Intramolecular Photocyclisation of Molecules containing both 3-Phenylcyclopentenone and Uracil Rings

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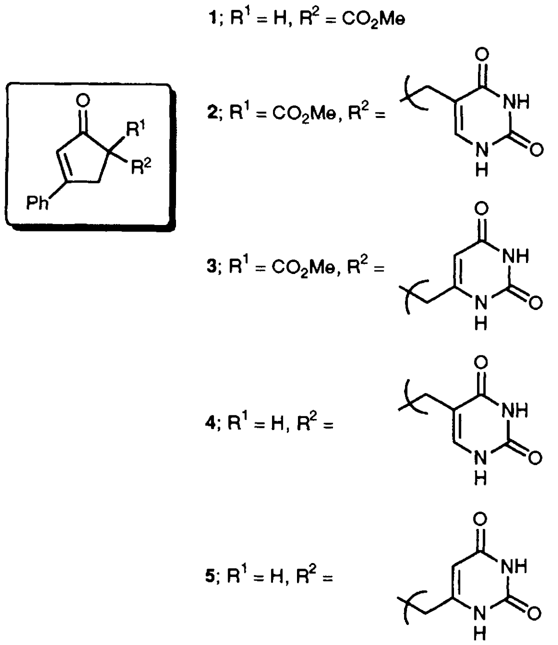
Photolysis of both 3-phenyl-(5- and 6-uracilylmethyl)cyclopentenones give single products which have been identified as 5,7-diaza-10-phenyl[7.2.1.0^{5,9}]tetracyclododecane-2,6,8-trione and 6,8-diaza-10-phenyl[7.2.1.0^{5,9}]tetracyclododecane-2,5,7-trione, respectively.

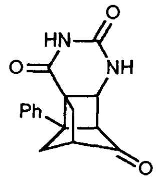
The cycloaddition reactions of pyrimidines are an important class of photochemical reactions of DNA[1] that are responsible for the formation of the principal photoproduct in UV-irradiated DNA (the [2 + 2] dimers of thymine), as well as being the basis for a successful phototherapeutic procedure (the treatment of psoriasis by psoralens). Surprisingly, relatively little work has been carried out with other classes of photoactive compounds and pyrimidines. In particular there has been no systematic study of the cycloadditions of cyclic enones to nucleic acids.[1,2]

We are currently embarking on such a study of substituted 3-phenylcyclopent-2-enones, planning to exploit the rich photocycloaddition chemistry of these compounds[3–5] and the long lifetime of the triplet state in solution that allows convenient monitoring by laser flash photolysis.[6] Synthetic methods are readily available, which allow the preparation of derivatives, that can bind to DNA. In this communication we present the results of experiments which show that these enones can add efficiently to thymines. By covalently linking the enone and pyrimidine derivatives, we hoped to maximise the chances of reaction, and the yield of photoadduct, and to minimise side reactions. We have previously shown that this is the case for enones linked to allyl groups[3] and to naphthalenes[4] and recently Lhomme and coworkers have reported a similar approach for the addition of psoralens to thymidines.[7]

Hatanaka *et al.*[8] have recently described the synthesis of 5-alkoxycarbonyl cyclopentenones. We have used their method to make 5-methoxycarbonyl-3-phenylcyclopentenone **1**. Alkylation of this molecule with 5- and 6-chloromethyluracils afforded the uracil esters **2** and **3**, respectively. Basic ester hydrolysis and concomitant decarboxylation afforded the required starting materials **4** and **5**, respectively.

Photolysis (Hanovia 450 W medium pressure Hg lamp; Pyrex filter, 3–4 h) of both **4** and **5** in acetonitrile afforded single photoproducts in quantative yield (HPLC and NMR spectroscopy of the photoreaction 'mixture'). Their structures follow from their elemental analyses, high resolution MS, IR and ^{1}H- and ^{13}C-spectra, using 2D- and NOE (nuclear Overhauser effect) measurements. In the product from **4**, the ^{1}H spectrum showed a singlet δ 3.55 assigned to the 4-H. When this signal is irradiated, the NOEs were shown at the 5- (4.2%) and 12-*endo* (4.0%) protons. Irradiation of the 5-NH caused NOEs at the 4-proton (5.3%), and the 3-proton (2.9%). The IR spectrum (Nujol) shows the expected carbonyl peaks at 1754 (cyclopentanone) 1711 (amide C=O) and





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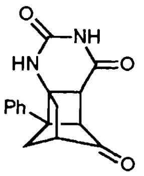

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1654 cm^{-1} (urea C=O). These results, among others, show that the photoproduct possesses the regiochemistry shown in **6**.

The product from **5** understandably lacks a distinctive signal around δ 3.5, but when the 8-NH signal is irradiated the NOEs are shown by the *ortho*-phenyl (4%) protons, thus demonstrating that the product is **7**. In the IR spectrum (Nujol), carbonyl peaks were found at 1745 (cyclopentanone), 1700 (amide) and 1650 cm^{-1} (urea).

These results show that photoadducts form readily between cyclopentenones and uracil rings giving a single product. It is of interest that the regiochemistry of the products is identical, and that the mode of cycloaddition is independent of the polarity of the uracil carbon–carbon double bond. This confirms our earlier results where the polarity of the ene does not affect the regiochemistry of the product.[5] The above results encourage us to prepare water-soluble cationic cyclopentenone derivatives to facilitate formation of adducts with thymine bases in DNA *via inter*molecular cycloaddition.

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