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SPECIFIC REARRANGEMENTS OF DIHYDROPYRIMIDINEDIONES TO PYRIDONES VIA DIAZACYCLOOCTATETRAENE INTERMEDIATES

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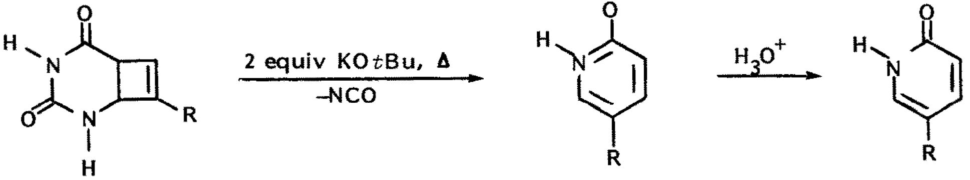
Abstract: *The rearrangement of a uracil-alkyne photoadduct has been studied by* ^{13}*C- and* ^{15}*N-labeling experiments. A diazacyclooctatetraene intermediate suggested as an intermediate from these labeling studies has been independently prepared and shown to undergo rapid rearrangement to a pyridone.*

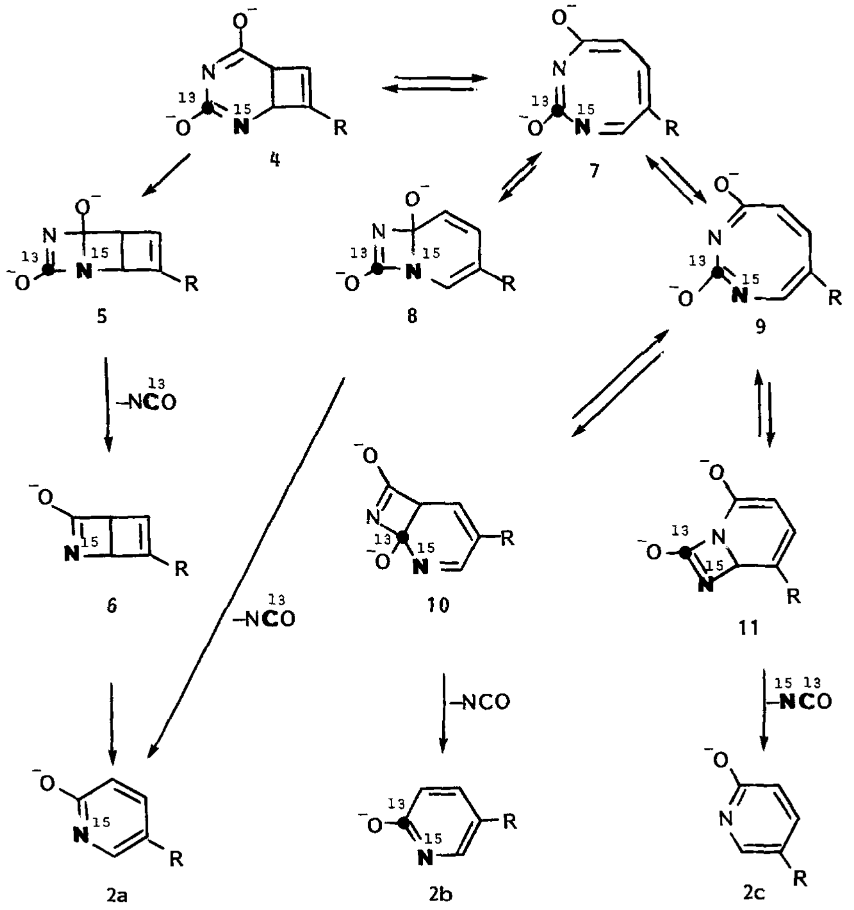
Uracil-alkyne photoadducts 1 undergo an interesting reaction to basic media to afford pyridones in good yield.[1] All attempts to detect an intermediate in the 1 → 2 reaction having failed, we turned to labeling studies to help elucidate the reaction mechanism. As outlined in Scheme I, there are four routes from 1 to 2 via the "dianion" 4.[2] Three of these involve an unknown diazacyclooctatetraene-type species (4 → 7 → 8 → 2a, 4 → 7 → 9 → 10 → 2b, and 4 → 7 → 9 → 11 → 2c) while the fourth (4 → 5 → 6 → 2a) involves a Dewar pyridone-type intermediate. Valence isomerizations[3,4] and bond reorganizations[4,5] in cyclooctatetraene and its derivatives are of much interest,[3-5] and these same processes would be of intrinsic interest in heterocyclic analogs of cyclooctatetraene[6] (e.g., 7 and 15). We report here on the highly specific nature of this base-mediated fragmentation of pyrimidinedione-alkyne photoadducts to pyridones using ^{13}C- and ^{15}N-labeling experiments. In addition, a 1,3-diaza-4,6-octadiene-2,4-dione ring system has been synthesized and shown to undergo specific conversion to a pyridone in basic media.



1 2 3

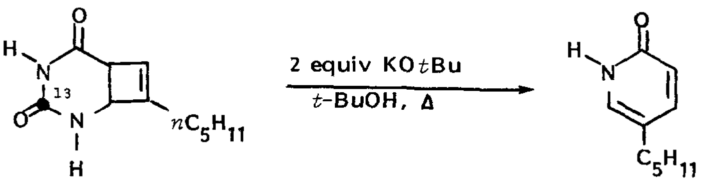
Inspection of Scheme I indicates that appropriate ^{13}C and ^{15}N labeling could rigorously establish several facets of the rearrangement. First, if bond isomerization between 7 and 9 is fast relative to fragmentation, the same 5-alkylpyridone could derive from the bicyclic intermediates 8, 10, and 11. However, ^{13}C and ^{15}N labeling at the indicated positions would rigorously establish the specificity of the fragmentation. Thus, one sequence affords exclusively ^{15}N-labeled compound, 2a, while a second gives ^{15}N- and ^{13}C-labeled compound, 2b, and the third gives product

Scheme I. Mechanistic Possibilities for Pyridone Formation from Uracil-Alkyne Photoadduct



with no label, 2c. Of course, a combination of these pathways would necessarily complicate the labeling results.

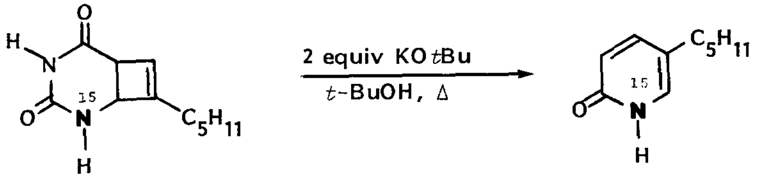
Uracil-$^{13}C_2$ was prepared by hydrogenation of 6-chlorouracil-$^{13}C_2$ which itself was prepared from urea ^{13}C (90 atom % ^{13}C).[10] For the subsequent photocycloaddition work, it was diluted with



1-$^{13}C_2$ 3

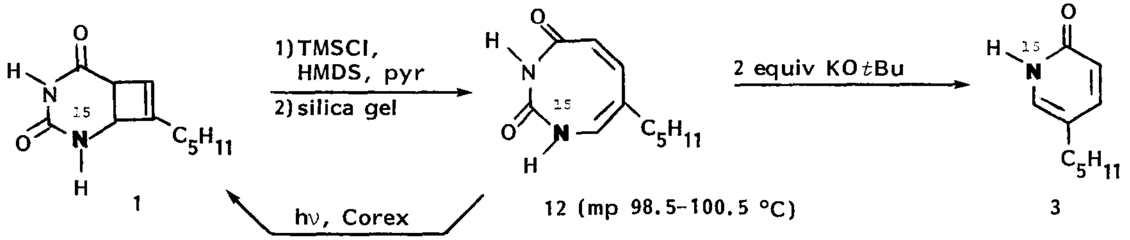
uracil to afford uracil-$^{13}C_2$ (10 atom % ^{13}C). Treatment of 1-$^{13}C_2$ with potassium *t*-butoxide in refluxing *t*-butyl alcohol gave pyridone showing no enhancement of ^{13}C in the ^{13}C NMR relative to a standard sample of pyridone. This rigorously excludes the pathway 4 → 7 → 9 → 10 → 2b.

To further study the mechanism, uracil-$^{15}N_1$ was prepared from hydrolysis/decarboxylation of 5-cyanouracil-$^{15}N_1$ which itself was prepared from ammonium ^{15}N chloride (95 atom % ^{15}N).[11] For the photocycloaddition reaction with 1-heptyne, this was diluted with uracil to give uracil-$^{15}N_1$ (28 atom % ^{15}N). Fragmentation of this adduct with base followed by analysis of ^{15}N by ^{15}N NMR spectroscopy using formamide as an internal reference showed >95% retention of ^{15}N in the pyridone. This ^{15}N-labeling study thus excludes the 4 → 7 → 9 → 11 → 2c reaction pathway.[12]



1-$^{15}N_1$ 3-$^{15}N_1$

The two remaining mechanistic considerations (4 → 5 → 6 → 2a and 4 → 7 → 8 → 2a) are indistinguishable by the above labeling studies, and as noted earlier, all attempts to isolate an intermediate in the reaction of 1 (R = C_5H_{11}) failed. However, if 1 was reacted with trimethylsilyl chloride/hexamethyl disilazane and then silica gel added to the reaction mixture, 12 was isolated in 70% yield. The structural assignment for 12 is supported by its ^1H NMR [($CDCl_3$, δ) 8.30 (br s, 1 H), 7.52 (br s, 1 H), 6.15 (AB q, J_{AB} = 15.0 Hz, $\Delta\nu_{AB}$ = 30 Hz, 2 H), 5.90 (br s, 1 H), 2.10 (t, J = 7 Hz, 2 H), 1.4-1.2 (m, 6 H), and 0.86 (t, J = 5 Hz, 3 H)]; ^{13}C NMR [($CDCl_3$) 167.74, 157.20, 137.99, 133.91, 125.44, 121.26, 33.51, 31.08, 27.78, 22.25, and 13.88]; exact mass spectrum; and its photoisomerization to 1.



1 12 (mp 98.5-100.5 °C) 3

In contrast to the five-hour reaction time for conversion of 1 to 3, 12 yielded the pyridone 3 in five minutes. When 12-$^{15}N_1$ was employed in the reaction, the pyridone 3-$^{15}N_1$ was formed with complete retention of ^{15}N. These results strongly favor the pathway 4 → 7 → 8 → 2a over the 4 → 5 → 6 → 2a sequence.

Summary: Strong evidence has been presented for the involvement of an eight-membered ring diazacyclooctatetraene intermediate in the fragmentation reaction of uracil-alkyne photocycloadducts to pyridones. The favored reaction pathway involves two valence isomerizations via six-electron disrotatory processes followed by a dianion mediated retro 2+2 cycloaddition. In addition, ring-expanded nitrogen base compounds (i.e., 12) are available via a photocycloaddition-valence isomerization sequence. These latter compounds, readily prepared in two steps from commercially available materials, should facilitate a study of the chemistry of diazacyclooctatetraene-like systems. This type of two-carbon ring expansion may be useful in other heterocyclic systems.[13]

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(10) The reaction sequence was analogous to that used for preparation of unlabeled chlorouracil. *Org. Syn. Coll.* Vol 2, 60; Bredereck, H.; Bräuninger, A.; Mayer, D.; Vollmann, H. *Chem. Ber.* 1959, *92*, 2937. Cresswell, R. M.; Wood, H. C. S. *J. Chem. Soc.* 1960, 4768.

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