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TOPOCHEMICAL PHOTOREACTIONS OF AROMATIC RETINOIDS ✝

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Abstract - The aromatic retinoid 1a exists in three crystal modifications. The centric α-1a yields the centrosymmetric photocycloadduct 2, whereas the γ-modification of 1a does not react photochemically. Deviations from this commonly accepted pattern are the occurrence of a second centric modification α_1-1a instead of the usual β-type and of two different photocycloadducts 3 and 4 derived therefrom in a ratio of 5 : 1. This ratio results from the probability of the excited molecule to react with its neighbours which are shifted against each other in the crystal lattice. Substitution of the ethyl ester group in 1a by a diethylamide (1d) leads to E/Z-isomerization only, though the shortest distance of 3.66 Å between two molecules is suitable for a [2+2]-photocycloaddition across the centre of symmetry. The packing diagrams of α-1a, α_1-1a, and of 1d as well as the structures of 1a, 1d, and 2 have been determined by X-ray analyses, whereas the structures of 3, 4, and 5 could be deduced from ^{1}H- and ^{13}C-NMR data including homo- and heteronuclear 2D and interproton Overhauser experiments.

INTRODUCTION

The aromatic retinoid 1a is a drug against the serious skin disease psoriasis[1]. Its generic name is etretinate and it crystallizes from ethanol without incorporating the solvent. Dispersed on a glass plate α_1-1a was exposed to daylight but not to direct solar radiation. Nevertheless, the former transparent yellow crystals became quickly opaque and additional signals appeared in the ^{1}H-NMR spectrum of 1a. This caused us to study the evidently photochemical transformation of crystalline α_1-1a and the photochemical behaviour of other crystal modifications and crystalline derivatives of 1a.

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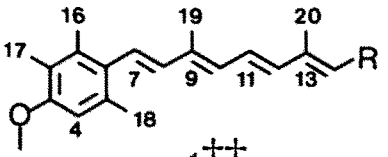

1†† 1a R = COOEt
1b R = CONHEt
1c R = COOH
1d R = CON(Et)$_2$

Figure 1. Substrates which were irradiated in the solid state.

POLYMORPHISM OF ETRETINATE

Beside the highest melting α_1-modification mentioned above we prepared two additional crystal modifications of etretinate (1a) using different solvents and crystallization temperatures (see exp. part). The corresponding ^{1}H-NMR spectra and elementary analyses showed that the orignal molecule 1a remained unchanged and that also no solvents were incorporated into the resulting α- and γ-modifications.

Table 1. Characterization of the crystal modifications of etretinate*

Properties	α-1a	α_1-1a	γ-1a
m.p.	90.7°C	105.6°C	79.1°C
packing	centric (Fig.3)	centric (Fig.6)	unknown
photoreactivity	1 cycloadduct	2 cycloadducts	no reaction

*No single crystals suitable for a X-ray analysis could be obtained from γ-1a. Therefore, we prepared X-ray powder diagrams of each modification to confirm the existence of three different crystal modifications of 1a.

PHOTOREACTIONS

An aqueous suspension of crystals of α-1a, α_1-1a, and γ-1a was circulated rapidly along the light source and irradiated with visible light. Though we did not use a strong light source but only a 150 W mercury high pressure lamp combined with a liquid cut-off filter α-1a and α_1-1a reacted surprisingly fast: 1.5 g α-1a were almost totally transformed after 1 hour and 5.0 g α_1-1a after 5 hours. The modification α-1a yielded one crystalline product (2) and α_1-1a an amorphous mixture of 2 products (3 and 4). In contrast to α-1a and α_1-1a the corresponding γ-modification did not react photochemically, even when we extended the wavelengths of the radiation to the uv (λ>300 nm) and the irradiation time to 12 hours. Above 528 nm α_1-1a did not react by direct irradiation nor upon photolysis in the presence of rose bengal which was dissolved in the water of the suspension. Rose bengal was chosen because it sensitizes [4+2]-photocycloadditions of 1a in ethanolic solution[2].

††The numbering of the C-atoms does not follow IUPAC rules but was chosen in analogy to the corresponding retinoic acid.

Motretinide is the generic name of an additional aromatic retinoid which is used against the skin disease acne[1]. Motretinide 1b reacted photochemically as little as the free acid 1c. Both compounds are slightly soluble in water and absorb at shorter wavelengths than α-1a and α_1-1a. Therefore, 1b and 1c were suspended in t-butyl methyl ether and irradiated with light $\lambda > 300$ nm. As one reason for the different photochemical behaviour of crystalline 1b and 1c compared with α-1a and α_1-1a we suppose a drastic change of their crystal lattices by possible hydrogen bridges (Fig.2).

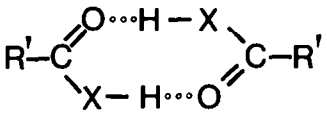

Figure 2.
Possible hydrogen bridges

To check our hypothesis we prepared the diethyl amide 1d which is not able to form hydrogen bridges. Indeed, crystalline 1d reacted photochemically but instead of the expected [2+2]-dimerization E/Z-isomerization took place.

RESULTS

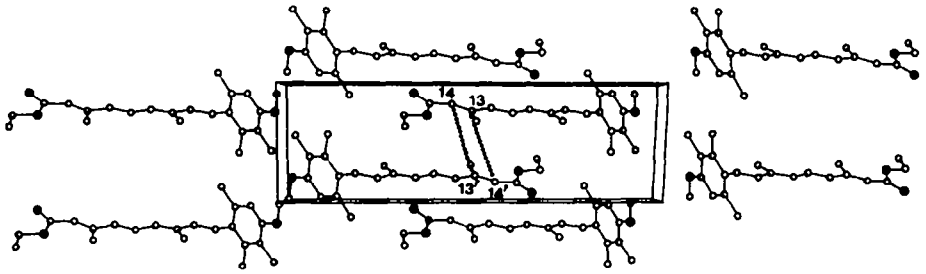

Figure 3. Packing diagram of α-1a. Crystal data[3]: Triclinic, $P\bar{1}$, a = 6.440(5), b = 7.316(7), c = 22.568(23) Å, α = 89.59(8), β = 93.98(7), γ = 107.94(7)°, Z=2. Distances of the reacting centres: C(13),C(14') = C(14),C(13') = 3.66, C(13),C(13') = 3.87 Å, R = 0.0540. View along the a axis.

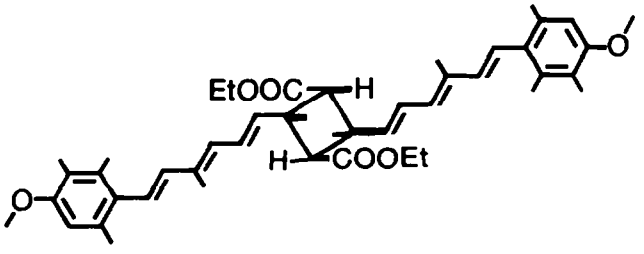

Figure 4. Structure of the [2+2]-cycloadduct 2 photochemically derived from α-1a. Crystal data[3]: Triclinic $P\bar{1}$, a = 8.411(2), b = 8.742(2), c = 27.259(6) Å, α = 94.862(3), β = 94.212(3), γ = 89.911(3)°, Z=2, R = 0.0650.

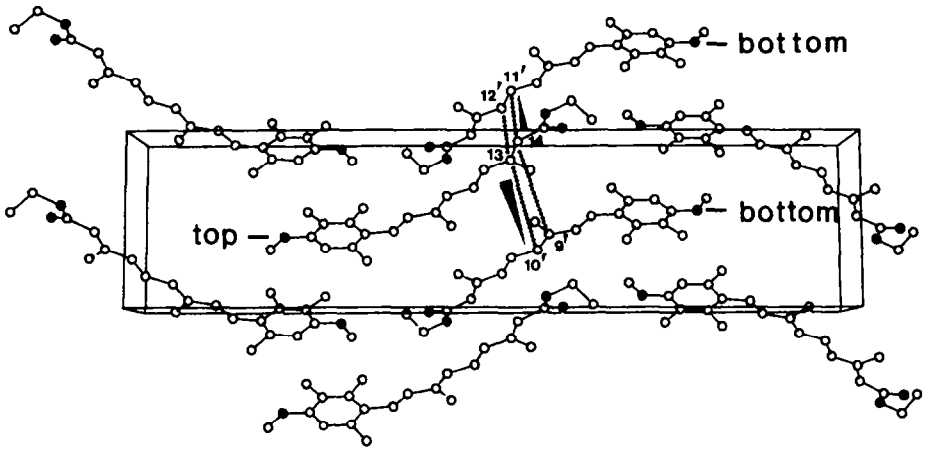

Figure 5. Packing diagram of α_1-1a. Crystal data[3]: Monoclinic, $P2_1/c$, a = 6.302(5), b = 36.985(15), c = 8.944(9) Å, β = 90.88(7)°, Z=4, R = 0.0630. View along the a axis.

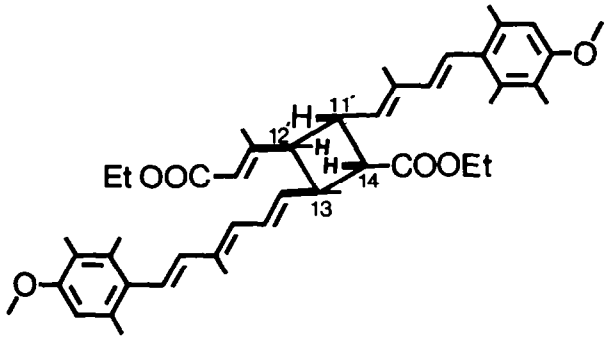

Figure 6. Structure of the [2+2]-cycloadduct 3 derived photochemically from α_1-1a. Distances of the reacting centres (arrow upward in Fig.5): C(13),C(12') = 3.829, C(14),C(11') = 3.816, C(12'),C(14) = 3.583 Å.

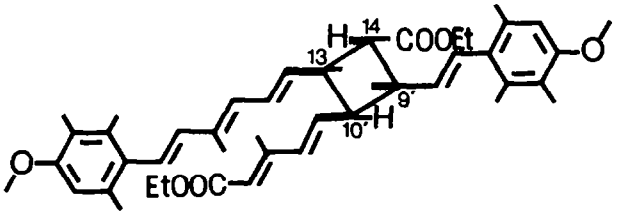

Figure 7. Structure of the [2+2]-cycloadduct 4, also derived photochemically from α_1-1a. Distances of the reacting centres (arrow downward in Fig.5): C(13),C10') = 4.319, C(14),C(9') = 4.464, C(13),C(9') = 4.046 Å.

Corresponding to the distances between the reacting centres in α_1-1a the photoproducts 3 and 4 (Fig.6 resp. Fig.7) are formed in a ratio of about 5:1. The stereochemistry on the four-membered ring of 2 was elucidated from a X-ray analysis of 2. The structures of 3 and 4 were deduced from ^{1}H- and ^{13}C-NMR data, especially from the results of Nuclear Overhauser Experiments (NOE) which are presented in Tab.3 and 4. The steric arrangement on the cyclobutane rings and the (E)-configuration of the double bonds is shown in Fig.6 and 7, whereas the formation of 3 and 4 on the basis of packing effects in the crystal is indicated by dotted lines in Fig.5 and will be discussed below.

Table 2. Relevant Nuclear Overhauser Effects of 3 (in %, 400 MHz, $CDCl_3$)

	irradiation of								Conclusions:
observed NOE at	Me 19	Me 20	H 14	H 14'	Me 20'	H 12'	H 11'	Me 19'	cis:
H-7	~8								Me20 /H-12'
H-11	~8	3.8	2.7						H-11'/H-14
H-12		1.1	1.9	8.3	~1.7		2.3		H-11'/H-14'
Me20						0.7			H-10'/H-12'
H-14		~0.6					5.9	1.3	
H-14'						1.6	10.2	1.6	trans:
Me20'		1.8				1.1			
H-12'		7.8	0	4.7	3.8			0.8	
H-11'			2.3					4.2	Me20/H-14
H-10'						3.8			H-14/H-12'
Me19'							1.3		
H-7'								6.3	

Table 3. Relevant Nuclear Overhauser Effects of 4 (in %, 400 MHz, $CDCl_3$)

	irradiation of										Conclusions:
observed NOE at	Me 16	Me 18	Me 19	Me 20	H 14	Me 20'	H 10'	Me 19'	Me 18'	Me 16'	cis:
H-4		6.7									Me20 /H-10'
H-7	<0	~5.4	~7.5								Me19'/H-14
H-8	<0	~4.7									Me19'/H-8'
H-11			~8.9	~3.6	7.4						Me19'/H-11'
H-12				3.6	2.7			~2.2			
H-14				1.3				7.4			trans:
H-12' } H-11' }						7.4	3	6±3			
H-10'				7.1				1.3			Me20 /H-14
H-8'				3.6			3	4.9	~3	~3	Me19'/H-10'
H-7'							5.4	4.9	~2.5	~3	
H-4'									7.8		

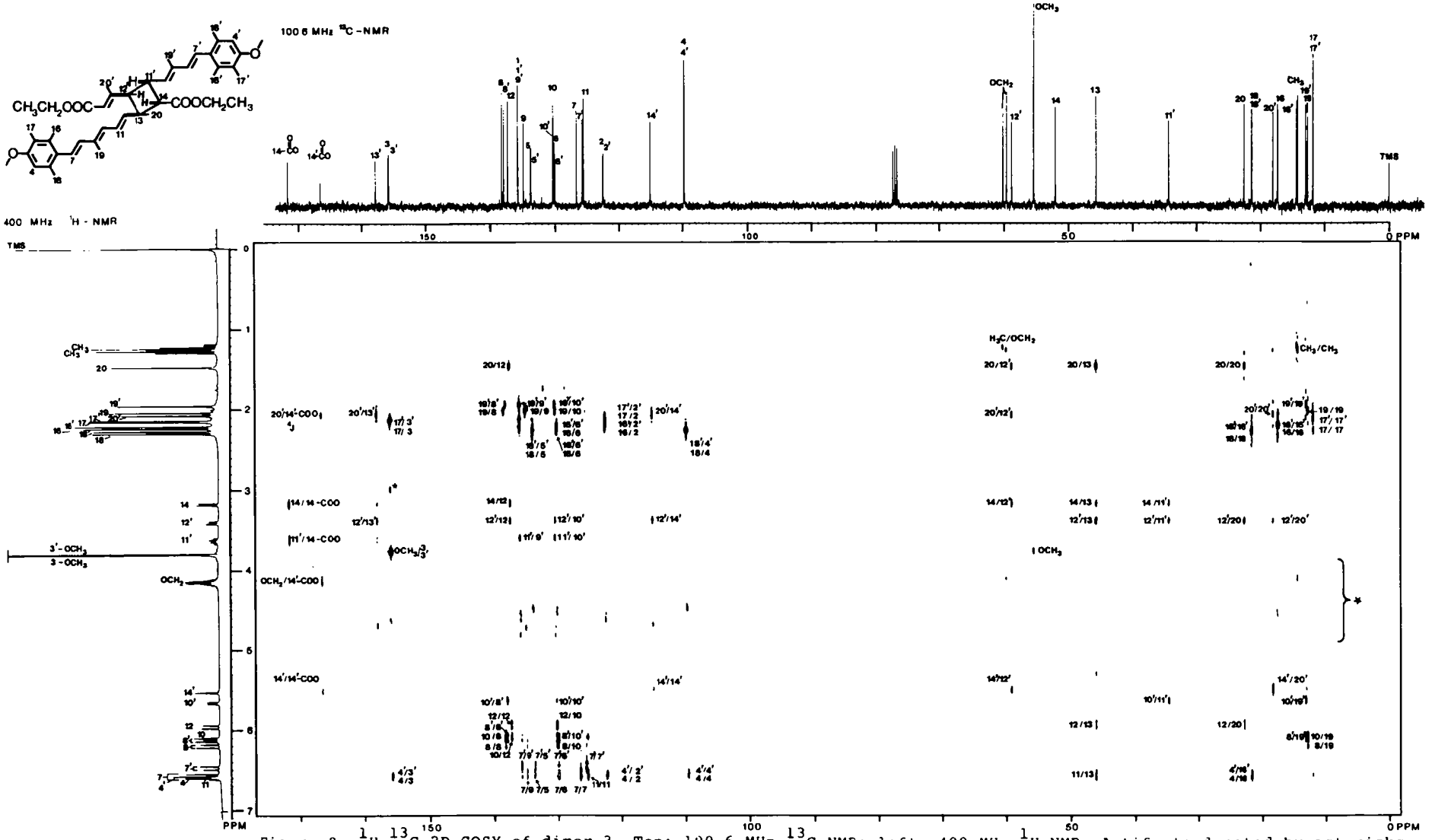

Figure 8. $^{1}H,^{13}C$ 2D COSY of dimer 3. Top: 100.6 MHz ^{13}C-NMR; left: 400 MHz ^{1}H-NMR. Artifacts denoted by asterisks.

The conclusions drawn from spectroscopic data strongly rely on the correctness of the spectral assignments. By application of two-dimensional chemical shift correlation experiments (2D COSY) the ^{1}H- and ^{13}C-NMR spectra of 2, 3, and 4 could readily be assigned. At first the homonuclear proton 2D COSY experiments were performed in normal and in delayed COSY versions with additional delays of 0.1 to 0.15 sec in order to enhance cross peaks caused by long-range proton couplings. Thus, relatively strong cross peaks between protons separated by up to 7 intervening bonds became detectable. Normally the corresponding very small couplings are not measurable, even in very highly resolved 1D spectra. However, they provide relevant information which considerably simplifies the assignments of the proton signals in related structural subunits of the photodimers. For example, the aromatic protons 4 and 4' showed cross peaks with their neighbouring methoxy protons as well as with the methyl protons in ortho and para position, i.e. with 18-Me, 16-Me and 18'-Me, 16'-Me, respectively ($^{4}J_{H,H}$ and ^{6}J). In general, the connectivity to the protons of 17-Me and 17'-Me (^{5}J) was too weak to be observed. However, 17-Me protons of a given phenyl could be linked to 16-Me (^{5}J) and/or to 18-Me (^{7}J) from the corresponding cross peaks. 16-Me and 18-Me protons were also linked by cross peaks to H-C(7) (^{5}J) and H-C(7) to H-C(8) (^{3}J). The protons of 19-Me were connected with H-C(8), H-C(10), and H-C(12) (^{6}J) and so forth. In this way the signals of the two subunits of the dimers were readily assigned, though in many cases the differnces between the chemical shifts of corresponding protons were rather small.

In a similar manner heteronuclear $^{1}H,^{13}C$ 2D COSY experiments were performed to assign the ^{13}C-signals unumbiguously. In a first step the polarization transfer delays were tuned to one band couplings (protonated C-atoms) and in a second experiment to long-range $^{n}J_{C,H}$-couplings (mainly n=2 and 3). The latter performance is especially useful since protons and C-atoms within a distance of two and three bonds can be identified from corresponding cross peaks in the 2D plot. From this we obtained information on the different overlapping structural elements and an unequivocal assignment of the signals due to the unprotonated C-atoms.

In order to demonstrate the great value of long-range $^{1}H,^{13}C$-COSY experiments we present in Fig.8. the results obtained for dimer 3. For convenience, the assigned ^{1}H-spectrum (left) and the ^{13}C-spectrum (top) are shown together with the 2D contour plot. In addition to connectivities caused by two and three bond $J_{C,H}$-couplings a few one bond connectivities are shown which were already known from the first experiment. Finally, as an exception from the general rule one four bond connectivity (20'-Me/14'-CO) could be detected. Furthermore, indicated by asterisks some artifacts with intensities less than a few percent of the main cross peaks can be seen as mirror images of very strong peaks symmetrically displaced with respect to the centre of the proton range.

A wealth of structural information is deduced from the 2D plot by entering on a horizontal line which starts from a given proton or by entering on a vertical line which starts from a given carbon signal. Thus, H-C(14) is linked to the attached 14-carboxyl, to 12-C, 12'-C, 13-C, and 11'-C by two and three bond connectivities. 13-C is linked to H-C(20), H-C(14), H-C(12'), H-C(12), and H-C(11) defining the position of the cyclobutane ring. In this way, complete structures can be derived in a straight-forward manner. The complete assignments of all signals are presented in the experimental part.

By preparing the diethyl amide 1d we tried to avoid hydrogen bridges (Fig.2) which we expected to prevent a [2+2]-photocycloaddition in solid motretinide 1b. Single crystals to check the packing of solid 1d could be obtained only by crystallizing 1d from water containing ethyl acetate. Unfortunately, in this way by incorporating 0.5 mol water, hydrogen bridges were created again. Because of the clearness of their representation in Fig.9 only hydrogen bridges directed towards the adjacent carbonyl are marked by dotted lines which start from the oxygen atoms of the water.

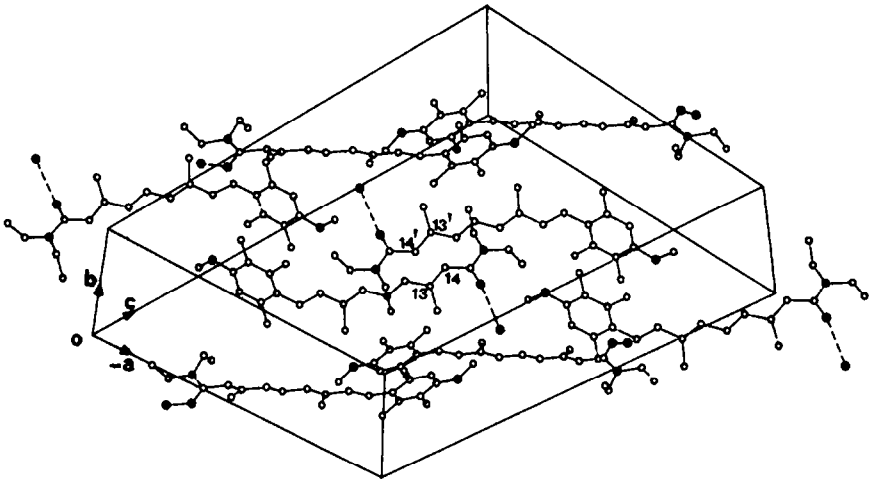

Figure 9. Packing diagram of 1d · 0.5 H_2O. Crystal data[3]: Monoclinic I2/a; a = 20.958(6), b = 7.782(2), c = 28.041(7) Å, β = 99.62(2)°, Z=8, R = 0.0547.

Whereas the monoethyl amide 1b and the free acid 1c did not react, irradiation with visible light caused a transformation of the crystalline diethyl amide 1d · 0.5 H_2O. In contrast to the etretinate modifications α-1a and α_1-1a the result was not a [2+2]-cycloaddition but a E/Z-isomerization yielding in a first step the 13-cis isomer, which then reacts further (Fig.9). This photochemical isomerization was accompanied by a complete destruction of the original crystal lattice.

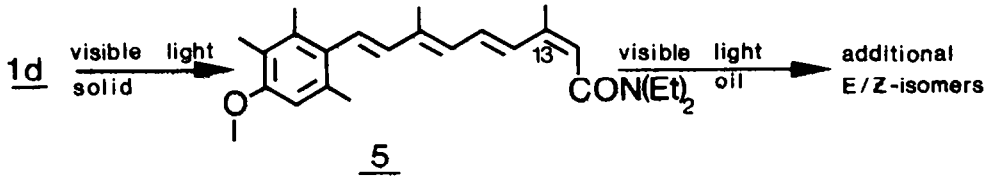

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Figure 10. Photochemical E/Z-isomerization of 1d 0.5 H_2O

The photochemical behaviour of the oily mixture consisting of all-trans 1d and of the corresponding 13-cis isomer 5 equals that of etretinate 1a in solution. After prolonged irradiation of dissolved 1a most of the possible mono-, di-, and tri-cis isomers could be isolated and characterized by means of NMR-data[4].

DISCUSSION

From the photochemical behaviour of crystalline cinnamic acids and other olefinic compounds[5] the following pattern of topochemical photocycloadditions is commonly accepted (Tab.4).

Table 4. Connection between crystal geometry and photochemical behaviour

packing type	nearest-neighbour relation	distance of the double bonds [Å]	[2+2]-photo-cycloadduct
α	centre of symmetry	3.4 - 4.1	centrosymmetric
β	translation	3.9 - 4.2	mirror symmetry
γ	translation	4.7 - 5.1	none

Results according to the usual pattern: The topochemical photoreaction of α-1a reported here, is in accordance with the well known reactions in the centric α-type packing. The distance between the reacting double bonds is about 3.66 Å and the photocycloaddition proceeds across the centre of symmetry (Fig.3) yielding the centrosymmetric dimer 2. Also in accordance with the results of earlier studies[6,7], the crystalline substrate α-1a is transformed into a product-crystal quite similar to the starting crystal. The α-modification of 1a is triclinic, $P\bar{1}$ as well as the photoproduct resulting therefrom.

Deviations from the usual pattern: Examples of the formation of two different [2+2]-photocycloadducts from one and the same crystal modification are rare in the literature. 4-Chlorocoumarin (4-cc) shows such a behaviour. In α_1-1a as in 4-cc the molecules are packed according to the β-type packing and in both cases a distance between the reactive centres appears which is well above the accepted limit (4.46 Å resp. 4.47 Å). Because the reactive double bonds in 4-cc exhibit no π overlap and because the consumption of 25% needs an irradiation time of 200 hours the reactivity of 4-cc is thought to be non-topochemical in nature but due to defects in the crystal[8]. In contrast α_1-1a exhibits considerable π overlap (see arrows in Fig.5) and 81% were consumed within 5 hours irradiation. Therefore, we believe the photodimerizations in α_1-1a to be topochemical reactions.

Though the packing type of α_1-1a is centric, the photodimerizations do not proceed across a centre of symmetry. The reacting double bonds are shifted against each other. Compared with α-1a (Fig.3) the reacting double bond of one chain is moved out of C(13'),C(14') to C(11'),C(12') yielding the photoproduct 3 and secondly to C(9'),C(10') giving photoproduct 4. The reason for this displacement of reacting double bonds within one chain is the fact that the translation in the lattice does not proceed parallel to the side chains of the etretinate molecules but inclines at an angle of about 45°.

Mechanistic considerations: Dissolved in the liquid where α_1-1a was suspended a triplet sensitizer was not able to cause cyclodimerization in the crystals. This could be due to inefficiency in energy transfer in a heterogenous system as well as to the fact that these dimerizations proceed via a singlet state. Analogous to the formation of one photodimer from α-1a the simultaneous appearence of two [2+2]-photocycloadducts from one and the same crystal modification (α_1-1a) can be rationalized in terms of an activation which is concentrated on a C(13),C(14) double bond (e.g. on the top of Fig.5). In α_1-1a this activated double bond has the possibility to react with double bonds of adjacent molecules over different distances: Attack of the C(12'),C(11') double bond over a distance of 3.83 A is demonstrated in Fig.5 by an upward arrow and attack of the C(10'),C(11') double bond over a distance of 4.46 Å by a downward arrow. The ratio of 5 : 1 of the resulting dimers 3 (shorter distance) and of 4 (longer distance) reflects the probability of each reaction.

Not only distances between functional groups are important for the understanding of topochemical reactions but also π-interactions[9,10]. In α_1-1a one would expect that C(13),C(14) would react with C(14'),C(13') across the centre of symmetry, where the distance of 3.79 Å is smaller than in direction of C(12'),C(11'). But this is not the case. In addition to the postulated π overlap of the reacting double bonds one has to consider that in 1a the C,C-conjugation is elongated by the ester carbonyl. This might be helpful to create a light-induced activation of the C(13),C(14) double bond which then attacks a suitable double bond of an adjacent ground state molecule, even over different distances as in α_1-1a. The preferred 13-cis isomerization of 1a in solution fits in with that general picture.

E/Z-Isomerization in crystalline 1d: Fig.9 shows a packing diagram of the α-type with a distance of C(13),C(14) to C(14'),C(13') of 3.66 Å favourable for a photochemical [2+2]-cycloaddition across the centre of symmetry. Nevertheless, in solid 1d we only obtained 13-cis isomerization. We are aware of the fact that substitution of the ethyl ester in 1a by a diethyl amide (1d) increases the excitation energy. The hydrogen bridges between the incorporated water molecules and the amide carbonyls exhibit the same effect. As a result of these effects the excitation state of solid 1d presumably differs in its multiplicity from those of the crystal modifications of the ester 1a. This would mean that in topochemical reactions beside distances of the reacting centres and beside π-interactions also the excitation state may determine the reaction mode.

Finally it has to be mentioned that E/Z-isomerizations in the solid state are known for a long time. But in contrast to our centrosymmetric example 1d they predominantly occur from the β-packing type[11].

Acknowledgements - The authors are indebted to Prof. V. Ramamurthy for helpful discussions. Valuable assistence with spectra by Dr. M. Grosjean, Mr. A. Bubendorf (IR), and Mr. W. Meister (MS) is gratefully acknowleged. We also thank Mr. F. Wild for the differential scanning calorimetric measurements as well as Mr. A. Ritter and Mr. St. Doppler for their skillful performance of the experiments.

EXPERIMENTAL PART

General remarks: M.ps. of the three crystal modifications of 1a were determined in a closed aluminum capsule using a TA 2000B Mettler differential scanning calorimeter. All other m.ps. were measured on a Büchi SMP-20 in open capillaries and are uncorrected. IR-spectra (KBr) in cm^{-1} were recorded on a Nicolet FT/IR 7199 and mass spectra on a MS 9 from AEI, Manchester, updated with a ZAB console+ data system 3000. Only significant signals in m/z are given (relative intensity in per cent referring to the basis signal = 100 %). NMR-spectra in $CDCl_3$, δ in ppm relative to TMS (= 0 ppm) as internal standard. Coupling constants ^3J in Hz. ^{1}H-NMR spectra at 400 MHz and ^{13}C-NMR spectra at 100.6 MHz were recorded on a WM-400 Bruker Spectrospin FT-NMR spectrometer combined with an ASPECT 3000 computer with 320K memory.
The assignment of the ^{1}H-NMR signals of 2, 3, and 4 was supported by 2D COSY, by decoupling, and by 1D NOE. The ^{13}C-NMR signals were assigned by heteronuclear 2D COSY experiments. Every 2D spectrum was acquired in the absolute value mode with acquisition times in the range of 1 hour to about 48 hours. Standard microprograms of the Bruker Software Library were used.
For the ^{1}H,^{13}C COSY of Fig.8 the following acquisition parameters were applied. F_2: Time domain 4K, acquisition time 0.13 sec, sweepwidth 18 512 Hz, digital resolution 9.0 Hz/pt. F_1: Time domain 200, zero-filling to 512 points, sweepwidth 2 958 Hz, time increment 207 μsec, digital resolution 5.8 Hz/pt. The delays were 2 (relaxation), 0.06 and 0.038 sec (polarization transfer); 384 scans and 4 dummy scans were acquired. The acquisition times of one bond ^{1}H,^{13}C 2D experiments with correspondingly stronger cross peaks could be reduced by 75%.

General procedure of irradiation: Irradiations were performed at 15-20°C using a 150 W high pressure mercury lamp (TQ 150 from Heraeus, Hanau, FRG.) placed into a double-walled pyrex immersion well which contained the liquid cut-off filter. The filter solution was circulated by a pump through an external heat-exchanger and the immersion well was fitted in a pyrex reaction vessel equipped with condensor, Argon inlet tube, and on the bottom with a centrifugal pump which pressed the crystal suspension upward through a bypass, in this way causing its circulation along the lamp. Filter A (0.5 cm) eliminated all light below 395 nm and consisted of 24.5 g $CuSO_4 \cdot 5H_2O$, 5.3 g $Fe_2(SO_4)_3 \cdot 5H_2O$, 1.8 g $FeSO_4 \cdot 1\text{-}2H_2O$, 38.5 ml conc. H_2SO_4 and 1015 ml distilled H_2O. Filter B (0.5 cm) eliminated all light below 528 nm and consisted of 624 g $FeCl_3\ 6H_2O$ and 240 ml 25% HCl, filled up with distilled water to give 1800 ml filter solution.

Preparation of the crystal modifications of 1a:
Modification α-1a: 3 g 1a were dissolved in 300 ml boiling t-butyl methyl ether. The stirred solution was slowly cooled down to -40°C, then 480 ml MeOH were added dropwise. When the solution became slightly opaque the stirring was stopped and the mixture kept over night at this temperature. Yield 1.4 g (46.7%) α-1a. M.p. 90.5°C when the heating was started at 70°C and proceeded with 2°C per minute. M.p. 91.0°C when the heating was started at 50°C and proceeded with 5°C per minute.
Modification α_1-1a: 20 g 1a were dissolved in 300 ml boiling t-butyl methyl ether. The solution was slowly cooled down to -40°C and a first fraction of α_1-1a filtered off. After adding 200 ml MeOH the cooling was continued to reach -65°C. Standing over night at that temperature a total yield of 17.7 g (88.6%) α_1-1a was obtained. M.p. 104.9°C when the heating was started at 60°C and proceeded with 2°C per minute. M.p. 106.6°C when the heating was started at 60°C and proceeded with 5°C per minute.
Modification γ-1a: 3 g 1a were dissolved in 300 ml boiling 2-propanone. The stirred solution was slowly cooled down to -60°C. After 70 ml MeOH had been added dropwise the solution became opaque and was allowed to stand for two hours at that temperature. Yield 2.33 g (77.7%) γ-1a. M.p. 78.4°C when the heating was started at 60°C and proceeded with 2°C per minute. M.p. 79.8°C when the heating was started at 60°C and proceeded with 5°C per minute.

Preparation of a substrate which was not available for our experiments:
All-trans-N,N-diethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide 1d · 0.5 H_2O. To a solution of 20 g 1c in 250 ml benzene 0.6 ml PCl_3 (60 mmol) were added. The resulting mixture was stirred for 1.5 hours at 30°C. After evaporation of the solvent the residue was dissolved in 200 ml ether. Then this etheral acid chloride solution was added dropwise to a chilled (5°C) solution of 18 ml diethylamine in 200 ml ether and stirred for 2 hours. Evaporation of the solvent and dissolution of the residue in 150 ml ethyl acetate (with a water content of about 2%). Separation of the precipitated $NH(Et)_2$ HCl and the not consumed 1c by filtration over silica gel gave a solution from which the diethylamide crystallized by chilling. Yield 16.4 g (69.9%) 1d·0.5 H_2O, m.p. 103-104°C. Exact mass M=390.57 (calc. for $C_{25}H_{35}NO_2$ 0.5 H_2O). For ^{13}C-NMR data see G. Englert[13]. Confirmation of the structure by X-ray analysis (for crystal data see Fig.9).

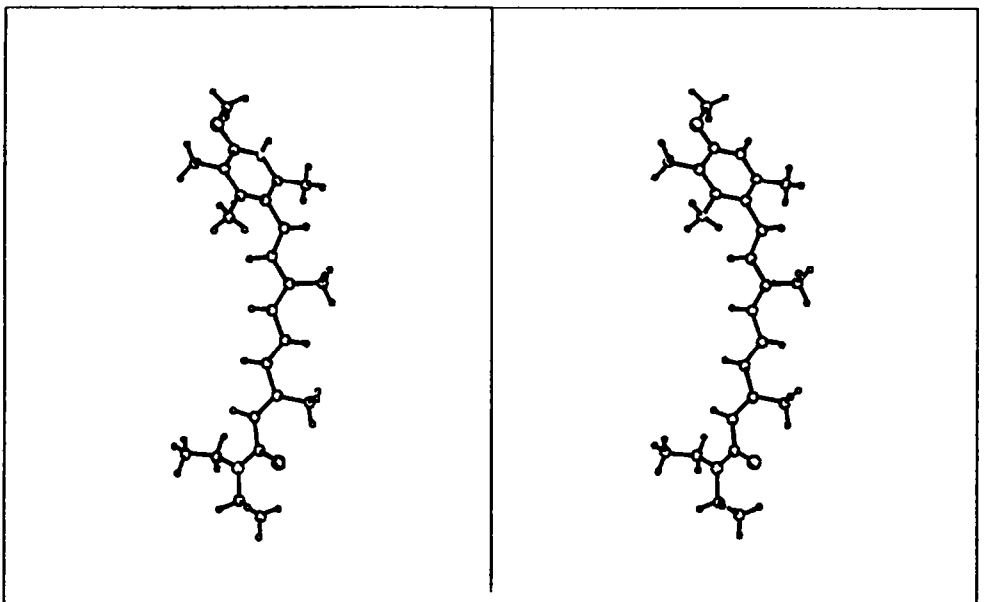

Figure 11. Stereoprojection of 1d (water molecule omitted).

Photoreactions:
Diethyl-2β,4α-bis[(all-E)-6-(4-methoxy-2,3,6-trimethyl)-4-methyl-1,3,5-hexatrienyl]-2,4-dimethyl-1α,3β-cyclobutane dicarboxylate 2. A suspension of 1.5 g (4.2 mmol) α-1a in 220 ml H_2O was irradiated for 1 hour using filter A. Consumption of α-1a: 93.3%. Recrystallization of dimer 2 from ether, m.p. 118°C. IR 1726, 1686, 1594, 1181, 1168, 1122, 976. MS 708 (8, M^+), 355 (11), 354 (39), 339 (14), 281 (41), 251 (16), 203 (61), 163 (100), 150 (64), 131 (14),91 (13). Exact mass M=708.98 (calc. for $C_{46}H_{60}O_6$). ^{1}H-NMR δ 1.292 (t, J=7.2, $2CH_2\underline{CH_3}$), 1.463 (s, 20- and 20'-Me), 2.046 (s, 19- and 19'-Me), 2.169 (s, 17- and 17'-Me), 2.247 (s, 16- and 16'-Me), 2.305 (s, 18- and 18'-Me), 3.346 (s, H-C(14) and H-C(14')), 3.629 (s, 2MeO), 4.180 (qa, $2\underline{CH_2}CH_3$), 6.106 (d, J=11.2, H-C(10) and H-C(10')), 6.162 (d, J=16, H-C(8) and H-C(8')), 6.204 (d, J=15, H-C(12) and H-C(12')), 6.513 (dd, J_1=15.5, J_2=11.3, H-C(11) and H-C(11')), 6.536 (d, J=16, H-C(7) and H-C(7')), 6.593 (s, H-C(4) and H-C(4')). ^{13}C-NMR δ 11.83 (qa, 17/17'-Me), 12.72 (qa, 19/19'-Me), 14.43 (qa, $2CH_2\underline{CH_3}$), 17.38 (qa, 16/16'-Me), 21.37 (qa, 18/18'-Me), 24.87 (qa, 20/20'-Me), 42.30 (s, 13/13'-C), 55.42 (qa, 2MeO), 56.53 (d, 14/14'-C), 60.01 (t, $2\underline{CH_2}CH_3$), 109.85 (d, 4/4'-C), 122.53 (s, 2/2'-C), 124.93 (d, 11/11'-C), 126.31 (d, 7/7'-C), 130.22 (s, 6/6'-C), 130.61 (d, 10/10'-C), 134.47 (s, 9/9'-C), 135.79 (s, 1/1'-C), 138.50 (d, 12/12'-C), 139.85 (d, 8/8'-C),155.92 (s, 3/3'-C), 170.43 (s, 2carbonyl-C on 14/14'-C). Confirmation of the structure of 2 by X-ray analysis (for crystal data see Fig.4).

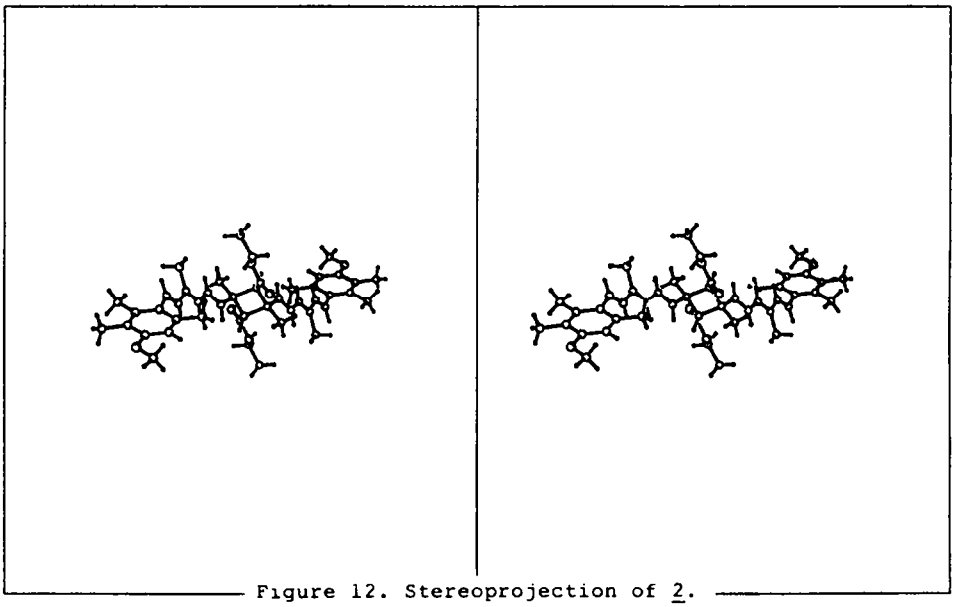

Figure 12. Stereoprojection of 2.

Ethyl (E)-3α-(ethoxycarbonyl)-2α-[(all-E)-4-(4-methoxy-2,3,6-trimethylphenyl)-2-methyl-1,3-butadienyl]-4β-[(all-E)-6-(4-methoxy-2,3,6-trimethylphenyl)-4-methyl-1,2,5-hexatrienyl]-α-methyl-1β-cyclobutane acrylate 3
and
Ethyl 5-[3α-(ethoxycarbonyl)]-2α-[(E)-4-methoxy-1,2,6-trimethylstyryl]-4β-[(all-E)-6-(4-methoxy-2,3,6-trimethylphenyl)-4-methyl-1,3,5-hexatrienyl]-2,4-dimethyl-1β-cyclobutyl]-3-methyl-2,4-pentadienoate 4.

A suspension of 5 g (14.1 mmol) α_1-1a in 230 ml H_2O was irradiated for 5 hours using filter A. Consumption of α_1-1a: 81%.

Dimer 3: Recrystallized from petrol ether 2.75 g (67.9%), m.p. 131°C. IR 1715, 1642, 1593, 1155, 1121, 972. MS 708 (10,M^+), 545 (6), 403 (5), 355 (8), 354 (16), 339 (5), 281 (15), 229 (8), 204 (12), 203 (54), 163 (100), 150 (38), 131 (5), 29 (10). Exact mass 708.98 (calc. for $C_{46}H_{60}O_6$). ^{1}H-NMR δ 1.239 and 1.272 (2t, J= 7, $2CH_2\underline{CH_3}$), 1.476 (s,20-Me), 1.953 (s,19-Me), 2.039 (s,19-Me), 2.074 (s, 20'-Me), 2.136 (s,17'-Me), 2.150 (s,17-Me), 2.207 (s,16'-Me), 2.234 (s,16-Me), 2.268 (s,18'-Me), 2.296 (s,18-Me), 3.178 (d, J=9, 14-H), 3.409 d, J=11, 12'-H), 3.629 (m,11'-H), 3.789 (s,3'-MeO), 3.800 (s,3-MeO), 4.142 (m, $2\underline{CH_2}CH_3$) 5.517 (s,14'-H), 5.651 (d, J=7.7, 10'-H), 5.952 (d, J=15.2, 12-H), 6.105 (d, J=10, 10-H), 6.114 (d, J=16.5, 8'-H), 6.193 (d, J=16.1, 8-H), 6.466 (d, J=16.4, 7'-H), 6.565 (d, J=16.5, 7-H), 6.573 and 6.594 (2s, aromat.4'-H,4-H), 6.580 (dd,-J_1=15, J_2=12, 11-H). ^{13}C-NMR δ 11.84 (2qa,17/17'-Me), 12.76 (qa,19-Me), 13.05 (qa,19'-Me), 14.32 and 14.47 (2qa, $2CH_2\underline{CH_3}$), 17.36 and 17.41 (16- and 16'-Me), 18.12 (qa,20'-Me), 21.35 (qa,18'-Me), 21.40 (qa,18-Me), 22.68 (qa,20-Me), 34.44 (d, 11'-C), 45.78 (s,13-C), 52.02 (d,14-C), 55.45 (2qa, 2MeO), 58.84 (d,12'-C), 59.61 and 60.17 (2t, $2\underline{CH_2}CH_3$), 109.84 and 109.86 (2d,4- and 4'-C), 115.22 (d, 14'-C), 122.49 and 122.56 (2s,2- and 2'-C), 125.64 (d,11-C), 125.84 (d,7'-C), 126.74 (d,7-C), 130.03 and 130.13 (2s,6- and 6'-C), 130.31 and 130.36 (2d,10- and 10'-C), 133.70 and 133.78 (2s,5- and 5'-C), 134.98 and 135.77 (2s,9- and 9'-C), 135.83 (2s,1- and 1'-C), 137.37 (d,12-C), 138.00 (d,8'-C), 138.31 (d,8-C), 155.87 and 155.96 (2s,3- and 3'-C), 157.91 (s,13'-C), 166.56 (s, carbonyl-C on 14'-C), 171.77 (s, carbonyl-C on 14-C). NOE see Table 3.

Dimer 4: Recrystallized from petrol ether 0.49 g (12.1%), m.p. 128°C. IR 1730, 1707, 1610, 1593, 1160, 1119, 976. MS 708 (12,M^+), 545 (10), 355 (16), 354 (32), 339 (5), 281 (20), 204 (16), 203 (76), 163 (100), 150 (52). Exact mass 708.98 (calc. for $C_{46}H_{60}O_6$). ^{1}H-NMR δ 1.255 and 1.277 (2t, J=7, $2CH_2\underline{CH_3}$), 1.374 (s,19'-Me), 1.406 (s,20-Me), 2.044 (s,19-Me), 2.138 (s,17'-Me), 2.150 (s,17-Me), 2.199 (s,16'-Me), 2.236 (s,16-Me), 2.256 (s,18'-Me), 2.297 (s,18-Me), 2.319 (s,20'-Me), 3.183 (d, J=8.9, 10'-H), 3.284 (s,14-H), 3.792 (s,3'-MeO), 3.802 (s,3-MeO), 4.153 and 4.169 (2qa, $2\underline{CH_2}CH_3$), 5.751 (s,14'-H), 5.899 (d, J=15.2, 12-H), 6.045 (d, J=16.5, 8'-H), 6.109 (d, J=10.6, 10-H), ~6.176 (d, J=16, 12'-H), 6.206 (d, J=16.5, 8-H), ~6.22 (dd, 11'-H), 6.280 (d, J=16.4, 7'-H), 6.549 (dd,-J_1=15, J_2=11), 6.565 (d, J=16.5, 7-H), 6.574 and 6.597 (2s, aromat.4'-H,4-H). ^{13}C-NMR δ 11.81 and 11.85 (2qa, 17/17'-Me), 12.76 (qa,19-Me), 14.18 (qa,20'-Me), 14.34 and 14.42 (2qa, $2CH_2\underline{CH_3}$), 17.24 and 17.42 (2qa, 16'- and 16-Me), 21.18 and 21.39 (2qa, 18'- and 18-C), 25.16 (qa,20-C), 25.31 (qa,19'-C), 43.44 (s,9'-C), 43.94 (s,13-C), 55.53 (2qa, 2MeO), 55.64 (d,14-C), 57.22 (d,10'-C), 59.69 and 59.96 (2t, $2\underline{CH_2}CH_3$), 109.87 and 109.99 (2d,4'- and 4-C), 118.86 (d,14'-C), 122.47 and 122.67 (2s,2'- and 2-C), 125.48 (d,11-C), 126.39 and 126.67 (2d,7'- and 7-C), 130.15 and 130.28 (2s,6'- and6-C), 130.32 (d,10-C), 133.63 (d+s, 11'- and 5'-C), 133.83 (s,5-C), 134.72 (s,9-C), 135.77 and 135.89 (2s,1'- and 1-C), 136.33 (d, 12'-C), 138.42 (d,8-C), 140.65 (d,12-C), 140.79 (d,8'-C), 151.75 (s,13'-C), 155.97 and 156.07 (2s,3'- and 3-C), 167.09 (s, carbonyl-C on 14'-C), 171.39 (s,carbonyl-C on 14-C). NOE see Table 4.

Photosensitation experiment: 2 g (5.6 mmol) α_1-1a suspended in a solution of 50 mg rose bengal in 230 ml H_2O were irradiated for 8 hours using filter B. No reaction occurred.

Photoisomerization:
(2Z,4E,6E,8E)-N,N-diethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide 5.

A suspension of 2 g 1d 0.5 H_2O in 250 ml H_2O was irradiated for 6 hours using filter A. Consumption of 1d 0.5 H_2O: 67%. The product was a mixture consisting of four components, mainly of 5 but also of further mono- and di-cis isomers. Reduction of the irradiation time to 0.5 hours and flash-chromatography (silica gel, dichloromethane-ethyl acetate = 1:1) yielded after recrystallization from hexane 55 mg (2.75%)5,m.p. 121.5°C. IR 1615, 1590, 1567, 1265, 1217, 1025, 968. MS 381 (58,M^+), 281 (75), 232 (44), 218 (58), 201 (40), 186 (38), 171 (30), 163 (94), 153 (48), 150 (42), 141 (21), 126 (100), 115 (18), 100 (99), 91 (35), 72 (46), 69 (19), 43 (20), 41 (24), 29 (30). Exact mass 381.56 (calc. for $C_{25}H_{35}NO_2$).

^{1}H-NMR δ 1.145 and 1.166 (2t, J=6.5, $2CH_2\underline{CH_3}$), 2.037 (d, J=6, 20-Me), 2.068 (s, 19-Me), 2.174 (s,17-Me), 2.227 (s,16-Me), 2.287 (s,18-Me), 3.340 and 3.440 (2qa, J=6.5, $2\underline{CH_2}CH_3$), 3.806 (s,MeO), 5.879 (s,14-H), 6.223 (d, J=16.3, 8-H), 6.228 (d, J ~11, 10-H), 6.594 (s,4-H), 6.614 (d, J ~16, 7-H), 6.820 (dd, J_1=15, J_2=11, 11-H), 7.132 (d, J=15.3, 12-H). ^{13}C-NMR δ 11.90 (qa,17-Me), 12.89 (qa,19-Me), 13.25 and 14.43 (2qa, $2CH_2\underline{CH_3}$), 17.48 (qa,16-Me), 20.42 (qa,20-Me), 21.46 (qa, 18-Me), 39.67 and 42.67 (2t, $2\underline{CH_2}CH_3$), 55.59 (qa,MeO), 110.06 (d,4-C), 120.97 (d,14-C), 122.76 (s,2-C), 127.47 (d,7-C), 129.22 (d,11-C), 130.13 (s,6-C), 130.79 (d,12-C), 131.38 (d,10-C), 133.96 (s,5-C), 135.99 (s,1-C), 137.60 (s,9-C), 138.55 (d,8-C), 142.68 (s,13-C), 156.16 (s,3-C), 167.11 (s,carbonyl-C).

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