

Tröger's Base. An Alternate Synthesis and a Structural Analog with Thromboxane A₂ 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 A₂ (TxA₂) synthase, with an ED₅₀ 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 TxA₂ 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 1887¹ and was structurally characterized in 1935² 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 A₂ (TxA₂) 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 structures⁵ and, second, we wish to report the TxA₂ synthetase inhibitory activity of 5, a compound whose structural features fall outside the structure-activity correlations found for most TxA₂ synthetase inhibitors.

Results and Discussion

Chemistry. In our synthesis of the TxA₂ synthetase inhibitor, sodium furegrelate,^{3,4} the formylation of a phenol in the ortho position was achieved⁴ with the use of hexamethylenetetramine in trifluoroacetic acid—a modification⁶ 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 C₂₇H₂₄N₄, which is the sum of two molecules of 4 (C₁₂H₁₂N₂ 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 resemblance to those of the classical Tröger's base synthesis since hexamethylenetetramine (3) is known to be a convenient source of methylenamine

(CH₂=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.

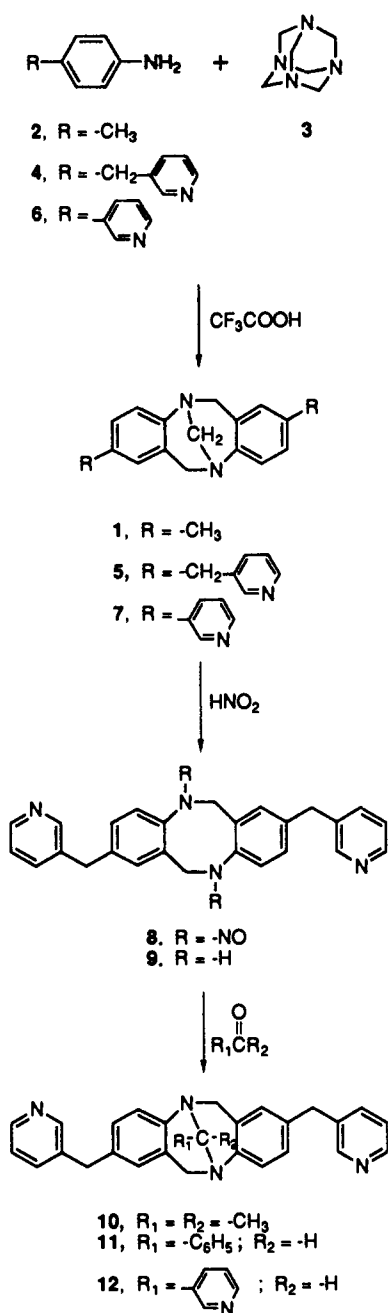
Of further interest was the fact that compound 5 was a potent inhibitor of the enzyme TxA₂ synthetase (see the following section). We therefore sought to obtain additional analogs of this structural type. When the closely related aniline 6 was allowed to react with hexamethylenetetramine in trifluoroacetic 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 TxA₂ synthetase assay. For this reason and because of other intervening activities, we did not pursue further this potential class of TxA₂ synthetase inhibitors.

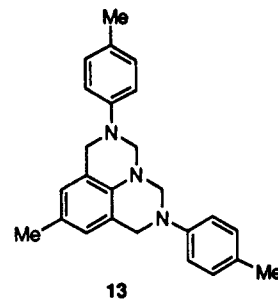
However, we have examined one additional question of chemistry and that is whether, and to what extent, Tröger's base (1) itself will be produced by our alternate reaction conditions, *i.e.*, hexamethylenetetramine in trifluoroacetic acid. When *p*-toluidine (2) and hexamethylenetetramine (3) were allowed 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

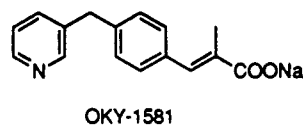
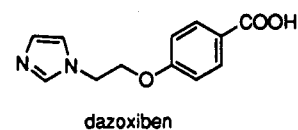
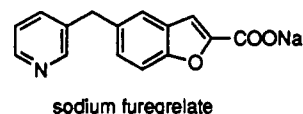


characterize it as Tröger's base, 1. The empirical formula of the compound, mp 145–147 °C, was found from the mass spectrum and elemental analysis to be C₂₅H₂₇N₃. The ratio of signals in the ¹H NMR spectrum of this compound was as follows: aromatic, 4:4:2; -CH₂-, 4:4; and -CH₃, 6:3 (the two methylene signals coincidentally fall at the same chemical shift in CDCl₃ but have different chemical shifts when the spectrum is run in C₆D₆). 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



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 TxA₂ 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 H₂ (PGH₂). Thirty seconds after addition of PGH₂, the incubation mixture was passed over rabbit aorta strips and the response of the strip taken as a measure of TxA₂ concentration. In this way, the ED₅₀ values summarized in Table I were obtained for the compounds described in this paper. For comparison, the ED₅₀ values for sodium furegrelate⁴, dazoxiben,¹¹ and OKY-1581¹² are included in Table I. These three compounds are among a number of TxA₂ 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.



The majority of TxA₂ 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. Tx_A₂ 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 ED₅₀ is the concentration causing a 50% reduction in the generation of Tx_A₂ as assayed on the rabbit aortic strip (see ref 3). Test accuracy for inhibition of Tx_A₂ synthesis will reflect statistically significant ($p < 0.05$) differences in potency when compounds differ in potency by $1/2$ log unit or more, i.e. 10 ng/mL is different from 30 ng/mL; 30 ng/mL is different from 10 or 100 ng/mL. ED₅₀ 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 μ m in thickness, 1 in. \times 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% HNO₃ in 1:1 H₂SO₄/H₂O 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-*i*]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 Na₂CO₃. 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 Na₂CO₃ (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 (Na₂SO₄), 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 CH₂Cl₂ 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 (CDCl₃, 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), (C₆D₆, 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); ¹³C NMR (CDCl₃,

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. (C₂₅H₂₇N₃) 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–H₂O 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 CF₃COOH 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–H₂O 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 (CDCl₃, 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 CF₃COOH was removed under reduced pressure, water was added, and the solution was made alkaline by the addition of solid Na₂CO₃. The alkaline mixture was extracted thoroughly with EtOAc, and the extracts were dried (Na₂SO₄), 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- μ m 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 (CDCl₃, TMS) δ 8.44 (m, 4H, pyridine C₂H and C₆H), 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, NCH₂N), 4.09 (d, 2H, J_{gem} = 16.8 Hz), 3.84 (s, 4H, PyCH₂Ar); ¹³C NMR (CDCl₃, 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 (C₂₇H₂₄N₄ requires 404.2001), no other major fragmentation peaks. Anal. (C₂₇H₂₄N₄): 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 CF₃COOH was removed, water (25 mL) was added, and the solution was made alkaline with solid Na₂CO₃ and was extracted with EtOAc (2x) and with CH₂Cl₂ (2x). The two separate extracts were dried (MgSO₄), filtered, and concentrated to give oils (0.810 g from EtOAc and 0.301 g from CH₂Cl₂) 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₂₅H₃₀N₄ requires 376.1679), 375 *m/e*. Anal. (C₂₅H₃₀N₄) 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 NaNO₂ (8.8 g, 127 mmol) in H₂O (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 CH₂Cl₂, and the extracts were dried (MgSO₄), filtered, and concentrated. The solid residue was dissolved in CH₂Cl₂, treated with activated charcoal, filtered, and crystallized from CH₂Cl₂–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% CH₃OH in CHCl₃) of a sample quenched in aqueous Na₂CO₃–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 CH₂Cl₂ (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 (MgSO₄), filtered, and concentrated separately. From the CH₂Cl₂ extract there was obtained a crystalline solid which was recrystallized from CH₂Cl₂–hexane, giving 1.363 g of pale yellow crystals, mp 197–207 °C. A sample was dissolved in hot CH₃OH, treated with activated charcoal, filtered, and crystallized from a reduced volume of CH₃OH, giving colorless crystals of 9: mp 228–229 °C; ¹H NMR (CDCl₃, 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, ArCH₂NH), 3.83 (s, 4H, PyCH₂Ar); IR (mull) 3254, 3208, 3178, 1616, 1575, 1300, 1276 cm⁻¹. Anal. (C₂₈H₂₄N₄) 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 (CDCl₃, TMS) δ 8.44 (m, 4H, Py C₂ and C₆ protons), 7.40 (d, 2H, Py C₄ 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, ArCH₂Py), 1.39 (s, 6H, CH₃); mass spectrum, 432.2322 (100, C₂₉H₂₈N₄ 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 (MgSO₄), 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 (CDCl₃, TMS) δ (8.45 (m, 4H, Py C₂ and C₆ protons), 6.90–7.70 (m, 13H, aromatic), 6.77 (s, 1H, Ar C₁ or C₇ proton), 6.43 (s, 1H, Ar C₇ or C₁ proton), 5.30 (s, 1H, C₁₃ proton), 4.80 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 4.28 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 4.16 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 3.85 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 3.82 (s, 2H, ArCH₂Py), 3.70 (s, 2H, ArCH₂Py); mass spectrum, 480.2311 (100, C₃₃H₂₈N₄ 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 (CDCl₃, TMS) δ 8.88 (s, 1H, py C₂ proton), 8.47 (m, 5H, py C₂ and C₆ protons), 7.90 (br d, 1H, *J* = 8 Hz, py C₄ proton), 6.93–7.56 (m, aromatic protons), 6.82 (s, 1H, C₁ or C₇ proton), 6.50 (s, 1H, C₁ or C₇ proton), 5.33 (s, 1H, C₁₃ proton), 4.82 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 4.31 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 4.13 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 3.92 (d, 1H, *J* = 16 Hz, C₆ or C₁₂ proton), 3.88 (s, 2H, ArCH₂Py), 3.76 (s, 2H, ArCH₂Py); mass spectrum, 481.2256 (100, C₃₂H₂₇N₅ requires 481.2266) *m/e*.

References

- Tröger, J. On Several Bases Formed From Nascent Formaldehyde. *J. Prakt. Chem.* 1887, 36, 225–245.
- Spielman, M. A. The Structure of Tröger's Base. *J. Am. Chem. Soc.* 1935, 57, 583–585.
- Gorman, R. R.; Johnson, R. A.; Spilman, C. H.; Aiken, J. W. Inhibition of Platelet Thromboxane A₂ Synthase Activity by Sodium 5-(3-Pyridinylmethyl)benzofuran-2-carboxylate. *Prostaglandins* 1983, 26, 325–342.
- Johnson, R. A.; Nidy, E. G.; Aiken, J. W.; Crittenden, N. J.; Gorman, R. R. Thromboxane A₂ Synthase Inhibitors. 5-(3-Pyridylmethyl)benzofuran-2-carboxylic Acids. *J. Med. Chem.* 1986, 29, 1461–1468.
- (a) This method has been disclosed: Johnson, R. A. Dibenzo Diazacines. U.S. Pat. 4,447,607, May 8, 1984. The experimental details for the synthesis of 5 were inadvertently omitted from this patent but a description of the synthesis of 7 was included; the method has been cited: Webb, T. H.; Suh, H.; Wilcox, C. S. Enantioselective and Diastereoselective Molecular Recognition of Allicyclic Substrates in Aqueous Media by a Chiral, Resolved Synthetic Receptor. *J. Am. Chem. Soc.* 1991, 113, 8554–8555. (b) For another alternate synthesis of a Tröger's base structure, see: Becker, D. P.; Finnegan, P. M.; Collins, P. W. Isolation of a Highly Functionalized Tröger's Base Derivative via a Novel Reaction. *Tetrahedron Lett.* 1993, 34, 1889–1892.
- Smith, W. E. Formylation of Aromatic Compounds with Hexamethylenetetramine and Trifluoroacetic Acid. *J. Org. Chem.* 1972, 37, 3972–3973.
- Duff, J. C. A New General Method for the Preparation of *o*-Hydroxyaldehydes from Phenols and Hexamethylenetetramine. *J. Chem. Soc.* 1941, 547–550.
- Blazevic, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. Hexamethylenetetramine, A Versatile Reagent in Organic Synthesis. *Synthesis* 1979, 161–176.

- (9) Cooper, F. C.; Partridge, M. W. Cyclic Amlidines. Part V. 5:11-*endo*-Substituted 5:6:11:12-Tetrahydro-2:8-dimethylphenhomazines. *J. Chem. Soc.* 1957, 2888-2893.
- (10) Farrar, W. V. Reactions of Formaldehyde with Aromatic Amines. *J. Appl. Chem. (London)* 1964, 389-399.
- (11) (a) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, O.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Takanori, O.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. Highly Selective Inhibitors of Thromboxane Synthetase. 1. Imidazole Derivatives. *J. Med. Chem.* 1981, 24, 1139-1148. (b) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. Selective Thromboxane Synthetase Inhibitors. 1. 1-[(Aryloxy)alkyl]-1*H*-imidazoles. *J. Med. Chem.* 1985, 28, 1427-1432.
- (12) Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Mijamota, T.; Taniguchi, K.; Hayashi, M.; Iizuka, K.; Nakazawa, M. Highly Selective Inhibitors of Thromboxane Synthetase. 2. Pyridine Derivatives. *J. Med. Chem.* 1981, 24, 1149-1155.
- (13) (a) Collington, E. W.; Finch, H. Thromboxane Synthetase Inhibitors and Receptor Antagonists. *Ann. Rep. Med. Chem.* 1990, 25, 99-108. (b) Cross, P. E.; Dickinson, R. P. Thromboxane Synthetase Inhibitors and Antagonists. *Ann. Rep. Med. Chem.* 1987, 22, 95-105.
- (14) Berrentini, M.; De Cunto, M.; Parise, P.; Grasselli, S.; Nenci, G. G. "In vitro" and "ex vivo" Effects of Picotamide, a Combined Thromboxane A₂ Synthetase Inhibitor and Receptor Antagonist, on Human Platelets. *Eur. J. Clin. Pharmacol.* 1990, 39, 495-500.