

CYCLOPHANES I. THE SYNTHESIS OF MIXED N-UNSUBSTITUTED[2.2](2,5)PYRROLOPHANES

James F. Haley, Jr. and Philip M. Keehn \*

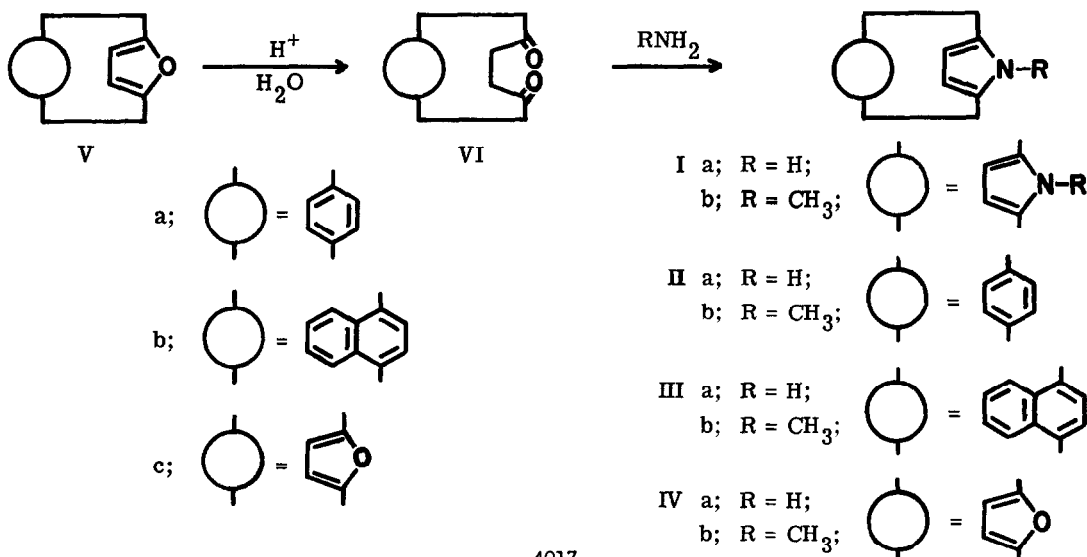
Department of Chemistry, Brandeis University - Waltham, Massachusetts, 02154

(Received in USA 3 August 1973; received in UK for publication 3 September 1973)

The syntheses of [2.2]cyclophanes containing heteroaromatic nuclei have been previously reported in the literature.<sup>1</sup> Among some of the common heteroaromatic nuclei which have been incorporated into the [2.2]cyclophane macrocycle are furan,<sup>2, 3, 4, 5</sup> thiophene,<sup>2, 6</sup> and pyridine.<sup>6, 7, 8</sup> However, except for the recent synthesis of NN'-dimethyl[2.2](2,5)pyrrolophane (Ib),<sup>9</sup> the literature is devoid of [2.2](2,5)pyrrolophanes. Of special interest are those in which the nitrogen is unsubstituted. We now report the first synthesis of a series of mixed N-unsubstituted[2.2](2,5)pyrrolophanes, specifically[2.2](2,5)pyrroloparacyclophane (IIa), [2.2](2,5)pyrrolo(1,4)naphthalenophane(IIIa), and [2.2](2,5)pyrrolofuranophane(IVa). Our ultimate goal is the synthesis of the parent [2.2](2,5) pyrrolophane (Ia).

In general, the synthetic scheme (see Scheme I) involves generating a  $\gamma$  diketone (VI), from the appropriate furanophane, (V), by acid hydrolysis in the absence of light and oxygen. The crystalline diketones<sup>10</sup> are then cyclized to the pyrrolophanes by treatment with ammonia via a Paal-Knorr Reaction.<sup>11</sup> This cyclization has previously been employed by Waserman and Bailey<sup>9</sup> in the preparation of Ib.

Scheme I



We have also attempted the Paal-Knorr cyclization with methylamine and met with success in the preparation of IIb. Attempts to prepare IIIb and IVb, under the same conditions as those used for IIb, led to recovered starting material.

Table I summarizes some of the physical and spectral data of the new compounds. The spectral data for VIb and VIc are consistent with the structure proposed.<sup>3</sup> Of particular interest are the NMR spectra<sup>12</sup> of VIb and VIc, which indicate unrestricted conformational mobility in VIc and restricted mobility in VIb. Analysis of conformational changes in the above compounds will be published in a future communication.

The assignment of structures to IIa,b, IIIa, and IVa is based on spectroscopic analysis.<sup>3, 4, 9</sup> 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  $\pi$ - $\pi$  interactions (244m $\mu$ ) in the ultraviolet spectra of [2.2] cyclophanes,<sup>13</sup> is only observed for IIIa; however, this band is sometimes not observed in [2.2] cyclophanes containing a five membered heterocyclic nucleus.<sup>4</sup> The presence of the pyrrole hydrogen is indicated by the sharp absorptions at ca. 3400cm<sup>-1</sup> in the infrared spectra of all but IIb.

The NMR spectra of IIa,b, IIIa, and IVa conclusively prove the cyclophane structure of these compounds. The benzenoid protons in IIa and IIb appear as a AA'XX' multiplet suggesting that the two rings are frozen parallel to one another,<sup>20</sup> 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(Va), which exhibits, in its room temperature spectrum, a singlet for the benzenoid protons<sup>3, 12</sup> 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 appears at 2.5 $\tau$ .<sup>14, 15</sup> In pyrrolophanes IVa, IIa, and IIIa, respectively, this absorption appears at 3.6 $\tau$ , 5.0 $\tau$ , and 6.3 $\tau$ .<sup>15</sup> Additionally, the chemical shift of the N-methyl group in IIb appears 0.72ppm upfield from that observed in 1,2,5-trimethylpyrrole.<sup>16</sup> This data clearly indicates that the substituent on the nitrogen is positioned above an aromatic plane and enjoys the increasing anisotropic shielding influence of the aromatic nuclei.<sup>17, 18</sup> This property is typical and consistent with the cyclophane structures proposed.

Finally, the appearance of the  $\beta$ -pyrrole protons in IIa, b and IIIa at chemical shifts nearly identical to those in 2,5-dimethylpyrrole and 1,2,5-trimethylpyrrole<sup>19</sup> indicates a minimum of transannular shielding by the parallel aromatic rings. In addition, the pyrrole protons in IVa appear at a chemical shift similar to that of the NN'-dimethyl[2.2](2,5)pyrrolophane previously assigned an anti-configuration by Wasserman and Bailey.<sup>9</sup> These facts, coupled with the above noted significant upfield shifts of the nitrogen substituent, demonstrate that IIIa and IVa exist in the more stable anti-conformation.<sup>4, 20</sup>

Further studies on this series of pyrrolophanes as well as on the synthesis of Ia are presently in progress. We believe that this method of cyclophane preparation will prove useful in synthesizing thiophene and deuterated analogues of cyclophanes I-IV.

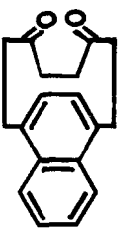



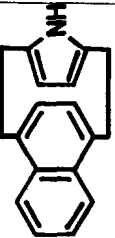

Compound	Structure	Melting Pt. <sup>a</sup> (Cryst. Sol)	Yield <sup>b</sup> %	NMR( $\tau$ ) <sup>c</sup>	IR( $\text{cm}^{-1}$ ) <sup>d</sup>	UV $\lambda$ max in $\text{m}\mu(\log \epsilon)^e$	f, h MS
V <b>lb</b>		158-159° (EtOH/H <sub>2</sub> O)	71	2. 2 (AA' BB', 4H) 2. 83 (s, 2H) 6. 6 (m, 4H) 7. 55 (m, 4H) 8. 67 (m, 4H)	1680 (C=O)	231 (4. 65) 297. 5 (3. 70)	266, 168 144, 100
V <b>lc</b>		109-110° (H <sub>2</sub> O)	68	4. 2 (s, 2H) 7. 45 (s, 2H) 7. 45 (A <sub>2</sub> B <sub>2</sub> , 8H)	1700 (C=O)	222 (3. 56) 292(sh)(1. 94)	206, 108 107, 99
II <b>b</b>		212-214° (EtOH/H <sub>2</sub> O)	53 <sup>g</sup>	3. 46(AA' XX', 4H) 4. 4 (s, 2H) 7. 15 (m, 8H) 7. 5 (s, 3H)	---	204. 5 (3. 99) 226. 5 (3. 89) 269(sh)(2. 75) 279(sh)(2. 61)	211, 107 104
II <b>a</b>		197-198° (Hexane)	55	3. 28(AA' XX', 4H) 4. 55(d, 2H; J=2.5Hz) 5. 00(broad s, 1H) 7. 4 (m, 8H)	3400 (N-H)	219 (4. 3) 269(sh)(2. 98) 286(sh)(2. 79)	197, 104 93
III <b>a</b>		111-112° (EtOH/H <sub>2</sub> O)	83	2. 3(AA' XX', 4H) 3. 5 (s, 2H) 4. 5 (d, 2H; J=3.0Hz) 6. 2 (broad s, 1H) 9. 4 (m, 2H) 9. 3 (m, 2H)	3450(N-H)	226. 5(4. 28) 243(sh)(4. 13) 301(3. 43)	247, 144 93
IV <b>a</b>		131-132° (EtOH/H <sub>2</sub> O)	65	3. 6(broad s, 1H) 3. 95(s, 2H) 4. 05(d, 2H; J=3.0Hz) 7. 35(m, 8H)	3408(N-H)	22 <sup>g</sup> (4. 00)	187, 93 94

TABLE I. Physical and Spectral Properties of IIa, IIb, IIIa, IVa, V**lb** and V**lc**.

a-Uncorrected; b-Recrystallized; c-CDCl<sub>3</sub>/1%TMS; d-KBr; e-EtOH(abs); f-m/e; g-Reaction carried out at 100°C; g-Satisfactory elemental analysis (i. e., within 0.3%) have been obtained for all new compounds

Acknowledgement - We wish to acknowledge the partial support of this work from the following institutions: NSF, Grant GU-3852; NIH, Biomedical Sciences Support Grant RR-7044-07; ACS, PRF-2786-G1.

References

1. B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, 1964.
2. H. E. Winberg, F. S. Fawcett, W. E. Mochel and C. W. Theobald, J. Amer. Chem. Soc., **82**, 1428 (1960).
3. D. J. Cram, C. S. Montgomery and G. R. Knox, J. Amer. Chem. Soc., **88**, 515 (1966).
4. H. H. Wasserman and P. M. Keehn, Tetrahedron Lett., 3227 (1969).
5. H. Wynberg and R. Helder, Tetrahedron Lett., 4317 (1971).
6. J. R. Fletcher and I. O. Sutherland, Chem. Comm., 1504 (1969).
7. I. Gault, B. J. Price and I. O. Sutherland, Chem. Comm., 540 (1967).
8. V. Boekelheide, I. D. Reingold and M. Tuttle, Chem. Comm., 406 (1973).
9. H. H. Wasserman and D. J. Bailey, Chem. Comm., 107 (1970).
10. Compound VIa has been synthesized previously by Cram. See ref. (3).
11. L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, Inc., New York, 1968.
12. G. M. Whitesides, B. A. Pawson and A. C. Cope, J. Amer. Chem. Soc., **90**, 639(1968).
13. R. C. Helgeson and D. J. Cram, J. Amer. Chem. Soc., **88**, 509 (1966).
14. Data obtained in our laboratories.
15. The values given are for the centers of very broad singlets. They are approximate due to the difficulty in observing the bands. There is no doubt however about their positions because the protons are easily observed during integration.
16. J. H. Goldstein and G. S. Reddy, J. Chem. Phys., **36**, 2644 (1962).
17. F. A.L. Anet and G. E. Schenck, J. Amer. Chem. Soc., **93**, 556 (1971).
18. A. G. Anastassiou and H. Yamamota, Chem. Comm., 286 (1972).
19. R. A. Jones, T. Spotswood and P. Cheuycht, Tetrahedron, **20**, 4469 (1967).
20. See the following communication.