Nontemplate Synthesis of Macrocyclic Tetraimine Schiff Bases Incorporating Dithienylmethane Units[1)]

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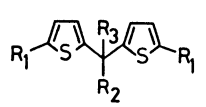
Synopsis. Novel 26- and 28-membered macrocyclic tetraimine Schiff bases incorporating four thiophene units as ring constituents were synthesized by a nontemplate method starting from bis(5-formyl-2-thienyl)methane derivatives and aliphatic diamines under high-dilution conditions.

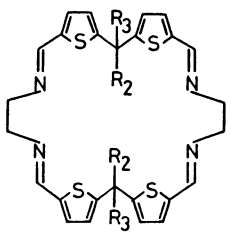
Recently, much attention has been given to the synthesis and characterization of macrocyclic tetraimine Schiff bases and their metal complexes.[2)] In addition to ligands, macrocyclic Schiff bases are potential precursors[3)] of the cyclic tetramines, which are also ligands,[4)] and potential inclusion hosts[5)] for organic molecules. Although several macrocyclic Schiff bases incorporating a heteroaromatic unit as a ring constituent have been reported,[6)] most of them have been derived from 2,6-pyridinedicarbonyl compounds and isolated as metal complexes. In spite of growing interest as mixed donor macrocyclic ligands, macrocyclic Schiff bases incorporating a heteroaromatic unit other than a pyridine nucleus have received less attention. Regarding the thiophene family, for example, it is limited to those[7-9)] derived from 2,5-thiophenedicarbaldehyde, all of which contain two thiophene units as a ring constituent. We investigated the synthesis of a novel-type macrocyclic Schiff bases (**3** and **4**)[5)] which contain four thiophene units, namely two di-2-thienylmethane units substituted at the methylene bridges. The results are reported.

Macrocyclic Schiff bases have generally been synthesized by the condensation of dicarbonyl compounds with diamines by employing a metal template procedure. However, it is rather difficult to isolate metal-free Schiff bases from the metal complex, because of the instability of the macrocycles under demetalation conditions. Only a few examples[3,5,7,9)] for the nontemplate synthesis of macrocyclic Schiff bases have been reported, including those prepared by the [2+2] condensation of 2,5-thiophenedicarbaldehyde with α,ω-alkanediamines[7,9)] under reflux in ethanol.



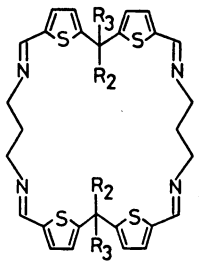
1, 2

1a: R_1=H, R_2=R_3=-CH_3
1b: R_1=H, R_2=-CH_3, R_3=-C_2H_5
1c: R_1=H, R_2=-CH_3, R_3=-c-C_3H_7
2a: R_1=-CHO, R_2=R_3=H
2b: R_1=-CHO, R_2=R_3=-CH_3
2c: R_1=-CHO, R_2=-CH_3, R_3=-C_2H_5
2d: R_1=-CHO, R_2=-CH_3, R_3=-c-C_3H_7



3

3a: R_2=R_3=H
3b: R_2=R_3=-CH_3
3c: R_2=-CH_3, R_3=-C_2H_5
3d: R_2=-CH_3, R_3=-c-C_3H_7



4

4: R_2=R_3=-CH_3

The 26-membered macrocycles, **3a—d**, which contain four thiophene units, could also be synthesized in high yields in the absence of a template metal by using a high-dilution procedure. Thus, when equimolar amounts of bis(5-formyl-2-thienyl)methane derivatives, **2a—d**, and 1,2-ethanediamine were allowed to react in a highly diluted $CHCl_3$ solution at room temperature, the expected **3a—d** were obtained in 70—86% yields. The 28-membered macrocycle (**4**) was obtained similarly by the condensation of **2a** and 1,3-propanediamine, but in rather low yield (18%). The condensation of **2b** with 1,4-butanediamine or 1,6-hexanediamine for the synthesis of 30- or 34 membered macrocycles gave no macrocyclic imines, but only polymeric materials. These results indicate that 1,2-ethanediamine is the most suitable building block for the construction of the macrocyclic tetraimine Schiff bases derived from bis(5-formyl-2-thienyl)methane derivatives, **2a—d**. The reason why **2** efficiently undergoes the [2+2] condensation with 1,2-ethanediamine, but not with its higher homologs, is not clear at present. The contribution of the facile precipitation of the products in the reaction media as well as the conformation of the starting dicarbonyl compounds were suggested to be the result of efficient [2+2] condensation of 2,5-pyrrole- or 2,5-thiophenedicarbaldehyde with 2-hydroxy-1,3-propanediamine.[9)] However, this is not the case regarding the condensation of **2** with 1,2-ethanediamine; products **3** and **4** are soluble in the reaction media, $CHCl_3$, and are derived from the same dicarbonyl compound, **2**. There must be a favoured mutual positioning between the two end groups of the noncyclic intermediates in the final stage of the ring closure between **2** and 1,2-ethanediamine.

The structures of **3a—d** and **4** were determined by elemental analysis as well as spectral data (MS, IR, ^1H and ^{13}C NMR). The IR spectra display an absorption band in the 1620—1630 cm^{-1} region (C=N stretching band). The ^1H NMR spectra show singlets at δ 8.15—8.18, while ^{13}C NMR singlets at ca. 156 ppm are ascribable to the four equivalent imine protons and imine

carbons, respectively. Any signals due to aldehyde and primary amine were not detected in the IR and NMR spectra.

All of the macrocyclic Schiff bases oblained are, contrary to our expectation, only slightly soluble in most solvents, except $CHCl_3$. Variatons of the alkyl group at the methylene bridges and of amine produced little effect on solubility. This makes it difficult to utilize **3** (or **4**) as inclusion hosts or a precursor for the macrocyclic polyamines.

Experimental

All melting points are uncorrected. The ^1H and ^{13}C NMR spectra were obtained on a Hitachi R-90H (90.0 MHz) and Hitachi R-90H (22.6 MHz) spectrometer, using TMS as an internal reference. The IR and Mass spectra were recorded on Hitachi EPI-S2 and UMU-5MG spectrometers. 2,2-Di(2-thienyl)propane (**1a**) and 2,2-bis(5-formyl-2-thienyl)propane (**2b**) were obtained according to methods described in the literature.[10]

Synthesis of 2,2-Di(2-thienyl)butane (1b). The procedure is a modification of the method used for the synthesis of **1a**.[10] 2-Butanone (48.3 g, 0.67 mol) was added to a mixture of thiophene (84 g, 1 mol) and 72% aqueous H_2SO_4 (126 g) over a period of 30 min at room temperature; the mixture was then stirred at 70—75 °C for 4 h. The cooled mixture was extracted with $CHCl_3$ (300 ml×2) and washed with water and dried over Na_2SO_4. After removing the solvent, the residue was distilled under reduced pressure to give **1b** (41.8 g, 38%). Colorless oil, bp 108—115 °C/3 Torr (1 Torr=133.322 Pa). IR ($CHCl_3$) 2980, 2950, 850, and 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (3H, t, J=7.2 Hz), 1.78 (3H, s), 2.23 (2H, q, J=7.2 Hz), 6.82 (2H, d, J=2.4 Hz), 6.85 (2H, d, J=4.2 Hz), and 7.08 (2H, d,d, J=4.2, 2.4 Hz); MS m/z 222 (M^+, 28%). Anal. ($C_{12}H_{14}S_2$) C, H.

Synthesis of 2,2-Di(2-thienyl)-3-methylbutane (1c). By a similar procedure used for the preparation of **1b**, **1c** was obtained in 19% yield. Yellow oil, bp 137—145 °C/5 Torr. IR ($CHCl_3$) 2970, 2860, and 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (6H, d, J=5.4 Hz), 1.75 (3H, s), 2.40—2.80 (1H, m), and 6.80—7.20 (3H, m); MS m/z 236 (M^+, 11%). Anal. ($C_{13}H_{16}S_2$) C, H.

Synthesis of Bis(5-formyl-2-thienyl)methane (2a). This compound was not obtained in satisfactory yield by the reported procedure.[11] Another route described below was used. A solution of bis(5-bromo-2-thienyl)methane[12] (6.3 g, 19 mmol) in dry ether (40 ml) was added over a period of 10 min to 15% buthyllithium-hexane solution (19 g) in dry diethyl ether (30 ml) at −40 °C—−50 °C under N_2 atmosphere. Then, *N*,*N*-dimethylformamide (DMF) (2.8 g, 38 mmol) in dry diethyl ether (20 ml) was added over a period of 5 min; the mixture stirred for 1 h at room temperature. After this solution was added to crushed ice (100 g) the ether layer was washed successively by a 5% HCl aqueous solution, a saturated $NaHCO_3$ solution, and a saturated NaCl solution and then dried over Na_2SO_4. After removing the solvent, the crude product was crystallized with ethanol to give **2a** (1.9 g, 42%). Colorless prisms, mp 95 °C (lit.[11] 95 °C). IR (KBr) 1645 cm^{-1} (CHO); ^1H NMR ($CDCl_3$) δ=4.43 (2H, s), 7.00 (2H, d, J=3.6 Hz), 7.62 (2H, d, J=3.6 Hz), and 9.83 (2H, s, CHO); MS m/z 236 (M^+, 100%).

Synthesis of 2,2-Bis(5-formyl-2-thienyl)butane (2c). To a mixture of **1b** (22.2 g, 0.1 mol) and DMF (9.2 g, 0.13 mol), $POCl_3$ (19.2 g, 0.13 mol) was added under cooling in a water bath with stirring. The mixture was stirred at 80—90 °C for 1 h and then cooled to room temperature. DMF (9.2 g, 0.13 mol) and $POCl_3$ (19.2 g, 0.13 mol) were added to this mixture. After heating at 80 °C for 2 h, the reaction mixture was poured into crushed ice (100 g), neutralized with sodium acetate, and then extracted with $CHCl_3$ (250 ml×2). The $CHCl_3$ layer was washed with water (200 ml×2) and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (Wako C-200, hexane/ethyl acetate=1/1) to give the crude product, which was recrystallized from ethanol gave **2c** (12.2 g, 48%). Yellow powder, mp 63—63.5 °C. IR (KBr) 2975, 2950, 2850, 1655, and 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (3H, t, J=6.9 Hz), 1.80 (3H, s), 2.24 (2H, q, J=6.9 Hz), 6.91 (2H, d, J=3.6 Hz), 7.53 (2H, d, J=3.6 Hz), and 9.74 (2H, s, CHO); MS m/z 278 (M^+, 14%). Anal. ($C_{14}H_{14}S_2$) C, H.

Synthesis of 2,2-Bis(5-formyl-2-thienyl)-3-methylbutane (2d). Diformyl compound **2d** was obtained in 55% yield by a similar procedure to that used for the synthesis of **2c**. Pale-yellow powder, mp 88—89.5 °C. IR (KBr) 1660 and 1650 cm^{-1} (CHO); ^1H NMR ($CDCl_3$) δ=0.94 (6H, d, J=6.0 Hz), 1.80 (3H, s), 2.47—2.90 (1H, m), 7.07 (2H, d, J=3.6 Hz), 7.59 (2H, d, J=3.6 Hz), and 9.78 (2H, s, CHO); MS m/z 292 (M^+, 12%). Anal. ($C_{15}H_{16}O_2S_2$) C, H.

Synthesis of 31,32,33,34-Tetrathia-3,6,18,21-tetraazapentacyclo[26.2.1.1^{8,11}.1^{13,16}.1^{23,26}]tetratriaconta-1(30),2,6,8,10,13,15,17,21,23,25,28-dodecaene (3a). A solution of **2a** (0.25 g, 1.0 mmol) in $CHCl_3$ (20 ml) and a solution of 1,2-ethanediamine (0.06 g, 1.0 mmol) in $CHCl_3$ (20 ml) were added simultaneously to the $CHCl_3$ (20 ml) over a period of 1.5 h with stirring at room temperature. After stirring for 30 min, the reaction mixture was filtered in order to remove any insoluble precipitate; the filtrate was then dried over Na_2SO_4 and concentrated. The yellow powder, thus obtained, was washed with ethanol (20 ml×2) giving **3a** (2.2 g, 83%). Colorless powder, mp 158—165 °C (decomp). IR (KBr) 2820, 1620, and 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.83 (8H, s), 4.20 (4H, s), 6.73 (4H, d, J=3.6 Hz), 7.03 (4H, d, J=3.6 Hz), and 8.15 (4H, s); MS m/z 520 (M^+, 10%). Anal. ($C_{26}H_{24}N_4S_4$) C, H.

Synthesis of 12,12,27,27-Tetramethyl-31,32,33,34-tetrathia-3,6,18,21-tetraazapentacyclo[26.2.1.1^{8,11}.1^{13,16}.1^{23,26}]tetratriaconta-1(30),2,6,8,10,13,15,17,21,23,25,28-dodecaene (3b). (Typical procedure) The solution of 2,2-bis(5-formyl-2-thienyl)propane (2.6 g, 10 mmol) in $CHCl_3$ (50 ml) and 1,2-ethanediamine (0.6 g, 10 mmol) in $CHCl_3$ (100 ml) were added simultaneously to 50 ml of $CHCl_3$ over a period of 15 h with stirring at room temperature; the mixture was stirred for an additional 30 h. After usual work-up, the crude product was obtained as yellow powder, which was recrystallized with $CHCl_3$-hexane to give **3b** (2.4 g, 84%). Pale-yellow powder, mp 233—236 °C (decomp). IR (KBr) 2970, 2930, 2830, 1630, and 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.80 (12H, s), 3.79 (8H, s), 6.74 (4H, d, J=3.6 Hz), 6.99 (4H, d, J=3.6 Hz), and 8.18 (4H, s); ^{13}C NMR ($CDCl_3$) δ=32.41, 40.92, 61.07, 123.61, 130.04, 155.83, and 158.09; MS m/z 576 (M^+, 26%). Anal. ($C_{30}H_{32}N_4S_4$) C, H, N.

The cyclic tetraimines, **3c**, **3d**, and **4a**, were synthesized in a similar manner.

12,27-Diethyl-12,27-dimethyl-31,32,33,34-tetrathia-3,6,18,21-tetraazapentacyclo[26.2.1.1^{8,11}.1^{13,16}.1^{23,26}]tetratriaconta-1(30),2,6,8,10,13,15,17,21,23,25,28-dodecaene (3c). Yield 86%. Pale yellow powder, mp 197—200 °C. IR (KBr) 2970, 2930, 2830, 1630, and 790 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 (6H, t, J=7.2 Hz), 1.78 (6H, s), 2.22 (4H, q, J=7.2 Hz), 3.80 (8H, s), 6.75 (4H, d, J=3.6 Hz), 7.00 (4H, d, J=3.6 Hz), and 8.15 (4H, s); ^{13}C NMR ($CDCl_3$) δ=9.71, 27.96, 37.11, 44.70, 61.04, 124.06, 129.98, 140.28, 155.86, and 157.33; MS m/z 604 (M^+, 28%). Anal. ($C_{32}H_{36}N_4S_4$) C, H, N.

12,27-Diisopropyl-12,27-dimethyl-31,32,33,34-tetrathia-3,6,18,21-tetraazapentacyclo[26.2.1.1^{8,11}.1^{13,16}.1^{23,26}]tetratriaconta-1(30),2,6,8,10,13,15,17,21,23,25,28-dodecaene (3d). Yield 70%. Pale yellow powder, mp 188—191 °C. IR (KBr) 2980, 2840,

and 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 (12H, d, J=6.2 Hz), 1.70 (6H, s), 2.30—2.50 (2H, m), 3.79 (8H, s), 6.87 (4H, d, J=3.6 Hz), 7.03 (4H, d, J=3.6 Hz), and 8.17 (4H, s); ^{13}C NMR ($CDCl_3$) δ=18.42, 22.17, 39.18, 48.11, 61.07, 124.09, 130.01, 139.95, 155.93, and 157.08; MS m/z 632 (M^+, 5%). Anal. ($C_{34}H_{40}N_4S_4$) C, H, N.

13,13,29,29-Tetramethyl-33,34,35,36-tetrathia-3,7,19,23-tetraazapentacyclo[28.2.1.1^{9,12}.1^{14,17}.1^{25,28}]hexatriaconta-1(32), 2,7,9,11,14,16,18,23,25,27,30-dodecaene (4). Yield 14%. Colorless powder, mp 270—275 °C. IR (KBr) 2975, 2840, and 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40—2.40 (16H, m), 3.53 (8H, t, J=7.2 Hz), 6.76 (4H, d, J=3.6 Hz), 7.00 (4H, d, J=3.6 Hz), and 8.20 (4H, s); ^{13}C NMR ($CDCl_3$) δ=31.74, 32.38, 40.89, 58.60, 123.54, 129.64, 140.56, 154.46, and 157.94; MS m/z 604 (M^+, 1%). Anal. ($C_{32}H_{36}N_4S_4$) C, H, N.

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