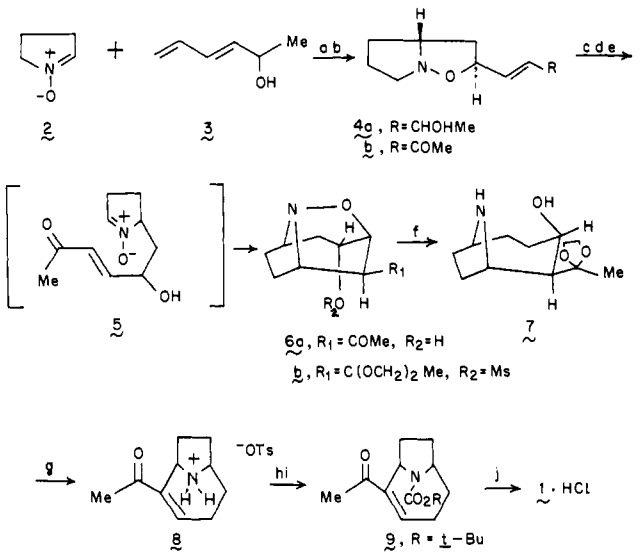
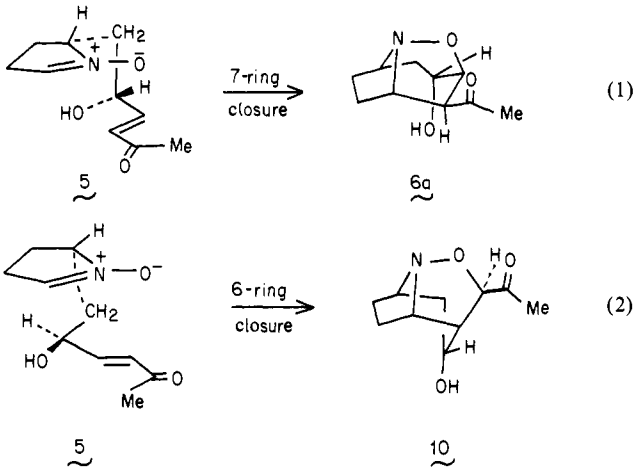
Scheme I



(a) heat, benzene (70%); (b) MnO_2, celite, CH_2Cl_2 (96%); (c) MCPBA, CH_2Cl_2 (71%); (d) $(CH_2OH)_2$, *p*-TsOH, benzene (96%); (e) MsCl, Et_3N (94%); (f) $LiAlH_4$, $NiCl_2$, THF (−40°); (g) *p*-TsOH, acetone; (h) $NaHCO_3$, H_2O; (i) $(t\text{-BuCO})_2O$, $CHCl_3$; (j) 3NHCl, EtOAc.

yield from **4b**. It has already been reported[18] that such *N*-alkenylnitrones can cyclize to produce either the product of 6-ring closure (e.g., **10**) or that of 7-ring closure (e.g., **6a**). A preference was observed in most cases for the transition state resulting in 6-ring closure. This was attributed to diminished strain when compared to its counterpart leading to 7-ring closure.[18] Clearly, nitrone **5** can undergo either 6- or 7-ring closure (cf. eq 1 and 2).



We believed that **5** might overcome the normal predilection for 6-ring closure because of the natural tendency of nitrones, in intermolecular cycloaddition reactions, to afford the adduct with the nitrone oxygen bound to the β-carbon of the dipolarophilic α,β-unsaturated carbonyl system.[17,19-21]

We could only identify a single cycloadduct from **5** (i.e., **6a**).[22] This adduct appears to be of kinetic origin since it is formed conveniently at 45 °C. This fortunate circumstance results in the construction of the ring system of anatoxin-*a*. Subsequent ketalization and mesylation results in the formation of ketal mesylate **6b**. Finally, treatment of **6b** with a 1:1 (molar) mixture of $LiAlH_4/NiCl_2$ in THF (−40 °C) leads to **7**. When direct conversion into anatoxin-*a* by acid hydrolysis proved to be problematic, the hydroxy ketal **7** was treated with a stoichiometric amount of *p*-toluenesulfonic acid in acetone to induce both trans ketalization and dehydration, thereby affording the *p*-toluenesulfonic acid salt (i.e., **18**) of the natural product. For purposes of purification, the crude salt **8** was treated with 2 equiv of sodium bicarbonate and di-*tert*-butyl dicarbonate.[23] The resultant *tert*-butyl carbamate **9** (43% overall yield from mesylate **6b**) was subjected to acid hydrolysis[24] to give anatoxin-*a* hydrochloride. The ^1H NMR, IR, and mass spectral comparisons of the synthetic material with the natural product confirmed the successful outcome of the synthetic effort.

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Registry No. (±)-**1**·HCl, 70470-07-4; **2**, 24423-88-9; (±)-**3**, 3280-51-1; **4a**, 92844-74-1; (±)-**4b**, 92844-75-2; **5**, 92844-79-6; (±)-**6a**, 92844-76-3; (±)-**6b**, 92844-77-4; (±)-**7**, 92844-78-5; (±)-**8**, 92844-80-9; (±)-**9**, 92998-50-0.

Supplementary Material Available: Experimental section for **4a,b**, **6a,b**, **7**, **9**, and **1**·HCl and tables of mass spectral data for **4a**, **6a,b**, **7**, **9**, and **1**·**HCl** (9 pages). Ordering information is given on any current masthead page.

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1,8-Biphenylenediol Forms Two Strong Hydrogen Bonds to the Same Oxygen Atom

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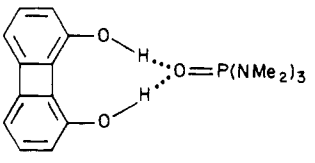
The molecular geometry of 1,8-biphenylenediol is such that the two hydroxyl groups should be capable of forming hydrogen bonds simultaneously to the same basic atom. This expectation is now supported by the isolation and X-ray structure determination of crystalline adducts of the diol[1] with *N,N,N',N',N'',N''*-hexamethylphosphoramide (**1**)[2] and with 1,2,6-trimethyl-4-pyridone[3,4] and 2,6-dimethyl-γ-pyrone.[5]



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(1) Blatchly, J. M.; Garner, D. V.; McOmie, J. F. W.; Watts, M. L. *J. Chem. Soc. C* **1968**, 1545-1549.
(2) Prepared by dissolving the diol (mp 222 °C) in the amide (HMPA) and removing excess amide by heating in a high vacuum. Recrystallized from cyclohexane containing a little chloroform: mp 132-134 °C.
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(4) Adduct prepared by dissolving equimolar amounts of the pyridone (mp 245-245.5 °C) and diol in acetonitrile and allowing the solvent to evaporate slowly. Decomposes without melting at 268-271 °C.
(5) Adduct prepared by dissolving equimolar amounts of pyrone (mp 133-137 °C) and diol in chloroform and crystallized by slow evaporation, first from chloroform–cyclohexane and then from ethyl acetate: mp 182-183 °C.

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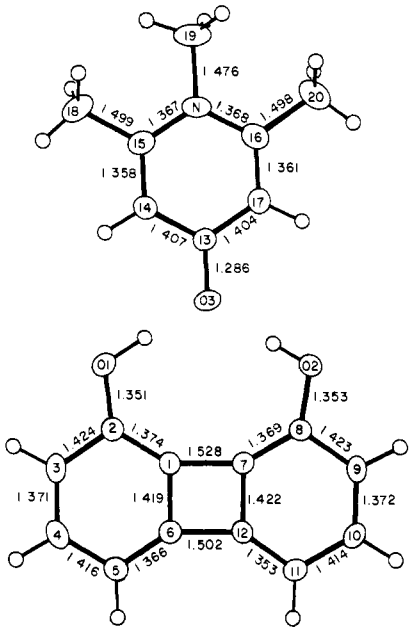

Figure 1. ORTEP drawing[13] displaying the labeling scheme and bond distances (Å) for the 1,8-biphenylenediol-1,2,6-trimethyl-4-pyridone complex with non-hydrogen atoms drawn at the 50% probability level and hydrogen atoms drawn with an artificial radius. The estimated standard deviations on the bond distances are 0.003-0.004 Å.

An ORTEP drawing of the structure of the 1,2,6-trimethyl-4-pyridone adduct is shown in Figure 1.[6] The two components are almost coplanar.[7] The O-H···O distances are 2.545 (3) and 2.548 (3) Å and the angles are 177 (3)° and 174 (3)°. Those of the pyrone adduct are 2.585 (2) and 2.589 (2) Å and 176 (3)° and 178 (3)°; those for the HMPA adduct are 2.601 (5) and 2.613 (5) Å and 168 (5)° and 172 (5)°. In his review of strong hydrogen bonds[8] Emsley lists one property of strong A-H···B hydrogen bonds as an overall bond length that is smaller than the summed van der Waals radii of A and B by at least 0.3 Å. This sum minus 0.3 Å is 2.70 Å for O-H···O and 2.75 Å for N-H···O.

The existence of the complexes in solution is established by vapor pressure osmometry determinations of molecular weight in toluene at 56.7 °C. Calcd for 1, 363.4; found; 374. Calcd for the pyrone complex, 308.3; found; 293. The pyridone complex was not soluble enough for its molecular weight to be determined.

There are other crystal structures known in which one molecule forms two hydrogen bonds to a given basic atom of a second molecule, but we know of no case in which these are two *strong* hydrogen bonds. The stronger pair in a crown ether-guanidinium ion complex, for example, are 2.90 and 2.94 Å[9] and in the case of urea are 2.98 and 3.04 Å.[10] A search of the Cambridge Crystallographic Data File by Murray-Rust and Glusker for precise data on hydrogen bonding to ketones and esters with O···X distances less than 3 Å yielded about 500 structures, of which 24 had two hydrogen bonds to the oxygen atoms.[11] Only two of these involved a diacid forming two hydrogen bonds to a given basic atom in another molecule. In the stronger of these two double hydrogen bonds, a urea derivative formed N-H···O hydrogen bonds of length 2.871 and 2.919 Å to the oxygen atom of acetone.[12] It is possible that 1,8-biphenylenediol is unique in having been shown to form two strong hydrogen bonds to a given basic atom in another molecule, with neither the acid nor the base being electrically charged. However, in view of the ubiquity of hydrogen bonds in nature, it is likely that unrecognized multiple hydrogen bonding acids are active as complexing agents and as catalysts in natural systems.

We are currently engaged in preparing additional adducts of the diol and its derivatives, in studying the catalytic activity of such diols in reactions subject to catalysis by hydrogen bonding, and in measuring equilibrium constants for hydrogen bonding of such diols to bases in poorly hydrogen bonding media and in aqueous solution.

Acknowledgment. We are greatly indebted to Dr. Jenny P. Glusker for additional details on her research,[11] to Dr. C.-S. Wu of Ashland Chemical Co. for molecular weight determinations, and to the National Science Foundation for Grant CHE-8114770.

Registry No. 1, 93136-30-2; (1,2,6-trimethyl-4-pyridone)(1,8-biphenylenediol) adduct, 93136-31-3; (2,6-dimethyl-α-pyrone)(1,8-biphenylenediol) adduct, 93184-34-0.

Supplementary Material Available: Positional and thermal parameters and structure factors (13 pages). Ordering information is given on any current masthead page.

(6) All data sets were measured by the ω-2θ scan method on a Syntex $P\bar{1}$ diffractometer equipped with graphite monochromated MoKα radiation and an LT-1 low-temperature system. The 1,8-biphenylenediol-hexamethylphosphoramide adduct crystallizes with $Z = 4$ in $P2_1/n$ in a cell of dimensions $a = 8.527$ (1) Å, $b = 15.099$ (4) Å, c = 15.354 (3) Å, and $\beta = 95.17$ (1)° at -56 °C. At lower temperatures these crystals appear to undergo a destructive phase transition. The final refinement on the 2351 F_o values [$F_o^2 > 2\sigma(F_o^2)$] yielded R (on F) of 0.077 for 234 variables (anisotropic non-hydrogen atoms, isotropic hydroxyl hydrogens, remainder of hydrogen atoms fixed). The rather high R index for this adduct results from large thermal motion for both molecules and/or positional disorder of the diol. The 1,8-biphenylenediol-1,2,6-trimethyl-4-pyridone adduct crystallizes with $Z = 4$ in $P2_1/n$ in a cell of dimensions $a = 7.639$ (1) Å, b = 22.130 (4) Å, c = 9.411 (1) Å, and $\beta = 90.66$ (1)° at -123 °C. The final refinement on the 2188 F_o values [$F_o^2 > 3\sigma(F_o^2)$] yielded R (on F) of 0.048 for 225 variables (anisotropic non-hydrogen atoms, isotropic hydroxyl hydrogens, remainder of hydrogen atoms fixed). The 1,8-biphenylenediol-2,6-dimethyl-γ-pyrone adduct crystallizes with $Z = 2$ in $P\bar{1}$ in a cell of dimensions $a = 8.983$ (1) Å, b = 13.450 (2) Å, c = 6.926 (1) Å, $\alpha = 85.15$ (1)°, $\beta = 106.19$ (1)°, and $\gamma = 109.72$ (1)° at -125 °C. The final refinement on the 2592 F_o values [$F_o^2 > 1.5\sigma(F_o^2)$] yielded R (on F) of 0.048 for 240 variables (anisotropic non-hydrogen atoms, isotropic methyl and hydroxyl hydrogens, remainder of hydrogen atoms fixed).

(7) The dihedral angle between the best least-squares planes for the two components is 3.2 (1)° for the pyridone adduct and 4.8 (1)° for the pyrone adduct.

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An Unprecedented Triisocyano Diterpenoid Antibiotic from a Sponge

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We recently reported the structure of kalihinol A (**1**), a highly functionalized diisocyano diterpenoid antibiotic from a Guam sponge, *Acanthella* sp.[3] The Bio-Sil A fraction from the isolation of **1** was resolved on HPLC (RP-18, MeOH/water, 3:1) into

(1) UNESCO Fellow from the University of Calcutta, 1983.

(2) On sabbatical leave from the University of West Florida, Pensacola, FL, 1983.

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