to impart a yellow color. Stirring was continued for 1 h and the resulting solution, showing no change in appearance, was then concentrated on a rotary evaporator. The residue was taken up in 30 mL of 3 N HCl and stirred for 1 h at room temperature, basified (50% KOH), and thoroughly extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give 1.33 g of a colorless oil. Purification was carried out with a Harrison Chromatotron using a 4-mm silica gel rotor and petroleum ether, acetone, and triethylamine (80:50:8) eluate. The solvent was removed under vacuum to afford 550 mg (22%) of (2′*S*,5′*R*)-5-(3-hydroxypropyl)nicotine (**7**) as a clear, colorless viscous oil which could not be distilled without decomposition: R_f 0.56 (80:50:8 petroleum ether–acetone–Et_3N); $[\alpha]_D$ −80.2° (*c* 0.32, CH_2Cl_2); ^{1}H NMR[19] ($CDCl_3$) δ 1.40–1.95 (br m, 8), 2.13 (s, 3), 2.43 (m, 1), 3.18 (m, 1), 3.6 (m, 2), 4.9 (br s, 1, OH), 7.2 (dd, *J* = 8, 2 Hz, 1), 7.6 (dt, *J* = 8, 2 Hz, 1), 8.45 (m, 2); ^{13}C NMR[19] ($CDCl_3$) δ 27.23, 27.68, 29.57, 32.56, 38.09, 62.61, 65.76, 69.65, 123.90, 135.08, 138.66, 148.96, 149.77; dipicrate, mp 128–130 °C.

Anal. (dipicrate) Calcd for $C_{25}H_{26}N_8O_{15}$: C, 44.25; H, 3.86; N, 16.51. Found: C, 44.43; H, 4.02; N, 16.32.

(2′*S*,4′*R*)-4′-(2-Hydroxyethyl)nicotine (8). To a solution of 10.4 mL (0.0741 mol) of diisopropylamine in 200 mL of THF under nitrogen at −20 °C was added 27.5 mL (0.0684 mol) of 2.5 M *n*-butyllithium in hexane such that the temperature did not rise above −20 °C. The solution was stirred keeping the temperature below −20 °C for 10 min; it was then cooled to −70 °C. To the solution was added a solution of 10.0 g (0.057 mol) of (*S*)-cotinine[13] in 50 mL of THF over 15 min. The resultant yellow solution was stirred at −70 °C for 30 min and then added over 20 min via a double-tipped needle to a solution of 10.1 mL (0.0625 mol) of *tert*-butyl bromoacetate in 50 mL of THF at −70 °C. The cloudy mixture was stirred at −70 °C for 15 min and then at room temperature for 16 h. The mixture was quenched with 100 mL of 10% aqueous HCl and washed with 2 × 100 mL of ether. The aqueous layer was basified with concentrated aqueous NaOH and extracted with 3 × 100 mL of ether. The ehtereal layers were combined, dried with $MgSO_4$, and filtered, and the resultant solution was evaporated to yield 7.55 g of a viscous red oil. Purification by the Harrison Chromatotron (silica gel GF plate with 1:1 petroleum ether/acetone eluent) provided 5.88 g (35%) of **17** as a viscous oil which was utilized directly in the next step.

To a solution of 1.183 g (4.08 mmol) of **17** in 45 mL of THF under nitrogen was added 23.1 mL (24.48 mmol) of 1.06 M borane in THF at room temperature. The mixture was heated at reflux for 24 h. After being allowed to cool, the mixture was carefully quenched with 30 mL of 6 N aqueous HCl and then refluxed for 3 h. The mixture was then concentrated to a volume of approximately 25 mL and washed with 4 × 25 mL of ether. The aqueous layer was basified and extracted with 3 × 25 mL of methlene chloride. The organic layers were combined and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to a viscous oil. Bulb-to-bulb distillation [oven temperature 110–120 °C (0.1 mm)] afforded 0.40 g (48%) of (2′*S*,4′*R*)-4′-(2-hydroxyethyl)nicotine (**8**) as a clear, colorless, viscous oil: $[\alpha]^{20}_D$ −136° (*c* 0.434, CH_2Cl_2); ^{1}H NMR[19] ($CDCl_3$) δ 1.66–1.73 (m, 2, CH_2CH_2OH), 1.90–1.97 (m, 2, H-3′), 2.08 (dt, *J* = 9.4, 1 Hz, 1, H-5′a), 2.16 (s, 3, N-CH_3), 2.44–2.51 (m, 1, H-4′), 3.20 (t, *J* = 8.3 Hz, 1, H-2′), 3.37 (dd, *J* = 9.4, 3.4 Hz, 1, H-5′b), 3.67 (t, *J* = 6.9 Hz, 2, CH_2OH), 7.26 (dd, *J* = 7.8, 4.9 Hz, 1), 7.70 (dt, *J* = 7.8, 2.0 Hz, 1), 8.48 (dd, *J* = 4.9, 1), 8.51 (d, *J* = 2.0 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 33.34, 37.90, 40.40, 47.74, 61.37, 63.94, 67.96, 123.61, 134.97, 138.92, 148.43, 149.25; IR (film) 3300 cm^{-1}.

Precise mass determined for M^+: Calcd for $C_{12}H_{18}H_2O$ 206.1419, found 206.1470.

(19) A number of additional weak resonances were observed, assigned to the minor diastereoisomer formed in the reduction step.

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Synthesis of [3.3]Heterophanes Containing the Pyridine, Furan, and Thiophene Rings by the TosMIC Method[1]

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[3.3](2,5)- and [3.3](2,6)pyridinophanes as well as [3]metacyclo[3](2,5)furanophane (**20**) and [3]metacyclo[3](2,5)thiophenophane (**23**) have been synthesized by the conventional or modified TosMIC coupling reaction, followed by acid treatment and reduction. ^{1}H NMR data suggest that the stable conformation of the [3.3]metacyclophane-2,11-dione system (**3**, **6**, **19**, and **22**) is anti, whereas that of the [3.3]metacyclophane system (**4**, **7**, **20**, and **23**) is syn. In [3.3](2,5)pyridinophanes (**17a–d**) the average deshielding effects for protons located pseudogeminal and pseudoortho to a nitrogen atom are found to be 0.28 and 0.15 ppm, respectively, as compared to those pseudopara to the nitrogen.

In a previous paper,[2] we reported a new general method for the synthesis of [3.3]cyclophanes. This method takes advantage of the coupling reaction between (*p*-tolylsulfonyl)methyl isocyanide (TosMIC[3]) and an appropriate bis(halomethyl) compound, followed by acid hydrolysis and reduction of the carbonyl groups.[4] We now report an application of this method to the synthesis of [3.3]heterophanes.

Various synthetic methods have been developed to prepare [2.2]heterophanes, and their chemistry has been

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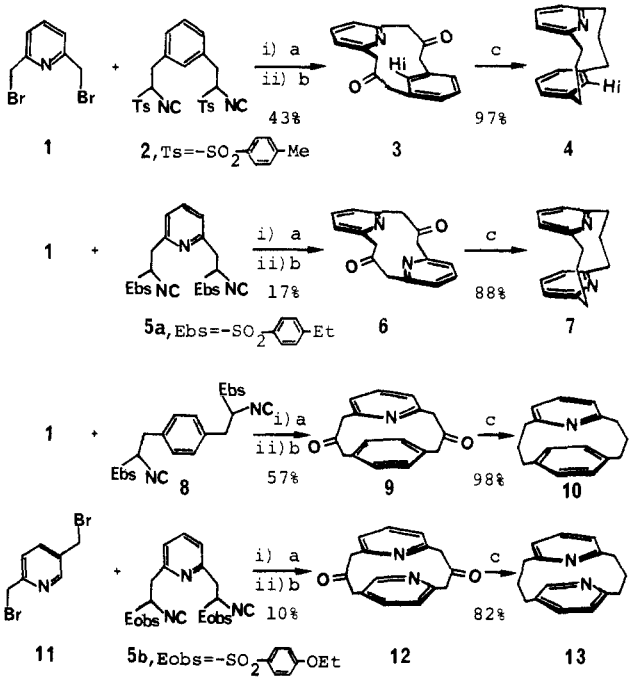
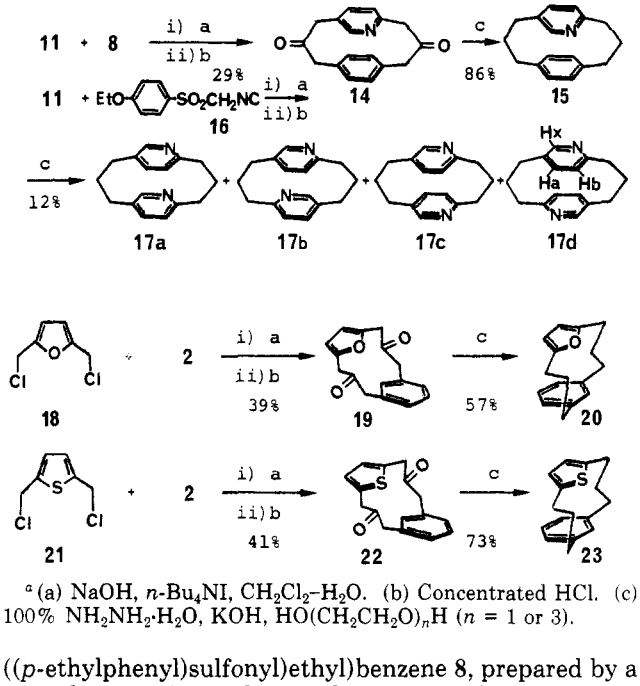
0022-3263/86/1951-1551$01.50/0

Scheme I



Scheme II



[a] (a) NaOH, n-Bu_4NI, CH_2Cl_2–H_2O. (b) Concentrated HCl. (c) 100% $NH_2NH_2 \cdot H_2O$, KOH, $HO(CH_2CH_2O)_nH$ (n = 1 or 3).

studied in detail.[5] However, there are only a few reports on [3.3]heterophanes mainly because simple and useful synthetic methods for their preparation have not been developed so far. Y. Miyahara of our laboratory reported the unique method of preparing [3.3]thiophenophanes which utilizes the condensation of diketo sulfides with glyoxal, followed by reduction of the carbonyl groups.[6] Moreover, W. Flitsch et al. synthesized [3.3](2,5)-pyrrolophane, as a synthetic precursor to 1,4:8,11-diimino[14]annulene, by the Dieckmann cyclization of tetraethyl 1,1′-bipyrrole-2,5,2′,5′-tetraacetate, followed by acid treatment and reduction.[7] I. Tabushi et al. also reported the synthesis of tetraethyl [3.3](2,5)thiophenophane-2,2,10,10-tetracarboxylate.[8] In recent years [3.3]-pyridinophane derivatives have found some applications as pyridoxal models.[9] In this paper we wish to describe the synthesis of [3.3]pyridinophanes as well as [3.3]furano- and thiophenophane.

Results and Discussions

Synthesis. The synthetic routes to and yields of [3.3]pyridinophanes as well as [3.3]furanophane **20** and thiophenophane **23** are shown in Schemes I and II.

Generally speaking, the TosMIC adducts with bis(halomethyl)benzene derivatives have poor solubilities in CH_2Cl_2. Compound **2** is the only exception and is readily soluble in CH_2Cl_2. But 1,4-bis(2-isocyano-2-tosylethyl)-benzene is sparingly soluble even in refluxing CH_2Cl_2. In order to increase their solubilities, we developed ((*p*-ethylphenyl)sulfonyl)methyl isocyanide (EbsMIC) or ((*p*-ethoxyphenyl)sulfonyl)methyl isocyanide (EobsMIC) in place of TosMIC.[10] As expected, 1,4-bis(2-isocyano-2-((*p*-ethylphenyl)sulfonyl)ethyl)benzene **8**, prepared by a procedure similar to that used for the synthesis of **2**, was found to have sufficient solubility in CH_2Cl_2. In the case of 2,6-bis(bromomethyl)pyridine(**1**), we also utilized EbsMIC or EobsMIC in place of TosMIC because of the poor solubility of the TosMIC adduct in CH_2Cl_2 or dimethyl sulfoxide (Me_2SO). The EbsMIC or EobsMIC adducts with **1** were, in fact, found to be highly soluble in CH_2Cl_2 or even in MeOH. We used the crude adducts in the coupling reaction without purification because the high solubility of the adducts in MeOH made the purification difficult. We also attempted to prepare EbsMIC adduct with 2,5-bis(bromomethyl)pyridine (**11**) but we could not isolate the adduct probably due to instability of dibromide **11** and its adduct in alkaline solution.

The coupling reaction of **1** and **2** in the presence of NaOH and tetra-*n*-butylammonium iodide (n-Bu_4NI) in a mixture of CH_2Cl_2 and water under phase-transfer conditions, followed by acid treatment afforded ketone **3** in 43% yield. The ketone **3** was converted into **4** by the Wolff–Kishner reduction in 97% yield. 2,6-Bis(bromomethyl)pyridine (**1**) was coupled with the crude EbsMIC adduct **5a** to give ketone **6** in 17% yield. This was reduced to [3.3](2,6)pyridinophane(**7**) in 88% yield.

In the [3.3]metaparacyclophane system, we prepared [3]paracyclo[3](2,6)pyridinophane (**10**) and [3](2,6)-pyridino[3](2,5)pyridinophane (**13**). In the synthesis of **13**, 2,5-bis(bromomethyl)pyridine (**11**) was coupled with the crude EobsMIC adduct **5b** to afford **12** in 10% yield.

In the [3.3]paracyclophane system, [3]paracyclo[3]-(2,5)pyridinophane (**15**) and four isomeric [3.3](2,5)-pyridinophanes (**17a–d**) were prepared. As previously described, we failed to prepare the EbsMIC adduct with 2,5-bis(bromomethyl)pyridine (**11**). Therefore we employed a one-step cyclization method. The coupling reaction of **11** with EobsMIC (**16**), followed by reduction of the crude ketones afforded [3.3](2,5)pyridinophanes (**17a–d**) as a mixture of all possible isomers in 10% yield with the following molar ratio: **17a** (pseudogeminal):**17b** (pseudoortho):**17c** (pseudometa):**17d** (pseudopara) = 3:3:1:1 based on ^1H NMR spectra. Repeated preparative

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TLC on silica gel with CH_2Cl_2–EtOH (19:1) effected the isolation and purification of the pseudometa isomer **17c** and pseudopara isomer **17d**. Attempts to separate the pseudogeminal isomer **17a** and the pseudoortho isomer **17b** by chromatographic methods failed because of their similar chromatographic mobility. However, fractional sublimation (50–80 °C, 0.1 mmHg) was successful in effecting this separation. The pseudoortho isomer **17b** was much more volatile than the pseudogeminal isomer **17a**. The structure of four isomers was confirmed by comparison of their ^1H NMR data with those of [2.2](2,5)pyridinophanes reported by Jenny et al.[11]

The TosMIC method was also successfully applied to other heterophanes. The coupling reaction of 2,5-bis(chloromethyl)furan (**18**) and **2** afforded the ketone **19** in 39% yield. Reduction of **19** gave the furanophane **20** in 57% yield. Similarly 2,5-bis(chloromethyl)thiophene (**21**) was coupled with **2** to give **22** in 41% yield. Subsequent reduction of **22** afforded the thiophenophane **23** in 73% yield.[12]

As described above, the TosMIC method is a promising method for the synthesis of [3.3]heterophanes. The coupling reaction, however, resulted in low yields when crude adducts (**5a** and **5b**) were used without purification. One-step cyclization also suffered from low yields (**17a–d**). We are now studying purification procedures for the adducts.

Conformation. ^1H NMR data suggest that the stable conformation of the [3.3]metacyclophane-2,11-dione systems (**3**, **6**, **19**, and **22**) is anti, whereas that of the [3.3]metacyclophane systems (**4**, **7**, **20**, and **23**) is syn. The upfield shift of the inner aromatic proton (Hi) of **3** to 6.50 ppm from its normal position of ca 7.00 ppm in *m*-xylene is caused by the shielding effect of the transannularly located pyridinoid ring. This suggests that the stable conformation of **3** is anti. In fact, pyridine protons of **3** show very similar chemical shifts to the equivalent protons of the anti-fixed [2]metacyclo[2](2,6)pyridinophane.[13]

On the other hand, the inner aromatic proton in **4** appears at a normal position (7.27 ppm), while both the pyridine and benzene protons show upfield shifts compared with the equivalent protons of 2,6-lutidine and *m*-xylene. These data suggest that the stable conformation of **4** is syn.

Similar phenomena were observed in the ^1H NMR spectra of all the [3.3]metacyclophane systems.[14] This result is consistent with that found in the parent [3.3]metacyclophane and its 2,11-dione, and supports our view that all gauche interactions of the two trimethylene bridges in the syn form causes the main driving force of the preferred syn conformation in the [3.3]metacyclophanes.[15]

The benzenoid ring protons of [3]paracyclo[3](2,6)pyridinophane (**10**) and its dione (**9**) appear as singlets at 6.21 and 6.37 ppm, respectively. We observed that the meta-bridged benzene ring of [3.3]metaparacyclophane undergoes rapid inversion, but the rotation of the para-bridged benzene ring is restricted at room temperature.[16] The equivalence of the benzenoid ring protons in **9** and **10** suggests the rapid inversion of the pyridine ring. Similarly rapid inversion of the 2,6-bridged pyridine ring is considered to occur in **12** and **13**.

Table I. ^1H NMR Spectra of the Aromatic Protons in Four Isomeric [3.3](2,5)Pyridinophanes (17a–d)[a]

	H_a[b]	H_b	H_x[c]
2,5-lutidine	7.35	7.01	8.30
17a (pseudogeminal)	7.00	6.59	8.05
17b (pseudoortho)	6.98	6.62	8.18
17c (pseudometa)	7.13	6.88	7.88
17d (pseudopara)	7.28	6.77	7.86

[a] $CDCl_3$, ppm. [b] J_{ab} = 8 Hz. [c] J_{ax} = 2 Hz.

Table II. Diamagnetic Upfield Shifts of the Pyridine Protons in Four Isomeric [3.3](2,5)Pyridinophanes (17a–d) Relative to the Equivalent Proton of 2,5-Lutidine

	pseudo-geminal H[a]	pseudo-ortho H	pseudo-meta H	pseudo-para H
17a (pseudogeminal)		0.25	0.42	0.35
17b (pseudoortho)	0.12		0.37	0.39
17c (pseudometa)	0.13	0.22		0.42
17d (pseudopara)	0.07	0.24	0.44	

[a] The proton pseudogeminal to a nitrogen.

^1H NMR Spectra. Table I denotes the ^1H NMR spectra of the aromatic protons observed for the four isomeric [3.3](2,5)pyridinophanes (**17a–d**), as well as those of 2,5-lutidine for the model compound, which is included for the comparison purpose. Table II shows the diamagnetic upfield shifts of the aromatic protons in **17a–d** relative to the equivalent protons of 2,5-lutidine.

The location of the nitrogen in the transannular ring affects the chemical shifts of the protons in the ring under consideration. The protons pseudogeminal to a nitrogen exhibit significant downfield shifts (average value 0.28 ppm) as compared to those pseudopara to the nitrogen. The pseudoortho protons also show downfield shifts (average value 0.15 ppm) about half as great as those found for the pseudogeminal protons. Jenny et al. synthesized [2.2](2,5)pyridinophanes by the Hofmann elimination reaction and separated all four isomers by gas chromatography.[11] They reported that the average deshielding effects for protons located pseudogeminal and pseudoortho to a nitrogen atom are 0.38 and 0.19 ppm, respectively. The magnitude of the de hielding effect of the [3.3] system (**17**) is smaller than that of the [2.2] system. This is interpreted in terms of the difference in transannular distance in [2.2]- and [3.3](2,5)pyridinophanes.

Experimental Section

General Comments. All melting points were uncorrected. The ^1H NMR spectra were recorded on either a Hitachi R-20B (60 MHz) or a JEOL EX-90Q (90 MHz) spectrometer. Chemical shifts are recorded as δ values (ppm) relative to internal Me_4Si. Mass spectra were obtained on a Hitachi RMU-6MG mass spectrometer at ionization energy of 70 eV; m/z values reported include the parent ion peak. Elemental analyses were performed by the Service Centre of the Elementary Analysis of Organic Compounds affiliated to the Faculty of Science in Kyushu University.

Distilled CH_2Cl_2 was used for the coupling reaction. Silica gel chromatography utilized Wako gel C-300 for column chromatography, Merck silica gel PF_{254} for preparative TLC, and Merck

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silica gel 60 F_{254} (0.2 mm on aluminum) for analytical purposes.

2,6-Bis(bromomethyl)pyridine (1) was prepared from commercially available 2,6-bis(hydroxymethyl)pyridine by treatment with hydrobromic acid (30 wt % solution in acetic acid).[17] 2,5-Bis(bromomethyl)pyridine (11) was obtained by reduction of diethyl pyridine-2,5-dicarboxylate with sodium borohydride according to the procedure reported by Matsumoto et al.,[18] followed by bromination with hydrobromic acid. 2,5-Bis(chloromethyl)-furan (18),[19] 2,5-bis(chloromethyl)thiophene (**21**)[20] and TosMIC[21] were prepared according to the literature methods.

1,3-Bis(2-isocyano-2-(tolylsulfonyl)ethyl)benzene (2). Although the synthetic procedure for this compound was already reported,[2] we wish to describe an improved procedure.

To a stirred mixture of *n*-Bu_4NI (7 g), 80 g of NaOH dissolved in 320 mL of water and 500 mL of CH_2Cl_2 was added in one portion TosMIC (80 g, 410 mmol, 1.8 equiv) dissolved in 500 mL of CH_2Cl_2 at room temperature. After the mixture had been stirred for 30 min, 2,6-bis(bromomethyl)benzene (30 g, 114 mmol) dissolved in 500 mL of CH_2Cl_2 was added in one portion at room temperature. The mixture was stirred for an additional 2 h, washed with water, and concentrated to a volume of ca. 1 L. The concentrate was diluted with MeOH (1 L) and stored overnight in a freezer. The precipitate was collected, washed with MeOH, and air-dried to give colorless powder (42.7 g, 76%).

[3]Metacyclo[3](2,6)pyridinophane (4). A 3-L, four-necked round-bottomed Morton flask was equipped with a mechanical stirrer and a 200-mL dilution head to which was fitted with a reflux condenser. A 500-mL-pressure-equalizing dropping funnel was attached to the top of the condenser. The flask was charged with *n*-Bu_4NI (0.9 g, 2.4 mmol), 1.5 L of CH_2Cl_2, and 20 g of NaOH dissolved in 150 mL of water. The mixture was stirred and heated to reflux. To the mixture was added dropwise a mixture of 1 (3.30 g, 12.5 mmol) and 2 (6.09 g, 12.4 mmol) in 0.5 L of CH_2Cl_2 over a 7-h period. The mixture was refluxed for an additional 1.5 h. After cooling, the mixture was washed with water (500 mL) and concentrated to a volume of 200 mL. To the concentrate was added 25 mL of concentrated HCl, and the mixture was stirred for 30 min at room temperature. The mixture was made alkaline by the addition of aqueous KOH solution and extracted with CH_2Cl_2 (150 mL × 3). The combined CH_2Cl_2 solution was washed with water, dried over $MgSO_4$, and filtered. Removal of the solvent afforded dark yellow oil, which was purified by silica gel chromatography with AcOEt–hexane (1:2) to give **3** as faintly yellow crystals (1.43 g, 43%). **3**: colorless plates from AcOEt; mp 145–146 °C; R_f (silica gel, AcOEt–hexane, 2:3) 0.20; ^1H NMR (δ, $CDCl_3$) 3.69 (s, 4, benzylic), 3.82 (s, 4, benzylic), 6.50 (br s, 1, benzene), 7.08 (AB_2, J = 8 Hz, 2, pyridine), ca. 7.14 (br s, 3, benzene), 7.50 (AB_2, J = 8 Hz, 1, pyridine); MS, m/z M^+ 265. Anal. Calcd for $C_{17}H_{15}O_2N$: 76.96; H, 5.70; N, 5.28. Found: C, 76.77; H, 5.78; N, 5.34.

A mixture of the diketone **3** (443 mg, 1.67 mmol), KOH (3 g, 53.5 mmol), 100% hydrazine hydrate (15 mL, 309 mmol), and triethylene glycol (20 mL) was heated at 120 °C for 2 h and then 200 °C for 2.5 h. The cooled reaction mixture was poured into water (100 mL) and extracted with diethyl ether (50 mL × 4). The combined ether solution was washed with water, dried over $MgSO_4$, filtered, and evaporated in vacuo to give **4** as colorless crystals (385 mg, 97%). **4**: colorless crystals by sublimation (65–75 °C, 0.9 mmHg); mp 88–89 °C; ^1H NMR (δ, $CDCl_3$) 2.0–2.5 (m, 4, $-CH_2CH_2CH_2-$), 2.5–3.2 (m, 8, benzylic), 6.50 (AB_2, J = 7 Hz, 2, pyridine), 6.5–6.8 (m, 3, benzene), 7.06 (AB_2, J = 7 Hz, 1, pyridine), 7.27 (br s, 1 , benzene); MS, m/z M^+ 237. Anal. Calcd for $C_{17}H_{19}N$: C; 86.03; H, 8.07; N; 5.90. Found: C, 86.00; H, 8.17; N, 5.88.

[3.3](2,6)Pyridinophane (7). 2,6-Bis(2-isocyano-2-((*p*-ethylphenyl)sulfonyl)ethyl)pyridine (**5a**) was prepared from 1 (6.0 g, 22.7 mmol) and EbsMIC (11.4 g, 54.5 mmol) by a similar procedure described for **2**. The CH_2Cl_2 solution of the crude product was concentrated to dryness in vacuo at room temperature. The resulting brown semisolid (14.4 g) was used in the next coupling reaction without purification. To a refluxed mixture of *n*-Bu_4NI (2.4 g, 6.5 mmol), NaOH (51 g), water (270 mL), and CH_2Cl_2 (1.5 L) was added a mixture of 1 (9.27 g, 35.0 mmol) and crude **5a** in CH_2Cl_2 (0.5 L) over a period of 7 h with stirring. The mixture was refluxed for an additional 2 h. Similar workup as described for **3** and subsequent purification by silica gel (280 g) chromatography eluted with AcOEt afforded colorless crystals (1.21 g, 17%). **6**: colorless crystals by sublimation (130–150 °C, 0.2 mmHg); mp 263–264 °C; R_f (silica gel, AcOEt–hexane, 1:2) 0.33; ^1H NMR ($CDCl_3$–Me_2SO-d_6) 3.79 (s, 8, benzylic, 7.18 (AB_2, J = 7 Hz, 4, pyridine), 7.60 (AB_2, J = 7 Hz, 2, pyridine); MS, m/z M^+ 266. Anal. Calcd for $C_{16}H_{14}O_2N_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.12; H, 5.40; N, 10.47.

The diketone **6** (1.19 g, 4.47 mmol) was reduced to **7** (940 mg, 88%) in a similar manner as described for **4** except the reaction solvent (ethylene glycol). **7**: colorless crystals by sublimation (120 °C, 0.2 mmHg); R_f (silica gel, CH_2Cl_2–EtOH, 10:1) 0.49; mp 169–170 °C; ^1H NMR (δ, $CDCl_3$) 2.3–3.2 (m, 12, $-CH_2CH_2-$), 6.43 (AB_2, J = 7 Hz, 4, pyridine), 6.99 (AB_2, J = 7 Hz, 2, pyridine); MS, m/z M^+ 238. Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.35; H, 7.65; N, 11.75.

[3]Paracyclo[3](2,6)pyridinophane (10). A mixture of *n*-Bu_4NI (2 g, 5.4 mmol), CH_2Cl_2 (1.5 L), and NaOH (40 g) dissolved in water (200 mL) was heated to reflux with stirring. To the mixture was added dropwise a mixture of 1 (6.36 g, 24.0 mmol) and 8 (12.5 g, 24.0 mmol) in CH_2Cl_2 (1 L) over an 11-h period. The mixture was refluxed for an additional 2 h. The reaction mixture was worked up in a similar manner as described for **3**. Purification of the crude product by silica gel chromatography with AcOEt, and subsequent recrystallization from AcOEt afforded **9** (3.65 g, 57%) as colorless prisms. **9**: mp 182–183 °C; ^1H NMR (δ, $CDCl_3$) 3.71 (s, 4, benzylic), 3.75 (s, 4, benzylic), 6.37 (s, 4, benzene), 7.01 (AB_2, J = 8 Hz, 2, pyridine), 7.34 (AB_2, J = 8 Hz, 1, pyridine); MS, m/z M^+ 265. Anal. Calcd for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.84; H, 5.82; N, 5.25.

A mixture of **9** (3.65 g, 13.8 mmol), KOH (15 g), 100% hydrazine hydrate (80 mL), and ethylene glycol (180 mL) was heated to reflux for 66 h. Similar workup of the reaction mixture as described for **4** afforded **10** (3.20 g, 98%) as colorless crystals. **10**: colorless crystals by sublimation (60–75 °C, 1 mmHg); mp 95.5–96.5 °C; ^1H NMR (δ, $CDCl_3$) 1.9–3.0 (m, 12, $-CH_2CH_2CH_2-$), 6.21 (s, 4, benzene), 6.71 (AB_2, J = 8 Hz, 2, pyridine), 7.32 (AB_2, J = 8 Hz, 1, pyridine); MS, m/z M^+ 237. Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 85.70; H, 8.13; N, 5.91.

[3](2,6)Pyridino[3](2,5)pyridinophane (13). 2,6-Bis(2-isocyano-2-((*p*-ethoxyphenyl)sulfonyl ethyl)pyridine (**5b**) was prepared from 1 (6.0 g, 22.7 mmol) and EobsMIC (12.3 g, 54.6 mmol) by a similar procedure described for **2**. The CH_2Cl_2 solution of the crude product was filtered, and the filtrate was used in the coupling reaction without purification. Similar synthetic and purification methods were used as described for **3**. **12** (0.62 g, 10%): colorless crystals by sublimation (130–140 °C, 0.2 mmHg); mp 146–147 °C; R_f (silica gel, CH_2Cl_2-2-propanol, 20:1) 0.30; ^1H NMR (δ, $CDCl_3$) 3.5–4.3 (m, 8, benzylic), 6.74 (*ABX*, J_{ab} = 8 Hz, 1, pyridine) 7.00 ($A'B_2$, $J_{a'b'}$ = 7 Hz, 2, pyridine) 7.01 (*ABX*, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 1, pyridine), 7.36 ($A'B_2$, $J_{a'b'}$ = 7 Hz, 1, pyridine), 8.25 (AB*X*, J_{ax} = 2 Hz, 1, pyridine); MS, m/z M^+ 266. Anal. Calcd for $C_{16}H_{14}O_2N_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.14; H, 5.41; N, 10.40. **13** (82%): colorless oil; ^1H NMR (δ, $CDCl_3$) 1.8–3.2 (m, 12, $-CH_2CH_2CH_2-$), 6.57 (*ABX*, J_{ab} = 8 Hz, 1, pyridine), 6.75 ($A'B_2$, $J_{a'b'}$ = 8 Hz, 2, pyridine), 6.86 (*ABX*, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 1, pyridine), 7.34 ($A'B_2$, $J_{a'b'}$ = 8 Hz, 1, pyridine), 8.02 (AB*X*, J_{ax} = 2 Hz, 1, pyridine); MS, m/z M^+ 238. Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.36; H, 7.53; N, 11.70.

[3]Paracyclo[3](2,5)pyridinophane (15). A mixture of *n*-Bu_4NI (1 g, 2.52 mmol), CH_2Cl_2 (1.5 L), and NaOH (15 g) dissolved in water (100 mL) was heated to reflux with stirring. To the mixture was added dropwise a mixture of 11 (1.87 g, 7.06 mmol) and 8 (3.64 g, 6.99 mmol) in CH_2Cl_2 (400 mL) over a 6-h period. The mixture was refluxed for an additional 2 h. The reaction mixture was worked up in a similar manner as described for **3**.

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Purification of the crude product by silica gel chromatography with AcOEt–hexane (4:1) and subsequent sublimation (140–150 °C, 1 mmHg) afforded **14** (0.532 g, 29%) as colorless crystals. **14**: colorless crystals from CH_2Cl_2–MeOH; mp 228 °C dec; ^1H NMR (δ, $CDCl_3$) 3.4–4.3 (m, 8, benzylic), ca. 6.81 (m, 2, benzene), 6.83 A*B*X, J_{ab} = 8 Hz, 1, pyridine), 7.14 (m, 2, benzene), 7.24 (*A*BX, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 1, pyridine), 8.14 (AB*X*, J_{ax} = 2 Hz, 1, pyridine); MS, m/z M^+ 265. Anal. Calcd for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.86; H, 5.60; N, 5.35.

A mixture of **14** (0.35 g, 1.32 mmol), KOH (2.4 g), 100% hydrazine hydrate (12 mL), and ethylene glycol (20 mL) was refluxed for 3.5 h. Similar workup of the reaction mixture as described for **4** and purification by sublimation (70–80 °C, 1 mmHg) gave **15** (0.27 g, 86%) as colorless crystals. **15**: mp 80.5–81.5 °C; ^1H NMR (δ, $CDCl_3$) 1.7–3.2 (m, 12, $-CH_2CH_2CH_2-$), 6.60 (*A*BX, J_{ab} = 8 Hz, 1, pyridine), 6.63 (br s, 2, benzene), ca. 6.83 (m, 1, benzene), ca. 6.90 (m, 1, benzene), 7.03 (*A*BX, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 1, pyridine), 7.95 (AB*X*, J_{ax} = 2 Hz, 1, pyridine).

[3.3](2,5)Pyridinophanes (17a–d). A mixture of *n*-Bu_4NI (3 g, 8.1 mmol), 50 g of NaOH dissolved in 100 mL of water, and 1.5 L of CH_2Cl_2 was stirred and refluxed. To the mixture was added dropwise a mixture of **11** (10 g, 37.8 mmol) and ((*p*-ethoxyphenyl)sulfonyl)methyl isocyanide (8.5 g, 37.7 mmol) in 0.5 L of CH_2Cl_2 over a period of 5 h. The mixture was refluxed for an additional 4 h. After similar workup as described for **3**, a dark brown solid (3.88 g) was obtained. The coupling reaction was repeated twice in the same scale. The combining crude products were purified by silica gel chromatography (silica gel 150 g, CH_2Cl_2–MeOH, 30:1–15:1) to afford a yellowish brown solid (1.72 g) as a mixture of isomers.

The Wolff–Kishner reduction of the ketone (1.72 g, 6.46 mmol) gave **17** (1.06 g, 12% overall yield) as a faintly yellow solid. Repeated preparative TLC (silica gel, CH_2Cl_2–EtOH, 19:1) afforded the pseudopara isomer **17d** (106 mg), the pseudometa isomer **17c** (97 mg), and a mixture of the pseudoortho isomer **17b** and pseudogeminal isomer **17a** (a 1:1 mixture, 560 mg). R_f values (silica gel, CH_2Cl_2–EtOH, 9:1) are as follows: 0.29 for **17a**, 0.30 for **17b**, 0.44 for **17c**, and 0.49 for **17d**. Separation of **17a** and **17b** was effected by fractional sublimation (50–80 °C, 0.1 mmHg). The pseudoortho isomer **17b** was volatilized over the range of 50–80 °C, but the pseudogeminal isomer **17a** remained unvolatilized. **17a** (pseudogeminal): colorless crystals by sublimation (100 °C, 0.12 mmHg); mp 172–173.5 °C; ^1H NMR (δ, $CDCl_3$) 1.7–3.4 (m, 12, $-CH_2CH_2CH_2-$), 6.59 (*A*BX, J_{ab} = 8 Hz, 2, pyridine), 7.00 (*A*BX, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 2, pyridine), 8.05 (AB*X*, J_{ax} = 2 Hz, 1, pyridine); MS, m/z M^+ 238; R_f (silica gel, CH_2Cl_2–EtOH, 9:1) 0.29. Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.55; H, 7.70; N, 11.75.

17b (pseudoortho): colorless crystals by sublimation (50 °C, 0.1 mmHg); mp 83–85 °C; ^1H NMR (δ, $CDCl_3$) 1.7–3.3 (m, 12, $-CH_2CH_2CH_2-$), 6.62 (*A*BX, J_{ab} = 8 Hz, 2, pyridine), 6.98 (*A*BX, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 2, pyridine), 8.18 (AB*X*, J_{ax} = 2 Hz, 2, pyridine); MS, m/z M^+ 238; R_f (silica gel, CH_2Cl_2–EtOH, 9:1) 0.30. Anal. Found: C, 80.57; H, 7.47; N, 11.76.

17c (pseudometa): colorless crystals by sublimation (110 °C, 1 mmHg); mp 115.5–117 °C; ^1H NMR (δ, $CDCl_3$) 1.8–3.3 (m, 12, $-CH_2CH_2CH_2-$), 6.88 (*A*BX, J_{ab} = 8 Hz, 2, pyridine), 7.13 (*A*BX, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 2, pyridine), 7.88 (AB*X*, J_{ax} = 2 Hz, 2, pyridine); MS, m/z M^+ 238; R_f silica gel, CH_2Cl_2–EtOH, 9:1) 0.44. Anal. Found: C, 80.42; H, 7.71; N, 11.66.

17d (pseudopara): colorless crystals by sublimation (110 °C, 1 mmHg); mp 156–158 °C; ^1H NMR (δ, $CDCl_3$) 1.7–3.3 (m, 12, $-CH_2CH_2CH_2-$), 6.77 (*A*BX, J_{ab} = 8 Hz, 2, pyridine), 7.28 (*A*BX, J_{ab} = 8 Hz, J_{ax} = 2 Hz, 2, pyridine), 7.86 (AB*X*, J_{ax} = 2 Hz, 2, pyridine); MS, m/z M^+ 238; R_f (silica gel, CH_2Cl_2–EtOH, 9:1) 0.49. Anal. Found: C, 80.26; H, 7.68; N, 11.70.

[3]Metacyclo[3](2,5)furanophane (20). To a refluxed mixture of *n*-Bu_4NI (1 g, 2.52 mmol), CH_2Cl_2 (1.5 L), and NaOH (15 g) dissolved in water (100 mL) was added dropwise a mixture of **18** (1.4 g, 8.48 mmol) and **2** (3.8 g, 7.71 mmol) in CH_2Cl_2 (400 mL) over a 6-h period with stirring. The mixture was refluxed for an additional 2 h. The cooled reaction mixture was washed with water and concentrated to a volume of 200 mL. The concentrate was treated with concentrated HCl (10 mL) at room temperature for 5 min. The mixture was worked up in a similar manner as described for **3**. Purification of the crude product by silica gel chromatography with AcOEt–hexane (1:2) afforded **19** (0.763 g, 39%) as colorless crystals. **19**: colorless needles from diethyl ether; mp 151–152 °C; R_f (silica gel, hexane–AcOEt, 2:1) 0.44; ^1H NMR (δ, $CDCl_3$) 3.51 (s, 4, benzylic), 3.67 (s, 4, benzylic), 5.90 (br s, 1, benzene), 6.28 (s, 2, furan), 7.05–7.35 (m, 3, benzene); MS, m/z M^+ 254. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.52; H, 5.59.

A mixture of **19** (0.2 g, 0.786 mmol), KOH (2.2 g), 100% hydrazine hydrate (6 mL), and ethylene glycol (15 mL) was refluxed for 1.5 h. Similar workup of the mixture as described for **4** afforded **20** (0.101 g, 57%) as colorless crystals. **20** (57%): colorless plates by sublimation (70–80 °C, 1 mmHg); mp 51.5–52.5 °C; ^1H NMr (δ, $CDCl_3$) 1.9–3.0 (m, 12, $-CH_2CH_2CH_2-$), 5.16 (s, 2, furan), 6.55–7.20 (m, 3, benzene), 6.95 (br s, 1, benene); MS, m/z M^+ 226. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.68; H, 7.99.

[3]Metacyclo[3](2,5)thiophenophane (23). A mixture of *n*-Bu_4NI (1.2 g, 3 mmol), CH_2Cl_2 (1.5 L), and NaOH (20 g) dissolved in water (70 mL) was heated to reflux with stirring. To the mixture was added a mixture of **21** (1.7 g, 9.61 mmol) and **2** (4.5 g, 9.13 mmol) in CH_2Cl_2 (400 mL) over a 5.5-h period. The mixture was refluxed for an additional 3 h. The mixture was worked up in a similar manner as described for **3**. Purification of the crude product by silica gel chromatography with AcOEt–hexane (1:3) afforded **22** (1.0 g, 41%) as colorless crystals. **22**: colorless needles from hexane–AcOEt; mp 206–207 °C; R_f (silica gel, hexane–AcOEt, 2:1) 0.36; ^1H NMR (δ, $CDCl_3$) 3.63 (br s, 4, benzylic), 3.78 (q, J = 17 Hz, 4, benzylic), 6.01 (br s, 1, benzene), 6.93 (s, 2, thiophene), ca. 7.11 (m, 3, benzene); MS, m/z M^+ 270. Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.09; H, 5.22. Found: C, 70.81; H, 5.11.

A mixture of **22** (0.594 g, 2.2 mmol), KOH (6 g), 100% hydrazine hydrate (18 mL), and ethylene glycol (30 mL) was refluxed for 2.5 h. Similar workup of the mixture as described for **4** afforded **23** (0.389 g, 73%). **23**: colorless crystals by sublimation (70–80 °C, 1 mmHg); mp 37–38 °C (lit.[12] mp 39–40 °C, ^1H NMR (δ, $CDCl_3$) 1.7–3.2 (m, 12, $-CH_2CH_2CH_2-$), 5.92 (s, 2, thiophene), 6.26 (br s, 1, benzene), 6.65 (AB_2, J = 9 Hz, 2, benzene), 6.93 (AB_2, J = 9 Hz, 1, benzene); MS, m/z M^+ 242. Anal. Calcd for $C_{16}H_{18}S$: C, 79.29; H, 7.48. Found: C, 79.14; H, 7.62.

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