Photocyclization of Aryl- and Heteroaryl-2-propenoic Acid Derivatives. Synthesis of Polycyclic Heterocycles

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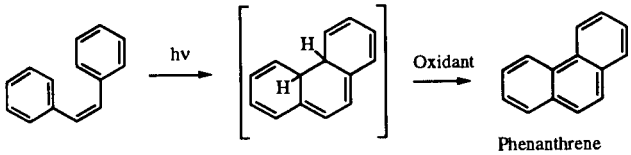
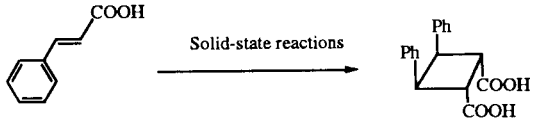
The stilbenes have been widely utilized as a versatile intermediate reagent for the synthesis of polycyclic hydrocarbon derivatives in photocylization reactions [1-3]. Their usual reactions initiated by light can be systematized as dimerizations, isomerizations and cyclizations [4-7]. The photocyclization of stilbenes occurs with a wide range of substituted stilbenes, including those bearing electron-withdrawing substituents such as carboxyl or cyano groups on the olefin and various polycyclic and heterocyclic analogs. Since the direct introduction of some specified substituents into polycyclic hydrocarbon or heterocyclic nuclei is not always easy, efforts have been directed in the first step of the synthesis to the construction of the ring bearing the useful functionalized groups, for example, carboxyl or cyano groups. The photocyclization of stilbenes bearing these groups yields polycyclic hydrocarbons or heterocyclic carboxylic acids or carbonitriles. These substances are very important as the key intermediates for the synthesis of useful derivatives such as biologically active compounds. This review describes the synthetic utility of the photocyclization of aryl- and heteroarylpropenoic acids and their derivatives primarily in the preparation of heterocyclic compounds and the reactions of their photocyclized products.



Phenanthrene

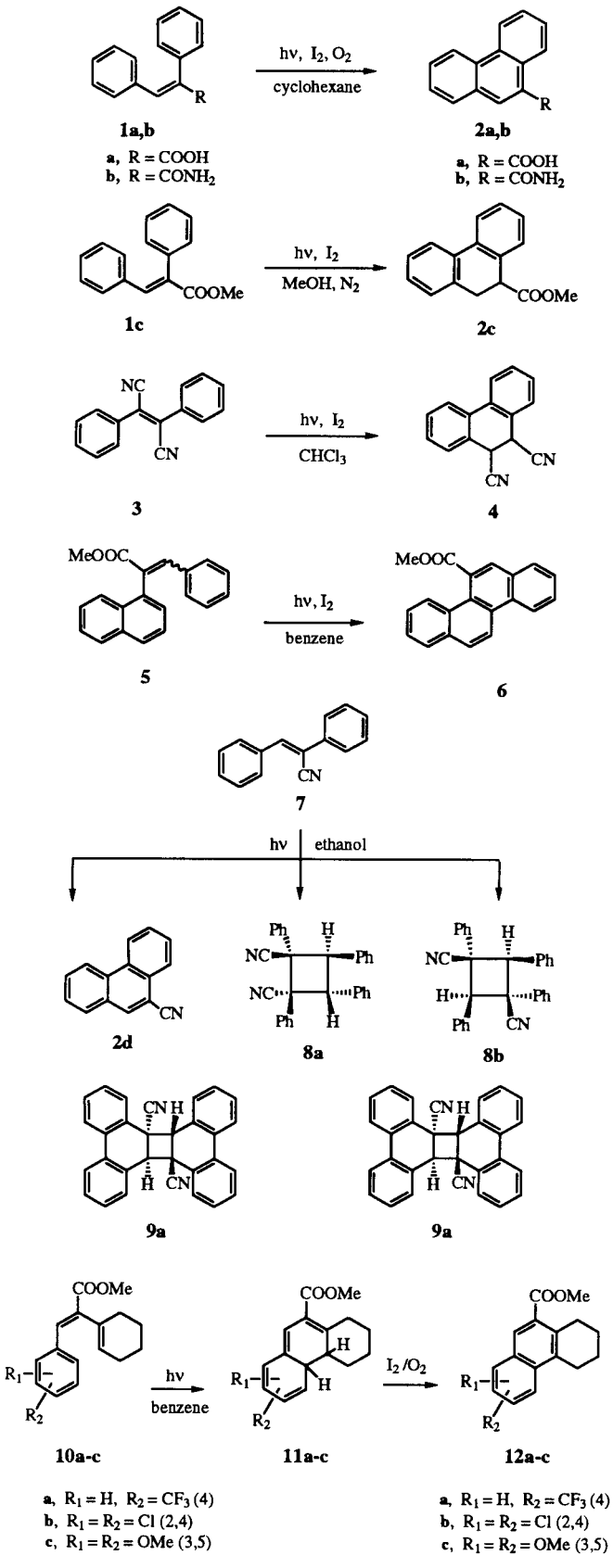


α-Truxillic acid

In a study of the photoconversion of stilbenes to phenanthrenes, Wood and Mallory reported that the photocyclization of 2,3-diphenylpropenoic acid (**1a**) in the presence of iodine and oxygen in thiophene free benzene gave the corresponding 9-phenanthrenecarboxylic acid (**2a**) in 72% yield [8]. Wood and Mallory determined the most satisfactory conditions that have been developed for preparative-scale photocyclization reactions. These involve the irradiation using an unfiltered mercury arc of an open-air stirred solution of 0.01 mole of the stilbene derivative and 0.0005 mole of iodine dissolved in 1 l of cyclohexane or benzene. The results obtained from these conditions suggest that using a mixture of two oxidants, iodine and dissolved oxygen, is superior to the results achieved when using oxygen alone [8]. Similarly, irradiation of *cis*-α-phenylcinnamide **1b** in the presence of oxygen give the corresponding phenanthrene derivatives **2b** in good yields [9]. In the absence of oxidants, certain dihydrophenanthrene derivatives undergo hydrogen shifts to give isomeric dihydrophenanthrenes. For example, the photocyclization of methyl 2,3-diphenylpropenoate (**1c**) in methanol solution gave 9-carbomethoxy-9,10-dihydrophenanthrene (**2c**) [10b]. Similarly, the phocyclization of dinitrile **3** in degassed benzene solution gave **4** [9]. Methyl 5-chrysenecarboxylate (**6**) is prepared by the photocyclization of **5** in the presence of iodine in benzene [11]. In the case of irradiation of propenecarbonitrile **7**, dimerization products **8a,b, 9a,b** are also identified along with a normal photocylization product **2d** (Scheme 1) [9]. The photocyclization of **10a-c** also gave the corresponding methyl 1,2,3,4-tetrahydrophenanthrene-5-carboxylates **12a-c** in good yields, respectively (Scheme 1) [12].

Irradiation of *cis*-2,3-diphenylpropenoic acid (**1a**) in the presence of tetramethylethylene in degassed ether gives *trans*-1,2-diphenyl-3,3,4,4-tetramethylcyclobutane (**14**) in 67% yield [13]. The mechanistic path of the reaction is believed to involve initial isomerization of *cis*-α-phenylcinnamic acid to the *trans*, *cis*-β-lactones. The *cis*-β-lactone **13** is isolated in 79% yield. Irradiation of the *cis*-β-lactone **13** in a degassed ether solution containing tetramethylethylene gives *trans*-1,2-diphenyl-3,3,4,4-tetramethylcyclobutane (**14**) in 85% yield. This result shows that *cis*-2,3-diphenyl-3-propiolactone (**13**) is a plausible intermediate in the formation of *trans*-1,2-diphenyl-3,3,4,4-tetramethylcyclobutane (**14**). The photoisomerization of α,β-disubstituted acrylic acids **1d-s** to β-lactones **13, 15** is shown to be quite general when one substituent is phenyl (Shown in Table 1). Irradiation of *trans*-2,3-diphenylpropenoic acid in benzene gives *cis*-2,3-diphenyl-3-propiolactone as the only isolated

Scheme 1



product. The yield is substantially lower than that from *cis*-2,3-diphenylpropenoic acid, and the reaction is slower. A qualitative study of the effect of *para* substituents in the α- and β-phenyl rings of *cis*-phenylpropenoic acid has revealed a striking dependence on the nature of the substituent. In the α-phenyl group electron-donation substituents facilitate reaction and electron-withdrawing

Scheme 2

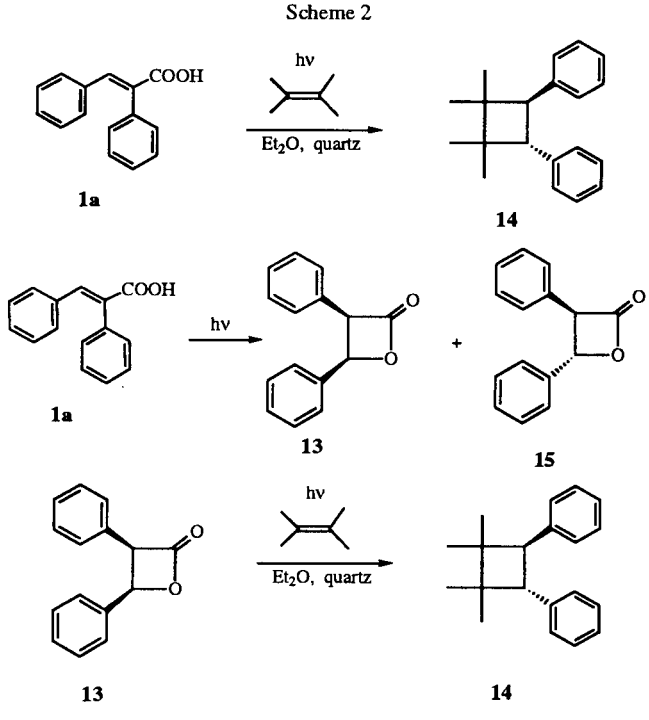
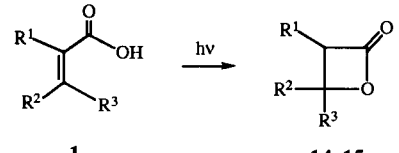


Table 1
β-Lactone Formation from Arylacrylic Acids

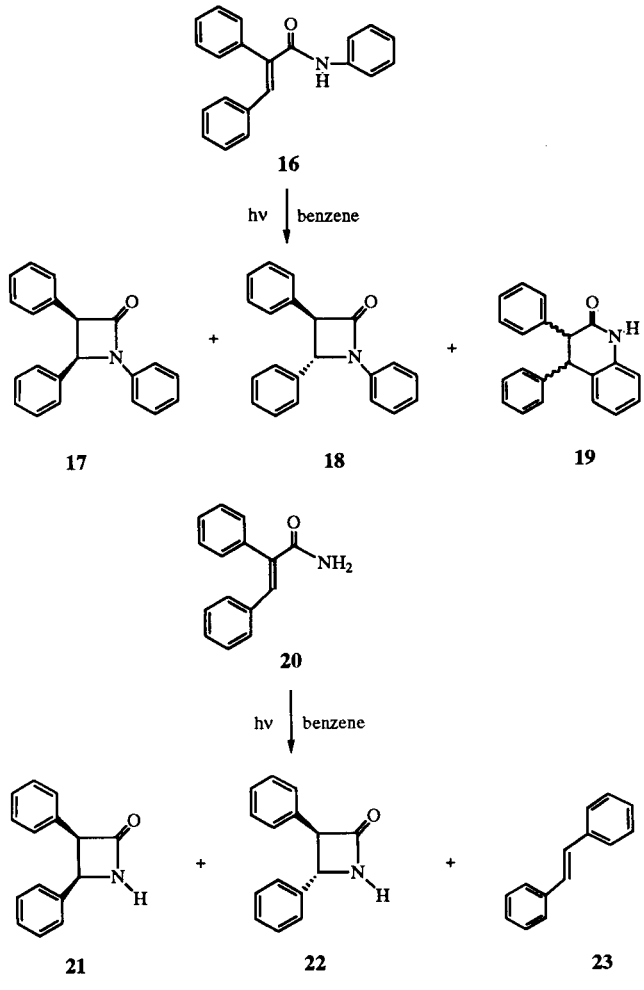


No.	R^1	R^2	R^3	Irradiation time, hr	β-Lactone *trans/cis* ratio
1	C_6H_5	C_6H_5	H	21	0.3
2	*p*-Me-C_6H_4	C_6H_5	H	23.5	0.9
3	C_6H_5	*p*-Me-C_6H_4	H	28.5	0.3
4	*p*-Cl-C_6H_4	C_6H_5	H	72	0.6
5	C_6H_5	*p*-ClC_6H_4	H	26	0.8
6	*p*-F-C_6H_4	C_6H_5	H	41	1.0
7	*p*-CN-C_6H_4	C_6H_5	H	72	All *cis*
8	C_6H_5	*p*-CN-C_6H_4	H	5	0.7
9	*p*-NO_2-C_6H_4	C_6H_5	H	72	No lactone
10	C_6H_5	*p*-NO_2-C_6H_4	H	36	1.0
11	*p*-MeO-C_6H_4	C_6H_5	H	10.5	1.0
12	C_6H_5	*p*-MeO-C_6H_4	H	96	No lactone
13	Me	C_6H_5	H	16 days	All *cis*
14	C_6H_5	Me	H	4	All *trans*
15	C_6H_5	C_6H_5	C_6H_5	12	Only one

substituents retard reaction. In the β-phenyl ring the substituent effect is reversed (Scheme 2, Table 1) [13].

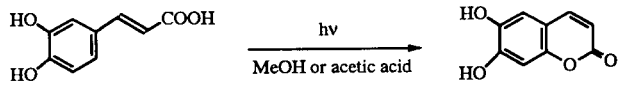
Irradiation of *cis*-α-phenylcinnamanilide (**16**) in benzene for 23 hours gives *trans*-1,3,4-triphenyl-2-azetidinone **18**, *cis*-1,3,4-triphenyl-2-azetidione (**17**), and a third substance which is tentatively identified as 3,4-diphenyl-3,4-dihydrocarbostyril (**19**). Irradiation of *cis*-α-phenylcinnamamide (**20**) in degassed benzene for 70 hours gives a complex mixture from which it is possible to isolate *trans*-stilbene (**23**), *cis*-3,4-diphenyl-2-azetidinone (**21**), *trans*-3,4-diphenyl-2-azetidinone (**22**), and an unidentified product (Scheme 3) [13].

Scheme 3



Oxidative photocyclization of 3,4-dihydroxycinnamic acid (caffeic acid) (**24**) in the presence of oxygen in glacial acetic acid gives 6,7-dihydroxycoumarin (esculetin) (**25**) in 10% yield (Scheme 4) [14]. This photocyclization also occurred in dilute acetic acid or in methanol, but more slowly. These reported results strongly suggests that a photochemically induced oxidative cyclization could account, at least in part, for the synthesis of coumarins from cinnamic acids *in vivo*.

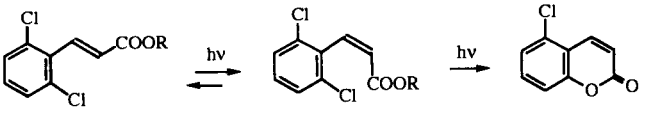
Scheme 4



24 caffeic acid **25** esculetin

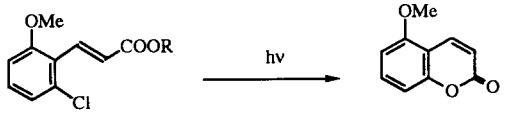
On uv irradiation, 2,6-dichlorocinnamic acid (**26a**) and its esters **26a-h** undergo photocyclization with elimination of the elements of HCl or RCl (R = alkyl or aryl) to yield 5-chlorocoumarin (**28**) (Scheme 5) [15,16]. The photocycloelimination is observed only with 2,6-disubstituted cinnamic acid derivatives. Irradiation of the related 2,4-dichloro analogs gives no trace of coumarin and additional products. In order to elucidate the process by which these compounds undergo their photocyclization, two other compounds, methyl 2-chloro-6-methoxycinnamate and its free acid were irradiated and yielded 5-methoxycoumarin as the product with no trace of 5-chlorocoumarin. Irradiation of methyl 2,6-dimethoxycinnamate and ethyl 2,4,6-trimethoxycinnamate only gave *cis-trans* photoisomerization. From these examples, it was concluded that the loss of the chlorine atom in the *ortho* position led to the ring closure and formation of the coumarin product [15]. Low-temperature irradiation monitored by

Scheme 5



26a-h **27** **28a**

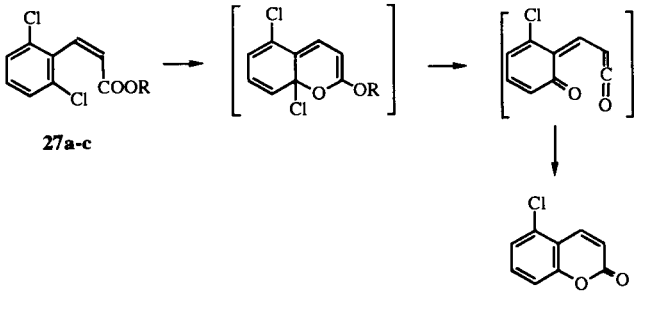
R = H, Me, Et, *iso*-Pr, *t*-Bu, *n*-Octyl, Ph, Ph-Br(4)



26i,j **28b**

R = H, Me

Scheme 6

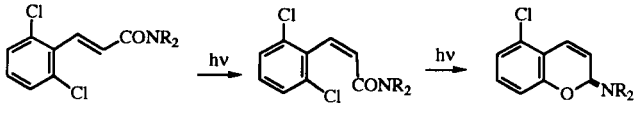


27a-c **28a**

infrared and optical spectrophotometry enabled the identification of *o*-quinomethyl ketene as one of the intermediates of this reaction and leading to a proposed mechanism for the photocycloelimination (Scheme 6 and 8).

2,6-Dichlorocinnamide (**29a**) and its *N*-methyl **29b** and *N,N*-dimethyl **29c** derivatives also undergo this same photocyclization; a chlorine atom and the group attached to the nitrogen are eliminated to give the iminocoumarins **31a-c** (Schemes 7 and 8) [16]. The latter was readily hydrolyzed in the presence of moisture to the 5-chlorocoumarin (**28**).

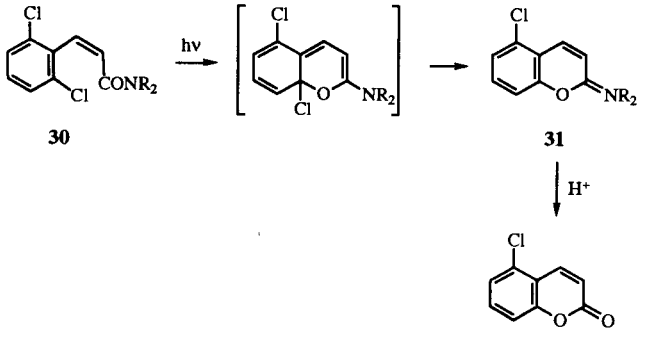
Scheme 7



29a-c **30a-c** **31a-c**

a, $NR_2 = NH_2$
b, $NR_2 = NHMe$
c, $NR_2 = NMe_2$

Scheme 8

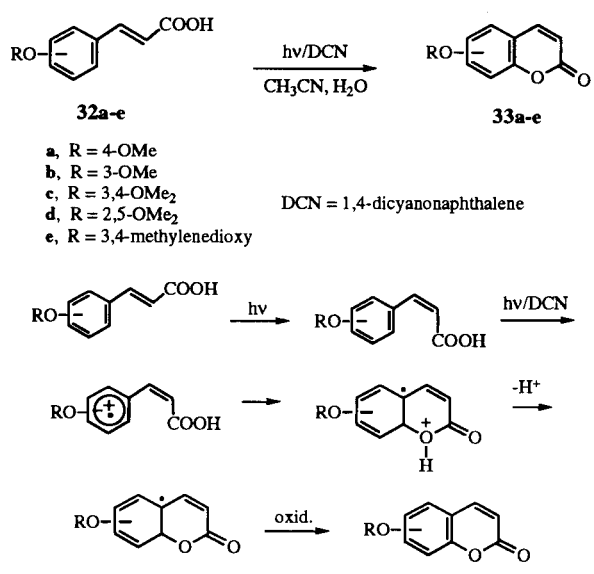


30 **31** **28a**

Pandey, *et al.*, have reported a single electron transfer initiated photocyclization of substituted cinnamic acids **32a-e** to the corresponding coumarins **33a-e** (Scheme 9) [17]. Irradiation of a solution containing substituted cinnamic acids (bearing electron-rich substituents) and 1,4-dicyanonaphthalene as an electron acceptor in a mixture of acetonitrile and water (80:20) saturated with oxygen using a 125 Watt mercury lamp for 4-6 hours gives the corresponding coumarins as a single photoproduct in 60-80% yield. Cinnamic acid fails to give the cyclized product under these circumstances [17].

The oxidative photocyclization of stilbenecarboxylic acid **34** in the presence of iodine gives the desired chrysenecarboxylic acid **35** as the major product in 58% yield along with a small amount of lactone **36** [18]. This ratio is dependent on the irradiation time. The irradiation of **35** is carried out under identical conditions and **35** itself is found to be slowly transformed to lactone **36**. Compound

Scheme 9



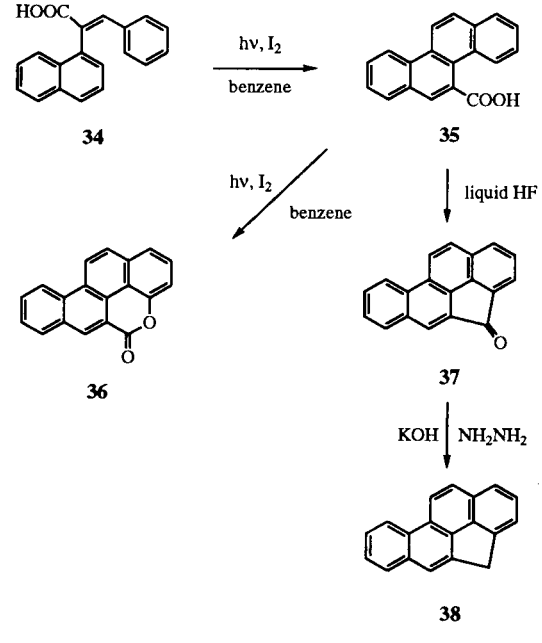
32a-e **33a-e**

a, R = 4-OMe
b, R = 3-OMe
c, R = 3,4-OMe_2
d, R = 2,5-OMe_2
e, R = 3,4-methylenedioxy

DCN = 1,4-dicyanonaphthalene

35 is a key intermediate of methanochrysene **38**. Cyclization of acid **35** in liquid HF gives the pentacyclic ketone **37** in 65% yield. A modified Wolff-Kishner reduction of this ketone gives **38** in 60% yield. The formation of lactone **36** from carboxylic acid **34** involves an unusual intramolecular photoaddition of arenecarboxylic acid. Such a transformation can be rationalized in terms of a 6π-electrocyclization involving the carbonyl group followed by oxidation of the dihydroaromatic lactone. The high mutagenicity of lactone **36** is of interest since this compound is analogous to the mutagenic and carcinogenic PAH benzo[*a*]pyrene [11] (Scheme 10).

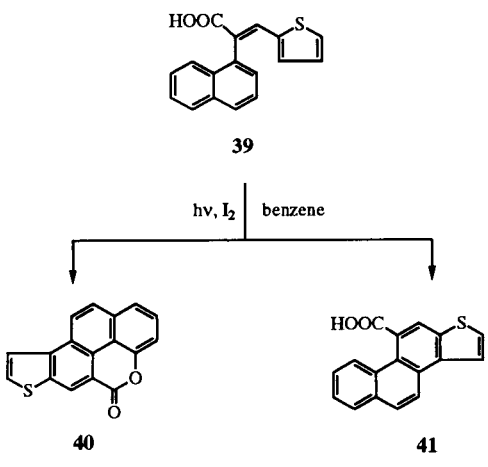
Scheme 10



34 **35** **36** **37** **38**

The irradiation of 2-(1-naphthyl)-3-(2-thienyl)propenoic acid (**39**) in the presence of iodine and oxygen in benzene gives the a mixture of a new lactone **40** and phenanthro[2,1-*b*]thiophene-10-carboxylic acid (**41**) in 2 and 28% yields, respectively (Scheme 11) [19].

Scheme 11



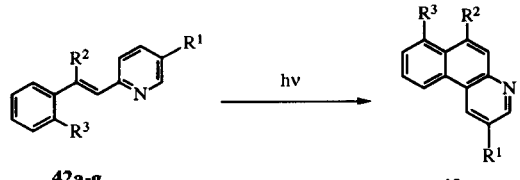
The photochemical behavior of a series of 2-stilbazole derivatives has been investigated [20-26]. The photochemical cyclization of stilbene and its derivatives has received considerable attention, but the photochemistry of stilbazoles has not been thoroughly investigated until Kumler's investigation [20,21]. The 2-stilbazole derivative **42a**, upon solution phase photolysis in the presence of oxygen, is converted in moderate yield into the corresponding benzo[*f*]quinoline (**43a**). The results of irradiation of other compounds **42b-g** is shown in Scheme 12 [20]. Photolysis of **42e** in *t*-butyl alcohol through Corex for 5 hours, followed by column chromatography on alumina, led to isolation of both **43e** (11%) and **43c** (6%) [21]. The formation of **43c**, which formally corresponds to loss of the elements of HCl, can be rationalized in a number of ways. Loss of substituents other than hydrogen during photocyclizations has been seen in a number of cases and the substituents "lost" include Cl, Br, CH_3, COOH, I, and OCH_3 (Scheme 12) [20]. Prolonged irradiation of the acetamidostilbazole **42f** resulted in a complex mixture of photoproducts from which the expected benzo[*f*]quinoline **43f** could not be isolated by column chromatography. Failure to isolate **43f** from photolysis of **42f** is thus probably due to the photodecomposition of **43f** under the reaction conditions.

Irradiation of nitrostilbazole **42g** under a wide variety of experimental conditions (variation of solvent, wavelength, and oxidizing agent) resulted in disappearance of the starting material; however, the expected photocyclization product **43g** could not be detected in the photolysate. Previous workers have noted that stilbenes containing nitro substituents would not undergo the photocyclization reaction [1b].

In an attempt to increase the yield of the photocyclization reaction and perhaps decrease the yield of undesirable byproducts, a study of the effect of various experimental parameters on the photocyclization of the nitrile **42b** was carried out. The effect of solvent, wavelength and additives on this reaction is also investigated, and the results are summarized in Scheme 13 and Table 2. It can readily be seen that polar solvents generally increase the rate of disappearance of the starting material, but the amount of photocyclized material isolated is generally less than in nonpolar solvents. The major exception to this generalization is the use of *t*-butyl alcohol as the solvent. Photolysis of the stilbazole **42c** in *t*-butyl alcohol containing small amounts of benzene as the solvent required 4 hours for complete disappearance of starting material and benzo[*f*]quinoline **43c** was isolated in 64% yield. In comparison, photolysis of this substrate in benzene as the solvent required 23 hours and the isolated yield of **43c** was 70% [20].

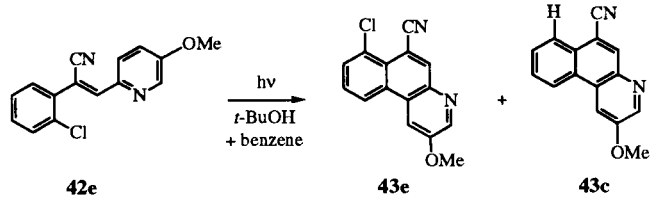
From the photolysis of the cyanostilbazole **42b** in cyclohexane solution in the presence of oxygen, the expected

Scheme 12



42a-g **43a-g**

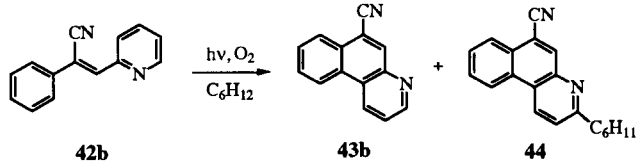
	R^1	R^2	R^3	Yield (%)
a	H	H	H	35
b	H	CN	H	58
c	OMe	CN	H	70
d	H	COOMe	H	25
e	OMe	CN	Cl	6
f	H	H	NHCOMe	no
g	H	H	NO_2	no



42e **43e** **43c**

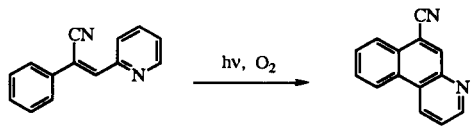
11% 6%

Scheme 13



42b **43b** **44**

Table 2
Effect of Solvent and Additives on the Photolysis of **42b**



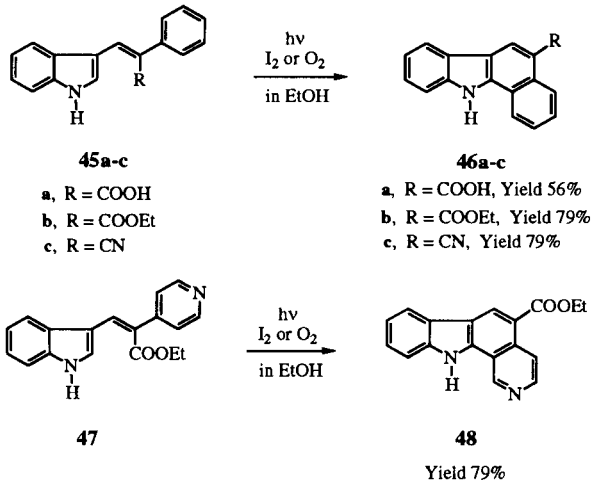
42b **43b**

Entry	Solvent	Filter	Irradiation time, hr	Yield of **43b**, %
1	C_6H_{12}	Corex	34.0	38
2	C_6H_6	Corex	27.0	70
3	CH_3CN	Vycor	7.0	17
4	CH_3CN	Corex	5.0	30
5	DME	Corex	4.5	0
6	C_2H_5OH	Corex	2.5	14
7	C_2H_5OH, $CuBr_2$	Vycor	8.0	0
8	t-C_4H_9OH	Corex	3.0	62

benzo[*f*]quinoline-6-carbonitrile (**43b**) is isolated in 58% yield. A minor photoproduct, 3-hexylbenzo[*f*]quinoline-6-carbonitrile (**44**) is isolated in 8.4% yield [10a].

Photolysis of **45a-c** in the presence of iodine or oxygen produced the corresponding cyclodehydrogenated products **46a-c**, respectively. The photolysis of the 3-pyridyl derivatives **47** proceeded predictably to give the expected pyridocarbazoles **48** in 79% yield [27].

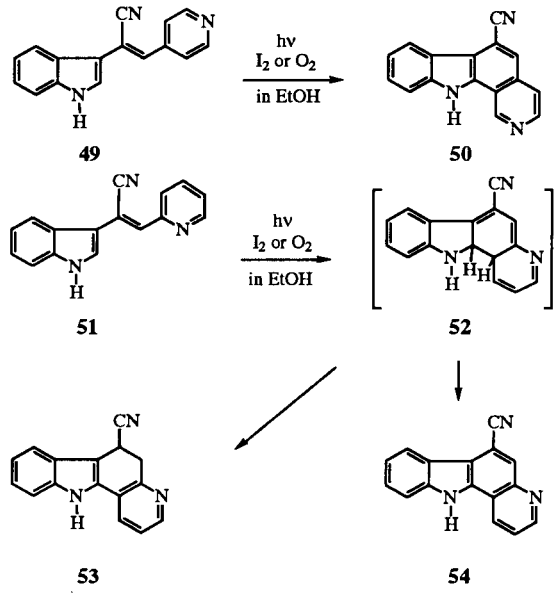
Scheme 14



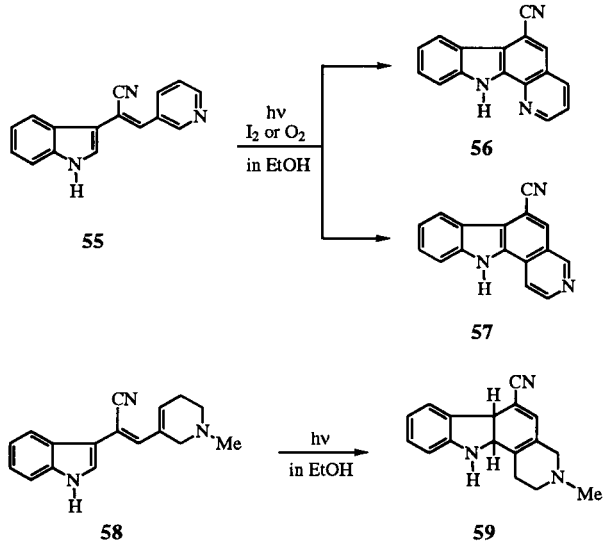
Irradiation of **49** in ethanol gives 6-cyano-11*H*-pyrido-[3,4-*a*]carbazole **50**. The photocyclization of **51** gives a mixture of 5,6-dihydropyrido[3,2-*a*]carbazole-6-carbonitrile (**53**) and 11*H*-pyrido[3,2-*a*]carbazole-6-carbonitrile (**54**) (Scheme 15) [28]. Irradiation of **55** gives a mixture of **56** and **57** (Scheme 16) [28]. Thal, *et al.*, have reported that the irradiation of **58** under nitrogen in ethanol gives the cyclized product **59** [29].

Irradiation of compound **60** and **49** gives a mixture of 11*H*-pyrido[3,4-*a*]carbazole derivatives (**61**, **50**) along with **62**, **63**, and **64** (Scheme 17) [29].

Scheme 15



Scheme 16

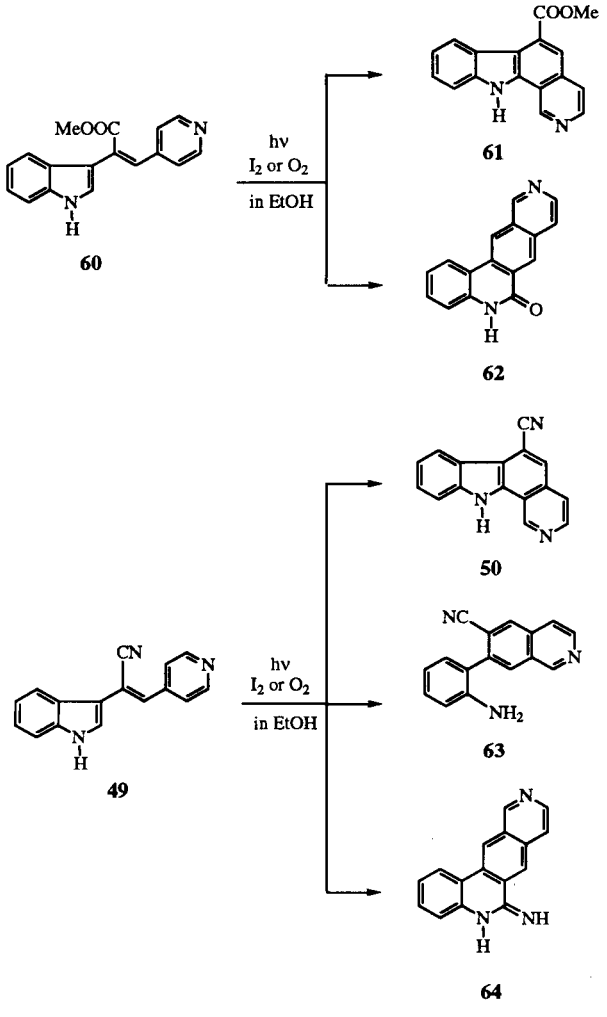


Irradiation of **58** in the absence of oxygen gives a mixture of the expected cyclized products **59**, **65** and the spiro compound **66** (Scheme 18) [29].

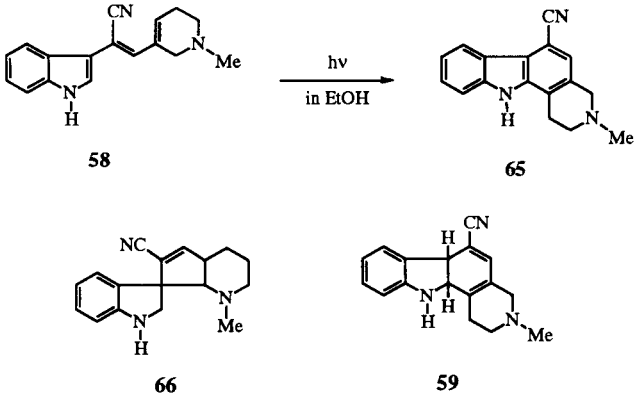
Irradiation of an ethanolic solution of **67** with a high-pressure Hanovia lamp in the presence of ferric chloride or iodine led to two products, **68** and **69** in 5 and 30% yields, respectively. The heterocycle **68**, containing a highly hindered pyridine nitrogen, is unreactive toward methylation, whereas **69** yielded a pyridinium salt **70** on treatment with methyl iodide, which could be converted into the piperidine derivative **71** on sodium borohydride reduction (Scheme 19) [30].

Irradiation of an ethanolic solution of **67** under nitrogen with a high-pressure Hanovia lamp yielded a complex

Scheme 17



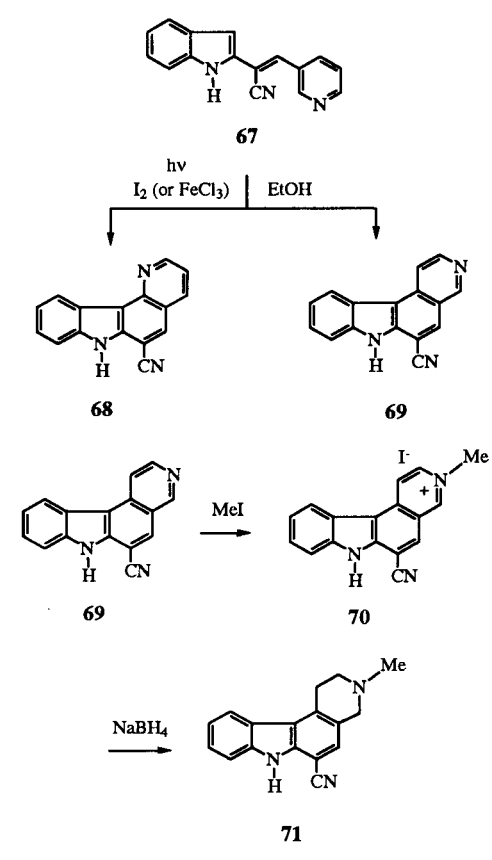
Scheme 18



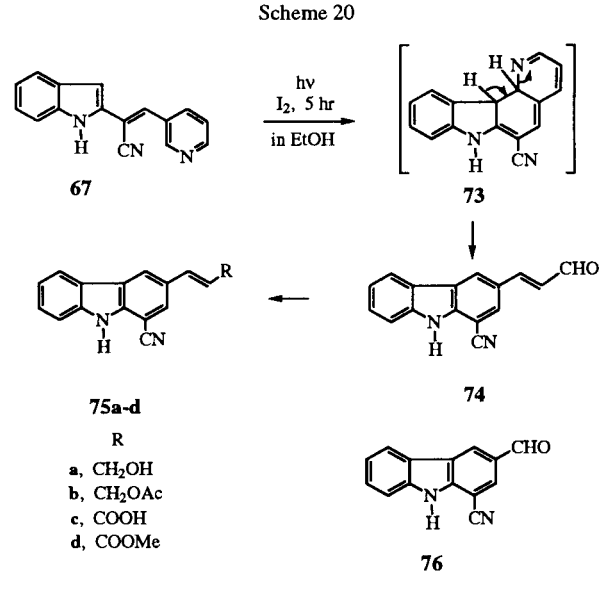
mixture from which a product to which structure **74** is assigned could be isolated in 30% yield. Compound **74** is an important intermediate of **75a-d** (Scheme 20) [30].

The photoconversion of some iodophenyl(thienyl)ethylenes and iodothienyl(thienyl)ethylenes to naphthothiophenes and benzodithiothiophenes respectively has been carried out. When a solution of methyl 2-(2-iodophenyl)-*trans*-3-(2-thienyl)-2-propenolate (**77**) in cyclohexane is photolysed with a high-pressure mercury lamp, iodine is released almost at once and after 6 hours methyl naphtho[2,1-*b*]thiophene-5-carboxylate (**78**) is obtained. A small

Scheme 19



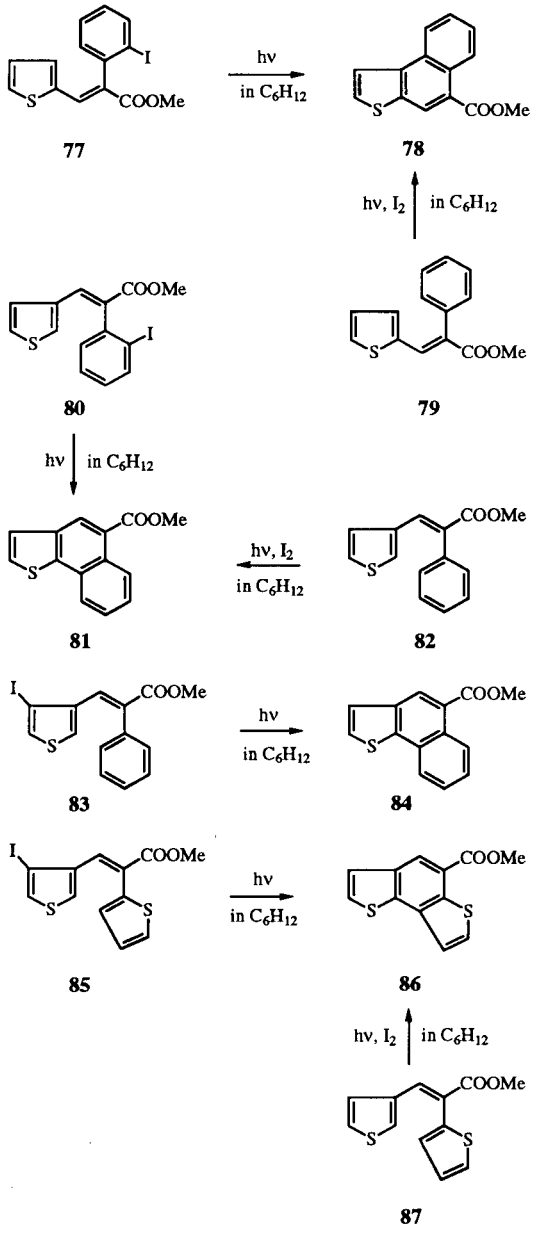
Scheme 20



quantity of a *cis-trans* mixture of the dehalogenated products **79** and **82** always accompanies the cyclization products **78** and **81**, respectively. Compounds **78** and **81** are identified by comparison with the authentic compound obtained from the photocyclization, in the presence of iodine, of methyl 2-phenyl-*trans*-3-(2-thienyl)-2-propenoate (**79**) and methyl 2-phenyl-*trans*-3-(3-thienyl)-2-propenoate (**82**). When methyl 2-phenyl-*trans*-3-[3-(4-iodo)thienyl]-2-propenoate (**83**) is irradiated with uv light, it gives **84** as the sole cyclization product. Similarly when methyl 2-(2-thienyl)-*trans*-3-[3-(4-iodo)thienyl]-2-propenoate (**85**) is irradiated, a single substitution product, methyl benzo[1,2-*b*:3,4-*b'*]dithiophene-5-carboxylate (**86**) is obtained, identical with the product isolated in the photocyclization of methyl 2-(2-thienyl)-*trans*-3-(3-thienyl)-2-propenoate (**87**). The results suggest that the intermediate in these cyclizations is likely to be a dihydro-derivative, which suffers dehydrogenation, rather than form an aryl radical which effects intramolecular substitution (Scheme 21) [31].

The above oxidative photocyclization of thiophene derivatives is applicable to prepare biologically active substances. A series of substituted alkylaminomethylnaphtho[2,1-*b*]thiophene-4-methanols **91** has been synthesized and screened for anitimalarial activity. The key step in the synthesis of the naphtho[2,1-*b*]thiophene ring system **89** is accomplished by photooxidative cyclization of arylthienylethylenes **88** (Scheme 22, Table 3) [32]. The side chains are attached by the classical five-step synthesis involving diazo ketone intermediates **90**->**91** (Scheme 22) [32,33].

Scheme 21



Scheme 22

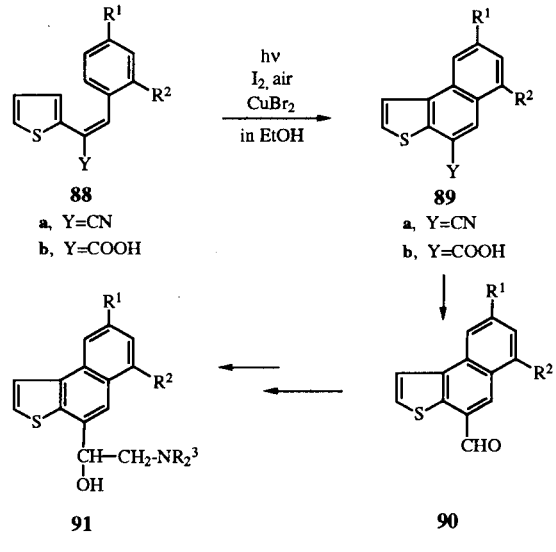
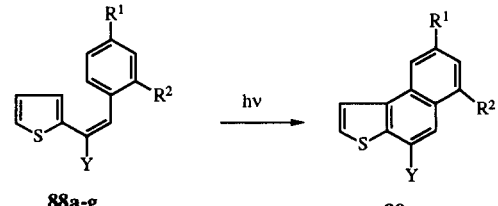
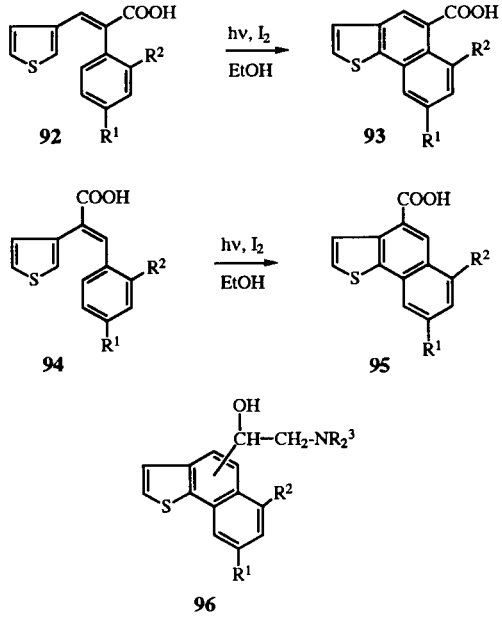


Table 3
4-Functionalized Naphtho[2,1-*b*]thiophenes



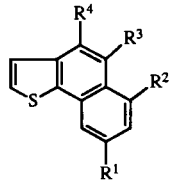
No.	R^1	R^2	Y	Mp, °C	Yield, %
89a	H	H	CN	124-125	60
b	CF_3	H	CN	183-184	51
c	Cl	Cl	CN	268-269	20
d	H	H	COOH	282-283	80
e	CF_3	H	COOH	306-307	85
f	Br	H	COOH	332-333	15
g	Cl	Cl	COOH	337-339	15

Scheme 23



Naphtho[1,2-*b*]thiophene-4-carboxylic acids **93** and naphtho[1,2-*b*]thiophene-5-carboxylic acids **95**, prepared by photooxidative cyclization of 2-(3-thienyl)-3-aryl-2-propenoic acids **92** and 2-aryl-3-(3-thienyl)-2-propenoic acids **94** (shown in Table 4), respectively, are converted into α-(alkylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanols as antimalarials **96** by the conventional five-step route involving bromomethyl ketone intermediates. It is interesting to note that photooxidative cyclization of 2-(3-thienyl)-3-phenyl-2-propenoic acids **92a** proceeds rapidly and in good yields; however their isomers, the 2-phenyl-3-(3-thienyl)-2-propenoic acids **94**, require relatively long irradiation times and the photooxidative cyclization yields are poor (Scheme 23) [34].

Table 4
Naphtho[1,2-*b*]thiophenes

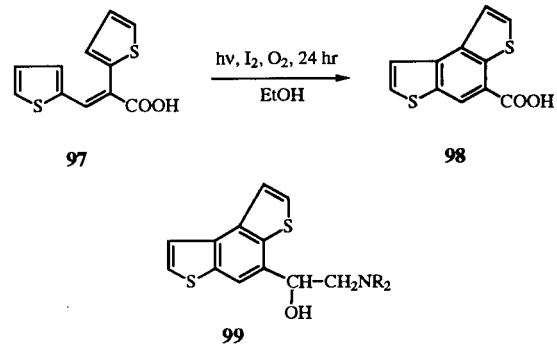


93a-d, 95a-d

No.	R^1	R^2	R^3	R^4	Mp, °C	Yield, %
93a	H	H	COOH	H	250-251	20
b	CF_3	H	COOH	H	232-233	22
c	Br	H	COOH	H	295-296	15
d	Cl	Cl	COOH	H	248-250	8
95a	H	H	H	COOH	260-261	61
b	CF_3	H	H	COOH	272-273	74
c	Br	H	H	COOH	321-322	73
d	Cl	Cl	H	COOH	333-334	76

Benzo[1,2-*b*:4,3-*b'*]dithiopheneethanolamines **99** are also synthesized in order to search for antimalarial activity. The synthesis of the benzodithiophene **98** is obtained in 57% yield by the photocyclization of dithienylpropenoic acid (**97**) in a similar manner to that described for the naphthothiopheneethanolamines and is outlined in Scheme 24. Compound **97** is readily obtained by condensation of thiophene-2-carboxyaldehyde and thiophene-2-acetic acid under modified Perkin reaction conditions (Scheme 24) [35].

Scheme 24



Karminski-Zamola *et al.*, have reported the photochemistry of number of 2-phenyl-3-(2-furyl)propenoic acids **100** under aerobic conditions to give substituted naphtho[2,1-*b*]furancarboxylic acids **101**, 2,3-epoxy-2,3-dihydrofuro[3,2-*b*]pyran-5-ones **103**, 7a-hydroxy-3a,7a-dihydrofuro[3,2-*b*]pyran-5-ones **104** and 7a-hydroxy-3a,7a-dihydrofuro[3,2-*b*]pyran-5-one (**105**). The type of the product, yield and composition of the possible mixture is strongly substituent dependent (Scheme 25 and Table 5) [36].

Scheme 25

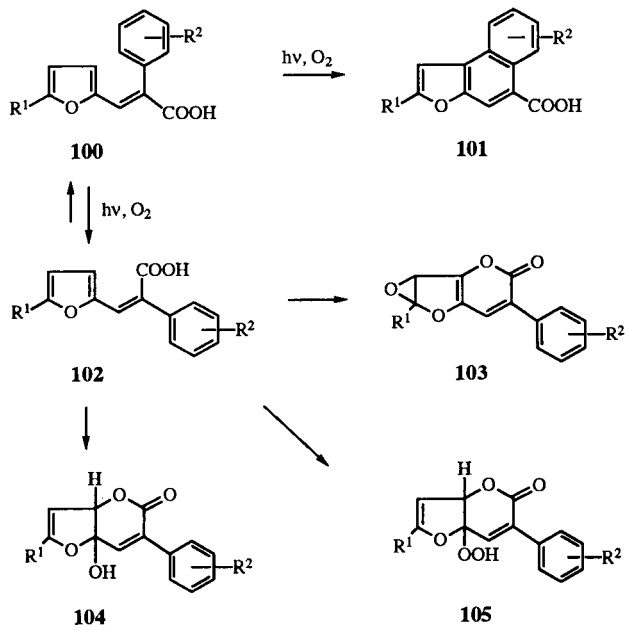
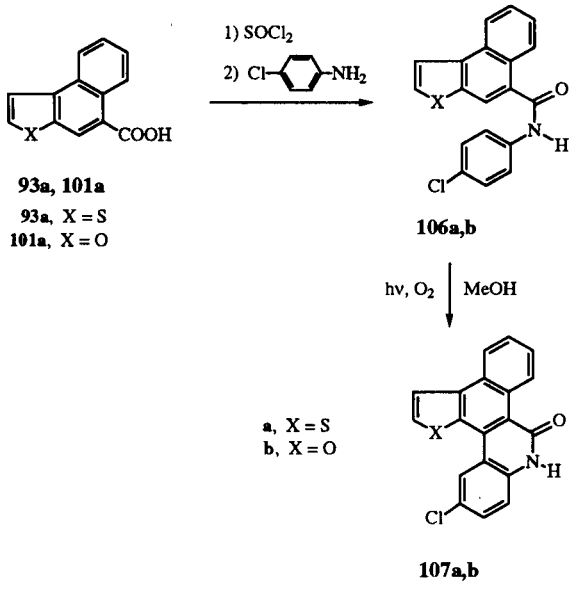


Table 5
UV Irradiation of 2-Aryl-3-furylpropenoic Acids

No	Starting acid (100) R^1	R^2	Irrad. (hours)	Product	Yield %	Reagent Acid (100)
1	H	4-CH_3	48	**101b + 103a**	30 + 30	–
2	H	3-CH_3	67	–	–	67
3	H	4-OCH_3	72	–	–	15
4	H	3-OCH_3	100	**101c**	50	–
5	H	4-Cl	48	**103b**	15	30
6	H	3-Cl	125	–	–	–
7	H	4-NO_2	98	–	–	80
8	5-CH_3	4-CH_3	48	–	–	–
9	5-CH_3	3-CH_3	48	**104a**	40	–
10	5-CH_3	4-OCH_3	48	**105**	48	–
11	5-CH_3	3-OCH_3	98	–	–	–
12	5-CH_3	4-Cl	48	**104b**	60	10
13	5-CH_3	3-Cl_3	72	–	–	–
14	5-CH_3	4-NO_2	30	–	–	–

5-Naphtho[2,1-*b*]thiophene-5- and naphtho[2,1-*b*]furan-5-carboxylic acids **93a, 101a** are synthesized by photochemical dehydrocyclization of **92a** and **100**. From these acids carboxanilides **106a,b** are prepared from their chlorides using thionyl chloride and *p*-chloraniline. The irradiation of **106a** and **b** in methanol gave **107a,b** in 20 and 64% yields, respectively (Scheme 26) [37].

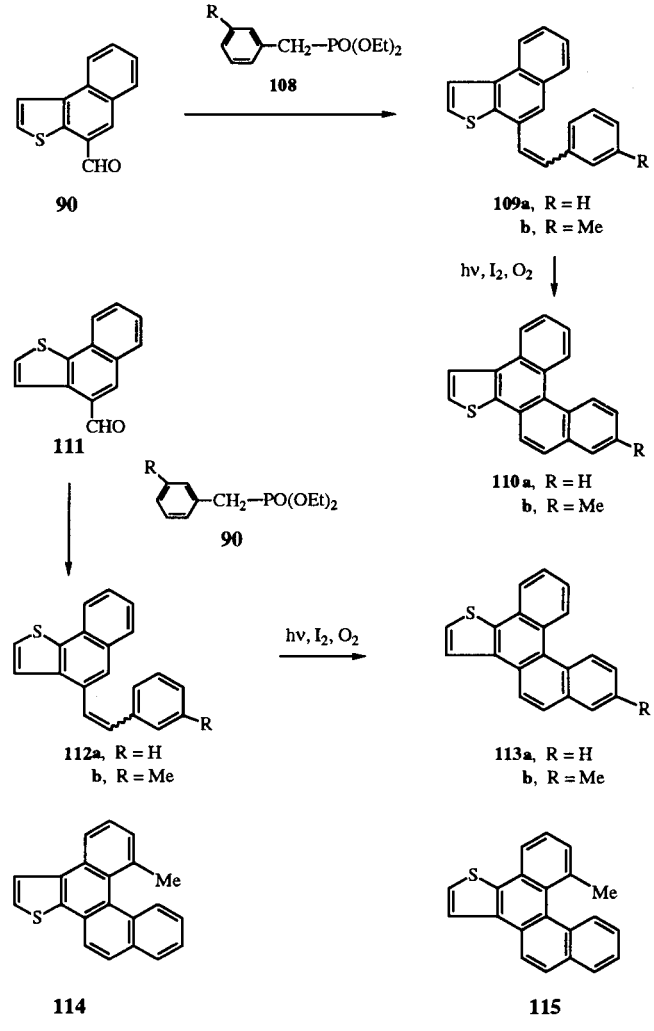
Scheme 26



The detailed characterization of polycyclic aromatic compounds in such a complex mixture as coal liquids and shale oils by capillary column gas chromatography-mass spectrometry has been reported. Using these methods, many polycyclic aromatic sulfur heterocycles have been separated and identified from coal gasification tar, coal liquids and shale oils. We have reported the synthesis of many polycyclic thiophene derivatives using photocyclization of a styrylthiophene [38-44].

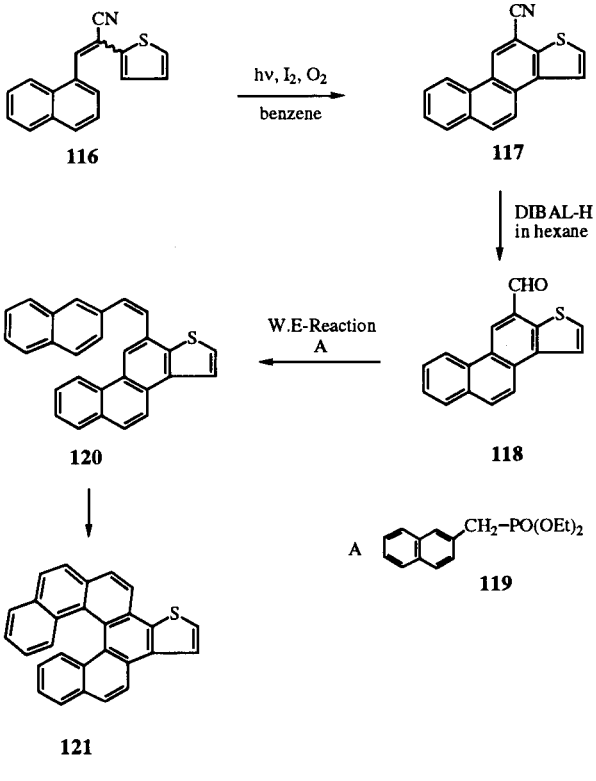
We have reported the synthesis polycyclic thiophene compounds such as phenanthro[1,2-*b*]- and [2,1-*b*]thiophene derivatives using aldehyde compound **90** (See Scheme 22) as the key intermediate. Condensation of **90** with diethyl benzylphosphonates **108a** or **b** under Wadsworth-Emmons conditions gives the styryl intermediates, **109a** or **b** in good yield followed by photocyclization to afford benzo[3,4]phenanthro[1,2-*b*]thiophenes **110a,b**. The preparation of the benzo[3,4]phenanthro[2,1-*b*]thiophenes **13a,b** were conducted in a nearly identical fashion as shown in Scheme 27. We have also reported the synthesis of compounds **114** and **115**. Total assignments of the ^{1}H-and ^{13}C-nmr spectra based on long range optimized heteronuclear proton-carbon two-dimensional chemical shift correlation were reported [45]. X-Ray crystal structures were determined for **113a** and **114**. Both molecules show distances between the bay region H^1-H^{13} and C^1Me-H^{13} of 2.03 and 2.28 Å, respectively, which are responsible for the out of plane distortions of the ring systems [45].

Scheme 27



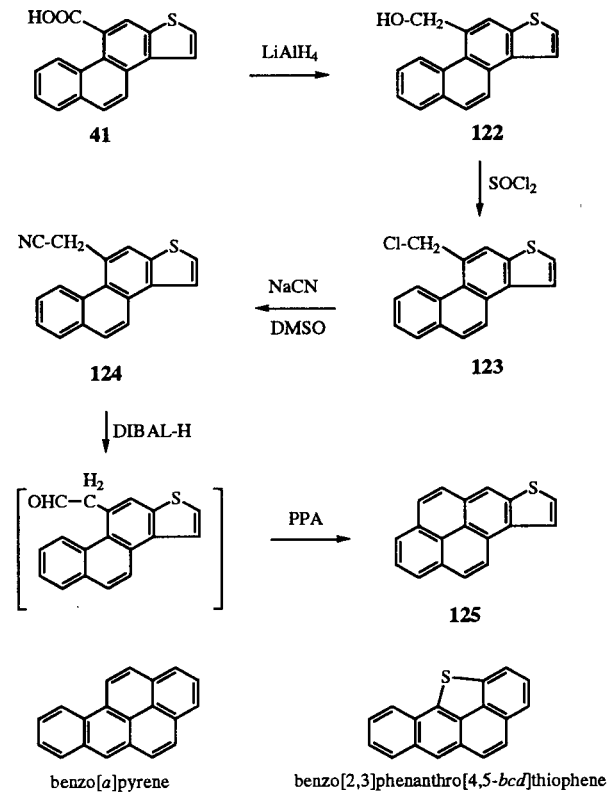
Benzo[5,6]naphtho[2',1':3,4]phenanthro[1,2-*b*]thiophene (**121**) required the initial preparation of 1-cyano-1-(2'-thienyl)-2-(1"-naphthyl)ethene (**116**) which is obtained from the condensation of thiophene-2-acetonitrile and 1-naphthalenecarboxyaldehyde. Photocyclization of **116** in benzene afforded 11-cyanophenanthro[2,1-*b*]thiophene (**117**) which is converted to the corresponding aldehyde **118** by reaction with diisobutylaluminium hydride in hexane. Reaction of **118** with 2-naphthylmethyldiethylphosphonate (**119**) under Wadsworth-Emmons conditions gives the required ethene **120** for the final photocyclization to the desired benzo[5,6]naphtho[2',1':3,4]phenanthro[1,2-*b*]thiophene (**121**). Photocyclization of **120** in benzene in the presence of iodine and a stream of dry air for 5 hours gives the desired **121** in a 75% yield (Scheme 28). The nmr assignments required concerted utilization of two-dimensional nmr techniques which included: COSY, direct and long-range optimized heteronuclear chemical shift correlation and heteronuclear relayed coherence transfer experiments [46].

Scheme 28

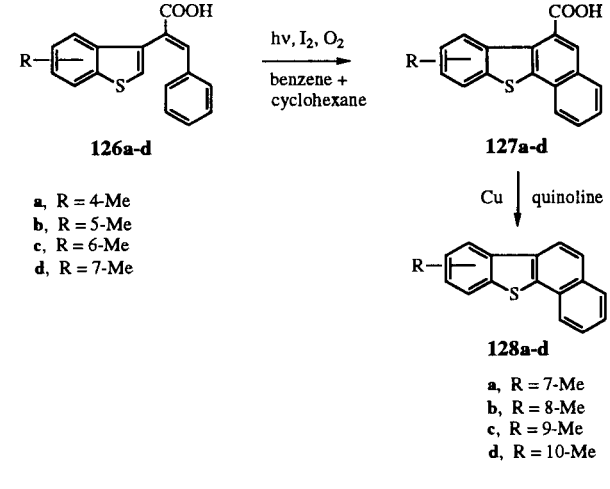


It is known that benzo[*a*]pyrene has been the most extensively investigated among the large number of polycyclic hydrocarbons. The pentacyclic thiophene compound, benzo[2,3]phenanthro[4,5-*bcd*]thiophene possesses mutagenic activity like benzo[*a*]pyrene. Compound **41** can be used as a key intermediate for the synthesis of **125** which is a thia analog of benzo[*a*]pyrene. Lithium aluminium hydride (LAH) reduction of **41** gave 10-hydroxymethylphenanthro[2,1-*b*]thiophene (**122**). The reaction of thionyl chloride on **122** gave the 10-chloromethyl compound **123** which is converted with sodium cyanide in DMSO into the 1-cyanomethyl compound **124**. The cyano compound **124** is reduced to the aldehyde with diisobutylaluminium hydride and the resulting aldehyde is cyclized with polyphosphoric acid to the desired compound **125** [47].

Scheme 29



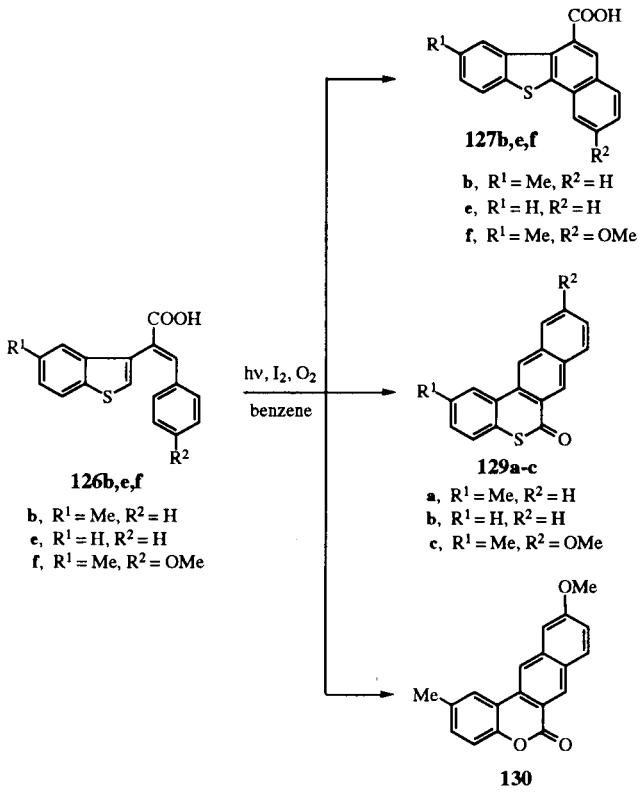
Scheme 30



The 3-styryl compounds **126a-d** are readily prepared by the condensation between acetic acid derivatives and benzaldehyde in the presence of triethylamine in acetic anhydride solution. The photocyclization of **126a-d** is carried out in a mixture of dry benzene and cyclohexane in the presence of iodine and air. Decarboxylation of **127a-d** with copper in quinoline proceeded smoothly to give the required compounds **128a-d** in 36, 52, 48, and 60% yields, respectively from **127a-d** (Scheme 30) [48].

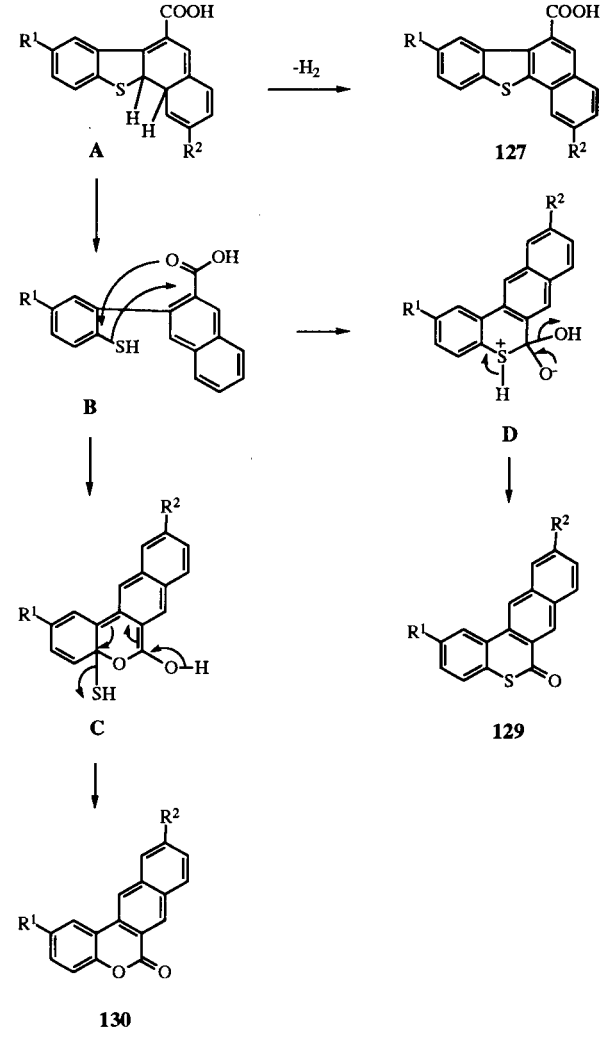
While the photocyclization of thiophene derivatives was being studied, it was found that a general oxidative cyclization reaction along with a new unexpected photocyclization reaction occurred, leading to compounds identified as new fused thiopyran and pyran derivatives. In the earlier work we did not investigate the nature of the byproducts present in low percentages occurring upon photocyclization. Therefore it was necessary to reinvestigate the photocyclization of thienyl-2-propenoic acid derivatives. Compounds **126b,e** upon irradiation in a benzene-cyclohexane mixture in the presence of iodine and air afforded a separable mixture of two compounds **127b,e** in 48 and 63% yields, respectively, together with **129a** in 6% yield and **129b** in 15% yield. Photocyclization of **126f** under the same conditions provided a separable mixture of three compounds, **127c** in 73% yield, **129c** in 3% yield, and **130c** in 4% yield. Compounds **129a-c** represent a novel polycyclic ring system and these three products are 6*H*-benzo[*e*]-naphtho[2,3-*c*]thiopyran-6-one derivatives. The third compound **130c** obtained is 10-methoxy-2-methyl-6*H*-benzo-[*b*]naphtho[2,3-*d*]pyran-6-one (Scheme 31) [49].

Scheme 31



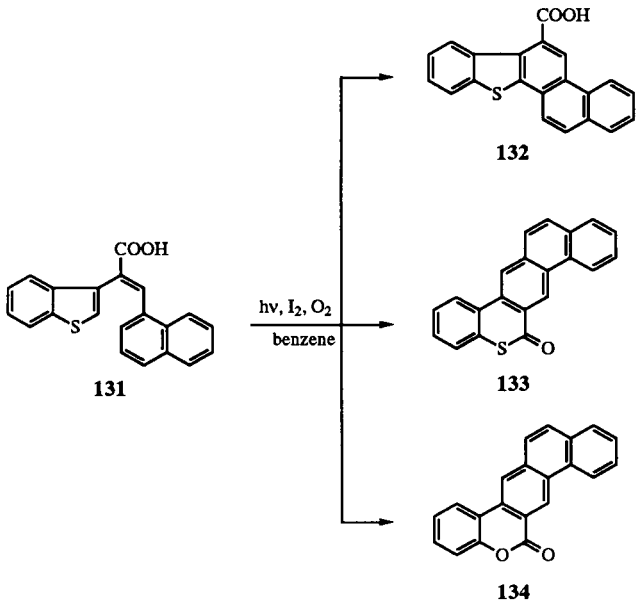
In order to explain the formation of compounds **127, 129** and **130**, we propose the following reaction pathway. The photocyclization of **126** provides the unisolable proposed dihydro intermediate **A** which can either lose a hydrogen molecule to afford the main product **127** or suffers ring opening of the thiophene ring to give the intermediate **B** in which the mercapto group attacks the carboxyl carbonyl group to afford species **D** which upon loss of a molecule of water provides the novel ring system **129**. The formation of **130** is obtained by the loss of hydrogen sulfide from **C** (Scheme 32).

Scheme 32



Photocyclization of **131** in benzene-cyclohexane afforded three products **132, 133,** and **134**. The expected benzo[*b*]-phenanthro[2,1-*d*]thiophene-6-carboxylic acid (**132**) is obtained in 44% yield. The second product of the

Scheme 33

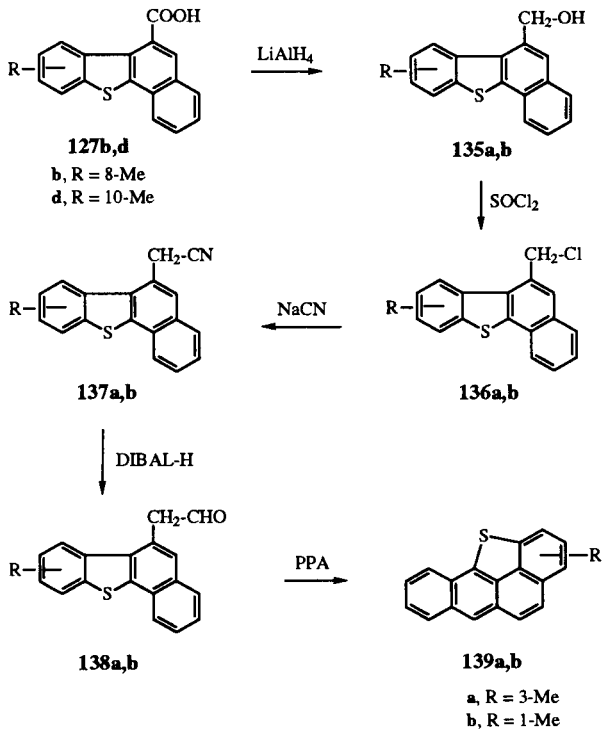


photocyclization is 6*H*-benzo[*b*]phenanthro[2,3-*d*]thiapyran-6-one (**133**) obtained in 2% yield. The third product is 6*H*-benzo[*b*]phenanthro[2,3-*d*]pyran-6-one (**134**) obtained in 6% yield (Scheme 33) [50].

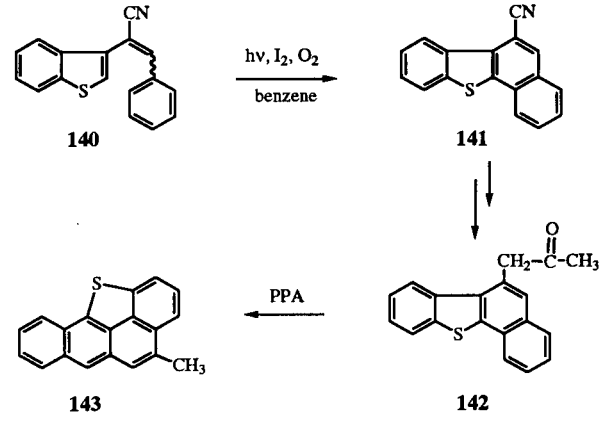
The mutagenic activity of benzo[2,3]phenanthro[4,5-*bcd*]-thiophene prompted us to initiate a program to provide the monomethylbenzo[2,3]phenanthro[4,5-*bcd*]thiophenes so that they could be tested for mutagenic activity and also to determine their presence in coal liquids and related coal-derived products.

For the synthesis of 1-methyl **139a** and 3-methylbenzo-[2,3]phenanthro[4,5-*bcd*]thiophene (**139b**), 8-methyl- **127a** and 10-methylbenzo[*b*]naphtho[2,1-*d*]thiophene-6-carboxylic acid (**127d**) served as the starting materials, respectively. Lithium aluminium hydride reduction of **127b,d** gave **135a,b** which are used to prepare the corresponding 6-cyanomethyl compounds **137a,b** *via* the chlorination of **135a,b** and cyanation in good yields. When **137a,b** are

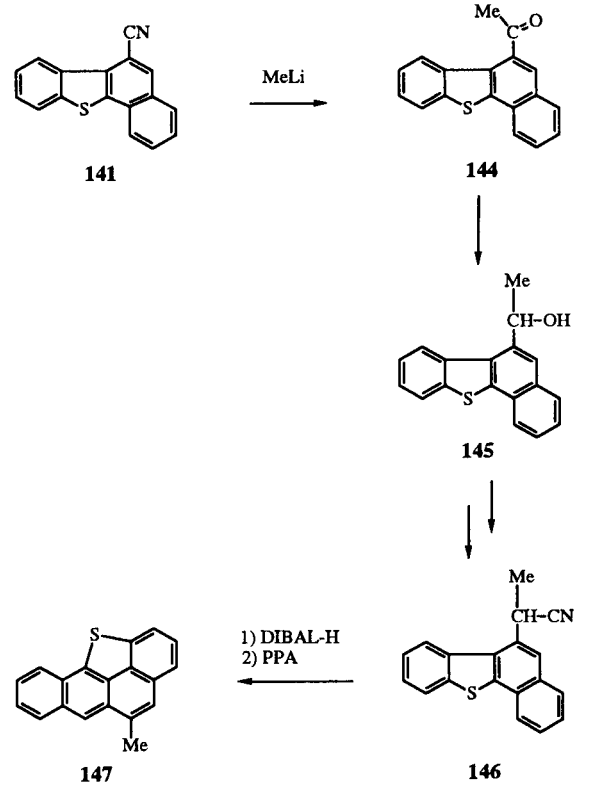
Scheme 34



Scheme 35



Scheme 36

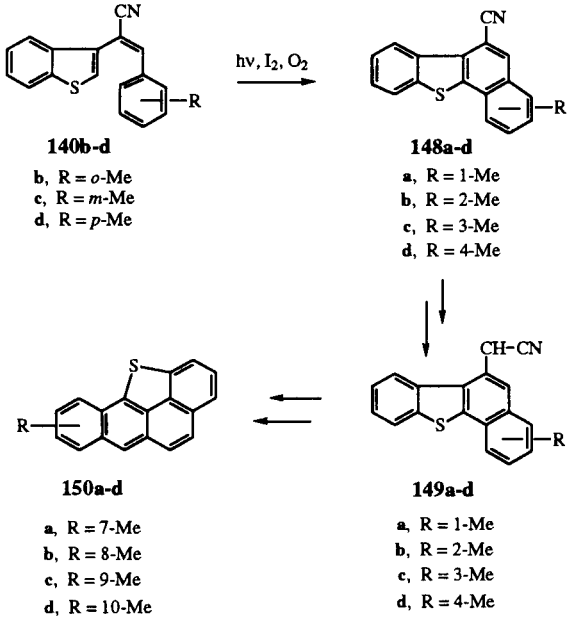


allowed to react with diisobutylaluminium hydride (DIBAL-H), aldehydes **138a,b** are obtained respectively. Cyclization of **138a,b** with polyphosphoric acid (PPA) produced **139a,b**, respectively (Scheme 34) [51].

4-Methyl- (**143**) and 5-methylbenzo[2,3]phenanthro[4,5-*bcd*]thiophene (**147**) has been synthesized in several steps from 6-cyanobenzo[*b*]naphtho[2,1-*d*]thiophene (**141**). Compound **141** is a key intermediate in the synthesis of **143** and **147** and it is prepared by the photocyclization of 2-([1]benzothien-3-yl)-3-phenylpropenenitrile (**140**) (Schemes 35 and 36) [51].

The synthesis of 7-, 8-, 9-, and 10-methylbenzo[2,3]phenanthro[4,5-*bcd*]thiophenes **150a-d** are accomplished in six steps from methyl substituted 6-cyanobenzo[*b*]naphtho[2,1-*d*]thiophene derivatives **148a-d** which are obtained by the photocyclization of **140b-d** (Scheme 37) [51].

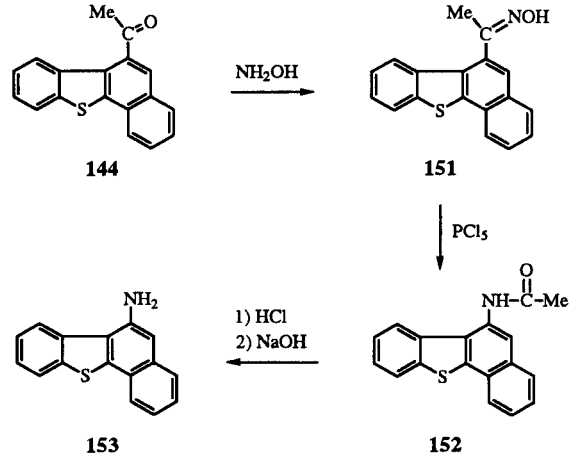
Scheme 37



6-Acetylbenzo[*b*]naphtho[2,1-*d*]thiophene (**144**) which is also obtained by the treatment of **141** with methyllithium (Scheme 36) is used to prepare 6-aminobenzo[*b*]naphtho[2,1-*d*]thiophene (**153**) (Scheme 38) [52].

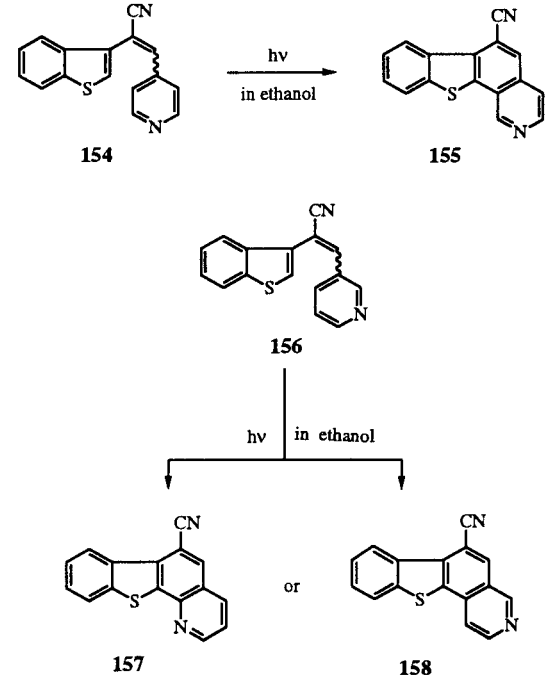
The photochemical behavior of a series of benzo[*b*]thiophene derivatives **154** is investigated as a part of a program directed toward the synthesis of various thia-analogs of indole alkaloids. Irradiation of compound **154** would be expected to cause rapid *trans-cis* isomerization and subsequent cyclization to the dihydro compound which should be readily oxidized to [1]benzothieno-[3,2-*h*]isoquinoline (**155**). Like the stilbene derivative, photolysis of **154** in the presence of oxygen gives the desired compound **155** in good yield. Compound **156** also

Scheme 38

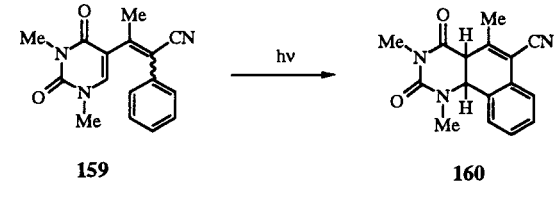


cyclizes very rapidly to only one compound, **157** or **158**. This compound is very insoluble in most organic solvents and nmr could not be used to differentiate between structures **157** and **158** (Scheme 39) [53].

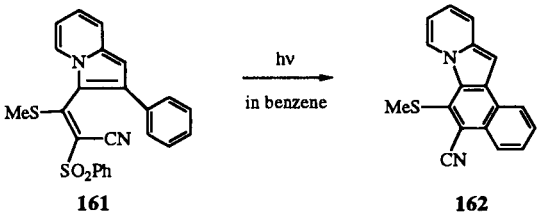
Scheme 39



Scheme 40

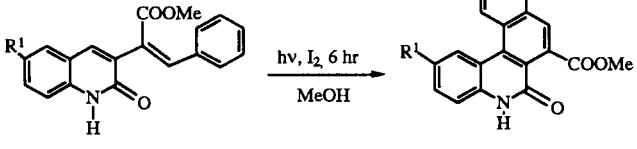


Scheme 41



161 162

Scheme 42

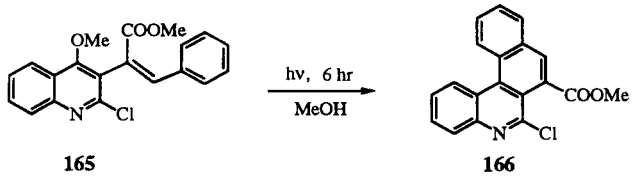


163a-c 164a-c

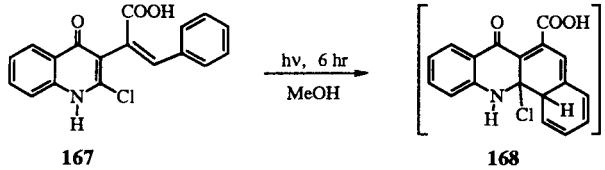
a, R^1 = H
b, R^1 = Cl
c, R^1 = Me

a, R^1 = H
b, R^1 = Cl
c, R^1 = Me

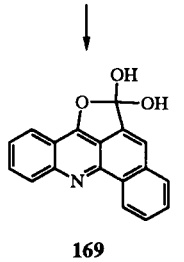
Scheme 43



165 166

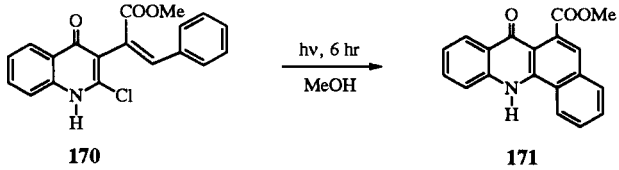


167 168



169

MeOH



170 171

Irradiation of **159** leads to photocyclization with prototropy to yield **160** (Scheme 40) [54].

Naphthoindolizine **162** is obtained by the photocyclization of **161** and subsequent elimination of phenylsulfinylic acid in benzene (Scheme 41) [55].

Shanmugam *et al.*, have reported a new method for the construction of benzo[*k*]phenanathridine systems based on the photolysis of 4-phenyl-3-vinylquinolines. Photolysis of **163a-c** in the presence of iodine gives 7-methoxycarbonylbenzo[*k*]phenanthridones **164a-c** (Scheme 42) [56-58].

Compound **165** readily undergoes photocyclization in methanol. The product obtained is identified as the known benzo[*k*]phenanthridine **166**, resulting from an eliminative photocyclization involving the 4-methoxy group. The photocyclization of **167** is isolated as the *gem*-diol **169**. Hydrolysis of **169** gives **171**. Product **171** is identical with the product obtained by photolysis of **170** (Scheme 43) [56-58].

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