615 (5, M**), 613 (9, M*), 611 (5, M), 524 (40, M** - $HCOOCH_3$ - OCH_3), 522 (100, M* - $HCOOCH_3$ - OCH_3), 520 (39, M - $HCOOCH_3$ - OCH_3), 510 (13), 464 (13), 462 (8), 217 (10), 105 (12), 79 (11).

Anal. Calcd for $C_{24}H_{23}Br_2NO_8$ (mol wt 613.28): C, 47.00; H, 3.78; Br, 26.06; N, 2.28. Found: C, 46.84; H, 3.83; Br, 26.17; N, 2.02.

Acknowledgment. We are grateful to Mr. Thomas Robison for his helpful suggestions in preparing the manuscript. C.K.L. thanks the Korean Science and Engineering Foundation for a research grant.

Registry No. 1b, 74965-13-2; **2a**, 74965-14-3; **2b**, 74965-15-4; **3b**, 74965-16-5; DMAD, 762-42-5.

Synthesis and Some Stereochemical Aspects of [2.2](2,5)Furano(3,6)pyridazinophane and Its *N*-Oxide

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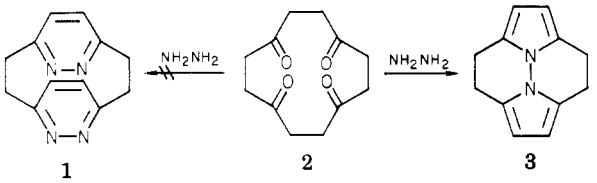
Received June 13, 1980

The synthesis of [2.2](2,5)furano(3,6)pyridazinophane (**6**), the first reported [2.2]pyridazinophane, is described. This comprises only the second known π-excessive/π-deficient [2.2]heterophane. Ultraviolet spectral studies indicate that there is some transannular interaction between the pyridazine and furan rings. A phane containing a 12-membered ring is also formed during the synthesis of the title compound. The chiral *N*-oxide **12** is the first reported *N*-oxide in the para-substituted [2.2]heterophane class.

During an attempted synthesis of [2.2](3,6)-pyridazinophane (**1**) from the tetraketone **2**, we obtained the unexpected nitrogen-bridged tetrahydroannulene **3**.[1]



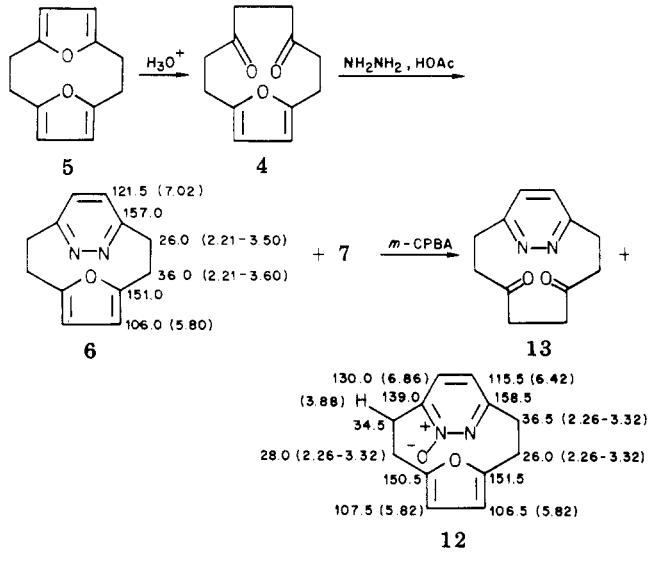
1 2 3

Thus, any potential synthesis of a pyridazinophane demanded a different synthetic approach. The intermediate compound **4** was prepared by hydrolysis of the furanophane **5**[2] in order to ascertain whether a pyridazinophane can be generated from a cyclic diketone. Treatment of the diketone **4** with hydrazine afforded two products, **6** and **7**, in essentially equal yields (Scheme I). An elemental analysis coupled with a mass spectral determination establishes $C_{12}H_{12}N_2O$ as the correct molecular formula for compound **6**, thus identifying it as the expected [2.2]-(2,5)furano(3,6)pyridazinophane. The ^1H NMR spectrum of this compound has singlets at δ 5.80 and 7.02, respectively. These values compare with δ 5.80 for the aromatic protons in 2,5-dimethylfuran (**8**) and δ 7.20 for the similar protons in 3,6-dimethylpyridazine (**9**). Thus, the pyridazine ring protons in the heterophane **6** are shielded with respect to those in 3,6-dimethylpyridazine (**9**), by 0.18 ppm, while the phane structure has no effect on the chemical shift of the ring protons of the furan ring.

We have already reported identical observations for the furanopyridinophane (**10**).[4a] The formation of the heterophane **6** constitutes only the second example of a [2.2]-heterophane containing a π-excessive as well as a π-deficient ring.

Compound **7** has a molecular formula of $C_{24}H_{28}N_4O_2$ as determined by elemental analysis and mass spectrum. This is, to our knowledge, the first reported instance of the formation of a 12-membered ring during the condensation of a 1,4-diketone with hydrazine (as is well-known, this reaction generally affords dihydropyridazines and pyridazines[3]). Interestingly, the yield of the compound can be increased to essentially 100% by appropriate variations of the reaction conditions (see Experimental Section). The infrared spectrum of this compound has no absorption in the N-H region but has a weak band at 1633 cm^{-1}, indicative of the presence of a N=N grouping. The ^1H NMR spectrum shows an AB system for four furan protons centered at δ 5.79, a complex multiplet in the region δ 1.26-3.78, equivalent to 22 protons, and an ABX system with H_x (two olefinic protons) resonating at δ 4.72. The ^{13}C NMR spectrum of this compound shows 12 dif-

Scheme I[a]



[a] Numbers in parentheses are ^1H NMR chemical shifts (δ). The others are ^{13}C NMR chemical shifts (δ).

(1) Paudler, W. W.; Stephan, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 4468.
(2) Haley, J. F.; Keehn, P. M. *Tetrahedron Lett.* **1973**, 4017.
(3) (a) Joule, J. A.; Smith, G. F. "Heterocyclic Chemistry"; Van Nostrand Reinhold Co.: London, 1975. (b) Bradamante, S.; Pagani, G.; Marchesini, A.; Pagnoni, U. M. *Ind. Chim. (Paris)* **1973**, *55*, 962. (c) Tisler, M.; Stanovnik, B. *Adv. Heterocycl. Chem.* **1968**, *9*, 000.

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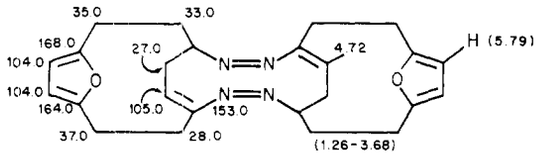
ferent carbons. Three of them are ascribable to the presence of the 2,5-disubstituted furan rings, two to the different olefinic carbons (153, 105 ppm, respectively) and six to the different sp^3 carbons. Thus we are dealing with a symmetrical dimer.

These data lead us to propose structure **7a** for this

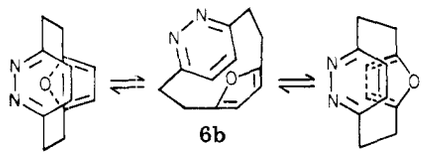


7a

^{13}C NMR chemical shifts in parts per million from Me_4Si. Numbers in parentheses are ^1H NMR chemical shifts.

compound.[4c] Barring any unusual carbon-skeletal rearrangements, this appears to be the only structure consistent with the spectral data. Further structural studies on this compound are in progress.

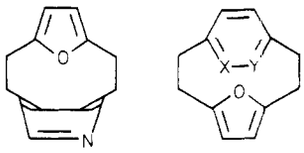
As in all of the other known cyclophanes, a knowledge of the stereochemistry of the furanopyridazinophane **6** is also of interest. One must consider the possible existence of the following equilibria:



6a 6b 6c

Since the ^1H NMR spectrum of this compound is unchanged between −60 and 110 °C, the absence of these equilibria in this temperature range is established (see Experimental Section). Thus, we are either dealing with a rapidly rotating isomer or the completely locked syn isomer **6a**. This conclusion is in agreement with the reported thermal stability of the related furanopyridinophane and establishes that the steric interaction in the heterophanes **6** and **10** is similar, but different from the furanoparacyclophane **11** where restricted rotation of the benzene ring has been observed only at low temperatures (−40 °C).[4b] In order to clarify the stereochemistry of the system, we took recourse to the synthesis of the furanopyridazinophane *N*-oxide **12**. As described later, a field effect from the oxygen atom is only found on one α-methylenic hydrogen. As the furanoid protons are unaffected, the stereochemical orientation of this compound is in the syn form. The similarity of the methylenic region in this compound to the same region in furanopyridazinophane **6** (with the exception to be noted later) leads one to conclude that the orientation of the two systems is similar and locked in the syn form (see Scheme I).

An X-ray crystallographic analysis of the furanopyridinophane **10** has shown that the pyridine ring in this compound is not planar, while the furan ring is.[7] Furthermore, the nitrogen of the pyridine ring is relatively closely situated to the oxygen of the furan ring.



10

6, X = Y = N
10, X = CH; Y = N
11, X = Y = CH

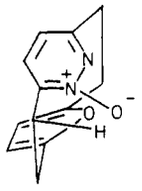
The similar shielding effects of the ring hydrogens in the pyridinophane **10** and in the pyridazinophane **6** allow one to conclude that the two ring systems have very similar, if not identical, stereochemistry; i.e., the pyridazine nitrogens are in a syn relationship to the furan oxygen and the angle between the two ring systems is close to the 23° angle shown to exist in the pyridinophane **10**.[7] The conclusion is therefore that the order of steric interaction in the cavity of these systems decreases in the order =N—N= ≥ =CH—N= > =CH—CH=. This is the reverse of the order observed in the metacyclophanes, where it has been shown that an aromatic CH is sterically more demanding than a nitrogen with its lone pair.[7,8]

Oxidation of furanopyridazinophane **6** with 1 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) gave two products, $C_{12}H_{12}N_2O_2$ (**12**) and $C_{12}H_{14}N_2O_2$ (**13**), in yields of 40% and 20%, respectively (Scheme I). Compound **13** is readily identified as the dioxopyridazinophane **13** by its ^1H NMR and infrared spectra (see Experimental Section).

Compound **12** has the correct molecular formula for the expected furanopyridazinophane *N*-oxide. The mass spectrum of this compound shows the anticipated M − 16 ion, typical for *N*-oxides. The remaining fragment ions are identical with those obtained from the furanopyridazinophane **6** itself.

The ^1H NMR spectrum of the *N*-oxide **12** when compared to that of the non-*N*-oxide **6** shows that H-4 and H-5 in the *N*-oxide are shielded by 0.6 and 0.16 ppm, respectively. In pyridazine *N*-oxide itself H-4 and H-5 are shielded by 0.5 and 0.1 ppm. Thus, qualitatively at least, the same effects are operative in the furanopyridazinophane *N*-oxide **12** as in pyridazine *N*-oxide.

The interesting feature of the ^1H NMR spectrum of the *N*-oxide is the fact that one of the methylene protons resonates at δ 3.88 (ABCD pattern), considerably deshielded (by about 0.7 ppm) with respect to the other methylene protons in the compound. An examination of molecular models[10] shows that one of the methylene protons is close enough to the *N*-oxide oxygen to experience a deshielding field effect. The field effect approximation



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(10) Prentice-Hall molecular models were used.

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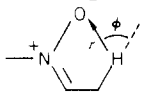
developed by Buckingham[11] and others[12] allows one to calculate the anticipated chemical shift changes when field effects are operative. This is shown by eq 1, where r is the

$$\Delta\delta = -14.4 \cos\frac{\phi}{r^2} - \frac{17}{r^4} \quad (1)$$

distance between the proton in question and the atom generating the field effect, while ϕ is the angle, as indicated below. This calculated field effect is 0.7 when $\phi = 70°$,



and $r = 2.6$ Å. Both of these values are readily discerned from an examination of molecular models. As only one proton experiences this effect, the *N*-oxide **12** is frozen in the syn form.

There now remains the need to examine these systems with respect to possible interactions between the π-excessive furan and the π-deficient pyridazine ring.

The ^{13}C NMR spectrum of the furanopyridazinophane is not significantly altered relative to its constituent monomers, but ^{13}C NMR spectroscopy is not as sensitive to ring deformations as is UV spectroscopy. X-ray crystallography[7] has established that the furan ring is not deformed in the furanopyridinophane **10** and is relatively perpendicular to the deformed pyridine ring. This is probably also true for the furan ring in the furanopyridazinophane **6**. The bathochromic shift in the furanoid absorption[14] can therefore be ascribed to transannular interactions between the furan oxygen and the pyridazine and pyridine rings, respectively, in both furanopyridazinophane and furanopyridinophane. Work is currently underway to measure the effects of electron-donating substituents on the π-excessive ring and/or electron-withdrawing substituents on the π-deficient ring.

Experimental Section

NMR spectra were obtained with a Varian HA-100 spectrometer, mass spectra with a Hitachi Perkin-Elmer RMU-6M instrument, and ultraviolet spectra with a Cary-14 spectrometer. Infrared spectra were recorded on a Beckman Acculab 1 instrument. The ^{13}C NMR spectra were obtained with a Hitachi Perkin-Elmer R-26 instrument. Elemental analyses were determined by the Analytical Services Laboratory of the University of Alabama Chemistry Department. Melting points are uncorrected.

Preparation of Furanopyridazinophane 6. Dioxofuranophane **4** (0.206 g, 1 mmol) was dissolved in 50 mL of refluxing glacial acetic acid in a 100-mL flask fitted with a reflux condenser and drying tube. A threefold excess of hydrazine hydrate (95%, 0.500 g) was added all at once. The progress of the reaction was monitored by TLC (Eastman silica gel sheets; mobile phase, ether). Two further additions of hydrazine were required before TLC revealed the absence of starting compound. The total reaction time was 12 h. After cooling, the reaction mixture was poured into 150 mL of ice-cold sodium carbonate solution (~10%). The basic solution was extracted with three 150-mL portions of chloroform. The combined chloroform layers were washed with water and dried over anhydrous sodium carbonate. Filtration and solvent evaporation yielded a yellow oil (200 mg). The oil was chromatographed on neutral alumina (Brockman grade III), using a dry column. Elution with ether and recrystallization from benzene gave the tetrahydroannulene **7** as colorless crystals (20–40%): mp 193–194 °C; ^1H NMR ($CDCl_3$) δ 5.79 (m, 4 H), 4.72 (m, 2 H), 1.26–3.68 (m, 22 H); mass spectrum, m/e (M^+) 375 ($-N_2$), 203, 202, 202, 135, 107, 94; IR (Nujol) 1633 (N=N), 1565 (C=C) cm^{-1} (no N-H). Anal. Calcd for $C_{24}H_{28}N_4O_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 17.20; H, 7.01; N, 13.57.

Elution with chloroform/ethyl acetate (1:1) and recrystallization from acetone/hexane gave colorless crystals of [2.2](2,5)furano(3,6)pyridazinophane (20–40%): mp 174–176 °C; ^1H NMR ($CDCl_3$) δ 7.02 (s, 2 H), 5.80 (s, 2 H), 2.2–3.36 (m, 8 H); mass spectrum, m/e 200, 172, 107, 94. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 604; N, 13.99. Found: C, 71.45; H, 6.20; N, 13.79.

Preparation of Tetrahydroannulene 7. The same procedure was followed as in the previous reaction with the following changes. (i) The reaction temperature was 70–80 °C. (ii) Nitrogen gas was bubbled through the solvent (HOAc) for 15 min prior to combination of the reagents and throughout the reaction time (18 h). (iii) The crude product was recrystallized without prior chromatography in high yield.

Preparation of Furanopyridazinophane *N*-Oxide 14. Furanopyridazinophane **6** (0.060 g, 3×10^{-4} mol) was dissolved in 15 mL of methylene chloride (Sargent-Welch reagent grade) at room temerature. *m*-Chloroperbenzoic acid (Aldrich, 85%) (0.060 g, 3×10^{-4} mol) was dissolved in 15 mL of methylene chloride and this was combined with the other solution. Stirring was continued for 48 h, with monitoring by TLC (Eastman Silica gel sheets; mobile phase, chloroform). The flask was protected from light with aluminum foil throughout the reaction. The yellow solution was poured into NaOH solution (final pH ~10–12). The aqueous layer was extracted with two 20-mL portions of chloroform. The combined chloroform extracts were washed with two 50-Ml portions of H_2O and then dried over anhydrous sodium carbonate. Filtration and solvent evaporation yielded 50 mg of a yellow oil. This oil was chromatographed on nondeactivated silica gel (Davison Chemicals). Band 1 eluted with chloroform and yielded 16 mg (20% of theory) of clear yellowish crystals of 3,6-dioxo[8](3,6)pyridazinophane (**15**): ^1H NMR ($CDCl_3$) δ 7.71 (s, 2 H), 2.67–3.3 (m, 12 H); mass spectrum, m/e 218 (M^+), 184 (p), 157, 143, 129, 127, 114, 101. Band 2 was eluted with chloroform/MeOH (3:1) and afforded 32 mg of clear yellowish crystals of furanopyridazinophane *N*-oxide **18**: ^1H NMR ($CDCl_3$) δ 6.64 (m, 2 H, AB), 2.26–3.32 (m, 7 H), 3.88 (m, 1 H, ABCD); mass spectrum, m/e 216 (M^+), 200 (M – 16), 172, 108, 94. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.32; H, 5.74; N, 12.70. Variable-temperature studies were carried out in pyridine solution from 30 to 110 °C by the method of Nelson,[14] using a sealed external Me_4Si standard. Deuteriochloroform was the solvent used for the –60 to 30 °C temperature range, with internal Me_4Si standard.

Acknowledgment. We gratefully acknowledge the University of Alabama for support of this work in the form of a Graduate Council Research Fellowship to M.D.B.

Registry No. **4**, 51460-20-9; **6**, 74965-64-3; **7**, 74978-10-2; **12**, 74965-65-4; **13**, 74965-66-5.

(14) 2,5-Dimethylfuran: UV (EtOH λ_{max} 220 nm (log ϵ 3.90); UV (hexane) λ_{max} 216 nm (3.80). Furanopyridazinophane **6**: UV (EtOH) λ_{max} 224 nm (log ϵ 3.80), 277 (3.35), 325 (3.40); UV (hexane) λ_{max} 222 nm (log ϵ 3.81), 278 (3.34), 340 (3.05).

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