of 50% aqueous NaOH; solids were broken up and mixed well with base. The aqueous mixture was extracted with CH_2Cl_2, and the extracts were dried ($MgSO_4$), filtered, and concentrated. The solid residue was dissolved in CH_2Cl_2, treated with activated charcoal, filtered, and crystallized from CH_2Cl_2–hexane. A first crop of **8** (3.309 g, 7.35 mmol), 73%) was obtained as a crystalline solid, mp 200–202 °C. Because this compound is a bisnitrosoamine, further handling for analytical work was avoided and the compound was used directly in the next step.

2,8-Bis(3-pyridylmethyl)-5,6,11,12-tetrahydrodibenzo[*b,f*]-[1,5]diazocine (9). A solution of cuprous chloride (2.20 g, 22 mmol) in concentrated aqueous HCl (12 mL) was added to a solution of **8** (3.309 g, 7.35 mmol) in glacial acetic acid (50 mL). A dark, thick precipitate formed. The mixture was warmed (5 min) on a steam bath, additional concentrated HCl (15 mL) was added, and the mixture was warmed another 10 min. TLC (10% CH_3OH in $CHCl_3$) of a sample quenched in aqueous Na_2CO_3–EtOAc showed a 1:1 ratio of starting material and a new product which was not changed by additional heating. More acidic CuCl (2.20 g in 10 mL) was added, some foaming was observed, and after 10 min of warming, TLC indicated that starting material was consumed. The mixture was poured onto ice, made alkaline by careful addition of aqueous NaOH, and extracted with CH_2Cl_2 (emulsion). The emulsion was filtered through Celite, and the filter pad and aqueous phase of the filtrate were further extracted with EtOAc. The organic extracts were dried ($MgSO_4$), filtered, and concentrated separately. From the CH_2Cl_2 extract there was obtained a crystalline solid which was recrystallized from CH_2Cl_2–hexane, giving 1.363 g of pale yellow crystals, mp 197–207 °C. A sample was dissolved in hot CH_3OH, treated with activated charcoal, filtered, and crystallized from a reduced volume of CH_3OH, giving colorless crystals of **9**: mp 228–229 °C; ^1H NMR ($CDCl_3$, TMS) 8.44 (m, 4H), 7.43 (m, 2H), 7.18 (m, 2H), 6.82 (d, 2H), 6.78 (m, 2H), 6.52 (d, 2H), 4.46 (s, 4H, $ArCH_2NH$), 3.83 (s, 4H, $PyCH_2Ar$); IR (mull) 3254, 3208, 3178, 1616, 1575, 1300, 1276 cm^{-1}. Anal. ($C_{26}H_{24}N_4$) C, calcd: 79.56; found: 78.99; H, N.

2,8-Bis(3-pyridylmethyl)-13,13-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (10). A solution of **9** (0.196 g, 0.50 mmol) in acetone (50 mL) was heated at reflux temperature for 6 h. The solvent was removed under reduced pressure, leaving a gummy residue (0.206 g). The residue was chromatographed over silica gel (10 g) packed as a slurry in acetone. The column was eluted with acetone (25-mL fractions), and the product **10** (0.187 g, 0.43 mmol, 86%) was eluted in fractions 6–19 as a viscous gum: ^1H NMR ($CDCl_3$, TMS) δ 8.44 (m, 4H, Py C_2 and C_6 protons), 7.40 (d, 2H, Py C_4 proton), 6.52–7.23 (m, 8H, aromatic), 4.65 (d, 2H, J = 16 Hz, NCH_{ax}), 4.06 (d, 2H, J = 16 Hz, NCH_{eq}), 3.78 (s, 4H, $ArCH_2Py$), 1.39 (s, 6H, CH_3); mass spectrum, 432.2322 (100, $C_{29}H_{28}N_4$ requires 432.2314), 417 (51), 389 (11), 375 (16), and 235 (17) m/e.

2,8-Bis(3-pyridylmethyl)-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (11). A mixture of **9** (0.196 g, 0.50 mmol) and benzaldehyde (0.061 g. 5.75 mmol) in toluene (50 mL) was heated to reflux temperature in an apparatus fitted with a Dean–Stark trap for 45 min and then left at room temperature for 1 week. Crystals were removed by filtration and were shown by their infrared spectrum to be unreacted **9**. Evaporation of the filtrate left a viscous gum (0.066 g). The crystals and benzaldehyde (0.079 g) in toluene were heated at the reflux temperature of toluene for 5 h, after which reaction was complete. The solvent was removed under reduced pressure, and the residue was dissolved in 0.1 N HCl and washed twice with ether. The aqueous phase was made alkaline with 1 N NaOH and extracted (3x) with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated, and the residue (0.140 g) was combined with the 0.066 g from above and chromatographed over a Merck size A Lobar silica gel column. The column was eluted with acetone (10-mL fractions), and the desired product **11** (0.156 g, 0.32 mmol, 64%) was eluted in fractions 7–11 as a viscous gum: ^1H NMR ($CDCl_3$, TMS) δ (8.45 (m, 4H, Py C_2 and C_6 protons), 6.90–7.70 (m, 13H, aromatic), 6.77 (s, 1H, Ar C_1 or C_7 proton), 6.43 (s, 1H, Ar C_7 or C_1 proton), 5.30 (s, 1H, C_{13} proton), 4.80 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 4.28 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 4.16 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 3.85 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 3.82 (s, 2H, $ArCH_2Py$), 3.70 (s, 2H, $ArCH_2Py$); mass spectrum, 480.2311 (100, $C_{33}H_{28}N_4$ requires 480.2314), 389 (16), 297 (15), 284 (28) m/e.

2,8-Bis(3-pyridylmethyl)-13-(3-pyridyl)-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (12). A mixture of **9** (0.196 g, 0.50 mmol) and pyridine-3-carboxaldehyde (0.072 g, 0.67 mmol) in toluene (50 mL) was heated to reflux temperature for 16 h in an apparatus fitted with a Dean–Stark trap. Solvent was removed under reduced pressure, and the residue was chromatographed over a Merck size A Lobar silica gel column. The column was eluted with acetone (10-mL fractions), and the pure product **12** (0.184 G, 0.38 mmol, 76%) was found in fractions 9–16 and was a viscous gum: ^1H NMR ($CDCl_3$, TMS) δ 8.88 (s, 1H, py C_2 proton), 8.47 (m, 5H, py C_2 and C_6 protons), 7.90 (br d, 1H, J = 8 Hz, py C_4 proton), 6.93–7.56 (m, aromatic protons), 6.82 (s, 1H, C_1 or C_7 proton), 6.50 (s, 1H, C_1 or C_7 proton), 5.33 (s, 1H, C_{13} proton), 4.82 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 4.31 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 4.13 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 3.92 (d, 1H, J = 16 Hz, C_6 or C_{12} proton), 3.88 (s, 2H, $ArCH_2Py$), 3.76 (s, 2H, $ArCH_2Py$); mass spectrum, 481.2256 (100, $C_{32}H_{27}N_5$ requires 481.2266) m/e.

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