β-Tricarbonyl Compounds. Part 2.[1] Synthesis of 5,7-Dihydroxy-8-isobutyryl-2,2-dimethyl-2*H*-chromen and the Antibiotics Uliginosin B-iBiB and Uliginosin B-iBiV

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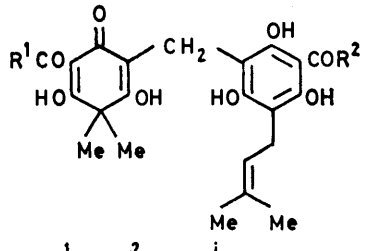
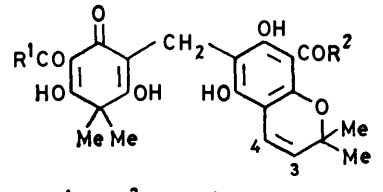
Several routes to 5,7-dihydroxy-8-isobutyryl-2,2-dimethyl-2*H*-chromen were investigated and it was eventually prepared, together with the 6-isobutyryl isomer, by cyclodehydrogenation of 2',4',6'-trihydroxy-3'-(3-methylbut-2-enyl)isobutyrophenone using DDQ. A rottlerone exchange between the 8-isobutyrylchromen and albaspidin-iBiB then afforded uliginosin B-iBiB. Uliginosin B-iBiB and uliginosin B-iBiV have also been prepared by cyclodehydrogenation of the corresponding derivatives of uliginosin A. Natural uliginosin B contains a homologue (*M* + 14) which is probably uliginosin B-iViB. 7-Hydroxy-2,2-dimethyl-2*H*-chromens react with DDQ to form 3-*O*-(2,3-dichloro-5,6-dicyano-4-hydroxyphenyl) ethers.

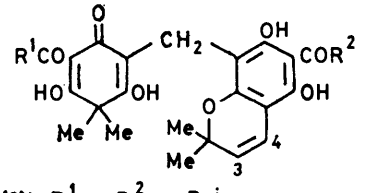
THE Mexican plant *Hypericum uliginosum* HBK produces two antibiotics, uliginosin A (1) and uliginosin B (4), both of which are contaminated with (*M* + 14) homologues.[2,3] In Part 1 [1] we described the synthesis of



(1) $R^1 = R^2 = Pr^i$
(2) $R^1 = Bu^i$; $R^2 = Pr^i$
(3) $R^1 = Pr^i$; $R^2 = Bu^i$



(4) $R^1 = R^2 = Pr^i$
(5) $R^1 = Bu^i$; $R^2 = Pr^i$
(6) $R^1 = Pr^i$; $R^2 = Bu^i$
(7) is 3,4-dihydro-(4)

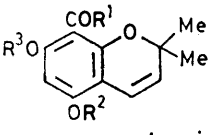


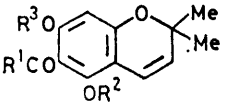
(8) $R^1 = R^2 = Pr^i$
(9) $R^1 = Pr^i$; $= R^2 = Bu^i$
(10) is 3,4-dihydro-(8)

uliginosin A-iBiB (1), uliginosin-A-iViB (2), uliginosin A-iBiV (3), dihydrouliginosin B-iBiB (7), and isodihydrouliginosin B-iBiB (10), and showed by mass spectrometry that the minor component in natural uliginosin A is most likely uliginosin A-iViB (2). We now describe the synthesis of uliginosin B-iBiB (4) and uliginosin B-iBiV (6) but the natural contaminant is probably uliginosin B-iViB (5).

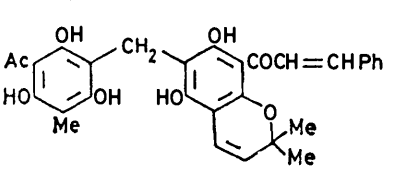
RESULTS AND DISCUSSION

The syntheses described in Part 1 were effected by a rottlerone exchange between an albaspidin, *e.g.* (11), and a phenolic component, either an acylphloroglucinol, *e.g.* (60), or an acylchromandiol, *e.g.* (42). To extend this method to the synthesis of uliginosin B-iBiB (4) it is necessary to prepare 5,7-dihydroxy-8-isobutyryl-2,2-dimethyl-2*H*-chromen (12). 2,2-Dimethylchromens





(12) $R^1 = Pr^i$; $R^2 = R^3 = H$ (13)
(14) $R^1 = R^2 = Me$; $R^3 = H$ (15)
(16) $R^1 = R^3 = Me$; $R^2 = H$ (17)
(18) $R^1 = R^2 = Me$; $R^3 = H$ (19)
(20) $R^1 = PhCH{=}CH$; $R^2 = R^3 = H$
(21) $R^1 = Pr^i$; $R^2 = Me$; $R^3 = H$
(23) $R^1 = Me$; $R^2 = R^3 = H$ (24)

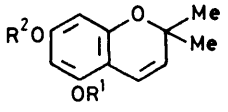


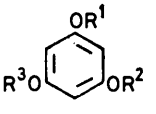
(25)

occur in nature;[4,5] in particular, alloevodionol (14), evodionol (15), isoevodionol (17), and their *O*-methyl ethers (18) and (19) have structures related to the required acylchromen (12). Rottlerin (25), the anthelmintic principle of the silk dye kamala, has a structure related to uliginosin B; here 8-cinnamoyl-5,7-dihydroxy-2,2-dimethylchromen (20) is linked to 2',4',6'-trihydroxy-3'-methylacetophenone by a methylene bridge. Several routes have been developed for the synthesis of chro-

mens [4-6] but, in general, these methods have only been applied to, or been successful with, chromens which have no free unchelated phenolic hydroxy groupings. We investigated several of these routes concurrently before we achieved the synthesis of the required chromen (12).

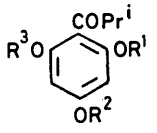
Attempts to synthesize 5,7-*Dihydroxy*-8-*isobutyryl*-2,2-*dimethyl*-2H-*chromen* (12).—(i) *Routes based on* 5,7-*dihydroxy*-2,2-*dimethyl*-2H-*chromen* (26). Theoretically, acylation of the unknown 5,7-dihydroxy-2,2-dimethyl-2*H*-chromen (26) should yield the desired acylchromen

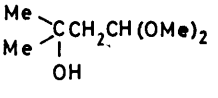




(26) $R^1 = R^2 = H$
(27) $R^1 = R^2 = Me$
(28) $R^1 = R^2 = MeC_6H_4SO_2$
(29) $R^1 = MeC_6H_4SO_2$; $R^2 = H$
(30) $R^1 = H$; $R^2 = MeC_6H_4SO_2$

(31) $R^1 = R^2 = R^3 = MeC_6H_4SO_2$
(32) $R^1 = H$; $R^2 = R^3 = MeC_6H_4SO_2$
(33) $R^1 = CMe_2C{\equiv}CH$; $R^2 = R^3 = MeC_6H_4SO_2$
(34) $R^1 = CMe_2C{\equiv}CH$; $R^2 = R^3 = H$
(35) $R^1 = CMe_2C{\equiv}CH$; $R^2 = MeC_6H_4SO_2$; $R^3 = H$





(39)

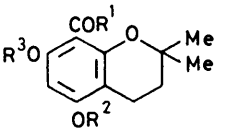
(36) $R^1 = R^2 = R^3 = H$
(37) $R^1 = R^3 = H$; $R^2 = CMe_2C{\equiv}CH$
(38) $R^1 = R^3 = H$ $R^2 = Me$

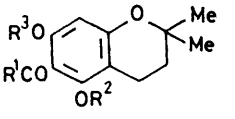
(12) but the stability of the chromen ring to acylation conditions is doubtful.[7] Nevertheless we attempted the synthesis of 2,2-dimethyl-2*H*-chromen-5,7-diol (26). Attempts to demethylate the known [8] dimethyl ether (27) with either boron tribromide or aluminium tribromide led to complete decomposition. Accordingly attempts were made to prepare phloroglucinol mono-(α,α-dimethylpropargyl) ether (34) which should [9] cyclize to the chromendiol (12). The mono-ether (34) could not be prepared by direct treatment of phloroglucinol with 3-chloro-3-methylbut-1-yne,[10] but partial alkaline hydrolysis [11] of phloroglucinol tris(toluene-*p*-sulphonate) (31) gave the diester (32) which gave the ether (33) on treatment with an excess of 3-chloro-3-methylbut-1-yne. This ether (33) could only be isolated as a crude oil but it readily cyclized to the crystalline chromen (28) when heated under reflux in *NN*-dimethylaniline. In warm methanolic potassium hydroxide solution this chromen underwent partial hydrolysis to a mixture of the two mono-esters (29) and (30), which could not be separated. The presence of two isomers in the hydrolysate was only detected in the n.m.r. spectrum, where the slightly different styryl groups gave rise to two overlapping AB quartets. Attempts to hydrolyse the mixture further resulted in serious decomposition and the dihydroxychromen (26) could not be isolated. Similarly the acetylenic ether (33) was only partially hydrolysed to the mono-ester (35) which decomposed on more vigorous treatment.

(ii) *Routes based on* 2′,4′,6′-*trihydroxyacylphenones*. We also investigated this acetylenic ether route [9] with the acyl group already *in situ*. Direct treatment of 2′,4′,6′-trihydroxyisobutyrophenone (36) with 3-chloro-3-methylbut-1-yne gave a complex mixture of products from which the required ether (37) could not be isolated. In contrast, treatment of 2′,4′,6′-trihydroxyisobutyrophenone 4′-methyl ether (38) with 3-chloro-3-methylbut-1-yne gave the chromen (21) directly. Attempts to demethylate this product (21) with either aluminium tribromide or boron tribromide resulted in decomposition. Attempts to prepare the 4′-benzoyl or 4′-*p*-tolylsulphonyl esters of 2′,4′,6′-trihydroxyisobutyrophenone, in order to prepare the chromen with more labile protecting groups, were also unsuccessful.

2,2-Dimethyl-2*H*-chromens have been satisfactorily prepared by the pyridine-catalysed condensation [6] of phenols with 3-hydroxy-3-methylbutanal dimethyl acetal (39). However, treatment of 2′,4′,6′-trihydroxyisobutyrophenone with the acetal (39) gave a mixture of products which could not be resolved by column chromatography. At about the same time Donnelly and Shannon [12] investigated the reaction of 2′,4′,6′-trihydroxyacetophenone with 2 mol of the acetal (39) and isolated six products. The homologous acetylchromens (23) and (24) were isolated in low yield as an unstable mixture, which was only resolved after reduction to the corresponding chromans (40) and (41).

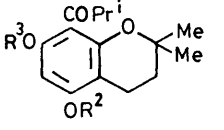
(iii) *Routes based on* 5,7-*dihydroxy*-8-*isobutyryl*-2,2-*dimethyl*-2H-*chroman* (42). Initially this route was considered the most promising since Cardillo *et al.*[13]

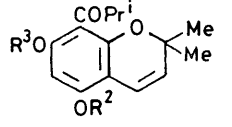




(40) $R^1 = Me$; $R^2 = R^3 = H$
(42) $R^1 = Pr^i$; $R^2 = R^3 = H$
(44) $R^1 = R^2 = Me$; $R^3 = H$

(41)
(43)





(42) $R^2 = R^3 = H$
(45) $R^2 = R^3 = CH_2Ph$
(47) $R^2 = R^3 = Me$
(49) $R^2 = Me$; $R^3 = H$
(50) $R^2 = R^3 = Ac$
(51) $R^2 = R^3 = COPh$
(52) $R^2 = R^3 = MeC_6H_4SO_2$
(53) $R^2 = MeC_6H_4SO_2$; $R^3 = H$
(54) $R^2 = CH_2OMe$; $R^3 = H$

(12)
(46)
(48)
(21)

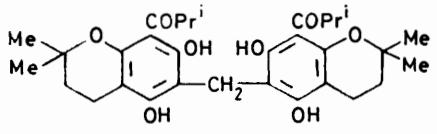
(55)

had dehydrogenated the chroman dihydroalloevodionol (44) to alloevodionol (14) by use of the high potentialquinone 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). The dihydroxychroman (42) did not react cleanly with DDQ in boiling benzene, and a complex mixture of products was indicated by t.l.c. Similar mixtures were obtained when the reaction was carried out at room temperature in either benzene or diethyl ether, and the required chromen (12) could not be isolated. Since DDQ is known to effect the oxidative coupling of phenols, it was assumed that such reactions had occurred and that it was necessary to protect the hydroxy groups before oxidation with a group that could be removed without destroying the labile 2,2-dimethylpyran ring of the chromen. First, however, we wished to confirm that the acylchroman system was dehydrogenated to the required chromen with DDQ. To this end the dibenzyl (45) and the dimethyl (47) ethers of 5,7-dihydroxy-8-isobutyryl-2,2-dimethylchroman (42) were prepared. Both ethers were cleanly oxidized by DDQ in boiling benzene; the initial dark green solutions fading to a pale yellow colour with the concomitant precipitation of 2,3-dichloro-5,6-dicyanohydroquinone. The purified products had the same R_F, when examined by t.l.c., as the starting materials but gave more intense blue colourations with the dye Fast Blue Salt B. The i.r. spectra of starting materials and products were also very similar, except for a weak band at *ca.* 1 640 cm^{-1} (C=C stretch) in the products. N.m.r. spectroscopy, however, readily established that the products were mixtures of the required chromens (46) or (48) and the corresponding starting materials (45) or (47).

Methylation of the chroman (42) gave first the 5-*O*-methyl ether (49), in good yield, and then the di-*O*-methyl ether (47), after more drastic treatment. We established that this 5-methyl ether (49) was smoothly demethylated back to the parent chroman (42) using boron tribromide in benzene, but the use of aluminium tribromide in carbon disulphide led to ring-opening and -closing to give a mixture of the 6- (43) and 8-isobutyrylchromans (42). This 5-methyl ether (49) was readily dehydrogenated with DDQ to a mixture of the chromen (21) and the chroman starting material, in the ratio 2 : 1. The product could not be purified but the pure chromen (21) has been prepared from (38) (see above). When the chromen–chroman mixture was treated with a further portion of DDQ there was no significant increase in the chromen–chroman ratio and considerable loss of material. A DDQ–chromen adduct was isolated, the structure of which is discussed below.

In view of the instability of the chromens towards acids, protecting groups were sought which could be removed under basic conditions. However, the diacetyl (50), dibenzoyl (51), bis-(*p*-tolylsulphonyl) (52) and 5-*p*-tolylsulphonyl (53) esters of the chroman (42) all failed to react with DDQ even after prolonged treatment in boiling xylene. No deep colouration was formed in solutions of these esters after the addition of the quinone, indicating that the charge-transfer complexes were not being formed. The reason for this may be partly steric but is more probably due to the reduced electron density on the aromatic ring of these chroman esters.

Methoxymethyl and tetrahydropyranyl ethers are reported to be readily cleaved by very mild treatment with inorganic acids. With chlorodimethyl ether under strictly anhydrous conditions, the dihydroxychroman (42) gave the 5-methoxymethyl ether (54). In the presence of a trace of moisture the only product was the known [1] methylene bis-chroman (56) which was also



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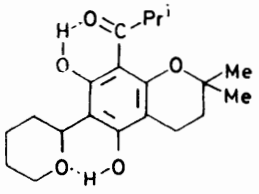

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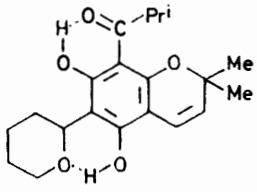

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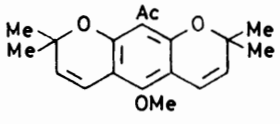

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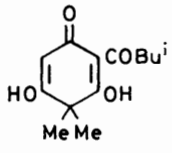


(61)

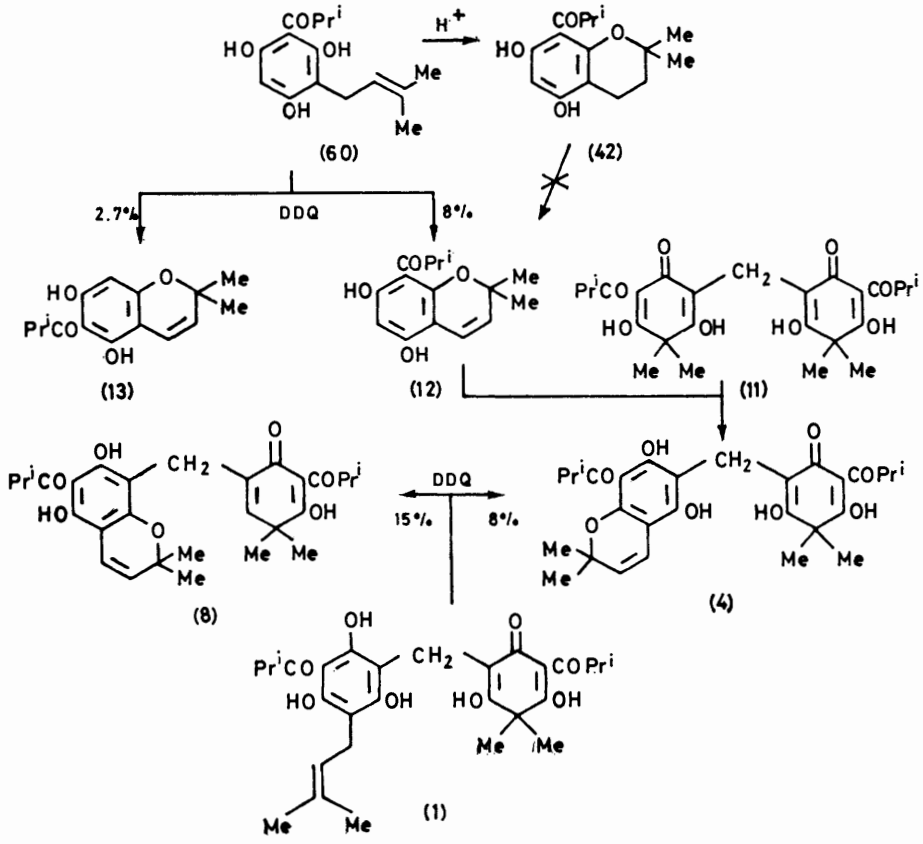
obtained by hydrolysis of the methoxymethyl ether (54) in hot aqueous acetic acid containing a trace of sulphuric acid. In contrast, the monomeric parent chroman (42) was recovered in good yield, free of (43) and (56), by hydrolysis of the methoxymethyl ether in methanol containing a trace of sulphuric acid. Dehydrogenation of the methoxymethylchroman (54) with DDQ gave a mixture of the chromen (55) (83%) and the original chroman. When this mixture was heated for a short period in acidified methanol only one major product was indicated by t.l.c. This had the same R_F as the chroman (42) but gave a more intense blue-purple colour with Fast Blue Salt B, as expected for the required chromen (12). However, attempts to purify the chromen led to mixtures with lower chromen–chroman ratios (n.m.r.), and in which 6-acyl derivatives were shown to be present by t.l.c. Further treatment of the chromen–chroman mixture with DDQ gave no improvement in the chromen–chroman ratio and gave rise to another DDQ–chromen adduct, the structure of which is discussed later.

Treatment of the parent chroman (42) with 2,3-dihydropyran in the presence of either hydrochloric or toluene-*p*-sulphonic acid gave the 6-*C*-alkylated product

(57) without any trace of the tetrahydropyranyl-*O*-ether. The product showed two exchangeable hydroxy proton signals in the n.m.r. spectrum but no signal in the τ 4.0 region for the aromatic 6-proton. The lower-field hydroxyl resonance (τ −4.22) was readily assigned to the chelated 7-hydroxy proton but the higher-field signal (τ 0.42), was sharp, and at much lower field than is normal for free 5-hydroxy protons. This, and an OH stretching band at 3 230 cm^{-1} which was unaffected by dilution, suggest that there is intramolecular hydrogen bonding between the 5-hydroxy proton and the pyran ethereal oxygen as shown in (57). This *C*-alkylated chroman was cleanly oxidized by DDQ to a mixture of the chromen (58) (75%) and the starting material (57). The unexpectedly smooth oxidation of this 5,7-dihydroxychroman (57) is probably due to the fact that both hydroxys are chelated by intramolecular hydrogen bonds.

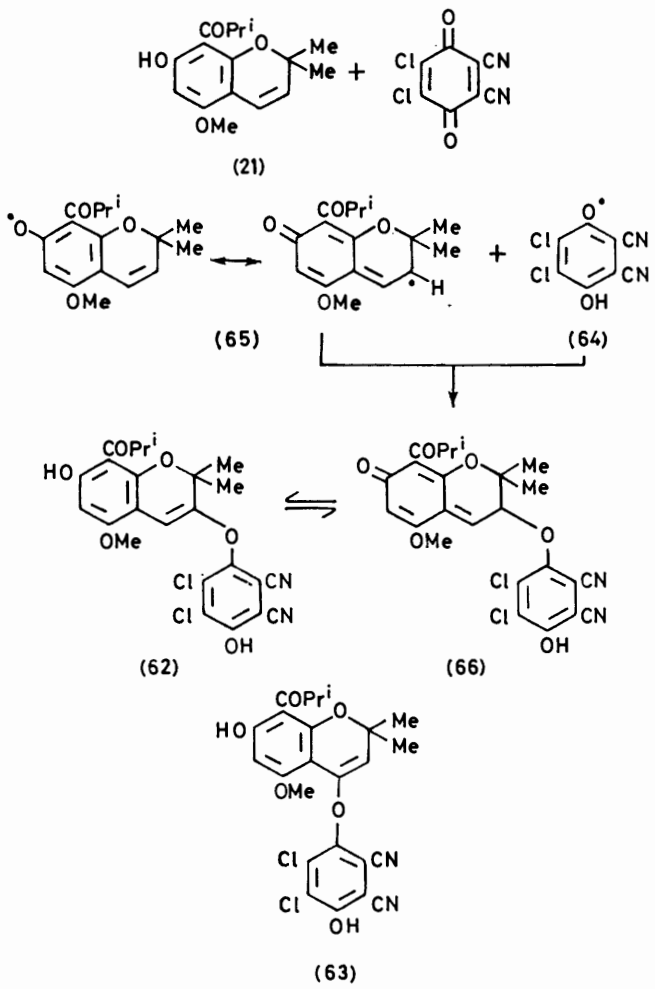
Finally we showed that DDQ had no effect on albaspidin iBiB (11) but partially dehydrogenated the methylene-bis-chroman (56) to the corresponding chromen(s). Accordingly, attempts were made to dehydrogenate dihydrouliginosin B-iBiB (7) to uliginosin B-iBiB (4), but, as before, the reaction led to an inseparable mixture of the desired antibiotic (4) and its dihydroderivative. Thus, in our hands, the dehydrogenation of chromans to chromens using DDQ never goes to completion and gives an inseparable mixture of chromen and chroman. Cardillo *et al.*[13] used this method to prepare alloevodionol (14) and franklinone (59) but provided no n.m.r. data for their products; it seems likely therefore that these products were contaminated with the parent chromans.

(iv) *Cyclodehydrogenation of* o-(3-*methylbut*-2-*enyl*)-*phenols*. The chroman starting materials (42) and (43) described in the previous section were prepared [1] by acid treatment of 2',4',6'-trihydroxy-3'-(3-methylbut-2-enyl)isobutyrophenone (60). Cyclodehydrogenation of the same compound (60) should give a mixture of the desired chromens (12) and (13) and this is the proposed [14] biogenetic route to natural products containing the 2,2-dimethylchromen ring. *In vitro* such cyclodehydrogenations were first carried out [15,16] using the high potential quinone DDQ. Our initial attempts to dehydrogenate the isobutyrophenone (60) with an equimolecular amount of DDQ gave a complex mixture of products. Similar mixtures were obtained using tetrachloro-1,2-benzoquinone (*o*-chloranil) but tetrachloro-1,4-benzoquinone (chloranil) failed to react with the phenol (60). With the benefit of our experience with chroman substrates, we repeated the oxidation of (60) using 0.7 mol DDQ. T.l.c. of the product then showed only two major spots which had the same R_F as those of the chromans (42) and (43), but which gave much more intense colours



SCHEME 1

with Fast Blue Salt B than those given by the chromans. The two chromens (12) and (13) were separated by column chromatography when the n.m.r. spectrum of both exhibited the typical AB quartets at τ *ca.* 4.5 and 3.5 of the 3- and 4-protons of the 2,2-dimethylchromen ring, but lacked the triplets at higher field characteristic



SCHEME 2

of the corresponding chromans. The assignment of structures to the two products followed from those of the chromans.[1]

Synthesis of Uliginosin B and Analogues thereof (*Scheme* 1).—With, 5,7-dihydroxy-8-isobutyryl-2,2-dimethylchromen (12) available, the synthesis of uliginosin B-iBiB (4) was achieved by a rottlerone exchange with albaspidin iBiB (11) as described for the analogues of uliginosin A.[1] The synthetic product was identical with the natural product provided by Dr. F. Johnson except for a slight depression (*ca.* 1.5 °C) in the mixed melting point. This was not unexpected in view of the known contamination of the natural product with an (M + 14) homologue.

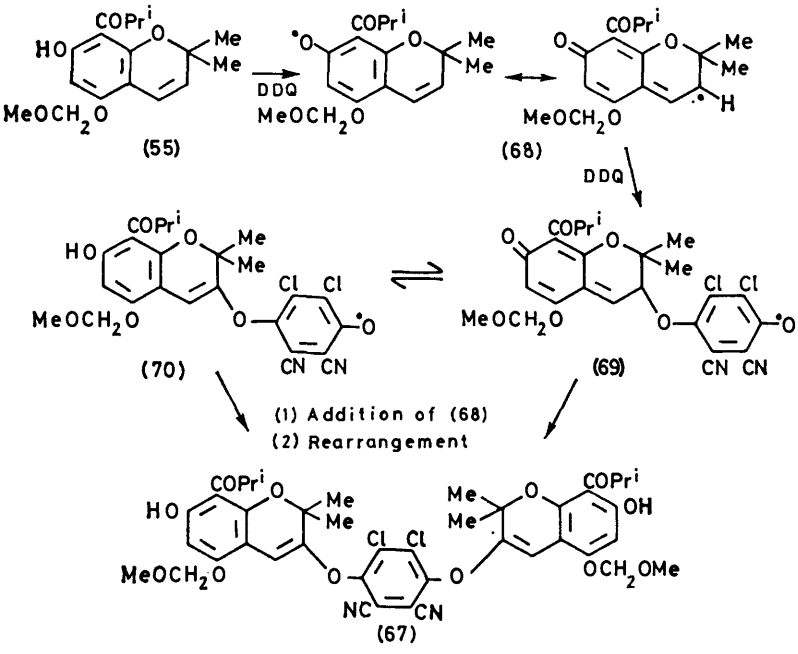
Some time before we achieved this synthesis we investigated [17] the cyclodehydrogenation of uliginosin A-iBiB (1) using DDQ in boiling benzene, and isolated uliginosin B-iBiB (4) identical with the natural product. It was also identical with the synthetic product (4) prepared from the chromen (12). In the initial experiment we did not encounter the alternative cyclization product isouliginosin B-iBiB (8), but when the experiment was repeated at room temperature two products were obtained which were separated by column chromatography. The first product eluted from the column was uliginosin B-iBiB (4) which was followed by the unknown isouliginosin B-iBiB (8). The orientation of the two isomers was readily confirmed by comparison of the pattern of signals given by the hydroxy protons in the n.m.r. spectrum with those in the spectra of the known [1] dihydro-compounds (7) and (10). In a similar manner cyclodehydrogenation of uliginosin A-iBiV (3) gave rise to uliginosin B-iBiV (6) and isouliginosin B-iBiV (9).

Nature of the Impurity in Natural Uliginosin B.—Comparison of the mass spectra of natural uliginosin B and synthetic uliginosin B-iBiB (4) suggested that the ions of *m/e* 512, 497 (M — Me), and 250 were due to the contaminant. Of these, the ion at *m/e* 250 is diagnostic [1] of a filicinic acid ring with a five-carbon acyl group, *e.g.* (61). This suggests that uliginosin B-iViB (5), which we have not synthesized, is the natural impurity. Support for this view also comes from examination of the mass spectrum of uliginosin B-iBiV (6), which shows prominent ions at *m/e* 276 and 261. Ions of these masses are found in the spectra of natural uliginosin B and synthetic uliginosin B-iBiB (4) but they are much less intense than in (6). If uliginosin B-iBiV (6) had been the natural contaminant these ions should have been more intense in the natural product than in the synthetic uliginosin B-iBiB (4) but this was not the case. Thus the natural contaminants of both uliginosin A (1) and B (4) are the homologues (2) and (5), in which the filicinic acid moiety contains an isovaleryl side chain.

Structure of DDQ–Chromen Adducts.—As described above, treatment of 7-hydroxy-8-isobutyryl-5-methoxy-2,2-dimethylchroman (49) with DDQ effected partial dehydrogenation to the chromen (21). Treatment of the chromen–chroman mixture with a further portion of DDQ did not increase the chromen–chroman ratio but led to the formation of a DDQ–chromen adduct, $C_{24}H_{20}Cl_2N_2O_6$. The same adduct was obtained when a pure sample of the chromen (21) [from 2′,6′-dihydroxy-4′-methoxyisobutyrophenone (38) and 3-chloro-3-methylbut-1-yne] was treated with DDQ. The base peak in the mass spectrum of the adduct, at *m/e* 275, is formed from the molecular ion by direct loss of the stable hydroquinone radical (64), which implies that the product is an ether. The position of the ether linkage can be limited to either C-3 (62) or C-4 (63) of the pyran ring by reference to the n.m.r. spectrum, which closely resembles that of the parent chromen (21) but only shows a signal for one olefinic proton at τ 4.76. This value, when compared with the values for the 3-proton

(τ 4.55) and the 4-proton (τ 3.38) of the parent chromen (21), immediately suggests structure (63) for the adduct but this argument neglects the anisotropy of the hydroquinone ring. Molecular models demonstrate that in either isomer (62) or (63) the olefinic proton is located close to the centre of the hydroquinone ring and will thus be shielded by the secondary field associated with any induced ring-current. Any such shielding would bring the calculated [18] chemical shift of the 4-proton in (62) closer to the observed value but displace that calculated for the 3-proton in (63) to even higher field. Also in the n.m.r. spectrum, the signal for the 2,2-dimethyl group in the adduct is at slightly lower field than in the corresponding unsubstituted chromen (21). This shift is more easily rationalized on the basis of structure (62) than (63). The mass spectrum of the adduct can be explained [19] on the basis of either structure, but in the i.r. spectrum the C=C stretching band of the adduct (1 665 cm^{-1}) is at higher frequency than that in the parent chromen (21) (1 645 cm^{-1}) which again favours (62) in which the ether linkage would reduce the conjugation of the styryl double bond with the phloroglucinol ring. Finally, current theories of the oxidation of phenols by DDQ support structure (62) for the adduct and exclude structure (63). Thus as proposed [20] for the oxidation of phenols and hydroxystilbenes, the charge transfer complex between (21) and DDQ breaks down by a one-electron process to the DDQH· semiquinone radical (64) and the resonance-stabilized phenoxyl radical (65) (Scheme 2). These two radicals then collapse to give the *para*-quinone allide (66) which will rearrange to the more stable chromen (62). Neither this mechanism, nor alternative ionic mechanisms,[19] can explain the formation of (63). Since we completed this work Turner [21] has described the formation of similar ethers between tricyclic styrenes and DDQ.

A second DDQ–chromen adduct was obtained when a mixture of 7-hydroxy-8-isobutyryl-5-methoxymethyleneoxy-2,2-dimethyl-2*H*-chromen (55) and the corresponding chroman (54) was treated with a further portion of DDQ. This adduct analysed for $C_{42}H_{42}Cl_2N_2O_{12}$ indicating that it was formed from two molecules of the chromen (55) for each molecule of DDQ. The bis-ether structure (67) is proposed since, unlike (62), this adduct is insoluble in dilute alkali and therefore does not possess an unchelated phenolic hydroxy group. The similarity of the chemical shifts of the olefinic protons and of the protons of the *gem*-dimethyl group to those of the analogous protons in the mono-ether (62) indicates that the position of substitution in the chromen ring is the same in both adducts. Furthermore, the bis-ether would appear to be symmetrical since the two olefinic protons in the adduct resonate as a two-proton singlet. The bis-ether (67) can arise (Scheme 3) if the resonance-stabilized radical (68) adds across the quinone to give (69). This new radical, or a tautomer thereof (70), can then collapse with a second molecule of (68) to give the bis-ether (67).



SCHEME 3

EXPERIMENTAL

For general methods used see Part 1.[1] The mass-spectral details for natural Uliginosin B and compounds (4), (5), (8), (9), (12), (62), and (67) are deposited as Supplementary publication No. SUP 22564 (15 pp.), as are experimental details for the preparation and spectral properties of compounds (50)—(53).*

* For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1978, Index issue.

Attempts to synthesize 5,7-*Dihydroxy*-8-*isobutyryl*-2,2-*dimethyl*-2H-*chromen* (12).—(i) *Routes based on* 5,7-*dihydroxy*-2,2-*dimethyl*-2H-*chromen* (26). (a) *Phloroglucinol tris*(*toluene*-p-*sulphonate*) (31). A solution of anhydrous phloroglucinol (100 g) and toluene-*p*-sulphonyl chloride (500 ml) was heated on a steam-bath for 1.5 h and then poured with vigorous stirring into 2 l of water. The precipitate crystallized from ethanol to give the triester (31) (426 g, 91%) as prisms, m.p. 89—90 °C (lit.,[11] m.p. 82—83 °C) (Found: C, 55.25; H, 4.25; S, 16.1. Calc. for $C_{27}H_{24}O_9S_3$: C, 55.1; H, 4.1; S, 16.35%); $\nu_{max.}$ 1 700, 1 200, 1 180, 1 115, 1 095, 985, 895, 885, 815, 765, and 745 cm^{-1}; $\tau(CDCl_3)$ 7.55 (9 H, s, 3 × Ar-*Me*), 3.35 (3 H, s, 2-H, 4-H, and 6-H), 2.68 (6 H, d, *J* 9 Hz, 3 × 3′-H, and 3 × 5′-H), and 2.38 (6 H, d, *J* 9 Hz, 3 × 2′-H and 3 × 6′-H).

(b) *Phloroglucinol bis*(*toluene*-p-*sulphonate*) (32). The foregoing triester (425 g) was partially hydrolysed with 25% aqueous methanolic potassium hydroxide solution (400 ml) using the method of Kampouris [11] to give phloroglucinol bis(toluene-*p*-sulphonate) (32) (230 g, 73%) as prisms, m.p. 109—110 °C (from benzene–cyclohexzne) (lit.,[11] 126—127 °C from acetic acid) (Found: C, 55.5; H, 4.3; S, 14.5. Calc. for $C_{20}H_{18}O_7S_2$: C, 55.3; H, 4.15; S, 14.7%); $\nu_{max.}$ 3 550—3 100, 1 620, 1 600, 1 190, 1 180, 1 160, 1 095, 1 005, 990, and 865 cm^{-1}; $\tau(CDCl_3)$ 7.58 (6 H, s, 2 × Ar-*Me*), 3.75 (m) and 3.50 (m) (3 H, 2-H, 4-H, and 6-H), 2.68 (4 H, d, *J* 9 Hz, 2 × 3′-H and 2 × 5′-H), and 2.38 (4 H, d, *J* 9 Hz, 2 × 2′-H and 2 × 6′-H).

(c) 1-(1,1-*Dimethylprop*-2-*ynyloxy*)3,5-*bis*-(p-*tolylsulphonyloxy*)*benzene* (33). A mixture of phloroglucinol bis(toluene-*p*-sulphonate) (32) (26 g), 3-chloro-3-methylbut-1-yne (24 g), dried potassium carbonate (10 g), and potassium iodide (16 g) in dry acetone (250 ml) was stirred and heated under reflux for 48 h. Inorganic material was removed by filtration and the filtrate evaporated. A solution of the residual oil in ether, after washing successively with 2N sodium hydroxide and water, was dried and evaporated. The residue would not recrystallize from any of the common solvents, even after the material had been purified through its silver salt. On attempted distillation under high vacuum, the oily residue rapidly charred and then exploded. However, the acetylenic ether (33) was obtained as a buff solid (20 g), m.p. 60—64 °C, when a solution of the oil in a small volume of ethanol was allowed to evaporate slowly at room temperature; $\nu_{max.}$ ($CHCl_3$) 3 300, 1 610, 1 600, 1 455, 1 380, 1 195, 1 185, 1 125, 1 095, 990, and 870 cm^{-1}; $\tau(CCl_4)$ 8.5 (6 H, s, CMe_2), 7.60 (7 H, s, 2 × Ar-*Me* and C≡CH), 3.70 (m) and 3.28 (m) (3 H, 2-H, 4-H, and 6-H), 2.78 (4 H, d, *J* 9 Hz, 2 × 3′-H and 2 × 5′-H), 2.43 (4 H, d, *J* 9 Hz, 2 × 2′-H, and 2 × 6′-H). However, even this material could not be recrystallized satisfactorily and was used without further purification.

(d) 2,2-*Dimethyl*-5,7-*bis*-(p-*tolylsulphonyloxy*)-2H-*chromen* (28). A solution of the bis-(*p*-tolylsulphonyl) acetylenic ether (33) (10 g) in dimethylaniline (50 ml) was heated under reflux for 8 h, cooled, diluted with ether, and then washed with 2N sulphuric acid and water. The ethereal solution was dried and evaporated to give the *bis*-(p-*tolylsulphonyloxy*)*chromen* (28) (7.6 g, 76%) as pale yellow prisms, m.p. 120—121 °C, (from ethanol) (Found: C, 59.7; H, 4.7; S, 13.0. $C_{25}H_{24}O_7S_2$ requires C, 60.0; H, 4.85; S, 12.8%); $\nu_{max.}$ ($CHCl_3$) 1 610, 1 600, 1 580, 1 480, 1 430, 1 380, 1 190, 1 180, 1 120, 1 095, 1 045, and 995 cm^{-1}; $\tau(CDCl_3)$ 8.75 (6 H, s, CMe_2) 7.58 (6 H, s, 2 × Ar-*Me*), 4.58 (1 H, d, *J* 10 Hz, 3-H), 3.8 (1 H, d, *J* 10 Hz, 4-H), 3.67 (2 H, S, 6-H and 8-H), and 2.7 (m) and 2.4 (m) (8 H, 8 × Ar-H).

(e) *Hydrolysis of the chromen ester* (28). A suspension of the chromen (5 g) in 10% methanolic potassium hydroxide (22 ml) was heated on a steam-bath for 10 min. The precipitated potassium toluene-*p*-sulphonate was removed by filtration and the filtrate diluted with water (50 ml), acidified with hydrochloric acid, and then extracted with ether (2 × 25 ml). The ethereal extracts were combined, washed with water, dried, and evaporated. The residue was extracted with hot cyclohexane (2 × 25 ml) and the extracts evaporated to give a pale yellow solid (3 g), m.p. 98—109 °C, which could not be purified further. Spectral data suggest that the material is a mixture of 5-hydroxy-2,2-dimethyl-7-(*p*-tolylsulphonyloxy)-2*H*-chromen (30) and 7-hydroxy-2,2-dimethyl-5-(*p*-tolylsulphonyloxy) chromen (29); $\nu_{max.}$ ($CHCl_3$) 3 560—2 800, 1 610, 1 595, 1 500, 1 440, 1 380, 1 195, 1 185, 1 145, 1 115, 1 095, 1 040, and 1 000 cm^{-1}; $\tau(CDCl_3)$ 8.75 (s) and 8.69 (s) (6 H, CMe_2), 7.62 (3 H, s, Ar-*Me*), 4.70 (d, *J* 10 Hz), 4.51 (d, *J* 10 Hz), 4.1—3.7 (m) and 3.49 (d, *J* 10 Hz) (4 H, 3-, 4-, 6-, and 8-H), 2.75 (2 H, d, *J* 9 Hz, 3′- and 5′-H), and 2.32 (2 H, d, *J* 9 Hz, 2′- and 6′-H).

(f) *Hydrolysis of the acetylenic ether* (33). A suspension of the ether (33) (5 g) and 20% aqueous methanolic potassium hydroxide (11 ml) was stirred at room temperature until all the solid had dissolved. Water (50 ml) was added and the aqueous layer washed with chloroform (2 × 25 ml). The aqueous solution was acidified with hydrochloric acid and extracted with ether (2 × 25 ml). Evaporation of the dried ethereal extracts gave a yellow oil, which could not be distilled or further purified. Spectral data suggest that this material is principally the mono-ester 3-(1,1-dimethylprop-2-ynyl)phloroglucinol 1-toluene-*p*-sulphonate (35); $\nu_{max.}$ ($CHCl_3$) 3 550—2 700, 3 300, 1 600, 1 375, 1 195, 1 180, 1 140, 1 115, 1 095, 995, and 850 cm^{-1}; $\tau(CDCl_3)$ 8.50 (6 H, s, CMe_2), 7.58 (3 H, s, Ar-*Me*), 7.40 (1 H, s, C≡CH), 3.7 (m) 3.55 (m), and 3.4 (m) (3 H, 2 H, 4-H, and 6-H), 2.68 (2 H, d, *J* 9 Hz, 3′-H and 5′-H), and 2.30 (2 H, d, *J* 9 Hz, 4′-H and 6′-H).

(ii) *Routes based on* 2′,4′,6′-*Trihydroxyisobutyrophenone* (36). (a) 2′,6′-*Dihydroxy*-4′-*methoxyisobutyrophenone* (38). Anhydrous phloroisobutyrophenone (36) (6 g), dimethyl sulphate (4.2 g), and potassium bicarbonate (10 g) were heated under reflux in anhydrous benzene overnight. Inorganic material was then removed by filtration and the filtrate evaporated to dryness. The residue was extracted with boiling cyclohexane (3 × 75 ml) and the extract cooled to yield 2′,6′-*dihydroxy*-4′-*methoxyisobutyrophenone* (38) (0.4 g, 6%), m.p. 162—163 °C (from benzene–light petroleum) (Found: C, 63.0; H, 6.6. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7%); $\nu_{max.}$ 3 280, 3 500—2 200, 1 640, 1 590, 1 295, 1 240, 1 165, 1 100, 985, 965, and 820 cm^{-1}; $\tau[(CD_3)_2CO]$ 8.85 (6 H, d, *J* 7 Hz, $CHMe_2$), 6.24 (3 H, s, OMe), 6.03 (1 H, sept. *J* 7 Hz, COCH), 4.04 (2 H, s, 3- and 5-H), and −1.6 (1 H, br s, hydrogen-bonded OH).

(b) 8-*Isobutyryl*-7-*hydroxy*-5-*methoxy*-2,2-*dimethyl*-2H-*chromen* (21). A mixture of 2′,6′-dihydroxy-4′-methoxyisobutyrophenone (38) (1 g), 3-chloro-3-methylbut-1-yne (5 ml), dried potassium carbonate (5 g), and potassium iodide (5 g) in dry acetone (50 ml), was stirred and heated under reflux for 48 h. Inorganic material was removed by filtration and the filtrate evaporated. The residue was chromatographed on a column of silica gel. The fraction

eluted by benzene gave an oil (0.3 g) which slowly solidified. Crystallization from methanol gave the *5-methoxychromen* (21) as pale yellow platelets, m.p. 67—68 °C (Found: C, 69.3; H, 7.4; M^+, 276.136 7. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.3% M, 276.136 2); $\nu_{max.}$ ($CHCl_3$) 3 300—2 400, 1 645, 1 615, 1 590, 1 465, 1 450, 1 385, 1 260, 1 155, 1 125, 975, 960, and 885 cm^{-1}; τ($CDCl_3$) 8.75 (6 H, d, *J* 7 Hz, $CHMe_2$), 8.45 (6 H, s, CMe_2), 6.10 (s) and 6.10 (m) (4 H, OMe and COCH), 4.55 (1 H, d, *J* 10 Hz, 3-H), 3.92 (1 H, s, 6-H), 3.38 (1 H, d, *J* 10 Hz, 4-H), and —3.92 (1 H, s, chelated OH).

(iii) *Routes based on 5,7-dihydroxy-8-isobutyryl-2,2-dimethylchroman* (42); *protected derivatives.* (a) *5,7-Dibenzyloxy-8-isobutyryl-2,2-dimethylchroman* (45). 8-Isobutyryl-5,7-dihydroxy-2,2-dimethylchroman (42) (1 g) in dry acetone (50 ml) was heated under reflux with benzyl chloride (1 ml), potassium iodide (1 g), and anhydrous potassium carbonate (1 g) for 3 d. The crude product gave the *dibenzyl ether* (45) (0.6 g, 36%) on treatment with light petroleum as prisms, m.p. 127—128 °C (from methanol) (Found: C, 78.5; H, 7.2. $C_{29}H_{32}O_4$ requires C, 78.3; H, 7.25%); $\nu_{max.}$ 1 695, 1 605, 1 500, 1 225, 1 165, 1 145, 1 110, 740, and 710 cm^{-1}; τ($CDCl_3$) 8.84 (6 H, d, *J* 6.6 Hz $COCHMe_2$), 8.69 (6 H, s, CMe_2), 8.24 (2 H, t, *J* 6.6 Hz, 3-CH_2), 7.5—6.5 (3 H, m, 4-CH_2 and COCH), 4.98 (4 H, s, 2 × OCH_2Ph), 3.84 (1 H, s, 6-H), and 2.75—2.5 (10 H, m, 10 × Ar-H).

(b) *8-Isobutyryl-5,7-dimethoxy-2,2-dimethylchroman* (47). 8-Isobutyryl-5,7-dihydroxy-2,2-dimethylchroman (42) (3 g) in dry acetone (100 ml) was heated under reflux with dimethyl sulphate (10 ml) and anhydrous potassium carbonate (18 g) for 6 h. More dimethyl sulphate (10 ml) was added and heating continued under reflux for a further 15 h. Inorganic material was removed by filtration and the filtrate evaporated to give an oil. Treatment of the oil with cold ether liberated the *dimethyl ether* (47) (1.5 g, 45%) as prisms, m.p. 139—140 °C (from cyclohexane) (Found: C, 70.05; H, 8.45. $C_{17}H_{24}O_4$ requires C, 69.8; H, 8.25%); $\nu_{max.}$ 1 690, 1 603, 1 590, 1 240, 1 210, 1 155, 1 110, 915, and 810 cm^{-1}; τ($CDCl_3$) 8.86 (6 H, d, *J* 6.6 Hz, $COCHMe_2$), 8.72 (6 H, s, CMe_2), 8.27 (2 H, t, *J* 6.6 Hz, 3-CH_2), 7.41 (2 H, t, *J* 6.6 Hz, 4-CH_2), 6.97 (1 H, sept, *J* 6.6 Me, COCH), 6.24 (3 H, s, OMe), 6.17 (3 H, s, OMe), and 3.96 (1 H, s, Ar-H).

(c) *8-Isobutyryl-7-hydroxy-5-methoxy-2,2-dimethylchroman* (49). 8-Isobutyryl-5,7-dihydroxy-2,2-dimethylchroman (42) (4 g), anhydrous potassium carbonate (4 g), and methyl iodide (2 ml) in acetone (50 ml) were stirred and heated under reflux for 1.5 h. Inorganic material was removed by filtration and the filtrate evaporated to give a pale yellow oil which slowly solidified. Crystallization from methanol afforded the *mono-methyl ether* (49) (2.8 g, 66%) as pale yellow prisms, m.p. 68—69 °C (Found: C, 69.05; H, 7.8. $C_{16}H_{22}O_4$ requires C, 69.05; H, 7.95%); $\nu_{max.}$ (CCl_4) 3 300—2 500, 1 625, 1 590, 1 450, 1 385, 1 230, 1 165, 1 145, and 1 115 cm^{-1}; τ($CDCl_3$) 8.80 (6 H, d, *J* 6.6 Hz, $CHMe_2$), 8.60 (6 H, s, CMe_2), 8.23 (2 H, t, *J* 6.6 Hz, 3-CH_2), 7.42 (2 H, t, *J* 6.6 Hz, 4-CH_2), 6.18 (s) and 6.18 (sept) (4 H, OMe and COCH), 3.98 (1 H, s, 6 H), and —4.00 (1 H, s, chelated 7-OH).

(d) *Demethylation of 8-isobutyryl-7-hydroxy-5-methoxy-2,2-dimethylchroman* (49). (A) *With aluminium tribromide.* A solution of the ether (49) (1 g) and anhydrous aluminium tribromide (2.9 g) in carbon disulphide (50 ml) was stirred overnight at room temperature. The solvent was evaporated and the green gel-like complex decomposed by the addition of water (20 ml). The product was extracted into ether (50 ml) and the extract washed with water (2 × 25 ml). The ethereal solution was extracted with 2N sodium hydroxide (2 × 25 ml) and the alkaline extract acidified with hydrochloric acid and re-extracted with ether (2 × 25 ml). Evaporation of the dried extract gave an orange-yellow powder (0.2 g) which was shown by t.l.c. to be a mixture of the 6- and 8-isobutyrylchromans (43) and (42).

(B) *With boron tribromide.* A solution of the ether (49) (1 g) in dry benzene (10 ml) was added dropwise to a well stirred solution of boron tribromide in dry benzene (25 ml). An oil separated which gradually stiffened on stirring. After 3 h the solvent was evaporated off and the product isolated as in the previous experiment. Evaporation of the phenolic extract gave a yellow solid (0.5 g) which was shown by t.l.c. to be the 8-isobutyrylchroman (42) contaminated with a small amount of the 6-isobutyryl isomer (43). Crystallization of this solid from benzene gave pure 8-isobutyryl-5,7-dihydroxy-2,2-dimethylchroman (0.15 g), identical with an authentic sample.

(e) *8-Isobutyryl-7-hydroxy-5-methoxymethyleneoxy-2,2-dimethylchroman* (54). Freshly dried potassium carbonate (5 g) was added to a solution of 8-isobutyryl-5,7-dihydroxy-2,2-dimethylchroman (42) (1.3 g) and chloromethyl methyl ether (0.75 ml) in dry acetone (25 ml). The flask was sealed with a calcium chloride drying tube and the mixture stirred overnight at room temperature. Inorganic material was removed by filtration and the filtrate evaporated to give the *mono-methoxymethyl ether* (54) (1.25 g, 82%), m.p. 95—96 °C (from methanol) (Found: C, 65.9; H, 7.7. $C_{17}H_{24}O_5$ requires C, 66.2; H, 7.85%); $\nu_{max.}$ ($CHCl_3$) 3 500—2 300, 1 620, 1 590, 1 225(br), 1 160, 1 140, 1 110, 1 065, and 960 cm^{-1}; τ(CCl_4) 8.86 (6 H, d, *J* 6.6 Hz, $CHMe_2$), 8.63 (6 H, s, CMe_2), 8.25 (2 H, t, *J* 6.6 Hz, 3-CH_2), 7.45 (2 H, t, *J* 6.6 Hz, 4-CH_2), 6.58 (s) and 6.25 (sept, *J* 6.6 Hz) (4 H, OMe and COCH), 4.90 (2 H, s, OCH_2O), 3.97 (1 H, s, ArH), and —3.30 (1 H, s, chelated 7-OH).

(f) *Hydrolysis of 8-isobutyryl-7-hydroxy-5-methoxymethyleneoxy-2,2-dimethylchroman* (54). (A) *In methanol.* A solution of the ether (54) (0.31 g) in methanol (10 ml) containing 1 drop of concentrated sulphuric acid was heated under reflux for 3 h. The cooled solution was diluted with water (50 ml) and extracted with ether (2 × 25 ml). The solvent was evaporated off and the residue recrystallized from cyclohexane to give yellow prisms (0.21 g, 90%), identical with an authentic sample of 8-isobutyryl-5,5-dihydroxy-2,2-dimethylchroman (42).

(B) *In aqueous acetic acid.* A solution of the ether (54) (0.25 g) in 80% acetic acid (5 ml) containing 2 drops of concentrated sulphuric acid, was heated on a steam-bath for 45 min. On cooling the solution a bright yellow solid crystallized (0.2 g, 91%), identical with an authentic [1] sample of methylenebis-(9-isobutyryl-5,7-dihydroxy-2,2-dimethylchroman) (56).

(g) *Attempted synthesis of the 5-tetrahydropyranyl ether of 8-isobutyryl-5,7-dihydroxy-2,2-dimethylchroman* (42). (A) The chroman (42) (0.5 g) was added, with stirring, to a solution of 2,3-dihydropyran (0.5 g) and toluene-*p*-sulphonic acid (0.01 g) in dry benzene (20 ml), and the mixture stirred at room temperature overnight. The solvent was evaporated off and the residue chromatographed on a column of silica gel. The fraction eluted by benzene yielded an oil, which crystallized from methanol to give *8-isobutyryl-5,7-dihydroxy-2,2-dimethyl-6-(tetrahydropyran-2-yl)chroman* (57) as pale yellow prisms (0.33 g, 50%), m.p. 94—95 °C (Found: C, 68.75; H, 8.2. $C_{20}H_{28}O_5$

requires C, 68.95; H, 8.1%); $\nu_{max.}$ (CCl_4) 3 230, 3 400—2 500, 1 615, 1 385, 1 330, 1 240, 1 190, 1 150, 1 120, 1 085, 1 045, and 910 cm^{-1}; τ($CDCl_3$) 8.85 (6 H, d, *J* 6.6 Hz, $CHMe_2$), 8.62 (6 H, s, CMe_2), 8.25 (8 H, m, 3-CH_2, 3′-CH_2, 4′-CH_2, and 5′-CH_2), 7.40 (2 H, t, *J* 6.6 Hz, 4-CH_2), 6.7—5.6 (2 H, m, COCH and 6′-CH_2), 5.00 (1 H, m, 2′-H), 0.42 (1 H, s, 5-OH), and −4.22 (1 H, s, chelated 7-OH).

(B) The experiment was repeated using concentrated hydrochloric acid (1 drop) as catalyst. Isolation of the product in a similar manner gave the chroman (57), identical to the above sample.

(C) The experiment was repeated using 2,3-dihydropyran (1 ml) as solvent and toluene-*p*-sulphonic acid (0.01 g) as catalyst. Again the product was the *C*-alkylated chroman (57).

Action of 2,3-Dichloro-5,6-dicyanobenzo-1,4-quinone (DDQ) on Protected Derivatives of 8-Isobutyryl-5,7-dihydroxy-2,2-dimethyl-chroman (42).—*General method.* A solution of the chroman (0.001 mol) and DDQ (0.001 mol) in dry benzene (25 ml) was heated under reflux for 1 h and then cooled. Any precipitate was removed by filtration and the filtrate evaporated. The residue was chromatographed on a column of silica gel and the fraction first eluted with chloroform was collected. The solvent was evaporated and, when possible, the residue was recrystallized from a suitable solvent and its i.r. and n.m.r. spectra determined.

(i) *8-Isobutyryl-7-hydroxy-5-methoxy-2,2-dimethylchroman* (49). This compound (5 g) reacted with DDQ (4.5 g) under the above conditions to give a bright yellow solid (1.9 g) which was shown by n.m.r. to be a mixture of starting material and the corresponding 8-isobutyryl-7-hydroxy-5-methoxy-2,2-dimethylchromen (21) in the ratio 1 : 2.

When a solution of the reactants in benzene was stirred overnight at room temperature, a mixture of similar composition to that above was obtained but the yield (3.3 g) was much improved. The percentage of chromen in the mixture could not be improved either by distillation or by fractional crystallization from methanol or light petroleum.

A sample of the above mixture (9 g) in benzene (50 ml) was stirred overnight at room temperature with DDQ (4.5 g) and after filtration the solvent was evaporated. The residue was extracted with boiling light petroleum (3 × 50 ml) to leave a pale brown solid (7 g). This material crystallized from ethanol to give 3-(2,3-*dichloro*-5,6-*dicyano*-4-*hydroxyphenoxy*)-7-*hydroxy*-8-*isobutyryl*-5-*methoxy*-2,2-*dimethyl*-2H-*chromen* (62) (5 g) as yellow prisms, m.p. 246—247 °C (Found: C, 57.5; H, 4.2; N, 5.45; Cl, 14.15%; M^+, 502.068 6. $C_{24}H_{20}N_2O_6Cl_2$ requires C, 57.25; H, 4.0; N, 5.55; Cl, 14.1%. $C_{24}H_{20}N_2O_6\ ^{35}Cl_2$ requires *M*, 502.069 8); $\nu_{max.}$ ($CHCl_3$) 3 500w, 3 400—2 400, 2 250w, 1 665, 1 620, 1 590, 1 450, 1 425, 1 275, 1 160, and 1 105 cm^{-1}; τ[$(CD_3)_2CO$] 8.75 (6 H, d, *J* 7 Hz, $CHMe_2$), 8.19 (6 H, s, CMe_2), 6.23 (3 H, s, OMe), 6.05 (1 H, sept, *J* 7 Hz, COCH), 5.00 (1 H, s, 4′-OH), 4.45 (1 H, s, 3-H), and 3.90 (1 H, s, 6-H); τ($CDCl_3$), 8.76 (6 H, d, *J* 7 Hz, $CHMe_2$), 8.25 (6 H, s, CMe_2), 7.1 (1 H, br s, 4′-OH), 6.20 (s) and 6.20 (m) (4 H, OMe and COCH), 4.72 (1 H, s, 3-H), 3.92 (1 H, s, 6-H), and −3.70 (1 H, s, chelated 7-OH).

The light petroleum extracts were evaporated and the residue chromatographed as in the general method. The yellow solid (4 g) obtained was shown by n.m.r. to be a mixture of chroman (49) and chromen (21) in the improved ratio 1 : 3.

This mixture was again treated with DDQ at room temperature and the product isolated in the normal manner. Examination of the yellow solid obtained (1 g) by n.m.r. spectroscopy showed that there had been no further improvement in the concentration of the chromen (21).

(ii) *8-Isobutyryl-7-hydroxy-5-methoxymethyleneoxy-2,2-dimethylchroman* (54). This gave a yellow solid (0.16 g, 53%) which was shown by n.m.r. to be a mixture of chroman and the corresponding 8-isobutyryl-7-hydroxy-5-methoxymethyleneoxy-2,2-dimethylchromen (55) in the ratio 1 : 5. Recrystallization from methanol gave yellow prisms, m.p. 76—77 °C (Found: C, 66.5; H, 7.05. $C_{27}H_{22}O_5$ requires C, 66.7; H, 7.2%), but n.m.r. indicated that the chromen content of the mixture had not been improved.

The experiment was repeated using the chroman (54) (15 g) and DDQ (11.5 g) and the crude product chromatographed on silica gel. Elution with benzene gave a mixture of chroman (54) and chromen (55) (5.5 g) in the ratio 1 : 4. Further elution with benzene gave a yellow solid (1.1 g) which crystallized from dimethylformamide to give *1,4-bis-(8-isobutyryl-7-hydroxy-5-methoxymethyleneoxy-2,2-dimethyl-2H-chromen-3-yloxy)-2,3-dichloro-5,6-dicyanobenzene* (67) (0.6 g) as yellow prisms, m.p. 252 °C (decomp.) (Found: C, 60.6; H, 4.95; N, 3.3; Cl, 8.7%; M^+, 836.209 9. $C_{42}H_{42}O_{12}Cl_2N_2$ requires C, 60.25; H, 5.05; N, 3.35; Cl, 8.45. $C_{42}H_{42}O_{12}{}^{35}Cl_2N_2$ requires *M*, 836.211 4); $\nu_{max.}$ 3 500—2 500, 1 665, 1 625, 1 585, 1 265, 1 155, 1 130, 1 100, 1 065, 960, and 950 cm^{-1}; τ($CDCl_3$) (Varian HA-100 spectrometer) 8.77 (12 H, d, *J* 7 Hz, 2 × $CHMe_2$), 8.22 (12 H, s, 2 × CMe_2), 6.58 (6 H, s, 2 × OMe), 6.2 (2 H, sept, *J* 7 Hz, 2 × COCH), 4.87 (4 H, s, 2 × OCH_2O), 4.72 (2 H, s, 2 × 4-H), 3.72 (2 H, s, 2 × 6-H), and −3.60 (2 H, s, 2 × chelated 7-OH).

(iii) *Dihydrouliginosin B* (7). Compound (7) (0.32 g) gave a pale yellow solid (0.07 g), which was shown by n.m.r. to be a mixture of starting material and a small amount of uliginosin B; the chromen CH=CH signals were present but were too weak to be accurately integrated.

Synthesis of 6-Isobutyryl-5,7-dihydroxy-2,2-dimethyl-2H-chromen (13) *and 8-Isobutyryl-5,7-dihydroxy-2,2-dimethyl-2H-chromen* (12).—DDQ (3.0 g, 0.014 mol) in dry benzene (20 ml) was added over 20 min to a refluxing solution of 2′,4′,6′-trihydroxy-3′-(3-methylbut-2-enyl)isobutyrophenone (60) (5.28 g, 0.02 mol) in benzene (120 ml). The precipitated hydroquinone was removed by filtration, the filtrate evaporated, and the residue chromatographed on a column of silica gel. Elution with benzene gave a broad yellow band shown by t.l.c. to be principally one compound, giving a spot which had an identical R_F value to 6-isobutyrylchroman (43), but which gave a much darker purple colour with Fast Blue Salt B than the chroman. Later fractions were contaminated by a second compound giving a spot with an identical R_F value to 8-isobutyrylchroman (42) but which again gave a much darker purple colour with Fast Blue Salt B than this chroman. Those fractions which were shown to be principally the former compound were combined and evaporated and the residue crystallized from cyclohexane to give *6-isobutyryl-5,7-dihydroxy-2,2-dimethyl-2H-chromen* (13) (0.1 g, 2.7%) as yellow needles, m.p. 120—121 °C (Found: C, 68.3; H, 7.0. $C_{15}H_{18}O_4$ requires C, 68.75; H, 6.9%); $\lambda_{max.}$ (acid EtOH) 273 and 294 nm; $\lambda_{max.}$ (alkaline EtOH) 242, 291, and 395 nm; $\nu_{max.}$ ($CHCl_3$) 3 550—2 200, 1 620, 1 425, 1 385, 1 220(br), 1 150, and 895 cm^{-1}; τ($CDCl_3$) 8.85 (6 H, d, *J* 7 Hz, $CHMe_2$), 8.61 (6 H, s, CMe_2), 6.2 (1 H, sept, *J* 7 Hz,

COCH), 4.66 (1 H, d, J 10 Hz, 3-H), 4.30 (1 H, s, 8-H), 3.47 (1 H, d, J 10 Hz, 4-H), 2.68 (1 H, s, OH), and −3.30 (1 H, s, chelated OH).

Further elution with 2% ether in benzene gave a second yellow band which was a mixture of the same two compounds. The fractions were therefore combined and re-chromatographed as above. The fraction eluted by benzene gave the above chromen (13) (0.05 g) as a tar. The fraction eluted by 2% ether in benzene gave a yellow gum (0.6 g) which crystallized from cyclohexane to give *8-isobutyryl-5,7-dihydroxy-2,2-dimethyl-2H-chromen* (12) (0.3 g, 8%) as yellow prisms, m.p. 102—103 °C (Found: C, 68.5; H, 7.1. $C_{15}H_{18}O_4$ requires C, 68.75; H, 6.9%); $\lambda_{max.}$ (acid EtOH) 279.5 nm; $\lambda_{max.}$ (alkaline EtOH) 290 and 327 nm; $\nu_{max.}$ ($CHCl_3$) 3 560—2 300, 1 640, 1 610, 1 425, 1 385, 1 260, 1 150, 1 120, 1 095, 1 005, and 885 cm^{-1}; τ($CDCl_3$) 8.85 (6 H, d, J 7 Hz, $CHMe_2$), 8.55 (6 H, s, CMe_2), 6.2 (1 H, sept, J 7 Hz, COCH), 4.70 (1 H, d, J 10 Hz, 3-H), 4.16 (1 H, s, 6-H), 3.57 (1 H, d, J 10 Hz. 4-H), 3.20 (1 H, s, 5-OH), and −3.85 (1 H, s, chelated 7-OH).

Synthesis of Uliginosin B-iBiB (4).—(*i*) A solution of DDQ (0.69 g) in benzene (10 ml) was added over 30 min to a stirred solution of uliginosin A-iBiB (1) (1.5 g) in benzene (50 ml). The precipitated hydroquinone was removed, the filtrate evaporated, and the residue chromatographed on a column of silica gel. Elution with benzene–light petroleum (2.5 : 1) gave a broad yellow band, which on t.l.c. gave a spot with an R_F value similar to that of dihydrouliginosin B (7). Further elution gave a mixture of this compound and one with a similar R_F to isodihydrouiliginosin B (9). However, with the spray reagent Fast Blue Salt B the spots gave a more intense blue colour than the corresponding chromans (7) and (9) [isodihydrouliginosin B (9) and dihydrouliginosin B (7) give faint pink colours with this reagent whilst uliginosin A (1) gives a deeper colour]. Later fractions gave the second material in a nearly pure state. The fractions containing principally the former compound were collected and the solvent evaporated. Treatment of the residue with ethanol gave *uliginosin B-iBiB* (4) (0.12 g, 8%) as yellow plates, m.p. 142.5—143.5 °C (from ethanol–nitromethane), mixed m.p. 141—142 °C (lit.,[3] 142 °C), (Found: C, 67.2; H, 7.0. $C_{28}H_{34}O_8$ requires C, 67.45; H, 6.9%); $\lambda_{max.}$ (cyclohexane) 231 (ε 29 000) and 270 nm (34 590); $\nu_{max.}$ (CCl_4) 3 400—2 200, 3 150, 2 650, 1 640, 1 605, 1 470, 1 430, 1 305, 1 365, 1 285, 1 200, 1 135, and 925 cm^{-1}; τ(CCl_4) 8.80 (12 H, d, J 7 Hz, 2 × $CHMe_2$), 8.5 (12 H, s, $OCMe_2$ and CMe_2), 6.51 (2 H, s, methylene bridge), 6.4—5.6 (2 H, m, 2 × COCH), 4.65 (1 H, d, J 10 Hz, chromen 3-H), 3.32 (1 H, d, J 10 Hz, chromen 4-H), 0.00 (1 H, s, OH), −1.18 (1 H, s, OH), −6.40 (1 H, s, OH), and −8.79 (1 H, s, OH).

The fractions containing principally the second compound were collected and the solvent evaporated off. Treatment of the residue with light petroleum gave *isouliginosin B-iBiB* (8) (0.23 g, 15%) as yellow prisms, m.p. 165—167 °C (from ethyl acetate) (Found: C, 67.2; H, 6.8%; M^+, 498.225 5. $C_{28}H_{34}O_8$ requires C, 67.45; H, 6.9%; M, 498.225 3); $\nu_{max.}$ (CCl_4) 3 400—2 200, 3 220, 2 700, 1 640, 1 605, 1 470, 1 430, 1 385, 1 285, 1 240, 1 195, 1 130, and 1 005 cm^{-1}; τ(CCl_4) 8.84 (12 H, d, J 7 Hz, 2 × $CHMe_2$), 8.51 (s) and 8.48 (s) (12 H, $OCMe_2$ and CMe_2), 6.55 (2 H, s, methylene bridge), 5.98 (2 H, sept, J 7 Hz, 2 × COCH), 4.65 (1 H, d, J 10 Hz, chromen 3-H), 3.40 (1 H, d, J 10 Hz, chromen 4-H), 1.15 (1 H, s, OH), −1.40 (1 H, s, OH), −3.80 (1 H, s, OH), and −8.35 (1 H, s, OH).

(*ii*) Sodium hydride (0.057 g), 8-isobutyryl-5,7-dihydroxy-2,2-dimethyl-2*H*-chromen (12) (0.3 g), and albaspidin-iBiB (11) (0.28 g) were heated under reflux in ethanol (10 ml) for 45 min and the product isolated in the usual manner.[1] Treatment of the crude product with cold ethanol gave uliginosin B-iBiB (36) (0.15 g, 51%) identical with that obtained, above, by oxidative cyclization of uliginosin A-iBiB (1).

Uliginosin B-iBiV (6) *and Isouliginosin B-iBiV* (9).—Uliginosin A-iBiV (3) (0.76 g) was treated with DDQ (0.34 g) and the products isolated by column chromatography as described above. Evaporation of the first fractions gave *uliginosin B-iBiV* (6) (0.2 g, 26%) as yellow prisms, m.p. 143—145 °C (from ethanol) (Found: C, 67.75; H, 7.1; M^+, 512.240 9. $C_{29}H_{36}O_8$ requires C, 67.95; H, 7.1%, M, 512.2 410); $\nu_{max.}$ (CCl_4) 3 400—2 200, 3 150, 2 650, 1 645, 1 605, 1 480, 1 430, 1 365, 1 200, 1 135, and 925 cm^{-1}; τ(CCl_4) 9.04 (6 H, d, J 7 Hz, CH_2CHMe_2), 8.84 (6 H, d, J 7 Hz, $COCHMe_2$), 8.55 (12 H, s, $OCMe_2$ and CMe_2), 8.2—7.5 (1 H, m, CH_2CHMe_2), 7.13 (2 H, d, J 7 Hz, $COCH_2$), 6.60 (2 H, s, methylene bridge), 5.9 (1 H, sept, J 7 Hz, COCH), 4.75 (1 H, d, J 10 Hz, chromen 3-H), 3.50 (1 H, d, J 10 Hz, chromen 4-H), 0.26 (1 H, s, OH), −0.90 (1 H, s, OH), −5.95 (1 H, s, OH), and −8.32 (1 H, s, OH).

Evaporation of the latter fractions gave *isouliginosin B-iBiV* (9) (0.1 g, 13%) as yellow prisms, m.p. 150—151 °C (from light petroleum) (Found: C, 67.6; H, 7.05%; M^+, 512.241 9. $C_{29}H_{36}O_8$ requires C, 67.95; H, 7.1%; M, 512.241 0); $\nu_{max.}$ (CCl_4) 3 500—2 200, 3 220, 2 650, 1 640, 1 605, 1 470, 1 430, 1 385, 1 365, 1 295, 1 195, 1 160, 1 120, 1 005, and 885 cm^{-1}; τ(CCl_4) 9.08 (6 H, d, J 7 Hz, CH_2CHMe_2), 8.86 (6 H, d, J 7 Hz, $COCHMe_2$), 8.57 (s) and 8.54 (s) (12 H, $OCMe_2$ and CMe_2), 8.3—7.6 (1 H, m, CH_2CHMe_2) 7.06 (2 H, d, J 7 Hz, $COCH_2$), 6.61 (2 H, s, methylene bridge), 5.9 (1 H, sept, J 7 Hz, COCH), 4.71 (1 H, d, J 10 Hz, chromen 3-H), 3.40 (1 H, d, J 10 Hz, chromen 4-H), 1.10 (1 H, s, OH), −1.28 (1 H, s, OH), −3.86 (1 H, s, OH), and −8.72 (1 H, s, OH).

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REFERENCES

[1] Part 1, T. Meikle and R. Stevens, *J.C.S. Perkin I*, 1978, 1303.
[2] H. L. Taylor and R. M. Brooker, *Lloydia*, 1969, **32**, 217.
[3] W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, 1968, **90**, 4716.
[4] F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, p. 220.
[5] E. E. Schweizer and D. Meeder-Nycz in 'Chromenes, Chromanones, and Chromones,' ed. G. P. Ellis, Wiley, New York, 1977, p. 11.
[6] W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *J. Chem. Soc.* (*C*), 1971, 811, and references cited therein.
[7] R. Huls and S. Brunelle, *Bull. Soc. chim. belges*, 1959, **68**, 325.
[8] W. Bencze, J. Eisenbeiss, and H. Schmid, *Helv. Chim. Acta*, 1956, **39**, 923.
[9] J. Hlubucek, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1971, **24**, 2347.
[10] G. F. Hennion and A. P. Boisselle, *J. Org. Chem.*, 1961, **26**, 725.

[11] E. M. Kampouris, *J. Chem. Soc.*, 1965, 2651; *J. Chem. Soc.* (*C*), 1968, 2125.
[12] W. J. G. Donnelly and P. V. R. Shannon, *J.C.S. Perkin I*, 1972, 25.
[13] G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24**, 4825.
[14] W. D. Ollis and I. O. Sutherland, ' Recent Developments in the Chemistry of Natural Phenolic Compounds,' Pergamon Press, London, 1961, p. 84.
[15] I. R. Campbell, C. H. Calzadilla, and N. J. McCorkindale, *Tetrahedron Letters*, 1966, 5170.
[16] G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1971, **27**, 1875.
[17] T. Meikle and R. Stevens, *Tetrahedron Letters*, 1972, 4787.
[18] C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, 1966, **49**, 164.
[19] T. Meikle, Ph.D. Thesis, C.N.A.A., 1975.
[20] H. D. Becker, *J. Org. Chem.*, 1965, **30**, 982, 989; 1969, **34**, 1198, 1203, 1211.
[21] A. B. Turner, *Chem. and Ind.*, 1976. 1030.