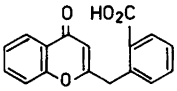
Synthesis of Benzylchromones and Benzoxanthones Related to Natural Products

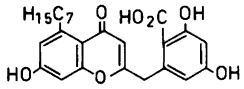
ANDERS KJÆR and DANA KJÆR

Department of Organic Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark

An array of procedures is available for the synthesis of naturally occurring chromones and flavones. None of them have been applied, however, to the synthesis of the homoflavone carboxylic acid skeleton *1*.

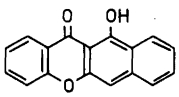


1

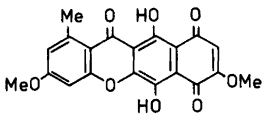


2

We were attracted to this system because of its presence in the unique, naturally occurring homoflavone, siphulin *2*, a constituent of the North Scandinavican lichen *Siphula ceratites* (Wahlenberg) Fr., isolated and identified by Bruun several years ago.[1] Apart from being the only homoflavone of natural derivation, siphulin, an obvious polyketide, carries distinction as the sole chromone carboxylic acid among natural products. On cyclization, the 2-(*o*-carboxybenzyl)-chromone system *1* could conceivably provide an entrance into the tetracyclic



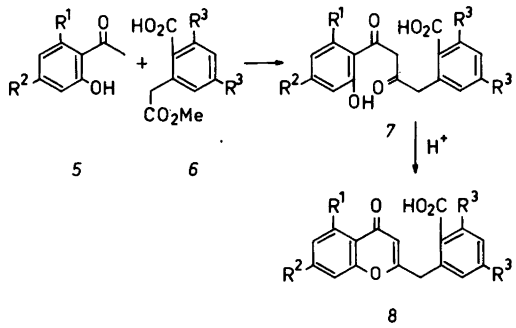
3



4

class of 11-hydroxy-12*H*-benzo[*b*]xanthen-12-ones *3* with the biochrome bikaverin *4*, a long-standing interest of ours,[2] as a conspicuous member. Both siphulin *2* and bikaverin *4* possess structural features of potential biological interest. With a view to studying the structure-activity relationships within the two classes of compounds, efficient synthetic routes, leading, at will, to 2-(*o*-carboxybenzyl)chromones of the siphulin type, or 11-hydroxy-12*H*-benzo[*b*]xanthen-12-ones, structurally related to bikaverin, were explored.

0302-4369/82/060417-03$02.50



5 *6* *7* *8*

We observed that enolates of *o*-hydroxyacetophenones *5*, generated in tetrahydrofuran by means of sodium hydride, reacted smoothly with methyl *o*-carboxyphenylacetates *6* to give enolised 1,3-diketones *7*, which, in turn, were easily converted by acid into the desired, colourless homoflavone acids *8* in satisfactory yields (Table 1).

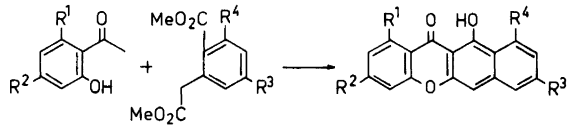
2-Hydroxy-4-methoxy-6-heptylacetophenone *5* ($R^1 = C_7H_{15}$, $R^2 = OMe$) was produced by subjecting sphaeropherol (5-heptylresorcinol), in its turn arising from alkaline hydrolysis and decarboxylation (see Experimental) of methyl 2,4-dihydroxy-6-heptyl benzoate,[3] to Houben-Hoesch acetylation, followed by selective methylation. 3,5-Dimethoxyhomophthalic acid was conveniently prepared by metalation and carbonization of di-*O*-methyl orsellinic acid, according to Hauser,[4] and was converted into its monomethyl ester *6* ($R^3 = OMe$) on brief exposure to methanolic HCl. Attempts to demethylate siphulin tri-*O*-methyl ether (*8*, $R^1 = C_7H_{15}$; $R_2 = R_3 = OMe$), under various conditions, were accompanied by extensive decarboxylation.

Substituting the acid esters *6* with the dimethyl homophthalates *9* in the Claisen-type condensation resulted in a surprisingly efficient, one step synthesis

Table 1. 2-(*o*-Carboxybenzyl)-chromones *8*,[a] synthesized from *5* and *6*.

R^1	R^2	R^3	M.p. °C	Yield %[b]
H	H	H	209	55
H	OMe	H	245	55
Me	OMe	H	244	52
Me	OMe	OMe	205	68
C_7H_{15}	OMe	OMe[c]	167–168[c]	77

[a] All compounds were recrystallized from ethanol and gave analytical figures within ±0.3% of the calculated values; their ^1H and mass spectra were in agreement with structure *8*. [b] The yields refer to analytically pure products. [c] Siphulin trimethyl ether; Lit.[1] m.p. 166–167 °C.



5 9 10

of the yellow 11-hydroxy-12*H*-benzo[*b*]xanthen-12-ones *10*, a number of which were produced by varying the *o*-hydroxyacetophenone and dimethyl homophthalate reactants (Table 2). The fully substituted derivative *10* ($R^1 = Me$, $R^2 = R^3 = R^4 = OMe$) has been further elaborated into bikaverin. This conversion, and several other aspects of the work outlined above, will be described in a forthcoming publication.

Experimental. Melting points (uncorr.) are determined in capillary tubes in a heated block. ^1H NMR spectra are recorded in $CDCl_3$ solutions at 90 MHz on a Bruker HX-90E instrument.

Sphaeropherol (5-heptylresorcinol). Methyl 2,4-dihydroxy-6-heptylbenzoate [3] (10.6 g) was dissolved in dimethyl sulphoxide (120 ml). After adding a solution of potassium hydroxide (12.1 g) in water (25 ml), the mixture was heated, in an argon stream, to 115 °C for 2.5 h. After cooling, the mixture was poured onto ice and conc. hydrochloric acid. The reaction product was extracted with ether, the ether solution was washed with sodium bicarbonate solution and water and dried. On evaporation a brownish solid remained, which was recrystallized first from light petroleum and then from aqueous acetic acid to give pure spaeropherol monohydrate (7.3 g, 81%), m.p. 56 °C (Lit.[1] m.p. 54–55 °C).

(2,4-Dihydroxy-6-heptylacetophenone) and an isomer. A suspension of anhydr. zinc chloride (2.0 g) in anhydr. ether (20 ml), containing sphaeropherol (3.15 g), was saturated at 0 °C with anhydr. hydrogen chloride. Acetonitrile (0.9 g) was added, and a slow stream of hydrogen chloride was maintained for 4 h. The reaction mixture was kept at 0 °C for 3 days, at the end of which the precipitate (2.5 g) was filtered off and subjected to hydrolysis on boiling with sulphuric acid (5 ml 5 N in 200 ml of water) for 1 h. Extraction with ether and recrystallization of the product from light petroleum (with a few drops of ether) gave an analytical specimen of 2,4-dihydroxy-6-heptylacetophenone (*5*, $R^1 = C_7H_{15}$, $R^2 = OH$), m.p. 61–62 °C, anal. $C_{15}H_{22}O_3$: C, H. ^1H NMR: δ 0.88 (3H, t, *J* 6 Hz), 1.1–1.8 (10 H, m), 2.62 (3H, s), 2.80 (2H, t, *J* 6 Hz), 6.22 (2H, s), 6.34 (1H, s; exch. w. D_2O), 11.5 (1H, s; exch. w. D_2O).

The ether filtrate was washed with water (2 × 10 ml) and evaporated to give 0.4 g of unreacted sphaeropherol. On saturating the aqueous phase with dichloromethane, a solid separated (0.95 g). It was hydrolyzed as described above, yielding an additional crop of 2,4-dihydroxy-6-heptylacetophenone (0.23 g) (bringing the total yield, based on reacted spaeropherol, to 57%), and another product (0.17 g), m.p. 46–47 °C, anal. $C_{15}H_{22}O_3$: C, H, after separation on silica gel plates with hexane – diethyl ether – acetic acid (30:20:1) as an eluant. The ^1H NMR spectrum revealed its identity as *2,6-dihydroxy-4-heptyl-acetophenone*, supposedly owing its unparalleled formation in a Houben-Hoesch synthesis to the bulkiness of the alkyl grouping of the substrate: δ 0.85 (3H, t, *J* 6 Hz), 1.1–1.8 (10 H, m), 2.44 (2H, t *J* 6 Hz), 2.67 (3H, s), 6.16 (2H, s), 9.52 (2H, s (br); exch. w. D_2O).

2-Hydroxy-4-methoxy-6-heptylacetone. To a solution of 2,4-dihydroxy-6-heptylacetophenone (1.5 g) in acetone (8 ml), covered with argon, were added, portionwise, a total of 0.85 g of dimethyl sulphate and 5.3 ml of 10% sodium hydroxide while the solution was maintained at 45 °C. After mixing the reagents, the solution was kept at 45 °C for 4 h and then poured onto ice and conc. hydrochloric acid. The oily material was extracted with ether and purified by flash chromatography on silica gel with hexane – ethyl acetate – acetic acid (85:15:1) as the mobile phase. The monomethyl ether (1.10 g, 70%), previously described by Bruun as an oily degradation product of siphulin,[1] was characterized by its ^1H NMR spectrum: δ 0.84 (3H, t, *J* 7 Hz), 1.1–1.8 (10H, m), 2.61 (3H, s), 2.82 (2H, t, *J* 7 Hz), 3.76 (3H, s), 6.22 (2H, s), 12.1 (1H, s; exch. w. D_2O).

Dimethyl 3-methoxy-homophthalate. 3-Hydroxy-homophthalic acid [7] (5 g), dissolved in anhydr. acetone, was stirred with silver oxide (prepared from 12 g of silver nitrate) and methyl iodide (25 ml) at 25 °C for 48 h. After filtration and evaporation, the dimethyl 3-methoxy homophthalate distilled as a colourless oil (5.4 g, 90%), b.p. 140–143 °C (1.7 mmHg) (Lit.[8]: b.p. 117–124 °C (0.3 mmHg)).

Methyl 2-carboxy-3,5-dimethoxyphenylacetate. 3,5-Dimethoxyhomophthalic acid (1 g) was dissolved in methanol (8 ml), containing 0.4 ml of methanol, saturated with hydrogen chloride. After 1 h at 22 °C, the solution was evaporated and the acid ester was recrystallized from ethyl acetate (1.24 g, 91%), m.p. 128–129 °C, anal. $C_{12}H_{14}O_6$: C, H.

Dimethyl 3,5-dimethoxyhomophthalate. 3,5-Dimethoxyhomophthalic acid [4] (1.9 g) was dissolved in methanol (10 ml) to which methanol (10 ml), saturated with hydrogen chloride, was added. The

Table 2. 11-Hydroxy-12*H*-benzo[*b*]xanthen-12-ones *10*,[a] synthesized from *5* and *9*.

R^1	R^2	R^3	R^4	M.p. °C	Yield %[b]
H	H	H	H	203 – 205[c]	70
H	OMe	H	H	183 – 184	63
Me	OMe	H	H	209 – 211	52
H	OMe	H	OMe	245 – 247(d.)	38
Me	OMe	H	OMe	252 – 254(d.)	42
Me	OMe	OMe	OMe	260 – 262(d.)	23

[a] All compounds were recrystallized from dichloromethane-hexane and gave analytical figures within ±0.2% of the calculated values; all exhibited ^{1}H and mass spectra in agreement with structure *10*. [b] The yields refer to analytically pure products. [c] Identical with a specimen (m.p. 198 – 203 °C), prepared, in about 1% yield, by a Nencki type of reaction;[5] described also (m.p. 205 – 209 °C) as the product of a photoinduced cyclization of unknown generality.[6]

solution was refluxed for 2 h, evaporated to dryness, and the residue taken up in ether. The solution was washed with sodium bicarbonate solution and water, dried and evaporated. The ester solidified on standing, m.p. 39 – 41 °C (previously reported as an oil[9,10]).

General procedure for the synthesis of 2-(o-carboxybenzyl)-chromones (Table 1) and 11-hydroxy-12H-benzo-[b]*xanthen-12-ones (Table 2).* To a stirred suspension of sodium hydride (40 mM) in anhydrous tetrahydrofuran, kept in a slow stream of argon, a solution of the *o*-hydroxyacetophenone (10 mM) in tetrahydrofuran (5 ml) was slowly added, followed by a solution of the mono- or diester (10 mM) in tetrahydrofuran (5 – 10 ml). The mixture was refluxed for 5 h, cooled and poured into 6 M hydrochloric acid (50 ml). After standing overnight, the products were collected by filtration and/or extracted with ether or chloroform. The acid derivatives, *8*, were freed of non-acid contaminants by distribution between sodium bicarbonate and ether (or chloroform), and were isolated by acidification of the aqueous phase, and reextraction. All reaction products were produced in analytically pure form by repeated recrystallizations (Tables 1 and 2), in a few cases preceded by chromatographic purification.

Acknowledgement. This paper is submitted in honour of Professor Holger Erdtman on the occasion of his 80th birthday in appreciation of his contributions to organic chemistry.

1. Bruun, T. *Acta Chem. Scand. 19* (1965) 1677.
2. Kjær, D., Kjær, A., Pedersen, C., Bu'Lock, J. D. and Smith, J. R. *J. Chem. Soc. C* (1971) 2792.
3. Djura, P. and Sargent, M. V. *Austr. J. Chem. 29* (1976) 899.
4. Hauser, F. M. and Rhee, R. P. *J. Org. Chem. 42* (1977) 4155.
5. Henderson, W. A., Jr. and Ullman, E. F. *J. Am. Chem. Soc. 87* (1965) 5424.
6. Sammes, P. G. and Wallace, T. W. *J. Chem. Soc. Perkin Trans. 1* (1975) 1845.
7. Wagatsuma, S., Higuchi, S., Ito, H., Nakano, J., Naoi, Y., Sakai, K., Matsui, T., Takahashi, Y., Nishi, A. and Sano, S. *Org. Prep. Proced. 5* (1973) 65.
8. Arai, Y., Kamikawa, T., Kubota, T., Masuda, Y. and Yamamoto, R. *Phytochemistry 12* (1973) 2279.
9. Hardegger, E., Rieder, W., Walser, A. and Kugler, F. *Helv. Chim. Acta 49* (1966) 1283.
10. Mukherjee, J., Chatterjea, J. N. and Sengupta, S. C. *Ind. J. Chem. 13* (1975) 859.

Received February 24, 1982.