Isolation of Cross-Coupling Products in Model Studies on the Photochemical Modification of Proteins by Tiaprofenic Acid

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Keywords: Proteins / Cross coupling / Drug research / Photochemistry / Toxicology

To gain insight into the chemical nature of drug-induced photoallergy, model studies have been carried out on the photochemical modification of proteins by tiaprofenic acid. Irradiation of decarboxylated tiaprofenic acid (DTPA) in the presence of *p*-cresol leads to C–C- and C–O-connected *p*-cresol "dimers", together with DTPA hydrodimers. The *p*-cresol–DTPA cross-coupling product was not detected in this reaction. However, a product of this type is formed using a more hindered phenol, such as 2,6-di-*tert*-butylphenol. Similar results are obtained when tiaprofenic acid (TPA) or its methyl ester are used as photosensitizers. The observed formation of "dimers" can be related to protein photo-crosslinking, through the coupling of two tyrosine units. On the other hand, phenol–(D)TPA cross-coupling may be relevant to the understanding of drug–protein photobinding.

Introduction

A number of organic compounds have been shown to photosensitize a variety of processes in biological systems.[1] Though some of these compounds occur naturally in living organisms, many others are of synthetic origin. This is the case for the so-called photosensitizing drugs, which can produce phototoxic and/or photoallergic side effects.[2] Thus, it has been demonstrated that antiinflammatory agents such as tiaprofenic acid (TPA, **1**) are frequently associated with photosensitivity disorders[3] and mediate photosensitized damage to lipids,[4] proteins[5,6] and nucleic acids.[7,8]

A satisfactory understanding of the drug-photosensitized reactions of target biomolecules is essential to establish the molecular bases of the observed photobiological effects. In this connection, the photochemistry of TPA in the presence of proteins has attracted recent attention as a model for studying the mechanisms of TPA-induced photoallergy.[5] It has been established that this drug sensitizes the photooxidation of proteins; His, Tyr and Trp are the reactive amino acid units. His undergoes TPA-photosensitized oxidation according to a Type-II (singlet oxygen) mechanism, while in the case of Tyr a Type-I (radical) mechanism predominates. Both reaction pathways seem to be operative in the photooxidation of Trp. Moreover, it has been established that UV irradiation of proteins in the presence of TPA results in the formation of higher molecular-weight protein aggregates (protein photo-crosslinking). Finally, using radiolabelled TPA it has been possible to detect significant drug−protein photobinding,[6] which appears to be responsible for hapten formation, the first event in the onset of photoallergy.

In spite of these efforts, little is known about the chemical nature of TPA-photosensitized processes in proteins, and the structures of the drug−protein adducts have still to be elucidated. To gain some insight into this matter, in the present work we have undertaken model studies on the TPA-photosensitized modification of proteins. For this purpose, we selected *p*-cresol (PC, **3**) as a simple analogue of Tyr, which appears to be the key amino acid involved. In some experiments, for practical reasons, we used decarboxylated tiaprofenic acid (DTPA, **2**) instead of the parent drug **1**; this is because both compounds share the same chromophore and exhibit the same behavior towards whole proteins, but the lack of the carboxylate moiety in DTPA facilitates solubilization in organic solvents and chromatographic purification of the photoproducts.

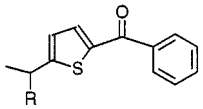

Figure 1. Chemical structures of tiaprofenic acid (**1**) and decarboxylated tiaprofenic acid (**2**)

We report herein that irradiation of DTPA in the presence of *p*-cresol leads to C−C- and C−O-connected PC "dimers", together with DTPA dihydrodimers. A cross-coupling phenol−DTPA product was not detected in this reaction. However, a product of this type was formed when a more hindered phenol was used, such as 2,6-di-*tert*-butylphenol. Similar results were obtained using TPA or its methyl ester.

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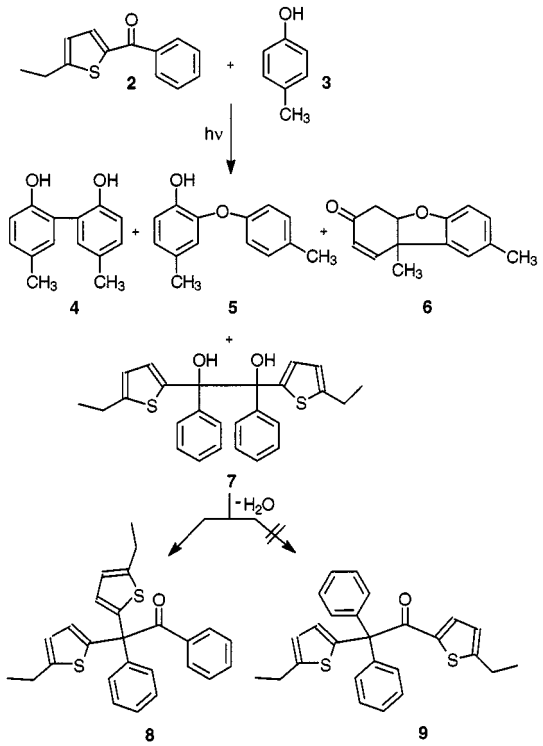
Results and Discussion

Irradiation of a methanolic solution of *p*-cresol (**3**, 10 mM) and DTPA (**2**, 10 mM), using light from a mercury lamp filtered through Pyrex glass, led to a complex mixture. Its preliminary fractionation by column chromatography allowed separation of two types of photoproducts (Scheme 1), namely the known *p*-cresol "dimers" **4**−**6** and the two possible DTPA dihydrodimers **7** (as a 1:1 diastereomeric mixture).[10]



Scheme 1. Photoproducts obtained after irradiation of a methanolic solution of DPTA (**2**) in the presence of *p*-cresol (**3**)

Separation of the two diastereomers **7a** and **7b** could be accomplished by HPLC. They were characterized by their ^{1}H-NMR, ^{13}C-NMR and IR spectra, but it was not possible to obtain satisfactory elemental analyses. This was due to the fact that the dihydro dimers partially rearranged during purification to give pinacolone **8** (Scheme 1). The formation of only one of the two possible pinacolones **8** and **9** demonstrates the much greater migratory aptitude of the thienyl group compared to the less nucleophilic phenyl group. In view of this complicating factor, attempts were made to obtain stable derivatives. Thus, treatment of compound **7a** with phenylboronic acid led to boronate **10**, which gave reproducible C, H, S elemental analysis values within experimental error. However, when the other diastereomer **7b** was treated in the same way, it rearranged to the pinacolone **8**. The stereochemistry of boronate **10** was assigned as *RR/SS* by NOE measurements on its 200-MHz ^{1}H-NMR spectrum. Thus, an NOE (4.33% enhancement) between the thiophene 3-H and the phenyl 2′- or 6′-H was indicative of a mutual *cis* relationship of these groups (Figure 2).

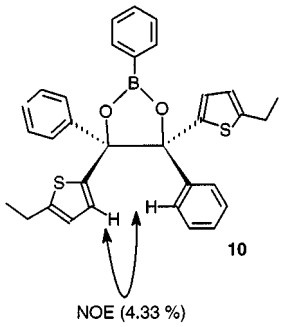


Figure 2. Stereochemistry assignment of boronate **10** based on NOE analysis

The structures of both the pinacol diastereomers were unambiguously established according to an X-ray crystal-structure analysis of a carefully crystallized sample of the first eluted isomer **7a**.

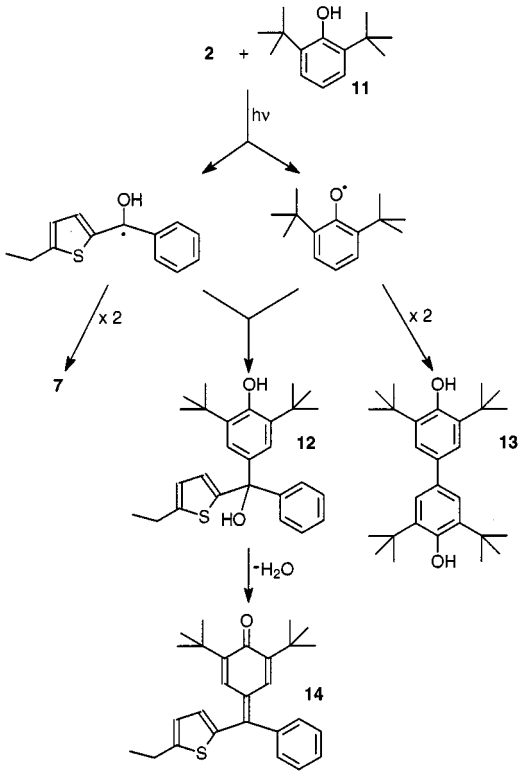
In spite of thorough GC/MS and HPLC/MS analysis of the photolyzate obtained upon irradiation of ketone **2** in the presence of *p*-cresol, no DTPA−phenol coupling products could be detected in the mixture. In principle, both C−C- and C−O-connected cross-coupling products could have been formed. However, the latter would be hemiketals and could easily be hydrolyzed back to the starting materials. The formation of phenol "dimers" **4**−**6** and of ketone "dimers" **7**, but not of cross-coupling products, may be rationalized as follows: Dehydrogenation of *p*-cresol by the triplet state of **2** must lead to a phenoxy/ketyl radical pair enclosed in a solvent cage.[11−13] The triplet multiplicity of the radical pair is inherited from the precursor excited state, and hence intersystem crossing to the singlet state is a prerequisite for recombination. This allows sufficient time for the radical partners to escape from the solvent cage.

In this context, it is noteworthy that significant drug−protein photobinding has been detected using radiolabelled compounds.[6] This could be due to a pre-association of the drug in the protein environment, which would help in keeping the ketyl radical derived from (D)TPA in close proximity to the protein binding site(s).

Photochemical reactions of phenols with benzophenones have been previously studied by Becker.[14] The formation of phenol−ketone coupling products was reported to occur only when 2,6-disubstituted phenols were used. Thus, photolysis of benzophenone in the presence of 2,6-di-*tert*-butylphenol (**11**) results in oxidation of the phenol by the n→π* triplet state of benzophenone. However, no pinacolization occurs; instead, coupling of the ketyl radical with the phenoxyl radical, followed by tautomerization, gives rise to a triaryl carbinol, which undergoes conversion to a 3,5-disubstituted fuchsone in a non-photochemical process. Yields of the adduct were higher in acetone than in methanol.

In order to increase the likelihood of obtaining phenol−ketone coupling products in our case, compound **2** was irradiated in the presence of the disubstituted phenol **11**

for 1 h. After separation of the resulting mixture by column chromatography, ^{1}H- and ^{13}C-NMR spectra of the relevant fractions indicated the presence of dimers **7** (27%), the phenol dimer **13** (30%), and the pursued ketone−phenol coupling product, fuchsone **14** (6%, Scheme 2).

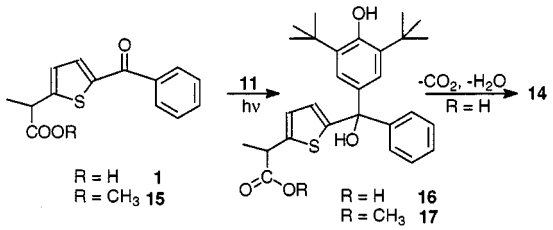


Scheme 2. Photoproducts obtained after irradiation of a methanolic solution of DPTA (**2**) in the presence of 2,6-di-*tert*-butylphenol (**11**)

Unreacted starting ketone **2** (70%) and 2,6-di-*tert*-butylphenol (30%) were also recovered. The structure of **14** was assigned on the basis of its spectral data and confirmed by X-ray analysis of a recrystallized sample. The immediate precursor of fuchsone **14** was envisaged as being carbinol **12**. By analogy with the known reactivity of benzophenone, the isolation of **12** could be expected to be favored upon irradiation in acetone, which was indeed found to be the case. In fact, using acetone as solvent, compound **12** was the only cross-coupling product detected, and could be satisfactorily purified and characterized. Compound **12** was also characterized crystallographically.

The contrasting behavior observed with *p*-cresol and 2,6-di-*tert*-butylphenol is most probably related to the different degrees of steric hindrance in the vicinity of the OH group. The bulky *tert*-butyl groups prevent coupling of the disubstituted phenoxyl radical through the oxygen atom, which then reverts to the starting compounds by hemiketal formation.

The parent drug **1** was also irradiated in acetone in the presence of phenol **11**. After evaporation of the solvent, ^{1}H-NMR analysis of the photolyzate revealed that it consisted of a mixture of the starting reagents and, surprisingly, the decarboxylated fuchsone **14**. In order to ascertain whether loss of carbon dioxide had taken place photochemically,[15] prior to coupling with the phenol, or thermally after formation of the expected carbinol **16**, several assays were performed. Thus, a mixture of **1** and **11** (1:1.3 ratio) was irradiated in deuterated acetone for 0.5 h. NMR analysis of the mixture showed that the phenol "dimer" **13** and a new compound with ^{13}C-NMR shifts at δ = 80.2 (q) and δ = 174.4 (s) were the only photoproducts formed. These signals could, in principle, be assigned to carbinol **16** (Scheme 3). Interestingly, when the solvent was evaporated and a new spectrum was obtained after subsequent redissolution of the residue, compound **14** was the only cross-coupling product detected. This result may be explained in terms of a concerted dehydration-decarboxylation process catalyzed by the carboxylic acid moiety of **16** (Scheme 3). In order to confirm the structure of the unstable carbinol intermediate **16**, the methyl ester **15** was irradiated under the same conditions (Scheme 3). After evaporation of the solvent and fractionation of the residue by column chromatography, the cross-coupling product **17** (55.7%) was obtained in pure form. The presence of two signals at δ = 80.4 and δ = 173.9 in its ^{13}C-NMR spectrum confirmed the structural assignment for the highly reactive carbinol **16**.



Scheme 3. Formation and subsequent dehydration of carbinols **16** and **17** upon irradiation of TPA (**1**) or its methyl ester (**15**) in the presence of 2,6-di-*tert*-butylphenol (**11**)

The observation of cross-coupling products **12**, **16** and **17** indicates that phenoxyl and ketyl radicals can undergo coupling prior to escape from the solvent cage. Therefore, the failure to detect products of this type when *p*-cresol was used could be due to formation of the unstable C−O coupling product. It seems reasonable to assume that the previously observed photobinding of TPA to proteins is due to C−C coupling of the substrate to tyrosine units, which would be favored by the steric hindrance provided by the protein matrix.

Conclusion

Irradiation of (D)TPA in the presence of phenols causes ketone dimerization (pinacolization), C−O/C−C phenol coupling, and phenol−ketone cross-coupling reactions. The latter is experimentally detected only when the phenol is unable to form hemiketals. This suggests that the previously observed protein photo-crosslinking may be due, at least in part, to a coupling of Tyr units. It also explains the formation of drug−protein covalent photoadducts, which is the primary photochemical step in the generation of photoanti-

gens in vivo, and sheds some light on the possible chemical nature of photobinding products. Both types of photosensitized protein modification could result in the development of drug-directed antibodies and the appearance of photoallergy as a cell-mediated immunological response.

Experimental Section

General: Tiaprofenic acid (TPA) was extracted from TORPAS, produced by Rousell Laboratories (Caracas, Venezuela). Decarboxytiaprofenic acid (DTPA) was prepared as previously described in detail.[4][15] – ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian Unity 300 MHz spectrometer; chemical shifts (δ) are reported in ppm relative to TMS. – Combustion analyses were performed at the Instituto de Química Bio-Orgánica of the CSIC in Barcelona. – High-resolution mass spectra were recorded with a VG AUTOSPEC instrument at the SCSIE in Valencia.

Irradiation of DTPA in the Presence of *p*-Cresol: A degassed 10^{-2} M methanolic solution of DTPA (200 mg, 0.93 mmol) and *p*-cresol (100 mg, 0.93 mmol) in a Pyrex tube was irradiated for 1 h with light from a 125-W medium-pressure mercury lamp placed inside a quartz immersion well, under continuous magnetic stirring. After evaporation of the solvent, the residue was chromatographed (hexane/ethyl acetate, 10:1) to give 4-methyl-2-(5-methyl-2-hydroxyphenyl)phenol (**4**, 4 mg, 4%), 4-methyl-2-(4-methylphenoxy)phenol (**5**, 2 mg, 2%), 4a,9b-dihydro-8,9b-dimethyldibenzo[*b*,*d*]furan-3(4*H*)-one (**6**, 1 mg, 1%), and 1,2-bis(5-ethyl-2-thienyl)-1,2-diphenylethane-1,2-diol (**7**, 40 mg, 20%, as a 1:1 diastereomeric mixture). Separation of diastereoisomers **7a** and **7b** was accomplished by HPLC (hexane/ethyl acetate, 10:1). In the course of purification, the dihydrodimers partially rearranged to 2,2-bis(5-ethyl-2-thienyl)-1,2-diphenyl-1-ethanone (**8**).

7a: ^{1}H NMR: δ = 1.25 (t, *J* = 9 Hz, 6 H), 2.85 (q, *J* = 9 Hz, 4 H), 3.25 (s, 2 H), 6.6 (m, 2 H), 6.75 (m, 2 H), 7.1 (m, 6 H), 7.35 (m, 4 H). – ^{13}C NMR: δ = 148.0 (s), 145.2 (s), 142.1 (s), 127.7 (d), 127.5 (d), 127.5 (d), 127.2 (d), 127.0 (d), 122.7 (d), 122.6 (d), 82.9 (s), 23.25 (t), 15.7 (q). – IR (Nujol): $\tilde{\nu}$ = 3532 cm^{-1}.

7b: ^{1}H NMR: δ = 1.25 (t, *J* = 8 Hz, 6 H), 2.75 (q, *J* = 8 Hz, 4 H), 3.4 (s, 2 H), 6.6 (m, 2 H), 6.65 (m, 2 H), 7.1–7.4 (m, 10 H). – ^{13}C NMR: δ = 147.7 (s), 145.1 (s), 141.1 (s), 128.5 (d), 128.3 (d), 127.65 (d), 127.2 (d), 127.0 (d), 122.7 (d), 83.3 (s), 23.2 (t), 15.7 (q). – IR (Nujol): $\tilde{\nu}$ = 3529 cm^{-1}.

Pinacolone 8: ^{1}H NMR: δ = 1.25 (t, *J* = 9 Hz, 6 H), 2.75 (q, *J* = 9 Hz, 4 H), 6.5 (m, 2 H), 6.6 (m, 2 H), 7.1–7.4 (m, 8 H), 7.65 (m, 2 H). – ^{13}C NMR: δ = 197.8 (s), 148.2 (s), 144.4 (s), 144.0 (s), 137.1 (s), 131.9 (d), 130.9 (d), 129.2 (d), 128.6 (d), 127.9 (d), 127.7 (d), 127.4 (d), 122.1 (d), 65.6 (s), 23.3 (t), 15.6 (q). – IR (Nujol): $\tilde{\nu}$ = 1680 cm^{-1}. – $C_{26}H_{24}OS_2$ (416.6): calcd. C 74.94, H 5.80, S 15.40; found C 75.07, H 5.94, S 14.99.

Formation of (4*S*,5*S*/4*R*,5*R*)-4,5-Bis(5-ethyl-2-thienyl)-2,4,5-triphenyl-1,3,2-dioxaborolane (10): Compound **10** was obtained from pinacol **7a** according to a literature method for the synthesis of boronates.[16] To a stirred suspension of phenylboronic acid (39 mg, 0.32 mmol) and $MgSO_4$ (1 g) in benzene (10 mL) was added pinacol **7a** (140 mg, 0.32 mmol) dissolved in benzene (5 mL). The mixture was stirred for about 12 h at room temperature and then filtered. The filtrate was concentrated and the crude product was purified by chromatography (CH_2Cl_2/hexane, 2:1) to afford **10** (80 mg, 48%). – ^{1}H NMR: δ = 1.0 (t, *J* = 7 Hz, 6 H), 2.5 (q, *J* = 7 Hz, 4 H), 6.1 (m, 2 H), 6.25 (m, 2 H), 7.2 (m, 6 H), 7.5 (m, 3 H), 7.6 (m, 4 H), 8.1 (d, *J* = 8 Hz, 2 H). – ^{13}C NMR: δ = 147.5 (s), 144.6 (s), 140.9 (s), 135.5 (d), 132.0 (d), 127.5 (d), 127.7 (d), 127.5 (d), 127.3 (d), 126.6 (d), 122.3 (d), 93.3 (s), 23.1 (t), 15.7 (q). – $C_{32}H_{29}BO_2S_2$ (520.5): calcd. C 73.78, H 5.61, S 12.32; found C 73.72, H 5.86, S 12.18.

Irradiation of DTPA in the Presence of 2,6-Di-*tert*-butylphenol: A 10^{-2} M methanolic solution of DTPA (65 mg, 0.30 mmol) and 2,6-di-*tert*-butylphenol (62 mg, 0.30 mmol) in a Pyrex tube was irradiated for 1 h with light from a 125-W medium-pressure mercury lamp placed inside a quartz immersion well, under continuous magnetic stirring. After evaporation of the solvent, the residue was chromatographed (hexane/dichloromethane, 3:2) to give 2,6-di-*tert*-butylphenol (19 mg, 0.09 mmol), 2,6-di(*tert*-butyl)-4-[3,5-di(*tert*-butyl)-4-hydroxyphenyl]phenol (**13**, 19 mg, 0.05 mmol, 30%), 4-[1-phenyl-1-(5-ethyl-2-thienyl)]methylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**14**, 9 mg, 0.02 mmol, 6%), DTPA (44 mg, 0.21 mmol), and "dimer" **7** (17 mg, 0.04 mmol, 27%).

Fuchsone 14: ^{1}H NMR: δ = 1.2 (s, 9 H), 1.35 (t, *J* = 7.5 Hz, 3 H), 1.4 (s, 9 H), 2.9 (q, *J* = 7.5 Hz, 2 H), 6.9 (d, *J* = 4 Hz, 1 H), 6.95 (d, *J* = 3 Hz, 1 H), 7.0 (d, *J* = 4 Hz, 1 H), 7.3–7.5 (m, 5 H), 7.8 (d, *J* = 3 Hz, 1 H). – ^{13}C NMR: δ = 186.0 (s), 154.5 (s), 148.4 (s), 147.6 (s), 146.6 (s), 140.9 (s), 140.8 (s), 133.9 (d), 132.1 (d), 131.6 (d), 131.1 (d), 129.3 (d), 128.7 (s), 127.8 (d), 124.5 (d), 35.4 (s), 35.2 (s), 29.6 (q), 29.4 (q), 23.8 (t), 15.5 (q). – IR (KBr): $\tilde{\nu}$ = 1599 cm^{-1}. – M.p. 145°C. – HRMS (CI): calcd. for $C_{27}H_{33}OS$ 405.2252; found 405.2269.

Carbinol 12: Irradiation of DTPA in the presence of 2,6-di-*tert*-butylphenol in acetone was performed under the same conditions. NMR analysis of the resulting mixture revealed the formation of 2,6-di(*tert*-butyl)-4-[5-ethyl-2-thienyl(hydroxy)phenylmethyl]phenol (**12**, 80% yield). The product was purified by column chromatography (hexane/ethyl acetate, 15:1) and recrystallized from petroleum ether at –20°C. – ^{1}H NMR: δ = 1.2 (t, *J* = 7 Hz, 3 H), 1.3 (s, 18 H), 2.7 (q, *J* = 7 Hz, 2 H), 2.8 (s, 1 H), 5.1 (s, 1 H), 6.4 (m, 1 H), 6.5 (m, 1 H), 7.0 (s, 2 H), 7.2–7.4 (m, 3 H). – ^{13}C NMR: δ = 153.1 (s), 150.0 (s), 147.6 (s), 147.0 (s), 137.0 (s), 134.8 (d), 127.6 (d), 127.2 (d), 126.4 (d), 124.4 (d), 122.3 (d), 80.3 (s), 34.4 (s), 30.2 (q), 23.5 (t), 15.8 (q). – IR (KBr): $\tilde{\nu}$ = 3620, 3575 cm^{-1}. – M.p. 124–125°C. – $C_{27}H_{34}O_2S$ (422.2): calcd. C 76.74, H 8.18, S 7.57; found C 77.10, H 8.14, S 7.67.

Irradiation of TPA in the Presence of 2,6-Di-*tert*-butylphenol: An acetone solution (17 mL) of TPA (3.0 g, 11.54 mmol) and 2,6-di-*tert*-butylphenol (7.0 g, 33.98 mmol) in a Pyrex tube was irradiated for 0.5 h. After evaporation of the solvent, analysis of the mixture by NMR revealed the presence of fuchsone **14** (31% on the basis of NMR integrals).

Irradiation of TPA Methyl Ester in the Presence of 2,6-Di-*tert*-butylphenol: An acetone (25 mL) solution of tiaprofenic acid methyl ester (**15**,[17] 1.0 g, 3.65 mmol) and 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol) in a Pyrex tube was irradiated for 2.5 h with light from a 125-W medium-pressure mercury lamp placed inside a quartz immersion well, under continuous magnetic stirring. After evaporation of the solvent, the residue was chromatographed (hexane/ethyl acetate, 2:1) to give methyl 2-{5-[3,5-di(*tert*-butyl)-4-hydroxyphenyl(hydroxy)phenylmethyl]-2-thienyl}propanoate (**17**, 975 mg, 2.03 mmol, 55.7%). – ^{1}H NMR: δ = 1.3 (s, 18 H), 1.5 (d, *J* = 7.1 Hz, 3 H), 2.8 (s, 1 H), 3.6 (s, 3 H), 3.9 (q, *J* = 7.1 Hz, 1 H), 5.2 (s, 1 H), 6.5 (m, 1 H), 6.7 (m, 1 H), 7.0 (s, 2 H), 7.2–7.4 (m, 5 H). – ^{13}C NMR: δ = 173.9 (s), 153.15 (s), 151.7 (s), 146.7 (s), 142.8 (s), 137.0 (s), 134.9 (s), 127.7 (d), 127.2 (d), 127.2 (d), 126.2 (d), 124.4 (d), 123.9 (d), 123.8 (d), 80.4 (s), 52.2 (q), 40.9 (d), 34.4 (s), 30.2 (q), 19.2 (q), 19.1 (q). – IR (KBr): $\tilde{\nu}$ = 3640, 3540,

1732 cm^{-1}. – M.p. 125–126°C. – $C_{29}H_{36}O_4S$ (480.6): calcd. C 72.24, H 7.55, S 6.67; found C 72.25, H 7.52, S 6.44.

Crystallographic Data Collection and Structure Determination: A summary of the crystallographic data and refinement results is given in Table 1. X-ray crystal structures with selected bond lengths [Å] and angles [°] are shown in Figures 3–5.

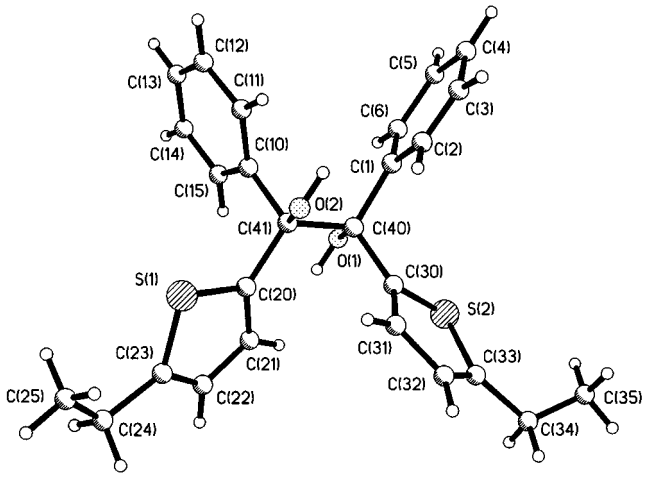


Figure 3. Molecular structure of **7a**; selected bond lengths [Å] and angles [°][: C(40)–C(41) 1.37(2), C(40)–O(1) 1.69(2), C(40)–C(1) 1.53(2), C(40)–C(30) 1.48(2), C(41)–O(2) 1.70(2), C(41)–C(10) 1.53(2), C(41)–C(20) 1.57(2); C(41)–C(40)–C(30) 112.5(10), C(41)–C(40)–C(1) 115.8(12), C(30)–C(40)–C(1) 112.6(9), C(41)–C(40)–O(1) 89.1(12), C(30)–C(40)–O(1) 105.4(13), C(1)–C(40)–O(1) 106.3(10), C(40)–C(41)–C(10) 121.7(12), C(40)–C(41)–C(20) 119.0(10), C(10)–C(41)–C(20) 110.0(9), C(40)–C(41)–O(2) 90.4(12), C(10)–C(41)–O(2) 109.5(11), C(20)–C(41)–O(2) 101.5(12)

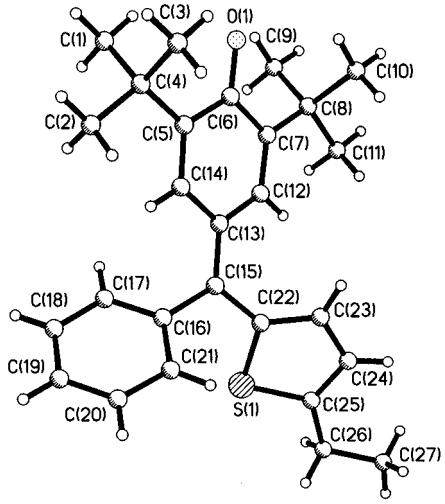


Figure 4. Molecular structure of **14**; selected bond lengths [Å] and angles [°]: C(6)–O(1) 1.241(3), C(5)–C(4) 1.518(4), C(7)–C(8) 1.526(4), C(5)–C(14) 1.354(4), C(7)–C(12) 1.348(4), C(14)–C(13) 1.440(4), C(12)–C(13) 1.437(3), C(13)–C(15) 1.392(4), C(15)–C(16) 1.491(3), C(15)–C(22) 1.460(4); C(25)–S(1)–C(22) 93.33(13), C(16)–C(15)–C(13) 120.9(2), C(22)–C(15)–C(16) 116.8(2), C(13)–C(15)–C(22) 122.3(2), O(1)–C(6)–C(5) 120.1(3), O(1)–C(6)–C(7) 120.5(3), C(15)–C(13)–C(12) 122.4(2), C(15)–C(13)–C(14) 120.7(2)

Compound 7a: A well-shaped crystal of dimensions 0.33 × 0.25 × 0.20 mm was mounted on a Siemens P4 single-crystal diffractometer for data collection using monochromated Mo-K_α radiation. An orthorhombic cell was obtained and the space group $P2_12_12_1$ was confirmed in the course of the structure determination. 1756 independent reflections were collected (1.83° < θ < 22.48°), *hkl* range 0, 0, 0 to 6, 18, 23. Lorentz and polarization corrections were applied, as well as a semiempirical absorption correction based on ψ scans (max. and min. transmission 0.2701 and 0.2540). The structure was solved by direct methods and refined by full-matrix least-squares analysis on F^2 (SHELXTL).[18] Hydrogen atoms were geometrically positioned. The refinement converged at $R1 = 0.0764$ [$I > 2\,\sigma(I)$] and $wR2 = 0.2355$ (all data). Largest peak and hole in the final difference map +0.49, −0.29 eÅ^{-3}.

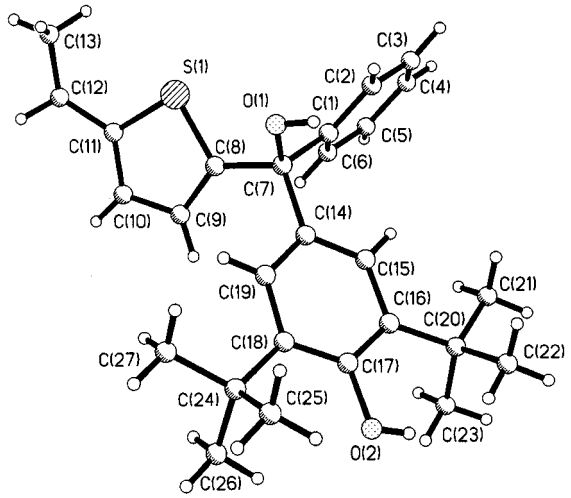


Figure 5. Molecular structure of **12**; selected bond lengths [Å] and angles [°]: O(1)–C(7) 1.450(3), C(7)–C(14) 1.544(4), C(17)–O(2) 1.383(3), C(18)–C(24) 1.540(4), C(16)–C(20) 1.536(4), C(7)–C(8) 1.520(4), C(7)–C(1) 1.534(4), C(8)–C(9) 1.354(4), C(9)–C(10) 1.413(4), C(10)–C(11) 1.339(4), C(11)–S(1) 1.719(3), S(1)–C(8) 1.722(3); C(11)–S(1)–C(8) 92.76(14), C(8)–C(7)–O(1) 109.4(2), C(1)–C(7)–O(1) 110.3(2), C(14)–C(7)–O(1) 108.5(2), C(18)–C(17)–O(2) 120.0(2), C(16)–C(17)–O(2) 116.4(3)

Compound 12: A well-shaped crystal of dimensions 0.25 × 0.25 × 0.20 mm was mounted on a Siemens P4 single-crystal diffractometer for data collection using monochromated Mo-K_α radiation. A triclinic cell was obtained and the space group $P1$ was confirmed in the course of the structure determination. 3146 independent reflections were collected (2.00° < θ < 22.48°), *hkl* range −6, −10, −22 to 6, 10, 22. Lorentz and polarization corrections were applied. The structure was solved by direct methods and refined by full-matrix least-squares analysis on F^2 (SHELXTL).[18] Hydrogen atoms were geometrically positioned. The refinement converged at $R1 = 0.0472$ [$I > 2\,\sigma(I)$] and $wR2 = 0.1593$ (all data). Largest peak and hole in the final difference map +0.44, −0.34 eÅ^{-3}.

Compound 14: A well-shaped crystal of dimensions 0.23 × 0.23 × 0.20 mm was mounted on a Siemens P4 single-crystal diffractometer for data collection using monochromated Mo-K_α radiation. A monoclinic cell was obtained and the space group $C2/c$ was confirmed in the course of the structure determination. 3161 reflections were collected, of which 3109 were independent (R_{int} = 0.0119), (2.06° < θ < 22.51°), *hkl* range 0, 0, −13 to 41, 11, 12. Lorentz and polarization corrections were applied, as well as a semiempirical absorption correction based on ψ scans (max. and min. transmission 0.3283 and 0.2923). The structure was solved by direct methods and refined by full-matrix least-squares analysis on F^2 (SHELXTL).[18] Hydrogen atoms were geometrically positioned.

The refinement converged at $R1 = 0.0529$ [$I > 2\sigma(I)$] and $wR2 = 0.1754$ (all data). Largest peak and hole in the final difference map $+0.25$, -0.29 eÅ^{-3}.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre under deposition nos. CCDC-102165, -102166, and -102167. Copies of the data can be obtained on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

The authors are indebted to FIS (Grant No. 95-1498), the European Union (Grant No. BMH-4-97-2590) and the Spanish Ministerio de Asuntos Exteriores (Mutis fellowship to Z. S.) for financial support. We also thank the Servicio de Difracción de Rayos X de la UPV for single-crystal X-ray analysis facilities.

Table 1. Crystallographic data for **7a**, **12** and **14**

	7a	**12**	**14**
empirical formula	$C_{26}H_{26}O_2S_2$	$C_{27}H_{34}O_2S$	$C_{27}H_{32}OS$
a [Å]	6.135(2)	5.9825(8)	38.908(7)
b [Å]	16.844(5)	9.9012(10)	10.259(2)
c [Å]	22.289(7)	20.499(2)	12.276(2)
α [°]	90	87.157(8)	90
β [°]	90	83.677(9)	103.770(13)
γ [°]	90	86.119(19)	90
V [Å^3]	2303.4(12)	1203.0(2)	4759.4(14)
Z	4	2	8
formula weight	434.59	422.60	404.59
space group	$P2_12_12_1$	*P*1	*C*2/*c*
T [°C]	20	20	20
λ [Å]	0.71073	0.71073	0.71073
$\rho_{calcd.}$ [g cm^{-3}]	1.253	1.167	1.129
μ [cm^{-1}]	2.51	1.54	1.50
*R*1 [$I > 2\sigma(I)$]	0.0764	0.0472	0.0529
*wR*2 (all data)	0.2355	0.1593	0.1754

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Received July 16, 1998
[O98326]