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ACCESS TO THE 1,3,4,6-TETRAAZAPENTALENE RING SYSTEM

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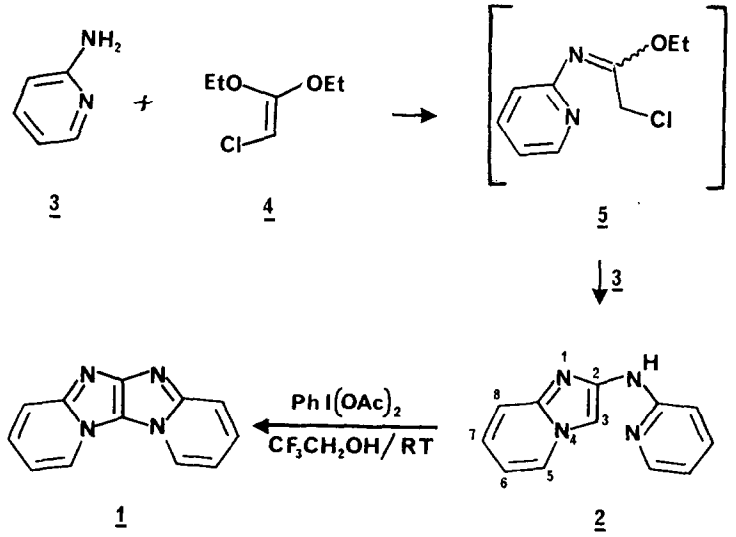
Abstract: An oxidative cyclization method is described for synthesizing molecules containing the 1,3,4,6-tetraazapentalene ring system.

With the goal of linking complementary ribo- and deoxyribonucleosides in a dimensionally defined manner, we have devised a convenient route to model compound 1, which incorporates the rare 10π-electron 1,3,4,6-tetraazapentalene ring system as its central feature. The only reference to the synthesis of 1,3,4,6-tetraazapentalene (imidazo[4,5-d]imidazole) itself is to the photochemical transformation of 4-aminoimidazo-5-carbonitrile.[1] The only previously described synthesis of a tetracyclic system incorporating the tetraazapentalene core is for dibenzotetraazapentalenes that can be represented only as hybrids of charge-separated contributors.[2] Dipyrido[1,2-a:2',1'-f]-1,3,4,6-tetraazapentalene (Scheme I, 1) can be visualized as consisting of two etheno-bridged heterocycles[3] fused back to back. The first step in the two-step synthesis is a refinement of the preparation reported by Kato, Yamamoto,

Scheme I



and Takeda.[4] 2-(2-Pyridylamino)imidazo[1,2-a]pyridine (2)[5] was obtained in 90% isolated yield when a stirred melt of 2-aminopyridine (3) (2.2 mmol) and 2-chloroketene diethylacetal (4)[6] was heated at 60 °C for 1 hour, presumably by way of the intermediate 2-aminopyridine-N^2-(O-ethyl-2-chloroacetimidate) (5).

The problem of cyclizing compound 2 to 1 is essentially one of forming a bond between two electron-rich centers, namely, the pyridine ring-nitrogen and C3 of the imidazo[1,2-a]pyridine moiety. This necessitates a reversal of polarization at one center. If a photochemical ring closure were to occur, it would probably result in the formation of a carbon-carbon bond[7] instead of the desired carbon-nitrogen bond. It was possible to halogenate compound 2 in chloroform with NBS[8] or, less satisfactorily, with NCS, at the 3-position of the bicyclic nucleus. However, neither halogenated compound underwent subsequent intramolecular nucleophilic addition-elimination at C3. We achieved the ring closure of 2 to 1 by an oxidative route that presumably occurs via an intermediate with positive charge delocalized over the N4-C3-C2-N^2 system of 2. Iodobenzene diacetate (IBD),[9] which has had widespread use as an oxidant in amine chemistry,[10] proved to be the appropriate reagent.[11] When a 0.04 M solution of compound 2 in 2,2,2-trifluoroethanol (TFE) was treated dropwise with a 0.04 M solution of IBD (1 mol equiv.) in TFE, the desired intramolecular cyclization took place efficiently and rapidly at room temperature. The reaction was essentially complete following mixing (30 min), as indicated by a single product spot on TLC. We selected the solvent TFE as optimal because of its high ionizing power and low nucleophilicity.[12] The reaction also proceeded, although less cleanly, in acetic acid but did not proceed in solvents such as $CHCl_3$, THF, CH_3CN, or dioxane. These observations strongly suggest that the reaction occurs by an ionic mechanism.

The oxidation product of 2 with IBD possesses the molecular formula $C_{12}H_8N_4$ based on microanalytical and mass spectroscopic data.[13] That it has a plane or center of symmetry was evident from the ^1H NMR spectrum of the $C_{12}H_8N_4$ product, determined in either $CDCl_3$ or CD_3OD solution. The spectrum showed only four discrete multiplet proton resonances, in contrast to the ^1H NMR spectrum of the precursor 2, which exhibited nine different, readily discernible proton signals. A plane of symmetry, as in dipyrido[1,2-a:2',1'-f]-1,3,4,6-tetraazapentalene (1), was dictated by the ^{13}C NMR spectrum, which showed seven discrete ^{13}C resonances, ruling out the possibility of the isomeric centrosymmetric structure, dipyrido[1,2-a:1',2'-e]-1,3,4,6-tetraazapentalene for which there would be only six ^{13}C resonances.[14]

For such a polycyclic molecule (1), the moderate water solubility is unexpected. The

compound is highly *fluorescent* in aqueous pH 7 phosphate buffer, and the fluorescence is detectable at concentrations $\geq 10^{-9}$ M. This efficient two-step method involving oxidative cyclization is applicable to the synthesis of a wide variety of heterocycles containing the central 10π electron system of 1,3,4,6-tetraazapentalene. It also provides the key to the examination of the chemistry of this unusual ring system.

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5. M.p. 164-166 °C (aqueous ethanol) (lit.[4] 165-167 °C); R_f (CH_3OH-$CHCl_3$, 1:4, v/v) 0.45; ^1H NMR ($CDCl_3$) δ (ppm) 6.75 (m, 2) and signals for single H's at 6.81 (d), 7.14 (m), 7.43 (d), 7.50 (m), 8.10 (d), 8.17 (s, 3-H), 8.31 (d), and 8.46 (br s); ^{13}C NMR [$(CD_3)_2SO$] δ (ppm) 98.1, 110.4, 110.9, 113.9, 114.3, 123.5, 126.1, 136.8, 141.0, 144.2, 147.4, 154.4. MS (EI, 70 eV) 210 (M^+, 100), 209 (44), 194 (5), 170 (4), 162 (8), 134 (18), 132 (9), 118 (9).
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8. 3-Bromo-2-(2-pyridylamino)imidazo[1,2-a]pyridine was obtained by treatment of 2 with an equivalent of NBS in $CHCl_3$ at 20 °C during 22 h, followed by chromatography on neutral alumina, $CHCl_3$ as eluant, and recrystallization from CH_2Cl_2/Et_2O: m.p. 150-151 °C (dec.); MS (m/e) 288, 290 (M^+); IR ($CDCl_3$) ν 1400 cm^{-1} (N-H); ^1H NMR δ (ppm) 6.6-8.2 (m, 8) with no singlet corresponding to a 3-H. Anal. calcd for $C_{12}H_9BrN_4$: C, 49.84; H, 3.14; N, 19.38; Br, 27.64. Found: C, 49.92; H, 3.04; N, 19.27; Br, 27.47.
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13. The name of 1 according to IUPAC rules of organic nomenclature as well as Chemical Abstracts practice is pyrido[1'',2'':1',2']imidazo[4',5':4,5]imidazo[1,2-a]pyridine (courtesy of Dr. Kurt L. Loening, Director of Nomenclature, CA). The compound is isolated (∿ 50% loss on work-up) by evaporation of the reaction mixture in vacuo followed by gradient chromatography on silicagel using CH_3OH-$CHCl_3$, 0-5%, combination and re-evaporation of the appropriate fractions (TLC) to dryness in vacuo, and recrystallization from water or absolute ethanol: pale yellow crystals, m.p. >300 °C; R_f (CH_3OH-$CHCl_3$, 1:4, v/v) 0.51; ^1H NMR (CD_3OD) δ (ppm) 7.08 (m, 2), 7.43 (m, 2), 7.62 (d, 2), 8.87 (d, 2, protons adjacent to N); ^{13}C NMR (CD_3OD) δ (ppm) 112.7, 116.7, 117.2, 126.0, 127.3, 148.4, 153.4; high resolution MS (FAB) m/e found 209.0823 ($C_{12}H_9N_4$ (MH^+) requires 209.0828; low resolution MS (FAB) m/e 209 (MH^+, 56), 179 (5), 167 (11), 152 (48), 135 (98), 119 (100), 103 (74); UV (pH 7 phosphate buffer λ_{max}, nm (ε) 233 (26,700), 255 (sh, 25,800), 260 (26,700), 284 (11,200), 296 (9,300), 338 (18,200), 354 (16,300); fluorescence λ^{em}_{max} 391 nm, λ^{ex}_{max} 354 nm (pH 7 phosphate buffer). Anal. calcd for $C_{12}H_8N_4$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.02; H, 4.06; N, 27.06.

14. We thank Dr. Michael P. Groziak and Mr. Gary L. Clauson for obtaining the definitive ^{13}C NMR spectrum.

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