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Photoreaction Between Benzoylthiophenes and *N*-BOC-Tryptophan Methyl Ester‡

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ABSTRACT

Drug-induced photoallergy requires as the first step formation of covalent drug-protein photoadducts. One of the key amino acids involved in this process is tryptophan (Trp). In this context, several diaryl ketones, including 2-benzoylthiophene (BT), [2-(5-benzoyl-5-thienyl)]-2-methylpropanoic methyl ester (TPA methyl ester) and 4-(2-thienylcarbonyl)phenyl]-2-methylpropanoic methyl ester (SUP methyl ester) have been irradiated in the presence of *N*-BOC-(*L*)-tryptophan methyl ester. Laser flash photolysis has allowed to detect three neutral radicals (ketyl, indolyl and skatolyl radicals) resulting from formal hydrogen-atom abstraction. This correlates well with the isolation of homodimers, as well as with cross-coupling products, in the preparative irradiation. The main cross-coupling products were in all cases lactones arising from the reaction of the Trp-derived skatolyl radicals with the corresponding ketyl radicals. These lactones were obtained as the (4*R*) stereoisomers with remarkable diasteroselectivity. No coupling products through the phenyl *p*-position of BT or TPA methyl ester were found. By contrast, ketone homodimers and cross-coupling products arising from reaction through the thienyl 5-position were obtained when using BT and SUP methyl ester; this is very interesting, because stable LAT-derived products are difficult to isolate.

INTRODUCTION

It is well known that anti-inflammatory drugs containing the 2-benzoylthiophene chromophore, tiaprofenic acid (TPA), and suprofen (SUP), can photosensitize damage to proteins; histidine (His), tyrosine (Tyr) and tryptophan (Trp) are the reactive amino acid units (1–4). Previous studies have been performed to gain insight into the chemical nature of the photoproducts that lead to phototoxic and/or photoallergic side effects (5–7). In a first approach (5,6), model studies on drug-induced photoreactions of the Trp moiety have been done using 2-benzoylthiophene (BT) and indole (InH). It has been demonstrated that the BT triplet (π,π^*) achieves formal hydrogen abstraction from InH in a process involving electron transfer at a hydrogen-bonded BT–HIn exciplex coupled with proton transfer. The BT ketyl (BTH) and indolyl (In) radicals are generated with high rate constants and quantum yields close to 1; however, low conversion of the starting reagents is obtained after 100 h of irradiation (Scheme 1). Analysis of the resulting complex mixture by GC/MS and NMR has shown that BT pinacols (BTH-BTH), InH dimers (In-In) and products arising from radical cross-coupling between In (through the 3-position) and BTH (through the ketyl carbon or the thienyl 5-position) are formed. These studies suggest that InH is not the best model to investigate the nature of Trp modification in proteins, because in the isolated photoproducts In radicals couple through the 3-position, which is not available in the amino acid. Time-resolved studies (7) have shown that with 3-methylindole (CH_3InH) not only BTH and *N*-centered indolyl (CH_3In) radicals but also C-centered skatolyl (CH_2InH) radicals are generated. Accordingly, product studies have shown the formation of BTH-BTH, together with three indolyl homodimers and four cross-coupling products (Scheme 1). These cross-coupling compounds arise from skatolyl radicals (involving the methylene position or the ring 2-position) and BTH radicals (via the ketyl carbon or through the thienyl 5-position).

The formation of C-centered skatolyl radicals is of special interest because these species appear to be involved in several processes of biological interest (8–11). Furthermore, previous results have evidenced reactivity differences between TPA and SUP (12), which share the same chromophore and differ only in the position of the propionic acid side chain, which is linked to the thiophene or the benzene ring (Chart 1). Therefore, an extension of the above-mentioned studies to the irradiation of the amino acid (Trp) in the presence of TPA, SUP or BT appeared necessary.

Product studies carried out in the present work have shown that in all cases the main cross-coupling product is a lactone arising from the reaction between Trp-derived skatolyl radicals and ketyl radicals.

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Abbreviations: BT, 2-benzoylthiophene; BTH, 2-benzoylthiopheneketyl radical; BTH-BTH, pinacols; CH_3In, *N*-centered indolyl radicals; CH_2InH, C-centered skatolyl radicals; CH_3InH, 3-methylindole; In, indolyl; InH, indol; In-In, Indol dimmers; SUP, suprofen; TPA, tiaprofenic acid; Trp, tryptophan.
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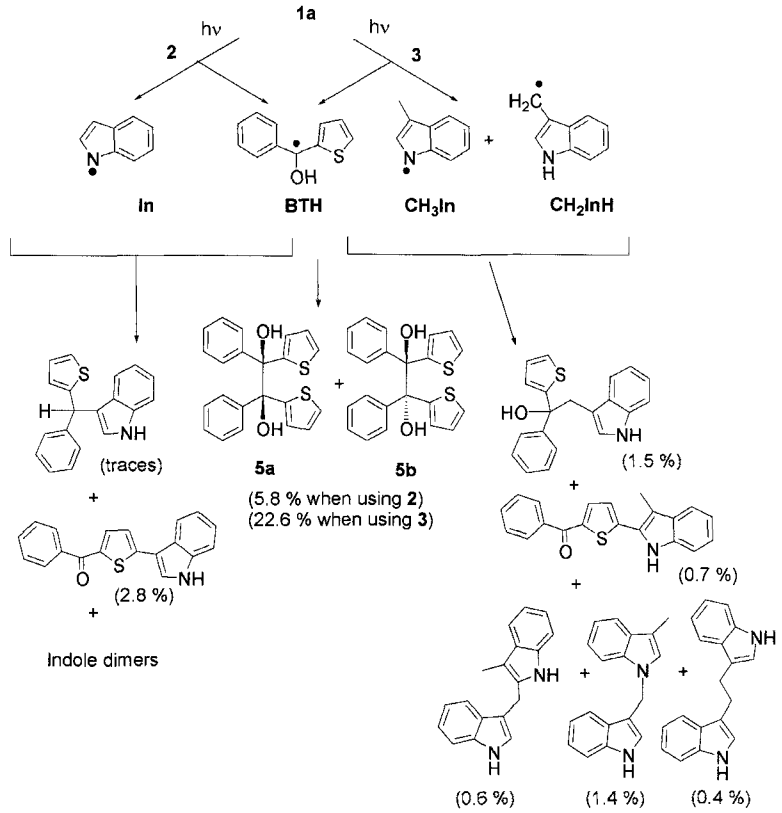


Scheme 1. Product formation in the photoreaction of BT in the presence of indole and 3-methylindole.

MATERIALS AND METHODS

General. ^{1}H-NMR, ^{13}C-NMR, Distortionless Enhancement by Polarization Transfer (DEPT) and Correlation Spectroscopy (COSY) spectra were recorded in a 300 MHz spectrometer; chemical shifts (δ) are reported in ppm relative to TMS. The coupling constants (*J*) are in hertz (Hz). Nuclear Overhauser Effect Spectroscopy (NOESY) spectra were recorded in 400 or 500 MHz spectrometers using $CDCl_3$ solvent. Column chromatography was performed on silica gel 60 (0.040–0.063 mm), and HPLC was carried out using a LiChrospher® Si60 (10 μm) silica column (Merck KGaA, Darmstadt, Germany). Compounds SUP, InH, CH_3InH and *N*-BOC-(*L*)-tryptophan were purchased from Sigma-Aldrich (St. Louis, MO). High-resolution mass spectrometry was conducted at the SCSIE in Valencia, Spain.

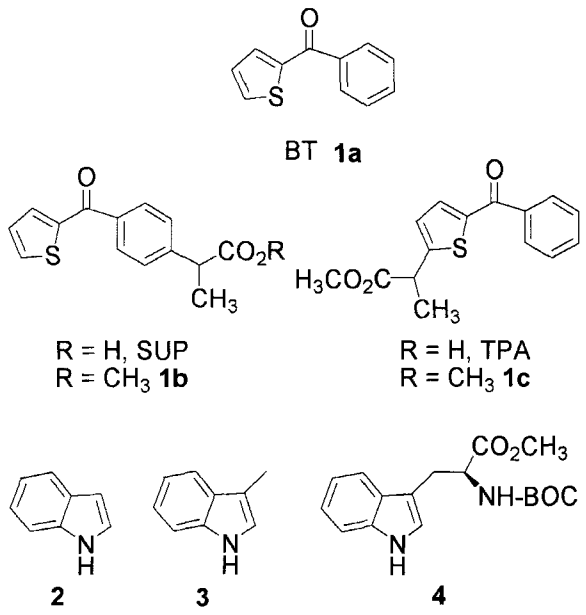


Chart 1.

Laser flash photolysis. Laser flash photolysis experiments were carried out by using the third harmonics (355 nm) of a pulsed Nd:YAG laser (mLFP-111; Luzchem Research, Ottawa, Ontario, Canada). The pulse duration was 10 ns and the energy of the laser beam was 18 mJ/pulse. A Lo255 Oriel xenon lamp was employed as detecting light source. The mLFP-111 apparatus consisted of the pulsed laser, the Xe lamp, a 77200 Oriel monochromator and an Oriel photomultiplier (PMT) system made up of a 77348 side-on PMT, 70680 PMT housing and a 70705 PMT power supply. The oscilloscope was a TDS-640A Tektronix. The output signal was transferred to a personal computer for data analysis.

General procedure of irradiation. A degassed acetonitrile solution of the ketone and *N*-BOC-(*L*)-Trp-OMe in a Pyrex tube was irradiated for 200 h with a 125 W medium-pressure mercury lamp inside a quartz immersion well, under continuous magnetic stirring. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/ethyl acetate, 10/1, 5/1 and 3/1) and then submitted to semipreparative HPLC. The isolated yields and the characterization data of the products follow:

BT (**1a**, 0.19 *M*)/*N*-BOC-(*L*)-Trp-OMe (**4**, 0.19 *M*): 1,2-diphenyl-1,2-dithien-2-ylethane-1,2-diol (**5a** and **5b**, 153.5 mg, 15.9%), {5-[hydroxy-(phenyl)thien-2-ylmethyl)]thien-2-yl}(phenyl) methanone (**6**, 4.0 mg, 0.4%), *tert*-butyl 4-(1*H*-indol-3-yl)-2-oxo-5-phenyl-5-(2-thienyl)tetrahydrofuran-3-ylcarbamate(**7**, 5.8 mg, 0.7%), methyl 3-[*N*-(5-benzoylthien-2-yl)-1*H*-indol-3-yl]-2-(*N*-*tert*-butoxycarbonylamino)propanoate (**8**, 11.1 mg, 1.3%).

6. ^{1}H NMR($CDCl_3$): δ3.1 (s, 1H); 6.84 (d, J = 4.5 Hz, 1H); 6.90–6.92 (m, 2H); 7.25–7.31 (m, 4H); 7.41–7.54 (m, 4H); 7.54 (t, J = 7.5 Hz, 2H); 7.78 (d, J = 7.4 Hz, 2H). MS *m/z* 376 (M^+ 11), 299 (26), 271 (66), 105 (100). HRMS Calcd for $C_{22}H_{16}O_2S_2$: 376.0592. Found: 376.0604.

7. ^{1}H NMR ($CDCl_3$): δ1.15–1.25 (m, 18H); 4.49 (d, J = 8.0 Hz, 1H); 4.58 (d, J = 8.1 Hz, 1H); 4.87 (dd, 1H); 4.97 (d, J = 7.0 Hz, 1H); 5.03 (d, J = 7.0 Hz, 1H); 5.24 (dd, 1H); 6.50 (m, 1H), 6.56–6.60 (m, 2H); 6.85–7.19 (m, 12H); 7.22–7.29 (m, 5H); 7.37 (t, J = 7.5 Hz, 2H); 7.55 (d, J = 7.8 Hz, 2H); 7.66 (d,

J = 7.8 Hz, 2H); 7.90 (s, 1H); 8.09 (s, 1H). MS m/z 301 (100), 267 (21), 207 (12). HRMS Calcd for $C_{27}H_{26}N_2O_4S$: 474.161329. Found: 474.161591.

8. ^{1}H NMR ($CDCl_3$): δ1.49 (s, 9H); 3.25 (m, 2H) 3.65 (s, ^{3}H); 4.64 (m, 1H); 5.07 (m, 1H), 7.02 (d, J = 4.2 Hz, 1H); 7.15 (s, 1H); 7.28 (t, J = 7.5 Hz, 2H); 7.44–7.49 (m, ^{3}H); 7.53–7.55 (m, 2H); 7.76 (d, J = 8.1 Hz, 1H); 7.82 (d, J = 7.8 Hz, 2H). MS m/z 404 (2), 316 (100), 210 (5), 105 (23). HRMS Calcd for $C_{28}H_{28}N_2O_5S$: 504.171894. Found: 504.170036.

SUP methyl ester(**1b**, 0.25 *M*)/*N*-BOC-(*L*)-Trp-OMe (**4**, 0.25 *M*): *N*-BOC-(*L*)-Trp-OMe dimers (100.3 mg, 3.6%), methyl 2-(4-{1,2-dihydroxy-2-[4-(1-methoxycarbonylethyl)phenyl]-1,2-*di*thien-2-ylethyl}phenyl) propanoate (**9a** and **9b**, 402.9 mg, 22.1%), methyl 2-[4-(hydroxy{5-[4-(1-methoxycarbonylethyl)benzoyl]thien-2-yl}thien-2-ylmethyl)phenyl]propanoate (**10**, 1.1 mg, 0.6%) and methyl 2-{4-[4-[(*tert*-butoxycarbonyl) amino]-3-(1*H*-indol-3-yl)-5-oxo-2-thien-2-yltetrahydrofuran-2-yl]phenyl}propanoate (**11a** and **11b**, 7.0 mg, 0.4%).

9a. ^{1}H NMR ($CDCl_3$): δ1.38 (d, J = 7.2 Hz, ^{3}H); 1.42 (d, J = 7.2 Hz, ^{3}H); 3.15 (s, 2H); 3.57–3.64 (m, 8H); 6.64 (m, 2H); 6.84 (m, 2H); 6.96 (d, J = 8.1 Hz, 2H); 7.08 (d, J = 8.4 Hz, 2H); 7.16 (d, J = 5.4 Hz, 2H); 7.22 (m, 2H); 7.51 (d, J = 8.5 Hz, 2H). (FAB)HRMS Calcd for $C_{30}H_{30}O_6S_2(-H_2O)$ 532.1378. Found: 532.1361.

9b. ^{1}H NMR ($CDCl_3$): δ1.40 (d, J = 6.9 Hz, 6H); 3.31 (s, 2H); 3.58 (s, 6H); 3.62 (m, 2H); 6.78 (m, 2H); 6.82–6.85 (m, 2H); 7.05 (d, J = 8.4 Hz, 4H); 7.16 (m, 2H); 7.19–7.22 (m, 4H). (FAB)HRMS Calcd for $C_{30}H_{30}O_6S_2(-OH)$ 533.1456. Found: 533.1421.

10. ^{1}H NMR ($CDCl_3$): δ1.43 (d, J = 7.2 Hz, ^{3}H), 1.47 (d, J = 7.2, ^{3}H); 3.14 (s, 1H); 3.60 (s, ^{3}H); 3.62 (s, ^{3}H); 3.68 (q, J = 7.2 Hz, 1H); 3.74 (q, J = 7.2 Hz, 1H); 6.84 (m, 1H); 6.89–6.92 (m, 2H); 7.22 (d, J = 8.4 Hz, 2H); 7.26 (dd, J_1 = 2.55 Hz, J_2 = 1.2 Hz, 1H); 7.34 (d, J = 8.4 Hz, 2H); 7.38 (d, J = 8.4 Hz, 2H); 7.44 (d, J = 3.9 Hz, 1H); 7.75 (d, J = 8.4 Hz, 2H). MS m/z 548 (M^+ 1), 464 (59), 405 (100), 341 (19), 301 (19), 241 (34), 191 (41), 131 (39), 103 (25). HRMS Calcd for $C_{30}H_{28}O_6S_2$: 548.1327. Found: 548.1329.

11a and **11b.** The amount of this compound was too small for obtaining reliable NMR data. MS m/z 387 (100), 328 (20), 216 (8), 130 (6). HRMS Calcd for $C_{31}H_{32}N_2O_6S$: 560.198109. Found: 560.199341.

TPA methyl ester(**1c**, 0.25 *M*)/*N*-BOC-(*L*)-Trp-OMe (**4**, 0.25 *M*): methyl 2-(5-{1,2-dihydroxy-2-[5-(1-methoxycarbonylethyl)thien-2-yl]-1,2-diphenylethyl}thien-2-yl)propanoate. (**12a** and **12b**, 937.9 mg, 33.7%), *N*-BOC-(*L*)-Trp-OMe dimers (29.9 mg, 1.1%), methyl 2-{5-[4-[(*tert*-butoxycarbonyl)amino]-3-(1*H*-indol-3-yl)-5-oxo-2-phenyltetrahydrofuran-2-yl]thien-2-yl}propanoate (**13**, 14.9 mg, 0.5%).

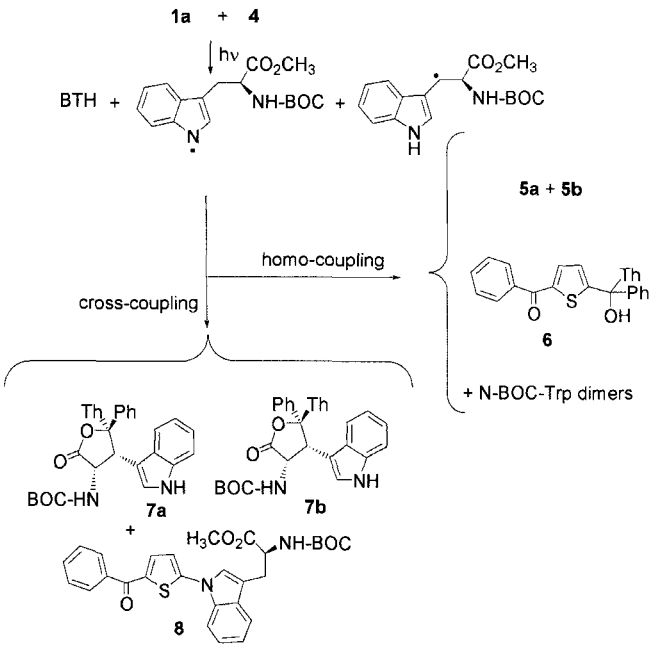
12a and **12b.** ^{1}H NMR($CDCl_3$): δ1.40 (d, J = 7.2 Hz, ^{3}H); 1.42 (d, J = 7.2 Hz, ^{3}H); 3.32 (s, 1H); 3.41 (s, 1H); 3.55–3.58 (m, 6H); 3.75–3.83 (m, 2H), 6.60–6.64 (m, ^{3}H), 6.70 (m, 1H); 6.99–7.14 (m, 6H); 7.25–7.27 (m, 4H). (FAB) HRMS Calcd for $C_{30}H_{30}O_6S_2(-H_2O)$ 532.1378; Found: 532.1281.

13. ^{1}H NMR ($CDCl_3$): δ1.20–1.30 (m, 18H), 1.51 (d, J = 7.2 Hz, ^{3}H); 1.52 (d, J = 7.3 Hz, ^{3}H); 3.50 (s, ^{3}H); 3.60 (q, J = 7.2 Hz, 1H); 3.69 (s, ^{3}H); 3.88 (q, J = 7.2 Hz, 1H); 4.52 (d, J = 8.1 Hz, 1H); 4.68 (d, J = 8.1 Hz, 1H); 4.89 (dd, 1H); 4.97 (d, J = 6.9 Hz, 1H); 5.04 (d, J = 7.2 Hz, 1H); 5.30 (dd, J = 7.5 Hz, 1H); 6.34 (d, J = 3.6 Hz, 1H); 6.41 (t, J = 4 Hz, 1H); 6.59 (s, 1H); 6.78 (bs, 1H); 6.91 (bs, 1H); 6.92–7.36 (m, 13H); 7.43 (t, J = 7.5 Hz, 2H); 7.56 (t, J = 6.5 Hz, 1H); 7.59 (d, J = 8.0 Hz, 1H); 7.69 (d, J = 8.1 Hz, 2H); 7.94 (s, 1H); 8.16 (s, 1H). MS m/z 387 (M^+ 100), 328 (81), 216 (69), 157 (19), 130*. HRMS Calcd for $C_{31}H_{32}N_2O_6S$: 560.198109. Found: 560.191673.

RESULTS

Photoreaction between BT and *N*-BOC-Trp methyl ester

Irradiation of deaerated acetonitrile solution of BT (**1a**) and *N*-BOC-(*L*)-tryptophan methyl ester (**4**) in equimolar amounts, using the Pyrex-filtered light from a medium pressure mercury lamp, led to a complex mixture containing the known pinacols (two diastereoisomers, **5a** and **5b**; 5,13) together with Trp homodimers, two



Scheme 2. Product formation in the photoreaction of BT in the presence of *N*-BOC-Trp methyl ester.

other compounds with apparent $M^{+\bullet}$ at m/z 301, another with apparent $M^{+\bullet}$ at m/z 404 and a last one with $M^{+\bullet}$ at m/z 376 (Scheme 2).

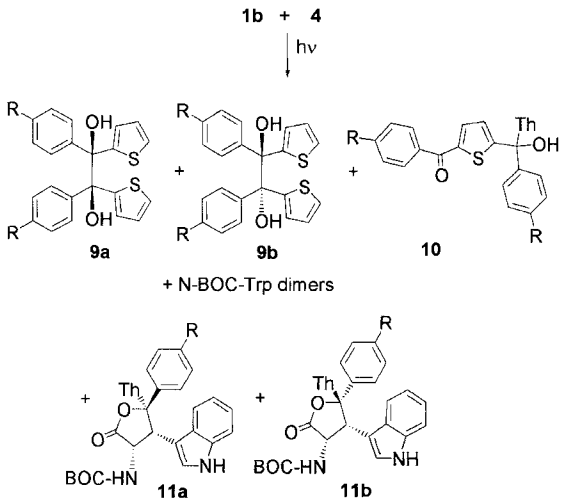
Purification by column chromatography, followed by semi-preparative HPLC, was performed to achieve isolation and characterization of these compounds. Attempts to separate the two isomeric photoproducts with the 301 ion were unfruitful. Their analysis by HRMS showed that they have actually an exact mass of 474.1616; the ^{1}H-NMR data agreed well with structures **7a** and **7b**. Also, COSY experiments allowed us to determine that the two doublets at δ = 4.49 ppm (J = 8.0 Hz) and 5.04 ppm (J = 7.5 Hz) and the apparent triplet at 5.24 ppm belong to the same compound. The other isomer presented the two doublets centered at 4.58 ppm (J = 8.0 Hz) and 4.98 ppm (J = 7.5 Hz), together with the triplet at 4.87 ppm. The signals at 4.49 and 4.58 ppm were attributed to the N-H on the basis of deuteration experiments. The coupling constant between the lactone 3-H and 4-H (7.5 Hz) was a strong evidence for a *cis* relationship; further confirmation was obtained by NOESY measurements performed on the analogous lactone **13** arising from **1c** (see below).

On the other hand, ^{1}H-NMR data for the product with apparent $M^{+\bullet}$ 404 (actual $M^{+\bullet}$ 504, HRMS: 504.1700) agreed well with structure **8**. Thus, comparison with *N*-BOC-(*L*)-Trp methyl ester showed that the amino acid chain remained unaltered and that the signal of the indolyl hydrogen (usually found at δ higher than 7.9 ppm) was absent; besides, the characteristic pattern of the deshielded *ortho* benzoyl hydrogens at δ = 7.82 ppm was present. Finally, in the case of the compound with $M^{+\bullet}$ 376, the singlet at 3.10 ppm (1H, interchangeable by D_2O), together with a characteristic pattern in the aromatic region, supported the assignment of structure **6** to this compound.

Photoreaction between the methyl esters of SUP and *N*-BOC-Trp

When SUP methyl ester (**1b**) was used instead of BT under the same irradiation conditions, GC/MS analysis of the complex

* The preparation of the analogous benzophenone derivative has been reported. It is obtained after bromine addition to a THF solution (at –70 °C) containing the product resulting from benzophenone radical anion coupling (see ref. 23).



Scheme 3. Product formation in the photoreaction of SUP methyl ester with *N*-BOC-Trp methyl ester.

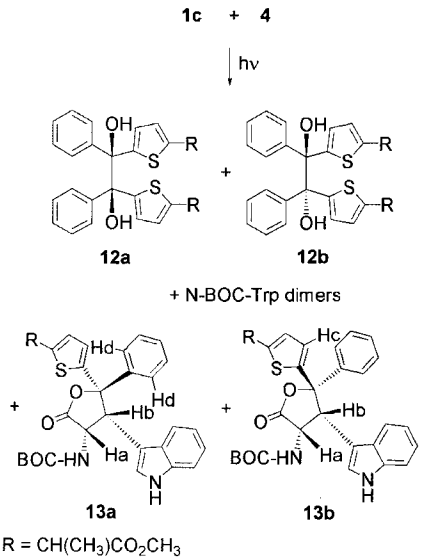
mixture showed the formation of the corresponding SUP pinacols **9** and Trp homodimers, together with the SUP homodimer **10** and lactones **11** (Scheme 3).

The structures of all the above compounds were assigned by comparison of the spectral data with those of the analogous BT-derived compounds.

Photoreaction between the methyl esters of TPA and *N*-BOC-Trp

Similar experiments were performed using TPA methyl ester (5) (**1c**). In this case, GC/MS analysis of the complex mixture also showed formation of pinacols **12**, together with Trp homodimers and lactones **13** (Scheme 4). However, no compounds related to **6** or **10** were isolated.

To establish the relative stereochemistry of the chiral centers present in compounds **13a** and **13b** NOESY experiments were



Scheme 4. Product formation in the photoreaction of TPA methyl ester with *N*-BOC-Trp methyl ester.

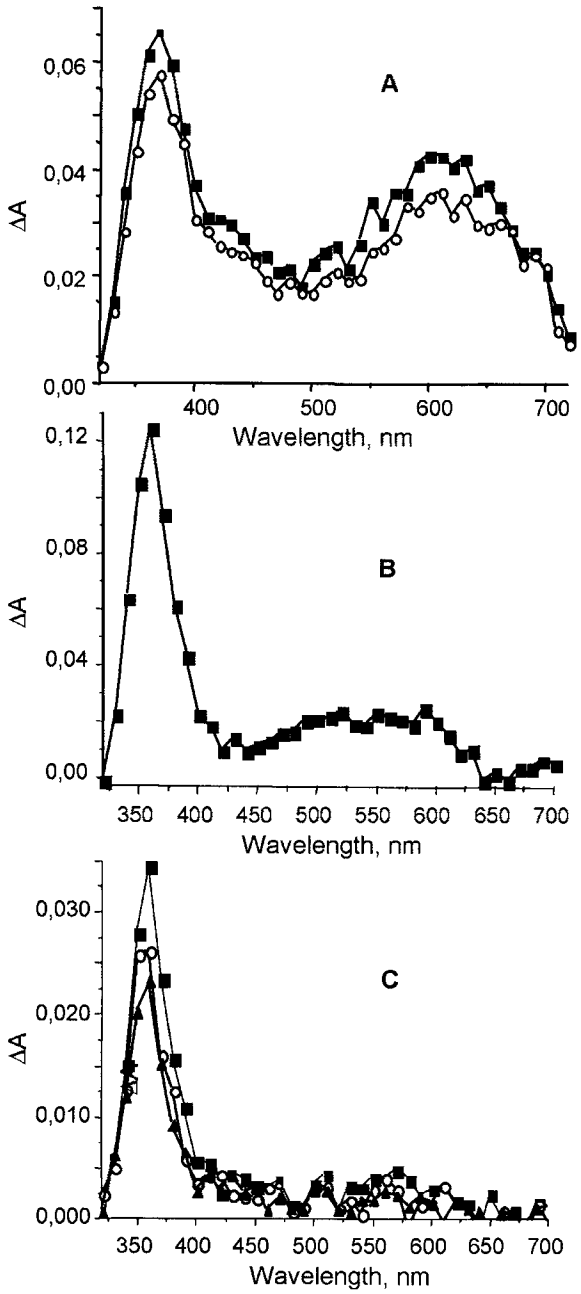
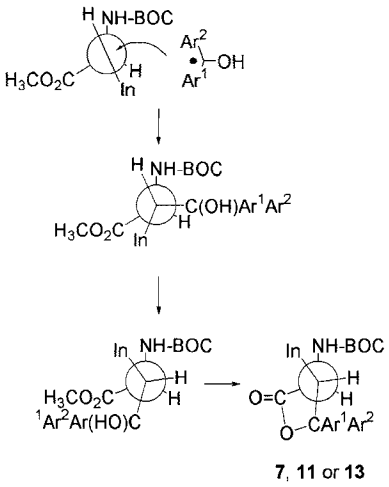


Figure 1. Transient absorption spectra recorded following laser excitation (355 nm) of **1b** (1.5×10^{-3} *M*) in deaerated acetonitrile. A: 0.5 (■) and 1 μs (○) after the laser pulse. B: in the presence of **4** (35.8×10^{-2} *M*) 0.5 μs after the laser pulse. C: in the presence of **4**, 120 (■), 200 (○) and 270 (▲) μs after the laser pulse.

performed. A clear interaction between Ha (δ = 4.84 ppm for compound **13a** and 4.99 ppm for **13b**) and Hb (δ = 4.93 ppm for compound **13a** and 5.26 ppm for **13b**) was observed. A closer inspection of the aromatic region showed other important NOESY interactions, between Ha and Hc (δ = 6.36, thienyl) for **13b** and between Ha and Hd (δ = 7.64, phenyl) for **13a**.

Transient species in the photolysis of 1b in the presence of 4

The triplet-triplet transient absorption spectrum of **1b** (λ_{max} at 350 nm and 600 nm) (14) was observed after 355 nm laser excitation in deaerated acetonitrile solutions with a 10 ns



7, **11** or **13**

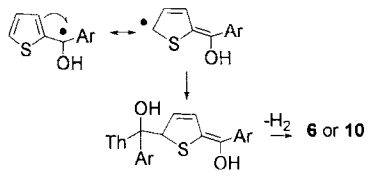
Scheme 5. A tentative explanation of the diastereoselectivity in the formation of lactones **7**, **11** and **13**.

Nd:YAGlaser pulse (Fig. 1A). According to previous studies (7,15), in the presence of **4** three transient species should be formed: ketyl radical, indolyl radical and Trp-derived skatolyl radical (Fig. 1B). The broad, long wavelength absorption band in the visible region is clearly because of the overlap of the spectra of the indolyl (λ_{max} at 520 nm) (16) and the ketyl radical (λ_{max} at 580 nm) (6). This absorption band decayed faster than the sharp 350 nm signal, which could indicate the presence of the Trp-derived skatolyl radical. Formation of this species was indeed expected, because it is the necessary reaction intermediate leading to several of the isolated products (**7**, **11** and **13**). Because related skatolyl radicals are known to be very long-lived under anaerobic conditions (17), the spectra were measured at very long times after the laser pulse. As a matter of fact, the transient spectrum of this long-lived, C-centered radical (λ_{max} at 350 nm and no significant absorption beyond 400 nm) was indeed observed (Fig. 1C). Similar spectra were obtained in the case of **1a** and **1c**.

DISCUSSION

As in the related photochemical reaction of indole or 3-methylindole with BT, long irradiation times were needed to obtain sufficient amounts of the photoproducts. This indicates that recombination within the radical pairs (see Scheme 1) occurs to a large extent, regenerating the starting materials.

The main (or exclusive) cross-coupling products were lactones **7**, **11** and **13**; they were obtained with remarkable stereoselectivity (only the 4*R* stereoisomers were isolated). This could be because of the combination of two effects: (1) planarization of the skatolyl radical (to favor delocalization of its unpaired benzylic electron) and (2) steric strain between the amidyl and indolyl moieties, which favors conformation for the attack to the prochiral center *anti* to the carboxymethoxy at the adjacent carbon (Scheme 5). Two diastereoisomeric esters should be obtained if planarization of the ketyl radicals is faster than radical combination. In agreement with this, two diastereoisomeric lactones derived from cyclization of those esters were obtained (this process could take place during the chromatography isolation). A similar rationalization has been used to explain the formation of analogous lactones in related photoreactions of benzophenone with other amino acids (18). Also, asymmetric induction involving radicals that are flanked by an



Scheme 6. Formation of compounds **6** and **10**.

ester and a stereogenic center bearing a heteroatom has been demonstrated in some reactions (19,20).

Moreover, the isolation of ketone homodimers coupled through the thienyl 5-position is remarkable. This type of compounds should arise from reaction of two ketyl radicals via the ketyl carbon of one of them with the delocalized radical at the 5-position of the other one (Scheme 6). Although coupling products of this type have been proposed for phenyl ketones, the only evidence for their formation has been obtained via UV spectra of the photomixtures; attempts to isolate them have been unfruitful (21–24). In the case of the LAT-derived products obtained in the present work, aromatization giving the thienyl ring would compete with regeneration of the starting products.

Finally, it should be mentioned that the yields of cross-coupling products here obtained are rather low, taking into account the efficient photobinding of the BT chromophore to proteins (2). This could be because of the fact that in solution the radicals can escape from the solvent cage, whereas in the protein the ketyl radicals and the protein-derived radicals are tightly bound, increasing the probability of cross-coupling products formation.

In summary, irradiation of acetonitrile solutions of BT in the presence of *N*-BOC-(*L*)-tryptophan methyl ester leads to homodimers derived from coupling of two ketyl radicals. The main cross-coupling product is in all the cases a lactone arising from the reaction between Trp-derived skatolyl radicals and the corresponding ketyl radicals. In accordance with previous studies, no coupling products through the phenyl *p*-position have been isolated when this position is free (BT and TPA methyl ester). By contrast, ketone homodimers and cross-coupling products arising from coupling through the thienyl 5-position are obtained when using BT and SUP methyl esters. This is not possible in TPA, because of the presence of the bulky substituent at the thienyl 5-position. These facts can be relevant in relation to the photobiological effects produced by benzoylthiophene-derived drugs.

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