Synthesis of Psoralen Analogues Based on Dibenzo[furan]

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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 properties have 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$_3$COOH. For example, cyclization of 1a with palladium acetate in AcOH gave 2a in 15 % yield, compared to 12 % yield in CF$_3$COOH. 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.
Demethylation of derivatives 2 with BBr₃, 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] (Scheme 2).

**Scheme 2**

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\begin{align*}
\text{i)} & \quad \text{BuLi, TMEDA (=N,N,N',N'-tetramethylethane-1,2-diamine), dry Et₂O, reflux;} \\
\text{ii)} & \quad (BuO)₃B, 0 \degree C; \\
\text{iii)} & \quad H₂O₂, 0 \degree C, reflux.
\end{align*}
\]

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 CICONE₂ 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

\[
\begin{align*}
3a & : R^1 = OH, R^2 = R^3 = H \\
3b & : R^1 = R^3 = H, R^2 = OH \\
3c & : R^1 = R^2 = H, R^3 = OH \\
4a & : R^1 = OCONEt_2, R^2 = R^3 = H \\
4b & : R^1 = R^3 = H, R^2 = OCONEt_2 \\
4d & : R^1 = R^2 = H, R^3 = OCONEt_2 \\
i) & \text{ClCONEt}_2 / \text{dry pyridine} / 85 \degree C.
\end{align*}
\]

Scheme 4

\[
\begin{align*}
4d & : R^1 = R^3 = H, R^2 = OCONEt_2 \\
3a & : R^1 = R^2 = H, R^3 = OH \\
3c & : R^1 = OH, R^2 = R^3 = H \\
5a & : R^1 = OH, R^2 = OH \\
5b & : R^1 = CH_2OH \\
5c & : R^1 = OH, R^2 = OH \\
5d & : R^1 = CH_2OH \\
i) & 1. \text{sec-BuLi, TMEDA, THF, } -78\degree C; 2. \text{DMF.} \\
ii) & 1. \text{CHCl}_3 , \text{NaOH , H}_2\text{O , } \Delta 2. \text{HCl.}
\end{align*}
\]

Knoevenagel condensation [16] of ortho-hydroxylaldehydes 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 °C. 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., $\lambda_{\text{max}} [\log \varepsilon \text{ [mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}].$ IR Spectra: Diffus IR-Bomem-MB FT-IR spectrometer; in cm$^{-1}$. 
H-NMR Spectra: Varian Unity Plus at 300 MHz($^1$H) and 75.4 Hz ($^{13}$C); $^1$H and $^{13}$C assignments are based on irradiation and DEPT-45 experiments, resp.; CDCl$_3$ solns.(if not stated otherwise), $\delta$ 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 CHNS-932.

2. Diphenyl Ethers: General Method
A mixture of bromoanisole (=bromo(methoxy)benzene; 5.62 g, 30 mmol), phenol (3.5 g, 37 mmol), $\text{K}_2\text{CO}_3$ (2.1 g, 15 mmol), and Cu$_2$O (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)