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In a one-step alkylation, ring-closure 7-hydroxycoumarins are condensed in acid media with allyl and homoallyl halides or alcohols to linear 6,7-dihydro-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]dipyran-2-ones. If both carbon-6 and carbon-8 are unsubstituted in the original coumarin, cyclization to angular isomers 9,10-dihydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-2-ones competes. These compounds are higher ring homologs of psoralens and angelicins commonly employed in phototherapy of skin disorders.

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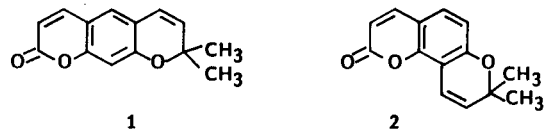
Psoralens, also known as linear furocoumarins, are used in the treatment of a number of proliferative diseases of the skin including psoriasis and mycosis fungoides [1-3]. Although of considerable potential benefit in the photochemotherapy of cancers and the phototreatment of psoriasis, one of the major concerns in the use of psoralens in such protocols is their long established ability to associate with and, upon irradiation, to alkylate and crosslink DNA. The latter are molecular events believed to be associated with the undesirable side-effects of PUVA therapy, namely long term mutagenic/carcinogenic effects arising from error-prone repair processes [4-6].

Recently, it has been shown that psoralens bind to specific high affinity receptors on epidermal target cells [7]. These receptors are distinct from nuclear DNA and are covalently modified by the combination of psoralens and UVA light. Photoactivation of the drug-receptor complex leads to the inhibition of binding of epidermal growth factor (EGF) to its receptor [8]. Inhibition of EGF action has been invoked as a possible mechanism for arresting malignant cell growth [9]. Our research has been targeted toward the synthesis and biological evaluation of psoralen analogs which exhibit the ability to inhibit EGF binding. In recent studies from our laboratories we have been able to show that certain dihydropsoralens and dihydrobenzodipyran-2-ones possess the beneficial photobiology of inhibition of EGF receptor binding while being structurally unable to crosslink DNA as they lack the second site of unsaturation found in the psoralens [10].

We have reported a facile synthesis of dihydro, monofunctional psoralens by a selective palladium-catalyzed transfer hydrogenation which has been extended to include the pyranocoumarins, structural homologs of the psoralens [11,12]. This method, while useful, required the availability of the corresponding unsaturated benzodipyran-2-ones. Herein we wish to report an efficient one-step acid-catalyzed synthesis of reduced derivatives of the natural products, xanthyletin **1** and seselin **2**, structurally related to the psoralens (linear furocoumarins) and to the angelicins (angular furocoumarins). This process requires only the availability of the preformed 7-hydroxycoumarin derivatives and may be carried out successfully with a wide variety of pentenyl halides and alcohols.



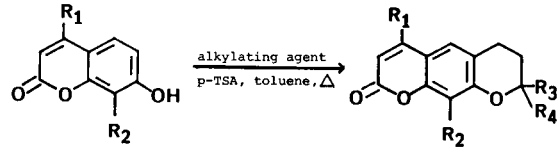
1 2

FIGURE 1

Xanthyletin, seselin and other dihydrobenzodipyran-2-ones have been isolated from botanical materials [13]. In addition, *de novo* low yield syntheses of xanthyletin and seselin have been reported by the boron trifluoride-etherate catalyzed allylation of appropriate salicylaldehydes followed by elaboration of the coumarin ring system by Perkin condensation [14]. Another approach condenses the sodium salt of 7-hydroxycoumarin with 3,3-dimethylallyl bromide but here again, the desired products were obtained in poor yield (>10%) [15].

We have observed that 7-hydroxycoumarins can be reacted with an appropriate alkylating agent under acidic conditions to afford directly the desired cyclized product

Scheme 1



3 R_1 = H; R_2 = I

4 R_1 = CH_3; R_2 = I

5 R_1, R_2 = CH_3

6 R_1, R_2, R_3, R_4 = CH_3

7 R_1, R_2, R_3 = CH_3; R_4 = H

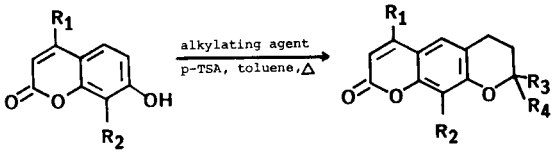
8 R_1, R_3, R_4 = CH_3; R_2 = H

9 R_1, R_2 = H; R_3, R_4 = CH_3

in good yield (45-60%). Furthermore, the alkylating agents may be the corresponding allyl halides, alcohols or even the homoallylic alcohols for all of these give the same product. This result can most likely be attributed to the *in situ* formation of equivalent allylic alkylating species. The acid catalysts used were *p*-toluenesulfonic acid or benzenesulfonic acid. Reflux times were between 3-5 hours and the products were readily purified by flash chromatography on silica gel. In this manner, selected methyl substituted dihydrobenzodipyran-2-ones were prepared (Scheme 1).

When the original 7-hydroxycoumarin employed is unsubstituted on both carbon #6 and carbon #8, mixtures of the linear isomer (6,7-dihydrobenzo[1,2-*b*:5,4-*b'*]dipyran-2-ones) and the angular isomer (9,10-dihydrobenzo[1,2-*b*:-3,4-*b'*]dipyran-2-ones) result (Scheme 2). The angular isomers can be recognized by their ^{1}H-nmr spectra. A coupled A-B doublet of doublets (J = 9 Hz) is present for the protons on carbons #5 and #6 on the benzenoid ring.

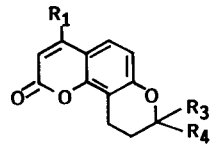
Scheme 2



10 R_1, R_2 = H
11 R_1 = CH_3; R_2 = H

8 and 9

and



12 R_1, R_3, R_4 = CH_3
13 R_1 = H; R_3, R_4 = CH_3

If only linear isomers are desired, this may be achieved in three ways: (1) selection of a coumarin bearing an alkyl substituent in position #8 to preclude closure to the angular isomer and (2) introduction of a blocking iodine atom onto the carbon #8 position which is subsequently removed in the cyclization process to force closure in one direction. This technique has been used successfully in the Claisen rearangement of propargyl ethers [16]. As a third alternative, chromatographic separation of the linear and angular isomers is possible when both are formed in the reaction mixture.

By this one-step procedure, the following dihydrobenzodipyan-2-ones were obtained: 6,7-dihydro-4,8,8,10-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]dipyran-2-one **6**, 6,7-dihydro-4,8,10-trimethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]dipyran-2-one **7**, 6,7-dihydro-4,8,8-trimethyl-2*H*,8*H*-benzo[1,2-*b*:-5,4-*b'*]dipyran-2-one **8**, 6,7-dihydro-8,8-dimethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]dipyran-2-one **9**, 9,10-dihydro-4,8,8-trimethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one **12** and 9,10-dihydrobenzo-8,8-dimethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]-dipyran-2-one **13**.

The photobiology of some fully unsaturated pyranocoumarin derivatives have been studied [17], in particular, the ability of these compounds to induce crosslinks in DNA [18]. It was discovered that many of these compounds, including the angular pyranocoumarins, are capable of undergoing a covalent photoreaction with DNA resulting in the formation of diadducts or interstrand crosslinks. Additionally, the results of this study indicated a clear relationship between the mutagenic activity of these analogs and their capacity to crosslink DNA.

Our biological studies indicate that the novel dihydro derivatives prepared herein act as inhibitors of epidermal growth factor binding similar to the photoactivated psoralens even even though the former are structurally unable to crosslink DNA. Our studies indicate that these derivatives act as inhibitors of epidermal growth factor binding similar to the action of photoactivated psoralens [12]. Therefore, these dihydrobenzodipyran-2-ones represent a psoralen-like therapeutc classes which lacks the mutagenic/carcinogenic potential of their model parents, the linear furocoumarins and the unsubstituted benzodipyran-2-ones.

EXPERIMENTAL

Melting points (uncorrected) were determined using a Thomas-Hoover melting point apparatus. Analytical thin layer chromatography (tlc) was performed on silica gel plates 60-F254 (Whatman) developed with methylene chloride. Preparative column chromatography was performed using silica gel (Merck, 60 Å). The ^{1}H-nmr spectra were recorded on a JEOL FX-90Q spectrometer using deuteriochloroform as the solvent. Chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS), s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants are given in Hertz (Hz). Combustion analyses were provided by Robertson Microanalytical Laboratory, Madison, NJ. The 7-hydroxycoumarins employed herein were available from commercial sources or were synthesized as noted.

6,7-Dihydro-4,8,8,10-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]-dipyran-2-one (**6**).

The 4,8-dimethyl-7-hydroxycoumarin **5** (0.95 g, 5.0 mmoles), 1-chloro-3-methyl-2-butene (1.4 g, 7.5 mmoles) and *p*-toluenesulfonic acid (0.095 g, 0.50 mmole) in 25 ml of toluene were heated at reflux with stirring for 3 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue, a dark brown oil, was flash chromatographed on silica gel using methylene chloride as eluent. Fractions were analyzed by tlc (silica:dichloromethane), pooled and the solvent evaporated under reduced pressure. The crude product was recrystallized from 95% methanol to yield white crystals, 0.80 g (62%), mp 149-150°; ^{1}H-nmr (deuteriochloroform): δ 1.38 (s, 6H, C_8-CH_3's), 1.80 (t, J = 6.8 Hz, 2H, C_6-CH_2),

2.42 (d, J = 1.2 Hz, 3H, C_4-CH_3), 2.76 (t, J = 6.8 Hz, 2H, C_7-CH_2), 6.12 (q, J = 1.2 Hz, 1H, C_3-H), 7.19 (s, 1H, C_5-H).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.41; H, 6.98. Found: C, 74.02; H, 6.85.

Other alkylating agents suitable for use in this reaction include 1-bromo-3-methyl-2-butene, 3-methyl-2-buten-1-ol, 2-methyl-3-buten-2-ol, 3-methyl-3-buten-1-ol and 2-chloro-3-butene. The yields of the product were comparable in all cases (59-63%). The following dihydrobenzo-dipyran-2-ones were prepared by the above general method with modifications as noted.

6,7-Dihydro-4,8,10-trimethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]dipyran-2-one (**7**).

This compound was prepared from 4,8-dimethyl-7-hydroxycoumarin (**5**) (0.95 g, 7.5 mmoles), 1-chloro-2-butene (0.68 g, 7.5 mmoles) and benzenesulfonic acid (0.089 g, 0.50 mmole). The product was obtained as shiny white crystals, mp 159-160° (methanol); ^{1}H-nmr (deuteriochloroform): δ 1.55 (d, 3H, C_8-CH_3), 1.82-2.11 (m, 2H, C_7-CH_2), 2.32 (s, 3H, C_{10}-CH_3), 2.42 (d, 3H, J = 1.2 Hz, C_4-CH_3), 2.85 (t, 2H, C_6-CH_2), 4.17 (m, 1H, C_8-H), 6.12 (q, 1H, J = 1.2 Hz, C_3-H), 7.23 (s, 1H, C_5-H).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.23; H, 6.60.

Other alkylating agents suitable for use in this reaction include 2-chloro-3-butene, 3-buten-2-ol and 3-buten-1-ol with yields of 50-60%.

6,7-Dihydro-4,8,8-trimethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]dipyran-2-one (**8**).

This compound was prepared from 4-methyl-8-iodo-7-hydroxycoumarin (**4**) [16] (2.27 g, 7.5 mmoles), 1-bromo-3-methyl-2-butene (1.12 g, 7.5 mmoles) and *p*-toluenesulfonic acid (0.095 g, 0.50 mmole). The product was isolated as white needles, mp 174-175° (methanol); ^{1}H-nmr (deuteriochloroform): δ 1.30 (s, 6H, C_8-CH_3's), 1.85 (t, 2H, J = 6.6 Hz, C_6-CH_2), 2.30 (d, 3H, J = 1.2 Hz, C_4-CH_3), 2.77 (t, 2H, J = 6.6 Hz, C_7-CH_2), 6.02 (q, 1H, J = 1.2 Hz, C_3-H), 6.65 (s, 1H, C_{10}-H), 7.19 (s, 1H, C_5-H).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.66; H, 6.77.

Here, too, the alternative pentenyl allylation agents used in the synthesis of **6** gave yields of 55-62%.

6,7-Dihydro-8,8-dimethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b'*]dipyran-2-one (Dihydroxanthyletin) (**9**).

This compound was prepared from 8-iodo-7-hydroxycoumarin (**3**) [16] (2.16 g, 7.5 mmoles), 1-chloro-3-methyl-2-butene (1.4 g, 7.5 mmoles) and *p*-toluenesulfonic acid (0.095 g, 0.50 mmole). The product was isolated as white crystals, mp 123-124° (methanol), lit [14] 124-125°; ^{1}H-nmr (deuteriochloroform): δ 1.36 (s, 6H, C_8-CH_3's), 1.83 (t, 2H, J = 6.7 Hz, C_7-CH_6), 2.84 (t, 2H, J = 6.7 Hz, C_7-CH_2), 6.24 (d, 1H, J = 9.4 Hz, C_3-H), 6.72 (s, 1H, C_{10}-H), 7.15 (s, 1H, C_5-H), 7.65 (d, 1H, J = 9.4 Hz, C_4-H).

Alternative pentenyl agents (1-bromo-3-methyl-2-butene, 3-methyl-2-butene-1-ol, 2-methyl-3-butene-2-ol and 3-methyl-3-buten-1-ol) gave equivalent yields (45-60%).

9,10-Dihydro-4,8,8-trimethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one (**12**).

This compound was prepared from 4-methyl-7-hydroxycoumarin (**11**) (0.88 g, 7.5 mmoles), 1-bromo-3-methyl-2-butene (1.12 g, 7.5 mmoles) and benzenesulfonic acid (0.089 g, 0.50 mmole). The product was isolated after flash column chromatography as white needles, mp 160-162° (methanol); ^{1}H-nmr (deuteriochloroform): δ 1.36 (s, 6H, C_8-CH_3's), 1.80 (t, 2H, J = 6.5 Hz, C_9-CH_2), 2.40 (d, 3H, J = 0.97 Hz, C_4-CH_3), 2.79 (t, 2H, J = 6.5 Hz, C_{10}-CH_2), 6.12 (q, 1H, J = 0.97 Hz, C_3-H), 6.80 (d, 1H, J = 8.8 Hz, C_6-H), 7.29 (d, 1H, J = 8.8 Hz, C_5-H).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found; C, 73.82; H, 6.56.

Comparable yields were obtained with isostructural pentenylation agents.

9,10-Dihydro-8,8-dimethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one (Dihydroseslin) (**13**).

This compound was prepared from 7-hydroxycoumarin (**10**) (0.81 g, 7.5 mmoles), 1-chloro-3-methyl-2-butene (1.4 g, 7.5 mmoles) and *p*-toluenesulfonic acid (0.095 g, 0.50 mole). The product was isolated after flash column chromatography as white crystals, mp 103-104° (methanol), lit [19] mp 103-104°; ^{1}H-nmr (deuteriochloroform): δ 1.25 (s, 6H, C_8-CH_3's), 1.84 (t, 2H, J = 6.9 Hz, C_9-CH_2), 2.91 (t, 2H, J = 6.9 Hz, $C_{10}CH_2$), 6.20 (d, 1H, J = 9.4 Hz, C_3-H), 6.73 (d, 1H, J = 8.9 Hz, C_6-H), 7.18 (d, 1H, J = 8.9 Hz, C_5-H), 7.56 (d, 1H, J = 9.4 Hz, C_4-H).

Here, again, the isostructural allylation agents gave comparable results.

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