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INFLUENCE OF THE STEREOCHEMISTRY ON THE RATE OF CYCLIZATION OF CIS AND TRANS-O-HYDROXYARYL ALKENYL KETONES. MECHANISTIC IMPLICATIONS

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Abstract - Irradiation of the aryl trans-2-butenoates **4b-e** affords the corresponding photo-Fries products **1b-e**, together with their cis isomers **3b-e**. After separation by means of HPLC, the kinetics of the basic cyclization of the trans and cis-o-hydroxyketones **1b-e** and **3b-e** to the chromanones **2b-e** were studied. The mechanistic implications of the obtained data are discussed.

INTRODUCTION

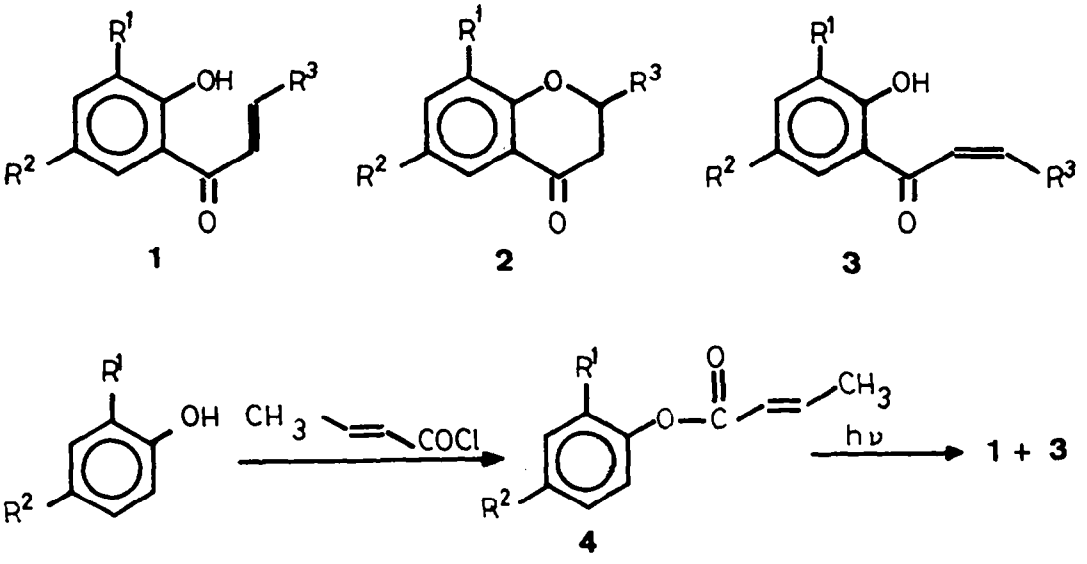
In the last decade, a great deal of theoretical and experimental work has been directed to gain a better understanding of ring forming reactions, since these processes are very common and important in organic chemistry[1].

Perhaps, one of the best known cyclization modes is the 6-Endo-Trig one, exemplified by the well-studied conversion of o-hydroxychalcones into flavanones (for instance, the conversion of **1a** into **2a**), which is enzymatically catalyzed in plants and appears to be involved in the biosynthesis of flavonoids[2-4].

We are currently interested in the stereoelectronic effects governing ring closure, and more specifically in the cyclizations related to the o-hydroxychalcone-flavanone transformation[5-6]. In this context, it appeared to us that the study of the influence of the stereochemistry of the double bond in the trans-and cis-o-hydroxyphenyl alkenyl ketones **1b-e** and **3b-e** on the rate of cyclization could be helpful in order to achieve a more precise and complete picture of this paradigmatic process. There is an obvious lack of information in the literature concerning this type of effect, probably because no general synthetic entry to cis-ketones such as **3** has been developed as yet. This prompted us to undertake the present investigations.

RESULTS AND DISCUSSION

The trans-and cis-o-hydroxyaryl alkenyl ketones **1b-e** and **3b-e** were expediently synthesized according to the scheme. In the first step, trans-2-butenoyl chloride was allowed to react with 4-methoxy-, 4-methyl-, 4-ethyl-, and 2,4-dimethylphenol in the presence of a base, affording the corresponding esters **4b-e**.[7-8].

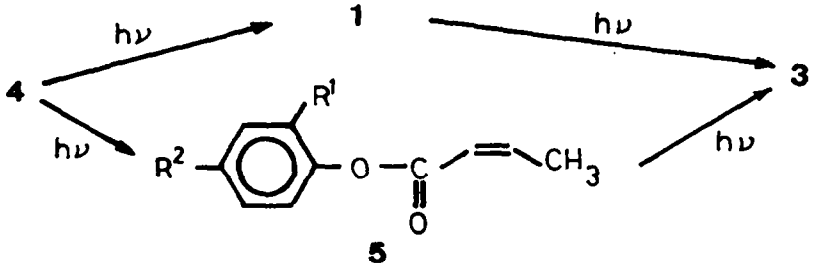


a $R^1 = R^2 = H$, $R^3 = Ph$; **b** $R^1 = H$, $R^2 = OCH_3$, $R^3 = CH_3$;

c $R^1 = H$, $R^2 = R^3 = CH_3$; **d** $R^1 = H$, $R^2 = CH_2\,CH_3$, $R^3 = CH_3$

e $R^1 = R^2 = R^2 = CH_3$

These compounds were subsequently submitted to the conditions of a photo-Fries rearrangement, giving mixtures of the desired products **1b-e**[9] and **3b-e**. The resolution of each photomixture was achieved by means of semipreparative HPLC. In all cases, the trans stereoisomers **1b-e** were the major isolated products. In principle, two alternative reaction pathways could account for the formation of the cis-ketones **3b-e** as minor products.



The first one might involve trans-cis photoisomerization of the starting butenoates **4b-e**, followed by photo-Fries rearrangement of the cis isomers **5b-e**. In connection with this possibility, it is worth mentioning that, in the course of studies dealing with the photochemical rearrangements of aryl cinnamates into o-hydroxychalcones, a partial trans-cis photoisomerization of the cinnamates has been observed, although this has not been accompanied by the isolation of the corresponding cis-chalcones.[10] The second pathway leading from **4b-e** to **3b-e** would involve a combination of the same two individual processes of the first pathway, but in the inverse sequence, i.e. the photorearrangement of the esters **4b-e** to the ketones **1b-e**, followed by trans-cis photoisomerization of these compounds. In this context, it must be said that the vast majority of o-hydroxyaryl ketones have a marked reluctance to undergo any photochemical reaction different from the termally reversible proton transfer from the phenolic to the ketonic oxygen, a process that usually provides a very efficient energy wasting channel.[11] Furthermore in the particular case of trans-o-hydroxychalcones, it has been reported that their irradiation results in a partial cyclization to the corresponding flavanones, instead of producing any degree of trans-cis photoisomerization.[12]

In view of these precedents, we decided to irradiate the trans-o-hydroxyaryl alkenyl ketone **1b**, in order to disclose whether it cyclizes to the chromanone **2b**, undergoes a trans-cis photoisomerization or is light stable. In fact, we found that the compound **1b** was easily photoisomerized under our reaction conditions to the corresponding cis-ketone **3b**. This evidence, together with the failure to detect any isomerization of the trans-butenoates during the photolysis, inclined us to consider the second pathway as most plausible to explain the formation of **3b**. Nonetheless, the first pathway cannot be completely ruled out on this basis.

The easy accessibility of the trans and cis-o-hydroxyaryl alkenyl ketones **1b-e** and **3b-e** allowed us to study their cyclization to the chromanones **2b-e**[9-13] under basic conditions. The system used was sodium acetate in dimethylsulfoxide for practical reasons. Preliminary experiments had shown that the weakly basic sodium acetate was able to induce a relatively slow cyclization of **1b-e** and **3b-e** at room temperature, so that the rate constants could be determined with the necessary accuracy. Other bases, like sodium hydroxide, tetraethylammonium hydroxide or potassium carbonate induced a cyclization process too fast to be conveniently monitored by means of the available techniques (data not given). On the other hand, the choice of the solvent was made taking into consideration the solubility of the substrates, as well as that of the base, in order to achieve in all cases an homogeneous system.

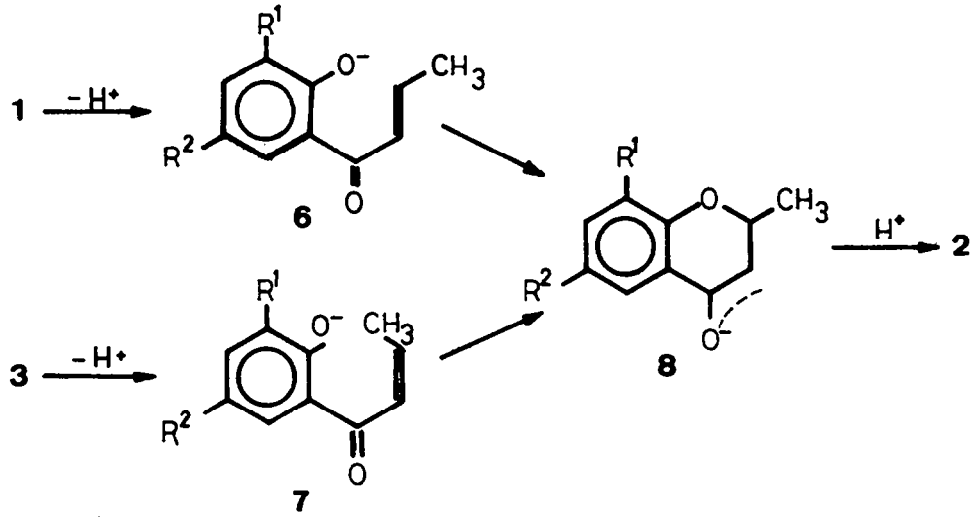
Under the above conditions, the trans and cis-ketones **1b-e** and **3b-e** were smoothly converted into the corresponding chromanones. The rate constants for these processes are given in the Table.

10^3 x Rate coefficients for the cyclizations of **1** and **3** (s^{-1})

	1	**3**
b	3.2	1.9
c	2.21	2.05
d	2.11	1.96
e	1.76	1.13

By analogy with the existing literature data concerning the related cyclizations of o-hydroxychalcones and o-hydroxyaryl alkynyl ketones, it could be

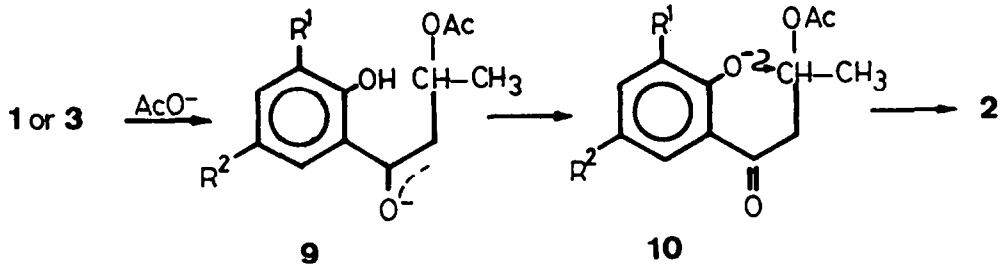
in principle assumed that the cyclizations studied here occur through intramolecular conjugate addition of the phenolate anions **6** and **7**, generated from the neutral substrates **1** and **3** by loss of a proton in the basic medium.



This would be supported by the fact that the attempted cyclizations of **1b-e** and **3b-e** under neutral or acidic conditions proceeded very slowly, so that no appreciable conversion was observed after several hours. On the other hand, the experimental rate constants should be nearly the same as those of the individual ring closure steps (process **6** or **7** ⟶ **8**), unless the reverse reaction (ring opening) would have a significant contribution in the kinetic equation. To check this possibility, we submitted pure samples of the chromanones **2b-e** to the conditions employed for the cyclization, observing that no detectable amounts of the ketones **1b-e** or **3b-e** were formed after several hours.

Hence, the values of the experimental rate constants given in the Table could serve as an indication of the facility of the ring closure process in each particular case. Unfortunately, the most noticeable aspect of our results is the small rate variatons for the different substrates, a fact that makes it difficult to detect a marked effect associated with a given structural feature or to establish clearcut trends. Nonetheless, it appears that the cyclization of the cis-o-hydroxyaryl alkenly ketones **3b-e** is slightly slower than that of their trans isomers **1b-e**, as it could be qualitatively expected according to the distortion of the bond angles and distances to achieve the approach trajectories required for 6-Endo-Trig attack, due to steric reasons.[1,14] Thus if one considers the average rate values within the trans and the cis series, the former are higher, although -it must be admitted- by a small factor. This effect is best observed in the case of the methoxy derivatives **1b** and **3b** and the dimethyl derivatives **1e** and **3e**, where the electron-donating ability of the substituents increases the nucleophilicity of the phenolic hydroxy group. In principle, we had expected more serious hindrance for the cyclization of the cis-o-hydroxyaryl alkenyl ketones **3b-e**. In our opinion, the above results suggest that a second mechanism involving conjugate addition of the acetate ion, followed by intramolecular nucleophilic

substitution may be also responsible for the formation of the chromanones **2**, competing with the direct cyclization of the phenolates **6** or **7**.



If such a view is taken, an increase in the contribution of the second mechanism would result in an approximation between the values of the rates of the trans and cis substrates. In connection with this idea, it is interesting that the treatment of o-hydroxyacrylophenone with acetic anhydride, in the presence of sodium acetate leads to 2',3-diacetoxypropiophenone, as a result of acetylation of the phenolic hydroxy group and subsequent conjugate addition of acetate ion.[15]

In summary, our results suggest that the basic cyclization of the trans and cis-o-hydroxyaryl alkenyl ketones **1b-e** and **3b-e** takes place via two competitive mechanisms: loss of a proton, followed by 6-Endo-Trig cyclization of the resulting phenolate anions **6** or **7** and/or conjugate addition of the base, followed by 6-Exo-Tet intramolecular nucleophilic substitution. The contribution of the first mechanism should be more important with the increasing nucleophilicity of the phenolate anions. while the reverse is true for the second mechanism. Finally, the 6-Endo-Trig process is clearly influenced by the stereochemistry of the double bond, being slower for a cis spatial arrangement, as it can be best observed in the case of the methoxy derivatives **1b** and **3b** and the dimethyl derivatives **1e** and **3e**.

EXPERIMENTAL

General. M.ps were determined with a Büchi 510 apparatus and are uncorrected. Ir spectra were obtained in CCl_4 solns with a Perkin-Elmer 781 spectrophotometer; ν_{max} (cm^{-1}) is given only for the main bands. ^{1}H-nmr spectra were measured in CCl_4 with a 60-MHz Varian 360 EM instrument; chemical shifts are reported in δ (ppm) values, using TMS as internal standard. The combustion analyses were performed at the Instituto de Química Bio-Organica of C.S.I.C. in Barcelona. Isolation and purification were done by flash column chromatography on silica gel Merck 60, 70-230 mesh, using hexane as eluent and a Waters isocratic HPLC equipment provided of a semipreparative microporasil column, using hexane-ethyl acetate as eluent.

Preparation of the aryl esters 4.
Compounds **4b** and **4c** were prepared as described.[7-8] For the preparation of **4d** and **4e** the following procedure was used: the phenol (9 g, 73.6 mmol) and pyridine (1 ml) were added to trans-butenoyl cloride (16 g, 153 mmol). The reaction mixture was refluxed for 3h. The cooled solution was then poured into a mixture of concentrated hydrocloric acid (10 ml) and ice (50 g). The products were extracted with dichloromethane and the extracts were washed with aqueous sodium hydroxide (10%) and water, dried and evaporated to leave an oil. The yields were 76% (for **4d**) and 84% (for **4e**).

Irradiations

General procedure. A soln of 1 g of the substrate in 400 ml of freshly distilled hexane was irradiated at r.t. with a 125 W medium pressure mercury lamp inside a quartz immersion well. The photoproducts were isolated, after removal of the solvent, with silica gel flash-column chromatography, using hexane as eluent, and subsequently by HPLC.
Irradiation of **4b**. The photoproducts isolated after 8 h were **1b** (300 mg, 30%) and **3b** (100 mg, 10%).
Irradiation of **4c**. The photoproducts isolated after 10 h were **1c** (280 mg, 28%) and **3c** (60 mg, 6%).
Irradiation of **4d**. The photoproducts isolated after 14 h were **1d** (270 mg, 27%) and **3d** (80 mg, 8%).
Irradiation of **4e**. The photoproducts isolated after 14 h were **1e** (250 mg, 25%) and **3e** (70 mg, 7%).
Irradiation of **1b**. After 3 h a mixture of **1b** (74%) and **3b** (26%).

Cyclizations

Kinetic methods. The kinetics of the reactions was studied with a Beckman 3600 spectrophotometer by following the change in absorbance with time at a wavelength of 275 nm. The general procedure was follows: to 3 ml of a ca 10^{-4} M solution of the o-hydroxyketone in dimethylsulphoxide, which had been equilibrated a 25°C, 0.2 ml of a saturated solution of sodium acetate in dimethylsulphoxide were added to initiate the reaction. Absorbance measurements were made until the reaction rate had diminished to less than 0.1% over a period of 10 min. At this stage, the corresponding chromanone was the only observable reaction product. All the compounds studied provided data which exhibited good pseudofirst-order kinetics. Rate constants were calculated using a least-squares computer program, the accuracy of the experimental points being estimated for the correlation coefficient and the t-Student test.

Preparative cyclization. A solution of the o-hydroxyaryl ketone (200 mg) in hexane (100 ml) together with aqueous sodium hydroxide (10%, 25 cm^3) was stirred at r.t. for 5 h. The organic layer was washed with water, dried, and evaporated to give the pure chromanone. Yields were nearly quantitative in all cases.

Spectral and analytical data of the new compounds.

Trans-4-ethylphenyl 2-butenoate **4d.** Oil; analysis: C 74.91 H 7.56% (Calcd. for $C_{12}H_{14}O_2$: C 75.56 H 7.41%); ir : 1745 (C = O); ^{1}H-nmr : 7.50 - 6.90 (m, 5H, ArH, =CHCH$_2$), 6.05 (d, J=14 Hz, COCH=), 2.68 (q, 2H, CH_2CH_3), 1.95 (d, J=8 Hz, 3H, =CHCH$_3$), 1.23 (t, 3H, CH_2CH_3).

Trans-2,4-dimethylphenyl 2 - butenoate **4e.** Oil; analysis: C 75.46 H 7.57% (Calcd. for $C_{12}H_{14}O_2$: C 75.76 H 7.41%); ir : 1740 (C = O); ^{1}H-nmr : 7.40 - 6.95 (m, 4H, ArH, =CH-CH$_3$), 6.05 (d, J=16 Hz, 1H, COCH=), 2.30 (s, 3H, ArCH$_3$), 2.15 (S, 3H, Ar-CH$_3$), 1.93 (d, J=7 Hz, 3H, =CH-CH$_3$)

Cis-1-(2-hydroxy-5-methoxyphenyl)-2-buten-1-one **3b.** Oil; analysis : C 68.34 H 6.41% (Calcd. for $C_{11}H_{12}O_3$: C 68.74 H 6.29%); ir : 1650 (C = O); ^{1}H-nmr : 11.97 (s, 1H, OH), 7.17 - 6.70 (m, 5H, ArH, CH=CH), 3.73 (s, 3H, OCH$_3$), 2.20 (d, J=6 Hz, 3H, CH$_3$).

Trans-1-(2-hydroxy-5-methoxyphenyl)-2-buten-1-one **1b.** M.p 48°C; analysis : C 68.95 H 6.49% (Calcd. for $C_{11}H_{12}O_3$: C 68.74 H 6.29%), ir : 1650 (C = O); ^{1}H-nmr : 12.50 (s, 1H, OH), 7.25 - 6.80 (m, 5H, ArH, CH=CH), 3.80 (s, 3H, OCH$_3$), 1.97 (d, J=6 Hz, 3H, CH$_3$).

Cis-1-(2-hydroxy-5-methylphenyl)-2 buten-1-one **3c.** Oil; analysis : C 74.64 H 6.58% (Calcd. for $C_{11}H_{12}O_2$: C 74.97 H 6.86%); ir : 1650 (C = O); ^{1}H-nmr : 12.43 (s, 1H, OH), 7.60 (br s, 1H, 6-ArH), 6.23 - 7.50 (m, 3H, 3,4-ArH, =CHCH$_3$), 6.06 (d, J=12 Hz, 1H, COCH=), 2.30 (d, J=3 Hz, 3H, =CHCH$_3$), 2.13 (s, 3H, ArCH$_3$).

Cis-1-(2-hydroxy-5-ethylphenyl)-2-buten-1-one **3d.** Oil; analysis : C 76.01 H 7.47% (Calcd. for $C_{12}H_{14}O_2$: C 75.76 H 7.41%); ir : 1645 (C = O); ^{1}H-nmr : 12.37 (s, 1H, OH), 7.5 (br s, 1H, 6-ArH), 7.37 - 6.2 (m, 4H, 3,4-ArH, HC=CH), 2.60 (q, 2H, CH_2CH_3), 2.15 (d, J=6 Hz, 3H, CH$_3$) 1.20 (t, 3H, CH_2CH_3).

Trans-1-(2-hydroxy-5-ethylphenyl)-2-buten-1-one **1d.** Oil; analysis : C 75.61 H 7.63% (Calcd. for $C_{12}H_{14}O_2$: C 75.76 H 7.41%); ir : 1650 (C = O); ^{1}H-nmr : 12.30 (s, 1H, OH), 7.43 (br s, 1H, 6-ArH), 7.33 - 6.70 (m, 4H, 3,4-ArH, CH=CH), 2.80 - 2.30 (m, 2H, CH_2CH_3), 2.00 (d, J=5 Hz, 3H, CH$_3$), 1.20 (t, 3H, CH_2CH_3).

Cis-1-(2-hydroxy-3,5-dimethylphenyl)-2-buten-1-one **3e.** Oil; analysis : C 75.33 H 7.48% (Calcd. for $C_{12}H_{14}O_2$: C 75.76 H : 7,41%); ir : 1660 (C = O); ^{1}H-nmr : 12.7 (s, 1H, OH), 7.43 (br s, 1H, 6-ArH), 7.23 (br s, 1H, 4-ArH), 7.00 - 6.45 (m, 2H, HC=CH), 2.25 (d, J=4 Hz, 3H, =CH-CH$_3$), 2,17 (s, 6H, 3,5-ArCH$_3$)

Trans-1-(2-hydroxy-3,5-dimethylphenyl)-2-buten-1-one **1e.** M.p 43-44°C; analysis : C 75.69 H 7.45% (Calcd. for $C_{12}H_{14}O_2$: C 75.76 H 7.41%); ir : 1655 (C = O); ^{1}H-nmr : 12.56 (s, 1H, OH), 7.27 (br s, 1H, 6-ArH), 6.96 (m, 3H, 4-ArH, CH=CH), 2.23 and 2.17 (2s, 6H, 3,5-ArCH$_3$), 2.00 (d, J=5 Hz, 3H, =CHCH$_3$).

6-Ethyl-3-methyl-4-chromanone **2d.** Oil; analysis : C 75.78 H 7.57% (Calcd. for $C_{12}H_{14}O_2$: C 75.76 H 7.41%); ir : 1695 (C = O); ^{1}H-nmr : 7.70 (d, J=2 Hz, 1H, 5-ArH) 7.30 (dd, J_1=8 Hz, J_2=2 Hz, 1H, 7-ArH), 6.80 (d, J=8 Hz, 1H, 8-ArH), 4.50 (m, 1H, CH), 2.60 (m, 4H, CH_2CH_3, COCH$_2$) 1.45 (d, J=6 Hz, 3H, CHCH$_3$), 1.20 (t, 3H, CH_2CH_3).

REFERENCES

1. For an important work concerning the rules that govern ring closure processes see J.E. Baldwin, J. Chem. Soc., Chem. Comm. 1976, 734. This paper has received several hundreds of citations since the date of publication.
2. J.E. Baldwin, R.C. Thomas, L.I. Kruse and L. Silberman, J. Org. Chem., 1977, 42, 3847.
3. K.B. Old and L. Main, J. Chem. Soc. Perkin Trans. II, 1982, 1309.
4. A. Grouiller, P. Thomassery and H. Pacheco, Bull. Soc. Chim. France, 1973, 3448.
5. H. Garcia, S. Iborra, J. Primo and M.A. Miranda, J. Org. Chem., 1986, 51, 4432.
6. J. Primo, R. Tormo and M.A. Miranda, Heterocycles, 1982, 19, 1819.
7. Reference for compound **4b**: A.B. Sen, S.S. Parmar, J. Indian Chem. Soc., 1951, 28, 661.
8. Reference for compound **4c**: J. Colonge, R. Chambard, Bull. Soc. Chim. France, 1953, 573.
9. The methyl substituted derivative had been previously described (Ref. 2).
10. H. Garcia, S. Iborra, M.A. Miranda and J. Primo, Heterocycles, 1985, 23, 1983 and references therein.
11. W. Kloepffer, Adv. Photochem., 1977, 10, 311.
12. R. Matsushima and I. Hirao, Bull. Chem. Soc. Japan, 1980, 53, 518.
13. Reference for compounds **2b** and **2e**: O. Dann, G. Volz and O. Huber, Liebigs Ann. Chem., 1954, 587, 16.
14. J.E. Baldwin, J. Chem. Soc., Chem. Comm., 1976, 739.
15. J.A. Donelly and D.E. Maloney, Tetrahedron, 1979, 35, 2883.