Synthesis and Conformation of [2.2](2,5)Furano(2,5)pyridinophane

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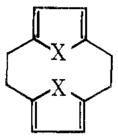
The synthesis of [2.2](2,5)furano(2,5)pyridinophane by a "cross-breeding" reaction between 2,5-dimethylene-2,5-dihydrofuran and 2,5-dimethylene-2,5-dihydropyridine is described. The conformation of the compound is such that the furan ring is essentially perpendicular to the pyridine ring with the oxygen function of the furan ring closer to the C_3–C_4 than to the N–C_6 bond.

Reports describing the syntheses of cyclophanes and studies describing their physical and chemical properties abound.[1] For example, in a series of very elegant papers, Cram and coworkers[2] have shown that in [2.2]paracyclophanes there exist transannular interactions between the benzene rings in these systems. These studies have been extended to include mixed [2.2]paracyclophanes where one ring is pyridinoid and the other is benzenoid.[3]

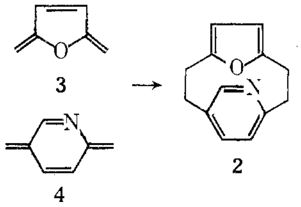
The four isomeric [2.2](2,5)pyridinophanes have also been recently synthesized,[4] as have been the two cyclophanes **1a** and **1b**.[5,6]



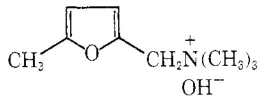
1a, X = O
b, X = NCH_3

We became interested in preparing the mixed heterocyclophane **2**, since it represents the first example of a mixed heterocyclophane composed of a π-deficient (pyridine) and a π-excessive (furan) ring.

The most reasonable approach to the synthesis of compound **2** appeared to us to be *via* a "cross-breeding" dimerization of compounds **3** and **4**. In this type of reaction, it is, of course, to be anticipated that the furan dimer **1a**, as well as the isomeric [2.2](2,5)pyridinophanes, will also be formed. Compounds **3** and **4** were generated *in situ* from the quaternary hydroxides **5** and **6**, respectively; the cross-breeding reaction was carried out in refluxing toluene, and the reaction mixture was subjected to dry-column chromatography. The proportions of the various possible products expected were those reported in Table I. Along with these cyclophanes, a substantial amount of the ether **7**, as observed in the formation of the pyridinophanes,[4] was obtained.



3 → 2
4



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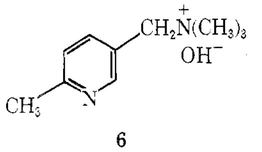

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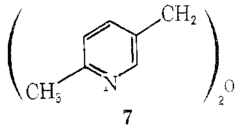

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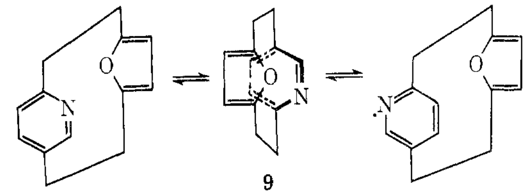
Table I
Reaction Products Distribution

Compd[a]	% of total product
	48
21a	18
Mixture of [2,2](2,5)pyridinophanes[b]	4
7	30

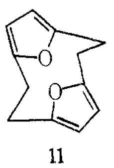
[a] See text for structures. [b] Identified by pmr spectra (*cf.* ref 4).

The desired compound, **2**, was identified by its correct elemental analysis, mass spectrometric molecular weight, and pmr spectrum. It is obvious that compound **2** could exist as conformer **8**, **9**, or **10** or as a rapidly equilibrating mixture of these three conformers. The latter possibility appears to be a fairly unlikely one in view of the fact that Dreiding models rule out a facile interconversion of the structures. In order to establish the correct structure for this mixed paracyclophane an analysis of its uv and pmr spectra was undertaken.



8 9 10

A comparison of the uv spectra of the furanophane **1a** with that of compound **2** shows that the furan absorption in compound **2** (λ_{max} 224 nm) is the same as that found in the furanophane (λ_{max} 222 nm). In the latter instance it has been established that the compound exists in the staggered conformation **11**.



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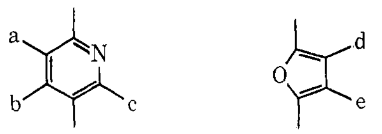
Consequently, one can suggest that there is no transannular interaction of the π clouds of the furan ring with those of the pyridine ring in compound **2**.

The furan protons of the furan dimer **1a** (δ 6.05 ppm) are deshielded by 0.25 ppm in comparison to 2,5-dimethylfuran (δ 5.80 ppm), while those of the mixed dimer **2** resonate at δ 5.69 and 5.75 ppm, respectively (see Table II). Thus, in the staggered conformation of the furan dimer **11** the furan protons are subject to a deshielding effect, while in the configuration of the mixed dimer **2**, the protons are experienc-

Table II
Pmr Spectral Data[a]

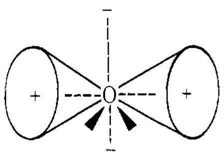


Compd[b]	H_a	H_b	H_c	H_d	H_e
2,5-Dimethylfuran				5.80	
2,5-Dimethylpyridine	7.00	7.34	8.30		
1a[c]				6.05	
2[d]	6.90	7.16	7.72	5.69	5.75

[a] In parts per million (δ). [b] Dilute solutions in $CDCl_3$. [c] See text for structures. [d] The pmr spectrum, in $CDCl_3$ or DMSO, is temperature independent from −50 to 60°, and in C_5D_5N from room temperature to 110°.

ing a slight shielding effect, with respect to the furan protons in 2,5-dimethylfuran. Thus, these protons are not influenced by the pyridine ring anisotropic effects. There are, however, significant shielding effects operating on the pyridine ring of dimer **2** where the α, γ, and δ protons are shielded, with respect to those in 2,5-dimethylpyridine, by 0.58, 0.18, and 0.10 ppm, respectively. Consequently, one must conclude that compound **2** exists neither as conformer **8** nor conformer **10.**

In view of the fact that the pyridine α proton in compound **2** is considerably more shielded than are the γ and δ protons, and keeping in mind that the estimated anisotropic effects in ether-type oxygens are represented by drawing **12,** one can strongly suggest that the correct room-temperature configuration for compound **2** in solution is representation **9** with the furan oxygen somewhat more closely situated toward the N_1–C_6 bond than toward the C_4–C_5 bond.



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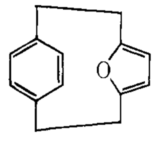
A variable-temperature pmr study of compound **2** (110° in C_5D_5N to room temperature, and room temperature to −50° in $CDCl_3$) showed no spectral changes in this temperature region. This behavior is surprising in view of the report that compound **13** is described as undergoing the type of inversion as indicated for the similar conformers **8** and **10.**[9]



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Experimental Section

Nmr spectra were obtained with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 80 eV. Elemental analyses were determined by the Analytical Services Laboratory of the University of Alabama Chemistry Department.

6-Methyl-*N*,*N*′-dimethylnicotinamide. Ethyl 2-methyl-5-ethylnicotinate[8](25.5 g, 0.15 mol) was stirred at room temperature with an excess of a saturated aqueous solution of dimethylamine. After 30 hr, the clear reaction mixture was extracted with $CHCl_3$ and washed with 50 ml of H_2O and 2 × 50 ml of a saturated aqueous solution of NaCl. The organic layer was dried over anhydrous Na_2CO_3. The reaction mixture was distilled at 115–120° (1 Torr) and 12.5 g (50% yield) of product was collected: mol wt 164 (mass spectrum); pmr spectrum δ_{TMS} ($CDCL_3$) 7.67 (1 H, d of d), 7.18 (1 H, d), 8.54 (1 H, d), 3.05 [6 H, $-N(CH_3)_2$, s], 2.56 (3 H, $-CH_3$, s).

2-Methyl-5-dimethylaminomethylpyridine. 6-Methyl-*N*,*N*′-dimethylnicotinamide (8.55 g, 0.052 mol) in 100 ml of ether was added dropwise to a slurry of $LiAlH_4$ (1.9 g in 100 ml of ether) and the reaction mixture was refluxed with stirring overnight. Water (2.7 ml) was then added to destroy the excess of $LiAlH_4$. The reaction mixture was then filtered, the filtrate was dried over anhydrous Na_2CO_3, the solvent was evaporated, and the product was distilled at 53–55° (1 Torr). The product, 3.59 g (46.1% yield), was collected: mol wt 150 (mass spectrum); pmr spectrum δ_{TMS} ($CDCl_3$) 8.38 (1 H, d), 7.53 (1 H, 2 d), 7.10 (1H, 5 d), and singlets at 3.38 (2 H, $-CH_2-$), 2.53 (3 H, $-CH_3$), and 2.22 [6 H, $-N(CH_3)_2$], respectively.

2-Methyl-5-trimethylaminomethylpyridinium Iodide. 2-Methyl-5-dimethylaminomethylpyridine (3.59 g, 0.024 mol) was dissolved in 50 ml of ether, and methyl iodide (4.48 g, 0.031 mol) in 50 ml of ether was added slowly with stirring at room temperature. After stirring overnight, the reaction mixture was filtered and the off-white solid was washed with ether and dried (6.4 g, 91.7% yield).

Anal. Calcd for $C_{10}H_{17}N_2I$: C, 41.11; H, 5.87; N, 9.59. Found: C, 41.00; H, 6.17; N, 9.37.

[2.2](2,5)Furano(2,5)pyridinophane. 2-Methyl-5-trimethylaminomethylpyridinium iodide (1.2 g, 0.004 mol) and 5-methyl-2-furfuryltrimethylammonium iodide (1.1 g, 0.004 mol) were dissolved in 100 ml of water and the resulting solution was stirred with 2.5 g of freshly prepared Ag_2O for a period of 1 hr. The mixture was filtered and the filtrate was freeze-dried. The remaining solid was suspended in 300 ml of toluene, a small amount of hydroquinone was added, the stirred mixture was heated at reflux, and the water that was formed was collected in a Dean-Stark trap. After 2 hr, no more trimethylamine was formed and the reaction was judged complete. The reaction mixture, after cooling to room temperature, was filtered and the filtrate was concentrated *in vacuo* to dryness. The remaining oily material was then subjected to dry-column chromatography (15 × 1 in., neutral alumina, 100–200 mesh, Brockman grade III), using ether as a developing solvent. By examining the behavior of the reaction mixture on tlc (identical conditions with the dry-column chromatogram) (visualization with I_2), the location of the various components on the dry-column chromatogram was ascertained. The various zones were then collected and the compounds were extracted from the alumina with methylene chloride. In this manner four different components were obtained.

These compounds were identified respectively as (1) [2.2](2,5)furanophane (**1a**, 250 mg, 16%, mp 189–191° dec) by comparison with an authentic sample;[6] (2) [2.2](2,5)furano(2,5)pyridinophane [100 mg, 6.3%, mp 86–87° after vacuum sublimation at 60° (1 Torr)] (*Anal.* Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.63; N, 7.05. Found: C, 78.11; H, 6.89; N, 6.78) (*cf.* also pmr and uv data in tables); (3) a mixture of the isomers of [2.2](2,5)pyridinophane (20 mg, 1.2%) by comparison with the reported pmr spectra, and the mass spectrometric molecular weight of 210;[4] (4) the ether **7** (190 mg, 10.3%) by comparison with an authentic sample.[4]

Registry No.—**1a**, 5088-46-0; **2**, 51849-29-7; **7**, 34107-45-4; 6-methyl-*N*,*N*-dimethylnicotinamide, 51849-30-0; ethyl 2-methyl-5-ethylnicotinate, 22701-39-9; dimethylamine, 124-40-3; 2-methyl-5-dimethylaminomethylpyridine, 51849-31-1; 2-methyl-5-trimethylaminomethylpyridinium iodide, 51849-32-2.

References and Notes

(1) For a review, see F. Voegtle and P. Neumann, *Synthesis*, 85 (1973).
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(3) J. Bruhin and W. Jenny, *Chimia*, **26**, 420 (1972).
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(9) (a) J. F. Haley, Jr., and P. M. Keehn, *Tetrahedron Lett.*, 4017, 4021 (1973); (b) G. M. Whitesides, B. A. Pawson, and A. C. Cope, *J. Amer. Chem. Soc.*, **90**, 639 (1968).