Acta Chemica Scandinavica B 33 (1979) 475—482

Syntheses and ^{13}C NMR Spectra of Some 5-Chloro-substituted Lichen Xanthones *

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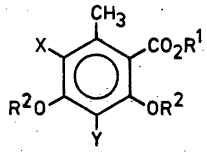
The total synthesis of seven lichen xanthones and several other derivatives of 1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (norlichexanthone *5a*) confirmed previously suggested revisions for the structures of this group of compounds. However, the original structures for 2,5,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl (*5l*) and 2,5,7-trichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (*5m*) were found to be correct. A key substrate in the xanthone syntheses was methyl 3-chloro-2,4-dihydroxy-6-methylbenzoate (*1i*). In the preparation of *1i* two unusual iodo rearrangements were observed. The ^{13}C NMR spectra of eight chloroxanthones are presented in Table 3.

In a previous report in this series [3] the preparation of several derivatives of norlichexanthone (*5a*) (1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one), the parent compound of all lichen xanthones, was described. Most lichen xanthones are chloro-substituted and occur frequently as methyl ethers [4] and therefore the number of possible structures becomes very large. ^1H NMR analysis of the derivatives of *5a*, however, facilitated the structural elucidation and it was suggested that of previously isolated seventeen chloroxanthones ten of the tentatively assigned structures had to be revised. In two cases this was confirmed by total synthesis of the natural products.[3,5] Additional support for the structures was later obtained from two independent studies on the ^{13}C NMR spectra of lichen xanthones.[2,6]

The method used in the synthesis of the xanthones was based on the acylation of ethers of 1,3,5-trihydroxybenzene (*2a*) or orcinol (*3a*) (3,5-dihydroxytoluene) with ethers of orsellinic acid (*1a*) (2,4-dihydroxy-6-methylbenzoic acid) or 2,4,6-trihydroxybenzoic acid (*2b*) in the presence of trifluoroacetic anhydride (TFAA).[3] The benzophenones *4* thus formed could easily be cyclized to the desired xanthones after selective removal of the protective groups. However, it was not possible to prepare 5-chloro derivatives of *5a* due to failure of acylation of the methyl ether of 4-chloroorcinol (*3b*) and to difficulties in obtaining 3-chloroorsellinic acid (*1b*) or a derivative thereof. This report describes one useful route for the preparation of the methyl ester *1i* and of seven naturally occurring xanthones.



1a $R^1=R^2=X=Y=H$
1b $R^1=R^2=X=H$; $Y=Cl$
1c $R^1=R^2=CH_3$; $X=Y=H$
1d $R^1=R^2=CH_3$; $X=I$; $Y=H$
1e $R^1=CH_3$; $R^2=Y=H$; $X=I$
1f $R^1=R^2=Y=H$; $X=I$
1g $R^1=R^2=X=H$; $Y=I$
1h $R^1=CH_3$; $R^2=H$; $X=I$; $Y=Cl$
1i $R^1=CH_3$; $R^2=X=H$; $Y=Cl$
1j $R^1=X=H$; $R^2=Bz$; $Y=Cl$
1k $R^1=Y=H$; $R^2=Bz$; $X=Cl$
1l $R^1=H$; $R^2=Bz$; $X=Y=Cl$

* See Refs. 1 and 2.

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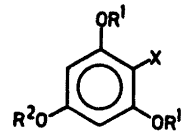
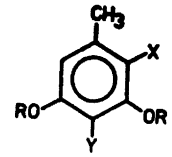


2a $R^1=R^2=X=H$
2b $R^1=R^2=H$; $X=CO_2H$
2c $R^1=R^2=Bz$; $X=H$
2d $R^1=R^2=Bz$; $X=CO_2H$
2e $R^1=R^2=CH_3$; $X=H$
2f $R^1=CH_3$; $R^2=Bz$; $X=Cl$



3a $R=X=Y=H$
3b $R=CH_3$; $X=H$; $Y=Cl$
3c $R=Y=H$; $X=I$

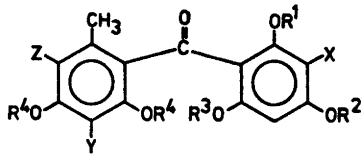
RESULTS AND DISCUSSION

One method of synthesis of *1i* from methyl acetoacetate and methyl crotonate has been published in a patent from the perfume industry.[7] However, the great availability of orsellinic acid (*1a*) [8] from earlier synthetic work [3] suggested a route from that compound. Direct chlorination of *1a* yields the 5-chloro derivative as the main product.[9] Therefore a 5-iodo derivative was needed which could selectively be deiodinated after chlorination. This method has been used previously,[9] but direct iodination of *1a* or its methyl ester resulted in formation of the 3-iodo derivatives.[3,10] The structures of these products were deduced by ^{13}C NMR spectroscopy [3] and from the syntheses below. Iodination of the methyl ether ester *1c*, however, gave the 5-iodo isomer (not identical with the methyl ether ester obtained by methylation of 3-iodoorsellinic acid (*1g*)). Chlorination of *1d* by several methods resulted in demethylation and formation of products with unknown structures. Probably addition takes place for steric reasons and because of the high reactivity of the orcinol nucleus.[11] Therefore *1d* was demethylated with 2 mol of boron tribromide (BBr_3) to give the ester *1e* in good yield (82 %, the rest soluble in a pH = 7 buffer consisted of 5-iodoorsellinic acid (*1f*)). By using larger amounts of reagent less ester was formed and also some deiodinated products. With 6 mol of BBr_3 the yield of ester decreased to 30 % and, unexpectedly, the acid part consisted mainly of 3-iodoorsellinic acid (*1g*) (33 % total yield). The rearrangement of *1f* under these conditions was attributed to the high concentration of hydrogen bromide generated during the work-up and was confirmed in a separate control experiment. This type of rearrangement has been observed in bromination of similar compounds.[12] Thus, for example, bromination of methyl 2-hydroxy-4-methoxy-6-methylbenzoate gives the 5-bromo isomer. However, if this is allowed to remain in contact with the hydrogen bromide generated during the reaction, rearrangement to the 3-bromo isomer occurs. It is remarkable, however, that only the acid (and not the ester) rearranges in this case. Further, if the acid *1g* is decarboxylated, a new rearrangement takes place and 2-iodoorcinol *3c* (^1H NMR) is formed. Chlorination of *1e* with chlorine in acetic acid gave the ester *1h* which quantitatively could be deiodinated with Raney nickel alloy to give the desired *1i*.

Monochloroxanthones

^1H NMR analysis of the monochloroxanthones of the lichen *Lecanora straminea* (Wahlbg.) Ach. suggested a mixture of 4- and 5-chloronorlichexanthone.[3] They could not be separated by TLC

Table 1.



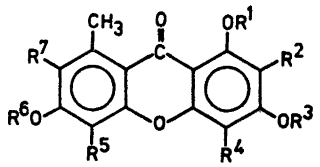
Compound	R^1	R^2	R^3	R^4	X	Y	Z
4a	Bz	Bz	Bz	Bz	H	Cl	H
4b	H	H	H	H	H	Cl	H
4c	CH_3	CH_3	CH_3	Bz	H	Cl	H
4d	CH_3	CH_3	CH_3	H	H	Cl	H
4e	CH_3	CH_3	Bz	Bz	Cl	Cl	H
4f	CH_3	CH_3	H	H	Cl	Cl	H
4g	H	CH_3	H	H	Cl	Cl	H
4h	CH_3	CH_3	Bz	Bz	Cl	Cl	Cl
4i	CH_3	CH_3	H	H	Cl	Cl	Cl
4j	H	CH_3	H	H	Cl	Cl	Cl

but structural assignment was inferred from spectra of the mixture and of reference compounds and from the synthesis of the 4-chloro analogue. To obtain the 5-chloroxanthone *5b*, acid *1j* was reacted with ether *2c* to give *4a* (Table 1). Hydrogenolysis of *4a* gave the benzophenone *4b* which underwent ring-closure in boiling water to form the expected product. The ^{1}H NMR spectrum of the compound strongly supports its occurrence in the lichen.

The monochloroxanthone of *L. vinetorum* Poelt et Hun.,[18] vinetorin, has been given the revised structure 5-chloro-3-*O*-methylnorlichexanthone (*5d*; see Table 2).[3,6] To verify this a total synthesis of the compound was performed from acid *1j* and ether *2e*. The product (*4c*) was hydrogenolyzed to give benzophenone *4d* which, after ring-closure (loss of methanol) in potassium hydroxide – ethanol, furnished the xanthone *5c*. Selective demethylation (BBr_3) gave the natural product (^{1}H NMR, m.m.p.).

The acylation reaction, with formation of the protected benzophenones, is frequently accompanied by an important side-reaction, *viz.* formation of symmetrical benzophenones.[14] The first step in the acylation with TFAA is the formation of an unsymmetrical anhydride (acyl trifluoroacetate)[15,16] which acts as the acylating agent. The benzophenones thus formed are sometimes cleaved on either side of the carbonyl function (probably as a Wheland intermediate) with formation of new unsymmetrical anhydrides, ready to attack unconsumed starting material so that symmetrical benzophenones are formed. In the synthesis of *4a* above it was found that, when the reaction was performed at room temperature, a considerable amount of a by-product was formed within a few minutes. Spectroscopic analysis of the compound, however, suggested formation of the symmetrical anhydride of acid *1j*. Therefore the reaction was performed at lower temperature (0 °C) in combination with excess of ether *2c*. In this case, *4a* could be isolated in high yield. When *1j* was reacted with ether *2e* at 25 °C, by contrast, benzophenone *4c* was the main product. In the reaction of the 5-chloro analogue (*1k*) with *2c* as reported earlier,[3] benzophenone formation was quantitative at 25 °C. In both substrates (*1j* and *1k*) the chloro substituent is *meta* to the carbonyl function and one would expect the inductive effect on reactivity of the acyl trifluoroacetates to be approximately equal. A steric interaction of the *ortho* oxygen substituent (flanked by the chloro atom) in the acylation step is more likely responsible for this difference in reactivity[17] and offers an explanation for the reluctance of the ether *3b* to react with *2d*.

Table 2.



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7
5a	H	H	H	H	H	H	H
5b	H	H	H	H	Cl	H	H
5c	CH_3	H	CH_3	H	Cl	H	H
5d	H	H	CH_3	H	Cl	H	H
5e	H	H	CH_3	Cl	Cl	H	H
5f	H	H	H	Cl	Cl	H	H
5g	H	H	CH_3	Cl	Cl	CH_3	H
5h	H	Cl	CH_3	H	Cl	H	H
5i	H	Cl	CH_3	H	Cl	CH_3	H
5j	H	Cl	H	H	Cl	H	H
5k	H	H	CH_3	Cl	Cl	H	Cl
5l	H	Cl	CH_3	H	Cl	H	Cl
5m	H	Cl	H	H	Cl	H	Cl
5n	H	Cl	H	Cl	H	CH_3	H
5o	H	H	H	Cl	Cl	H	Cl

Dichloroxanthones

Of the previously isolated eight dichloroxanthones of lichen origin only two have been synthesized by unambiguous methods.[3,5] To prepare the dichloroxanthone of *L. straminea*[18] (revised structure *5f*)[3] the acid *1j* and ether *2f* were condensed. After hydrogenolysis of the product (*4e*) formed, benzophenone *4f* was obtained which, after ring-closure, gave the xanthone *5e*. Demethylation of *5e* with $AlCl_3$ in chlorobenzene afforded the natural product (^{1}H NMR, IR). Methylation of *5e* gave another natural product *5g*, identical (TLC, micro-IR) with the dichloroxanthone of *Buellia glaziouana* (Krempelh.) Müll. Arg.[19]

Recently the isolation and structural elucidation of the lichen metabolite 2,5-dichloro-3,6-di-*O*-methylnorlichexanthone (*5i*) from *Per-*

tusaria aleianta Nyl. was reported.[6] A convenient synthesis of that compound was devised from the benzophenone *4f*. It has been demonstrated that 2,2',6-trihydroxybenzophenones (*e.g. 4b*) very easily dehydrate in boiling water to give xanthones.[3] With a chloro substituent in the "phloroglucinol-part" of the benzophenone, only 2-chloronorlichexanthones (and not 4-chloro) were formed. Therefore *4f* was first selectively demethylated with BBr_3 to give the *p*-methoxybenzophenone *4g*. Boiling this in water, however, did not result in ring-closure, but by applying high pressure (sealed tube, 120 °C) the desired 2,5-dichloroxanthone *5h* (61 %) was obtained. In this reaction selectivity was less pronounced and the isomer *5e* was also formed (18 %). With KOH – ethanol, ring-closure was found to be very slow and only *5e* was isolated but in low yield. Methylation of *5h* gave the *Pertusaria* xanthone confirmed by comparison with the original sample. Demethylation of *5h* gave *5j* not found in nature but used here as a reference compound for ^{13}C NMR spectroscopy (Table 3).

Trichloroxanthones

The trichloroxanthone of *L. capistrata* (Darb.) Zahlbr. was tentatively assigned the structure 2,5,7-trichloro-3-*O*-methylnorlichexanthone (*5l*) [19] and another, found in *L. flavido pallescens* Nyl. and *L. sulphurata* (Ach.) Nyl., the structure 2,5,7-trichloronorlichexanthone (*5m*).[19] The latter was never isolated but its structure was inferred from MS and TLC-analysis of the methylated extract. The ^1H NMR value given for the aromatic proton of the xanthone from *L. capistrata* ($\delta = 6.58$, DMSO-d_6) however, was later found to be in better agreement with a 4,5,7-trichloro structure *5k*.[3] To test this a synthesis of *5k* was performed from *1l* and *2f*. In the acylation step forcing conditions (reflux, prolonged heating) had to be used because of the low reactivity of *2f*. To prevent anhydride formation of *1l*, trifluoroacetic acid (TFA) was added to the reaction mixture and a considerable increase in the yield of *4h* was obtained (from 10 % without to 53 % with TFA added). However, the symmetrical benzophenone of *2f* was also formed (^1H NMR, MS) and therefore a compromise had to be made in choosing the proper reaction time.

The effect of TFA in this reaction is most certainly to suppress the formation of the symmetrical anhydride according to the equilibrium [20]

$$ArCO\text{-}O\text{-}COCF_3 + ArCO_2H \rightleftharpoons ArCO\text{-}O\text{-}COAr + CF_3CO_2H$$

so that more acyl trifluoroacetate is available to attack the ether, although TFA is also known to have a catalytic effect on the acylation reaction itself.[20]

Hydrogenolysis of *4h* and ring-closure of the product *4i* gave the desired xanthone *5k* with a shift value for the 2-H of 6.65. Unfortunately, no original sample was available for comparison, but a reinvestigation of the lichen (TLC) displayed that the synthetical product was not identical with the lichen xanthone. Evidently, ^1H NMR spectroscopy is not a good method to differentiate between the 2 and 4 positions in this particular case.[3] To prepare the isomer *5l*, benzophenone *4i* was demethylated and the product (*4j*) dehydrated. In this case the synthetic product was identical (TLC, MS, ^1H NMR: $\delta = 6.61$) with the lichen xanthone. The reinvestigation of the lichen (TLC, MS) also displayed that it most likely contains thiophaninic acid (*5n*) known to occur in several lichens.[4] Demethylation of xanthone *5l* gave *5m*. Co-chromatography of *5m* with an extract of *L. sulphurata* confirmed its occurrence in the lichen.

Demethylation of *5k* above gave 4,5,7-trichloronorlichexanthone (*5o*), used here as reference substance for ^{13}C NMR spectroscopy (Table 3). The assignments were based on methods described earlier [2] and in all cases excellent additivity is observed.

EXPERIMENTAL

Melting points were measured with a Leitz melting point microscope and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, Royal College of Agriculture and by the Analytical Department, Institute of Chemistry, University of Uppsala, Uppsala. ^1H and ^{13}C NMR spectra were recorded on a Jeol FX 60 and 100. IR spectra were recorded on a Perkin-Elmer 177 (KBr-discs) and mass spectra on an LKB 9000 instrument.

Methyl 2,4-dimethoxy-5-iodo-6-methylbenzoate (1d). 2,4-Dihydroxy-6-methylbenzoic acid *1a* [8]

Table 3. ^{13}C NMR shift values for some derivatives of norlichexanthone.[a]

Compound	C–1	C–2	C–3	C–4	C–4a	C–10a	C–5	C–6	C–7	C–8	C–8a	C–9a	Me	CO	OMe	Temp./°C
5a (5-Cl)	162.7	98.1	164.6	93.2	155.8	153.4	104.5	158.0	115.1	139.9	111.3	101.7	22.9	180.6		25
5d (5-Cl, 3OMe)	162.3	97.0	165.3	91.6	155.6	153.4	104.5	158.2	115.2	140.0	111.2	102.4	22.9	180.7	55.9	25
5e (4,5-diCl, 3OMe)	160.8	95.0	160.4	97.7	150.0	153.1	104.9	158.3	115.4	139.8	110.8	102.4	22.1	180.6	56.5	70
5h (2,5-diCl, 3OMe)	160.4	102.4	158.8	90.5	153.8	153.4	104.6	157.2	115.6	140.2	110.9	102.4	22.9	180.4	56.9	25
5j (2,5-diCl)	158.1	101.7	160.2	93.4	153.6	153.4	104.6	158.5	115.3	140.1	111.0	101.9	22.8	180.5		25
5k (4,5,7-triCl, 3OMe)	160.5	95.2	160.8	97.6	149.7[b]	151.2[b]	106.8	154.4	120.2	136.7	110.9	102.4	17.6	179.8	56.6	65
5o (4,5,7-triCl)	160.4	98.4	160.6	97.2	151.4	150.7	106.9	154.5	120.3	137.0	111.2	102.1	17.9	180.0		25
5m (2,5,7-triCl)	160.3[b]	101.4	159.9[b]	93.3	153.1	152.5	106.9	158.2	123.2	135.9	107.0	101.7	18.5	179.3		25[c]

[a] Spectra recorded in 5 mm tubes using DMSO-d_6 as solvent. Shift values, in ppm from TMS, were converted using [δ (TMS) = δ (DMSO-d_6 + 39.5 ppm)]. [b] Assignments may be reversed. [c] Spectrum measured in micro probe.

was methylated by improved methods[21] to give *1c* (97 %), m.p. 43–45 °C (benzene), lit.[22] 44–45 °C. *1c* (6.7 g) was dissolved in dry ether (75 ml) and iodine (8.1 g) was added. Yellow mercuric oxide (7.3 g) was added in small portions with stirring during 15 min. The mixture was refluxed for 20 min and the ether was then evaporated. Chloroform (200 ml) was added and the slurry treated with 100 ml portions of aqueous potassium iodide (10 %) until all mercury salts had dissolved. After washing with water, drying, and evaporation of the solvent, the product was recrystallized from cyclohexane. Yield 9.8 g white needles (92 %), m.p. 134.5–135 °C. Anal. $C_{11}H_{13}IO_4$: C, H, I. MS(IP 70 eV): 336 (M). ^1H NMR [$(CD_3)_2CO$]: δ 2.35 (3H, s), 3.82 (3H, s), 3.87 (3H, s), 3.94 (3H, s), 6.65 (1H, s).

*Methyl 2,4-dihydroxy-5-iodo-6-methylbenzoate (*1e*).* Ester *1d* (9.0 g) was dissolved in dichloromethane (60 ml) and the solution cooled to −80 °C. A solution of BBr_3 (5.2 ml) in the same solvent was added and the mixture allowed to slowly reach room temperature. Stirring was continued under nitrogen overnight. After evaporation, ether (400 ml) was added and the solution treated with a phosphate buffer (pH = 7.0, 3 × 75 ml). The water layer was acidified (2 M HCl) and extracted with ether. Evaporation gave practically pure 2,4-dihydroxy-5-iodo-6-methylbenzoic acid (*1f*) (1.3 g, 17 %) which was recrystallized from benzene as white needles, m.p. 178–179 °C. Anal. $C_8H_7IO_4$: C, H, I, MS(IP 70 eV): 308 (M). ^1H NMR[$(CD_3)_2CO$]: δ 2.82 (3H, s), 6.48 (1H, s). After washing with water, the ether layer above was evaporated to give *1e* (6.8 g, 82 %). An analytical sample was obtained from benzene as white needles, m.p. 128–130 °C (varies slightly with the rate of heating). Anal. $C_9H_9IO_4$: C, H, I. ^1H NMR [$(CD_3)_2CO$]: δ 2.69 (3H, s), 3.93 (3H, s), 6.47 (1H, s). When 6 mol BBr_3 were used, the reaction was performed at 0 °C. 2,4-Dihydroxy-3-iodo-6-methylbenzoic acid (*1g*) was isolated as described for *1f*. M.p. 182–183 °C (benzene), lit.[9] 172.5–174 °C. ^1H NMR[$(CD_3)_2CO$]: δ 2.53 (3H, bs), 6.47 (1H, bs).

Rearrangement of 1g *to 3,5-dihydroxy-2-iodotoluene (*3c*).* The acid *1g* was heated in a glass tube at 180 °C until evolution of gas ceased. After work-up, the product was recrystallized from chloroform, m.p. 97–98.5 °C (sinters at 87 °C), lit.[23] 87 °C. MS(IP 70 eV): 250 (M). ^1H NMR[$(CD_3)_2CO$]: δ 2.32 (3H, t, J 0.6 Hz), 6.38 (2H, qq, J 2.7 Hz, J 0.6 Hz), 8.33 (1H, s), 8.74 (1H, s).

*Methyl 3-chloro-2,4-dihydroxy-5-iodo-6-methylbenzoate (*1h*).* Ester *1e* (1.7 g) was dissolved in acetic acid (10 ml) and a solution of chlorine in the same solvent (400 mg in 8 ml) was added dropwise under subdued light. After 15 min water (10 ml) was added and the precipitate collected. Recrystallization from acetic acid–water yielded *1h* as white needles, (1.6 g, 83 %), m.p. 107–110 °C. Anal. $C_9H_8ClIO_4$: C, H, I.

MS(IP 70 eV): 342 (M). ^{1}H NMR[$(CD_3)_2CO$]: δ 2.70 (3H, s), 3.98 (3H, s).

*Methyl 3-chloro-2,4-dihydroxy-6-methylbenzoate (*1i*)*. Ester *1h* (0.75 g) was dissolved in 2 M NaOH (15 ml) and treated with Raney nickel alloy (1.2 g) for 2 min. The solution was immediately filtered into cold 2 M HCl (6 ml) and the precipitate extracted with ether. Evaporation gave *1i* (0.47 g, *ca.* 100 %) which was recrystallized from benzene, m.p. 133–134°C, lit.[7] 139–140 °C. Anal. $C_9H_9ClO_4$: C, H, Cl. ^{1}H NMR[$(CD_3)_2CO$]: δ 2.47 (3H, broad s), 3.96 (3H, s), 6.48 (1H, broad s), 12.2 (1H, s). MS(IP 70 eV): 216 (M). Shift values for methyl 5-chloro-2,4-dihydroxy-6-methylbenzoate: δ 2.58 (3H, s), 3.95 (3H, s), 6.47 (1H, s), 11.0 (1H, s).

*2,4-Dibenzyloxy-3-chloro-6-methylbenzoic acid (*1j*)*. Ester *1i*, dissolved in DMF (10 ml), was treated with K_2CO_3 (6 g) and benzyl bromide (1.8 ml). The mixture was heated at 70 °C for 1 hr or until the violet colour disappeared. After work-up, the product was triturated with light petroleum to give *methyl 2,4-dibenzyloxy-3-chloro-6-methylbenzoate* (4.8 g, 87 %), m.p. 103–103.5 °C (thick white needles, hexane). Anal. $C_{23}H_{21}ClO_4$: C, H, Cl. MS (IP 70 eV): 396 (M). ^{1}H NMR[$(CD_3)_2CO$]: δ 2.29 (3H, bs), 3.80 (3H, s), 5.06 (2H, s), 5.23 (2H, s), 6.95 (1H, bs), 7.1–7.7 (10H, m). This ester was hydrolyzed as described before,[24] to give *1j* as an amorphous powder (91 %), m.p. 146.5–147 °C (benzene–light petroleum). Anal. $C_{22}H_{19}ClO_4$: C, H, Cl. MS (IP 70 eV): 382 (M). ^{1}H NMR[$(CD_3)_2CO$]: δ 2.37 (3 H, bs), 5.11 (2H, s), 5.27 (2H, s), 6.99 (1H, bs), 7.1–7.7 (10H, m).

*2,4-Dibenzyloxy-3,5-dichloro-6-methylbenzoic acid (*1l*)*. Ester *1i* (3.7 g) was dissolved in acetic acid (20 ml) and at 40 °C a solution of chlorine in the same solvent (1.3 g, 18 ml) was added with vigorous stirring. Then the mixture was heated to 60 °C and after 15 min evaporated *in vacuo* to approx. 20 ml. After cooling, the precipitate was collected and dried to give methyl 3,5-dichloro-2,4-dihydroxy-6-methylbenzoate (3.6 g). Another crop (0.3 g, total yield 91 %) was obtained by heating the mother liquor and adding an equal amount of hot water, m.p. 118–119 °C, lit.[25] 115 °C. This ester was benzylated as described for *1j*. Yield 89 %, m.p. 77–78 °C (light petroleum), lit.[24] 77–78 °C. Hydrolysis of the ester according to Ref.[24] gave *1l*, m.p. 186–188 °C, lit.[23] 185–187 °C.

Synthesis of xanthones

The general procedure for the synthesis and hydrogenolysis of benzylbenzophenones has been described before.[3]

*5-Chloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (*5b*)*. Acid *1j* (77 mg) and ether *2c*[3] (158 mg) were dissolved in dichloromethane (2 ml) and TFAA (55 μl) was added at 0 °C. After 5 min the mixture was poured into ether–water and washed several times with 2 M NaOH (the salt of unchanged *1j* was only sparingly soluble in alkaline solution and appeared as a third layer between organic and aqueous phases) and then with water. After evaporation of the ether, the product was separated on silica gel [0.5 mm plates, eluent: toluene–acetic acid (19:1)] to give benzophenone *4a* (R_F = 0.49, 113 mg, 74 %) as a colourless gum homogeneous on TLC, which did not crystallize. MS(IP 13 eV): 760 (M). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.12 (3H, bs), 4.60 (2H, s), 4.85 (4H, s), 5.15 (2H, s), 5.23 (2H, s), 6.39 (2H, s), 6.71 (1H, bq, J = 0.5 Hz), 7.1–7.7 (25H, m). *2,4-Dibenzyloxy-3-chloro-6-methylbenzoic anhydride* was also obtained as a non-crystalline gum (R_F = 0.72, 7 mg) homogeneous on TLC. MS (IP 13 eV): 746 (M). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.32 (6H, bs), 5.05 (4H, s), 5.29 (4H, s), 6.99 (2H, bs), 7.1–7.7 (20 H, m). IR (film): 1790 (s), 1710 cm). Benzophenone *4a* was hydrogenolyzed (Pd/C, H_2), the product dissolved in acetone and added to hot water. After cooling, the crystals were filtered off and recrystallized from acetone to give xanthone *5b* as yellow needles, m.p. 304–305 °C. Anal. $C_{14}H_9ClO_5$: C, H, Cl. MS [IP 70 eV; *m/e* (% rel. int.)]: 294 (34, M) 292 (100, M), 263, (5, [M–CHO]), 257 (4, [M–Cl]), 229 (2). ^{1}H NMR [100 MHz, $(CD_3)_2CO$] δ 2.77 (3H, d, J 0.98 Hz, CH_3), 6.25 and 6.44 (2H, ABq, J 2.4 Hz, 2-H and 4-H), 6.88 (1H, q, J 0.98 Hz, 7-H), 9.8 (1H, bs, OH), 10.0 (1H, bs, OH), 13.23 (1H, s, OH).

*5-Chloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one (vinetorin,* 5d*)*. Equimolar amounts of acid *1j* and ether *2e* were condensed with TFAA and the product hydrogenolyzed without prior purification. Recrystallization from methanol gave benzophenone *4d* (74 %) as yellow needles, m.p. 177–180 °C. Anal. $C_{17}H_{17}ClO_6$: C, H, Cl. MS [IP 70 eV; (% rel. int.)]: 354 (1, M), 352 (3, M), 321 (23, [M–OCH_3]), 195 (5, ArCO), 185 (5, ArCO), 168 (100, ArH). ^{1}H NMR [$(CD_3)_2CO$]: δ 1.90 (3H, s, CH_3), 3.75 (6H, s, 2 × OCH_3), 3.88 (3H, s, OCH_3), 6.34 (2H, s, 3′-H and 5′-H), 6.39 (1H, s, 5-H), 9.63 (1H, bs, OH), 14.42 (1H, s, OH). This was boiled in KOH/ethanol (3h.) as described earlier.[3] Recrystallization from methanol gave xanthone *5c* (67 %) as white needles, m.p. 321–323 °C (d.). Anal. $C_{16}H_{13}ClO_5$. MS [IP, 70 eV; *m/e* (% rel. int.)]: 322 (24, M), 320 (71, M), 319 (12, [M–1)], 305 (11, [M–CH_3]), 302 (100, [M–H_2O]), 291 (14, [M–CHO]), 290 (18, [M–CH_2O]), 289 (14, [M–CH_3O]), 285 (4, [M–Cl]), 274 (17). ^{1}H NMR (DMSO-d_6): δ 2.65 (3H, bs, CH_3), 3.84 and 3.90 (6H, s, 2 × OCH_3), 6.46 and 6.59 (2H, ABq, J = 2.2 Hz, 2-H and 4-H), 6.74 (1H, bs, 5-H). Demethylation of *5c* with BBr_3 (2 mol)[3] gave xanthone *5d*, which crystallized from ethyl acetate as pale yellow needles (61 %) m.p. 256–256.5 °C, lit.[17] 243–245 °C.

*4,5-Dichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (*5f*) and 3,5-di-*O*-methyl ether (*5g*)*. Equimolar amounts of acid *1j* and ether

2f were condensed and after recrystallization from dichloromethane–light petroleum, the benzophenone *4e* (44 %) was obtained as white crystals, m.p. 166–166.5 °C. Hydrogenolysis of *4e* afforded benzophenone *4f* (quantitatively), which crystallized from benzene as pale yellow needles, m.p. 167–168 °C. Anal. $C_{16}H_{14}Cl_2O_6$: C, H, Cl. MS [IP 70 eV; *m/e* (% rel. int.)]: 374 (16, M), 372 (22, M), 357 (13, [M–CH_3]), 343 (15, [M–CHO]), 215 (61, ArCO), 187 (41, Ar), 185 (100, ArCO), 157 (11, Ar). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.10 (3H, d, *J* 0.7 Hz, CH_3), 3.44 (3H, s, 2′-OCH_3), 3.97 (3H, s, 4′-OCH_3), 6.49 (1H, s, 5′-H), 6.51 (1H, q, *J* 0.7 Hz, 5-H), 9.4 (1H, bs, OH), 12.4 (1H, bs, OH).

Ring-closure of *4f* in KOH/ethanol during 2h gave the xanthone *5e* (77 %), yellow needles after recrystallization from acetone, m.p. 255–257 °C. Anal. $C_{15}H_{10}Cl_2O_5$: C, H, Cl. MS [IP 70 eV; *m/e* (% rel. int.)]: 344 (11, M), 342 (64, M), 340 (100, M), 311 (8, [M–CH_3O]), 310 (5, [M–CH_3OH]), 297 (9), 276 (10). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.77 (3 H, d, *J* 0.7 Hz, CH_3), 4.05 (3H, s, OCH_3), 6.55 (1H, s, 2-H), 6.91 (1H, q, *J* 0.7 Hz, 7-H), 13.31 (1H, s, OH).

Demethylation of *5e* was done with $AlCl_3$ (4 mol) in refluxing chlorobenzene (3.5 h). After evaporation of the solvent, ice-water was added and the crude product extracted with ether (containing 10 % acetone). After washing with water the ether layer was evaporated to give *5f* (68 %). The water layer was allowed to stand overnight and the crystals were filtered off to give another crop (30 %) of *5f*. Recrystallization from acetone gave yellow needles, m.p. 291–293 °C (d), lit.[18] 273–274 °C (d). Treatment of *5e* with diazomethane gave the 3,6-di-*O*-methyl-ether *5g*, which was recrystallized from ethyl acetate, m.p. 283–283.5 °C, lit.[18] 250–251 °C.

2,5-Dichloro-1,3,6-trihydroxy-8-methyl-9H-xanthen-9-one (5j) and 3,6-di-O-methyl ether (5i). Benzophenone *4f* was demethylated with BBr_3 (6 mol) to give benzophenone *4g* (91 %), which crystallized from acetone–water as yellow needles, m.p. *ca.* 123–135 °C (dehydrat.). Anal. $C_{15}H_{12}Cl_2O_6$: C, H, Cl. MS [IP, 70 eV; *m/e* (% rel. int.)]: 362 (4, M), 360 (18, M), 358 (24, M), 343 (16, [M–CH_3]), 340 (12, [M–H_2O]), 201 (100, ArCO), 187 (25, ArCO), 173 (3, Ar), 157 (8, Ar). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.10 (3H, d, *J* 0.5 Hz, CH_3), 3.92 (3H, s, OCH_3), 6.19 (1H, s, 5′-H), 6.45 (1H, q, *J* 0.5 Hz, 5-H), 8.4 (1H, bs, OH), 8.9 (1H, bs, OH), 10.90 (1H, s, OH), 11.67 (1H, s, OH).

Ring-closure of *4g* was performed by heating 20 mg in 40 ml water in a sealed tube at 120–130 °C for 3 h. After cooling, the product was filtered off and chromatographed on silica gel (precoated plates, 0.5 mm, eluent: benzene–ether–acetic acid (14:6:1)). Three bands were obtained: unreacted *4g* (3 mg, R_F 0.40), xanthone *5e* (7 mg, 18 %, R_F 0.65) and xanthone *5h* (23 mg, 61 %, R_F 0.60). Needles from ethyl acetate, m.p. 296–297 °C (sealed tube, subl.). Anal. $C_{15}H_{10}Cl_2O_6$: C, H, Cl. MS [IP 70 eV; *m/e* (% rel. int.)]: 344 (12, M), 342 (65, M), 340 (100, M), 339 (7, [M–H]), 325 (8, [M–CH_3]), 311 (9, [M-OCH_3]), 310 (6, [M-CH_3OH]), 297 (10), 276 (8). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.73 (3H, bs, CH_3), 4.07 (3H, s, OCH_3), 6.72 (1H, s, 4-H), 6.87 (1H, narrow m, 7-H), 13.9 (1H, bs, OH).

Demethylation of *5h* with $AlCl_3$ as described for *5e* gave xanthone *5j* (83 %), m.p. 267–268 °C (acetone–water), lit.[6] 245–247 °C. Methylation of *5h* with diazomethane gave xanthone *5i*, m.p. 314–316 °C (ethyl acetate), lit.[6] 299–300 °C.

4,5,7-Trichloro-1,3,6-trihydroxy-8-methyl-9H-xanthen-9-one (5o) and 3-O-methyl ether (5k). Acid *1l* (2 mol), ether *2f* (1 mol), TFAA (4 mol), and TFA (2 mol) were refluxed in dichloromethane for 0.5 h. After work-up, the mixture was separated on a silica gel column (eluent: light petroleum–ether 1:1), to give benzophenone *4h* (53 %), m.p. 166–166.5 °C. From experiments where TFA was omitted, *2,4-dibenzyloxy-3,5-dichloro-6-methylbenzoic anhydride* was isolated, m.p. 86.5–87.5 °C (ether). Anal. $C_{44}H_{34}Cl_4O_7$: C, H, Cl. MS [IP 14 eV; *m/e* (% rel. int.)]: 509 (2), 507 (4), 492 (4), 490 (5), 403 (12), 401 (54), 399 (89, ArCO), 308 (16, ArCO-C_7H_7), 271 (10), 181 (11), 92 (13), 91 (100). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.32 (6H, s), 5.07 (4H, s), 5.11 (4H, s), 7.36 (20H, m). ^{13}C NMR ($CDCl_3$): δ 17.3 (CH_3, q, ^1J 130 Hz), 74.9 (CH_2O, tdt, ^1J 147 Hz, ^3J 4 Hz, ^4J 1Hz), 76.8 (CH_2O, tdt, ^1J 147 Hz, ^3J 3 Hz, ^4J 2 Hz), 122.0 (C-3, s), 125.2 (C-1 m? hidden), 126.6 (C-5, q, ^3J 5Hz), 126.5, 128.3 and 128.4 (*o*-C, *p*-C and *m*-C in benzylic groups, dm, ^1J 160 Hz), 134.5 (C-6, q, ^2J 6 Hz), 135.5 and 135.7 (α-C in benzylic groups, m), 151.5 (C-2, s) 153.8 (C-4, s), 161.0 (C=O). IR (KBr): 1792 (s), 1731 (m). Hydrogenolysis of the benzophenone *4h* above gave *4i* after recrystallization from benzene (89 %) as yellow needles, m.p. 191–192 °C. Anal. $C_{16}H_{13}Cl_3O_6$: C, H, Cl. MS [IP 70 eV; *m/e* (% rel. int.)]: 410 (5, M), 408 (14, M), 406 (14, M), 391 (6, [M–CH_3]), 219 (51, ArCO), 215 (31, ArCO), 188 (100, ArH). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.22 (3H, s, CH_3), 3.38 (3H, s, 2′-OCH_3), 4.01 (3H, s, 4′-OCH_3), 6.53 (1H, s, 5′-H), 8.8 (1H, bs, OH), 13.0 (1H, bs, OH), 14.6 (1H, bs, OH).

Ring-closure of *4i* with KOH/ethanol (2h) gave the xanthone *5k*, which crystallized from ethyl acetate as yellow needles (87 %), m.p. 294–295 °C. Anal. $C_{15}H_9Cl_3O_5$: C, H, Cl. MS [IP 70 eV; *m/e* (% rel. int.)]: 380 (4, M), 378 (32, M), 376 (97, M), 374 (100, M), 372 (2, [M–H]), 345 (7, [M–CHO]), 344 (5, [M–CH_2O]), 331 (8), 310 (10).

Demethylation of *5k* with $AlCl_3$ as described for *5e* gave the xanthone *5o*, recrystallized from acetone–water as yellow needles (67 %), m.p. 307–308 °C. (d.). Anal. $C_{14}H_7Cl_3O_5$: C, H, Cl. MS [IP 70 eV; *m/e* (% rel. int.)]: 364 (33, M), 362 (99, M), 360 (100, M), 359 (5, [M–H]), 331 (5, [M–CHO]), 325 (10, [M–Cl]),

297 (6). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.97 (3H, s, CH_3), 6.46 (1H, s, 2-H), 13.29 (1H), s, OH).

2,5,7-Trichloro-1,3,6-trihydroxy-8-methyl-9H-xanthen-9-one (5m) and 3-O-methyl-ether (5l). Benzophenone *4i* was demethylated with BBr_3 as described for *4f* to yield ketone *4j*, which crystallized from benzene as light yellow needles, m.p. *ca.* 127–140 °C. Anal. $C_{15}H_{11}Cl_3O_6$: C, H, Cl. MS [IP 13 eV; *m/e* (% rel. int.)]: 396 (33, M), 394 (96, M), 392 (100, M), 374 (15, [M–H_2O]), 221 (14, ArCO), 201 (19, ArCO), 192 (10, ArH), 174 (ArH). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.18 (3H, s, CH_3), 3.94 (3H, s, OCH_3), 6.20 (1H, s, 5'-H), 9.0 (2H, bs, 2×OH), 11.8 (1H, bs, OH).

Ring-closure in a sealed tube as described for *4g* gave xanthone *5l*. Yield 53 %, R_F 0.65 (together with *5k*, 18 % R_F 0.75) m.p. 296–297 °C (acetone), lit.[19] m.p. 279–282 °C. Demethylation of *5l* as described for *5e* afforded xanthone *5m*, recrystallized from acetone–water as yellow needles, m.p. 250–251 °C. Anal. $C_{14}H_7Cl_3O_6$: C, H, Cl. MS [IP 70 eV; (% rel. int.)]: 366 (4, M), 364 (33, M), 362 (98, M), 360 (100, M), 359 (6, [M–H]), 331 (4, [M–CHO]), 325 (10, [M–Cl]), 297 (5). ^{1}H NMR [$(CD_3)_2CO$]: δ 2.97 (3H, s, CH_3), 6.67 (1H, s, 4-H), 13.80 (1H, s, OH).

TLC analysis of lichens

Voucher specimens are to be found at the herbarium of Uppsala Botanical Museum. *Buellia glaziouana* from Easter Isl. (Chile), collected 1917, reference designation C & I Skottsberg; *Lecanora capistrata*, Falkland Isl. (Gr.Br.), 1917, Skottsberg, 53; *L. sulphurata*, Bulgaria, 1924, Szatala.

The lichens were extracted with acetone (*ca.* 20 mg in 3 ml) for 24 h and co-chromatographed with the synthetic xanthones on silica gel plates (0.25 mm) in three systems: Dichloromethane–acetone (4:1), toluene–acetic acid (4:1), benzene–ether–acetic acid (14:6:1).

Acknowledgements. Financial support of the work by a grant from the Hierta-Retzius' Fund and from the Swedish Natural Science Research Council are gratefully acknowledged. I also wish to express my sincere thanks to Dr. R. Moberg for generous gifts of the lichens examined and to Dr. S. Huneck for a sample of xanthone *5i*.

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Received February 23, 1979.