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Intramolecular [2+2] Photocycloaddition Of Juxtaposed 4-Pyridone Moieties

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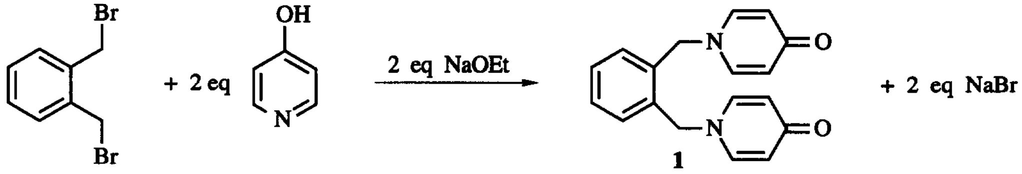
Abstract: Refluxing 4-hydroxypyridine and α,α'-dibromo-*o*-xylene in an ethanolic sodium ethoxide solution affords α,α'-di-(4-pyridon-1-yl)-*o*-xylene (**1**) which undergoes a novel [2+2] photocycloaddition reaction in 3:7 ethanol–ether giving *cis,syn,cis*-12,13-benzo-1,10-diazatetracyclo[8.4.2.$0^{5,15}$.$0^{6,16}$]hexadeca-2,8-diene-4,7-dione (**2**). The structure of **2** was determined by x-ray crystallographic analysis.

We became interested in the photocycloaddition chemistry of 4-pyridones as a route to rigid analogs of certain brain receptor ligands. The photocycloaddition chemistry of 2-pyridones has been well documented. Their [4+4] dimerizations have been known since the early 1960s.[1] Juxtaposed 2-pyridone moieties have been reported to undergo intramolecular [2+2], [4+2][2] and [4+4][3] cycloadditions. *N*-alkyl-2-pyridones tethered to alkenes gave [2+2] photoproducts.[4]

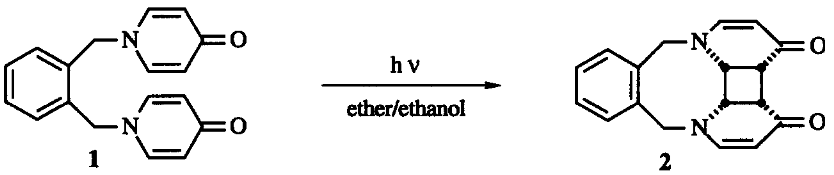
We are unaware of any examples of photocycloadditions involving 4-pyridones. The photolysis of 4-pyridone[5] and *N*-methyl-4-pyridone[6] resulted in reductive addition of protic solvents. Certain sterically hindered *N*-alkyl-4-pyridones underwent photoisomerization reactions.[7] Guerry and coworkers[8] were unable to effect a cycloaddition reaction between *N*-alkyl-4-pyridones and tethered alkenes. On the other hand, certain 5,6-dihydro-4-pyridones give both intra- and intermolecular photocycloaddition products with activated alkenes.[9]

We reasoned that *N*-alkyl-4-pyridones might be made to undergo photocycloadditions in the same fashion as analogous heterocycles like γ-pyranones,[10] cyclic vinylogous amides[11] and pyrimidines.[12] It was conceivable that the expected 4-pyridone [2+2] photoproducts had been formed but were susceptible to photoreversion to the extent that appreciable amounts of product never built up. Under appropriate conditions, [2+2] and [4+2] 2-pyridone photoproducts have been observed to undergo photodecyclization.[2] Our approach was to choose a substrate and conditions such that the 4-pyridone photocycloadduct precipitated from solution as it was formed. Herein we report the first [2+2] photocycloaddition reaction involving a 4-pyridone moiety.

Photosubstrate **1** was prepared as follows. 4-Hydroxypyridine (5.09 g, 53.5 mmol) was dissolved in 1.07 M ethanolic sodium ethoxide (50 mL). *α,α'*-Dibromo-*o*-xylene (7.06 g, 26.8 mmol) was added and the stirred solution was refluxed for 6 h. Filtration, evaporation of the solvent in vacuo, flash chromatography (silica gel, ethanol) and crystallization from methanol by ether diffusion gave 6.97 g (89%) of photosubstrate **1**[13,14] as colorless needles.



A stirred, nearly saturated solution of **1** (104 mg, 0.356 mmol) in 3 mL of ethanol and 7 mL of diethyl ether was irradiated (Rayonet Srinivasan-Griffin Photochemical Reactor, 254 nm, air cooled) in a quartz tube for 2 h. Filtration of the semi-crystalline precipitate gave 81 mg (78%) of analytically pure **2**.[15] Crystallization in the absence of light from acetic acid by ether diffusion gave 74 mg (71%) of **2**•HOAc as colorless needles suitable for x-ray crystallographic analysis (see below). Yields averaging 37% were obtained when the photolysis reaction was not stirred. Irradiation of **1** in ethanol produced no precipitate and only a trace of **2** in solution, as visualized by TLC. Irradiation of a stirred suspension of **1** in 12:1 ether–ethanol resulted in near quantitative recovery of **1**. The photocycloaddition reaction leading to **2** was photoreversible. Thus, while a colorless solution of **2** in CD_3CO_2D in an NMR tube in the dark was stable over a 48-h period, exposure to ambient light for 48 h resulted in quantitative conversion into a colorless solution of **1**.



X-ray crystallographic analysis of **2**•HOAc established the *cis,syn,cis* configuration of **2** (Figure 1). The phenyl rings are positioned such that the molecules are cup shaped in these crystals.[16] Each molecule of **2** has a molecule of acetic acid hydrogen bonded to one of the carbonyl oxygens.

In conclusion, we report the first example of a [2+2] photocycloaddition reaction involving an *N*-alkyl 4-pyridone. Synthetic strategies employing [2+2] photocycloadditions may well be applicable to other 4-pyridones, leading to strained heterocycles that incorporate a vinylogous amide moiety.

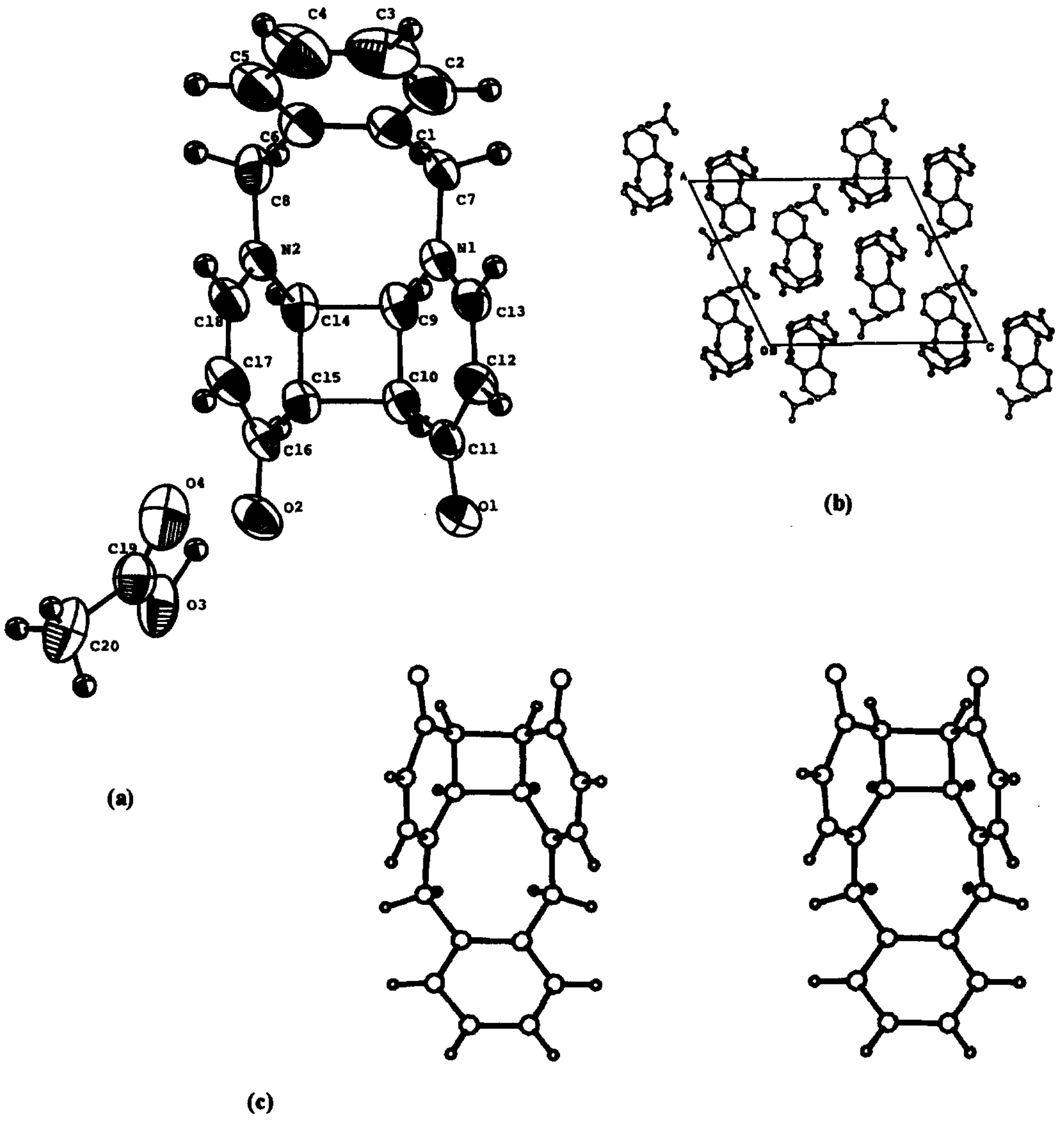


Figure 1. (a) Projection of 2 and acetic acid normal to the cyclobutyl ring, the non-hydrogen atoms are shown as 20% thermal ellipsoids. (b) Display of molecular packing in the unit cell. (c) Stereo pair of 2.

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14. **1**: colorless needles, mp. 239-241°C; ^{1}H-NMR (300 MHz, CD_3OD) δ 5.31 (s, 4 H), 6.48 (d, J = 7.4 Hz, 4 H), 7.15 (m, 2 H), 7.45 (m, 2 H), 7.80 (d, J = 7.4 Hz, 4 H); ^{13}C-NMR (75 MHz, CD_3OD) δ 57.90, 118.94, 130.18, 130.78, 134.76, 143.26, 180.92; UV (CH_3OH) γ max = 267 nm (ε = 37000); IR (KBr) 1638 cm^{-1}; Anal. found: C, 69.28; H, 5.95; N, 8.85%. Calcd for $C_{18}H_{16}N_2O_2 \bullet H_2O$: C, 69.66; H, 5.85; N, 9.03%.
15. **2**: colorless blades, mp. 298°C (decomp.); ^{1}H-NMR (300 MHz, CD_3OD) δ 3.69 (m, 2 H), 4.37 (m, 2 H), 4.49 (d, J = 14.4 Hz, 2 H), 4.73 (d, J = 7.8 Hz, 2 H), 4.80 (d, J = 14.4 Hz, 2 H), 7.32 (d, J = 7.8 Hz, 2 H), 7.40 (m, 4 H); ^{13}C-NMR (75 MHz, CD_3CO_2D) δ 45.81, 56.41, 60.65, 129.48, 131.61, 134.60, 156.79, 187.80; UV (CH_3OH) γ max = 326 nm (ε = 24000); IR (KBr) 1631 cm^{-1}; Anal. found: C, 73.70; H, 5.28; N, 9.27%. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.59%.
16. Crystal experimental data; $C_{18}H_{16}N_2O_2 \cdot CH_3CO_2H$, MW 352.39, monoclinic, space group $P2_1/n$, $a = 14.688(5)$, $b = 7.447(3)$, $c = 17.380(3)$ Å, $\beta = 114.86(2)°$, $V = 1725(1)$ Å^3, monochromatic MoK$_\alpha$ radiation, $\mu = 0.89$ cm^{-1}, $\lambda = 0.71069$ Å, 2848 independent reflections, 1575 observed, $R = 0.066$, $R_w = 0.078$. The positions of nonhydrogen atoms were visualized in an E-map generated using SHELXS and the TEXSAN program was used for the calculations. Anisotropic refinement gave hydrogen peaks in the expected positions. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at Cambridge X-ray Crystallographic Data Centre.

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