Synthesis of Psoralen Analogues Based on Dibenzofuran

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Abstract.

The syntheses of four novel psoralen derivatives, **6a-d**, of the benzofurocoumarin (=benzofuro[1]benzopyranone) type containing an ester group are described. These compounds might be of interest in PUVA (psoralen long-wave ultraviolet radiation) therapy. The overall efficiency of the synthetic procedure is greatly limited by the low yields for the penultimate step, *i.e.* formylation of the dibenzofuranols **3a,c** or protected dibenzofuranol **4d** to the carboxaldehydes **5** (*Scheme 4*). However, the final stage to form the pyranone ring from 5a-d proceeds smoothly (*Scheme 5*).

1. Introduction.- Benzopsoralens, which may be considered as benzofuro-fused coumarin systems (=benzofuro[1]benzopyranone), have previously been synthesized and their biological propertieshave been studied [1] [2]. Introduction of a benzene ring fused to the furan moiety, or bulky or electron-withdrawing substituents at the pyranone ring have been proposed as potential ways to inhibit adduct formation with DNA [3]. In addition, *Gia et al.* [2] have shown that the introduction of an ester group into a benzopsoralen can provide derivatives, which are efficient photosensitizers of singlet oxygen. Recently, the photophysical properties of three such compounds have been investigated, and it was shown that two of them could

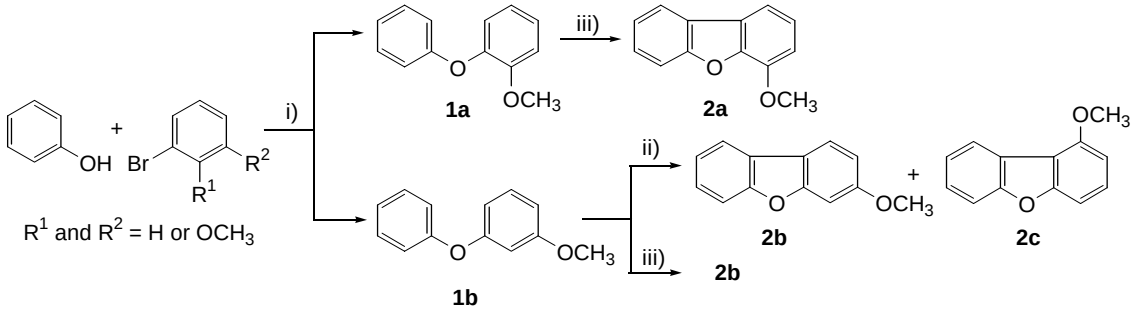
photochemically sensitize singlet-oxygen generation, with a quantum efficiency near unity. This efficiency is unusual for psoralens, but is in accord with their measured long triplet lifetimes, and with their proposed state diagrams [4].

The purpose of this study was to synthesize new derivatives of this general type, that have different fusion sites between the benzofuro and benzopyranone moieties, as a prelude to the study of their potential usefulness as photosensitizers for PUVA (psoralen long-wave ultraviolet radiation) therapy. In the present work, we describe the preparation and characterization of four new psoralen analogues, that are potentially, strongly protected against DNA-adduct formation, in which both the furan ring is benzo-fused and the pyran ring is substituted with an electron withdrawing group.

2. Results and discussion.- The synthesis of the dibenzofuran moiety of the benzopsoralens may be achieved by several methods. One approach involves *Goldberg*-type coupling [5] between phenol and bromoanisoles to give biphenyl ethers, which can then be cyclized. Thus we obtained the diphenylethers **1a-b** in 78 and 93 % yield, respectively (*Scheme 1*).

Cyclisation of compounds of type **1** to the dibenzofuran system has been achieved either by oxidative coupling with palladium acetate [6] or by photolysis [7]. We found that cyclization with palladium acetate gave slightly better yields in AcOH than with CF_3COOH. For example, cyclization of **1a** with palladium acetate in AcOH gave **2a** in 15 % yield, compared to 12 % yield in CF_3COOH. Cyclization of **1b** with palladium acetate in AcOH gave only **2b** in 22 % yield. On the other hand photochemical cyclization of **1b** produced both MeO-substituted dibenzofurans **2b** and **2c,** in 9 % and 30 % yield respectively *(Scheme 1).* Irradiation of **1a** under the same conditions gave only a complex mixture of unidentified products.

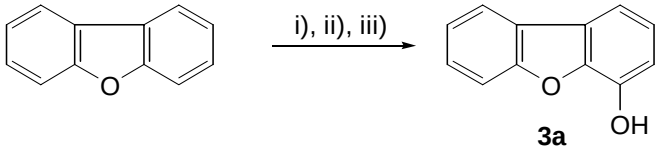
Scheme 1



i) K_2CO_3 / Cu_2O / reflux. ii) C_6H_{12} / hν (150 W) / I_2. iii) $Pd(OAc)_2$ / AcOH or CF_3CO_2H (**1a**), Δ.

Demethylation of derivatives **2** with BBr_3, in dichloromethane [8] gave the corresponding dibenzofuranols **3a-c** in high yields (94- 100 %). Another satisfactory route to the dibenzofuranol **3a** was the hydroxylation of commercial dibenzofuran by lithiation (*N,N,N',N'*-tetramethylethane-1,2-diamine(TMEDA), BuLi) followed by treatment with tributylborate and hydrogen peroxide [9] (S*cheme 2*).

S*cheme 2*

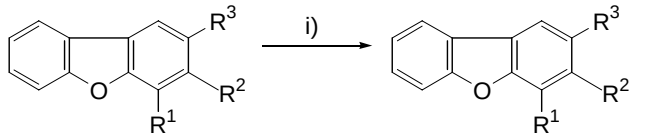


i) BuLi, TMEDA (=N,N,N',N'-tetramethylethane-1,2-diamine), dry Et_2O, reflux; ii) $(BuO)_3B$, 0 ºC; iii) H_2O_2, 0 ºC, reflux.

To synthesize the coumarin part of the psoralen, several methods of formylation of dibenzofuranols **3a - c** and of the commercially available dibenzofuran-2-ol **(3d)** were attempted. The first approach involved protection of the OH function C(2), C(3) or C(4) by conversion to the corresponding carbamates **4a,b,d,** which were obtained in good yields by reacting the benzopyranols **3** with $ClCONEt_2$ in pyridine [10] (*Scheme 3*) [11]. Subsequent formylation of 4d by the method of *Snieckus* (*sec*-BuLi and TMEDA/THF at -78°C, DMF treatment and hydrolysis) giving two aldehydes **5a** and **5b** (*Scheme 4*) in equal amounts (12% each). However, when the same procedure was applied to dibenzofuran-3-yl and dibenzofuran-4-yl **4b** and **4a**, respectively, only

starting material was recovered. Similarly, attempted *Vilsmeier* formylation [12] of compounds **3a** and **3b**, and *Duff* formylation [13] of **3c** were unsuccessful, and none of the expected aldehydes could be detected. Finally, formylation of the dibenzofuranols **3a** and **3c** was attempted by the *Reimer-Tiemann* method [14], [15] (*Scheme 4*), and although the aldehydes **5c** and **5d** were obtained, the yields were low (13 and 17 % resp.).

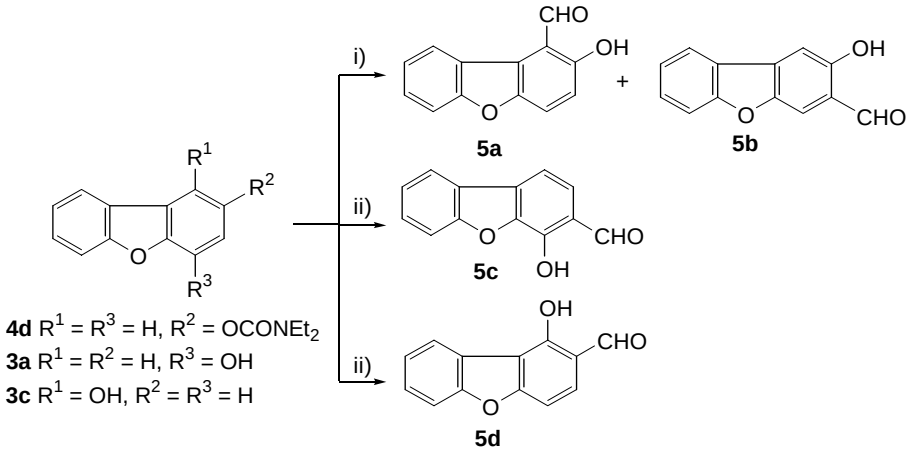
Scheme 3



3a R^1 = OH, R^2 = R^3 = H **4a** R^1 = $OCONEt_2$, R^2 = R^3 = H
3b R^1 = R^3 = H, R^2 = OH **4b** R^1 = R^3 = H, R^2 = $OCONEt_2$
3d R^1 = R^2 = H, R^3 = OH **4d** R^1 = R^2 = H, R^3 = $OCONEt_2$

i) $ClCONEt_2$ / dry pyridine / 85 ºC.

Scheme 4



4d R^1 = R^3 = H, R^2 = $OCONEt_2$
3a R^1 = R^2 = H, R^3 = OH
3c R^1 = OH, R^2 = R^3 = H

i) 1. *sec*-BuLi, TMEDA, THF, -78°C; 2. DMF. ii) 1. $CHCl_3$, NaOH , H_2O , Δ; 2. HCl.

Knoevenagel condensation [16] of *ortho*-hydroxyaldehydes **5a-d** with diethyl malonate, using piperidine and AcOH (*Scheme 5*) afforded the corresponding final products **6a-d**, in moderate to good yields. The structures of the products were

confirmed by elemental analysis, mass spectrometry, IR spectroscopy and also ^{1}H-NMR and ^{13}C-NMR spectroscopy.

3. Conclusions. - The synthesis of the benzopsoralens **6a-d** requires the formylation of relevant intermediate dibenzofuranols **3**. Dibenzofuran-2-ol (**3d**) is commercially available and **3a-c** can be obtained in a three step synthesis involving sequential condensation of phenol with the appropriate bromoanisole, cyclization of the biphenyl ether, and demethylation of the resultant methoxydibenzofuran. Formylation proved difficult, and, when reactions were successful, yields were low. However, cyclization of the *o*-hydroxyaldehydes **5a-d** with diethyl malonate proceeded smoothly, readily giving the benzopsoralens **6a-d** in yields ranging from 20 to 87 %. Studies on the therapeutic and/or toxic properties of the four novel compounds **6a-d** described in this paper are under way.

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Experimental Part

1. *General.* Light petroleum ether refers to solvent boiling in the range 40 - 60 ºC. The photochemical experiments were conducted in a *Heraeus* UV-reactor system with a medium-pressure Hg vapor immersion lamp (150 W). Column chromatography (CC) : *Merck* silica gel 60 (70-230 mesh or 230-400 mesh). M.p.: *Gallenkamp* apparatus; uncorrected; for some compounds no solvent of crystallization is indicated, since the m.p. was determined for the compound obtained

from CC. UV Spectra: *HITACHI 2000* ; EtOH sols., λ_{max} [log ε [mol^{-1} dm^3 cm^{-1}]. IR Spectra: *Diffus IR-Bomem-MB* FT-IR spectrometer; in cm^{-1}.

H-NMR Spectra: *Varian Unity Plus* at 300 MHz(^1H) and 75.4 Hz (^{13}C); ^1H and ^{13}C assignments are based on irradiation and DEPT-45 experiments, resp.; $CDCl_3$ solns.(if not stated otherwise), δ in ppm, rel. to internal $SiMe_4$ or solvent, resp., *J* in Hz. EI-MS and HR-MS. EI-MS and HR-MS *AutoSpecE* spectrometer; in m/z (rel. %). Elemental analyses: *Leco CHN*S-932.

2. *Diphenyl Ethers: General Method*

A mixture of bromoanisole (=bromo(methoxy)benzene; 5.62 g, 30 mmol), phenol (3.5 g, 37 mmol), K_2CO_3 (2.1 g, 15 mmol), and Cu_2O (6.6 g, 46 mmol) was heated at reflux for 1 h. Another portion of phenol (0.5 g, 5 mmol) was added, and reflux was continued for another 1.5 hours. After cooling, $CHCl_3$ (100 ml) was added, and the solids were separated by filtration. The org. soln. was washed with a 1 M NaOH (5x 25 ml), dried ($MgSO_4$), and evaporated. The product was used without further purification.

2-Methoxyphenyl Phenyl Ether (=1-Methoxy-2-phenoxybenzene