Synthesis of Siphulin, a Naturally Occurring Homoflavone

ANDERS KJÆR and DANA KJÆR

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

Siphulin, the only homoflavone known in Nature, is synthesized from 2-hydroxy-4-benzylxy-6-heptylacetophenone and methyl 2-carboxy-3,5-dibenzylxyhomophthalate, 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.

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.\(^2\) Oxsiphulin (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.\(^1\)

Scheme 2.

0302-4369/85 $2.50
© 1985 Acta Chemica Scandinavica
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-heptylacetonaphone, prepared as described in our recent paper,\(^3\) proceeded less selectively than the corresponding O-methylation.\(^5\) Thus, a nearly 1:1 mixture of the crystalline 2-hydroxy-4-benzyloxy-6-heptylacetonaphone (7) and the oily 2,4-dibenzoyloxy-6-heptylacetonaphone resulted from treating the dihydric phenol with benzyl bromide, or benzyl chloride, and potassium carbonate in refluxing acetone.

The crystalline monomethyl 3,5-dibenzoyloxymorphthalate (8) was easily produced by selective esterification of the unknown 3,5-dibenzoyloxymorphhalic acid, a useful, protected polyketide synthon accessible through benzylaition of dimethyl 3,5-dihydroxyxymorphthalate,\(^4,8,9\) 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-Benzylaition, 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.

![Diagram](image)

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-benzylprotopsiphulin 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-Benzylaition of 2,4-dihydroxy-6-heptylacetonaphone.** 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-heptylacetonaphone\(^3\) (2 mmol), and the mixture was refluxed for 1.5 h. After filtration and evaporation, the reaction products were separated by

chromatography on SiO₂-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-benzylxy-6-heptylacetophenone (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. C₂₇H₂₉O₅: C, H. ¹H 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, ArCH₂), 5.01 (2H, s, OCH₂Ph), 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-dibenzylxy-6-heptylacetophenone (0.75 mmol, 42 %, on the basis of non-recovered starting material). ¹H NMR: δ 0.9 (3H, t, J 6 Hz), 1.2–1.7 (10H, m), 2.44 (3H, s, MeCO), 2.50 (2H, m, ArCH₂), 5.00 (4H, s, 2 x OCH₂Ph), 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−PhCH₂]), 181 (5), and 91 (100).

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

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

An identical experiment in which the heating period was extended to 64 h gave two major reaction products, separated by chromatography on SiO₂-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-dibenzyloxyhomophtalate (10) (3.1 mmol), separating from methanol in colourless needles, m.p. 101–103 °C. Anal. C₇₀H₇₀O₄: C, H. ¹H NMR: δ 2.95 (1H, dd, H₆A (or H₆B)), JAB 13 Hz, JAC (or BC) 6 Hz), 3.30 (1H, dd, H₅B (or HA), JAB 13 Hz, JBC (or AC) 8 Hz), 3.52 (3H, s, aliph. CO₂Me), 3.80 (3H, s, arom. CO₂Me), 4.00 (1H, dd, H₆C, JAC 6 Hz, JBC 8 Hz), 5.00 (4H, s, 2 x OCH₂Ph), 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-Dibenzyloxyhomophtalate. A solution of dimethyl 3,5-dibenzyloxyhomophtalate (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. C₇₀H₇₀O₄: C, H. ¹H NMR: δ 3.87 (2H, br.s, CH₂CO₂H), 4.98 (2H, s, OCH₂Ph), 5.08 (2H, s, OCH₂Ph), 6.55 (2H, s, O-subst. ArH), 7.32 (10H, s, Ph).

Methyl 2-carboxy-3,5-dibenzyloxyhomophtalate (8). To a solution of 3,5-dibenzyloxyhomophtalate (3.6 mmol) in methanol (7.5 ml) was added methanol, saturated with anhyd. 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. C₇₀H₇₀O₄: C, H. ¹H NMR: δ 3.67 (3H, s, OMe), 3.96 (2H, s, CH₂CO₂Me), 5.05 (2H, s, OCH₂Ph), 5.14 (2H, s, OCH₂Ph), 6.55 (1H, d, J 1.5Hz, O-subst. ArH), 6.63 (1H, d, J 1.5 Hz, O-subst. ArH), 7.35 (10H, s, 2 x Ph).

Tri-O-benzylprotopsiphin (11). A solution of 2-hydroxy-4-benzylxy-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-dibenzyloxyhomophtalate (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 SiO₂-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-dibenzoyloxyhomophthalic acid (0.45 mmol); from the middle band, tri-O-benzylprotopsiphulin (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_{6}: C, H. 1H NMR: δ 0.90 (3H, t, J 6 Hz), 1.1–1.7 (10H, m), 2.82 (2H, s, H	extsubscript{A} and H	extsubscript{B}), 3.00 (2H, t, J 7 Hz, ArCHO	extsubscript{2}), 3.14 (1H, d, J 13 Hz, H	extsubscript{C} (or H	extsubscript{D})), 3.86 (1H, d, J 13 Hz, H	extsubscript{D} (or H	extsubscript{E})), 5.00, 5.06, 5.11 (each 2H, s, OCH	extsubscript{2}Ph), 6.40 (2H, s, ArH in CO	extsubscript{2}-subst.ring), 4.40 (2H, s, OH). 6.48 (1H, d, J 2.5 Hz, ArH in C	extsubscript{7}-subst.ring), 6.58 (1H, d, J 2.5 Hz, ArH in C	extsubscript{7}-subst. ring), 7.35 (15H, br.s, 3 x Ph). MS: 696 (14, [M−H	extsubscript{2}O]), 652 (36, [M−H	extsubscript{2}O−CO	extsubscript{2}]), 581 (21), 562 (94), and 491 (100).

Tri-O-benzylsiphulin (9). A solution of tri-O-benzylprotopsiphulin (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	extsubscript{45}H	extsubscript{46}O	extsubscript{6}: C, H. 1H NMR: δ 0.85 (3H, t, J 6 Hz), 1.0–1.8 (10H, m), 3.14 (2H, t, J 7 Hz, ArCHO	extsubscript{2}), 4.15 (2H, br.s, C−CH	extsubscript{2}−C), 5.01, 5.03, 5.10 (each 2H, s, OCH	extsubscript{2}Ph), 5.85 (1H, s, vinylic H), 6.54 (1H, d, J 1.5 Hz, ArH in C	extsubscript{7}-subst.ring), 6.58 (1H, d, J 1.5 Hz, ArH in C	extsubscript{7}-subst.ring), 6.67 (2H, s, ArH in CO	extsubscript{2}H-subst. ring), 7.35 (15H, br.s, 3 x Ph). MS: 696 (13, M), 652 (38 [M−CO	extsubscript{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-benzylprotopsiphulin.

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, 1H NMR, and MS) with an authentic specimen of siphulin ascertained the identity and homogeneity of the synthetic specimen.

Acknowledgement. The authors are grateful to Professor S. Shibata, The University of Tokyo, Japan, for the generous gift of an authentic specimen of siphulin, and to Dr. J. Øgaard Madsen for recording the mass spectra.

REFERENCES

Received April 17, 1984.