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Polyquinanes by [4 + 4] Cycloaddition–Transannular Cyclization

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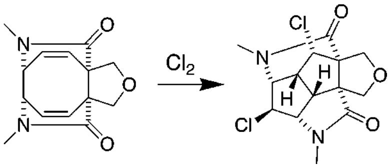
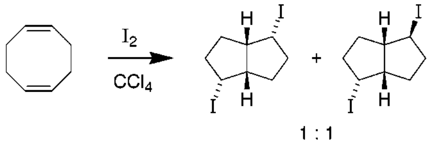
ABSTRACT



Photocycloaddition of 2-pyridones yields a rigid polycyclic product containing a 1,5-cyclooctadiene. The cis isomer, with the alkenes in close proximity, undergoes a transannular reaction when treated with chlorine to give a polyquinane product. The chlorination reaction involves migration of an amide nitrogen and forms a single isomer, generating eight stereogenic centers in two steps.

The topological connection between a cyclooctane and fused five-membered rings has long been recognized. Transannular ring closure has been accomplished via carbanions,[1] carbocations,[2] radicals,[3] carbenes,[4] pinacol coupling,[5] and electrocyclic reactions.[6] The parent 1,5-cyclooctadiene was shown by Uemura et al.[7] to yield a mixture of two isomeric diquinanes when treated with iodine, Scheme 1. Other halogens, however, failed to yield the bicyclooctane under similar conditions.

Scheme 1. Cyclooctadiene Yields Diquinanes[7]



Explorations of 2-pyridone [4 + 4] cycloadditions by several labs have shown it to be a versatile method for construction of functionalized 1,5-cyclooctadienes.[8] We have reported conditions for both cis-selective[9] and trans-selective[10] reactions. The ability to readily generate cis pyridone photoproducts containing a tub-shaped cyclooctadiene suggested that these products might be a useful route to polyquinanes.

Unlike the conformationally mobile 1,5-cyclooctadiene parent, the doubly bridged cyclooctadiene found in pyridone photoproducts is very inflexible. Moreover, there were regiochemical issues with **1**, Scheme 2. The alkenes can be

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[1] MacDougall, J. M.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 7445−7450.

[2] Davis, A. P.; Hughes, G. J.; Lowndes, P. R.; Robbins, C. M.; Thomas, E. J.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1934−1941. Riches, B. H.; Kitching, W. *J. Chem. Soc., Chem. Commun.* **1996**, 1907−1908.

[3] Belotti, D.; Cossy, J.; Pete, J. P.; Portella, C. *J. Org. Chem.* **1986**, *51*, 4196−4200. Forbes, J. E.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 2565−2568. Curran, D. P.; Shen, W. *Tetrahedron* **1993**, *49*, 755−770.

[4] Regitz, M.; Rüter, J. *Chem. Ber.* **1969**, *102*, 3877−3890. Whitesell, J. K.; White, P. D. *Synthesis* **1975**, 602−603. Murata, S.; Suzuki, M.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 247−254.

[5] Cope, A. C.; Kagan, F. *J. Am. Chem. Soc.* **1958**, *80*, 5499−5502. Pauw, J. E.; Weedon, A. C. *Tetrahedron Lett.* **1982**, *23*, 5485−5488.

[6] Matlin, A. R.; Lahti, P. M.; Appella, D.; Straumanis, A.; Lin, S.; Patel, H.; Jin, K.; Schrieber, K. P.; Pauls, J.; Raulerson, P. *J. Am. Chem. Soc.* **1999**, *121*, 2164−2173.

[7] Uemura, S.; Fukuzawa, S.-i.; Toshimitsu, A.; Okano, M.; Tezuka, H.; Sawada, S. *J. Org. Chem.* **1983**, *48*, 270−273.

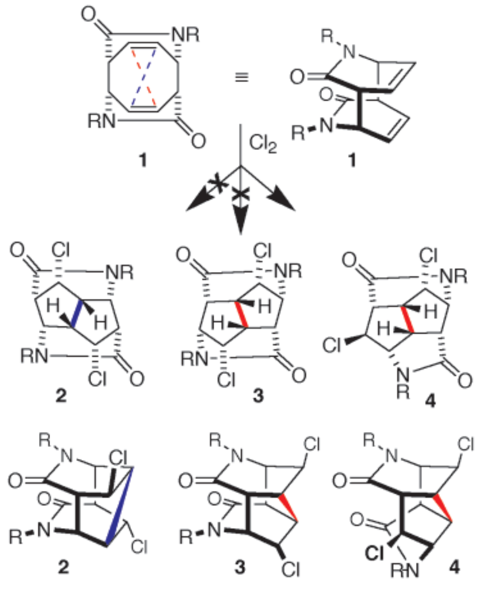
[8] Sieburth, S. McN. The Inter- and Intramolecular [4 + 4] Photocycloaddition of 2-Pyridones and Its Application to Natural Product Synthesis. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI: Greenwich, CT, 1999; Vol. 5, pp 85−118.

[9] Sieburth, S. McN.; McGee, K. F., Jr. *Org. Lett.* **1999**, *1*, 1775−1777.

[10] Sieburth, S. McN.; Lin, C.-H. *J. Org. Chem.* **1994**, *59*, 3597−3599.

10.1021/ol016076x CCC: $20.00

Scheme 2. Two Products, **2** and **3**, Expected from the Pyridone Dimer **1** and the Actual Product **4** (R = *n*-Butyl)

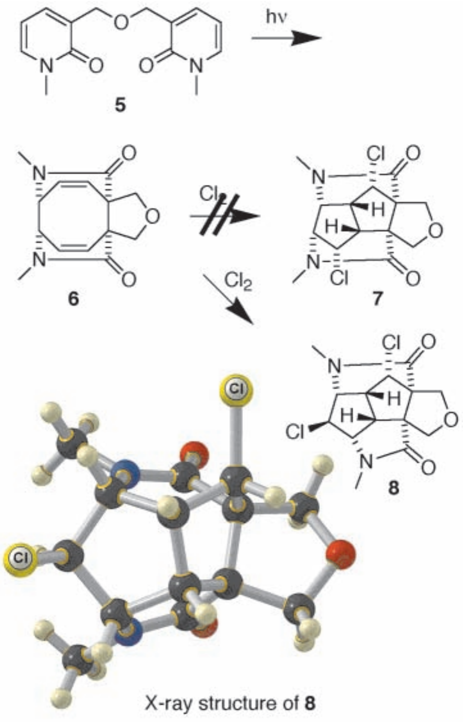


combined in two different ways, with the anticipated products **2** and **3** having different carbon skeletons.

Our initial experiments with **1** (R = *n*-butyl) seemed to confirm that a transannular closure had occurred but without regioselectivity; both proton and carbon NMR suggested a 1:1 mixture of structures **2** and **3**. Dimer **1** is C_2 symmetric, with nine ^{13}C NMR signals, and twice that number were seen for the product, consistent with a mixture of the C_2 symmetric products **2** and **3**. On the basis of subsequent experiments, however, the product was neither **2** nor **3** but was instead a single product, **4**, without symmetry and resulting from migration of one of the amide nitrogens.

The structure of **4** was deciphered, in part, by comparison with the chlorination product of the intramolecular head-to-head photocycloaddition adduct **6**,[11] Scheme 3. Substrate **6** was initially chosen because, with its altered symmetry relative to **1**, a straightforward chlorination reaction was expected to yield only one product, **7**, not two as expected from **1** (Scheme 2). This reaction *did* yield a single product, isolated in 45% yield. Nevertheless, subsequent X-ray crystallography showed that while the desired carbon−carbon bond had been formed, a nitrogen migration gave **8**, exchanging the expected positions of nitrogen and chlorine, with one chlorine at a carbon originally connected to nitrogen but with inverted stereochemistry.[12]

Scheme 3. Chlorination of **6** Yields the Single, but Unexpected, Product **8**



The formation of **8** is consistent with the mechanism shown in Scheme 4. On the basis of steric effects, chlorination of **6** can occur on only one face of the equivalent alkenes and is assumed to involve initial formation of a chloronium ion, **9**. Direct opening of this ion with chloride is blocked by the remaining alkene. Opening of the chloronium ion can result in either of two secondary carbocations **10** and **13**. Electronic considerations would lead one to expect **10** to be the more stable carbocation, because it is farther from the electronegative amide nitrogen.[13] In each case, a new carbon−carbon bond is then formed to the remaining alkene, yielding a new secondary carbocation (**11** and **14**). Each of these could be trapped by the chloride counterion to yield **12** and **7**. Instead, carbocation **14** is intercepted by the adjacent amide nitrogen, forming an aziridinium ion, **15**. This aziridinium could be opened in two different ways, yielding **16**, an epimer of **7**, or **8**. Both of the pathways leading to **8** and **16** are sterically and electronically similar. Molecular mechanics calculations suggest that **8** is substantially lower in energy than the other possible products shown.[14]

It seems unlikely that the opening of chloronium ion **9** could be influenced directly by the nitrogen that eventually migrates in this transformation. One explanation for the domination of the pathway leading to **8** would be a reversibility of reaction steps, with formation of the penultimate aziridinium ion **15** as the committed transformation.

Additional experiments with methyl-substituted pyridone dimers has shown that stabilization of the initial carbocation can alter the pathway. Photodimerization of 1,4-dimethyl-2-pyridone gave three products, with the unusual cis head-to-head dimer **17** as a minor component. Chlorination of this

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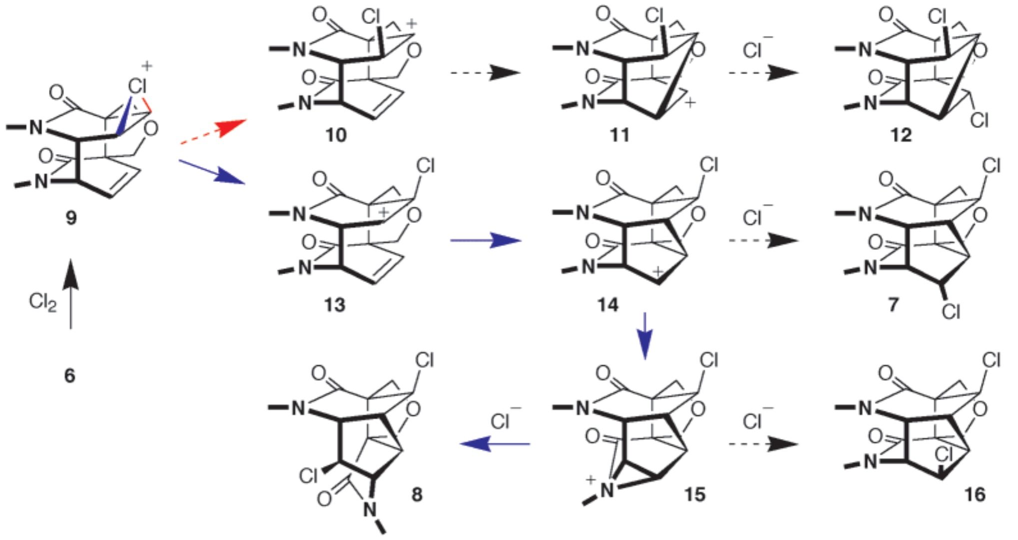
[11] Sieburth, S. McN.; Siegel, B. *J. Chem. Soc., Chem. Commun.* **1996**, 2249−2250.

[12] Compound **8** crystallizes in the triclinic space group $P1$ with $a = 6.9014$ (12) Å, $b = 7.6944$ (13) Å, $c = 8.3578$ (14) Å, $\alpha = 65°$, $\beta = 82°$, $\gamma = 65°$, $V = 1457.1$ (5) Å^3, and $Z = 1$. Final least squares refinement using 1314 unique reflections with $I > 3\sigma(I)$ gave R (R_w) = 0.0437 (0.1182).

[13] Bienvenüe-Goëtz, E.; Ratsimandresy, B.; Ruasse, M. F.; Dubois, J. E. *Tetrahedron Lett.* **1982**, *23*, 3273−3276. Yamabe, S.; Tsuji, T. *Chem. Phys. Lett.* **1988**, *146*, 236−242.

[14] Chem3D minimization yields the following strain energies (kcal/mol): **7** (57.7), **8** (52.7), **12** (57.8), **16** (57.0).

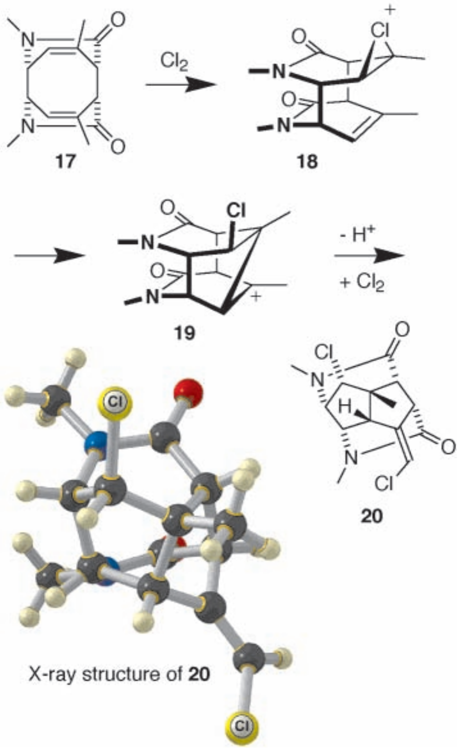
Scheme 4. Chlorination of **6** Leads to Regiospecific Ring Opening, Nitrogen Migration, and Stereospecific and Site-Specific Aziridinium Opening



dimer, Scheme 5, which is structurally close to **6** (Scheme 4), again gave one primary product (43%), whose structure, **20**, was solved by X-ray crystallography.[15]

Notably, compound **20** results from transannular ring closure *without* rearrangement. The mechanism leading to this product is easily rationalized as resulting from opening of the initial chloronium ion **18** to yield a tertiary carbocation. Ring closure to the nearby alkene forms the two fused five-membered rings and gives a second tertiary cation, **19** (compare with **11**, Scheme 4). Without a nearby amide nitrogen, the cation loses a proton to form the exocyclic alkene. Under the reaction conditions, this alkene is chlorinated again, losing a second proton and generating a vinyl chloride.

Scheme 5. Methyl Substitution Can Alter the Chloronium Ion Opening



The reaction pathway leading to **20**, in contrast to that proposed in Scheme 4, is initiated by the chloronium ion opening away from the amide nitrogen, presumably due to the formation of the more stable cation, although reversibility of the reaction steps leading to the second tertiary cation cannot be discounted.

We believe that these are the most rigid cyclooctadienes to undergo this transannular ring closure. The two-step sequence described here generates complex polyquinanes with up to eight new stereogenic centers from achiral aromatic pyridones. In each case, the carbon skeleton of the [4 + 4] adduct is retained in the product, despite the molecular rearrangements observed. These studies are continuing.

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Supporting Information Available: Experimental details and spectral data for **4**, **8**, and **20** and crystallographic details for **8** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Compound **20** crystallizes in the monoclinic space group $P2_1/n$ with $a = 9.025$ (2) Å, $b = 12.062$ (3) Å, $c = 13.651$ (3) Å, $\beta = 105.219(4)°$, $V = 1433.9$ (6) Å, and $Z = 4$. Final least squares refinement using 3292 unique reflections with $I > 3\sigma(I)$ gave R (R_w) = 0.0515 (0.1259).