Novel Photosensitizers for the *E*/*Z*-Isomerization of Trienes.[1] Part 1. Syntheses and Application

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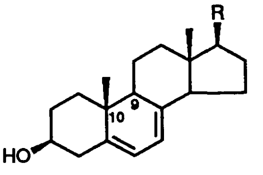
Uranine and its thioxanthene and selenoxanthene analogues, as well as the disodium salts of *o*-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)benzenesulphonic acid and its thioxanthene and selenoxanthene analogues, show different photosensitizer properties in the *E*/*Z*-isomerization of trienes. This has been verified by applying them to the technically useful conversion of tachysterol into previtamin D. The syntheses of the novel photosensitizers with thioxanthene and selenoxanthene moieties are also described.

The preparation of vitamin D_3 (**4**) implies a photochemical step, in which the 9,10 bond of provitamin D_3 (**1**) is cleaved by irradiation with appropriate UV light to give the *Z*-triene previtamin D_3 (**2**).[2] With increasing consumption of **1** the photochemically formed **2** competes with **1** in the light absorption. Hereby, **2** is photoisomerized in part into the *E*-triene tachysterol$_3$ (**3**).[2] Before the thermal transformation of **2** into **4**, the by-product **3** is usually separated from the reaction mixture, *e.g.* as a Diels–Alder adduct with maleic anhydride.[3] Since the appearance of **3** lowers the yield of **2** considerably (and hence of the vitamin) in technical processes the irradiation of **1** with light of $\lambda < 300$ nm is stopped at conversion rates $<50\%$ of **1**. The formation of **3** certainly does not then exceed 15% (Fig. 1).



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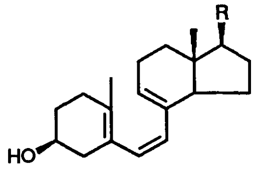

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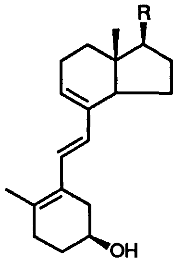

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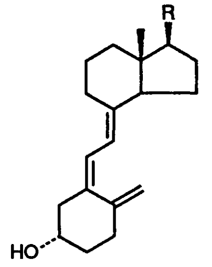

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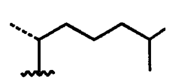

According to Snoeren *et al.*[4] irradiation of tachysterol trimethylsilyl ether in the presence of fluoren-9-one with light $\lambda > 370$ nm gave a mixture of the corresponding trimethylsilyl ethers of **2** and **3** in the ratio 8:2. Eyley and Williams[3] then irradiated **1** up to 75% conversion. They then added fluoren-9-one to the reaction mixture, which was irradiated again. Incorporation of this second irradiation step into the reaction sequence provided a general method for increasing the yield of **2**, though it is not feasible for a manufacturing process, because the sensitizer can only be eliminated by column chromatography.

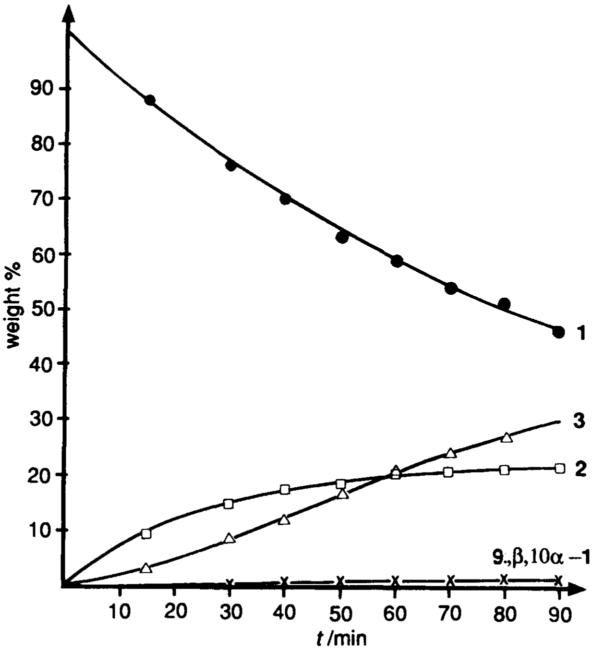

Fig. 1 Irradiation of **1** using a lamp mainly emitting light at $\lambda = 254$ nm

Results and Discussion

With disodium salts,* which were derived from compounds represented by the general formulae **5** and **6**, we now introduce a new type of sensitizer for the photochemical *E*/*Z*-isomerization of **3**. To our knowledge this is the first time that such compounds have been used as sensitizers for the photochemical *E*/*Z*-isomerization of trienes. The structures **5a**, **b** and **6a** are known, whereas **5c** and **6b**, **c** are new, and the essential features of their syntheses will be given below. In the following discussion the disodium salts of the benzoic acids corresponding to lactone **5** and of the benzene sulphonic acids **6** will be distinguished from the latter by the subscript 1, *e.g.* $\mathbf{5a}_1$–$\mathbf{c}_1$ and $\mathbf{6a}_1$–$\mathbf{c}_1$.

Rose Bengal and eosine disodium salt also photosensitize the partial isomerization of **3** into **2**, but for a manufacturing process they are economically unsuitable because of their inferior efficiency and high molecular weights, 1017.65 and 691.88, respectively. Thus, the successful progress in our preliminary experiments with $\mathbf{5a}_1$–$\mathbf{c}_1$ and $\mathbf{6a}_1$–$\mathbf{c}_1$ prompted us to

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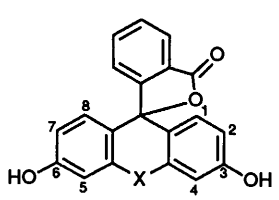
* Since the Li and K salts were considerably less effective, only the Na salts were taken into account.



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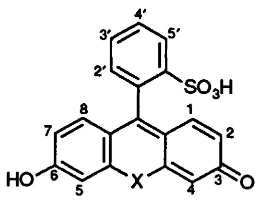

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5a, **6a** X = O
5b, **6b** X = S
5c, **6c** X = Se

Table 1 Photosensitized (*E*/*Z*)-isomerization of **3** into **2**

Sensitizer	λ_{max}/nm[a]	ε dm^3 mol^{-1} cm^{-1} [a]	*t*/h	Conversion of **3** (%)[b]
5a$_1$[c]	490.3	74 630	5	64.7
5b$_1$	511.9	48 760	1.17	89.7
5c$_1$	522.6	65 650	0.66	87.0
6a$_1$[c]	495.8	80 350	3	44.0
6b$_1$	519.3	60 440	0.75	92.4
6c$_1$	528.8	68 360	0.50	88.0

[a] In 0.1 mol dm^{-3} NaOH. [b] Determined by HPLC. [c] Continuously added because of the rapid light-induced formation of a red precipitate.

prepare **2** by double irradiations on a relatively large scale; *i.e.* to start in each case the first irradiation step with **1** (225 g) dissolved in *tert*-butyl methyl ether (TBME) (4.5 dm^3). Using a high power low-pressure mercury lamp (see the Experimental) the photoreaction of the first irradiation step proceeded as shown in Fig. 1. Since our strong low-pressure mercury lamp emits not only light of 254 nm (92%) but also 302 nm (1%) and 313 nm (7%), a small amount of 9β,10α-**1**, known as lumisterol$_3$, was also formed by the latter. Therefore, an irradiation of 55 min under the conditions mentioned above yielded a reaction mixture consisting of 60.5% **1**, 20.0% **2**, 18.4% **3** and 1.1% 9β,10α-**1**.

After conversion of 39.5% of **1** the solution was pumped into another photoreactor, equipped with a 2 kW medium-pressure mercury lamp and a liquid cut-off filter for the elimination of light at $\lambda < 400$ nm.[5] The disodium salt of the respective sensitizer derived from **5** or **6** dissolved in methanol, was then added and the second irradiation was performed. In Table 1 the increase of the desired **2** is expressed as a percentage of the converted **3**, whereas the irradiation time given defines the time required to reach the photostationary state. More impressive is the increase in **2** when it is related to consumed **1**, expressed as a percentage. One can then recognize that the 50.6% of **2** resulting from the first irradiation step is enhanced to 93.7% of **2** by using the most effective sensitizer (**6b$_1$**) in the second irradiation. Similar results were observed with 1α,25-dihydroxy analogues of **1**–**4**.

In contrast with 9-fluorenone[3] the photosensitizers **5a$_1$**–**c$_1$** and **6a$_1$**–**c$_1$** can be separated from the reaction mixture by extraction. Since they are insoluble in TBME, their solubility is firstly reduced by extraction of the reaction solution with water, which together with part of the corresponding sensitizer removes most of the MeOH from the TBME–MeOH mixture. This enables the complete separation of the photosensitizer by a second extraction with dilute aqueous NaOH. After removal of the dried TBME the **1** remaining was separated from the residue by precipitation with MeOH. Thermal isomerization of **2** into **4** up to a ratio of 15:85, crystallization of **4** from methyl formate at −20 °C, and repeated thermal isomerization of the remaining **2** confirmed the increase of **2** compared with its yield in the first irradiation step. This was particularly significant when not only the weight of the crystalline fractions of **4** was considered but also the HPLC analysis of the last mother liquor with respect to its content of **2** and **4**.

The synthesis of the known **5b**[6] as well as the synthesis of the novel **6b**[7] starts with the preparation of 3-iodoanisole (**8**) from *m*-anisidine (**7**) *via* its diazonium chloride and with the separate preparation of the 3-methoxythiophenol sodium salt (**10**) by reaction of EtONa with the corresponding thiophenol (**9**). Heating **8** with **10** and powdery copper gave 1,1′-thiobis(3-methoxybenzene) (**11**).[6] The key intermediate *m*,*m*′-thiodiphenol (**12**) was obtained from **11** by ether cleavage with HI in AcOH. Melting **12** with phthalic anhydride in the presence of zinc chloride yielded **6b** (path *a*), whereas an analogous procedure with 2-sulphobenzoic acid cyclic anhydride and toluene-4-sulphonic acid instead of zinc(II) chloride led to **6b** (path *b*, Scheme 1).

For the syntheses of the novel compounds **5c**[7] and **6c**[7] a similar route was used, which differed from the former by the mode of preparation of **15**, the seleno analogue to **10**. Melting KCN with selenium powder gave KSeCN[8] which reacted with the diazonium chloride derived from **7** to yield **13**.[9] On heating **13** with NaOH the diselenide **14** was formed.[10] The reaction of Marciano and Passerini[11] was then modified in order to prepare **15** by reduction of **14** in 1,4-dioxane–EtOH with NaBH$_4$ in the presence of excess NaOH (Scheme 2).

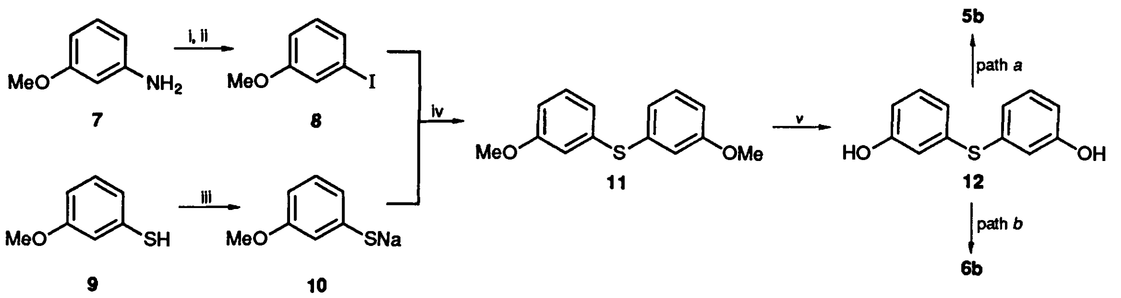
Thermal reaction of **8** with **15** in the presence of powdery copper yielded **16**,[6] the seleno analogue of **11**, from which the key intermediate **17** corresponding to **12** (Scheme 1) was obtained by subsequent ether cleavage. When a mixture consisting of **17**, phthalic anhydride, and trifluoromethanesulphonic acid was heated, the benzoic acid **5c** was formed. Thermal reaction of **17** with 2-sulphobenzoic acid cyclic anhydride and toluene-4-sulphonic acid as acid catalyst also led to the benzenesulphonic acid (**6c**).

Experimental

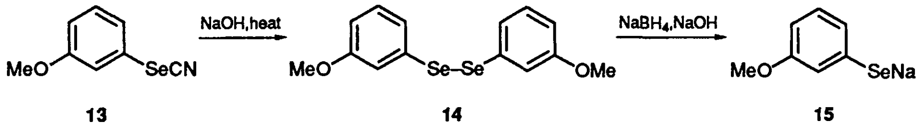
The UV spectra of the sensitizer solutions in 0.1 mol dm^{-3} NaOH were recorded on a Perkin-Elmer Lambda 9, and the IR spectra on a Nicolet FT/IR 719. The ^{1}H NMR spectra were taken on a Bruker-Spectrospin WM 250, HX-90, and WP 80 CW, respectively, using Me$_4$Si as the standard. The mass spectra were determined on a MS 9 from AEI, Manchester, updated with ZAB console and data system 3000. HPLC was carried out on a Waters 440 instrument with a 50 cm Spherisorb S-5CN column and hexane containing 0.6% MeCN and 0.8% decanol as the eluent, with 2-phenylpropan-2-ol as the internal standard. The pressure was 8 MPa and the flow 0.9 cm^3 min^{-1}. All coupling constant values *J* are given in Hz.

Materials.—The starting material **1** as well as **2** and **4** for reference were taken from our vitamin D$_3$ production. Fluorescein (**5a**) was obtained from Fluka. The 3′,6′-dihydroxyspiro[isobenzofuran-1(3*H*),9′-thioxanthen]-3-one (**5b**) and sulphonefluorescein (**6a**) were prepared according to literature methods.[6,12]

General Procedure for the Double Irradiation Experiments.—The first irradiation was performed in an apparatus equipped with a quartz insert containing the high-power low pressure mercury immersion lamp XI2-70 from ABB (Baden, Switzerland) characterized by an electrical power input of 1.5 kW and a light output of 3.8 × 10^{-1}, 6.8 × 10^{-3} and 3.5 × 10^{-2} einstein h^{-1} at 254, 302 and 313 nm, respectively. While being passed through the photoreactor, Ar was bubbled through the irradiated solution which also circulated through an external heat exchanger at the rate of 22 dm^3 min^{-1}. A solution of **1** (225



Scheme 1 Preparation of **5b** and **6b** *via* the common intermediates **11** and **12**. *Reagents and conditions:* i, $NaNO_2$, HCl; ii, KI; iii, EtONa; iv, Cu, heat, −NaI; v, HI, AcOH.



Scheme 2 Preparation of the 3-methoxyselenophenol sodium salt **15**

g, 0.588 mol) in *tert*-butyl methyl ether (4.5 dm^3) was irradiated for 55 min in this way to reach a conversion of 39.5% of **1**. This solution was pumped into another apparatus with a 2 kW medium pressure mercury lamp (TQ 2020 from Heraeus, Hanau, FRG) placed into a double-walled quartz immersion well which contained a liquid cut-off filter.[5] Circulation was as described above. Before the second irradiation was started, a methanolic solution of the sensitizer **5** resp. (**6**) combined with 2 equiv. MeONa was added to give a sensitizer concentration of 0.3 mmol dm^{-3} (**5a**$_1$–**c**$_1$; **6a**$_1$–**c**$_1$). Because of their rapid consumption concentrated methanolic solutions of (**5a**$_1$) resp. (**6a**$_1$) were added continuously during the irradiation.

Syntheses.—3′,6′-*Dihydroxyspiro*[*isobenzofuran*-1(3H),9′-*selenoxanthen*]-3-*one* (**5c**). A mixture of *m,m*′-selenodiphenol (**17**) (5 g, 18.9 mmol) and phthalic anhydride (5.85 g, 39.5 mmol) was heated to 80 °C. This darkened immediately when trifluoromethanesulphonic acid (5 cm^3) was added and the temperature rose to 120 °C. After being stirred for 1 h at 90 °C, aq. NaOH (100 cm^3; 2 mol dm^{-3}) was added to the cooled melt and the resulting solution was stirred for 2 h at 60 °C. Dilution with water (150 cm^3) and dropwise addition of H_2SO_4 (150 cm^3; 2 mol dm^{-3}) led, after 16 h in the dark, to a precipitate which was purified by repeated flash chromatography on silica gel with ethyl acetate–dichloromethane (1:1) as the eluent to yield **5c**·acetone (2.33 g, 27.3%), m.p. 150 °C (decomp.) (from propanol–acetone); (Found: C, 60.9; H, 4.10; Se, 17.4. $C_{20}H_{12}O_4Se{\cdot}C_3H_6O$ requires C, 60.94; H, 4.00; Se, 17.42%); ν_{max}(KBr)/cm^{-1} 3272 (OH) and 1735 (γ-lactone); δ_H(80 MHz, [$^2H_6$]DMSO) 6.66 (2 H, dd, $J_{2,4} = J_{7,5}$ 2.5, $J_{2,1} = J_{7,8}$ 9, 2-H, 7-H), 6.91 (2 H, d, $J_{1,2} = J_{8,7}$ 9, 1-H, 8-H), 7.16 (2 H, d, $J_{4,2} = J_{5,7}$ 3, 4-H, 5-H), 7.61–8.05 (4 H, m, Ar) and 9.90 (2 H, br s, 2 OH); *m/z* 396 (M^+, 18), 393 (9), 351 (100), 349 (56), 347 (19), 335 (30), 333 (17) and 331 (8).

o-(6-*Hydroxy*-3-*oxo*-3H-*thioxanthen*-9-*yl*)*benzenesulphonic acid* (**6b**). A mixture of *m,m*′-thiodiphenol (**12**) (32.8 g, 0.15 mmol), 2-sulphobenzoic acid cyclic anhydride (30.4 g, 0.16 mmol), and toluene-4-sulphonic acid monohydrate (71.4 g) was kept for 9 h at 150 °C. The melt was chilled to 60 °C, then MeOH (300 cm^3) was added and the suspension thus formed was stirred for 1 h. The separated and rinsed precipitate was suspended in MeOH (360 cm^3) and dissolved by adding aq. NaOH (10 cm^3; 2 mol dm^{-3}). Dropwise addition of aq. H_2SO_4 (50 cm^3; 2.5 mol dm^{-3}) caused the crystallization of **6b** (39.2 g, 68%), m.p. 268 °C (decomp.) (Found: C, 59.2; H, 3.25; S, 16.2; $C_{19}H_{12}O_5S_2$ requires C, 59.36; H, 3.15; S, 16.68%); ν_{max}(KBr)/cm^{-1} 3418 (OH), 1597 (CO, conj.) and 1224 (SO_3^-); δ_H(250 MHz, [$^2H_6$] DMSO) 7.23 (2 H, dd, $J_{2,4} = J_{7,5}$ 2.5, $J_{2,1} = J_{7,8}$ 9.5, 2-H, 7-H), 7.27 (1 H, br d, $J_{2',3'}$ 8, 2′-H), 7.56 (2 H, d, $J_{1,2} = J_{8,7}$ 9.5, 1-H, 8-H), 7.60 (1 H, ddd, $J_{3',2'} = J_{3',4'}$ 8, 3′-H), 7.70 (2 H, d, $J_{4,2} = J_{5,7}$ 2.5, 4-H, 5-H) overlapped with 7.71 (1 H, ddd, $J_{4',3'} = J_{4',5'}$ 8, 4′-H) and 8.03 (1 H, d, $J_{5',4'}$ 8, 5′-H).

o-(6-*Hydroxy*-3-*oxo*-3H-*selenoxanthen*-9-*yl*)*benzenesulphonic acid* (**6c**). A mixture of *m,m*′-selenodiphenol (**17**) (5 g, 18.9 mmol), and 2-sulphobenzoic acid cyclic anhydride (3.47 g, 18.9 mmol) was added to a melt of toluene-4-sulphonic acid monohydrate (5 g) and stirred for 2.5 h at 140 °C. After being cooled to 50 °C the red mass was dissolved in 25% aq. NH_3 (150 cm^3). Together with some of the water, the excess NH_3 was evaporated off and the solution was diluted with water (250 cm^3). The mixture was allowed to stand overnight which caused the precipitation of impurities which were filtered off. Dropwise addition of H_2SO_4 (40 cm^3; 7 mol dm^{-3}) resulted in the crystallization of **6c** which was purified by repeating the procedure of dissolution in aqueous NH_3, filtration and precipitation with H_2SO_4 to yield **6c**·H_2O (2.70 g, 31.9%), decomp. > 300 °C (Found: C, 50.6; H, 3.0; S, 7.0; Se, 17.50. $C_{19}H_{12}O_5SSe{\cdot}H_2O$ requires C, 50.79; H, 3.14; S, 7.13; Se, 17.57%); ν_{max}(KBr)/cm^{-1} 3430 (OH), 1585 (CO, conj.) and 1222 (SO_3^-); δ(90 MHz, [$^2H_6$] DMSO) 7.14 (2 H, dd, $J_{2,4} = J_{7,5}$ 3, $J_{2,1} = J_{7,8}$ 9.5, 2-H, 7-H), 7.25 (1 H, br d, $J_{2',3'}$ 8, 2′-H), 7.67 (2 H, d, $J_{1,2} = J_{8,7}$ 9.5, 1-H, 8-H) overlapped with 7.70 (1 H, ddd, $J_{3',2'} = J_{3',4'}$ 8, 3′-H), 7.93 (2 H, d, $J_{4,2} = J_{5,7}$ 3, 4-H, 5-H) overlapped with 7.94 (1 H, ddd, $J_{4',3'} = J_{4',5'}$ 8.5, 4′-H) and 8.09 (1 H, d, $J_{5',4'}$ 8, 5′-H).

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