Tetrahedron, Vol. 37, pp 1437 to 1439, 1981
Printed in Great Britain.

0040-4020/81/071437-03$02.00/0

NUCLEAR ISOPRENYLATION OF POLYHYDROXYACETOPHENONES

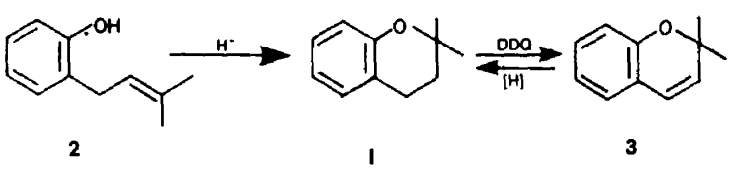
ACID CATALYSED CONDENSATION WITH ISOPRENE

V. K. AHLUWALIA* and K. K. ARORA
Department of Chemistry, University of Delhi, Delhi-110007, India

(*Received in UK 23 September* 1980)

Abstract—A novel method of nuclear isoprenylation leading to the exclusive formation of 2,2-dimethylchromans has been achieved by the direct condensation of polyhydroxyacetophenones with isoprene in presence of phosphoric acid. Acetylchromans, thus obtained, are dehydrogenated with DDQ to given corresponding 2,2-dimethylchromenes. Using this method, synthesis of number of naturally occurring chromenes, *viz.* riparichromene A (**6**), eupatoriochromene (**10**), encecalin (**11**), isoevodionol (**16**), evodionol (**17**) and methylevodionol (**18**) has been affected.

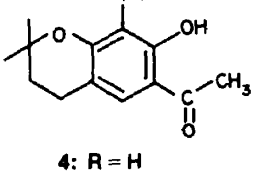
Phenolic natural products bearing isoprenoid substituents exhibit a wide variety of structural types,[1] both with respect to the polyphenolic moiety (e.g. coumarins, flavonoids, xanthones, chromones and quinones etc) and the C_5-isoprenyl unit (most frequently either as open chain form or as hetero-oxygen ring, *viz.* 2,2-dimethylchromene or 2,2-dimethyldihydropyranol). In the course of structural elucidation of natural products bearing either of these substitution patterns the compound is converted into a derivative having the 2,2-dimethylchroman structure (**1**), either by acid catalysed cyclization of the *o*-hydroxy-3,3-dimethylallyl group (**2**) or by hydrogenation of the chromene double bond (**3**). In spite of these facile interconversions, the unsubstituted 2,2-dimethylchroman unit occurs very infrequently among phenolic natural products but compounds containing chroman unit have to be synthesised for comparison purposes. Moreover, the discovery of Cardillo *et al.*[2] that chromans can be dehydrogenated to chromenes by DDQ, also provides a convenient method for synthesis of many natural products containing the latter group which have been difficult to prepare by the methods previously available. In the past such chromans have been prepared by (i) Clemmensen reduction of 2,2-dimethylchromanones[3] (ii) by treatment of dihydrocoumarins with methyl magnesium iodide[4] or (iii) by direct condensation of phenols with 2-methyl-but-3-ene-2-ol[5] in aqueous acid solution. Methods (i) and (ii) suffer from the disadvantage that the appropriate starting materials are often difficult to prepare. The method (iii) invariably yields a mixture of products from which the chromans are obtained by fractional distillation. Further the yield in all the above methods is poor. So a convenient method was desired for the synthesis of chromans.



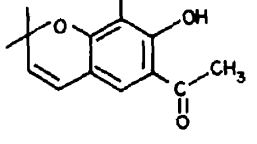
2 1 3

We, hereby report a new and elegant method for nuclear isoprenylation leading to the synthesis of chromans in one step. The method involves the condensation of phenolic compounds with isoprene (2-methyl-1,3-butadiene) in presence of phosphoric acid as catalyst. The chromans, thus obtained are dehydrogenated with DDQ to give corresponding chromenes, many of them are found to occur in nature. These chromans and chromenes are also useful intermediates for the synthesis of large number of naturally occurring flavonoids.

Condensation of 2,3,4-tridydroxyacetophenone (gallacetophenone) with isoprene was carried out as a test case which gave only one product (**4**; yield 85%). It gave positive ferric reaction and its elemental analysis showed the introduction of one isoprene unit. It was assigned the structure 6-acetyl-7,8-dihydroxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**4**) on the basis of its NMR spectrum which showed only one singlet at δ 7.01 for one aromatic proton along with a six protons singlet at δ 1.40, two triplets of two protons each at δ 1.82 and 2.73, three protons singlet at δ 2.51 and two singlets (exchanged with D_2O) at δ 5.32 and 12.38 of one proton each. On partial methylation with dimethyl sulphate (1.1 mole) 4 gave 6-acetyl-7-hydroxy-8-methoxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**5**), which on dehydrogenation with DDQ afforded 6-acetyl-7-hydroxy-8-methoxy-2,2-dimethyl-2H-1-benzopyran (**6**). It was identical with the naturally occurring riparichromene-A isolated from *Eupatorium riparium*.[6,7]



4: R = H
5: R = CH_3

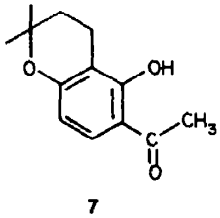


6

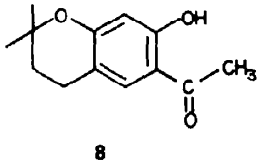
2,4-Dihydroxyacetophenone (resacetophenone) on similar reaction gave a mixture of two major products

along with a minor product which were separated by column chromatography. The first major component was identified as 6-acetyl-5-hydroxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**7**) on the basis of its characteristic ferric reaction, elemental analysis and NMR spectrum which showed, besides other signals, two doublets (J = 9 Hz) at δ 6.28 and 7.44 of one proton each indicating the presence of two ortho-coupled aromatic protons. The second major component was identified as 6-acetyl-7-hydroxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**8**) on the basis of its NMR spectrum which showed besides other signals, two singlets at δ 6.24 and 7.35 of one proton each indicating the presence of two para aromatic protons. The third minor component was insoluble in sodium carbonate (5%) or sodium hydroxide (2%) solution. It showed negative ferric reaction indicating the absence of a chelated hydroxyl group. Its elemental analysis indicated the introduction of two isoprene units and finally the dichroman structure **9** was confirmed for this compound on the basis of its NMR spectrum.

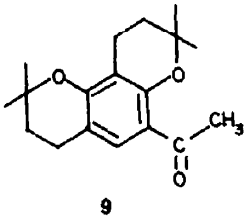
Compound **8** on dehydrogenation with DDQ gave 6-acetyl-7-hydroxy-2,2-dimethyl-2H-1-benzopyran (**10**) which was found to agree with the description given for natural eupatoriochromene.[6,8,9] Since **10** has already been methylated to corresponding methyl ether (**11**) by Anthonsen,[6] who named it methyleupatoriochromene, though it had been earlier called encecalin after its isolation from *Encelia californica*,[10] the present synthesis of hydroxy compound constitutes also the total synthesis of encecalin.[8-10] Similarly, **7** on dehydrogenation with DDQ afforded 6-acetyl-5-hydroxy-2,2-dimethyl-2H-1-benzopyran (**12**) which has not been obtained from natural sources but has been synthesised earlier by other methods.[11,12] Its methyl ether, called isoencecalin[13] (**13**) is also known synthetically.



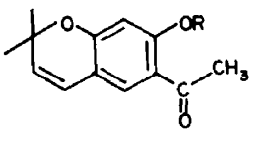
7



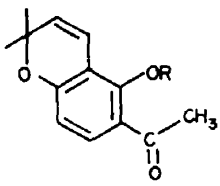
8



9

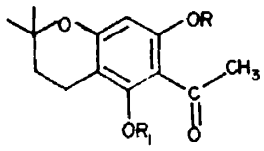


10: R = H
11: R = CH_3



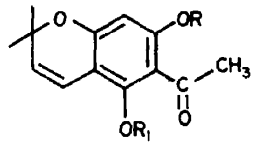
12: R = H
13: R = CH_3

2,4-Dihydroxy-6-methoxyacetophenone, when subjected to similar reaction, gave two major products (**14** and **15**) which were separated by column chromatography. They were assigned the structures 6-acetyl-5-hydroxy-7-methoxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**14**) and 6-acetyl-7-hydroxy-5-methoxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**15**) on the basis of their NMR spectral data and the reaction with DDQ to give the corresponding naturally occurring chromenes, *viz.* 6-acetyl-5-hydroxy-7-methoxy-2,2-dimethyl-2H-1-benzopyran (isoevodionol)[8,14] **16** and 6-acetyl-7-hydroxy-5-methoxy-2,2-dimethyl-2H-1-benzopyran (evodionol)[9,15,16] **17**. On methylation, **17** is known to give 6-acetyl-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (methylevodionol) **18**, which is also known to occur in nature.[17]



14, 15

	R	R_1
14:	CH_3	H
15:	H	CH_3



16–18

	R	R_1
16:	CH_3	H
17:	H	CH_3
18:	CH_3	CH_3

EXPERIMENTAL

M.ps have been taken in H_2SO_4 and are uncorrected. NMR spectra were recorded on Perkin–Elmer R-32 spectrometer with TMS as an intermal standard.

Reaction of 2,3,4-trihydroxy acetophenone with isoprene

6-Acetyl-7,8-dihydroxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**4**). A soln of isoprene (0.8 ml) in xylene (2.0 ml) was added to a mixture of 2,3,4-trihydroxyacetophenone (1.0 g), orthophosphoric acid (90%; 0.6 ml) and xylene (2.0 ml) with constant stirring at 30–35° during 8 hr. Stirring was continued for further 12 hr and then ether (25 ml) added. It was washed successively with 2% Na_2CO_3 aq and water, dried (Na_2SO_4) and the solvent distilled off to give **4**. It crystallised from benzene–petroleum ether as pale yellow needles (1.1 g), m.p. 124–5° (lit.[7] m.p. 122–4°). NMR($CDCl_3$) δ: 1.40 (s, 6H, $C(CH_3)_2$); 1.82 (t, J = 7 Hz, 2H, H3); 2.51 (s, 3H, $COCH_3$); 2.73 (t, J = 7 Hz, 2H, H4); 5.32 (s, 1H, exchanged with D_2O, OH at C_8); 7.01 (s, 1H, H5); 12.38 (s, 1H, exchanged with D_2O, OH at C_7).

6-Acetyl-7-hydroxy-8-methoxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (**5**). **4** (0.5 g) in dry acetone (25.0 ml) was refluxed for 5 hr with Me_2SO_4 (0.23 ml) in presence of anhyd K_2CO_3 (2.0 g). It was filtered, inorganic salts washed with hot acetone and combined filtrate distilled. The solid product obtained after addition of crushed ice was filtered, washed successively with 5% Na_2CO_3 aq and water. It was crystallised from benzene–petroleum ether to give colourless needles of **5** (0.5 g) m.p. 102–3°. (Found: C, 67.0; H, 7.3. $C_{14}H_{18}O_4$ requires: C, 67.2; H, 7.2%). NMR($CDCl_3$) δ: 1.39 (s, 6H, $C(CH_3)_2$); 1.81 (t, J = 7 Hz, 2H, H3), 2.49 (s, 3H, $COCH_3$); 2.71 (t, J = 7 Hz, 2H, H4); 3.81 (s, 3H, OCH_3); 7.17 (s, 1H, H5); 12.44 (s, 1H, exchanged with D_2O, OH at C_7).

6-Acetyl-7-hydroxy-8-methoxy-2,2-dimethyl-2H-1-benzopyran (Ripariochromene-A) (**6**). **5** (0.2 g) in dry benzene (10 ml) was refluxed for 8 hr with DDQ (0.2 g). The soln was filtered, washed successively with 1% $NaHCO_3$ aq, water, dried (Na_2SO_4) and distilled. The residue thus obtained, on crystallisation from petroleum ether afforded **6** (0.18 g) as pale yellow prisms m.p. 90–91° (lit.[7] m.p. 90–91°). NMR($CDCl_3$) δ: 1.49 (s, 6H, $C(CH_3)_2$), 2.52 (s, 3H, $COCH_3$); 3.87 (s, 3H, OCH_3); 5.56 (d, J = 10 Hz, 1H, H3); 6.25 (d, J = 10 Hz, 1H, H4); 7.10 (s, 1H, H5); 12.8 (s, 1H, exchanged with D_2O, OH at C_7).

Reaction of 2,4-dihydroxyacetophenone with isoprene

A soln of isoprene (0.86 ml) in xylene (2.0 ml) was added to mixture of 2,4-dihydroxyacetophenone (1.0 g), orthophosphori

acid (90%; 0.7 ml) and xylene (2.0 ml) with constant stirring at 30–35° during 8 hr. Stirring was continued for further 12 hr and then working up the reaction gave a product which was found to be mixture of three products. Hence it was subjected to column chromatography and the column eluted, successively, with (i) petroleum ether (ii) benzene: petroleum ether (1:19) and (iii) benzene:petroluem ether (1:9) giving the following three fractions.

Fraction A, crystallised from petroleum ether, yielding **7** (0.25 g), m.p. 69–70° (lit.[11] m.p. 72°). NMR($CDCl_3$) δ: 1.31 (s, 6H, $C(CH_3)_2$); 1.76 (t, J = 7 Hz, 2H, H3); 2.48 (s, 3H, $COCH_3$); 2.64 (t, J = 7 Hz, 2H, H4); 6.28 (d, J = 9.0 Hz, 1H, H8); 7.44 (d, J = 9.0 Hz, 1H, H7) and 13.14 (s, exchanged with D_2O, OH at C_5).

Fraction B, crystallised from petroleum ether, yielding **8** (0.2 g), m.p. 118–9° (lit.[7] m.p. 118–9°). NMR($CDCl_3$) δ: 1.31 (s, 6H, $C(CH_3)_2$); 1.79 (t, J = 7 Hz, 2H, H3); 2.48 (s, 3H, $COCH_3$); 2.71 (t, J = 7 Hz, 2H, H4); 6.24 (s, 1H, H8); 7.35 (s, 1H, H5) and 12.44 (s, exchanged with D_2O, OH at C_7).

Fraction C, crystallised from benzene–petroleum ether yielding **9** (0.1 g), m.p. 78–79° (Found: C, 74.6; H, 8.6; $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.3%). NMR($CDCl_3$) δ: 1.30 and 1.34 (each s, each 6H, $2 \times C(CH_3)_2$); 1.75 (t, J = 7 Hz, 4H, H3 and H3'); 2.50–2.76 (m, 7H, H4, H4' and $COCH_3$); 7.43 (s, 1H, H5).

6-Acetyl-7-hydroxy-2,2-dimethyl-2H-1-benzopyran (eupatoriochromene) (**10**). **8** (0.5 g) in dry benzene (20 ml) was refluxed for 8 hr with DDQ (0.57 g) and worked up as described. The residue thus obtained, on crystallisation from petroleum ether gave **10** (0.45 g) as pale yellow needles m.p. 75–6° (lit.[6] 76°). NMR($CDCl_3$) δ: 1.41 (s, 6H, $C(CH_3)_2$); 2.49 (s, 3H, $COCH_3$); 5.51 (d, J = 10 Hz, 1H, H3); 6.20 (d, J = 10 Hz, 1H, H4); 6.28 (s, 1H, H8); 7.22 (s, 1H, H5) and 13.2 (s, 1H, exchanged with D_2O, OH at C_7).

6-Acetyl-5-hydroxy-2,2-dimethyl-2H-1-benzopyran (**12**). **7** (0.5 g) in dry benzene (20 ml) was refluxed for 8 hr with DDQ (0.57 g) and worked up as described. The residue thus obtained, on crystallisation from petroleum ether gave **12** (0.45 g) as pale yellow needles m.p. 104° (lit.[11] 104–5°). NMR($CDCl_3$) δ: 1.36 (s, 6H, $C(CH_3)_2$); 2.47 (s, 3H, $COCH_3$); 5.58 (d, J = 10 Hz, 1H, H3); 6.32 (d, J = 9 Hz, 1H, H8); 6.44 (d, J = 10 Hz, 1H, H4); 7.31 (d, J = 9 Hz, 1H, H7); 13.42 (s, 1H, exchanged with D_2O, OH at C_5).

Reaction of 2,4-dihydroxy-6-methoxyacetophenone with isoprene

A soln of isoprene (0.72 ml) in xylene (2.0 ml) was added to a mixture of 2,4-dihydroxy-6-methoxyacetophenone (1.0 g), orthophosphoric acid (90%; 0.58 ml) and xylene (2.0 ml) with constant stirring at 30–35° during 8 hr. Stirring was continued for a further 12 hr and then working up the reaction gave a product which was found to be a mixture of two major products. Hence it was subjected to column chromatography and the elution of the column with (i) benzene:petroleum ether (1:19) and (ii) benzene:petroleum ether (1:9) gave following two fractions.

Fraction A, crystallised from benzene–petroleum ether yielding 14 (0.3 g), m.p. 92–3° (lit.[7] 93–4°). NMR($CDCl_3$) δ: 1.32 (s, 6H, $C(CH_3)_2$); 1.76 (t, J = 7 Hz, 2H, H3); 2.58 (triplet superimposed with a singlet, 5H, H4 and $COCH_3$); 3.80 (s, 3H, OCH_3); 5.82 (s, 1H, H8); 14.44 (s, 1H, exchanged with D_2O, OH at C_5).

Fraction B, crystallised from benzene–petroleum ether yielding 15 (0.3 g), m.p. 52° (lit.[7] 51–2°). NMR($CDCl_3$) δ: 1.34 (s, 6H, $C(CH_3)_2$); 1.77 (t, J = 7 Hz, 2H, H3); 2.68 (triplet superimposed with a singlet, 5H, H4 and $COCH_3$); 3.78 (s, 3H, OCH_3); 6.14 (s, 1H, H8); 13.0 (s, 1H, exchanged with D_2O, OH at C_7).

6 - Acetyl - 5 - hydroxy - 7 - methoxy - 2,2 - dimethyl - 2H - 1 - benzopyran (isoevodionol) (**16**). **14** (0.2 g) in dry benzene (10 ml) was refluxed for 8 hr with DDQ (0.2 g) and worked up as described. The residue thus obtained, on crystallisation from petroleum ether gave **16** (0.17 g) as pale yellow plates m.p. 129° (lit.[14] m.p. 128–9°).

6 - Acetyl - 7 - 7 - hydroxy - 5 - methoxy - 2,2 - dimethyl - 2H - 1 - benzopyran (evodionol) (**17**). **15** (0.2 g) in dry benzene (10 ml) was refluxed for 8 hr with DDQ (0.2 g) and worked up as described. The residue thus obtained, on crystallisation from benzene–petroleum ether gave (**17**) (0.18 g) as colourless plates m.p. 86° (lit.[9] m.p. 86–86.5°).

Acknowledgement—Our thanks are due to CSIR, New Delhi, India for the financial assistance.

REFERENCES

[1]W. D. Ollis and I. O. Sutherland, *Isoprenoid Units in Natural Phenolic Compounds.* In *Chemistry of Natural Phenolic Compounds* (Edited by W. D. Ollis), p. 74. Pergamon Press, Oxford (1961).
[2]G. Cardillo, R. Cricchio and L. Merlini, *Tetrahedron* **24**, 4825 (1968).
[3]H. B. Bhat and K. Venkataraman, *Ibid.* **19**, 77 (1963).
[4]R. Adams, C. K. Cain and S. Loewe, *J. Am. Chem. Soc.* **63**, 1977 (1941).
[5]R. J. Molyneux and L. Jurd, *Tetrahedron* **26**, 4743 (1970).
[6]T. Anthonsen, *Acta Chem. Scand.* **23**, 3605 (1969).
[7]B. S. Bajwa, P. Lal and T. R. Seshadri, *Ind. J. Chem.* **11**(2), 100 (1973).
[8]B. S. Bajwa, P. Lal and T. R. Seshadri, *Ibid.* **9**(1), 17 (1971).
[9]V. K. Ahluwalia, C. Prakash and R. Gupta, *Tetrahedron* to be published.
[10]L. F. Bjeldanes and T. A. Geissmann, *Phytochem.* **8**, 1293 (1969).
[11]J. Nickl, *Ber. Dtsch. Chem. Ges.* **91**, 1372 (1958).
[12]A. C. Jain, P. Lal and T. R. Seshadri, *Ind. J. Chem.* **7**(11), 1072 (1969).
[13]S. K. Mukerjee, S. C. Sarkar and T. R. Seshadri, *Ind. J. Chem.*, **8**(10), 861 (1970).
[14]R. D. Allan, R. L. Correll and R. J. Wells, *Tetrahedron Letters* 4673 (1969).
[15]L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 2376 (1950).
[16]K. D. Kirby and M. D. Sutherland, *Aust. J. Chem.* **9**, 411 (1956).
[17]M. E. Baldwin, I. R. C. Bick, A. A. Komzak and J. R. Price, *Tetrahedron* **16**, 206 (1961).