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

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Contents

I. Introduction

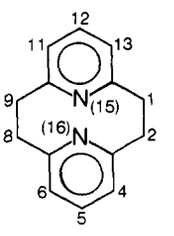
Although synthetic procedures for the construction of macrocycles containing subheterocyclic units have been known for about a century, it has only been within the past score that these compounds have been shown to possess unique chemical and biochemical properties. Numerous reviews have dealt with various 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.

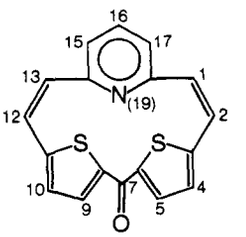
This review will be limited in scope to the synthetic aspects leading to macrocycles possessing, specifically, pyridine, furan, and thiophene subunits. For convenience a macrocyclic ring will be defined by a 11- or larger atom ring; however, several smaller (9- and 10-) membered rings have been included 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 rules[288] are applied to the herein described macrocycles, extremely complicated and nearly impossible names can result. In order to partially circumvent this problem, Phane nomenclature[289-291] 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).

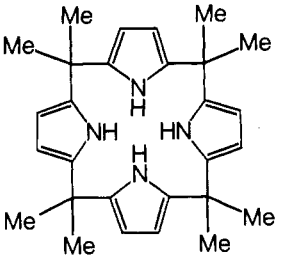




The numbering scheme is shown on the parent structures in the tables.

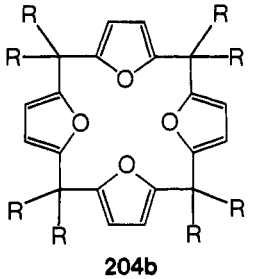
III. Historical Examples

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 Baeyer[323] via the condensation of pyrrole and acetone in the presence of mineral acid. Shortly thereafter, Dennstedt[324] 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 tetrazaquaterene structural backbone, at least one misassignment[326] was made for the product from the reaction of pyrrole and cyclohexanone; the structure was later reassigned.[303]



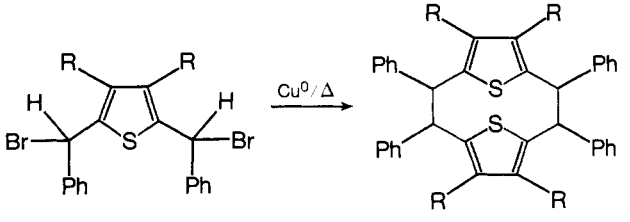
405b

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 Brown[194] synthesized "tetraoxaquaterene" **204b** by polycondensation of furan and 3-pentanone in the presence of mineral acid (the Baeyer procedure[323] except for the substitution of furan for pyrrole); direct comparison[194] of the original 1906 sample[195] with **204b** established the macrocyclic skeleton, thus confirming the structure of the first macrocycle containing a furan subunit.



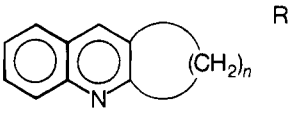
204b

In 1930, Steinkopf proposed[294] the first macrocycle which incorporated a thiophene ring. However, he later corrected[299] 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, Methcohn[298] 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]

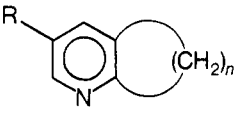


268b

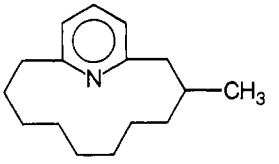
In 1933, the first macrocycle which incorporated a pyridine ring (**163a**) was prepared by Ruzicka et al.[122] from cyclopentadecanone (commonly known as Exalton) and 2-aminobenzaldehyde via a base-catalyzed condensation. The first nonbenzo-fused analog **159a** was synthesized 12 years later by Prelog and Geyer.[118] Although the 2,3-bridged backbone was constructed first, the most widely known pyridine macrocycle is that of "muscopyridine". 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]



163a



159a



5i

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-one[462] 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 muscopyridine (**5j**) was accomplished[17] 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]

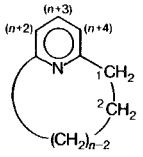
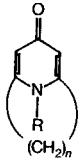
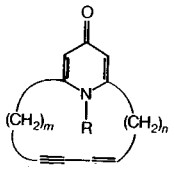
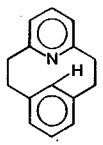
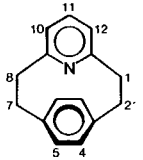
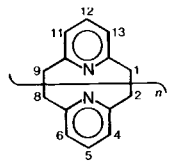
Compound	n	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available[a]	Metal complex(es) general comments[d]	Ref
	6	H	1		A, C, D		93[b]
	7	H	2a	[70–73 (3)]	A–C		2, 4, 14, 93[b]
		4-D	2b	[103 (7)]	A		4
		1-CO_2Me	2c	[84 (0.03)]	A		4
		1-OH	2d	53.5–54.0 [95 (0.01)]	A		4
		1-(=O)	2e	33.5–34.5	A		4, 14
		1-$(OMe)_2$	2f	[85 (0.06)]	A		4
		1-(=O); 2,2-$(Me)_2$	2g	[77 (0.07)]	B–D		5
		2,2-$(Me)_2$	2h	[49 (0.2)]	A–D		5
		1-($=CH_2$)	2i	[70 (2.0)]	A–D		14
		1-($=CMe_2$)	2j	[117–118 (0.5)]	A–D		14
		1-($=C(C_6H_5)_2$)	2k	116–118	A–D		14
		1-$C(C_6H_5)_2OH$	2l	162–163	A, B		14
	8	H	3				93[b]
	9	H	4				93[b]
	10	H	5a	15.6–16.6 [152–158 (3.7)]	B, C	*N*-Oxide (79–80.5°); picrolonate (183–185°)	17, 93[b]
		12-OH	5b	201–202	B, C	Subl: 125–130° (0.1)	17
		12-OAc	5c				17
		1-OH	5d	88–89	B, C		17
		1-OAc	5e				17
		1-(=O)	5f	47–48	B, C	DNP (191–192°)	17
		1-(=O); 2-Me	5g	Oil	B	Picrolonate (113–115°)	17
		1-(=O); 2,2-$(Me)_2$	5h	[150–160 (0.36)]	B, C		17
		(±)-2-Me	5i	[138–143 (2.2)]	B, C	Picrolonate (163–166°)	17
		(+)-2-Me	5j			$[\alpha]_D^{25}$ +13.31°; picrolonate (163–166°)	17, 21
		13-Me	5k	103–105	B, C	Picrolonate [274° dec]	1, 489
					A–D	Isolated <1% yield	3
		2,2-$(Me)_2$	5l	Oil	B	Picrolonate [170–172° dec]	17
		1,2,9,10-De(H)$_4$:N→O	5m				20
	12		6				93[b]
	26	29-ONH_2	7				94
	26	R = H	8a	184–185	B		94
	26	R = NH_2	8b	129–130	B		94

TABLE I (Continued)

Compound	n	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available[a]	Metal complex(es) general comments[d]	Ref
	$m = n =$ 11	R = H	**9**	177–178	B		94
		H	**10**		A	VTNMR study	6, 37
		H	**11a**	80.5–81.5	A, B, D	VTNMR study[8]	9
				83–84			7
		1(2),7(8)-$(SMe)_2$	**11b**	152–153	A, D		9
		1(2),7(8)-$[S^+(Me)_2]_2$ $2BF_4^-$	**11c**				9
		16-H (BF_4^-)	**11d**	179–183	A–C		9
		16 N→O	**11e**	165–167	A, B, D		9
		1,2,7,8-De$(H)_4$	**11f**	157–158	A, C, D		9
		1,2,7,8-De$(H)_4$	**11g**			X-ray study	10
		16-H (BF_4^-)	**11h**	207–210	A, C		9
		1,2,7,8-De$(H)_4$	**11i**				
		16-BF_3	**11j**	204–206	A, C		9
	1	H	**12a**	256–258		PES[262]	11–13, 16, 18, 19, 37, 98, 262
					A		6, 7, 15
	1	*trans*-1,8-$(SMe)_2$	**12b**	234–235		Isomer A	12
	1	1,8(9)-$(SMe)_2$	**12c**	167–168		Isomer B	12
	1	1,8(9)-$(SMe_2)_2^+$	**12d**				12
	1	1,2,8,9-De$(H)_4$	**12e**	127.5–128	A, C		12
	2	H	**13**	191–192	A		13
	3	H	**14**		A	Subl: 150–160° (0.01)	13, 19
				205–206	A		16
	4	H	**15**	158–159	A	Subl: 200–210° (0.01)	13
	5	H	**16**	160–161	A		13, 16
	6	H	**17**				13
	7	H	**18**				16

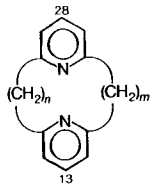
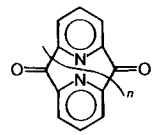
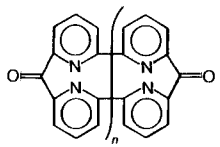
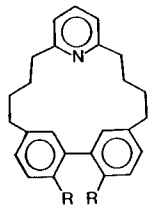
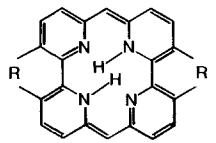
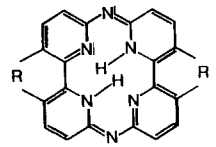
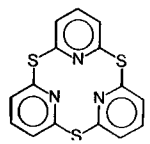
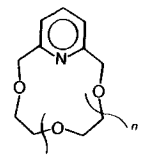
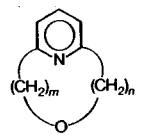
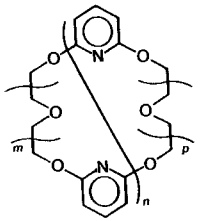
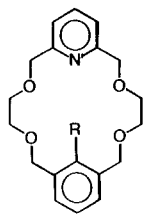
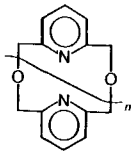
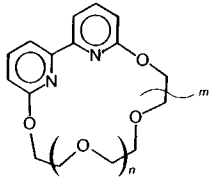
	n = 2; m = 3–6	H	19a–d				405b
	n = m = 10	13, 28-$(Me)_2$	**20**	103–105	B		3
	2	H	**21**	134.5–135	A, B		102
	1	H	**22**	176–178	A, B		102
	2	H	**23**	185–187	A, B		102
	3	H	**24**	196–199 dec	A		102
	4	H	**25**	218–221	A		102
	—	R = OMe	**26**	154.5–156.5	A, B	Lythraceous alkaloids	134–136
		R = (–CH=CH–)	**27**		B–D	Light sensitive	308
		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 (±0.2)	23, 24
		3,4:12,13-Dibenzo	**30b**	132 dec	A	K, Co, Na, NH_4, Ag, Pr, Rb, Ba, Hg	374
		3,4:12,13-Dibenzo; N→O	**30c**	159 dec	A	K	374

TABLE I (Continued)

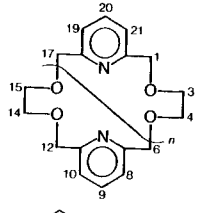
Compound	*n*	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available [a]	Metal complex(es) general comments[d]	Ref
	*m* = *n* = 4	H	31				93b
	*n* = 0; *m* = 2	H	32a	83–84	A, B		25, 487
	n = 0; *m* = 2	(±)-2-Me	32b	54–55	A, B, D	CMR	487
	n = 0; *m* = 3	H	33	76–78	A, B, D		25, 487
	n = 0; *m* = 4	H	34	[155–160 (0.15)]	A, B, D		487
	n = 1; *m* = *p* = 0	H	35	215–216	A, B		25, 487
	n = 1; *m* = 0; *p* = 1	H	36	94.5–95.5	A–C		25, 487
	n = 1; *m* = *p* = 1	H	37	111–112	A–C		25, 487
	n = 1; *m* = *p* = 2	H	38a	117–120	A		25, 487
	n = 1; *m* = *p* = 2	2,17(24)-(Me)$_2$	38b	109–110	A, B, D	Isomer A	487
			38c	Oil	A, B, D	Isomer B	487
			38d	Oil	A, B, D	Isomer C	487
	n = 1; *m* = 2; *p* = 3	H	39	71–72	A, B, D		487
	n = 1; *m* = *p* = 3	H	40	83–84	A, B, D		487
	n = 1; *m* = *p* = 4	H	41	90–91	A, B, D		487
	n = 2; *m* = *p* = 1	H	42	120.5–121.5	A, B		25, 487
		R = CO_2H	43a	172–181	A, D		34
		R = CO_2Me	43b	Oil	A, D		34



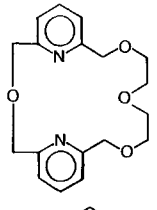
1	H	44	172–175	A	pK_a 7.9 (<3)	23, 24
2	H	45	125–128	A	pK_a 5.3 (3.7)	
					tert-Butylammonium thiocyanate (1:1) (198–201°)	23, 24
3	H	46	173–176	A	pK_a 4.8 (>3)	23, 24



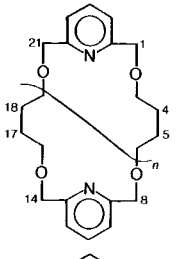
n = 1; m = 1	H	47	Oil	A, B		39
n = 2; m = 1	H	48		A, B		39
n = 1; m = 2	H	49	145–146	A, B		39
n = 2; m = 2	H	50		A, B		39



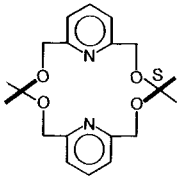
1	H	51a	147–148		pK_a 5.3 (3.6)	23, 24
1	3,4:14,15-Dibenzo	51b	184–186			23
1	3(R),4(R),14(R),15(R)-(CONMe$_2$)$_4$	51c	224		$[\alpha]_D^{25}$ +107°	100



	H	52			(Impure sample)	23

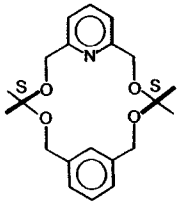
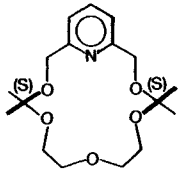
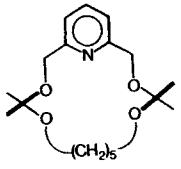
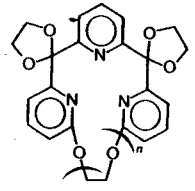
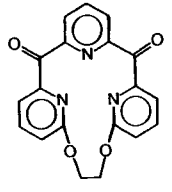
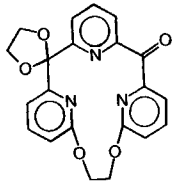


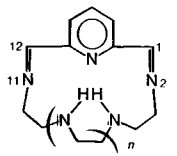
1	4,5:17,18-Dibenzo	53	142–143	A, C	NaSCN (195–196°)	26
2	4,5:17,18-Dibenzo	54	129–130	C		26
3	4,5:17,18-Dibenzo	55	108–109	C		26
4	4,5:17,18-Dibenzo	56	104–105	C		26



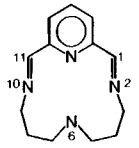
	H	57	288–292 dec	A	$[\alpha]_{546}^{25}$ -302°	23, 92

TABLE I (Continued)

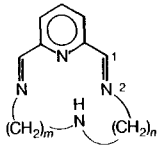
Compound	*n*	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available[a]	Metal complex(es)/ general comments[d]	Ref
		H	58			$[\alpha]_{578}^{25}$ -283°	92
		H	59			$[\alpha]_{578}^{25}$ -242°	92
		H	60			$[\alpha]_{578}^{25}$ -250°	92
	1	H	61	209–211	A, B		39, 102
	2	H	62	161–163	A, B		39
		H	63	122–124	A, B		39, 102
		H	64		A, B		39



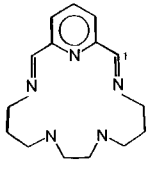
	1	H	65a
	1	1,12-$(Me)_2$(abr:"B")	65b
		1,12-$(Me)_2$; 3,4;9,10-dibenzo	65c
		1,12-$(Me)_2$; 1,2,11,12-$(H)_4$ (abr: pyane N_5)	65d
	2	1,12-$(Me)_2$ (abr: "A")	66



		H	67a
		1,11-$(Me)_2$ (formerly cyp[41]; CR[44])	67b
		1,11-$(Me)_2$; 6-CH_2CH_2-$N(Me)_2$	67c
		1,11-$(Me)_2$; 1,2,10,11-$(H)_4$ (Abr: CRH or CR + 4H)	67d
		1,11-$(Me)_2$; 1,2,10,11-$(H)_4$; 6-CH_2CH_2N-$(Me)_2$	67e
		1,11-$(Me)_2$; 1,2-di(H)	67f
		1,6,11-$(Me)_3$(Abr: N-Me CR)	67g
		1,11-$(Me)_2$; 5,6-de(H)	67h

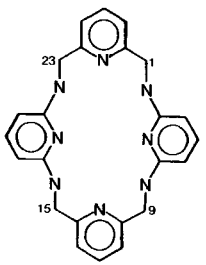
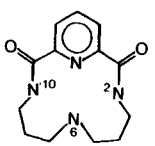
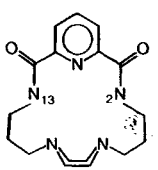
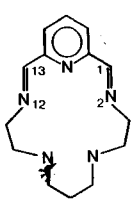
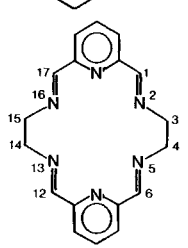
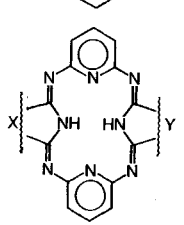


	(m = 2) 4	1,11-$(Me)_2$ (abr: 2,4-CR)	68
	(m = 3) 4	1,12-$(Me)_2$ (abr: 3,4-CR)	69
	(m = 3) 2	1,10-$(Me)_2$ (abr: 3, 2-CR)	70



		1,14-$(Me)_2$	71
		Fe, Mn, Zn	279
[B, C, Mossbauer[59])[c]		Fe[x-ray],[279] Mn, Zn	55–59, 275, 279, 392–397
(B, C, x-ray[97])[c]		Mg	97
		Mn, Zn [x-ray: Mn-$(ClO_4)_2$]	36
(B,C)[c]		Fe, Co, Ni, Cu	273
		Fe	55
(B, C)[c]		Zn	40
(A–C)[c]		Co	40–44, 277
(A–C, ESR, [48]x-ray[49,322])[c]		Ni	40, 45–49, 52, 322
(B, C, ESR)[c]		Cu	45, 278
(B, C)[c]		Zn	40, 44
(B)[c]		Ni	342
(B, C)[c]		D isomer (131–134°)	52
(B, C)[c]		Meso isomer(83–85°)	52
(A–C)[c]		From meso: Co[d]	44, 50, 51
(A–C,ESR[48], x-ray[322])[c]		From meso: Ni	46–48, 53, 322
(B, C, Mossbauer)[c]		Fe	54, 274
(B, C, ESR)[c]		Cu	278
		Ni[$(ClO_4)_3^-$(diamagnetic); $(ClO_4)_2^-$ (paramagnetic)]	342, 501
(A–C, ESR[48])[c]		Ni	47, 48
(B, C)[c]		Zn, Cu	40
(A–C, ESR[48])[c]		Ni	47, 48
(B, C)[c]		Ni, Cu	460
(B, C)[c]		Ni, Cu, Zn	40
(B, C)[c]		Attempted	40
		Mn	394

TABLE I (Continued)

Compound	*n*	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available[a]	Metal complex(es) general comments[d]	Ref
		1,9,15,23-$(C{=}O)_4$	**72**	>360			431
		6-Me;	**73**	164–166		Cu [mp 196–198° dec]	29
		H	**74**	226–228			29
		H	**75a**			Fe, Mn, Zn	279
		1,13-$(Me)_2$ (abr: "C")	**75b**		(B, C, x-ray[279])[c]	Mg, Fe, Mn	97, 275, 279, 393–395
		3,4:14,15-Dibenzo (abr: HADA)	**76a**			Theoretical calculations	61
		1,6,12,17-$(Me)_4$, 3,4:14,15-dibenzo (abr: tmed)	**76b**	300/1 mm (subl)	(B–D, ESR)[c]	Cu	60
		X = Y = 	**77a**				65
		X = Y = 	**77b**		C		63, 64

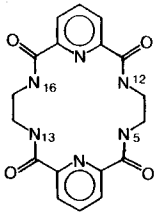
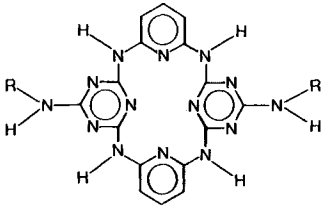
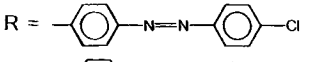
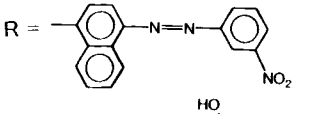
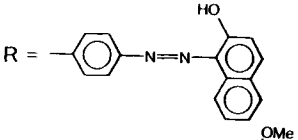
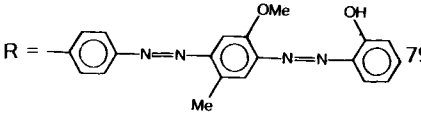
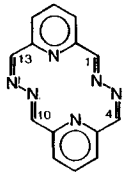
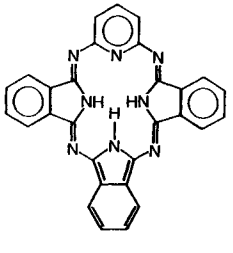
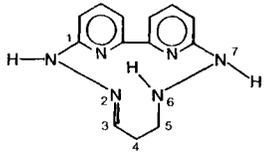
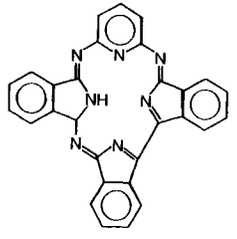
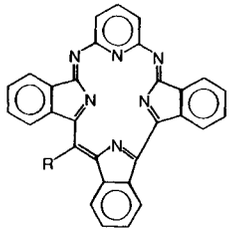
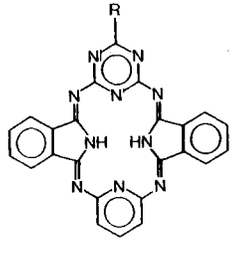
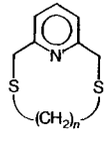
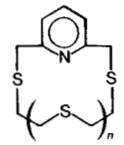
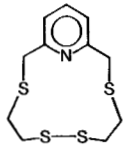
	X = Y = 	77c				65
	X = Y = 	77d		C		64, 66, 95
	X = Y = 	77e			Theoretical calculations	61
	(abr: OAPI)					
	H	78a	>250			29, 431
	2,5,13,16-$(Tos)_4$	78b				29
	R = 	79a		C	Cu	62
	R = 	79b		C	Cu	62
	R = 	79c		C	Cu	62
	R = 	79d		C	Cu	62
	1,4,10,13-$(Me)_4$	80		(B, C, x-ray)[c]	Fe	96
		81		(C, D)[c]	Ni, Cu, Au	272

TABLE I (Continued)

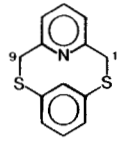
Compound	*n*	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available[a]	Metal complex(es) general comments[d]	Ref
		3,5,5-$(Me)_3$	82			Ni	280
		H	83		C, D	Cu	321
		R = (2-cyano-phenyl)	84		B–D	Cu	321
		R = OH	85			Cu, Co	384
	2	N→O	86	152–154	A	VTNMR	27
	3	H	87a	78–79	A		28
	3	N→O	87b	107–109	A	VTNMR	27
	4	N→O	88	98–99	A	VTNMR	27
	5	N→O	89	147–148	A	VTNMR	27, 283
	6	N→O	90	138–140	A	VTNMR	27
	7	N→O	91	89	A	VTNMR	27
	8	N→O	92	73–75	A	VTNMR	27
	9	N→O	93	117–120	A	VTNMR	27
	10	N→O	94	54–55	A	VTNMR	27



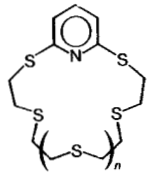
0	H	95	74–77	A		431
1	H	96a	162–163	A	Ag (mp 217–219°; A)	29, 431
					Hg (mp 198–200° dec; A)	29
					Ag, Hg, Au, Pd, Pt, Co	431
1	N→O	96b	151–152	A, D		283
1	5-sulfoxide	96c	171–174	A		431
2	H	97	131–133	A	Cd, Co, Ni	29, 431



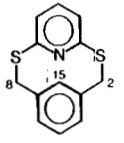
	H	98	151–153 (subl)	A	Zn	431



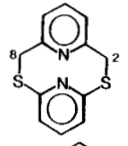
	H	99	172–173	A		30, 31



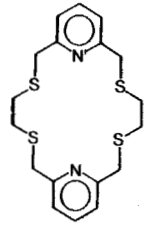
	H	100		A, B		



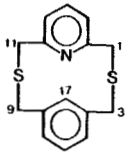
	H	101a	195–196	A		30, 37
	15-Me	101b	129–131	A		33
	15-OMe	101c	206–208			33
	15-F	101d	142–144	A		30
	15-Cl or Br	101e			(Attempted)	30



	H	102	228–229	A		30

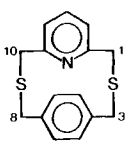
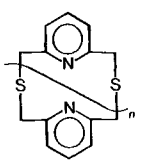
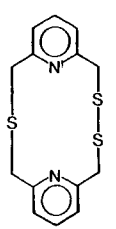
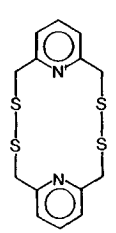
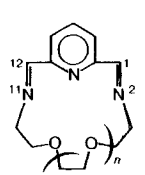


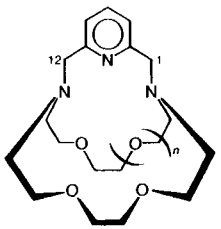
	H	103	213–216	A	Fe, Co, Ni	431



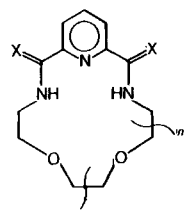
	H	104a	173–175	A		32
	17-Me	104b	135–136	A		33
	17-F	104c	174–175	A		32
	17-NO_2	104d	159–160			99

TABLE I (Continued)

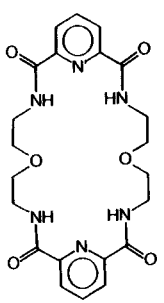
Compound	n	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available[a]	Metal complex(es) general comments[d]	Ref
		H	105a	177–178	A, C, D		7, 9
		2,9-[SMe(BF_4)]$_2$	105b				9
		2-Sulfone	105c	228–230	A, B (D^{429})		428
		N→O;2,9-bis-(sulfone)	105d	>340	A, B, D (D^{429})		9, 428
		N→O; 2-sulfoxide	105e	226–228 dec	A, B (D^{429})		428
		2-sulfoxide; 9-sulfone	105f	>250 dec	A, B, (D^{429})		428
		N→O; 2,9-bis(sulfoxide)	105g	220–250 (color change)	A (D^{429})	Sublimed: 220–245° (0.002)	428
		N→O; 2-sulfoxide; 9-sulfone	105h	>300	A, B (D^{429})		428
	1	H	106a	220–222	A		18, 32
				230–230.5			12, 98
		$(N→O)_2$	106b	211 d	A		27
		$(N→O)_2$; bis(sulfone)	106c				18
		Bis(sulfone)	106d				18
		[SMe(BF_4)]$_2$	106e				12
	2	H	107				18
				185–188	A, D		98
		H	108		A, D		98
		H	109	150–152	A, D		98
	1	3,4:9,10-Dibenzo	110			Mn, Zn	36



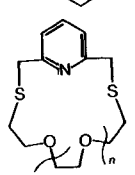
0	1,12-$(C{=}O)_2$	111a	275–276			427
	1,12-$(C{=}O)_2$	111b	185–186	A		427
1	H	112	95–96	A, D, CMR	pK_a 8.31; Li, Na, K, Rb, Cs, Mg, Ca, Sr, Ba	427



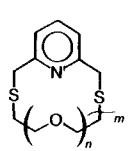
0	H; X = O	113a	228–230	A, D		29, 374
	2,11-$(Tos)_2$; X = H	113b	175–177	A, D		29, 374
1	H; X = O	114a	200–201	A, D		29, 374
	2,11-$(Tos)_2$; X = H	114b	184–185	A, D		29, 374
2	H; X = O	115a	127–129	A, D		29, 374
	2,11-$(Tos)_2$; X = H	115b	163–165	A, D		29, 374



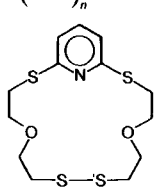
	H	116	338–340 (subl)	A, D		29, 374



0	H	117	133–135	A, D		35, 374
1	H	118	90–91	A, D	Na	35, 374
2	H	119a	58–59	A, B[c], D	Na, Co, Cu, K, Ba	35, 374
	N→O	119b	Oil	A, B[c], D	Na, K, NH_4^+, Ba	35, 374
	N→O; bis (sulfone)	119c	198–201	A, D		374
3	H	120				35

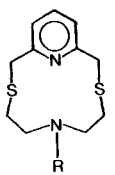
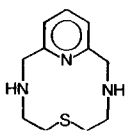
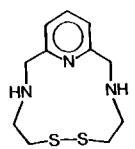
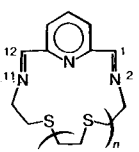
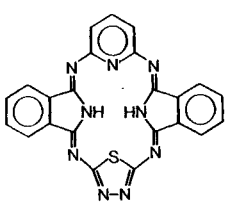
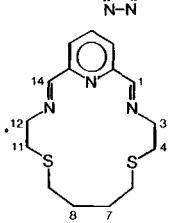
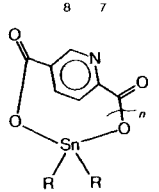


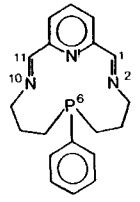
1; m = 1	H	121	92–94; 110–112[374]	A, D		29, 374
2; m = 1	H	122	75–77	A, D		29, 374
3; m = 1	H	123	73–76	A, B[c], D	Ag	29, 374
1; m = 2	H	124	168–170	A, D		374

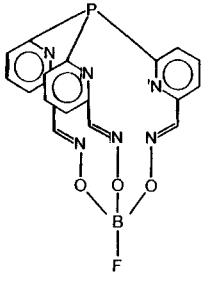


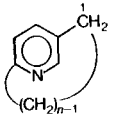
	H	125		A		39

TABLE I (Continued)

Compound	n	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available[a]	Metal complex(es) 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
	1	3,4:9,10-Dibenzo	129			Mn, Zn	36
			130			Cu, Co, Ni, Zn	38
		1,14-$(Me)_2$ 3,4:7,8: 11,12-Tribenzo-	131			Zn, Cd	276
	2	R = Et R = *i*-Pr	132a 132b	>300 dec 250 dec			137 137

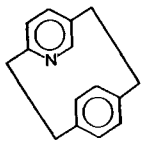
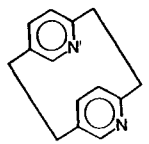
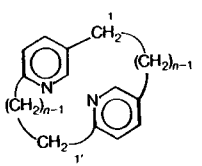
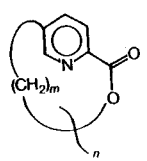
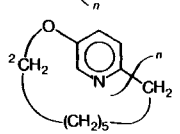
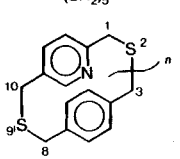
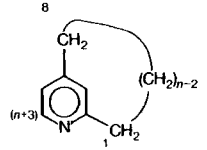
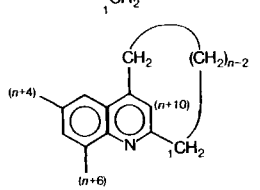






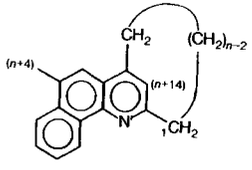
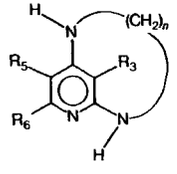
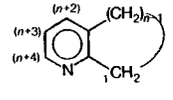
	1,11-$(Me)_2$	133a			Ni	67
	1,11-$(Me)_2$; 1,2,10, 11-$(H)_4$ (abr: pn_2-H_4)["meso"]	133b			Ni	67
	1,11-$(Me)_2$; 1,2,10, 11-$(H)_4$; 6-S	133c		D		67
	(abr: $P_{cc}BF$)	134			Fe, Zn, Ni, Co	68
				X-ray[c]	Fe	69
				X-ray[c]	Ni	70
8	H	135a	[70–75 (0.01)]	A–C		84
	1-(=O)	135b	43–48 [105–110 (0.02)]	A–C		84
	1-OH	135c	[125–135 (0.02)]	A, B	Isomeric mixture	84
	1-OAc	135d	[110–115 (0.01)]	A	Isomeric mixture	84
9	(±)-H	136a	[80–81 (0.04)]	A–C		84
	(+)-H	136b	[80 (0.01)]		$[\alpha]_D$ +152°, $[\alpha]_{365}$ +1074°	84
	1-OH	136c	[145–146 (0.03)]	A, B	Mixture	84
			Oil	A, B	Isomer B	84
			96–97	A, B	Isomer A	84
	1-OAc	136d	47–59 [135–140 (0.01)]		Mixture	84
			70–72	A	Isomer A	84
			66–68	A	Isomer B	84
	1-(=O)	136e	[105–115 (0.03)]	A–C		84
10	H	137a	[75–78 (0.01)]	A–C		84
	1-OH	137b	[155–160 (0.02)]	A, B	Mixture	84
	1-OAc	137c	[125–130 (0.01)]	A	Mixture	84
	1-(=O)	137d	79–82 [140–150 (0.01)]	A–C		84
11	H	138a	[90–95 (0.03)]	A–C		84
	1-OH	138b	[140–145 (0.03)]	A, B	Mixture	84
	1-OAc	138c	[110–115 (0.02)]	A	Mixture	84
	1-(=O)	138d	35–37 [120–130 (0.03)]	A–C		84
12	H	139a	[100 (0.01)]	A–C		84
	1-OH	139b	[140–150 (0.03)]	A, B		84
	1-OAc	139c	[100–110 (0.02)]	A, B		84
	1-(=O)	139d	45–48 [120–130 (0.02)]	A–C		84

TABLE I (Continued)

Compound	*n*	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
			**141**		A	4 isomers(separable)	85–88
	8	1 = 1′ = (=O)$_2$	**142**	107–108	A–C		84
	9	1 = 1′ = (=O)$_2$	**143a**	147–148	A–C		84
		H	**143b**	94.5-97.5	A–C		84
	1, *m* = 9	H	**144**	103–104	A, B		84
	m = 12	H	**145**	38–40	A, B		84
	2, *m* = 9	H	**146**	72–73	A, B		84
	2	2-(=O); 9, 10, 11, 12,13,14-[carpaine] (H)$_6$	**147**	119–120 [subl: 120 (0.05)]	D	$[\alpha]_D^{12}$ + 24.7°; *N*,*N*′-(Me)$_2$ [mp 79–81°]	104, 105, 130 127, 128, 468
	1	H	**148a**	204–205	A		89
		2,9-Bis(sulfone)	**148b**	330 dec			85, 89
	2	H	**149**	217–218	A	Two isomers	89
	9	H	**150a**	[115–120 (0.3)]	A	MeI (127–128°)	107, 108
		12-Me	**150b**	[105–110 (0.2)]	A, B		106
	6	H	**151a**	62–63	A, C	HCl (230–234°)	110
		16-Cl	**151b**	67–68	A, C	Picrate (192.5–193.5°)	110
	8	H	**152a**	44–45	A, C	Picrate (166.5–167.5°)	109, 110
		18-Cl	**152b**	64.5–66	A, C	Picrate (201–203°); pK_a 5.03)	110

10	H	153a	62–63	A, C	HCl (230–234°)	109, 110
	N→O	153b	119–121			117
	1-Cl (syn)	153c	109–110	A		117
	20-Cl	153d	81.5–82.5	A, C	Picrate (176–178°); pK_a 2.88	110, 113, 114
				A–C	HCl (194–221°)	109, 113
	20-Cl; 1-*d* (syn)	153e	81–82	A	N→O (122.5–123.5°)	111
	20-Cl; N→O	153f	125–127	A, C		109, 113, 117
	20-Cl; 1,1,10,10-$(d)_4$	153g				129
	20-Cl; 1-OH	153h	139–158			109
	Syn isomer	153i	160–162	A, C		129, 109, 113, 114, 116
	N→O	153j	174–175	A		113
	Anti isomer	153k	205.5–207	A, C		129, 109, 113, 114, 116
	N→O	153l	220–230	A		113
	20-Cl; 1-(=O)	153m	136–137.5	A–C		109, 132
	20-Cl; 1-Br (syn)	153n	149.5–151	A, C	N→O (186–188°)	109, 114, 129
	20-Cl; 1-Br (anti)	153o	152–153	A		114, 129, 132
	20-Cl; 1,10-$(Br)_2$	153p	133.5–135	A, C	Picrate (183.5–185°)	109
	20-Cl; 1-OAc (syn)	153q	116–118 118–119	A	Labeled *d*	112, 114 129
	20-Cl; 1-OAc (anti)	153r	149–150	A	Labeled *d*	112, 114, 129
	1(anti), 20-$(Cl)_2$	153s	140–140.5	A, D		112, 132
	1 (syn), 20-$(Cl)_2$	153t	144–145	A, C		112, 113
	N→O	153u	189.5–191	A		113
	20-Cl; 1-OTos (syn)	153v	104–107	A–D	Recryst: $CHCl_3$–pet. ether	112–114, 129
					recryst: ether	112
	N→O (syn)	153w	145	A		113
	20-Cl; 1-OTos (anti)	153x	122–123	A, B		113, 114, 129
	N→O (anti)	153y	166–167	A		113
	20-Cl; 1-OCH_2CH_3(syn)	153z	Oil	A, C	Picrate (189–191.5°)	116, 129
	N→O (syn)	153aa	Oil	A		113
	20-Cl; 1-OCH_2CH_3 (anti)	153bb	107.5–110	A, C		116, 129
	N→O (anti)	153cc	176–178	A		113
	20-Cl; 1-$OCOC_6H_5$ (syn)	153dd	147–148	A–C		113
	N→O (syn)	153ee	Oil	A	HCl (146–150°)	113
	20-Cl; 1-$OCOC_6H_5$ (anti)	153ff	116–118	A–C		113

TABLE I (Continued)

Compound	n	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available[a]	Metal complex(es) general comments[d]	Ref
		N→O (anti)	153gg	176–178	A		113
		20-Cl; 1-OPO(OCH_2CH_3)$_2$(syn)	153hh	84.5–86.5	A–D		113
		20-Cl; 1-OCHO (syn)	153ii	122–122.5	A, B		114
		14,20-$(Cl)_2$	153jj	77–79	A		117
		N→O	153kk	159–160			117
		14,20-$(Cl)_2$; 1-OPO(OCH_2CH_3)$_2$	153ll	114–116	A–C		113
		14-Br; 20-Cl	153mm	96–98			114
		14,16,20-$(Cl)_3$	153nn	159–160	A		117
	6	10-Br; 20-Cl	154	187–189	C		115
	10	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-$COCH_2N(C_4H_9)_2$	155d			Unstable	115
		14-COCl; 24-Cl	155e	202-206	B		115
		14-$COCH_2N(C_7H_{15})_2$	155f			Unstable	115
		14-CO_2H; 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-$COCH_2Br$; 24-Cl	155j	207–208	B		115
		14-$CHOHCH_2N(C_7H_{15})_2$; 24-Cl	155k	130–131	B	Isomer A	115
				Oil	B	Isomer B	115
		14-$CHOHCH_2N(C_4H_9)_2$	155l	Oil	B	Mixed racemates	115
		14-(2-pyrCHOH); 24-Cl	155m	173–186	A, B	Isomer A	115
				174–176	A, B	Isomer B	115
		14-(2-pyrCO); 24-Cl	155n	147–149	B		115
	9	$R_3 = R_5 = (Cl)_2$; $R_6 = F$	156	Oil	A, D		131
	12	$R_3 = R_5 = (Cl)_2$; $R_6 = F$	157	[175–180 (3.5)]	A, D		131
	10	H	158	[165–175 (3.7)] 21.8–23.4	B, C	Picrate (154–155°)	17
	13	H	159a	[125–127 (0.007)]		Picrate (137–138°)	118, 119
		17-Cl	159b	130–131		Picrate (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

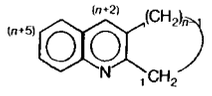
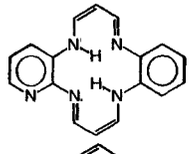
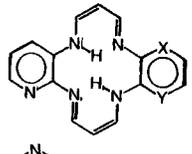
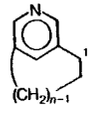
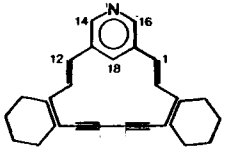
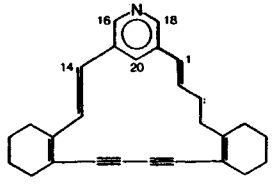
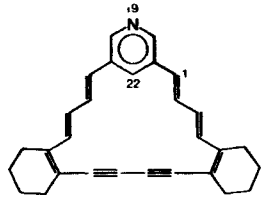
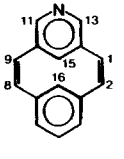
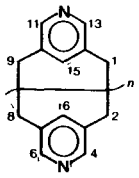
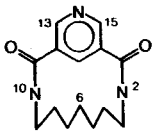
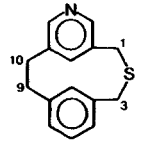
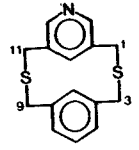
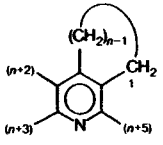
		15,17-$(OH)_2$; 16-$CO_2CH_2CH_3$	159f	280–300			118
		$(H)_6$(cis)	159g			Picrate (194–195°)	118
		$(H)_6$ (trans)	159h			Picrate (202–203°)	118
	10	H	160a	[255 (25)]; 75		Picrate (185°)	124
		15-Me	160b	[238 (11)]; 61		Picrate (196°)	124
		15-Br	160c	[260 (13)]; 91		Picrate (231°)	124
		15,16-$(Me)_2$	160d	93		Picrate (221°)	124
		12-CO_2H	160e	314			124
		15-Me, 12-CO_2H	160f	>365			124
		15-Br, 12-CO_2H	160g	>365			124
		15,16-$(Me)_2$; 12-CO_2H	160h	>365			124
	11	H	161a	80		Picrate (175°)	120
		13-CO_2H	161b	>320 (subl)			120
	12	H	162a	76		Picrate (159°)	121
		14-CO_2H	162b	310			121
	13	H	163a	[200–205 (0.15)]		Picrate (169–171°)	122
		18-Me	163b	Oil		Picrate (165°)	121
		18-Me; 15-CO_2H	163c	307			121
		18-Br	163d	55		Picrate (194–195°)	123
		15-Me	163e			(TCNQ complex: mp 147–153°)	338
		15-CO_2H	163f	297–298			337
	14	H	164a			Picrate (173°)	121
		19-CO_2H	164b	280			121
	15	H	165a			Picrate (172°)	121
		20-CO_2H	165b	250 dec			121
		8,9-De$(H)_2$	165c			Picrate (161°)	121
		8,9-De$(H)_2$; 17-CO_2H	165d	256			121
		8,9-De$(H)_2$; 17-CO_2H; 20-Br	165e	270 dec			123
		H	166	262–264	B–D	Co, Cu	126
		(X = N; Y = CH)	167a	320	B, D	Cu	126
		(X = CH; Y = N)	167b				
	7	9,11$(Me)_2$	168		A(CMR)	Picrate (171–172°), Picrolonate (259°)	432
	9	11,13-$(Me)_2$	169a	Oil	A		71
	9	11,13-$(Me)_2$; 12-NH_2-(ClO_4^-)	169b	249	A		72
	9	11,12,13-$(Me)_3$-(ClO_4^-)	169c	226	A, B		72

TABLE I (Continued)

Compound	n	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-$C_6H_5(ClO_4^-)$	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-$CO_2CH_2CH_3$; 18-H	170d	Mp (dec)	A, D		75
		15-$COCH_3$; 18-CH_2CH_3	170e		A		78
		15-$COCH_3$; 18-H	170f	Mp (dec)	A, D		75
		15-$CO_2CH_2CH_3$; 18-CH_2CH_3	170g	Mp (dec)	A		78
		15,18-$(Me)_2$	170h	230 dec	B		76
		15-Me; 18-CH_2CH_3	170i	230 dec	A		76, 78
		15-Me; 18-$CH_2CH_2CH_3$	170j	200 dec	A		76
		15-Me; 18-*n*-Bu	170k	220 dec	A		76
		15-H; 18-CH_3	170l	Mp (dec)		K (anion formation)	77
		15-H; 18-CH_2CH_3	170m	Mp (dec)		K (anion formation)	77, 78
		20-H; 17-$CO_2CH_2CH_3$	171	Mp (dec)	A, C		79
		H	172a	Mp (dec)	A		80
		22-H; 19-$CO_2CH_2CH_3$	172b	Mp (dec)	A, C		80
		11,13,15,16-$(Me)_4$	173a			HCl; $K_{1/2}$ ~ 8 s (MeOH)	73
		8,9-$(H)_2$; 11,13,15,16-$(Me)_4$	173b	89.1–89.6	A–C		73
		1,2,8,9-$(H)_4$	173c	169–171[subl: 60–65 (0.3)]	A		74

	1	H	174	236–237	A, D	81, 82, 101
	2	H	175a	259–260	A, D	82
		4,6,11,13,15,16-(Me)$_6$	175b	244–246	A	73
	3	H	176	277–278	A, D	13, 82
	4	H	177			13
		H	178a	334–337 (dec)	A, B, D	83, 493
		6-OH	178b	316–318 (dec)	A, B, D	83, 493
		6-O-*t*-Bu	178c	310–312 (dec)	A, B, D	83
		14-$CH_2C_6H_5$(Br^-)	178d	261–262 (dec)	A, B	83
		6-OH; 14-$CH_2C_6H_5$-(Br^-)	178e	239–241 (dec)	A–C	83
		6,13-$(OH)_2$; 14-$CH_2C_6H_5$	178f		A	83
	1	H	179	90–92 [subl: 55–60 (0.01)]	A	74
		H	180	177–178	A	74
	10	15-Me; 12-CN; 13-OH	181	281.5–282	B, C	125

[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. 93b [c] Spectral data of the complex. No corresponding data available for ligand. [d] Temperatures given in °C.

TABLE II. Heterocycles Containing the Furan Subunit[a]

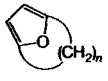
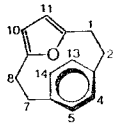
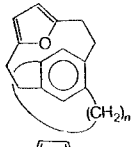
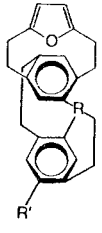
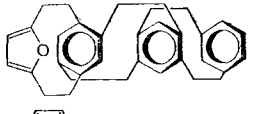
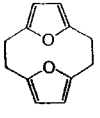
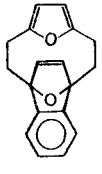
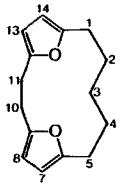
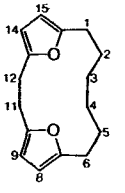
Compound	Double bond position	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Complex(es)/comments[g]	Ref
	4,5:5,6	n = 7; 2-(=O)	182	69–70	A–D	Reactions of DNP (mp 202–203°)	177, 260, 183
		n = 8; H	183a	[104–106 (11)]	A–C		176, 187
		n = 8; $(H)_4$	183b	[96 (2)]			370, 454
		n = 8; $(H)_4$; 1,8-$(Br)_2$	183c	116–118	A–D	Exo, exo isomer	454
			183d	74.5–75.5	A–D	Endo,exo isomer	454
		n = 8; 3,6-$(=O)_2$	183e	109–110	A–C	VTNMR study[471]	184
	(*Z*)-4,5	n = 8; 3,6-$(=O)_2$	183f			Proposed intermediate	373

TABLE II (Continued)

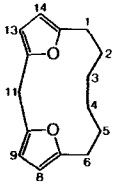
Compound	Double bond position	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Complex(es)/comments[g]	Ref
		H	**184a**	68–68.5	A[217], C	Reactions of [498]	179–181, 217
		4,14-d_2	**184b**	66.5–67.0	A		178
		4,14-$(Me)_2$	**184c**	63–64.5	A, C	VTNMR	188
		4,5-Benzo	**184d**	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			259
		n = 10	**186**	74–75		Reactions of[485]; Chiral[485]	259
		R = R′ = H	**187a**	117–118	A, C		217
		R = R′ = Me	**187b**	127–128	A, C	VTNMR	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
		H				Reactions of	165, 166, 181, 186, 218, 268, 373, 484, 496–498
		H			A	VTNMR studies	15
	(Z)-1,2	1-Cl	**189b**	Oil	A		167
		1,(2 or 7)-$(Me)_2$	**189c**	146–148	B, C	Mixture of isomers	186
		1,(2 or 7)-$(CH_2C_6H_5)_2$	**189d**	182–186		Mixture of isomers	186
		H	**190**	125–126	A, D	Bis adduct (mp 224°)	165



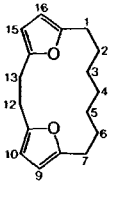
	1-(=O)	**191a**				141
(*Z*)-1,2; (*Z*)-4,5; (*Z*)-10, 11	H	**191b**	110	A–D		140, 144
(*E*)-1,2; (*Z*)-4,5; (*Z*)-10, 11	3-(=O)	**191c**	Red oil	A–D	Nonplanar; non-diatropic	164, 173
(*Z*)-1,2; (*Z*)-4,5; (*Z*)-10, 11	3-(=O)	**191d**	158–160	A–D	Nonplanar; non-diatropic	164, 173
(*E*)-1,2; (*E*)-4,5; (*Z*)-10,11	3-(=O); 2,4-$(CO_2Me)_2$	**191e**	170	A–D		142, 164
(*E*)-1,2; (*E*)-4,5; (*Z*)-10,11	3-(=O); 2,4-$(COOCO)_2$	**191f**	>300	A–D	Appreciable diamagnetic ring current	142, 164, 173
(*E*)-1,2; (*E*)-4,5; (*Z*)-10,11	3-(=O); 2,4-$(CO_2H)_2$	**191g**	>300	A–C		142, 164, 173
(*E*)-4,5; (*Z*)-10,11	3-(=O); 2,4-$(CO_2Me)_2$	**191h**	155–156	A–D		164



(*Z*)-5,6; (*Z*)-11,12	2-OH; 4-(=O)	**192a**		A, D		143
(*Z*)-5,6; (*Z*)-11,12	2,4-$(OH)_2$	**192b**	150–152	A–D		143
(*Z*)-1,2; (*Z*)-5,6; (*Z*)-11,12	H	**192c**	145	A, C, D	Decoupling studies	150
(*Z*)-1,2; (*Z*)-5,6; (*Z*)-11,12	3,4-$(Br)_2$	**192d**	138	D	Not isolated	150
(*Z*)-2,3; (*Z*)-5,6; (*Z*)-11,12	4-(=O)	**192e**				143
(*Z*)-2,3; (*E*)-5,6; (*Z*)-11,12	4-(=O); 3,5-$(CO_2Me)_2$	**192f**		A–D		143
(*Z*)-2,3; (*E*)-5,6; (*Z*)-11,12	4-(=O); 3,5-$(CO_2H)_2$	**192g**	>300			143
(*Z*)-2,3; (*Z*)-5,6; (*Z*)-11,12	4-(=O); 3-CO_2H	**192h**				143
(*Z*)-1,2; (*E*)-3,4; (*Z*)-5,6; (*Z*)-11,12	H	**192i**	167–170	A–D		150

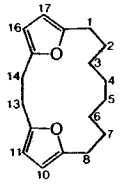
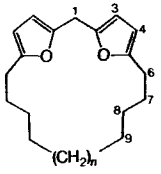
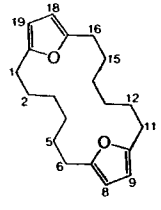
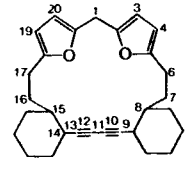
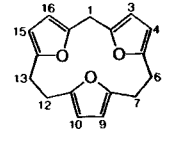


(Z)-1,2; (*Z*)-5,6	11-(=O)	**193a**	148–150	A–D		158
(Z)-1,2; (*Z*)-5,6	11-(=O); 3-Br	**193b**	Unstable oil		Not identified	158
(Z)-1,2; (*E*)-3,4; (*Z*)-5,6	11-2H	**193c**	103–105	A–D	Decoupling studies	158
(Z)-1,2; (*E*)-3,4; (*Z*)-5,6	11-(=O)	**193d**	212–215	A–D	Conformationally mobile, VTNMR	158



( )-1,2; ( )-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
	( )-1,2; ( )-7,8; (*Z*)-13,14	H	**195**	146–148		Probably *Z*,*Z* orientation	150
	(*E*)-6,7; (*Z*)-8,9; (*Z*)-11,12; (*E*)-13,14	*n* = 1; 1-2H	**196a**	130–133	A, C, D		163
	(*E*)-6,7; (*Z*)-8,9; (*Z*)-11,12; (*E*)-13,14	*n* = 1; 1-(=O)	**196b**	171-174	A, C, D		163
	(*E*)-6,7; (*Z*)-8,9; (*Z*)-12,13; (*E*)-14,15	*n* = 2; 1-$(H)_2$	**196c**	141–143	A, C, D		163
	(*E*)-6,7; (*Z*)-8,9; (*Z*)-12,13; (*E*)-14,15	*n* = 2; 1-(=O)	**196d**	165–168	A, C, D		163
	(*E*)-6,7; (*Z*)-8,9; (*Z*)-13,14; (*E*)-15,16	*n* = 3; 1-$(H)_2$	**196e**	173–177	A, C, D		163
	(*E*)-6,7; (*Z*)-8,9; (*Z*)-13,14; (*E*)-15,16	*n* = 3; 1-(=O)	**196f**	114–120	A, C, D		163
	(*E*)-1,2; (*Z*)-3,4; (*E*)-5,6; (*E*)-11,12; (*Z*)-13,14; (*E*)-15,16	2,4,13,15-$(Me)_4$	**197a**			Unsuccessful Wittig cyclization[b]	175
	(*Z*)-1,2; (*Z*)-5,6; (*Z*)-11,12; (*E*)-15,16	3,4: 13,14-Dibenzo	**197b**	230–234	A–D	Nonplanar	154
	(*Z*)-1,2; (*E*)-5,6; (*E*)-11,12; (*E*)-15,16	3,4: 13,14-Dibenzo	**197c**	202-204	A–D	Nonplanar	154
	(*Z*)-1,2; (*E*)-5,6; (*Z*)-11,12; (*E*)-15,16	3,4: 13.14-Dibenzo	**197d**	209–211	A–D	Nonplanar	154
	(*E*)-1,2; (*E*)-5,6; (*E*)-11,12; (*E*)-15,16	3,4: 13,14-Dibenzo	**197e**	330–332	A–D	Sublimed [180° (0.1)]	154, 174
	(*E*)-6,7; (*E*)-16,17	$1-(H)_2$	**198a**	270–271 dec	A, D		163, 172
	(*E*)-6,7; (*E*)-16,17	1-(=O)	**198b**	>270 dec	A, C, D	Atropic (NMR)	163, 172
	(*Z*)-6,7; (*Z*)-12,13	1-(=O)	**199a**	236–237	A–D		162
				233–236	A–C	Paramagnetic ring current	160
	(*Z*)-6,7; (*Z*)-12,13	$1-(H)_2$	**199b**	90–92	A, D	No paramagnetic ring current	160, 162

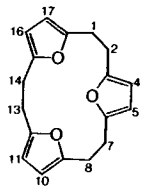
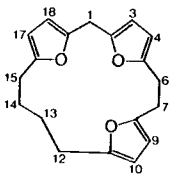
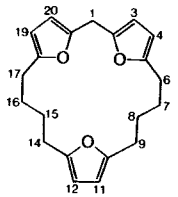
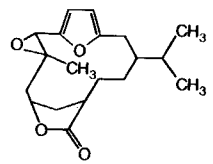
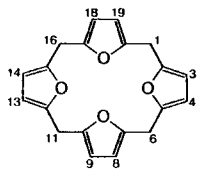
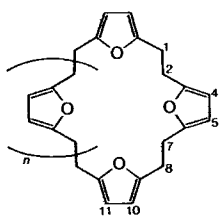
	(*Z*)-6,7; (*Z*)-12,13	1-OMe	**199c**	141–142	A, D	Small paramagnetic ring current	160, 162
	(*E*)-6,7; (*E*)-12,13	1-(=O); 7,12-$(CO_2Me)_2$	**199d**	206–208	A, D		160, 162
	(*E*)-6,7; (*E*)-12,13	1-(=O); 7,12-$(CO_2H)_2$	**199e**	295 dec	D		162
	(*Z*)-1,2; (*Z*)-7,8; (*Z*)-13,14	H	**200a**	215–216	A–C	Peripheral conjugation, aromatic stability[434]	146–148, 155
					D		149
	(*E*)-1,2; (*Z*)-7,8; (*Z*)-13,14	1-CO_2Me	**200b**	89–91	A–C		147
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,7,14-$(CO_2Me)_3$	**200c**	147–150	A–C	Limited peripheral conjugation	146, 147
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,14-$(CO_2H)_2$; 7-CO_2Me	**200d**	Dec	A–C		147
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,7,14-$(CO_2H)_3$	**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	A, D	X-ray; perhydro[168,343,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)/comments[g]	Ref
		1-Et; 1,6,6,11,11,16, 16-$(Me)_7$	**204e**	195–195.5			
		1,1-$(Et)_2$; 6,6,11,11, 16,16-$(Me)_6$	**204f**	209–209.5			169
		1,6,11,16-$(Me)_4$; 1,6, 11,16-$(Et)_4$	**204g**	174			169, 192
		1-CO_2Me; 1,6,6,11,11, 16,16-$(Me)_7$	**204h**	172.5			192
		1-CO_2Et; 1,6,6,11,11, 16,16-$(Me)_7$	**204i**	169.5			192
		1-$[(CH_2)_5]$; 6,6,11,11, 16,16-$(Me)_6$	**204j**	182.3–183.3	A, B		303
		1,11-$[(CH_2)_5]_2$; 6,6, 16,16,-$(Me)_4$	**204k**	208.2–209.2	A, B		303
		1,6,11,16-$[(CH_2)_5]_4$	**204l**	268–269	A, B		303
		1-CO_2H; 1,6,6,11,11, 16,16-$(Me)_7$	**204m**	250 dec			192
		1-CH_2CO_2Me; 1,6,6, 11,11,16,16-$(Me)_7$	**204n**	179			192
		1-CH_2CO_2Et; 1,6,6, 11,11,16,16-$(Me)_7$	**204o**	165			192
		1-CH_2CO_2H; 1,6,6, 11,11,16,16-$(Me)_7$	**204p**	248.5–249.5			192
		1-$CH_2CH_2CO_2Me$; 1, 6,6,11,11,16,16-$(Me)_7$	**204q**	157.5			192
		1-$CH_2CH_2CO_2Et$; 1, 6,6,11,11,16,16-$(Me)_7$	**204r**	153	A, B	Perhydro-[isomers; oil]	192, 500
		1-$CH_2CH_2CO_2H$; 1,6, 6,11,11,16,16-$(Me)_7$	**204s**	225.5–226			192
		1-CH_2Cl; 1,6,6,11,11, 16,16-$(Me)_7$	**204t**	219.5–220			192
		1,11-$(CH_2Cl)_2$; 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; paramagnetic ring current	148, 155

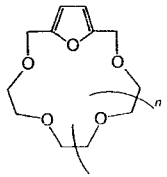
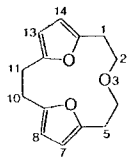
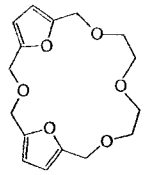
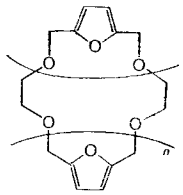
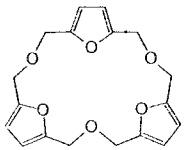
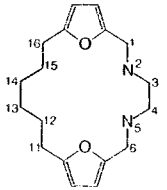
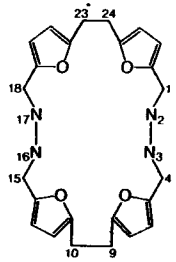
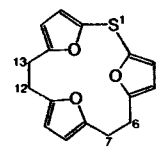
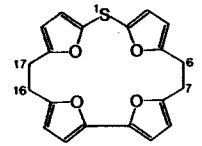
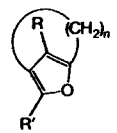
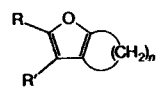
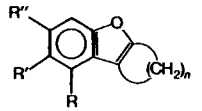
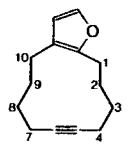
	(*Z*)-1,2; (*E*)-7,8; (*Z*)-13,14; (*E*)-19,20	*n* = 1; H	**205c**				155
	1,2; 7,8; 13,14; 19, 20; 25, 26	*n* = 2; H	**206**	218–220 dec	A–C	Isomer A, confign unknown	148, 155
				192–194 dec	A–C	Isomer B, confign unknown	148, 155
	1,2; 7,8; 13,14; 19, 20; 25,26; 31,32	*n* = 3; H	**207**	250–252	A, C	Confign unknown; no paramagnetic ring current	155
		*n* = 1; H	**208**	[150 (0.01)]	A, D	Pt[e]	170, 171, 467
		n = 2; H	**209**	~0 [150(0.01)]	A, D	DMAD adduct (mp 55–60°)	24, 167, 170, 467
		n = 3; H	**210**				171
		n = 4; H	**211**	[230 (0.1)]	A, D		170, 467
	(*Z*)-1,2; (*Z*)-4,5; (*Z*)-10, 11	H	**212**	255 dec	A–D	Paramagnetic ring current	140, 144
		H	**213**	69–70			167
		*n* = 1; H	**214a**	109–111			24, 167
		n = 1; 3(*R*), 12(*R*), 13(*R*)-$(CONH_2)_4$	**214b**			Proposed synthesis	223
		n = 2; H	215				24
		n = 3; H	**216**	250 (0.01)			170, 467
		H	**217**	124–126			24, 167
	(*E*)-5,6; (*E*)-11,12; (*E*)-15,16	1,2-Oxa; 3,4: 13,14 -Dibenzo	**218a**	180–181	B–D		174
	(*E*)-5,6; (*E*)-11,12; (*E*)-15,16	1-(=0); 3,4: 13,14-Dibenzo	**218b**	289–291	A–D		174
	(*E*)-5,6; (*E*)-11,12; (*E*)-15,16	3,4: 13,14-Dibenzo	**218c**	268	A–D		174

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	7,12-$(CO_2Me)_2$[a]	**220b**	205–206	A–D		157, 161
	(*E*)-6,7; (*E*)-12,13	7,12-$(CO_2H)_2$	**220c**	>260 dec			157
	(*Z*)-6,7; (*Z*)-16,17	H	**221**	170–171	A–D	No diamagnetic ring current	157, 161
		*n* = 6; R = R′ = H	**222**			Attempted synthesis	229
		n = 7; R = R′ = H	**223**			Attempted synthesis; dimer isolated	229
		n = 9; R = R′ = H	**224a**	[65–70 (0.05)]	A		205
		n = 9; R = H; R′ = Me	**224b**	[72–75 (1.5)]	A–C	VTNMR[206]	206, 229
				[91–92 (0.05)]	A–B		228
		*n* = 10; R = Me; R′ = H	**225**	[104–108 (0.9)]	A, B, D	n_D^{20} 1.5089	221
		*n* = 10; R = R′ = H; R″ = OAc	**226a**			Ketolactones via ozonolysis	219
		n = 10; R = R′ = [–CH = CH–]$_2$; R″ = OAc	**226b**			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		208

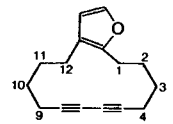
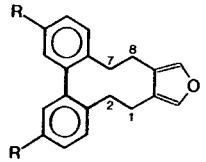
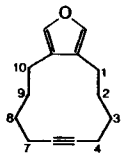
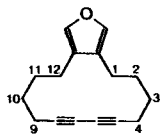
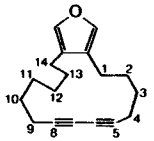
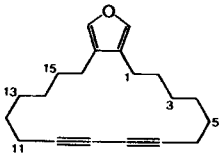
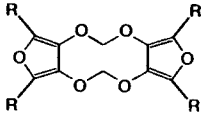
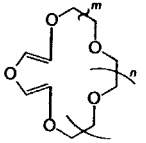
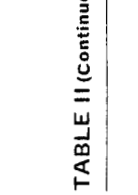
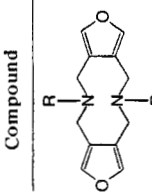
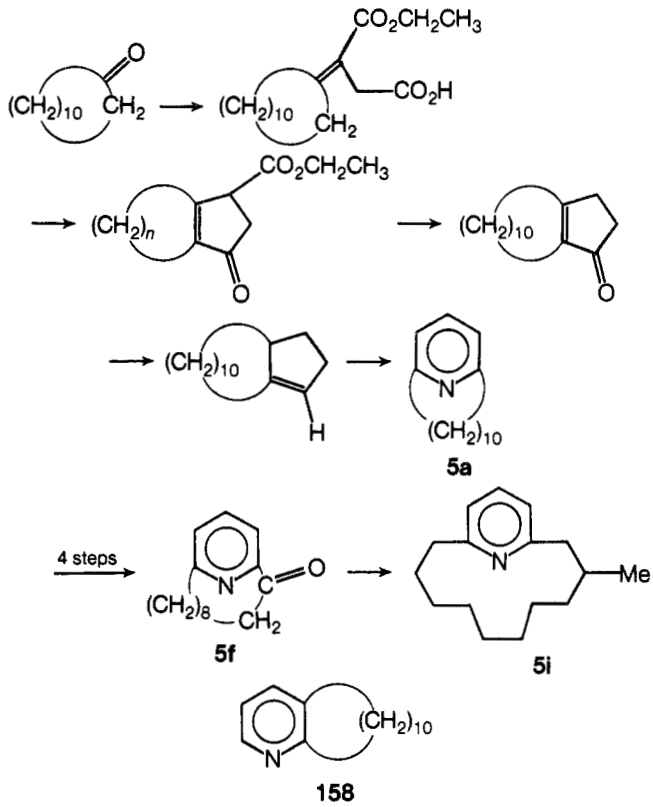
	(*E*)-1,2; (*Z*)-3,4; (*Z*)-9,10; (*E*)-11,12	4,9-$(Me)_2$	**228a**	134–135	A, C, D		209
	(*E*)-1,2; (*E*)-11,12	4,9-$(Me)_2$; 3,10-$(OH)_2$	**228b**				209
	(*Z*)-1,2; (*E*)-7,8*f*	R = H	**229a**		A	NMR of both conformers	214
	(*Z*)-1,2; (*E*)-7,8	R = $CH(Me)_2$	**229b**	Oil	A, C, D		214
	(*E*)-1,2; (*E*)-7,8*f*	R = H	**229c**	113	A–D	Isomer A (higher R_f) (major)	207, 215
				100–101	A–C	Isomer B (lower R_f) (major)	207, 215
	(*E*)-1,2; (*Z*)-3,4; (*Z*)-7,8; (*E*)-9,10	4,7-$(Me)_2$	**230**	131–132	A, C, D		208, 458
	(*E*)-1,2; (Z)-3,4; (*Z*)-9,10; (*E*)-11,12	4,9-$(Me)_2$	**231a**	Dec	A, C, D	Weakly diatropic[210,213]	209, 210, 212–214, 458
	(*E*)-1,2; (*E*)-11,12	4,9-$(Me)_2$; 3,10-$(OH)_2$	**231b**				210
	(*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	Weakly diatropic, conformationally mobile	211
	(*E*)-1,2; (*Z*)-3,4; (*Z*)-9,10; (*E*)-11,12; (*E*)-13,14	4,9-$(Me)_2$	**232**	137–140	A	Weakly paratropic	458
	(*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 diatropic	458
		R = CO_2Et	**234**	213*o*	A, B		204
		*n* = 0; *m* = 1; H	**235**		A, CMR	Na, K	304
		n = 1; *m* = 1; H	**236**		A, CMR	Na, K	304
		n = 2; *m* = 1; H	**237**		A, CMR	Na, K	304
		n = 3; *m* = 1; H	**238**		A, CMR	Na, K	304
		n = 4; *m* = 1; H	**239**		A, CMR	Na, K	304
		n = 5; *m* = 1; H	**240**		A, CMR	Na, K	304
		n = 0; *m* = 2; H	**241**		A, CMR	Na, K	304
		n = 1; *m* = 2; H	**242**		A, CMR	Na, K	304
		n = 2; *m* = 2; H	**243**		A, CMR	Na, K	304

TABLE II (Continued)

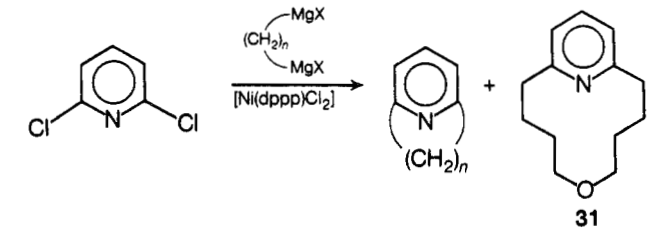
Compound	Double bond position	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Complex(es)/comments[g]	Ref
		R = Et	244a	78–79		$(MeI)_2$ (242–244 dec)	433
		R = Pr	244b	47–48 [165–167 (1)]	A[436]	$(MeI)_2$ (267–268 dec)	433
		R = Bu	244c	63–63.5	A[436]	$(MeI)_2$ (255–257 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 has been reported.[214] [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 (**5l**). 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]

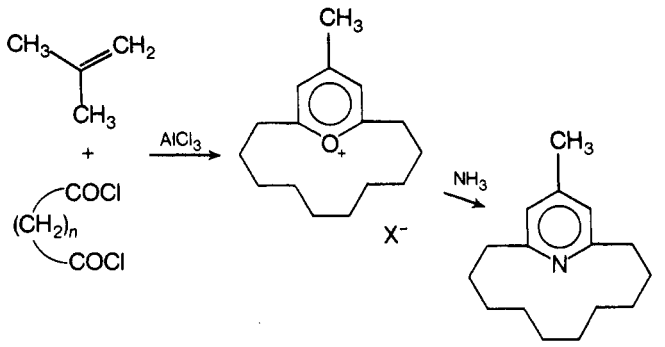


More recently, the one-step construction of racemic muscopyridine has been accomplished via cyclocoupling the di-Grignard of 2-methyl-1,10-dibromodecane with 2,6-dichloropyridine in the presence of a catalytic amount of a nickel–phosphine complex [Ni(dppp)Cl_2].[93] A 20% yield of **5l** was realized 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]



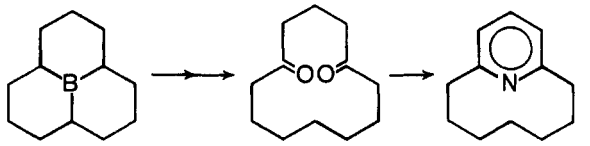
Balaban et al. have utilized a bicyclic pyrylium salt, 4-methyl-2,6-decamethylenepyrylium perchlorate, as a convenient intermediate in a synthesis of an isomer of muscopyridine.[1] These pyrylium salts are prepared by diacylation of isobutene with the corresponding diacyl chloride in nitromethane in the presence of anhydrous aluminum chloride.[301] Treatment of the pyrylium perchlorate with ammonia in *tert*-butyl alcohol[302] gave substituted [10](2,6)pyridinophane (**5k**) in low yield. Several years later, Georgi and Rétey[3] 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]



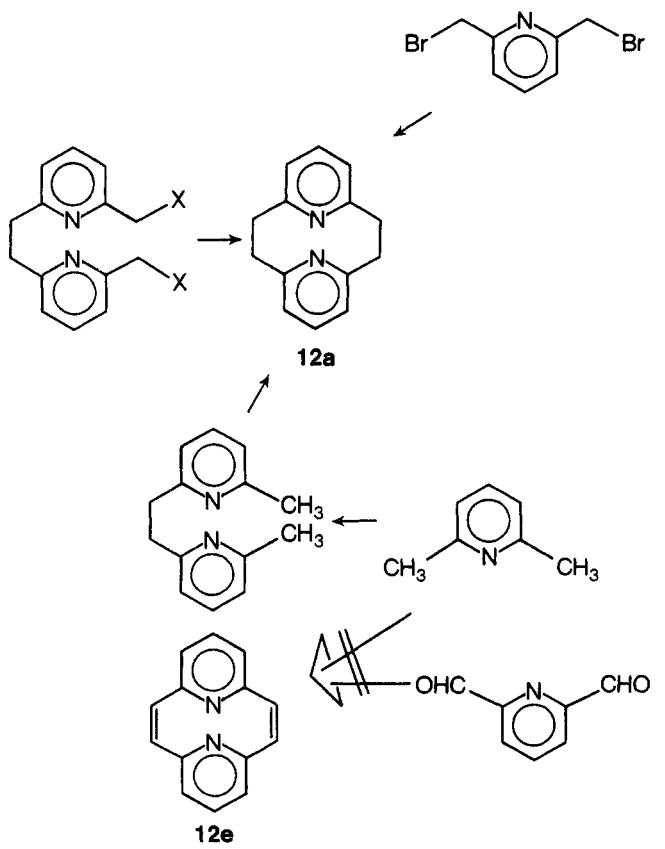
5k

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.



2a

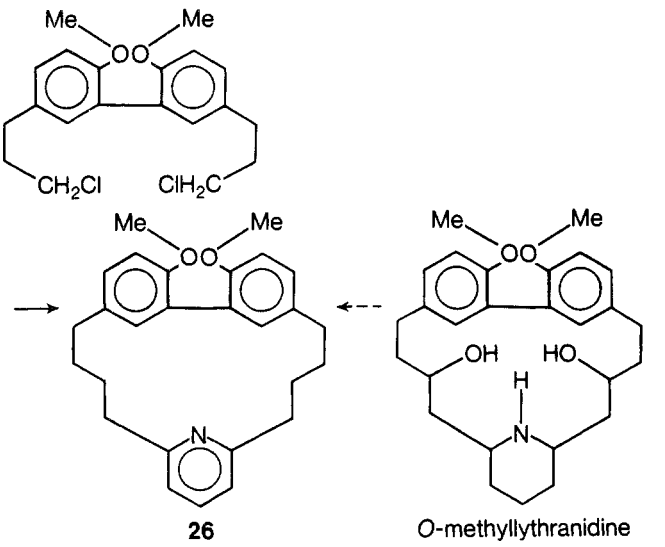
Carbon–carbon σ-bond formation is typically accomplished by reaction of an organometallic reagent with an activated site possessing a good leaving group. After the attempted simple condensation of 2,6-pyridinedicarboxaldehyde with 2,6-dimethylpyridine in the presence of acetic anhydride failed to cyclize 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]



12a

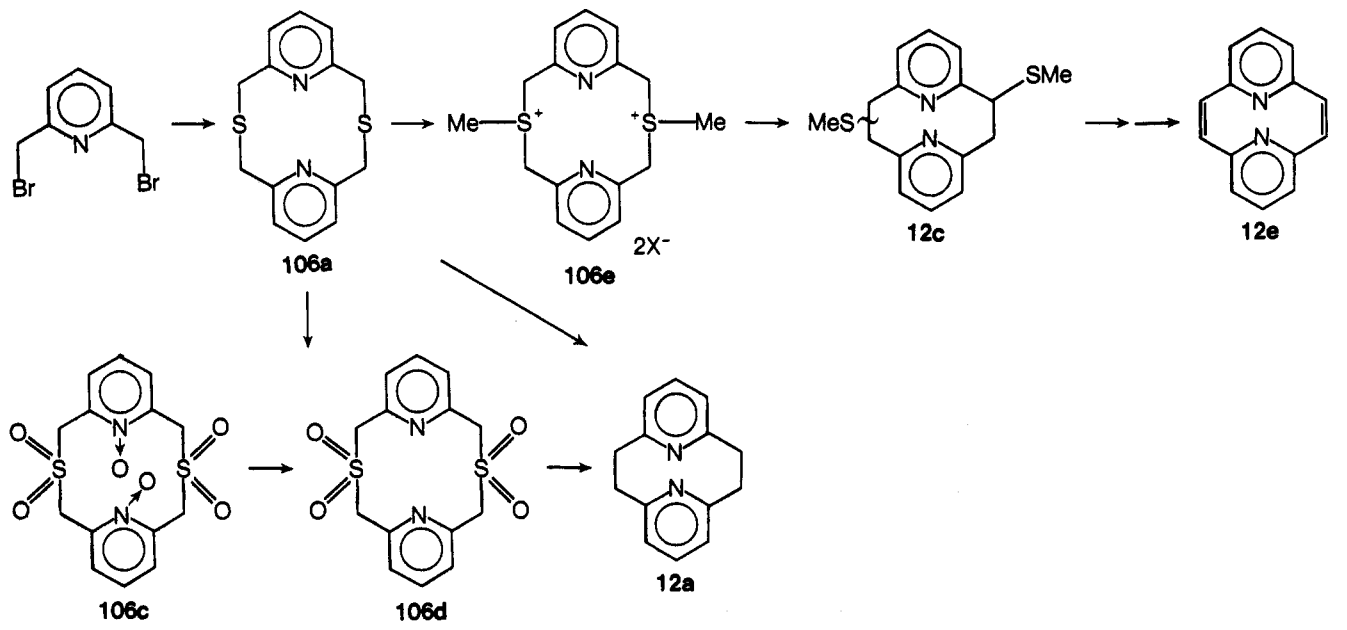
12e

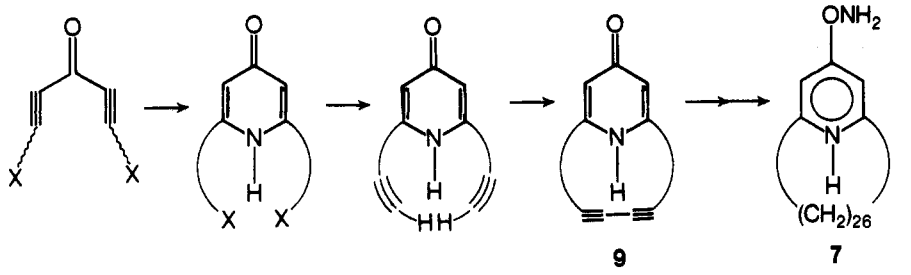
This selective metalation–nucleophilic displacement sequence has been demonstrated in the synthesis of a degradation product from the alkaloid *O*-methyllythranidine (from *Lythrium anceps* Makino, a herb grown in Japan).[306] Condensation of a substituted dichloride with 2,6-lutidine in the presence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



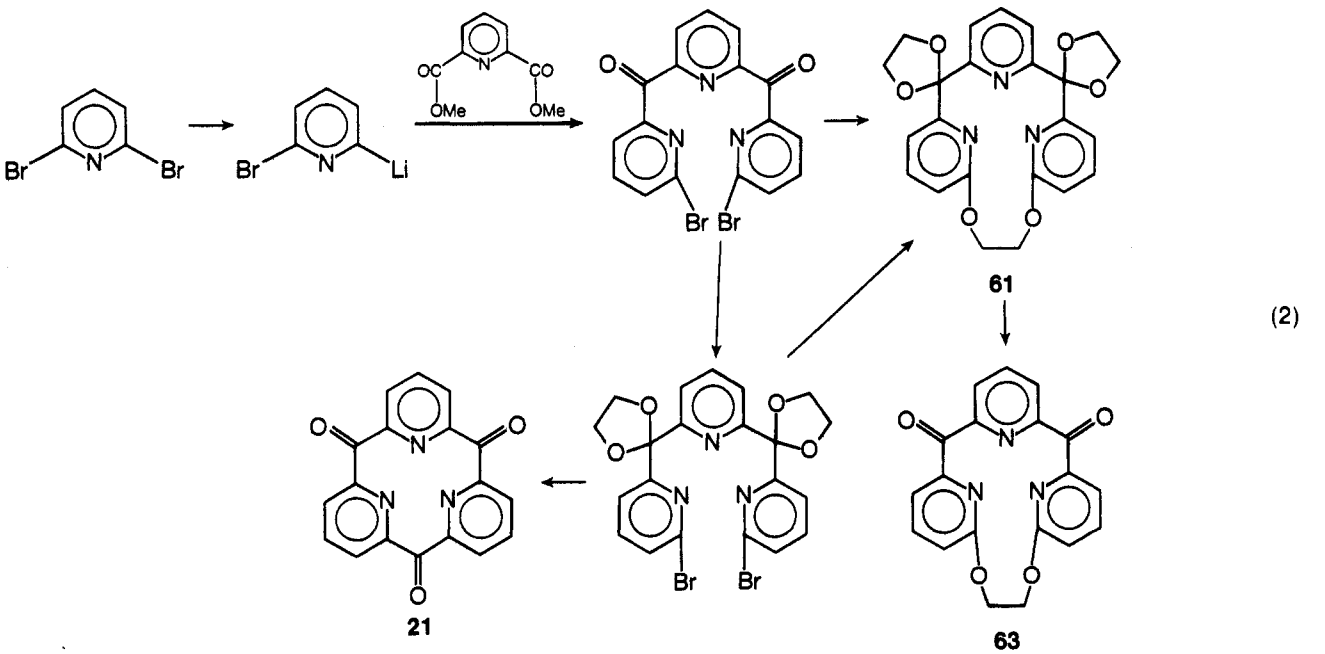
26 *O*-methyllythranidine

Several different syntheses of pyridinophanes from dithiacyclophane 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 Lawson[12] 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)phenoxide, 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 Rasmussen[18] 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-


Br
Br
106a
Me
Me
2X⁻
106e
MeS
SMe
12c
12e
106c
106d
12a


X
X
X
X
H
H
H
ONH2
(CH2)26
9
7

(1)


Br
Br
Br
Li
OC
CO
OMe
OMe
Br Br
61
Br
Br
21
63
21c
21b

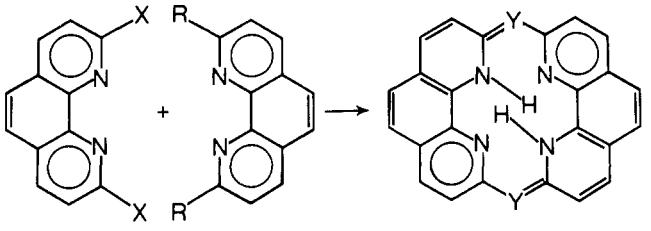
(2)

tion,[307] sulfur dioxide extrusion (procedure 2) under pyrolytic conditions (680 °C/0.01 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 metalated 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 carbonate[309] affording (60%) the diketal along with an unexpected ethereal macrocyclic diketal **61.** Hydrolysis of **61** gave the cyclic diketone **63,** whose PMR spectrum showed an eight-bond long-range *W* coupling between positions 12 and 7(18), thus, indicating the planar nature of this ring system. The dibromo diketal 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]

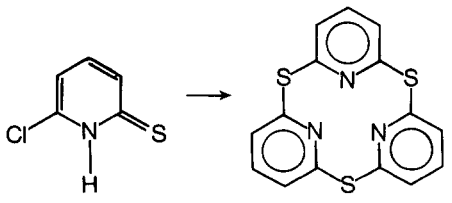
An efficient nontemplate synthesis of the novel carbon-bridged macrocycle **27,** in which the pyridine rings are confined within 1,10-phenanthroline units, was reported by Ogawa, wherein 2,9-dimethyl-1,10-phenanthroline and 2,9-dichloro-1,10-phenanthroline are thermally condensed at 260 °C for 4 h.[308]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



27, Y = CH
28, Y = N

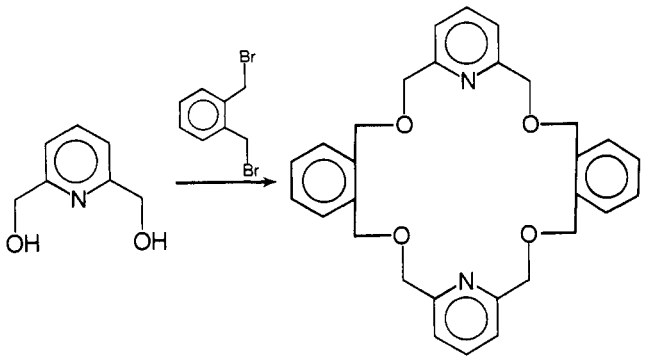
R = CH_3 or NH_2

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 P_2S_5 at 130°.[22] Although no physical data have been cited, an x-ray analysis has established that **29** possesses a nonplanar conformation.[22]

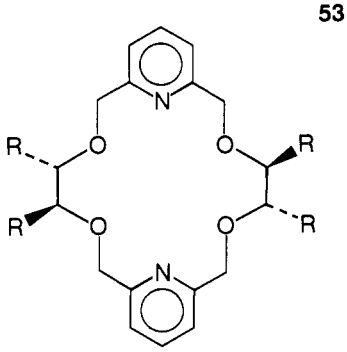


29

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 oligiomers, 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]

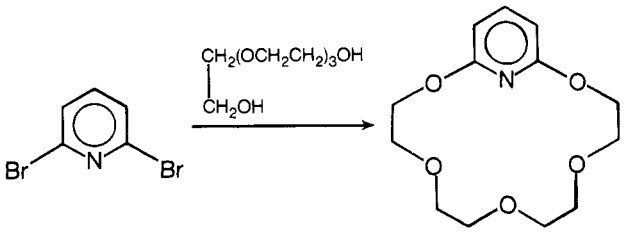


53

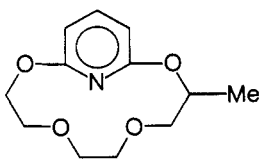


51c, R = $CONMe_2$

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 tetraoxamuscopyridine **32b**[39] as well as various macrocycles which possess other types of subheterocyclic ring(s).



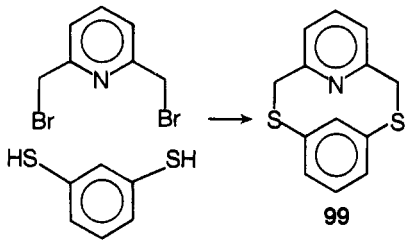
33a



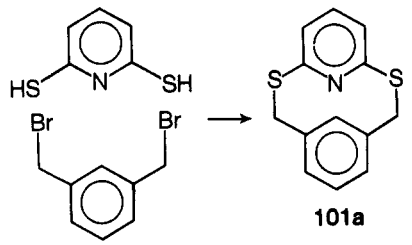
32b

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(mercaptomethyl)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.**

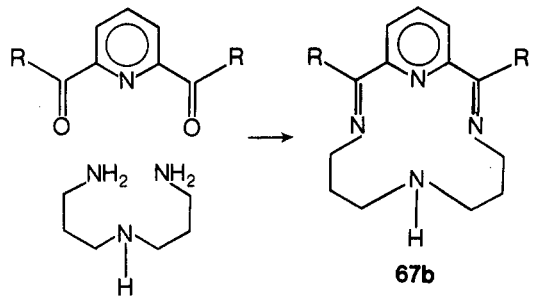


99

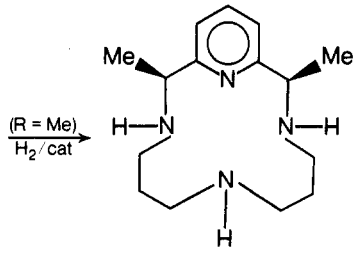


101a

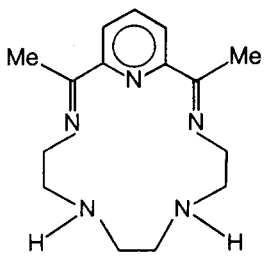
Carbon-nitrogen-bridged pyridine macrocycles generally have been produced by a Schiff-base condensation of either 2,6-pyridinedicarboxaldehyde or 2,6-diacetylpyridine and a substituted bis(primary amine). Curry and Busch reported the first



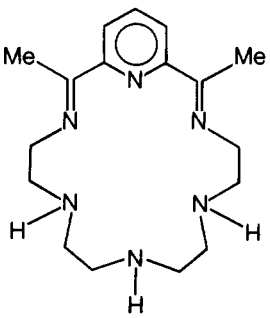
67b



67d (meso)



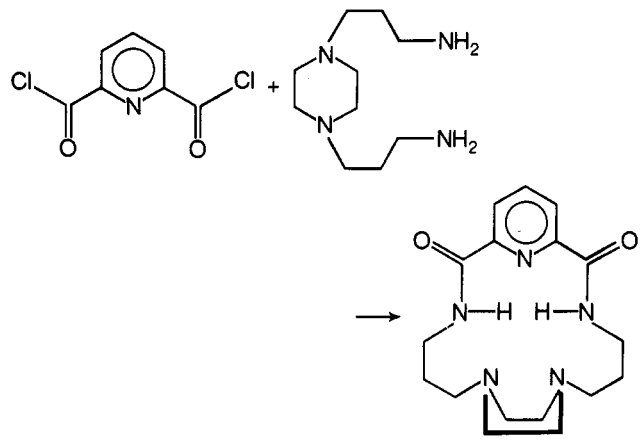
65b



66

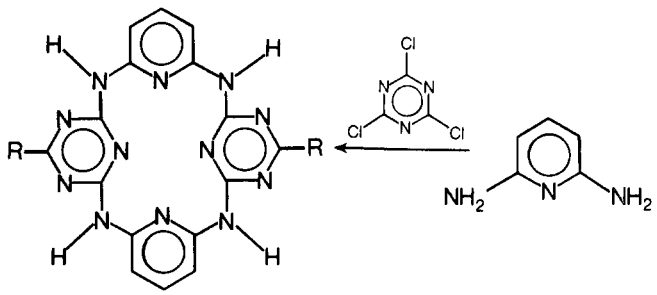
penta- and hexadentate macrocycles (**65b** and **66,** respectively) to be prepared in this series through the utilization of metal ion catalysis.[55] It has been demonstrated that metal ions can cause striking improvements in the formation of macrocyclic products over competing linear polymerization; 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 aza-bridged 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]

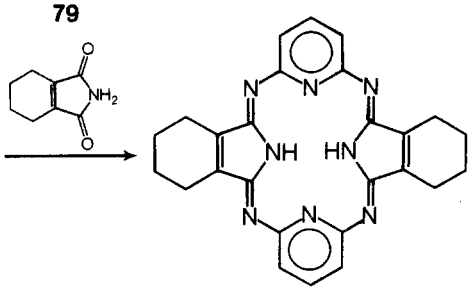


74a

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 dichloride[62] with 2,6-diaminopyridine.



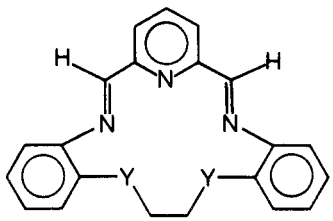
79



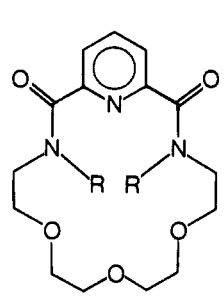
77d

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 Mn^{2+} and Zn^{2+} to the preparation of a series of pen-

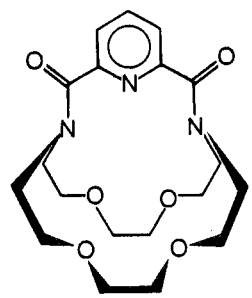
tadentate (N and O or S) macrocyclic ligands, e.g., **110**.[36] The x-ray analysis of the **65c** manganese complex demonstrated that the donor atoms define the five equatorial positions of a distorted pentagonal bipyramid.[36] Vögtle et al. have reacted 2,6-pyridinedicarbonyl chloride with diversified 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]



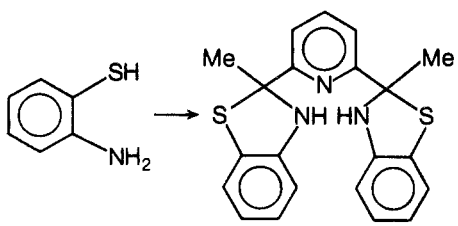
65c, Y = N; **110**, Y = O; **129**, Y = S

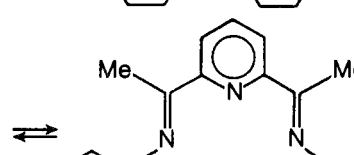


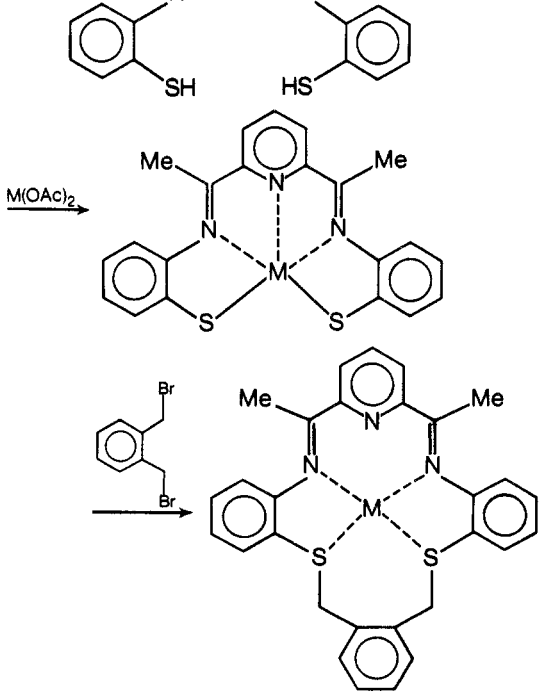
115



111



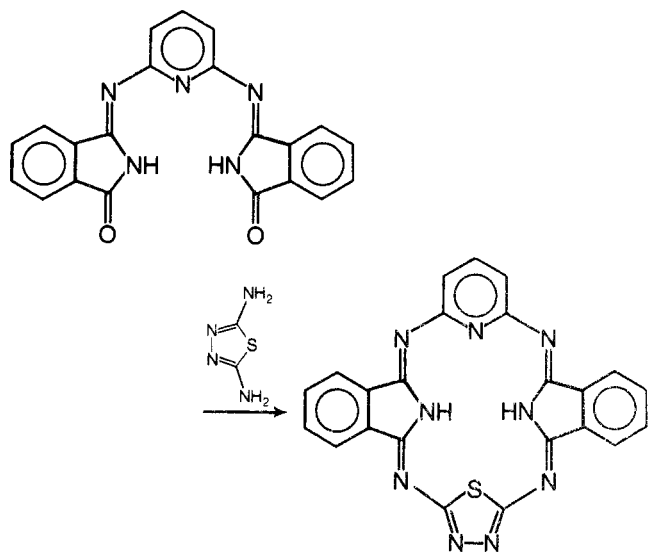




131

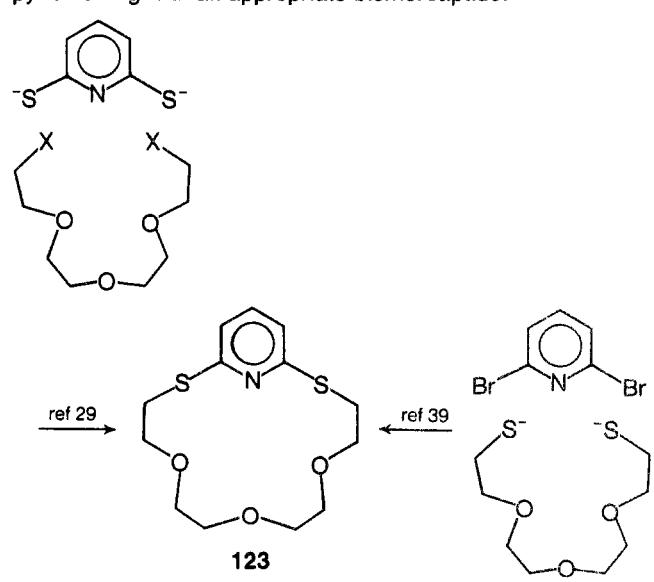
Recently, Londoy[327] and Busch[311] have shown that aldehydes and ketones react with 2-aminobenzenethiol to generate predominately the corresponding benzothiazolines. When 2,6-diacetylpyridine was reacted with 2-aminobenzenethiol, the expected bis(benzothiazoline) was isolated.[276,403] Treatment of 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-iminoisoindolinylidene derivative in boiling butanol for 40 h.[38]



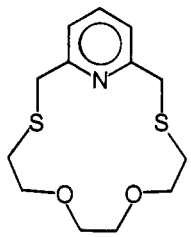
130

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]



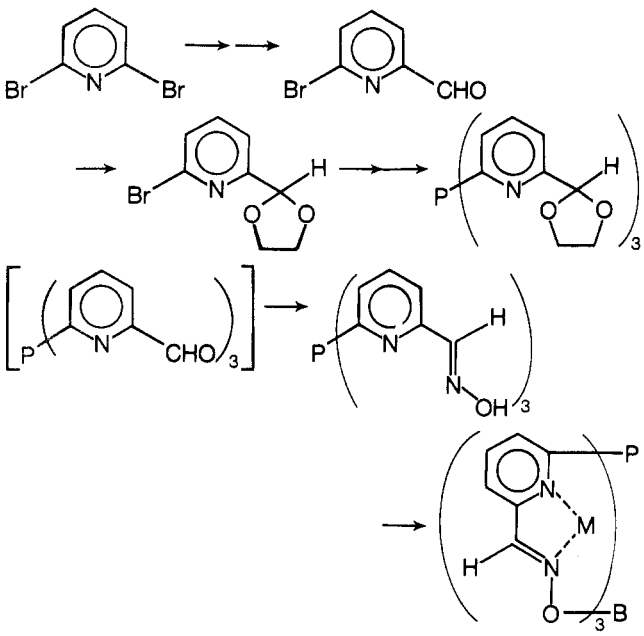
123

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]



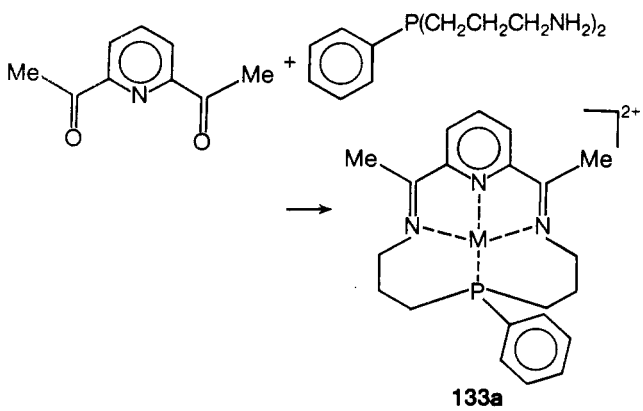
119a

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. Anaerobic 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.



134

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

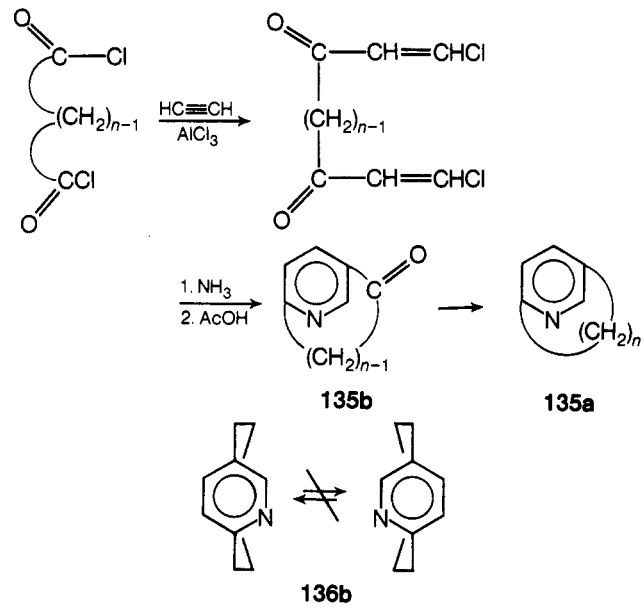


133a

prepared by refluxing an ethanolic solution of 2,6-diacetylpyridine, 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

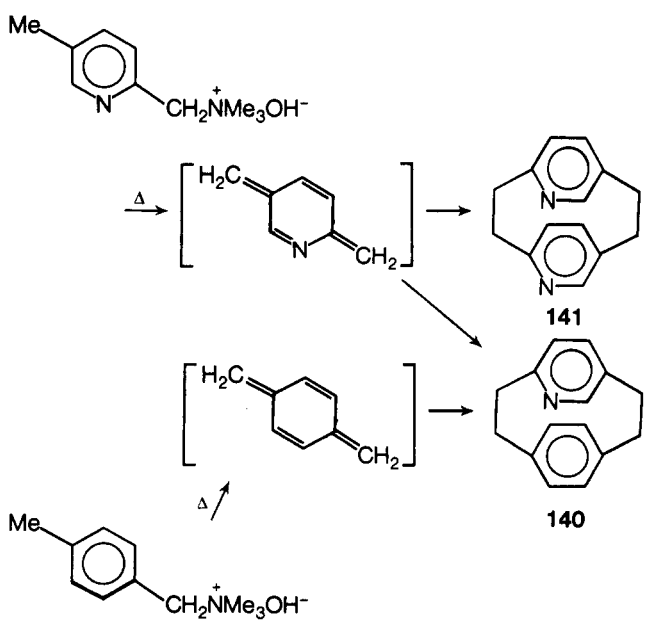
Carbon-bridged [*n*](2,5)pyridinophanes were first constructed by Gerlach and Huber in 1968.[84] In general, bis(β-aminovinyl)diketones were subjected to an acid-catalyzed cyclization generating the [*n*](2,5)pyridinophan-*n*-ones (**135b**), which were converted to the [*n*](2,5)-pyridinophanes by standard 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] (±)-[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]



135b 135a

136b

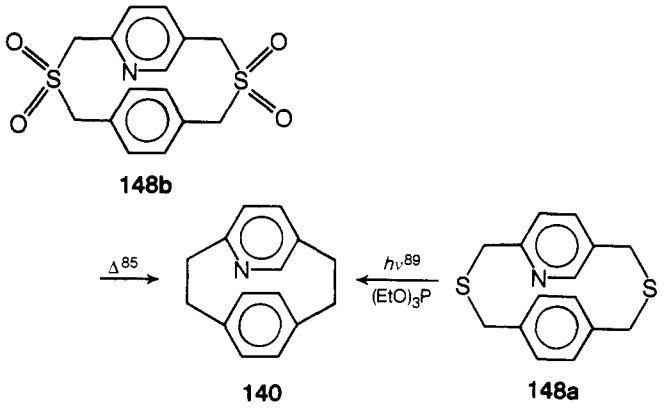
Bruhin and Jenny synthesized [2]paracyclo[2](2,5)pyridinophane by a thermal 1,6-Hofmann elimination from an intimate



141 140

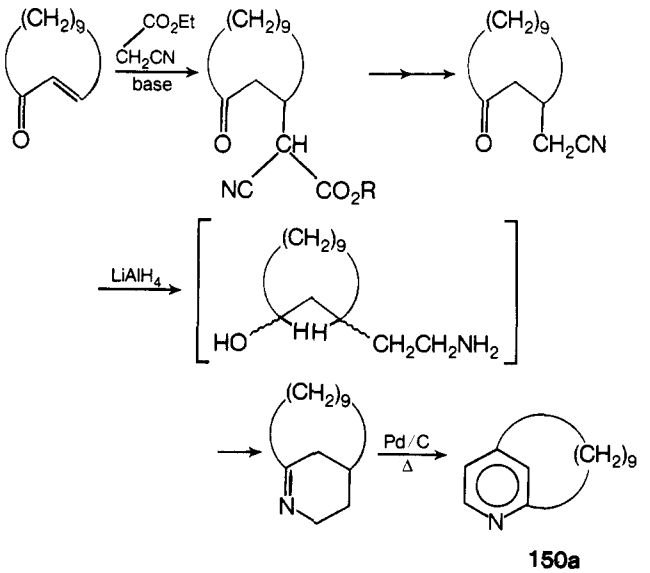
mixture of (4-methylbenzyl)trimethylammonium hydroxide and (5-methyl-2-picolinyl)trimethylammonium hydroxide via the *crossed condensation of the intermediates.*[85] *Isomeric* [2.2]-(2,5)pyridinophanes were also isolated from this reaction[85] as well as from thermolysis of either (2-methyl-5-picolinyl)trimethylammonium 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 Bruhin and Jenny in their quest for **140.** Thermolysis[85] of **148b** prepared by the procedure of Vögtle,[328] or the photolysis[89] of **148a** in the presence of triethyl phosphite gave the desired [2]paracyclo[2](2,5)pyridinophane (**140**).

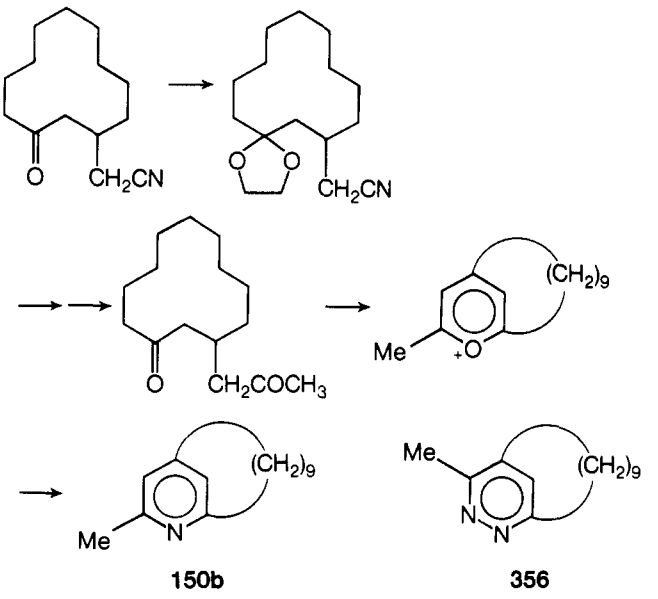


3. 2,4-Pyridino

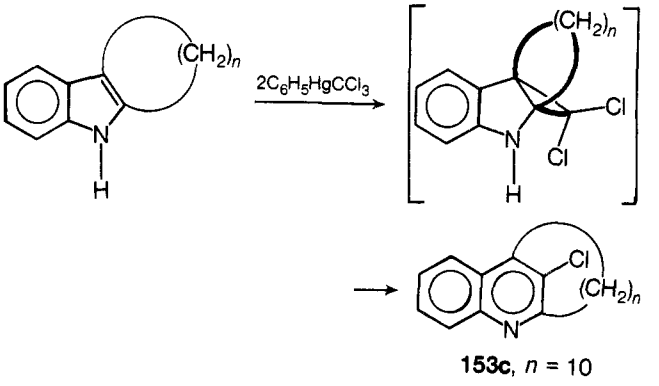
The *carbon-bridged* [9](2,4)pyridinophane was first synthesized by Italian workers[107] from 2-cyclododecenone by initial treatment with ethyl cyanoacetate under Michael conditions. The resultant cyano keto ester was hydrolyzed under alkaline conditions and subsequently decarboxylated to the γ-cyano 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]



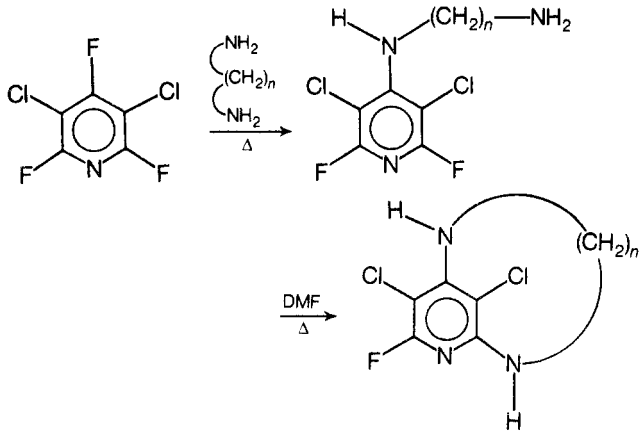
An alternate approach to substituted [9](2,4)pyridinophanes is via the corresponding pyrylophanium salt.[106] 3-Cyanomethylcyclododecanone[107] was ketalized under standard conditions and treated with methylmagnesium bromide in tetrahydrofuran; *upon hydrolysis, the 3-acetonylcyclododecanone was isolated.* Reaction of this diketone with trityl perchlorate in boiling acetic acid afforded the 12-methyl[9](2,4)pyrylophanium perchlorate, which upon treatment with ammonium acetate gave **150b** in 80% yield. When the intermediary pyrylophanium 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]



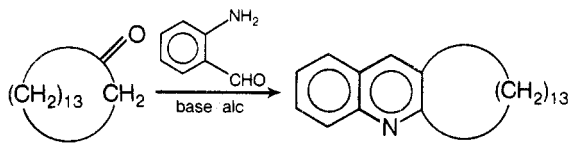
The only *carbon–nitrogen-bridged* (2,4)pyridinophane was recently synthesized by Wakefield et al.,[131] when 3,5-dichlorotrifluoropyridine was treated with an appropriate long-chained (9 or 12 carbon atoms) primary diamine. The intermediate diamines can be isolated, and, when subjected to heating in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



156, $n = 9$
157, $n = 12$

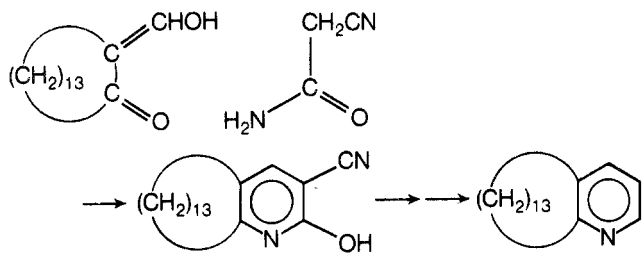
4. 2,3-Pyridino

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]



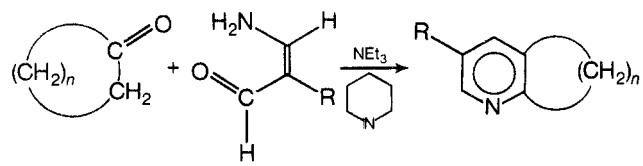
163a

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.

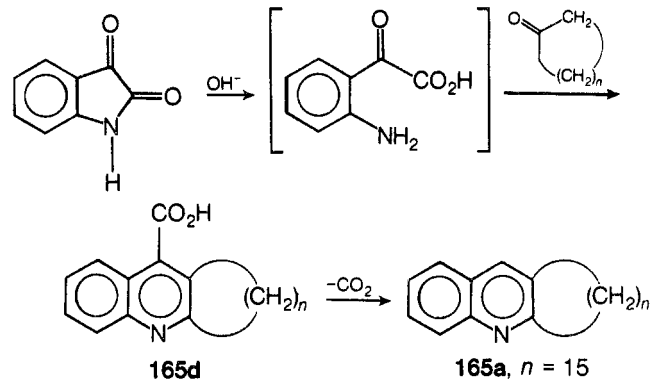


159d **159a**

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-polymethylenepyridines.

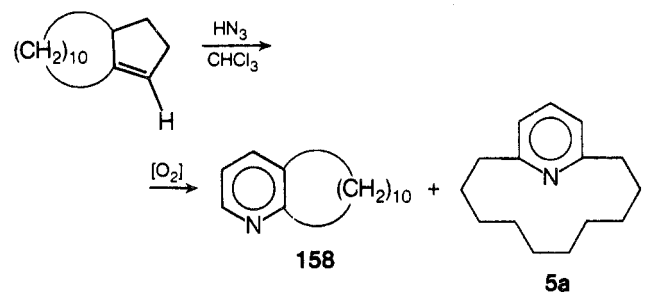


The classic Pfitzinger condensation[335,336] has been utilized by Buu-Hoï et al. to synthesize 2,3-polymethylenequinolines.[120,121,123,124,337] The condensation of isatin with cycloheptadecanone (dihydrocivetone) gave **165d,** which subsequently was decarboxylated to afford **165a.** Remote unsaturation within the macrocyclic ring **165a** can also be achieved via this condensation reaction through the use of the appropriate unsaturated cyclic ketone.[123,124]



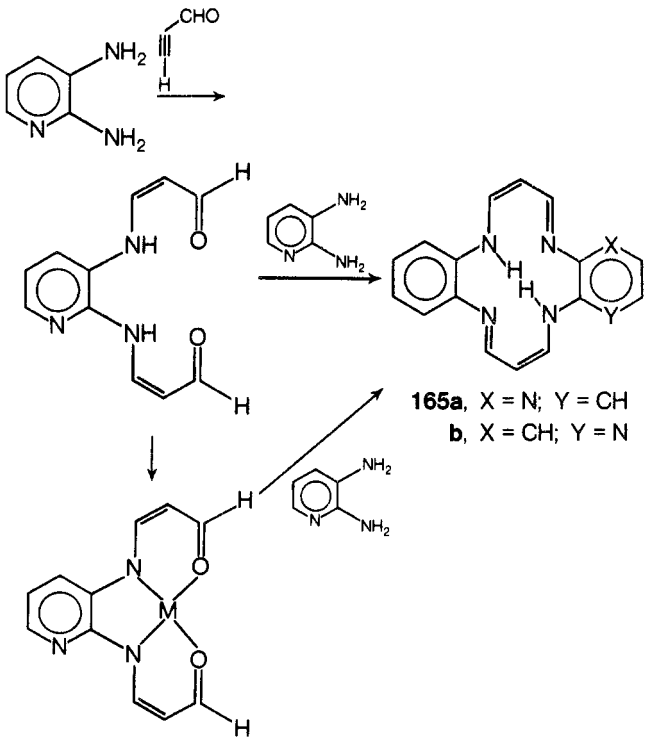
165d **165a**, $n = 15$

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]



158 **5a**

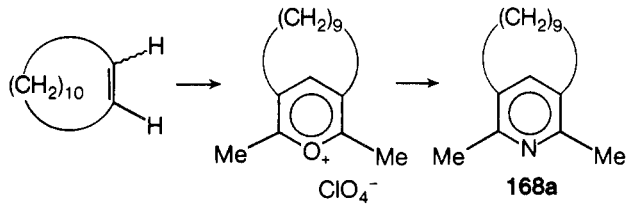
Carbon–nitrogen 2,3-pyridino macrocycles were prepared by Müller and Wöhrle from 2,3-diaminopyridine and propynal in a 1:1 ratio with or without the aid of a metal ion template.[126] The reaction proceeded through an intermediate (complex) and then cyclized to the 14-membered macrocycles **167a** or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



165a, X = N; Y = CH
b, X = CH; Y = N

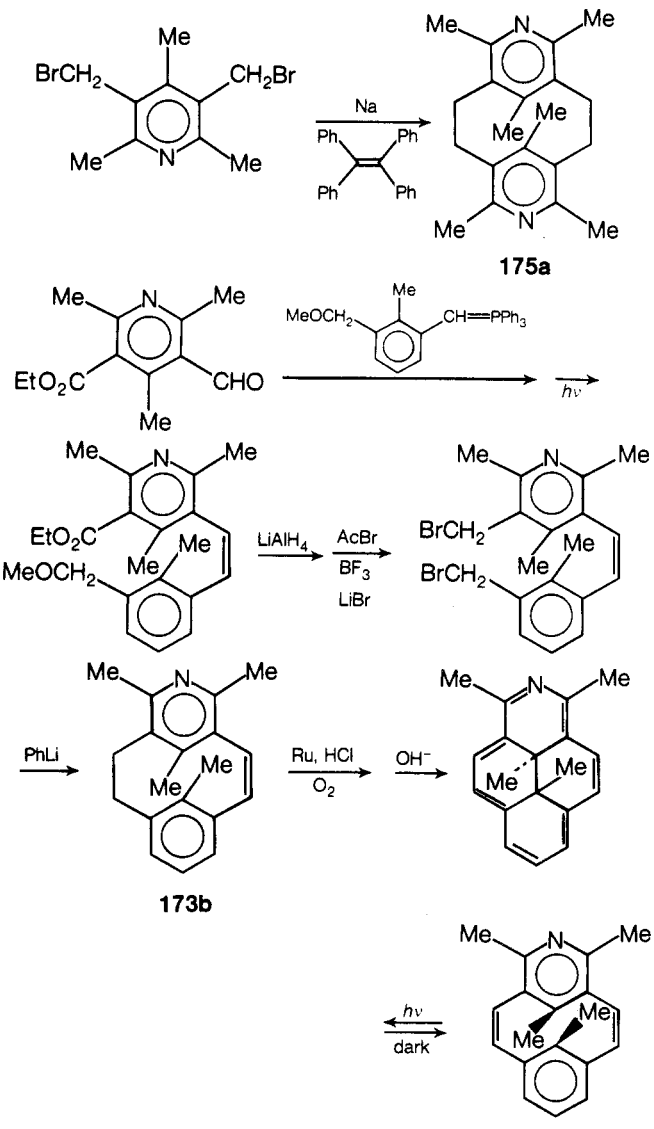
5. 3,5-Pyridino

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.[72]

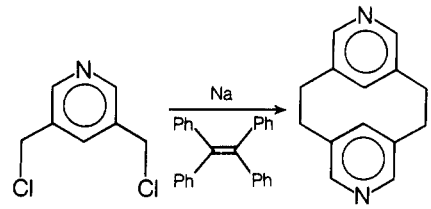


168a

Boekelheide and Pepperdine 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-methylbenzyl)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 metacyclophane-1,9-diene (**173a**) was a facile process; however, a dark thermal isomerization has been shown to be an equally rapid reaction ($K_{1/2}^{MeOH}$ = 8 s at 17 °C).[73]

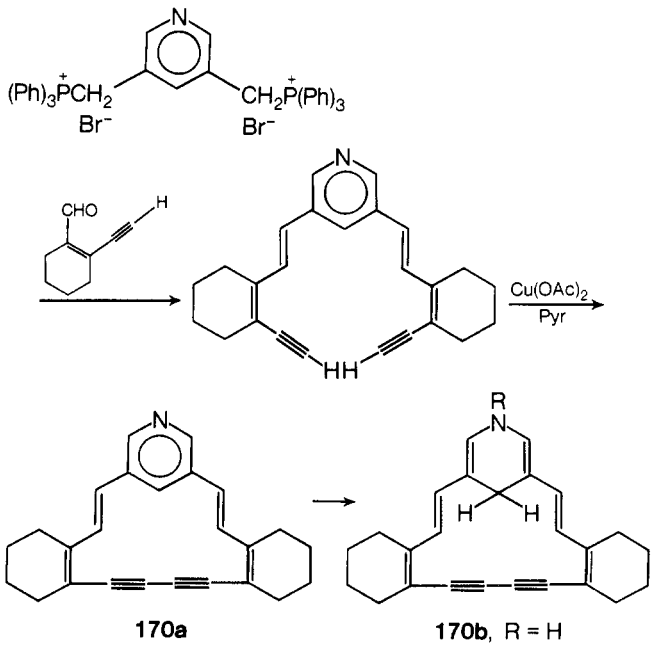


Jenny and Holzrichter synthesized [2.2](3,5)pyridinophane (**174**) in a manner analogous to that presented in their previous papers specifically via the reaction of 3,5-bis(chloromethyl)-pyridine with sodium in the presence of tetraphenylethylene.[81,82] Not only was the [2.2] member isolated (2%),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



174

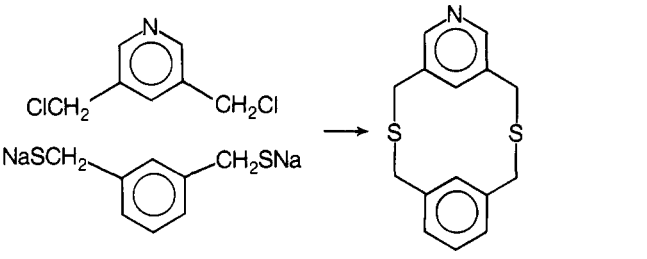
Sondheimer et al. in a series of elegant papers have described the synthesis of several new aromatic macrocyclic heteroannulenes.[75-80] The general mode of construction can be demonstrated by the synthesis of **170b.**[75] The di-Wittig reagent prepared from 3,5-bis(bromomethyl)pyridine was reacted 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



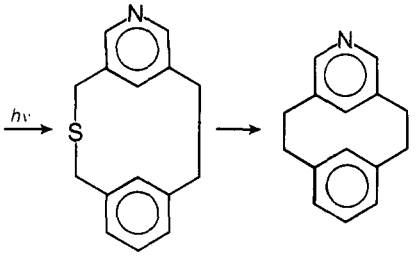
170a **170b**, R = H

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]

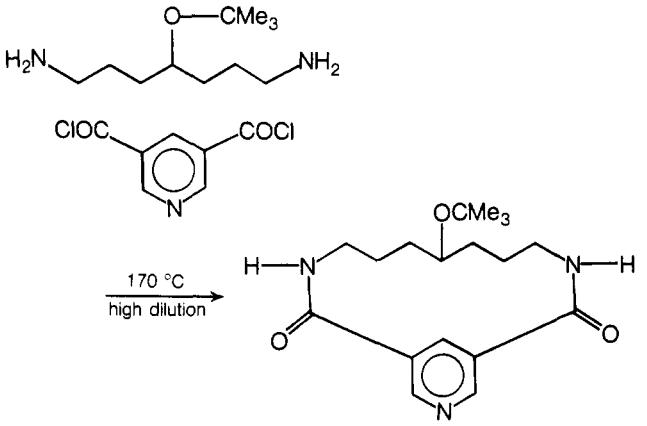


180



179 **173c**

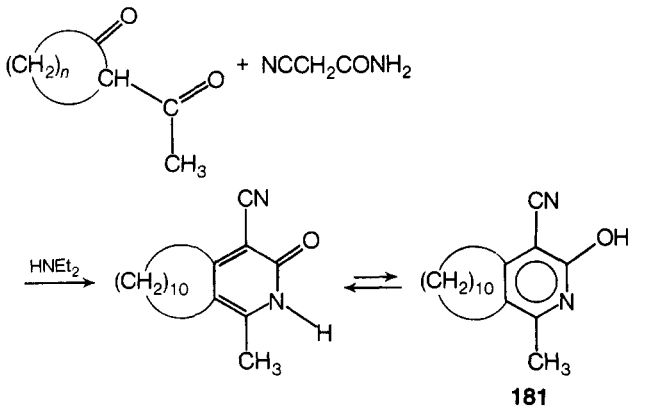
Carbon–nitrogen 3,5-pyridino macrocycle **178c** was synthesized by Overman[83] via a high-dilution cyclization of 3,5-pyridinedicarbonyl chloride and a substituted diamine,[493] following the procedure of Stetter.[339]



178c

6. 3,4-Pyridino

Freeman and Ito have reported the simple conversion of 2-acylcyclanones into substituted 5*H*-2-pyridines, as well as 3,4-polymethylene pyridines.[125] The reaction of 2-acetylcyclododecanone with 2-cyanoacetamide in the presence of diethylamine gave (50%) macrocycle **181.** The functionality can be removed by literature procedures.[340]



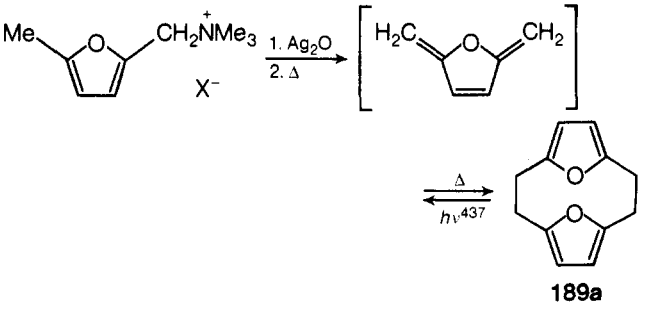
181

B. Furan as the Subunit

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

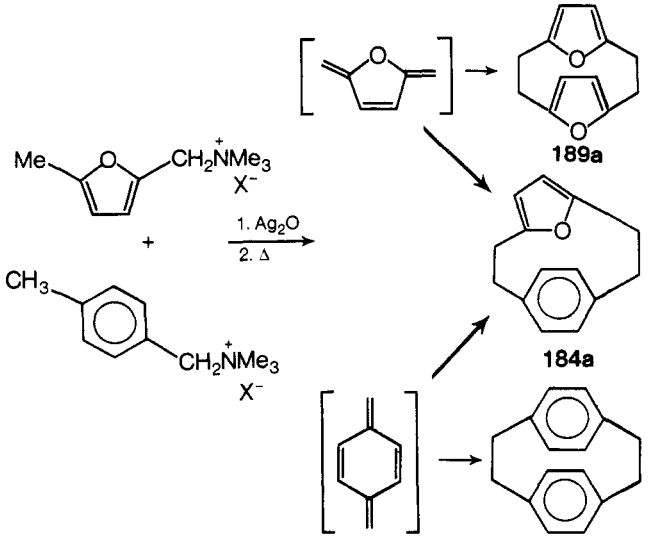
1. 2,5-Furano

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-furfuryl)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 Winberg[186] 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]



189a

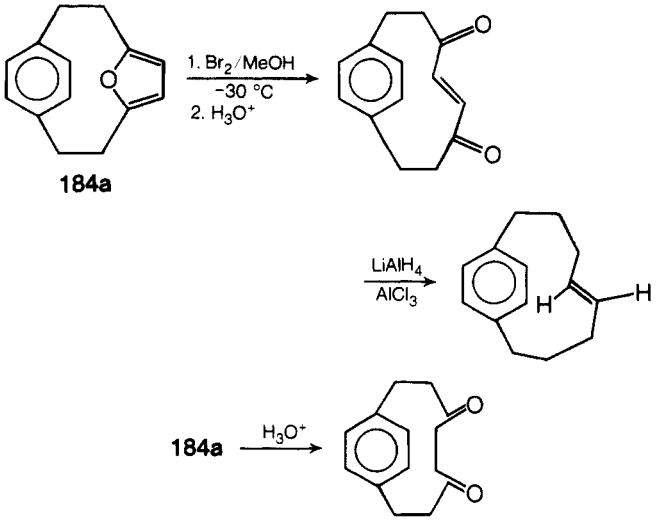
Cross-cycloadditions of 2,5-dimethylene-2,5-dihydrofuran with numerous other reactive trienes or tetraenes have been reported. These 1,6 to 1,6 cycloaddition reactions have afforded a vast array of mixed cyclophanes: [2.2](2,5)furanoparacyclo-



189a **184a**

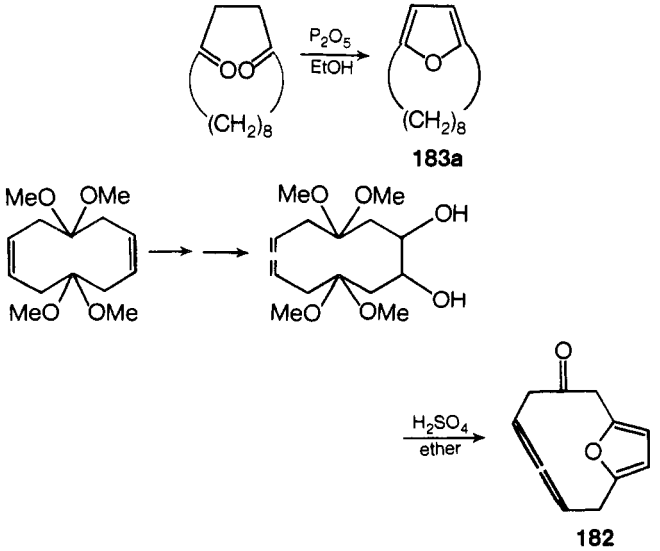
phanes,[178,180,181,184] [2.2](2,5)furano(1,4)naphthalenophanes,[184,189] [2.2](2,5)furano(9,10)anthracenophane,[190] [2.2](2,5)furano(1,4)anthracenophane,[191] and multilayered furanophanes.[188,217,259,485,486]

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 Pawson[179] utilized the procedure of Cram and Knox[180] 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).



184a

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 oxaquadricyclane.[260]

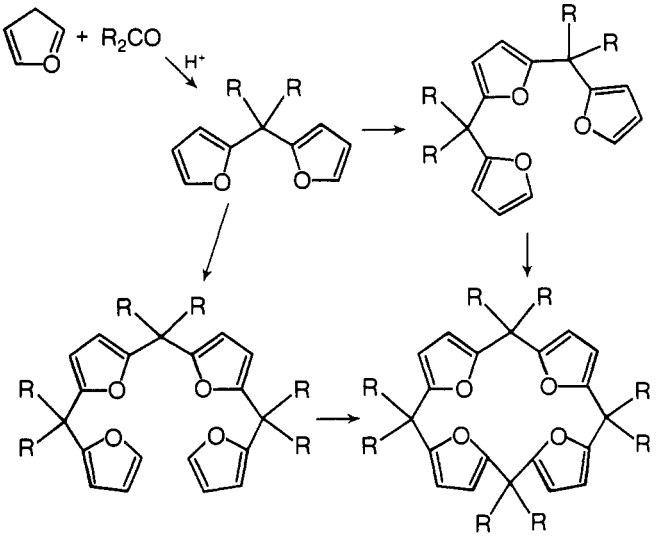


183a

182

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]

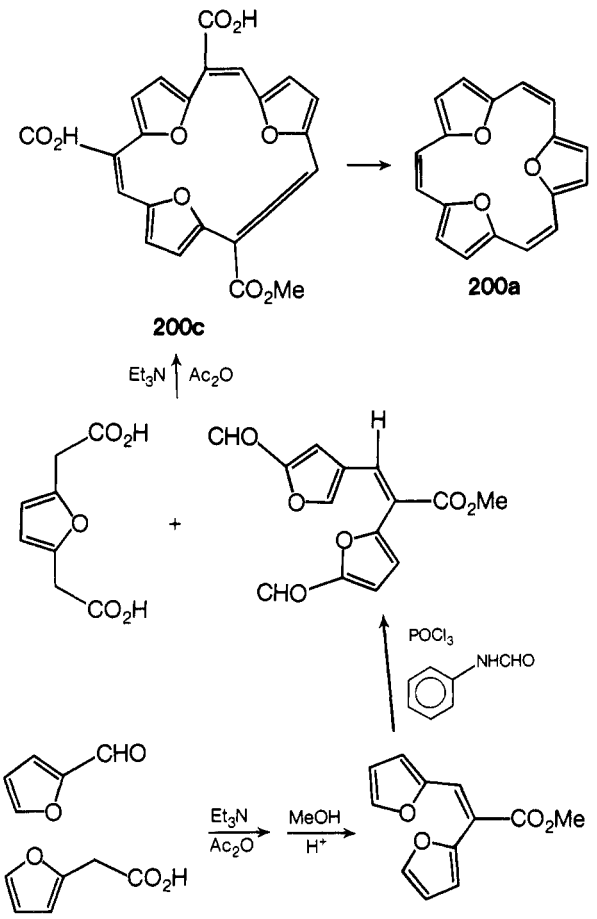
One of the largest classes of furan-containing macrocycles is that of "tetraoxaquaterene". ["Quaterene" denotes a macrocycle composed of four methylene-bridged 1,4-disubstituted cyclopentadienes.][169] The 16-membered macrocycle **204** was synthesized in low yield by simple acid-catalyzed condensation 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]



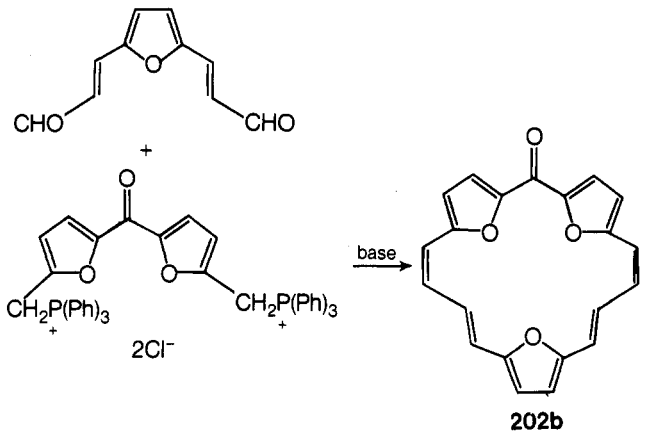
204

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-formal-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-



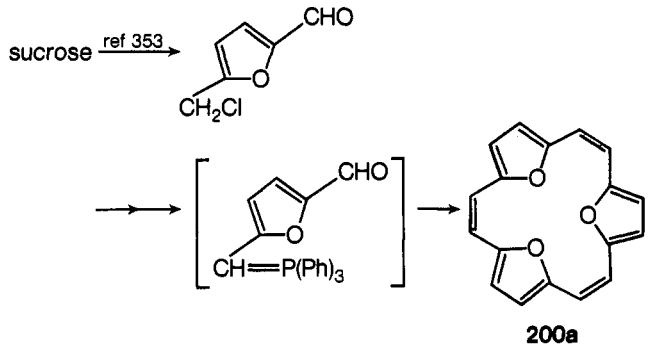
thesis of the parent annulene structure, is via bis-Wittig reagents (reviewed in ref 351). A typical illustration of this cyclization was reported for the Wittig reaction of a diacrolein[352] with an appropriate bis-phosphonium salt[162] in the presence of lithium ethoxide to afford (15%) annulenone **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).



202b

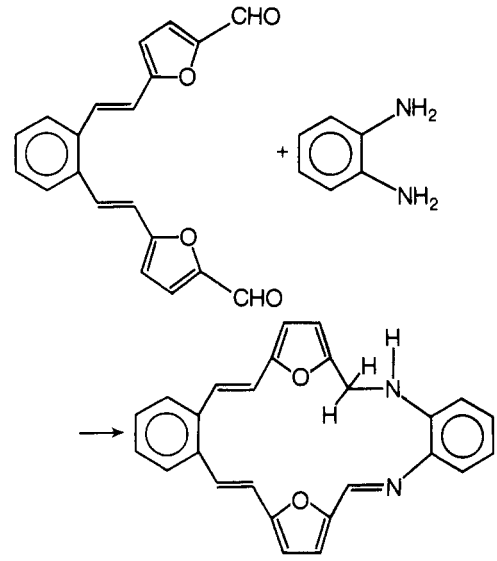
Elix has reported a synthesis of annulenes from sucrose[148] via an appropriately substituted Wittig reagent prepared from 5-chloromethyl-2-furfural.[353] The slow addition of lithium ethoxide to this phosphonium salt in dimethylformamide resulted in an intermolecular cyclocondensation to give (0.07%) 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, Saikachi et al. prepared several novel *carbon–nitrogen-bridged* furan macrocycles.[174] When di-*trans*-1,2-bis[β-(5′-formyl-2′-

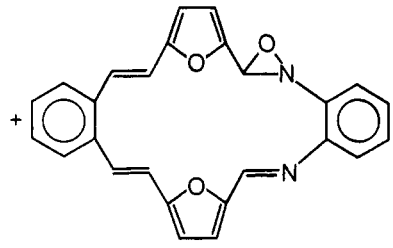


200a

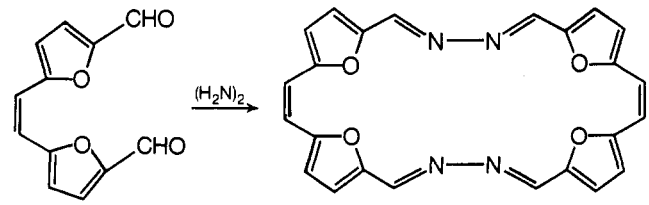
furyl)vinyl]benzene was condensed with *o*-phenylenediamine, the expected annelated diaza[20]annulene dioxide was not formed but rather **218c, 218b,** and **218a** were isolated in 15, 1, and 15.7%, respectively. However, when *cis*-α,β-bis(5′-formyl-2′-furyl)ethylene was reacted with hydrazine, the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



218c



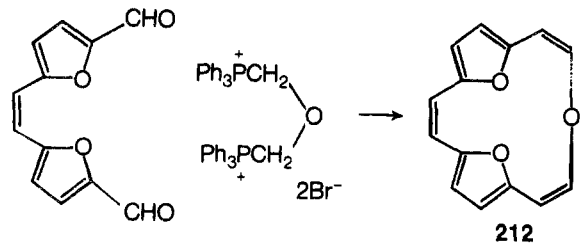
218a + 218b



219

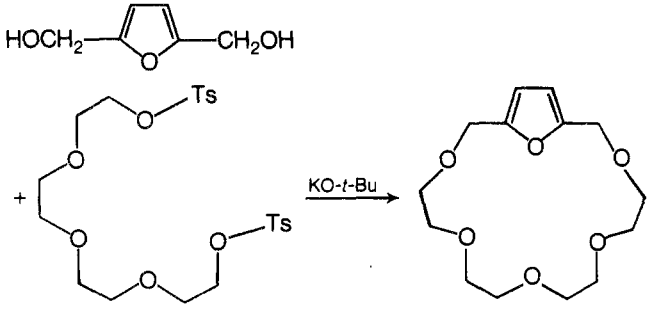
Several *carbon–oxygen-bridged* furan macrocycles have been reported. Ogawa et al.[140,144] prepared hetero[15]annulenone **212** by the Wittig reaction of a known dialdehyde[174] and (dimethyl ether)-α,α′-bis(triphenylphosphonium bromide)[354] with lithium methoxide. Spectral data have excluded the 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-



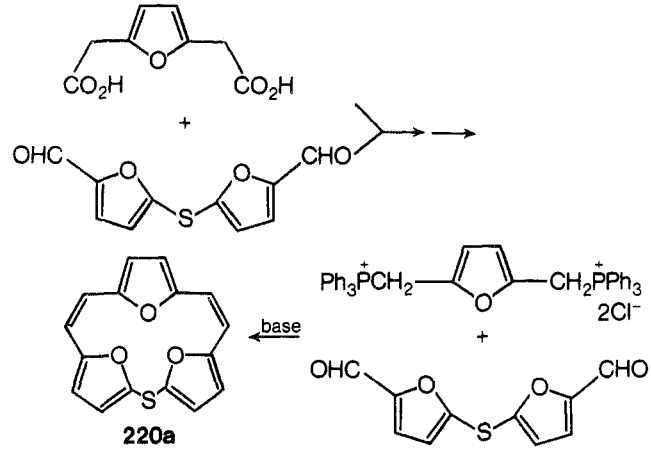
212

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]



209

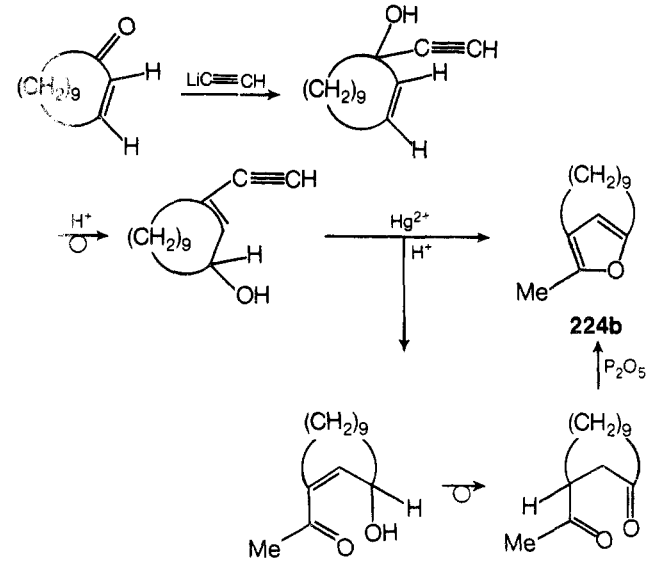
The *carbon–sulfur-bridged* furan macrocycle related to **220a** has been prepared by a Perkin condensation of a known dialdehyde[355] with furan-2,5-diacetic acid,[356] followed by decarboxylation to afford only traces of the thia[17]annulene (**220a**).[161] However, when the same dialdehyde was reacted 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]



220a

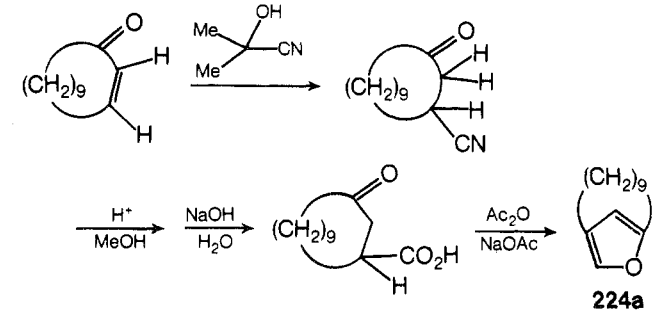
2. 2,4-Furano

Carbon-bridged furanophanes have been prepared by two similar procedures. When a mixture of *cis- and trans*-2-cyclododecenone[358] 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]



224b

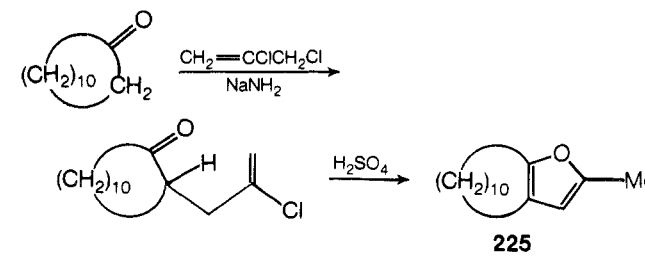
The unsubstituted [9](2,4)furanophane was prepared[205] from the same cyclododecen-2-one by initial treatment with acetone cyanohydrin in aqueous alcohol in the presence of sodium carbonate to afford 3-cyanocyclododecanone. Direct conversion of the nitrile to the methyl ester was accomplished by treatment 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.



224a

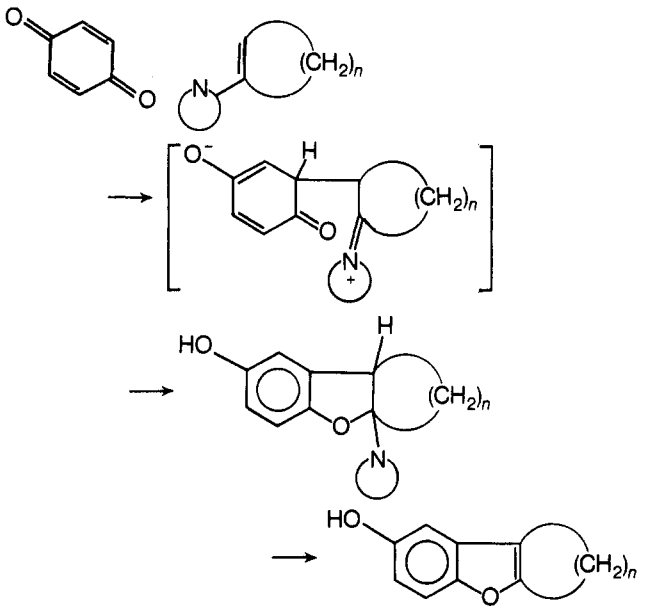
3. 2,3-Furano

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.

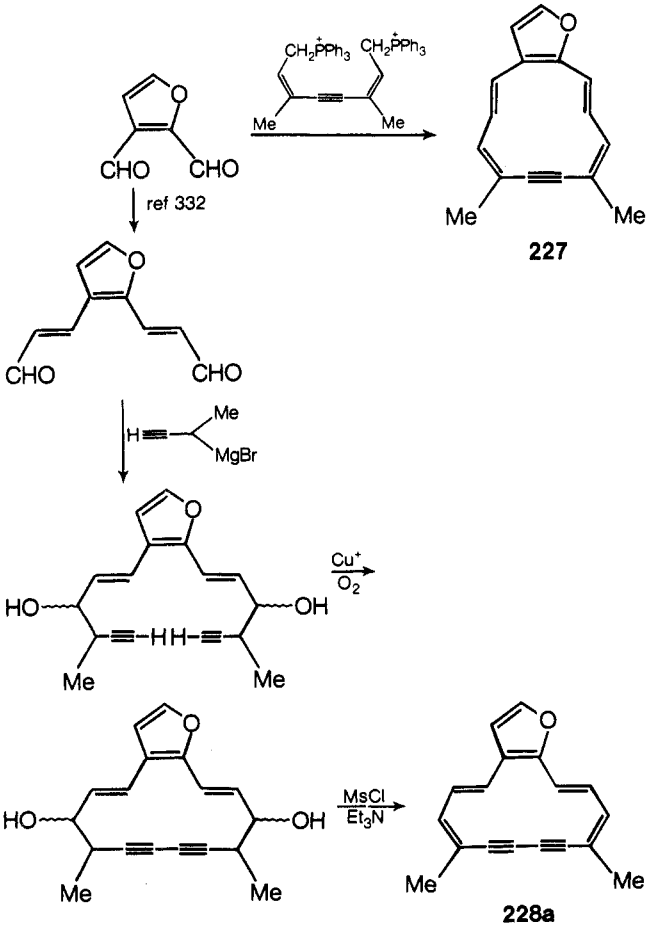


225

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: $-CH_2OH \rightarrow -CH_2Br \rightarrow -CH_2P^+(Ph)_3Br$] 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]annulene[209] **228a** was synthesized from the same dialdehyde by initial conversion[352] to the bisvinylogue, 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]

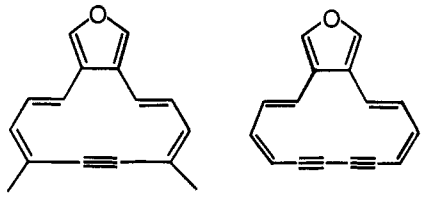


227

228a

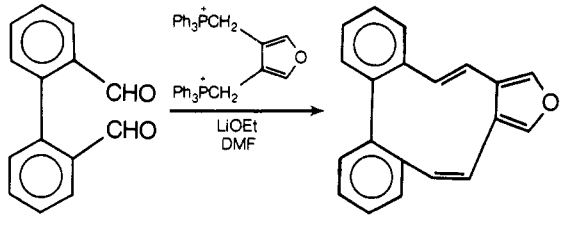
4. 3,4-Furano

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]

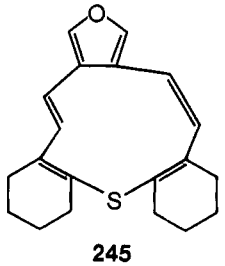


230 **231a**

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 letter[207] 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 paper[214] 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]



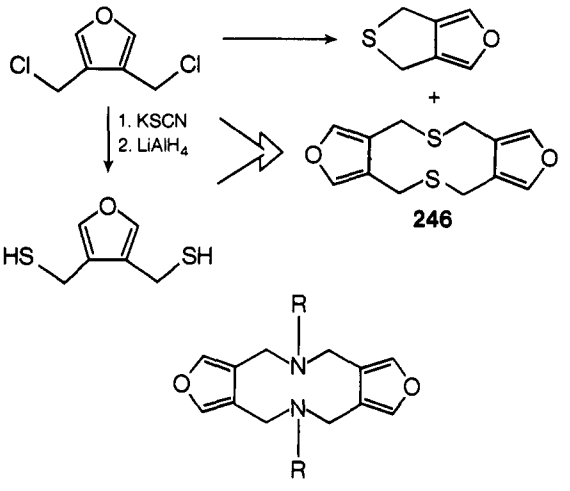
229a



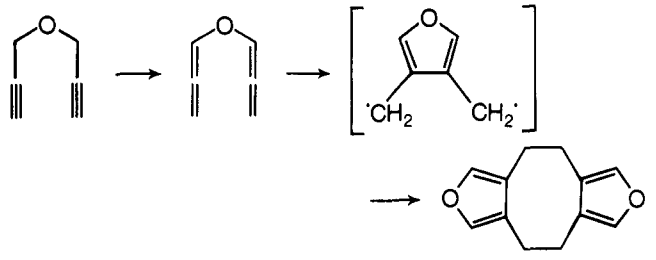
245

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

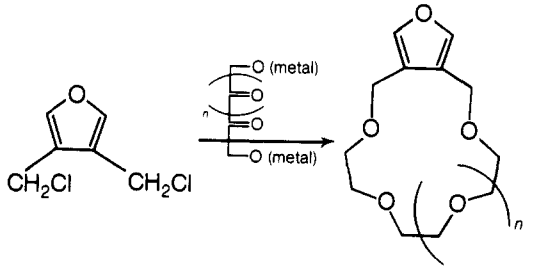
yield.[435] The same macrocycle **246** was obtained from the reaction of 3,4-bis(chloromethyl)furan and 3,4-bis(mercaptomethyl)furan.[435] The corresponding *carbon–nitrogen-bridged* analog **244** was prepared from 3,4-bis(chloromethyl)furan and a primary amine.[433,436]



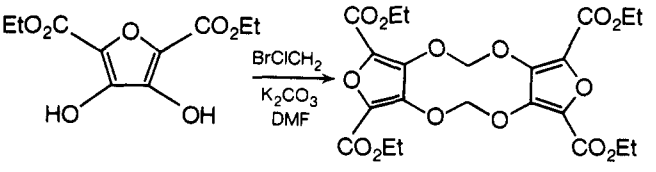
Treatment of dipropargyl ether with freshly prepared potassium *tert*-butoxide in *tert*-butyl alcohol at 0 °C led to the formation of bisfuranocyclooctadiene, the intermediacy of a diallenyl ether, and then diradical; macrocyclic products were not reported, however, as expected.[453]



Only a limited number of *carbon–oxygen-bridged* 3,4-furano macrocycles has been reported. Recently, Reinhoudt 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]



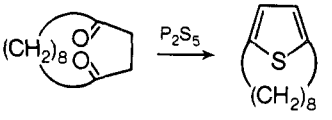
234

C. Thiophene as the Subunit

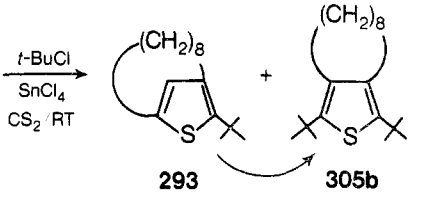
Macrocycles possessing only the thiophene subunit are tabulated in Table III. Certain limited aspects of thiophene macrocycles have been reviewed.[298,367,375] Several of the procedures utilized in the synthesis of furan-containing macrocycles have also been applied to construction of the thiophene analogs; 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 $SnCl_4$ 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!

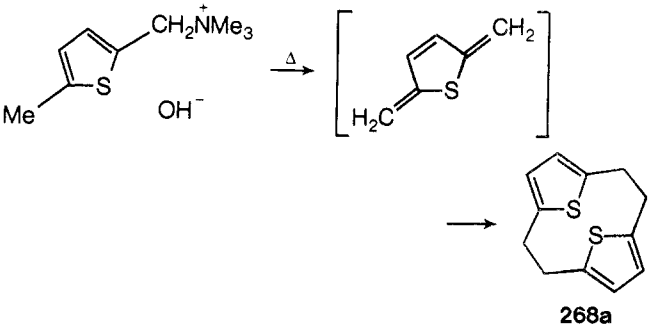


247a



293 305b

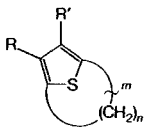
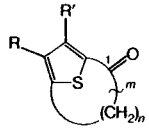
Thiophenophanes can be prepared in low yield by the procedure of Winberg et al., in which (5-methyl-2-thienyl)trimethylammonium hydroxide was pyrolyzed at 150 °C.[186] The 2,5-dimethylene-2,5-dihydrothiophene intermediate was not isolated in this reaction; however, it has been isolated (at liquid nitrogen temperatures) from the pyrolysis of 2-ethyl-5-methylthiophene at 825 °C[372] and has been shown to undergo spontaneous polymerization. The x-ray analysis of the 1:1 adduct of benzotrifuroxan 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]

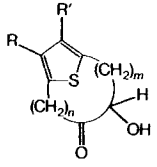


268a

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.

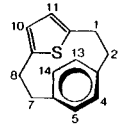
TABLE III. Macrocycles Containing the Thiophene Subunit[a]

Compound	Double bond position	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Complexes(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*-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*-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-CO_2Et	**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–Et;2-CO_2Et	**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-CO_2Et	**255b**	[160 (0.15)]; 52.8–55		n^{20}D 1.5360	251, 367
		$m = 1; n = 12$; 2-Me; 2-CO_2Et	**255c**	53–55			256

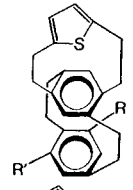


m = 1; n = 12; 2-Et; 2-CO_2Et	**255d**	65–66			256
m = 1; n = 12; 2-C_3H_7; 2-CO_2Et	**255e**	82–83.5			256
m = 2; n = 5; R = R′ = H	**256**	[180–200.5 (10^{-5})], 142–143.5	C		233, 234, 252, 367
m = 2; n = 6; R = R′ = H	**257**	[120–180 (0.005)]; 107.8–109.3	C		234, 367
m = 2; n = 7; R = R′ = H	**258**	[150–200 (10^{-5})]; 97–98	C		234, 367
m = 2; n = 8; R = R′ = H	**259a**	[150–200 (10^{-5})]; 83.5–85	C	Semicarbazone (mp 191.5–193.5°)	233, 234, 252, 367
m = 2; n = 8; R = R′ = H; 2,15-$(CO_2Et)_2$	**259b**	132.5–134			251, 261, 367
m = 2; n = 9; R = R′ = H	**260**	[180–200 (10^{-5}–10^{-6})]; 102–104			233, 234, 236, 252, 261
m = 2; n = 10; R = R′ = H; 2,17-$(CO_2Et)_2$	**261**				240, 261
m = 3; n = 5; R = R′ = H	**262**	89–90.5	C		234, 367

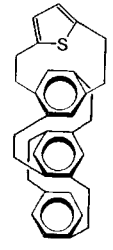
m, n = 4; R = H	**263a**	[169–178 (1)]; 69.5–71		Positive test with Bi_2O_3	249, 252, 367
m = n = 4; R = R′ = Me	**263b**	117–119		Positive test with Bi_2O_3	249, 367
m = 5; n = 4; R = H	**264**	[167–169 (0.3)]; 62–64		Positive test with Bi_2O_3	249, 367



H	**265a**	230–231 (sealed tube)	A, C		217
4,14-$(Me)_2$	**265b**	125–126	A, C	VTNMR	188
4,5-Benzo	**265c**	182–183	A, C, D	Anti isomer	191
	265d	142–143	A, C, D	Syn isomer	191
4,5-(2,3-Naphtho)	**265e**	~195 dec	A, D	Anti only isolated	191
4,5;13,14-Dibenzo)	**265f**	~100 dec	A, C, D		191

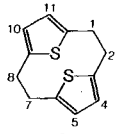
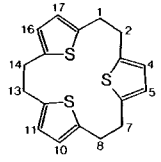
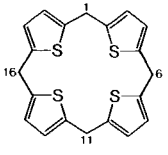
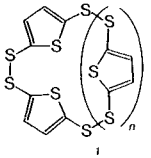
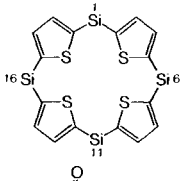
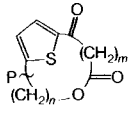


R = R′ = H	**266a**	~175 dec	A, C		217
R = R′ = Me	**266b**	149–151.5 dec	A, C	VTNMR	188

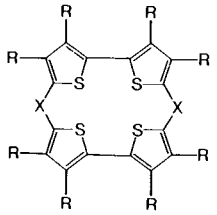


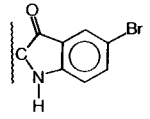
H	**267**	~195 dec	A, C		217

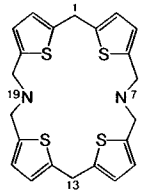
TABLE III (Continued)

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	C_{2n} symmetry[286] X-ray	186, 188, 191, 246, 286, 253
		1,2,7,8-$(C_6H_5)_4$; 4,5,-10,11-$(Br)_4$	**268b**	250–255		Probable structure[298]	297
		H	**269a**				191
	(*Z*)-1,2; (*Z*)-7,8; (*Z*)-13,14	H	**269b**	74.5–75.5 (subl: 70)	A–C	No peripheral conjugation, aromatic stability[434]	151, 152
					D		149
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,7,14-$(CO_2Me)_3$	**269c**	257–259	A–C		151, 152
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,7,14-$(CO_2H)_3$	**269d**	>360	B, C	Unsuccessful resolution	151, 152
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,14-$(CO_2H)_2$; 7-CO_2Me	**269e**	Dec	A		151, 152
		1,1,6,6,11,11,16,16-$(Me)_8$	**270a**	338	A, B, D		199, 200
		1,11-$(OH)_2$; 1,6,6,11,-16,16-$(Me)_6$	**270b**	280 dec	A, B		199, 248
		1,11-$(=CH_2)_2$; 6,6,-16,16-$(Me)_4$	**270c**	250 dec			199, 248
		1,11-$(OH)_2$; 1,11-$(H)_2$; 6,6,16,16-$(Me)_4$	**270d**	280 dec	A, B, D		199, 248
		$n = 2$	**271**		A, D		255, 442
		1,1,6,6,11,11,16,16-$(Me)_8$	**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

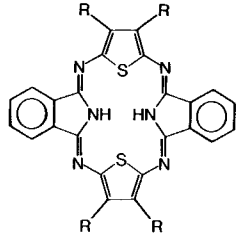
$p = 1; m = 3; n = 5;$ H	**275**	114–115			237
$p = 1; m = 4; n = 3;$ H	**276**	70–71	A,[224], D		224, 225, 245, 363, 444
$p = 1; m = 5; n = 2;$ H	**277**	134–135	D		245, 363, 444
$p = 1; m = 5; n = 4;$ H	**278**		A[224]		224, 225
$p = 1; m = 1; n = 6;$ H	**279**				245
$p = 2; m = 2; n = 5;$ H	**280**	166–167	A,[224], D		224, 245, 444



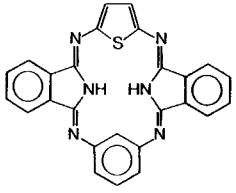
R = H; X = Hg	**281**			Improbable structure[298]	295
R = H; X = 	**282**	130		Poor analysis; amorphous powder Improbable structure[298]	294



1,1,7,13,13,19-(Me)$_6$	**283**	168.5–170		Picrate (mp 155.5–157°)	243

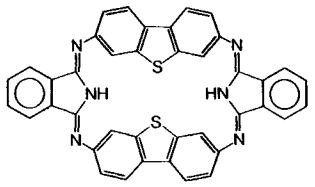
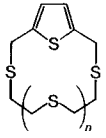
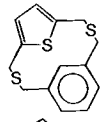
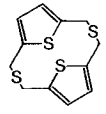
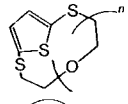
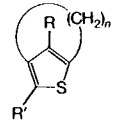
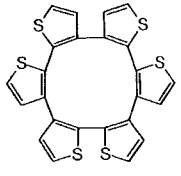


R = CN	**284**				257



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
		Bissulfone	**286**	378–380	B, C		258
		n = 1; H	**287**	127–129	A	Cu	431
		H	**288**	210	A		246
		H	**289**	234 dec	A		246
		n = 3; H	**290**				35
		n = 6; R = H; R′ = Me	**291**	[68–74 (3)]	A–D		229, 230
		n = 7; R = H; R′ = Me	**292**	[120–(3)]	A–D		229
		n = 8; R = H; R′ = t-Bu	**293**	Oil	A, C (CMR)		220
		n = 9; R = R′ = H	**294a**	[80–85 (0.03)]	A		205
		n = 9; R = H; R′ = Me	**294b**	[115 (3)][227] [105–110 (0.4)][228]	A–D		228, 229
		n = 10; 10-(=O); R = H; R′ = Me	**295**	55–56	A	4-NO_2PhNHNH$_2$(Z isomers)	227, 282
		n = 11; 11-(=O); R = H; R′ = Me	**296**	37.7–38.5	A	4-NO_2PhNHNH$_2$ (mp 165–168°)	227, 282, 365
		n = 12; 12-(=O); R = H; R′ = Me	**297**	Oil	A	4-NO_2PhNHNH$_2$ (mp 178–179°)	226, 282, 365
		H	**298**	>420	A	Centrosymmetric structure	404

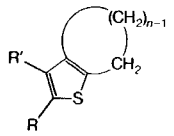
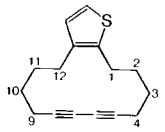
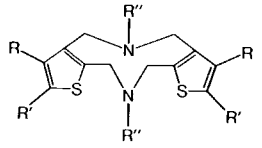
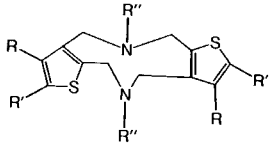
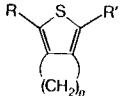
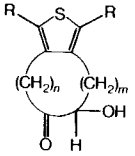
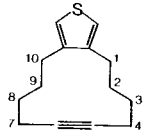
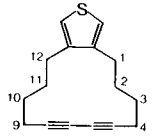
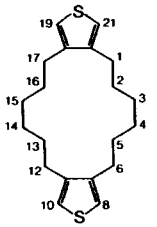
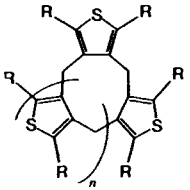
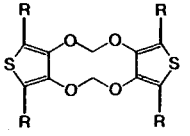
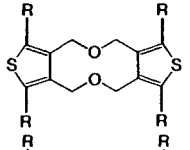
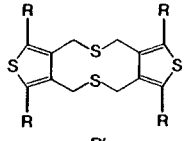
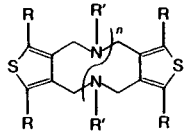
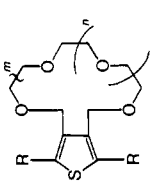
		n = 10; 10-(=O); R = Me; R′ = H	**299**				227, 282
		n = 11, 11-(=O); R = Me; R′ = H	**300**				227, 282, 365
		n = 12; 12-(=O); R = Me; R′ = H	**301**	48	A	4-NO_2PhNHNH_2 (reported)	226, 365
	(E)-1,2, (Z)-3,4; (Z)-9,10; (E)-11,12	4,9-$(Me)_2$	**302a**	169–170	A, C, D		209
	(E)-1,2; (E)-11,12	4,9-$(Me)_2$; 3,10-$(OH)_2$	**302b**				209
		R = Me; R′ = CO_2Me; R″ = Et	**303**	142–143	A–D		319
		R = Me; R′ = CO_2Me; R″ = Et	**304**	218–219	A–D		319
		n = 8; R = R′ = H	**305a**	Oil	A, C, D		220
		n = 8, R = R′ = t-Bu	**305b**	96–96.4	A, C (CMR), D		220
		n = 8; R = R′ = CO_2Me	**305c**	129.5–130.5	A, C, D		220
		n = 8; R = H; R′ = t-Bu	**305d**	51–51.5	A, C (CMR), D		220
		n = 8; R = H; R′ = CO_2Me	**305e**	63–65	A, C, D		220
		m = n = 5; R = Me	**306**	105.5–107		Positive test with Bi_2O_3	249, 367
						Tosyl derivate (mp 126–128°)	249
	(E)-1,2; (Z)3,4; (Z)-7,8; (E)-9,10	4,7-$(Me)_2$	**307**	157–158	A, C, D		208
	(E)-1,2; (Z)-3,4; (Z)-9,10; (E)-11,12	4,9-$(Me)_2$	**308**	182 dec	A, C, D		209

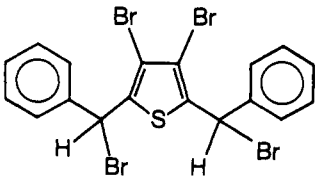
TABLE III (Continued)

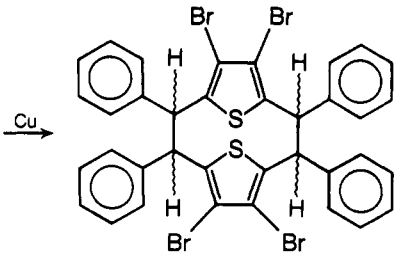
Compound	Double bond position	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Complex(es)/comments[b]	Ref
	(*E*)-1,2; (*E*)-5,6; (*E*)-12,13; (*E*)-16,17	3,4:14,15-Dibenzo 8,10,19,21-(Me)$_4$	**309**	235–240 dec	A–D	Unstable in air	232
		n = 1; R = Me	**310**	244–245; 200 (subl)	A, D	Conformationally mobile	231
		n = 2; R = Me	**311**	>370 (subl 300)	D		231
		R = CO_2Et	**312**	209–210	A, B		204
		R = Me	**313a**	233–235			357
		R = Cl	**313b**	270–271	A–C		317
		R = *t*-Bu	**313c**	220–221	A, B	Reassignment of structure[317]	317, 318
		R = Br	**314a**	275 dec	D		319
		R = Me	**314b**	173–184			357
		n = 1; R = Cl; R′ = Et	**315a**	102.5–103.5	A–C		319
		n = 1; R = Me; R′ = Et	**315b**	88–88.5		Picrate (250°)	320, 357
		n = 1; R = Me; R′ = *i*-Pr	**315c**	152–153		Picrate (186°)	320, 357
		n = 1; R = Me; R′ = *i*-Bu	**315d**	119–120			357
		n = 1; R = Me; R′ = *t*-Bu	**315e**	209–210		Dipicrate (195–197°)	320
		n = 1; R = Me; R′ = $-(CH_2)_5-$[2Cl$^-$]	**315f**	242		Dipicrate	320

n = 1; R = Me; R′ = 2 (Et) [2Cl⁻]	315g	202–204				
n = 2; R = Me; R′ = Et	316	182.5–183				
n = 0; m = 1; R = Me	317		A, CMR	Na, K	304	
n = 1; m = 1; R = Me	318		A, CMR	Na, K	304	
n = 2; m = 1; R = Me	319		A, CMR	Na, K	304	
n = 3; m = 1; R = Me	320		A, CMR	Na, K	304	
n = 4; m = 1; R = Me	321		A, CMR	Na, K	304	
n = 5; m = 1; R = Me	322		A, CMR	Na, K	304	
n = 6; m = 1; R = Me	323		A, CMR	Na, K	304	
n = 0; m = 2; R = Me	324		A, CMR	Na, K	304	
n = 1; m = 2; R = Me	325		A, CMR	Na, K	304	
n = 2; m = 2; R = Me	326		A, CMR	Na, K	304	



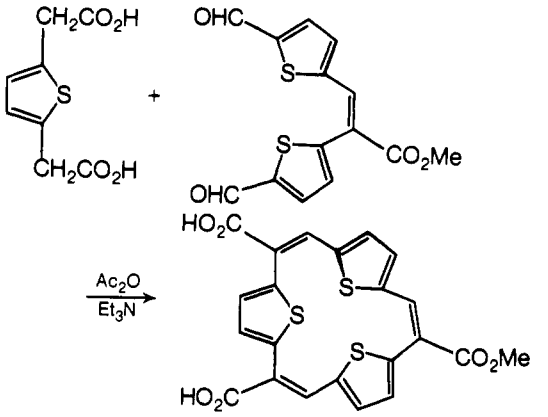
[a] Spectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS. [b] Temperatures given in °C.



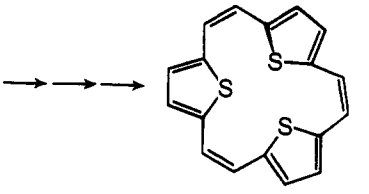


268b

[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]



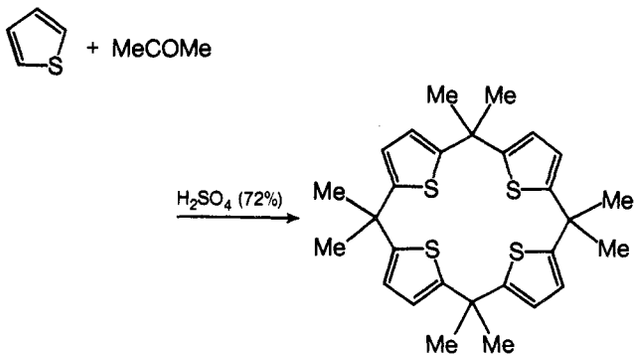
269e



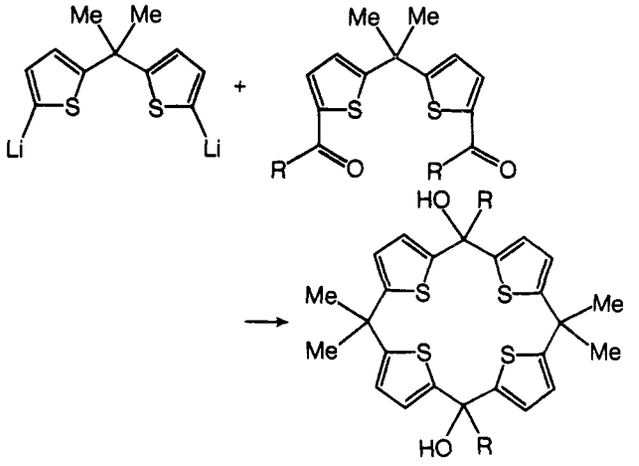
269b

Although pyrrole and furan reacted with acetone and hydrochloric acid to generate porphyrinogen[323-325] and tetraoxaquaterene,[169,194,195] respectively, initial attempts to prepare tetrathiaquaterene 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-



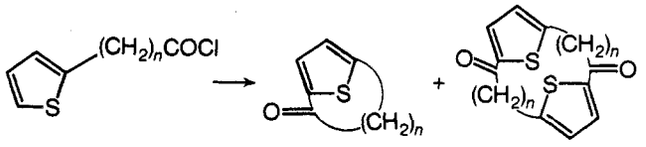
270a



270d, R = H
270b, R = Me

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.

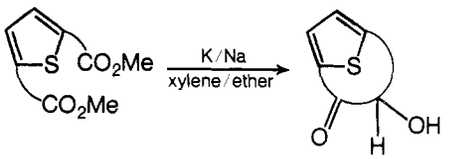
The Friedel–Crafts acylation of an appropriate terminal 2-thienyl straight-chain acyl chloride gave rise to both monomeric (intramolecular) and dimeric (intermolecular) products when subjected to either aluminum chloride/etherate in carbon disulfide (ref 233, 234, 238), stannic chloride in benzene at +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,



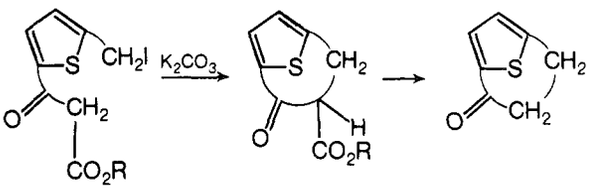
251–255 **256–260**

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%).

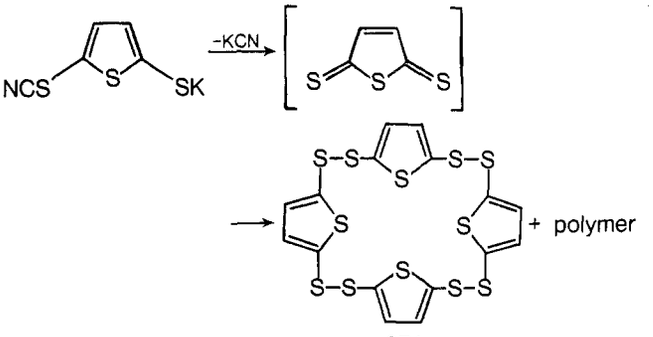


The third procedure utilized by these Russian workers was the intramolecular cyclization of an activated methylene group with an iodomethylene group in the presence of finely pulverized potassium carbonate (ref 240, 241, 250, 251, 261, 286) in methyl ethyl ketone, potassium *tert*-butoxide,[239] or other 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).

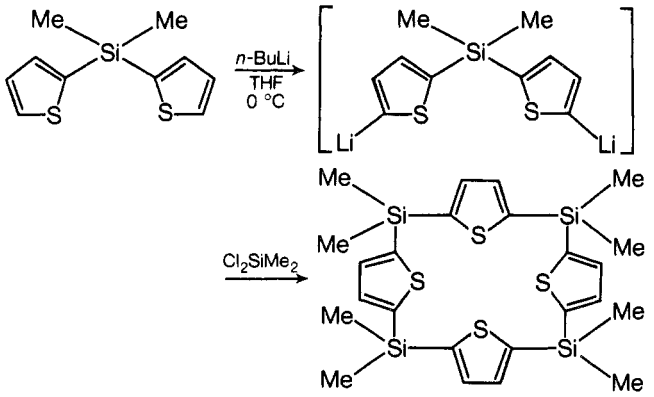
The only known *sulfur-bridged* thiophene macrocycle was reported by Todres et al. when 5-thiocyanato-2-thienyl mercaptide (stable in absolute tetrahydrofuran) was treated with acetic acid.[255] This mercaptide probably decomposed through the unstable trithiomaleic anhydride intermediate, which underwent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



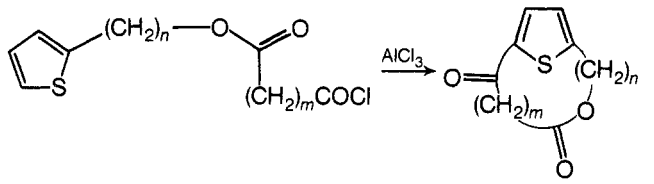
271

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-silapropane 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**).

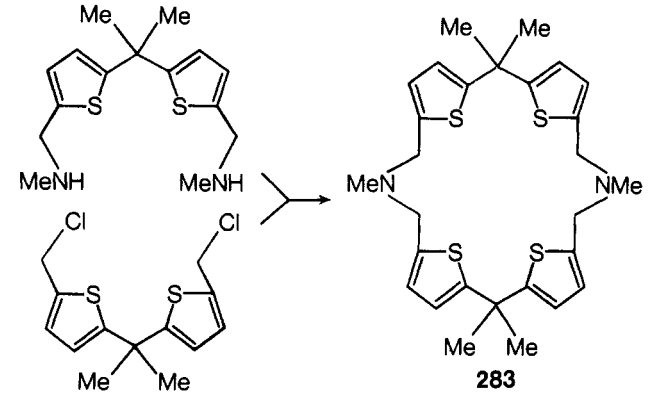


272

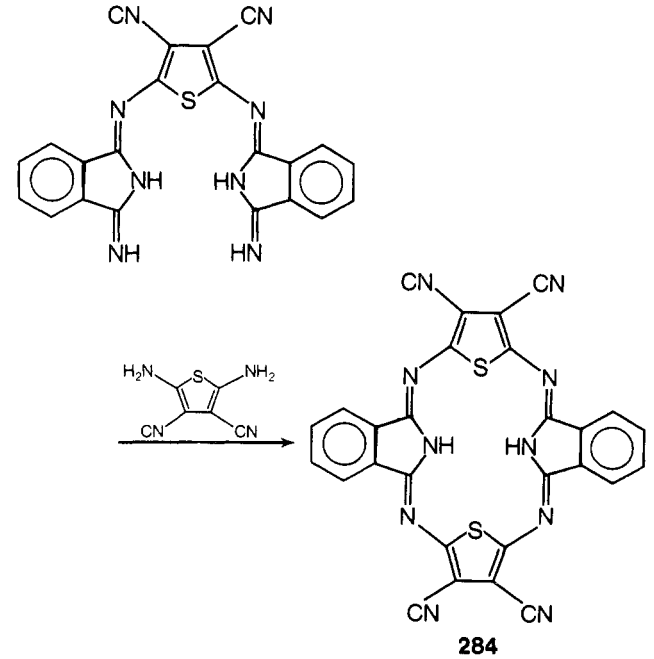


273-279

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]



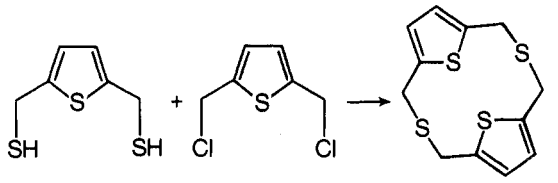
283



284

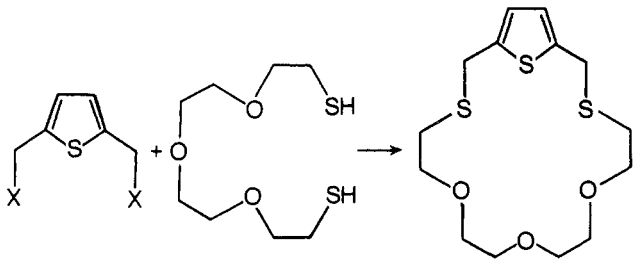
A thiophenedicarbonitrile derivative, prepared (48%) by the reaction of 1-amino-3,3-diethoxyisoindoline with 2,5-diamino-3,4-dicyanothiophene, was treated with a second equivalent of the diamine to give (58%) the desired heteromacrocycle **284.** The corresponding benzene derivative **285**[257] as well 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(mercaptomethyl)thiophene with either 2,5-bis(chloromethyl)thiophene or 1,3-bis(bromomethyl)benzene, respectively, under high-dilution conditions.[246]



289

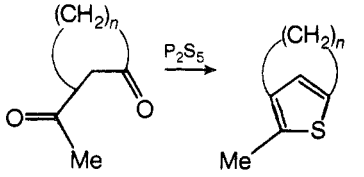
A *carbon–sulfur–oxygen-bridged* thiophenophane **290** has been reported by Vögtle and Weber; no experimental details were presented.[35] However, **290** was probably synthesized in a manner similar to their previous heterocyclic examples.[27-29,31-33]



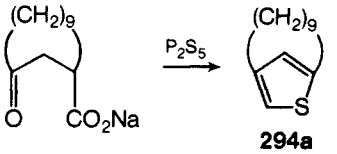
290

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-acetylcycloalkanone 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]

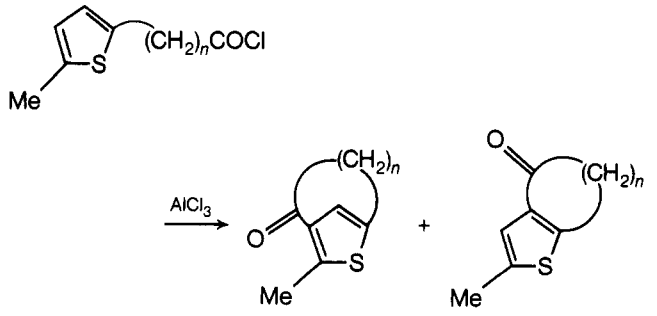


Bradamante et al. reported the preparation of the unsubstituted [9](2,4)thiophenophane **294a** by the gentle warming of the sodium salt of 3-ketocyclododecanecarboxylic acid with P_2S_5.[205]



294a

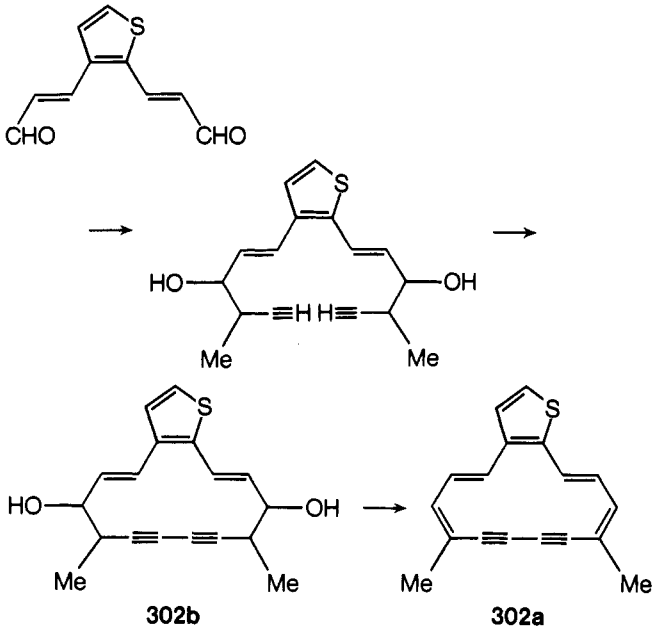
Gol'dfarb et al. prepared a series of (2,4)thiophenophan-1-ones by an intramolecular Friedel–Crafts acylation reaction of ω-(5-methyl-2-thienyl)alkanoyl chlorides in the presence of aluminum chloride.[226,227] Substitution at the 3 or 4 position occurred since the 5 position was blocked with an alkyl 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.

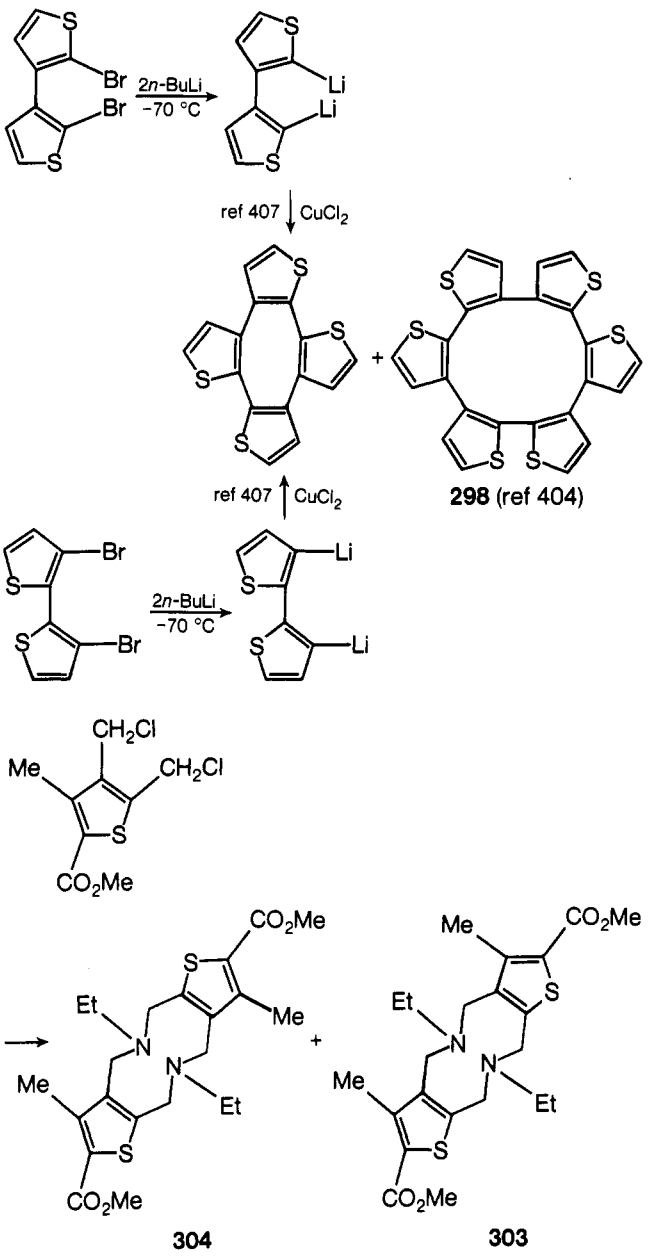
[14]Annuleno[*b*]thiophene **302b** has been prepared by Sondheimer et al. from thiophene-2,3-dicarboxaldehyde.[209] Their procedure was essentially the same as for the construction of **228a** (see section B.3).[210]



302b **302a**

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%).

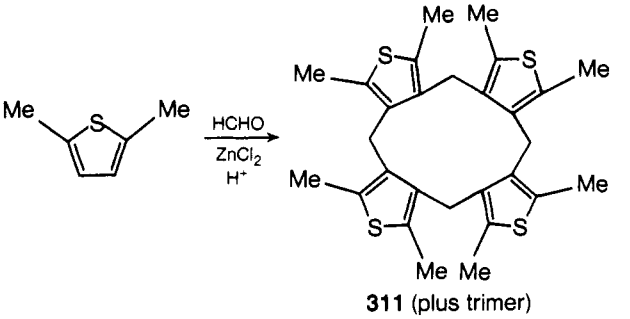


298 (ref 404)

304 **303**

4. 3,4-Thiopheno

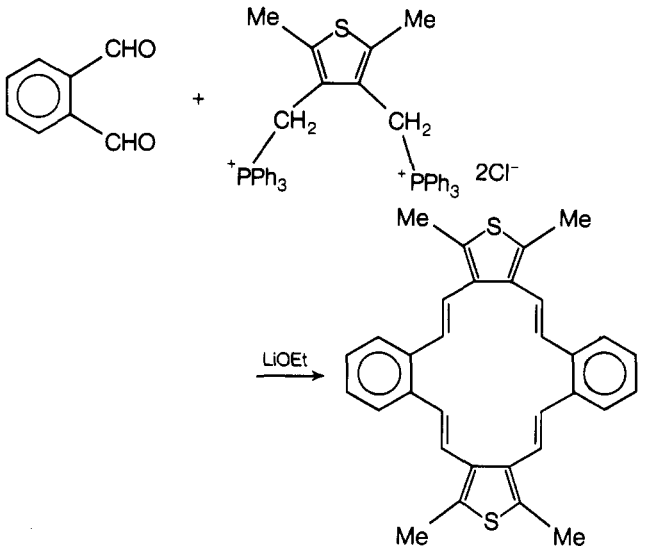
Trimeric and tetrameric 3,4-disubstituted thiophene cyclic units coupled by a *carbon bridge* have been reported by Meth-Cohn. When an equimolar mixture of 2,5-dimethylthiophene and formaldehyde in acetic acid was added dropwise to refluxing acetic acid containing zinc chloride and a little mineral acid,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



311 (plus trimer)

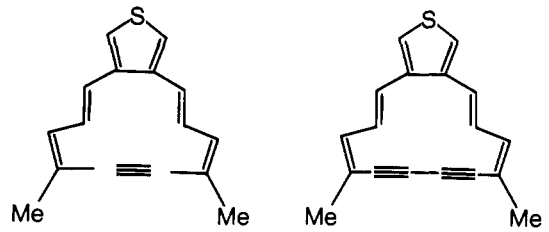
Reaction of *o*-phthalaldehyde with 2,5-dimethylthiophene-3,4-bis(methylenetriphenylphosphonium chloride) in the pres-

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]



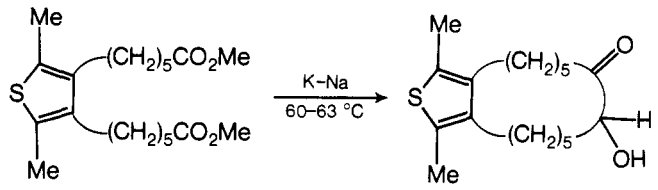
309

Sondheimer et al. reported the synthesis of both [12]annuleno[*c*]thiophene[208] (**307**) and [14]annuleno[*c*]thiophene[209] (**308**) by previously discussed procedures (section B.3, except that thiophene was substituted for furan).



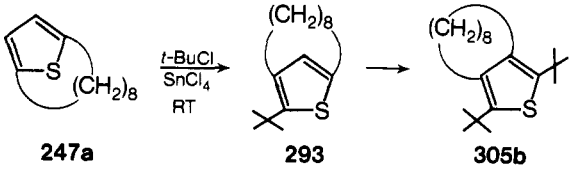
307 **308**

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]



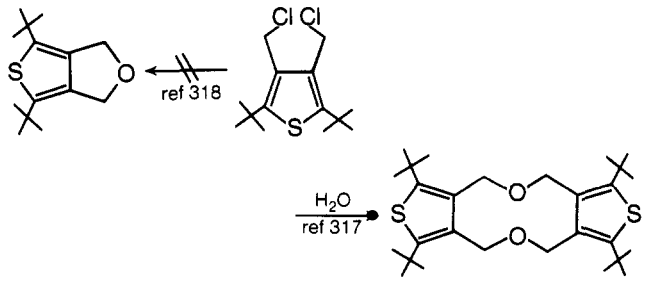
306

[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]



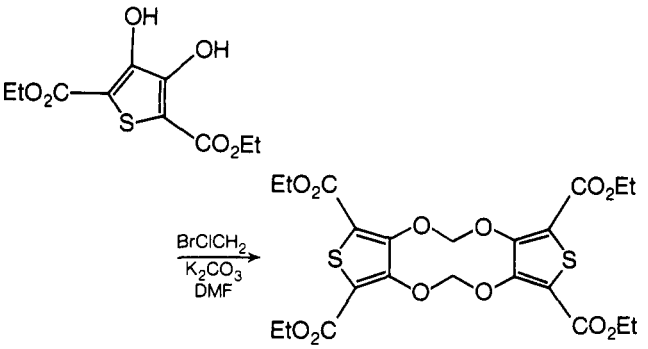
247a **293** **305b**

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 tetrachloro[317] and tetramethyl[357] derivatives have been prepared in a similar manner.



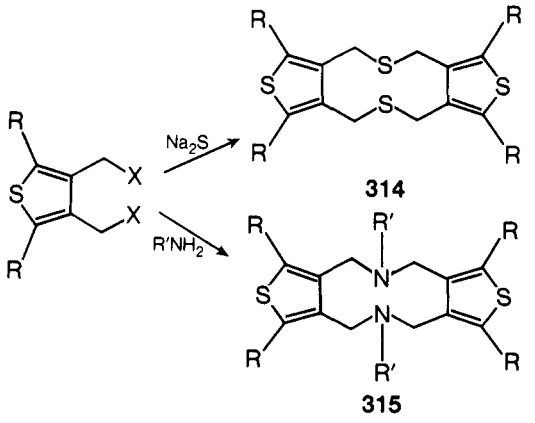
313c

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]



312

Zwanenburg 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]



314

315

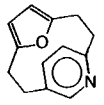
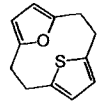
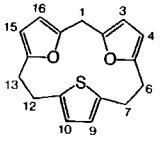
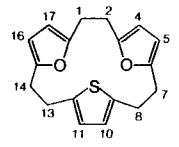
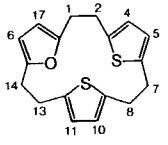
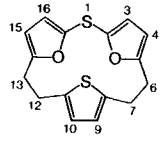
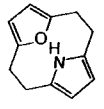
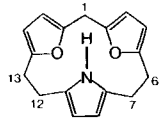
V. Synthesis of Macrocycles Possessing Two or More Different Subheterocyclic Rings

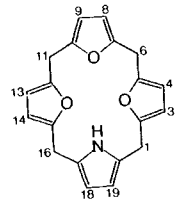
Table IV is a compilation of the macrocycles which possess a combination of pyridine, furan, and/or thiophene subheterocyclic rings.

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

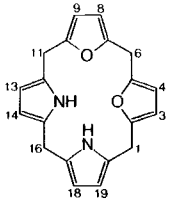
Wong and Paudler have recently reported the first mixed heterocyclophane which is composed of both a π-deficient pyridine subunit and a π-excessive furan ring.[88] Construction

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

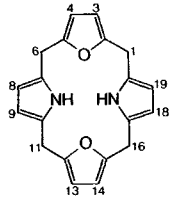
Compound	Double bond position	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available	Complex(es)/comments	Ref
		H	**327**	86–87	A, C	No VTNMR changes, x-ray[448]	88
		H	**328**		A	Conformational studies	6
	(*Z*)-6,7; (*Z*)-12,13	1-(=O)	**329a**	148–150	A–D	No paramagnetic ring current	160, 162
	(*Z*)-6,7; (*Z*)-12,13	1-$(H)_2$	**329b**	Yellow oil	A, D		162
	(*Z*)-6,7; (*Z*)-12,13	1-H; 1-OMe	**329c**	Orange oil	A, D		162
	(*Z*)-1,2; (*Z*)-7,8; (*Z*)-13,14	H	**330**	250–251 dec	A–C	Aromatic (NMR), aromatic stability[434]	145, 254
					D		149
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2,8,13-$(CO_2H)_3$	**331a**	>360	A–C		145, 254
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2,8,13-$(CO_2Me)_3$	**331b**	192–193	A–C		145, 254
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	13,8-$(CO_2H)_2$; 2-CO_2Me	**331c**	>250 dec	A–C		254
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2,7,14-$(CO_2Me)_3$	**331d**	210–212	A–C		145, 254
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2,7,14-$(CO_2H)_3$	**331e**	>360 dec	A–C		145, 254
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2,7-$(CO_2H)_2$; 13-CO_2Me	**331f**	>250 dec	A–C		254
	(*Z*)-1,2; (*Z*)-7,8; (*Z*)-13,14	H	**332**	103–103.5	A–C	No peripheral conjugation, aromatic stability[434]	146, 153
					D		149
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2-CO_2Me; 8,13-$(CO_2H)_2$	**333a**	dec			153
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2,8,13-$(CO_2Me)_3$	**333b**	256–257	A–C		153
	(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	2,8,13-$(CO_2H)_3$	**333c**	>340 dec	A–C		153
	(*Z*)-6,7; (*Z*)-12,13	H	**334**	81–83	A, C	No diamagnetic ring current	161
				84.5–85.5	A–D		157
	(*E*)-6,7; (*E*)-12,13	7,12-$(CO_2Me)_2$[b]	**335a**	193–195	A–C		157, 161
	(*E*)-6,7; (*E*)-12,13	7,12-$(CO_2H)_2$	**335b**	>300 dec			157
		H	**336a**	131–132	A–D	VTNMR studies	8, 184
		2,2,4,5,7,7-$(D)_6$	**336b**		A	VTNMR conformationally rigid	185
	(*Z*)-6,7; (*Z*)-12,13	1-$(H)_2$	**337a**	126–128	A, D	Paramagnetic ring current	159, 162
	(*Z*)-6,7; (*Z*)-12,13	1-(=O)	**337b**	299–300 dec	A–D	Paramagnetic ring current	159, 162



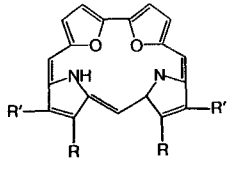
1,1,6,6,11,11,16,16-$(Me)_8$	**338**	223			193



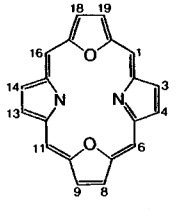
1,1,6,6,11,11,16,16-$(Me)_8$	**339**	260 dec			193



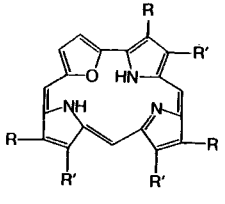
1,1,6,6,11,11,16,16-$(Me)_8$	**340**	230.5			193



R = R′ = Me	**341a**	>300	C, D	HBr (mp >300°; A, C)[c]	182, 198
R = R′ = Et	**341b**	167–169	A, C, D	HBr (mp >300°; A, C)[c]	182, 198
R = Et; R′ = Me	**341c**	230–232	A, C, D	HBr (mp >300°; A, C)[c]	182, 198
R = Et; R′ = Me; N-Me(I)	**341d**				203
R = Et; R′ = Me; N-Et(I)	**341e**				203
R = Et; R′ = Me; N,N′-$(Me)_2$ (I)	**341f**		A		203
R = Et; R′ = Me; N,N′-$(Et)_2$ (Br)	**341g**			Partial resolution	203

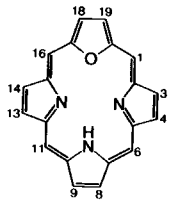
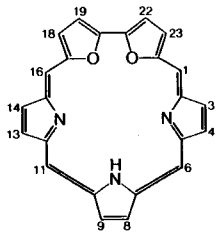
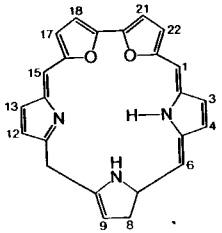
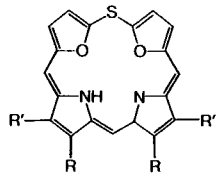
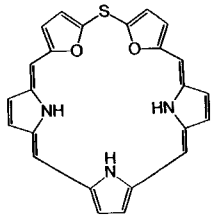


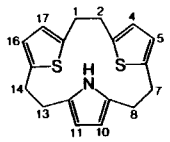
3,14-$(Me)_2$; 4,13-$(Et)_2$	**342**		A, C	DiHBr (mp >300°; A, C)	202, 197



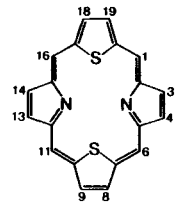
R = Me; R′ = Et	**343a**		A		182
R = R′ = Et	**343b**	197.5–199.5	A, C, D		198

TABLE IV (Continued)

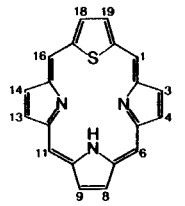
Compound	Double bond position	Substituents	Compd no.	Physical data Mp[bp (mm)], °C	Spectral data available	Complex(es)/Comments	Ref
		3,8,14-$(Me)_3$; 4,9,13-$(Et)_3$	**344**	>300	A, C	HBr (mp >300°)	197, 202
					(C, D)[d]	Ni (mp >300°, paramagnetic)	197, 202
					(A, C)[d]	Zn (mp >300°)	197, 202
						Cu	202
		3,4,8,9,13,14-$(Me)_6$	**345a**		D		182, 198
		3,9,14-$(Me)_3$; 4,8,13-$(Et)_3$	**345b**	>300	A	Large ring current (NMR)	182, 196, 201, 202
					A, C	Dihydro perchlorate (mp > 300°)	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, D		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	**348**			"Probable precursor"	196



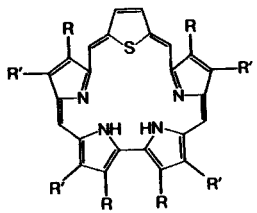
(*Z*)-1,2; (*Z*)-7,8; (*Z*)-13,14	H	**349a**	129–130	A, C, D	Nonaromatic; nonplanar; aromatic stability[434]	156
				D		149
(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1-CO_2Me; 8,13-$(CO_2H)_2$	**349b**	>180 dec	A, B		156
(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,8,13-$(CO_2Me)_3$	**349c**	288	A–D		156
(*E*)-1,2; (*E*)-7,8; (*E*)-13,14	1,8,13-$(CO_2H)_3$	**349d**	>360 dec	A–C		156



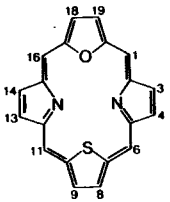
3,14-$(Me)_2$; 4,13-$(Et)_2$	**350**	>300	A, C, D	"Aromatic macrocycle"	197, 201, 202, 222



3,8,14-$(Me)_3$; 4,9,13-$(Et)_3$	**351a**	263–264	A, C, D	Zn (unstable)	197, 202
1,6,11,16-$(C_6H_5)_4$	**351b**	>350	B–D	Fe	222



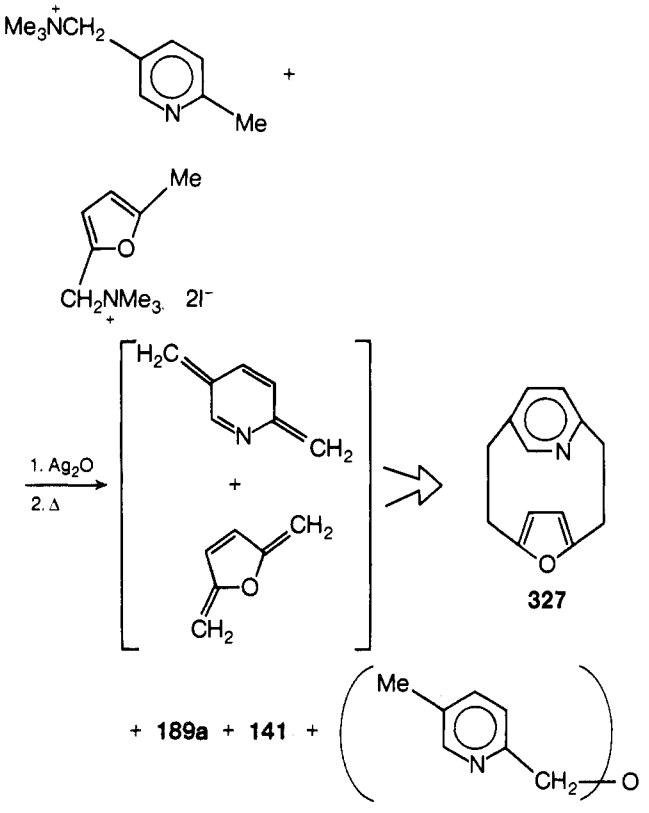
R = Et; R′ = Me	**352**	>300	A, C, D		196



3,14-$(Me)_2$; 4,13-$(Et)_2$	**353**	>300	A, C		197, 202

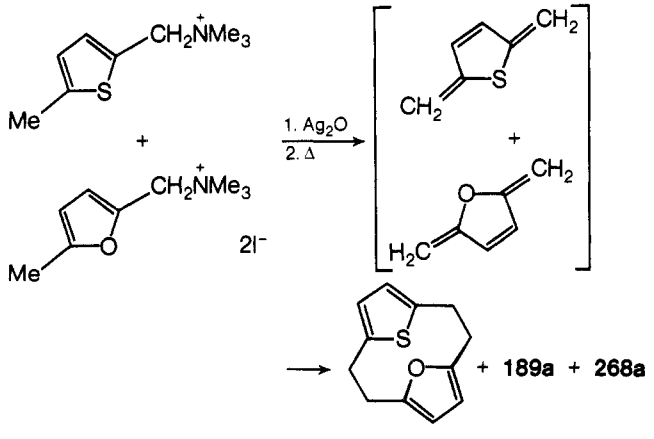
[a] Spectral data cited in the literature: A = PMR; B = IR; C = UV; D = Ms. [b] In ref 157, this compound was drawn incorrectly (e.g., **17**). [c] Reference 182b is a correction to the previous article.[182a] [d] Spectral data of complex. [e] Reference 171.

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-picolyl) ether.



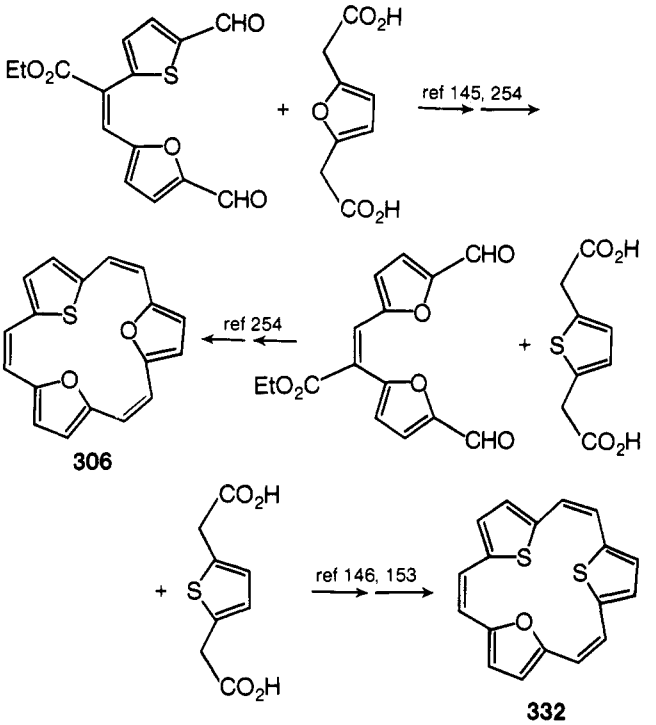
B. Combination of 2,5-Furano and 2,5-Thiopheno Subunits

The simplest member (**328**) of these subunits was prepared by Fletcher and Sutherland[6] 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]



328

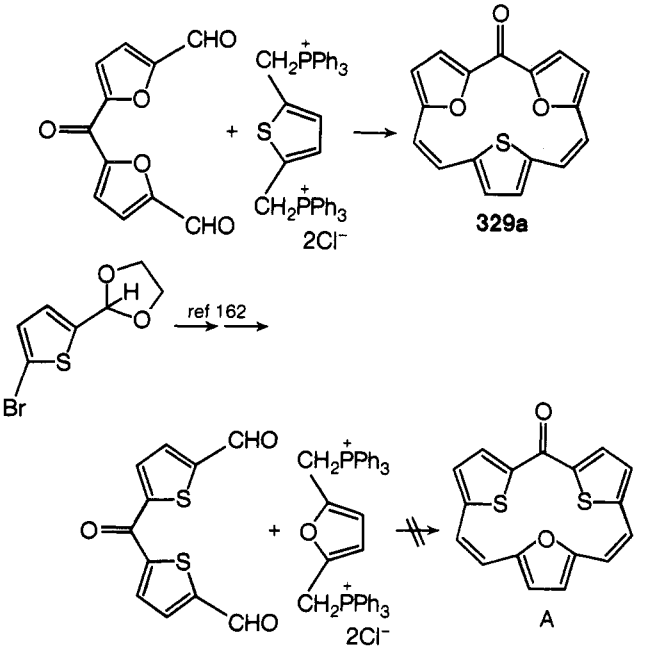
Badger and co-workers carried out the synthesis of two "cross-breed" [18]annulenes in order to ascertain the aromatic character of the $(4n + 2)$ π-electron systems. Both the [18]-annulene trisulfide[151,152] and trioxide[146] had been previously reported by these workers, and the general mode of construction of **330** and **332** reflects their earlier procedures. The appropriate



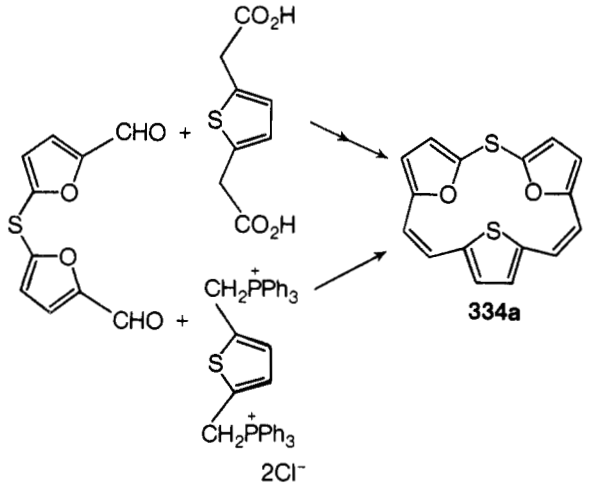
332

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 data[149] 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

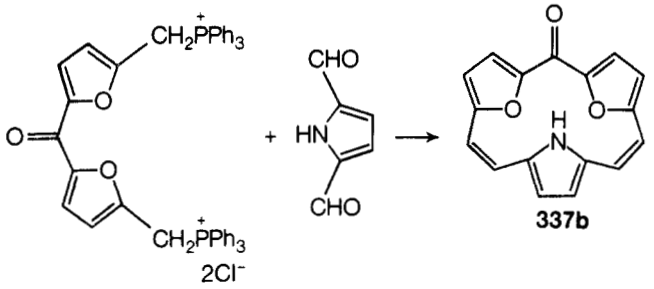


routes: (a) Perkin condensation, esterification, saponification, and decarboxylation; and (b) a diformyl compound[355] with a bis-Wittig reagent.[161] The degree of aromatic character of **329a** and **334a** has been determined by NMR analyses.

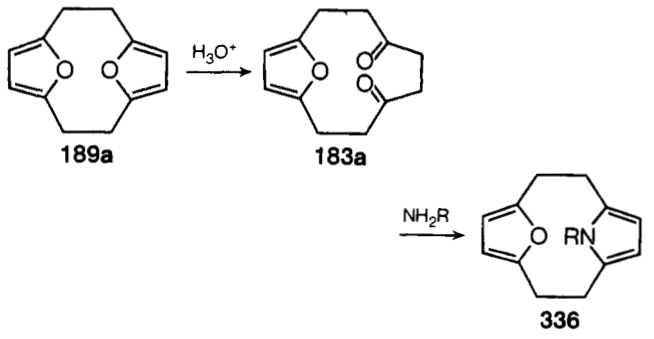


C. Combination 2,5-Furano and 2,5-Pyrrolo Subunits

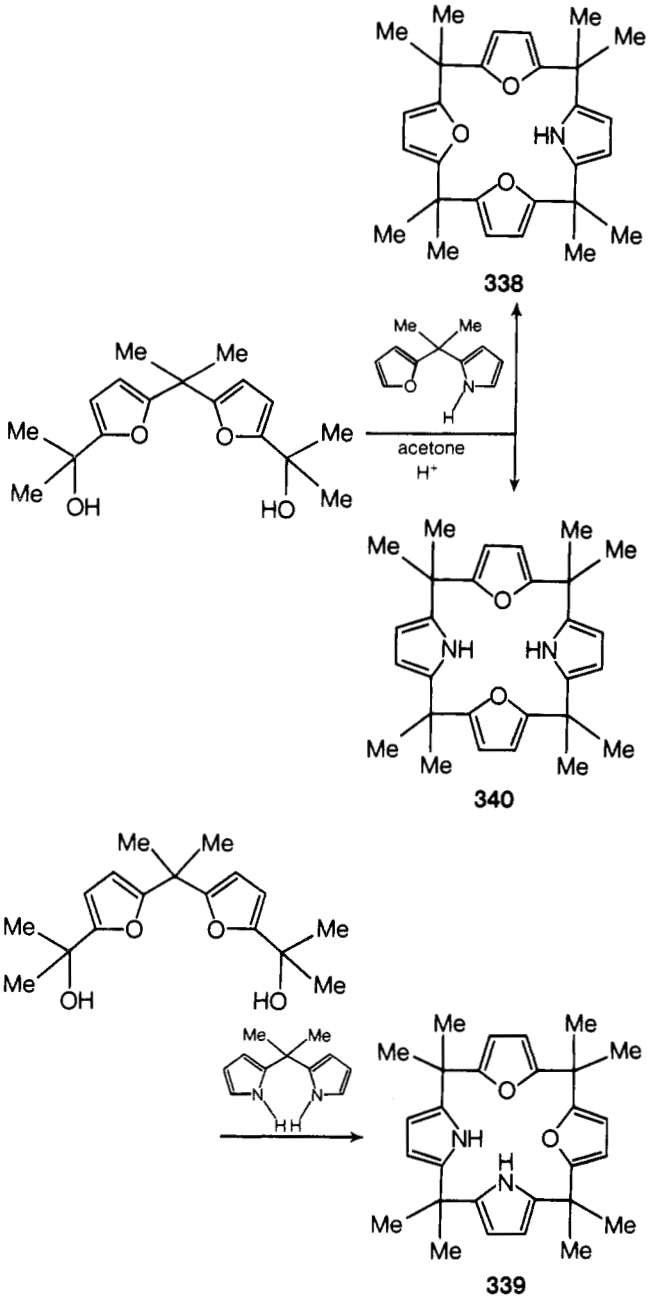
Cresp and Sargent extended the above bis-Wittig reaction sequence (of **329a**) to the preparation of [17]annulenone **337b.**[159,162] A Wittig reaction between the ketonic bis-Wittig reagent and pyrrole-2,5-dicarboxaldehyde afforded (13.8%) 8,11-imino-2,5:14,17-diepoxy[17]annulenone **(337b)** . Annulenone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



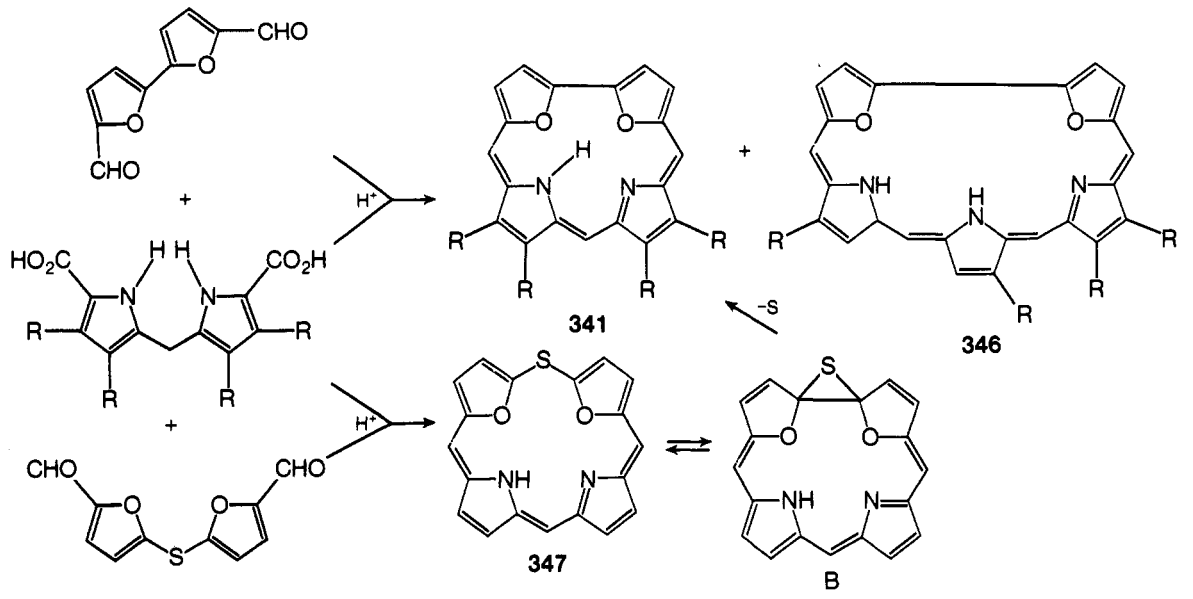
[2.2](2,5)Furanophane **189a** was partially hydrolyzed under acidic conditions in the absence of light and air to generate **183a** which was conveniently cyclized upon treatment with ammonia or a primary amine (Paal–Knorr reaction), by the procedure of Wasserman and Bailey,[218] to afford **336.**[184,185]



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 various combinations, **338, 340,** and **339** were prepared via this procedure.[193]

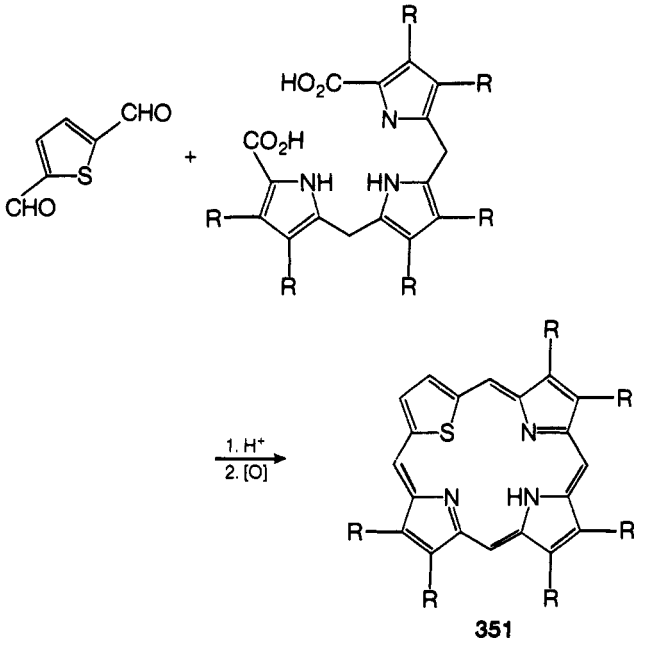


Grigg et al. have reported two procedures for construction of new aromatic macrocyclic systems, which are related to porphin and corroles,[182] utilizing the MacDonald porphin synthesis.[376] The more direct approach to **341** was via the acid-catalyzed condensation of a 5,5′-diformylbifuran with a substituted dipyrrolylmethane 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]



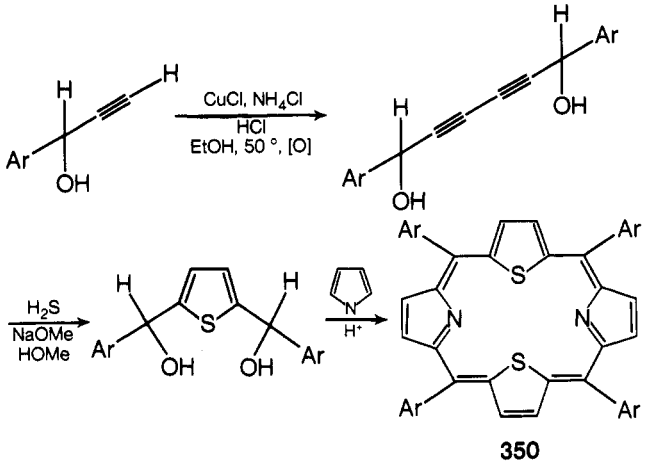
D. Combination of 2,5-Thiopheno and 2,5-Pyrrolo Subunits

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]



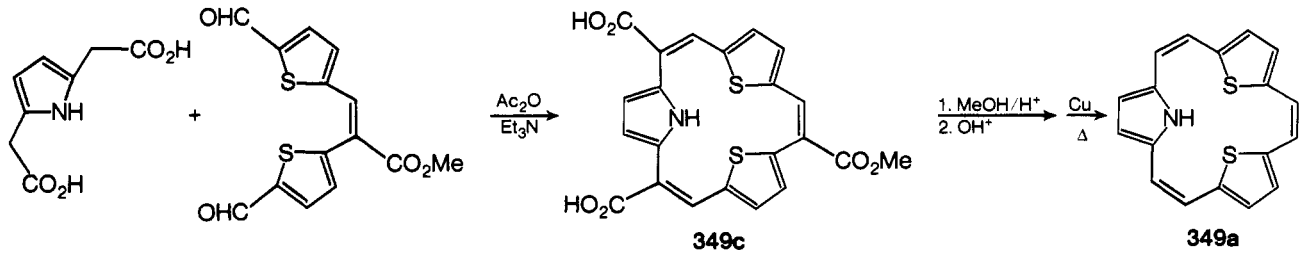
Badger et al. have reported the synthesis of **349a** by their previously discussed procedures (see section V.B) from pyrrole-2,5-diacetic acid and methyl *cis*-α,β-bis(5-formyl-2-thienyl)acrylate.[156] The electron impact studies of **349a** have been reported,[149] and NMR studies have indicated that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

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/benzene, chloroacetic acid/toluene, or propionic acid to afford (4–10%) the desired substituted dithiaphorphyrin **350**.[222]

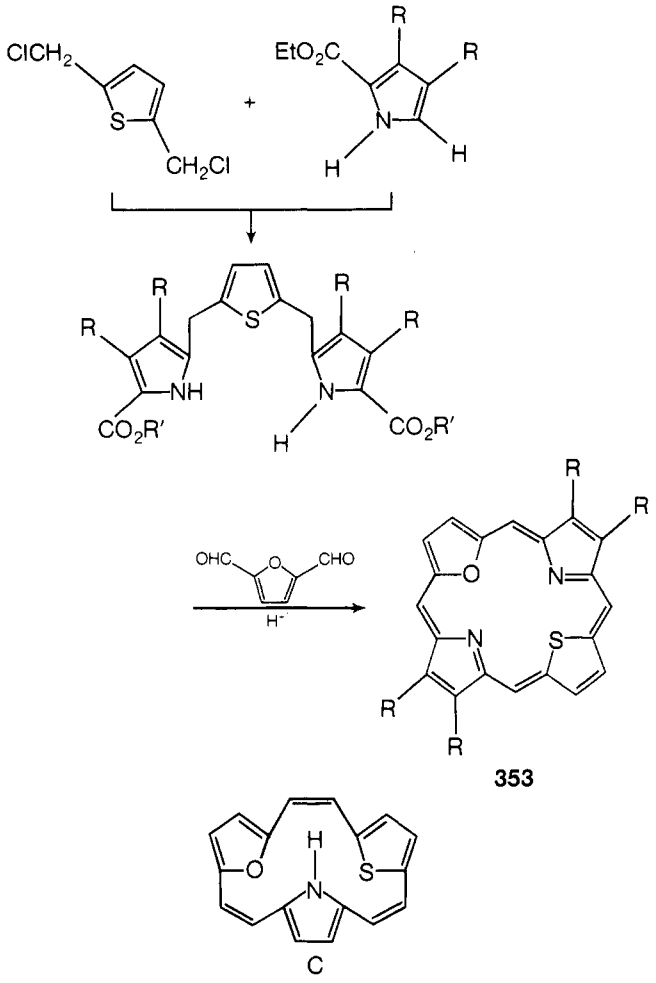


E. Combination of 2,5-Furano, 2,5-Thiopheno, and 2,5-Pyrrolo Subunits

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 porphin 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.**



353

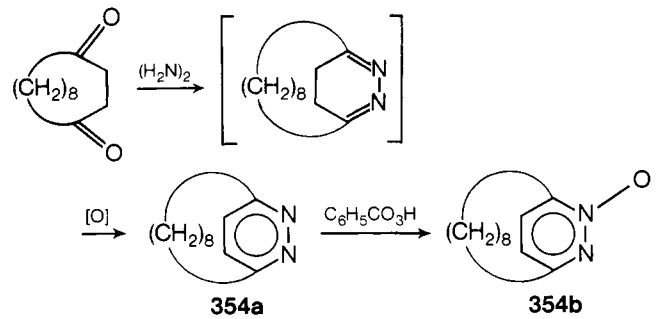
C

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.

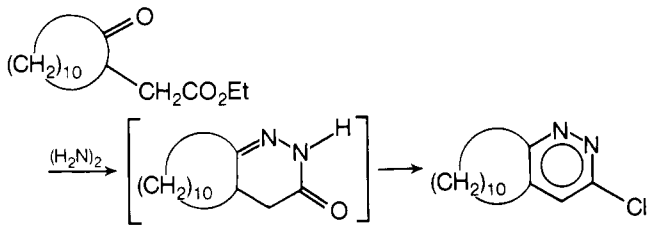
A. Miscellaneous Six-Membered Rings

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]



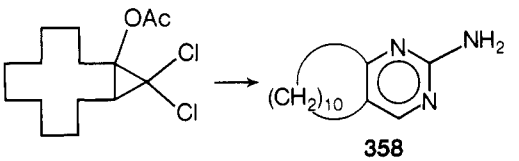
354a 354b

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]



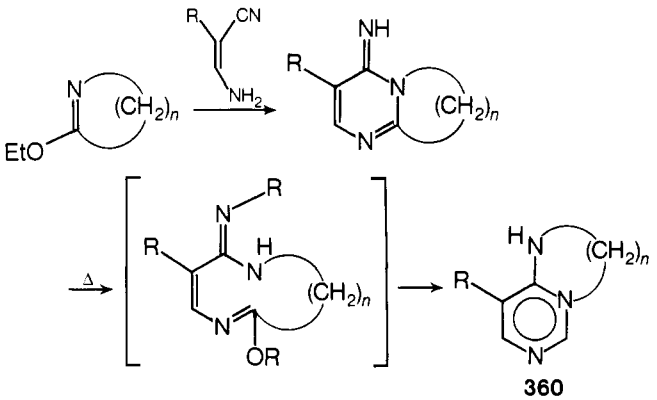
357

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]



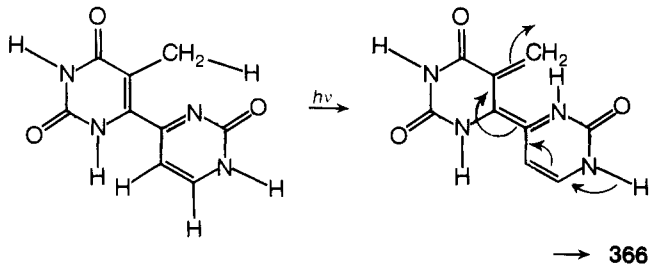
358

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]



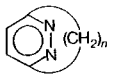
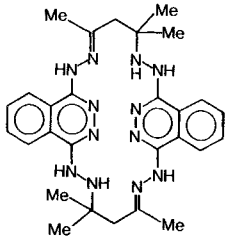
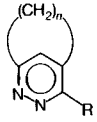
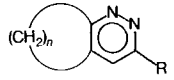
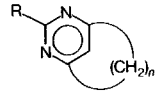
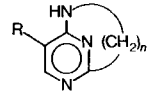
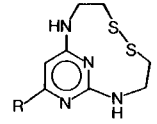
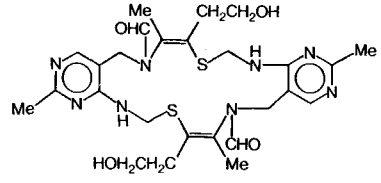
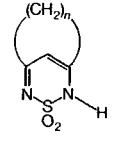
360

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]



→ 366

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

Compound	n	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Metal complex(es)/general comments	Ref
	8	H	**354a**	59–60	A–C	Temperature-dependent NMR	133
		N→O	**354b**	[140–150 (0.1)]	A, B, D	"Chiral ansa compound"	133
		H	**355**		B	Ni	438
	9	R = Me	**356**	92	A, B	Di- and tetrahydro intermediates isolated and characterized	106
	10	R = (NH=CMe$_2$)	**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_2Et	**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

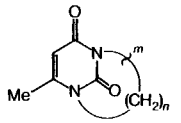
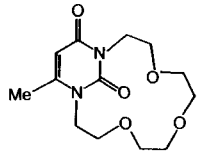
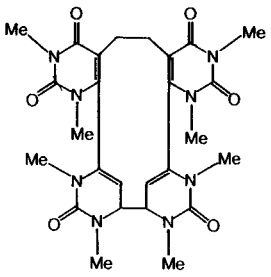
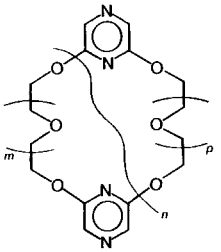
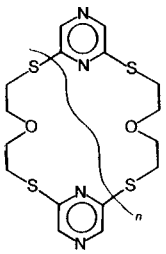
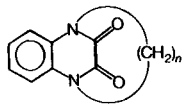
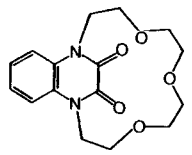
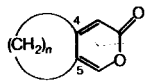
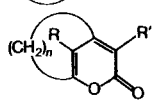
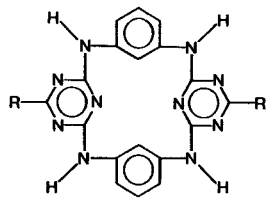
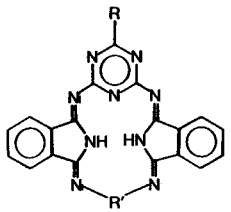
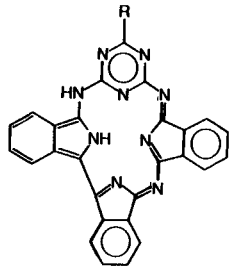
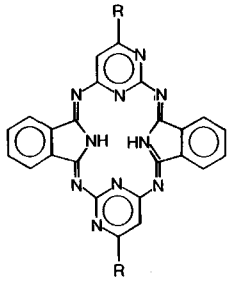
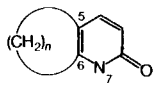
	$m = 2; n = 6$	H	**364**	160–164		Isomers possible	263, 389
		H	**365**	92–94		K, NH_4	263, 389
		H	**366**	>300	A, C	Trans, syn configuration	378, 379
	$n = 0; m = 2$	H	**367**	130–131	A, B, D	Methiodide (mp 203°)	39
	$n = 0; m = 3$	H	**368**	86–87	A, B	Methiodide (mp 186–189°)	39
	$n = 0; m = 4$	H	**369**	72–74	A, B		39
	$n = 1; m = p = 1$	H	**370**	136–137	A, B, D		39
	$n = 1; m = p = 2$	H	**371**	125–127	A, B	Methiodide (mp 211°)	39
	$n = 1; m = p = 3$	H	**372**	75–76	A, B		39
	$n = 2; m = p = 1$	H	**373**	110–111	A, B, D		39
	$n = 1$	H	**374**	118–119	A, B, D		39
	$n = 2$	H	**375**	155–156	A, B, D		39
	10	H	**376**	172–174			389
		H	**377**	184		Mg, K, Cs	263, 389

TABLE V (Continued)

Compound	*n*	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Metal complex(es)/general comments	Ref
	10	6-Me	**378**	101.5	A–D		264
	11	6-Me	**379**	99	A–D		264
	11	R = R′ = H	**380a**	97–98	A–D		264, 267
	11	R = Me; R′ = Ac	**380b**	84–85	A–D		264, 267
	12	R = R′ = H	**381**	67°	A–D		264
		R = NH_2	**382a**				139, 382, 383
		R = PhNH	**382b**				139, 381–383
		R = *p*-$HO_2CC_6H_4NH$-	**382c**				382
		R = piperidino	**382d**				382
		R = 4-sulfo-]-naphthyl-amino	**382e**				382
		R = *p*-NHC_6H_4-N=NPh	**382f**				382
		R = OH; R′ = 1,3-C_6H_4–	**383a**			Cu, Ni, Co	384
		R = Cl; R′ = 1,3-C_6H_4–	**383b**			Cu	385
		R = Cl; R′ = 4-chloro-2,6-pyrimidine-pyrimidinediyl	**383c**			Cu	384
		R = Cl; R′ = HNNH	**383d**			Ni, Cu, Co	384
		R = C_6H_5	**384**		C, D	Cu	441

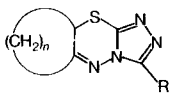


	R = OH	**385**		C	Co, Ni	439
	R = H	**386**	475–477	A		406



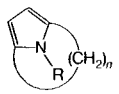
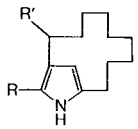
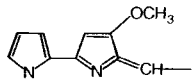
8	1-C_6H_5; 3-OH; 4-H	**387a**	252		449
8	1-C_6H_5; 3-OH; 4-Me	**387b**	283		449
8	1-C_6H_5; 3-H; 4-OH	**387c**	271		449
8	1-C_6H_5; 3-Me; 4-OH	**387d**	289		449
8	1-C_6H_5; 3-H; 4-OMe	**387e**	155		449
9	1-C_6H_5; 3-OH; 4-H	**388a**	245		449
9	1-C_6H_5; 3-OH; 4-Me	**388b**	289		449
9	1-C_6H_5; 3-H; 4-OH	**388c**	268		449
9	1-C_6H_5; 3-Me; 4-OH	**388d**	291		449
9	1-C_6H_5; 3-H; 4-OMe	**388e**	153		449
10	1-C_6H_5; 3-OH; 4-H	**389a**	252		449
10	1-C_6H_5; 3-OH; 4-Me	**389b**	286		449
10	1-C_6H_5; 3-H; 4-OH	**389c**	252		449
10	1-C_6H_5; 3-Me; 4-OH	**389d**	297		449
10	1-C_6H_5; 3-H; 4-OMe	**389e**	167		449

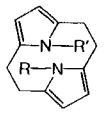
TABLE V (Continued)

Compound	n	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Metal complex(es)/general comments	Ref
	10	R = alkyl, Ph, c-Pr, $EtOCH_2CH_2$–, $MeOCH_2$–, $EtOCH_2$–, $C_6H_5OCH_2$	**390**			Data in patent	457

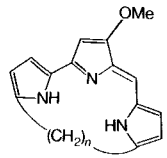
[a] Spectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS.

TABLE VI. Partial List of Macrocycles Containing a Five-Membered Subheterocyclic Ring[a]

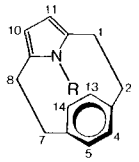
Compound	n	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Metal complex(es)/general comments	Ref
	8	R = H	**391a**	154–154.5	A–C	NMR study	176, 187
		R = Me	**391b**	[95–97 (3)]	A, B		176
		R = $–CH_2CH=CH_2$	**391c**	[75–78 (0.095)]	A, B		176
		R = C_6H_5	**391d**	54–54.5	A–C		176
		R = 4-MeC_6H_4	**391e**	94–94.5	A–C		176
		R = 3,4,5-$Me_3C_6H_2$	**391f**	95–95.5	A–C		176
		R = 2-MeC_6H_4	**391g**	[140–150 (0.02)]	A–C		176
		R = 1,4-C_6H_4–	**391h**	180 dec	A–C		176
		R = 1,4-(2,5-$Me_2C_6H_2$)–	**391i**	250 dec	A–C		176
		R = 1,4-(2,3-$Me_2C_6H_2$)–	**391j**	250 dec	A–C		176
		R = Me; 3,6-(=O)$_2$	**391k**	97–98	A, B, D		218
		R = 4-BrC_6H_4; 3,6-(=O)$_2$	**391l**	137–139	A, B, D		452
		R = R′ = H	**392a**	90–92	A, B, D		446
		R = H; R′ = Et	**392b**	[109–111 (0.2)]; 59–61	A, B, D		399, 445, 447
		R = 	**392c**	219–221	A–D	(dl)-"Metacycloprodigiosin"	399, 400, 447
		R′ = Et		208–209	A–D	HCl (218–220°); $[\alpha]_D^{20}$ –2370°	400, 445, 447
		R = CHO; R′ = Et	**392d**	109–112	A		400, 447
		R = Me; R′ = H	**392e**	107–107.5	A–D	Conformational studies	229
		R = Me; R′ = H; N-Ph	**392f**	[145 (0.095)]	A–D	Conformational studies	229
		R = Me; R′ = H; N-*o*-tolyl	**392g**	[150 (0.1)]; 46.5–47.5	A–D	Conformational studies	229
		R = Me; R′ = H; N-*p*-tolyl	**392h**	[150 (0.08)]; 39–40	A–D	Conformational studies	229
		R′ = H; R = CO_2Et	**392i**	127–129	A–D		446
		R′ = H; R = CO_2H	**392j**	120 ($–CO_2$)	A–D		446



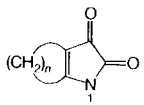
		R = R′ = Me	**393a**	144–145	A, B, D	218, 402
		R = R′ = H	**393b**	163–165	A–D	402
		R = R′ = $-CO_2Et$	**393c**		Attempted synthesis	402
		R = R′ = $-(CH_2)_2-$	**393d**	198–202 dec	A, D Suggested synthesis[402]	452
		R = Me; R′ = H	**393e**	78–79	A–D	402
		R = 4-BrC_6H_4; R′ = H	**393f**	137–140 dec (anti)	A, D Syn and anti isomers	452
		R = $-CH_2C_6H_5$; R′ = H	**393g**	84–85	A–D	402



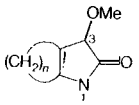
		H	**394**		A, C, D Isolation and characterization	401, 480



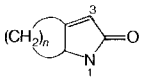
		R = H	**395a**	197–198	A–D VTNMR study	8, 184
		R = Me	**395b**	212–214	A, C, D VTNMR study	8, 184
		R = H; 4,5-benzo	**395c**	111–112	A–D VTNMR study	8, 184



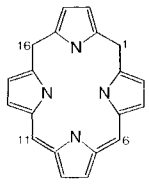
	8	1-C_6H_5	**396**	225–227		449
	9	1-C_6H_5	**397**	213		449
	10	1-C_6H_5	**398**	196		449



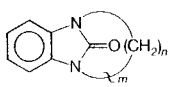
	8	1-C_6H_5; 3-OMe	**399a**	82		449
	8	1-C_6H_5; 3-OEt	**399b**	62		449
	9	1-C_6H_5; 3-OMe	**400a**	71		449
	9	1-C_6H_5; 3-OEt	**400b**	61–63		449
	10	1-C_6H_5; 3-OMe	**401a**	76		449
	10	1-C_6H_5; 3-OEt	**401b**	57		449



	8	1-C_6H_5; 3-OCH_3	**402a**	95		449
	8	1-C_6H_5; 3-OEt	**402b**	87		449
	9	1-C_6H_5; 3-OMe	**403a**	102–104		449
	9	1-C_6H_5; 3-OEt	**403b**	91		449
	10	1-C_6H_5; 3-OMe	**404a**	106		449
	10	1-C_6H_5; 3-OEt	**404b**	95		449

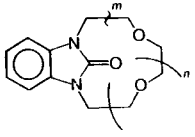
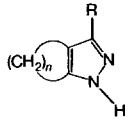
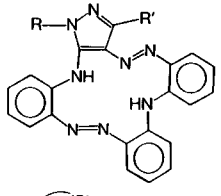
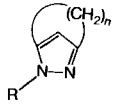


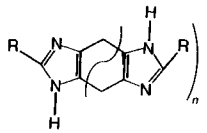
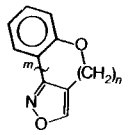
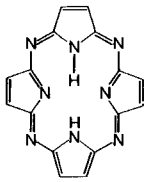
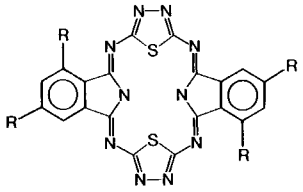
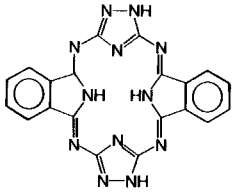
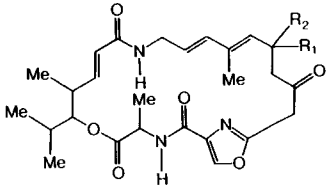
		1,6,11,16-[$-(CH_2)_5-$]$_4$	**405a**	272–272.5	A, B Incorrect structural assignment[326]	303
		1,1,6,6,11,11,16,16-$(Me)_8$	**405b**			323
		N,N,N,N-$(Me)_4$; 3,4,8,9,13,14,18,19-$(CH_2CO_2H)_8$	**405c**	233	A, D Octamethyl ester (mp 218°)	451



	$m = 1; n = 10$	H	**406**	129–130		398, 389
	$m = 1; n = 12$	H	**407**	107–108		389, 398
	$m = 2; n = 5$	H	**408**	173	Li, Ca, Sr, Ba, NH4	263, 389
	$m = 2; n = 6$	H	**409**	211	Ca	263, 389

TABLE VI (Continued)

Compound	n	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Metal complex(es)/ general comments	Ref
	$m = 2; n = 7$	H	**410**	102–105		Li, Ca	263, 389
	$m = 2; n = 8$	H	**411**	189–190			263, 389
	$m = 2; n = 10$	H	**412**	139–140		Ca, NH_4	263, 389
	$m = 3; n = 4$	H	**413**	218–219		Ca, Sr	263, 389
	$m = 3; n = 6$	H	**414**	151–152			389
	$m = 1; n = 2$	H	**415**	117–118		Li, Na, Ca, Sr, K, Cs	263, 389
	$m = 1; n = 5$	H	**416**	[95–100 (0.05)]		Mg, Li, Na, Ca, Sr, K, Ba, Cs	263, 389
	$m = 2; n = 0$	H	**417**	197–199		Mg, Li, Na, Ca, Sr, Ba, NH_4^+	263, 389
	$m = 2; n = 1$	H	**418**	114		Mg, Li, Na, Ca, Sr, Ba	263, 389
	9	H	**419**	[100–105 (0.2)]	A		205
	10	R = Me	**420a**	63–65	A, C		269
		R = Et	**420b**	79–80 (glass)	A, C		269
		R = H	**420c**	[160(0.025)]; 88.5–89°	A, B	n_D^{28} 1.5305	271
		R = C_6H_5; R′ = Me	**421**			Ni (also isomers)	450
	6	R = H	**422**	[~106–107 (0.01)]	A–D	Mixture of isomers	270
	7	R = H	**423a**	71.5–72	A–D	Conformational study[229]	229, 390
		N-C_6H_5; R = H	**423b**	[125–128 (0.08)]; 33–34.5	A–D	Conformational study[229]	229, 390
	9	R = H	**424**	[130–135 (0.05)]; 107	A, B	HCl	205
				109–109.7	A–D		206
	10	R = H	**425**	92.5–93	A–C		271
	11	R = H	**426a**	150–151	A, C		269
		R = Me	**426b**	137	A, C		269

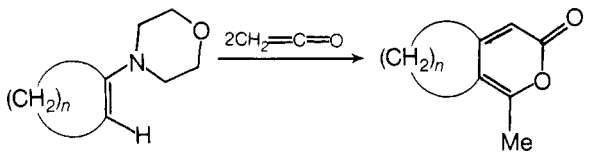
	2	$R = C_6H_5$	**427**	>250	A, B, D		265
	3	$R = C_6H_5$	**428**	>250	A, B, D		265
	$m = 2; n = 3$	H	**429**	236–237	A		138
	$m = 2; n = 4$	H	**430**	168	A		138
		H	**431**			MO–LCAO calculations	455
						(Other aza derivatives were also considered)	455
		$R = SO_3H$	**432**			Co	456
		H	**433**		C	Co, Ni, Zn, Co, Cd	439
		$R' = R^2 = O$	**434a**				440
		$R' = H; R^2 = OH$	**434b**				440

[a] Spectral data cited in the literature: A = PMR; B = IR; C = UV; D = MS.

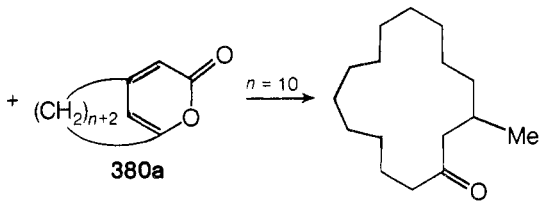
Vitamin B_1 derivatives (e.g., **362**) have been easily synthesized (55%) from thiamine hydrochloride upon treatment with aqueous sodium hydroxide, formaldehyde, and diethylamine.[386]

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-pyrones **379** and **380** from 1-morpholinocyclododec-1-ene[264] via the procedure of Hünig and Hoch.[423] Pyrone **380a** was converted into racemic muscone by saponification and subsequent hydrogenation.[264]

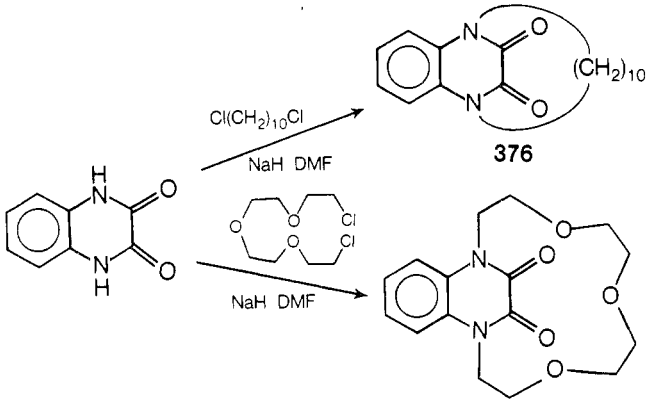


379



380a

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.[263,389,464]



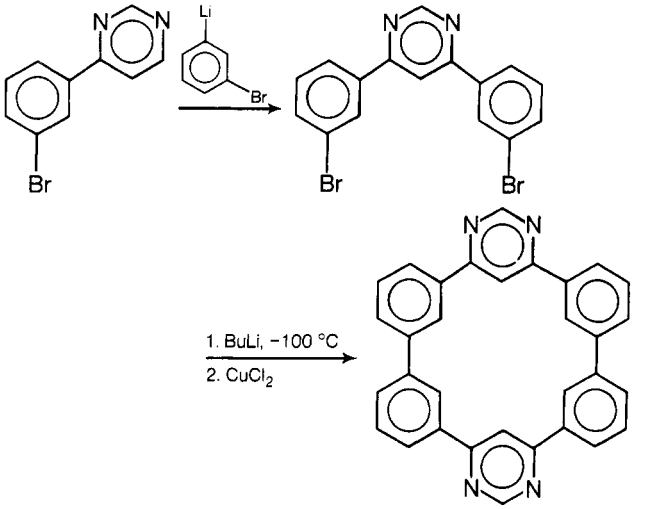
376

377

Synthesis of heterocyclic cyclopolyaromatics 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]

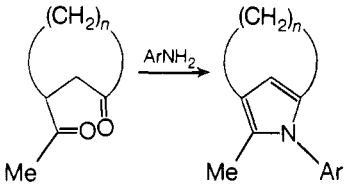
B. Miscellaneous Macrocycles with Five-Membered Subunits

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-acetylcycloalkanones into (2,4)pyrrolophanes (**392e**) by treatment with substituted anilines.[229] Other heterophanes have been synthesized from suitable macrocyclic 1,4-diones: pyrazolophanes (ref



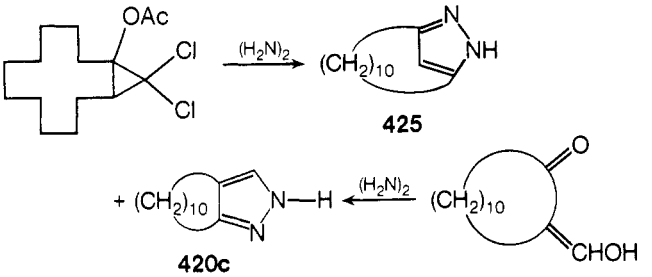
386

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



392e

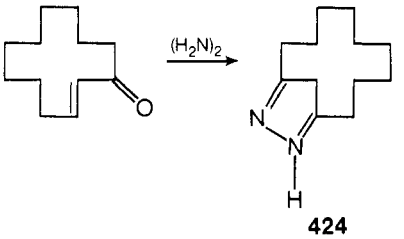
Parham's procedure for the synthesis of pyrazoles from cyclopropanes has proven to be a convenient route to pyrazolophanes **420c** and **425.**[270,271] **420c** was also prepared from 2-hydroxymethylenecyclododecanone.[271]



425

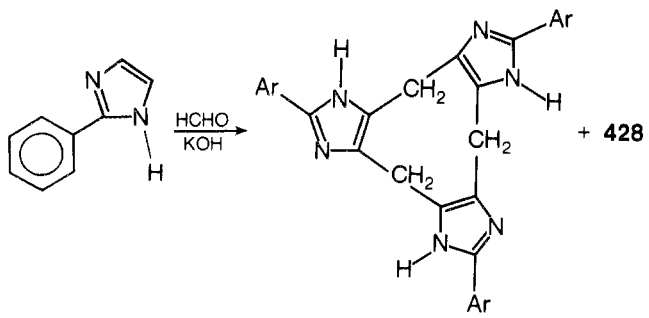
420c

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

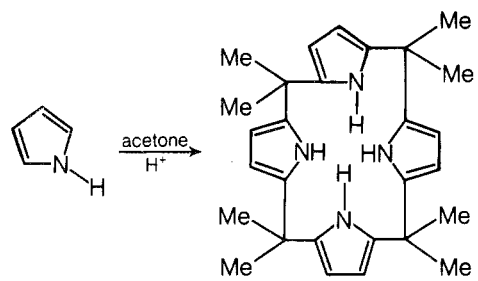


424

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]



427



405b

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 sulfoxide 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)-dithia[*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*-isopropylidenepyridoxine.[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-dihydropyridine, 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 dihydropyridine 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]

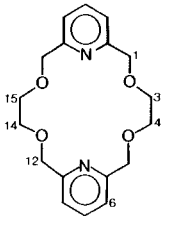
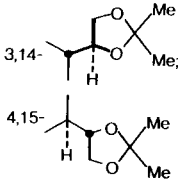
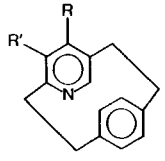
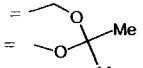
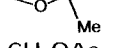
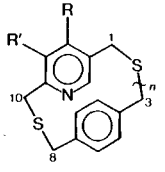
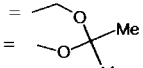
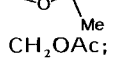
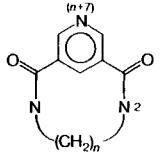
IV.C.3. The Wittig reaction of 2,2′-bis(triphenylphosphiomethyl)biphenyl dibromide and thiophene-2,3-dicarboxaldehyde afforded an 18% yield of 9,13-dihydrotriphenyleno[2,3-*b*]-thiophene via the intermediacy of 1,2:3,4-dibenz[7,8-*b*]thieno[10]annulene (**457**), which was too unstable for isolation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

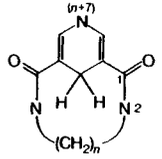
VI.A. The reaction of 1-(ω-bromobutyl)uracil with the sodium salt of *p*-toluenesulfamide gave (10%) **458** as a high-melting crystalline compound.[465]

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]

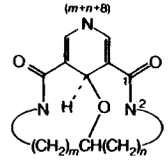
VI.B. The structure of griseoviridin (**460a**),[473,474,476] a metabolite of *Streptomyces griseus,* has been revised[475] as based on the chemical and detailed ^1H and ^{13}C NMR and mass spectral studies. The relationship of **460a** to other related cyclic microbial peptides and possible biogenetic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

TABLE VII. Addendum Table

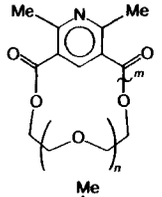
Compound	n	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Metal complex(es)/ general comments	Ref
			To Table I				
	1		**51d**	147–149	A	$[\alpha]_D$ ($CHCl_3$) –22°; K_a; $C_6H_5CH_2NH_3^+$ (SCN^-); t-$BuNH_3^+$	491
	1	R′ =  R = 	**140b**				478
	1	R′ = CH_2OAc; R = OAc	**140c**				478
	1	R′ =  R = 	**148c**				478
	1	R′ = CH_2OAc; R = OAc	**148d**				478
	1	R′ = CHO; R = OH	**148e**	218–219 dec			478
	7	14-(2,6-$Cl_2C_6H_3CH_2$)(Br^-)	**178g**	288–290	A, B		493
	7	6-OH; 14-(2,6-$Cl_2C_6H_3CH_2$)(Br^-)	**178h**	254–255	A, B		493
	7	6-(=O)	**178i**	313–316	A, B		493
	7	6-(=O); 14-2,6-$Cl_2C_6H_3CH_2$)(Br^-)	**178j**	257–259	A, B		493
	7	6- 	**178k**	266–267	A, B		493
	5	H	**435**	236–238	A, B		493
	6	H	**436**	298–300	A, B		493
	8	H	**437**	341–343	A, B		493
	9	7-OH	**438a**	352–354	A, B		493
	9	7-OH; 16-(2,6-$Cl_2C_6H_3CH_2$)(Br^-)	**438b**	224–226	A, B		493
	9	7-(=O)	**438c**	323–325	A, B		493
	9	7-(=O); 16-(2,6-$Cl_2C_6H_3CH_2$) (Br^-)	**438d**	221–223	A, B		493
	9	7-(=O); 16-CH_3 (I^-)	**438e**	262–266	A, B		493
	9	7- 	**438f**	347–351 dec	A, B		493



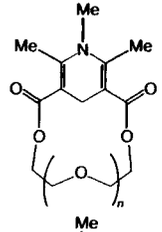
7	6-(=O); 14-(2,6-$Cl_2C_6H_3CH_2$) (Br^-)	**439**	265–268	A–C		493
8	15-(2,6-$Cl_2C_6H_3CH_2$)	**440**	230–231 dec	A–C		493
9	7-(=O); 16-(2,6-$Cl_2C_6H_3CH_2$)	**441a**	215–217	A–C		493
9	7-(=O); 16-CH_3	**441b**	231–234	A–C		493



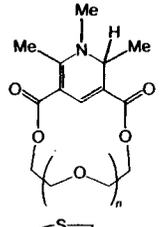
$m = n = 3$	14-H	**442a**		C		493
$m = n = 3$	15-OH; 16-H	**442b**		C		493
$m = n = 4$	16-H	**443**		C		493



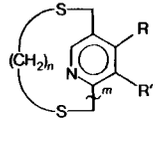
$m = 1; n = 2$	H	**444**	167–169	A, C		492
$m = 1; n = 3$	H	**445**	90–92		$Me(ClO_4^-)$ salt (mp 190–193°)	492
$m = 2; n = 0$	H	**446**	196–198	A, C		492
$m = 2; n = 1$	H	**447**				492
$m = n = 2$	H	**448**				492
$m = 2; n = 3$	H	**449**				492



$n = 3$	H	**450**	110–113			492

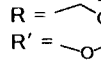
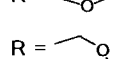
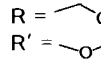
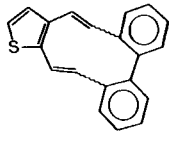
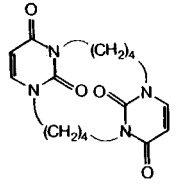
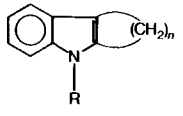


$n = 3$	H	**451**	131.5–133			492

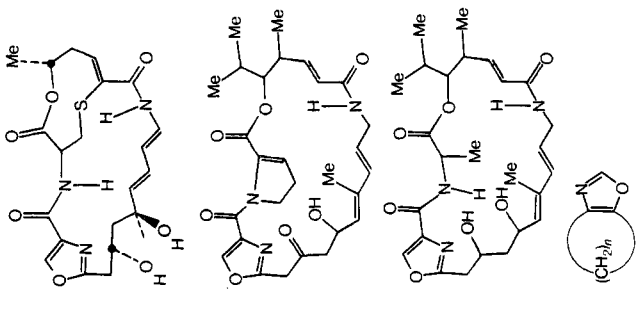


$m = 1; n = 4$	R = R′ = H	**452a**	Oil			478
$m = 1; n = 4$	R = R′ =	**452b**	145			478
$m = 1; n = 6$	R = R′ = H	**453a**	129			478
$m = 1; n = 6$	R = R′ =	**453b**	169			478
$m = 1; n = 6$	R = CH_2OAc; R′ = OAc	**453c**	122			478
$m = 1; n = 8$	R = R′ = H	**454a**	Oil			478
$m = 1; n = 8$	R = R′ =	**454b**	Oil			478

TABLE VII (Continued)

Compound	*n*	Substituents	Compd no.	Physical data Mp [bp (mm)], °C	Spectral data available	Metal complex(es)/ general comments	Ref
	$m = 1; n = 8$	R′ = CH_2OAc; R = OAc	**454c**	Oil			478
	$m = 2; n = 4$	R =  R′ = 	**455**	150			478
	$m = 2; n = 6$	R =  R′ =	**456**	Oil			478
			To Table II				
	1	H	**204v**	140–142	A, B	Perhydro [isomers; oil]	500
	1	1,11-($CH_2CH_2CO_2Et$); 1,6,6,11,16,16-$(Me)_6$	**204w**	126–128	A, B	Prehydro [isomers; oil]	500
	2	1,1,6,6,11,11,16,16,-21,21-$(Me)_{10}$	**204x**	Oil	A, B	Prehydro [isomers; oil]	500
	3	1,1,6,6,11,11,16,16 21,21,26,26-$(Me)_{12}$	**204y**	182	A, B	Perhydro [isomers (!); mp 75–80°]	500
			To Table III				
		H	**457**			Proposed intermediate	464
			To Table V				
		H	**458**	>340	B, C		465
			To Table VI				
	10	R = $COCH_2CH(Me)NH_2$	**459**	231–233	A–D		472

H	**460a**	161–163 dec	A–D	$[\alpha]_D$ −232°; HCl (>190°) HBr (>300°); perchlorate (>190°)	473–475 473–475
N, N-Diacetate	**460b**	136–140 dec	A, B, D		
	461				477
	462			Antibiotic A-2315	477
H	**463**	[84–85° (0.15)]		Reactions of	484



10

VI.B. 4,5-Decamethyleneoxazole (**463**)[484] was prepared in 46% yield by treatment of 2-hydroxycyclododecanone with formamide in sulfuric acid by a modification of the procedure of Bredereck and Gompper.[502]

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