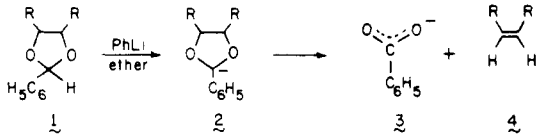
Communications to the Editor

Dianion Mediated Cycloreversions. A Novel Pyrimidinedione to Pyridone Conversion

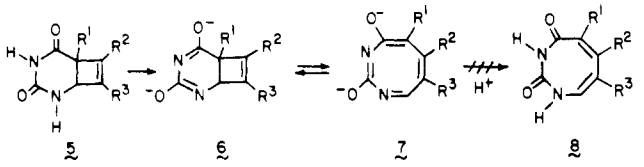
Sir:

Cycloreversion reactions of monoanionic species have been of mechanistic interest and of considerable synthetic utility, especially in olefin synthesis.[1,2] The driving force for many of these cycloreversions has been attributed to the increased stability of the product anion (e.g., **3**) relative to the intermediate anion (e.g., **2**). By contrast cycloreversions derived from

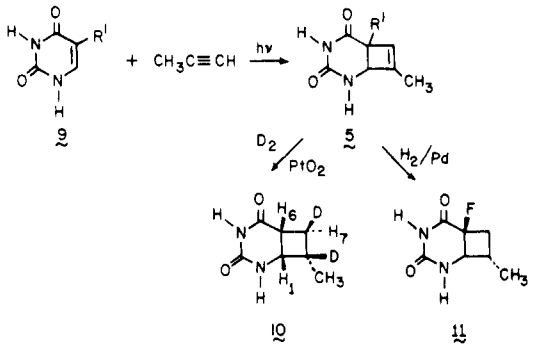


dianions in which coulombic repulsion would be expected to afford an additional driving force for cleavage to two monoanionic species have not been the subject of any systematic study. In connection with studies directed toward the synthesis of ring-expanded nitrogen bases[3] (e.g., **8**), we conceived of routes involving valence tautomerization of the dianions of uracil–acetylene photoadducts to diazacyclooctatetraene dianions which would be converted to **8** on workup (Scheme I).[4] However, we have found that dianions of **5** do not afford a route to ring-expanded nitrogen bases but undergo a novel, facile cycloreversion to pyridones. We report herein this interesting cycloreversion for dianions derived from uracil-, 5-fluorouracil-, and thymine–acetylene cycloadducts. The overall process comprises a pyrimidinedione to pyridone conversion.

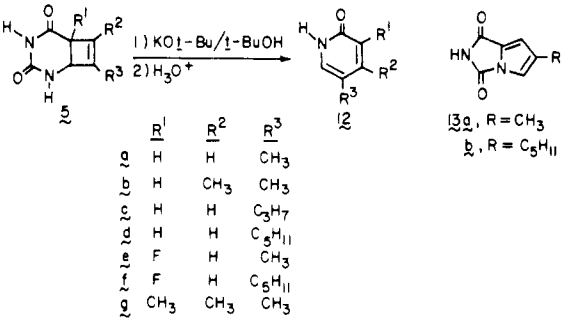
Scheme I. Projected Route from Uracil–Acetylene Cycloadducts to Ring-Expanded Nitrogen Bases



Scheme II



Scheme III



The photochemical cycloaddition of uracil to acetylenes (Table I), while affording only modest yields of adduct, was especially convenient in that primarily one regioisomer was formed.[9,10] The orientation of the propyne–uracil adduct, **5a** (R^1 = H), was established by reduction with deuterium to **10** (Scheme II). Compound **10** showed in its ^{1}H NMR spectrum (pyridine) H_1 as a doublet of doublets at δ 4.10 (J = 8.5, 2.5 Hz), H_6 as a doublet of doublets at 3.28 (J = 8.7, 6.0 Hz), and H_7 as a doublet at 1.80 (J = 6.0 Hz). When the N–H coupling was washed out with deuterium oxide, H_1 appeared as a clean doublet (J = 8.5 Hz), thus establishing the regioselectivity shown in **5a**. The 5-fluorouracil–propyne cycloadduct was established as **5e** (R^1 = F) by hydrogenation to the known **11**.[11]

When the uracil–propyne cycloadduct, **5a**, was refluxed for 4 h in dry *tert*-butyl alcohol containing 2 equiv of potassium *tert*-butoxide, workup, followed by silica gel chromatography, afforded a new compound of molecular formula C_6H_7NO (Scheme III). On the basis of its UV,[12] ^{1}H NMR,[14] and

Table I. Photocycloaddition Reactions of Uracil[a] and Their Rearrangement Reactions

pyrimidinedione	acetylene (M)	cycloadduct[b,c] yield, %	cycloadduct[b,c] mp,[d] °C	pyridone yield,[e] %	pyridone mp, °C
uracil	propyne (0.62)	43	241–242[f]	60	181–183
	2-butyne (0.33)	54	260–261	65	213–214
	1-pentyne (0.33)	30	240–241	84	68–69
	1-heptyne (0.33)	31	223–224	83	64–65
	3-hexyne (0.33)	31	249–250	70	43–45
5-fluorouracil	propyne (0.62)	31	273–275	50	144–145[g]
	1-heptyne (0.29)	29	229–230	70	43–45[g]
thymine	2-butyne (0.36)	32	293–295	83	229–230

[a] Uracil concentrations, 22.3 × 10^{-3} M; 5-fluorouracil concentrations, 19.0 × 10^{-3} M; thymine concentration, 23.9 × 10^{-3} M. [b] Irradiations were conducted in 200 mL of 4:1 acetone–water using Corex-filtered light from a 450-W medium-pressure source, 0.5 g requiring ~1.5 h for complete disappearance of uracil. [c] The remaining uracil was largely accounted for as dimers. [d] Melting point with decomposition. [e] Isolated yields of crystalline material. [f] A minor uncharacterized product was also formed in this irradiation. [g] A second compound was isolated in 17 and 9% yield, respectively.

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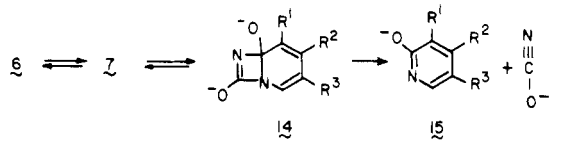
melting points,[15] the rearrangement product has been established as 5-methyl-2-pyridone (**12a**). This rearrangement appears quite general since the cycloadducts of uracil (**5a–d**), 5-fluorouracil (**5e,f**), and thymine (**5g**) undergo smooth conversion to pyridone. Only for the adducts **5e** and **5f** was a second rearrangement product noted. These compounds, formed in 17 and 9% yields, respectively, have been tentatively assigned as the novel pyrrole derivatives **13a** and **13b**, based on their ^{1}H NMR, ^{13}C NMR, UV, and combustion analyses. The structural assignments for the previously unknown pyridones are based on spectroscopy (^{13}C NMR, ^{1}H NMR, UV) and analytical data.

This unusual **5** → **12** conversion is another interesting rearrangement emanating from treatment of dihydropyrimidinediones with base.[11] Since 1 equiv of potassium *tert*-butoxide does not effect rearrangement, we surmise dianions of **5** are required for rearrangement. A reasonable mechanism involves ring opening of the dianion to **7** followed by an alternate mode of ring closure to **14** and fragmentation to the pyridone anion.[17,18] The facile **14** → **15** cycloreversion may be



related to the separation of charge resulting from the cleavage of **14** or reflect alkoxide acceleration of a reverse [2 + 2] cycloaddition. Prominent rate accelerations of [3,3][20] and [1,3][21] shifts by alkoxide moieties have already proven of mechanistic interest and synthetic value.[22] Anions and dianions of other carbo- and heterocyclic systems may also undergo facile rearrangements of the type noted here; additional studies in this area are currently in progress.[23]

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References and Notes

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(4) Relatively little is known concerning the chemistry of aza-[5] and diazacyclooctatetraenes.[6] The parent azacyclooctatetraene is especially unstable, and the chemistry of these systems is largely undefined.[7,8]
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(12) $\lambda_{max(H_2O)}$ 227 nm (log ϵ 4.01) and 302 (3.81) compared with that reported[13] for 5-methylpyridone, $\lambda_{max(H_2O)}$ 227 nm (log ϵ 3.81) and 302 (3.76).
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(15) The 5-methyl isomer has mp 181–183 °C, while the 4-methylpyridone has mp 124–125 °C.[16]
(16) "Pyridine and Its Derivatives, Supplement Part III", Abramovitch, R. A., Ed.; Wiley: New York, 1974, p 8661.
(17) All attempts to isolate an intermediate (i.e., **8**) by interrupting the reaction of **5a** and **5d** at various conversions to pyridone have been unsuccessful. An absorption at ~280 nm in the UV was observed in several cases, but the small yield of material prevented characterization. The use of additional trapping agents for intermediates in these reactions will be explored.
(18) The residue (primarily inorganic) from the reactions shows only five IR (KBr) absorptions at 2185 (vs), 1306 (m), 1212 (m), 652 (m), and 642 (m) cm^{-1}. Waddington[19] reports a mull IR (either Nujol or hexachlorobutadiene) of potassium cyanate showing five absorptions at 2170, 1300, 1205, 636, and 626 cm^{-1}.
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(23) All new compounds gave satisfactory combustion analyses or exact mass measurement (**5e, 5g,** and **12c**).

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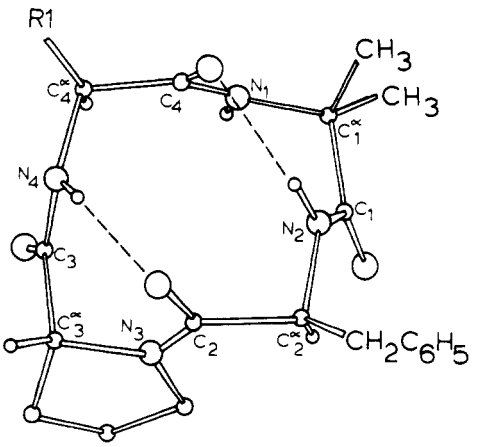
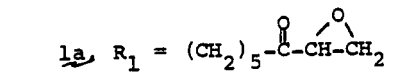
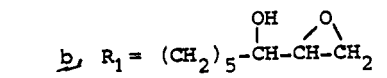
Stereoselective Hydrogenation of Dehydrophenylalanine in a Cyclic Tetrapeptide. Synthesis of [Ala^4]-Chlamydocin

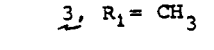
Sir:

Chlamydocin, cyclo[A^{i}bu-L-Phe-D-Pro-(L-2-amino-8-oxo-9,10-epoxidecanoic acid)] (**1a**), a cyclic tetrapeptide isolated from culture filtrates of *Diheterosporia chlamydosporia*









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