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Synthesis of Siphulin, a Naturally Occurring Homoflavone

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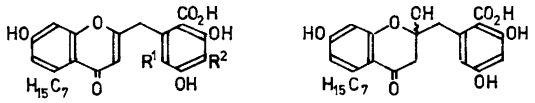
Siphulin, the only homoflavone known in Nature, is synthesized from 2-hydroxy-4-benzyloxy-6-heptylacetophenone and methyl 2-carboxy-3,5-dibenzyloxyhomophthalate, reacting, in the presence of sodium hydride, to give tri-*O*-benzylprotosiphulin, convertible, on acid-induced dehydration, into tri-*O*-benzylsiphulin. Hydrogenolysis of the latter affords siphulin, unavailable by demethylation of the previously synthesized tri-*O*-methylsiphulin due to concomitant decarboxylation.



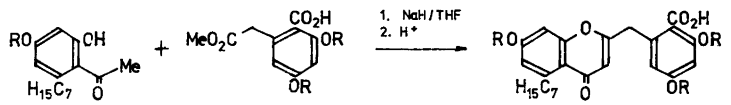
1, $R^1 = R^2 = H$
2, R^1, or R^2 = OH; R^2, or R^1 = H

3

Scheme 1.

Siphulin (*1*)[1] stands out as the sole naturally occurring homoflavone, isolated from the Northern hemisphere lichen *Siphula ceratites* (Wahlenb.) Fr.;[1,2] *S.* species, endemic to the Southern hemisphere are reported as being devoid of siphulin.[2] Oxysiphulin (*2*) and protosiphulin (*3*) are known congeners of siphulin in *S. ceratites* of Canadian provenance.[2] The homoflavone framework of siphulin (*1*) is strongly suggestive of a dodecaketide derivation, setting it biogenetically apart from the mixed acetate-shikimic acid origin obtaining for the flavones. Structural uniqueness, a need for specifically labelled material, and curiosity about biological function and properties, together made siphulin a target for our synthetic efforts; the results are reported below.

Recently, we described an efficient synthesis of tri-*O*-methylsiphulin (*6*) involving the base-promoted condensation of 2-hydroxy-4-methoxy-6-heptylacetophenone (*4*) and the monomethyl ester of 3,5-dimethoxyhomophthalic acid (*5*), followed by acid-induced cyclization.[3] The synthetic product possessed properties identical with those reported for authentic *6*, produced from siphulin of natural derivation.[1]



4, R = Me
7, R = CH_2Ph

5, R = Me
8, R = CH_2Ph

6, R = Me
9, R = CH_2Ph

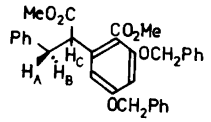
Scheme 2.

0302-4369/85 $2.50

Unfortunately, this approach to siphulin was thwarted by several unsuccessful attempts at the removal of the *O*-methyl groups. Invariably, demethylation was accompanied by decarboxylation, hardly surprising in view of the ease with which siphulin is known to undergo decarboxylation.[1] To circumvent this obstacle, recourse was taken to the *O*-benzylated derivatives, (*7*) and (*8*), in an otherwise analogous approach.

Mono-benzylation of 2,4-dihydroxy-6-heptylacetophenone, prepared as described in our recent paper,[3] proceeded less selectively than the corresponding *O*-methylation.[3] Thus, a nearly 1:1 mixture of the crystalline 2-hydroxy-4-benzyloxy-6-heptylacetophenone (*7*) and the oily 2,4-dibenzyloxy-6-heptylacetophenone resulted from treating the dihydric phenol with benzyl bromide, or benzyl chloride, and potassium carbonate in refluxing acetone.

The crystalline monomethyl 3,5-dibenzyloxyhomophthalate (*8*) was easily produced by selective esterification of the unknown 3,5-dibenzyloxyhomophthalic acid, a useful, protected polyketide synthon accessible through benzylation of dimethyl 3,5-dihydroxyhomophthalate,[4,8,9] followed by alkaline hydrolysis in aqueous dimethyl sulphoxide. Prolonged treatment with excess benzyl bromide must be avoided since the *C*-benzylated ester (*10*) becomes a quantitatively significant component of the reaction mixture under such conditions. *O*-Benzylation, as here described, compares favourably with the procedure previously reported.[5] Attempts at carbonisation of ethyl di-*O*-benzylorsellinate under anion-forming conditions, modelled after the successful carbonisation of the dianion of the analogous dimethoxy-*O*-toluic acid,[7] led only to complex and uninviting reaction mixtures.



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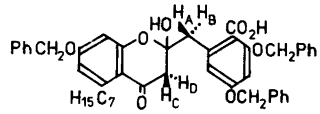

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Subjected to reaction in tetrahydrofuran, the dianion of (*7*) combined with the anion of (*8*), both generated *in situ* by means of sodium hydride, to give a crystalline product to which we assigned the tri-*O*-benzylprotosiphulin structure (*11*) on the basis of spectroscopical data (see Experimental). On acid treatment, *11* easily underwent dehydration to give tri-*O*-benzylsiphulin (*9*), hydrogenolysis of which proceeded unexceptionally to give a nearly quantitative yield of siphulin (*1*), indistinguishable, by i.r., ^{1}H NMR, and mass spectrometry, as well as by t.l.c. comparison in several solvent systems, from an authentic specimen of siphulin, isolated from *S. ceratites*.

EXPERIMENTAL

General. Melting points (uncorrected) are determined in capillary tubes in a heated block. ^{1}H NMR spectra are recorded in $CDCl_3$ solutions at 90 MHz on a Bruker HX-90E spectrometer; mass spectra on a VG-Micromass 7070 F instrument, IP 70 e V. Microanalyses were performed at the LEO company by Mr. G. Cornali and his staff.

O-Benzylation of 2,4-dihydroxy-6-heptylacetophenone. Benzyl bromide (2.1 mmol) was added to a stirred suspension of anhydr. potassium carbonate (8 mmol) in acetone (10 ml), containing 2,4-dihydroxy-6-heptylacetophenone[3] (2 mmol), and the mixture was refluxed for 1.5 h. After filtration and evaporation, the reaction products were separated by

chromatography on SiO_2-plates, with hexane: ether (6:1) as the solvent. A slowly moving band contained unchanged starting material (0.21 mmol).

From a faster moving second band, the desired *2-hydroxy-4-benzyloxy-6-heptyl-acetophenone* (*7*) (0.74 mmol, 42 %, on the basis of non-recovered starting material) was obtained as colourless needles, m.p. 45 °C (from hexane). Anal. $C_{22}H_{28}O_3$: C,H. ^{1}H NMR: δ 0.9 (3H, t, J 6 Hz), 1.2–1.7 (10 H,m), 2.60 (3H, s, MeCO), 2.80 (2H, t, J 7 Hz, $ArCH_2$), 5.01 (2H, s, OCH_2Ph), 6.45 (2H, s, ArH), 7.35 (5H, br.s, Ph), 13.0 (1H, s, OH). MS: [*m/e* (% rel. int.)]: 340 (7, M), 325 (4, [M–Me]), 91 (100).

The fastest moving band contained the oily *2,4-dibenzyloxy-6-heptylacetophenone* (0.75 mmol, 42 %, on the basis of non-recovered starting material). ^{1}H NMR: δ 0.9 (3H, t, J 6 Hz), 1.2–1.7 (10H, m) 2.44 (3H, s, MeCO), 2.50 (2H,m, $ArCH_2$), 5.00 (4H, s, 2 x OCH_2Ph), 6.45 (2H, s, ArH), 7.36 (5H, s, Ph), 7.39 (5H, s, Ph). MS: [*m/e* (% rel. int.)]: 430 (3, M), 415 (2, [M–Me]), 339 (20, [M–$PhCH_2$]), 181 (5), and 91 (100).

Benzylations, conducted with benzyl chloride under similar conditions, proceeded more sluggishly and without improved selectivity.

Benzylation of dimethyl 3,5-dihydroxyhomophthalate. A solution of benzyl bromide (22 mmol) in acetone (10 ml) was added, in the course of 45 min, to a suspension of anhydr. potassium carbonate (80 mmol) in acetone (50 ml), containing dimethyl 3,5-dihydroxyhomophthalate[4,8,9] (10 mmol). The mixture was heated to reflux for 12 h, cooled, filtered, and evaporated to give the crystalline *dimethyl 3,5-dibenzyloxyhomophthalate* (9 mmol, 90 %), separating from methanol as colourless needles, m.p. 86 °C (Lit.[5] m.p. 85–86 °C). The present benzylation procedure represents a considerable improvement over that previously reported.[5]

An identical experiment in which the heating period was extended to 64 h gave two major reaction products, separated by chromatography on SiO_2-plates (hexane: ether, 3:2). The slowest moving band contained the dibenzyloxy ester (4.7 mmol) described above whereas a faster moving band afforded a crystalline product, identified as the *dimethyl α-C-benzyl-3,5-dibenzyloxyhomophthalate* (10) (3.1 mmol), separating from methanol in colourless needles, m.p. 101–103 °C. Anal. $C_{32}H_{30}O_6$: C,H. ^{1}H NMR: δ 2.95 (1H, dd, H_A (or H_B), J_{AB} 13 Hz, $J_{AC\ (or\ BC)}$ 6 Hz), 3.30 (1H, dd, H_B (or H_A), J_{AB} 13 Hz, $J_{BC\ (or\ AC)}$ 8 Hz), 3.52 (3H, s, aliph. CO_2Me), 3.80 (3H, s, arom. CO_2Me), 4.00 (1H, dd, H_C, J_{AC} 6 Hz, J_{BC} 8 Hz), 5.00 (4H, s, 2 x OCH_2Ph), 6.50 (1H, d, J 1.5 Hz, *O*-subst. ArH), 6.68 (1H, d, J 1.5 Hz, *O*-subst. ArH), 7.19 (5 H, d, J 2 Hz, Ph), 7.32 (5H, s, Ph), 7.35 (5H, s, Ph). MS: [*m/e* (% rel.int.)]: 510 (5, M), 479 (2, [M–OMe]), 387 (7), 181 (10), 180 (4), 91 (100).

3,5-Dibenzyloxyhomophthalic acid. A solution of dimethyl 3,5-dibenzyloxyhomophthalate (5 mmol) and potassium hydroxide (27 mmol) in dimethyl sulphoxide (25 ml) and water (6 ml) was heated at 110 °C for 2 h. After cooling, the mixture was poured into 1 M hydrochloric acid (35 ml) and water (50 ml) when most of the acid separated. An additional crop was obtained from the filtrate by ether extraction. The acid (4.5 mmol, 90%) separated in tiny, colourless needles from acetone: hexane, m.p. 156–157 °C. Anal. $C_{23}H_{20}O_6$: C,H. ^{1}H NMR: δ 3.87 (2H, br.s, CH_2CO_2H), 4.98 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 6.55 (2H, s, *O*-subst. ArH), 7.32 (10H, s, Ph).

Methyl 2-carboxy-3,5-dibenzyloxyhomophthalate (8). To a solution of 3,5-dibenzyloxyhomophthalic acid (3.6 mmol) in methanol (7.5 ml) was added methanol, saturated with anhydr. HCl (1.5 ml). Separation of the monoester started after a few min. It was isolated after 1 h at 20 °C and separated from acetone: hexane in colourless prisms (3.3 mmol, 92 %), m.p. 133 °C. Anal. $C_{24}H_{22}O_6$: C,H. ^{1}H NMR: δ 3.67 (3H, s, OMe), 3.96 (2H, s, CH_2CO_2Me), 5.05 (2H, s, OCH_2Ph), 5.14 (2H, s, OCH_2Ph), 6.55 (1H, d, J 1.5 Hz, *O*-subst. ArH), 6.63 (1H, d, J 1.5 Hz, *O*-subst. ArH), 7.35 (10H, s, 2 x Ph).

Tri-O-benzylprotosiphulin (11). A solution of 2-hydroxy-4-benzyloxy-6-heptylacetophenone (*7*) (0.38 mmol) in tetrahydrofuran (5 ml) was added, in the course of 10 min, to a stirred suspension of sodium hydride (7.6 mmol, 55–60 % oil suspension) in tetrahydrofuran (30 ml). After another 10 min, a solution of methyl 2-carboxy-3,5-dibenzyloxyhomophthalate (*8*) (0.76 mmol) in tetrahydrofuran (5 ml) was added, and the reaction mixture was heated to reflux for 4 h. It was then poured into ice and conc. hydrochloric acid (4.5 ml) and extracted with chloroform. After washing with water, drying, and evaporation, the chloroform extract deposited a crystalline residue, which was separated into three components by chromatography on SiO_2-plates in hexane–ether–formic acid (20:30:1): the

fastest moving band contained unreacted phenone (*7*) (0.14 mmol), and the very slowly moving band 3,5-dibenzyloxyhomophthalic acid (0.45 mmol); from the middle band, tri-*O*-benzylprotosiphulin (*11*) (0.23 mmol, 59 % (or 84 % yield based on consumed phenone (*7*)) was isolated as colourless needles, m.p. 126–128 °C (from ether). Anal. $C_{45}H_{46}O_8$: C,H. ^{1}H NMR: δ 0.90 (3H, t, *J* 6Hz), 1.1–1.7 (10H, m), 2.82 (2H, s, H_A and H_B), 3.00 (2H, t, *J* 7 Hz,$ArCH_2$), 3.14 (1H, d, *J* 13 Hz, H_C (or H_D)), 3.86 (1H, d, *J* 13 Hz, H_D (or H_C)), 5.00, 5.06, 5.11 (each 2H, s, OCH_2Ph), 6.40 (2H, s, ArH in CO_2-subst.ring), 6.40 (2H, s, OH), 6.48 (1H, d, *J* 2.5 Hz, ArH in C_7-subst.ring), 6.58 (1H, d, *J* 2.5 Hz, ArH in C_7-subst. ring), 7.35 (15H, br.s, 3 x Ph). MS: 696 (14, [M–H_2O]), 652 (36, [M–H_2O–CO_2]), 581 (21), 562 (94), and 491 (100).

Tri-O-benzylsiphulin (9). A solution of tri-*O*-benzylprotosiphulin (0.22 mmol) in chloroform (1 ml) containing a few drops of trifluoroacetic acid was kept at 40 °C for 3 h. The residue was recrystallized from dichloromethane and ether to give tri-*O*-benzylsiphulin (*9*) as colourless prisms (0.21 mmol, 96 %), m.p. 116–118 °C. Anal. $C_{45}H_{44}O_7$: C,H. ^{1}H NMR: δ 0.85 (3H, t, *J* 6 Hz), 1.0–1.8 (10H, m), 3.14 (2H, t, *J* 7 Hz, $ArCH_2$), 4.15 (2H, br.s, C–CH_2–C), 5.01, 5.03, 5.10 (each 2H, s, OCH_2Ph), 5.85 (1H, s, vinylic H), 6.54 (1H, d, *J* 1.5 Hz, ArH in C_7-subst.ring), 6.58 (1H, d, *J* 1.5 Hz, ArH in C_7-subst.ring), 6.67 (2H, s, ArH in CO_2H-subst.ring), 7.35 (15H, br.s, 3 x Ph). MS: 696 (13, M), 652 (38 [M–CO_2]), 562 (93), and 491 (100).

Alternatively, tri-*O*-benzylsiphulin may be obtained from the reaction mixture from the condensation of *7* and *8* by leaving it in acid solution overnight, thus bypassing the isolation of tri-*O*-benzylprotosiphulin.

Siphulin (1). A solution of tri-*O*-benzylsiphulin (0.26 mmol) in ethyl acetate (10 ml) was shaken with palladium on charcoal (10 %, 60 mg) in a hydrogen atmosphere for 4 h. After filtration, evaporation, and recrystallization from aqueous methanol, siphulin (0.24 mmol, 92 %) was obtained as colourless needles. Comparison (T.L.C., IR, ^{1}H NMR, and MS) with an authentic specimen of siphulin ascertained the identity and homogeneity of the synthetic specimen.

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