Chromens and Citrans derived from Phloroacetophenone and Phloroglucinaldehyde by Citral Condensation: Regioselectivity, Mechanism, and *X*-Ray Crystal Structures

By **Michael J. Begley, Leslie Crombie,* Richard W. King, David A. Slack,** and **Donald A. Whiting,*** Department of Chemistry, University of Nottingham, Nottingham NG7 2RD

The monochromen produced by low-temperature pyridine-catalysed condensation of phloroacetophenone with citral has structure (15), not the isomeric structure (17): on further heating of compound (15), or by direct reaction at higher temperature, two isomeric citrans (5) and (7) (8 : 1) are formed. Similar conclusions are reached for the chromen and citrans from phloroglucinaldehyde. The structure of the major acetyl citran (5) and of the major formyl citran (6) are established by *X*-ray studies of these strained species in which the aromatic ring assumes a shallow 'boat' form. During heating in pyridine, the chromens (15) and (16) isomerise to the chromens (17) and (18), which undergo more ready electrocyclisation giving the citrans (5) and (6), respectively: a mechanistic scheme is proposed.

Investigation of the acid-catalysed cyclisation of the chromen (15) shows that the citran (7) and the isopropenyl compound (38) are formed: no evidence to support a citran rearrangement in this reaction was found.

A WIDE variety of structural form is shown by natural meroterpenoids derived from monoterpenes and phenols. Apart from the corresponding chromens these include the tetracyclic 'citran' (1) and 'cyclol' (2) units found in bruceol,[1] deoxybruceol,[2] eriobrucinol and hydroxyeriobrucinol,[2] rubranine,[3] cannabicitran,[4,5] cannabicyclol,[4,6] and carbazole alkaloids such as mahanimbidine [7,8] (curryangin or murrayazoline) and bicyclomahanimbine.[8] We have previously demonstrated the synthesis of such structures through the pyridine-catalysed chromenylation of resorcinols with citral, followed by further cyclisation.[4,9-12] During this work [13] we became conscious of insecurities in the assignment of orientations in this field. Thus, the assignment of structure (4) to rubranine [3] rests on its synthesis,[10] which involves citral–pinocembrin (3) condensation, and proceeds through the chromen (9). However, structure (4) for rubranine follows only if further cyclisation of (9) proceeds without rearrangement. Although structure (4) emerges as sound, the present work shows that this type of premise is untenable in certain cases. Another stimulus was that the citral–pyridine reactions with acetylphloroglucinol (10) [14,15] and 5,7-dihydroxycoumarin (11) [9] were reported to form the citrans (5) and (12), respectively, *i.e.* to form products of different terpenoid orientation despite electronic factors in structures (10) and (11) which would be expected to cause similar behaviour.

For these reasons, and because of the necessity to establish structures for further synthetic work, we examined in detail the pyridine-catalysed reactions of citral with acetyl- and formyl-phloroglucinol. In this paper we report the structures of the resulting chromens and citrans; in the course of the work a new rearrangement has been uncovered.

Condensation of acetylphloroglucinol with citral (1 mol. equiv.) and pyridine at 110 °C for 6 h gave three products, the bischromen (13) and a mixture (76%) of the two citrans (5) and (7) (8 : 1 by ^{1}H n.m.r. analysis). The major isomer (5) was purified by repeated crystallisation and had spectroscopic data closely similar to those reported by Winternitz *et al.*[15] and by Kane and Grayek.[14] These authors, using the same reaction, did not observe the minor citran (7) and adopted structure (5) for the major product on the basis of its identity with the product (5) from retro-aldolisation of rubranine (4).[3] Structure (4) for the latter rests in turn on earlier chemical evidence [10] and we have now set it on a firmer foundation by *X*-ray analysis of the citran (5), m.p. 138—140° (see Figure 1 and discussion later). With structure (5) confirmed, structure (4) for rubranine is also confirmed, since the two compounds are interconvertible by aldol or retro-aldol reactions involving benzaldehyde.

The citral-resacetophenone condensation was then repeated using the same reactant ratios, but at 40 °C for 16 h. Products (5), (7), and (13) were obtained, but in addition a monochromen (31%) was isolated. Most spectroscopic data for this compound matched those reported,[15,16] except that two phenolic hydroxy-resonances at τ 1.90 and −3.78 were noted in place of the single

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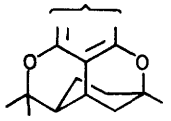
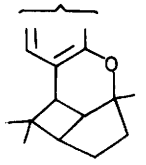
[8] S. P. Kureel, R. S. Kapil, and S. P. Popli, *Tetrahedron Letters*, 1969, 3857.
[9] L. Crombie and R. Ponsford, *J. Chem. Soc.* (*C*), 1971, 788.
[10] W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *J. Chem. Soc.* (*C*), 1971, 804.
[11] W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 998.
[12] D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 1007.
[13] M. J. Begley, L. Crombie, R. W. King, D. A. Slack, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1976, 138; L. Crombie, D. A. Slack, and D. A. Whiting, *ibid.*, p. 139; M. J. Begley, L. Crombie, D. A. Slack, and D. A. Whiting, *ibid.*, p. 141.
[14] V. V. Kane and T. L. Grayek, *Tetrahedron Letters*, 1971, 3991.
[15] J. L. Montero and F. Winternitz, *Tetrahedron*, 1973, **29**, 1243; G. Combes, J. L. Montero, and F. Winternitz, *Compt. rend.* (*C*), 1972, 1313.
[16] J. L. Montero, Thesis, Montpellier, 1973.

resonance at −3.80. These, and a bathochromic u.v. shift of +36 nm in basic solution, tend to support structure (15) for this chromen rather than the 2′,6′-dihydroxyacetophenone version (17). To confirm the structure, the chromen was monomethylated (81%) with diazomethane and the product was compared with the monochromen obtained (74%) by condensing 2′,6′-dihydroxy-4′-methoxyacetophenone (19) with citral in pyridine at 90 °C. This second chromen can only have structure (22), and the diazomethane product proved to be identical with it [i.r., u.v., and ^{1}H and ^{13}C n.m.r. spectra; formation of the same monoacetate (23) and *p*-nitrobenzoate (24), m.p. 89—91°]. Chromenylation of 2′,4′-dihydroxy-6′-methoxyacetophenone (20) gave the crystalline isomer (25), m.p. 88—90°, with spectroscopic data clearly different from those of (22). The structure (25) followed from shifts of the chromen proton resonances on acetylation to (26).

Similar reactions were then examined for phloroglucinaldehyde (27). With citral and pyridine at 110 °C, two formylcitrans (6) and (8) (6 : 1) were obtained; this pair



(1)



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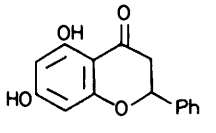
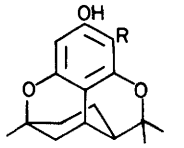
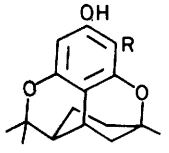


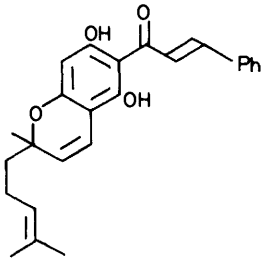
(3)



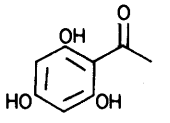
(4) R = CO·CH
(5) R = CO·CH=CH·Ph
(6) R = CHO



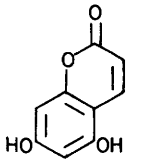
(7) R = COMe
(8) R = CHO



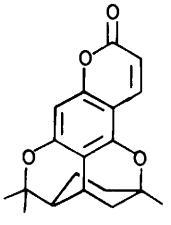
(9)



(10)



(11)



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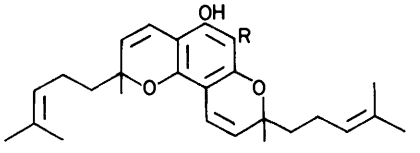
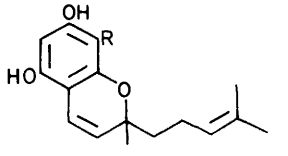
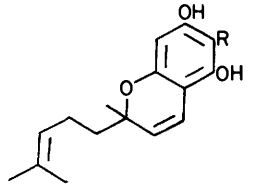


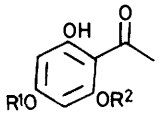
(13) R = COMe
(14) R = CHO



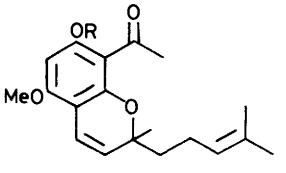
(15) R = COMe
(16) R = CHO



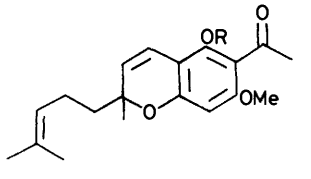
(17) R = COMe
(18) R = CHO



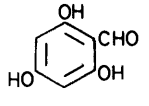
(19) R^1 = Me, R^2 = H
(20) R^1 = H, R^2 = Me
(21) R^1 = R^2 = Me



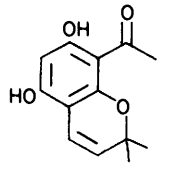
(22) R = H
(23) R = COMe
(24) R = CO·C_6H_4·NO_2-*p*



(25) R = H
(26) R = COMe



(27)



(28)

could be separated by t.l.c. (multiple elution), and were thus isolated. The structure of the major isomer (6) was solved from *X*-ray data using direct phase-determining

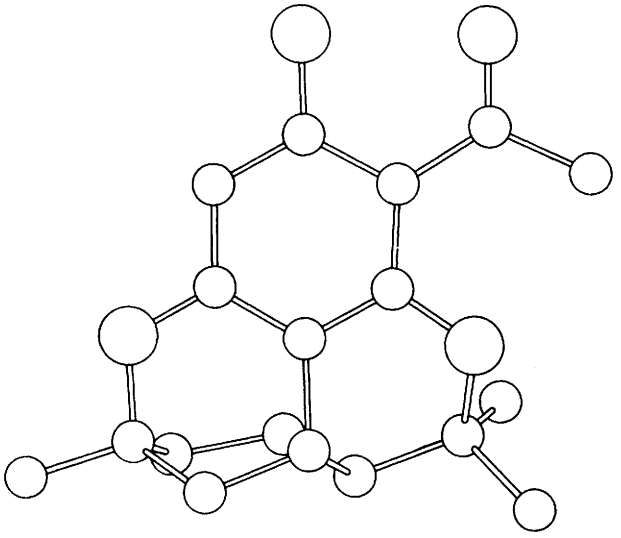


FIGURE 1 *X*-Ray structure of acetylcitran (5)

methods (Figure 2). Repeating the condensation at 40 °C for 16 h enabled the isolation of the intermediate formylmonochromen, as well as the bischromen (14).

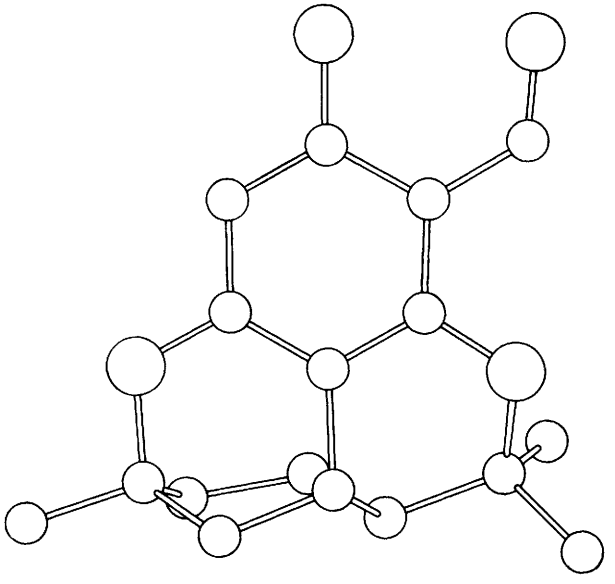


FIGURE 2 *X*-ray Structure of formylcitran (6)

The former was assigned structure (16) on the grounds of the close parallel between its spectroscopic data and those for (15): particularly relevant are the hydroxy-resonances at τ 1.87 and −1.94, and the bathochromic u.v. shift of 36 nm on basification. Both (15) and (16) gave only weak light absorption (500—700 nm) in the Gibbs reaction, as required by the proposed structures.

From these results it appears that the initial chromenylation of phloroacetophenone and phloroglucinaldehyde is essentially regiospecific, leading to an orientation opposite to that found in the citrans produced in a higher temperature reaction. In a related reaction between phloroacetophenone and 4,4-dimethoxy-2-methylbutan-2-ol the major product is reported to be (28), *i.e.* the orientation is parallel to those of (15) and (16), though here the second chromen isomer was detected by n.m.r.[17] Heating the chromens (15) and (16) in pyridine at 110 °C led to the same citran products as obtained from a direct aldehyde–phenol reaction at this temperature. Thus a chromen rearrangement is involved and the situation, and its proposed explanation, are summarised in Scheme 1.

In hot pyridine, the chromens (15) and (16) equilibrate with the ketonic isomer (30) from which the minor citran products (7) and (8) are formed by intramolecular Diels–Alder reaction as discussed earlier.[18,*] However, (15) and (16) are also involved in reversible electrocyclic ring opening to (29) : *EZ*-isomerisation of the latter ensues to form (31), from which the isomeric chromens (17) and (18), and hence, *via* (32), the major citrans (5) and (6), arise. Prolonged heating of the isomeric citrans (8) and (6) separately, in pyridine, failed to bring about interconversion, so the Diels–Alder stages (30) ⟶ (8) and (32) ⟶ (6) must be essentially irreversible. The predominance of the citrans (5) and (6) relative to (7) and (8) reflects the chelate stabilisation of (32) relative to (30). A similar transition-state stabilising factor appears to govern orientations in the chromenylation reaction itself, as pointed out earlier.[12,18] A significant feature is that it operates in an alternative sense as between chromen and citran formation [*cf.* the bond localisation in (30) with that in (32)]. Because of reversibility between the chromens it is the unfavoured chromen orientation that leads to the favoured citran arrangement.

The crystal structures of the acetylcitran (5) and the formylcitran (6) mentioned earlier were determined by direct methods from four-circle diffractometer data (2 037 and 1 798 reflections, respectively) and refined by least-squares and difference-Fourier methods to $R = 4.2\%$ for (5) and 4.8% for (6). Crystallographic numbering for the two citrans is shown in Figure 3 and bond lengths and angles are displayed in Figures 4—7, together with an indication of their standard deviations. Bonding to hydrogen is not shown, but all C–H bond lengths were

* Cannon *et al.*[19] have recently reported the *X*-ray crystal structure of (35) formed by heating (33) at 230 °C. Its origins can be explained analogously to citran formation *via* electrocyclisation (34) as shown. The mechanism can also be applied to the cyclisation of mahanimbine to mahanimbidine.[20]

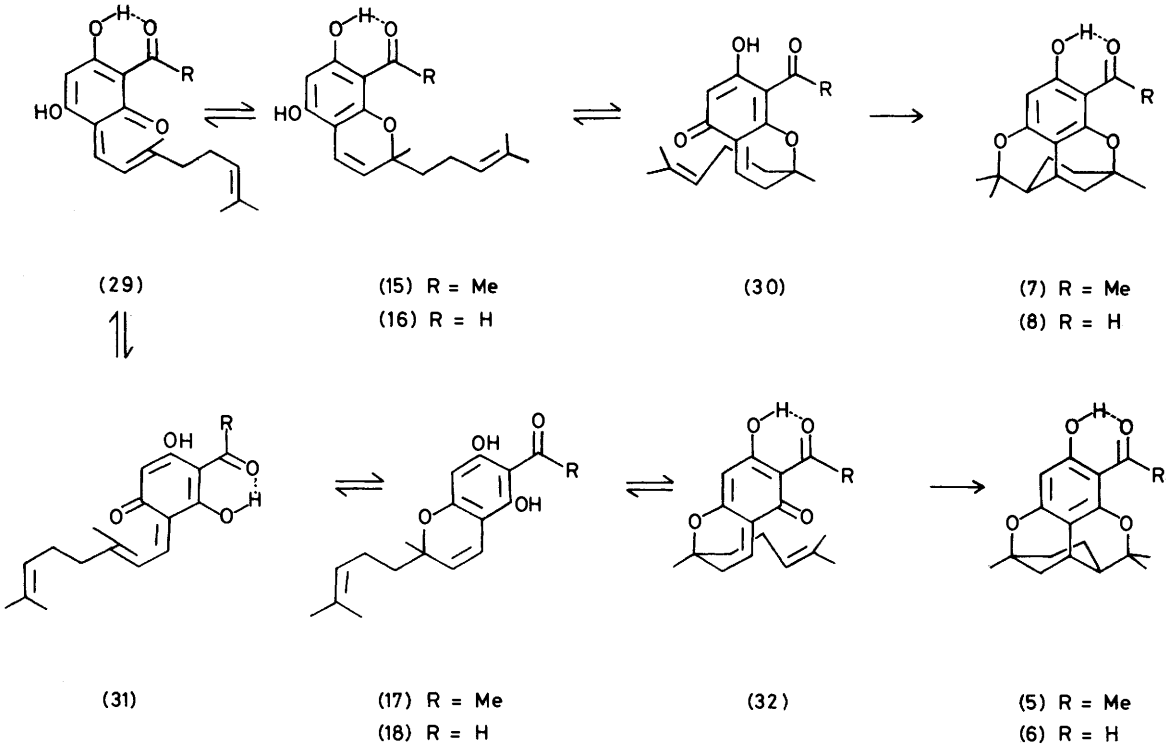
[17] W. J. G. Donnelley and P. V. R. Shannon, *J.C.S. Perkin I*, 1972, 25.

[18] D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1973, 580, 582.

[19] J. R. Cannon, I. A. McDonald, A. F. Sierakowski, A. H. White, and A. C. Willis, *Austral. J. Chem.*, 1975, **28**, 57.

[20] N. S. Narasimhan and S. L. Kelkar, *Indian J. Chem.*, 1976, 430.

in the range 0.91—1.08 Å (σ 0.03 Å) and all bond angles, at sp^3-hybridised carbon atoms involving hydrogen, were between 102 and 115° (σ 2°). No bond length or angle deviates significantly from its expected value, and the lengths and angles display remarkable consistency between the two citran structures. In each case an intra-



SCHEME 1

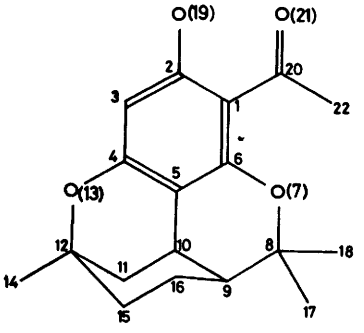


FIGURE 3 Crystallographic numbering scheme for acetyl- and formyl-citrans

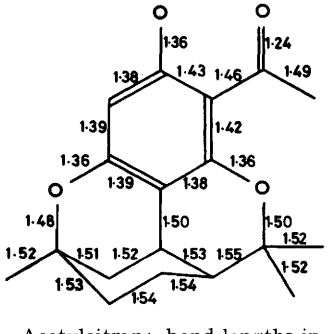


FIGURE 4 Acetylcitran: bond lengths in Å (largest standard deviation 0.003 Å)

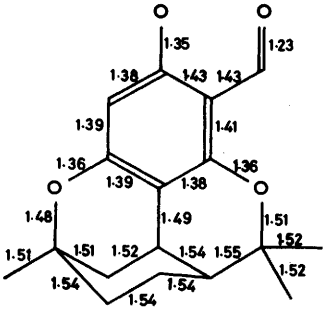


FIGURE 5 Formylcitran: bond lengths in Å (largest standard deviation 0.004 Å)

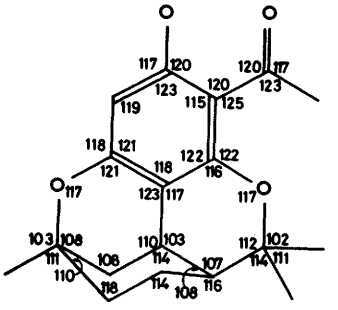


FIGURE 6 Acetylcitran: bond angles (degrees; largest standard deviation 0.03°); additional angles: O(7)–C(8)–C(17), 106°; C(9)–C(8)–C(18), 111°; C(11)–C(12)–C(14), 113°; O(13)–C(12)–C(15), 112°

molecular hydrogen bond was observed, OH(19)–O(21) 2.50 Å in the acetylcitran (5) and 2.61 Å in the formylcitran (6).

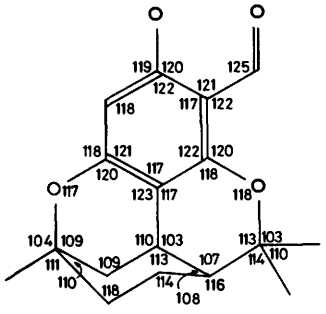


FIGURE 7 Formylcitran: bond angles (degrees; largest standard deviation 0.03°); additional angles: O(7)–C(8)–C(17), 105°; C(9)–C(8)–C(18), 111°; C(11)–C(12)–C(14), 113°; O(13)–C(12)–C(15), 111°

Torsion angles are displayed in Tables 1 and 2. These reveal the strained nature of the structures, with considerable deviation from idealised values: again there is excellent consistency within the data. The strain is demonstrated by a study of the mean plane through the aromatic ring which reveals considerable deviation from planarity. Thus C(2) and C(5) are 0.06 and 0.11 Å above the mean plane, respectively, with the remaining atoms, C(1) 0.02 Å, C(3) 0.01 Å, C(4) 0.07 Å, and C(6) 0.06 Å below the plane, thus producing an aromatic shallow ' boat ' conformation. Distortion at C(5) is indeed confirmed by the summation of the bond angles at that atom to 357.6°, a significant deviation from the 360° required for planarity. Oxygen atoms O(7) and O(13), directly linked to the phenyl ring, are displaced 0.28 and 0.35 Å, respectively, below the mean plane through the ring [C(1) to C(6)] by cyclisation.

The arrangement of molecules in the unit cell is shown in Figure 8 for the acetylcitran and Figure 9 for the formylcitran. These reveal the totally different packing of the two citrans, presumably due to the slight difference in overall molecular shape. No intermolecular contacts less than the sum of the van der Waals radii were discovered in either structure.

Our revision of the structure of the chromen obtained from citral and phloroacetophenone from (17) to (15) has other chemical repercussions. Thus, it has been reported that this chromen, on treatment with camphorsulphonic acid, gave three products formulated as the

TABLE 1

Torsion angles (degrees) for acetylcitran (5)

C(6)–C(1)–C(2)–C(3)	−5.7	C(6)–C(1)–C(2)–O(19)	178.7	C(20)–C(1)–C(2)–C(3)	174.1
C(20)–C(1)–C(2)–O(19)	−1.5	C(2)–C(1)–C(6)–C(5)	−5.6	C(2)–C(1)–C(6)–O(7)	173.6
C(20)–C(1)–C(6)–C(5)	174.7	C(20)–C(1)–C(6)–O(7)	−6.2	C(2)–C(1)–C(20)–O(21)	0.6
C(2)–C(1)–C(20)–C(22)	−179.3	C(6)–C(1)–C(20)–O(21)	−179.7	C(6)–C(1)–C(20)–C(22)	0.4
C(1)–C(2)–C(3)–C(4)	4.8	O(19)–C(2)–C(3)–C(4)	−179.4	C(2)–C(3)–C(4)–C(5)	7.3
C(2)–C(3)–C(4)–O(13)	−170.8	C(3)–C(4)–C(5)–C(6)	−18.2	C(3)–C(4)–C(5)–C(10)	179.3
O(13)–C(4)–C(5)–C(6)	159.9	O(13)–C(4)–C(5)–C(10)	−2.7	C(3)–C(4)–O(13)–C(12)	162.8
C(5)–C(4)–O(13)–C(12)	−16.3	C(4)–C(5)–C(6)–C(1)	17.3	C(4)–C(5)–C(6)–O(7)	−161.9
C(10)–C(5)–C(6)–C(1)	−179.1	C(10)–C(5)–C(6)–O(7)	1.7	C(4)–C(5)–C(10)–C(9)	106.4
C(4)–C(5)–C(10)–C(11)	−15.0	C(6)–C(5)–C(10)–C(9)	−56.4	C(6)–C(5)–C(10)–C(11)	−177.8
C(1)–C(6)–O(7)–C(8)	−136.2	C(5)–C(6)–O(7)–C(8)	43.0	C(6)–O(7)–C(8)–C(9)	−27.3
C(6)–O(7)–C(8)–C(17)	97.9	C(6)–O(7)–C(8)–C(18)	−146.1	O(7)–C(8)–C(9)–C(10)	−28.3
O(7)–C(8)–C(9)–C(16)	92.2	C(17)–C(8)–C(9)–C(10)	−148.8	C(17)–C(8)–C(9)–C(16)	−28.3
C(18)–C(8)–C(9)–C(10)	85.4	C(18)–C(8)–C(9)–C(16)	−154.1	C(8)–C(9)–C(10)–C(5)	66.1
C(8)–C(9)–C(10)–C(11)	−174.9	C(16)–C(9)–C(10)–C(5)	−59.6	C(16)–C(9)–C(10)–C(11)	59.4
C(8)–C(9)–C(16)–C(15)	−164.4	C(10)–C(9)–C(16)–C(15)	−44.3	C(5)–C(10)–C(11)–C(12)	47.9
C(9)–C(10)–C(11)–C(12)	−67.0	C(10)–C(11)–C(12)–O(13)	−65.8	C(10)–C(11)–C(12)–C(14)	−179.2
C(10)–C(11)–C(12)–C(15)	56.2	C(11)–C(12)–O(13)–C(4)	49.7	C(14)–C(12)–O(13)–C(4)	169.4
C(15)–C(12)–O(13)–C(4)	−71.1	C(11)–C(12)–C(15)–C(16)	−46.6	O(13)–C(12)–C(15)–C(16)	73.5
C(14)–C(12)–C(15)–C(16)	−172.2	C(12)–C(15)–C(16)–C(9)	41.4		

TABLE 2

Torsion angles (degrees) for formylcitran (6)

C(6)–C(1)–C(2)–C(3)	−5.7	C(6)–C(1)–C(2)–O(19)	179.0	C(20)–C(1)–C(2)–C(3)	173.5
C(20)–C(1)–C(2)–O(19)	−1.3	C(2)–C(1)–C(6)–C(5)	−5.8	C(2)–C(1)–C(6)–O(7)	171.8
C(20)–C(1)–C(6)–C(5)	175.0	C(20)–C(1)–C(6)–O(7)	−7.4	C(2)–C(1)–C(20)–O(21)	1.8
C(6)–C(1)–C(20)–O(21)	−179.1	C(1)–C(2)–C(3)–C(4)	4.4	O(19)–C(2)–C(3)–C(4)	179.7
C(2)–C(3)–C(4)–C(5)	8.4	C(2)–C(3)–C(4)–O(13)	−168.4	C(3)–C(4)–C(5)–C(6)	−19.3
C(3)–C(4)–C(5)–C(10)	178.9	O(13)–C(4)–C(5)–C(6)	157.4	O(13)–C(4)–C(5)–C(10)	−4.4
C(3)–C(4)–O(13)–C(12)	164.5	C(5)–C(4)–O(13)–C(12)	−12.3	C(4)–C(5)–C(6)–C(1)	17.8
C(4)–C(5)–C(6)–O(7)	−159.8	C(10)–C(5)–C(6)–C(1)	−179.3	C(10)–C(5)–C(6)–O(7)	3.1
C(4)–C(5)–C(10)–C(9)	106.2	C(4)–C(5)–C(10)–C(11)	−14.9	C(6)–C(5)–C(10)–C(9)	−55.7
C(6)–C(5)–C(10)–C(11)	−176.8	C(1)–C(6)–O(7)–C(8)	−139.0	C(5)–C(6)–O(7)–C(8)	39.6
C(6)–O(7)–C(8)–C(9)	−22.1	C(6)–O(7)–C(8)–C(17)	102.6	C(6)–O(7)–C(8)–C(18)	−142.0
O(7)–C(8)–C(9)–C(10)	−30.7	O(7)–C(8)–C(9)–C(16)	90.4	C(17)–C(8)–C(9)–C(10)	−150.6
C(17)–C(8)–C(9)–C(16)	−29.4	C(18)–C(8)–C(9)–C(10)	84.4	C(18)–C(8)–C(9)–C(16)	−154.5
C(8)–C(9)–C(10)–C(5)	66.0	C(8)–C(9)–C(10)–C(11)	−175.2	C(16)–C(9)–C(10)–C(5)	−59.9
C(16)–C(9)–C(10)–C(11)	58.9	C(8)–C(9)–C(16)–C(15)	−165.2	C(10)–C(9)–C(16)–C(15)	−44.6
C(5)–C(10)–C(11)–C(12)	48.4	C(9)–C(10)–C(11)–C(12)	−66.5	C(10)–C(11)–C(12)–O(13)	−64.9
C(10)–C(11)–C(12)–C(14)	−179.2	C(10)–C(11)–C(12)–C(15)	56.4	C(11)–C(12)–O(13)–C(4)	47.0
C(14)–C(12)–O(13)–C(4)	167.4	C(15)–C(12)–O(13)–C(4)	−73.5	C(11)–C(12)–C(15)–C(16)	−47.0
O(13)–C(12)–C(15)–C(16)	73.0	C(14)–C(12)–C(15)–C(16)	−172.6	C(12)–C(15)–C(16)–C(9)	41.8

citran (7) (15%), (36) (30%), and (37) (45%).[15] In order to rationalise these products of differing terpenoid orientation it was proposed[15] that the chromen, then thought to be (17), partly cyclised with retention of the

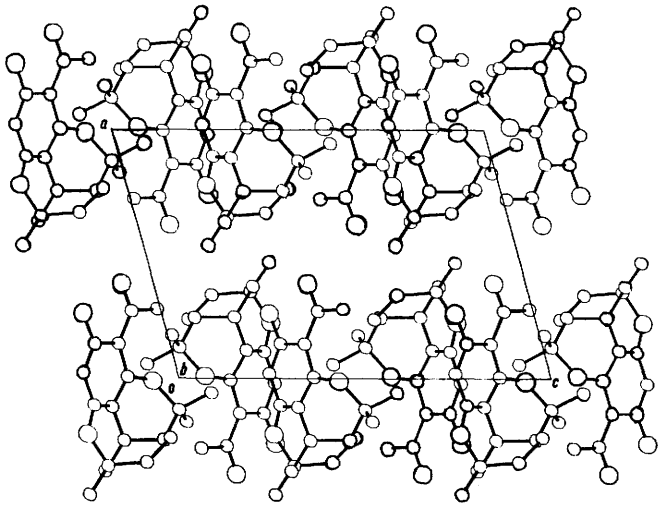


FIGURE 8 Acetylcitran: arrangement of molecules within the unit cell

original orientation and partly underwent rearrangement *via* a species [*cf.* (43)] which allowed rotation and reclosure in the opposite sense. With revision of the chromen structure (17) to (15) it is (37), not (7) or (36),

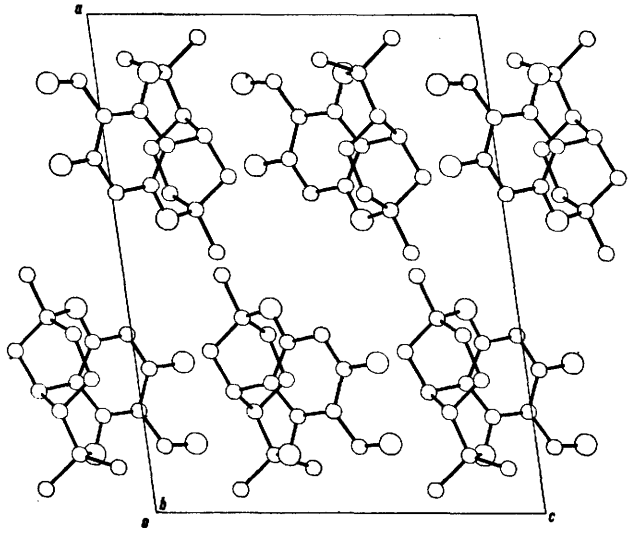
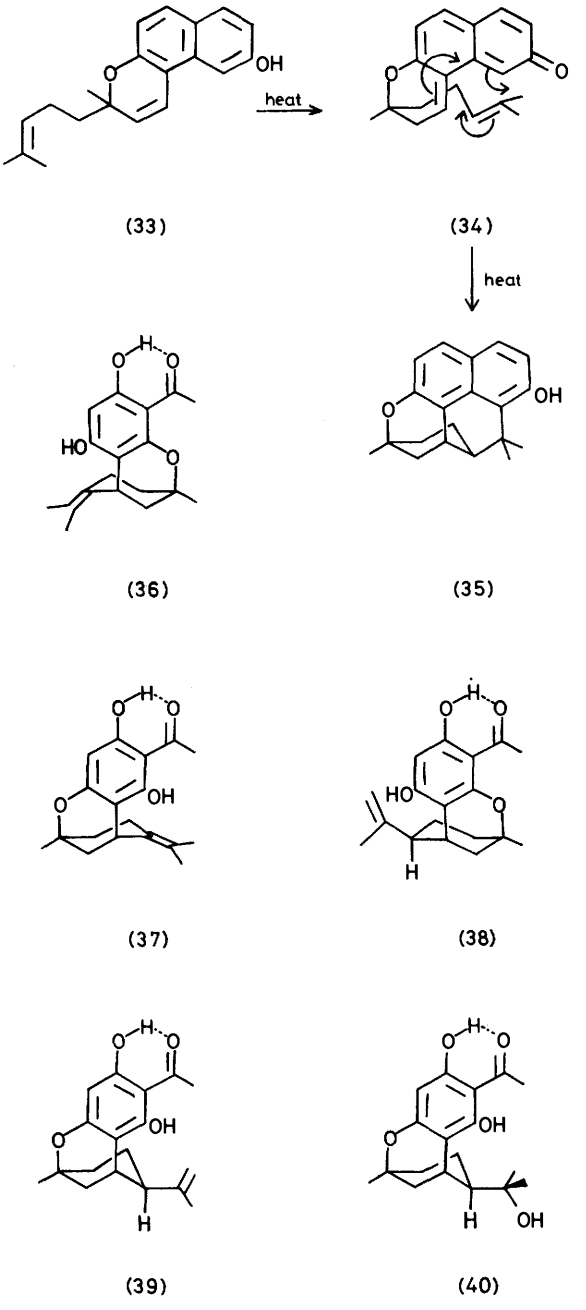


FIGURE 9 Formylcitran: arrangement of molecules within the unit cell

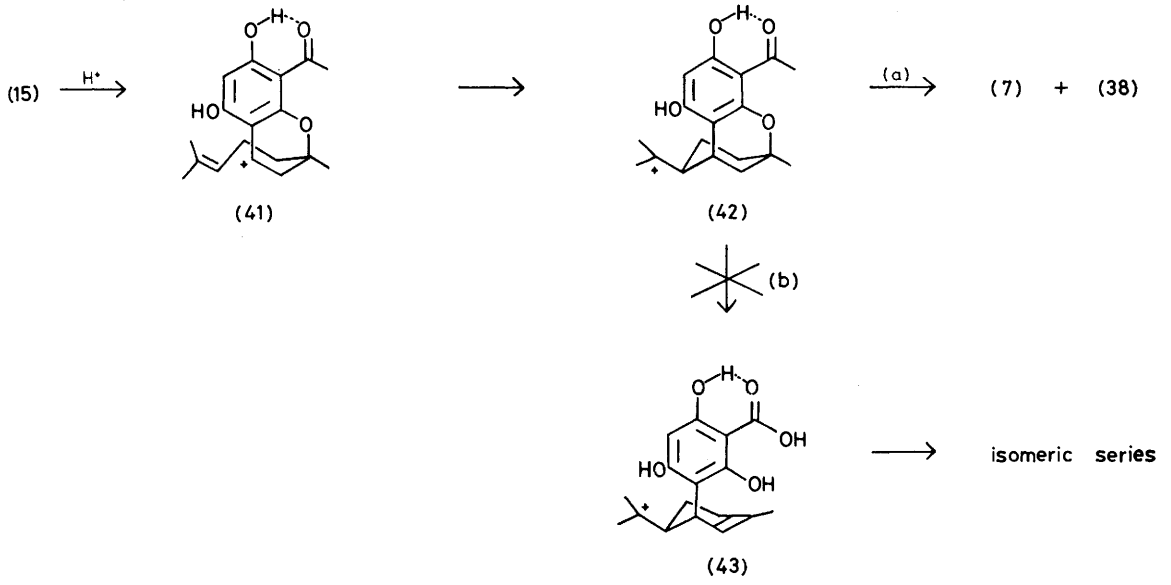
which becomes the unexpected rearranged product of acid-catalysed cyclisation.

In our laboratory, reaction of the chromen (15) with camphorsulphonic acid in benzene gave the citran (7) (36%), the isopropenyl compound (38) (37%) having the same terpenoid orientation as (7), and minor products, probably mainly of cyclol character (12%). To clear up the situation further, we have prepared both pairs of isopropylidene [(36) and (37)] and isopropenyl [(38) and (39)] isomers from the citrans (5) and (7). Thus the citran (5) with camphorsulphonic acid gave the isopropylidene derivative (37) together with the tertiary alcohol (40); with acetic acid the isopropenyl isomer of the same



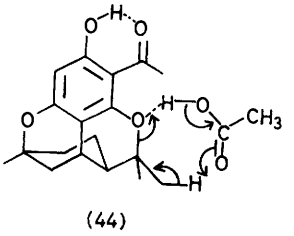
orientation (39) was obtained. Similarly (7) gave (36) and (38), and spectroscopic data support the four structures. None of our compounds [(36), m.p. 222—224°; (37), m.p. 143—145°; (38), m.p. 206—207°; (39), m.p. 182—184°] has characteristics compatible with those

reported for the anomalous product, m.p. 115—116° assigned structure (37). We thus have no evidence from our own work to support rearrangement in the products from acid-catalysed cyclisation of (15). Reaction proceeds as in Scheme 2, path (a), with protonation of the chromen to give the benzylic cation (41), which cyclises to the new ion (42) and may be trapped internally as (7) or deprotonated to (38); path (b) is not required. The production of the more stable isopropylidene isomer [(36) or (37)] from the citrans [(7) or (5)] by using a stronger acid is understandable: production of the isopropylidene



SCHEME 2

forms (38) and (39) with acetic acid suggests a reaction within associated molecules as shown (44).



EXPERIMENTAL

Analytical and spectroscopic data (n.m.r., u.v., and i.r.) for compounds described in this section are listed in Supplementary Publication No. SUP 22106 (28 pp.).* M.p.s were determined with a hot-stage microscope. Silica gel G was used in analytical t.l.c.; for preparative work, silica gel HF_{254} (1 mm layers) was employed. Organic solutions were dried over magnesium sulphate and evaporated at reduced pressure.

Reaction of 2,4,6-Trihydroxybenzaldehyde with Citral and Pyridine at 110 °C.—2,4,6-Trihydroxybenzaldehyde (1.54 g, 0.01 mol), citral (1.54 g, 0.01 mol), and pyridine (1.0 g, 0.013 mol) were heated at 110 °C with stirring for 6 h. The product was diluted with chloroform and chromatographed on silica gel HF_{254} plates [45 × 45 cm; elution with n-hexane–ether (3 : 1)]. Two products were isolated, the less polar of which, a pale yellow gum, was identified as the *bischromen* (14) (350 mg, 16%).

The more polar product was isolated as a white solid (1.90 g, 69%). Examination of the products obtained directly from the plates by n.m.r. indicated the presence of a mixture of the two formylcitrans (6) and (8) in the ratio 6 : 1. Repeated crystallisations from ethanol yielded the pure *citran* (6), m.p. 127—128°. This compound was subjected to *X*-ray analysis (below).

Examination of the mother liquors from the recrystallisations showed the presence of a mixture of the formylcitrans (6) and (8) in the ratio 2 : 1. Separation was achieved by t.l.c. (0.3 mm layers; multiple elution with hexane) to provide the minor *citran* (8), m.p. 143—145°.

Reaction of 2,4,6-Trihydroxybenzaldehyde with Citral and Pyridine at 40 °C.—2,4,6-Trihydroxybenzaldehyde (1.54 g, 0.01 mol), citral (1.54 g, 0.01 mol), and pyridine (1.0 g, 0.013 mol) were heated at 40 °C, with stirring, for 16 h. The solution was diluted with chloroform and chromatographed on silica gel HF_{254} [preparative plates, 45 × 45 cm; elution with n-hexane–ether (3 : 1)]. Two products were isolated: the less polar was identified as the formylbischromen (14) (380 mg, 18%), as above. The more polar product was isolated as a brown oil and was further purified by column chromatography [elution with n-hexane–ether (3 : 1)]. Evaporation yielded the *monochromen* (16), a pale yellow oil (804 mg, 28%), which darkened when subjected to further chromatography.

Action of Heat on the Formylmonochromen (16).—The monochromen (16) (150 mg, 0.000 52 mol) was heated with pyridine (100 mg, 0.001 2 mol) at 110 °C for 7 h. The solution was diluted with chloroform and chromatographed on silica gel HF_{254} [preparative plates, 20 × 20 cm; elution with chloroform–acetone (19 : 1)]. The major product was

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

obtained as a white solid (95 mg, 63%), identified by n.m.r. as a mixture of the two formylcitrans (6) and (8) in the ratio 6 : 1.

Reaction of 2′,4′,6′-Trihydroxyacetophenone with Citral and Pyridine at 110 °C.—2′,4′,6′-Trihydroxyacetophenone (1.68 g, 0.01 mol), citral (1.52 g, 0.01 mol), and pyridine (0.79 g, 0.01 mol) were heated at 110 °C, with stirring, for 6 h. T.l.c. indicated two products. The pyridine was evaporated off and the residual brown gum chromatographed on silica gel HF_{254} [preparative plates, 45 × 45 cm; elution with n-hexane–ether (3 : 1)]. Two products were isolated, the less polar of which, a pale yellow gum, was identified as the known [15] acetylbischromen (13) (410 mg, 19%). The more polar product was isolated as a white solid (2.3 g, 76%). Examination of the product directly from the plates by n.m.r. indicated the presence of a mixture of the two acetylcitrans (5) and (7) in the ratio 8 : 1.

Repeated crystallisations from ether–n-hexane yielded the citran (5), m.p. 138—140°; this specimen was subjected to *X*-ray analysis (see below). Its n.m.r. data were parallel to those reported [14,15] (lit., m.p. 140°).

Examination of the mother liquors from the recrystallisations showed the presence of a mixture of the acetylcitrans (5) and (7) in the ratio 3 : 2. The n.m.r. data for the acetylcitran (7) were identical with those for the compound obtained from acid-catalysed isomerisation of the monochromen (15).

Reaction of 2′,4′,6′-Trihydroxyacetophenone with Citral and Pyridine at 40 °C.—2′,4′,6′-Trihydroxyacetophenone (1.68 g, 0.01 mol), citral (1.52 g, 0.01 mol), and pyridine (0.79 g, 0.01 mol) were heated at 40 °C, with stirring, for 16 h. T.l.c. indicated three products. The solution was diluted with chloroform and chromatographed on silica gel HF_{254} [preparative plates, 45 × 45 cm; elution with n-hexane–ether (3 : 1)]. The least polar product was identified as the acetylbischromen (13) (704 mg, 32%). The product of intermediate polarity was identified as a mixture of the acetylcitrans (5) and (7) (440 mg, 15%). The most polar product was isolated as a dark orange oil and was further purified by column chromatography [elution with n-hexane–ether (3 : 1)]. Evaporation yielded the *acetylmonochromen* (15) as a pale yellow oil (931 mg, 31%).

Methylation of 2′,4′,6′-Trihydroxyacetophenone with Diazomethane.—2′,4′,6′-Trihydroxyacetophenone (10.0 g) was dissolved in dry ethanol (125 ml). The solution was cooled to 0 °C and ethereal diazomethane (containing *ca.* 2.8 g of diazomethane) was added dropwise with stirring. The solution was then left overnight at room temperature. T.l.c. indicated three products. The ether was evaporated off and the resulting yellow solid was chromatographed on a dry column of Woelm silica [elution with chloroform–acetone (19 : 1)]. The least polar compound was obtained as a pale yellow solid (483 mg), which crystallised from aqueous ethanol to yield 2′,4′-dimethoxy-6′-hydroxyacetophenone as needles, m.p. 82—84° (lit.,[21] 85—88°).

The second most polar compound was obtained as a yellow solid (2.50 g), which crystallised from aqueous ethanol to yield 2′,6′-dihydroxy-4′-methoxyacetophenone as needles, m.p. 138—139° (lit.,[21] 136—137°).

The most polar compound was obtained as a yellow solid (200 mg) which crystallised from aqueous ethanol to yield 2′,4′-dihydroxy-6′-methoxyacetophenone as white needles, m.p. 206—207° (lit.,[21] 205—207°).

Methylation of the Acetylmonochromen (15) *with Diazomethane.*—The acetylmonochromen (750 mg) was dissolved in dry ethanol (50 ml) and cooled to 0 °C. Ethereal diazomethane (100 ml containing *ca.* 0.5 g of diazomethane) was added dropwise with stirring. The solution was allowed to warm to room temperature and stirred for a further 3 h. T.l.c. indicated one product. The solvent was evaporated off and the residue chromatographed on a dry column of Woelm silica (elution with chloroform). The *methyl ether* (22) was isolated as a pale yellow oil (640 mg, 18%).

Reaction of 2′,6′-Dihydroxy-4′-methoxyacetophenone with Citral and Pyridine at 90 °C.—2′,6′-Dihydroxy-4′-methoxyacetophenone (546 mg, 0.003 mol), citral (462 mg, 0.003 mol), and pyridine (237 mg, 0.003 mol) were heated with stirring at 90 °C for 18 h. T.l.c. indicated one product. The pyridine was evaporated off and the residue chromatographed on a dry column of Woelm silica [elution with n-hexane–ether (3 : 1)]. The only product was isolated as a pale yellow oil (703 mg, 74%), identical with the acetylmonochromen methyl ether (22).

Reaction of 2′,4′-Dihydroxy-6′-methoxyacetophenone with Citral and Pyridine at 90 °C.—2′,4′-Dihydroxy-6′-methoxyacetophenone (136 mg, 0.000 75 mol), citral (115 mg, 0.000 75 mol), and pyridine (400 mg, 0.005 mol) were heated with stirring at 90 °C for 18 h. The pyridine was evaporated off and the residue chromatographed on a dry column of Woelm silica [elution with n-hexane–ether (3 : 1)]. The only product, the *chromen* (25), was isolated as a pale yellow solid (68 mg, 29%), m.p. 88—90° (from aqueous ethanol).

Acetylation of the Monochromen Methyl Ether (22).—The monochromen methyl ether (22) (50 mg) was stirred at room temperature with dry pyridine (1.0 ml) and acetic anhydride (0.5 ml). After 6 h t.l.c. indicated that all the starting material had been consumed. The solution was poured onto ice, acidified with 10% hydrochloric acid, and extracted with ether. The extracts were washed with saturated sodium hydrogen carbonate solution, then water, and dried. Evaporation followed by chromatography on a dry column of Woelm silica [elution with n-hexane–ether (3 : 1)] yielded the *acetate* (23) as a gum (50 mg).

Acetylation of the Acetylmonochromen Methyl Ether (25).—The monochromen methyl ether (25) (10 mg) was stirred at room temperature with dry pyridine (1.0 ml) and acetic anhydride (0.5 ml) for 6 h. Work-up and chromatography as before yielded the *acetate* (26) as a gum (9 mg).

p-*Nitrobenzoylation of the Acetylmonochromen Methyl Ether* (22).—The monochromen methyl ether (22) (75 mg) obtained by methylation of the chromen (15) was dissolved in dry pyridine (5 ml) and cooled to 0 °C. Freshly crystallised *p*-nitrobenzoyl chloride (400 mg) was added and the solution stirred at room temperature overnight. The mixture was poured onto ice and acidified with 2N-hydrochloric acid. The solution was then extracted with ether, and the extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated. The residual oil was chromatographed on silica gel HF_{254} [preparative plates, 20 × 20 cm; elution with n-hexane–ether (3 : 1)]. The major product was obtained as a pale yellow oil which crystallised from ethanol during 2 months at 0 °C to yield the p-*nitrobenzoate* (24) (40 mg), m.p. 90—91°.

A similar benzoylation of the chromen methyl ether

[21] A. Sonn and W. Bülow, *Ber.*, 1925, **58**, 1691.

obtained by chromenylation of 2′,6′-dihydroxy-4′-methoxyacetophenone yielded a yellow solid, m.p. 89—91°, identical with the *p*-nitrobenzoate isolated in the previous reaction (t.l.c. and n.m.r., i.r., u.v., and mass spectra) (mixed m.p. 89—91°).

Reaction of the Acetylmonochromen (15) *with* (+)-*Camphorsulphonic Acid.*—The acetylmonochromen (15) (1.0 g, 0.003 mol) was dissolved in dry benzene (50 ml) and refluxed for 18 h in the presence of (+)-camphorsulphonic acid (50 mg). The volume was then reduced to *ca.* 10 ml and the product was taken up in ether, washed with saturated sodium hydrogen carbonate solution and water, and dried. Evaporation yielded a pale yellow oil which was chromatographed on silica gel HF_{254} [preparative plates, 45 × 45 cm, elution with chloroform–acetone (25 : 1)]. Three bands were visible on u.v. irradiation. The least polar yielded a white solid which crystallised from ethanol to provide the acetylcitran (7) (364 mg, 36%), m.p. 168—170° (lit.,[15] 170—171°). Spectroscopic data were parallel to those reported.[15]

The next band in order of increasing polarity yielded a pale yellow oil (120 mg, 12%). N.m.r. indicated the presence of a mixture of at least two compounds which could not be separated by further chromatography. The most polar compound isolated was a white solid which was further purified by preparative chromatography on silica gel HF_{254} plates [elution three times with n-hexane–acetone (6 : 1)]. It crystallised from ether–petroleum (b.p. 60—80 °C) to form the isopropenyl ether (38) (374 mg, 37%), m.p. 182—184°.

Reaction of the Acetylcitran (5) *with* (+)-*Camphorsulphonic Acid.*—The acetylcitran (5) (500 mg) was dissolved in dry benzene (50 ml) and refluxed with (+)-camphorsulphonic acid (50 mg) for 12 h. The volume was reduced to *ca.* 10 ml, and the residue taken up in ether. The product was washed with saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation yielded a pale yellow solid which was chromatographed on silica gel HF_{254} [preparative plates, 20 × 20 cm; elution with chloroform–acetone (20 : 1)]. Two products were obtained. The least polar was a solid which crystallised from ether–petroleum (b.p. 60—80 °C) to give the *isopropylidene ether* (37), m.p. 143—145° (324 mg, 65%). The more polar product was the *8′-hydroxy-ether* (40), which crystallised from methanol, m.p. 194—196° (82 mg, 16%).

Reaction of the Acetylcitran (7) *with* (+)-*Camphorsulphonic Acid.*—The acetylcitran (7) (100 mg) was dissolved in dry benzene (10 ml) and refluxed with (+)-camphorsulphonic acid (10 mg) for 18 h. T.l.c. indicated one product. The benzene was evaporated off and the residue was separated by preparative layer chromatography on silica gel HF_{254} [elution with chloroform–acetone (20 : 1)]. The isopropylidene ether (36) was obtained (77 mg, 77%) which crystallised from ether–light petroleum (b.p. 60—80 °C) as white needles, m.p. 222—224° (lit.,[15] 226—228°).

Reaction of the Acetylcitran (5) *with Acetic Acid.*—The acetylcitran (5) (250 mg) was refluxed with acetic acid (10 ml) for 2 h. T.l.c. indicated one product. The solvent was removed and the resulting white solid was taken up in ether. The solution was washed with saturated sodium hydrogen carbonate solution, and then with water. Drying followed by evaporation yielded the isopropenyl ether (39), which crystallised from cyclohexane; yield 185 mg (74%); m.p. 206—207° (lit.,[3] 204—206°).

Crystallographic Analyses of the Acetylcitran (5) *and the Formylcitran* (6).—Suitable specimens of the acetylcitran (5) were recrystallised from ether–n-hexane and of the formylcitran (6) from ethanol. Oscillation and Weissenberg photographs were taken to establish unit-cell dimensions and space group. For intensity measurement a crystal of dimensions *ca.* 0.3 × 0.3 × 0.5 mm^3 (5) or 0.2 × 0.6 × 0.6 mm^3 (6) was mounted on an automatic, computer-controlled four-circle diffractometer. Unit-cell dimensions were refined by a least-squares fit on the positions of 12 peaks found on the diffractometer. Intensity data were collected with Mo-K_α radiation for $2\theta \leqslant 50°$ by use of an ω—2θ scan. Reflections with a net count greater than 3.0σ were considered observed and used in the subsequent structure refinement. A total of 2 922 (5) or 2 625 (6) independent reflections was measured, of which 2 037 (5) or 1 798 (6) were considered observed. No absorption corrections were made. Data reduction and subsequent crystallographic calculations were performed by using the '*X*-Ray '70' system of programs.[22] Atomic scattering factors were taken from ref. 23.

TABLE 3

Acetylcitran (5): atomic co-ordinates with standard deviations in parentheses

Atom	*x*	*y*	*z*
C(1)	−0.139 9(1)	0.159 4(1)	0.138 1(1)
C(2)	−0.139 8(2)	0.064 7(1)	0.203 0(1)
C(3)	−0.019 2(2)	0.011 0(1)	0.254 1(1)
C(4)	0.107 7(1)	0.056 1(1)	0.247 9(1)
C(5)	0.113 9(1)	0.160 5(1)	0.200 5(1)
C(6)	−0.006 2(1)	0.201 4(1)	0.137 1(1)
O(7)	0.010 4(1)	0.283 8(1)	0.072 1(1)
C(8)	0.125 5(2)	0.265 9(1)	0.022 6(1)
C(9)	0.246 4(2)	0.192 8(1)	0.085 4(1)
C(10)	0.248 7(1)	0.213 2(1)	0.192 9(1)
C(11)	0.370 3(2)	0.155 2(1)	0.264 9(1)
C(12)	0.350 3(2)	0.025 7(1)	0.254 5(1)
O(13)	0.225 1(1)	−0.006 2(1)	0.286 7(1)
C(14)	0.465 8(2)	−0.041 9(2)	0.324 6(2)
C(15)	0.336 2(2)	−0.009 6(1)	0.148 0(1)
C(16)	0.237 6(2)	0.061 3(1)	0.066 7(1)
C(17)	0.056 8(2)	0.214 0(2)	−0.076 8(1)
C(18)	0.173 2(2)	0.389 2(2)	0.011 6(1)
O(19)	−0.261 8(1)	0.019 2(1)	0.211 3(1)
C(20)	−0.271 6(2)	0.205 3(1)	0.079 0(1)
O(21)	−0.383 7(1)	0.162 9(1)	0.085 4(1)
C(22)	−0.279 5(2)	0.302 8(2)	0.009 2(2)
H(3)	−0.022(2)	−0.059(2)	0.292(1)
H(9)	0.329(2)	0.224(2)	0.073(1)
H(10)	0.248(2)	0.296(1)	0.206(1)
H(11A)	0.373(2)	0.181(2)	0.335(1)
H(11B)	0.455(2)	0.176(2)	0.250(1)
H(14A)	0.443(2)	−0.125(2)	0.319(2)
H(14B)	0.476(2)	−0.015(2)	0.400(2)
H(14C)	0.554(3)	−0.023(2)	0.310(2)
H(15A)	0.310(2)	−0.093(2)	0.140(1)
H(15B)	0.434(2)	−0.005(2)	0.141(1)
H(16A)	0.259(2)	0.044(2)	0.006(1)
H(16B)	0.140(2)	0.034(2)	0.059(1)
H(17A)	−0.014(2)	0.267(2)	−0.115(1)
H(17B)	0.130(2)	0.200(2)	−0.109(2)
H(17C)	0.009(2)	0.140(2)	−0.065(2)
H(18A)	0.221(2)	0.421(2)	0.076(1)
H(18B)	0.091(2)	0.437(2)	−0.025(1)
H(18C)	0.242(2)	0.386(2)	−0.026(2)
H(19)	−0.329(3)	0.063(2)	0.163(2)
H(22A)	−0.378(2)	0.320(2)	−0.024(2)
H(22B)	−0.231(2)	0.288(2)	−0.039(2)
H(22C)	−0.231(2)	0.371(2)	0.042(2)

[22] J. M. Stewart, F. A. Kindell, and J. C. Baldwin, University of Maryland Technical Report, TR 67—58, 1967 (revised 1970).

[23] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1965.

Crystal data. Acetylcitran (5). $C_{18}H_{22}O_4$, $M = 302.374$. Monoclinic, $a = 9.938(2)$, $b = 11.569(2)$, $c = 14.136(2)$, $\beta = 105.09(2)°$, $U = 1\,569.23$ Å^3, $Z = 4$, $D_c = 1.28$ g cm^{-3}, $F(000) = 648$. Space group $P2_1/c$ uniquely from systematic absences. Mo-K_α radiation, $\lambda = 0.710\,69$ Å; μ(Mo-K_α) = 0.96 cm^{-1}.

TABLE 4

Formylcitran (6): atomic co-ordinates with standard deviations in parentheses

Atom	x	y	z
C(1)	0.204 6(1)	0.599 9(3)	0.491 7(2)
C(2)	0.289 2(1)	0.654 1(3)	0.532 6(2)
C(3)	0.358 5(1)	0.588 2(3)	0.488 7(2)
C(4)	0.343 6(1)	0.475 5(3)	0.397 3(2)
C(5)	0.261 8(1)	0.447 2(3)	0.341 8(2)
C(6)	0.194 5(1)	0.488 7(3)	0.397 6(2)
O(7)	0.117 6(1)	0.413 6(2)	0.361 9(1)
C(8)	0.116 9(1)	0.223 4(3)	0.323 9(2)
C(9)	0.203 3(1)	0.165 5(3)	0.288 9(2)
C(10)	0.243 5(1)	0.330 2(3)	0.242 6(2)
C(11)	0.325 3(2)	0.290 3(3)	0.195 9(2)
C(12)	0.392 0(1)	0.234 2(3)	0.290 1(2)
O(13)	0.411 0(1)	0.386 1(2)	0.366 8(1)
C(14)	0.477 1(2)	0.193 4(4)	0.252 9(3)
C(15)	0.359 3(2)	0.075 3(3)	0.350 7(2)
C(16)	0.268 4(1)	0.085 9(3)	0.381 2(2)
C(17)	0.090 7(2)	0.116 7(4)	0.419 1(2)
C(18)	0.046 5(2)	0.220 6(4)	0.225 5(2)
O(19)	0.303 1(1)	0.763 0(2)	0.621 6(1)
C(20)	0.134 0(2)	0.654 7(3)	0.544 9(2)
O(21)	0.139 4(1)	0.753 3(3)	0.626 2(1)
H(3)	0.419(2)	0.609(4)	0.527(2)
H(9)	0.189(1)	0.084(3)	0.224(2)
H(10)	0.198(1)	0.386(3)	0.187(2)
H(11A)	0.342(1)	0.394(3)	0.155(2)
H(11B)	0.318(2)	0.194(4)	0.139(2)
H(14A)	0.522(2)	0.158(4)	0.323(3)
H(14B)	0.470(2)	0.102(4)	0.197(2)
H(14C)	0.496(2)	0.297(4)	0.212(2)
H(15A)	0.358(2)	−0.023(4)	0.295(2)
H(15B)	0.403(2)	0.050(4)	0.421(2)
H(16A)	0.270(1)	0.149(3)	0.450(2)
H(16B)	0.249(2)	−0.029(4)	0.400(2)
H(17A)	0.133(2)	0.142(4)	0.489(2)
H(17B)	0.091(2)	−0.008(4)	0.400(2)
H(17C)	0.031(2)	0.152(5)	0.433(2)
H(18A)	0.064(2)	0.288(4)	0.163(2)
H(18B)	0.040(2)	0.087(4)	0.194(3)
H(18C)	−0.003(2)	0.258(4)	0.249(3)
H(19)	0.249(2)	0.785(6)	0.642(3)
H(20)	0.077(2)	0.611(4)	0.507(2)

Formylcitran (6). $C_{17}H_{20}O_4$, $M = 288.347$. Monoclinic, $a = 15.867(4)$, $b = 7.564(2)$, $c = 12.152(2)$, $\beta = 98.04(2)°$, $U = 1\,444.14$ Å^3, $Z = 4$, $D_c = 1.33$ g cm^{-3}, $F(000) = 616$. Space group $P2_1/c$ uniquely from systematic absences. Mo-K_α radiation, $\lambda = 0.710\,69$ Å; μ(Mo-K_α) = 1.01 cm^{-1}.

Both structures were solved by direct methods using the Multan program.[24] Reflections with $E > 1.7$ were used [250 for (5) and 234 for (6)] and the best sets of phases produced had figures of merit 1.140 4 (5) or 1.108 7 (6). In each case a subsequent E map based on these phases revealed all non-hydrogen atom positions as the largest peaks on the map. Block-diagonal least-squares refinements of atomic parameters were commenced, initially with isotropic temperature factors and later including anisotropic vibrations. After apparent convergence with agreement factor R 0.100 (5) or 0.097 (6), difference-Fourier syntheses were calculated. These revealed the approximate positions of all the hydrogen atoms as the largest peaks in the maps. The hydrogen atoms were then included in the refinement with isotropic temperature factors. Analyses of the agreement of F_o and F_c suggested the adoption of weighting schemes of the form $w = 1$ for $|F_o| < 10.0$ and $w = (10.0/|F_o|)^2$ for $|F_o| > 10.0$ (5) or $w = 1/\{1 + [(|F_o| - 7.5)/7.5]^2\}$ (6). Further refinement finally converged when the largest parameters shifts were $<0.6\sigma$, lowering R to 0.042 (5) or 0.048 (6) after totals of 19 cycles (5) or 12 cycles (6). Final difference maps were calculated which showed no peaks or depressions >0.2 e Å^{-3}. Final atomic co-ordinates are listed in Tables 3 and 4; temperature factors and observed and calculated structure factors are listed in Supplementary Publication No. SUP 22106.

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[7/680 *Received*, 22*nd April*, 1977]

[24] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 360.