Tetrahedron Letters, Vol.31, No.35, pp 5031-5034, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

# SOLID STATE PHOTODIMERIZATION OF PSORALEN DERIVATIVES

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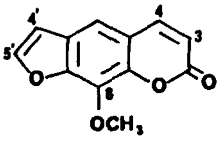
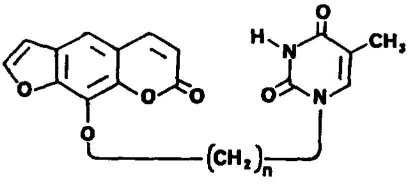
Abstract : Stereoselective reversible photodimerization of 8-alkoxypsoralen 1-thymine derivatives occurs in the solid state with topochemical control, the reactive pyrone double bonds of the monomers being favourably oriented in the crystal to produce only the exo head-to-tail dimer.

Psoralens are compounds of wide photobiological interest[1,2,3]. For example, 8-methoxypsoralen 8-MOP 1 is used in the phototherapy of skin diseases like psoriasis and vitiligo. The photobiological activity is related, at least partly, to 2+2 photocycloaddition onto pyrimidine bases of DNA[4]. To investigate the interactions and the photoreactions between psoralens and nucleotide bases, we have previously reported the synthesis and study of model compounds like 2 and 3 in which the base is linked to the psoralen ring by different polymethylene bridges[5-9]. The crystal structures of such models have also been determined[10,11]. We report here an unusual photodimerization which occurs in the crystalline state for two of these models 2e and 3e (n = 5).

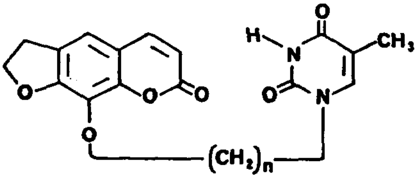
In contrast to compound 2d (n = 4) for which no particular interaction of the ring-ring stacking type (psoralen-thymine, psoralen-psoralen or thymine-thymine) was observed in the solid[10], X-ray structure analysis[12] of crystals of 2e and 3e, as obtained in the dark



1 : 8-MOP



2 (c,d,e,f,l) : n=3,4,5,6,12

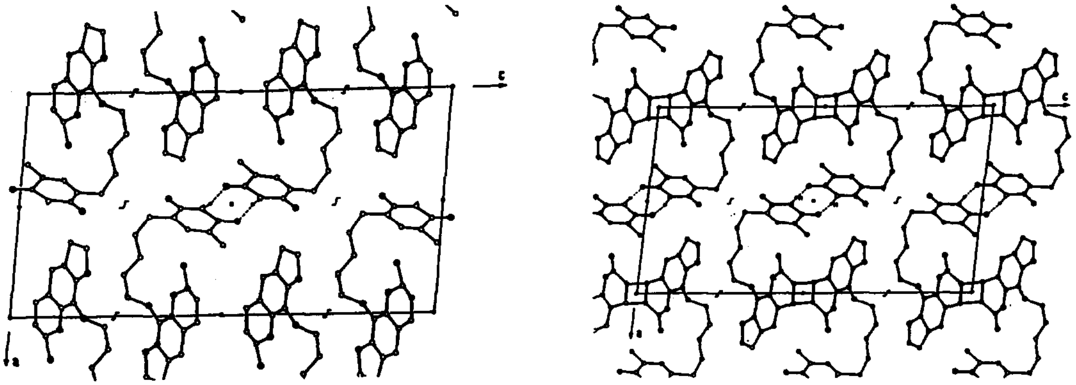


3 (c,d,e,f) : n=3,4,5,6

from alcoholic solutions, showed the 3,4 double bonds of the psoralen rings to be lying over each other at a distance of 3.5 A (Figure 1) which appears favourable to a photodimerization in the crystal[13]. When crystals of either 2e and 3e were exposed to daylight or to an artificial light source ( $\lambda$ = 365 nm), HPLC analysis showed that a highly selective reaction had occured with excellent yield (one photoproduct, over 99 %). The identity of the dimeric product involving the 3,4 double bond of psoralen was established by $^1$H NMR, mass spectroscopy and elemental analysis[14]. Reirradiation at 254 nm in DMSO led to photoreversion to the starting compound 2e or 3e which confirms that a [2+2] photoaddition had occurred[15].

A crystal of the dimer of 2e was obtained with some difficulties and found to be isostructural with the corresponding monomer (Figures 1 and 2). Molecular packings are similar and photodimerization requires only a translational movement to reduce the distances between the C(3) and C(4) atoms[16-19]. Thus, the model compounds 2e lead to psoralen dimers having the exo head-to-tail configuration, quite clearly controlled by the favourable arrangement of the reactive double bonds of the monomers in the crystal. Presumably, the same stereoselective photoaddition occurs for the model compound 3e.

Photodimerization involving the pyrone double bonds of psoralens has been observed under various conditions : in the solid state[20-24], in frozen solution[23,25] and in organic solvents[23,25-29], but little has been reported on the reaction stereochemistry. For 8-MOP and its derivatives, stereoselectivity has been described only in organic solvents to give "pyrone-pyrone" exo head to head dimers[26-28]. The reaction appears less selective for psoralen in the solid state[24] and for 4,5',8-trimethypsoralen (TMP) in dichloromethane[29]. For example, irradiation of TMP leads to a mixture of six principal photoproducts, three of which were identified as a "pyrone-pyrone" exo head to tail dimer, a "pyrone-furan" endo head to head dimer and a bicyclomer resulting from a double cycloaddition between pyrone and furan double bonds. The present stereoselective intermolecular photodimerization in the crystal therefore represents a new mode of addition which emphasizes the effect that appropriate local arrangement can have on regio- and stereoselectivity.



Figures 1 and 2 : Packing of the compound 2e and its photodimer down the b axis

This result can be compared to the psoralen-thymine photoreaction. In solution, models give an intramolecular photoaddition of thymine and psoralen, and only at the pyrone double bond[7,8]. When, in contrast, psoralen photoreacts with DNA[1-4], both pyrone and furan adducts are formed, which suggests that on intercalation certain geometries for reactive double bonds are imposed. As in the crystal, the course of the reaction is thus largely determined by geometric factors.

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12. Crystals of monomers 2e and 3e were obtained by slow cooling from a boiling ethanol/isopropanol mixture. The monomers are isostructural. Crystal data of monomer 2e : $C_{21}H_{20}N_2O_6$, M = 396.4, monoclinic, P2$_1$/c, crystal size 0.1 x 0.1 x 0.3 mm, a = 13.562 (3) ; b = 5.321 (2) ; c = 25.522 (6) Å ; ß =95.98 (5)° ; V = 1831.9 Å$^3$ ; D$_c$ = 1.43 g/cm$^3$, Z = 4. Structure was solved by MULTAN 78 [ P. Main, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq and M.M. Wolfson, Univ. of York (England) and Louvain (Belgium) ] and refined by least square methods to R = 0.05. Crystal data of monomer 3e : $C_{21}H_{22}N_2O_6$, M = 398.4, monoclinic, space group P2$_1$/c, crystal size 0.05 x 0.1 x 0.2 mm, a = 13.519 (3) ; b = 5.345 (2) ; c = 25.934 (7) Å ; ß = 95.79 (3)° ; V = 1865 Å$^3$ ; D$_c$ = 1.42 g/cm$^3$, Z = 4 ; R = 0.07.
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14. Crystals of 2e or 3e (obtained from ethanolic solutions) were irradiated at 365 nm with a 125 W high pressure mercury lamp Philips HPW. The crystals were then pulverized with ultrasound in dichloromethane. Repetitive washings and filtrations removed the unreacted starting material and pure dimer was finally obtained as an insoluble white powder. Yields 90 %. Photodimer of 2e : mp : 247-249°C (decomposition). $^1$H NMR (DMSOd$_6$, 80 MHz); δppm : 11.10 (broad s, 2H, 2NH) ; 7.95 (d, 2H, J = 2Hz, 2 C$_5$, H) ; 7.45 (d, 2H, J < 1Hz, 2C$_6$H Thy) ; 7.15 (s, 2H, 2C$_5$ H) ; 6.90 (d, 2H, J = 2Hz, 2C$_4$, H) ; 4.30 (m, 6H) ; 1.70 (d, 6H, J < 1Hz, 2CH$_3$ Thy) ; 2.0-1.2 (m, 12H). MS (CI, methane), m/z : 794 (100,(M+1)$^+$) ; 793 (54, M$^+$). Analysis, $C_{42}H_{40}N_4O_{12}$ ; calc. %C : 63.63, %H : 5.09, %N : 7.07 ; found %C :

63.37, %H : 5.12, %N : 7.18. Photodimer of 3e : mp : 239-241°C (decomposition). $^1$H NMR (DMSOd$_6$, 80 MHz), δppm : 11.10 (broad s, 2H, 2NH) ; 7.50 (d, 2H, J < 1Hz, 2C$_6$H Thy) ; 6.70 (s, 2H, 2C$_5$H) ; 4.55 (t, 4H, J = 9Hz, 2 O-CH$_2$) ; 4.0 (m, 6H) ; 3.6 (m, 6H) ; 3.10 (t, 4H, J = 9Hz, 2 N-CH$_2$) ; 1.70 (d, 6H, J < 1Hz, 2CH$_3$ Thy) ; 2.0 to 1.0 (m, 12H). MS (CI, methane), m/z : 798 (100, (M+1)$^+$) ; 399 (32). Analysis,C$_{42}$H$_{44}$N$_4$O$_{12}$ ; calc. %C : 63.31, %H : 5.57, %N : 7.03 ; found %C : 62.99, %H : 5.57, %N : 7.04.

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16. Crystal data of photodimer of 2e : C$_{42}$H$_{40}$N$_4$O$_{12}$, M = 792.8, monoclinic, space group P2$_1$/c, crystal size 0.025 x 0.05 x 0.1 mm ; a = 13.882 (5) ; b = 5.251 (1) ; c = 24.881 (7) Å ; ß = 97.21 (4)° ; V = 1799.3 Å$^3$ ; D$_c$ = 1.46 g/cm$^3$, Z = 2. This crystal showed poor diffraction spectra and the time constant had to be increased during data acquisition. No decay was observed in the three reference intensities. Refinement by least squares procedures with independent atoms converge to R = 0.13. The bond lengths and angles are near the usual values except for the length of the bonds between the two pyrone rings in the cyclobutane which were found equal to 1.75 A. Such abnormally long bonds for a cyclobutane[17] have been observed previously in the structure of photodimers of 1,1'-trimethylenebisthymine[18] and 1,3-dimethylthymine[19] and have been related to a dissociation of the dimer into monomer by X radiation. For the present psoralen-psoralen photodimer, a similar dissociation is possible. Since dimer and monomer are isostructural, the dissociation cannot be followed by measuring reference reflexions as any variations are indiscernible. Sections of electron density distribution show a minor anomaly in the cyclobutane environment (at the limits of experimental errors) which is in accord with a partial decomposition of the crystal under X radiation. If the bond length of 1.75 Å is attributed to a decomposition of 10 % of the molecules, the refinement assigning 90 % occupancy to the cyclobutane atoms and 10 % occupancy for the same atoms as monomer, leads to a R factor of 0.13 with an entirely satisfactory geometry for the cyclobutane.
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**(Received in France 12 June 1990)**