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Interaction Between Furocoumarins and Pyrimidine Bases in a Linked System. The Crucial Choice of the Link

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INTERACTION BETWEEN FUROCOUMARINS AND PYRIMIDINE BASES IN A LINKED SYSTEM. THE CRUCIAL CHOICE OF THE LINK

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Abstract A specific interaction between psoralen and pyrimidine bases (thymine), revealed in crystals of compound III, induced under UV light a topochemical photocycloaddition between the double bonds of thymine and pyrone ring of psoralen. The crystallographic analysis of compound I, II and III demonstrated the minor perturbation displayed by the trioxyethylene chain on the chromophore packing modes.

INTRODUCTION

The biological activity of psoralen derivatives is still an active field of investigation. The activity of these drugs used for treating some skin deseases, is generally described in two steps : i) the formation in the dark of a molecular complex of intercalation type with DNA bases; ii) the photoreactivity of the dark complex, under UV light, leading to mono and double cycloadducts (cross linking) where the [3,4] or/and [4', 5'] double bonds of psoralen are involved (fig.1).

Although a great deal of work has been published on this topic[1,2], little is known about the geometry of the dark complex which was mainly studied by UV absorption spectroscopy in fluid media[3]. X-ray structure analysis was proved to be an ideal technique for determining the geometry of complexes when crystals are available; so far for the DNA

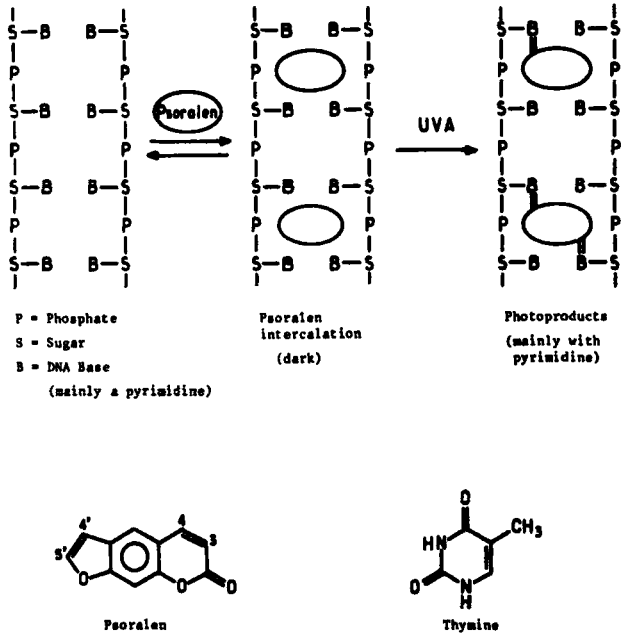
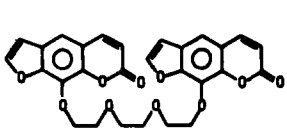


FIGURE 1. Schematized psoralen photoreactivity with DNA

psoralen dark complex it has not been possible to consider this technique. In order to identify any psoralen-thymine interactions that may be contributing to the binding observed in the furocoumarins-DNA system, we designed a model compound III having a trioxyethylene chain between a pyrimidine base (thymine, which is found to be the most photoreactive base toward furocoumarins) and psoralen. (Attempts to effect a direct crystallization between psoralen and thymine met with failure). The choice of the chain linking the two interacting moieties is very important. It was shown in anthracenic series[4], that polyoxyethylene chains are very flexible and display in fluid solution, only a minor perturbation of the mutual interaction between the chromophores fixed at their extremities in contrast to n-alkane chains[4,5]. For checking the behaviour of the chain in the

solid state, the X-ray structure of the symmetrical bichromophores I and II[6] were solved.

This paper concerns the crystal structures of compounds I, II and III, the conformational behaviour of the triethyleneoxyde chain in the solid state and the first direct evidence of a specific interaction between psoralen and thymine in the crystal which allows a topochemical transformation into the corresponding photocycloadducts.



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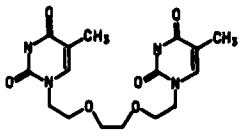

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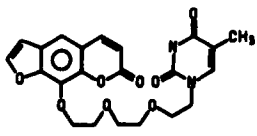

III

RESULTS AND DISCUSSION

The synthesis of compounds I, II and III are described elsewhere[7].

1. 1,8-bis(-8-oxypsoralen)-3,6 dioxaoctane (I).

Monocrystals of compound I were grown from an acetone-benzene solution by slow evaporation. The crystallographic data are :

Space group P_1

a = 9.929 (2) Å	α = 99.76 (2)°	
b = 11.096 (4) Å	β = 96.72 (2)°	Z = 2
c = 11.413 (2) Å	γ = 106.99 (2)°	

A projection of the crystalline structure along [001] is shown in figure 2.

The aromatic rings are packed, in the crystal, in layers. A comparison with analogous single chromophore derivatives (psoralen[8] and 8-methoxypsoralen[9]) indicates a non-prohibiting factor of the flexible chain on the stacking of the

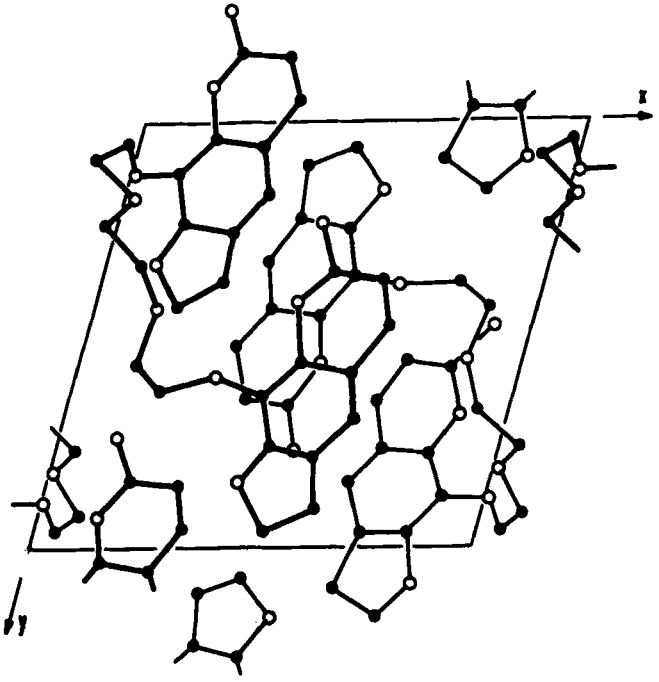

FIGURE 2. Projection along [001] of compound I.

tricyclic rings.

2. 1,8-bis (thym-1 yl)-3,6 dioxaoctane (II).

Crystals of compound II were obtained from an ethyl acetate solution in the same conditions as I. The crystallographic data are :

Space group $P_{\bar{1}}$

a = 12.356 (1) Å	α = 116.08 (2)°	
b = 9.341 (2) Å	β = 96.10 (1)°	Z = 2
c = 8.524 (2) Å	γ = 92.58 (1)°	

Figure 3 gives a projection along [001] and the packing mode of the pyrimidine rings in which hydrogen-bonded pairs of thymine form stacks. These results have to be compared with the crystal structure of 1-methyl thymine[10]. The triethyleneoxyde chain is flexible enough for the pyrimidine bases

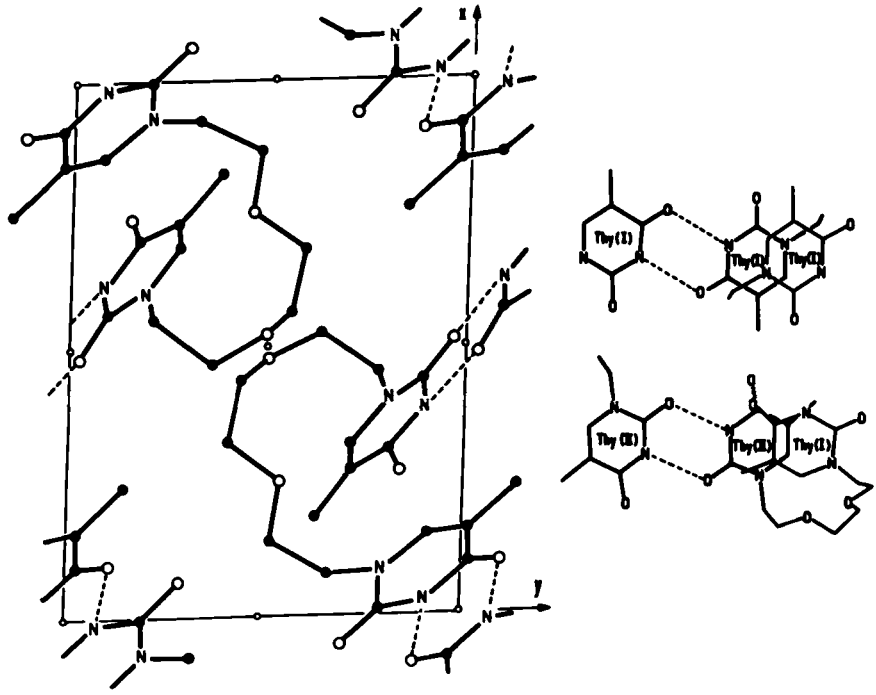

FIGURE 3. Projection along [001] and packing mode of thymine moieties.

to be linked by the classical double hydrogen bonds.

3. 1-(8-oxypsoralen)-8 (thym-1 yl)-3,6-dioxaoctane (III).

A solution of compound III in a mixture of benzene and dichloromethane gave by slow evaporation available crystals. The crystallographic data are :

Space group $P_{\bar{1}}$

$a = 14.414\ (4)$ Å $\quad \alpha = 121.02\ (2)^\circ$

$b = 10.340\ (3)$ Å $\quad \beta = 90.23\ (2)^\circ \quad Z = 2$

$c = 10.757\ (3)$ Å $\quad \gamma = 109.26\ (3)^\circ$

The [001] projection of the structure is given in figure 4

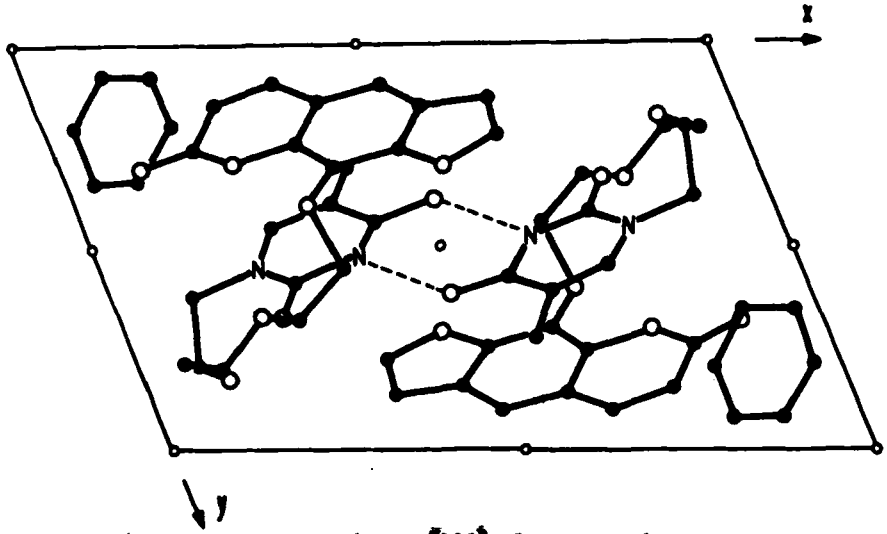

FIGURE 4. Projection along [001] of compound III.

The above crystal structures show that the polyoxyethylenic chain displays different conformations which are dependent on the nature of the end groups. As previously published by Dale[11], the chain may be described as a sequence of anti (a) and gauche ($g^{\pm}$) bounds. For compounds I, II and III the sequences of the chain are respectively $g^- g^- g^- a g^- a a g^+ a$, $g^- a a g^+ a g^+ a$ and $g^+ a a g^- a a a a$. This conformationnal behaviour in the crystal is mainly due to the chromophore packing mode and results from weak energy barriers in the C-O-C sequence between the different possible conformers, in opposition to polymethylenic chains[12]. Due to the flexibility of the polyoxyethylene link, the molecular packing of III might be analyzed as following : i) Formation of coplanar pairs of bases associated by strong hydrogen bonds. ii) Interaction and complexation of the psoralen ring with the pairs of bases.

The planes (figure 5) formed with the pyrimidine bases and the psoralen moiety are nearly parallel (angle$\simeq 3^{\circ}$); the distance (3,5 Å) between the double bonds of pyrone ring [3,4] and thymine is propitious for a topochemical photocycloaddition[13]. This specific overlapping between thymine pairs and psoralen is reminiscent to the description given by Dall' Acqua[14] for the cross linkage of DNA by psoralen (figure 6).

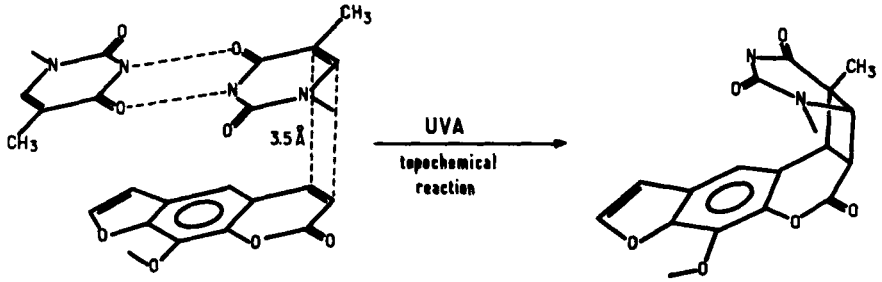

FIGURE 5. Molecular overlapping in crystals of III and photoreactivity.

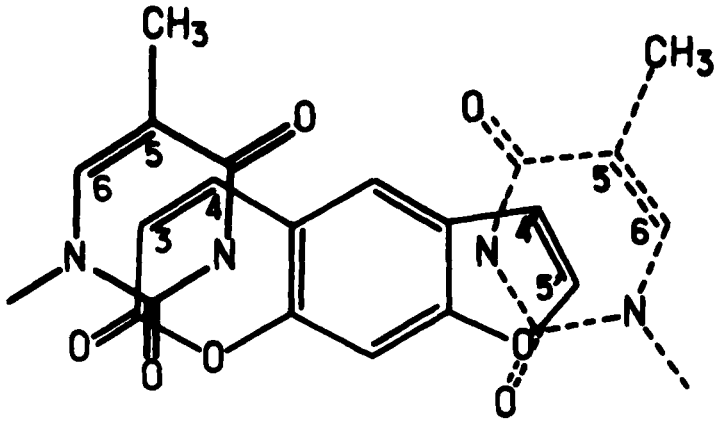

FIGURE 6. Model proposed by Dall'Acqua[11] for the intercalation of psoralen in DNA (cross linkage).

However a second interaction corresponding to the overlapping between thymine and furan ring is not observed in crystals of III. This interaction seems to be less favourable in the solid although some photoproducts have been recently isolated involving [4',5'] bond of psoralen and thymine[2,15].

The irradiation of monocrystals of compound III, under nitrogen atmosphere, with UV light $\geq$ 340nm (liquid filter : lead acetate 7g, sodium bromide 540g in water 1 liter) leads nearly quantitatively to a white amorphous photoproduct (m. p. $>$ 220°C) with the total destruction of the parent solid. The photoproduct insoluble in the usual organic solvents, was analyzed by IR and UV techniques on solid KBr pellets. The UV spectrum indicated a net decrease of the absorption band of the coumarin chromophore (400-320nm). In IR we observed the total disappearence of the strong ν c=c at 1580 cm^{-1} (in compound III) supporting the reactivity of the pyrone ring[16] and a new absorption at 1755 cm^{-1} ascribable to the saturation of the double bonds conjugated with the carbonyl groups[16]. These spectroscopic data indicate the formation of a cyclobutane ring between the double bonds of thymine and coumarin part of psoralen under UV light as expected from a topochemical reaction in crystals of III.

CONCLUSION

From a crystallographic study of compounds I, II and III, the triethyleneoxyde chain was found to display different conformations in the solid depending on the molecular packing of the chromophores linked at its ends. Moreover, the specific overlapping between psoralen and thymine pairs observed in crystals of III brings new informations about the geometry and the photoreactivity of the already postulated

dark complex between furocoumarins and DNA bases.

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