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THE PHOTOSENSITIZED CYCLOADDITION OF URACIL TO VINYLENE CARBONATE: A ROUTE TO 5-(FORMYLMETHYL)URACIL AND (±)-5-(4',5'-DIHYDROXYPENTYL)URACIL

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The photochemistry of the nucleic acid bases has been extensively studied as a model for photochemical transformations of DNA and RNA (1). Most of the studies thus far have addressed themselves either to the isolation and characterization of new photoproducts or investigation of excited state properties and the mechanism of photoproduct formation. In the present communication the photoreaction of uracil with vinylene carbonate is described. The resulting [2 + 2] photoadducts 2a and 2b react with aprotic base to give 5-(formylmethyl)uracil (3), a potentially useful intermediate for the elaboration of extended carbon chains in the 5-position of uracil. This particular two step sequence was reported recently as a means to convert cycloalkenones to 2-formylmethyl-2-cycloalkenones (2).

A solution of uracil and vinylene carbonate (14-18-fold excess) in water-acetone (2.4:1.0, v/v) was irradiated until the uv absorbance at 260 nm had decreased by 95% (14-16 hr)(3). The acetone and water were removed *in vacuo* to give a white solid, which on washing with cold acetone gave a mixture of 2a and 2b (5:2, 75-87% yield). The isomers were separated and obtained analytically pure by chromatography on silica gel (4). Tentative assignment of stereochemistry follows from the nmr data in Table I (5). Gamba and Mondelli (6) have suggested that for cyclobutane rings the sign of the cross-ring four-bond couplings (^{4}J) is a much more reliable indicator of the cis-trans orientation of the interacting protons than is the relative magnitude of the vicinal coupling constants between cis and trans protons (7). Specifically, when ^{4}J is positive the coupled protons are cis, and conversely when ^{4}J is negative the coupled protons are trans. Spin decoupling experiments allowed us to assign all of the peaks and coupling constants for the major isomer and all but the cross-ring $^4\underline{J}$ coupling constants ($\underline{J}_{ac}$ and $\underline{J}_{bd}$) in the minor isomer. The spectrum resolution allowed us to place an upper limit on the magnitude of $\underline{J}_{ac}$ and $\underline{J}_{bd}$ in the minor isomer 2b of ±1.0 Hz. Spin tickling experiments on the major isomer established that all coupling constants are positive. Both these spin tickling results and the data in Table I point to the cis-syn-cis configuration 2a for the major isomer.

TABLE I

Nmr Data[a] for 2a and 2b

Proton	Chemical shifts[b]			Coupling constants,[c] Hz	
	2a	2b		2a	2b
H_a	5.33	5.25	$\underline{J}_{ab}$	5.7	6.2
H_b	5.19	5.12	$\underline{J}_{ac}$	2.2	-
H_c	4.25	4.26	$\underline{J}_{ad}$	5.8	1.9
H_d	3.80	3.80	$\underline{J}_{bc}$	4.4	2.4
H_e	7.90	8.06	$\underline{J}_{bd}$	1.9	-
H_f	10.51	10.54	$\underline{J}_{cd}$	9.9	9.9
			$\underline{J}_{ce}$	3.0	3.3

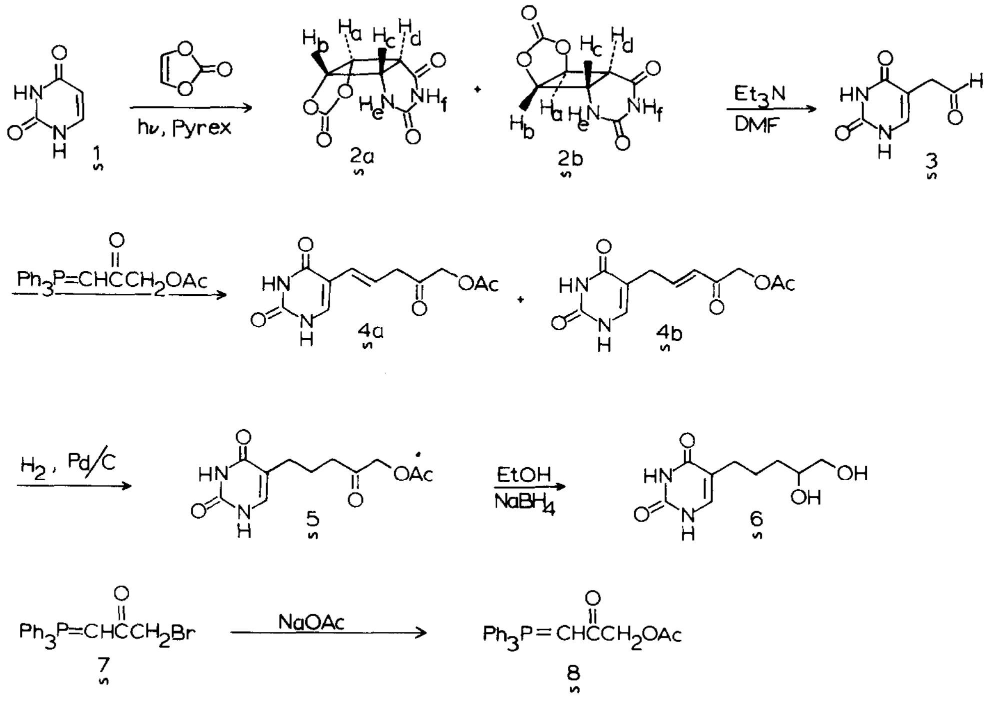
(a) Chemical shifts and coupling constants were determined on a Varian HR-220 (220 MHz) spectrometer and spin tickling experiments were carried out on a Varian HA-100 (100 MHz) instrument.

(b) δ values, ppm from tetramethylsilane.

(c) All coupling constants reported are positive.

Neither isomer showed absorption in the uv spectrum above 240 nm. The cis-anti-cis isomer 2b (ν_{max}^{KBr} 1864, 1746, 1696, and 1278 cm^{-1}) and the cis-syn-cis isomer 2a (ν_{max}^{KBr} 1819 and 1725 cm^{-1}) did not melt, but both slowly resinified on heating to 320°. Treatment of the mixed photoproducts with triethylamine in dimethylformamide (DMF) followed by silica gel chromatography gave the aldehyde 3 (40% yield) in a purity suitable for subsequent conversions. The structure of the aldehyde followed from nmr, ir, uv, and mass spectral evidence. The high resolution electron impact mass spectrum gave a parent ion at $\underline{m}/\underline{e}$ 154.0374 (calcd for

$C_6H_6N_2O_3$: m/e 154.0378). The aldehyde was further characterized as its 2,4-dinitrophenylhydrazone: (4) mp 256-257°; λ_{max}^{MeOH} 361.5 nm (ε 21,000), 262 (16,600), 212 (20,300).



(+)-5-(4',5'-Dihydroxypentyl)uracil (6) was recently isolated from the DNA of *Bacillus subtilis* phage SP-15 (8) and its structure proved by synthesis (9). As a first example of the synthetic utility of 5-(formylmethyl)uracil, we have devised a facile synthesis of racemic 6.

(Bromomethylcarbonylmethylene)triphenylphosphorane (7) (10) was treated with anhydrous sodium acetate in DMF to give (acetoxymethylcarbonylmethylene)triphenylphosphorane (8) in 68% yield. Reaction of phosphorane 8 with aldehyde 3 in refluxing acetonitrile gave a 1:1 mixture of the two isomeric trans alkenes 4a and 4b. The mixture of isomers was characterized by uv and nmr data and then converted directly by catalytic hydrogenation in methanol-water over palladium on carbon to 5-(4'-oxo-5'-acetoxypentyl)uracil (5) (4) (34% overall yield from 3): mp 234-237°; $\lambda_{max}^{H_2O}$ 265nm (ε 7,600), 207 (9,800). Reduction of 5 with sodium borohydride in refluxing ethanol gave 5-(4',5'-dihydroxypentyl)uracil (6) (4) in 78% yield: mp 217-220°. The nmr, ir, and mass spectra of an analytical sample of **6** corresponded well with the published spectra (8,9).

The applicability of this approach to the insertion of carbon chains into the 5-position of other nucleic acid pyrimidine bases and their nucleosides is currently under study.

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3. All irradiations were carried out under nitrogen in a water-cooled Pyrex apparatus placed in a Rayonet RPR-100 photoreactor with 16 3000-Å lamps.

4. Satisfactory elemental analysis and complete characterization by uv, ir, nmr, and mass spectroscopy were obtained.

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