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Construction of Synthetic Macroyclic Compounds Possessing Subheterocyclic Rings, Specifically Pyridine, Furan, and Thiophene

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I. Introduction

Although synthetic procedures for the construction of macrocycles containing subheterocyclic units have been known for about a century, it has only been within the past score that these compounds have been shown to possess unique chemical and biochemical properties. Numerous reviews have dealt with various limited aspects of these compounds;⁴⁰⁸ however, none has presented the detailed preparative procedures to specific macrocycle systems. We herein attempt to review both the

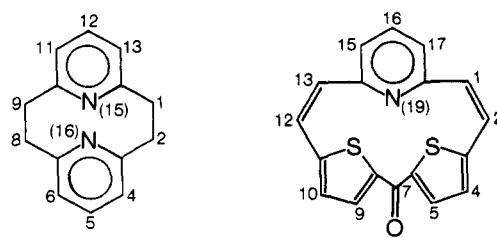
historical as well as modern methodology leading to the construction of these macrocycles.

This review will be limited in scope to the synthetic aspects leading to macrocycles possessing, specifically, pyridine, furan, and thiophene subunits. For convenience a macrocyclic ring will be defined by a 11- or larger atom ring; however, several smaller (9- and 10-) membered rings have been included in order to define the lower limits in a specific synthesis. Macrocycles of biological origin are not included, unless they were synthesized or degraded to smaller important fragments. Porphyrins and related systems have been omitted because of the vastness of the area; however, several very simple pyrrole macrocycles have been included.

This review attempts to tabulate the majority of the known literature examples of these macrocycles through December 1976. Section II defines the numbering system used throughout the text and tables. Section III presents the first historical examples of the four main subheterocyclic classes. Sections IV and V review the major synthetic routes to macrocycles possessing pyridine, furan, and/or thiophene. Section VI deals with a limited number of important miscellaneous subheterocyclic classes which have, for the most part, been prepared from a key intermediate described in sections IV and V.

II. Nomenclature and Numbering

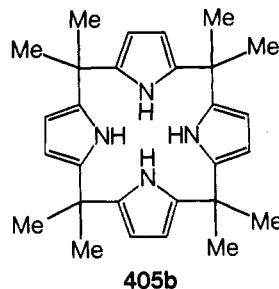
Numerous nomenclature and numbering rules have been proposed and adapted for the easy identification of the structures of organic molecules. In general when the conventional IUPAC rules²⁸⁸ are applied to the herein described macrocycles, extremely complicated and nearly impossible names can result. In order to partially circumvent this problem, Phane nomenclature²⁸⁹⁻²⁹¹ has been used, in part, in this review and appears to be a move in the right direction. However, since a drawn structure is unambiguous, this review will skirt the greatest part of the problem of communication by inclusion of the parent structures and will indicate the site(s) of substitution by adopting a modified numbering scheme proposed by Gol'dfarb et al.²³³ as well as others.²⁹² Thus, when the location of substituents is necessary, the atom adjacent to the subheterocyclic ring will be designated as atom number one with all atoms in the largest continuous ring being numbered in succession with substituted positions taking preference when necessary (see examples).



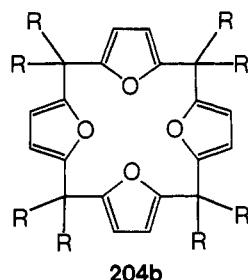
The numbering scheme is shown on the parent structures in the tables.

III. Historical Examples

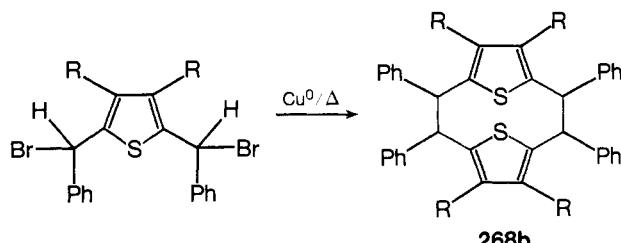
Although macrocycles which possess the pyrrole subunit are not within the primary objective of this review, it is interesting to note that the first documented macrocycle possessing a (pyrrole) subheterocyclic ring (**405b**) was synthesized in 1886 by Baeyer³²³ via the condensation of pyrrole and acetone in the presence of mineral acid. Shortly thereafter, Dennstedt³²⁴ and then Chelintzev and Tronov,³²⁵ in a series of papers, reported numerous modifications to the original Baeyer procedure. Although in these early papers most macrocyclic products possessed the tetraazaquaterene structural backbone, at least one misassignment³²⁶ was made for the product from the reaction of pyrrole and cyclohexanone; the structure was later re-assigned.³⁰³



In 1906, the first probable macrocycle, which included a furan ring, was isolated from the reaction of ethyl 2-furanoate and ethylmagnesium iodide;¹⁹⁵ even though the compound originally was identified as 3-(2'-furanyl)pent-2-ene. Wright et al.¹⁶⁹ and then Beals and Brown¹⁹⁴ synthesized "tetraoxaquaquerene" **204b** by polycondensation of furan and 3-pentanone in the presence of mineral acid (the Baeyer procedure³²³ except for the substitution of furan for pyrrole); direct comparison¹⁹⁴ of the original 1906 sample¹⁹⁵ with **204b** established the macrocyclic skeleton, thus confirming the structure of the first macrocycle containing a furan subunit.

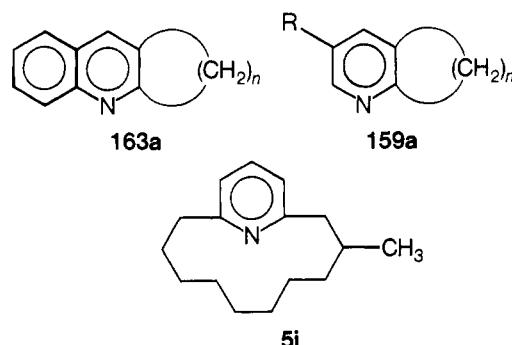


In 1930, Steinkopf proposed²⁹⁴ the first macrocycle which incorporated a thiophene ring. However, he later corrected²⁹⁹ his assignment of this cyclic structure to a nonmacrocyclic analog. In another series of classical papers, Steinkopf proposed cyclic mercury-bridged thiophenes.^{293,295,296} Recently, Meth-Cohn²⁹⁸ has suggested that Steinkopf's mercury compounds were probably polymeric, rather than macrocyclic compounds, in view of the imposed degree of strain in the mercury bond angles. In 1941, Steinkopf reported the synthesis of the first



reasonable cyclic thiophene macrocycle **268b** through a standard coupling reaction.²⁹⁷

In 1933, the first macrocycle which incorporated a pyridine ring (**163a**) was prepared by Ruzicka et al.¹²² from cyclopentadecanone (commonly known as Exalton) and 2-aminobenzaldehyde via a base-catalyzed condensation. The first nonbenzo-fused analog **159a** was synthesized 12 years later by Prelog and Geyer.¹¹⁸ Although the 2,3-bridged backbone was constructed first, the most widely known pyridine macrocycle is that of "muscopryidine". Prelog et al. isolated **5j** in 1946 from the odoriferous constituents of natural musk from the musk deer (*Moschus moschiferus*),²¹ and later Büchi et al. synthesized **5i** from cyclododecanone in a lengthy ten-step sequence.¹⁷



IV. Synthesis of Macrocycles Possessing a Subheterocyclic Ring

Tables I-IV are compilations of the majority of reported macrocycles containing one or more pyridine, thiophene, and/or furan subheterocyclic ring(s). Each table contains the parent structure, location and type of substitution, compound number for easy text reference, reported physical data, an indication of the spectral information cited in the literature, and general comments which may be of importance for specific listing. Certain macrocycles possess complexation properties; therefore, the metal ions that have been reported to be incorporated in that ligand have been abbreviated in these tables. Tables V and VI contain selected macrocycles which possess either a six- or five-membered subunit, respectively, as well as a limited number of representative compounds that contain only the pyrrole subunit. These miscellaneous examples are included since they were cited in one of the included references.

A. Pyridine as the Subunit

Macrocycles possessing only the pyridine subunit are tabulated in Table I.

1. 2,6-Pyridino

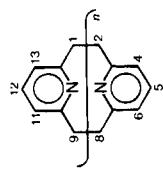
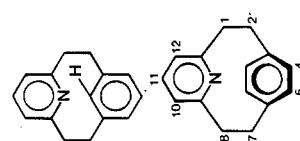
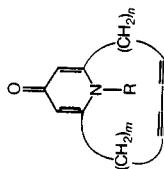
The classical example of a carbon-bridged 2,6-disubstituted pyridine unit contained within a macrocycle was constructed by Büchi et al.¹⁷ The Stobbe condensation of cyclododecanone with ethyl succinate gave an exocyclic carboxylic acid, which was subsequently cyclized with either zinc chloride in acetic acid or preferably polyphosphoric acid to a δ -keto β,γ -unsaturated ester. Hydrolysis and concomitant decarboxylation generated the expected α,β -unsaturated ketone. Wolff-Kishner reduction of bicyclo[10.3.0]pentadec-1(12)-en-13-one¹⁶² gave two isomeric olefins, from which, fortuitously, the trisubstituted olefin was isolated as the major (70%) isomer. A subsequent Schmidt reaction followed by dehydrogenation over 10% palladium on carbon at ca. 250 °C afforded an equal mixture of macrocycles: **5a** and its 2,3-isomer **158**, both in about 4% overall yield.

Conversion of **5a** into muscopryidine (**5j**) was accomplished¹⁷ by α -substitution of the corresponding pyridine N-oxide in the presence of acetic anhydride.³⁰⁰ Hydrolysis of **5e** afforded **5d**,

TABLE I. Macrocycles Containing the Pyridine Subunit^a

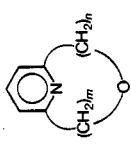
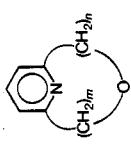
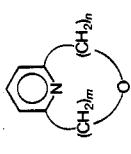
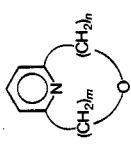
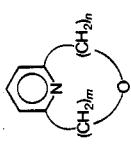
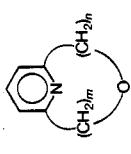
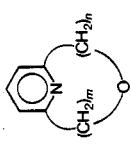
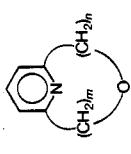
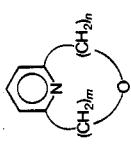
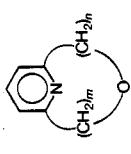
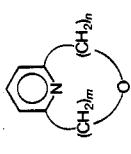
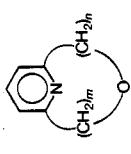
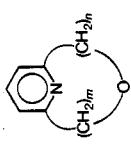
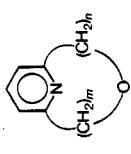
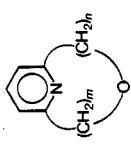
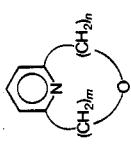
TABLE I (Continued)

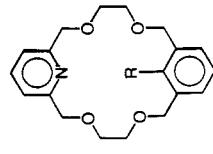
| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) general comments ^d | Ref |
|----------|----------|--|-----------|-----------------------------------|---|--|---|
| | 11 | R = H | 9 | 177–178 | B | | 94 |
| | H | | 10 | | A | VTNMR study | 6, 37 |
| | H | | 11a | 80.5–81.5 83–84 152–153 | A, B, D | VTNMR study ^e | 9 7 9 |
| | | 1(2),7(8)-(SMe) ₂ 1(2),7(8)-[S ⁺ (Me) ₂] ₂ | 11b | | A, D | | 9 |
| | | 2BF ₄ ⁻ | 11c | | A–C | | 9 |
| | | 16-H (BF ₄ ⁻) | 11d | 179–183 | A, B, D | | 9 |
| | | 16-N ⁺ O | 11e | 165–167 | A, C, D | | 9 |
| | | 1,2,7,8-De(H) ⁴ | 11f | 157–158 | X-ray study | | 9 |
| | | 1,2,7,8-De(H) ⁴ | 11g | | A, C | | 10 |
| | | 16-H (BF ₄ ⁻) | 11h | 207–210 | | | 9 |
| | | 1,2,7,8-De(H) ⁴ | 11i | | | | 9 |
| | | 16-BF ₃ | 11j | 204–206 | A, C | | 9 |
| | H | | 12a | 256–258 | PESS ^{2,62} | | 11–13, 16, 18, 19, 37, 98, 262 |
| | | | | | A | | 6, 7, 15 |
| | | | | | Isomer A Isomer B | | 12 |
| | | | | | | | 12 |
| | | | | | | | 12 |
| | | | | | | | 12 |
| | | | | | | | 12 |
| | | | | | | | 13, 19 |
| | | | | | | | 16 |
| | | | | | | | 13 |
| | | | | | | | 13, 16 |
| | | | | | | | 13 |
| | | | | | | | 16 |



| | | | | | |
|------------------------------|---|-----|------------------------------------|----------------|--|
| <i>n</i> = 2; <i>m</i> = 3-6 | H | | 19a-d | | 405b |
| <i>n</i> = <i>m</i> = 10 | 13, 28-(Me) ₂ | 20 | 103-105 | | 3 |
| 2 | H | 21 | 134.5-135 | A, B | 102 |
| | | | | | |
| 1 | H | 22 | 176-178 | A, B | 102 |
| 2 | H | 23 | 185-187 | A, B | 102 |
| 3 | H | 24 | 196-199 dec | A | 102 |
| 4 | H | 25 | 218-221 | A | 102 |
| | | | | | |
| — | R = OMe | 26 | 154.5-156.5 | A, B | Lythraceous alkaloids 134-136 |
| | | | | | |
| | | | | B-D | Light sensitive 308 |
| | | | | | |
| | R = (-CH=CH-) | 27 | | | |
| | | | | | |
| | R = (-CH=CH-) | 28 | 450; subl: 400 (10 ⁻⁴) | A, B, D | Co, Cu, Ni 90, 91, 103, 308 |
| | | | | | |
| | H | 29 | | X-ray analysis | 22 |
| | | | | | |
| 3 | H | 30a | 40-41 | A | pK _a 4.8 (\pm 0.2) |
| | 3,4:12,13-Dibenzo | 30b | 132 dec | A | K, Co, Na, NH ₄ , Ag, Pr, Rb, Ba, Hg |
| | 3,4:12,13-Dibenzo; N \rightarrow O | 30c | 159 dec | A | K 374 374 |

TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data ^b Mp/bp (mm), ^c °C | Spectral data available ^a | Metal complex(es) general comments ^d | Ref |
|---|--|--------------|-----------|---|--------------------------------------|--|---------|
|  | <i>n</i> = <i>n</i> = 4 | H | 31 | | | | 93b |
|  | <i>n</i> = 0; <i>m</i> = 2 | H | 32a | 83–84 | A, B | | 25, 487 |
|  | <i>n</i> = 0; <i>m</i> = 2 | (±)-2-Me | 32b | 54–55 | A, B, D | CMR | 487 |
|  | <i>n</i> = 0; <i>m</i> = 3 | H | 33 | 76–78 | A, B, D | | 25, 487 |
|  | <i>n</i> = 0; <i>m</i> = 4 | H | 34 | [155–160 (0.15)] | A, B, D | | 487 |
|  | <i>n</i> = 1; <i>m</i> = <i>p</i> = 0 | H | 35 | 215–216 | A, B | | 25, 487 |
|  | <i>n</i> = 1; <i>m</i> = 0; <i>p</i> = 1 | H | 36 | 94.5–95.5 | A–C | | 25, 487 |
|  | <i>n</i> = 1; <i>m</i> = 1 | H | 37 | 111–112 | A–C | | 25, 487 |
|  | <i>n</i> = 1; <i>m</i> = 2 | H | 38a | 117–120 | A | | 25, 487 |
|  | <i>n</i> = 1; <i>m</i> = 2, 17(24)-(Me) ₂ | | 38b | 109–110 | A, B, D | Isomer A | 487 |
|  | <i>n</i> = 2; <i>p</i> = 2 | | 38c | Oil | A, B, D | Isomer B | 487 |
|  | <i>n</i> = 1; <i>m</i> = 2; <i>p</i> = 3 | | 38d | Oil | A, B, D | Isomer C | 487 |
|  | <i>n</i> = 1; <i>m</i> = 3 | H | 39 | 71–72 | A, B, D | | 487 |
|  | <i>n</i> = 1; <i>m</i> = 4 | H | 40 | 83–84 | A, B, D | | 487 |
|  | <i>n</i> = 2; <i>m</i> = 1 | H | 41 | 90–91 | A, B, D | | 487 |
|  | <i>n</i> = 2; <i>m</i> = 2 | H | 42 | 120.5–121.5 | A, B | | 25, 487 |



R = CO₂H
R = CO₂Me

172–181
Oil

A, D
A, D

34
34

| | | | | | |
|---|--|-----|--------------------|-------------------------------------|--------|
| 1 | H | 44 | 172–175 125–128 | A | 23, 24 |
| 2 | H | 45 | | A | 23, 24 |
| 3 | H | 46 | 173–176 | A | 23, 24 |
| | $n = 1;$ $m = 1$ | 47 | Oil | A, B | 39 |
| | $n = 2;$ $m = 1$ | 48 | | A, B | 39 |
| | $n = 1;$ $m = 2$ | 49 | 145–146 | A, B | 39 |
| | $n = 2;$ $m = 2$ | 50 | | A, B | 39 |
| | | | | | |
| | | | | pK_a 5.3 (3.6) | 23, 24 |
| | | | | $[\alpha]_D^{25} + 107^\circ$ | 23 |
| | | | | | 100 |
| | | | | (Impure sample) | 23 |
| | | | | | |
| 1 | H | 51a | 147–148 | A, C | 23, 24 |
| 1 | 3,4:14,15-Dibenzo | 51b | 184–186 | C | 26 |
| 1 | 3(R),4(R),14(R), 15(R)-(CONMe ₂) ₄ | 51c | 224 | C | 26 |
| | | | | C | 26 |
| | | | | C | 26 |
| | | | | | |
| 1 | H | 52 | | A | 23, 92 |
| | | | | $[\alpha]_{S,6}^{25} - 302^\circ$ | |
| | | | | | |
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |

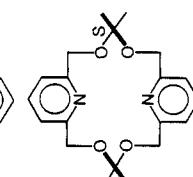
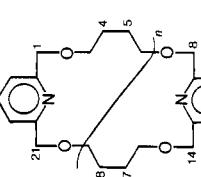
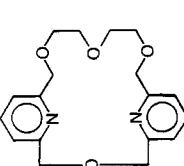
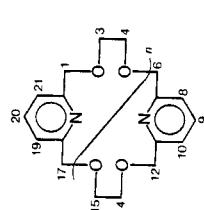
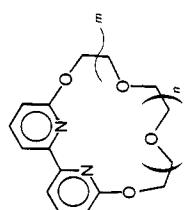
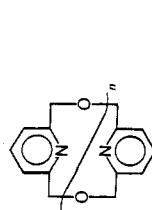


TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es)/ general comments ^d | Ref |
|----------|----------|--------------|-----------|-----------------------------------|--------------------------------------|---|---------|
| | H | | 58 | | | | 92 |
| | H | | 59 | | $[\alpha]_{578}^{25} -242^\circ$ | | 92 |
| | H | | 60 | | $[\alpha]_{578}^{25} -250^\circ$ | | 92 |
| | H | | 61 | 209-211 161-163 | A, B | | 39, 102 |
| | H | | 62 | | A, B | | 39, 102 |
| | H | | 63 | 122-124 | A, B | | 39, 102 |
| | H | | 64 | | A, B | | 39 |

| | | | | |
|---|---|------------|---|--|
| 1 | H 1,12-(Me) ₂ (abr: "B") | 65a 65b | (B, C, Mossbauer ⁸⁹) ^c | Fe, Mn, Zn Fe[x-ray] ^{1,2} , Mn, Zn |
| | | | (B, C, x-ray ^{o7}) ^c | Mg Mn, Zn [x-ray: Mn- (C ₁₀ J) ₂] Fe, Co, Ni, Cu |
| 2 | 1,12-(Me) ₂ ; 1,2,11,12- (H) ₄ (abr: pyane N _s) 1,12-(Me) ₂ (abr: "A") | 65d 66 | (B,C) ^c | F ^e |
| | 1,12-(Me) ₂ (formerly cyp ¹¹ ; CR ⁴⁴) | 67a 67b | (B, C) ^c (A-C) ^c | Zn Co |
| | | | (A-C, ESR, ⁴⁸ X-ray ^{49,322}) ^c | Ni Cu |
| | | | (B, C, ESR) ^c | Zn Ni |
| | | | (B, C) ^c | 40, 45-49, 52, 322 45, 278 |
| | | | (B) ^c | 40, 44 342 |
| | | | (B, C) ^c | D isomer (131-134°) |
| | | | (B, C) ^c (A-C) ^c | 52 |
| | | | (A-C, ESR ⁴⁸ , X-ray ³²²) ^c | From meso: Co ^d From meso: Ni |
| | | | (B, C, Mossbauer) ^c | 44, 50, 51 46-48, 53, 322 |
| | | | (B, C, ESR) ^c | 54, 274 278 |
| | | | Ni[(ClO ₄) ₃ ⁻ (diamagnetic); (ClO ₄) ₂ ⁻ (paramag- netic)] | 342, 501 |
| | | | (A-C, ESR ⁴⁸) ^c | 47, 48 40 |
| | | | (B, C) ^c | |
| | | | (A-C, ESR ⁴⁸) ^c | 47, 48 |
| | | | (B, C) ^c | Ni, Cu |
| | | | (B, C) ^c | Ni, Cu, Zn |
| | | | (B, C) ^c | 40 |
| | | | (B, C) ^c | Attempted |
| | | | 1,14-(Me) ₂ | |

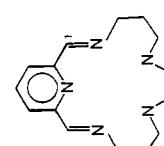
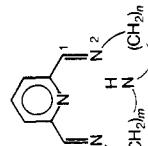
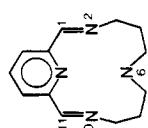
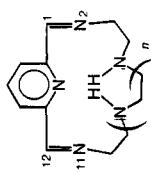


TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) general comments ^d | Ref |
|----------|----------|--|-----------|-----------------------------------|--|--|-------------------------------------|
| | | 1,9,15,23-(C=O), 6-Me; | 72 | >360 | | | 431 |
| | | | 73 | 164–166 | Cu [mp 196–198° dec] | | 29 |
| | H | | 74 | 226–228 | | | 29 |
| | H | 1,13-(Me) ₂ (abr: "C") | 75a | | (B, C, x-ray ^{27,29}) ^c | Fe, Mn, Zn Mg, Fe, Mn | 279, 97, 275, 279, 393–395 |
| | | 1,6,12,17-(Me) ₄ , 3,4: 14,15-dibenzo (abr: tmed) | 75b | | (B–D, ESR) ^c | Cu | Theoretical calculations 61 |
| | X = Y = | | 77a | | | | 65 |
| | X = Y = | | 77b | | | | 63, 64 |

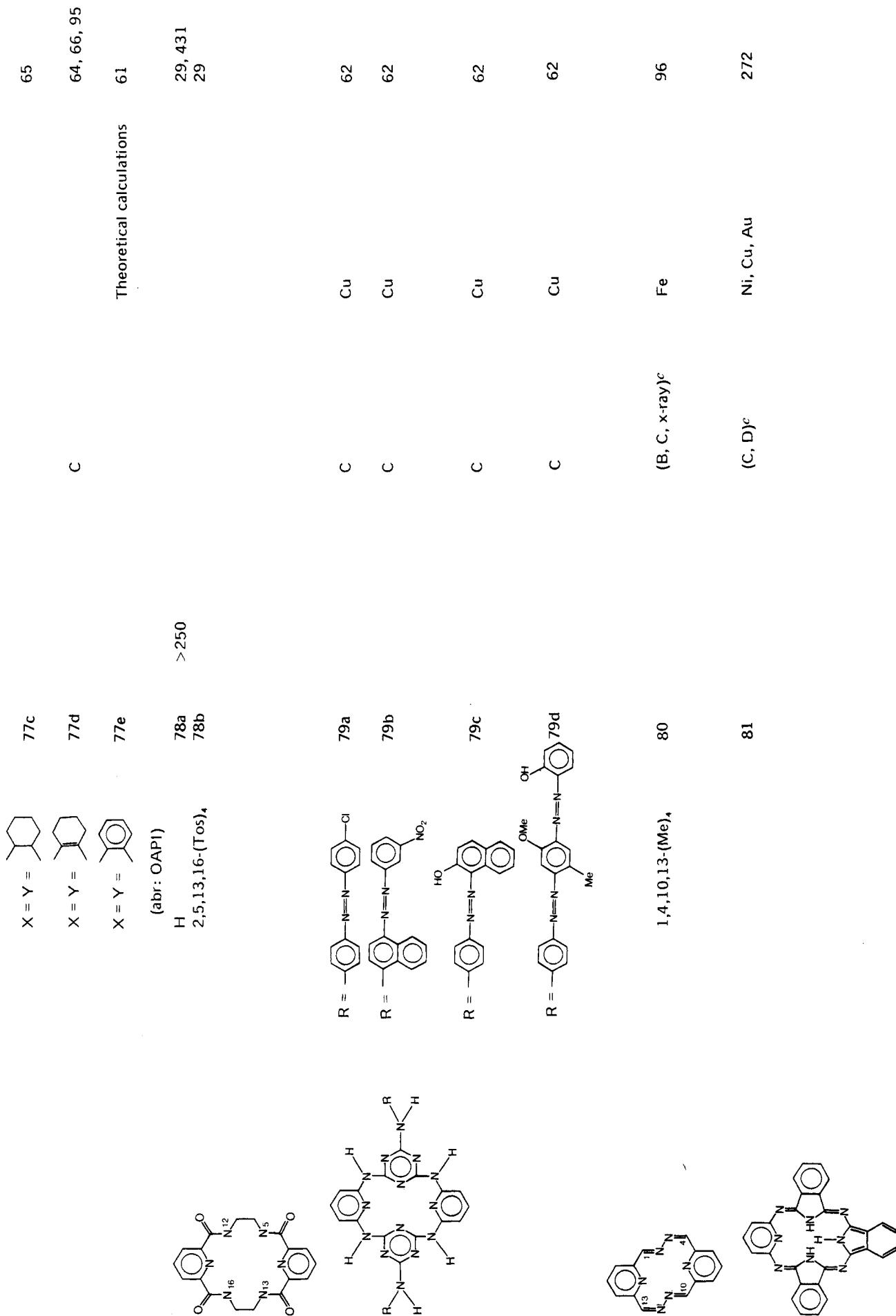


TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) general comments ^d | Ref |
|----------|-------------------------|--------------|-----------|-----------------------------------|--------------------------------------|--|---------|
| | 3,5,5-(Me) ₃ | | 82 | | | | 280 |
| | H | | 83 | | C, D | Ni | 321 |
| | R = (2-cyano-phenyl) | | 84 | | B-D | Cu | |
| | R = OH | | 85 | | | Cu, Co | 384 |
| | | | 86 | | 152-154 | A | 27 |
| | H | | 87a | 78-79 | A | A | 28 |
| | N→O | | 87b | 107-109 | A | A | 27 |
| | N→O | | 88 | 98-99 | A | A | 27 |
| | N→O | | 89 | 147-148 | A | A | 27, 283 |
| | N→O | | 90 | 138-140 | A | A | 27 |
| | N→O | | 91 | 89 | A | A | 27 |
| | N→O | | 92 | 73-75 | A | A | 27 |
| | N→O | | 93 | 117-120 | A | A | 27 |
| | N→O | | 94 | 54-55 | A | A | 27 |

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|---|---|--------------------|-----|------------------|--------|--|
|  | 0 | H | 95 | 74–77 162–163 | A A | 431 |
|  | 1 | H | 96a | 162–163 | A A | 29, 431 |
|  | 1 | N→O 5-sulfoxide | 96b | 151–152 | A, D | Ag (mp 217–219°; A) Hg (mp 198–200° dec; A) |
|  | 2 | H | 96c | 171–174 | A | Ag, Hg, Au, Pd, Pt, Co |
|  | | H | 97 | 131–133 | A | 283 |
|  | | H | 98 | 151–153 (subl) | A | Cd, Co, Ni |
|  | | Zn | | | | 431 |
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TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) ^b general comments ^c | Ref |
|----------|----------|---|-----------|-----------------------------------|--------------------------------------|---|------------------|
| | | H 2,9-15Me(BF ₄) ₂ | 105a | 177–178 | A, C, D | | 7, 9 |
| | | 2-Sulfone N→O,2,9-bis(sulfone) | 105b | 228–230 | A, B (D ⁴²⁹) | | 428 |
| | | N→O,2,9-bis(sulfone) | 105c | >340 | A, B, D (D ⁴²⁹) | | 9, 428 |
| | | N→O,2-sulfoxide 2-sulfoxide; 9-sulfone | 105d | 226–228 dec | A, B (D ⁴²⁹) | | 428 |
| | | N→O,2-sulfoxide 2-sulfoxide; 9-sulfone | 105e | >250 dec | A, B, (D ⁴²⁹) | | 428 |
| | | N→O,2,9-bis(sulfone) | 105f | 220–250 (color change) | A (D ⁴²⁹) | Sublimed: 220–245° (0.002) | 428 |
| | | N→O,2-sulfoxide; 9-sulfone | 105g | >300 | A, B (D ⁴²⁹) | | 428 |
| | | N→O,2-sulfoxide; 9-sulfone | 105h | | | | |
| | 1 | H | 106a | 220–2222 230–230.5 | A | | 18, 32 12, 98 |
| | | (N→O) ₂ (N→O) ₂ ; bis(sulfone) | 106b | 211 d | A | | 27 |
| | | Bis(sulfone) | 106c | | | | 18 |
| | | [SM ₂ (BF ₄) ₂] ₂ | 106d | | | | 18 |
| | | H | 106e | | | | 12 |
| | 2 | H | 107 | 185–188 | A, D | | 18 |
| | | H | 108 | | A, D | | 98 |
| | | H | 109 | 150–152 | A, D | | 98 |
| | | | 110 | | | | |
| | 1 | 3,4,9,10-Dibenzozo | | | | Mn, Zn | 36 |

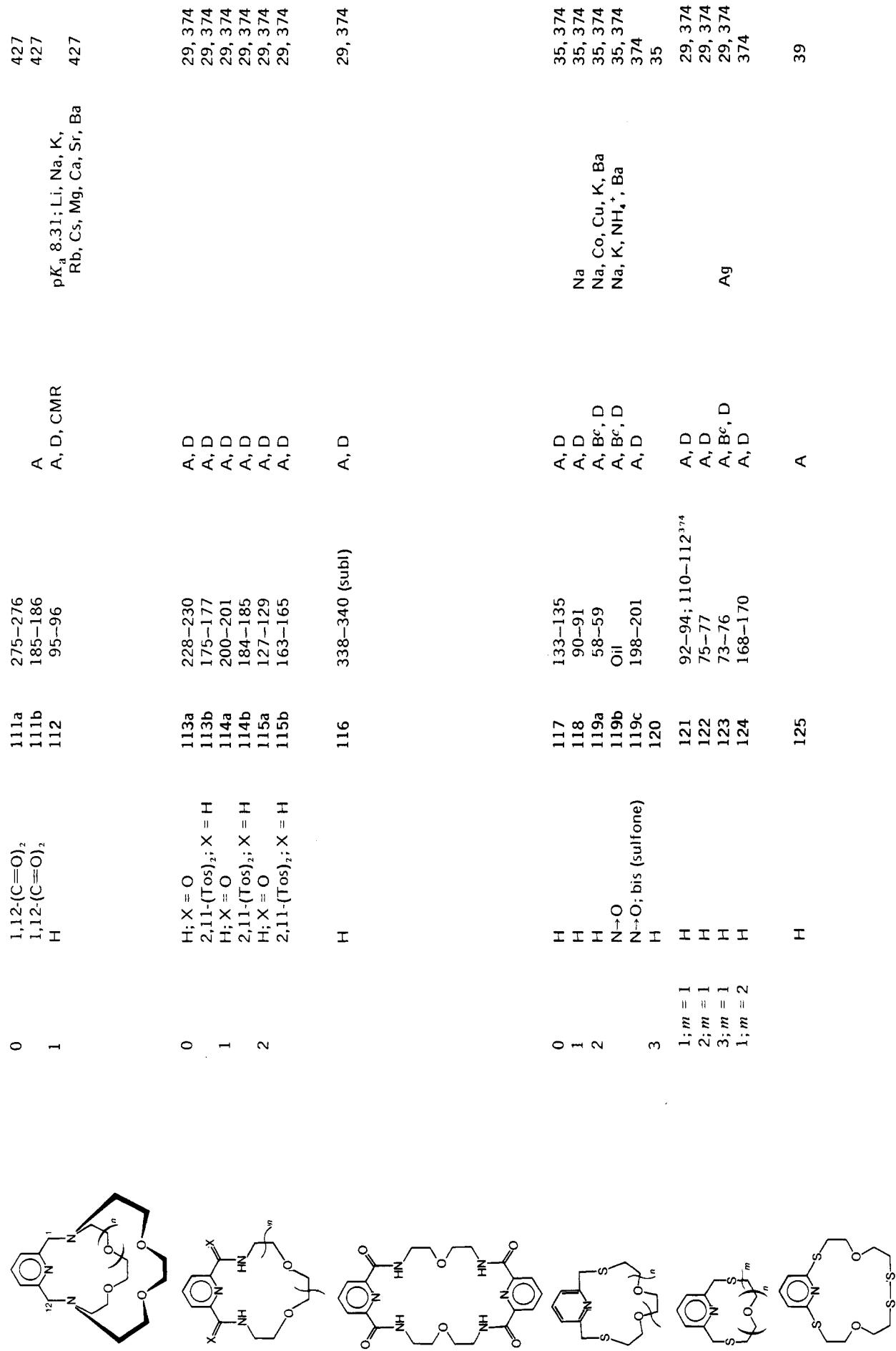


TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data ^b Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) ^c general comments ^d | Ref |
|----------|--|--------------|-----------|--|--------------------------------------|---|------------|
| | 5-Me | | 126 | 67–69 | A | Cu, Fe | 431 |
| | 1,9-(C=O) ₂ | | 127 | 242–243 | A | | 431 |
| | 1,10-(C=O) ₂ | | 128 | 234–236 | A | | 431 |
| | 3,4:9,10-Dibenzo | | 129 | | | Mn, Zn | 36 |
| | 1 | | | | | Cu, Co, Ni, Zn | 38 |
| | 1,14-(Me) ₂ , 3,4:7,8: 11,12-Tribenzo- | | | | | Zn, Cd | 131 |
| 2 | R = Et R = <i>i</i> -Pr | | | | 132a 132b | >300 dec 250 dec | 137 137 |

| | | |
|---|--|---|
| 1,11-(Me) ₂ | 67 | Ni |
| 1,11-(Me) ₂ ; 1,2,10, | 67 | Ni |
| 11-(H) ₄ (abr: pn ₂ , H) [“meso”] | 67 | D |
| 1,11-(Me) ₂ ; 1,2,10, 11-(H) ₄ ; 6-S | 67 | |
| (abr: P _{cc} BF) | 134 | F _e , Zn, Ni, Co |
| | | X-ray ^c |
| | | X-ray ^c |
| 8 | H 1.(=O) | [70–75 (0.01)] 43–48 [105–110 (0.02)] |
| | 135a 135b | A–C |
| 9 | 1-OH 1-OAc (±)-H (+)-H | [125–135 (0.02)] [110–115 (0.01)] [80–81 (0.04)] [80 (0.01)] |
| | 135c 135d 136a 136b | A, B A A–C |
| | 136c | [145–146 (0.03)] Oil 96–97 |
| | 136d | 47–59 [135–140 (0.01)] 70–72 66–68 |
| | 136e 137a 137b 137c 137d | A A A–C A–C A–C |
| 10 | 1-(=O) H 1-OH 1-OAc 1.(=O) | [105–115 (0.03)] [75–78 (0.01)] [155–160 (0.02)] [125–130 (0.01)] 79–82 [140–150 (0.01)] |
| | 138a 138b 138c 138d | A–C A–C A–C A–C |
| 11 | H 1-OH 1-OAc 1.(=O) | [90–95 (0.03)] [140–145 (0.03)] [110–115 (0.02)] 35–37 [120–130 (0.03)] |
| | 139a 139b 139c 139d | A A A–C A–C |
| 12 | H 1-OH 1-OAc 1.(=O) | [100 (0.01)] [140–150 (0.03)] [100–110 (0.02)] 45–48 [120–130 (0.02)] |

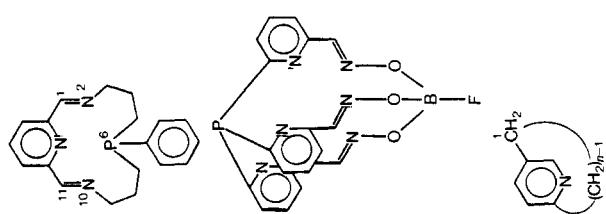
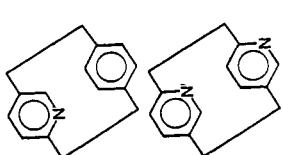
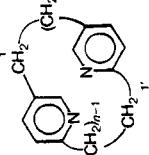
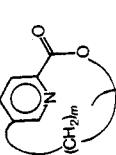
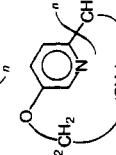
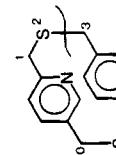
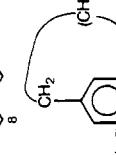
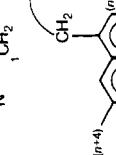
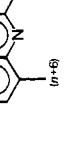


TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) general comments ^d | Ref |
|---|--|--------------|------------------------------|------------------------------------|--------------------------------------|---|-------------------------------|
|  | H | | 140 | 256–258 | A | | 85, 89 |
|  | H | | 141 | | A | 4 isomers(separable) | 85–88 |
|  | 1 = 1' = (==O) ₂ 1 = 1' = (==O) ₂ H | | | 142 143a 143b | A-C A-C A-C | | 84 84 84 |
|  | | | | 94.5–97.5 | | | |
|  | 1, <i>m</i> = 9 <i>m</i> = 12 2, <i>m</i> = 9 | H | 144 | 103–104 145 146 | A, B A, B A, B | | 84 84 84 |
|  | | | | 38–40 72–73 | | | |
|  | | | | | | | |
|  | | | 147 | 119–120 [subl: 120 (0.05)] | D | | |
|  | 2–{==O}; 9, 10, 11, 12, 13, 14-[carpaine] (H) ₆ | | | 148a 148b 149 | 204–205 330 dec 217–218 | A A A | |
|  | | | | | | Two isomers | 89 85, 89 89 |
| | 9 | H 12-Me | 150a 150b | [115–120 (0.3)] [105–110 (0.2)] | A A, B | MeI (127–128°) | 107, 108 106 |
| | 6 | H 16-Cl | 151a 151b 152a 152b | 62–63 67–68 44–45 64.5–66 | A, C A, C A, C A, C | HCl (230–234°) Picrate (192.5–193.5°) Picrate (166.5–167.5°) Picrate (201–203°); pK _a 5.03 | 110 110 109, 110 110 |

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|--|-------|-----------|------|---|
| H | 153a | 62–63 | A, C | HCl (230–234°) |
| $\text{N} \rightarrow \text{O}$ | 153b | 119–121 | A | 109, 110 117 |
| 1-Cl (<i>syn</i>) | 153c | 109–110 | A, C | 117 |
| 20-Cl | 153d | 81.5–82.5 | A, C | 110, 113, pK_a 2.88 HCl (194–221°) $\text{N} \rightarrow \text{O}$ (122.5–123.5°) |
| 20-Cl; 1- <i>d</i> (<i>syn</i>) | 153e | 81–82 | A–C | 114 109, 113 |
| 20-Cl; N→O | 153f | 125–127 | A, C | 111 109, 113, 117 |
| 20-Cl; 1,1,10,10-(<i>d</i>), 20-Cl; 1-OH | 153g | 139–158 | A, C | 129 109 |
| Syn isomer | 153i | 160–162 | A, C | 129, 109, 113, 114, 116 |
| $\text{N} \rightarrow \text{O}$ | 153j | 174–175 | A | 113 |
| Anti isomer | 153k | 205.5–207 | A, C | 129, 109, 113, 114, 116 |
| $\text{N} \rightarrow \text{O}$ | 153l | 220–230 | A | 113 |
| 20-Cl; 1-(=O) | 153m | 136–137.5 | A–C | 109, 132 |
| 20-Cl; 1-Br (<i>syn</i>) | 153n | 149.5–151 | A, C | 109, 114, 129 |
| 20-Cl; 1-Br (anti) | 153o | 152–153 | A | 114, 129, 132 |
| 20-Cl; 1,10-(Br), 20-Cl; 1-OAc (<i>syn</i>) | 153p | 133.5–135 | A, C | 109 |
| 20-Cl; 1-OAc (<i>anti</i>) | 153q | 116–118 | A | 112, 114 |
| 20-Cl; 1-OAc (<i>anti</i>) | 153r | 118–119 | A | 112, 114, 129 |
| 1(anti), 20-(Cl), 1(syn), 20-(Cl), $\text{N} \rightarrow \text{O}$ | 153s | 140–140.5 | A, D | 112, 132 |
| 20-Cl; 1-OTos (<i>syn</i>) | 153t | 144–145 | A, C | 112, 113 |
| 20-Cl; 1-OTos (<i>syn</i>) | 153u | 189.5–191 | A | 113 |
| 20-Cl; 1-OTos (<i>syn</i>) | 153v | 104–107 | A–D | Recryst: CHCl ₃ –pet. ether recryst: ether |
| $\text{N} \rightarrow \text{O}$ (syn) | 153w | 145 | A | 112 |
| 20-Cl; 1-OTos (anti) | 153x | 122–123 | A, B | 113, 114, 129 |
| $\text{N} \rightarrow \text{O}$ (anti) | 153y | 166–167 | A | 113 |
| 20-Cl; 1-OCH ₂ CH ₃ (syn) | 153z | Oil | A, C | 116, 129 |
| $\text{N} \rightarrow \text{O}$ (syn) | 153aa | Oil | A | 113 |
| 20-Cl; 1-OCH ₂ CH ₃ , (anti) | 153bb | 107.5–110 | A, C | 116, 129 |
| $\text{N} \rightarrow \text{O}$ (anti) | 153cc | 176–178 | A | 113 |
| 20-Cl; 1-OCOC ₆ H ₅ , (syn) | 153dd | 147–148 | A–C | 113 |
| $\text{N} \rightarrow \text{O}$ (syn) | 153ee | Oil | A | 113 |
| 20-Cl; 1-OCOC ₆ H ₅ , (anti) | 153ff | 116–118 | A–C | 113 |

TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) general comments ^d | Ref |
|----------|----------|---|-----------|-----------------------------------|--------------------------------------|--|----------------|
| | | N>O (anti) 20-Cl; 1-OPO(OCH ₂ - CH ₃) ₂ (syn) | 153gg | 176-178 84.5-86.5 | A | | 113 |
| | | 20-Cl; 1-OCHO (syn) | 153ii | 122-122.5 | A, B | | 114 |
| | | 14,20-(Cl) ₂ , N>O | 153jj | 77-79 | A | | 117 |
| | | 14,20-(Cl) ₂ ; 1-OPO- (OCH ₂ CH ₃) ₂ | 153ll | 159-160 114-116 | A-C | | 117 |
| | | 14-Br; 20-Cl | 153mm | 96-98 | | | 113 |
| | | 14,16,20-(Cl) ₃ , | 153nn | 159-160 | A | | 114 |
| | | 10-Br; 20-Cl | 154 | 187-189 | C | | 115 |
| | | 24-Cl | 155a | 129-131 | B, C | | 115 |
| | | 14-Br; 24-Cl | 155b | 200-201.5 | B | | 115 |
| | | 14-CN; 24-Cl | 155c | 231-232 | B | | 115 |
| | | 14-COCH ₂ N(C ₆ H ₅) ₂ | 155d | | Unstable | | 115 |
| | | 14-COCl; 24-Cl | 155e | 202-206 | B | | 115 |
| | | 14-COCH ₂ N(C ₆ H ₅) ₂ | 155f | | Unstable | | 115 |
| | | 14-CO ₂ H; 24-Cl | 155g | 280-282 | B | | 115 |
| | | 14-COMe; 24-Cl | 155h | 212-212.5 | B | | 115 |
| | | 14-COCHBr ₂ ; 24-Cl | 155i | 164 | B | | 115 |
| | | 14-COCH ₂ Br; 24-Cl | 155j | 207-208 | B | | 115 |
| | | 14-CHOHCH ₂ N-(C ₆ H ₅) ₂ ; 24-Cl | 155k | 130-131 | B | Isomer A Isomer B | 115 |
| | | 14-CHOHCH ₂ N-(C ₆ H ₅) ₂ | 155l | Oil | B | Mixed racemates | 115 |
| | | 14-(2-pyrCHOH); 24-Cl | 155m | 173-186 174-176 | A, B A, B | Isomer A Isomer B | 115 |
| | | 14-(2-oxrCO); 24-Cl | 155n | 147-149 | B | | 115 |
| | | R ₃ = R _s = (Cl) ₂ ; | 156 | Oil | A, D | | 131 |
| | | R _s = F | | | | | |
| | | R ₃ = R _s = (Cl) ₂ ; | 157 | [175-180 (3.5)] | A, D | | 131 |
| | | R _s = F | | | | | |
| | | H | 158 | [165-175 (3.7)] 21.8-23.4 | B, C | Picrate (154-155°) Picrate (137-138°) Picrate (130-131°) | 17 118, 119 |
| | | H | 159a | [125-127 (0.007)] | | | 118 |
| | | 17-Cl | 159b | 130-131 | | | 118 |
| | | 17-OH | 159c | 189-190 | | | 118 |
| | | 17-OH; 16-CN | 159d | 210-211 | | | 118 |
| | | 15,18-(H) ₂ ; 17,19-(OH) ₂ ; 16-CN | 159e | 247-248 | | | 118 |

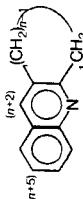
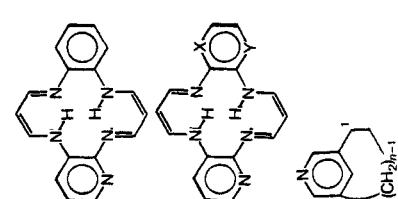
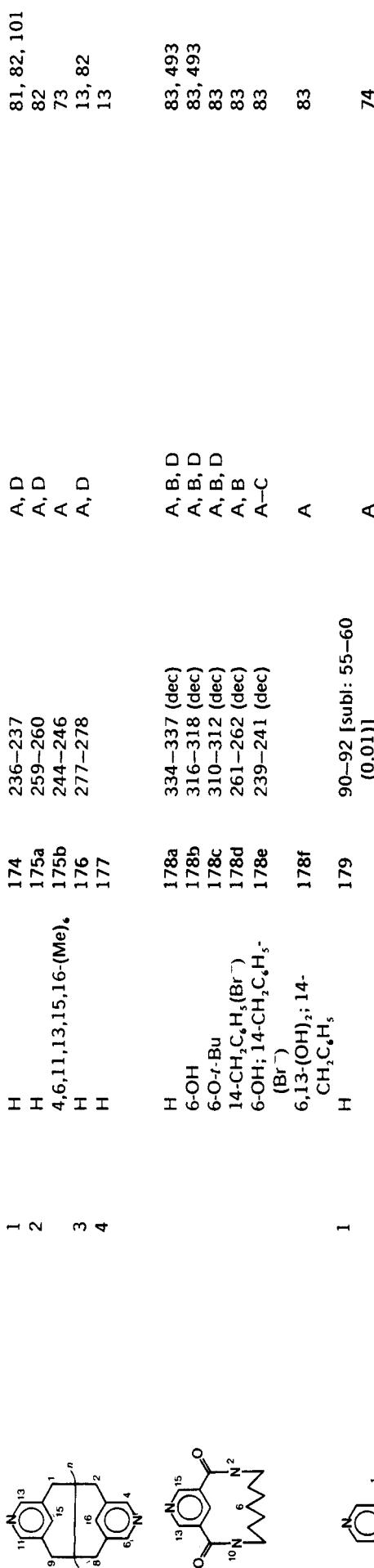
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|--|---|--|---|--|---|
| 15,17-(OH) ₂ ; 16-CO ₂ CH ₂ CH ₃ (H) ₆ (cis) (H) ₆ (trans) | 159f | 280–300 | | | 118 |
| 159g (H) ₆ | 159h | | Picrate (194–195°) Picrate (202–203°) | 118 | 118 |
| 10  | 160a 15-Me 15-Br 15,16-(Me) ₂ 12-CO ₂ H 15-Me, 12-CO ₂ H 15-Br, 12-CO ₂ H 15,16-(Me) ₂ ; 12-CO ₂ H | 160b 160c 160d 160e 160f 160g 160h | [255 (25)]; 75 [238 (11)]; 61 [260 (13)]; 91 93 314 >365 >365 >365 | Picrate (185°) Picrate (196°) Picrate (231°) Picrate (221°) | 124 124 124 124 124 124 124 |
| 11 H | 161a 13-CO ₂ H H | 161b 162a 162b 163a 163b 163c 163d 163e | 80 >320 (subl) 76 310 [200–205 (0.15)] Oil 307 55 | Picrate (175°) Picrate (159°) Picrate (169–171°) Picrate (165°) | 120 120 121 121 122 121 |
| 12 H | 14-CO ₂ H | 164a 164b | 280 | Picrate (194–195°) (TCNQ complex: mp 147–153°) | 123 |
| 13 H | 18-Me 18-Me; 15-CO ₂ H 18-Br 15-Me | 165a 165b 165c 165d 165e | 250 dec 165c 256 270 dec | Picrate (173°) Picrate (172°) Picrate (161°) | 337 121 121 121 |
| 14 H | 15-CO ₂ H 19-CO ₂ H | 164a 164b | 297–298 280 | Picrate (161°) | 121 |
| 15 H | 20-CO ₂ H 8,9-De(H) ₂ 8,9-De(H); 17-CO ₂ H 8,9-De(H); 17-CO ₂ H; 20-Br | 165a 165b 165c 165d 165e | 250 dec 165c 256 270 dec | Picrate (161°) | 121 |
| 16 H | | 166 | 262–264 | Co, Cu | 126 |
| (X = N; Y = CH) (X = CH; Y = N) | 167a 167b | 320 | B, D | Cu | 126 |
| 7 9,11(Me) ₂ | 168 | | A(CMR) | Picrate (171–172°), Picrolonate (259°) | 432 |
| 9 9  | 11,13-(Me) ₂ 11,13-(Me) ₂ ; 12-NH ₂ (ClO ₄ ⁻) 11,12,13-(Me) ₃ (ClO ₄ ⁻) | 169a 169b 169c | Oil 24.9 226 | A A A, B | 71 72 72 |

TABLE I (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available ^a | Metal complex(es) general comments ^d | Ref |
|----------|----------|---|-----------|-----------------------------------|--------------------------------------|--|--------|
| | 9 | 11,13-(Me) ₂ ; 12-C ₆ H ₅ (ClO ₄) ⁻ | 169d | 174 | A, B | | 72 |
| | | | | | | | |
| | | H | 170a | 249-250 | A, D | | 75 |
| | | 15,18-(H) ₂ | 170b | Mp (dec) | A, D | K (anion formation) | 75-77 |
| | | 15-Me; 18-H | 170c | Mp (dec) | A, C, D | | 75 |
| | | 15-CO ₂ CH ₂ CH ₃ ; 18-H | 170d | Mp (dec) | A, D | | 75 |
| | | 15-COCH ₃ ; 18-H | 170e | | A | | 78 |
| | | 18-CH ₂ CH ₃ | | | | | |
| | | 15-COCH ₃ ; 18-H | 170f | Mp (dec) | A, D | | 75 |
| | | 15-CO ₂ CH ₂ CH ₃ ; 18-CH ₂ CH ₃ | 170g | Mp (dec) | A | | 78 |
| | | 15,18-(Me) ₂ | 170h | 230 dec | B | | 76 |
| | | 15-Me; 18-CH ₂ CH ₃ | 170i | 230 dec | A | | 76, 78 |
| | | 15-Me; 18-CH ₂ CH ₂ -CH ₃ | 170j | 200 dec | A | | 76 |
| | | 15-Me; 18- <i>n</i> -Bu | 170k | 220 dec | A | K (anion formation) | 76 |
| | | 15-H; 18-CH ₃ | 170l | Mp (dec) | A | K (anion formation) | 77 |
| | | 15-H; 18-CH ₂ CH ₃ | 170m | Mp (dec) | | K (anion formation) | 77, 78 |
| | | 20-H; 17-CO ₂ CH ₂ CH ₃ | 171 | Mp (dec) | A, C | | 79 |
| | | | | | | | |
| | | | | | | | |
| | | H | 172a | Mp (dec) | A | | 80 |
| | | 22-H; 19-CO ₂ CH ₂ CH ₃ | 172b | Mp (dec) | A, C | | 80 |
| | | | | | | | |
| | | | | | | | |
| | | 11,13,15,16-(Me) ₄ | 173a | | | | 73 |
| | | 8,9-(H) ₂ ; 11,13,15,16-(Me) ₄ | 173b | 89.1-89.6 | | | 73 |
| | | 1,2,3,9-(H) ₄ | 173c | 169-171 [subl: 60-65 (0.3)] | A-C | | 74 |
| | | | | | | | |



^a Spectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS. ^b Samples were isolated by preparative gas-liquid chromatography and characterized by NMR, IR, MS, and elemental analysis. ^c IR spectral data of the complex. No corresponding data available for ligand. ^d Temperatures given in °C.

TABLE II. Heterocycles Containing the Euran Subunit^a

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comment ^g | Ref |
|---|----------------------|---|-----------|-----------------------------------|-------------------------|----------------------------------|---------------|
|  | 4,5:5,6 | $n = 7; 2(-\text{O})$ | 182 | 69–70 | A–D | Reactions of DNP (mp 202–203°) | 177, 260, 183 |
| | | $n = 8; \text{H}$ | 183a | [104–106 (11)] | A–C | | 176, 187 |
| | | $n = 8; (\text{H})_4$ | 183b | [96 (2)] | A–D | Exo, exo isomer | 370, 454 |
| | | $n = 8; (\text{H})_4; 1,8-(\text{B})_2$ | 183c | 116–118 | A–D | Endo-exo isomer | 454 |
| | | | 183d | 74.5–75.5 | A–D | VTNMR study ⁴⁷ | 454 |
| | | | 183e | 109–110 | A–C | Proposed intermedi- ate | 184 |
| | | $n = 8; 3,6-(=\text{O})_2$ | 183f | | | | 373 |
| | | $n = 8; 3,6-(=\text{O})_2$, (Z)-4,5 | | | | | |

TABLE II (Continued)

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comments ^g | Ref |
|----------|--|--------------|-----------|-----------------------------------|----------------------------|---|---|
| | H | | 184a | 68–68.5 | A ²¹⁷ , C | Reactions of ⁴⁹⁸ | 179–181, 217 |
| | 4,14- <i>d</i> ₂ | | 184b | 66.5–67.0 | A | | 178 |
| | 4,14-(Me) ₂ | | 184c | 63–64.5 | A, C | V ¹ TNMR | 188 |
| | 4,5-Benz ₂ O | | 184d | 164–165 | A, D | | 189, 268 |
| | 4,5:13,14-Dibenzo | | 184e | 170–174 | C | DMAD adduct (mp 212–213.5°) | 190 |
| | 4,5-(2,3-Naphtho) | | 184f | ~154 dec | A, D | | 191 |
| | | | | | | | |
| | | | | | | | |
| | n = 8 | | 185 | Oil | | Reactions of ⁴⁹⁸ ; | 259 |
| | n = 10 | | 186 | 74–75 | | Chiral ⁴⁸⁵ | 259 |
| | | | | | | | |
| | | | | | | | |
| | R = R' = H | | 187a | 117–118 | A, C | | 217 |
| | R = R' = Me | | 187b | 127–128 | A, C | V ¹ TNMR | 188, 486 |
| | | | | | | | |
| | | | | | | | |
| | H | | 188 | 176–178 | A, C | | 217 |
| | | | | | | | |
| | | | | | | | |
| | H | | 189a | 189–190° dec | A–C | D _{2H} , symmetry ¹⁸⁶ | 6, 88, 180, 181, 186, 188, 189, 190, 259, 485, 497 |
| | | | | | | Reactions of | 165, 166, 181, 186, 218, 268, 373, 484, 496–498 |
| | | | | | | | 15 |
| | | | | | | | |
| | H | | 189b | Oil | A | V ¹ TNMR studies | 167 |
| | (Z)-1,2-Cl | | 189c | 146–148 | A | Mixture of isomers | 186 |
| | 1,(2 or 7)-(Me) ₂ | | 189d | 182–186 | B, C | Mixture of isomers | 186 |
| | 1,(2 or 7)-(CH ₂ C ₆ H ₅) ₂ | | | | | | |
| | | | | | | | |
| | H | | 190 | 125–126 | A, D | Bis adduct (mp 224°) | 165 |

| | | | | | |
|--|---|--|---|--|--|
| $(Z)-1,2; (Z)-4,5; (Z)-10,11$ | 1-($\equiv O$) H | 191a 191b 191c 191d 191e 191f 191g 191h | 110 Red oil 158–160 170 >300 >300 155–156 | A–D A–D A–D A–D A–D A–D A–C A–D | 141 140, 144 164, 173 164, 173 142, 164 142, 164, 173 142, 164, 173 164 |
| $(E)-1,2; (Z)-4,5; (Z)-10,11$ | 3-($\equiv O$) 3-($\equiv O$) 3-($\equiv O$); 2,4-(CO ₂ Me) ₂ | 192a 192b 192c 192d 192e 192f 192g 192h | 150–152 145 138 | A, D A–D A, C, D D | 143 143 150 150 |
| $(Z)-1,2; (Z)-5,6; (Z)-11,12$ | 2-OH; 4-($\equiv O$) 2,4-(OH) ₂ H | 192b 192c 192d | 150–152 145 | Decoupling studies Not isolated | 143 |
| $(Z)-1,2; (Z)-5,6; (Z)-11,12$ | 3,4-(Br) ₂ | 192d | 138 | D | 143 |
| $(Z)-2,3; (Z)-5,6; (Z)-11,12$ | 4-($\equiv O$) | 192e | | | 143 |
| $(Z)-2,3; (E)-5,6; (Z)-11,12$ | 4-($\equiv O$); 3,5-(CO ₂ Me) ₂ | 192f | >300 | A–D | 143 |
| $(Z)-2,3; (E)-5,6; (Z)-11,12$ | 4-($\equiv O$); 3,5-(CO ₂ H) ₂ | 192g | >300 | A–D | 143 |
| $(Z)-2,3; (Z)-5,6; (Z)-11,12$ | 4-($\equiv O$); 3-CO ₂ H | 192h | | | 143 |
| $(Z)-1,2; (E)-3,4; (Z)-5,6; (Z)-11,12$ | H | 192i | 167–170 | A–D | 150 |
| $(Z)-1,2; (Z)-5,6$ | 11-($\equiv O$) | 193a | 148–150 | A–D | 158 |
| $(Z)-1,2; (Z)-5,6$ | 11-($\equiv O$); 3-Br | 193b | Unstable oil | Not identified | 158 |
| $(Z)-1,2; (E)-3,4; (Z)-5,6$ | 11-2H | 193c | 103–105 | Decoupling studies | 158 |
| $(Z)-1,2; (E)-3,4; (Z)-5,6$ | 11-($\equiv O$) | 193d | 212–215 | Conformationally mobile, VT NMR | 158 |
| $(\text{---})-1,2; (\text{---})-6,7;$ $(Z)-12,13$ | H | 194 | 94–96 | Probably Z, Z orientation | 150 |

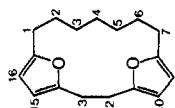
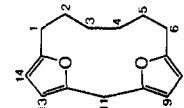
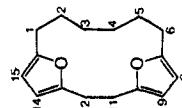
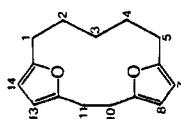


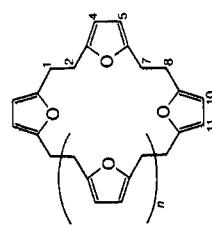
TABLE II (Continued)

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comments ^g | Ref |
|---|----------------------------------|--------------|--------------------|-----------------------------------|----------------------------|-----------------------------------|------------|
| (<i>E</i>)-1,2; (<i>E</i>)-7,8; (<i>Z</i>)-13,14 | H | | 195 | 146–148 | | Probably Z,Z orientation | 150 |
| | <i>n</i> = 1; 1-2H | 196a | 130–133 | | A, C, D | | 163 |
| | <i>n</i> = 1; 1-(=O) | 196b | 171–174 | | A, C, D | | 163 |
| | <i>n</i> = 2; 1-(H) ₂ | 196c | 141–143 | | A, C, D | | 163 |
| | <i>n</i> = 2; 1-(=O) | 196d | 165–168 | | A, C, D | | 163 |
| | <i>n</i> = 3; 1-(H) ₂ | 196e | 173–177 | | A, C, D | | 163 |
| | <i>n</i> = 3; 1-(=O) | 196f | 114–120 | | A, C, D | | 163 |
| Unsuccessful Wittig cyclization ^b | | | | | | | |
| | 2,4,13,15-(Me) ₄ | 197a | | | A–D | Nonplanar | 154 |
| | | 197b | 230–234 | | | | |
| | 3,4: 13,14-Dibenzo | 197c | | | | | |
| | 3,4: 13,14-Dibenzo | 197d | 202–204 209–211 | | A–D A–D | Nonplanar Nonplanar | 154 154 |
| | 3,4: 13,14-Dibenzo | 197e | 330–332 | | A–D | Sublimed [180° (0.1)] | 154, 174 |
| Atropic (NMR) | | | | | | | |
| | 1-(H) ₂ | 198a | 270–271 dec | | A, D | | 163, 172 |
| | 1-(=O) | 198b | >270 dec | | A, C, D | | 163, 172 |
| | 1-(=O) | 199a | 236–237 233–236 | | A–D A–C | Paramagnetic ring current | 162 |
| | 1-(H) ₂ | 199b | 90–92 | | A, D | No paramagnetic ring current | 160, 162 |

| | | | | | | |
|--|---|------|-------------|------------|---|---|
| (Z)-6,7; (Z)-12,13 | 1-O <i>Me</i> | 199c | 141–142 | A, D | Small paramagnetic ring current | 160, 162 |
| (E)-6,7; (E)-12,13 | 1-(=O); 7,12-(CO ₂ -Me) ₂ | 199d | 206–208 | A, D | | 160, 162 |
| (E)-6,7; (E)-12,13 | 1-(=O); 7,12-(CO ₂ H) ₂ | 199e | 295 dec | D | | 162 |
| (Z)-1,2; (Z)-7,8; (Z)-13,14 | H | 200a | 215–216 | A–C | Peripheral conjugation, aromatic stability ^{a,b} | 146–148, 155 |
| (E)-1,2; (Z)-7,8; (Z)-13,14 | 1-CO ₂ <i>Me</i> | 200b | 89–91 | D A–C | | 149 147 |
| (E)-1,2; (E)-7,8; (E)-13,14 | 1,7,14-(CO ₂ Me) ₃ | 200c | 147–150 | A–C A–C | Limited peripheral conjugation | 146, 147 |
| (E)-1,2; (E)-7,8; (E)-13,14 | 1,14-(CO ₂ H) ₂ ; 7-CO ₂ <i>Me</i> | 200d | Dec | | | 147 |
| (E)-1,2; (E)-7,8; (E)-13,14 | 1,7,14-(CO ₂ H) ₃ | 200e | >360 | B, C | | 146, 147 |
| (Z)-6,7; (E)-12,13; (Z)-14,15 | 1-2H | 201a | Yellow gum | A, D | | 163, 172 |
| (Z)-6,7; (E)-12,13; (Z)-14,15 | 1-(=O) | 201b | 208–209 | A, C, D | Diatropic (NMR) | 163, 172 |
| (Z)-6,7; (E)-8,9; (Z)-14,15; (E)-16,17 | 1-(=O) | 202a | 218–221 | A, C, D | | 163 |
| (Z)-6,7; (E)-8,9; (E)-14,15; (Z)-16,17 | 1-(=O) | 202b | Red gum | A, C, D | Atropic (NMR) | 163, 172 |
| (Z)-6,7; (E)-8,9; (E)-14,15; (Z)-16,17 | 1-2H | 202c | 142–144 | A | | 172 |
| | H | 203 | 212.5–213.5 | A–D | Synthesized from Pukalide | 391 |
| | 1,1,6,6,11,11,16,16-(Me) ₈ | 204a | 243 | | X-ray; perhydro ^{1,6,8,3,4,c} | 168, 169, 199, 266, 303, 343, 344 |
| | 1,1,6,6,11,11,16,16-(Et) ₈ | 204b | 249 | | | 169, 194, 195 |
| | 1,11-(Et) ₂ ; 1,6,6,11,16,16-(Me) ₆ | 204c | 178.5 | B | X-ray trans isomer (0 D) | 169 |
| | | 204d | 204 | B | X-ray cis isomer (0.77 D) | 169 |
| | | | | | | 169 |

TABLE II (Continued)

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comment ^{g,f} | Ref |
|--|--|--------------|-------------|-----------------------------------|----------------------------|--|----------|
| | 1-Et; 1,6,6,11,11,16, 16-(Me) ₇ | 204e | 195–195.5 | | | | 169 |
| | 1,1-(Et) ₂ ; 6,6,11,11, 16,16-(Me) ₆ | 204f | 209–209.5 | | | | 169, 192 |
| | 1,6,11,16-(Me) ₄ ; 1,6, 11,16-(Et) ₄ | 204g | 174 | | | | 192 |
| | 1-CO ₂ Me; 1,6,6,11,11, 16,16-(Me) ₇ | 204h | 172.5 | | | | 192 |
| | 1-CO ₂ Et; 1,6,6,11,11, 16,16-(Me) ₇ | 204i | 169.5 | | | | 303 |
| | 1-(CH ₂) ₃ ; 6,6,11,11, 16,16-(Me) ₆ | 204j | 182.3–183.3 | | A, B | | 303 |
| | 1,11-[(CH ₂) ₃] ₂ ; 6,6, 16,16-(Me) ₇ | 204k | 208.2–209.2 | | A, B | | 303 |
| | 1,6,11,16-[CH ₂] ₃ ¹ , 1-CO ₂ H; 1,6,6,11,11, 16,16-(Me) ₇ | 204l | 268–269 | | A, B | | 303 |
| | 1,6,11,16-[CH ₂] ₃ ¹ , 1-CO ₂ H; 1,6,6,11,11, 16,16-(Me) ₇ | 204m | 250 dec | | | | 192 |
| | 1-CH ₂ CO ₂ Me; 1,6,6, 11,11,16,16-(Me) ₇ | 204n | 179 | | | | 192 |
| | 1-CH ₂ CO ₂ Et; 1,6,6, 11,11,16,16-(Me) ₇ | 204o | 165 | | | | 192 |
| | 1-CH ₂ CO ₂ H; 1,6,6, 11,11,16,16-(Me) ₇ | 204p | 248.5–249.5 | | | | 192 |
| | 1-CH ₂ CH ₂ CO ₂ Me; 1, 6,6,11,11,16,16-(Me) ₇ | 204q | 157.5 | | | | 192 |
| | 1-CH ₂ CH ₂ CO ₂ Et; 1, 6,6,11,11,16,16-(Me) ₇ | 204r | 153 | | A, B | Perhydro-[isomers; oil] | 192, 500 |
| | 1-CH ₂ CH ₂ CO ₂ H; 1,6, 6,11,11,16,16-(Me) ₇ | 204s | 225.5–226 | | | | 192 |
| | 1-CH ₂ Cl; 1,6,6,11,11, 16,16-(Me) ₇ | 204t | 219.5–220 | | | | 192 |
| | 1,11-(CH ₂ Cl) ₂ ; 1,6,6, 11,16,16-(Me) ₆ | 204u | 211–211.5 | | | | 192 |
| (E)-1,2-(Z)-7,8-(E)- 13,14; (E)-19,20 | n = 1; H | 205a | 216–217 | | A–C | Isomer A, ^d paramagnetic ring current | 148, 155 |
| (E)-1,2-(E)-7,8-(E)- 13,14; (E)-19,20 | n = 1; H | 205b | 269–270 | | A–C | Isomer B; para- magnetic ring current | 148, 155 |



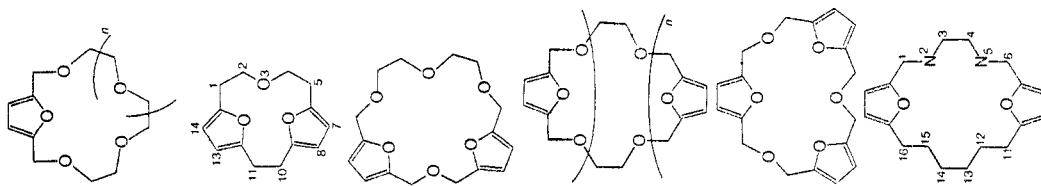
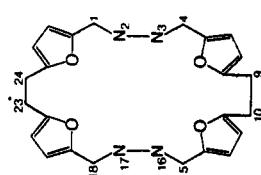
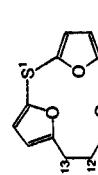
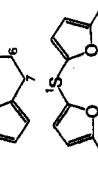
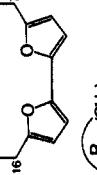
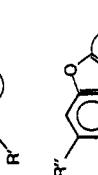
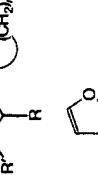
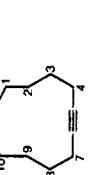


TABLE II (Continued)

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comments ^g | Ref |
|---|---|---|--------------|-----------------------------------|----------------------------|---|----------|
|  | (E)-1,2; (E)-3,4; (Z)-9,10; (E)-15, 16; (E)-17,18; (Z)-23,24 | H | 219 | 305 | B-D | | 174 |
|  | (Z)-6,7; (Z)-12,13 | H | 220a | 97-99 | A-D | No diamagnetic ring current | 157, 161 |
|  | (E)-6,7; (E)-12,13 (E)-6,7; (E)-12,13 | 7,12-(CO ₂ Me) ₂ 7,12-(CO ₂ H) ₂ | 220b 220c | 205-206 >260 dec | A-D | | 157, 161 |
|  | (Z)-6,7; (Z)-16,17 | H | 221 | 170-171 | A-D | No diamagnetic ring current | 157, 161 |
|  | n = 6; R = R' = H n = 7; R = R' = H | | 222 223 | | | Attempted synthesis Attempted synthesis; dimer isolated | 229 |
|  | n = 9; R = R' = H n = 9; R = H; R' = Me | | 224a 224b | [65-70 (0.05)] [72-75 (1.5)] | A A-C | VTNMR ^{20e} | 205, 229 |
|  | n = 10; R = Me; R' = H | | 225 | [91-92 (0.05)] [104-108 (0.9)] | A-B | | 228 |
|  | n = 10; R = R' = H; R' = OAc | | | | nD ²⁰ 1.5089 | | 221 |
|  | n = 10; R = R' = [-CH = CH-] ₂ ; R'' = OAc | | | | | Ketolactones via ozonolysis | 219 |
|  | (E)-1,2; (Z)-3,4; (Z)-7,8; (E)-9,10 | 4,7-(Me) ₂ | 227 | 100-102 | A, C, D | Ketolactones via ozonolysis | 219 |

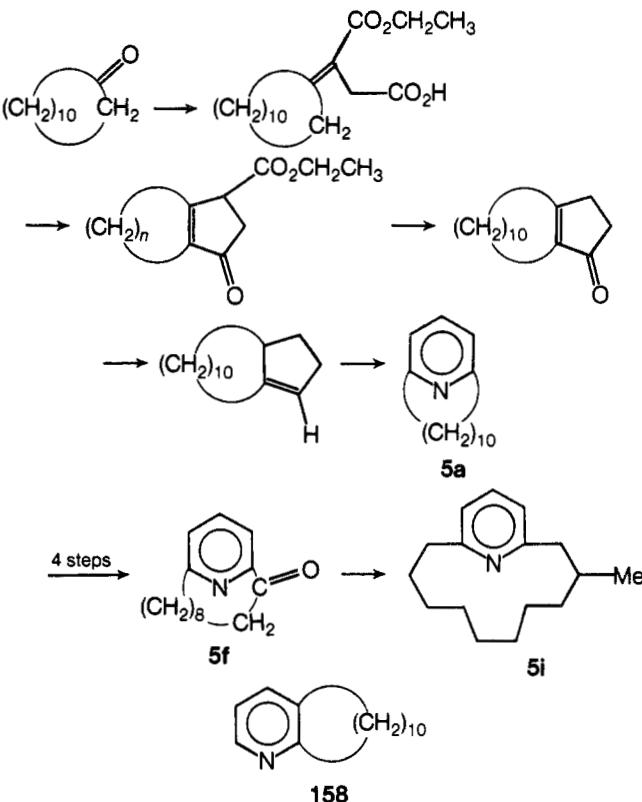
| | | | | | | |
|--|---|--|--------------|------------|---|-------------------|
| | (E)-1,2; (Z)-3,4; (Z)-9,10; (E)-11,12 (E)-1,2; (E)-11,12 | 4,9-(Me) ₂ | 228a | 134-135 | A, C, D | 209 |
| | (Z)-1,2; (E)-7,8f | R = H | 229a | | A | 214 |
| | (Z)-1,2; (E)-7,8 (E)-1,2; (E)-7,8f | R = CH(Me) ₂ R = H | 229b 229c | Oil 113 | A, C, D A-D | 214 |
| | (E)-1,2; (Z)-3,4; (Z)-7,8; (E)-9,10 | 4,7-(Me) ₂ | 230 | 131-132 | A, C, D | 207, 215 |
| | (E)-1,2; (Z)-3,4; (Z)-9,10; (E)-11,12 | 4,9-(Me) ₂ | 231a | Dec | Weakly diatropic ^{210,211} | 209, 210, |
| | (E)-1,2; (E)-11,12 | 4,9-(Me) ₂ ; 3,10-(OH) ₂ | 231b | | Weakly diatropic, conformationally mobile | 212-214, 458 |
| | (E)-1,2; (Z)-3,4; (Z)-9,10; (E)-11,12 | 3,4; 9,10-[CH ₂] ₄] ₂ | 231c | Dec | A, C, D | 210 |
| | (E)-1,2; (Z)-3,4; (Z)-9,10; (E)-11,12; (E)-13,14 | 4,9-(Me) ₂ | 232 | 137-140 | A | 211 |
| | (E)-1,2; (E)-3,4; (Z)-5,6; (Z)-11,12; (E)-13,14; (E)-15,16 | 6,11-(Me) ₂ | 233 | >150 dec | A-D | Weakly paratropic |
| | R = CO ₂ Et | | 234 | 213° | A, B | 458 |
| | n = 0; m = 1; H | | 235 | | A, CMR | Na, K |
| | n = 1; m = 1; H | | 236 | | A, CMR | Na, K |
| | n = 2; m = 1; H | | 237 | | A, CMR | Na, K |
| | n = 3; m = 1; H | | 238 | | A, CMR | Na, K |
| | n = 4; m = 1; H | | 239 | | A, CMR | Na, K |
| | n = 5; m = 1; H | | 240 | | A, CMR | Na, K |
| | n = 0; m = 2; H | | 241 | | A, CMR | Na, K |
| | n = 1; m = 2; H | | 242 | | A, CMR | Na, K |
| | n = 2; m = 2; H | | 243 | | A, CMR | Na, K |

TABLE II (Continued)

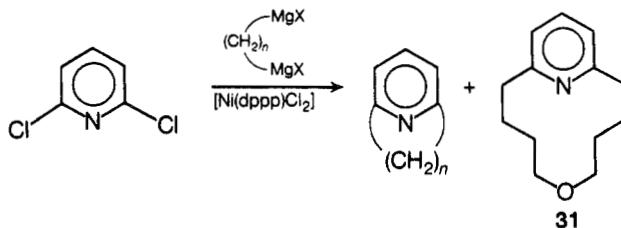
| Compound | Double bond position | Substituents | Compd no. | Physical data Mp / bp (mm), °C | Spectral data available | Complex(es)/comments ^g | Ref |
|----------|----------------------|--------------|-----------|-----------------------------------|----------------------------|-----------------------------------|-----|
| | R = Et | | 244a | 78–79 | | (Me) ₂ (242–244 dec) | 433 |
| | R = Pr | | 244b | 47–48 [165–167 (1)] | | (Me) ₂ (267–268 dec) | 433 |
| | R = Bu | | 244c | 63–63.5 | | (Me) ₂ (255–257 dec) | 433 |
| | (E)-1,2; (Z)-8,9 | H | 245 | 125.5–127 | A–D | Reactions of | 216 |
| | | H | 246 | 174–175 | A ⁴³⁶ | | 435 |

^a Spectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS. ^b The bisphosphonium salt eliminated triphenylphosphine, resulting in polymer formation. ^c The presence of salts in reaction mixture greatly improved the yield,¹⁶⁸ also see ref 266. ^d Isomer A thermally isomerized to the all-E configuration (isomer B). ^e NMR data also available on the platinum complex.^f References 207 and 215 reported the di-E configuration; the reassignment of this compound to the E, Z configuration (isomer A) has been reported.²¹ ^g Temperatures given in °C.

which was oxidized with chromium trioxide to give ketone **5f**. Direct alkylation of **5f** with potassium *tert*-butoxide and methyl iodide followed by a Wolff-Kishner reduction gave the desired racemic muscopyridine (**5i**). This racemic base was resolved by means of di-*p*-toluoyl-L-tartaric acid to give **5j**, whose picrolonate derivative was identical with that of the natural muscopyridine.²¹

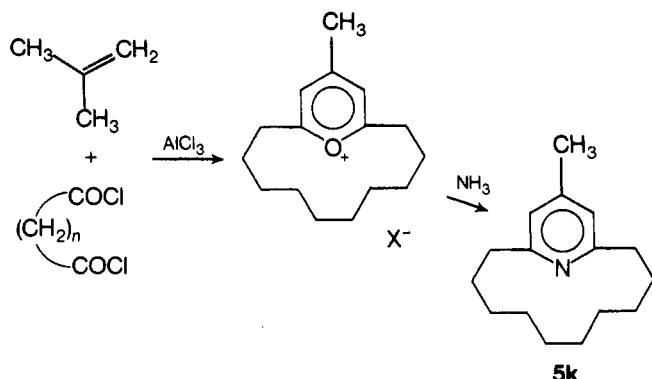


More recently, the one-step construction of racemic muscopyridine has been accomplished via cyclocoupling the di-Grignard of 2-methyl-1,10-dibromodecane with 2,6-dichloropyridine in the presence of a catalytic amount of a nickel-phosphine complex [Ni(dppp)Cl₂].⁹³ A 20% yield of **5i** was realized by this procedure. Further application of this cyclocoupling was successful in the preparation of several [n]-(2,6)pyridinophanes (*n* = 6–10, 12; 10–33%), [n]metacyclophanes (*n* = 8–10, 12; 3–22%), as well as an oxamethylene bridged pyridinophane (**31**).⁹³

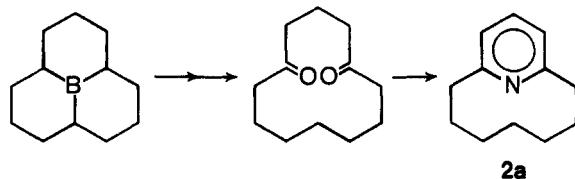


Balaban et al. have utilized a bicyclic pyrylium salt, 4-methyl-2,6-decamethylenepyrylium perchlorate, as a convenient intermediate in a synthesis of an isomer of muscopyridine.¹ These pyrylium salts are prepared by diacylation of isobutene with the corresponding diacyl chloride in nitromethane in the presence of anhydrous aluminum chloride.³⁰¹ Treatment of the pyrylium perchlorate with ammonia in *tert*-butyl alcohol³⁰² gave substituted [10](2,6)pyridinophane (**5k**) in low yield. Several years later, Georgi and Rétey³ repeated this procedure and ascertained that the isolated pyrylium salt was not monomeric in nature, but rather dimeric. Thus, the macrocycle originally isolated by Balaban et al.¹ was not **5k** but rather its dimer. The mass spectrum of this product has confirmed its dimeric structure.³

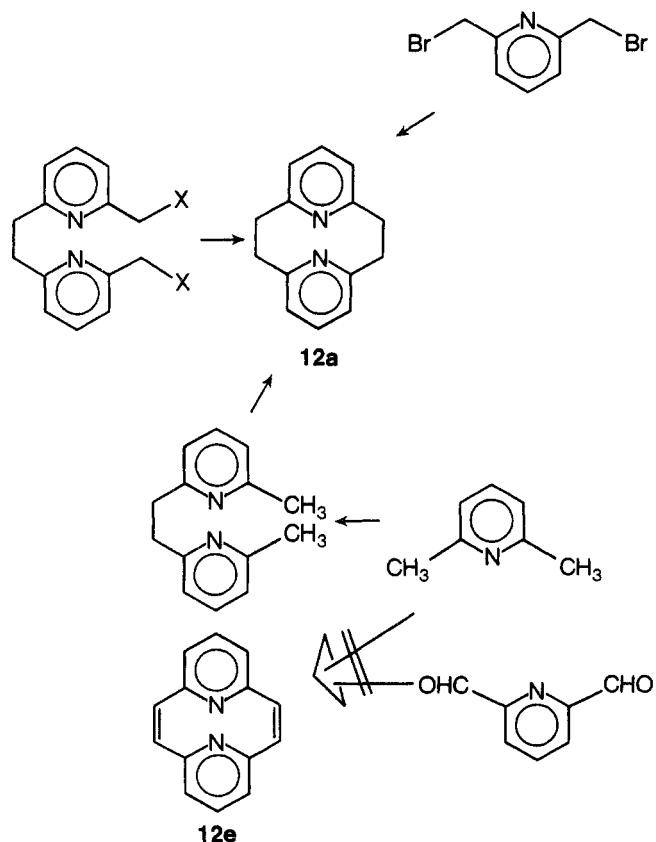
Besides dimer **20**, a second pyridine macrocycle was isolated (0.5%) and shown to be the desired monomer **5k**.³ An analogous reaction sequence has been utilized to prepare [7](2,6)pyridinophane (**2a**).^{2,4}



An alternate route to the construction of a pyridine ring involves precursors to pyrylium salts, that is, the macrocyclic 1,5-diketones; therefore, treatment of cyclododecane-1,5-dione with hydroxylamine afforded [7](2,6)pyridinophanes (**2a**).⁴ The desired 1,5-dione was prepared (30%) from boraperhydrophenalene by treatment with 1 equiv of acetic acid followed by a chromic acid oxidation.

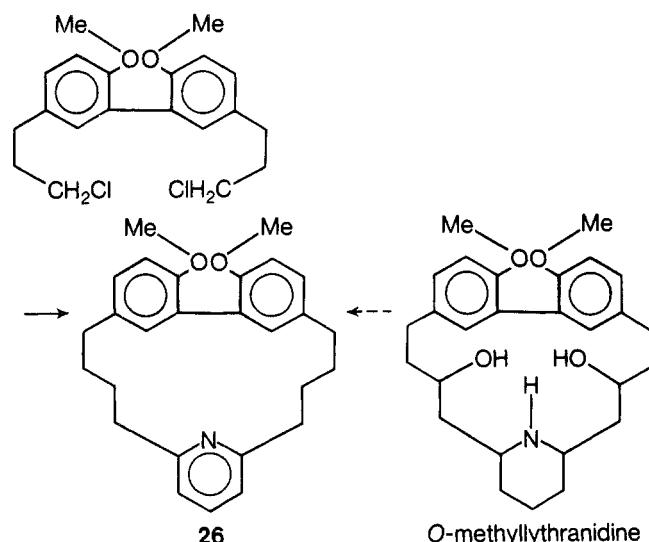


Carbon–carbon σ -bond formation is typically accomplished by reaction of an organometallic reagent with an activated site possessing a good leaving group. After the attempted simple condensation of 2,6-pyridinedicarboxaldehyde with 2,6-dimethylpyridine in the presence of acetic anhydride failed to cyclize to the desired **12e**,^{11,305} Baker et al. in a classic paper

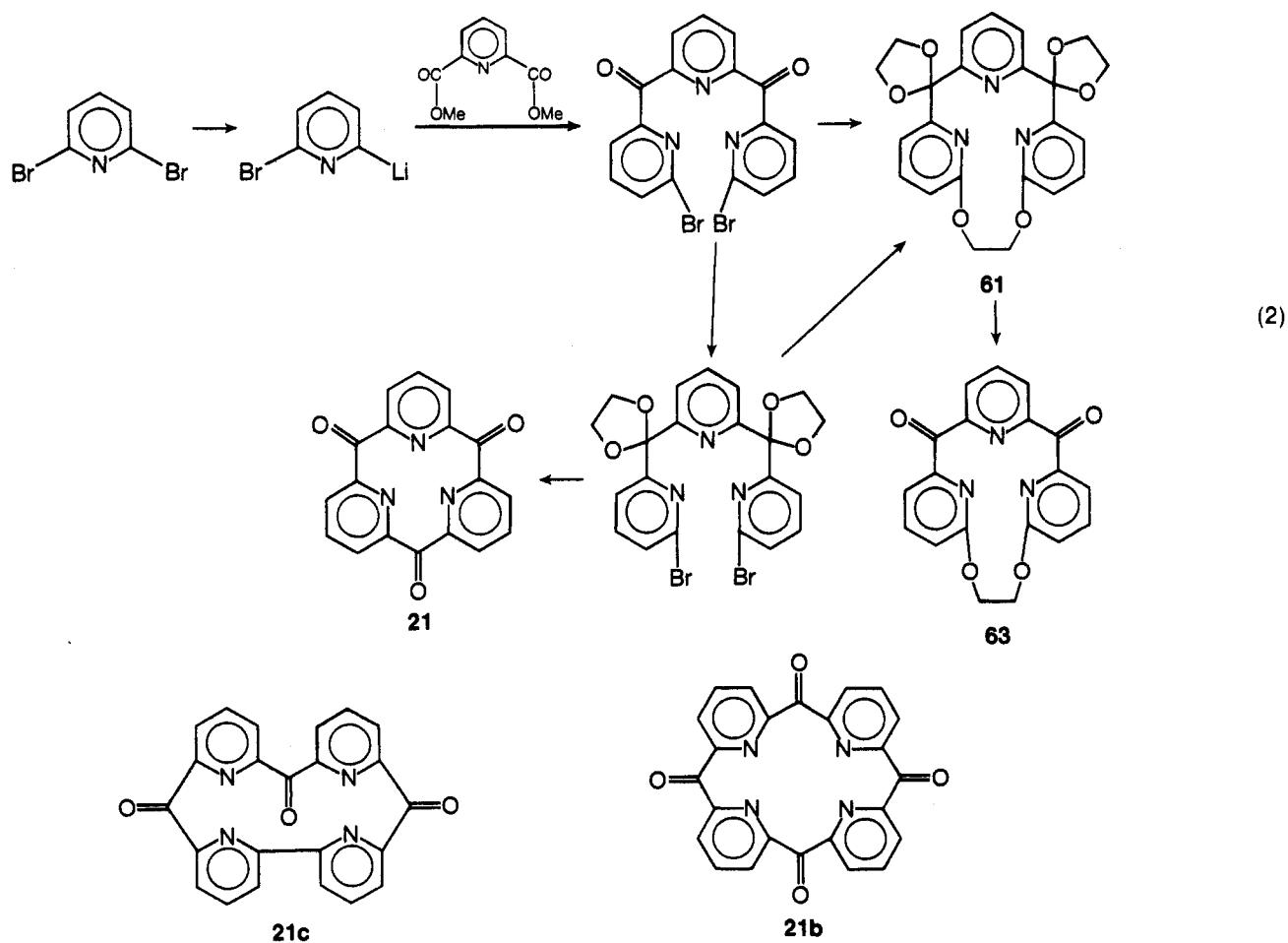
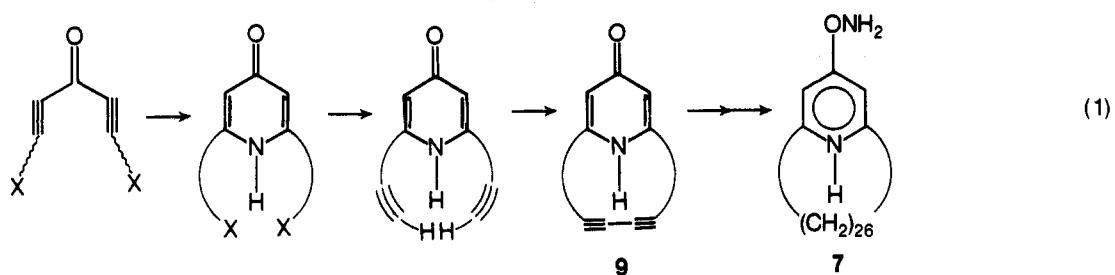
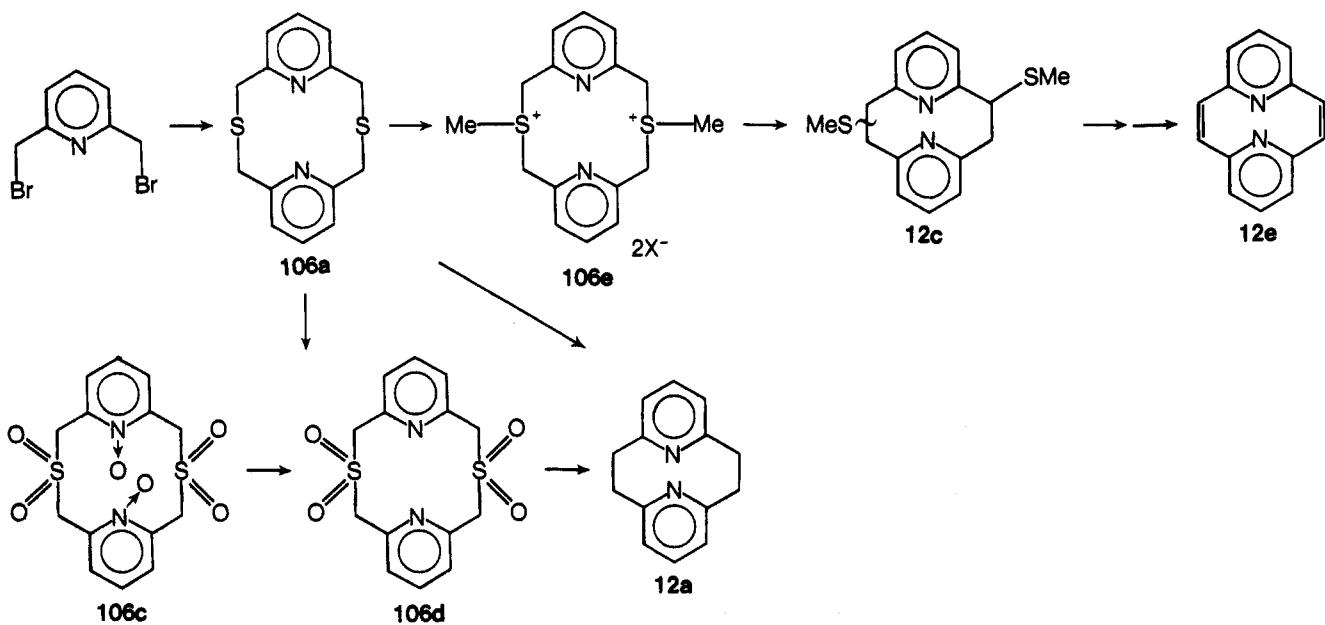


described the preparation of the first example of a [2.2](2,6)-pyridinophane (**12a**) through cyclization of 1,2-bis(6'-bromomethyl-2'-pyridyl)ethane by action of either butyllithium in ether or phenyllithium in benzene–ether.^{11,346} [2.2]Metacyclo-2,6-pyridinophane (**10**) was prepared in a similar manner upon treatment of the corresponding dibromide with butyllithium.⁶ The reaction of 2,6-bis(bromomethyl)pyridine with phenyllithium gave **12a** in 25% yield.¹² Cyclization of 1,2-bis(6'-halomethyl-2'-pyridyl)ethane by means of sodium and tetraphenylethylene in tetrahydrofuran afforded a separable mixture of 2,6-bridged pyridinophanes.^{13,16} Kauffmann et al. modified these procedures by initial selective metalation of the readily available 2,6-dimethylpyridine with butyllithium, followed by copper transmetalation, and subsequent oxidative coupling.¹⁹ Repetition of this metalation procedure on 1,2-bis(6'-methyl-2'-pyridyl)ethane gave **12a**, as well as dimer **14**.¹⁹

This selective metalation–nucleophilic displacement sequence has been demonstrated in the synthesis of a degradation product from the alkaloid *O*-methyllytranidine (from *Lythrum anceps* Makino, a herb grown in Japan).³⁰⁶ Condensation of a substituted dichloride with 2,6-lutidine in the presence of potassium amide in liquid ammonia gave the desired macrocycle **26**, thus establishing the gross structure of the natural product.¹³⁵



Several different syntheses of pyridinophanes from dithia-cyclophane precursors by a ring contraction have been reported to proceed by either: (1) two-step extrusion of sulfur by a Stevens rearrangement, followed by a Hofmann elimination; (2) thermal expulsion of sulfur dioxide from the corresponding sulfone; or (3) irradiation of sulfides in the presence of a trialkyl phosphite. Preparation of **12e** via procedure 1 has been reported by Boekelheide and Lawson¹² in which the reaction of 2,6-bis(bromomethyl)pyridine with sodium sulfide gave a dithia[3,3]-pyridinophane (**106a**).³² Dimethylation of **106a** using either Meerwein's reagent or dimethoxymethyl fluoroborate afforded the crude methylated product **106e** which upon treatment with potassium *tert*-butoxide effected a Stevens' rearrangement to give **12c**. Modification of this two-step procedure by using 2,6-di(*tert*-butyl)phenoxyde, as the base in the elimination step, gave rise to [2.2](2,6)pyridinophane (**12e**).¹² This technique for ring contraction and olefin formation has been applied to other pyridinophanes, such as **11f**.⁹ Martel and Rasmussen¹⁸ applied the second procedure (2) in the conversion of **106a** into [2.2](2,6)pyridinophane (**12a**). Oxidation of **106a** with 4 equiv of pertrifluoroacetic acid gave the bis-sulfone bis-*N*-oxide **106c**. Selective reduction of the *N*-oxide groups with iron in trifluoroacetic acid afforded the desired bis-sulfone **106d** in high yield. After failure of **106d** to undergo a Ramberg–Bäcklund reac-

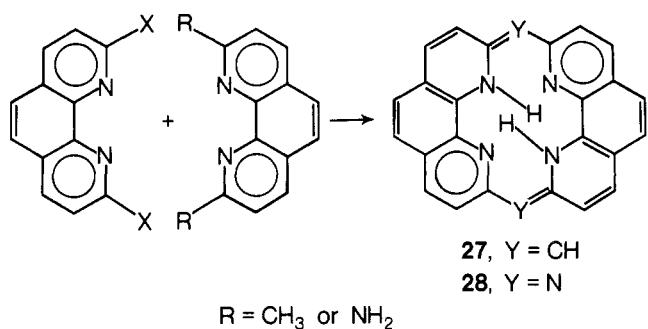


tion,³⁰⁷ sulfur dioxide extrusion (procedure 2) under pyrolytic conditions ($680^{\circ}\text{C}/0.01\text{ mm}$) gave (46%) pyridinophane **12a**.¹⁸ [2,2](2,6]Pyridinoparacyclophane (**11a**) was prepared (66%) in an analogous manner from **105d**.⁹ The most convenient synthesis of pyridinophanes is by photochemical extrusion of sulfur from a sulfide (procedure 3) as demonstrated by the irradiation of **103a** in trimethyl phosphite at room temperature for 48 h to generate **11a** (49%).⁷ Galuszko demonstrated that disulfides undergo similar sulfur extrusion–ring contraction.⁹⁸

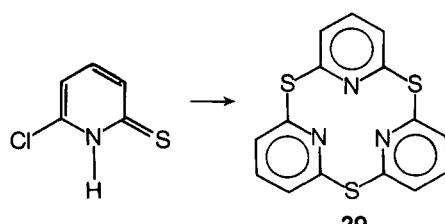
A novel approach to these macrocycles was recently demonstrated by Isele and Scheib by the formation of the pyridine nucleus from a disubstituted diynone, followed by a subsequent copper-catalyzed second cyclization of a terminal diyne.⁹⁴ Reduction of the triple bonds and O-amination with chloroamine and sodium hydride gave **7** (see eq 1).

The construction of a new series of pyridine macrocycles linked solely by carbonyl groups has been reported.¹⁰² 2,6-Dibromopyridine was metallated with butyllithium in tetrahydrofuran at -100°C to afford 2-bromo-6-lithiopyridine, which was reacted with 0.5 equiv of methyl 2,6-pyridinedicarboxylate at -90 to -100°C to give 2,6-bis(6'-bromo-2'-pyridoyl)pyridine. The resultant diketone was ketalized with bromoethanol in the presence of lithium carbonate³⁰⁹ affording (60%) the diketal along with an unexpected ethereal macrocyclic dikel **61**. Hydrolysis of **61** gave the cyclic diketone **63**, whose PMR spectrum showed an eight-bond long-range *W* coupling between positions 12 and 7¹⁸, thus, indicating the planar nature of this ring system. The dibromo dikel was dimetalated with butyllithium at -100°C , treated with ethyl chloroformate, and hydrolyzed to generate **21** in 3.5% overall yield (eq 2). This general procedure has been applied successfully to the synthesis of **21c** (a corrin model), **21b** (a porphyrin model), and **22**.³¹⁰

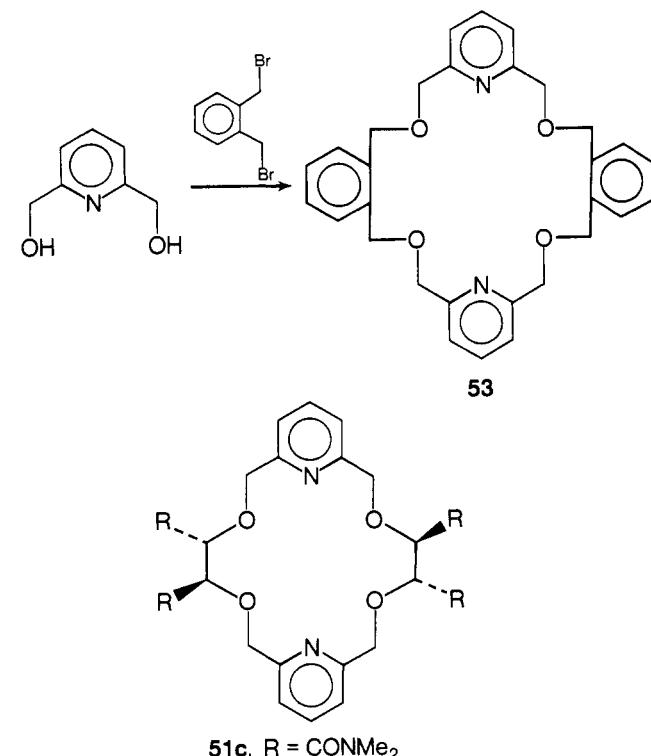
An efficient nontemplate synthesis of the novel carbon-bridged macrocycle **27**, in which the pyridine rings are confined within 1,10-phenanthroline units, was reported by Ogawa, wherein 2,9-dimethyl-1,10-phenanthroline and 2,9-dichloro-1,10-phenanthroline are thermally condensed at 260°C for 4 h.³⁰⁸ This procedure had been previously used for the preparation of the only known nitrogen-bridged pyridine macrocycle **28**.^{90,91,103}



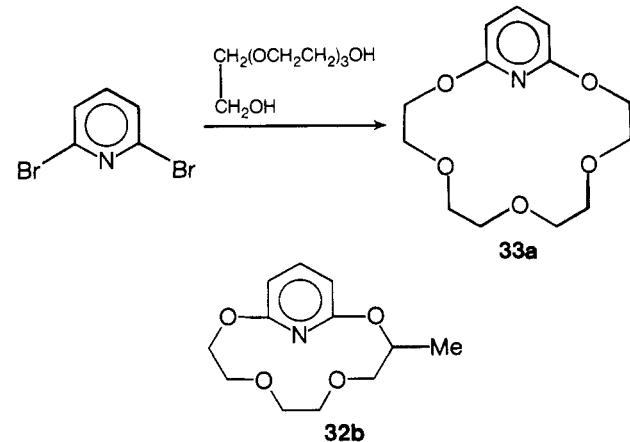
The only sulfur-bridged pyridine macrocycle **29** has been prepared by Undheim et al. through an intermolecular condensation of 6-chloropyridine-2-thione in the presence of P₂S₅ at 130° .²² Although no physical data have been cited, an x-ray analysis has established that **29** possesses a nonplanar conformation.²²



The majority of carbon–oxygen-bridged pyridine macrocycles can be divided into two general classes: (1) those possessing bridging oxygen atoms that are isolated from the pyridine nucleus and (2) those in which the bridging oxygen atoms are directly attached to the pyridine ring. The facile preparation of **53**, as well as its oligomers, was accomplished by treating 2,6-bis(hydroxymethyl)pyridine with sodium hydride in dimethoxyethane followed by dropwise addition of α,α' -dibromo-*o*-xylene.²⁶ Cram et al. have applied this general procedure to the construction of not only achiral, but also chiral compounds.^{23,24,34,92,488} Utilization of the bis(*N,N*-dimethylamide) of L-(+)-tartaric acid as the oxygen source in a modification of this cyclization procedure permitted the construction of **51c** in 15% yield.¹⁰⁰

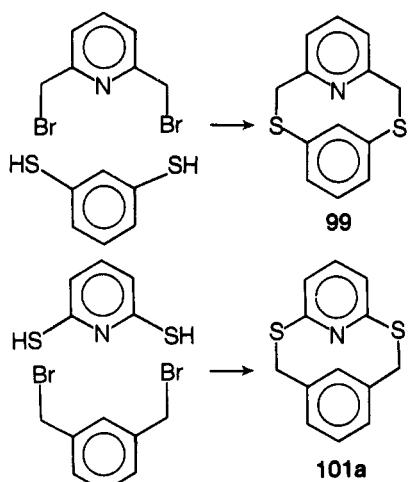


Newkome et al. have constructed the carbon–oxygen bridges via direct nucleophilic displacement of the 2,6-dihalo substituents of 2,6-dihalopyridine.^{25,102,487} When 2,6-dibromopyridine was subjected to the dianion of tetra(ethylene glycol) in xylene at 140°C , the desired 1:1 macrocycle was isolated along with the 2:2 cyclic ether and numerous acyclic intermediates.^{25,487} Further application of this procedure has been demonstrated in the construction of tetraoxamuscropyridine **32b**³⁹ as well as various macrocycles which possess other types of subheterocyclic ring(s).

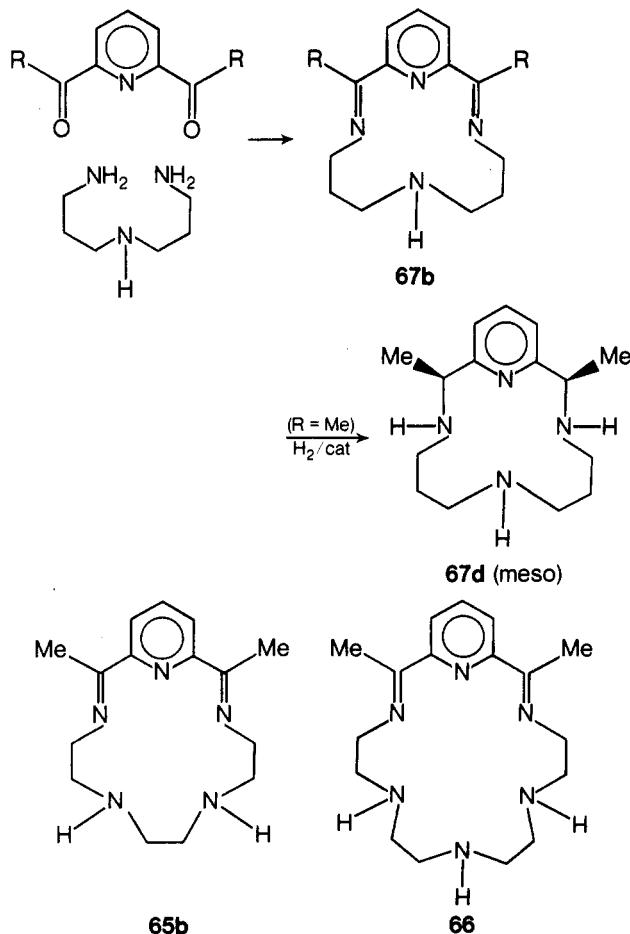


Carbon–sulfur-bridged pyridine macrocycles are also divided into two general classes: (1) those with isolated bridging sulfur

atoms and/or (2) those with bridging sulfur atoms which are directly connected to the subunit. Vögtle first demonstrated the construction of class (1) sulfur-bridged macrocycles, by treating 2,6-bis(bromomethyl)pyridine with dithioresorcinol to produce (29%) the desired **99**.³¹ Vögtle et al.,^{27-29,32,33,283,374,431} Boekelheide et al.,¹² Martel and Rasmussen,¹⁸ and Galuszko^{98,428,429} have utilized this procedure, whereas, Boekelheide et al.^{7,9} have also modified this procedure by condensation of 2,6-bis(mercaptopethyl)pyridine with a suitable dihalide. Vögtle et al.^{29,33,374} have successfully condensed 2,6-pyridinedithiol with an appropriate polymethylene dihalide, thus demonstrating a route to class (2) carbon-sulfur macrocycles, exemplified by **101a**.

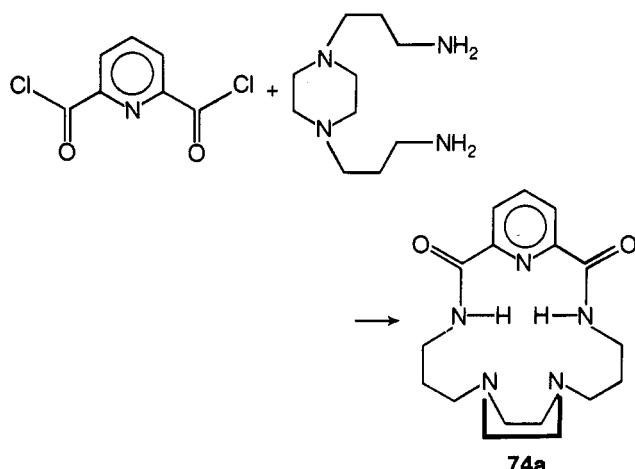


Carbon-nitrogen-bridged pyridine macrocycles generally have been produced by a Schiff-base condensation of either 2,6-pyridinedicarboxaldehyde or 2,6-diacetylpyridine and a substituted bis(primary amine). Curry and Busch reported the first

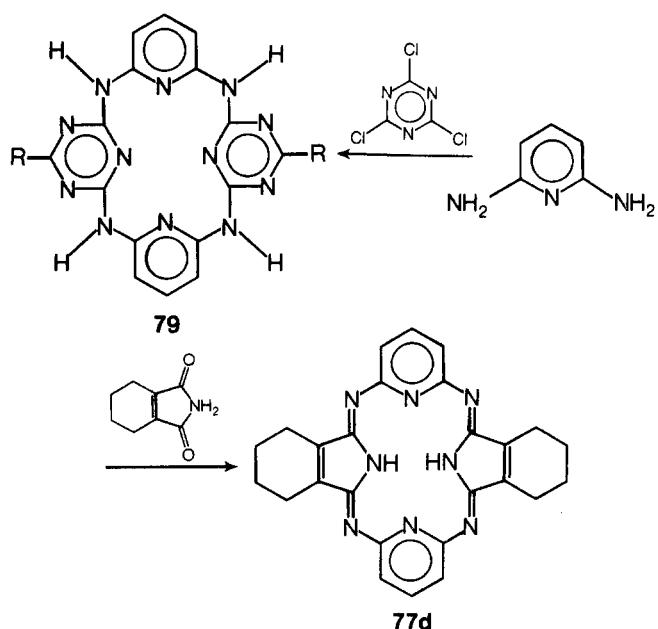


penta- and hexadentate macrocycles (**65b** and **66**, respectively) to be prepared in this series through the utilization of metal ion catalysis.⁵⁵ It has been demonstrated that metal ions can cause striking improvements in the formation of macrocyclic products over competing linear polymerization; this general phenomenon is known as the *template effect*. Application of the varied template effects to the synthesis of macrocyclic ligands has been reviewed.³¹¹⁻³¹⁵ This metal ion intervention in a Schiff-base condensation has been utilized by numerous researchers in the preparation of tetra- (ref 40, 42, 44-47, 52, 96, 272, 277, 278), penta- (ref 36, 55-57, 97, 273, 275, 392-395), and hexadentate (ref 55, 60) pyridine macrocycles. Catalytic reduction of the imine bonds in these bis-Schiff bases has afforded an additional series of related saturated tetra- (ref 41, 44, 48, 50, 52, 53, 274) and pentadentate (ref 273) ligands.

Vögtle et al.^{29,374,427,431} have synthesized a series of azabridged dilactams, e.g., **74a**, through the reaction of 2,6-pyridinedicarbonyl chloride with numerous diamines under high dilution conditions according to the procedure of Stetter and Marx.³¹⁶

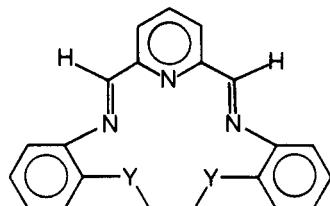


Borodkin et al. have reported the preparation of different macroheterocycles containing the pyridine subunit via the direct heating of either a dicarbonyl compound (an imide)^{38,64,65,95} or a dichloride⁶² with 2,6-diaminopyridine.

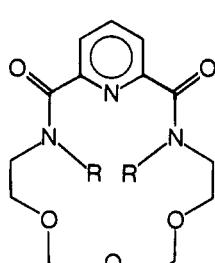


Carbon-nitrogen-oxygen (sulfur)-bridged pyridine macrocycles generally have been prepared by the previously discussed Schiff-base procedure. Alcock et al. have applied the template effect of Mn²⁺ and Zn²⁺ to the preparation of a series of pen-

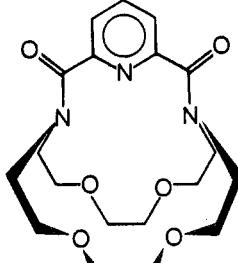
tadentate (N and O or S) macrocyclic ligands, e.g., **110**.³⁶ The x-ray analysis of the **65c** manganese complex demonstrated that the donor atoms define the five equatorial positions of a distorted pentagonal bipyramidal.³⁶ Vögtle et al. have reacted 2,6-pyridinedicarbonyl chloride with diversified ethereal bis(primary amines or amides) to get variable yields of the lactam-type macrocycles, e.g., **115**^{29,374,431} as well as pyridinophane cryptates, e.g., **111**.⁴²⁷



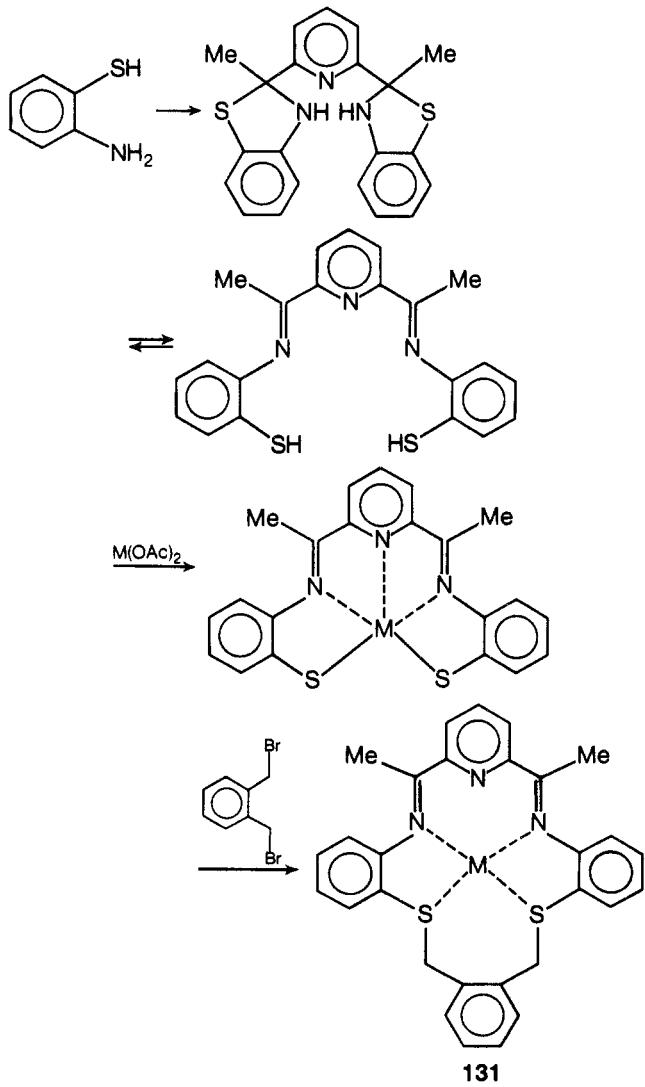
65c, Y = N; **110**, Y = O; **129**, Y = S



115



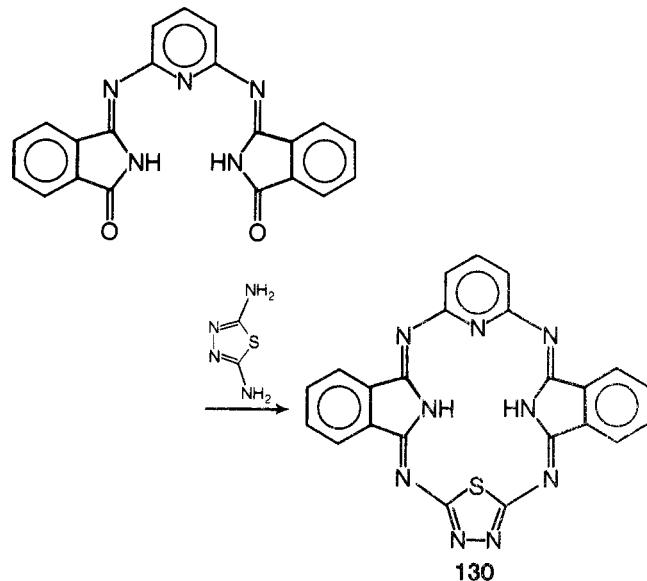
111



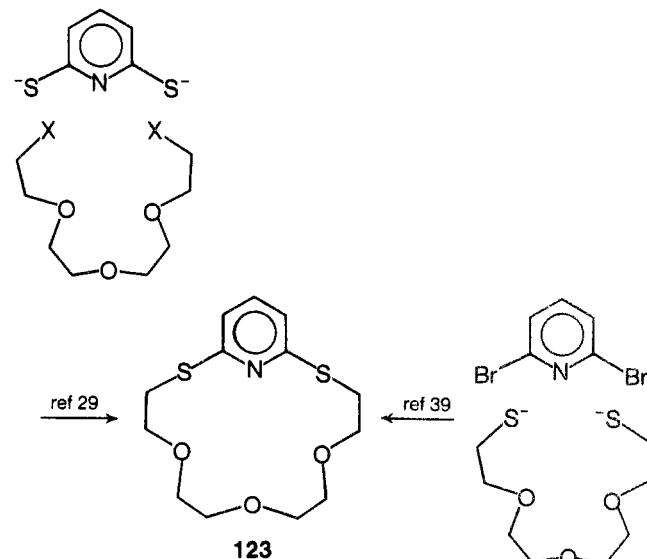
131

Recently, Londoy³²⁷ and Busch³¹¹ have shown that aldehydes and ketones react with 2-aminobenzenethiol to generate predominately the corresponding benzothiazolines. When 2,6-diacylpyridine was reacted with 2-aminobenzenethiol, the expected bis(benzothiazoline) was isolated.^{276,403} Treatment of this bisadduct with either zinc or cadmium acetate caused a shift in the bis(benzothiazoline)-bis(Schiff base) equilibrium favoring the Schiff base, which precipitated in the form of a pentadentate complex.⁴⁶¹ Subsequent reaction of this complex with α,α' -dibromo-*o*-xylene gave rise to a novel ring-closing S-alkylation, thus generating macrocycle **131**.²⁷⁶

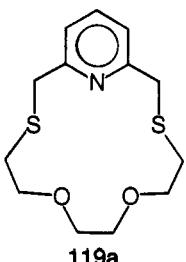
Borodkin et al. prepared **130** by heating 2,5-diamino-1,3,4-thiadiazole with an appropriate 1-iminoisindolinylidene derivative in boiling butanol for 40 h.³⁸



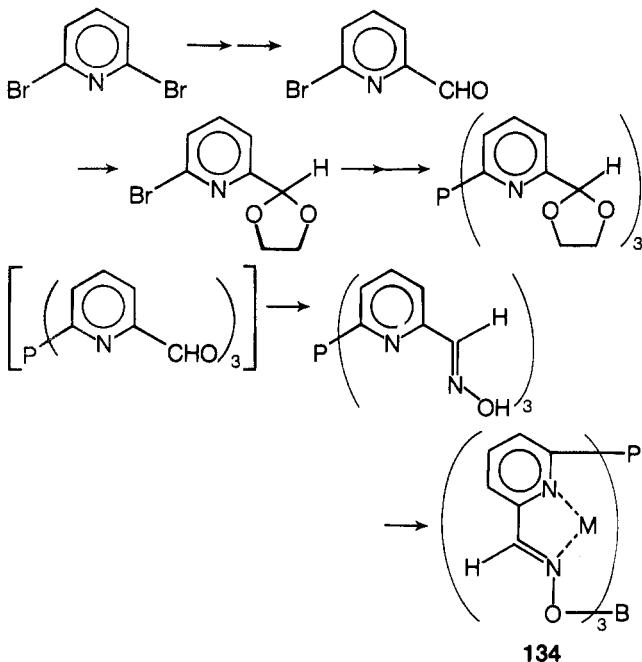
Carbon-sulfur-oxygen-bridged pyridine macrocycles have been reported by Vögtle et al. to be formed from 2,6-pyridinedithiol and the appropriate ethereal terminal dihalide or ditosylate.²⁹ Newkome et al. have approached the synthesis of these same molecules via direct nucleophilic substitution on the pyridine ring with an appropriate bismercaptide.³⁹



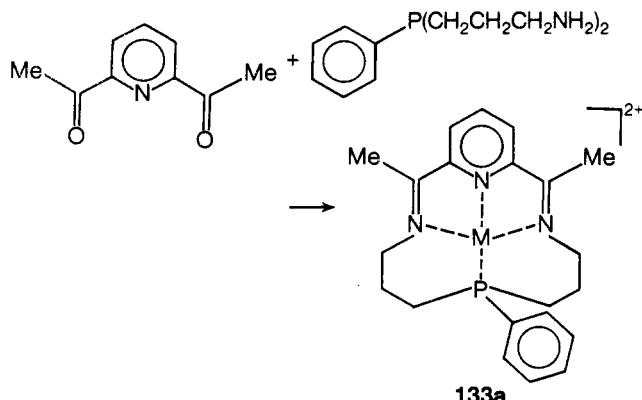
Vögtle and Weber prepared a related series of mixed heteroatom ligands (e.g., **119a**) under high-dilution conditions without the use of the template effect.^{35,374} The details concerning the mode of construction were not presented in the communication; however, **119a** will instantaneously solubilize the sodium ion (e.g., sodium permanganate) whereas potassium permanganate remains completely undissolved.^{35,374}



Phosphorus-bridged pyridine macrocycles have been quite limited in scope. Holm et al. reported the synthesis of a most unusual six-coordinate complex (**134**) with nonoctahedral stereochemistry.⁶⁸ 2,6-Dibromopyridine was converted to 2-bromo-6-lithiopyridine, then reacted with dimethylformamide at -80°C to afford 6-bromo-2-pyridinecarboxaldehyde. Treatment with ethylene glycol and *p*-toluenesulfonic acid yielded the corresponding ketal, which, after metalation at -100°C with butyllithium, was quenched with phosphorus trichloride to give tris[2-(1',3'-dioxolan-2'-yl)-6-pyridyl]phosphane. An aerobic acid hydrolysis and subsequent treatment with hydroxylamine yielded (90%) tris(2-aldoximo-6-pyridyl)phosphine. Encapsulation was accomplished by homogeneous anaerobic reaction of the metal (Fe^{2+} , Co^{2+} , Ni^{2+} , or Zn^{2+}) fluoroborate complex with distilled boron trifluoride etherate. The procedure of initial complexation of the metal ion within the ligand framework followed by "stitching up" the opening was certainly a novel approach to the encapsulation of metal ions.



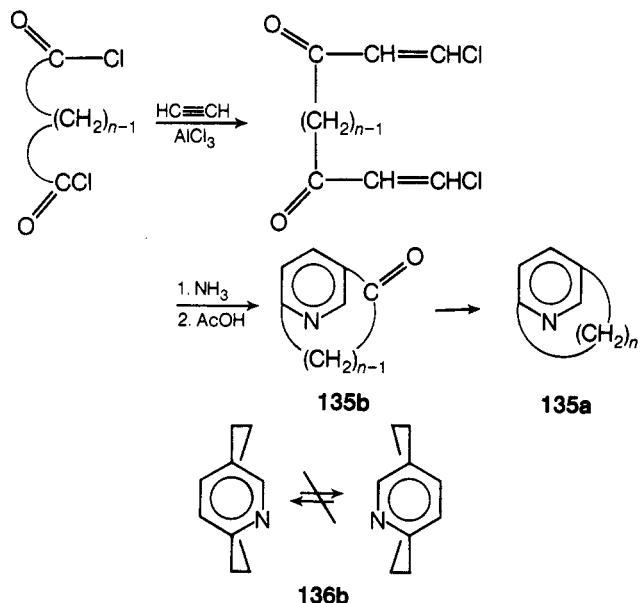
The first tetradentate macrocyclic ligand containing the 2,6-pyridino moiety and a phosphine bridging donor (**133a**) was



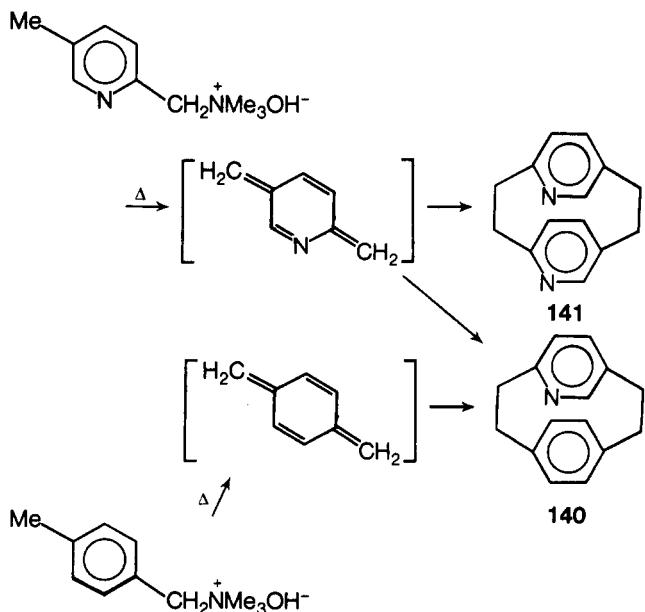
prepared by refluxing an ethanolic solution of 2,6-diacylpyridine, bis(3-aminopropyl)phenylphosphine, and nickel bromide hydrate.⁶⁷ Upon addition of ammonium hexafluorophosphate, the desired macrocyclic five-coordinate complex crystallized. Reduction of the imine bonds was easily carried out by treatment of **133a** with methanolic sodium borohydride.⁶⁷

2. 2,5-Pyridino

Carbon-bridged [*n*](2,5)pyridinophanes were first constructed by Gerlach and Huber in 1968.⁸⁴ In general, bis(β -amino-vinyl)diketones were subjected to an acid-catalyzed cyclization generating the [*n*](2,5)pyridinophan-*n*-ones (**135b**), which were converted to the [*n*](2,5)-pyridinophanes by standard Wolff-Kishner reduction. Numerous reactions and conformational stability studies were carried out on the lower members of this series, especially [*n*] < 12 .⁸⁴ The smallest bridged (2,5)pyridinophane yet reported possesses an eight-carbon atom bridge.⁸⁴ (\pm)-[9](2,5)Pyridinophane (**136a**) was resolved with the aid of (+)-2,2'-dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylic acid and was shown to be thermally stable.⁸⁴

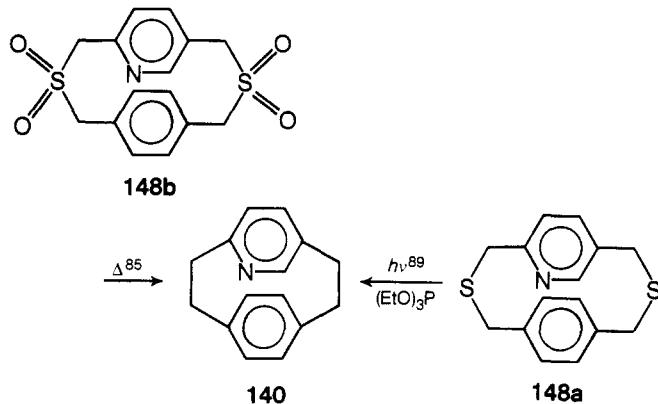


Bruhin and Jenny synthesized [2]paracyclo[2](2,5)pyridinophane by a thermal 1,6-Hofmann elimination from an intimate



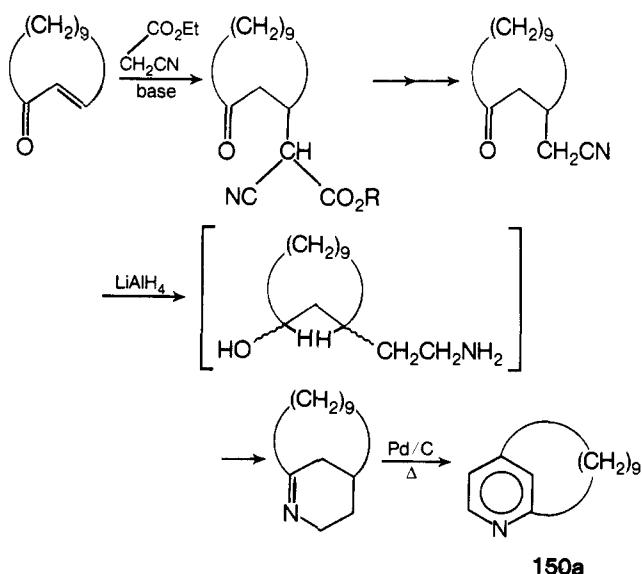
mixture of (4-methylbenzyl)trimethylammonium hydroxide and (5-methyl-2-picolinyl)trimethylammonium hydroxide via the crossed condensation of the intermediates.⁸⁵ Isomeric [2.2]-(2,5)pyridinophanes were also isolated from this reaction⁸⁵ as well as from thermolysis of either (2-methyl-5-picolinyl)trimethylammonium hydroxide^{87,88} or (5-methyl-2-picolinyl)trimethylammonium hydroxide.⁸⁶

Application of the previously mentioned ring contraction of a *sulfur-bridged* cyclophane has been successfully carried out by Bruhn and Jenny in their quest for **140**. Thermolysis⁸⁵ of **148b** prepared by the procedure of Vögtle,³²⁸ or the photolysis⁸⁹ of **148a** in the presence of triethyl phosphite gave the desired [2]paracyclo[2](2,5)pyridinophane (**140**).



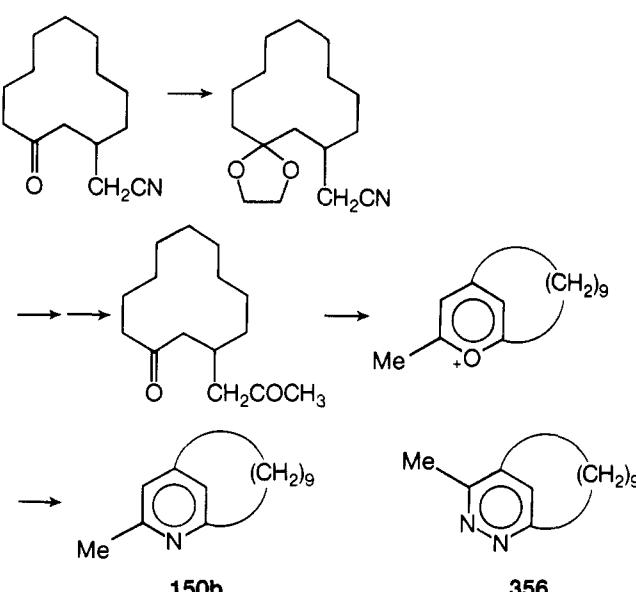
3. 2,4-Pyridino

The *carbon-bridged* [9](2,4)pyridinophane was first synthesized by Italian workers¹⁰⁷ from 2-cyclododecenone by initial treatment with ethyl cyanoacetate under Michael conditions. The resultant cyano keto ester was hydrolyzed under alkaline conditions and subsequently decarboxylated to the γ -cyano ketone. Reduction of this cyano ketone with lithium aluminum hydride gave a diastereomeric mixture of amino alcohols, which spontaneously cyclized to the disubstituted Δ^1 -piperideine. Dehydrogenation of the tetrahydropyridine nucleus with a catalytic amount of Pd-C in xylene and nitrobenzene gave **150a**. PMR spectral studies on **150a** failed to show the expected shielding effect of the π electron cloud upon the bridge methylene protons.¹⁰⁷

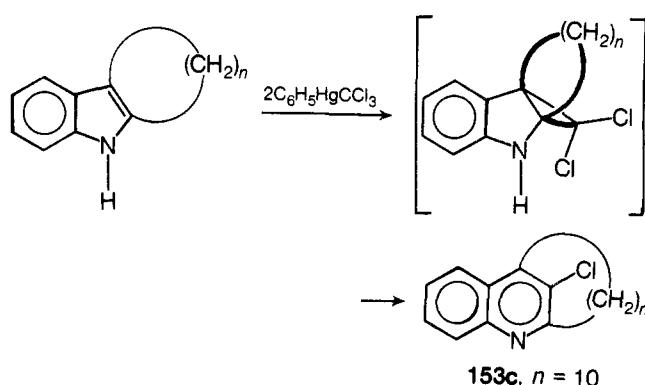


An alternate approach to substituted [9](2,4)pyridinophanes is via the corresponding pyrlophanium salt.¹⁰⁶ 3-Cyanometh-

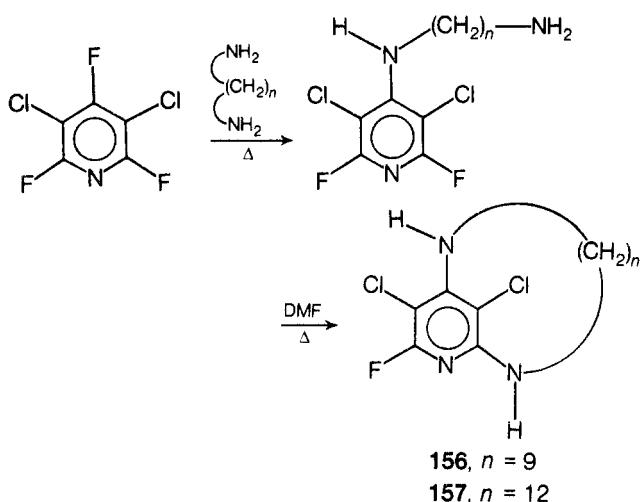
ylcyclododecanone¹⁰⁷ was ketalized under standard conditions and treated with methylmagnesium bromide in tetrahydrofuran; upon hydrolysis, the 3-acetylpyrlophanium was isolated. Reaction of this diketone with trityl perchlorate in boiling acetic acid afforded the 12-methyl[9](2,4)pyrlophanium perchlorate, which upon treatment with ammonium acetate gave **150b** in 80% yield. When the intermediary pyrlophanium salt was reacted with hydrazine, the first [9](4,6)pyridazinophane (**356**) was isolated.¹⁰⁶



Parham and co-workers synthesized a large series of benzo[2,4]pyridinophanes through a novel ring expansion reaction.¹¹⁰ The starting fused indoles were readily prepared by the Fischer indole synthesis;³²⁹⁻³³¹ treatment of these indoles with 2 equiv of phenyl(trichloromethyl)mercury afforded reasonable yields of the benzopyridinophanes. Both spectral and chemical evidence support the presence of a distorted aromatic system when the bridge is equal to or less than six carbon atoms. This general procedure has been applied to the synthesis of numerous [n](2,4)pyridinophanes.^{109,110,115,116} Hydrodechlorination of **153c** was easily accomplished by action of hydrazine and palladium on charcoal.^{332,333}

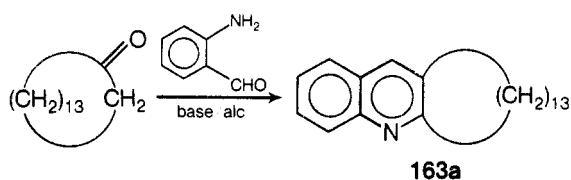


The only *carbon-nitrogen-bridged* (2,4)pyridinophane was recently synthesized by Wakefield et al.,¹³¹ when 3,5-dichlorotrifluoropyridine was treated with an appropriate long-chained (9 or 12 carbon atoms) primary diamine. The intermediate diamines can be isolated, and, when subjected to heating in *N,N*-dimethylformamide or *N,N*-dimethylaniline for an unspecified time, the cyclized compounds (e.g., **156**) were isolated.

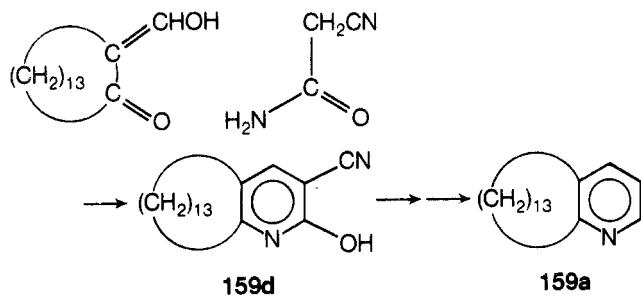


4. 2,3-Pyridino

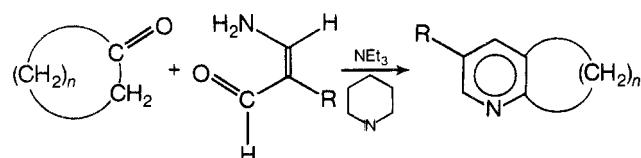
The carbon-bridged 2,3-pyridino macrocycles were generally synthesized by a base-catalyzed condensation reaction in order to construct a 2,3-disubstituted pyridine nucleus. 2,3-Tridecamethylenequinoline (163a) was synthesized by condensation of cyclopentadecanone (Exaltone) with 2-aminobenzaldehyde.¹²² These original macrocycles were prepared in order to permit evaluation of their physiological properties; 163a was reported to be physiologically inactive. 2,3-Polymethylenebenzopyridines have been recently reviewed.⁴⁴³



Prelog and Geyer also utilized a base-catalyzed condensation to generate the desired substituted pyridine nucleus 159d.^{118,119} The substituents were removed by standard methods.

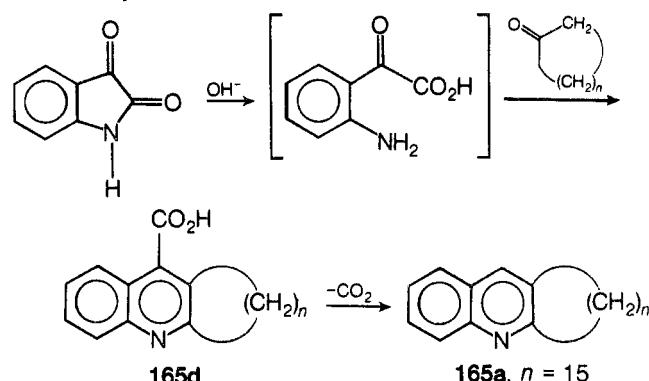


An alternate procedure to these macrocycles possessing the 2,3-pyridino moiety was recently described by Breitmaier and Bayer in which a cycloalkanone was reacted with 3-aminoacrolein in the presence of triethylamine and a trace of piperidinium acetate.³³⁴ Although their reported examples were limited to cyclic ketones of eight or less carbon atoms, this general procedure should be applicable to the construction of larger 2,3-polymethylenequinoxides.

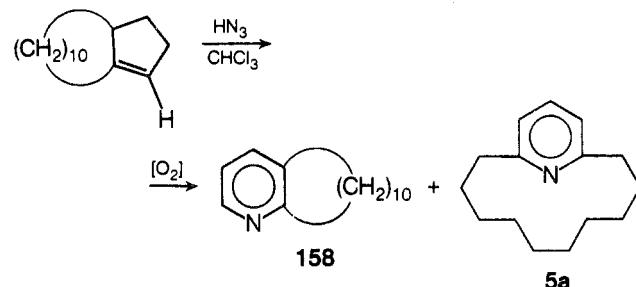


The classic Pfitzinger condensation^{335,336} has been utilized by Buu-Hoi et al. to synthesize 2,3-polymethylenequinolines.^{120,121,123,124,337} The condensation of isatin with cycloheptadecanone (dihydrocivetone) gave 165d, which subse-

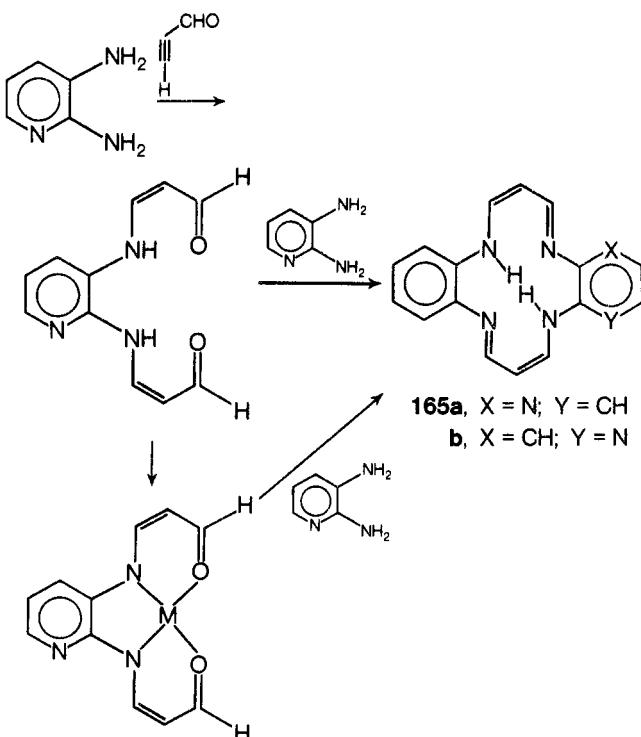
quently was decarboxylated to afford 165a. Remote unsaturation within the macrocyclic ring 165a can also be achieved via this condensation reaction through the use of the appropriate unsaturated cyclic ketone.^{123,124}



During the course of the synthesis of muscopyridine, bicyclo[10.3.0]pentadec-12-ene was subjected to Schmidt reaction conditions (HN_3 in CHCl_3), followed by oxidation, affording an equal mixture of both the anticipated macrocycle 5a as well as the unwanted 2,3-isomeric macrocycle 158.¹⁷ An explanation for the product distribution has been given.¹⁷

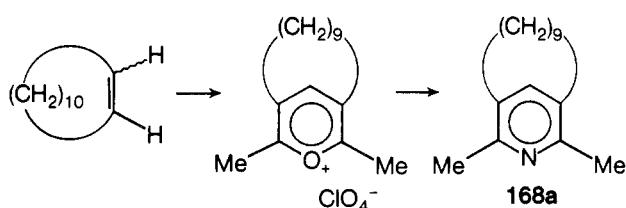


Carbon-nitrogen 2,3-pyridino macrocycles were prepared by Müller and Wöhrl from 2,3-diaminopyridine and propynal in a 1:1 ratio with or without the aid of a metal ion template.¹²⁶ The reaction proceeded through an intermediate (complex) and then cyclized to the 14-membered macrocycles 167a or 167b. Several metal complexes of 167a and 167b have been reported.¹²⁶

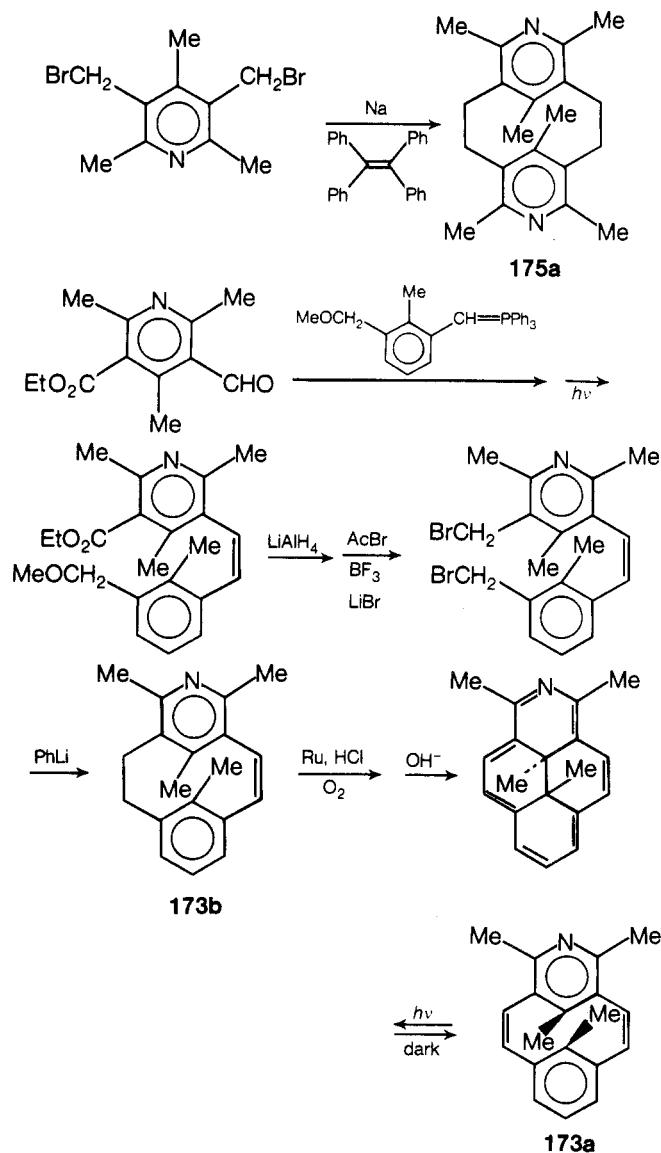


5. 3,5-Pyridino

Carbon-bridged 3,5-pyridino macrocycles have been synthesized by Balaban through the intermediary 3,5-bridged pyrylium salt.^{71,72,432} Diacetylation of cyclododecene was accomplished by addition of perchloric acid to an olefin in excess acetic anhydride without cooling. The black viscous residue (after extraction of the reaction mixture with ether) was extracted with boiling water affording 2,6-dimethyl-3,5-nonamethylenepyrylium perchlorate. Treatment of this salt with ammonia afforded the desired pyridine macrocycle **168a**,⁷¹ whereas, treatment with methylamine, aniline, or hydrazine gave the corresponding pyridinium perchlorate salts.

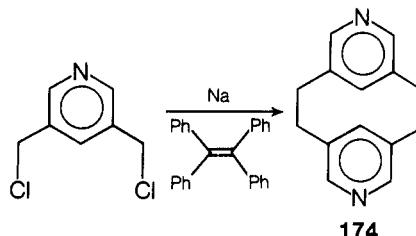


Boekelheide and Peppardine synthesized the metapyridinophane **175b** via the Wurtz coupling of the appropriate dihalide.⁷³ A more tedious route was employed by these researchers in the preparation of the related cyclophane **173a**.⁷³ 5-Ethoxycarbonyl-2,4,6-trimethylpyridine-3-carboxaldehyde underwent a smooth Wittig reaction with (3-methoxymethyl-2-methylben-

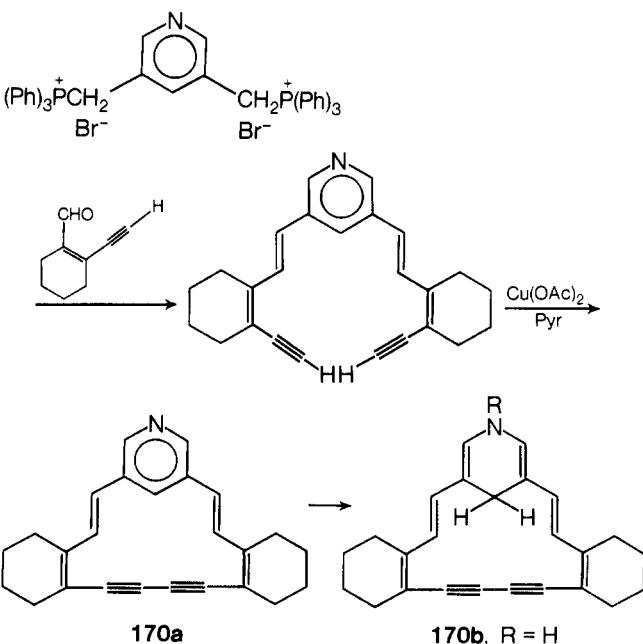


zyl)triphenylphosphonium bromide to afford a *cis*- and *trans*-stilbazole mixture. Photoisomerization converted the trans-rich product mixture (1:15) to a favorable 4:1 *cis*-*trans* ratio. The ester functionality was quantitatively reduced with lithium aluminum hydride and then subsequent conversion of both this alcohol group as well as simultaneous cleavage of the ether function to the dibromide was accomplished by reaction with acetyl bromide and boron trifluoride etherate in the presence of excess lithium bromide. Treatment of the dibromide with phenyllithium gave the metacyclophan-1-ene **173b**. Oxidation of **173b** with ruthenium and molecular oxygen in the presence of HCl gave a salt, which upon treatment with base generated the *trans*-1,3,15,16-tetramethyl-2-azadihydropyrene. Photoisomerization of the substituted dihydropyrene to the metacyclopane-1,9-diene (**173a**) was a facile process; however, a dark thermal isomerization has been shown to be an equally rapid reaction ($K_{1/2}^{\text{MeOH}} = 8 \text{ s at } 17^\circ\text{C}$).⁷³

Jenny and Holzrichter synthesized [2.2](3,5)pyridinophane (**174**) in a manner analogous to that presented in their previous papers specifically via the reaction of 3,5-bis(chloromethyl)-pyridine with sodium in the presence of tetraphenylethylene.^{81,82} Not only was the [2.2] member isolated (2%), but the [2.2.2]- and [2.2.2.2](3,5)pyridinophanes were also isolated in 4.2 and 1.5% yield, respectively.

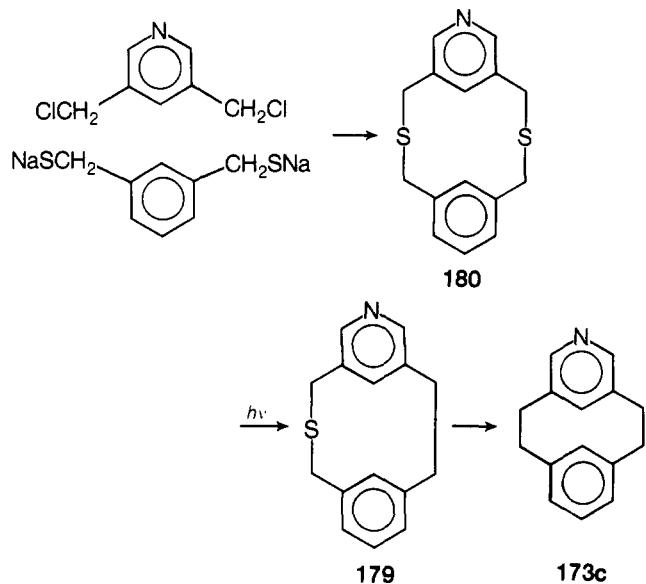


Sondheimer et al. in a series of elegant papers have described the synthesis of several new aromatic macrocyclic heteroannulenes.⁷⁵⁻⁸⁰ The general mode of construction can be demonstrated by the synthesis of **170b**.⁷⁵ The di-Wittig reagent prepared from 3,5-bis(bromomethyl)pyridine was reacted with 2 equiv of the appropriate ynenealdehyde to afford an isomeric mixture of olefins. The desired *trans*,*trans* isomer was isolated and oxidized with cupric acetate in pyridine at 55–60 °C for 1.5 h generating the polyunsaturated macrocycle **170a**. 1,4-Reduction of **170a** followed by the utilization of various trapping agents afforded a novel series of aza[17]annulene derivatives (**170b**). This synthetic route to the aza[17]annulenes has also

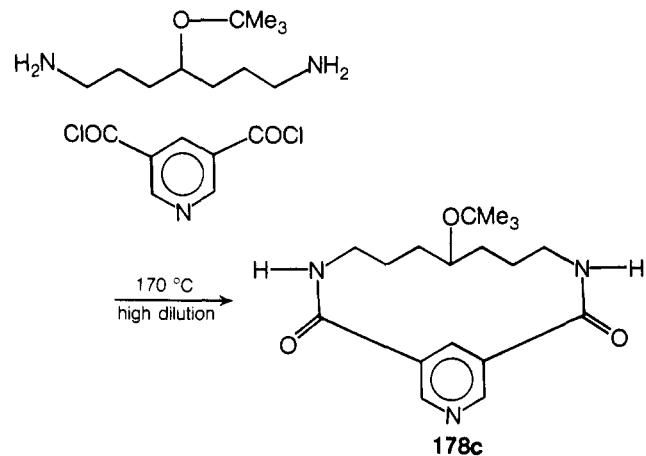


been applied to the synthesis of diatropic oxygen and sulfur analogs.^{78,341}

Carbon-sulfur-bridged 2,11-dithia[3]metacyclo[3](3,5)pyridinophane has been synthesized by a standard procedure and upon photolysis in the presence of triethyl phosphite gave 179 and then 173c.⁷⁴

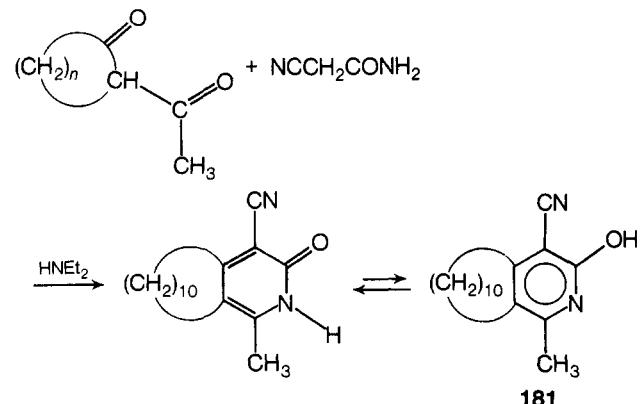


Carbon-nitrogen 3,5-pyridino macrocycle 178c was synthesized by Overman⁸³ via a high-dilution cyclization of 3,5-pyridinedicarbonyl chloride and a substituted diamine,⁴⁹³ following the procedure of Stetter.³³⁹



6. 3,4-Pyridino

Freeman and Ito have reported the simple conversion of 2-acetylcyclanones into substituted 5*H*-2-pyridines, as well as 3,4-polymethylene pyridines.¹²⁵ The reaction of 2-acetylcy-



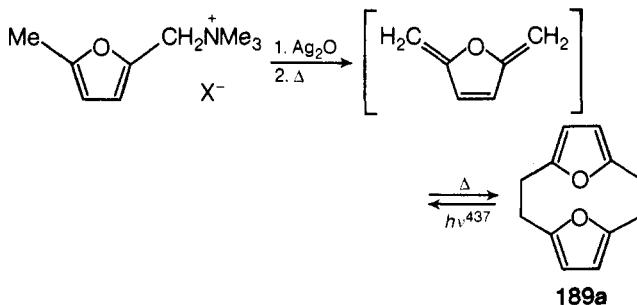
clododecanone with 2-cyanoacetamide in the presence of diethylamine gave (50%) macrocycle 181. The functionality can be removed by literature procedures.³⁴⁰

B. Furan as the Subunit

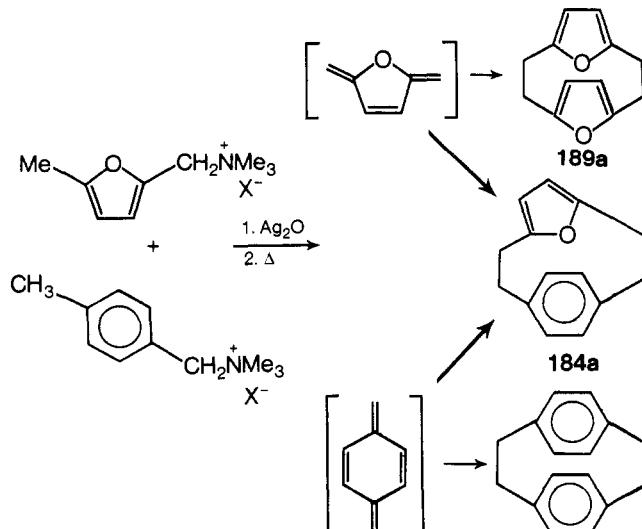
Macrocycles possessing only the furan subunit are tabulated in Table II.

1. 2,5-Furano

Of the *carbon-bridged* furanophanes, [2.2](2,5)furanophane (189a) has been the most widely investigated. Winberg et al. were the first to synthesize 189a via the pyrolysis of (5-methyl-2-furyl)trimethylammonium hydroxide at 150 °C at 3–4 mm pressure.¹⁸⁶ The intermediate 2,5-dimethylene-2,5-dihydrofuran was isolated from this reaction by trapping at –78 °C. Although this intermediate was stable at –78 °C, upon warming in the presence of radical inhibitors it dimerized (72%) to form 189a as well as a 1,6-coupled polymer possessing rearomatized furan rings. Both 5-ethylidene-2-methylene-2,5-dihydrofuran and 5-benzylidene-2-methylene-2,5-dihydrofuran were generated and dimerized separately; the stereochemistry of the(se) dimeric product(s) was (were) not ascertained.¹⁸⁶ This procedure of Winberg¹⁸⁶ has been successfully utilized by numerous researchers (ref 167, 178, 180, 181, 189–191, 281). The chemistry of 189a has also been widely investigated in cycloaddition reactions (ref 165, 166, 268) in conformational studies,¹⁵ and as a source of other cyclophanes (ref 181, 184, 186, 218, 281, 496–498). Photolysis of 189a with a low-pressure mercury lamp leads to a [6 + 6] photocleavage and thus generation of 2,5-dimethylene-2,5-dihydrofuran, which can be isolated at –78 °C.⁴³⁷

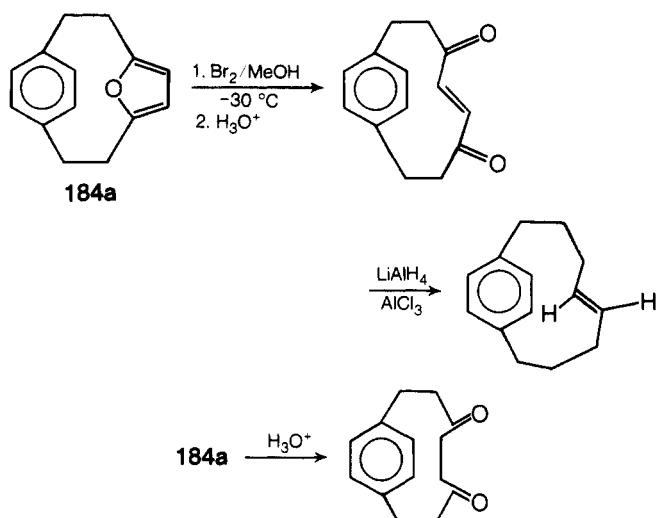


Cross-cycloadditions of 2,5-dimethylene-2,5-dihydrofuran with numerous other reactive trienes or tetraenes have been reported. These 1,6 to 1,6 cycloaddition reactions have afforded a vast array of mixed cyclophanes: [2.2](2,5)furanoparacyclo-

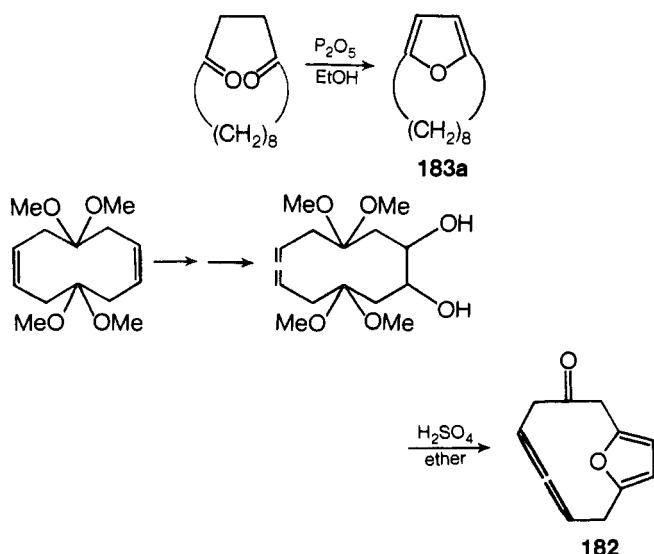


phanes,^{178,180,181,184} [2.2](2,5)furanophanes,^{184,189} [2.2](2,5)furan(1,4)naphthalenophanes,^{184,189} [2.2](2,5)furan(9,10)anthracenophane,¹⁹⁰ [2.2](2,5)furan(1,4)anthracenophane,¹⁹¹ and multilayered furanophanes.^{188,217,259,485,486}

These furanophanes have afforded a novel form of latent functionality of a 4- (or 6-) carbon atom moiety possessing varied substituents.^{347,348} In their molecular asymmetry studies, Cope and Pawson¹⁷⁹ utilized the procedure of Cram and Knox¹⁸⁰ to obtain **184a** as the convenient source to paracyclophanes, in which **184a** was oxidatively cleaved (bromine in methanol at -30 °C, followed by hydrolysis),^{180,181} then reduced with excess lithium aluminum hydride and aluminum chloride (1:3 ratio). Simple hydrolysis of the furan ring has also afforded a source of the 1,4-dione moiety (ref 178, 181, 184, 259, 281, 485).

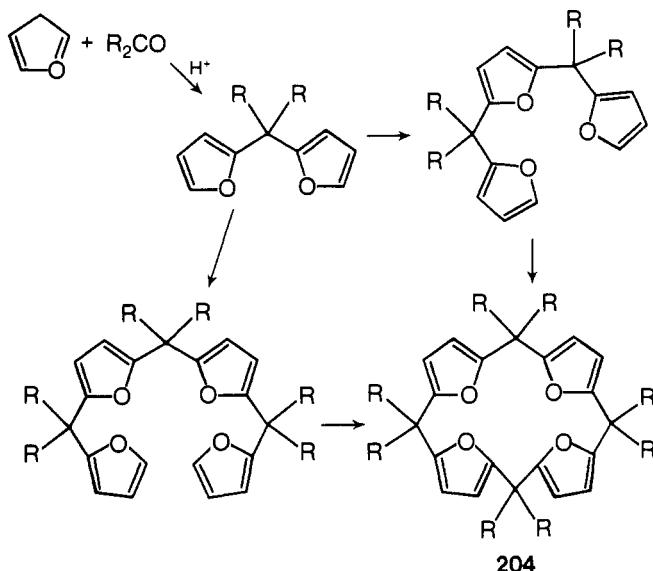


Synthesis of (2,5)furanophanes by dehydration of cyclic 1,4-diones has been reported. [8](2,5)Furanophane (**183a**) has been prepared (81%) from 1,4-cyclododecanedione^{176,187} upon treatment with phosphorus pentoxide in ethanol (the Paal-Knorr synthesis) according to the general procedure of Mukaiyama and Hata.³⁵⁰ In studies related to the reactions of cyclophanes, Helder and Wynberg needed large quantities of the starting 1,4-cyclododecanedione.²²⁰ Repetition of the earlier literature procedures^{349,370-371} resulted, however, in only moderate yields of the desired dione. Utilization of the Jones oxidation on the cyclobutanol intermediate afforded (55% overall) a much improved route to the dione; the mechanistic aspects of this conversion are not understood.²²⁰ Cycloadditions utilizing **183a** have afforded several novel structures, such as: a "paddlane"¹⁷⁷ and an octano-bridged oxaquadracyclane.²⁶⁰



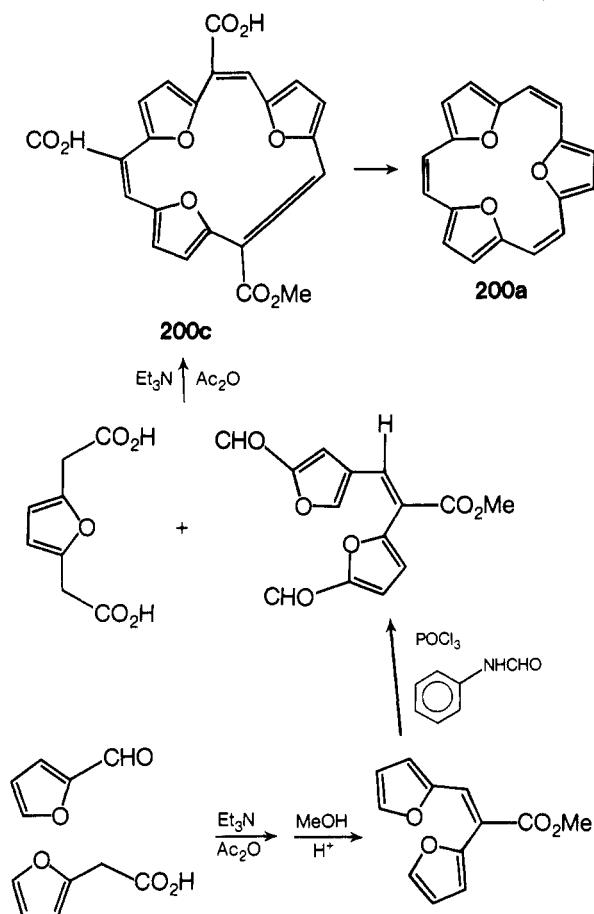
In search of monocyclic allenes, Garrett, Nicolaou, and Sondheimer isolated a novel allenic, macrocyclic tetraether, which upon treatment with 80% sulfuric acid in ether gave (63%) the unexpected furanophane **182**.¹⁸³ Catalytic hydrogenation of **182** afforded the reduced bicyclic ketone in 69% yield. Furanophane **182** "appears to be the first bridged aromatic system containing an allene group".¹⁸³ Mechanisms have been proposed for this novel transformation.¹⁸³

One of the largest classes of furan-containing macrocycles is that of "tetraoxaquaaterene". ["Quaterene" denotes a macrocycle composed of four methylene-bridged 1,4-disubstituted cyclopentadienes.]¹⁶⁹ The 16-membered macrocycle **204** was synthesized in low yield by simple acid-catalyzed condensation of furan and a dialkyl ketone (e.g., acetone).^{169,192-194,303,500} In general, such condensations have given rise to predominantly polymeric products; however, more recently, enhanced yields (~20%) of the desired macrocycles can be realized when metal ions are added to the reaction mixture (the template effect).^{168,266,343,344} Numerous intermediates have been isolated from these reactions and in certain cases can be converted to the macrocyclic system when subjected to additional acidic condensation conditions.^{169,192,194,500}

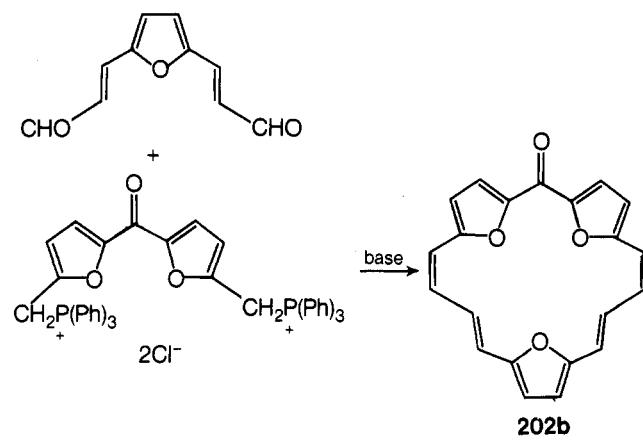


Over the past decade, studies of the physical and chemical properties of completely conjugated monocycles (annulenes) and ketones (annulenones) have been in vogue. Construction of these macrocycles generally has been via a base-catalyzed cyclocondensation. The [18]annulene trioxide synthesis will exemplify the basic mode of construction.^{146,147} The key intermediates, furan-2,5-diacetic acid and methyl *cis*- α,β -bis(5-formyl-2-furyl)acrylate, were subjected to a Perkin reaction (acetic anhydride and triethylamine) affording a low (1.05%) yield of annulene **200a**. The key intermediate methyl *cis*- α,β -bis(5-formyl-2-furyl)acrylate was prepared by (1) base-catalyzed condensation of 2-furylacetic acid with furfural; (2) esterification; and (3) direct formylation with phosphorus oxychloride and *N*-methylformanilide. Other formylation conditions caused either isomerization of the double bond, limited yields of the diformylated product, or a mixture of monoformylated products. Removal of the carboxylic acid groups was accomplished through initial saponification of **200c** to the triacid, then decarboxylation by treatment with quinoline and copper chromite at 200–205 °C to afford the desired unsubstituted [18]annulene trioxide (**200a**). This general cyclocondensation procedure utilizing either the Perkin reaction (an aldehyde and substituted acetic acid)^{110,162} or aldol condensation^{142,164} has been applied to the construction of numerous related annulenes.^{142,160,162,164}

An alternate, shorter procedure, albeit more convenient sy-

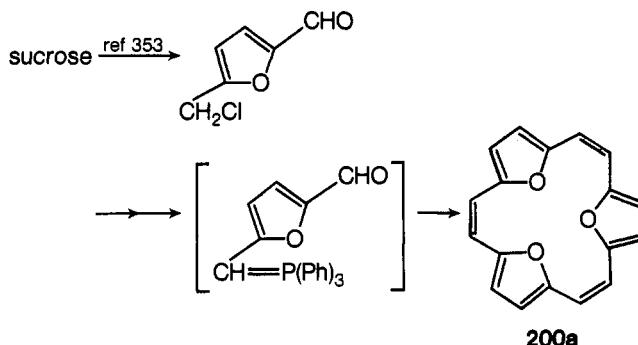


thesis of the parent annulene structure, is via bis-Wittig reagents (reviewed in ref 351). A typical illustration of this cyclization was reported for the Wittig reaction of a diacrolein³⁵² with an appropriate bis-phosphonium salt¹⁶² in the presence of lithium ethoxide to afford (15 %) annulenone **202b**.¹⁷² The bis-Wittig reagents have been used in the synthesis of varied annulenes (ref 140, 144, 150, 154, 174, 175) and annulenones (ref 158–160, 162, 163).

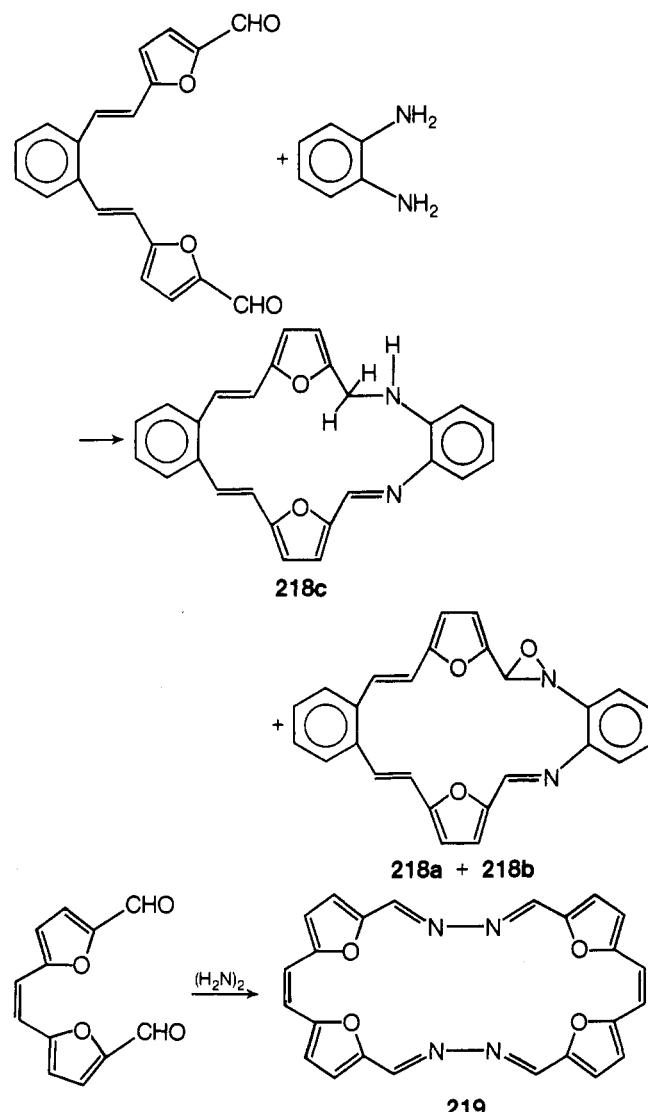


Elix has reported a synthesis of annulenes from sucrose¹⁴⁸ via an appropriately substituted Wittig reagent prepared from 5-chloromethyl-2-furfural.³⁵³ The slow addition of lithium ethoxide to this phosphonium salt in dimethylformamide resulted in an intermolecular cyclocondensation to give (0.07 %) trioxide **200a** along with two isomeric [24]annulene tetraoxides, two isomeric [30]annulene pentoxides, and an [36]annulene hexoxide of unknown configuration.^{148,155}

With the availability of polyunsaturated bis-aldehydes, Saito et al. prepared several novel carbon–nitrogen-bridged furan macrocycles.¹⁷⁴ When di-trans-1,2-bis[β-(5'-formyl-2'-

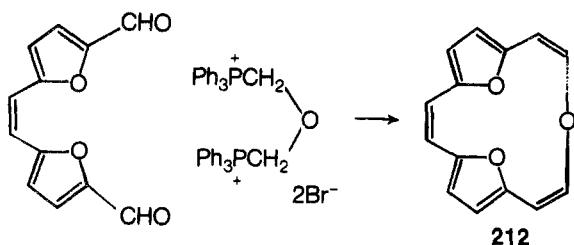


furyl)vinyl]benzene was condensed with o-phenylenediamine, the expected annelated diaza[20]annulene dioxide was not formed but rather **218c**, **218b**, and **218a** were isolated in 15, 1, and 15.7 %, respectively. However, when *cis*-α,β-bis(5'-formyl-2'-furyl)ethylene was reacted with hydrazine, the dimer **219** was isolated and no monomer or other disproportionation products were obtained.¹⁷⁴

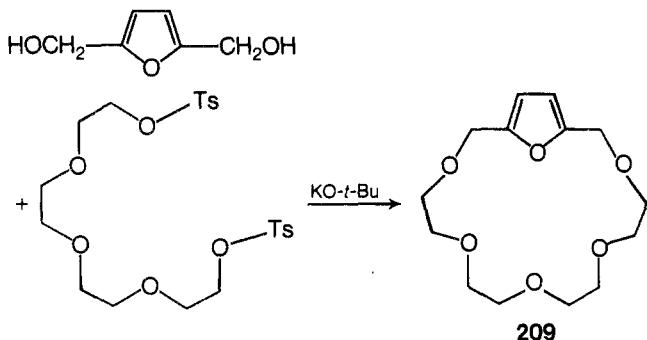


Several carbon–oxygen-bridged furan macrocycles have been reported. Ogawa et al.^{140,144} prepared hetero[15]annulenone **212** by the Wittig reaction of a known dialdehyde¹⁷⁴ and (dimethyl ether)-α,α'-bis(triphenylphosphonium bromide)³⁵⁴ with lithium methoxide. Spectral data have excluded the occurrence of valence tautomeric isomerism.

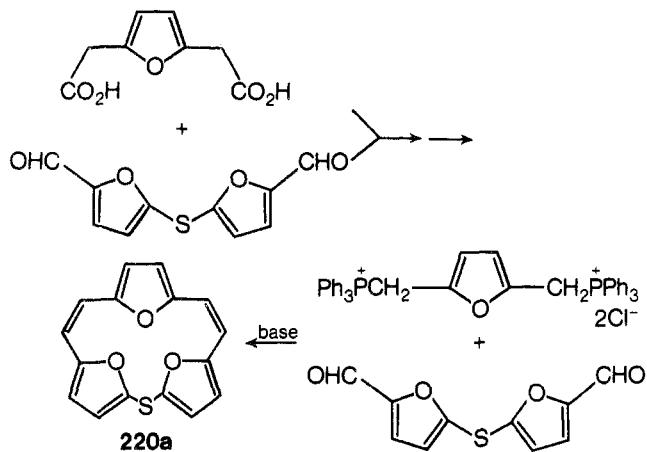
A large series of host compounds has been reported by Timko and Cram.¹⁶⁷ The pivotal starting material, 2,5-bis(hydroxy-



methyl)furan was prepared (55% overall) via a two-step sequence from sucrose. Macrocycle **209** was prepared (36%) by treatment of tetra(ethylene glycol) ditosylate with this diol in tetrahydrofuran in the presence of potassium *tert*-butoxide. The unique complexing properties of these ethereal furano macrocycles have been reported.²⁴ This general procedure has also been utilized by Reinhoudt and Gray in the synthesis of related crown ethers,^{170,467} and a modified procedure has been suggested to be applicable for the construction of chiral macrocyclic polyethers **214b**.²²³



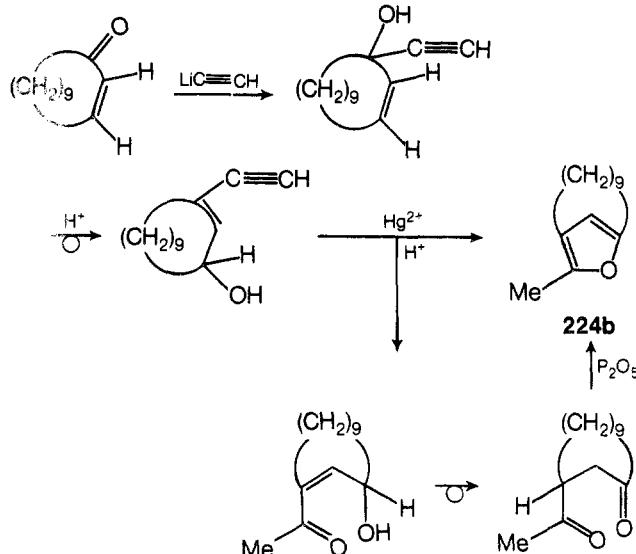
The carbon-sulfur-bridged furan macrocycle related to **220a** has been prepared by a Perkin condensation of a known dialdehyde³⁵⁵ with furan-2,5-diacetic acid,³⁵⁶ followed by decarboxylation to afford only traces of the thia[17]annulene (**220a**).¹⁶¹ However, when the same dialdehyde was reacted with the appropriate bis-Wittig reagent,¹⁷⁵ the desired macrocycle was prepared in 10% yield. The Wittig procedure has also been applied to the synthesis of thia[21]annulene (**221**).¹⁵⁷



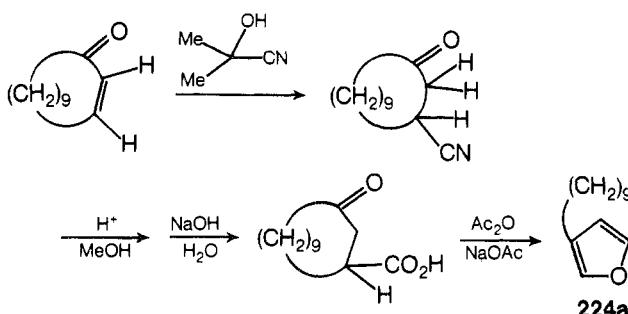
2. 2,4-Furano

Carbon-bridged furanophanes have been prepared by two similar procedures. When a mixture of *cis*- and *trans*-2-cyclododecenone³⁵⁸ was treated with lithium acetylide, 1,2-addition gave 1-ethynyl-2-cyclododecen-1-ol, which underwent an acid-catalyzed isomerization to 3-ethynyl-2-cyclododecen-1-ol. Subsequent treatment of this latter alcohol with mercuric sulfate under acidic conditions afforded 11-methyl-[9](2,4)-furanophane.^{206,229} 3-Acetylcyclododecanone was isolated as a by-product from the hydration of the alkyne bond as well as from the acidic hydrolysis of **224b**. It should be noted that application

of the Paal-Knorr reaction of 1,4-diketones via dehydrative conditions (P_4O_{10}) failed in the attempted preparation of [6]- and [7](2,4)furanophanes from the corresponding diones;²²⁹ however, 3-acetylcyclododecanone was converted to **224b** under these reaction conditions.²²⁸ In the attempted synthesis of [7](2,4)furanophane, a crystalline dimer was isolated; however, its structure was never elucidated.²²⁹

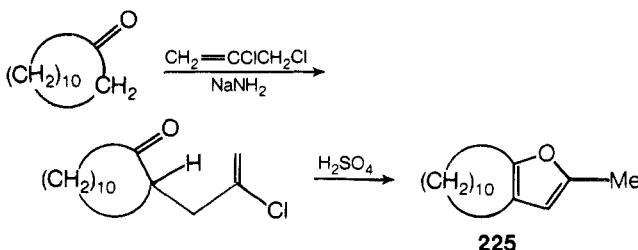


The unsubstituted [9](2,4)furanophane was prepared²⁰⁵ from the same cyclododecen-2-one by initial treatment with acetone cyanohydrin in aqueous alcohol in the presence of sodium carbonate to afford 3-cyanocyclododecanone. Direct conversion of the nitrile to the methyl ester was accomplished by treatment with hydrochloric acid in methanol; then saponification gave the corresponding γ -keto acid, which when subjected to acetic anhydride and sodium acetate gave a mixture of four components. [9](2,4)Furanophane was obtained (15%) from the mixture by distillation.

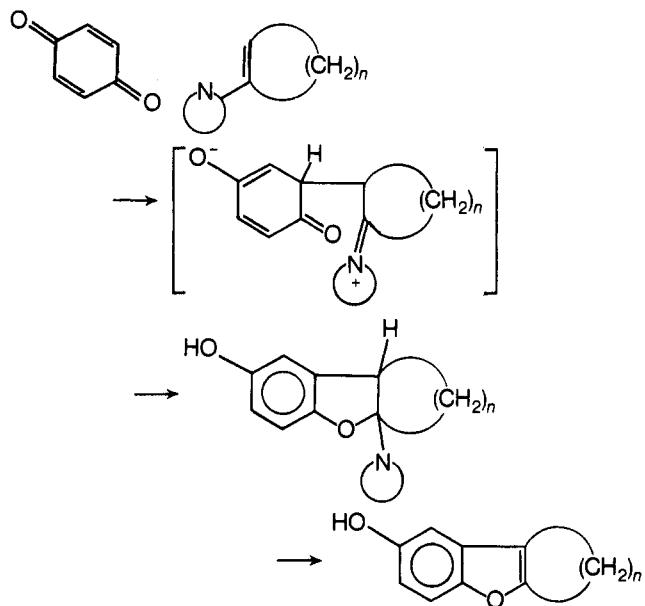


3. 2,3-Furano

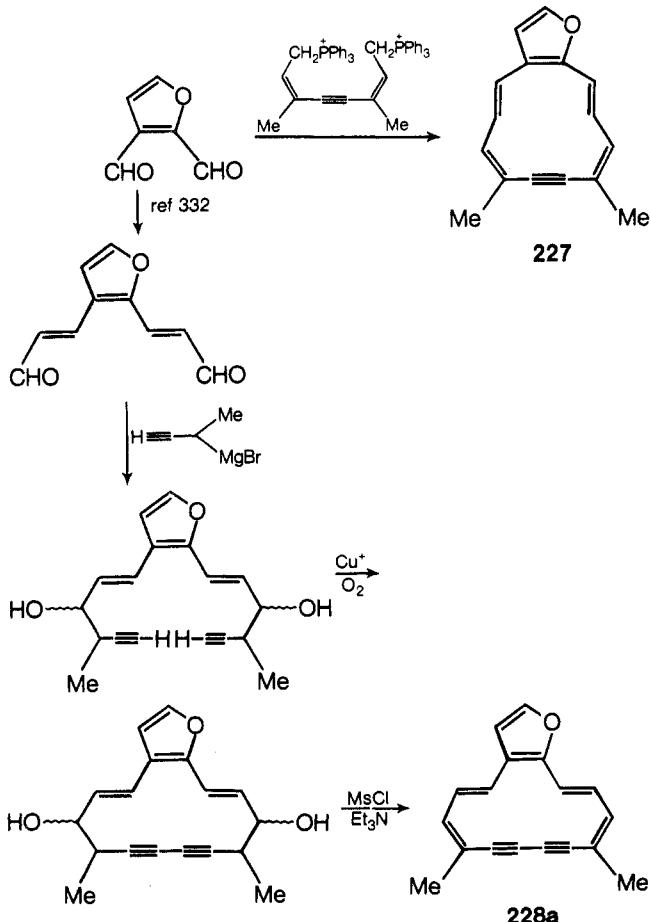
Only a limited number of *carbon-bridged* 2,3-furano macrocycles have been reported. McAndrew and Russell cyclized an appropriate chloro ketone in the presence of 90% sulfuric acid, according to the procedure of Nienhouse et al.,³⁵⁹ to generate **225** (66%).²²¹ The necessary chloro ketone was synthesized (62%) from cyclododecanone and 2,3-dichloroprop-1-ene in the presence of sodium amide.



In a recent communication, macrocyclic keto lactones were synthesized from the corresponding benzo- and naphthofurans,²¹⁹ which were in turn synthesized by the procedure of Domschke.³⁶⁰ No physical or spectral data were cited in this communication for these furans.²¹⁹ In general, the furan nucleus was prepared by the Michael addition of a macrocyclic enamine with a quinone, followed by cyclization, and subsequent β -elimination.³⁶⁰



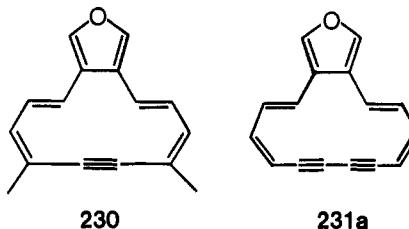
Sondheimer et al. prepared both [12]- and [14]annuleno[*b*]furans via a novel application of the Wittig reaction. The appropriate bis-Wittig reagent [prepared in 55% from the corresponding diol: $-\text{CH}_2\text{OH} \rightarrow -\text{CH}_2\text{Br} \rightarrow -\text{CH}_2\text{P}^+(\text{Ph})_3\text{Br}$] was



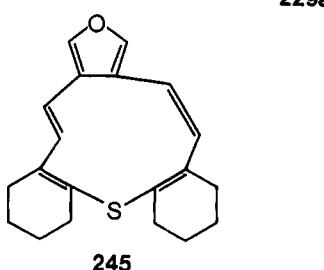
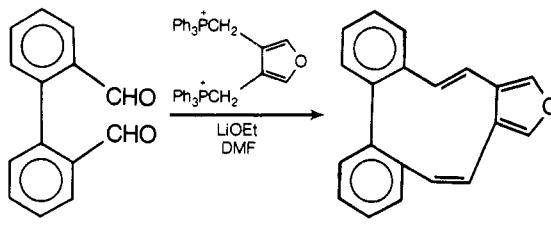
reacted with butyllithium in tetrahydrofuran, followed by addition of furan-2,3-dicarboxaldehyde to afford 227 in 0.6% isolated yield.²⁰⁸ The related [14]annulene²⁰⁹ 228a was synthesized from the same dialdehyde by initial conversion³⁵² to the bisvinylene, which was reacted with 1-methyl-2-propynylmagnesium bromide in ether at -30°C to give a mixture of diols. Coupling of the bisacetylene was accomplished by treatment with oxygen in the presence of cuprous chloride (Glazer coupling). The bis- β -elimination was carried out by treatment of the crude macrocyclic diol with mesyl chloride and triethylamine in dimethoxyethane at 0°C under an inert atmosphere to afford 228a. Overall conversion of the bis- α,β -unsaturated aldehyde to 228a was 15%.^{209,210}

4. 3,4-Furano

Sondheimer et al. applied the same synthetic modes of construction as shown directly above for the preparation of both the carbon-bridged 3,4-furano macrocycles 230,²⁰⁸ 231a^{210,212} and related annulenes.⁴⁵⁸ The bimolecular rate constants for the Diels-Alder reactions of maleic anhydride with the dehydroannuleno[*c*]furans have afforded reactivity criterion of aromaticity and antiaromaticity in macrocyclic annulenes.⁴⁵⁸

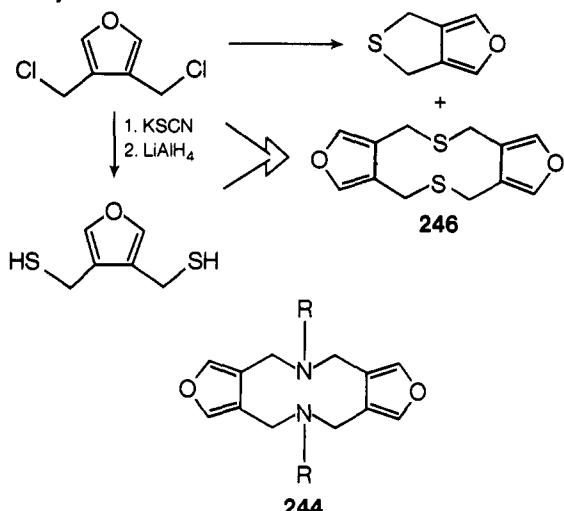


The Wittig reaction has been utilized in the preparation of other 3,4-furano macrocycles. Synthesis of 229a was accomplished by condensation of biphenyl-2,2'-dicarboxaldehyde and 3,4-furan bis(methylenetriphenylphosphonium chloride)³⁶¹ with lithium ethoxide in dimethylformamide.^{207,214,215} It is of particular interest to note that, in both the preliminary letter²⁰⁷ and full paper,²¹⁵ the products from this reaction were reported to be two conformational isomers which both possess the *E,E* configuration; however, in a later paper²¹⁴ the configurational assignment of these isomers was corrected to *E,Z*. Use of 3,4-furanbis(methyltriphenylphosphonium chloride) has been reported in the construction of several related medium-ring furan containing compounds,³⁶² as well as in the preparation of a carbon-sulfur-bridged thia[11]annulene 245.²¹⁶

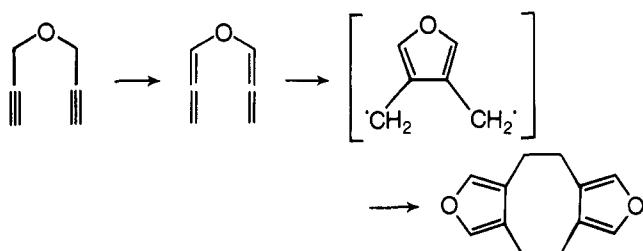


The main reaction product of 3,4-bis(chloromethyl)furan with sodium sulfide was the expected bicyclic compound; however, the ten-membered dithieocene 246 was also isolated in 16%

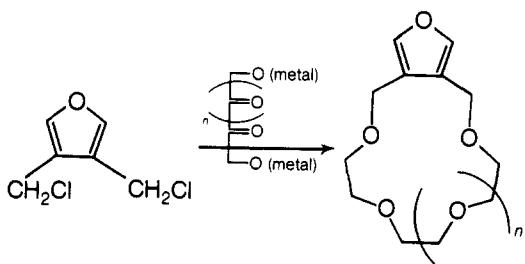
yield.⁴³⁵ The same macrocycle **246** was obtained from the reaction of 3,4-bis(chloromethyl)furan and 3,4-bis(mercaptopethyl)furan.⁴³⁵ The corresponding carbon–nitrogen-bridged analog **244** was prepared from 3,4-bis(chloromethyl)furan and a primary amine.^{433,436}



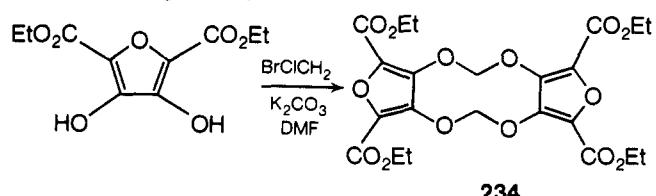
Treatment of dipropargyl ether with freshly prepared potassium *tert*-butoxide in *tert*-butyl alcohol at 0 °C led to the formation of bisfuranocyclooctadiene, the intermediacy of a diallenyl ether, and then diradical; macrocyclic products were not reported, however, as expected.⁴⁵³



Only a limited number of carbon–oxygen-bridged 3,4-furano macrocycles has been reported. Recently, Reinoudt et al. described the synthesis of a series of crown ethers which incorporated the 3,4-furano moiety.³⁰⁴ When 3,4-bis(chloromethyl)furan was reacted with a poly(ethylene glycolate), variable yields (6–43%) of the desired crown ether were realized. When small ($n = 1$ and 2) poly(ethylene glycolates) were used, the corresponding dimers were isolated; however, when $n > 2$, the 1:1 monomers were isolated exclusively.³⁰⁴



The methylation of diethyl 3,4-dihydroxy-2,5-furandicarboxylate with bromochloromethane in the presence of potassium carbonate gave (25%) **234** as well as a complex mixture of high molecular weight compounds.²⁰⁴

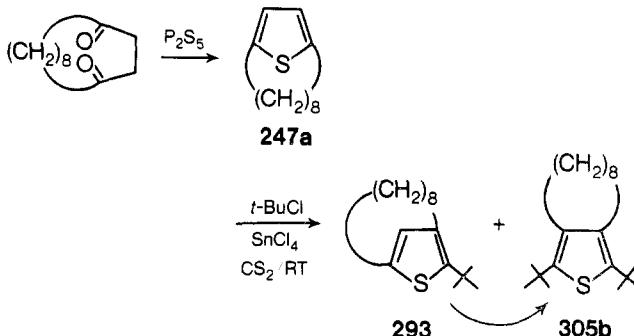


C. Thiophene as the Subunit

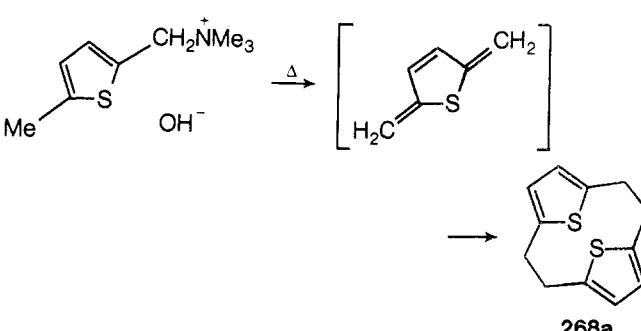
Macrocycles possessing only the thiophene subunit are tabulated in Table III. Certain limited aspects of thiophene macrocycles have been reviewed.^{298,367,375} Several of the procedures utilized in the synthesis of furan-containing macrocycles have also been applied to construction of the thiophene analogs; thus, where duplication has occurred, only a brief description will be used to illustrate the general mode of construction.

1. 2,5-Thiopheno

Dehydration of the appropriate cyclic 1,4-diketone in the presence of phosphorus pentasulfide at 80 °C afforded a carbon-bridged 2,5-thiopheno macrocycle;^{176,187,430} for example, **247a** was prepared (51%) via this procedure from 1,4-cyclododecanedione.²²⁰ Attempted Friedel–Crafts alkylation of **247a** with *tert*-butyl chloride in the presence of SnCl₄ in carbon disulfide at ambient temperature afforded **305b** rather than the expected 3,4-dialkylated product.²²⁰ A monoalkylated, intermediary rearrangement product was also isolated.²²⁰ Thus, care must be exercised when subjecting strained thiophenophanes to stringent reaction conditions!

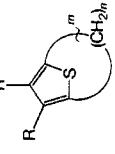
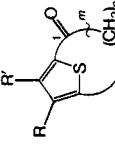


Thiophenophanes can be prepared in low yield by the procedure of Winberg et al., in which (5-methyl-2-thienyl)trimethylammonium hydroxide was pyrolyzed at 150 °C.¹⁸⁶ The 2,5-dimethylene-2,5-dihydrothiophene intermediate was not isolated in this reaction; however, it has been isolated (at liquid nitrogen temperatures) from the pyrolysis of 2-ethyl-5-methylthiophene at 825 °C³⁷² and has been shown to undergo spontaneous polymerization. The x-ray analysis of the 1:1 adduct of benzotri-furoxan and **268a** has been determined; **268a** has a trans- or step-like configuration.²⁵³ Cross-condensation of this intermediate with other reactive trienes has afforded a unique series of heterocyclophanes.^{188,191}



Steinkopf et al. reported the first purported thiophenophane example; when 3,4-dibromo-2,5-di(phenylbromomethyl)thiophene was treated with copper-bronze at elevated temperatures, a coupling reaction product **268b** was isolated.²⁹⁷ Since this compound (**268b**) was an amorphous solid for which a wide melting point, no spectral data, and suspicious analytical data were reported, a better characterization of the reaction products seems to be in order.

TABLE III. Macrocycles Containing the Thiophene Subunit^a

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comments ^b | Ref |
|---|----------------------|---|-----------|---|----------------------------|------------------------------------|--|
|  | | $m = 1; n = 8; R = R'$ $= H$ | 247a | [80–81 (15)] | A–C | | 176, 187, 220, 260 |
| | | $m = 1; n = 8; R = R'$ $= t\text{-Bu}$ | 247b | | | Attempted synthesis | 220 |
| | | $m = 1; n = 10; R = R'$ $= H$ | 248a | [67.5 (0.03)] | | | 235 |
| | | $m = 1; n = 10; R = R'$ $= Ac$ | 248b | 59–60.5 | C | Semicarbazone (mp 213–214°) | 235 |
| | | $m = 1; n = 11; R = R'$ $= H$ | 249a | 51–53 | A | | 430 |
| | | $m = 1; n = 11; R = H;$ $R' = Br$ | 249b | 45–46 [140–144 (5 × 10 ⁻³)] | A | | 430 |
| | | $m = 2; n = 10; R = R'$ $= H$ | 250 | [108.5–111 (0.8)]; 51.5–53.5 | | | 233–235, 252, 363 |
|  | | $m = 1; n = 8; R = R'$ $= H$ | 251 | | C | Semicarbazone (mp 191.5–193.5°) | 234, 285, 287, 367 |
| | | $m = 1; n = 9; R = R'$ $= H$ | 252a | [149–152 (1)]; 35.5–37.5 | A, C | Oxime (mp 133– 134.5°) | 224, 233–236, 285, 240, 287, 365–367 |
| | | $m = 1; n = 9; R = Me;$ $R' = H$ | 252b | 58.5–60 | | | 224, 282 |
| | | $m = 1; n = 9; R = H;$ $R' = Me$ | 252c | 90–91.5 | | | 224, 282 |
| | | $m = 1; n = 9; R' = H;$ $R = i\text{-Pr}$ | 252d | 80.5–81.5 | C | Semicarbazone (mp 188.5–189.6°) | 235 |
| | | $m = 1; n = 9; R' = H;$ $R = NO_2$ | 252e | 89.5–90 | C | | 235 |
| | | $m = 1; n = 10; R = R'$ $= H$ | 253a | [127.5–132 (0.05)]; 45–46.2 | C | Semicarbazone (mp 193.4–195.5°) | 234, 250, 251, 285, 287, 363, 365–367 |
| | | $m = 1; n = 10; R' =$ $H; R = Me$ | 253b | 40.5–42 | | | 244, 282 |
| | | $m = 1; n = 10; R' =$ $Me; R = H$ | 253c | 76.5–78.5 | | | 244, 282 |
| | | $m = 1; n = 10; R =$ $R' = H; 2\text{-CO}_2\text{Et}$ | 253d | [189–192 (0.15)]; 80 (5 × 10 ⁻⁵) subl | | | 239–242, 250, 251, 261, 286, 367 |
| | | $m = 1; n = 10; R =$ $R' = H; 2\text{-Et}; 2\text{-CO}_2\text{Et}$ | 253e | 61–62 | | | 256 |
| | | $m = 1; n = 11; R =$ $R' = H$ | 254 | [162–165 (0.5)]; 31–32 | C | Semicarbazone (mp 214–215°) | 234, 285, 287, 365– 367 |
| | | $m = 1; n = 12; R =$ $R' = H$ | 255a | [170–171 (0.2)] | C | Semicarbazone (mp 225.3–225.5°) | 234, 285, 287, 365– 367 |
| | | $m = 1; n = 12; R =$ $R' = H; 2\text{-CO}_2\text{Et}$ | 255b | [160 (0.15)]; 52.8–55 | | <i>n</i> ²⁰ D 1.5360 | 251, 367 |
| | | $m = 1; n = 12; 2\text{-Me}; 2\text{-CO}_2\text{Et}$ | 255c | 53–55 | | | 256 |

| | | | |
|--|------|---|---|
| $m = 1; n = 12; 2\text{-Et};$ | 255d | 65–66 | 256 |
| $2\text{-CO}_2\text{Et}$ | 255e | 82–83.5 | 256 |
| $m = 1; n = 12; 2\text{-C}_3\text{H}_7\text{-CO}_2\text{Et}$ | 256 | [180–200.5 (10^{-5})]; 142–143.5 | c |
| $= \text{H}$ | 257 | [120–180 (0.005)]; 107.8–109.3 | c |
| $m = 2; n = 6; \text{R} = \text{R}'$ | 258 | [150–200 (10^{-5})]; 97–98 | c |
| $= \text{H}$ | 259a | [150–200 (10^{-5})]; 83.5–85 | c |
| $m = 2; n = 7; \text{R} = \text{R}'$ | 259b | [132.5–134 | Semicarbazone (mp 191.5–193.5°) |
| $= \text{H}$ | 260 | [180–200 (10^{-5} – 10^{-6})]; 102–104 | 233, 234, 236, 252, 261 |
| $m = 2; n = 8; \text{R} = \text{R}'$ | 261 | | 240, 261 |
| $= \text{H}; 2,15\text{-}(\text{CO}_2\text{Et})_2$ | 262 | 89–90.5 | c |
| $m = 2; n = 9; \text{R} = \text{R}'$ | 263a | [169–178 (1)]; 69.5–71 | Positive test with Bi_2O_3 |
| $= \text{H}; 2,17\text{-}(\text{CO}_2\text{Et})_2$ | 263b | 117–119 | Positive test with Bi_2O_3 |
| $m = 3; n = 5; \text{R} = \text{R}'$ | 264 | [167–169 (0.3)]; 62–64 | Positive test with Bi_2O_3 |
| $= \text{H}$ | 265a | 230–231 (sealed tube) | c |
| $m, n = 4; \text{R} = \text{H}$ | 265b | 125–126 | A, C |
| $m = n = 4; \text{R} = \text{R}'$ | 265c | 182–183 | A, C, D |
| $= \text{Me}$ | 265d | 142–143 | A, C, D |
| $m = 5; n = 4; \text{R} = \text{H}$ | 265e | ~195 dec | A, D |
| H | 265f | ~100 dec | A, C, D |
| $4,14\text{-}(\text{Me})_2$ | | | 217 |
| $4,5\text{-Benzo}$ | | | 188 |
| $4,5\text{-}(2,3\text{-Naphtho})$ | | | 191 |
| $4,5\text{-}(13,14\text{-Dibenzo)}$ | | | 191 |
| $R = R' = H$ | 266a | ~175 dec | A, C |
| $R = R' = \text{Me}$ | 266b | 149–151.5 dec | A, C |
| H | 267 | ~195 dec | A, C |

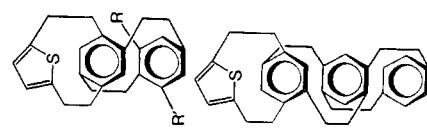
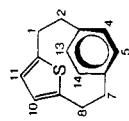
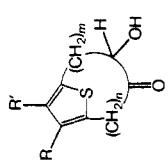


TABLE III (Continued)

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comments ^b | Ref |
|----------|---|--------------|-----------|-----------------------------------|----------------------------|---|--|
| | H | | 268a | 194.5–196 | A–C | <i>C</i> 2n symmetry ²⁸⁶ X-ray Probable structure ²⁹⁸ | 186, 188, 191, 246, 286, 253 297 |
| | 1,2,7,8-(C6H5)4; 4,5,- 10,11-(Bz)2 | | 268b | 250–255 | | | |
| | H | | 269a | 74.5–75.5 (subl: 70) | A–C | No peripheral con-jugation, aromatic stability ⁴³⁴ | 191 151, 152 |
| | (Z)-1,2; (Z)-7,8; (E)- 13,14 | H | 269b | | | | |
| | (E)-1,2; (E)-7,8; (E)- 13,14 | | 269c | 257–259 | D | | 149 151, 152 |
| | (E)-1,2; (E)-7,8; (E)- 13,14 | | 269d | >360 | A–C | Unsuccessful resolution | 151, 152 |
| | (E)-1,2; (E)-7,8; (E)- 13,14 | | 269e | Dec | A | | 151, 152 |
| | 1,14-(CO2H)2; 7-CO2Me | | 270a | 338 | A, B, D | | 151, 152 |
| | 1,1,6,6,11,11,16,16- (Me)s | | 270b | 280 dec | A, B | | 199, 200 |
| | 1,1,1-(OH)2; 1,6,6,11,- 16,16-(Me)s | | 270c | 250 dec | | | 199, 248 |
| | 1,11-(=CH2)2; 6,6,- 16,16-(Me)s | | 270d | 280 dec | A, B, D | | 199, 248 |
| | 1,11-(OH)2; 1,11- (H); 6,6,11,16- (Me)s | | 271 | | A, D | | 199, 248 |
| | n = 2 | | | | | | 255, 442 |
| | 1,1,6,6,11,11,16,16- (Me)s | | 272 | 224–226 | A, C, D | | 247 |
| | p = 1; m = 2; n = 5; H | | 273a | 67–68 | A ²²⁴ , D | X-ray analysis ⁴⁹⁹ | 224, 225, 245, 363, 444 |
| | p = 1; m = 2; n = 5; 2,3-benzo | | 273b | | | | 364 |
| | p = 1; m = 3; n = 4; H | | 274 | 113–114 | A ²²⁴ | X-ray analysis ⁴⁹⁹ | 444, 224, 225, 237, 238 |

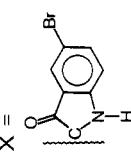
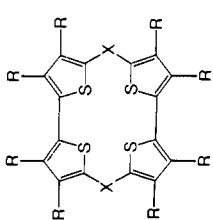
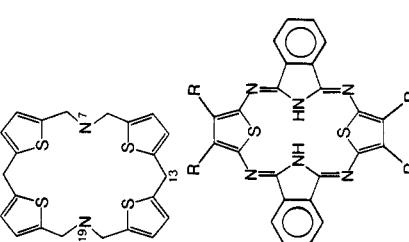
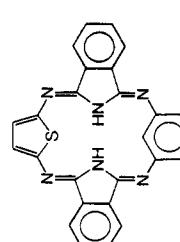
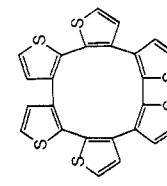
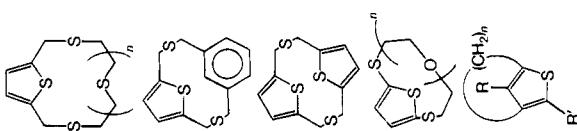
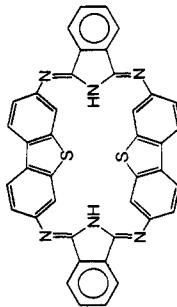
| | | | |
|---|-----|-----------|--|
| $p = 1; m = 3; n = 5;$ | 275 | 114–115 | 237 |
| H | | | |
| $p = 1; m = 4; n = 3;$ | 276 | 70–71 | A_{224}, D |
| H | | | 224, 225, 245, 363, 444 |
| $p = 1; m = 5; n = 2;$ | 277 | 134–135 | D |
| H | | | 245, 363, 444 |
| $p = 1; m = 5; n = 4;$ | 278 | | A_{224} |
| H | | | 224, 225 |
| $p = 1; m = 1; n = 6;$ | 279 | | 245 |
| H | | | |
| $p = 2; m = 2; n = 5;$ | 280 | 166–167 | A_{224}, D |
| H | | | 224, 245, 444 |
| $R = H; X = Hg$ | 281 | | Improbable structure ²⁹⁸ |
| $R = H; X =$ | 282 | 130 | Poor analysis; amorphous powder |
|  | | | Improbable structure ²⁹⁸ |
| $1,1,7,13,13,19-(Me)_6$ | 283 | 168.5–170 | Picrate (mp 155.5–157°) |
|  | | | |
| $R = CN$ | 284 | | 257 |
|  | | | |
| $R = CN$ | 285 | | 257 |
|  | | | |

TABLE III (Continued)

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comments ^b | Ref |
|----------|--------------------------------|--------------|-----------|---|----------------------------|---|---------------|
| | Bisulfone | | 286 | 378–380 | B, C | | 258 |
| | <i>n</i> = 1; H | | 287 | 127–129 | A | Cu | 431 |
| | H | | 288 | 210 | A | | 246 |
| | H | | 289 | 234 dec | A | | 246 |
| | <i>n</i> = 3; H | | 290 | | | | 35 |
| | <i>n</i> = 6; R = H; R' = Me | | 291 | [68–74 (3)] | A–D | | 229, 230 |
| | <i>n</i> = 7; R = H; R' = Me | | 292 | [1120–(3)] | A–D | | 229 |
| | <i>n</i> = 8; R = H; R' = t-Bu | | 293 | Oil | A, C (CMR) | | 220 |
| | <i>n</i> = 9; R = R' = H | | 294a | [80–85 (0.03)] | A | | 205 |
| | <i>n</i> = 9; R = H; R' = Me | | 294b | [1115 (3)] ²²⁷ [105–1110 (0.4)] ²²⁸ | A–D | | 228, 229 |
| | <i>n</i> = 10; 10-(=O); R = Me | | 295 | 55–56 | A | 4-NO ₂ PhNHNH ₂ (Z isomers) | 227, 282 |
| | <i>n</i> = 11; 11-(=O); R = Me | | 296 | 37.7–38.5 | A | 4-NO ₂ PhNHNH ₂ (mp 165–168°) | 227, 282, 365 |
| | <i>n</i> = 12; 12-(=O); R = Me | | 297 | Oil | A | 4-NO ₂ PhNHNH ₂ (mp 178–179°) | 226, 282, 365 |
| | H | | 298 | >420 | A | Centrosymmetric structure | 404 |



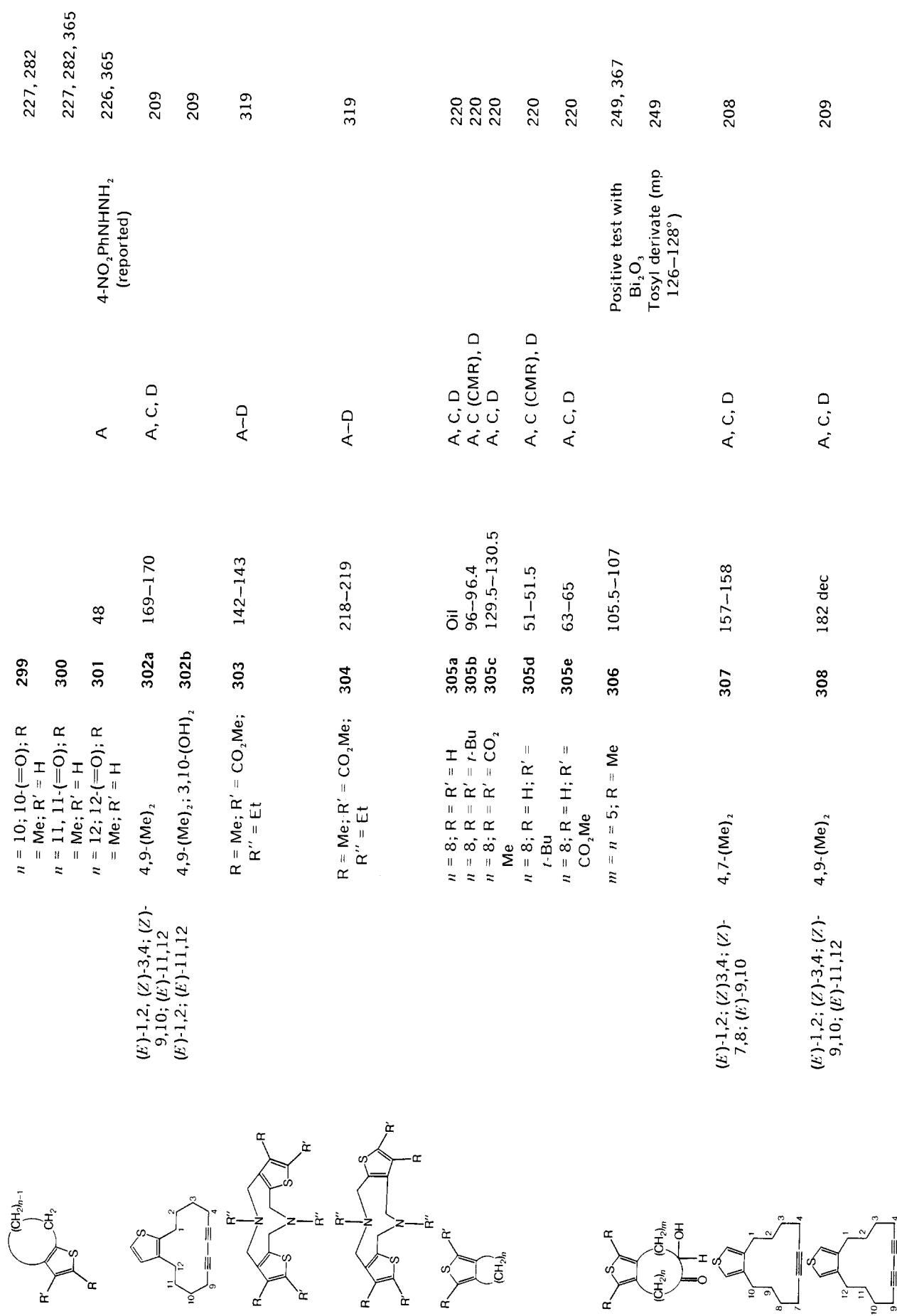
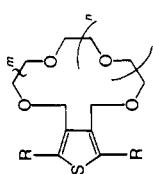


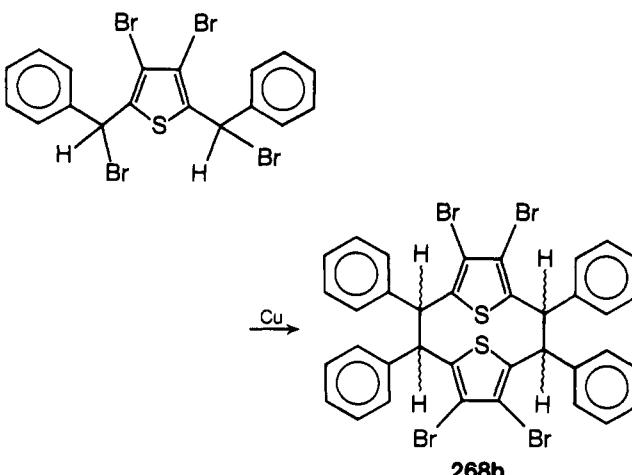
TABLE III (Continued)

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/comments ^b | Ref |
|---|---|--------------|---------------------|-----------------------------------|--|-----------------------------------|----------|
| (E)-1,2; (E)-5,6; (E)-12,13; (E)-16,17 | 3,4;14,15-Dibenzo 8,10,19,21-(Me), | 309 | 235–240 dec | A–D | Unstable in air | | 232 |
| <i>n</i> = 1; R = Me | | 310 | 244–245; 200 (subl) | A, D | Conformationally mobile | | 231 |
| <i>n</i> = 2; R = Me | | 311 | >370 (subl 300) | D | | | 231 |
| | | 312 | 209–210 | A, B | | | 204 |
| R = CO ₂ Et | | | | | | | |
| | | 313a | 233–235 | A–C | | | 357 |
| R = Me | | 313b | 270–271 | A, B | | | 317 |
| R = Cl | | 313c | 220–221 | | Reassignment of structure ^{a,17} | | 317, 318 |
| R = i-Bu | | | | | | | |
| | | 314a | 275 dec | D | | | 319 |
| R = Br | | 314b | 173–184 | | | | 357 |
| R = Me | | | | | | | |
| | | | | | | | |
| <i>n</i> = 1; R = Cl; R' = Et | | 315a | 102.5–103.5 | A–C | | | 319 |
| <i>n</i> = 1; R = Me; R' = Et | | 315b | 88–88.5 | | Picrate (250°) | | 320, 357 |
| <i>n</i> = 1; R = Me; R' = i-Pr | | 315c | 152–153 | | Picrate (186°) | | 320, 357 |
| <i>n</i> = 1; R = Me; R' = i-Bu | | 315d | 119–120 | | | | 357 |
| <i>n</i> = 1; R = Me; R' = i-Bu | | 315e | 209–210 | | Dipicrate (195– 197°) | | 320 |
| <i>n</i> = 1; R = Me; R' = -(CH ₂) ₅ -[2Cl] ₇ | | 315f | 242 | | Dipicrate | | 320 |

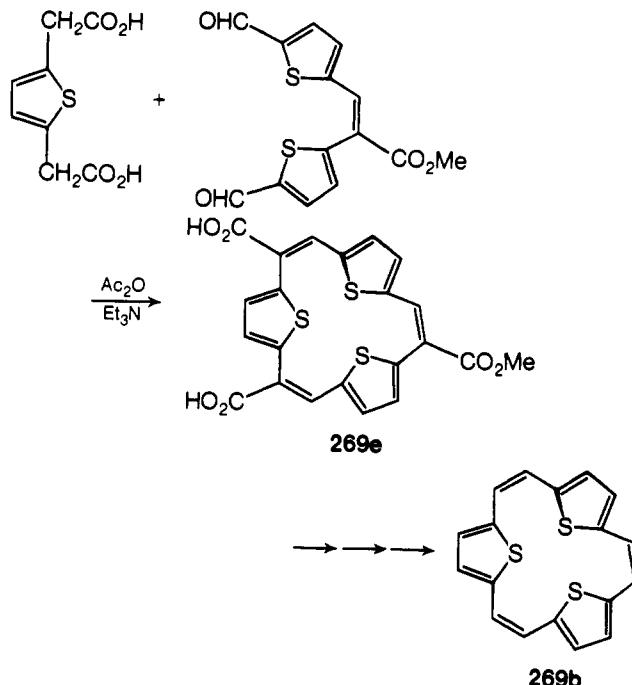
| | | | |
|--------------------------------------|------|-----------|-------------------------|
| $n = 1; R = Me; R' = 2 (Et) [2Cl^-]$ | 315g | 202–204 | (246–249°) |
| $n = 2; R = Me; R' = Et$ | 316 | 182.5–183 | Dipicrate (157–158°) |
| $n = 0; m = 1; R = Me$ | 317 | | 320 |
| $n = 1; m = 1; R = Me$ | 318 | | 320 |
| $n = 2; m = 1; R = Me$ | 319 | | 320 |
| $n = 3; m = 1; R = Me$ | 320 | | 320 |
| $n = 4; m = 1; R = Me$ | 321 | | 320 |
| $n = 5; m = 1; R = Me$ | 322 | | 320 |
| $n = 6; m = 1; R = Me$ | 323 | | 320 |
| $n = 0; m = 2; R = Me$ | 324 | | 320 |
| $n = 1; m = 2; R = Me$ | 325 | | 320 |
| $n = 2; m = 2; R = Me$ | 326 | | 320 |
| | | | 357 |
| | | | A, CMR Na, K |



^aSpectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS. ^bTemperatures given in °C.

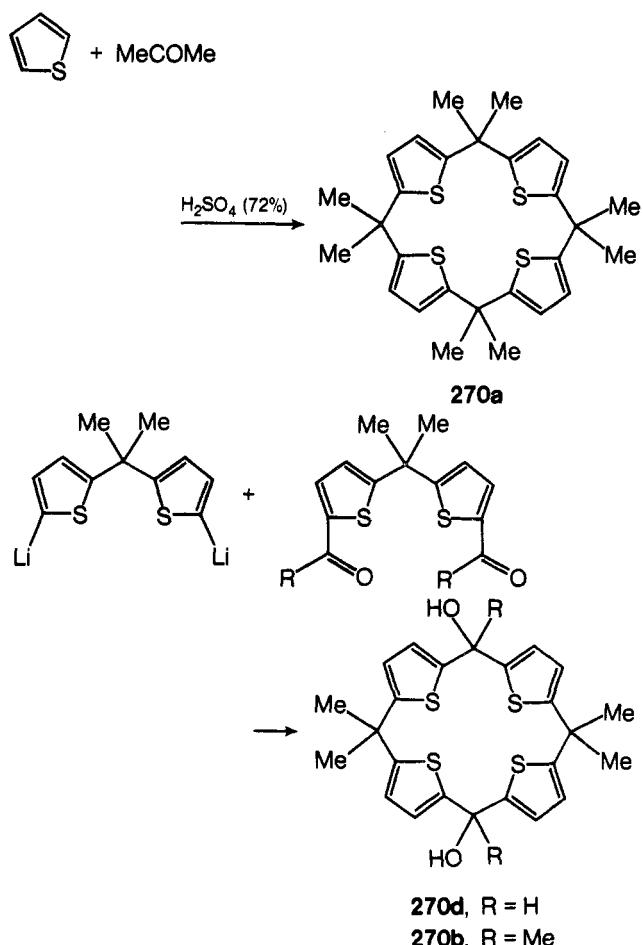


[18]Annulene trisulfide (**269b**) has been synthesized by cyclocondensation of thiophene-2,5-diacetic acid and methyl *cis*- α,β -bis(5-formyl-2-thienyl)acrylate under standard Perkin reaction conditions (acetic anhydride and triethylamine).^{151,152} Since it was difficult to work with the diacid, **269e** was converted via standard Fischer esterification to the desired triester **269c**. Alkaline hydrolysis of **269c** gave the triacid **269d**, which was decarboxylated with copper chromite in quinoline at 210–220 °C affording the unsubstituted [18]annulene trisulfide **269b**.^{151,152} All experimental evidence supported the fact that **269b** is a nonplanar, nonaromatic system in which the thiophene subunits are bridged by olefinic vinylene groups.¹⁵¹



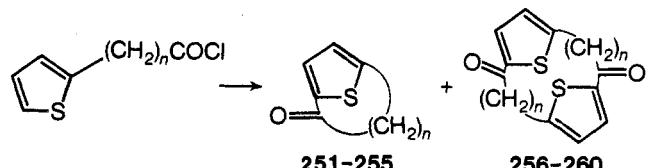
Although pyrrole and furan reacted with acetone and hydrochloric acid to generate porphyrinogen^{323–325} and tetraoxa-*quaterene*,^{169,194,195} respectively, initial attempts to prepare tetrathia-*quaterene* in an analogous manner failed. However, under more rigorous reaction conditions (thiophene, acetone, and 72% sulfuric acid),²⁰⁰ the residue was shown to contain the desired macrocycle **270a**.¹⁹⁹ Ahmed and Meth-Cohn also prepared several other members of this series by condensation of 2,2-bis(5'-lithio-2'-thienyl)propane with 2,2-bis(5'-formyl-2'-thienyl)propane to yield **270d**.^{199,248} Similarly when this dilithio reagent was reacted with 2,2-bis(5'-acetyl-2'-thienyl)propane, the corresponding hexamethyl analogue was prepared; dehydration of **270b** afforded diolefin **270c**.²⁴⁸

Gol'dfarb et al., in a series of papers, have described the utilization of 2,5-thiophene macrocycles as precursors to bio-



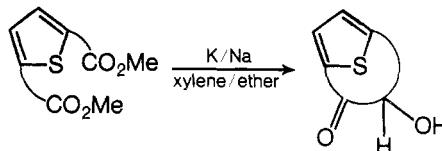
logically important sulfur-free macrocyclic compounds, for example, naturally occurring perfumes (Exaltone and related macrocyclic keto lactones) and macrolide antibiotics. These Russian workers have described three general procedures to these macrocycles: (a) Friedel-Crafts acylation; (b) acyloin condensation of a diester; and (c) S_N2 cyclization. The initial overview of their procedures was surveyed in 1959,²³³ however, since then numerous supportive papers have been published.

The Friedel-Crafts acylation of an appropriate terminal 2-thienyl straight-chain acyl chloride gave rise to both monomeric (intramolecular) and dimeric (intermolecular) products when subjected to either aluminum chloride/etherate in carbon disulfide (ref 233, 234, 238), stannic chloride in benzene at +5 °C (ref 233, 234, 252), aluminum chloride in ether (ref 252), aluminum chloride in chloroform (ref 234, 236, 238, 244, 245, 285, 287, 364), or aluminum chloride-ether in the presence of neutral alumina or silica gel (ref 236-238, 244, 282). In general, when $n = 3-5$, 2,3-disubstituted thiophenes were isolated; $n = 8-12$, 2,5-disubstituted monomeric thiophenes were obtained; and $n = 5-9$, 2,5-disubstituted dimeric thiophenes resulted.²³⁴ Interestingly, by the addition of silica gel (or alumina) to these Friedel-Crafts acylations and utilizing high-dilution conditions, *intramolecular cyclization products were favored*. As an important synthetic preparative note,²³⁶ addition of these adsorbents permitted: (1) increased addition rates of the acid chlorides, (2) reduction of solvent volumes, and (3) increased intramolecular cyclization products in the case of carbon bridges. It was assumed that when adsorbents are present in this reaction mixture,

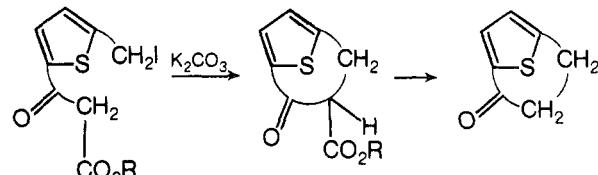


the adsorbent surface takes an active part in the intramolecular acylation reaction.²³⁸

The acyloin condensation has been applied to construction of these macrocycles, however, to a much more limited extent than one would expect! When methyl thiophene-2,5-dialkanoates were treated under high-dilution conditions in the presence of sodium in xylene/ether at 60 °C^{249,252} or of potassium/sodium alloy in the same solvent,²⁴⁹ the desired acyloin products were isolated (25-30%).

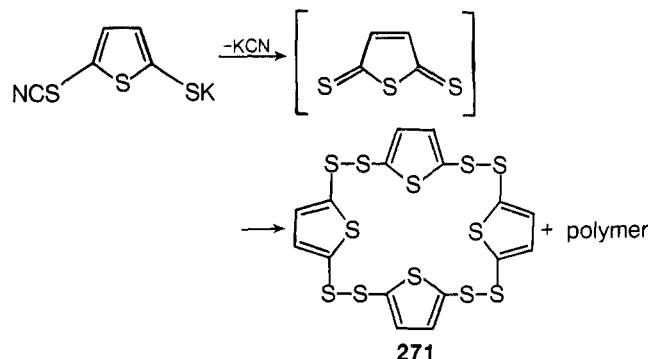


The third procedure utilized by these Russian workers was the intramolecular cyclization of an activated methylene group with an iodomethylene group in the presence of finely pulverized potassium carbonate (ref 240, 241, 250, 251, 261, 286) in methyl ethyl ketone, potassium *tert*-butoxide,²³⁹ or other alkali metal carbonates.²⁴² In general, no intermolecular cyclization products were isolated when potassium carbonate was used as the base.²⁴¹ In the presence of various alkali metal carbonates, the intramolecular cyclization rate increased with the radius of the alkali metal cation and surface area of the carbonate.²⁴²



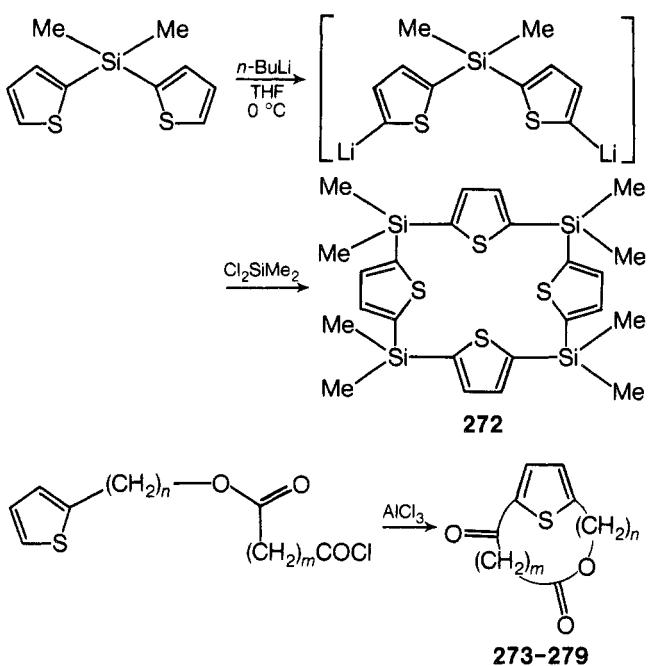
Conversion of these thiophene macrocycles to sulfur-free macrocycles via Raney-nickel desulfurization has been reported by Gol'dfarb et al. (ref 233, 235, 237, 244, 250-252, 256, 285, 365).

The only known *sulfur-bridged* thiophene macrocycle was reported by Todres et al. when 5-thiocyanato-2-thienyl mercaptide (stable in absolute tetrahydrofuran) was treated with acetic acid.²⁵⁵ This mercaptide probably decomposed through the unstable trithiomaleic anhydride intermediate, which underwent facile polymerization. The tetrameric disulfide macrocycle **271** was isolated in low yield from the mixture of oligomers.²⁵⁵

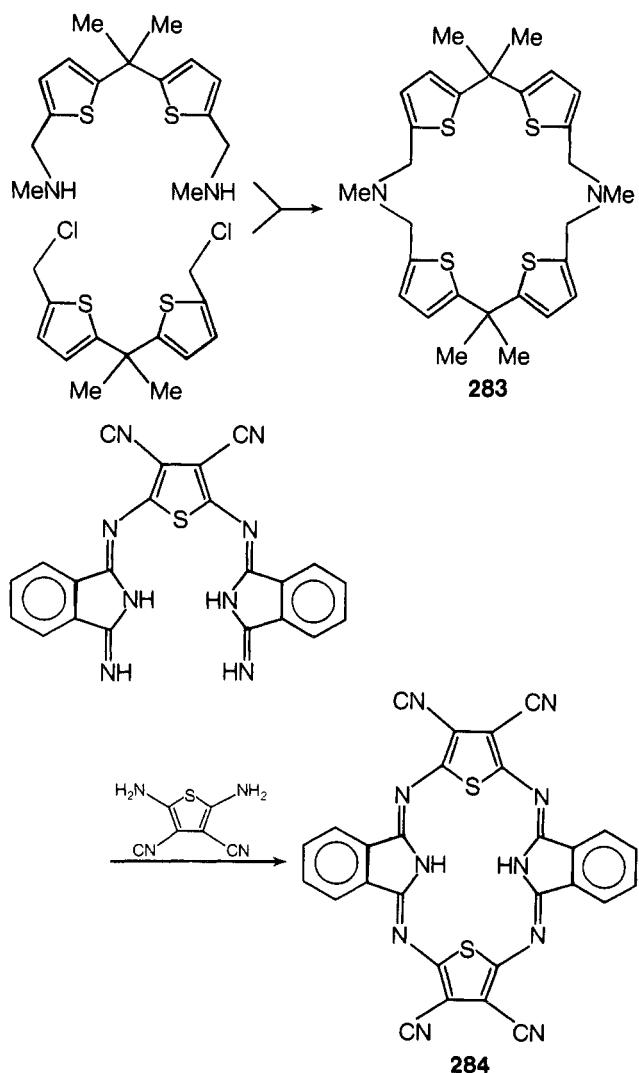


Kauffmann and Kniese reported the synthesis of a *silicon-bridged* macrocycle (silathiophenophane) **272** through the treatment of 2,2-bis(5'-lithio-2'-thienyl)-2-silapropene with dichlorodimethylsilane in tetrahydrofuran at 0 °C.²⁴⁷

Carbon-oxygen-bridged thiophene macrocycles were prepared by Gol'dfarb et al. in the search for a convenient source of macrocyclic keto lactones. Thiophene macrocycles were constructed (40-60%) by intra- and intermolecular cyclization of the corresponding acid chlorides in the presence of aluminum chloride^{225,237,238,245} (see **273-279**).

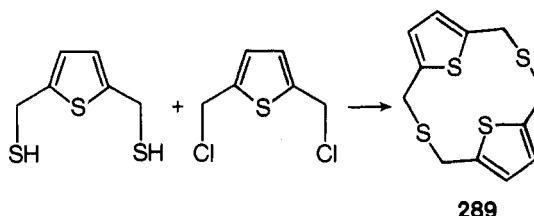


Gol'dfarb, et al. also reported the construction of a novel 2,5-carbon–nitrogen-bridged thiophene system by the reaction of 2,2-bis(5'-methylaminomethyl-2'-thienyl)propane with 2,2-bis(5'-chloromethyl-2'-thienyl)propane under very mild conditions (benzene at 40°C); the proposed macrocyclic structure **283** was marginally supported by physical data.²⁴³

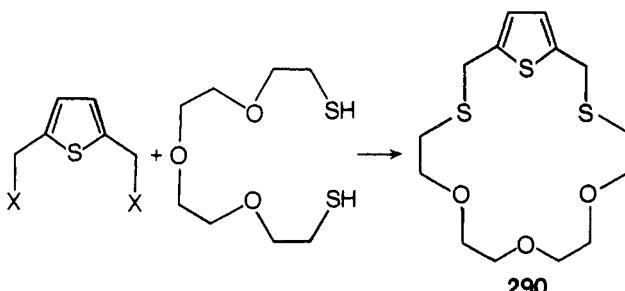


A thiophenedicarbonitrile derivative, prepared (48%) by the reaction of 1-amino-3,3-diethoxyisoindoline with 2,5-diamino-3,4-dicyanothiophene, was treated with a second equivalent of the diamine to give (58%) the desired heteromacrocycle **284**. The corresponding benzene derivative **285**²⁵⁷ as well as numerous other related derivatives^{387,388} were prepared in a similar manner.

The carbon-sulfur-bridged heterophanes **289** and **288** were prepared by the reaction of 2,5-bis(mercaptopethyl)thiophene with either 2,5-bis(chloromethyl)thiophene or 1,3-bis(bromomethyl)benzene, respectively, under high-dilution conditions.²⁴⁶

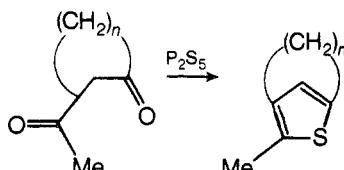


A carbon-sulfur–oxygen-bridged thiophenophane **290** has been reported by Vögtle and Weber; no experimental details were presented.³⁵ However, **290** was probably synthesized in a manner similar to their previous heterocyclic examples.^{27-29,31-33}

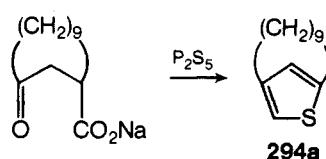


2. 2,4-Thiopheno

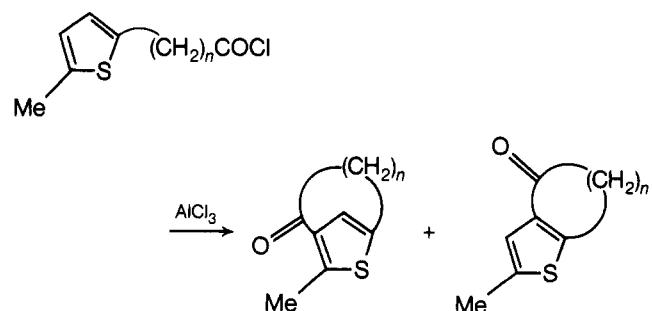
To date, all of the 2,4-thiopheno macrocycles possess a carbon bridge. The simplest general procedure to $[n](2,4)$ thiophenophane was the treatment of an appropriate 3-acetylcy cloalkanone with phosphorus pentasulfide.^{228,230} The smallest (2,4)thiophenophane yet reported contains a six-membered carbon bridge.^{229,230} As considered earlier in this review, [8]-(2,5)thiophenophane **247a** underwent monoelectrophilic substitution to rearrange to a substituted [8](2,4)thiophenophane.²²⁰



Bradamante et al. reported the preparation of the unsubstituted [9](2,4)thiophenophane **294a** by the gentle warming of the sodium salt of 3-ketocyclododecanecarboxylic acid with P_2S_5 .²⁰⁵



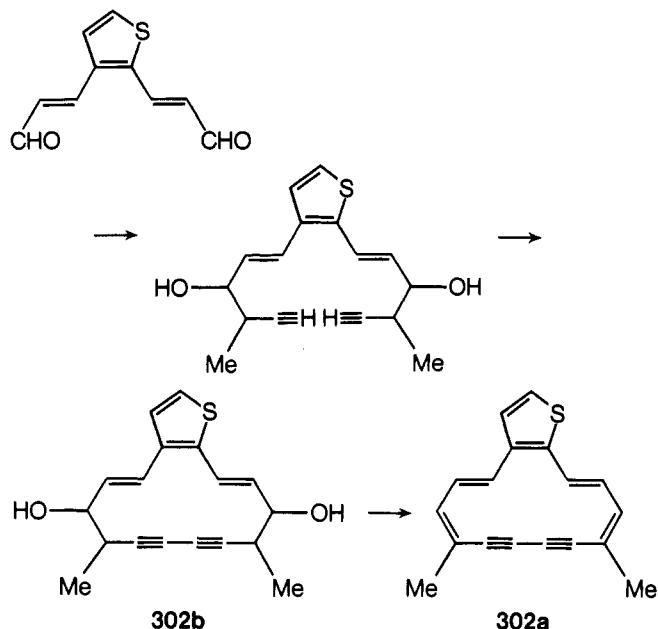
Gol'dfarb et al. prepared a series of (2,4)thiophenophan-1-ones by an intramolecular Friedel-Crafts acylation reaction of ω -(5-methyl-2-thienyl)alkanoyl chlorides in the presence of aluminum chloride.^{226,227} Substitution at the 3 or 4 position occurred since the 5 position was blocked with an alkyl group; in light of Helder and Wynberg's recently reported rearrangement of substituents at positions 2 and 5 on the thiophene nucleus under acylation conditions,²²⁰ care must be taken in the structural assignments of products derived by electrophilic substitution!



3. 2,3-Thiopheno

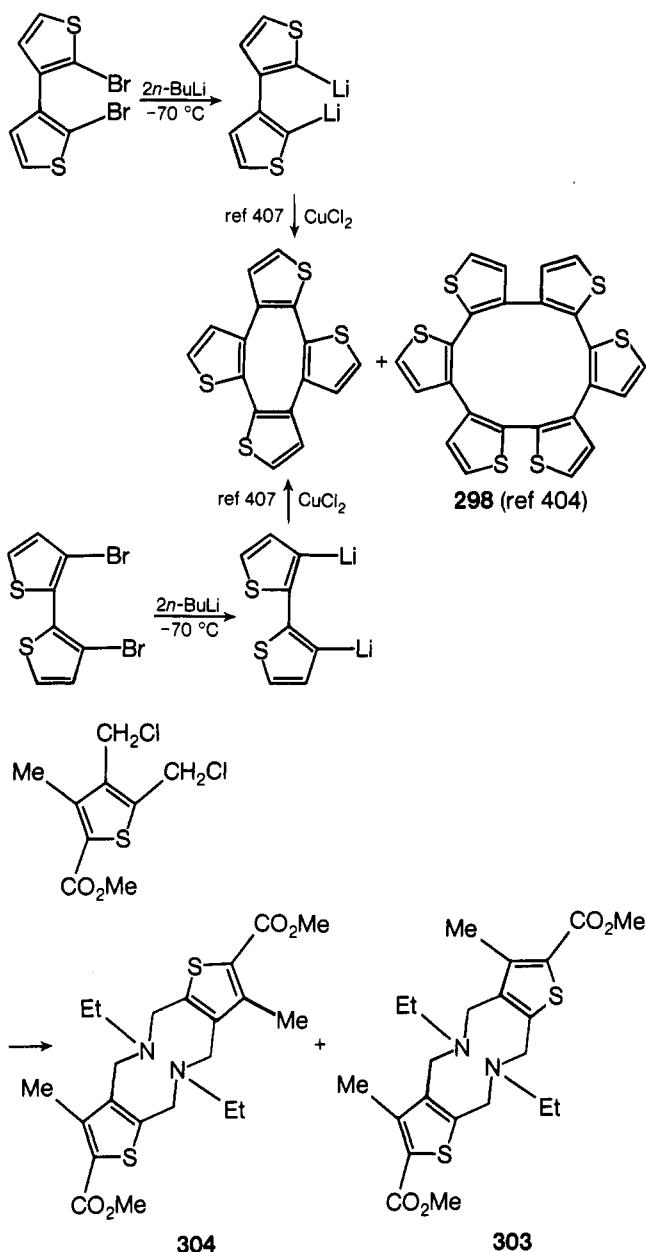
Gol'dfarb et al. reported the isolation of both the 2,4- as well as 2,3-disubstituted (*carbon-bridged*) acylation products (see above)^{226,227} via their standard reaction procedures.

[14]Annuleno[*b*]thiophene **302b** has been prepared by Sondheimer et al. from thiophene-2,3-dicarboxaldehyde.²⁰⁹ Their procedure was essentially the same as for the construction of **228a** (see section B.3).²¹⁰



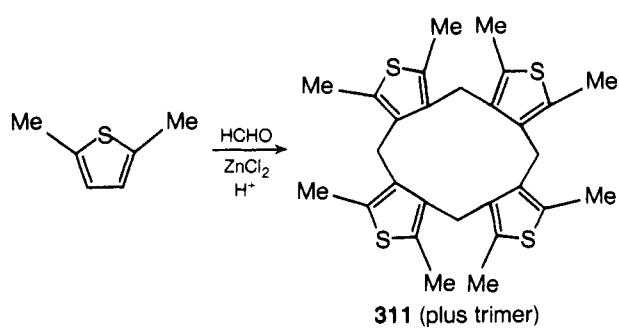
Kauffmann has recently described the synthesis of numerous cyclopolyaromatics via the oxidative coupling of organometallic intermediates with copper salts at reduced temperatures.^{405a} Cyclotetrathiophene was prepared by two similar procedures utilizing either 3-bromothiophene or 2,3-dibromothiophene;⁴⁰⁷ a small amount of **298** was isolated and characterized.⁴⁰⁴ A review by Kauffmann described the utilization of oxidative coupling reactions for the construction of heterocyclic arene (heteroaromatic) nuclei.^{405a,c}

An isomeric mixture of *carbon-nitrogen-bridged* 2,3-thiopheno macrocycles was isolated when methyl 4,5-bis(chloromethyl)-3-methylthiophene-2-carboxylate was reacted with ethylamine in acetonitrile.³¹⁹ The yields of both isomeric dimers **303** and **304** were low (<4%).



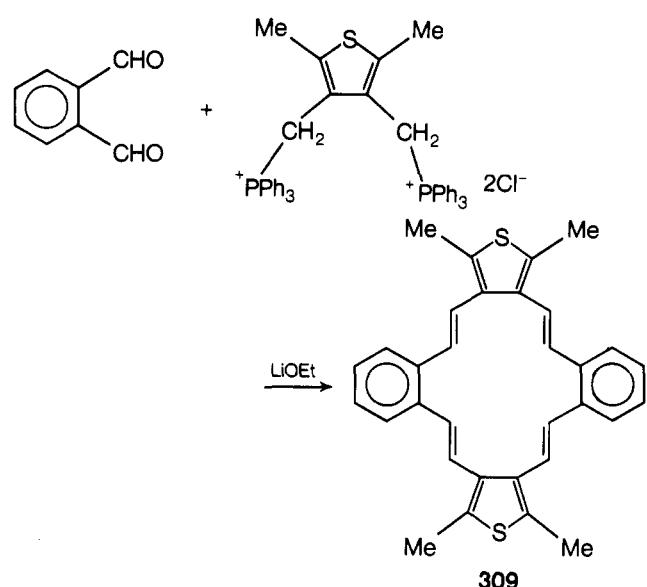
4. 3,4-Thiopheno

Trimeric and tetrameric 3,4-disubstituted thiophene cyclic units coupled by a *carbon bridge* have been reported by Meth-Cohn. When an equimolar mixture of 2,5-dimethylthiophene and formaldehyde in acetic acid was added dropwise to refluxing acetic acid containing zinc chloride and a little mineral acid, upon cooling, both the 9- and 12-membered (**311**) cyclic structures were isolated.²³¹

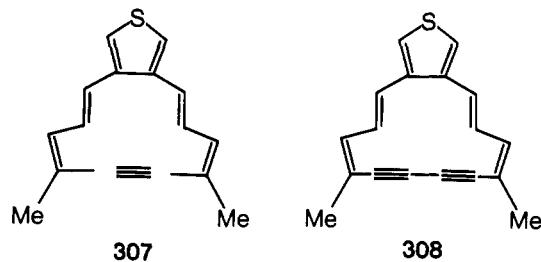


Reaction of *o*-phthalaldehyde with 2,5-dimethylthiophene-3,4-bis(methylenetriphenylphosphonium chloride) in the pres-

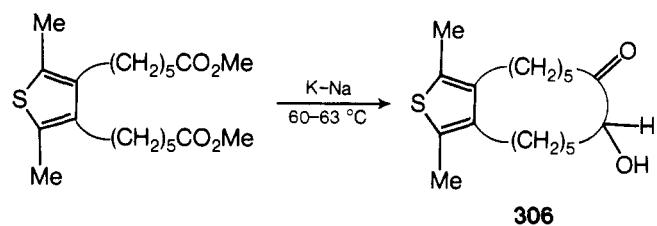
ence of lithium ethoxide afforded an easily oxidizable (purported) macrocycle **309** along with three geometrical isomers of *o*-bis[2-(2,4,5-trimethyl-3-thienyl)vinyl]benzene.²³²



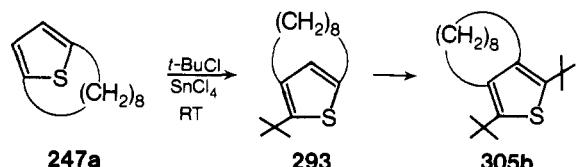
Sondheimer et al. reported the synthesis of both [12]annuleno[*c*]thiophene²⁰⁸ (**307**) and [14]annuleno[*c*]thiophene²⁰⁹ (**308**) by previously discussed procedures (section B.3, except that thiophene was substituted for furan).



Gol'dfarb et al. have applied their acyloin condensation procedure to the construction of **306**. Cyclization of the appropriate diester was conducted in the presence of finely divided potassium–sodium alloy in xylene at 60–65 °C; the yield of **306** was an amazing 70%.²⁴⁹

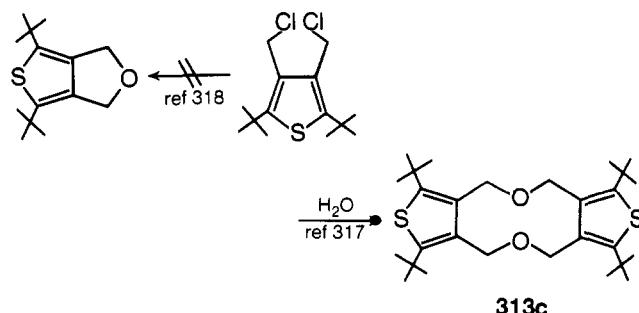


[8](2,5)-Thiophenophane (**247a**)¹⁷⁶ underwent a stepwise rearrangement to **293**, then to the substituted [8](3,4)-thiophenophane nucleus (**305b**) upon treatment with *tert*-butyl chloride under Friedel–Crafts conditions.²²⁰

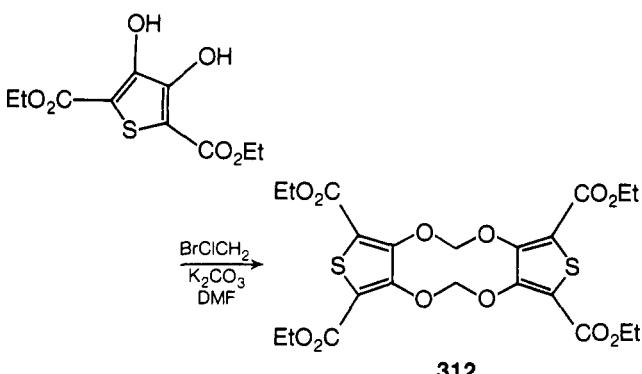


Recently, Zwanenberg and Wynberg treated 2,5-di-*tert*-butyl-3,4-bis(chloromethyl)thiophene with water, according to the procedure of Gol'dfarb and Kondakova,³¹⁸ isolating not the originally proposed substituted thieno[3,4-*c*]furan,³¹⁸ but rather the carbon–oxygen-bridged dimer **313c**.³¹⁷ The corresponding

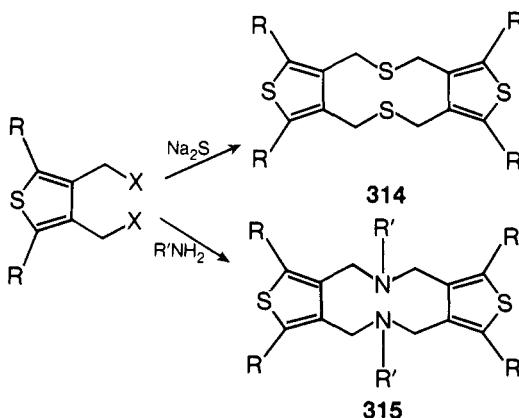
tetrachloro³¹⁷ and tetramethyl³⁵⁷ derivatives have been prepared in a similar manner.



Methylation of ethyl 3,4-dihydroxy-2,5-thiophenedicarboxylate with bromochloromethane and potassium carbonate in dimethylformamide gave macrocycle **312** as a minor product, along with ethyl 3,4-methylenedioxy-2,5-thiophenedicarboxylate as well as its S,S-dioxide.²⁰⁴



Zwanenberg and Wynberg reported the preparation of both carbon–sulfur- and carbon–nitrogen-bridged 3,4-disubstituted thiophene macrocycles. Treatment of 2,5-disubstituted bis(3,4-halomethyl)thiophene with either sodium sulfide or a primary amine derivative afforded, along with monomeric products, the expected dimers.³¹⁹ These studies parallel the original work of Gol'dfarb and co-workers some 8 years earlier.³²⁰



V. Synthesis of Macrocycles Possessing Two or More Different Subheterocyclic Rings

Table IV is a compilation of the macrocycles which possess a combination of pyridine, furan, and/or thiophene subheterocyclic rings.

A. Combination of 2,6-Pyridino and 2,5-Furano Subunits

Wong and Paudler have recently reported the first mixed heterocyclophane which is composed of both a π -deficient pyridine subunit and a π -excessive furan ring.⁸⁸ Construction

TABLE IV. Macrocycles Containing Combinations of Pyridine, Furan, Thiophene, and/or Pyrrole Subunits^a

| Compound | Double bond position | Substituents | Compd no. | Physical data Mp(bp (mm)), °C | Spectral data available | Complex(es)/comments | Ref |
|----------|-----------------------------|--------------|---------------------|----------------------------------|--|----------------------|-----|
| | H | 327 | 86–87 | A, C | No VTNMR changes, x-ray ^{4,48} | 88 | |
| | H | 328 | | A | Conformational studies | 6 | |
| | 1-(=O) | 329a | 148–150 | A–D | No paramagnetic ring current | 160, 162 | |
| | 1-(H) ₂ | 329b | Yellow oil | A, D | | 162 | |
| | 1-H; 1-OMe | 329c | Orange oil | A, D | | 162 | |
| | (Z)-1,2; (Z)-7,8; (Z)-13,14 | 330 | 250–251 dec | A–C | Aromatic (NMR), aromatic stability ^{4,34} | 145, 254 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 331a | >360 | D | | 149 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 331b | 192–193 | A–C | | 145, 254 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 331c | >250 dec | A–C | | 145, 254 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 331d | 210–212 | A–C | | 145, 254 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 331e | >360 dec | A–C | | 145, 254 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 331f | >250 dec | A–C | | 254 | |
| | (Z)-1,2; (Z)-7,8; (Z)-13,14 | 332 | 103–103.5 | A–C | No peripheral conju-ga-tion, aromatic sta-bility ^{4,34} | 146, 153 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 333a | dec | D | | 149 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 333b | 256–257 | A–C | | 153 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 333c | >340 dec | A–C | | 153 | |
| | (Z)-6,7; (Z)-12,13 | 334 | 81–83 | A, C | No diamagnetic ring current | 161 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 335a | 84.5–85.5 | A–D | | 157 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 335b | 193–195 >300 dec | A–C | | 157, 161 | |
| | (Z)-6,7; (Z)-12,13 | 336a | 131–132 | A–D | VTNMR studies | 8, 184 | |
| | (E)-1,2; (E)-7,8; (E)-13,14 | 336b | | A | VTNMR conforma-tionally rigid | 185 | |
| | 1-(H) ₂ | 337a | 126–128 | A, D | Paramagnetic ring current | 159, 162 | |
| | 1-(=O) | 337b | 299–300 dec | A–D | Paramagnetic ring current | 159, 162 | |

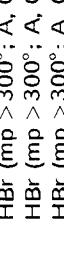
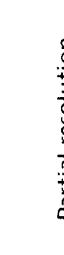
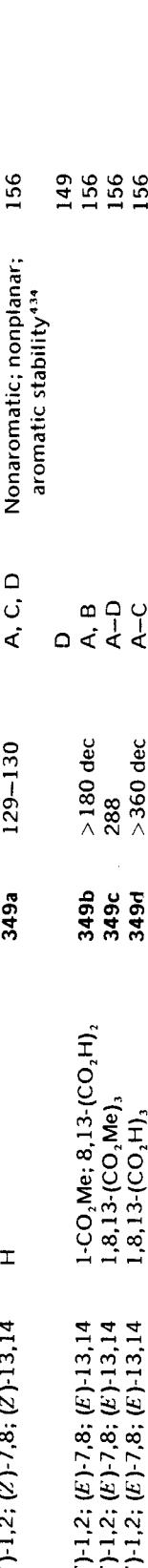
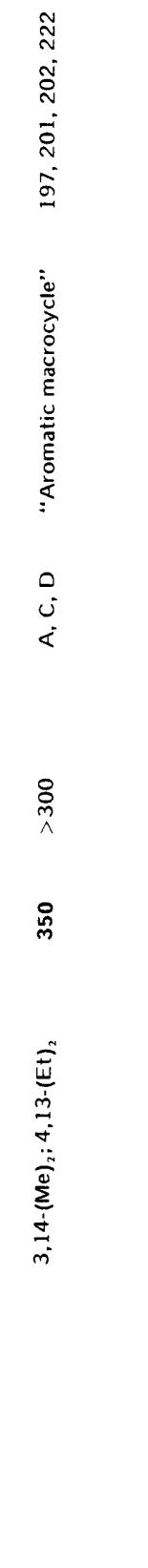
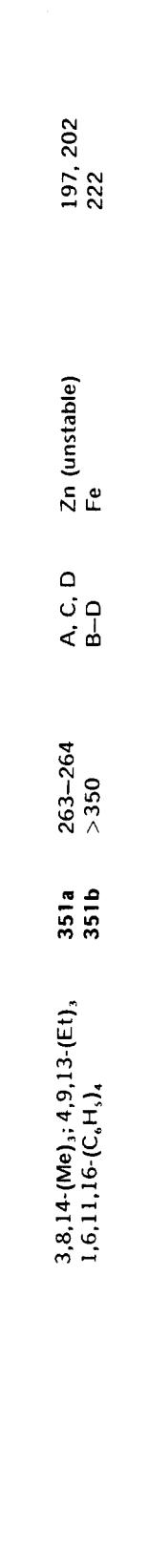
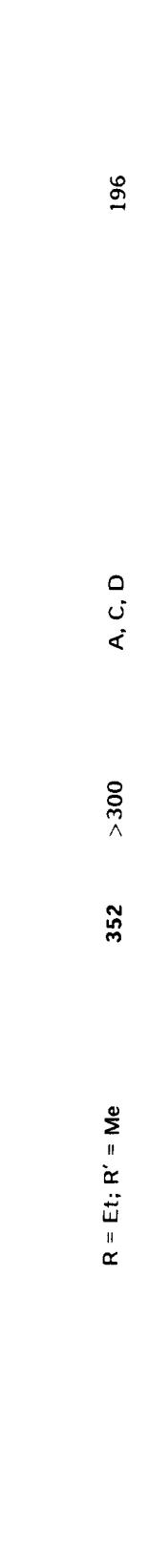
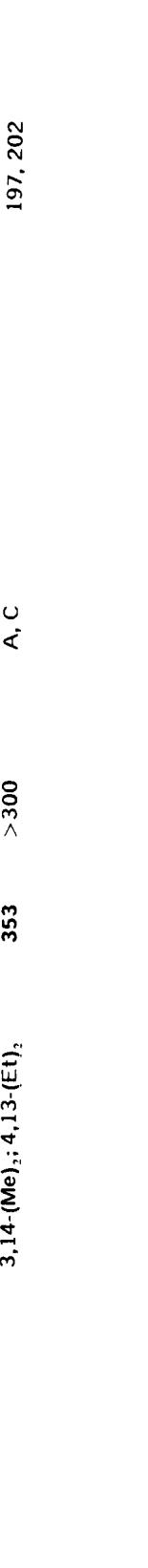
| | | | |
|---|--|------------------------------------|--------------------|
|  | 1,1,6,6,11,11,16,16-(Me) _s | 338 | 223 |
|  | 1,1,6,6,11,11,16,16-(Me) _s | 339 | 260 dec |
|  | 1,1,6,6,11,11,16,16-(Me) _s | 340 | 230.5 |
|  | 3,14-(Me) _i ;4,13-(Et) ₂ | 342 | |
|  | 3,14-(Me) _i ;4,13-(Et) ₂ | 342 | |
|  | R = Me; R' = Et | 341a | >300 |
|  | R = Et; R' = Me | 341b | 167-169 |
|  | R = Et; R' = Me; N-Me(I) | 341c | 230-232 |
|  | R = Et; R' = Me; N-Et(I) | 341d | |
|  | R = Et; R' = Me; N-Et(I) | 341e | A |
|  | R = Et; R' = Me; N,N'-Me ₂ (I) | 341f | |
|  | R = Et; R' = Me; N,N'-Et ₂ (Br) | 341g | 203 |
|  | A | | Partial resolution |
|  | C, D | HBr (mp > 300°; A, C) ^c | 203 |
|  | A, C, D | HBr (mp > 300°; A, C) ^c | 203 |
|  | A, C, D | HBr (mp > 300°; A, C) ^c | 203 |
|  | A, C, D | DiHBr (mp > 300°; A, C) | 202, 197 |
|  | R = Me; R' = Et | 343a | 182 |
|  | R = Et; R' = Et | 343b | 198 |
|  | A, C, D | A, C, D | |

TABLE IV (Continued)

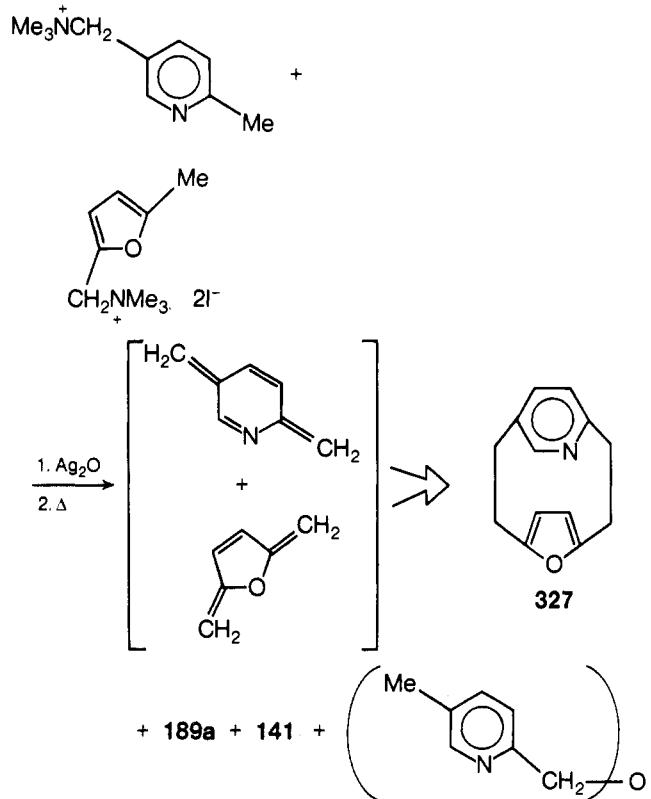
| Compound | Double bond position | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Complex(es)/Comments | Ref |
|----------|---|--------------|-----------|-----------------------------------|---|---------------------------|-----|
| | 3,8,14-(Me) ₃ ; 4,9,13-(Et) ₃ | 344 | >300 | A, C (C, D) ^d | HBr (mp >300°) Ni (mp >300°, para-magnetic) Zn (mp >300°) | 197, 202 197, 202 | |
| | 3,4,8,9,13,14-(Me) ₆ | 345a | >300 | D | Large ring current (NMR) | 182, 198 | |
| | 3,9,14-(Me) ₃ ; 4,8,13-(Et) ₃ | 345b | >300 | A A, C | Dihydro perchlorate (mp > 300°) | 182, 196, 201, 202 196 | |
| | 3,4,8,13-(Me) ₄ ; 9,12-(H) ₂ | 346a | >300 | C, D | | 196, 202 | |
| | 4,8,13-(Me) ₃ ; 3,9,12-(Et) ₃ | 346b | >300 | A, C, E | | 196, 202 | |
| | R = R' = Me | 347a | | | "Probable precursor" | 182 | |
| | R = Me; R' = Et | 347b | | | "Probable precursor" | 182 | |
| | R = R' = Et | 347c | | | "Probable precursor" | 182 | |
| | H | | | | "Probable precursor" | 196 | |

| | | | | |
|--|-----------------|----------|------------|---|
|  | 349a | 129–130 | A, C, D | Nonaromatic; nonplanar; aromatic stability ^{a,34} |
|  | 349b | >180 dec | D | 149 |
|  | 349c | 288 | A, B | 156 |
|  | 349d | >360 dec | A–D A–C | 156 |
|  | 350 | >300 | A, C, D | "Aromatic macrocycle" 197, 201, 202, 222 |
|  | 351a | 263–264 | A, C, D | 197, 202 |
|  | 351b | >350 | B–D Fe | 222 |
|  | R = Et; R' = Me | 352 | >300 | A, C, D |
|  | 353 | >300 | A, C | 197, 202 |

^aSpectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS. ^bIn ref 157, this compound was drawn incorrectly (e.g., 17). ^cReference 182b is a correction to the previous article.^{182a}

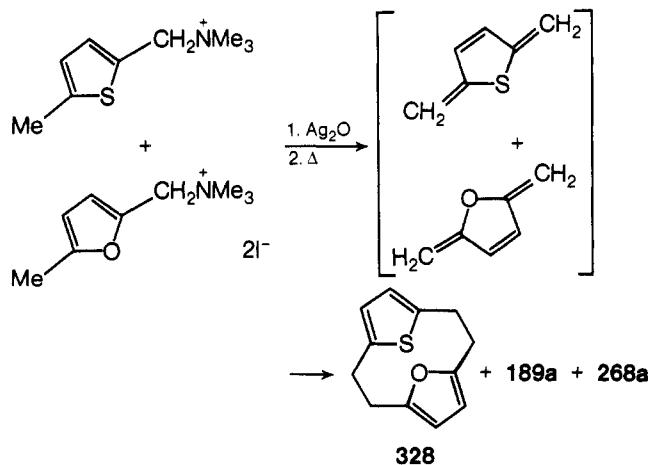
^dSpectral data of complex. ^eReference 171.

of this mixed heterocyclophane utilized the original Winberg procedure,¹⁸⁶ in which an equimolar mixture 2-methyl-5-trimethylaminomethylpyridinium hydroxide and 5-methyl-2-furfuryltrimethylammonium hydroxide (generated from the corresponding iodides) was heated in refluxing toluene to afford 327, 189a, and 141 as well as bis(5-methyl-2-picoly) ether.

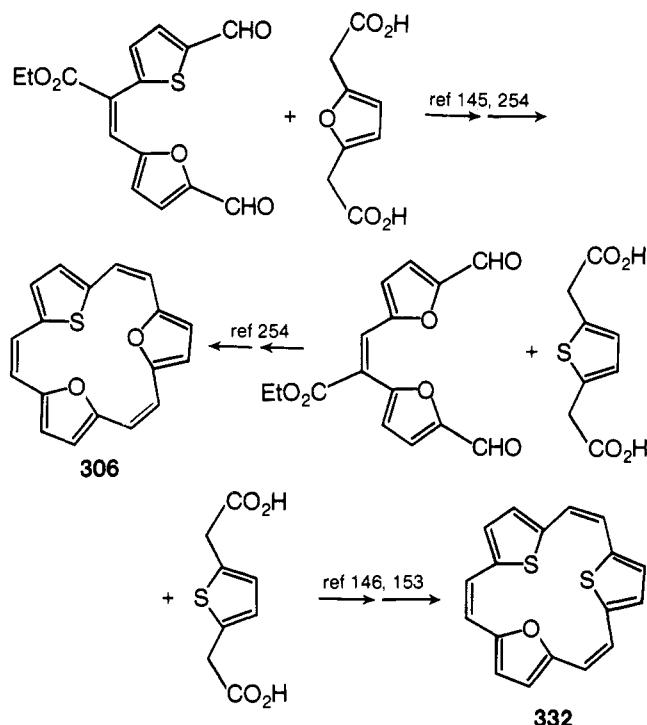


B. Combination of 2,5-Furano and 2,5-Thiopheno Subunits

The simplest member (328) of these subunits was prepared by Fletcher and Sutherland⁶ when the corresponding quaternary hydroxides were refluxed in xylene according to the Winberg procedure.¹⁸⁶ A 1:1:1 mixture of the three heterocyclophanes (328, 189a, 268a) was obtained in 26% overall yield; the physical data for 189a were not reported.⁶

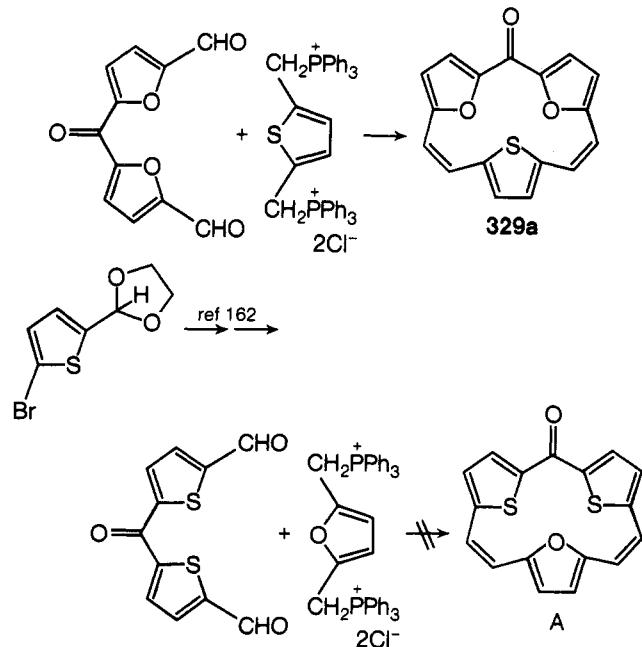


Badger and co-workers carried out the synthesis of two "cross-breed" [18]annulenes in order to ascertain the aromatic character of the $(4n + 2)$ π -electron systems. Both the [18]-annulene trisulfide^{151,152} and trioxide¹⁴⁶ had been previously reported by these workers, and the general mode of construction of 330 and 332 reflects their earlier procedures. The appropriate

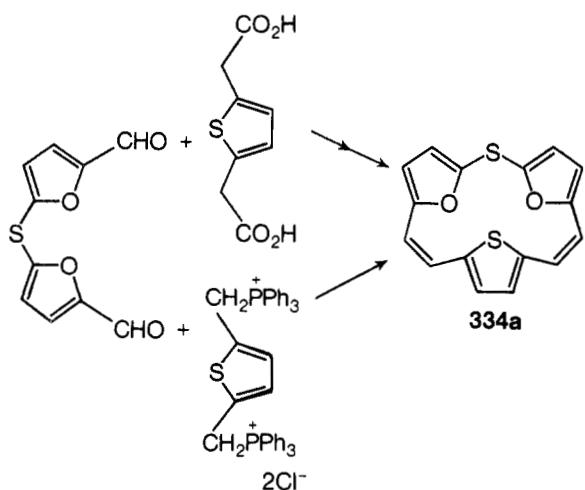


diacetic acid was condensed with a *cis*-diformyl acrylate under Perkin reaction conditions (acetic anhydride and triethylamine). Esterification of the diacid afforded the triester, which was saponified and decarboxylated with copper chromite in quinoline at 195–200 °C to afford the desired [18]annulene. Extensive NMR^{153,254} and mass spectral data¹⁴⁹ have been reported for these compounds; 330 was shown (via NMR) to be aromatic,^{145,254} whereas 332 was shown to be nonaromatic.^{146,153}

Cresp and Sargent reported the preparation of a related series of [17]annulenes, which incorporated either a carbonyl group or sulfur atom. This replacement of a double bond (e.g., in 334a) with a heteroatom possessing a lone pair of electrons will lead to a peripherally conjugated $(4n + 2)$ π -electron annulene. Annulenone 329a was prepared by reaction of bis(5-formyl-2-furyl) ketone with the appropriate thiophene bis-Wittig reagent.^{160,162} Although 329a was isolated in 8% yield, the analogous reaction of bis(5-formyl-2-thienyl) ketone with 2,5-furanbis(methyltriphenylphosphonium chloride) failed to give the desired annulenone A.¹⁶² The heteroannulene 334a was prepared by two

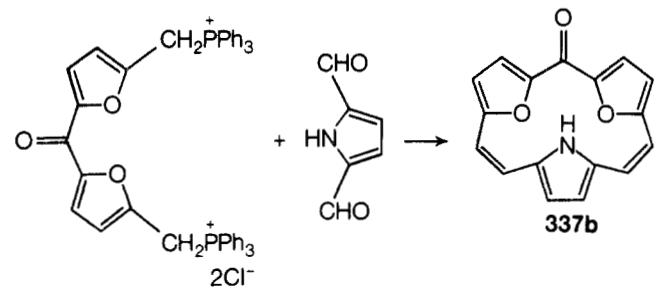


routes: (a) Perkin condensation, esterification, saponification, and decarboxylation; and (b) a diformyl compound³⁵⁵ with a bis-Wittig reagent.¹⁶¹ The degree of aromatic character of **329a** and **334a** has been determined by NMR analyses.

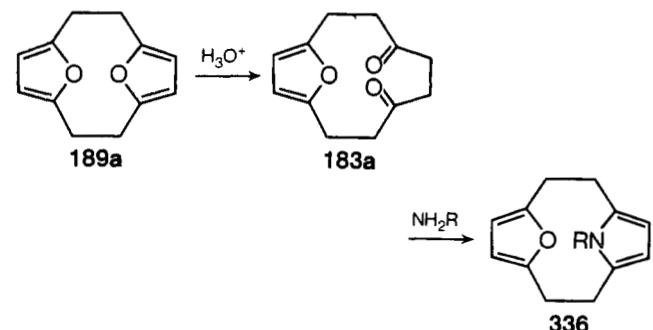


C. Combination 2,5-Furano and 2,5-Pyrrolo Subunits

Cresp and Sargent extended the above bis-Wittig reaction sequence (of **329a**) to the preparation of [17]annulenone **337b**.^{159,162} A Wittig reaction between the ketonic bis-Wittig reagent and pyrrole-2,5-dicarboxaldehyde afforded (13.8%) 8,11-imino-2,5:14,17-diepoxy[17]annulenone (**337b**). Annulenone **337b** was reduced to homoannulene **337a** by lithium aluminum hydride and aluminum chloride in anhydrous ether.^{159,162}

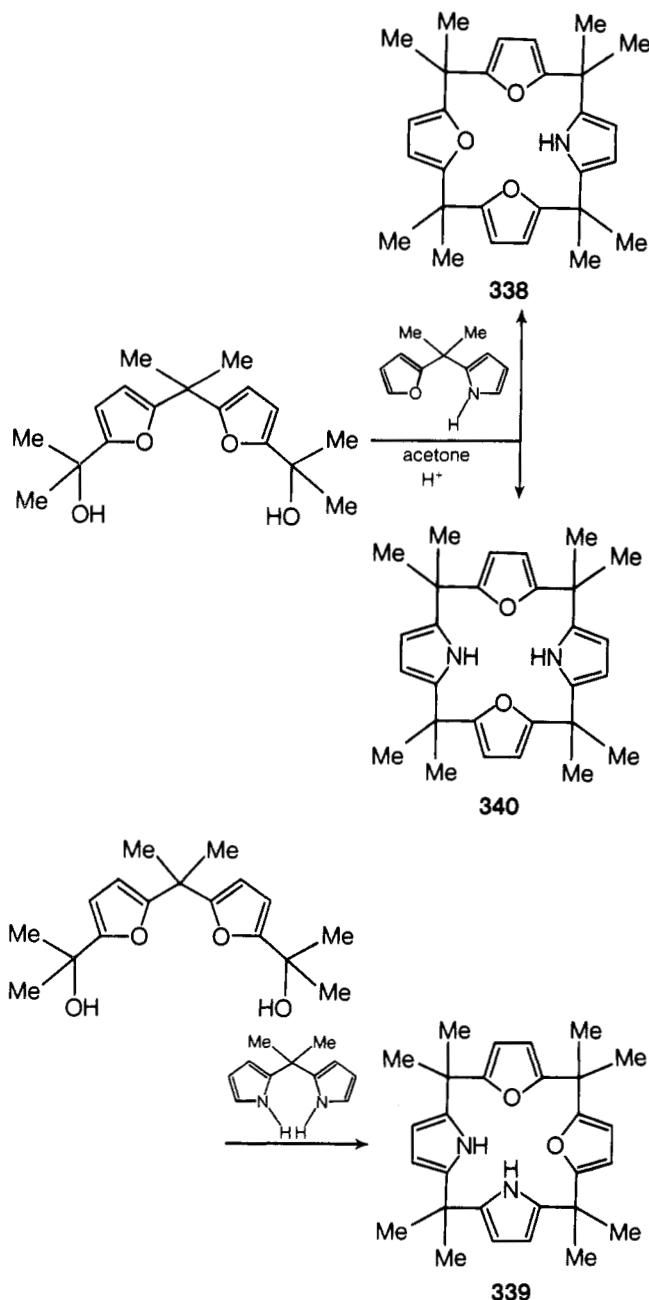


[2.2](2,5)Furanophane **189a** was partially hydrolyzed under acidic conditions in the absence of light and air to generate **183a** which was conveniently cyclized upon treatment with ammonia or a primary amine (Paal-Knorr reaction), by the procedure of Wasserman and Bailey,²¹⁸ to afford **336**.^{184,185}

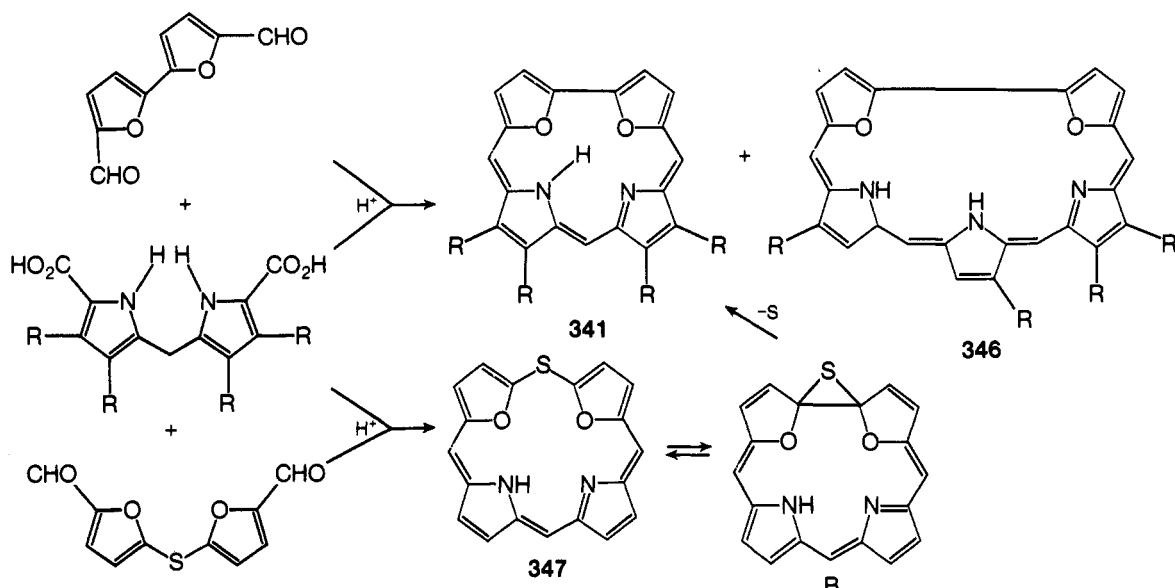


The synthesis of tetraoxaquaterenes has been considered earlier (section IV.B.1). Numerous intermediates were isolated and characterized in these studies;¹⁶⁹ subsequent treatment of these intermediates with pyrrole and acetone under acid conditions generated a series of "cross-breeds".¹⁹³ By use of var-

ious combinations, **338**, **340**, and **339** were prepared via this procedure.¹⁹³



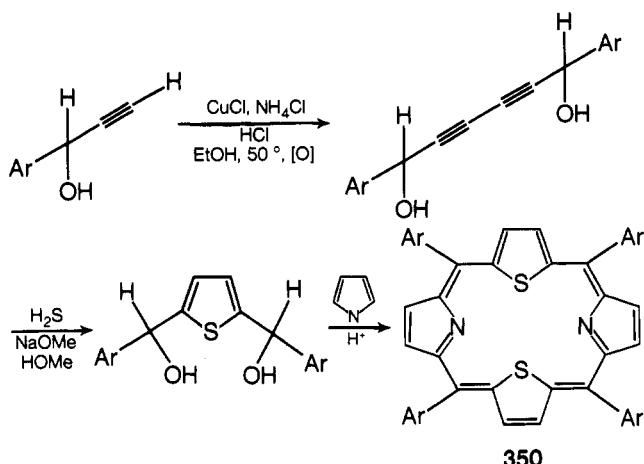
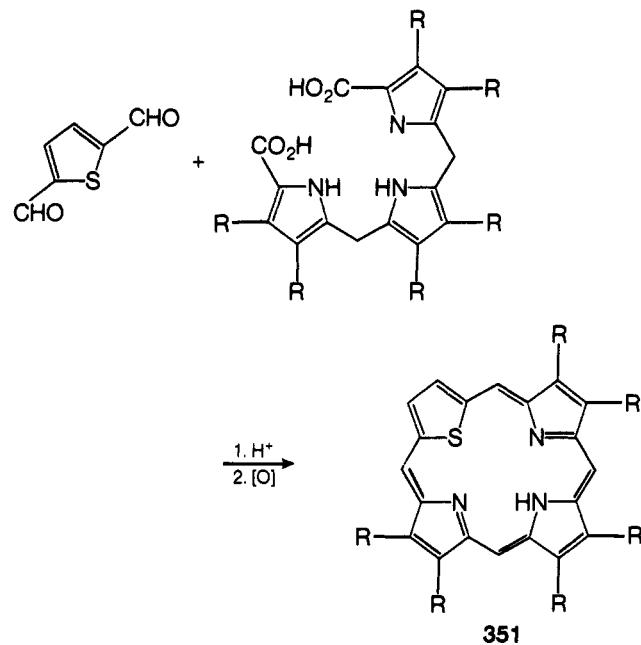
Grigg et al. have reported two procedures for construction of new aromatic macrocyclic systems, which are related to porphin and corroles,¹⁸² utilizing the MacDonald porphin synthesis.³⁷⁶ The more direct approach to **341** was via the acid-catalyzed condensation of a 5,5'-difomylbifuran with a substituted dipyrorylmethane diacid to give the expected product **341** along with a second macrocycle **346**, which had arisen from a cleavage-recombination process.¹⁸² A better synthesis of **346** was accomplished (27–30%) by the acid-catalyzed condensation of bis(5-formyl-2-furyl) sulfide with the same pyrrole diacids; only traces of the recombination product were detected.^{182,198,201} Sulfur extrusion from the nonaromatic 20- π -electron intermediate **347** probably proceeded to generate the 18- π -electron aromatic system **341**, since **B** has the correct symmetry for a disrotatory ring contraction with concerted expulsion of sulfur.^{182,201} These synthetic procedures have been applied to the synthesis of other 18- π - and 22- π -electron macrocyclic possessing furan, pyrrole, and thiophene subunits.^{196–198,202,203}



D. Combination of 2,5-Thiopheno and 2,5-Pyrrolo Subunits

Porphin analogues which possess the thiophene subunit have been reported by Grigg et al.; construction of these systems (e.g., 351) via the above procedures have been described above (see section V.C.).^{196, 197, 201, 202}

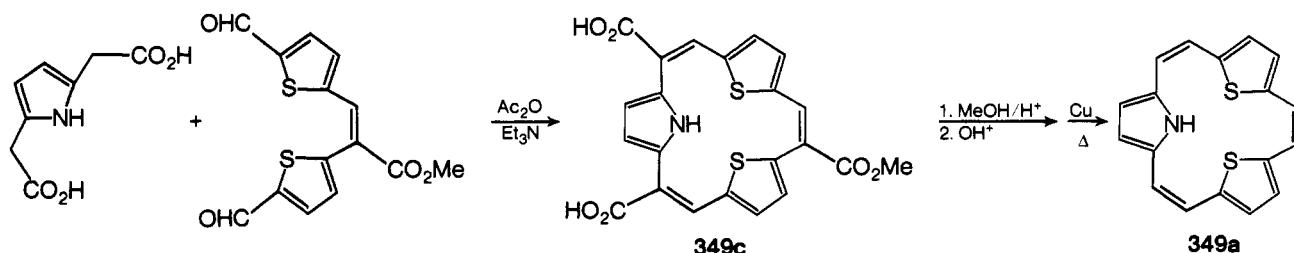
Ulman and Manassen have reported the second example of a dithiaporphin,²²² which was synthesized by a scheme differing from that of Grigg et al.¹⁹⁷ The key compound, 2,5-bis(phenylhydroxymethyl)thiophene, prepared by a known procedure,³⁷⁷ was reacted with pyrrole in either chloroacetic acid/toluene, chloroacetic acid/toluene, or propionic acid to afford (4–10%) the desired substituted dithiaporphyrin 350.²²²



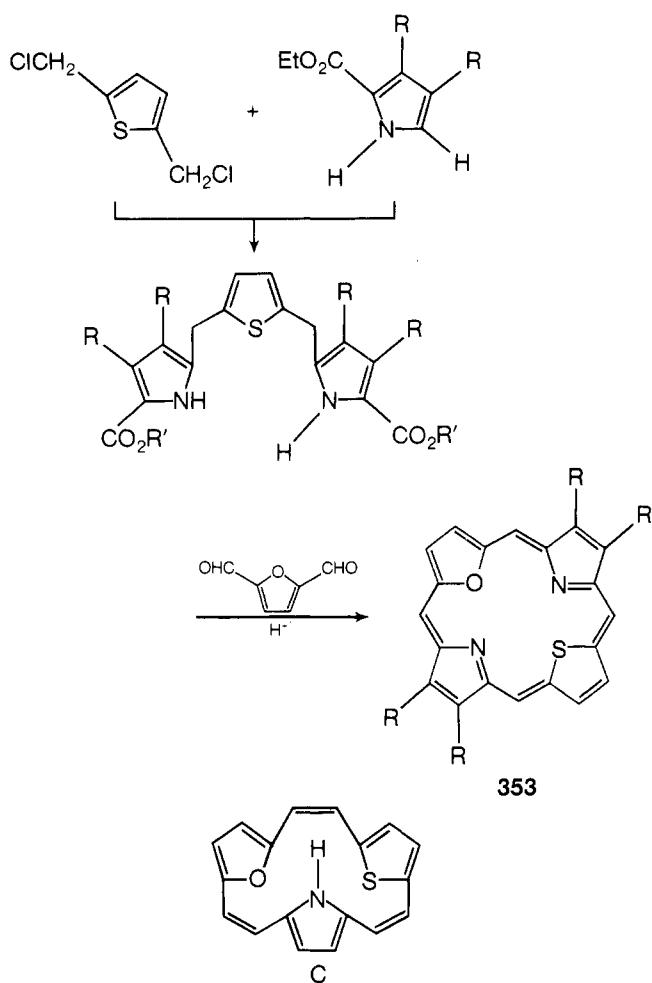
E. Combination of 2,5-Furano, 2,5-Thiopheno, and 2,5-Pyrrolo Subunits

Badger et al. have reported the synthesis of 349a by their previously discussed procedures (see section V.B) from pyrrole-2,5-diacetic acid and methyl *cis*- α, β -bis(5-formyl-2-thienyl)acrylate.¹⁵⁶ The electron impact studies of 349a have been reported,¹⁴⁹ and NMR studies have indicated that 349a is a stable, nonaromatic system.

Although Badger et al.¹⁵⁶ suggested that C was under investigation in their laboratories, to the best of our knowledge the synthetic details for this compound have never been reported. Grigg et al. have reported the only example of a porphyrin analogue which possesses these three different subunits.¹⁹⁷ The basic mode of preparation followed the previously discussed "3 + 1 approach" to the synthesis of these macrocycles. A convenient Friedel-Crafts reaction of 2 equiv of a substituted ethyl 2-pyrrolecarboxylate with 2,5-bis(chloromethyl)thiophene generated,



after hydrolysis, the necessary starting diacid. Condensation of this diacid with furan-2,5-dicarboxaldehyde gave (6%) the substituted porphin **353**.

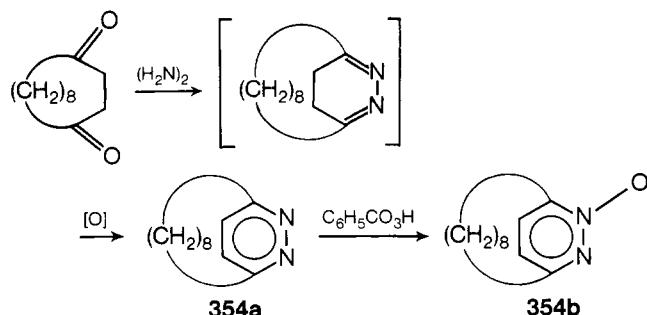


VI. Miscellaneous Multiple Ring Systems

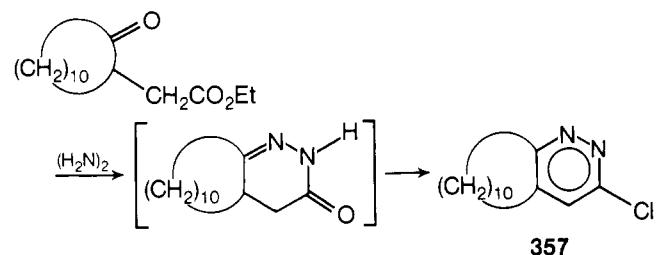
Tables V and VI are collections of miscellaneous macrocycles which possess six- and five-membered subheterocyclic rings, respectively. No exhaustive literature search has been made; rather, if previously considered intermediates were converted into a macrocycle with a novel subunit, these macrocycles have been included.

A. Miscellaneous Six-Membered Rings

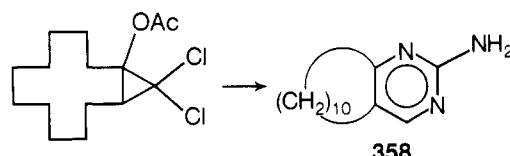
The diaza analog (**354a**) of [8]paracyclophane was synthesized from cyclododecane-1,4-dione by treatment with hydrazine hydrate in ethanol for 6 h, followed by facile dehydrogenation.¹³³ Oxidation of [8](3,6)pyridazinophane (**354a**) with 1 equiv of perbenzoic acid gave the mono-*N*-oxide **354b**; this is a chiral ansa compound.¹³³



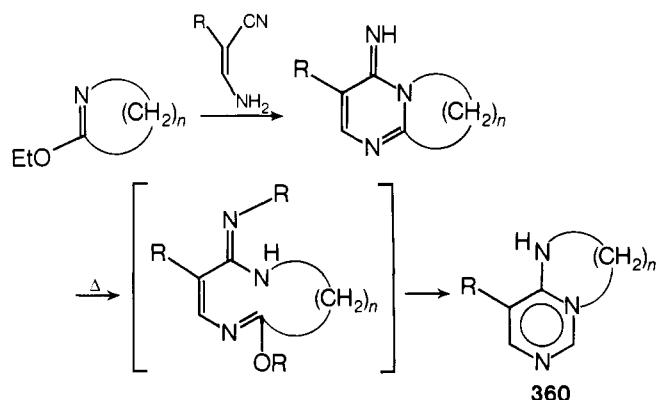
An alternate approach to cycloalka[*c*]pyridazines has utilized an appropriate enamine intermediate, 1-pyrrolidinylcyclododecene, which reacted with ethyl bromoacetate to give ethyl cyclododecanone-2-acetate. Cyclization with hydrazine gave a pyridazin-3-one, which was dehydrogenated and chlorinated to generate **357**.³⁸⁰



Parham et al. have described the facile ring opening of cyclopropyl acetates upon treatment with 95% hydrazine to afford a new substituted pyrazole nucleus.^{270,271} Treatment of the 1-acetoxy-13,13-dichlorobicyclo[10.1.0]tridecane with guanidine afforded 2-amino-4,5-decamethylenepyrimidine.^{345,422}



The Dimroth rearrangement has been utilized in the conversion of ethoxyhexahydroazocines, by treatment with aminomethylenemalononitrile, to two major products, the hexahydroimino-4*H*-pyrimidoazocinecarbonitrile and its β isomer **360**.³⁷⁷ The isolated imine was the favored product with short reaction time and was easily rearranged into **360** by prolonged boiling in butanol, possibly proceeding through a monocyclic intermediate.³⁷⁷



A pyrimidine phototetramer **366** has been isolated from prolonged photolysis (water with either **360** or 313 nm source) of 6,4'-[pyrimidin-2'-one]thymine via a possible 1,6 head-to-head-tail-to-tail dimerization.²⁷⁸ The crystal and molecular structure of **366** has been confirmed.²⁷⁹

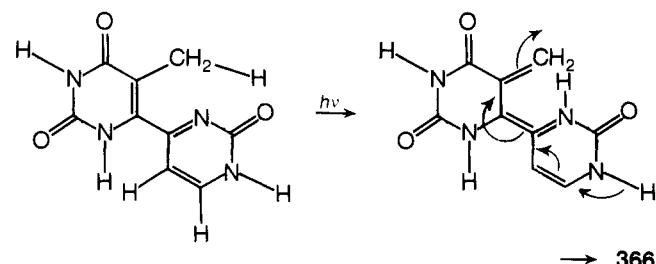


TABLE V. Partial List of Macrocycles Containing a Six-Membered Subheterocyclic Ring^a

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Metal complex(es)/general comments | Ref |
|----------|----------|---|--------------|-----------------------------------|----------------------------|--|---------------|
| | 8 | H N+O | 354a 354b | 59–60 [140–150 (0.1)] | A–C A, B, D | Temperature-dependent NMR "Chiral ansa compound" | 133 133 |
| | 9 | H | 355 | B | Ni | | 438 |
| | 9 | R = Me | 356 | 92 | A, B | Di- and tetrahydro intermediates isolated and characterized | 106 |
| | 10 | R = (NH=) C(Me ₂) ₂ | 357 | | | | 380 |
| | 10 | R = NH ₂ | 358 | 198–200 | A, B | | 345 |
| | 6 | R = CN | 359 | 103 | A, C, D | pK _a 4.39 | 377 |
| | 7 | R = CN | 360a | 126 | A, C, D | pK _a 4.18 | 377 |
| | 7 | R = CONH ₂ | 360b | 245 | A, C, D | pK _a 5.74 | 377 |
| | 7 | R = CO ₂ Et | 360c | ~94 | A, C | pK _a 6.12; picrate (184°) | 377 |
| | | R = Me | 361 | | | | 426 |
| | | | 362 | 284–289 | | | 386, 459, 466 |
| | 9 | H | 363 | 177 (subl: 100 (0.1)) | A | | 108 |

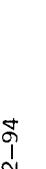
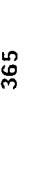
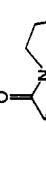
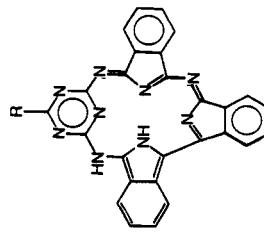
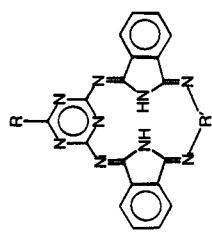
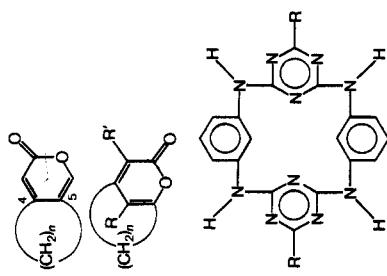
| | | | | | | |
|---|--------------------|-----|---------|----------------------------------|----------------------|----------|
|  | $m = 2; n = 6$ | H | 364 | 160–164 | Isomers possible | |
|  | H | 365 | 92–94 | K, NH ₄ | 263, 389 | |
|  | H | 366 | >300 | A, C Trans, syn configuration | 378, 379 | |
|  | H | 367 | 130–131 | A, B, D | 39 | |
|  | H | 368 | 86–87 | A, B | 39 | |
|  | H | 369 | 72–74 | A, B | 39 | |
|  | $n = 0; m = 2$ | H | 370 | 136–137 | A, B, D | 39 |
|  | $n = 0; m = 3$ | H | 371 | 125–127 | A, B | 39 |
|  | $n = 0; m = 4$ | H | 372 | 75–76 | Methiodide (mp 211°) | 39 |
|  | $n = 1; m = p = 1$ | H | 373 | 110–111 | A, B, D | 39 |
| | $n = 1; m = p = 2$ | H | 374 | 118–119 | A, B, D | 39 |
| | $n = 1; m = p = 3$ | H | 375 | 155–156 | A, B, D | 39 |
| | $n = 2; m = p = 1$ | H | 376 | 172–174 | 389 | |
| | $n = 2$ | H | 377 | 184 | Mg, K, Cs | 263, 389 |

TABLE V (continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Metal complex(es)/general comments | Ref |
|----------|----------|--|----------------------|-----------------------------------|----------------------------|------------------------------------|-------------------------------|
| | 10 | 6-Me 6-Me | 378 379 | 101.5 99 | A-D A-D | | 264 |
| | 11 | R = R' = H R = Me; R' = Ac R = R' = H | 380a 380b 381 | 97-98 84-85 67° | A-D A-D A-D | | 264, 267 264, 267 264 |
| | 11 | R = NH ₂ R = PhNH R = p-HO ₂ CC ₆ H ₄ -NH ₂ | 382a 382b 382c | | | | 139, 382, 383 139, 381-383 |
| | 12 | R = piperidino R = 4-sulfo-1-naphthyl-amino | 382d 382e | | | | 382 382 |
| | | R = p-NHC ₆ H ₄ H ₃ -N=NPhe | 382f | | | | 382 |
| | | R = OH; R' = 1,3-C ₆ H ₄ -Cl | 383a | | Cu, Ni, Co | | 384 |
| | | R = Cl; R' = 1,3-C ₆ H ₄ -Cl | 383b | | Cu | | 385 |
| | | R = Cl; R' = 4-chloro-2,6-pyrimidinediyI | 383c | | Cu | | 384 |
| | | R = Cl; R' = HNNH | 383d | | Ni, Cu, Co | | 384 |
| | | R = C ₆ H ₅ | 384 | | C, D | | 441 |



439

Co, Ni

385

R = OH

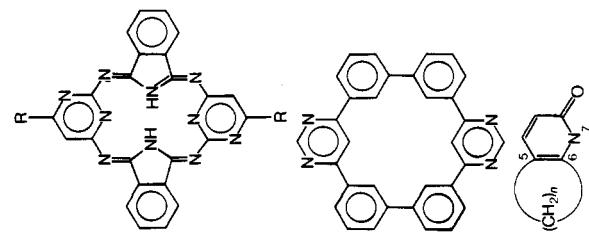
C

406

A

386 475-477

R = H



| | | | |
|----|---|------|-----|
| 8 | 1-C ₆ H ₅ ; 3-OH; 4-H | 387a | 252 |
| 8 | 1-C ₆ H ₅ ; 3-OH; 4-Me | 387b | 283 |
| 8 | 1-C ₆ H ₅ ; 3-H; 4-OH | 387c | 271 |
| 8 | 1-C ₆ H ₅ ; 3-Me; 4-OH | 387d | 289 |
| 8 | 1-C ₆ H ₅ ; 3-H; 4-OMe | 387e | 155 |
| 9 | 1-C ₆ H ₅ ; 3-OH; 4-H | 388a | 245 |
| 9 | 1-C ₆ H ₅ ; 3-OH; 4-Me | 388b | 289 |
| 9 | 1-C ₆ H ₅ ; 3-H; 4-OH | 388c | 268 |
| 9 | 1-C ₆ H ₅ ; 3-Me; 4-OH | 388d | 291 |
| 9 | 1-C ₆ H ₅ ; 3-H; 4-OMe | 388e | 153 |
| 10 | 1-C ₆ H ₅ ; 3-OH; 4-H | 389a | 252 |
| 10 | 1-C ₆ H ₅ ; 3-OH; 4-Me | 389b | 286 |
| 10 | 1-C ₆ H ₅ ; 3-H; 4-OH | 389c | 252 |
| 10 | 1-C ₆ H ₅ ; 3-Me; 4-OH | 389d | 297 |
| 10 | 1-C ₆ H ₅ ; 3-H; 4-OMe | 389e | 167 |

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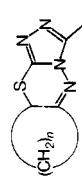
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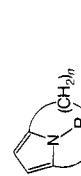
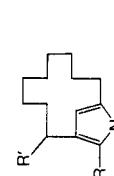
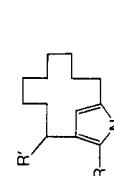
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TABLE V (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Metal complex(es)/general comments | Ref |
|---|----------|--|-----------|-----------------------------------|----------------------------|------------------------------------|-----|
|  | 10 | R = alkyl, Ph, c-Pr, EtOCH ₂ - CH ₂ -; Me- OCH ₂ -; EtOCH ₂ -; C ₆ H ₅ OCH ₂ , | 390 | | | Data in patent | 457 |

^aSpectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS.TABLE VI. Partial List of Macrocycles Containing a Five-Membered Subheterocyclic Ring^a

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Metal complex(es)/ general comments | Ref |
|---|---|---|---|---|--|---|---|
|  | 8 | R = H R = Me R = -CH ₂ CH=CH ₂ R = C ₆ H ₅ R = 4-MeC ₆ H ₄ R = 3,4,5-Me ₃ C ₆ H ₂ R = 2-MeC ₆ H ₄ R = 1,4-C ₆ H ₄ - R = 1,4-(2,5-Me ₂ C ₆ H ₂)- R = 1,4-(2,3-Me ₂ C ₆ H ₂)- R = Me; 3,6-(=O) ₂ R = 4-BrC ₆ H ₄ ; 3,6-(=O) ₂ | 391a 391b 391c 391d 391e 391f 391g 391h 391i 391j 391k 391l 392a 392b 392c | 154-154.5 [95-97 (3)] [75-78 (0.095)] 54-54.5 94-94.5 95-95.5 [140-150 (0.02)] 180 dec 250 dec 250 dec 97-98 137-139 [109-111 (0.2)]; 59-61 219-221 | A-C A, B A, B A-C A-C A-C A-C A-C A-C A-C A, B, D A, B, D A, B, D A, B, D A, B, D | NMR study | 176, 187 176 176 176 176 176 176 176 176 176 218 452 446 399, 445, 447 399, 400, 447 400, 445, 447 |
|  | R' = Et | | 208-209 | A-D | HCl (218-220°); [α] _D ²⁰ -2370° | | |
|  | R = CHO; R' = Et R = Me; R' = H R = Me; R' = H; N-Ph R = Me; R' = H; N- <i>p</i> -tolyl R = Me; R' = H; N- <i>p</i> -tolyl R' = H; R = CO ₂ Et R' = H; R = CO ₂ H | 392d 392e 392f 392g 392h 392i 392j | 109-112 107-107.5 [145 (0.095)] [150 (0.1)]; 46.5-47.5 1150 (0.08); 39-40 127-129 120 (-CO ₂) | A A-D A-D A-D A-D A-D A-D | Conformational studies Conformational studies Conformational studies Conformational studies Conformational studies Conformational studies Conformational studies | 229 229 229 229 229 229 229 | |

| | | | | |
|--|--|--------------------|---|-----------------|
| | 39a R = R' = Me R = R' = H R = R' = -CO ₂ Et R = R' = -(CH ₂) ₂ - R = Me; R' = H R = 4-BrC ₆ H ₄ ; R' = H R = -CH ₂ C ₆ H ₅ ; R' = H | 144-145 163-165 | A, B, D A-D | 218, 402 402 |
| | 39b R = R' = H | 163-165 | A, D A-D | 402 |
| | 39c R = R' = -CO ₂ Et | 198-202 dec | A, D A-D | 452 |
| | 39d R = R' = -(CH ₂) ₂ - | 78-79 | Suggested synthesis ^{40,2} | 402 |
| | 39e R = Me; R' = H | 137-140 dec (anti) | Syn and anti isomers | 452 |
| | 39f R = 4-BrC ₆ H ₄ ; R' = H | 84-85 | A, D A-D | 402 |
| | 39g R = -CH ₂ C ₆ H ₅ ; R' = H | | | |
| | 394 H | | A, C, D Isolation and characterization | 401, 430 |
| | 395a R = H | 197-198 | A-D | VTNMR study |
| | 395b R = Me | 212-214 | A, C, D A-D | VTNMR study |
| | 395c R = H; 4,5-benzo | 111-112 | A, C, D A-D | VTNMR study |
| | 396 1-C ₆ H ₅ | 225-227 | | 8, 184 |
| | 397 1-C ₆ H ₅ | 213 | | 8, 184 |
| | 398 1-C ₆ H ₅ | 196 | | 8, 184 |
| | 399a 1-C ₆ H ₅ ; 3-OMe | 82 | | 449 |
| | 399b 1-C ₆ H ₅ ; 3-OEt | 62 | | 449 |
| | 400a 1-C ₆ H ₅ ; 3-OMe | 71 | | 449 |
| | 400b 1-C ₆ H ₅ ; 3-OEt | 61-63 | | 449 |
| | 401a 1-C ₆ H ₅ ; 3-OMe | 76 | | 449 |
| | 401b 1-C ₆ H ₅ ; 3-OEt | 57 | | 449 |
| | 402a 1-C ₆ H ₅ ; 3-OCH ₃ | 95 | | 449 |
| | 402b 1-C ₆ H ₅ ; 3-OEt | 87 | | 449 |
| | 403a 1-C ₆ H ₅ ; 3-OMe | 102-104 | | 449 |
| | 403b 1-C ₆ H ₅ ; 3-OEt | 91 | | 449 |
| | 404a 1-C ₆ H ₅ ; 3-OMe | 106 | | 449 |
| | 404b 1-C ₆ H ₅ ; 3-OEt | 95 | | 449 |
| | 405a 1,6,11,16-[-(CH ₂) ₅] ₄ | 272-272.5 | A, B Incorrect structural assignment ^{32,6} | 303 |
| | 405b (Me) ₈ N ₃ N,N,N-(Me) ₄ ; 3,4, 8,9,13,14,18,19-(CH ₂ CO ₂ H) _n | | | 323 |
| | 406 m = 1; n = 10 | H | | 451 |
| | 407 m = 1; n = 12 | H | | |
| | 408 m = 2; n = 5 | H | | |
| | 409 m = 2; n = 6 | H | | |
| | | | | 398, 389 |
| | | | | 389, 398 |
| | | | | 263, 389 |
| | | | | 263, 389 |

TABLE VI (Continued)

| Compound | <i>n</i> | Substituents | Compd no. | Mp [bp (mm)], °C | Physical data available | Metal complex(es)/ general comments | Ref |
|----------|----------|---|----------------------|---|----------------------------|---|-------------------|
| | 9 | H | 419 | [100–105 (0.2)] | A | | 205 |
| | 10 | R = Me R = Et R = H | 420a 420b 420c | 63–65 79–80 (glass) [160(0.025)]; 88.5–89° | A, C A, C A, B | ²⁸ D 1.5305 | 269 269 271 |
| | 11 | R = C ₆ H ₅ ; R' = Me | 421 | | Ni (also isomers) | 450 | |
| | 12 | R = H R = H | 422 423a | [~106–107 (0.01)]; 71.5–72 | A–D | Mixture of isomers Conformational study ²²⁹ | 270 229, 390 |
| | 13 | N-C ₆ H ₅ ; R = H | 423b | [125–128 (0.08)]; 33–34.5 | A–D | Conformational study ²²⁹ | 229, 390 |
| | 14 | R = H | 424 | [130–135 (0.05)]; 107 | A, B | HCl | 205 |
| | 15 | R = H R = H R = Me | 425 426a 426b | 109–109.7 92.5–93 150–151 137 | A–D A–C A, C A, C | 206 271 269 269 | 270 229, 390 |

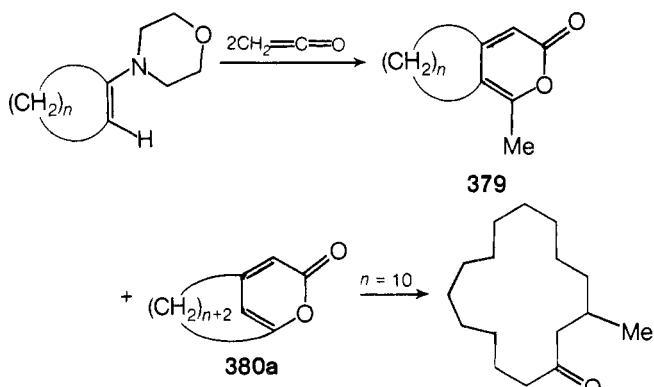
| | | | | |
|---|----------------------------------|------------|--------------|--|
| 2 | $R = C_6H_5$ $R = C_6H_5$ | 427 428 | >250 >250 | A, B, D A, B, D |
| 3 | $m = 2; n = 3$ $m = 2; n = 4$ | H H | 429 430 | 236–237 168 |
| | | H | 431 | |
| | | | | MO-LCAO calculations (Other azza derivatives were also considered) |
| | | | 432 | 455 455 |
| | | | | C Co |
| | | | 433 | C, Ni, Zn, Co, Cd |
| | | | 439 | |
| | | | | $R' = R^2 = O$ $R' = H; R^2 = OH$ |
| | | | | 434a 434b |
| | | | | |

^aSpectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS.

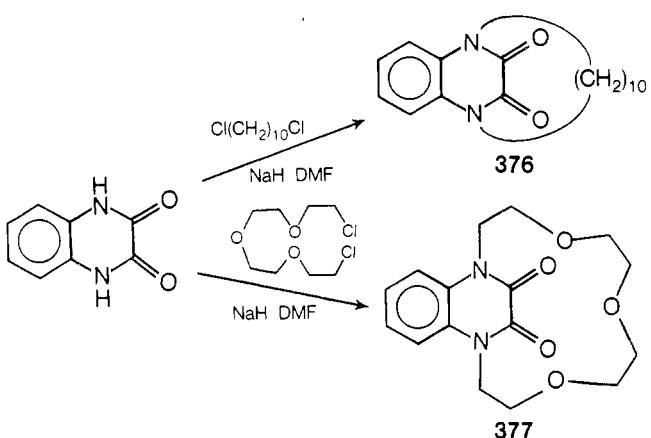
Vitamin B₁ derivatives (e.g., 362) have been easily synthesized (55%) from thiamine hydrochloride upon treatment with aqueous sodium hydroxide, formaldehyde, and diethylamine.³⁸⁶

The synthesis of numerous macroheterocyclic systems 382, 383, 130, and 85 has been reported by Borodkin et al. by the condensation of diamines with substituted triazines^{381–385,387} or diazines.⁴³⁹

Karpf and Dreiding synthesized macrocyclic 2-pyrone 379 and 380 from 1-morpholinocyclododec-1-ene²⁶⁴ via the procedure of Hünig and Hoch.⁴²³ Pyrone 380a was converted into racemic muscone by saponification and subsequent hydrogenation.²⁶⁴



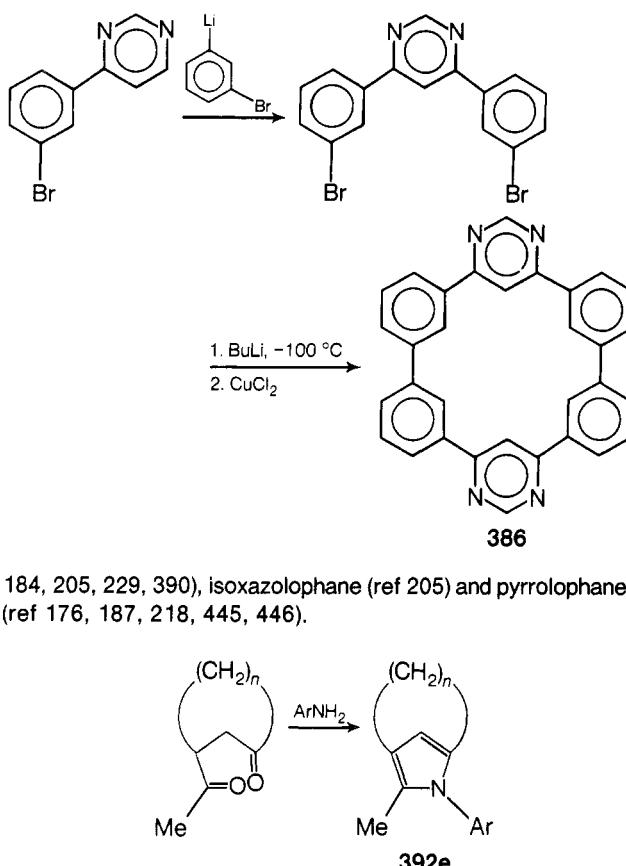
Htay and Meth-Cohn have described the preparation of N-bridged macroheterocycles (e.g., 376) by the simple treatment of an amide (quinoxaline-2,3-dione) with either a α,ω -dibromoalkane or a α,ω -dichloro ether in the presence of sodium hydride; the yield data seem to vary greatly depending upon both the initial heterocycle used as well as size of the bridging ring.^{263,389} This general procedure has also been applied to the inclusion of other heterocycles, such as benzimidazolones and uracils.^{263,389,444}



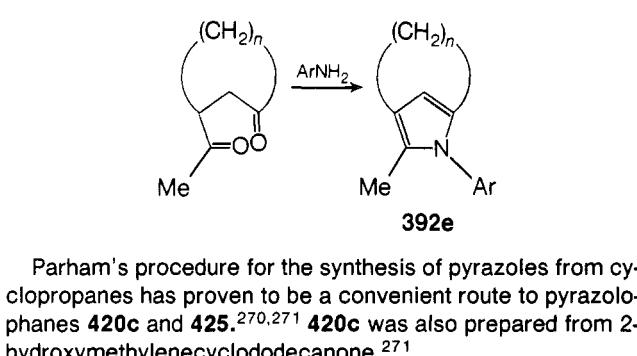
Synthesis of heterocyclic cyclopolymers containing the pyrimidine moiety has been demonstrated by the preparation of a cyclohexaaromatic compound 386 via the copper-catalyzed cyclization of a dilithio intermediate.⁴⁰⁶ This procedure described by Kauffmann should prove to be a very useful route to many novel macrocycles possessing diversified subunits.⁴⁶³

B. Miscellaneous Macrocycles with Five-Membered Subunits

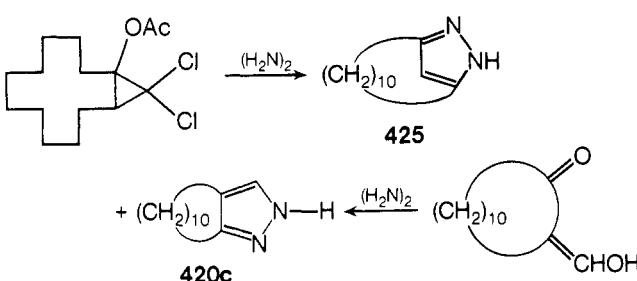
The general preparation of pyrrolophanes is via reaction of an appropriate 1,4-diketone with a primary amine; Hirano et al. demonstrated this procedure in the conversion of 2-acetylcloalkanones into (2,4)pyrrolophanes (392e) by treatment with substituted anilines.²²⁹ Other heterophanes have been synthesized from suitable macrocyclic 1,4-diones: pyrazolophanes (ref



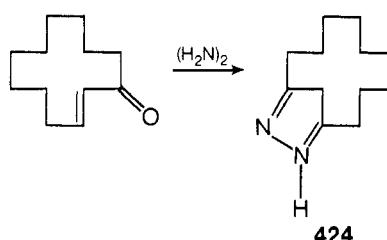
[184, 205, 229, 390], isoxazolophane (ref 205) and pyrrolophanes (ref 176, 187, 218, 445, 446).



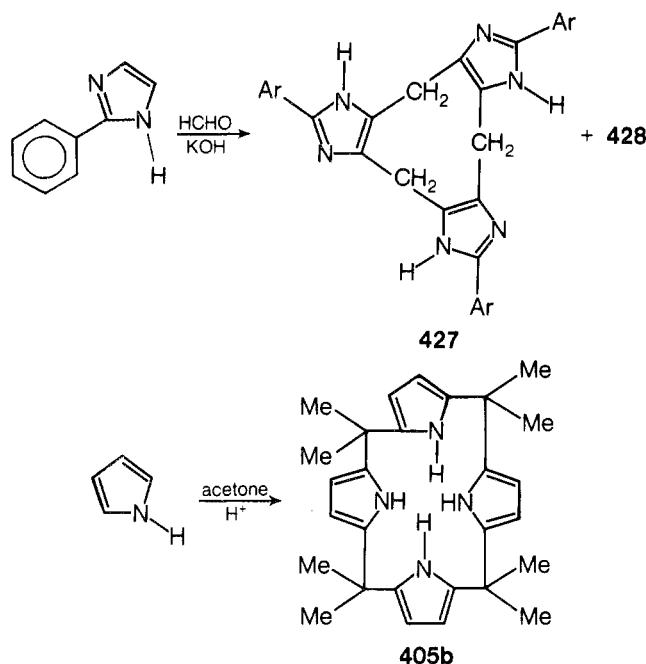
Parham's procedure for the synthesis of pyrazoles from cyclopropanes has proven to be a convenient route to pyrazolophanes 420c and 425.^{270,271} 420c was also prepared from 2-hydroxymethylenecyclododecanone.²⁷¹



[9](3,5)Pyrazolophane 424 was easily synthesized from cyclohexadec-2-en-1-one upon treatment with hydrazine hydrate.²⁰⁶



Reactions with numerous heterocyclic compounds with aldehydes and ketones in the presence of either mineral acid or base have generated a variety of unusual macrocyclic compounds. Sawa et al. reported the reaction of arylimidazoles with formaldehyde in the presence of base to generate the trimer 427 and tetramer 428,²⁶⁵ whereas numerous investigators have condensed pyrrole with aldehydes and ketones in the presence of acid to generate a porphyrin ring system, e.g., pyrrole with acetone afforded 405b.³²⁶



VII. Conclusions

This review has been concerned primarily with the synthetic routes to the known macrocycles which have incorporated subheterocyclic units, especially pyridine, furan, and/or thiophene. We have attempted to present the current technology for their construction and have tabulated the reported physical and chemical data. We have also pointed out both the synthetic generalities as well as the pitfalls for the known procedures. But most importantly, the tabulation of these macrocycles has indicated that the vast majority of synthetic as well as complexation studies have concentrated on a limited number of the now easily constructed compounds. Thus, from a complete review of the literature, the indications for future research in this area point in the direction of devising new synthetic methodology which will afford convenient routes to new classes of specifically designed macrocycles and the utilization of these compounds for specific metal ion complexation, phase-transfer reagents, general and specific catalysts, biological mimics, semiconductors, drugs, antibiotics, to mention just a few potential applications.

VIII. Addendum (see Table VII)

IV.A.1. 4-Methyl-[10](2,6)pyridinophane (**5k**) was synthesized (25%) by a novel intramolecular cyclization of an cyclododecanone oxime derivative upon treatment with POCl_3 in pyridine at 80 °C under an inert atmosphere.⁴⁸⁹

IV.A.1. Azimine, isolated from the leaves of *Azima tetracantha* Lam. (Salvadoraceae), has been shown spectrometrically to be a 22-membered analog of carpaine (**147**).^{468–470}

IV.A.1. The condensation of 1,2:5,6-di-O-isopropylidene-D-mannitol with 2,6-bis(bromomethyl)pyridine in dimethyl sulf oxide at 50 °C for 50 h with sodium hydride as base gave (7.5%) the dipyridyl-18-crown-6 (**51d**).⁴⁹¹ The temperature dependence of the ^1H NMR spectrum of the 1:1 complex between **51d** and benzylammonium thiocyanate in solution has been interpreted in terms of slow dissociation of the complex.⁴⁹¹

IV.A.2. Recently, a new series of substituted 2,(n+3)-di-thia[m](2,5)-pyridinophanes (**452–456**) have been prepared by the reaction of 1,n-alkanedithiols with 5'-deoxy-2',5'-dichloro-3,4'-O-isopropylidene-pyridoxine.⁴⁷⁸ Phane **148e** was synthesized from **148c**.⁴⁷⁸ The functionalized (2,5)pyridinophane derivatives (**452**, **453**) with ring sizes equal to or less than 14 members could be optically resolved into enantiomers.⁴⁷⁸

IV.A.4. An interesting study of the lithiation of cycloalkeno[*b*]quinolines by phenyllithium has shown that with small fused cycloalkeno rings (e.g., **160**; $n = 3, 4$), the α -lithiated product predominated, whereas, in the cases of larger rings (**160**, $n = 5, 6$), an increasing percentage of 1,2-addition products resulted.⁴⁷⁹ If this trend continues with fused macrocyclic rings, 1,2-addition products would be predicted.

IV.A.5. The transesterification of ethyl acetoacetate with poly(ethylene glycols) afforded quantitatively a new series of diketo diesters which upon treatment with a 40-fold excess of ammonium carbonate and aqueous formaldehyde (Hantzsch condensation), followed by dehydrogenation of the intermediary 1,4-dihdropyridine, gave monomers **444** and **445** as well as the corresponding dimers **446–449**.⁴⁹² In this communication,⁴⁹² the authors indicated that other aldehydes can be substituted for formaldehyde, thus affording an opportunity to incorporate diverse substituents into the 4 position of the pyridine ring. Macrocycle **445** was quaternized with MeOSO_2F in chloroform, followed by treatment with sodium perchlorate and reduced with sodium dithionite to generate the NADH model (**450**), which undergoes facile isomerization to the isomeric 1,2-dihydro compound **451**.⁴⁹²

IV.A.5. An improved high-dilution procedure was recently devised to increase the yields of macrocyclic products from the condensation of α,ω -alkyldiamines and the acid chloride of 2,6-pyridinedicarboxylic acid.⁴⁹³ For example, **437** was prepared in 41% yield by this new technique. Quaternization of the pyridine unit was accomplished by treatment with 2,6-dichlorobenzyl bromide and subsequent reduction of the resultant salt with sodium dithionite afforded the corresponding dihydro pyridine derivative.⁴⁹³ Diverse functionality has been introduced into the macrocyclic bridge and the effect of these substituents which are in the close proximity of the 4 position of either a dihydro-pyridine or pyridinium salt has been evaluated. No evidence was obtained to support either an intramolecular hydrogen transfer from the dihydropyridine moiety to a bridge carbonyl or hydride transfer from a bridge alcohol function to the pyridinium ring.⁴⁹³

IV.A. Vögtle and Frensch have recently described the synthesis of papaverine crown ethers.⁴⁹⁴

IV.B.1. A series of macrocyclic compounds possessing tetrahydrofuran subunits (perhydro **204a,r,v-y**) have been synthesized by an acid-catalyzed condensation of furan and carbonyl compounds followed by reduction.⁵⁰⁰ The macrocycles were shown to extract alkali metals, ammonium, and silver ions from aqueous media via the formation of a 1:1 macro-ring–metal complex with an estimated binding constant of more than 10^6 in chloroform.⁵⁰⁰

IV.B.1. The synthesis of chiral benzene-furan “hybrid” [2.2]paracyclophanes has been reported.⁴⁸⁵

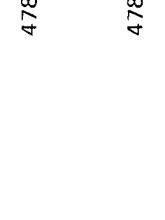
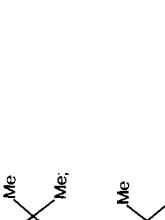
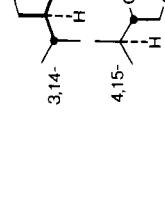
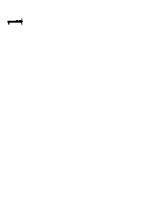
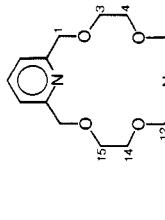
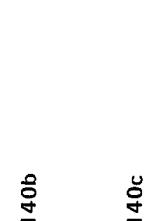
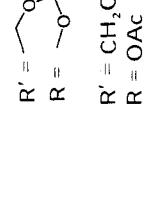
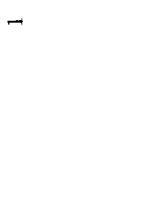
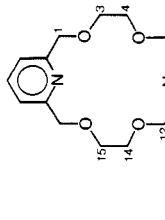
IV.C.3. The Wittig reaction of 2,2'-bis(triphenylphosphino-methyl)biphenyl dibromide and thiophene-2,3-dicarboxaldehyde afforded an 18% yield of 9,13-dihydrotriphenylene[2,3-*b*]-thiophene via the intermediacy of 1,2:3,4-dibenz[7,8-*b*]thiene[10]annulene (**457**), which was too unstable for isolation under the reaction conditions.⁴⁶⁴

VI.A. The reaction of 1-(ω -bromobutyl)uracil with the sodium salt of *p*-toluenesulfamide gave (10%) **458** as a high-melting crystalline compound.⁴⁶⁵

VI.B. Reactions of 1-phenyl-5-pyrazolidinone with various cyclic ketones gave 5-(3-aminopropanoyl)-5-*H*-cycloalk[*b*]indoles (e.g., **459**).⁴⁷²

VI.B. The structure of griseoviridin (**460a**),^{473,474,476} a metabolite of *Streptomyces griseus*, has been revised⁴⁷⁵ as based on the chemical and detailed ^1H and ^{13}C NMR and mass spectral studies. The relationship of **460a** to other related cyclic microbial peptides and possible biogenetic implications are considered.⁴⁷⁵ A related Antibiotic A-23[5 (**462**), isolated from *Actinoplanes philippinensis*, has been tentatively assigned.⁴⁷⁷

TABLE VII. Addendum Table

| Compound | <i>n</i> | Substituents | Compd no. | Physical data Mp [bp (mm)], °C | Spectral data available | Metal complex(es)/ general comments | Ref |
|----------|----------|---|-----------|-----------------------------------|----------------------------|---|-----|
| | 1 |  | 51d | 147–149 | A | $[\alpha]_D^{25} (CHCl_3) -22^\circ; K_a; C_6H_5CH_2NH_3^+$ $(SCN^-); t\text{-BuNH}_3^+$ | 491 |
| | 1 |  | 140b | | | | 478 |
| | 1 |  | 140c | | | | 478 |
| | 1 |  | 148c | | | | 478 |
| | 1 |  | 148d | | | | 478 |
| | 1 |  | 148e | 218–219 dec | | | 478 |
| | 7 |  | 178g | 288–290 | A, B | | 493 |
| | 7 |  | 178h | 254–255 | A, B | | 493 |
| | 7 |  | 178i | 313–316 | A, B | | 493 |
| | 7 |  | 178j | 257–259 | A, B | | 493 |
| | 7 |  | 178k | 266–267 | A, B | | 493 |
| | 5 |  | 435 | 236–238 | A, B | | 493 |
| | 6 |  | 436 | 298–300 | A, B | | 493 |
| | 8 |  | 437 | 341–343 | A, B | | 493 |
| | 9 |  | 438a | 352–354 | A, B | | 493 |
| | 9 |  | 438b | 224–226 | A, B | | 493 |
| | 9 |  | 438c | 323–325 | A, B | | 493 |
| | 9 | | 438d | 221–223 | A, B | | 493 |
| | 9 | | 438e | 262–266 | A, B | | 493 |
| | 9 | | 438f | 347–351 dec | A, B | | 493 |

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