for running the ^{13}C NMR spectra and the simulation plot of the proton spectrum of 8. We also thank Mr. Koji Goto of JEOL Analytical Instruments for running the 100-MHz proton spectrum of 8.

Registry No.—**1**, 57802-40-1; **2**, 61473-88-9; **2b**, 61473-89-0; **3**, 61473-90-3; **4**, 61394-83-0; **5**, 61394-84-1; **6**, 61394-85-2; **7**, 61394-86-3; **8**, 61394-87-4; bicyclo[2.2.1]hepta-2,5-diene, 121-46-0; *m*-chloroperbenzoic acid, 937-14-4; vinyl chloride, 75-01-4; styrene, 100-42-5; isobutylene, 115-11-7; α-methylstyrene, 98-83-9; ethylene, 74-85-1.

Supplementary Material Available. Normal and decoupled ^1H NMR spectra of **2**, **2a**, **3**, and **3a** in the C-12 methylene region, a plot of chemical shift of **3** protons vs. equivalents of $Eu(fod)_3$, the 100-Hz ^1H NMR of 8 and the simulated spectrum of 8, and ^1H NMR data for the compounds 4–8 and **4a**–**8a** (4 pages). Ordering information is given on any current masthead page.

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Cyclophanes. 10.[1] Synthesis and Conformational Behavior of [2.2](2,5)Pyrrolophanes[2]

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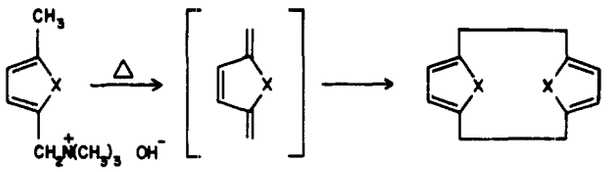
Attempted synthesis of [2.2](2,5)pyrrolophanes by 1,6-Hofmann elimination proved unsuccessful and led only to dipyrrolmethanes. [2.2](2,5)Pyrroloparacyclophane (**11a**), [2.2](2,5)pyrrolo(1,4)naphthalenophane (**12a**), and [2.2](2,5)pyrrolo(2,5)furanophane (**13a**) were prepared by Paal–Knorr cyclization of 3,6-diketo[8]paracyclophane (**10a**), 3,6-diketo[8](1,4)naphthalenophane (**10b**), and 3,6-diketo[8](2,5)furanophane (**10c**), respectively, with ammonia. Preparation of the analogous *N*-methyl derivatives **11b**, **12b**, and **13b** by Paal–Knorr cyclization using methylamine was successful only for the synthesis of *N*-methyl[2.2](2,5)pyrroloparacyclophane (**11b**). *N*-Methyl-[2.2](2,5)pyrrolophane (**17a**) and *N*-benzyl[2.2](2,5)pyrrolophane (**17b**) were also synthesized by Paal–Knorr cyclization of 1,4,7,10-cyclododecatetraone by successive treatment with the appropriate alkylamine and ammonia. Reductive cleavage of the benzyl group in **17b** with sodium afforded the parent [2.2](2,5)pyrrolophane (**1**). The spectral properties and structural assignment of the above pyrrolophanes are discussed. Variable temperature NMR studies on the above pyrrolophanes indicated that all aromatic rings in the above phanes are conformationally rigid on the NMR time scale with the exception of the pyrrole ring in **11a**. In this pyrrolophane the barrier to pyrrole ring rotation is 17 kcal/mol.

In the past two and one-half decades a substantial literature has accumulated concerning the synthesis and properties of cyclophanes.[4] The syntheses of [2.2]cyclophanes containing heteroaromatic nuclei have been extensively recorded and among some of the common heteroaromatic groups which have been incorporated into the cyclophane macrocycle are furan,[5] thiophene,[5a,6] pyridine,[7] and pyridazine.[7a,8] However, conspicuously absent from these ranks are those containing the pyrrole moiety.[9] Indeed, except for the recent synthesis of *N,N'*-dimethyl[2.2](2,5)pyrrolophane (**2**)[10] the literature is devoid of reports concerning [2.2]pyrrolophanes. Of special interest is the parent phane, [2.2](2,5)pyrrolophane (**1**). On the basis of relative properties, general chemical behavior, and stability,[11] pyrrole, like the analogous furan and thiophene ring systems, ought to exist as a stable aromatic entity within a [2.2]cyclophane macrocycle. Additionally, in view of the contemporary interest in rotational behavior of aromatic moieties within [2.2]cyclophanes,[12] the dynamic behavior of [2.2](2,5)pyrrolophanes, as compared with [2.2](2,5)furanophanes, [2.2](2,5)thiophenophanes, [2.2](2,6)pyridinophanes, and other [2.2]metaphanes, would prove of interest in defining the relative stéric bulk and intramolecular interactions of an N–H and N^- grouping as compared with O:, S:, N:, and C–H groupings during the rotational process in which these groups pass through the cavity of the cyclophane macrocycle. In view of the above we undertook the synthesis of a number of pyrrolophanes.

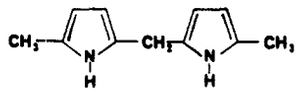
Hofmann Pyrolytic Route. Previous successful use of a 1,6-Hofmann elimination reaction on the appropriate quaternary ammonium hydroxide for the synthesis of **3**[5a] and **4**[5a] (see Scheme I) prompted us to attempt the synthesis of **2** by this method. A procedure quite analogous to that traditionally

Scheme I



5 a X=O
b X=S
c X=N-H

1 X=N-H
2 X=N-CH$_3$
3 X=O
4 X=S

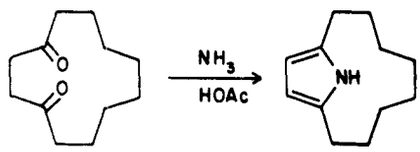


6

followed was used with the modification of strict exclusion of light and oxygen. However, pyrolysis of quaternary ammonium hydroxide **5c** afforded one major product in low yield, dipyrrylmethane **6**, but none of the expected pyrrolophane was observed.

Paal–Knorr Cyclization Route. This successful synthetic approach to the [2.2](2,5)pyrrolophanes is based on work of Nozaki[9b] and Wasserman[10a] in which the former synthesized [8](2,5)pyrrolophane (**7**) by cyclization of 1,4-cyclododecadione with ammonia (see Scheme II) and the latter synthesized *N*-methyl-3,6-diketo[8]pyrrolophane (**8**) and *N,N'*-

Scheme II



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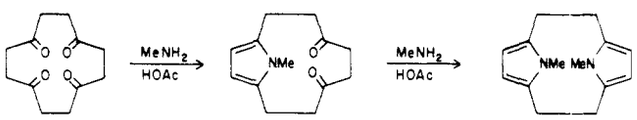
dimethyl[2.2](2,5)pyrrolophane (**2**) by cyclization of 1,4,7,10-cyclododecatetraone with methylamine (see Scheme III). Since the requisite 1,4-diketone synthon necessary for

Scheme III

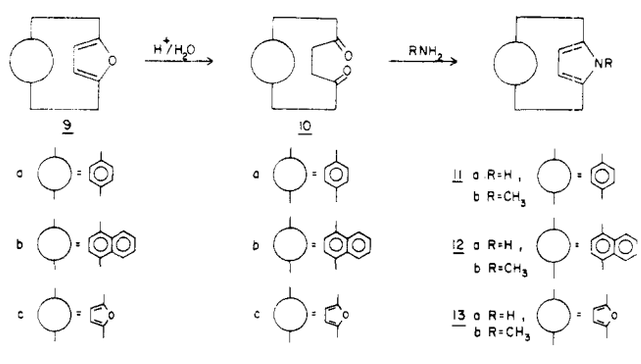


15 8 2

cyclization was potentially available from the furan containing phanes by hydrolysis, a series of mixed [2.2](2,5)pyrrolophanes was synthesized initially.

A. Pyrrolophanes from 3,6-Diketo[8]phanes. In general, the synthetic scheme (see Scheme IV) involved generating the

Scheme IV



9 10

11 a R=H, b R=CH$_3$
12 a R=H, b R=CH$_3$
13 a R=H, b R=CH$_3$

γ-diketone **10** from the appropriate furanophane **9** by acid hydrolysis in the absence of light and oxygen. The crystalline diketones were then cyclized to the pyrrolophanes by treatment with ammonia via a Paal–Knorr reaction.[11a] Thus 3,6-diketo[8](1,4)naphthalenophane (**10b**) and 3,6-diketo[8]-(2,5)furanophane (**10c**) were synthesized in 71 and 68% yield, respectively, as had been done previously by Cram[5b] for 3,6-diketo[8]paracyclophane (**10a**), by refluxing **9b** and **9c**, respectively, for 18 h at 105 °C and 17 h at 55 °C in an acetic acid/water/sulfuric acid medium.

Treatment of **10a, 10b,** and **10c** with ammonia in acetic acid at 80 °C in the dark under nitrogen followed by workup and chromatography afforded pyrrolophanes **11a, 12a,** and **13a** in 55, 86, and 67% yields, respectively.

The reaction of diones **10** with the more bulky methylamine was successful only for the preparation of *N*-methyl[2.2]-(2,5)pyrroloparacyclophane (**11b**) and as expected the reaction required elevated temperatures. Thus, when **10a** was treated with methylamine in acetic acid at 105 °C, **11b** was formed in 53% yield. While the reaction of methylamine with **10b** and **10c** was also carried out at higher temperatures only starting materials were recovered. The reason for the nonreactivity of **10b** and **10c** toward methylamine is not fully understood but is probably due, in the former, to the increased interaction of the *N*-methyl group with the outer fused portion of the naphthalene ring during the attack of the amine on the carbonyl. This steric interaction would be even more important during ring closure. What is surprising is that this does not force the formation of a *syn*-*N*-methyl[2.2](2,5)pyrrolo(1,4)-naphthalenophane from **10b** and that the reaction does not take place with **10c**. That **10a** reacts while **10b** and **10c** do not may be indicative of an attractive or stabilizing influence by the benzene ring during the formation of the pyrrole ring.

As was expected, reaction of **10a, 10b,** and **10c** with the exceptionally bulky *tert*-butylamine afforded only starting material.

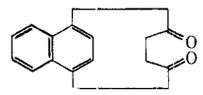
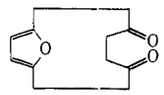
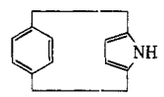
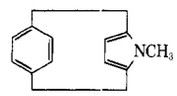
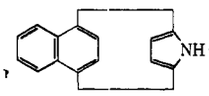
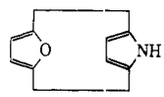
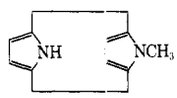
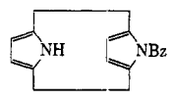
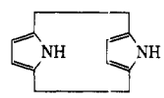
Characterization of 3,6-diketo[8]cyclophanes **10b** and **10c** followed from spectral analysis (see Table I) and the spectral data for **10b** and **10c** are consistent with the structures proposed. Of particular interest are the NMR spectra[13] of **10b** and **10c**, which indicate unrestricted conformational mobility of the furan ring in **10c** and the aliphatic chain in **10c** and **10b**, and restricted mobility of the naphthalene ring in **10b**.[14]

The assignment of structures to **11a,b, 12a,** and **13a** is based on spectroscopic analysis.[5b,c,10] All four pyrrolophanes exhibit mass spectral patterns which are typical for the cyclophane structure, i.e., a parent peak and major peaks corresponding to fragmentation of the molecule by cleavage of the two ethylene bridges. The band usually associated with transannular π–π interactions (244 nm) in the ultraviolet spectra of [2.2]-cyclophanes[15] is only observed for **12a**; however, this band is sometimes not observed in [2.2]cyclophanes containing a five-membered heterocyclic nucleus.[5c] The presence of the pyrrole hydrogen is indicated by the sharp absorption at ca. 3400 cm^{-1} in the infrared spectra of all but **11b**.

The NMR spectra of **11a,b, 12a,** and **13a** conclusively prove the cyclophane structure of these compounds. The benzenoid protons in **11a** and **11b** appear as an AA'XX' multiplet suggesting that the two rings are frozen parallel to one another, thus allowing one side of the benzene ring to encounter a greater portion of the shielding effects of the pyrrole ring. This is in sharp contrast to [2.2](2,5)furanoparacyclophane **9a**, which exhibits, in its room temperature spectrum, a singlet for the benzenoid protons[5b,13] due to the rapid rotation of the furan nucleus.

Of greatest interest, and a fact which lends support to the above structures, is the chemical shift of the pyrrole hydrogen. The chemical shift for this proton in 2,5-dimethylpyrrole is τ 2.52.[16] In pyrrolophanes **13a, 11a,** and **12a**, respectively, this

Table I. Physical and Spectral Properties of [2.2](2,5)Pyrrolophanes

Compd	Structure	Mp, °C[a] (crystn solvent)	Yield,[b] %	NMR, τ[c]	IR, cm^{-1}[d]	UV, λ_{max}, nm (log ϵ)[e]	MS[f]
10b		158–159 (EtOH/H_2O)	71	2.2 (AA'BB', 4 H) 2.83 (s, 2 H) 6.6 (m, 4 H) 7.55 (m, 4 H) 8.67 (m, 4 H)	1680 (C=O)	231 (4.65) 297.5 (3.70)	266, 168 144, 100
10c		109–110 (H_2O)	68	4.2 (s, 2 H) 7.45 (s, 4 H) 7.45 (AA'BB', 8 H)	1700 (C=O)	222 (3.56) 292 (sh) (1.94)	206, 108 107, 99
11a		197–198 (hexane)	55	3.28 (AA'XX', 4 H) 4.55 (d, 2 H, J = 2.5 Hz) 5.00 (broad s, 1 H) 7.4 (m, 8 H)	3400 (N–H)	219 (4.3) 269 (sh) (2.98) 286 (sh) (2.79)	197, 104 93
11b		212–214 (EtOH/H_2O)	53	3.46 (AA'XX', 4 H) 4.4 (s, 2 H) 7.15 (m, 8 H) 7.5 (s, 3 H)		204.5 (3.99) 226.5 (3.89) 269 (sh) (2.75) 279 (sh) (2.61)	211, 107 104
12a		111–112 (EtOH/H_2O)	83	2.3 (AA'BB', 4 H) 3.5 (s, 2 H) 4.5 (d, 2 H, J = 3.0 Hz) 6.2 (broad s, 1 H) 6.4 (m, 2 H) 7.5 (m, 6 H)	3450 (N–H)	226.5 (4.28) 243 (sh) (4.13) 301 (3.43)	247, 144 93
13a		131–132 (EtOH/H_2O)	65	3.6 (broad s, 1 H) 3.95 (s, 2 H) 4.05 (d, 2 H, J = 3.0 Hz) 7.35 (m, 8 H)	3408 (N–H)	222 (4.00)	187, 93 94
17a		78–79[g]	43	3.4 (broad s, 1 H) 3.71 (s, 2 H) 4.15 (d, 2 H, J = 2.9 Hz) 6.98 (s, 3 H) 7.15 (m, 8 H)	3450 (N–H)	204 (4.22) 219 (4.04) 240 (3.91)	200 107 93 92
17b		84–85[g]	17	3.45 (broad s, 1 H) 2.7–3 (m, 5 H) 3.8 (s, 2 H) 4.1 (d, 2 H, J = 2.6 Hz) 5.42 (s, 2 H) 7.27 (m, 8 H)	3450 (N–H)	206 (4.10) 240 (3.76) 263 (3.11) 270 (2.94)	276 183 182 168 93 91
1		163–164[g]	87	3.58 (broad s, 2 H) 4.16 (d, 4 H, J = 2.5 Hz) 7.43 (AA'BB', 8 H)	3450 (N–H)	218 (3.98) 254 (3.19)	186 185 94 93

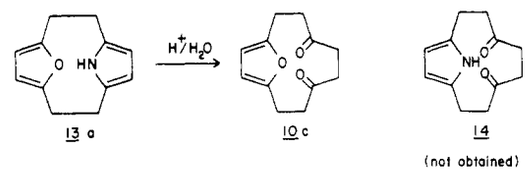
[a] Uncorrected. [b] Isolated. [c] $CDCl_3$/1% Me_4Si. [d] KBr. [e] EtOH (absolute). [f] m/e. [g] Sublimed.

absorption appears at τ 3.6, 5.0, and 6.3.[17] Additionally, the chemical shift of the *N*-methyl group in **11b** appears 0.72 ppm upfield from that observed in 1,2,5-trimethylpyrrole.[18] These data clearly indicate that the substituent on the nitrogen is positioned above an aromatic plane and enjoys the increasing anisotropic shielding influence of the aromatic nuclei.[19,20] This property is typical and consistent with the cyclophane structures proposed.

Finally, the appearance of the β-pyrrole protons in **11a,b** and **12a** at chemical shifts nearly identical with those in 2,5-dimethylpyrrole and 1,2,5-trimethylpyrrole[21] indicates a minimum of transannular shielding by the parallel aromatic ring. In addition, the pyrrole protons in **13a** appear at a chemical shift similar to those in *N,N'*-dimethyl[2.2](2,5)-pyrrolophane previously assigned an anti configuration by Wasserman and Bailey.[10] These facts, coupled with the above noted significant upfield shifts of the nitrogen substituent, demonstrate that **12a** and **13a** exist in the more stable anti conformation.[5c]

B. Pyrrolophanes from 1,4,7,10-Cyclododecatetraone (15). Initially it was supposed that **1** would be available from **13a** by selective hydrolysis of the more reactive furan ring[11b,22] followed by Paal–Knorr cyclization of 3,6-diketo[8](2,5)pyrrolophane (**14**) (see Scheme V). However treatment of **13a**

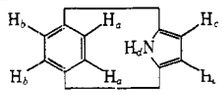
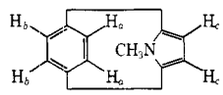
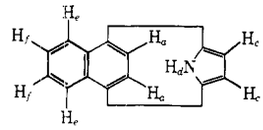
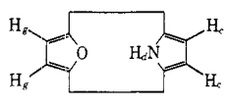
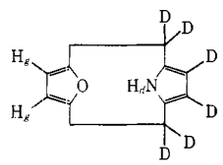
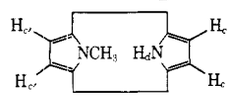
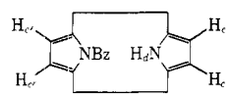
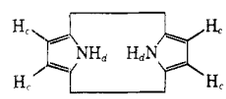
Scheme V



with 10% sulfuric acid in acetic acid for 16 h at 65 °C afforded only **10c**.

In addition, in light of the successful Paal–Knorr cyclizations described above, we attempted a synthesis of **1** by the reaction of tetraone **15** with ammonia but were unsuccessful.[23] *N*-Methyl[2.2](2,5)pyrrolophane (**17a**), *N*-benzyl[2.2](2,5)-

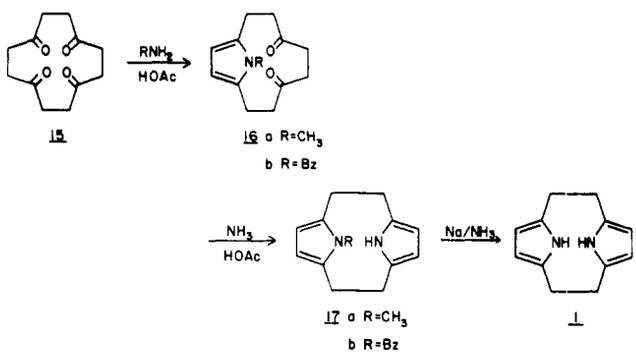
Table II. Chemical Shifts (τ) and Assignments for Protons in [2.2](2,5)Pyrrolophanes

Compd	Structure	a	b	c	d	e	f	g	Bridge
11a		3.29	2.85	4.55	5.0				7.40[a]
11b		3.88	3.05	4.40					7.15[a] 7.5 (NCH_3)
12a		3.50		4.50	6.2	1.95	2.36		6.25[a] and 7.50[a]
13a				4.05	3.6			3.95	7.35[a]
13a-d_6					3.6			3.9	7.3[a]
17a				c 4.15 c' 3.71	3.4				7.15[a] 6.98 (NCH_3)
17b				c 4.1 c' 3.8	3.45				7.27[a]
1				4.16	3.58				7.43[a]

[a] Multiplet center.

pyrrolophane (**17b**), and the parent pyrrolophane **1** were, however, successfully prepared from tetraone **15** as described in Scheme VI. Thus, **15** was treated in glacial acetic acid with

Scheme VI



methylamine for 10 min, affording dione **16a**.[10] The dione was not isolated but treated in situ with ammonia. Chromatography of the reaction mixture followed by sublimation afforded pyrrolophane **17a** in 43% yield.

Analogously, **15** was treated successively with benzylamine and ammonia and afforded a 17% yield of **17b** after chromatography and sublimation. Reductive cleavage of the benzyl group by sodium in liquid ammonia afforded the parent [2.2](2,5)pyrrolophane **1** in 87% yield after sublimation. Compounds **17a, 17b,** and **1** were characterized spectrally and the pertinent data are summarized in Table I.

Compounds **17a, 17b,** and **1**, respectively, exhibit the simple recognizable mass spectral characteristics of [2.2]cyclophanes showing a molecular ion for the phane (*m/e:* **17a,** 200; **17b,** 276; **1,** 186), and ions corresponding to the two fragments arising from, and indicative of, the cleavage of the ethylene bridges (*m/e:* **17a,** 107 and 93; **17b,** 183 and 93; **1,** 93). In addition compound **17b** exhibits a strong peak at *m/e* 91 associated with the loss of the benzyl group. The infrared spectra of the three compounds confirm the presence of a nitrogen–hydrogen bond, exhibiting, in each, an absorption at 3450 cm^{-1} characteristic of the N–H stretch. The ultraviolet absorption spectra of these compounds are not unusual. Compound **17b** exhibits two shoulders at 270 and 263 nm confirming the presence of the benzenoid group. All three compounds show absorptions, in the 240–250-nm region, usually associated with transannular π–π interactions.[15] The degree (if any) that these interactions enhance this absorption is not immediately evident since pyrrole nuclei normally absorb in this region, albeit with a much lower extinction coefficient.

The NMR spectra of the three cyclophanes were most significant and informative in elucidating their structures. Each compound exhibited broad absorptions at τ 3.4–3.6, indicative of the nitrogen-bound pyrrole proton. The chemical shift of these protons is similar to that observed in [2.2]-(2,5)furano(2,5)pyrrolophane **13a** (τ 3.6), illustrative of the similar anisotropic shielding effects of both the furan and pyrrole rings. The chemical shift of the β protons on the N-unsubstituted pyrrole nuclei in **17a, 17b,** and **1** is observed at about τ 4.1 and the peaks are split into doublets by the pyrrole N–H. These chemical shifts and coupling constants are similar to those found in **13a** (τ 4.05, J = 3.0 Hz). The analogous β protons on the N-substituted pyrrole rings in **17a** and **17b,** on the other hand, are found as sharp singlets at τ 3.7–3.8 and are positioned near the chemical shift of the β-pyrrole protons in **2** (τ 3.9).[10] Each compound also shows a complex absorption pattern at τ 7.3 for the eight protons on the ethylene bridges.

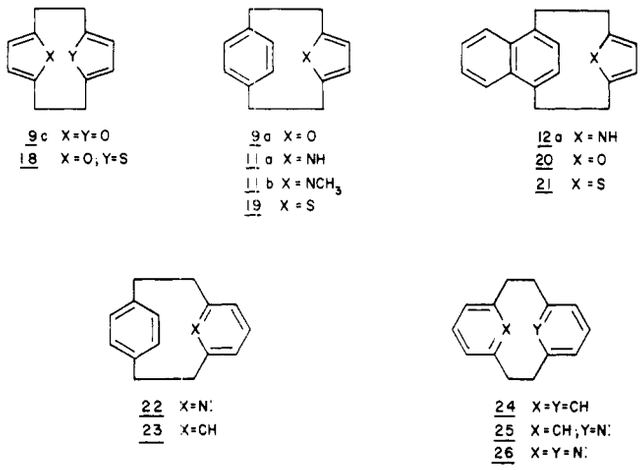


Figure 1.

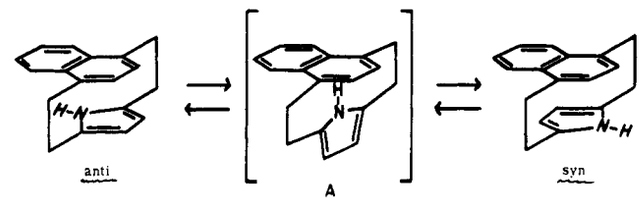


Figure 2.

Again, the shifts are similar to those found in **2** (τ 7.16)[10] and **13a** (τ 7.35). Additionally, **17a** exhibits a single absorption at τ 7 for the *N*-methyl protons, similar to that found in **2** (τ 6.95),[10a] and **17b** shows a singlet at τ 5.42 and a multiplet at τ 2.85 for the methylene and benzenoid protons of the benzyl group, respectively. The above data are entirely consistent with the assigned structures of **17a, 17b,** and **1.**

Conformational Behavior of Pyrrolophanes. The conformational behavior of numerous [2.2]cyclophanes has been studied internationally in various groups by variable temperature NMR spectroscopy. It has been demonstrated that the size of the cavity of the cyclophane macrocycle and the steric bulk of the groups passing through this cavity play a major role in determining the barrier to rotation of various aromatic groups.[6a,b,7a,b,8,13,25,26] For instance, cyclophanes (see Figure 1) **18**,[6a] **19**,[6c] **20**,[5c,6b] **21**,[6b] **24**,[25f] and **25**[6a] are rigid on the NMR time scale (E_{act} > 27 kcal/mol) while **9a**,[13] **9c**,[7a] **22**,[7c] **23**,[25a,26] and **26**[7a] are mobile, with coalescence temperatures (T_c, °C) and activation energies (E_{act}, kcal/mol) of −40, 11.1; 63, 16.8; −43.5, 10.7; 157, 20.6; and 13.5, 14.8, respectively. Because rotational behavior of the pyrrole nuclei in cyclophanes was not known, a variable temperature NMR study was carried out on the pyrrolophanes synthesized above.

The chemical shift data (ambient temperature) for the various protons in pyrrolophanes **11a, 11b, 12a, 13a, 17a, 17b,** and **1** are given in Table II.

At room temperature, the protons on the benzene nuclei in both compounds **11a** and **11b** appear as a well-separated AA'XX' multiplet, similar to that observed for **9a** at low temperatures, providing strong evidence for a frozen conformation for both **11a** and **11b.** Upon raising the sample temperature, **11a** exhibits a broadening and coalescence (T_c = 105 °C) of the multiplets associated with protons a and b until at 190 °C a sharp singlet at a point halfway between the original two multiplets is observed. This behavior is completely in accord with an averaging of the environment of these benzenoid protons by rapid flipping of the heterocyclic nucleus. At the above T_c the process requires a $\Delta G^{\ddagger}$ of ca. 17 kcal/mol.[27] This energy barrier is thus greater than that associated with either **22** or **9a,** but, as might be expected from the size of the N atom and the length of the N–H bond, less than that for **23.** The protons on the ethylene bridges, which give rise to an ABCD multiplet at ambient temperatures, show a corresponding spectral change and appear as a symmetrical AA'BB' multiplet at 190 °C.

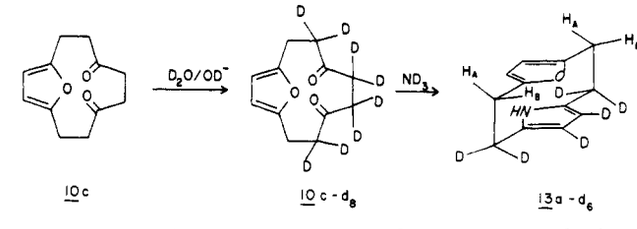
The variable temperature NMR behavior of **11b** was also examined. The NMR spectrum of **11b,** however, remained unchanged from ambient temperature to 190 °C, indicating a greater energy barrier for flipping. No broadening of the multiplets due to the benzenoid protons was observed up to 190 °C, suggesting an activation energy in excess of 27 kcal/mol,[7a,25a,26] an expectedly high barrier in view of the steric bulk of the methyl group.

A priori, it might be reasoned that **12a** should exhibit rotational behavior similar to that shown by **22, 23, 9a,** or **11a.** However, while the barriers to flipping in these compounds are for the most part due to the bulky size of the atoms or group of atoms passing through the cavity during the inversion process, there is an added interaction in **12a** which can contribute to the energy barrier in converting the anti to the syn conformation (see Figure 2). Inspection of models shows that the syn conformer is indeed more energetic due to an added transannular π–π interaction. The barrier to rotation would, therefore, be somewhat perturbed as compared with that of **11a,** depending upon the magnitude of this π–π interaction.

It was found that the aromatic region of the NMR spectrum of **12a** remained unchanged from room temperature to 190 °C. Apparently, despite the capability of the N–H to pass through an aromatic π cloud (as demonstrated from the data on compound **11a**), the syn conformer of **12a,** being relatively energy rich, is not populated to an appreciable extent. Thus, an averaged spectrum, nearly identical with that of the anti conformation, is obtained. While the above NMR data are not rich in conformational information, they do indicate that other influences,[28] aside from steric bulk, effect the flipping in these cyclophanes, and that the syn and anti conformations are substantially different in energy. It should be noted that compound **21** has been isolated by Misumi[6b] in both syn and anti forms but attempted thermal interconversion (similar to those described in Figure 2 for **12a**) resulted in decomposition. Thus, the barrier to rotation in **21** is high enough so that both forms are isolable but is too high for thermal interconversion without bond fragmentation (i.e., decomposition occurs prior to thiophene ring inversion). In contrast only the anti form of **12a** has been isolated, which indicates either a low syn to anti flipping barrier of the pyrrole ring or more likely a continued increase in energy due to greater π–π interaction as rotation continues from A to the syn form[1c] (see Figure 2).

The conformational behavior of **13a** between −35 and 190 °C was not easily interpreted from its NMR spectrum since the multiplet for the bridge protons is very narrow and it was very difficult to observe line broadening. The study was therefore carried out on the hexadeuterio analogue of **13a** (prepared as described in Scheme VII) to reduce the complexity of the absorption pattern for the protons α to the furan ring.

Scheme VII



The NMR spectrum of **13a**-d_6 at 60 MHz exhibits a deuterium broadened AB quartet (in contrast to the complicated

ABCD pattern in **13a**) for the bridge protons α to the furan ring. The deuterium decoupled 100-MHz spectrum of **13a**-d_6 shows the AB quartet more clearly. The separation between the A and B resonances is calculated[29] to be 12.7 Hz based on the coupling constant (J_{AB}) of 13.6 Hz as obtained from the deuterium decoupled spectrum. This deuterium decoupled spectrum remains unchanged upon heating the sample to 190 °C. For a minimum detectable line broadening of 0.5 Hz, the above data represent a rate constant for conformational flipping of the furan ring in **13a**-d_6 of <1 s^{-1} with an associated Arrhenius energy of activation greater than 27 kcal/mol. The data demonstrate that the furan ring is not flipping and since the steric bulk of the N–H group of the pyrrole ring has been shown above to be higher than that of the oxygen of the furan ring, it implies that the pyrrole ring is also conformationally rigid.

This system is analogous to the conformationally rigid [2.2](2,6)pyridinometacyclophane (**25**)[6a] and indicates the similar steric bulk of C–H–:N and N–H–:O groups as these groups attempt to pass through the cavity in their respective cyclophanes.

The multiplicity of the bridge protons in **1** (AA′BB′) indicates that, unlike the corresponding furan rings in [2.2]-(2,5)furanophane (**9c**),[7a] the pyrrole rings are not flipping. This conformational rigidity was predicted in light of the high activation energy (>27 kcal/mol) observed for the analogous cyclophane **13a**. Attempts, however, to detect the rotational process by variable temperature NMR techniques and to rigorously substantiate the above prediction proved fruitless owing to the decomposition of **1** at high temperatures. On the other hand, high-temperature NMR experiments on **17a** demonstrated conclusively that the pyrrole rings are not rotating at temperatures up to 190 °C and that the barrier to rotation is >27 kcal/mol. Though variable temperature NMR spectra were not obtained for **17b**, it seems likely that the results would be similar to that obtained for **17a**, i.e. the pyrrole rings are rigid on the NMR time scale.

Our present efforts are being directed toward the synthesis of [n.2.2]pyrrolophanes[10b] and the effect that removal of the proton from the nitrogen in these [2.2]pyrrolophanes will have on the rotational behavior of the pyrrole nucleus.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 735 grating spectrophotometer and a Perkin-Elmer Infracord Model 137 spectrophotometer and were calibrated with the 1601-cm^{-1} band of polystyrene. Nuclear magnetic resonance spectra were taken on Varian Model A-60A, Perkin-Elmer Model R-24, Perkin-Elmer Model R-32, and Bruker Model WH-90 spectrometers. Deuterium decoupled NMR spectra of **13a** were recorded on a Varian Model HA-100 spectrometer. Chemical shifts are reported in parts per million on a τ scale, using Me_4Si as an internal standard. Ultraviolet spectra were taken on Perkin-Elmer-Coleman Model 124 and Perkin-Elmer Model 202 spectrophotometers. Mass spectra were obtained using an A.E.I. Model MS-12 mass spectrometer. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz., and Galbraith Laboratories, Knoxville, Tenn.

[2.2](2,5)Pyrroloparacyclophane (11a). A three-neck flask, equipped with a condenser, serum cap, and glass stopper, was charged with glacial acetic acid (50 mL, purged with nitrogen for 15 min) and 3,6-diketo[8]paracyclophane (0.7 g, 3 mmol). The flask was wrapped in aluminum foil to exclude light and heated under nitrogen in an oil bath (80 °C) for 10 min. Precondensed liquid ammonia was distilled into the mixture via a disposable pipet placed through the serum cap and the nitrogen inlet at the top of the condenser was replaced with a drying tube (Drierite). The ammonia was allowed to bubble into the heated and stirred solution for 30 min. By this time the mixture had usually solidified. It was cooled in ice and made basic (pH 10) with ammonium hydroxide (concentrated). The light-yellow solution was extracted with chloroform (4 × 25 mL). The organic layer was washed several times with water until the wash was neutral and dried over anhydrous sodium sulfate. Removal of solvent in vacuo yielded a yellow-white solid. This was purified by chromatography on silica gel (elution with chloroform). Recrystallization from hexane afforded silky white needles of **11a** (0.35 g, 55%): mp 197–198 °C; NMR ($CDCl_3$) τ 3.28 (AA′XX′, 4 H), 4.55 (d, 2 H, J = 2.5 Hz), 5.0 (broad s, 1 H), 7.4 (m, 8 H); IR (KBr) 3400 (N–H), 2900, 1390, 1025, 874, 800, 765, 720 cm^{-1}; UV (EtOH) λ (log ϵ) 286 nm sh (2.79), 269 sh (2.98), 219 (4.0); MS m/e 197 (M$^+$), 104, 93.

Anal. Calcd for $C_{14}H_{15}N$ (mol wt 197.28): C, 85.24; H, 7.66; N, 7.10. Found: C, 85.15; H, 7.91; N, 7.21.

***N*-Methyl[2.2](2,5)pyrroloparacyclophane (11b).** A flask equipped with a condenser, serum cap, and glass stopper was charged with glacial acetic acid (10 mL, purged with nitrogen for 15 min) and 3,6-diketo[8]paracyclophane (0.25 g, 0.0012 mol). The flask was wrapped in aluminum foil to exclude light and heated under nitrogen in an oil bath (105 °C) for 10 min. Precondensed methylamine was bubbled into the hot acid solution for 90 min via a disposable pipet placed through the serum cap and the nitrogen inlet was replaced with a drying tube (Drierite). The orange reaction mixture was cooled, made basic (pH 10) with ammonium hydroxide (concentrated), and extracted with chloroform (4 × 25 mL). The light, orange organic layer was washed with water until the wash was neutral and dried over anhydrous sodium sulfate. Chromatography of the residue, after solvent removal on alumina with methylene chloride as eluent, afforded a yellow-white solid. Recrystallization from ethanol/water gave colorless, crystalline **11b** (0.15 g, 53%): mp 212–214 °C; NMR ($CDCl_3$) τ 3.46 (AA′XX′, 4 H), 4.4 (s, 2 H), 7.15 (m, 8 H), 7.5 (s, 3 H); IR (KBr) 3000, 1280, 1080, 870, 755, 720 cm^{-1}; UV (EtOH) λ (log ϵ) 279 nm sh (2.61), 269 sh (2.75), 226.5 (3.89), 204.5 (3.99); MS m/e 211 (M$^+$), 107, 104.

Anal. Calcd for $C_{15}H_{17}N$ (mol wt 211.31): C, 69.89; H, 6.84; N, 5.66. Found: C, 69.65; H, 6.82; N, 5.69.

3,6-Diketo[8](1,4)naphthalenophane (10b). A liquid mixture of glacial acetic acid (4.3 mL), water (2.2 mL), and 10% sulfuric acid (3 drops) was placed in a flask and purged with nitrogen for 15 min. To this solution was added [2.2](2,5)furano(1,4)naphthalenophane (0.467 g, 1.9 mmol). The flask was covered with aluminum foil to exclude light and was heated under nitrogen with magnetic stirring in an oil bath (105 °C) for 18 h. The resulting mixture, after cooling, was poured into water (10 mL) and the cloudy solution extracted with methylene chloride (4 × 20 mL). The light-yellow organic layer was washed with water (2 × 15 mL), a saturated solution of sodium bicarbonate (2 × 15 mL), and a saturated solution of sodium chloride (2 × 15 mL), and dried over anhydrous sodium sulfate. Removal of solvent in vacuo gave 0.43 g (88%) of crude white solid. Recrystallization from ethanol (95%) afforded 3,6-diketo[8](1,4)naphthalenophane (**10b**, 0.36 g 71%): mp 159–160 °C; NMR ($CDCl_3$) τ 2.2 (AA′BB′, 4 H), 2.83 (s, 2 H), 6.6 (m, 4 H), 7.55 (m, 4 H), 8.67 (m, 4 H); IR (KBr) 2950, 1680 (C=O), 814, 765 cm^{-1}; UV (EtOH) λ (log ϵ) 297.5 nm (3.70), 231 (4.35); MS m/e 266 (M$^+$), 168, 144, 100.

Anal. Calcd for $C_{18}H_{18}O_2$ (mol wt 266.34): C, 81.17; H, 6.81. Found: C, 81.05; H, 6.86.

[2.2](2,5)Pyrrolo(1,4)naphthalenophane (12a). A flask, equipped with a condenser, serum cap, and glass stopper, was charged with glacial acetic acid (10 mL) and purged with nitrogen (15 min) and to the acid was added 3,6-diketo[8](1,4)naphthalenophane (75 mg, 0.28 mmol). The flask was wrapped in foil to exclude light and heated in an oil bath (80 °C) for 10 min. Precondensed ammonia was bubbled into the solution (30 min) through the serum cap via a disposable pipet and the nitrogen inlet tube at the top of the condenser was replaced with a drying tube (Drierite). The yellow-orange solution was cooled in ice, made basic (pH 10) with ammonium hydroxide (concentrated), and extracted with chloroform (4 × 15 mL). The orange organic layer was washed several times with water, until the wash was neutral, and dried over anhydrous sodium sulfate. Removal of solvent in vacuo afforded an orange, solid residue. Purification by chromatography on silica gel, eluting with chloroform, gave **12a** (0.06 g, 86%). Recrystallization from ethanol/water afforded white needles: mp 111–112 °C; NMR ($CDCl_3$) τ 2.3 (AA′XX′, 4 H), 3.5 (s, 2 H), 4.5 (d, 2 H, J = 3.0 Hz), 6.2 (broad s, 1 H), 6.4 (m, 2 H), 7.5 (m, 6 H); IR (KBr) 3450 (N–H), 2950, 1170, 1010, 758, 705 cm^{-1}; UV (EtOH) λ (log ϵ) 301 nm (3.43), 243 sh (4.13), 226.5 (4.28); MS m/e 247 (M$^+$), 144, 93.

Anal. Calcd for $C_{18}H_{17}N$ (mol wt 247.34): C, 87.41; H, 6.93; N, 5.66. Found: C, 87.20; H, 6.73; N, 5.69.

3,6-Diketo[8](2,5)furanophane (10c). A flask charged with a liquid mixture of glacial acetic acid (54 mL), water (27 mL), and 10% sulfuric acid (1.2 mL) was purged with nitrogen (15 min) and to the solution was added [2.2](2,5)furanophane (4.43 g, 0.0235 mol). The flask was covered with aluminum foil to exclude light and heated in

an oil bath (70–80 °C) under nitrogen for 18 h. The resulting light-yellow mixture was poured into water (100 mL) and extracted with methylene chloride (4 × 50 mL). The yellow organic layer was washed with water (2 × 20 mL), a saturated solution of sodium bicarbonate (2 × 20 mL), and a saturated solution of sodium chloride (2 × 20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a white-yellow powder (4.0 g, 82.5%). Recrystallization from water afforded 3,6-diketo[8](2,5)furanophane **10c** (3.4 g, 68%), as colorless crystals: mp 109–110 °C; NMR ($CDCl_3$) τ 4.2 (s, 2 H), 7.45 (s, 4 H), 7.45 (AA'BB', 8 H); IR (KBr) 2940, 1700 (C=O), 1420, 1160, 1015, 805 cm^{-1}; UV (EtOH) λ (log ϵ) 292 nm sh (1.94), 222 (3.56); MS *m/e* 206 (M^+), 108, 107, 99.

Anal. Calcd for $C_{12}H_{14}O_3$ (mol wt 206.24): C, 69.89; H, 6.84. Found: C, 69.65; H, 6.82.

[2.2](2,5)Furano(2,5)pyrrolophane (13a). A flask equipped with a condenser, serum cap, and glass stopper was charged with glacial acetic acid (15 mL) and purged with nitrogen for 15 min. To this solution was added 3,6-diketo[8](2,5)furanophane (0.260 g, 1.3 mmol). The flask was wrapped in aluminum foil to exclude light and placed in an oil bath (80 °C) for 15 min. Precondensed ammonia was distilled into the solution (30 min) through the serum cap via a disposable pipet and the nitrogen inlet tube at the top of the condenser was replaced with a drying tube (Drierite). The reaction mixture was cooled in ice and made basic (pH 10) with ammonium hydroxide (concentrated). It was extracted with chloroform (4 × 20 mL) and the yellow organic layer washed several times with water until the wash was neutral and dried over anhydrous sodium sulfate. Removal of solvent in vacuo gave solid yellow product, 0.25 g. This solid was purified by chromatography on silica gel, eluting with chloroform, and recrystallized from ethanol–water affording colorless needles of **13a** (0.15 g, 67%), mp 131–132 °C. The crystals were light sensitive: NMR ($CDCl_3$) τ 3.6 (broad s, 1 H), 3.95 (s, 2 H), 4.05 (d, 2 H, J = 3.0 Hz), 7.35 (m, 8 H); IR (KBr) 3408 (N–H), 2920, 1170, 1010, 750 cm^{-1}; UV (EtOH) λ (log ϵ) 222 nm (4.0); MS *m/e* 187 (M^+), 94, 93.

Anal. Calcd for $C_{12}H_{13}NO$ (mol wt 187.24): C, 76.98; H, 7.00; N, 7.48. Found: C, 76.91; H, 7.05; N, 7.37.

***N*-Methyl[2.2](2,5)pyrrolophane (17a).** Methylamine (precondensed) was bubbled into a stirred and heated solution of 1,4,7,10-cyclododecatetraone (110 mg, 0.49 mmol) in glacial acetic acid (10 mL, purged with nitrogen for 15 min) in the dark for 10 min. The reaction system was purged with nitrogen and ammonia (precondensed) was distilled into the solution for 20 min. The "solid" brown-red reaction mixture was made basic (pH 10) with ammonium hydroxide (concentrated) and extracted with chloroform (5 × 15 mL). The brown organic layer was washed with water until the washings were neutral, dried over anhydrous sodium sulfate, and concentrated in vacuo to a brown residue. Preparative chromatography (silica gel/chloroform, R_f 0.72) afforded a light yellow, crystalline product. Sublimation afforded *N*-methyl[2.2](2,5)pyrrolophane (**17a**, 23 mg, 43%): NMR ($CDCl_3$) τ 3.71 (s, 2 H), 4.15 (d, 2 H, J = 2.9 Hz), 6.98 (s, 3 H), 7.15 (m, 8 H); IR (KBr) 3450 (N–H), 2950, 1170, 1010, 780, 760 cm^{-1}; UV (EtOH) λ (log ϵ) 240 nm (3.91), 219 (4.04), 204 (4.22); MS *m/e* 200 (M^+), 107, 93, 92.

Anal. Calcd for $C_{13}H_{16}N_2$ (mol wt 200.27): C, 77.96; H, 8.05; N, 13.99. Found: C, 77.83; H, 8.08; N, 13.73.

***N*-Benzyl[2.2](2,5)pyrrolophane (17b).** Benzylamine (135 mg, 1.26 mmol, distilled from sodium) was added to a heated solution (85 °C) of 1,4,7,10-cyclododecatetraone (100 mg, 0.45 mmol) in glacial acetic (10 mL) (purged with nitrogen for 15 min) under nitrogen and in the dark. After the reaction mixture had been heated and stirred for 1 h,[30] ammonia (precondensed) was bubbled into the light-orange solution for 30 min. The brown reaction mixture was cooled and made basic (pH 10) with ammonium hydroxide (concentrated). The mixture was extracted with chloroform (5 × 15 mL) and the organic layer was washed with water until the wash was neutral. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed in vacuo affording a red-brown oil. Purification by preparative chromatography (silica gel/chloroform, R_f 0.63) and sublimation yielded the white, crystalline *N*-benzyl[2.2](2,5)pyrrolophane (**17b**, 20 mg, 17%): mp 84–85 °C; NMR ($CDCl_3$) τ 2.7–3.0 (m, 5 H), 3.8 (s, 2 H), 4.1 (d, 2 H, J = 2.6 Hz), 5.42 (s, 2 H), 7.27 (m, 8 H); IR (KBr) 3450 (N–H), 3000, 1410, 1170, 755, 745, 705 cm^{-1}; UV (EtOH) λ (log ϵ) 270 nm (2.94), 263 (3.11), 240 (3.76), 206 (4.10); MS *m/e* 276 (M^+), 183, 182, 168, 93, 91.

Anal. Calcd for $C_{19}H_{20}N_2$ (mol wt 276.36): C, 82.57; H, 7.29; N, 10.14. Found: C, 82.51; H, 7.41; N, 9.97.

[2.2](2,5)Pyrrolophane (1). *N*-Benzyl[2.2](2,5)pyrrolophane (**17b**, 13 mg, 0.0471 mmol) was dissolved in tetrahydrofuran (2 mL, distilled from sodium). This solution was placed in a dry flask under nitrogen and precondensed ammonia was distilled from sodium into the flask. After about 15 mL had been condensed, the distillation was stopped and sodium (20 mg) was added in small portions. The dark blue reaction mixture was stirred for 1 h. The ammonia was allowed to evaporate from the reaction mixture. The last traces of ammonia and tetrahydrofuran were removed in vacuo leaving a residual white solid. Addition of water (10 mL) yielded a suspension, which was extracted with chloroform (4 × 10 mL). The organic layer was washed with water (1 × 10 mL) and dried over anhydrous sodium sulfate and the solvent removed in vacuo to afford a light yellow solid. Sublimation yielded white powdery [2.2](2,5)pyrrolophane **1** (7.5 mg, 87%), mp 163–165 °C dec. The compound decomposes slowly in light and air: NMR ($CDCl_3$) τ 3.58 (broad s, 2 H), 4.16 (d, 4 H, J = 2.5 Hz), 7.12–7.74 (AA'BB', 8 H); IR (KBr) 3450 (N–H), 2970, 1175, 1040, 765, 708 cm^{-1}; UV (EtOH) λ (log ϵ) 254 nm (3.19), 218 (3.98); MS *m/e* 186 (M^+), 185, 94, 93.

Anal. Calcd for $C_{12}H_{14}N_2$ (mol wt 186.24): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.35; H, 7.76; N, 15.31.

2,2,4,5,7,7-Hexadeuterio[2.2](2,5)furano(2,5)pyrrolophane (13a-d_6). 3,6-Diketo[8]furanophane (**10c**, 0.5 g, 2.4 mmol) in dioxane (5 mL, distilled from $LiAlH_4$) and D_2O (6 mL, 99.8%, Stohler) was stirred for 16 h in the dark in the presence of a trace of sodium. The reaction mixture was extracted with $CHCl_3$ (3 × 10 mL) and the extracts washed with saturated NaCl (20 mL) and dried over $MgSO_4$. Evaporation of solvent left crystalline diketone **10c-d_8** (0.440 g, 2.1 mmol, 85%): NMR ($CDCl_3$) τ 4.16 (s, 2 H), 7.09 (broad s, 4 H).

A solution of **10c-d_8** (300 mg, 1.4 mmol) in acetic acid-d_1 (7 mL, 99%, Stohler) was purged with nitrogen for 30 min and then ammonia-d_3 (99%, Stohler) was bubbled into the stirred solution at 80 °C in the dark. The solution was then cooled and basified to pH 10 with NH_4OH (concentrated). The solution was extracted with $CHCl_3$ (3 × 25 mL) and the extracts washed with water until neutral and then dried over Na_2SO_4. Evaporation of solvent afforded **13a-d_6** (245 mg, 1.3 mmol, 91%). Recrystallization from 95% EtOH gave white, crystalline material: mp 130–132 °C; NMR ($CDCl)_3$ τ 3.6 (broad s, 1 H), 3.91 (s, 2 H), 7.3 (deuterium broadened AB q, 4 H); MS *m/e* 193 (M^+), 99, 94. Analysis of the mass spectrum shows >70% hexadeuteration and >90% hexa- and pentadeuteration in the bridge positions α to the pyrrole ring. The effect of the pentadeuterated isomers on the NMR spectrum is negligible.

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Registry No.—**1**, 56634-48-1; **10b**, 51460-19-6; **10c**, 51460-20-9; **10c-d_8**, 61394-88-5; **11a**, 51053-69-1; **11b**, 51012-07-8; **12a**, 51012-08-9; **13a**, 51041-05-5; **13a-d_6**, 61394-89-6; **17a**, 56634-47-0; **17b**, 61394-90-9; 3,6-diketo[8]paracyclophane, 5297-49-4; [2.2](2,5)furano(1,4)-naphthalenophane, 25108-53-6; [2.2](2,5)furanophane, 5088-46-0; 1,4,7,10-cyclododecatetraone, 25887-95-0; methylamine, 74-89-5; benzylamine, 100-46-9; D_2O, 7789-20-0; ammonia-d_3, 13550-49-7.

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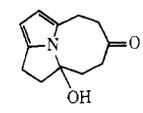

i

following spectral data: NMR ($CDCl_3$) τ 4.2 (AB q, 2 H, J = 3.1 Hz), 7.5 (m, 13 H); IR (KBr) 3280 (OH), 1690 cm^{-1} (C=O); MS *m/e* 205 (M^+), 204, 106, 92.
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Synthesis of Bicyclo[2.2.2]octenes and Bicyclo[3.2.2]nonenes by π-Cyclization

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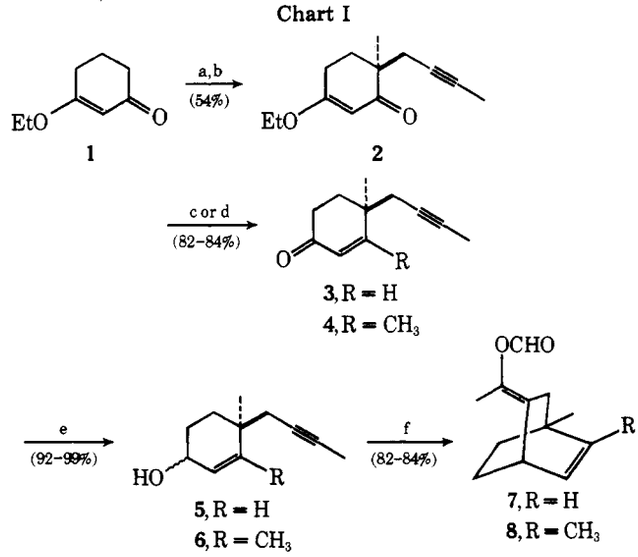
The (2-butynyl)cyclohexenols **5**, **6**, and **12** undergo cyclization to bicyclic enol formates **7**, **8**, and **13**, respectively, upon treatment with formic acid at room temperature. The trimethylsilylpropynyl analogue **17** cyclizes in the alternative sense to yield, after hydrolysis and protodesilylation, the bicyclo[3.2.2]nonenone **18**.

π-Cyclization (the interaction of a carbon–carbon multiple bond with a neighboring cationic center) has become an important method for the creation of carbocycles. The most extensive and definitive work in the area is that of Johnson and co-workers and concerns mainly the application of π-cyclization to the synthesis of steroids.[1,2] We have now found that π-cyclization provides a convenient synthesis of bicyclo[2.2.2]octenes and bicyclo[3.2.2]nonenes.

The method is typified by the synthesis of enol formates **7** and **8** (Chart I). Successive alkylation of enol ether **1**[3] by methyl iodide and 1-bromo-2-butyne[4] affords enol ether **2**, which may be reduced or treated with methyllithium to yield, after acid workup, enones **3** or **4**. Reduction of these materials affords allylic alcohols **5** and **6**. When these allylic alcohols are dissolved in 98% formic acid and kept at room temperature for 2 h, bicyclic enol formates **7** and **8** are produced in good yield (33–38% overall from enone **1**). The structures assigned are consistent with elemental compositions, infrared spectra, and both proton and carbon nuclear magnetic resonance spectra of the two compounds. Only one stereoisomer is produced in each case. Although the geometry of the double bond is unknown, it is probably *E*, as depicted in Chart I (anti addition).

Chart I



a, lithium diisopropylamide (LDA), THF, −78 °C, CH_3I; b, LDA, THF, −78 °C, $CH_3C{\equiv}CCH_2Br$; c, $LiAlH_4$, ether, H_3O^+; d, CH_3Li, H_3O^+; e, $LiAlH_4$; f, HCO_2H, 25 °C