Acid-catalysed Condensation of Isoprene with Phenols. Formation of 2,2-Dimethylchromans

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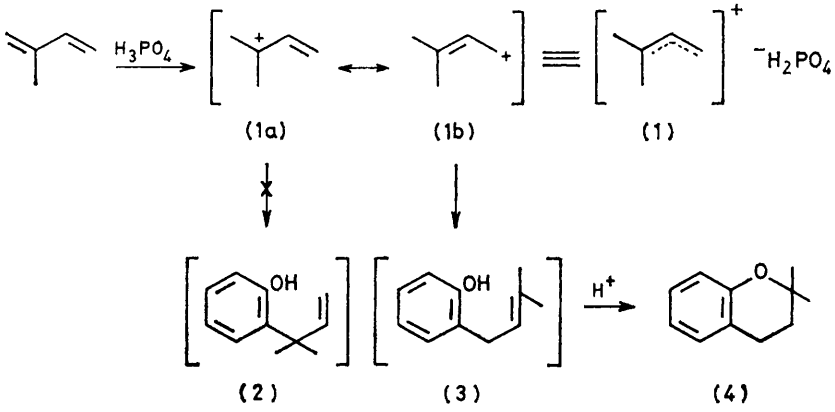
A novel method of nuclear isopentenylation which gives exclusively 2,2-dimethylchromans has been achieved by the direct condensation of phenols, *viz.* resorcinol, quinol, pyrogallol, and phloroglucinol, with 2-methylbuta-1,3-diene(isoprene) in the presence of orthophosphoric acid as catalyst. Condensation of 2-methylbut-3-en-2-ol with phenols in the presence of aqueous citric acid has been reinvestigated.

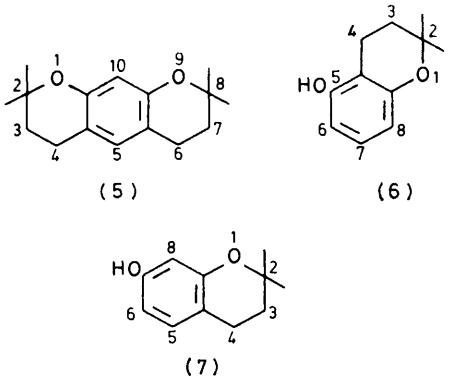
2,2-DIMETHYLCHROMENE rings or 3,3-dimethylallyl groups,[1] common in natural phenolic compounds, are converted into 2,2-dimethylchroman units, rare in natural products, by catalytic hydrogenation and acid-catalysed cyclisation, respectively.

The present paper describes a facile method for the nuclear isopentenylation of phenols to synthesise 2,2-dimethylchromans. The method consists of the condensation of phenols with 2-methylbuta-1,3-diene (isoprene) in the presence of catalytic amounts of orthophosphoric acid.

The acid-catalysed condensation of isoprene with phenols may be regarded as the chemical equivalent of proposed biogenetic pathways.[2-7] The mesomeric cation [which may exist as the ion pair (1)] required for this condensation can be generated by the protonation of isoprene. Either the mesomer (1a) or (1b) can alkylate the phenol to give *O*-(1,1-dimethylallyl)phenol (2) or *O*-(3,3-dimethylallyl) phenol (3), but of the two alkylated products, the product (3) is the one which is expected, thermodynamically, to be formed more readily. The allyl-phenol (3) undergoes acid-catalysed cyclisation to give the required chroman (4). The self-condensation of isoprene, the chief difficulty encountered while working with dienes, was minimised by slow addition of a dilute solution of isoprene in an inert solvent to a stirred suspension of phenols in a catalytic amount of orthophosphoric acid (85%) at 30—35 °C.

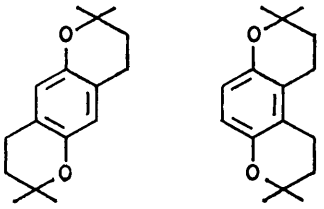
Thus, condensation of resorcinol with isoprene resulted in the formation of three products A, B, and C in the ratio of 1 : 2 : 5, respectively (overall yield 80%) which were separated by column chromatography over silica gel. Elemental analysis of compound A, m.p. 97—98 °C (the fastest moving fraction) showed the introduction of two isoprene units. Its ^{1}H n.m.r. spectral data showed two singlets of one proton each at δ 6.16 and 6.67 (2 Ar-protons), a singlet at δ 1.28 (gem-dimethyl groups) and two distinctive triplets at δ 1.77 and 2.66, each integrating for 4 protons, assigned to methylene groups. It was thus assigned the linear dichroman structure (5). Compound B, m.p. 121—121.5 °C, was identified as the monochroman (6) on the basis of elemental analysis and ^{1}H n.m.r. spectral data. Compound C, m.p. 67—68 °C, was found to be an isomer of compound B. In the aromatic region of its ^{1}H n.m.r. spectrum, it showed a doublet (*J* 2.5 Hz) at δ 6.18, a double doublet (*J* 8.5 Hz, 2.5 Hz) at δ 6.22, and a doublet (*J* 8.5 Hz) at δ 6.72, each integrating for one proton, which is characteristic of a 1,2,4-





trisubstituted benzene ring. Hence, compound C was assigned the structure (7).

Quinol (1,4-dihydroxybenzene), treated similarly, also gave a mixture of three products D, E, and F in the ratio of 3 : 2 : 5, respectively (overall yield 50%) which were separated by column chromatography. Compounds D, m.p. 157—158 °C, and E, m.p. 141—143 °C, were found to be isomeric dichromans from their elemental analysis. The ^{1}H n.m.r. spectra of D showed, besides other signals, a singlet of two aromatic protons at δ 6.43, whereas that of E showed a singlet at δ 6.53; so a clear distinction between the structures of compounds D and E could not be made. Even the application of nuclear Overhauser enhancement (n.O.e.) could not differentiate between the two structures, so either of the compounds can be assigned the structure (8) or (9). Skinner and Parkhurst [8] have described a compound, m.p. 159—161 °C, with a ^{1}H n.m.r. spectrum similar to that of compound D and they assign it the [4,5-*b*']-structure (8). In our opinion the evidence is ambiguous and does not exclude the [4,3-*b*']-isomer (9). Compound F, m.p. 75 °C, was assigned the structure (10) on the basis of its ^{1}H n.m.r. spectra and elemental analysis.



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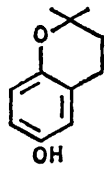
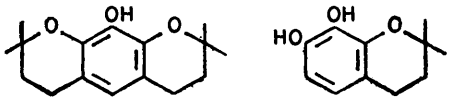


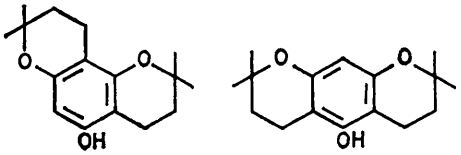
(10)

Similarly, pyrogallol on condensation with isoprene gave two compounds G and H in the ratio of 1 : 7, respectively (overall yield 80%) which were separated by column chromatography. Elemental analysis of compound G, m.p. 139—140 °C showed the introduction of two isoprene units and compound G was assigned the dichroman structure (11). Elemental analysis of the major compound H, m.p. 106—107 °C, indicated the introduction of one isoprene unit; this compound gave dimethyl ether on methylation, so it was assigned the monochroman structure (12), which was in agreement with its ^{1}H n.m.r. spectrum.



(11) (12)

Similarly, phloroglucinol on condensation with isoprene gave three compounds I, J, and K in the ratio of 5 : 4 : 5, respectively (overall yield 70%) which were separated by column chromatography. Compounds I m.p. 162—163 °C, and J m.p. 161—162 °C, were found, by elemental analysis, to be isomeric dichromans. Compound *J* gave a positive Gibb's test for an unsubstituted position *para* to the hydroxy-group. The ^{1}H n.m.r. spectrum of compound I showed four distinct triplets, of two protons each, at δ 1.66, 1.71, 2.48, and 2.52, whereas only two triplets, of four protons each, at δ 1.74 and 2.53 were observed in the ^{1}H n.m.r. spectrum of compound J. Compound I was, therefore, assigned the angular dichroman structure (13) and compound J was assigned the symmetrical, linear dichroman structure (14). Elemental analysis of compound K, m.p. 163—164 °C, indicated the introduction of only one isoprene unit and was assigned structure (15) on the basis of its ^{1}H n.m.r. spectrum which showed, besides other signals, two m-coupled aromatic protons as two doublets at δ 5.56 and 5.77 (*J* 2.5 Hz). Its structure was further confirmed by the ^{1}H n.m.r. spectrum of its dimethyl ether which showed, besides other signals, two signals at δ 3.69 and 3.72, of three protons each, for two methoxy-groups and a singlet at δ 5.99 of two aromatic protons.



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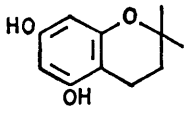

(15)

Molyneux and Jurd [9] have reported that 2-methylbut-3-en-2-ol condenses with phloroglucinol in the presence of 5% aqueous citric acid to yield the dichroman (14) (13%) and the monochroman (15) (18.5%), but the ^{1}H n.m.r. spectral data reported by them differs from those of the monochroman (15) prepared by us. So the condensation of 2-methylbut-3-en-2-ol with phloroglucinol under the conditions described [9] was repeated for comparative purposes. However, we found that three products were obtained (overall yield 40%), identical (m.p., mixed m.p., and i.r.) with compounds (13), (14), and (15). In view of the above discrepancy, the citric acid-catalysed condensation of 2-methylbut-3-en-2-ol with pyrogallol and resorcinol was also carried out. Pyrogallol gave the same two products as reported earlier,[9] but in the case of resorcinol three products were obtained (overall yield 50%) which were assigned the

structures (5), (6), and (7), whereas earlier only the monochroman (7) (55%) had been reported.[9]

The above condensation of phenols with isoprene provides a better route to the synthesis of 2,2-dimethylchromans than the previously available methods, the overall yield of the chromans being 50—80%. In the past, such chromans have been prepared by Clemmensen reduction of 2,2-dimethylchromanones,[10] by treatment of dihydrocoumarins with methyl magnesium iodide,[11] or by the condensation of phenols with 2-methylbut-3-en-2-ol[9] in the presence of aqueous citric acid. The first two methods require starting materials which are often difficult to prepare. Since the chromans can be dehydrogenated to the corresponding chromenes by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[12] this can provide a convenient route to the synthesis of more complex natural products containing the chromene group.

EXPERIMENTAL

Melting points were taken in a sulphuric acid bath and are uncorrected. ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R-32 (90 MHz) instrument for solutions in $CDCl_3$ with tetramethylsilane as the internal standard. Nuclear Overhauser enhancement (n.O.e.) studies were made on a Varian (60 MHz) model. Light petroleum refers to the fraction with b.p. 60—80 °C. Silica gel (60—120 mesh) was used for all column chromatographic separations.

Reaction of Resorcinol with 2-Methylbuta-1,3-diene.—A solution of 2-methylbuta-1,3-diene (isoprene) (1.6 ml) in light petroleum (5.0 ml) was added to a stirred mixture of resorcinol (2.0 g), orthophosphoric acid (85%, 2.0 ml), and light petroleum (5.0 ml) at 30—35 °C over 2 h. The mixture was stirred for a further 2 h and then neutralised with sodium hydrogencarbonate solution (5%). The mixture, thus obtained, was extracted with diethyl ether. The extract was washed with water, dried (Na_2SO_4), and distilled. The residue, thus obtained, was found by thin layer chromatography (t.l.c.) to be a mixture of three products. It was subjected to column chromatography and elution of the column with light petroleum gave the following three fractions, successively.

Fraction A, crystallised from light petroleum, yielded *2,3,4,6,7,8-hexahydro-2,2,8,8-tetramethylbenzo*[1,2-b;5,4-b']-*dipyran* (5) as needles (0.42 g), m.p. 97—98 °C (Found: C, 78.0; H, 8.9. $C_{16}H_{22}O_2$ requires C, 78.1; H, 8.9%); δ 1.28 (12 H, s, 2 × CMe_2), 1.77 (4 H, t, *J* 7 Hz, 3- and 7-H), 2.66 (4 H, t, *J* 7 Hz, 4- and 6-H), and 6.16 and 6.67 (each 1 H, each s, 5- and 10-H).

Fraction B, crystallised from benzene–light petroleum, yielded *5-hydroxy-2,2-dimethylchroman* (6) as needles (0.64 g), m.p. 121—121.5 °C (Found: C, 74.1; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.2; H, 7.8%); δ 1.32 (6 H, s, CMe_2), 1.79 and 2.65 (each 2 H, each t, *J* 7 Hz, 3- and 4-H, respectively), 6.31 (2 H, m, 6- and 8-H), and 6.89 (1 H, t, *J* 8.5 Hz, 7-H).

Fraction C, crystallised from benzene–light petroleum, yielded 7-hydroxy-2,2-dimethylchroman (7) as needles (1.24 g), m.p. 67—68 °C (lit.,[13] 72—73 °C) (Found: C, 74.1; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.2; H, 7.8%); δ 1.28 (6 H, s, CMe_2), 1.69 and 2.60 (each 2 H, each t, *J* 7 Hz, 3- and 4-H, respectively), 5.48 (1 H, s, exchanged with D_2O, 7-OH), 6.18 (1 H, d, *J* 2.5 Hz, 8-H), 6.22 (1 H, dd, *J* 8.5 Hz, 2.5 Hz, 6-H), and 6.72 (1 H, d, *J* 8.5 Hz, 5-H).

Reaction of 1,4-Dihydroxybenzene with Isoprene.—A solution of isoprene (1.6 ml) in light petroleum (5.0 ml) was added to a stirred mixture of 1,4-dihydroxybenzene (quinol) (2.0 g), orthophosphoric acid (85%, 2.0 ml), and light petroleum (5.0 ml) at 30—35 °C over 6 h. The mixture was stirred for a further 2 h and work-up as above gave a residue which was found to be a mixture of three products. It was subjected to column chromatography and the column was eluted successively with (*i*) light petroleum, (*ii*) benzene–light petroleum (1 : 19), and (*iii*) benzene–light petroleum (1 : 3) to give the following three fractions.

Fraction D, crystallised from chloroform, gave 2,3,4,7,8,9-hexahydro-2,2,7,7-tetramethylbenzo[1,2-*b*;4,5-*b*']dipyran (8) or 1,2,3,8,9,10-hexahydro-3,3,8,8-tetramethylbenzo[1,2-*b*;4,3-*b*']dipyran (9) as prisms (0.3 g), m.p. 157—158 °C (Found: C, 78.0; H, 9.0. $C_{16}H_{22}O_2$ requires C, 78.1; H, 8.9%); δ 1.27 (12 H, s, 2 × CMe_2), 1.72 and 2.67 (each 4 H, each t, *J* 7 Hz, 4 × CH_2), and 6.43 (2 H, s, 2 × Ar-H).

Fraction E, crystallised from benzene, gave compound (8) or (9) as needles (0.21 g), m.p. 141—143 °C (Found: C, 78.0; H, 8.9. $C_{16}H_{22}O_2$ requires C, 78.1; H, 8.9%); δ 1.27 (12 H, s, 2 × CMe_2), 1.77 and 2.53 (each 4 H, each t, *J* 7 Hz, 4 × CH_2), and 6.53 (2 H, s, 2 × Ar-H).

Fraction F, crystallised from chloroform, yielded 6-hydroxy-2,2-dimethylchroman (10) as needles (0.4 g), m.p. 75 °C (lit.,[14] 74—75 °C) (Found: C, 74.1; H, 7.8. $C_{11}H_{14}O_2$ requires C, 74.2; H, 7.8%); δ 1.27 (6 H, s, CMe_2), 1.72 and 2.67 (each 2 H, each t, *J* 7 Hz, 3- and 4-H, respectively), 5.0br (1 H, s, exchanged with D_2O, 6-OH), and 6.54 (3 H, m, 5-, 7-, and 8-H).

Reaction of Pyrogallol with Isoprene.—A solution of isoprene (1.5 ml) in light petroleum (5.0 ml) was added to a stirred mixture of pyrogallol (2.0 g), orthophosphoric acid (85%, 2.0 ml), and light petroleum (5.0 ml) at 30—35 °C over 2 h. The mixture was stirred for a further 2 h and work-up as above gave a residue which was found to be a mixture of two products. It was subjected to column chromatography and the column was eluted successively with (*i*) light petroleum–benzene (1 : 1) and (*ii*) benzene to give the following two fractions.

Fraction G, crystallised from benzene–light petroleum, gave 2,3,4,6,7,8-hexahydro-10-hydroxy-2,2,8,8-tetramethylbenzo[1,2-*b*;5,4-*b*']dipyran (11) as needles (0.2 g), m.p. 139—140 °C (lit.,[9] 139—140 °C) (Found: C, 73.2; H, 8.5. $C_{16}H_{22}O_3$ requires C, 73.3; H, 8.4%); δ 1.33 (12 H, s, 2 × CMe_2), 1.74 (4 H, t, *J* 7 Hz, 3- and 7-H), 2.66 (4 H, t, *J* 7 Hz, 4- and 6-H), 5.25 (1 H, s, exchanged with D_2O, 10-OH), and 6.28 (1 H, s, 5-H).

Fraction H, crystallised from dilute alcohol, gave 7,8-dihydroxy-2,2-dimethylchroman (12) as needles (1.0 g), m.p. 106—107 °C (lit.,[15] m.p. 99—100 °C) (Found: C, 68.0; H, 7.3. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.2%); δ 1.31 (6 H, s, CMe_2), 1.74 and 2.66 (each 2 H, each t, *J* 7 Hz, 3- and 4-H, respectively), 5.53br (2 H, s, exchanged with D_2O, 7- and 8-OH), and 6.43 (2 H, s, 5- and 6-H).

Reaction of Phloroglucinol with Isoprene.—A solution of isoprene (1.5 ml) in light petroleum (5.0 ml) was added to a stirred mixture of phloroglucinol (2.0 g), orthophosphoric acid (85%, 2.0 ml), and light petroleum (5.0 ml) at 30—35 °C over 2 h. The mixture was stirred for a further 2 h and work-up as above gave a residue which was found to be a mixture of three products. It was subjected to column chromatography and the column was eluted successively with (*i*) benzene (*ii*) benzene–ethyl acetate (19 : 1), and

(*iii*) benzene–ethyl acetate (9 : 1) to give the following three fractions.

Fraction I, crystallised from benzene–light petroleum, gave 2,3,4,8,9,10-hexahydro-5-hydroxy-2,2,8,8-tetramethylbenzo[1,2-*b*;3,4-*b*']dipyran (13) as needles (0.5 g), m.p. 162—163 °C (lit.,[16] 157.5—158 °C) (Found: C, 73.2; H, 8.4. $C_{16}H_{22}O_3$ requires C, 73.3; H, 8.4%); δ 1.27 (12 H, s, 2 × CMe_2), 1.66 and 1.71 (each 2 H, each t, *J* 7 Hz, 3- and 9-H), 2.48 and 2.52 (each 2 H, each t, *J* 7 Hz, 4- and 10-H), 4.72 (s, 1 H, exchanged with D_2O, 5-OH), and 5.86 (1 H, s, 6-H).

Fraction J, crystallised from benzene–light petroleum, gave 2,3,4,6,7,8-hexahydro-5-hydroxy-2,2,8,8-tetramethylbenzo[1,2-*b*;5,4-*b*']dipyran (14) as needles (0.4 g), m.p. 161—162 °C (lit.,[16] 161—162.5 °C) (Found: C, 73.2; H, 8.5. $C_{16}H_{22}O_3$ requires C, 73.3; H, 8.4%); δ 1.27 (12 H, s, 2 × CMe_2), 1.74 (4 H, t, *J* 7 Hz, 3- and 7-H), 2.53 (4 H, t, *J* 7 Hz, 4- and 6-H), 5.33 (1 H, s, exchanged with D_2O, 5-OH), and 5.94 (1 H, s, 10-H).

Fraction K, crystallised from dilute alcohol, gave 5,7-dihydroxy-2,2-dimethylchroman (15) as needles (0.37 g), m.p. 163—164 °C (lit.,[16] 163—164 °C) (Found: C, 68.0; H, 7.3. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.2%); δ[$(CD_3)_2SO$] 1.24 (6 H, s, CMe_2), 1.66 and 2.47 (each 2 H, each t, *J* 7 Hz, 3- and 4-H, respectively), 5.56 and 5.77 (each 1 H, each d, *J* 2.5 Hz, 6- and 8-H), and 8.52 and 8.83 (each 1 H, each s, exchanged with D_2O, 5- and 7-OH). Its dimethyl ether was obtained as an oil; δ 1.30 (6 H, s, CMe_2), 1.73 and 2.55 (each 2 H, each t, *J* 7 Hz, 3- and 4-H, respectively), 2.69 and 2.72 (each 3 H, each s, 5- and 7-OMe), and 5.99 (2 H, s, 6- and 8-H).

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REFERENCES

[1] L. Merlini, *Adv. in Heterocycl. Chem.*, 1975, **18**, 159.
[2] A. J. Birch, P. Eliot, and A. R. Penfold, *Aust. J. Chem.*, 1954, **7**, 169; A. J. Birch, *Fortschr. Chem. Org. Naturst.*, 1957, **14**, 186.
[3] J. W. Cornforth and G. Popjak, *Tetrahedron Lett.*, 1959, 29.
[4] D. H. R. Barton, P. De Mayo, G. A. Morrison, and H. Riastrick, *Tetrahedron*, 1959, **6**, 48.
[5] W. D. Ollis and I. O. Sutherland in ' Recent Developments in the Chemistry of Natural Phenolic Substances,' Pergamon, Oxford, 1961; W. D. Ollis, *Experinetia*, 1966, **22**, 777; W. D. Ollis and O. R. Gottlieb, *Chem. Commun.*, 1968, 1396.
[6] A. B. Turner, *Quart. Rev., Chem. Soc.*, 1964, **18**, 347.
[7] R. Mechoulam and T. Gaoni, *Fortschr. Chem. Org. Naturst.*, 1967, **25**, 201.
[8] W. A. Skinner and R. M. Parkhurst, *J. Chromatogr.*, 1964, **13**, 69.
[9] R. J. Molyneux and L. Jurd, *Tetrahedron*, 1970, **26**, 4743.
[10] H. B. Bhat and K. Venkataraman, *Tetrahedron*, 1963, **19**, 77.
[11] R. Adams, C. K. Cain, and S. Loewe, *J. Am. Chem. Soc.*, 1941, **63**, 1977.
[12] G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24**, 4825.
[13] W. Bridge, A. J. Crocker, T. Cubin, and A. Robertson, *J. Chem. Soc.*, 1937, 1530.
[14] J. A. Miller and H. C. S. Wood, *J. Chem. Soc. C*, 1968, 1837.
[15] J. H. Richards and A. Robertson, *J. Chem. Soc.*, 1948, 1610.
[16] M. L. Wolfrom and B. S. Wildi, *J. Am. Chem. Soc.*, 1951, **73**, 235.