Tetrahedron Vol. 47, No. 29, pp. 5437-5452, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

NEW SHORT STEP GENERAL SYNTHESIS OF ISOBENZOFURAN-1(3*H*)-ONES (PHTHALIDES) BASED ON A SINGLE OR DOUBLE β-SCISSION OF ALKOXYL RADICALS GENERATED FROM 1-ETHYL-BENZOCYCLOBUTEN-1-OLS AND FROM 1,3-DIHYDROISOBENZOFURAN-1-OLS; SYNTHESIS OF SOME NATURAL PHTHALIDES[1,2]

Kazuhiro Kobayashi, Masahito Itoh, Akiyoshi Sasaki, and Hiroshi Suginome*

Organic Synthesis Division, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

(*Received in Japan* 22 *March* 1991)

Key Words · Synthesis of Phthalides; Alkoxyl Radicals; Mercury(II) oxide-Iodine Reagent; Photolysis; Double β-Scission

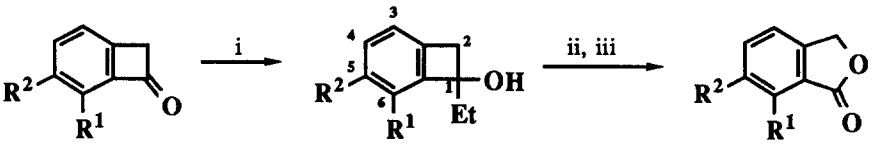
Abstract - New general methods are described for the synthesis of phthalides, 3-monosubstituted, and 3,3-disubstituted phthalides including naturally-occurring phthalides such as pierardine based on a regioselective single or double β-scission of the alkoxyl radicals generated by the photolysis of the hypoiodites of 1-ethyl benzocyclobuten-1-ols or 1,2-catacondensed benzocyclobuten-1-ols or 1,3-dihydro-1,3-alkanoisobenzofuran-1-ols. The formation paths of the phthalides, which involve a regioselective single or double β-scission of the alkoxyl radicals generated from 1-alkylbenzocyclobuten-1-ols and from catacondensed benzocyclobuten-1-ols, are discussed.

Isobenzofuran-1(3*H*)-ones (phthalides)[3] are a group of substances which are interesting in two respects. First, several substituted phthalides possessing biological activity have been found in nature.[4] Second, since Trueb and Eugster used a carbanion generated from phthalide for annelation,[5] a variety of methods using phthalides as key intermediates have been developed for the annelation of aromatic rings in the synthesis of tri- and tetracyclic aromatic natural products, such as anthracycline antibiotics[6] and in the phthalide isoquinoline alkaloids.[7]

Since the classical work by Wislicenus[8] and by Gabliel,[9] several methods for the synthesis of phthalides have been reported. These include preparations of phthalides by the oxidation of o-methylbenzoic acid,[10] the oxidation of polymethylbenzonitriles with fuming nitric acid,[11] by appropriate transformations of suitable ortho-lithiated benzyl alcohols, N,N-dialkylbenzylamine, or benzamides[12], and the reduction of phthalaldehydic acids prepared from o-bromobenzaldehydes.[13] Asymmetric syntheses of the chiral phthalides have also been reported.[14]

In this paper we give a full account of new, simple routes to 3-monosubstituted and 3, 3-disubstituted phthalides, as well as some naturally-occurring phthalides based on a rather novel approach[2]. The methods involve a regioselective single or double β-scission of alkoxyl radicals as the key step.

Our first method for the preparation of phthalides is based on simply the preparation of 1-ethylbenzocyclobuten-1-ols and the photolysis of their hypoiodites in benzene (outlined in Scheme 1).



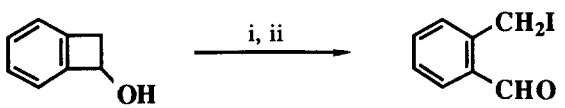
1a R^1=R^2=H	**2a**	**3a**
1b R^1=Cl, R^2=H	**2b**	**3b**
1c R^1=OMe, R^2=H	**2c**	**3c**
1d R^1=R^2=OMe	**2d**	**3d**

Reagents and conditions: i, EtMgBr, Et_2O, 0°C; ii, HgO-I_2, benzene; iii, hν.

Scheme 1.

Thus, irradiation of 1-ethylbenzocyclobuten-1-ol (**2a**), prepared from benzocyclobutenone (**1a**)[15,16] and ethylmagnesium bromide, in benzene containing mercury(II) oxide and iodine (3 equivalents each) with a 100-W high-pressure Hg arc through a Pyrex-filter at room temperature gave phthalides (**3a**) in a 41% yield. 7-Chloro- (**3b**), 7-methoxy- (**3c**),[17] and 6,7-dimethoxyphthalide (**3d**)[4a,4b] were similarly prepared from the corresponding 1-ethylbenzocyclobuten-1-ols (**2b**), (**2c**), and (**2d**) derived analogously from benzocyclobutenones (**1b**),[16] (**1c**),[16] and (**1d**)[16] in 54-67% yields. The 6,7-dimethoxyphthalide (**3d**) is a natural product (meconin) isolated by Freund[4a] and synthesized by W. H. Perkin, Jr.[4b]

The presence of the alkyl group attached to C-1 of benzocyclobuten-1-ols was found to be essential for the formation of the phthalides, since the photolysis of the hypoiodite of benzocyclobuten-1-ol (**4**)[18] under the above-mentioned conditions gave simply 2-iodomethylbenzaldehyde (**5**) arising from a β-scission (outlined in Scheme 2).

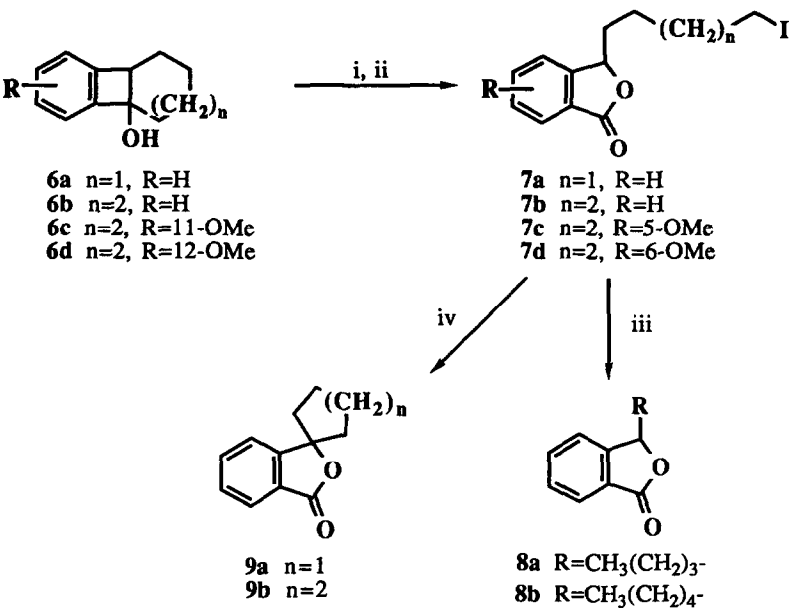


4 **5**

Reagents and conditions: i, HgO-I_2, benzene; ii, hν.

Scheme 2.

We then extended this new method to the synthesis of 3-substituted phthalides. The synthesis of 3-substituted phthalides consists of the preparation of catacondensed benzocyclobuten-1-ols and the photolysis of their hypoiodites generated *in situ* by an excess of mercury(II) oxide and iodine (outlined in Scheme 3).



Reagents and conditions: i, HgO-I_2, benzene; ii, hν; iii, Bu_3SnH, benzene-reflux; iv, $LiNPr^i_2$ (LDA), THF-HMPA, -78°C.

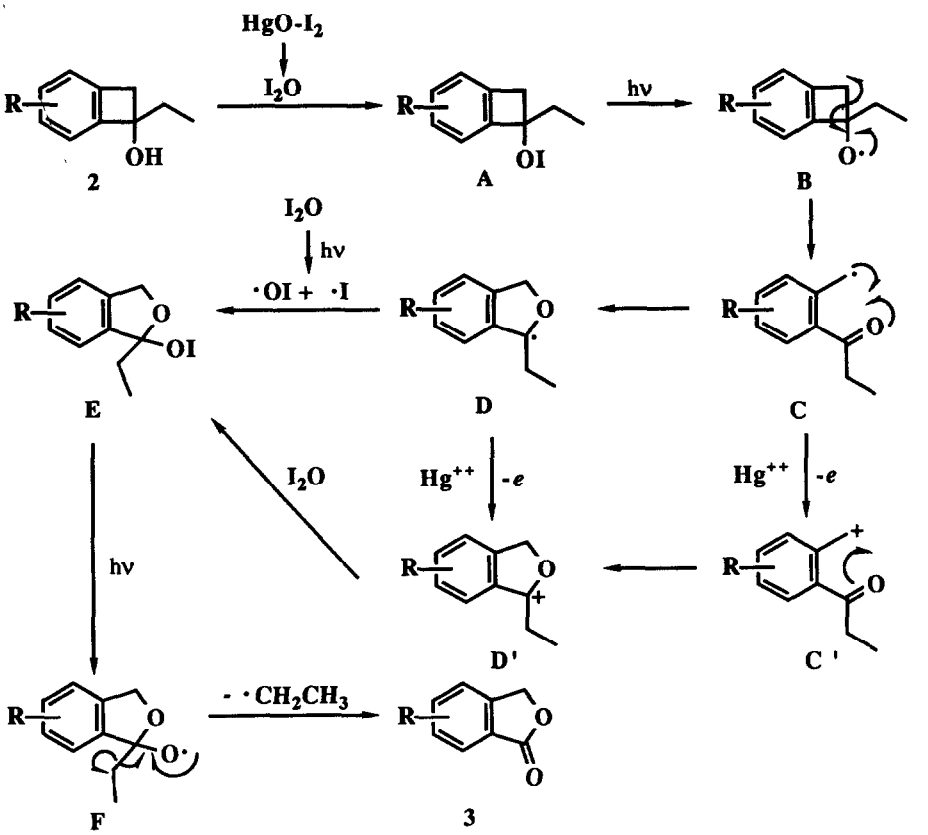
Scheme 3.

Thus, irradiation of 1,3,4,8b-tetrahydro-4a(2*H*)-biphenylenol (**6a**),[19] prepared according to the method of Caubere and colleagues,[20] in benzene under the same conditions as described for the photolysis of the hypoiodite of 1-ethyl-benzocyclobuten-1-ol (**2a**) gave 3-(4-iodobutyl)phthalide (**7a**) in 61% yield.

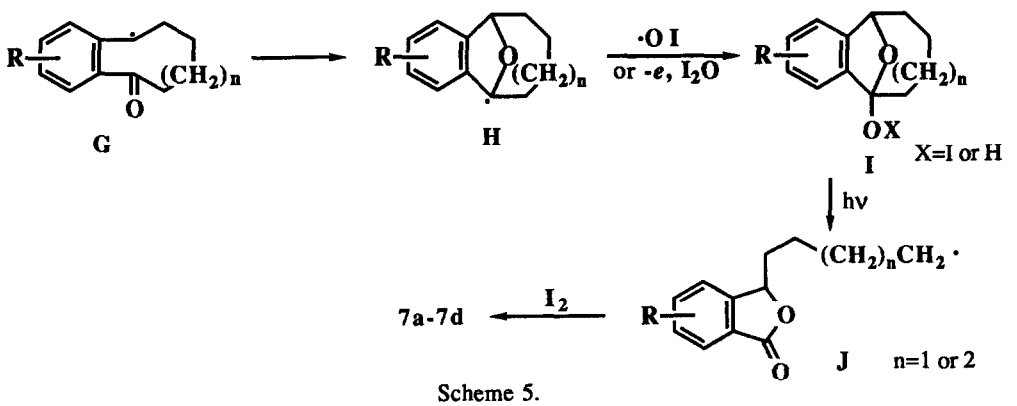
Similarly, a one-step reaction of homologous catacondensed benzocyclobuten-1-ol (**6b**) gave 3-(5-iodopentyl)phthalide (**7b**); a one-step reaction of a mixture of 2-methoxybiphenylenol (**6c**) and its 3-methoxy isomer (**6d**) afforded 3-(5-iodopentyl)-5-methoxyphthalide (**7c**) and its 6-methoxy isomer (**7d**). 3-(ω-Iodoalkyl)phthalides, such as (**7a-7d**), are useful compounds; the iodine atom can be either readily removed or substituted by nucleophiles in an intra- or intermolecular manner. For example, the reduction of iodide **7a** with tributyltin hydride in benzene under reflux gave (±)-3-butylphthalide (**8a**), a racemic form[21] of a constituent of celery[4d,14b], in 87% yield.

On the other hand, treatment of iodide (**7a**) with lithium diisopropylamide in THF-HMPA at-78°C for 30 min led to the formation of 3,-spirophthalide (**9a**) in 67% yield. Similarly, 3-pentylphthalide (**8b**) and 3-spiropentylphthalide (**9b**) can be prepared from catacondensed benzocyclobuten-1-ol (**6b**)[19] through 3-(5-iodopentyl)phthalide (**7b**), as outlined in Scheme 3.

The pathways which led to phthalides (**3a-3d**) from 1-ethylbenzocyclobuten-1-ols and to 3-(ω-iodoalkyl)phthalides (**7a-7d**) from catacondensed benzocyclobuten-1-ols (**6a-6d**) are outlined in Schemes 4 and 5.



Scheme 4.



Scheme 5.

These pathways are essentially parallel to those leading to the formation of iodo formates from the hypoiodites of steroidal cyclic alcohols upon irradiation.[22] The principal feature of this process is an intramolecular combination of a carbon-centered radical or an ion and a carbonyl oxygen generated by a regioselective β-scission of the alkoxyl radicals, a combination of the resultant species with iodine oxide or the iodoxyl radical to form a second hypoiodite and a final β-scission of the alkoxyl radical generated from the second hypoiodite.

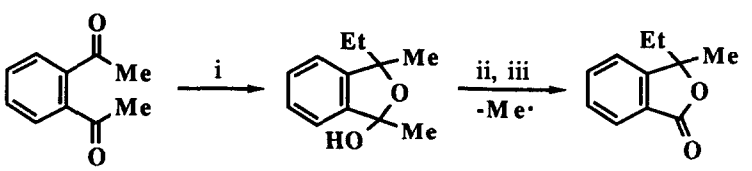
Thus, irradiation of the hypoiodite (A) of 1-ethylbenzocyclobuten-1-ols **2** generates a stabilized benzyl radical (C) *via* an alkoxyl radical (B) (Scheme 4). An intramolecular combination of the carbonyl oxygen and the carbon-centered radical (C) or the corresponding carbocation (C') formed by one-electron oxidation affords a cyclic radical (D) or the corresponding cation (D') which combines with the iodoxyl radical (·OI) or with the iodine oxide to generate a second hypoiodite (E). The second β-scission of alkoxyl radical (F) generated from hypoiodite (E) under the experimental conditions gives phthalides (**3a-3d**). An analogous path through radicals G, H, I, and J leads to 3-(ω-iodoalkyl)phthalides (**7a-7d**) (outlined in Scheme 5).

Hemiacetal (I; X=H, n=1, R=H) can, in fact, be isolated by discontinuing the photolysis of the hypoiodite of catacondensed benzocyclobuten-1-ol (**6a**) at an early stage of the reaction.

A limitation of the described method is that it can not be applied to the preparation of phthalides having three or less carbon chains attached to the 3-position. The involvement of the intermediates (I; X=I in Scheme 5) in the path leading to 3-(ω-iodoalkyl)phthalides (**7a-7d**) from the hypoiodites of catacondensed benzocyclobuten-1-ols, however, suggested a second new method for the general synthesis of 3-(ω-iodoalkyl)phthalides, simply based on the photolysis of the hypoiodites of type I hemiacetals.

In the following section of this paper, we describe this new synthesis of 3-(3-iodopropyl)- or 3-(4-iodobutyl)phthalides and a new synthesis of a racemic form of a naturally occurring 3-substituted phthalide, pierardine.[23]

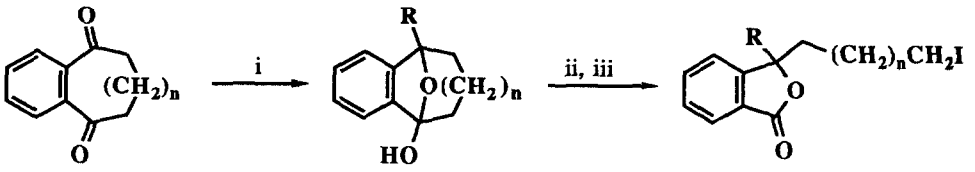
The preparation of a type I transannular hemiacetal has been reported by Hahn and Kryczka,[24] who prepared 9-ethyl-6,7,8,9-tetrahydro-5,9-epoxy-5*H*-benzocyclohepten-5-ol (**16a**)[24] by a treatment of 7,8-dihydro-5*H*-benzocycloheptene-5,9(6*H*)-dione (**15a**)[25] with ethylmagnesium bromide. We prepared analogous transannular hemiacetals (**13**), (**16b**), (**16d**) from acyclic and cyclic 1,4-diones by this method. The generation of alkoxyl radicals from these acetals (as described above) gave the expected 3, 3-disubstituted phthalides (outlined in Schemes 6 and 7) in fair to high yields.



12 **13** **14**

Reagents and conditions: i, EtMgBr, Et_2O, -78°C; ii, HgO-I_2, benzene; iii, hv.

Scheme 6.



15a n=1
15b n=2

16a n=1, R=Et
16b n=1, R=$CH_2CO_2Bu^t$
16c n=2, R=H
16d n=2, R=Et

17a n=1, R=Et
17b n=1, R=$CH_2CO_2Bu^t$
7a n=2, R=H
17d n=2, R=Et

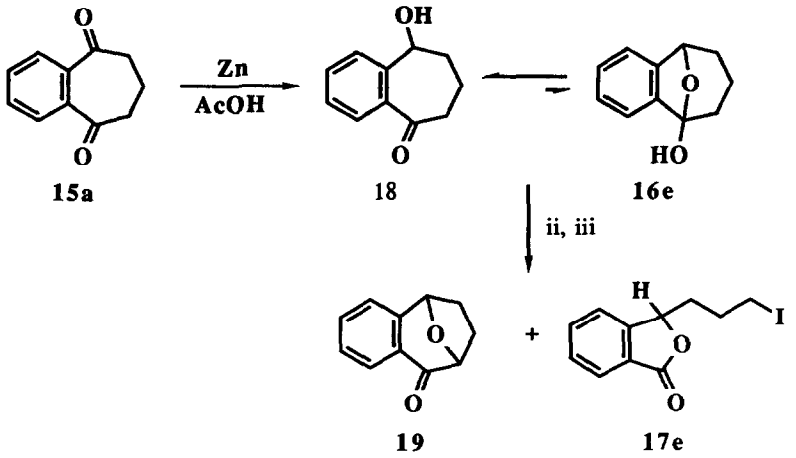
Reagents and conditions; i, EtMgBr, Et_2O, -78°C for **16a** and **16d**, $CH_3CO_2Bu^t$, $Mg[N(Pr^i)_2]_2$, Et_2O, 0°C for **16b**; ii, HgO-I_2, benzene; iii, hv.

Scheme 7.

Thus, the reaction of commercially available 1,2-diacetylbenzene (**12**) with ethylmagnesium bromide in diethyl ether gave 1,3-dimethyl-3-ethylisobenzofuran-1-ol (**13**) in 89 % yield. Irradiation of hemiacetal (**13**) in benzene containing mercury(II) oxide and iodine under the conditions described above gave 3-ethyl-3-methylphthalide (**14**)[26] in 36% yield (Scheme 6). Far better yields of phthalides (**17a-17d**) can be obtained from transannular hemiacetals (**16a-16d**) prepared by the reaction of fused cyclic 1,4-diones, (**15a**) and (**15b**), with Grignard reagents. Thus, we prepared two hemiacetals, (**16a**)[24] and (**16b**), by a treatment of 7,8-dihydro-5*H*-benzocycloheptene-5,9(6*H*)-dione (**15a**)[25] with ethyl magnesium bromide and with magnesium enolate of t-butyl acetate,[27] in 94 and 76% yields, respectively. Similarly, hemiacetal (**16d**) could be obtained by the reaction of 6,7,8,9-tetrahydrobenzocyclooctene-5,10-dione (**15b**)[28]with ethylmagnesium bromide in 57% yield.

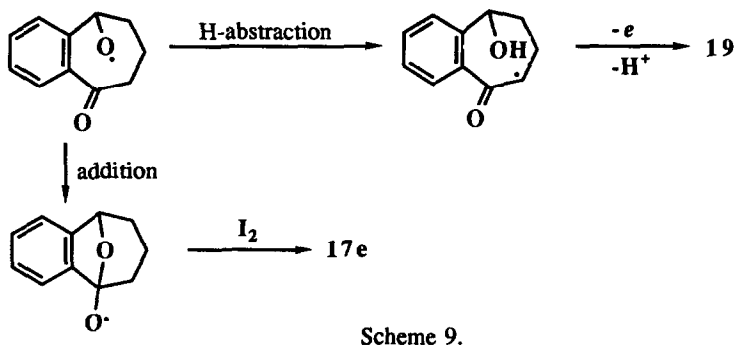
The transannular hemiacetals, (**16a**), (**16b**), and (**16d**), were subjected to photolysis under the conditions mentioned above to yield the corresponding 3-(ω-iodoalkyl)phthalides, (**17a**), (**17b**), and (**17d**), in 83, 97, and 58% yields, respectively. Hemiacetal (**16c**), isolated from the products of the photolysis of the hypoiodite of catacondensed benzocyclobuten-1-ol (**6a**) (as mentioned previously), gave the expected 3-monosubstituted phthalide (**7a**) in 89% yield.

It has been reported that in contrast to hemiacetal (**16c**), an attempted preparation of homologous transannular hemiacetal (**16e**) by the reduction of 1,4-dione (**15a**) with zinc in acetic acid afforded a hydroxy ketone (**18**)[24,29] in 82% yield. We confirmed by ^{1}H-NMR spectroscopy that the product of the reduction of (**15a**) existed entirely as a ring-opened form (**18**) in $CDCl_3$. Irradiation of the hypoiodite of hydroxy ketone (**18**) under the conditions described above gave 3-(3-iodopropyl)phthalide (**17e**) and a new ketone (**19**) in 36 and 32% yields. The structure of the new ketone (**19**), $C_{11}H_{10}O_2$ (high resolution mass spectrometry), was confirmed to be 6,7,8,9-tetrahydro-6,9-epoxybenzocyclohepten-5-one (**19**) by the IR, mass, and ^{1}H-NMR spectra (see Experimental). The phthalide (**17e**) can be formed either from hemiacetal form (**16e**) or from the ring-opened form (**18**), as outlined in Scheme 8. The ketone (**19**), on the other hand, is most probably formed *via* an intramolecular nucleophilic addition of hydroxyl oxygen to a carbocation which is formed by an intramolecular hydrogen abstraction by alkoxyl radical followed by one-electron oxidation of the resulting radical (as outlined in Scheme 9).



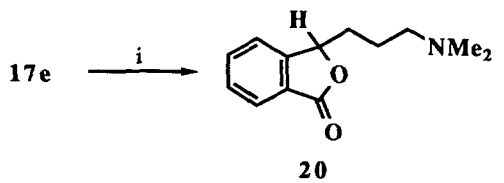
Reagents and conditions: i, Zn, AcOH; ii, HgO-I_2, benzene; iii, hν.

Scheme 8.



Scheme 9.

A displacement of the iodine atom of 3-(3-iodopropyl)phthalide (**17e**) with dimethylamine in methanol at 0°C gave a racemic form of naturally-occurring phthalide, pierardine (**20**)[23] in 23% yield (outlined in Scheme 10).



Reagents and conditions: i, $HNMe_2$, MeOH, 0°C.

Scheme 10.

EXPERIMENTAL

Mps. were recorded with a Yanagimoto melting point apparatus and are uncorrected. IR spectra were determined for Nujol mulls with a Hitachi 285 infrared spectrometer unless stated otherwise. The ^{1}H-NMR spectra were determined with either a Hitachi R-90B spectrometer (90 MHz) or a JNM-FX 270 spectrometer (270 MHz, Faculty of Pharmaceutical Sciences of this University). $CDCl_3$ was used as the solvent with $SiMe_4$ as an internal standard. PLC was carried out with Merck Kiesel gel 60-PF_{254}. The high- and low- resolution mass spectra were determined with a JEOL JMS-300 spectrometer (70 eV, Faculty of Pharmaceutical Sciences of this university). Elemental analyses were performed by the staff of the analytical laboratory of the Faculty of Pharmaceutical Sciences.

Preparation of 7-Ethylbicyclo[4.2.0]octa-1,3,5-trien-7-al (**2a**) *[General Procedure for the Preparation of 1-Ethylbenzocyclobuten-1-ol* (**2a-2d**)*]*. To a solution of benzocyclobutenone (**1a**)[15,16] (186 mg, 1.57 mmol) in diethyl ether (5ml), was added dropwise ethylmagnesium bromide (2M in diethyl ether solution, 2 mmol) at 0°C while stirring. After the solution was stirred for 15 min, the mixture was poured into iced water and extracted with diethyl ether. The extract was washed with aq. ammonium chloride and brine, and dried over anhydrous magnesium sulphate. The solvent was removed with the aid of rotary evaporator. The residue was subjected to PLC on silica gel (1:3 ethyl acetate-hexane) to give benzocyclobutenol (**2a**) (152 mg, 66%). An oil. IR (neat) 3330 cm^{-1} (OH); ^{1}H NMR (90 MHz) δ 1.06 (3H, t, *J* 7.3 Hz, -CH_2CH_3), 1.92 (2H, q, *J* 7.3 Hz, -CH_2CH_3), 3.10 (1H, d, *J* 4.3 Hz, 2-H), 3.36 (1H, d, *J* 4.3 Hz, 2-H), and 7.20 (4H, s, aromatic H); MS, *m/z* 148 (M^+, 3.8%), 119 [$(M-Et)^+$, 100], and 91 (68.7). (Found : M^+, 148.0876. $C_{10}H_{12}O$ requires *M*, 148.0887).

5-Chloro-7-ethylbicyclo[4.2.0]octa-1,3,5-trien-7-ol (**2b**). The reaction of 6-chlorobenzocyclobutenone (**1b**)[16] (190 mg, 1.25 mmol) with ethylmagnesium bromide (2 mmol) in diethyl ether (5 ml) under the above-mentioned conditions gave benzocyclobutenol (**2b**) (170 mg, 75%). An oil. IR (neat) 3350 cm^{-1} (OH); ^{1}H NMR (90 MHz) δ 1.04 (3H, t, *J* 7.3 Hz, -CH_2CH_3), 1.9-2.2 (2H, m, -CH_2CH_3), 3.09 (1H, d, *J* 14.3 Hz, 2-H), 3.35 (1H, d, *J* 14.3 Hz, 2-H), and 7.0-7.3 (3H, m, aromatic H); MS, *m/z* 182 (M^+, 1.4%), 153 [$(M-Et)^+$, 100], 125 (25.4), and 89 (19.3). (Found : M^+, 182.0483. $C_{10}H_{11}OCl$ requires *M*, 182.0498).

7-Ethyl-5-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-ol (**2c**). The reaction of 6-methoxybenzocyclobuteneone (**1c**)[16] (85 mg, 0.57 mmol) with ethylmagnesium bromide (1 mmol) in diethyl ether (3 ml) under the above-mentioned conditions gave benzocyclobutenol (**2c**) (85 mg, 0.57 mmol), mp 40-41.5°C (diethyl ether -hexane). IR (neat) 3400 cm^{-1} (br. OH); ^{1}H NMR (90 MHz) δ 1.02 (3H, t, *J* 7.3 Hz, CH_2CH_3), 1.8-2.1 (2H, m, CH_2 CH_3), 3.02 (1H, d, *J* 14.1 Hz, 2-H), 3.18 (1H, d, *J* 14.1 Hz, 2-H), 3.87 (3H, s, OMe), 6.6-6.8 (2H, m, aromatic H), and 7.1-7.3 (1H, m, aromatic H); MS, *m/z* 178 (M^+, 2.8%), 149 [$(M-Et)^+$, 100], and 91 (32.0). (Found: C, 73.89; H, 7.92. $C_{11}H_{14}O_2$ requires C, 74.12; H, 7.92).

7-Ethyl-4,5-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-ol (**2d**). The reaction of cyclobutenone (**1d**)[16] (105 mg, 0.59 mml) with ethylmagnesium bromide (1 mmol) in diethyl ether (3ml) gave benzocyclobutenol (**2d**) (89 mg, 73%), mp 64.5-65.0°C (hexane). IR 3310 cm^{-1} (OH); ^1H NMR (90 MHz) δ 0.95 (3H, t, *J* 7.3 Hz, $-CH_2CH_3$), 1.8-2.1 (2H, m, $-CH_2CH_3$), 2.94 (1H, d, *J* 13.9 Hz, 2-H), 3.33 (1H, d, *J* 13.9 Hz, 2-H), 3.82 (3H, s, OMe), 4.04 (3H, s, OMe), 6.65 (1H, d, *J* 7.7 Hz, aromatic H), and 6.83 (1H, d *J* 7.7 Hz, aromatic H); MS *m/z* 208 (M^+, 12.2%), 179 [$(M-Et)^+$, 100], and 136 (17.1). (Found: C, 69.16, H, 7.73. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74).

(a) *Preparation of Isobenzofuran-1(3H)-one* (**3a**). *(General Procedure for the Preparation of Phthalides).* Benzocyclobutenol (**2a**) (64 mg, 0.43 mmol) in benzene (30 ml) containing mercury(II) oxide (284 mg, 1.29 mmol) and iodine (331 mg, 1.29 mmol) was irradiated for 3 h with a 100-W high pressure mercury arc through a Pyrex filter while stirring in an atmosphere of nitrogen. Examination of the solution by TLC indicated that all the starting material was converted to the products. The photolysed solution was filtered through Celite and the filtrate was washed with aqueous sodium thiosulphate and then with water. After the solution was dried over anhydrous magnesium sulphate, the solvent was removed by rotary evaporator to give phthalide (**3a**) which was purified by PLC on silica gel (Rf 0.23; 1:3 ethyl acetate - hexane) (24 mg, 41%).

(b) *7-Chloroisobenzofuran-1(3H)-one* (**3b**). Irradiation of benzocyclobutenol (**2b**) (120 mg, 0.66 mmol) in benzene (40 ml) in the presence of mercury(II) oxide (428 mg, 1.98 mmol) and iodine (502 mg) for 1.5 h and work-up as mentioned above gave phthalide (**3b**) (62 mg, 56%), mp 144-145°C (diethyl ether-hexane). IR 1750 cm^{-1} (C=O); ^1H NMR (90 MHz) δ 5.26 (2H, s, 3-H), and 7.3-7.7 (3H, m, aromatic H); MS, *m/z* 168 (M^+, 37.4%) and 139 (100). (Found : C, 56.74; H, 3.01. $C_8H_5O_2Cl$ rquires C, 57.00; H, 2.99).

(c) *7-Methoxyisobenzofuran-1(3H)-one (3c)* Irradiation of benzocyclobutenol (**2c**) (80 mg, 0.45 mmol) in benzene (30 ml) containing mercury(II) oxide (288 mg, 1.35 mmol) and iodine (344 mg, 1.35 mmol) for 4h and work-up of the solution as mentioned above gave phthalide (**3c**) (40 mg, 54%), mp 105-107°C (diethyl ether-hexane) (lit.[17] 107-109°C).

(d) *6,7-Dimethoxyisobenzofuran-1(3H)-one* (**3d**). Irradiation of benzocyclobutenol (**3d**) (48 mg, 0.23 mmol) in benzene (15 ml) containing mercury(II) oxide (150 mg, 0.69 mmol) and iodine (175 mg, 0.69 mmol) for 1.5 h and work-up of the solution gave phthalide (**3d**) (30 mg, 67%), mp 99-100°C (diethyl ether - hexane) (lit.[12] mp 97-100°C).

Photoreaction of benzocyclobuten-1-ol Hypoiodite in the Presence of Mercury(II) Oxide and Iodine. -A solution of benzocyclobutenol (**4**)[18] (214 mg, 1.78 mmol) in benzene (100 ml) containing mercury(II) oxide (1.16 g, 5.34 mmol) and iodine (1.36 g, 5.34 mmol) was irradiated for 30 min. with a 100-W high pressure mercury arc through a Pyrex filter, as described for 1-ethyl derivative. The solution was worked up as usual. The product was subjected to PLC (1:3 ethyl acetate hexane) to yield 2-iodomethylbenzaldehyde (**5**) (178 mg, 41%). IR (neat) 2730, 1684 and 1655 cm^{-1} (CHO); ^1H NMR (90 MHz) δ 4.92 (2H, s, $-CH_2I$),7.3-7.8 (4H, m, aromatic H),

and 10.23 (1H, s, CHO); MS *m/z* 246 (M^+, 5.6%) and 119 [$(M-I)^+$, 100]. (Found M^+, 245.9523. C_8H_7IO requires *M*, 245.9541).

Preparation of Fused benzocyclobuten-1-ols.

*(a) Fused benzocyclobuten-1-ols (***6a***) and (***6b***).* These cyclobutenols were prepared according to the published procedure.[19]

*(b) Fused benzocyclobuten-1-ols (***6c***) and (***6d***).* The reaction of 4-bromoanisole (935 mg, 5 mmol) with cycloheptanone (560 mg, 5 mmol) in the presence of sodium amide (390 mg, 10 mmol) in THF (15 ml) was carried out in the same manner as the reported procedure for the synthesis of fused benzocyclobutenol (**6b**)[19] to give a 1:1 mixture of (**6c**) and (**6d**) as an oil (306 mg, 28%), Rf 0.40 (1:3 ethyl acetate - hexane). IR (neat) 3400cm^{-1} (OH); ^{1}H NMR (270MHz) δ 1.35-1.95 (8H, m, methylene protons), 2.05-2.15 (2H, m), 2.25 (1H, s, OH), 3.39 (1H, 2t *J* 11.36 Hz each, benzylic H), 3.775 and 3.783 (3H, 2s, OMe), 6.7-6.85 (2H, m, aromatic H), and 7.0-7.1 (1H, m, aromatic H); MS, *m/z* 218 (M^+, 18%) and 175 (100). (Found M^+, 218.1301. $C_{14}H_{18}O_2$ requires *M*, 218.1307).

*3-(4-Iodobutyl)isobenzofuran-1(3H)-one (***7a***).*

i) Irradiation of benzocyclobutenol (**6a**) (254 mg, 1.46 mmol) in benzene (100 ml) containing mercury(II) oxide (950 mg, 4.38 mmol) and iodine (1.12 g, 4.38 mmol) for 2.5 h gave 3-substituted phthalide (**7a**) (298 mg, 62%). IR(neat) 1759 cm^{-1} (C=O); ^{1}H NMR (270 MHz) δ 1.4-2.15 (6H, m, -$(CH_2)_3$-), 3.18 (2H, t, *J* 6.96 Hz, CH_2I), -5.48 (1H, dd, *J* 8.06 and 4.03 Hz, -CH-O), and 7.4-7.55 (2H, m, aromatic H); MS, *m/z* 316 (M^+, 3.7%), 189 [$(M-I)^+$, 65], and 133 [$(M - C_4H_8I$, 100)]. (Found : M^+, 315.9962. $C_{12}H_{13}O_2I$ requires *M*, 315.9984).

ii) A solution of benzocyclobutenol (**6a**) (300 mg, 1.72 mmol) in benzene (100 ml) containing mercury(II) oxide (1.12 g, 5.16 mmol) and iodine (1.31 g, 5.16 mmol) was irradiated with a 100-W high pressure Hg arc in a similar manner as described above. The irradiation was discontinued after 30 min and worked up as described above. The product was subjected to PLC (1:5 ethyl acetate-hexane) to give hemiacetal (**16c**) (134 mg, 41%) and (**7a**) (108 mg, 20%) Mp. 133-134°C (diethyl ether-hexane). IR (Nujol) 3400 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.0-1.2 (2H, m, -CH_2-), 1.5 - 1.7 (3H, m, -CH_2- and -HC*H*-), 2.0 - 2.3 (3H, m, -CH_2- and -HC*H*-), 5.28 (1H, d, *J* 6.23 Hz, benzylic H), 7.05 - 7.1 (1H, m, aromatic H), and 7.25 - 7.35 (3H, m, aromatic H); MS, *m/z* 190 (M^+, 47%) and 147 (100). (Found : C, 75.74 : H, 7.58. $C_{12}H_{14}O_2$ requires C, 75.76 : H, 7.42).

*3-(5-Iodopentyl)isobenzofuran-1(3H)-one(***7b***).* Irradiation of benzocyclobutenol (**6b**) (340 mg, 1.81 mmol) in benzene (100 ml) containing mercury(II) oxide (1.18 g, 5.43 mmol) and iodine (1.38 g, 5.43 mmol) for 1.5 h gave phthalide (**7b**) (245 mg, 41%). IR (neat) 1753 cm^{-1} (C=O) : ^{1}H NMR (270MHz) δ 1.45-1.6 (4H, m, -$(CH_2)_2$-), 1.75-1.8 (3H, m, -CH_2- and -HC*H*-), 2.0-2.15(1H, m, -HC*H*-), 3.53 (2H, t, *J* 6.60 Hz, -CH_2I), 5.50 (1H, dd, *J* 8.06 and 4.03 Hz, 3-H), 7.44 (1H, dd, *J* 7.70 and 0.74, aromatic H), 7.5-7.55 (1H, m, aromatic H), 7.65-7.7 (1H, m, aromatic H), and 7.90 (1H, d, *J* 7.69 Hz, 7-H); MS, *m/z* 330 (M^+, 16%), 203 [$(M - I)^+$, 31], and 133 [$(M - C_5H_{10}I)^+$, 100]. (Found : M^+ 330.0118. $C_{13}H_{15}O_2I$ requires *M*, 330.0123).

*3-(5-Iodopentyl)-5-methoxyisobenzofuran-1(3H)-one (***7c***) and 3-(5-iodopentyl)-6-methoxyisobenzofuran-1(3H)-one (***7d***).* Irradiation of a mixture of benzocyclobutenols (**6e**) and (**6d**) (218 mg, 1 mmol) in benzene (75 ml) containing mercury(II) oxide (651 mg, 3 mmol) for 3h gave a product mixture. It was subjected to PLC (1:3 ethyl acetate-hexane) to give phthalide (**7c**) (Rf 0.32) (40 mg, 11%) and (**7d**) (Rf 0.46) (94 mg, 26%). Phthalide (**7c**). IR (neat) 1752 cm^{-1} (C=O) ; ^1H NMR (270 MHz) δ 1.4 - 1.5 (4H, m, -$(CH_2)_2$-), 1.7-1.9 (3H, m, -CH_2- and HC*H*-), 2.0 - 2.1 (1H, m, -HC*H*-), 3.18 (2H, t, *J* 6.96 Hz, -CH_2I), 3.91 (3H, s, OMe), 5.39 (1H, dd, *J* 8.06 and 3.66 Hz, 3-H), 6.84 (1H, d, *J* 2.20 Hz, 4-H),7.03 (1H, dd, *J* 8.84 and 2.20 Hz, 6-H), and 7.80 (1H, d, *J* 8.80 Hz, 7-H); MS *m/z* 360 (M^+, 15%), 233 [$(M-I)^+$, 30], and 163 [$(M-C_5H_{10}I)^+$, 100]. (Found : M^+, 360.0236. $C_{14}H_{17}O_3I$ requires *M*, 360.0223). Phthalide (**7d**). IR (neat) 1756 cm^{-1} (C=O) ; ^1H NMR (270 MHz) δ 1.4-1.55 (4H, m, -(CH_2)-$_2$), 1.65-1.85 (3H, m, -CH_2- and -HC*H*-), 1.95-2.1 (1H, m, HC*H*), 3.17 (2H, t, *J* 6.96 Hz, -CH_2I), 3.87 (3H, s, OMe), 5.42 (1H, dd, *J* 7.70 and 4.03 Hz, 3-H), 7.22 (1H, dd, *J* 8.06 and 2.19 Hz, 5-H), 7.31 (1H, d, *J* 8.06 Hz, 4-H), and 7.32 (1H, d, *J* 2.19 Hz, 7-H); MS *m/z* 360 (M^+, 21%), 233 [$(M-I)^+$, 8], and 163 [$(M-C_5H_{10}I)^+$, 100]. (Found : M^+, 360.0236. $C_{14}H_{17}O_3I$ requires *M* 360.0223).

*3-Butylisobenzofuran-1(3H)-one (***8a***).* A mixture of iodide (**7a**) (92 mg, 0.29 mmol) and tributyltin hydride (170 mg, 0.58 mmol) in benzene (6 ml) was heated under reflux for 3h. After the removal of the solvent, the residue was subjected to PLC (1:3 ethyl acetate-hexane) to afford phthalide (**8a**)[21] (48 mg, 87%). IR (neat) 1752 cm^{-1} (C=O), ^1H NMR (270 MHz) δ 0.85-0.95 (3H, m, Me), 1.3-1.5 (4H, m, -$(CH_2)_2$-), 1.7-1.8 (1H, m, one of -CH_2-), 1.95-2.1 (1H, m, one of -CH_2-), 5.48 (1H, dd, *J* 8.06 and 4.03 Hz, 3-H), 7.44 (1H, dd, *J* 7.70 and 0.74 Hz, aromatic H), 7.5-7.55 (1H, m, aromatic H), 7.65-7.7 (1H, m, aromatic H), and 7.90 (1H, d, *J* 7.70 Hz, 7-H); MS *m/z* 190 (M^+, 6.3%) and 133 [$(M-Bu)^+$, 100].

*3-Pentylisobenzofuran-1(3H)-one (***8b***).* Reduction of iodide (**7b**) (110 mg, 0.33 mmol) in benzene (10 ml) with tributyltin hydride (190 mg, 0.66 mmol) as described above gave phthalide (**8b**) (46 mg, 68%). IR (neat) 1768 cm^{-1} (C=O); ^1H NMR (270 MHz) δ 0.89 (3H, t, *J* 6.96 Hz, Me), 1.25-2.55 (6H, m, -$(CH_2)_3$-), 5.48 (1H, dd, *J* 8.06 and 4.03 Hz, 3-H), 7.44 (1H, dd, *J* 7.69 and 1.10 Hz, aromatic H), 7.52 (1H, t, *J* 7.33, aromatic H), 7.67 (1H, dt, *J* 1.10 and 7.33 Hz, aromatic H), and 7.90 (1H, d *J* 7.69Hz, 7-H); MS, *m/z* 204 (M^+, 3.9%) and 133 [$(M-C_5H_{11})^+$, 100). (Found :M^+, 204.1153. $C_{13}H_{16}O_2$ requires M, 204.1151).

*3-Spirotetramethyleneisobenzofuran-1(3H)-one (***9a***).* To a solution of diisopropylamine (108 mg, 1.07 mmol) and HMPA (309 mg, 1.7 mmol) in THF (5ml) cooled to -78°C, was added butyllithium (1.24 mmol, 1.5M in hexane). To the solution, stirred for 5 min, was added iodide (**7a**) (200 mg, 0.63 mmol) in THF (5 ml). After the solution was stirred for half an hour, the solution was quenched with aqueous ammonium chloride and extracted with diethyl ether. The extract was washed with brine and dried over anhydrous magnesium sulphate. Removal of the solvent gave a product which was purified by PLC (1:3 ethyl acetate-hexane) to give spirophthalide (**9a**) (79 mg, 67%). IR (neat) 1755 cm^{-1} (C=O); ^1H NMR(270 MHz) δ 1.9-2.15 (8H, m, -$(CH_2)_4$-), 7.40 (1H, d, *J* 7.69 Hz, aromatic H), 7.45-7.55 (1H, m, aromatic H), and 7.86 (1H, d, *J* 7.69 Hz, 7-H); MS, *m/z* 188 (M^+, 66%) and 159 (100). (Found : M^+, 188.0835. $C_{12}H_{12}O_2$ requires *M*, 188.0836).

3-Spiropentamethyleneisobenzofuran-1(3H)-one (**9b**). This spirophthalide (**9b**) (86mg, 60%) was prepared by the treatment of iodide (**7b**) (240 mg, 0.72 mmol) with LDA (1.24 mmol) - THF (6 ml)-HMPA (357 mg, 1.96 mmol). The crude product was purified by PLC (1:3 ethyl acetate-hexane) and recrystallized from diethyl ether - hexane. Mp 75-76°C. IR (neat) 1755 cm^{-1} (C=O); ^1H NMR (90 MHz) δ 1.15-1.95 (10H, m, $-(CH_2)_5-$), 7.35-7.7 (3H, M, aromatic H), and 7.87 (1H, d, *J* 6.81 Hz, 7-H); MS, *m/z* 202 (M^+, 62%) and 159 (100). (Found : C, 76.93 ; H, 7.06. $C_{13}H_{14}O_2$ requires C, 77.20: H, 6.98).

1,3-Dihydro-1,3-dimethyl-3-ethylisobenzofuran-1-ol (**13**). To a stirred solution of commercially available 1,2-diacetyl benzene (**12**) (44 mg, 0.27 mmol) in diethyl ether (5 ml) kept at -78°C was added ethylmagnesium bromide (1 mmol) in diethyl ether (0.5 ml). The solution was stirred for 30 min at that temperature, then quenched with aqueous ammonium chloride and extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product which was purified by PLC (1:4 ethyl acetate-hexane) to give hemiacetal (**13**) (46 mg, 89%) as a 1:1 mixture of diastereomers. IR (neat) 3400 cm^{-1} (OH): ^1H NMR (90 MHz) δ 0.74 and 0.84 (3H, 2t, *J* 7.5 and 7.3 Hz,-CH_2CH_3), 1.05-2.05 (8.5H, m including 4s at 1.46, 1.56, 1.77, and 1.78, Me, CH_2CH_3, and OH), 2.64 (0.5H, br. s, OH), 7.0-7.15(m, aromatic H), and 7.25-7.35 (m, aromatic H); MS *m/z* 192 (M^+, 0.49%), 191 [$(M-H)^+$, 3.5], 175 [$(M-OH)^+$, 27], and 147 (100). (Found : M^+, 192.1142. $C_{12}H_{16}O_2$ requires *M*, 192.1150).

Preparation of 3-Ethyl-3-methylisobenzofuran-1(3H)-one (**14**). Hemiacetal (**13**) (46 mg, 0.24 mmol) in benzene (5 ml) containing mercury(II) oxide (0.16g, 0.72 mmol) and iodine (0.18 g, 0.72 mmol) was irradiated with a 100-W high pressure mercury arc through a Pyrex-filter under nitrogen atmosphere for 1.5 h while stirring. The mixture was filtered through Celite pad and the filtrate was washed with a 5% aqueous sodium thiosulphate and then with brine, dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product which was purified by PLC (1:5 ethyl acetate-hexane) to give phthalide (**14**)[25] (15mg, 36%).

9-Ethyl-6,7,8,9-tetrahydro-5,9-epoxy-5H-benzocyclohepten-5-ol (**16a**). This hemiacetal was prepared from 7,8-dihydro-5H-benzocycloheptene-5,9 (6*H*)-dione (**15a**)[25] according to the reported procedure[24].

9-Carbo(1,1-dimethylethoxy)methyl-6,7,8,9-tetrahydro-5,9-epoxy-5H-benzocyclohepten-5-ol (**16b**). To a stirred solution of magnesium enolate of t-butyl acetate (1 mmol), prepared *in situ* according to the previously reported procedure,[27] was added dione (**15a**) (0.25g, 1.4 mmol) in diethyl ether (7 ml) at 0°C. The solution was stirred for 30 min at that temperature and then quenched with aqueous ammonium chloride. The solution was extracted with diethyl ether and the organic layer was washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product which was purified by PLC (1:3 ethyl acetate-hexane, Rf 0.25) to give hemiacetal (**16b**) (0.31g, 76%). IR (neat) 3370 (OH) and 1728 cm^{-1} (ester C=O); ^1H NMR (90 MHz) δ 1.2-2.1 (15H, m, $-(CH_2)_3-$ and $-C(CH_3)_3$), 2.86 (2H, s, $-CH_2COO-$), 3.95 (1H, s, OH), and 7.1-7.6 (4H, m, aromatic H); MS, *m/z* 234 [$(M-C_4H_8)^+$, 33%] and 57 (100). (Found : M^+, 234,0908. $C_{13}H_{14}O_4$ ($M-C_4H_8$) requires 234.0892).

10-Ethyl-7,8,9,10-tetrahydro-5,10-epoxybenzocycloocten-5(6H)-ol (**16d**). To a stirred solution of ethylmagnesium bromide (0.45 mmol) in diethyl ether (3 ml) kept at -78°C was added 6, 7, 8, 9-tetrahydrobenzocyclooctene-5, 10-dione (**15b**) (15mg, 0.08 mmol) in diethyl ether (3 ml). The solution was stirred for 30 min at that temparature and then allowed to warm to room temperature. The solution was further stirred for one day, then quenched with aqueous ammonium chloride and worked up as in the case of the preparation of hemiacetal (**16b**). The product was purified by PLC (1:3 ethyl acetate-hexane) to give hemiacetal (**16d**). (14mg, 57%). IR (neat) 3380 cm^{-1} (OH) : ^1H NMR (90 MHz) δ 0.81 (3H, t, *J* 7.47 Hz, Me), 1.45-2.3 (10H, m, $-(CH_2)_4-$ and CH_2Me), 2.96 (1H, s, OH), 6.95-7.1 (1H, m, aromatic H), 7.25-7.35 (3H, m, aromatic H); MS *m/z* 218 (M^+, 69%) and 189 [$(M-Et)^+$, 100]. (Found : M^+, 218.1317.$C_{14}H_{18}O_2$ requires M^+, 218.1307).

Preparation of 3-Ethyl-3-(3-iodopropyl)isobenzofuran-1(3H)-one (**17a**). Hemiacetal (**16a**) (75 mg, 0.38 mmol) in benzene (25 ml) containing mercury(II) oxide (0.24g, 1.1 mmol) and iodine (0.28 g, 1.1 mmol) for 2h as described for the above-mentioned preparation of phthalide (**14**) gave phthalide (**17a**). The phthalide was purified by PLC (1:3 ethyl acetate-hexane) (0.10 g, 83%), mp 73-75°C (diethyl ether-hexane). IR (Nujol) 1744 cm^{-1} (C=O); ^1H NMR (90MHz) δ 0.71 (3H, t, *J* 7.3 Hz, Me), 1.05-2.4 (6H, m, $-(CH_2)_2-$), 3.09 (2H, *J* 6.37 Hz, $-CH_2I$), and 7.25-7.95 (4H, m, aromatic H); MS *m/z* 330 (M^+, 0.25%), 301 [$(M-Et)^+$, 55], and 203 [$(M-I)^+$, 100]. (Found : M^+, 330.0130. $C_{13}H_{15}IO_2$ requires *M*, 330.0117).

Preparation of 3-Carbo(1,1-dimethylethoxy)methyl-3-(3-iodopropyl)isobenzofuran-1(3H)-one (**17b**). Hemiacetal (**16b**) (0.18 g, 0.60 mmol) in benzene (30 ml) containing mercury(II) oxide (0.39 g, 1.8 mmol) and iodine (0.46 g, 1.8 mmol) was subjected to photolysis for 4h as mentioned above to give phthalide (**17b**) (0.24 g, 97%) after purification by PLC (1:4 ethyl acetate-Hexane). IR (neat) 1765 (lactone C=O) and 1722 cm^{-1}(ester C=O); ^1H NMR (90 MHz) δ 1.23 (9H, s, $C(CH_3)_3$), 1.5-2.4 (4H, m, $-(CH_2)_2-$), 2.94 (2H, s, $-CH_2COO-$), 3.09 (2H, t, *J* 6.6 Hz, $-CH_2I$), and 7.3-7.9 (4H, m, aromatic H); MS *m/z* 416 (M^+, 0.38%), 360 [$(M-C_4H_8)^+$, 25], 301 [$(M-CH_2COOC(CH_3)_3)^+$, 42], 233 (84), and 57 (100); (Found : M^+, 359.9887. $C_{13}H_{13}IO_4$ ($M-C_4H_8$) requires 359.9857.)

Preparation of 3-(4-Iodobutyl)isobenzofuran-1(3H)-one(**7a**). Hemiacetal (**16c**) (68 mg, 0.36 mmol), isolated in the photolysis of the hypoiodite of cyclobutenol (**6a**) mentioned above, in benzene (20 ml) containing mercury(II) oxide (0.24 g, 1.1 mmol) and iodine (0.28 g, 1.1 mmol) was photolyzed for 2h to afford phthalide (**7a**) (68 mg, 89%).

Preparation of 3-Ethyl-3-(4-iodobutyl)isobenzofuran-1(3H)-one (**17d**). Hemiacetal (**16d**) (11 mg, 0.05 mmol) in benzene (5 ml) containing mercury(II) oxide (35 mg, 0.15 mmol) and iodine (38 mg, 0.15 mmol) was photolyzed for 2.5 h as described for the preparation of phthalide (**17a**) to give phthalide (**17d**) (10 mg, 58%) after purification by PLC (1:3 ethylacetate-hexane). IR (neat) 1760 cm^{-1} (C=O); ^1H NMR (90 MHz) δ 0.71 (3H, t, *J* 7.3 Hz, Me), 0.9-2.3 (8H, m, $-(CH_2)_3-$and $-CH_2Me$), 3.08 (2H, t, *J* 7.0 Hz, $-CH_2I$), and 7.2-7.9 (4H, m, aromatic H) : MS *m/z* 344 (M^+, 41%), 315 [$(M-Et),^+$, 58], 217 [$(M-I),^+$ 93], and 161 [$(M-C_4H_8I)^+$, 100]. (Found M^+, 344.0270. $C_{14}H_{17}IO_2$ requires *M*, 344.0274).

Preparations of 3-(3-Iodopropyl)isobenzofuran-1(3H)-one (**17e**) *and 6,7,8,9-tetrahydro-6,9-epoxybenzocycloheptene-5-one* (**19**). A stirred solution of ketol (**18**) (0.15g, 0.83 mmol) in benzene (20 ml) containing mercury(II) oxide (0.54 g, 2.5 mmol) and iodine (0.63 g, 2.5 mmol) was irradiated with a 100-W high pressure mercury arc through a Pyrex-filter under nitrogen for 1 h 20 m. After filtering through a Celite pad the filtrate was washed with a 5% aqueous sodium thiosulphate and then brine. The solution was then dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* to give a residue which was subjected to PLC on silica gel (1:5 ethyl acetate - hexane) to give isobenzofuranone (**17e**) (Rf 0.37, 90 mg, 36%) and epoxybenzocycloheptenone (**19**) (Rf 0.39, 33 mg 32%). (**17e**): IR (neat) 1762 cm ^{1}(C=O); ^{1}H NMR (90 MHz) δ 1.65-2.4 (4H, m, -$(CH_2)_2$-), 3.24 (2H, t, *J* 6.3Hz, -CH_2I), 5.50 (1H, dd, *J* 7.3 and 3.5 Hz, -CHO), 7.4-7.75 (3H, m, aromatic H), and 7.90 (1H, dd, *J* 7.7 and 1.8 Hz, aromatic H); MS, *m/z* 302 (M^+, 0.11%), 1.75 [(M-I)$^+$, 53], and 131 [(M-C_3H_6I)$^+$, 100].(Found M^+, 301.9788 $C_{11}H_{11}IO_2$ requires *M*, 301.9804). (**19**): IR (neat) 1705 cm^{-1}(C=O); ^{1}H NMR (90MHz) δ 1.6 - 2.0 and 2.2 - 2.5 (4H, m, -$(CH_2)_2$-), 4.76 (1H, dd, *J* 6.2 and 1.8 Hz, -CHO-), 5.30 (1H, d, *J* 6.4 Hz, -CHO-), 7.15 - 7.6 (3H, m, aromatic H), and 8.00 (1H, dd, *J* 7.0 and 1.8 Hz, aromatic H) ; MS, *m/z* 174 (M^+, 70%) and 131 (100). (Found :M^+, 174.0652. $C_{11}H_{10}O_2$ requires *M*, 174.0681).

Synthesis of 3-[3-(Dimethylamino)propyl]isobenzofuran-1(3H)-one. (±)-Pierardine (**20**). A solution of phthalide (**17e**) (90 mg, 0.30 mmol) and dimethylamine (1 ml, 50% in water) in methanol (3 ml) was stirred at 0°C for 2h, then acidified with conc. hydrochloric acid and adjusted to pH 10. The solution was concentrated *in vacuo* and extracted with diethyl ether. The organic extract was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product which was purified by PLC (1:1 ethyl acetate-hexane) to give a racemic pierardine (**20**)[23] (15 mg, 23%). A viscous oil. IR (neat) 1762 cm^{-1} (lactonic C=O): ^{1}H NMR (90 MHz) δ 1.5-2.5 (6H, m, -$(CH_2)_3$-), 2.20 (6H, s, NMe_2), and 7.3-7.95 (4H, m, aromatic H).

References

1 Photoinduced Molecular Transformations. 121. Part 120. Kobayashi, K.; Shimizu, H.; Sasaki, A.; Suginome, H. *J. Org. Chem.*, in press .

2 Preliminary communication. Kobayashi, K.; Itoh, M.; Suginome, H. *Tetrahedron Lett.*, **1987**, *28*, 3369.

3 Hereafter, "phthalide" a trivial name for isobenzofuran-1(3*H*)-one, is used.

4 a) Freund, M. *Ber.*, **1889**, *22*, 456 and 459.
b) Edward, G. A.; Perkin, Jr., W. H.; Stoyle, F. W. *J. Chem. Soc.*, **1925**, *127*, 195.
c) Hochstein, R. A.; Pasternack, R. *J. Am. Chem. Soc.*, **1952**, *74*, 3905.
d) Barton, D. H. R.; de Vries, J. X. *J. Chem. Soc.*, **1963**, 1916.
e) Grove, J. F. *J. Chem. Soc., Perkin Trans. I*, **1972**, 2406.
f) A review on phthalide isoquinoline alkaloids. Shamma, M. "The Isoquinoline Alkaloids", Academic Press, New York, N. Y., **1972**, Chapter 19.
g) Leete, E. Boden, G. B.; *J.Am.Chem. Soc.*, **1976**, *98*, 6321 and references cited therein.
h) Danheiser, T. L.; Gee, S. K.; Perez, J. J. *Ibid.*, **1986**, *108*, 806 and references cited therein.

i) de Jesus, M. E; Horak, R. M.; Steyn, P.S. Vleggaar, R. J. *J. Chem. Soc. Perkin Trans. I.*, **1987**, 2253 and references cited therein.

5 Trueb, W.; Eugster, C. H. *Helv. Chim. Acta.*, **1972**, 969.

6 a) Broom, N. J. P.; Sammes, P. G. *J. C. S. Perkin Trans. I*, **1981**, 465.
b) Hauser, F. M. Rhee, R. P. *J. Org. Chem.*, **1978**, *43*, 178.
c) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.*, **1978**, 2263.
d) Broom, N. J.; Sammes, P. G. *J. C. S. Chem. Commun.*, **1978**, 162.
e) Kim, K. S.; Spatz, M. W.; Johnson, F.*Tetrahedron Lett.*, **1979**, 331.
f) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.*, **1979**, *44*, 2596.
g) Sammes, P. G. *J. C. S. Chem. Commun.*, **1979**, 33.
h) Contreras, L.; Maclean, D. B. *Can. J. Chem.*, **1980**, *58*, 2573.
i) Li, T. Wu, Y. L. *J. Am. Chem. Soc.*, **1981**, *103*, 7007.
j) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.*, **1983**, *48*, 3439.
k) Hauser, M. F.; Prasanna, S. Combs, D. W. *J. Org. Chem.*, **1983**, *48*, 1328.
l) Russella, R. W.; Krauss, A. S.; Warrener, R. N. Iruine, R. W. *Tetrahedron Lett.*, **1984**, *25*, 1517.
m) Franck, R. W.; John, T. V. *J. Org, Chem.*, **1980**, *45*, 1170.
n) Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. R. *Synthesis*, **1980**, 72.
o) Larock, R. C.; Fellows, C. A. *J. Org. Chem.*, **1980**, *45*, 363.
p) Kraus, G. A.; Pezzanite, J. O.; Sugimoto, H. *Tetrahedron Lett.*, **1979**, 853.
q) Larock, R. C. *Heterocycles*, **1982**, *18*, 397.

7 Snieckus, V.; *Heterocycles*, **1980**, *14*, 1649; Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aust. J. Chem.*, **1981**, *34*, 383, and references cited therein.

8 Wislicenus, J. *Ber.*, **1884**, *17*, 2178.

9 Gabriel. H. *Ibid.*, **1887**, *20*, 2224.

10 Fischer, C.; Wolffenstein, R. *Ibid*, **1904**, *37*, 3220.

11 Suzuki, H.; Hanafusa, T. *Synthesis*, **1974**, 53.

12 Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.*, **1975**, 1195; Trost, B. M.; Rerers, G. T.; Gold, J. M. *J. Org. Chem.*, **1980**, *45*, 1835; Noire, P. D.; Franck, R. W. *Synthesis*, **1980**, 882.; Beak, P.; Snieckus, V. *Acc. Chem. Res.*, **1982**, *15*, 306; Mills, R. J.; Snieckus, V. *Tetrahedron Lett.*, **1984**, *25*, 483; Desilva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.*,1978, 5099.

13 Sinhababu, A. K.; Borchart, R. T. *J. Org. Chem.*, **1983**, *48*, 2356.

14 (a) Jones, P.R.; Jarboe, C. J. *Tetrahedron Lett.*, **1969**,1849.
(b) Asami, M.; Mukaiyama, T. *Chem. Lett.*,**1980**, 17.
(c) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; BakerR. J. *Tetrahedron*, **1983**, *39*, 1991.

15 Durr, H.; Nickels, H.; Pacala, L. A.; Jones, M. *J. Org. Chem.*, **1980**, *45*, 973.

16 Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.*, **1982**, *47*, 2393.

17 Blair, J.; Brown, J. J.; Newbold, G. T. *J. Chem. Soc.*, **1955**, 708.

18 Cava, M.P.; Muth, K. *J. Am. Chem. Soc.*, **1960**, *82*, 652; Wasserman, H.; Solodar, J.; *Ibid.*, **1965**, *87*, 4002.

19 Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron*, **1985**, *41*, 399.

20 Caubere, P.; *Acc. Chem. Res.*, **1974**, *7*, 301; Carre, . C.; Viriot-Villaume, M. L.; Caubere, P.; *Synthesis*, **1977**, 48, and references cited therein.

21 Canonne, P.; Akssira, M.; *Tetrahedron Lett.*, **1984**, *25*, 3453; Canonne, P.; Plamondon, J.; Akssira, M.; *Tetrahedron*, **1988**, *44*, 2903.

22 Suginome, H.; Yamada, S. *J. Org. Chem.*, **1984**, *49*, 3753 ; *Ibid.*, **1985**, *50*, 2489.

23 Elander, M.; Leander, K.; Luning, B. *Acta. Chem. Scand.*, **1969**, *23*, 2177.
Elander, M.; Gawell, L.; Leander, K. *Ibid.*, **1971**, *25*, 721.

24 Hahn, W. E.; Kryczniki. *Roczniki Chem.*, **1979**, *53*, 1751.

25 Barltrop, J. A.; Johnson, A. J.; Meakins, G. D. *J. Chem. Soc.*, **1951**, 181.

26 Cozzi, P.; Carganico, G.; Orsini, G. *J. Med. Chem.*, **1983**, *26*, 1764; Vene, J.; Tirouflet, J. *Hebd. C. R. Seances Acad. Sci.*, **1948**, *227*, 1375.

27 Hiyama, T.; Kobayashi, K.; Nishide, K. *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 212; Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.*, **1983**, *23*, 1597.

28 McIntyre, D.; Proctor, G. R.; Rees, L. *J. Chem. Soc. C.*, **1966**, 987.

29 Buchanan, G. L.; Sutherland, J. K. *J. Chem. Soc.*, **1956**, 2620.