Tetrahedron Letters No. 21 , pp 1675-1678, 1975. Pergamon Press. Printed in Great Britain.

CYCLOPHANES IV: THE SYNTHESIS OF [2.2](2,5)PYRROLOPHANE[1]

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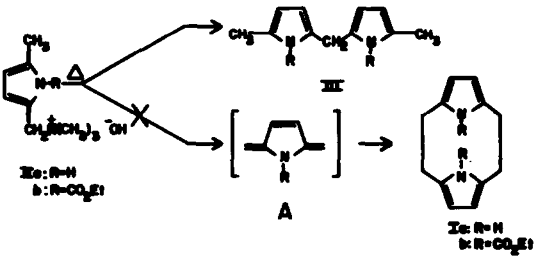
(Received in USA 31 March 1975; received in UK for publication 7 April 1975)

While numerous cyclophanes exist in which heteroaromatic nuclei (e.g. furan,[2-5] thiophene,[2,6] pyridine[6-8]) are incorporated into the cyclophane macrocycle, those which contain the pyrrole moiety[9] are conspicuously absent from these ranks. Recently, we reported the synthesis of a number of cyclophanes containing a single pyrrole nucleus.[1a] We now wish to report the successful completion of the synthesis of the parent unsubstituted nitrogen containing cyclophane, [2.2](2,5)pyrrolophane (Ia).

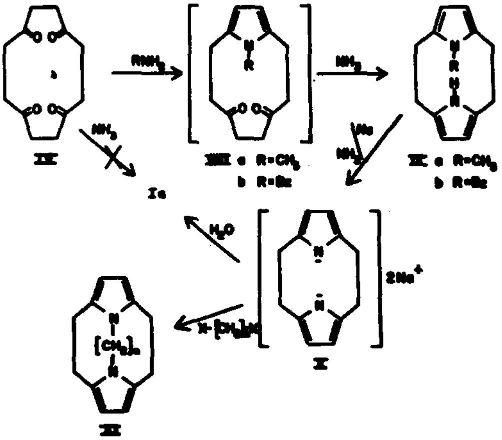
Attempts to synthesize Ia or b by the classical method[10] of dimerization of monomer A, afforded dipyrrylmethane (III), but none of the desired cyclophane, Ia or b. In addition, attempted synthesis of Ia by a Paal-Knorr[11] cyclization of 1,4,7,10-cyclododecatetraone (IV) with ammonia, proved fruitless,[12] although the method had been successfully employed to synthesize [2.2](2,5)-pyrroloparacyclophane, [2.2](2,5)pyrrolonaphthalenophane and [2.2](2,5)pyrrolo-(2,5)furanophane [1a] (V, VI and VII, respectively).

A successful synthetic approach to Ia was realized, as described in Scheme II, after it was observed that N-methyl[2.2](2,5)pyrrolophane (IXa)

SCHEME I



SCHEME II



could be prepared (43%,[13] after chromatography and sublimation, mp 78-79°) by successively treating tetraone IV with methylamine[9] and ammonia. Analogously, tetraone IV was converted to N-benzyl[2.2](2,5)pyrrolophane (IXb) (17%,[13] after chromatography and sublimation, mp 84-85°) by condensation with N-benzylamine[14] followed by immediate treatment, in situ, with ammonia. Reductive cleavage of the benzyl group by sodium in liquid ammonia afforded the desired cyclophane, Ia (87%, after sublimation, mp 163-165°).

The structures of cyclophanes IXa,b and Ia were confirmed by spectral analysis.[20] Compounds IXa,b and Ia respectively, exhibit the simple recognizable[16] mass spectral characteristics of [2.2]cyclophanes showing a molecular ion for the phane (m/e: IXa, 200; IXb, 276; Ia, 186), and ions corresponding to the two fragments arising from, and indicative of, the cleavage of the ethylene bridges (m/e: IXa, 107 and 93; IXb, 183 and 93; Ia, 93. In addition compound IXb exhibits a strong peak at m/e 91 associated with the loss of the benzyl group. The infrared spectra of the three compounds confirms 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 IXb 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.[17] 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 pmr spectra of the three cyclophanes were most significant and informative in elucidating their structures (See Table 1). Each compound exhibited broad absorptions at 3.4-3.6 τ, 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(VII) (3.6 τ),[1a] 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 IXa,b and Ia is observed

Table 1

PMR Spectral Data of Compounds IXa, IXb and Ia (τ; $CDCl_3$; internal standard, TMS)

IXa	IXb	Ia
3.4, broad s, 1H	3.4-3.5, broad s[15], 1H	3.58, broad s, 2H
3.71, s, 2H	2.7-3, m, 5H	4.16, d (J=2.5Hz), 4H
4.15, d (J=2.9Hz), 2H	3.8, s, 2H	7.43, A_2B_2, 8H
6.98, s, 3H	4.1, d (J=2.6Hz), 2H	
7.15, m, 8H	5.42, s, 2H	
	7.27, m, 8H	

at about 4.1 τ and the peaks are split into doublets by the pyrrole N-H. These chemical shifts and coupling constants are similar to those found in VII (4.05 τ, J = 3.0 Hz).[1a] The analogous β-protons on the N-substituted pyrrole rings in IXa and b on the other hand, are found as sharp singlets at 3.7-3.8 τ and are positioned near the chemical shift of the β-pyrrole protons in Ic (3.9 τ).[9] Each compound also shows a complex absorption pattern at 7.3 τ for the eight protons on the ethylene bridges. Again, the shifts are similar to those found in Ic (7.16 τ)[9] and VII (7.35 τ).[1a] Additionally, IXa exhibits a single absorption at 7 τ for the N-methyl protons, similar to that found in Ic (6.95 τ),[9] and IIb shows a singlet at 5.42 τ and a multiplet 2.85 τ for the methylene and benzenoid protons of the benzyl group, respectively. The above data is entirely consistent with the assigned structures for IXa,b and Ia.

It is important to note that the multiplicity of the bridge protons in Ia(A_2B_2) indicates that, unlike the corresponding [2.2](2,5)furanophane,[18] the pyrrole rings are not rotating. This conformational rigidity was predicted in light of the high activation energy (> 27 Kcal/mol) observed for the analogous cyclophane VII.[1b,c] Attempts, however, to detect the rotational process by variable temperature pmr techniques and rigorously substantiate the above prediction proved fruitless due to the decomposition of Ia at high temperatures. On the other hand, high temperature pmr experiments on IXa demonstrated conclusively that the pyrrole rings are not rotating at temperatures up to 190° C and that the barrier to rotation is > than 27 Kcal/mole.[19]

Since reduction of IXb probably involves the intermediacy of dianion X, we are presently studying the feasability of quenching the reaction mixture with dihaloalkanes of type $X-(CH_2)_n-X$ as a possible route to the unknown [n.2.2](1,2,5)pyrrolophanes, XI. In addition, variable temperature pmr studies are being carried out to determine what effect the removal of the N-H protons will have on the rotational process in these and other [2.2](2,5)pyrrolophanes.

Acknowledgement: We thank the National Science Foundation, Grant GU-3852, the National Institutes of Health Biomedical Sciences Support Grant RR-7044-07 and the donors of the Petroleum Research Fund, administered by the American Chemical Society, Grant 2786-G1, for support of this work.

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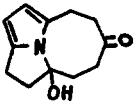
12. Along with much tarry material, a compound, whose structure has tentatively been assigned to be **i** by spectral analysis, was isolated from this reaction.

i



13. Yield based on starting tetraone.

14. Diketone VIIIb, unlike VIIIa,[9] was not isolated. The compound is air and light sensitive which precluded isolation for analytical purposes. Spectral data consistent with structure VIIIb however, have been obtained.

15. The value given is for the center of a very broad singlet. It is approximate due to the difficulty in observing the band. There is no doubt however, about its presence because the proton is easily observed during integration.

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20. Satisfactory analysis (within 0.3%) were obtained for all three compounds.