Notes

Synthesis and Crystal Structure of 2,4-Diaza-6,7-benzo-8-oxabicyclo[3.3.1]nonenes[1]

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Received March 9, 1984

Proton transfer reactions are one of the basic chemical transformations in chemistry,[2] and tautomeric proton exchange can serve as a convenient model for investigating the mechanisms of and the factors influencing this important class of reactions. Therefore, our first report of annular amidinic tautomerism in dihydropyrimidine systems was of considerable interest.[3] In connection with this work we determined the crystal structures of the 1,4-[4] and 1,6-dihydro tautomers[5] as well as the factors making possible the detection of such tautomerism.[6]

In order to further clarify the structural factors leading to tautomeric estimation in dihydropyrimidines, we attempted the synthesis of compounds of type **3**, where an *o*-hydroxy group is expected to stabilize the 1,4-dihydro tautomer even in solution via intramolecular hydrogen bonding. Using standard procedures for preparing dihydropyrimidines (condensation of α,β-unsaturated carbonyl compounds **1a** with benzamidine **2** in benzene with azeotropic removal of water), we isolated a colorless crystalline product in ca. 90% yield.

Although the elemental analysis and parent ion peak in the mass spectrum were in agreement with those of the desired product, other spectral data (IR, NMR), in fact, suggested that the material was not **3**, but rather a structural isomer of the target compound. Since the product was found to be sufficiently stable, and yielded crystals suitable for a diffraction study, a definitive structural determination was obtained by a complete X-ray analysis, showing an unexpected tricyclic bridgehead configuration **6a**. The overall molecular structure is shown in Figure 1 and detailed geometric data are given in Table 1–5 (supplementary material section). Salts with a similar structure were obtained by Girke[7] by reacting 2- and/or 4-substituted pyrimidines with resorcinol in trifluoroacetic acid/benzene (2:1).

A reasonable mechanism for the formation of **6a** is given in Scheme I. The initial Michael-type addition reaction of **1a** and **2** is followed by ring closure to the tetrahydropyrimidine **4a**, which is thermodynamically more stable than the open-chain product (ring–chain tautomerism). Compound **4a** then dehydrates to the highly reactive dihydropyrimdine **5a**, which is rapidly attacked by the phenolic hydroxy group before it undergoes either thermally allowed [1,5]-hydrogen migration to corresponding 1,6-dihydropyrimidine or imine–enamine tautomerism to 1,4-dihydropyrimidine. Similar dehydrations to highly reactive intermediate 4,5-dihydropyrimidine systems **5**, which are energetically less stable than the corresponding 1,4- or 1,6-pyrimidines,[8] may also occur in the course of

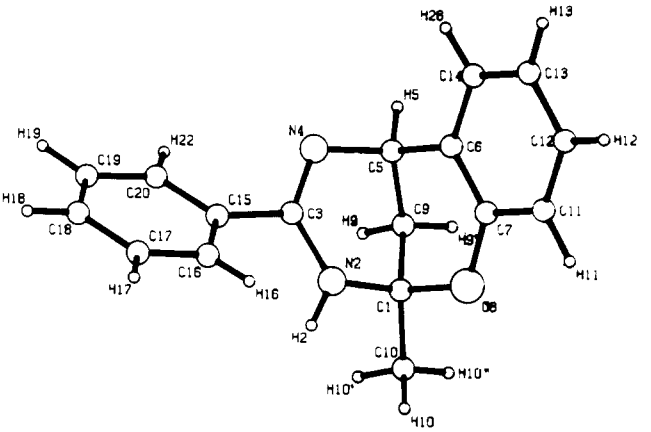
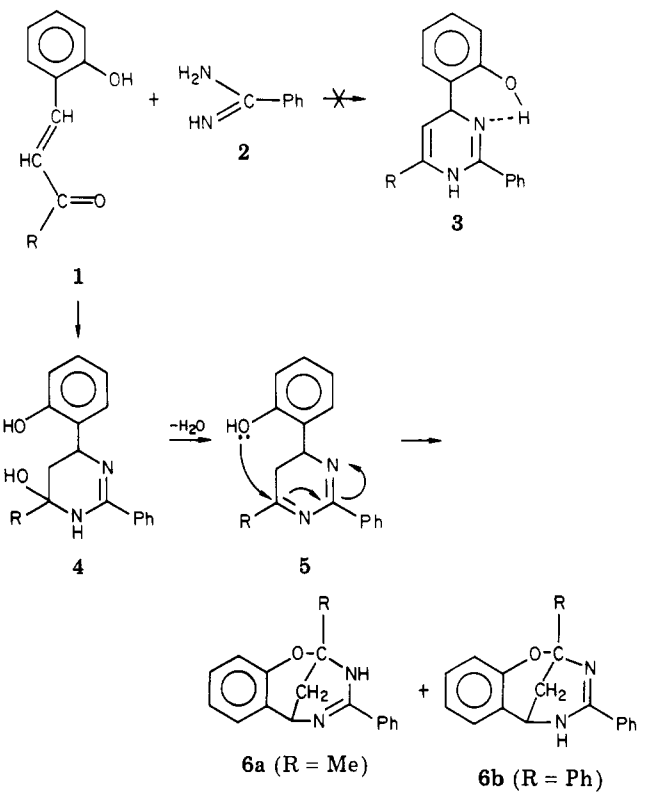


Figure 1. Molecular structure of 1-methyl-2,4-diaza-6,7-benzo-8-oxabicyclo[3.3.1]non-3-ene (**6a**). Selected bond lengths (Å): N(2)–C(1) 1.445 (2); O(8)–C(1) 1.454 (2); C(9)–C(1) 1.513 (2); C(3)–N(2) 1.369 (2); H(2)–N(2) 0.938 (32); N(4)–C(3) 1.292 (2); C(5)–N(4) 1.473 (2); C(6)–C(5) 1.511 (2); C(9)–C(5) 1.520 (2); C(7)–C(6) 1.398 (2); O(8)–C(7) 1.372 (2).

Scheme I



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(8) GAUSSIAN-70 ab initio calculations of the energy of unsubstituted dihydropyrimidines yielded the following order of stability 1,6 > 1,4 > 1,2 > 2.5 > 4,5 dihydropyrimidines. Weis, A. L.; Degen, U. (unpublished results).

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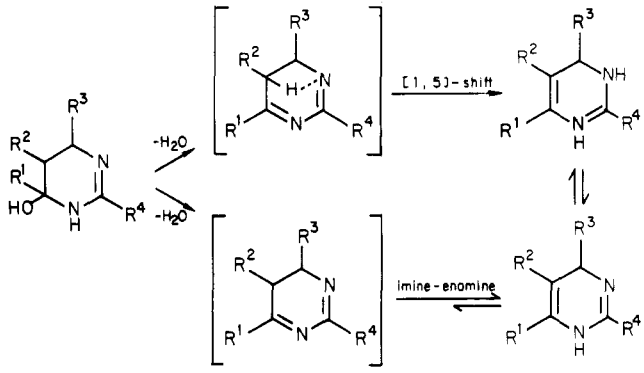
Scheme II



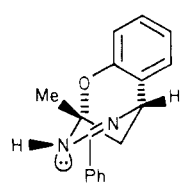
formation of other dihydropyrimidines,[9] namely, in the common production of dihydropyrimidines nonsubstituted at the nitrogen from α,β-unsaturated carbonyls and amidines. These unstable 4,5-dihydro intermediates, in the absence of other concurrent trapping moieties, such as the hydroxyl group in **5a**, eventually undergo a sigmatropic hydrogen shift to the corresponding stable 1,4- or 1,6-isomers, which, in solution, can be in tautomeric equilibrium with one another (Scheme II).[3-6] Further mechanistic studies to substantiate this conjecture are being carried out.

It should be noted that, by running the reaction in acetone at a low temperature, **4a** could be isolated. The intermediacy of this compound in the formation of **6a** was indeed demonstrated by its being treated with triethylamine under the original conditions used for the condensation and observing the formation of compound **6a**.

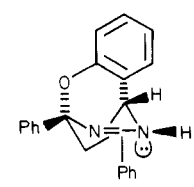
The tricyclic product **6a** was expected to exist in two equilibrating tautomeric structures. However, X-ray analysis of **6a** showed that, at least in the crystalline state, only one tautomeric form was observed (Figure 1).

When the identical reaction was carried out on **1b**, the NMR spectrum of the product was in general agreement with a tricyclic structure as was obtained previously. However, the NH proton in Me_2SO-d_6 solution appeared at 8.61 ppm, whereas in **6a** the NH proton occurred at 8.13 ppm. The difference in chemical shifts is analogous to that observed in other cyclic amidinic systems, where it has been attributed to the presence of two individual tautomeric forms. This observation suggested that, unlike the methyl-substituted product **6a**, the phenyl analogue exists in the tautomeric form **6b**, a fact confirmed by the X-ray diffraction analysis of the material which clearly showed that the NH proton is attached to N^4 (Figure 2).

The X-ray data clearly indicate the half-chair conformations of the tetrahydropyrimidinic parts of both **6a** and **6b** in which the NH, the C-5 proton, and Me or Ph are pseudoequatorial, whereas the C-1–O bond is pseudoaxial due to the "anomeric effect".[10]



6a



6b

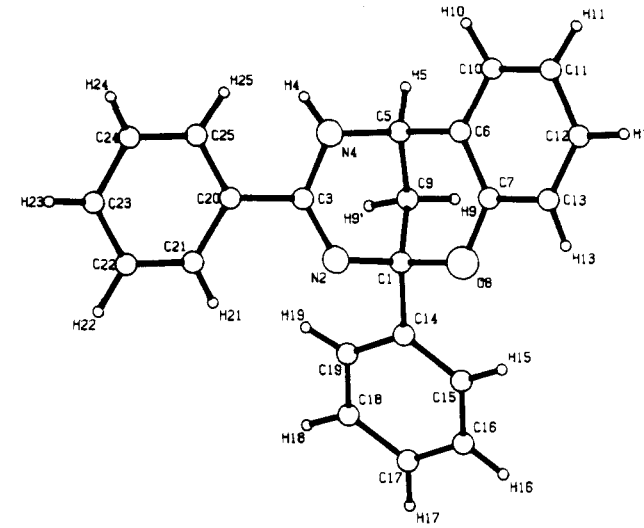


Figure 2. Molecular structure of 1-phenyl-2,4-diaza-6,7-benzo-8-oxabicyclo[3.3.1]non-2-ene (**6b**). Selected bond lengths (Å): N(2)–C(1) 1.445 (5); C(9)–C(1) 1.537 (6); O(8)–C(1) 1.456 (5); C(3)–N(2) 1.305 (5); N(4)–C(3) 1.353 (5); C(5)–N(4) 1.456 (6); C(6)–C(5) 1.510 (6); C(9)–C(5) 1.516 (6); C(7)–C(6) 1.397 (6); O(8)–C(7) 1.372 (5).

All attempts to bring about a tautomeric equilibration of isomers, **6a** or **6b**, in a variety of solvents (Me_2SO-d_6, $CDCl_3$) at several concentrations and different temperatures failed. This observation coincides with our recent observations[1,11] on the tautomerism of cyclic amidines, where we obtained indications that the tautomeric equilibrium in cyclic azine systems requires intermolecular proton transfer through an available NH···N hydrogen bond bridging. Such proton transfer requires neighboring molecules to assume a suitable geometry which will allow proton transfer to take place. In open-chain amidinic systems, such intramolecular transfer is possible because free rotation allows the molecule to assume a proper geometry for intramolecular N–H···N bridging. However, intramolecular H-bridging is not possible in most cyclic compounds and here, the less hindered, intermolecular, hydrogen bond forms. Moreover, presence in the molecules of a more basic (electron rich) center than N(sp^2)—in our case O—or a more acidic group than NH—as, for example, OH in hydroxytetrahydropyrimidines[9,11]—will discourage intermolecular NH···N bridging and lead to formation of the stronger OH···N or NH···O intermolecular hydrogen bonding, and the amidinic proton transfer will not take place.

Indeed, the crystal structure of these molecules indicates a strong intermolecular NH···O hydrogen bond, and no NH···N hydrogen bridging.

Experimental Section

General Procedures. Melting points were taken on a Fisher-Johns apparatus and were not corrected. Infrared spectra were measured with a Nicolet MX-1 fourier transform spectrometer. Proton NMR spectra were measured with Varian FT-80A and WH-270 Bruker fourier transform spectrometers. All chemical shifts are reported in units downfield from internal Me_4Si, and the J values are given in hertz. Mass spectra were determined with an Atlas MAT-731 or MAT-CH-4 spectrometer. Microanalyses were performed by the microanalytical laboratory at the Weizmann Institute.

Preparation of 2,4-Diaza-6,7-benzo-8-oxabicyclo[3.3.1]nonene 6. A solution of 1 (5 mmol) in 30 mL of dry benzene was

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added slowly at room temperature to a magnetically stirred solution of freshly prepared benzamidine **2** (5.5 mmol) (white solid prepared from equimolar amounts of benzamidine hydrochloride and sodium methoxide in absolute methanol with subsequent filtration of NaCl and evaporation of methanol at room temperature) in 30 mL of dry benzene. Water was removed from the deep red solution via azeotropic distillation (Dean–Stark trap), which then turned yellow. After removal of the solvent in vacuo, the residue was washed with a small amount of ether, affording pure **6**.

1-Methyl-2,4-diaza-6,7-benzo-8-oxabicyclo[3.3.1]non-3-ene (6a): yield, 87%; mp 193–4 °C (needles from ethanol); MS (70 eV), *m/e* 264 (M^+); IR (KBr) 3188, 3034, 2991, 2976, 2945, 2916, 2828, 1616, 1579, 1522, 1481, 1254, 1130, 1079, 882 cm^{-1}; ^1H NMR (Me_2SO-d_6) 8.13 (NH), 6.70–7.80 (complex 9 H Ar), 4.72 (H^5), 1.82–1.99 (CH_2), 1.77 (CH_3, s, 3 H). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.18; H, 6.24.

1-Phenyl-2,4-diaza-6,7-benzo-8-oxabicyclo[3.3.1]non-2-ene (6b): yield, 97%; mp 183–4 °C (needles from ethanol); MS (70 eV), *m/e* 326 (M^+); IR (KBr) 3163, 3135, 2963, 2861, 2818, 1595, 1558, 1534, 1491, 1482, 1325, 1237, 1124, 1064, 1004, 996, 923, 880, 850 cm^{-1}; ^1H NMR (Me_2SO-d_6) 8.61 (NH), 6.91–7.90 (complex 14 H Ar), 4.69 (H^5, t, J = 2.7 Hz), 1.86–2.08 (CH_2, dd, J = 2.7, J = 12 Hz). Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.56. Found: C, 80.92; H, 5.48.

2,6-Diphenyl-4-(2-hydroxyphenyl)-6-hydroxy-1,4,5,6-tetrahydropyrimidine (4b). A solution of **1b** (5.8 mmol) in 20 mL of dry acetone (the color changing from yellow to green) was added dropwise during 0.5 h to a magnetically stirred, cooled (–15 °C) solution of freshly prepared benzamidine in 20 mL of dry acetone. After having been left to stir overnight at room temperature, the solvent was removed in vacuo and the residue was trituated with 5 mL of ether, affording a white solid: yield 21%; mp 134–135 °C (from ethanol); MS (70 eV), *m/e* 326 (M^+); ^1H NMR ($CDCl_3$) 6.53–8.05 (complex 14 H Ar), 5.11 (H^4, dd, $J_{H^{5a}-H^4}$ = 12 Hz, $J_{H^{5e}-H^4}$ = 4 Hz), 2.40 (H^{5e}, dd, $J_{H^{5a}-H^{5e}}$ = 11 Hz, $J_{H^{5e}-H^4}$ = 4 Hz), 1.61 (H^{5a}, dd, $J_{H^{5a}-H^{5e}}$ = 11 Hz, $J_{H^{5a}-H^4}$ = 12 Hz). Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81. Found: C, 76.64; H, 5.78.

Conversion of 4b to the Tricyclic Bridgeheaded 6b. A solution of **4** (374 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in 40 mL of dry benzene was heated in a 100-mL flask equipped with an azeotropic distillation system (Dean–Stark) for 5 h (TLC control). It was cooled and stored in the freezer overnight. After filtering off unreacted starting material **4** (91 mg, 24%, mp = 132–3 °C) was obtained. The solution was concentrated, affording an orange residue (159 mg) which was trituated with 5 mL of diethyl ether, filtered, and washed again with 5 mL of diethyl ether, producing a white solid (142 mg, 40.3%, mp 183–4 °C) which was identical by all spectroscopic characteristics with **6b** and shows no melting point depression in admixture with authentic material.

X-ray Crystallographic Study of 6a. Single crystals of **6a**, suitable for analysis, were prepared by slow evaporation of an ethanolic solution. They were monoclinic: space group $C2/c$, a = 24.660 (3) Å, b = 12.134 (2) Å, c = 10.139 (1) Å, β = 114.26 (1)°, V = 2765.76 Å^3, Z = 8, D_c = 1.274 g cm^{-3}, D_m = 1.270 g cm^{-1}. A single crystal (0.2 × 0.3 × 0.4 mm^3) was mounted on an Enraf-Nonius CAD-4 diffractometer and a total of 2678 reflections (one quadrant) were measured by using Ni-filtered Cu Kα radiation up to θ – 78°. Intensities were corrected for Lorentz and polarization factors, yielding 2438 independent reflections with $F_o > 3\sigma(F_o)$. The structure was solved by using MULTAN and refined to R = 0.042. All hydrogen atoms were found from the difference Fourier map. A final difference map possessed no special features. The final atomic and bonding parameters are given in Table 1–5 (supplementary material section).

X-ray Crystallographic Study of 6b. Single crystals of **6b**, suitable for analysis, were prepared by slow evaporation of an ethanolic solution. They were monoclinic, space group $P2_1/a$, a = 8.969 (1) Å, b = 17.968 (3) Å, c = 10.595 (2) Å, β = 102.16 (1)°, V = 1669.12 Å^3, Z = 4, D_c = 1.303 g cm^{-3}, D_m = 1.289 g cm^{-3}. A single crystal (0.1 × 0.2 × 0.2 mm^3) was mounted on an Enraf-Nonius CAD-4 diffractometer and a total of 2345 reflections (one quadrant) were measured using graphite monochromated Mo Kα radiation up to θ – 25°. Intensities were corrected for Lorentz and polarization factors, yielding 1824 independent reflections with $F_o > 3\sigma(F_o)$. The structure was solved by using MULTAN and refined to R = 0.068. All hydrogen atoms were found from a difference Fourier map. A final difference map possessed no special features. The final atomic and bonding parameters are given in Tables 6–11 (supplementary material section).

Acknowledgment. Financial support by the G. M. J. Schmidt Fund for Preindustrial Research of the Harry Levine Center and the Ministry of Industry, Israel, is gratefully acknowledged. We thank Messrs. M. Bernstein and J. Fahima for skillful technical assistance and Mr. R. Heller for elemental analyses.

Registry No. **1a**, 6051-53-2; **1b**, 644-78-0; **2**, 618-39-3; **3a**, 91210-88-7; **3b**, 91210-89-8; **4a**, 91210-90-1; **4b**, 91210-93-4; **6a**, 91210-91-2; **6b**, 91210-92-3.

Supplementary Material Available: Tables of bond distances, bond angles, atomic coordinates, and isotropic and anisotropic thermal parameters for **6a** and **6b** (11 pages). Ordering information is given on any current masthead page.

Kinetic Solvent Parameters for Nucleophilic Substitution in Aqueous Acetonitrile

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Received February 28, 1984

Quantitative treatments of kinetic solvent effects upon spontaneous reaction are typically based upon linear free-energy relationships such as the Grunwald–Winstein equation[1] or extensions of it.[2-5] These equations permit estimation by interpolation or extrapolation of rate constants which cannot easily be measured, and the derived parameters may be mechanistically informative.

We are interested in spontaneous hydrolyses, some of which are too fast to be conveniently followed in water,[6] and one approach is to estimate the rate constant in water by extrapolation of rate constants in mixed aqueous organic solvents. The organic solvent should be unreactive to the substrate, stable, and easily purified and preferably optically transparent, so that reactions can be followed spectrophotometrically. Acetone absorbs at low wavelengths and dioxane is toxic and difficult to purify, but acetonitrile is a very convenient solvent and its mixtures with water have been used extensively in kinetic studies.[7] However, these mixtures have not been used widely for hydrolysis of alkyl halides or arenesulfonates.

The Y scale of solvent polarity has been based on solvolysis of *tert*-butyl chloride (*t*-BuCl) and solvent nu-

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