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# TOTAL SYNTHESES OF LICHEN XANTHONES

## REVISION OF STRUCTURES[1,2]

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**Abstract**—The preparations of several chlorinated derivatives of norlichexanthone **6a** by unambiguous methods are described. The $^1$H NMR spectra of these compounds are discussed and several structures previously assigned for lichen xanthones are questioned. The suggested revisions are summarized in Table 3.

### RESULTS AND DISCUSSION

All lichen xanthones found to date can be regarded as ring-chlorinated (1–4 Cl atoms) and/or O-methylated derivatives of norlichexanthone **6a** (1,3,6-trihydroxy-8-methylxanthene-9-one). A great number of lichen xanthones have been isolated and structurally determined at this institute.[3–7] The structural elucidation was based mainly on $^1$H NMR studies of the acetyl and/or methyl derivatives. Only a few, however, have been synthesized. By applying Shahs' method[8] ($POCl_3$ and $ZnCl_2$), orsellinic acid and phloroglucinol could be condensed to norlichexanthone **6a**, which, upon chlorination in acetic acid, yielded three different chloroxanthones all of which were found to be identical with natural products.[9] Attempts to prepare other chlorinated lichen xanthones by Shahs' method have proven unsuccessful and a convenient method for the ultimate confirmation of their structures was needed.

In a search for suitable precursors for biosynthetic studies on lichen xanthones, benzophenone **5a** was synthesized.[2] Condensation of the benzylether of phloroglucinol carboxylic acid **1a** with the same ether of orcinol **2a** using trifluoroacetic anhydride (TFAA) gave benzophenone **5b** which, after hydrogenolysis, yielded ketone **5a**. **5a**, however, was found to be very unstable and underwent facile cyclization to xanthone **6a**. This finding provided a convenient way to obtain chloroxanthones and, in cases in which ring-closure does not take place easily, alternative precursors for biosynthetic studies.

*Monochlorinated xanthones.*

Condensation of the acid **4a** with the ether **3a** in the presence of TFAA gave the benzophenone **5c** (95%). **5c** was also obtained from **2b** and **1a** (65%) and therefore the structure of **5c** is established. Hydrogenolysis afforded ketone **5d** which was found to dehydrate easily to xanthone **6b**. In the condensation of **1b** with **2a**, using the same conditions, the pentabenzyloxy benzophenone formed gave **5e** after removal of the benzyl groups. Even in this case ring-closure took place easily and of the two theoretically possible structures only xanthone **6c** (m.p. 313–14.5°) was formed. The structure of **6c** was established by the following synthesis. Acid **4b** was reacted with the symmetrical ether **3b** and the tetramethoxy benzophenone formed after hydrogenolysis was converted to the trimethoxy xanthone **6d** after prolonged heating in methanol/NaOH. This product was identical (m.m.p., IR) with the trimethyl ether obtained by methylation of **6c**, which therefore proves the structure of **6c** as 2-chloronorlichexanthone.

In the next synthesis acid **4c** was condensed with the symmetrical ether **3b**. Hydrogenolysis of the benzylketone formed gave **5f**, which was found to be stable even in boiling water. Treatment of **5f** in alkali, however, converted it to a monomethylxanthone (m.p. 249–50°). Demethylation of this xanthone with $AlCl_3$ gave a chloroxanthone that was not identical with **6c** and which is therefore 4-chloronorlichexanthone (**6e**). Evidentally, ring-closure of benzophenone **5f** occurs with methanolysis and not with dehydration and the monomethylxanthone formed is therefore **6f**. **6f** has been given the trivial name griseoxanthone B, a metabolite of certain strains of *Penicillium griseofulvum*.[10] To the author's knowledge this compound has not been synthesized before.

2-Chloronorlichexanthone (**6c**) has been reported as a metabolite of the lichen *Lecanora straminea*.[5] A reinvestigation of the original sample (2 mg) by FT $^1$H NMR (Fig. 1b), however, showed that it most likely consists of a mixture of two monochlorinated xanthones. Attempts to separate them by TLC were not successful but the existence of two compounds was established using analytical HPLC (Experimental). One of the xanthones should by comparison be 4-chloronorlichexanthone **6e**. In the aromatic region of the spectrum of **6e** (Fig. 1a) a sharp signal for the H–2 proton appears at $\delta = 6.39$ (all shift values mentioned in the text refer to spectra obtained in acetone-$d_6$ unless otherwise stated). Centered at $\delta \sim 6.78$ is a partially resolved multiplet corresponding to the protons in positions 5 and 7. This multiplet results from long-range coupling of the aromatic protons to the methyl group ($ABX_3$-system) and is often observed with orcinol derivatives.[11]. Irradiation at 166 Hz afforded an AB-quartet with parameters $|J_{AB}| = 2.3 \pm 0.1$, $\delta_A = 6.80$ and $\delta_B = 6.73$. Using these values with an NMR simulation program (Jeol FX 60/100 System Program) the calculated spectrum with best agreement to the observed (Fig. 1a) displayed *ortho*/*para* long-range couplings of magnitudes |0.7| and |0.4| Hz†, and therefore the shift values for the H-5 and H-7 protons of **6e** are $\delta = 6.80$ and

†Witiak *et al.*,[11] using first-order analysis, suggested equal coupling (0.6 Hz) of *ortho* and *para* protons to the methyl group in orcinol derivatives. Other examples, however, show that the *ortho* coupling is either approximately equal to, or larger than, the *para* coupling.[12]

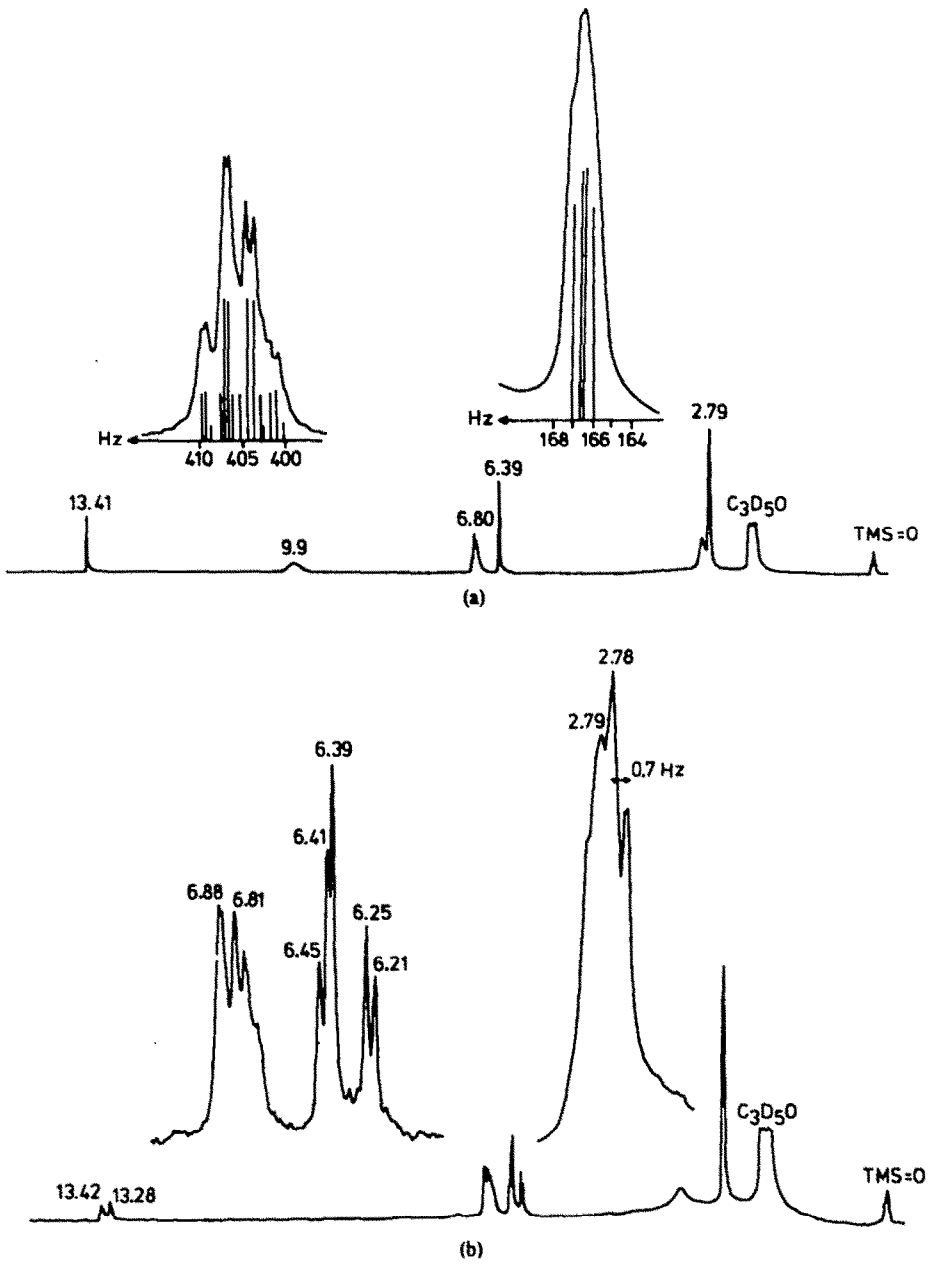
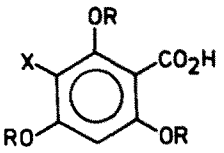



Fig. 1. $^1$H NMR spectra of (a) 4-chloronorlichexanthone (inserted the observed and calculated spectra for the methyl group and the H-5 and H-7 protons); (b) the monochloroxanthone-mixture of *L. straminea*.

6.73. All signals for **6e** are found in the spectrum of the mixture (Fig. 1b) (also in DMSO-$d_6$) which therefore certainly contains this xanthone. By exclusion the other xanthone should be 5-chloronorlichexanthone **6g** and this is further supported by the shift-values obtained on subtracting the spectrum of **6e** from that of the mixture. An AB-quartet centered at $\delta = 6.33$ ($J_{AB} = 2.3 \pm 0.1$ Hz, meta coupling) is in good agreement with the aromatic protons in positions 2 and 4 of norlichexanthone (**6a**, Table 1) and the low-field part of the aromatic region displays a quartet (not completely resolved) at $\delta = 6.88$ ($J = 0.7 \pm 0.1$ Hz) which results from long-range coupling between the proton in pos. 7 and the aromatic methyl group.

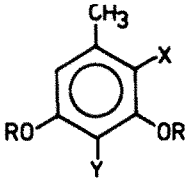
*L. vinetorum* has been reported to contain a monochlorinated xanthone, vinetorin (m.p. 243–5°),[13] for which the structure 2-chloro-6-0-methyl-norlichexanthone has been suggested. $^1$H NMR data, kindly supplied by Dr. Huneck are, however, in better agreement with a 5 or 7-chloro derivative of griseoxanthone C (**6h**, Table 1). An AB-quartet at $\delta = 6.40$ establishes the phloroglucinol-part of the molecule and a singlet at $\delta = 6.87$ lies in the region for a proton in both 5 and 7 positions. Therefore xantone **6i**, the 7-chloro analogue, was prepared from acid **4a** and ether **3c**. Hydrogenolysis of the benzylketone formed gave, after ring-closure, dimethylxanthone **6j**, which, after selective demethylation ($BBr_3$) of the Me group in pos. 1, yielded **6i**. Spectroscopic data and m.p. (283–4°) are not identical with those of vinetorin which therefore most certainly is 5-chloro-3-0-methyl-norlichexanthone.

Attempts to prepare a 5-chloroxanthone were not successful. Condensation of **2c** with **1a** did not take place



1a R= $PhCH_2$ ; X= H

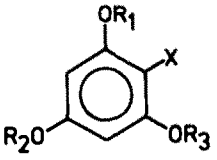
b R= $PhCH_2$ ; X= Cl



2a R= $PhCH_2$ ; X= H ; Y= H

b R= $PhCH_2$ ; X= Cl ; Y= H

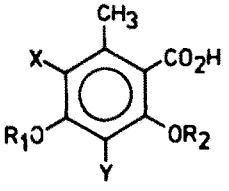
c R= $CH_3$ ; X= H ; Y= Cl



3a $R_1$= $R_2$= $R_3$= $PhCH_2$ ; X= H

b $R_1$= $R_3$= $CH_3$ ; $R_2$= $PhCH_2$ ; X= Cl

c $R_1$= $R_2$= $R_3$= $CH_3$ ; X= H



4a $R_1$= $R_2$= $PhCH_2$ ; X= Cl; Y= H

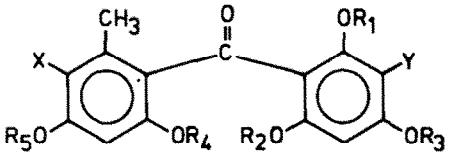
b $R_1$= $R_2$= $CH_3$ ; X= H ; Y= H

c $R_1$= $R_2$= $PhCH_2$ ; X= H ; Y= H

d $R_1$= $R_2$= $CH_3$ ; X= Cl ; Y= H

e $R_1$= $R_2$= $PhCH_2$ ; X= H ; Y= Cl

f $R_1$= $CH_3$ ; $R_2$= $PhCH_2$; X= H ; Y=H



| compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Y |
|---|---|---|---|---|---|---|---|
| 5a | H | H | H | H | H | H | H |
| b | $PhCH_2$ | $PhCH_2$ | $PhCH_2$ | $PhCH_2$ | $PhCH_2$ | H | H |
| c | $PhCH_2$ | $PhCH_2$ | $PhCH_2$ | $PhCH_2$ | $PhCH_2$ | Cl | H |
| d | H | H | H | H | H | Cl | H |
| e | H | H | H | H | H | H | Cl |
| f | $CH_3$ | H | $CH_3$ | H | H | H | Cl |
| g | H | H | H | H | H | Cl | Cl |

and prolonged heating resulted in complex mixtures. In the condensation reactions with TFAA better results were usually obtained with orsellinic acid derivatives than with phloroglucinol carboxylic acid derivatives; the acid of choice would therefore be the benzylether of 3-chloroorsellinic acid (**4e**). Iodination of orsellinic acid followed by chlorination and deiodination has been reported to give the desired product.[14] The $^{13}C$ NMR spectrum of the product was, however, identical with that of 5-chloro-orsellinic acid, obtained by direct chlorination of orsellinic acid. From the shift values in Table 2, it is easily seen that the iodination product of orsellinic acid is 3-iodoorsellinic acid. This finding was unexpected since substitution of orsellinic acid derivatives usually take place in the 5 position.[15]

*Di- and trichloroxanthones*

With an increasing number of Cl atoms in the substrates longer reaction times in the condensations with TFAA had to be used. In acylations of phloroglucinol derivatives however, the reaction has been shown to be reversible and cleavage of the benzophenones on both sides of the CO function results in formation of symmetrical and isomerized benzophenones as by-products.[16] A compromise thus had to be made in choosing the proper reaction conditions. In the syntheses of benzophenones with two Cl atoms the method was still found to be of preparative value.

In the next synthesis **4d** was reacted with the symmetrical **3b**. After hydrogenolysis and methanolysis, xanthone **6k** (total yield 39%) was obtained. Selective

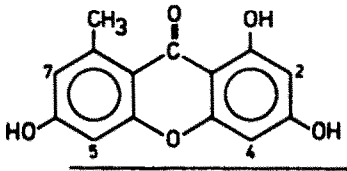



Table 1. $^1$H NMR shift values of norlichexanthone derivatives[a]

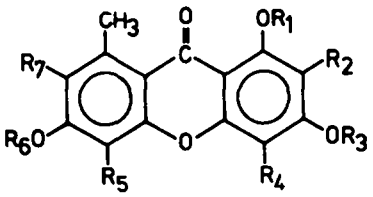
| compound (solvent)[b] | H-1 | H-2 | OH-3 | H-4 | H-5 | OH-6 | H-7 | $CH_3$ |
|---|---|---|---|---|---|---|---|---|
| 6a (A) | 13.44 | 6.19[d] | — | 6.32[d] | 6.71[bs] | — | 6.71[bs] | 2.79[bs] |
| 6h[2] (A) | 13.42 | 6.27[d] | 3.92[e] | 6.43[d] | 6.72[m] | — | 6.70[m] | 2.79[m] |
| | | ($J_{AB}$= 2.3, $J_{H_{ortho}-CH_3}$ = 0.2, $J_{H_{para}-CH_3}$ = 0.2 Hz)[f] | | | | | | |
| 6g (A) | 13.36 | 6.20[d] | 9.61[c] | 6.32[d] | 6.80[m] | 3.94[e] | 6.73[m] | 2.79[m] |
| | | ($J_{AB}$= 2.2, $J_{H_{ortho}-CH_3}$ = 0.8, $J_{H_{para}-CH_3}$ = 0.4 Hz)[f] | | | | | | |
| 6o (A) | 14.19 | Cl | 9.87 | 6.51 | 6.71[bs] | 9.87 | 6.71[bs] | 2.78[bs] |
| 6c (D) | 14.15 | Cl | 11.63[c] | 6.49 | 6.67 | 10.97[c] | 6.67 | 2.73 |
| 6d (C) | 4.05[c,e] | Cl | 4.05[c,e] | 6.67 | 6.69 | 3.86[e] | 6.69 | 2.87 |
| 6e (D) | 13.38 | 6.34 | 11.2[c] | Cl | 6.70 | —[c] | 6.70 | 2.73 |
| 6f (A) | 13.58 | 6.52 | 4.03[e] | Cl | 6.81[m] | — | 6.74[m] | 2.79[m] |
| | | ($J_{AB}$= 2.3, $J_{H_{ortho}-CH_3}$ = 0.8, $J_{H_{para}-CH_3}$ = 0.4 Hz)[f] | | | | | | |
| 6f (D) | 13.50 | 6.53 | 3.94[e] | Cl | 6.65 | — | 6.65 | 2.63 |
| 6b (A) | 13.29 | 6.19[d] | — | 6.30[d] | 6.92[bs] | — | Cl | 2.96[bs] |
| 6b (D) | 13.24 | 6.14[d] | —[c] | 6.28[d] | 6.87 | 10.9[c] | Cl | 2.90 |
| 6j (D) | 3.88[c,e] | 6.45[d] | 3.84[c,e] | 6.60[d] | 6.84 | 11.4 | Cl | 2.82 |
| 6i (A) | 13.26 | 6.29[d] | 3.93[e] | 6.45[d] | 6.97 | — | Cl | 2.99 |
| 6o (A) | 14.04 | Cl | — | 6.55 | 6.97 | — | Cl | 2.99 |
| 6o (D) | 13.99 | Cl | — | 6.48 | 6.87 | — | Cl | 2.89 |
| 6k (C) | 4.00[c,e] | Cl | 4.00[c,e] | 6.69 | 6.75 | 4.02[c,e] | Cl | 3.00 |
| 6n (A) | 13.31 | 6.38 | 5.34 | Cl | 7.01 | 5.34 | Cl | 2.95 |
| 6m (A) | 13.40 | 6.50 | 4.04[e] | Cl | 7.00 | — | Cl | 2.96 |
| 6p (D) | — | 6.58 | 3.99[e] | Cl | Cl | — | Cl | 2.78 |

[a] 1-2 % solutions with TMS as internal standard; [b] A= $C_5D_6O$, D= DMSO-$d_6$, C= = $CDCl_3$; [c] signals may be reversed; [d] doublet (meta-coupling, J= 2.1- 2.8 Hz); [bs] broad unresolved singlet; [m] multiplet ($ABX_3$-spectrum); [e] $OCH_3$-signal; [f] data from spectrum simulation of H-5, H-7, and $CH_3$-protons.

Table 2. $^{13}$C chemical shifts of orsellinic acids[a].

| compound | C1 | C2 | C3 | C4 | C5 | C6 | $CH_3$ | $CO_2H$ |
|---|---|---|---|---|---|---|---|---|
| orsellinic acid | 104.9 | 162.2[b] | 100.7[d] | 164.8[b] | 111.2[d] | 143.2 | 23.7 | 173.5 |
| 5-chloro- | 111.0[c,e] | 156.2[b] | 101.4[d] | 158.1[b] | 112.4[c,e] | 137.0 | 18.5 | 171.0 |
| 5-iodo- | 104.5 | 161.8[b] | 72.2[e] | 164.1[b] | 110.2[d] | 143.1 | 23.8 | 173.5 |

[a] δ-values, in PPM down-field from TMS (δ(TMS)= δ(DMSO-$d_6$ + 39.5 PPM); [b,c] assignments may be reversed; [d] doublet and [e] singlet at off-resonance.



| compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ |
|---|---|---|---|---|---|---|---|
| **6a** | H | H | H | H | H | H | H |
| **b** | H | H | H | H | H | H | Cl |
| **c** | H | Cl | H | H | H | H | H |
| **d** | $CH_3$ | Cl | $CH_3$ | H | H | $CH_3$ | H |
| **e** | H | H | H | Cl | H | H | H |
| **f** | H | H | $CH_3$ | Cl | H | H | H |
| **g** | H | H | H | H | Cl | H | H |
| **h** | H | H | $CH_3$ | H | H | H | H |
| **i** | H | H | $CH_3$ | H | H | H | Cl |
| **j** | $CH_3$ | H | $CH_3$ | H | H | H | Cl |
| **k** | $CH_3$ | Cl | $CH_3$ | H | H | $CH_3$ | Cl |
| **l** | H | Cl | $CH_3$ | H | H | $CH_3$ | Cl |
| **m** | H | H | $CH_3$ | Cl | H | H | Cl |
| **n** | H | H | H | Cl | H | H | Cl |
| **o** | H | Cl | H | H | H | H | Cl |
| **p** | H | H | $CH_3$ | Cl | Cl | H | Cl |
| **q** | H | H | H | H | H | $CH_3$ | H |

demethylation gave a dimethyl ether (2,7-dichlorolichexanthone **6l**), which was found to be identical (m.m.p., IR) with the dichloroxanthone of *L. populicola*[7] for which the structure 2,5-dichlorolichexanthone has been suggested. This structure is therefore wrong and should be **6l**.

Condensation of **4a** with **3b** gave, after hydrogenolysis and methanolysis, a monomethyl xanthone (**6m**) which, upon demethylation, gave 4,7-dichloronorlichexanthone **6a** with the shift-values shown in Table 1. This compound has not been found in *Nature*. When **1b** and **2b** were reacted, a pentabenzyloxy benzophenone was formed which, after removal of the benzylgroups, gave **5g**. This compound underwent cyclization in the same manner as **5e** to form **6o** (2,7-dichloronorlichexanthone, m.p. 298–9°). This substance was not identical with the dichloroxanthone (m.p. 273–4°) isolated from *L. straminea* and for which structure **6o** has been suggested.[4] The $^1$H NMR spectrum of the lichen xanthone showed two singlets, one at $\delta = 6.42$ which places one Cl in the 4 position (sec Table 1) and one at $\delta = 6.93$. This peak was broader suggesting coupling to the Me group but the peak could not be resolved. The shift value for the Me group ($\delta = 2.76$) is, however, a good indication that the Cl is in the 5-position. A chlorine *ortho* to the Me group of orcinol derivatives was found to cause a downfield shift for the Me group (0.17 ppm for 5-chloroorsellinic acid and 7-chloronorlichexanthone **6b**) but not with a Cl in the *para* position (e.g. 4-chloroorcinol). The proper structure for the lichen xanthone should therefore be 4,5-dichloronorlichexanthone.

Monochlorination of the dichloroxanthone of *L. straminea* yields arthothelin,[3,4] a trichloroxanthone (suggested structure 2,4,7-trichloronorlichexanthone) isolated from several *Lecanora* species.[17] The $^1$H NMR spectrum of arthothelin displays a quartet at $\delta = 6.95$ with a coupling constant (0.7 Hz) as expected for long-range coupling of an *ortho* proton to the Me group as described above. The shift-value for the Me group is $\delta = 2.78$ (doublet) and therefore the proper structure of arthothelin should be 2,4,5-trichloronorlichexanthone.

The chemical evidence which has been used for structural assignments of lichen xanthones, has been based on the finding of 2-chlororcinol in the alkali melt of arthothelin.[18] This reaction was re-investigated and 4-chlororcinol was prepared as a reference substance by demethylation of the dimethyl ether **2c** with $AlCl_3$ in benzene. The xanthone was treated at 270° with a mixture of NaOH and KOH and samples were taken after 5 and 25 min. After 5 min, trace amounts of 4-chlororcinol could be detected (TLC, MS) but only orcinol after 25 min. 2-Chlororcinol was not detected in any case.

The shift-values for the trichloroxanthone of *L. capistrata*[6] (given the structure 3-0-methyl-2,5,7-trichloronorlichexanthone) are by inspection (xanthone **6p**, Table 1) in better agreement with a 4,5,7-trichloroxanthone. The suggested revisions for the structures of chlorinated lichen xanthones are summarized in Table 3.

Since no $^1$H NMR data were available in the literature for xanthone **6q**[19] (6-0-methylnorlichexanthone) it was needed as a reference substance. Condensation of **4f** with **3a** gave a benzyl ketone which, after hydro-

Table 3. Suggested revisions of structures of chlorinated lichen xanthones.

| Earlier assignment positions | | Revised structure positions | | Reference |
|---|---|---|---|---|
| Cl | $OCH_3$ | Cl | $OCH_3$ | |
| 2 | | 4 and 5 | | 5 |
| 2 | 6 | 5 | 3 | 13 |
| 2,5 | 3 | 2,7 | 3 | 7 |
| 2,5 | 3,6 | 2,7 | 3,6 | 7 |
| 2,7 | | 4,5 | | 4 |
| 2,7 | 3,6 | 4,5 | 3,6 | 6 |
| 2,4,7 | | 2,4,5 | | 3 |
| 2,4,7 | 3 | 2,4,5 | 3 | 18 |
| 2,5,7 | | 4,5,7 | | 6 |
| 2,5,7 | 3 | 4,5,7 | 3 | 6 |

genolysis, yielded a tetrahydroxybenzo-phenone. After boiling in acetone/water the desired xanthone **6q** was obtained (overall yield 52%).

The instability of the 2,2',6-trihydroxybenzophenones was unexpected. No benzophenone could be purified on TLC (silica gel) without the co-occurrence of the respective xanthone. In solution (DMSO, acetone), ring-closure was found to be very slow, even upon addition of conc. HCl and is therefore not acid-catalyzed. Addition of water or base however caused rapid dehydration. H-bonding of the 2-OH of the benzophenone to the CO must be of importance in the cyclizations[20] since **5f** with one 6-OMe was stable even in boiling water. The mechanism of this reaction is under investigation.

## EXPERIMENTAL

All m.ps are uncorrected. Elemental analyses were performed by the Analytical Department, Institute of Chemistry, University of Uppsala and the Microanalytical Laboratory, Royal College of Agriculture, Uppsala. $^1$H NMR spectra were recorded on a Jeol FX 60, $^{13}$C NMR spectra on a Jeol FX 100. IR spectra were measured on a Perkin–Elmer 177 (KBr-discs), mass spectra on a LKB 9000 and UV spectra on a Varian Cary 118 spectrophotometer. The monochloroxanthone mixture of *L. straminea* was separated on a Waters M 6000 liquid chromatograph equipped with a M 440 UV (254 nm) detector. A reversed-phase column (Bondapak $C_{18}$, 3.9 mm × 30 cm) was used with MeOH/water (9:5) as eluant. $R_V$(4-chlorononorlichexanthone) = 16 ml, $R_V$(5-chlorononorlichexanthone) = 17 ml. TLC was carried out using Mercks precoated silica gel plates. Analyses (C, H, Cl) agreed within ± 0.4% units with the calculated values.

*0,0-Dibenzylorsellinic acid* (**4c**). Orsellinic acid[21,22] was benzylated according to ref.[2] to give *benzyl 0,0-dibenzylorsellinate*, yield 85%, *m.p.* 54–56° (hexane/THF); IR (KBr) $\nu_{CO}$ = 1724 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 2.27 (3H, s), 5.02 (4H, s), 5.31, (2H, s), 6.41 (2H, s), 7.3–7.4 (15H, m); MS(M$^+$) 438 ($C_{29}H_{26}O_4$). This ester was hexane/THF gave *benzyl 5-chloro-0,0-dibenzylorsellinate* (82%), petroleum ether) 100–01° (lit.[23] 100–01°).

*5-Chloro-0,0-dibenzylorsellinic acid* (**4a**). 5-Chloroorsellinic acid[14] was benzylated according to ref.[2]. Recrystallization from hexane/THF gave *benzyl 5-chloro-0,0-dibenzylorsellinate* (82%), m.p. 101–2°; IR(KBr) $\nu_{CO}$ = 1724 cm$^{-1}$; $^1$H NMR($C_3D_6O$) $\delta$ = 2.26 (3H, s), 5.16 (2H, s), 5.24 (2H, s), 5.32 (2H, s), 6.95 (1H, s), 7.35 (15H, m); MS(M$^+$) 472 ($C_{29}H_{24}O_4Cl$). This benzyl ester was hydrolyzed according to Ref.[2]. Recrystallization from benzene gave **4a** (72%), m.p. 163–64°; IR(KBr) $\nu_{CO}$ = 1696 cm$^{-1}$; $^1$H NMR($C_3D_6O$) $\delta$ = 2.36 (3H, s), 5.19 (2H, s), 5.25 (2H, s), 6.96 (1H, s), 7.41 (10H, m); MS(M$^+$) 382 ($C_{22}H_{19}O_4Cl$).

*5-Chloro-0,0-dimethylorsellinic acid* (**4d**). 0,0-Dimethylorsellinic acid[24] (0.98 g) was dissolved in $CH_2Cl_2$ (20 ml) and treated at 25° with a soln of sulphuryl chloride (0.68 g) in the same solvent (5 ml). Evaporation after 1 hr. and recrystallization from MeOH gave 0.96 g (83%), m.p. 210–11°; IR(KBr) $\nu_{CO}$ = 1696 cm$^{-1}$; $^1$H NMR($C_3D_6O$) $\delta$ = 2.33 (3H, s), 3.87 (3H, s), 3.94 (3H, s), 6.74 (1H, s); MS(M$^+$) 230 ($C_{10}H_{11}O_4Cl$).

*3-Chloro-0,0,0-tribenzylphloroglucinol carboxylic acid* (**1b**). Phloroglucinol carboxylic acid[25] (1.2 g) was dissolved in anhydrous ether (50 ml) and sulphuryl chloride (0.65 ml, 15% excess) in ether (15 ml) was added dropwise. After 2 hr the soln was poured onto ice and washed with water (5 × 40 ml). The ether layer was dried ($MgSO_4$) and evaporated to give 1.3 g crude product. Attempts to recrystallize the acid resulted in decarboxylation. The product (1.3 g) was benzylated according to Ref.[2]. Recrystallization from hexane gave *benzyl 3-chloro-0,0,0-tribenzylphloroglucinol carboxylate* (1.7 g, 43% total yield), m.p. 96–96.5°; IR(KBr) $\nu_{CO}$ = 1730 cm$^{-1}$; $^1$H NMR($CDCl_3$) $\delta$ = 4.91 (2H, s), 5.05 (4H, s), 5.21 (2H, s), 6.36 (1H, s), 7.2 – 7.6 (20H, m); MS(M$^+$) 564 ($C_{35}H_{29}O_5Cl$). The ester was hydrolyzed as in Ref.[2]. Recrystallization from benzene/petroleum-ether gave **1b** (83%), m.p. 133.5–34.5°; IR(KBr) $\nu_{CO}$ = 1689 cm$^{-1}$; $^1$H NMR($CDCl_3$) $\delta$ = 5.08 (2H, s), 5.11 (4H, s), 6.43 (1H, s), 7.2–7.7 (15H, m); MS(M$^+$) 474 ($C_{28}H_{23}O_5Cl$).

*0-Benzyleverninic acid* (**4f**). Everninic acid (4-0-methylorsellinic acid)[26] was benzylated as in Ref.[2]. Recrystallization from hexane gave *benzyl 0-benzyl-everninate* (69%), m.p. 68–68.5°; IR(KBr) $\nu_{CO}$ = 1722 cm$^{-1}$; $^1$H NMR($CDCl_3$) $\delta$ = 2.29 (3H, s), 3.75 (3H, s), 5.05 (2H, s), 5.31 (2H, s), 6.33 (2H, s), 7.33 (10H, m); MS(M$^+$) 362 ($C_{23}H_{22}O_4$). The ester was hydrolyzed as in Ref.[2]. Recrystallization from hexane gave **4f** (82%), m.p. 105–6°; IR(KBr) $\nu_{CO}$ = 1682 and 1690 cm$^{-1}$; $^1$H NMR($CDCl_3$) $\delta$ = 2.60 (3H, s), 3.82 (3H, s), 5.20 (2H, s), 6.47 (2H, s), 7.40 (5H, s); MS(M$^+$) 272 ($C_{16}H_{16}O_4$).

*2-Chloro-0,0-dibenzylorcinol* (**2b**). Orcinol was chlorinated with sulphuryl chloride by the usual method. Recrystallization from chloroform gave *2-chlororcinol* (84%), m.p. 139–41° (lit.[27] 138–40°); $^1$H NMR($C_3D_6O$) $\delta$ = 2.25 (3H, t, $J_{H_{meta}\text{-}CH_3}$ = 0.7 Hz, $J_{H_{para}\text{-}CH_3}$ = 0.5 Hz), 6.37 (2H, quartet of quartets, $\delta_{H_{meta}}$ = 6.34; $\delta_{H_{para}}$ = 6.40, $J_{AB}$ = 2.3 Hz), 8.26 (1H, s), 8.29 (1H, s); MS(M$^+$) 158 ($C_7H_7O_2Cl$). This compound was benzylated by the usual method. Recrystallization in methanol gave **2b** (62%), m.p. 75.5–76.5°; $^1$H NMR($CDCl_3$) $\delta$ = 2.35 (3H, s), 4.97 (2H, s), 5.08 (2H, s), 6.49 (2H, s), 7.2–7.5 (10H, m); MS(M$^+$) 338 ($C_{21}H_{19}O_2Cl$).

*4-Chlororcinol.* 4-Chloro-0,0-dimethylorcinol[29] (40 mg) was treated with $AlCl_3$ (120 mg) in refluxing benzene (5 ml) for 45 min. The solvent was evaporated and the residue treated with a

Table 4. Syntheses and hydrogenolysis of benzylbenzophenones.

| reaction (no) | benzylbenzophenone: time (min) | yield (%) | m.p. (°C) (solvent)[a] | MS ($M^+$) | formula | IR(KBr) $\nu_{CO}$ ($cm^{-1}$) | hydrogenolysis product: m.p. (°C) (solvent)[a] | MS ($M^+$) | formula | IR(KBr) $\nu_{CO}$ ($cm^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|---|
| 4a+3a (I) | 2 | 95 | 150.5-51 (A) | 760 | $C_{49}H_{41}O_6Cl$ | 1669 | | | | |
| 1b+2a (II) | 15 | — | —[b] | 760 | $C_{49}H_{41}O_6Cl$ | 1665 | | | | |
| 4b+3b (III) | 10 | 47 | 132-32.5 (A) | 456 | $C_{25}H_{25}O_6Cl$ | 1670 | 140.5-42 (C) | 366 | $C_{18}H_{19}O_6Cl$ | 1603 |
| 4c+3b (IV) | 15 | 61 | 75.5-77 (A) | 608 | $C_{37}H_{33}O_6Cl$ | 1646 | 181-82 (B) | 338 | $C_{16}H_{15}O_6Cl$ | 1613 |
| 4a+3c (V) | 3 | 87 | 120-21 (A) | 532 | $C_{31}H_{29}O_6Cl$ | 1662 | 132-33 (B) | 352 | $C_{17}H_{17}O_6Cl$ | 1605 |
| 4d+3b (VI) | 80 reflux | 50 | 189-90 (B) | 490 | $C_{25}H_{24}O_6Cl_2$ | 1668 | 196-97 (D) | 400 | $C_{18}H_{18}O_6Cl_2$ | 1604 |
| 4a+3b (VII) | 20 | — | 117-19 (A) | 642 | $C_{37}H_{32}O_6Cl_2$ | 1650 | 217-19[c] (E) | 372 | $C_{16}H_{14}O_6Cl_2$ | 1612 |
| 1b+2b (VIII) | 20 | 18[d] | —[b] | 794 | $C_{49}H_{40}O_6Cl_2$ | 1661 | | | | |
| 4f+3a (IX) | 15 | 81 | 141-42.5 (A) | 650 | $C_{45}H_{38}O_6$ | 1662 | | | | |

[a] Solvents: A (benzene/petroleum ether), B (benzene), C (methanol), D (benzene/hexane), E (acetone/water). [b] An analytical sample did not crystallise. [c] Over-all yield 29 %. [d] After chromatography on silica gel (petroleum ether/ether 1:1).

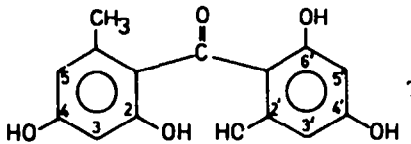



Table 5. $^1$H NMR shift values for hydroxybenzophenones in reactions I–IX[a].

| reaction | 2 | 3 | 4 | 5 | $CH_3$ | 2′ | 3′ | 4′ | 5′ | 6′ |
|---|---|---|---|---|---|---|---|---|---|---|
| I | 9.29 | 6.45 | 8.39 | Cl | 2.18 | 11.27 | 5.90 | 8.39 | 5.90 | 11.27 |
| II | 9.65 | 6.26 | 8.47 | 6.26 | 2.11 | 9.97 | 6.10 | 8.70 | Cl | 12.37 |
| III | 3.69[b] | 6.46 | 3.84[b] | 6.46 | 2.18 | 13.53 | 6.50 | 4.00[b] | Cl | 3.27[b] |
| IV | 10.3 | 6.27 | — | 6.27 | 2.09 | 10.3 | 6.50 | 3.95[b] | Cl | 3.47 |
| V | 12.99 | 6.46 | — | Cl | 2.08 | 3.75[b] | 6.33 | 3.88[b] | 6.33 | 3.75[b] |
| VI | 3.77[b] | 6.78 | 3.97[b] | Cl | 2.21 | 13.46 | 6.52 | 4.01[b] | Cl | 3.29[b] |
| VII | 8.8 | 6.51 | — | Cl | 2.22 | 13.30 | 6.51 | 4.00[b] | Cl | 3.39[b] |
| VIII | — | 6.46 | 10.30 | Cl | 2.18 | 9.67 | 6.10 | 8.49 | Cl | 12.96 |
| IX | 9.30 | 6.31 | 3.73[b] | 6.31 | 2.14 | 11.04 | 5.90 | 8.56 | 5.90 | 11.04 |

[a] 1–2 % solutions in $C_5D_6O$ with TMS as internal standard. All signals are singlets. OH- and $OCH_3$-signals may be reversed. [b] $OCH_3$-signal.

Table 6. Derivatives of norlichexanthone.

| xanthone | m.p. (°C) | MS ($M^+$) | formula | IR(KBr)[a] $\nu_{max}$ ($cm^{-1}$) | UV $\lambda_{max}^{EtOH}$ ($\varepsilon \cdot 10^{-3}$) |
|---|---|---|---|---|---|
| 6b | 292-93.5 | 292 | $C_{14}H_9O_5Cl$ | 1696 m, 1650 s, 1601 s | 243 (37.9), 254 (24.6), 268 (13.5), 313 (15.0), 352 (15.4) |
| 6j | 303-05 | 320 | $C_{16}H_{13}O_5Cl$ | 1622 s, 1602 s | |
| 6i | 283-84 | 306 | $C_{16}H_{11}O_5Cl$ | 1643 s, 1595 s | 241 (40.5), 254 (25.8), 266 (15.3), 311 (13.2), 357 (19.3) |
| 6c | 313-14.5 | 292 | $C_{14}H_9O_5Cl$ | 1650 sh, 1610 s | 244 (38.8), 270 (14.1), 316 (17.6), 347 (13.9) |
| 6d | 204-4.5 | 334 | $C_{17}H_{15}O_5Cl$ | 1650 s, 1621 s, 1598 s | |
| 6e | 288-89 | 292 | $C_{14}H_9O_5Cl$ | 1649 m, 1622 s, 1600 s | 242 (34.7), 253 (22.1), 270 (14.9), 312 (15.9), 346 (12.7) |
| 6f | 249-50 | 306 | $C_{15}H_{11}O_5Cl$ | 1649 s, 1619 s, 1606sh | 240 (32.9), 253 (22.0), 271 (10.4), 310 (17.0), 350 (10.4) |
| 6o | 298-99 | 326 | $C_{14}H_8O_5Cl_2$ | 1641 s, 1593 s | 245 (38.9), 260 (24.2), 270 (14.5), 319 (12.7), 358 (19.0) |
| 6k | 245.5-46.5 | 368 | $C_{17}H_{14}O_5Cl_2$ | 1657 s, 1618 s, 1590 s | |
| 6n | 290-93 | 326 | $C_{14}H_8O_5Cl_2$ | 1656 s, 1596 s | 243 (37.6), 255 (23.6), 270 (17.8), 313 (12.3), 360 (17.1) |
| 6m | 246-47 | 340 | $C_{15}H_{10}O_5Cl_2$ | 1640 s, 1590 s | 241 (39.6), 256 (22.3), 270 (15.6), 311 (9.8), 365 (21.8) |

[a] Abbreviations: s, strong; m, medium; sh, shoulder.

mixture of conc. HCl (5 ml) and ice (5 g); gave after work-up and recrystallization 4-chlororcinol (32 mg, 90%), m.p. 138–138.5°. TLC (silica gel, benzene/ether (7:3) $R_f$(2-chlororcinol) = 0.38, $R_f$(4-chlororcinol) = 0.58; $^1$H NMR ($C_3D_6O$) $\delta$ = 2.16 (3H, t, J = 0.6 Hz), 6.36 (2H, q, J = 0.6 Hz), 8.37 (2H, bs); MS($M^+$) 158 ($C_7H_7O_2Cl$).

0,0,0,-*Tribenzylphloroglucinol* (**3a**). **3a** was obtained by melting **1a**[2] at 145° during 45 min. Recrystallization from benzene/petroleum ether afforded **3a**, m.p. 94–5° (lit.[19] 86–87°).

*The ether* **3b** was prepared according to Ref.[20].

*General procedure for synthesis and hydrogenolysis of benzylbenzophenones* (*Tables* 4 *and* 5). Equimolar amounts (3 mmol) of substrates were dissolved in $CH_2Cl_2$ (5 ml) and a 2-fold excess freshly distilled TFAA was added under $N_2$. After reaction (2–80 min) the mixture was poured into MeOH (100 ml) and the soln was evaporated at 25° *in vacuo* to approx 10 ml. Water (50 ml) was added and the mixture extracted with ether; the ether layer washed with 5% $NaHCO_3$ and water, then dried ($MgSO_4$) and evaporated. In reactions VI and VII precipitation (of symmetrical benzophenones) occured when ether was added to the MeOH soln. The ppts were filtered off before washing the ether layer. Hydrogenolysis of the benzylbenzophenones (0.1 mmol) was done at 25° in EtOAc (5 ml, with addition of THF when solubility was low) over 10% Pd/C (5 mg/benzyl group) until $H_2$ uptake ceased. The yields were > 95% (10–30% was lost after recrystallization). All hydroxybenzophenones were light-yellow compounds.

*Preparation of xanthones* (*Table* 6)

(A) *Ring-closure of hydroxybenzophenones. Xanthones* **6b** and **6o** were obtained by recrystallizing the hydrogenolysis products from acetone/water. *xanthone* **6q** (m.p. 263–65°, lit.[19] 260–62°) and *xanthone* **6c** (chromatographed on silica gel, methylene chloride/acetone 4:1; *total* yield 32%) from MeOH/water.

*Xanthones* **6f**, **6j** and **6m** were obtained by refluxing the hydrogenolysis products in ethanolic KOH (1% soln) for 1 hr. After work-up the products were recrystallized from acetone (**6m**) and MeOH (**6f** and **6j**). The yields were > 95%.

*Xanthones* **6d** and **6k**. 100 mg hydroxybenzophenone was refluxed in a soln of MeOH (15 ml) and 3% NaOH aq (5 ml) overnight. The ppt was filtered off and the soln refluxed for another 12 hr and filtered again. The combined ppt was washed with water, dried and recrystallized from benzene, yields 70% (**6d**) and 78% (**6k**).

(B) *Demethylations.* Xanthones **6f** and **6m** were demethylated with $AlCl_3$ (2 moles) in refluxing benzene. Recrystallization (after work-up) from acetone/water gave *xanthones* **6e** (82%) and **6n** (74%). Xanthones **6j** and **6k** were demethylated with $BBr_3$ (1.5 moles) in methylene chloride under nitrogen for 10 min. After work-up *xanthone* **6i** was recrystallized from acetone and **6l** was purified by sublimation (m.p. 292–93°, lit.[7] 290–93°).

(C) *Methylations.* Xanthone **6c** was methylated with dimethyl sulphate in DMF by usual methods. Recrystallization from benzene/petroleum ether afforded *xanthone* **6d** (69%). Xanthone **6o** was methylated with diazomethane as in Ref.[3] to give *xanthone* **6l**.

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