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A Synthesis of the Lichen Xanthone Thiomelin

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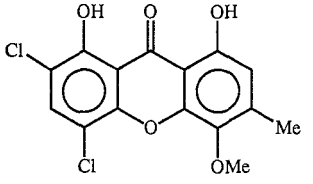
Abstract

A total synthesis of thiomelin (2,4-dichloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one) (1) has been achieved.

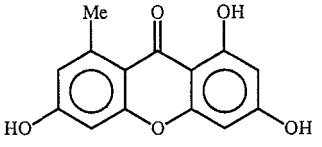
Introduction

The lichen xanthone thiomelin and its cogenors were first isolated by Leuckert and Mayrhofer in 1984[1] from the lichens *Rinodina thiomela* (Nyl.) Müll. Arg. and *R. lepida* (Nyl.) Müll. Arg. The structure (1) of thiomelin followed an X-ray crystal structure analysis performed on the corresponding diacetate,[2] while those of the cooccurring xanthones followed from a comparative study of the ^{1}H n.m.r. and mass spectral data of (1) and these derivatives. The isolation of thiomelin (1) was the first reported occurrence of a typical 'fungal' xanthone from a lichen, as all previously known lichen xanthones were derivatives of norlichexanthone (2), distinct from those found in the free-living fungi.

This paper reports the first total synthesis of thiomelin (1).



(1)



(2)

Synthetic Approaches to Thiomelin

The substitution pattern of thiomelin (1) precluded a normal Friedel–Crafts approach by using preformed orsellinic acid and phloroglucinol derivatives as used in the synthesis of norlichexanthone derivatives.[3–8] Instead, 3,5-dichloro-

[1] Leuckert, C., and Mayrhofer, H., *Herzogia*, 1984, **6**, 373.
[2] Elix, J. A., Gaul, K. L., Sterns, M., and Samsudin, M. W. bin, *Aust. J. Chem.*, 1987, **40**, 1169.
[3] Sundholm, E. G., *Tetrahedron*, 1978, **34**, 577.
[4] Elix, J. A., Musidlak, H. W., Sala, T., and Sargent, M. V., *Aust. J. Chem.*, 1978, **31**, 145.
[5] Sundholm, E. G., *Acta Univ. Ups. Abstr. Uppsala Diss. Fac. Sci.*, 1979, **526**, 1.
[6] Fitzpatrick, L., Sala, T., and Sargent, M. V., *J. Chem. Soc., Perkin Trans. 1*, 1980, 85.
[7] Sundholm, E. G., *Acta Chem. Scand., Ser. B*, 1979, **33**, 475.
[8] Elix, J. A., Jiang, H., and Portelli, V. J., *Aust. J. Chem.*, 1990, **43**, 1291.

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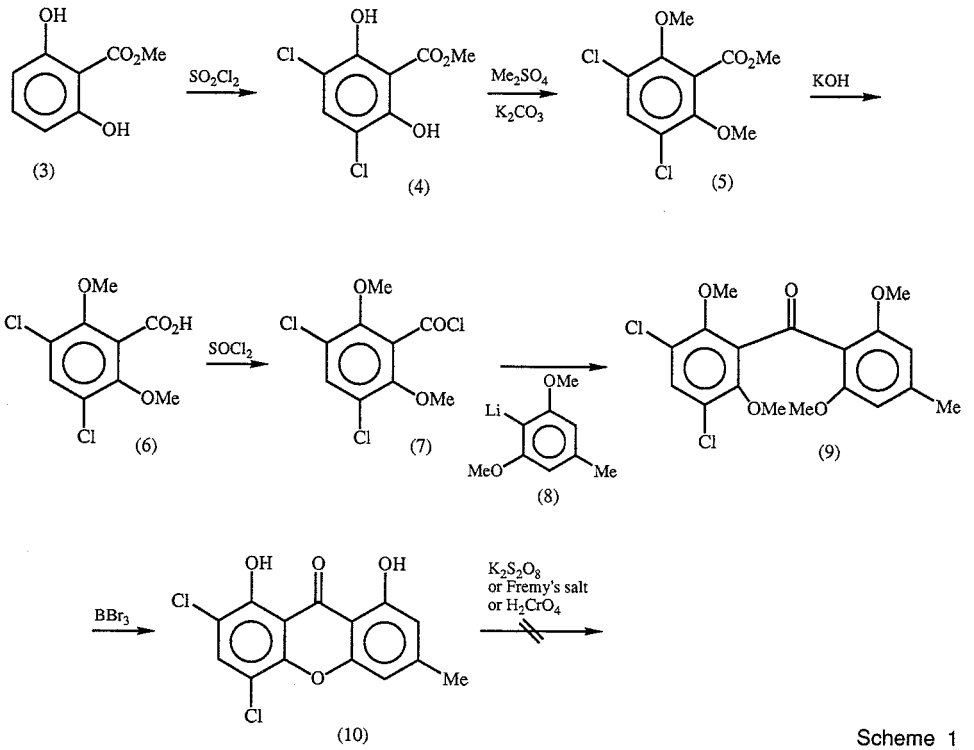
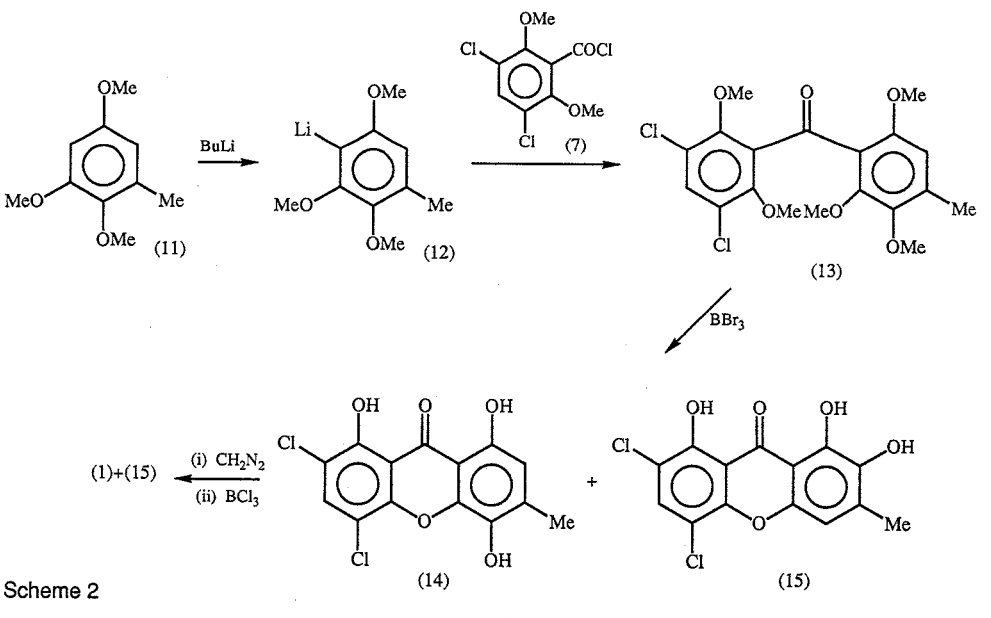
2,6-dimethoxybenzoyl chloride (7) and 2,6-dimethoxy-4-methylphenyllithium (8) were envisaged as key intermediates (Scheme 1), and (7) was prepared in the following manner. Methyl 2,6-dihydroxybenzoate (3) underwent facile chlorination with sulfuryl chloride to give methyl 3,5-dichloro-2,6-



Scheme 1



Scheme 2

dihydroxybenzoate (4). Treatment of (4) with dimethyl sulfate in the presence of potassium carbonate gave methyl 3,5-dichloro-2,6-dimethoxybenzoate (5), and subsequent alkaline hydrolysis afforded the corresponding acid (6). The key intermediate acid chloride (7) was prepared by treating the acid (6) with thionyl chloride in refluxing toluene. Condensation of the acid chloride (7) with 2,6-dimethoxy-4-methylphenyllithium (8) then afforded 3,5-dichloro-2,2′,6,6′-tetramethoxy-4′-methylbenzophenone (9) together with some unreacted acid. Treatment of the benzophenone (9) with boron tribromide effected demethylation and concomitant dehydration and ring closure of the intermediate tetrahydroxybenzophenone to give 2,4-dichloro-1,8-dihydroxy-6-methyl-9*H*-xanthene-9-one (10) in good yield. However, attempted hydroxylation of the xanthone (10) by treatment with potassium persulfate failed, as did attempted oxidation of (10) with potassium nitrosodisulfonate (Fremy's salt) or with chromic acid. Consequently an alternative but similar approach to thiomelin (1) was considered where all required substituents were present in the mononuclear precursors (Scheme 2).

Regioselective lithiation of 2,3,5-trimethoxytoluene (11) by reaction with butyllithium afforded 2,3,6-trimethoxy-4-methylphenyllithium (12). Addition of this lithio derivative (12) to 3,5-dichloro-2,6-dimethoxybenzoyl chloride (7) then gave the required benzophenone 3,5-dichloro-2,2′,3′,6,6′-pentamethoxy-4′-methylbenzophenone (13). Subsequent treatment of the benzophenone (13) with boron tribromide afforded a mixture of 2,4-dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (14) and 2,4-dichloro-1,7,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (15). Permethylation of this mixture of the xanthones [(14) and (15)] by treatment with excess diazomethane gave the corresponding tri-*O*-methyl derivatives, and subsequent demethylation of this mixture with boron trichloride afforded thiomelin (1) and (15). The latter reagent is known to be effective in cleaving 1,2-dimethoxybenzenes as well as alkoxy aromatics with an adjacent carbonyl group.[9] The preferential formation of the xanthone (15) is probably due to the *ortho* inductive effect of the methoxy (or hydroxy) group at position 3′ of benzophenone (13). The inductive effect of this oxygen functionality accentuates the strength of the adjacent hydrogen-bonding interaction which in turn directs cyclization in this manner. Other $-I$ substituents (e.g. halogens) are known to show similar selectivities.[3,5,8]

Experimental

The general experimental details have been reported previously.[8]

Methyl 3,5-Dichloro-2,6-dihydroxybenzoate (4)

Sulfuryl chloride (9·84 g) was added portionwise to a stirred solution of methyl 2,6-dihydroxybenzoate (3)[10] (4·7 g) in anhydrous ether (100 ml), and stirring continued at room temperature for 2 h. The precipitate was filtered and crystallized from ether to give *methyl 3,5-dichloro-2,6-dihydroxybenzoate* (4) (4·98 g, 61%) as colourless crystals, m.p. 163–164° (Found: C, 40·7; H, 2·5; Cl, 29·5. $C_8H_6Cl_2O_4$ requires C, 40·5; H, 2·6; Cl, 29·9%). ^{1}H n.m.r. ($CDCl_3$) δ 4·05, s, OMe; 7·45, s, ArH; 10·00, s, OH. Mass spectrum *m/z* 240 (2%), 238 (14), 236 (M, 21), 208 (10), 206 (72), 204 (100).

[9] McOmie, J. F. W., Watts, M. L., and West, D. E., *Tetrahedron*, 1967, **24**, 2289.
[10] Mauthner, F., *J. Prakt. Chem.*, 1929, **121**, 263.

Methyl 3,5-Dichloro-2,6-dimethoxybenzoate (5)

A solution of dimethyl sulfate (6·70 g) in anhydrous acetone (15 ml) was added dropwise to a stirred mixture of methyl 3,5-dichloro-2,6-dihydroxybenzoate (4) (4·9 g), anhydrous acetone (150 ml) and anhydrous potassium carbonate. The resultant mixture was stirred at room temperature for 16 h and then filtered. Evaporation of the filtrate gave a crude brown oil (5·8 g) which was distilled under reduced pressure to afford methyl 3,5-dichloro-2,6-dimethoxybenzoate (5·55 g, 90%) as a colourless oil, b.p. 165–168°/16 mm (lit.[11] 168°/16 mm). ^{1}H n.m.r. ($CDCl_3$) δ 3·90, s, OMe; 3·95, s, CO_2Me; 7·40, s, ArH.

3,5-Dichloro-2,6-dimethoxybenzoic Acid (6)

A mixture of methyl 3,5-dichloro-2,6-dimethoxybenzoate (5) (5·55 g), potassium hydroxide (5·64 g), water (10 ml) and dimethyl sulfoxide (175 ml) was stirred and heated at 80–90° for 24 h. The resulting orange solution was poured into cold, dilute hydrochloric acid and was extracted several times with ether. The combined ethereal solution was washed with water, dried ($MgSO_4$) and the solvent evaporated. The residue was crystallized from light petroleum to afford the acid (6) (4·1 g, 78%) as colourless needles, m.p. 100–102° (lit.[11] 104–106°) (Found: C, 43·4; H, 3·1; Cl, 28·2. Calc. for $C_9H_8Cl_2O_4$: C, 43·1; H, 3·2; Cl, 28·2%). ^{1}H n.m.r. ($CDCl_3$) δ 3·95, s, OMe; 5·45, br s, CO_2H; 7·50, s, ArH.

3,5-Dichloro-2,2′,6,6′-tetramethoxy-4′-methylbenzophenone (9)

A solution of butyllithium (6·9 ml, 1·6 M) in hexane was added to a stirred solution of 3,5-dimethoxytoluene (1·55 g) in anyhdrous ether (30 ml) in an atmosphere of nitrogen, and stirring continued at room temperature for 3 h. 3,5-Dichloro-2,6-dimethoxybenzoyl chloride (7) was prepared by refluxing a solution of 3,5-dichloro-2,6-dimethoxybenzoic acid (6) (1·9 g) and thionyl chloride (5 ml) in anhydrous toluene (80 ml) for 2 h. The toluene was then removed under reduced pressure and the crude acid chloride was dissolved in anhydrous ether (20 ml). The above lithiation mixture was then added dropwise to a stirred solution of the acid chloride over a period of 30 min in an atmosphere of nitrogen. This solution was stirred at room temperature for 2 h and then poured into cold, dilute hydrochloric acid. The solution obtained was extracted repeatedly with ether (4×50 ml) and the combined ethereal solution was washed with water and dried ($MgSO_4$). The residue obtained on evaporation of the solvent was purified by radial chromatography (SiO_2) by using 5% ethyl acetate/light petroleum as eluent. The major, slow moving band afforded the *benzophenone* (9) (0·63 g, 30%) which crystallized from cyclohexane in colourless prisms, m.p. 107–109° (Found: C, 56·2; H, 4·7; Cl, 19·0. $C_{18}H_{18}Cl_2O_5$ requires C, 56·1; H, 4·7; Cl, 18·4%). ^{1}H n.m.r. ($CDCl_3$) δ 2·25, s, ArMe; 3·70, 3·75, 2s, OMe; 6·20, s, H3′,5′; 7·31, s, H4. Mass spectrum *m/z* 388 (3%), 386 (7), 384 (M, 25), 357 (3), 355 (17), 323 (17), 233 (7), 179 (100), 165 (35), 152 (31).

2,4-Dichloro-1,8-dihydroxy-6-methyl-9H-xanthen-9-one (10)

Boron tribromide (0·75 g, 3 mmol) was added to a stirred solution of 3,5-dichloro-2,2′,6,6′-tetramethoxy-4′-methylbenzophenone (9) (0·2 g, 0·52 mmol) in anhydrous dichloromethane (10 ml) at −15°. The solution was allowed to warm to room temperature over a period of 4 h, and was then poured into cold, dilute hydrochloric acid (5 ml, 2 M) and extracted repeatedly with dichloromethane. The combined extracts were washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by radial chromatography (SiO_2) by using 15% ethyl acetate/light petroleum as eluent. The major band afforded the *xanthone* (10) (0·14 g, 86%) which crystallized from dichloromethane in yellow needles, m.p. 214–215° (Found: C, 53·9; H, 2·5; Cl, 22·8. $C_{14}H_8Cl_2O_4$ requires C, 54·05; H, 2·6; Cl, 22·8%). ^{1}H n.m.r. ($CDCl_3$) δ 2·50, s, ArMe; 6·70, 6·91, 2d, J 2·4 Hz, H5,7; 7·80, s, H3; 11·40, 12·49, 2s, OH. Mass spectrum *m/z* 314 (11%), 312 (63), 310 (M, 100), 283 (4), 281 (6), 155 (4).

[11] Doyle, F. P., Nayler, J. H. C., Waddington, H. R. J., Hanson, J. C., and Thomas, G. R., *J. Chem. Soc.*, 1963, 497.

2,3,5-Trimethoxytoluene (11)

A mixture of 2,4-dimethoxy-6-methylphenol[12] (5·09 g), methyl iodide (5·5 g) and anhydrous potassium carbonate (8 g) in dimethylformamide (50 ml) was stirred at room temperature under a nitrogen atmosphere for 16 h. The resultant mixture was poured into excess cold, dilute hydrochloric acid and was extracted with ether. The ethereal extract was washed in turn with saturated sodium hydrogen carbonate solution, dilute ammonium hydroxide solution, water and brine, and then dried ($MgSO_4$). Evaporation of the solvent afforded *2,3,5-trimethoxytoluene* (11) (4·11 g, 75%) as a colourless liquid (Found: C, 65·8; H, 7·5. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). ^1H n.m.r. ($CDCl_3$) δ 2·15, s, ArMe; 3·70, s, 2×OMe; 3·81, s, OMe; 6·20, s, ArH. Mass spectrum *m/z* 182 (M, 80%), 167 (100).

3,5-Dichoro-2,2′,3′,6,6′-pentamethoxy-4′-methylbenzophenone (13)

A solution of butyllithium (5·6 ml, 1·6 M) in hexane was added portionwise to a stirred solution of 2,3,5-trimethoxytoluene (11) (1·65 g) in anhydrous ether (80 ml) in an atmosphere of dry nitrogen, and stirring continued at room temperature for 3·5 h. Meanwhile, 3,5-dichoro-2,6-dimethoxybenzoyl chloride (7) was prepared by refluxing a solution of 3,5-dichloro-2,6-dimethoxybenzoic acid (6) (2·6 g) and thionyl chloride (8 ml) in anhydrous toluene (70 ml) for 2 h. The toluene and excess thionyl chloride were then removed by distillation under reduced pressure and the crude acid chloride was dissolved in anhydrous ether (20 ml). The above lithiation mixture was then added dropwise to a stirred solution of the acid chloride over a period of 30 min, and stirring continued at room temperature for 2 h. The solution was then poured into cold, dilute hydrochloric acid and extracted with ether (3×30 ml). The combined ethereal solution was washed in turn with water, saturated sodium hydrogen carbonate solution and brine, and then dried ($MgSO_4$) and evaporated. The residue was purified by radial chromatography (SiO_2) by using 5% ethyl acetate/light petroleum as eluent. The major band afforded the *benzophenone* (13) which crystallized from the eluent in off-white crystals, m.p. 114–116° (Found: C, 55·2; H, 5·0. $C_{19}H_{20}Cl_2O_6$requires C, 55·0; H, 4·8%). ^1H n.m.r. ($CDCl_3$) δ 2·20, s, ArMe; 3·55, 3·61, 2s, each 2×OMe; 3·65, s, OMe; 6·40, 7·31, 2s, ArH. Mass spectrum *m/z* 416 (68%), 414 (M, 100), 399 (16), 383 (22), 233, (78), 218 (22), 209 (86), 195 (42).

2,4-Dichloro-1,8-dihydroxy-5-methoxy-6-methyl-9H-xanthen-9-one (Thiomelin) (1) and 2,4-Dichloro-1,7,8-trihydroxy-6-methyl-9H-xanthen-9-one (15)

Boron tribromide (0·55 ml) in anhydrous dichloromethane (1·9 ml) was added to a stirred solution of the benzophenone (13) (0·60 g) in anhydrous dichloromethane (15 ml) at −15° in an atmosphere of dry nitrogen. After stirring at room temperature for 16 h, the solution was poured into cold, dilute hydrochloric acid and was extracted repeatedly with ether. The combined ethereal solution was washed with water, dried ($MgSO_4$) and evaporated. The residue crystallized from dichloromethane to afford a mixture of the *xanthones* (14) and (15) as yellow crystals m.p. 220–240° (Found: C, 51·6; H, 2·5. $C_{14}H_8Cl_2O_5$ requires, C, 51·4; H, 2·4%). All attempts to separate these two xanthones failed. ^1H n.m.r. ($CDCl_3/CD_3SOCD_3$) δ 2·35, s, ArMe; 7·01, s, ArH; 8·00, s, ArH; 8·20, br s, OH; 9·15, br s, OH; 11·20, s, bonded OH; 12·55, s, bonded OH.

The above mixture of xanthones (14) and (15) (0·4 g) was dissolved in acetone (10 ml) and treated with excess ethereal diazomethane at 0°. The solution was maintained at 0° for 3 h and then at room temperature for 16 h. The solvent was then evaporated and the residue redissolved in anhydrous dichloromethane (10 ml) and cooled to 0°. A solution of boron trichloride (0·19 ml) in dichloromethane (0·7 ml) was then added, and the resultant mixture stirred at room temperature for 16 h. The reaction mixture was then poured into cold, dilute hydrochloric acid, and the solution extracted repeatedly with ether. The combined ethereal extract was washed with water, dried ($MgSO_4$) and evaporated. The residue crystallized from dichloromethane to afford *2,4-dichloro-1,7,8-trihydroxy-6-methyl-9H-xanthen-9-one* (15) (0·29 g, 73%) as yellow needles, m.p. 282–283° (Found: C, 51·3; H, 2·5. $C_{14}H_8Cl_2O_5$

[12] Godfrey, I. M., Sargent, M. V., and Elix, J. A., *J. Chem. Soc., Perkin Trans. 1*, 1974, 1353.

requires C, 51·4; H, 2·4%). ^{1}H n.m.r. ($CDCl_3/CD_3SOCD_3$) δ 2·40, s, ArMe; 7·01, 8·00, 2s, ArH; 9·20, br s, OH; 11·20, 12·60, 2s, bonded OH. Mass spectrum *m/z* 330 (12%), 328 (64), 326 (M, 100), 297 (5), 163 (5), 149 (7).

The mother liquors from above were concentrated and the residue was purified by radial chromatography (SiO_2) by using 10–30% ethyl acetate/light petroleum. The faster moving band afforded thiomelin (1) (6·8 mg, 1·7%) which crystallized from dichloromethane/light petroleum as fine yellow threads, m.p. 185° alone or admixed with authentic material. The properties (t.l.c., h.p.l.c., ^{1}H n.m.r., mass spectrum) of this synthetic material were identical with those of natural thiomelin.[2] The slower, major band afforded a further quantity (22·3 mg) of the xanthone (15).

Acknowledgments

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