N-(p-Bromophenyl)[2.2](2,5)pyrrolophane. Synthesis and Self-Condensation

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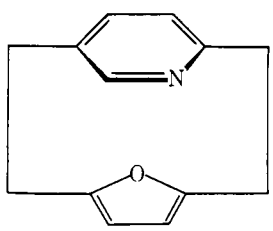
The N-(p-bromophenyl)[2.2](2,5)pyrrolophane was prepared and shown to exist in the anti structure. This compound readily rearranges to 13-(p-bromophenyl)-13,14-diazatetracyclo[8.2.1.1^{4,7}.0^{1,14}]tetradeca-4,6,11-triene. The structure of the latter was established by x-ray crystallographic analysis.

We have recently described the synthesis and structure of [2.2](2,5)furano(2,5)pyridinophane (1).[1,2] Contrary to expectations, the two rings are not parallel to each other in this molecule but the furan ring is inclined toward the pyridine at an angle of 23°. Interestingly, of the two heterocyclic rings in this system, only the pyridine ring is significantly nonplanar. These results prompted us to expand our investigations of heterocyclophanes in order to further examine their chemical, spectral, and stereochemical behavior.



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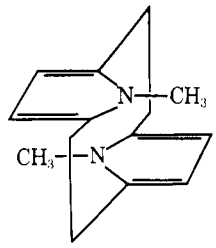

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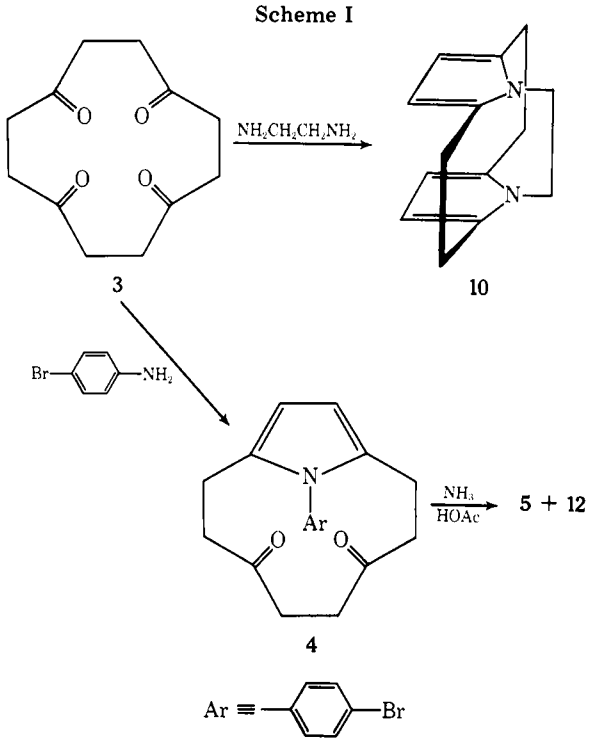
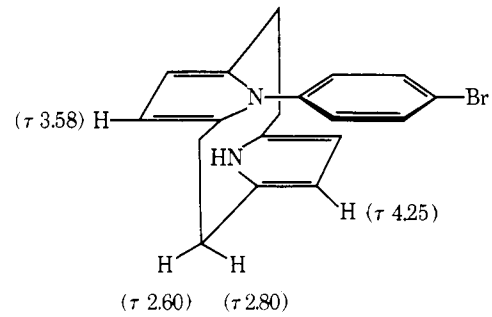
Wasserman and Bailey[3] originally described the synthesis of N,N'-dimethyl[2.2](2,5)pyrrolophane (2) and suggested that the compound exists in the indicated anti structure. Keehn and co-workers later continued these studies to include some other pyrrolophanes.[4]

In order to examine the stereochemical consequences of changing R in the pyrrolophanes such as 2, we prepared a series of these derivatives. This report describes the synthesis and structure determination of the products obtained from the reaction of compound 4 (see Scheme I) with ammonia. This reaction afforded two isomeric compounds, separable by HPLC, of molecular formula $C_{18}H_{17}N_2Br$. A priori, one might suggest that, because of the mode of formation, we are dealing with compounds 5 and 6, respectively. The temperature-insensitive ^{1}H NMR spectrum of the lower melting isomer was consistent with structure 5 or 6. The spectrum shows the presence of an aromatic A_2B_2 (τ 3.00, 2.66), an A_2 (τ 3.58) as well as the A_2 portion (τ 4.25) of an apparent A_2X system. The latter pattern, upon addition of D_2O to a solution of the compound, degenerates over time[5] to a two-proton singlet (τ 4.25). This change is in accord with a H → D exchange of the proton on the unsubstituted pyrrole ring. The question as to whether this product is 5 or 6 must now be answered.

Scheme I





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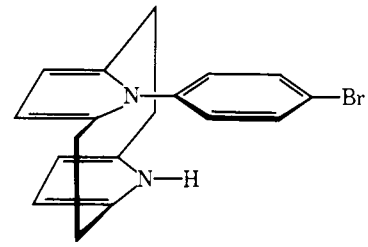

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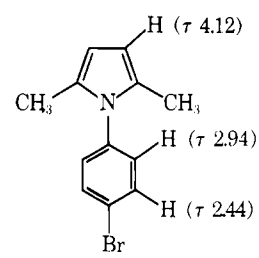
A comparison of the proton chemical shifts of the pyrroles 8 and 9 with those of the corresponding protons in the pyrrolophane isomer indicates that the substituted pyrrole protons in the latter are more deshielded ($\Delta\tau$ 0.54) than in the "monomer" 8, while the protons on the unsubstituted pyrrole are not significantly changed in going from the "monomer"



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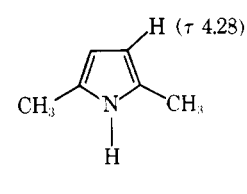

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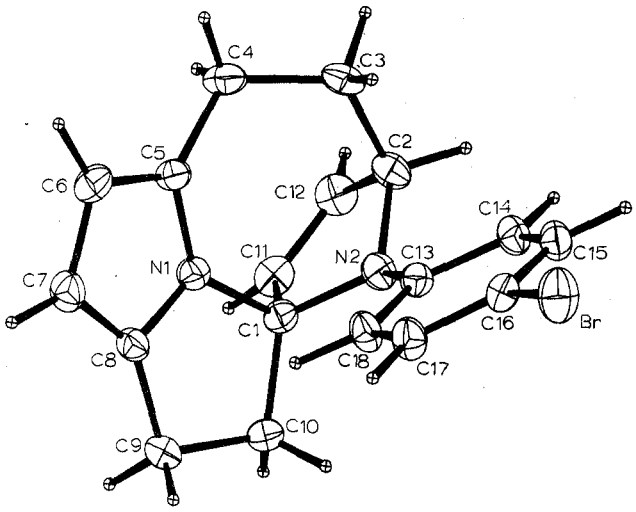
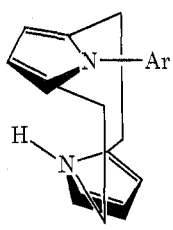


Figure 1. Molecular structure and atom numbering scheme for 13-(*p*-bromophenyl)-13,14-diazatetracyclo[8.2.1.1^{4,7}.0^{1,14}]tetradeca-4,6,11-triene. The atoms are represented as their 50% probability ellipsoids for thermal motion.

9 to the "dimer". Thus, the substituted pyrrole in the pyrrolophane is within the deshielding region of the unsubstituted pyrrole, while the substituted pyrrole has no significant effect ($\Delta\tau$ 0.03) upon the protons in the unsubstituted pyrrole ring. The only structure that is consistent with these data is the anti isomer **5** with nonparallel rings.



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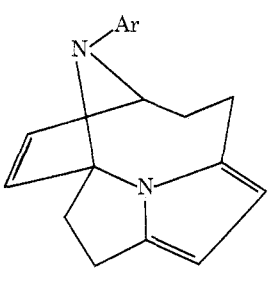
A more accurate assessment of the ring to ring angles in these systems will be published elsewhere. The fact that we are dealing with a modified anti structure is further confirmed by the ^{1}H NMR spectrum of compound **10**, prepared as indicated in Scheme I. A comparison of the pyrrole chemical shifts (τ 4.49) of this unique cage-type *syn*-pyrrolophane with those of 1,2,5-trimethylpyrrole (τ 4.26) clearly shows that the pyrrole protons in this pyrrolophane are within the *shielding* region of the opposite pyrrole ring, in contrast to the location of the pyrrole protons in the anti isomer **5**.

The ^{1}H NMR spectrum of the higher melting isomer must now be examined. None of the protons in this spectrum are subject to H → D exchange. Thus, we are not dealing with a structure which has an unsubstituted pyrrole ring. Detailed analysis of the deshielded region shows the presence of an aromatic A_2B_2 (τ 2.79, 3.86) system as well as an ABX ($\tau_{H_AH_B}$ 2.65, 4.24) and AB (τ 4.18, 4.35) pattern. These data could be accommodated by either structure **12** or **13**.



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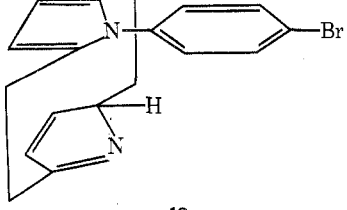

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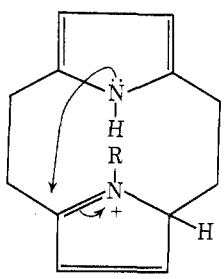
The observation that the olefinic protons of the ABX system are so greatly deshielded (τ 2.65, 2.88) seems to preclude structure **13**, especially in view of the fact that the pyrrole protons in the locked syn isomer are all more shielded than in the "monomeric" reference compound. Nevertheless, this analysis does not allow one to assign structure **12** to the compound with complete certainty.

Consequently, recourse was taken to a x-ray crystallographic analysis which proved that we are dealing with compound **12** rather than **13**. A computer-generated structure representation is given in Figure 1. Interestingly, when the anti isomer (**5**) is treated with acetic acid it is converted to compound **12**.

The acid-catalyzed transformation of compound **5** to compound **12** can be envisioned to occur via the C-protonated



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species **14** (typical for pyrroles) followed by bond formation and deprotonation as indicated.

Experimental Section[7]

Compound 4. 1,4,7,10-Cyclododecatetraone[6] (1.00 g, 4.5 mmol) and 3.87 g (22.5 mmol) of *p*-bromoaniline were dissolved in 50 ml of glacial HOAc and heated at 90 °C under a N_2 atmosphere for 40 min. The mixture was cooled, poured into cold NH_4OH, and extracted with $CHCl_3$. The extracts were washed successively with 5% HCl and water and dried over anhydrous K_2CO_3. Evaporation of the solvent gave a dark residue which was chromatographed on Brockman grade III neutral alumina using C_6H_6 as the eluent to yield 0.70 g (43.3%) of a yellow oil that gradually solidified. Further purification was accomplished by sublimation or recrystallization from acetone–water to give a yellow solid: mp 137–139 °C; ^{1}H NMR τ 2.42, 3.04 (A_2B_2, 4 H), 3.77 (s, 2 H), 8.5–7.0 (m, 12 H); ir 1705 cm^{-1} (C=O); mass spectrum mol wt 359, 361. Anal. Calcd for $C_{18}H_{18}NO_2Br$: C, 60.01; H, 5.04; N, 3.89. Found: C, 60.11; H, 5.07; N, 3.93.

Compounds 5 and 12. Compound **4** (250 mg, 0.70 mmol) was dissolved in 20 ml of glacial HOAc and added to 5 ml of liquid NH_3 cooled to −78 °C for 2 h. After cooling NH_4OH was added and the product was extracted with $CHCl_3$. The extracts were washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of the $CHCl_3$ yielded a dark residue which was chromatographed on Brockman grade II silica gel using 1:1 benzene–cyclohexane as the eluent. This afforded 24 mg of compound **12**, mp 137–140 °C dec, and 100 mg of compound **5**, mp 151.5–153 °C. These compounds can also be separated by HPLC using a 1-m Porasil A column, 4 ml/min flow rate, 20% $CHCl_3$–80% isooctane eluent. Compound **5**: ^{1}H NMR τ 2.76, 3.00 (A_2B_2, 4 H), 3.58 (s, 2 H), 4.25 (d, 2 H), 2.60, 2.80 (A_2B_2, 8 H) (the chemical shift of the hydrogen atom on nitrogen could not be immediately determined; however, integration indicates that it falls within this chemical shift range of the aromatic protons); mass spectrum mol wt 340, 342. Compound **12**: ^{1}H NMR τ 2.79, 3.86 (A_2B_2, 4 H), 2.88, 2.65, 4.24 (ABX, 3 H), 4.18, 4.35 (AB, 2 H), 6.7–8.6 (m, 8 H); mass spectrum mol wt 340, 342. Anal. Calcd for $C_{18}H_{17}N_2Br$: C, 63.36; H, 5.02; N, 8.21. Found for compound **5**: C, 63.25; H, 5.03; N, 8.14. Found for compound **12**: C, 63.62; H, 5.16; N, 8.03.

Compound 10. 1,4,7,10-Cyclododecatetraone (500 mg, 2.25 mmol) was dissolved in 6 ml of glacial HOAc and heated at 80 °C under a N_2 atmosphere. Ethylenediamine (1.3 g, 22.5 mmol, 1.5 ml) was added dropwise and the mixture was heated for 5 min. The reaction mixture was cooled, poured into cold NH_4OH, and extracted with $CHCl_3$. The organic layer was washed successively with 5% HCl, water, and saturated Na_2CO_3 solution and dried over anhydrous K_2CO_3. The $CHCl_3$ extract was evaporated and the residue obtained was chromatographed on Brockman grade III neutral alumina using benzene as the

eluent to give 190 mg (38%) of a white solid: mp 198–202 °C dec; ^{1}H NMR τ 4.49 (s, 4 H), 5.99 (s, 4 H), 7.15 (A_2B_2, 8 H); mass spectrum mol wt 212. Anal. Calcd for $C_{14}H_{16}N_2$: C, 72.83; H, 4.83; N, 22.35. Found: C, 72.83; H, 4.90; N, 22.42.

Conversion of Compound 5 to 12. Compound **5** (50 mg, 0.15 mmol) was dissolved in 5 ml of glacial HOAc and heated at 120 °C for 1 h. The mixture was cooled and added to cold NH_4OH. The aqueous solution was extracted with chloroform (3 × 50 ml) and the combined extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to dryness. The residue was examined using high-pressure liquid chromatography (HPLC) (column 0.5 m Dorasil A, 20% $CHCl_3$, 80% isooctane, Waters ALC 202 instrument) which revealed the presence of compound **12.** Isolation by preparative HPLC afforded 40 mg (80%) of compound **12.**

X-Ray Data Collection. The detailed data are available in the microfilm edition of this journal.[8]

Registry No.—**3,** 25887-95-0; **4,** 59547-39-6; **5,** 59547-40-9; **10,** 59547-41-0; **12,** 59547-42-1; *p*-bromoaniline, 106-40-1; ethylenediamine, 107-15-3.

Supplementary Material Available. A listing of all of the crystallographic data (8 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) J. L. Atwood, W. E. Hunter, C. Wong, and W. W. Paudler, *J. Heterocycl. Chem.*, **12,** 433 (1975).
(3) H. H. Wasserman and D. T. Bailey, *Chem. Commun.*, 107 (1970).
(4) (a) J. F. Haley, Jr., and P. M. Keehn, *Tetrahedron Lett.*, 4017 (1973); (b) S. Rosenfeld and P. M. Keehn, *ibid.*, 4021 (1973); (c) J. F. Haley, Jr., and P. M. Keehn, *ibid.*, 1675 (1975).
(5) The results of a study of these slow exchange rates and of the stereochemistry of these compounds will be published elsewhere.
(6) J. L. Atwood, D. C. Hrncir, C. Wong, and W. W. Paudler, *J. Am. Chem. Soc.*, **96,** 6132 (1974).
(7) ^{1}H NMR spectra were obtained with either a Varian HA-100 or a Hitachi Perkin-Elmer R20B NMR spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 70 eV. Elemental analyses were determined by the Analytical Services Laboratory of The University of Alabama Chemistry Department, and Atlantic Microlab, Inc., Atlanta, Ga. Melting points were uncorrected.
(8) See paragraph at end of paper regarding supplementary material.

Bishomoaromatic Interaction in the Disrotatory Ring Opening of Cyclopropyl Carbenoids

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Treatment of 9,9-dibromo-*cis*-bicyclo[6.1.0]nonanes **1, 3,** and **15** with butyllithium at −95 °C leads to corresponding *endo*-lithio-*exo*-bromo derivatives which upon addition of methyl iodide can be alkylated, leading to the *endo*-methyl-*exo*-bromo derivatives **2, 4,** and **16** respectively. Even the strained 9,9-dibromo-*trans*-bicyclo[6.1.0]nonane (**9**) is converted in this way to 9-bromo-9-methyl-*trans*-bicyclo[6.1.0]nonane (**10**). However, in the presence of a double bond (**5**) or a cyclopropyl ring (**7**) at $C_{4,5}$ the carbenoids generated with butyllithium at −95 °C undergo a very rapid ring opening to the corresponding allenes. This result may be explained by assuming a bishomoaromatic interaction which favors a facile disrotatory ring opening of the carbenoids.

Geminal dihalo compounds have been shown to produce carbenoid species on reaction with organolithiums.[1] In the specific instance of 1,1-dibromocyclopropanes, the transient carbenes generally prove to undergo either ring opening to allenes[2a–h] or specific insertion in C–H bonds.[3a–i] At very low temperatures (−70 to −105 °C) the geminal dibromocyclopropanes can be easily lithiated to 1-bromo-1-lithiocyclopropanes. The latter behave like anions and are able to undergo alkylation reactions.[4a–c]

Our present research, directed toward the synthesis of nine-membered-ring systems via ring expansions, required the synthesis of 9-*exo*-bromo-9-*endo*-methyl-*cis*-bicyclo[6.1.0]nonane derivatives. To this end a recently described method of Hiyama et al.[4a] was employed, which permits the stereoselective endo methylation of cyclopropylidenes derived from geminal dibromocyclopropanes. Upon reaction of 9,9-dibromo-*cis*-bicyclo[6.1.0]nonane (**1**) with butyllithium at −95 °C and subsequent treatment with excess of methyl iodide in THF, the desired 9-*exo*-bromo-9-*endo*-methyl-*cis*-bicyclo[6.1.0]nonane (**2**) was isolated in essentially quantitative yield. In a similar way, the acetonide of 4,5-*trans*-dihydroxy-9,9-dibromo-*cis*-bicyclo[6.1.0]nonane (**3**) was converted to the corresponding *endo*-methyl derivative (**4**) in 92% yield. However, on treatment of 9,9-dibromo-*cis*-bicyclo[6.1.0]-non-4-ene (**5**) with butyllithium and methyl iodide under identical conditions, 1,2,6-cyclononatriene (**6**) was formed, as evidenced readily by its NMR and ir spectral data.[5a–c] Similar anomalous behavior was observed when a cyclopropane was annelated at $C_{4,5}$.[6] Upon treatment of 10,10-dibromo-*cis,cis*-tricyclo[7.1.0.0^{4,6}]decane (**7**) with butyllithium–methyl iodide at −95 °C only *cis*-bicyclo[7.1.0]deca-