Tetrahedron. Vol 26, pp. 4667 to 4671. Pergamon Press 1970. Printed in Great Britain

CLAISEN REARRANGEMENTS—I
SYNTHESIS OF THE COUMARIN, PINNARIN

R. D. H. MURRAY* and M. M. BALLANTYNE
Department of Chemistry, University of Glasgow, Glasgow W.2

(*Received in the UK* 22 *June* 1970; *Accepted for publication* 3 *July* 1970)

Abstract—The natural coumarin, pinnarin (**9**) has been synthesised in four steps from **5**. Introduction of the 1,1-dimethylallyl unit at C-8 has been achieved in high yield by performing the Claisen rearrangement of the 3,3-dimethylallyl ether (**6**) in the presence of butyric anhydride. Unusually strong OH–π intramolecular H-bonding is observed in the IR spectrum of **8**.

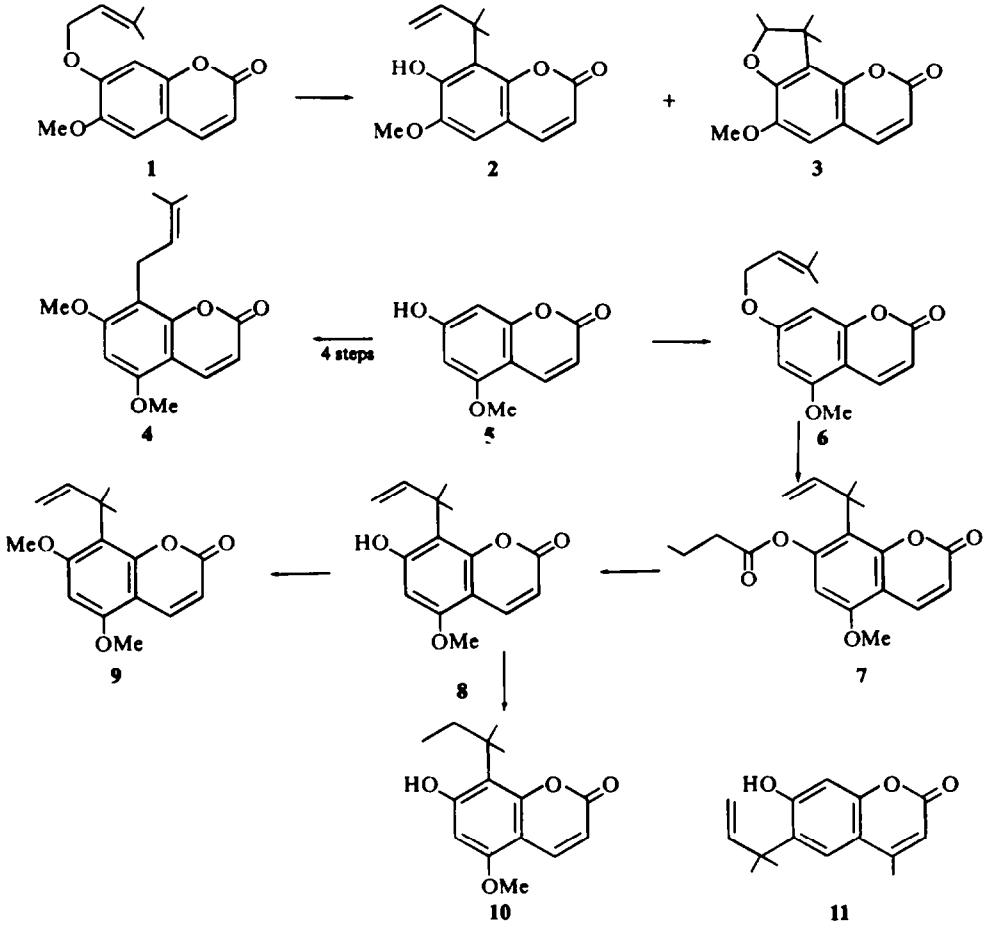
OUR interest[1,2] in the heartwood constituents of *Ptaeroxylon obliquum* led us to investigate[3] the Claisen rearrangement as a method for the synthesis of natural coumarins having the relatively uncommon 1,1-dimethylallyl side chain. Thus we found[3] that pyrolysis of the 3,3-dimethylallyl ether (**1**) afforded two of the *P. obliquum* coumarins, namely the desired *ortho* rearrangement product, obliquetin (**2**) and its cyclised isomer, nieshoutin (**3**). Extension of these studies to 1,1-dimethylallyl ethers has led[4] to the successful syntheses of osthenol and demethylsuberosin from umbelliferone and coumurrayin (**4**) from 7-hydroxy-methoxycoumarin (**5**). The high selectivity of rearrangement to the 8-position in this last example prompted us to investigate the Claisen rearrangement of the 3,3-dimethylallyl ether of **5**. This was thought[5] to be particularly relevant since it might provide confirmatory evidence for the structure of pinnarin[6] (**9**), a 5,7-dimethoxycoumarin containing a 1,1-dimethylallyl grouping which has been placed at C-8 on the basis of UV and NMR data.

7-Hydroxy-5-methoxycoumarin (**5**) was conveniently prepared from 5,7-diacetoxycoumarin.[7] However, we found it necessary to separate **5** from a small amount of the isomeric 5-hydroxy-7-methoxycoumarin by repeated fractional crystallization.

Pyrolysis of **6**, readily derived from **5** in 85% yield, at 185° in the absence of solvent not unexpectedly[3] led to a mixture of compounds. Bearing in mind the low yield (9%) of obliquetin obtained by this procedure,[3] a modification of the reaction conditions was sought to maximise the yield of the required *ortho*-(1,1-dimethylallyl)-phenol (**8**). In a study[8] of the Claisen rearrangement of 3,3-dimethylallyl oestrone ether, Jefferson and Scheinmann were able to trap the first formed phenol by carrying out the reaction in the presence of butyric anhydride. Using this method, the ether (**6**) was converted in high yield (92%) to a single butyrate whose NMR spectrum clearly indicated[3] that a 1,1-dimethylallyl unit had been inserted into the benzenoid ring. This butyrate could be firmly assigned structure **7** since it has been shown that coumarin 7-allyl[9] and 7-(1,1-dimethylallyl)[4,10] ethers on pyrolysis rearrange predominantly or exclusively to the C-8 position. Although some coumarin isoprenyl ethers have been found[11] to be thermally unstable giving isoprene with regeneration

of the parent phenol, surprisingly the butyrate of **5** was not isolated from the above experiment.

The ester **7**, when exposed to warm 0·2% NaOH–EtOH for one min, was converted to the phenol **8** (86%) the NMR of which was consistent with the proposed structure showing that no further rearrangement[3,8] had occurred. Reaction of **8** with MeI and K_2CO_3 in refluxing acetone gave a dimethyl ether which was identical (mp, mmp, TLC and IR) with a sample of natural pinnarin very kindly provided by Professor González.



An interesting feature of the IR spectrum of **8** is the remarkably low value, 3428 cm^{-1}, of the OH stretching frequency. It has been reported[12] that *o*-(1,1-dimethylallyl)-phenol displays both free OH (3615) and intramolecularly bonded OH (3494 cm^{-1}) bands. The absence of any free OH stretching frequency in the spectrum of **8** in addition to the considerably stronger OH–π intramolecular H-bond[13] is considered to be a consequence of the acidity of the coumarin 7-OH group and of the restricted rotation of the bulky 1,1-dimethylallyl residue. It was noticeable that for dihydro-demethylpinnarin (**10**) a steric buttressing effect[13] was in evidence, the free OH band

appearing as a doublet at 3629 and 3599 cm^{-1}. In agreement with the above hypothesis, intramolecular OH–π H-bonding was considerably weaker for the model compound[14] (11). The spectrum of this coumarin which possesses a similarly acidic OH group but has the 1,1-dimethylallyl grouping in the sterically less crowded 6-position, shows two OH stretching frequencies, bonded at 3475 and a less intense free OH band at 3593 cm^{-1}.

This synthesis of pinnarin provides strong evidence for the 1,1-dimethylallyl residue being attached to the C-8 position. Further, since **8** is formed from **5** in 67% yield, this pathway represents an efficient method for the incorporation of a 1,1-dimethylallyl unit *ortho* to a phenol.

EXPERIMENTAL

M.ps were determined with a Kofler hot stage apparatus. IR spectra were recorded for CCl_4 solns by Mrs. F. Lawrie on a Unicam SP 100 Mark II spectrophotometer. UV spectra were recorded for EtOH solns on a Unicam SP 800 spectrophotometer; λ (in base) refers to the above solns to which 2 drops 4N NaOH were added. NMR spectra of solns in $CDCl_3$ with TMS as internal standard were recorded by Mrs. S. Hamilton with a Varian T-60 spectrometer. Mass spectra were recorded by Mr. A. Ritchie with an AEI–GEC MS12 mass spectrometer. Microanalyses were performed by Mr. J. M. L. Cameron and his staff. Kieselgel G (Merck) was used for preparative TLC plates. Light petroleum refers to the fraction of b.p. 60–80°.

5-Methoxy-7-hydroxycoumarin (**5**)

K_2CO_3 (7 g) and MeI (7 ml) were added to a soln of 5,7-diacetoxycoumarin (3·5 g) in acetone (350 ml). After refluxing for 40 hr, more MeI (3·5 ml) was added and refluxing continued for a further 6 hr and another addition made. The inorganic solid was filtered off 3 hr later and washed with hot acetone. After evaporation of the solvent TLC examination revealed that some starting material still remained. The residue was then dissolved in acetone (350 ml), K_2CO_3 (7 g) and MeI (3·5 ml) added and the mixture refluxed for 6 hr. The solvent was evaporated and the residue dissolved in aqueous MeOH (50% v/v, 200 ml). The soln was heated on a steam bath for 15 min, allowed to cool and neutralised with dil HCl. Most of the solvent was then removed and the residue dissolved in a mixture of EtOAc and NaOH aq (0·5% w/v). The organic layer was washed with NaOH aq (0·5%) until the basic washings were colourless. The combined washings were carefully neutralised and set aside. The EtOAc soln was washed with brine to neutrality, dried and evaporated. Crystallization of the residue from MeOH afforded 5,7-dimethyoxycoumarin as pale yellow needles (0·16 g, 6%), m.p. 145–147° (lit.[7] m.p. 145°).

The neutralised washings were extracted with EtOAc and the organic layer washed with brine, dried and evaporated. Crystallization of the residue from MeOH afforded 5,7-dimethoxycoumarin as pale yellow 41%), m.p. 241–244° (lit.[7] m.p. 243–245°); λ_{max} 221, 247, 257 and 330 nm (log ε 4·02, 3·72, 3·74 and 4·14), λ_{max} (in base) 236, 271 and 374 nm (log ε 3·96, 3·79 and 4·29).

The mother liquors afforded a crystalline mixture (0·48 g, 19%) of **5** and 5-hydroxy-7-methoxycoumarin (~2:1) (identification from TLC behaviour and UV spectra, by comparison with authentic samples).

5-Methoxy-7-hydroxycoumarin butyrate

A soln of **5** (25 mg) and butyric anhydride (0·1 ml) in dry pyridine (0·2 ml) was kept for 2 hr, then diluted with iced water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated, the residual traces of pyridine being removed by azeotroping with C_6H_6. The residual solid was sublimed at 145°/0·15 mm to give *5-methoxy-7-hydroxycoumarin butyrate* as colourless needles (31 mg, 91%), m.p. 116–118°. (Found: C, 64·3; H, 5·3. $C_{14}H_{14}O_5$ requires: C, 64·1; H, 5·4%); NMR signals at τ 8·95 (3H, t, J = 7 Hz), 8·22 (2H, sextet, J = 7 Hz), 7·43 (2H, t, J = 7 Hz), 6·10 (3H, s), 3·76 (1H, d, J = 9·5 Hz), 3·54 (1H, d, J = 2 Hz), 3·34 (1H, d, J = 2 Hz) and 2·05 (1H, d, J = 9·5 Hz); mass spectral peaks at *m/e* 262 (M^+), 192, 165, 71 and 43 (relative abundance 11, 100, 39, 23 and 40%).

Dimethylallylation of **5**

A mixture of 5-methoxy-7-hydroxycoumarin (150 mg), K_2CO_3 (150 mg), dimethylallyl bromide (200 mg) and acetone (50 ml) were refluxed for 12 hr. After freeing from inorganic material which was washed with

hot acetone, the solvent was evaporated. The residue was dissolved in EtOAc, washed with brine, dried and evaporated. The resulting low melting solid on crystallization from ether–light petroleum gave 5-*methoxy*-7-O-(3,3-*dimethylallyl*)*coumarin* (**6**) as colourless needles (174 mg, 85%), m.p. 101–102°. (Found: C, 69·35; H, 6·1. $C_{15}H_{16}O_4$ requires: C, 69·2; H, 6·2%); NMR signals at τ 8·32 (6H, bs), 6·20 (3H, s), 5·55 (2H, bd, J = 6·5 Hz), 4·62 (1H, bt, J = 6·5 Hz), 3·99 (1H, d, J = 9·5 Hz), 3·80 (1H, d, J = 2 Hz), 3·70 (1H, d, J = 2 Hz) and 2.17 (1H, d, J = 9·5 Hz); mass spectral peaks at *m/e* 260, 245, 205, 193, 192, 164, 69 and 41 (relative abundance 5, 5, 6, 12, 100, 47, 35 and 31%).

Pyrolysis of **6**

Oxygen-free N_2 was passed over a suspension of **6** (60 mg) in N,N-diethylaniline (0·5 ml) and butyric anhydride (0·3 ml) contained in a 1 ml flask for 1 hr. The flask was then immersed in an oil bath at 185 ± 5°, shaken for 5 min to ensure that the melt had dissolved then kept at this temp under N_2 for 8 hr. The mixture was diluted with iced water (10 ml), set aside for 2 hr and then extracted with EtOAc. The organic layer was washed with dil HCl (1% w/v) to pH2, dil K_2CO_3 (5% w/v) to pH11, brine to neutrality, dried and evaporated. The residue was purified by preparative TLC [2 × EtOAc–light petroleum (3:7); then 1 × $CHCl_3$] and sublimed at 155°/0·02 mm. This afforded the *butyrate* (**7**) as colourless needles (70 mg, 92%), m.p. 162–164°. (Found: C, 68·8; H, 6·45. $C_{19}H_{22}O_5$ requires: C, 69·05; H, 6·7%); NMR signals at τ 8·97 (3H, t, J = 7 Hz), 8·39 (6H, s), ~8·31 (2H, m), 7·51 (2H, t, J = 7 Hz), 6·14 (3H, s), 5·14 (1H, bd, J = 10 Hz), 5·11 (1H, bd, J = 18 Hz), 3·76 (1H, dd, J = 10 and 18 Hz), 3·74 (1H, d, J = 9·5 Hz), 3·74 (1H, s), 1·98 (1H, d, J = 9·5 Hz); mass spectral peaks at *m/e* 330 (M^+), 315, 261, 260, 246, 245, 217, 205, 71 and 43 (relative abundance 23, 14, 9, 47, 16, 100, 16, 40, 27 and 42%).

5-*Methoxy*-7-*hydroxy*-8(1,1-*dimethylallyl*)*coumarin* (**8**)

The butyrate **7** (32 mg) was dissolved in EtOH (5 ml) with gentle heating. NaOH in EtOH (1% w/v, 1 ml) was added and the soln warmed on a steam bath for 1 min until a bright blue-green fluorescence appeared. The soln was then carefully neutralised with dil HCl (1% w/v) and most of the solvent evaporated. The remainder was diluted with water and extracted into EtOAc. After preparative TLC [2 × EtOAc–light petroleum (3:7)] the residue was crystallized from ether to give 7-*demethylpinnarin* (**8**) as colourless needles (22 mg, 86%), m.p. 161–166° dec. (Found: C, 69·05; H, 6·25. $C_{15}H_{16}O_4$ requires: C, 69·2; H, 6·2%); ν_{max} (0·024 M and 0·0024 M) 3428, 1755 (sh), 1739, 1626 and 1599 cm^{-1}; λ_{max} 225, 255, 262 and 332 nm (log ε 4·02, 3·87, 3·89 and 4·11), λ_{max} (in base) 253, 281 and 400 nm (log ε 3·91, 3·96 and 4·30); NMR signals at τ 8·29 (6H, s), 6·13 (3H, s), 4·63 (1H, d, J = 10·5 Hz), 4·54 (1H, d, J = 18 Hz), 3·86 (1H, d, J = 9·5 Hz), 3·74 (1H, s), 3·51 (1H, dd, J = 10·5 and 18 Hz), 2·71 (1H, s) and 1·98 (1H, d, J = 9·5 Hz); mass spectral peaks at *m/e* 261, 260, 246, 245, 217, 205 and 189 (relative abundance 10, 53, 22, 100, 43, 50 and 20%).

5-*Methoxy*-7-*hydroxy*-8(1,1-*dimethylpropyl*)*coumarin* (**10**)

The hydroxy–ether **8** (25 mg) in EtOAc (20 ml) was hydrogenated over 5% Pd-$BaSO_4$ (15 mg) for 2 hr. After freeing from catalyst and solvent, the *phenol* (**10**) crystallized from ether as pale yellow needles (20 mg, 80%), m.p. 222–226° dec. (Found: C, 68·85; H, 6·85. $C_{15}H_{18}O_4$ requires: C, 68·7; H, 6·9%); ν_{max} (sat soln) 3629, 3599, 1738 and 1625 cm^{-1}; NMR signals (in deuteropyridine) at τ 9·03 (3H, t, J = 7 Hz), 8·08 (6H, s), 7·73 (2H, q, J = 7 Hz), 6·30 (3H, s), 3·78 (1H, d, J = 9·5 Hz), 3·43 (1H, s) and 2·01 (1H, d, J = 9·5 Hz).

5,7-*Dimethoxy*-8(1,1-*dimethylallyl*)*coumarin* (**9**)

A mixture of **10** (34 mg), K_2CO_3 (100 mg), MeI (0·2 ml) and acetone (5 ml) was refluxed for 12 hr. Work up yielded **9** which crystallized from ether as colourless needles (30 mg, 84%), m.p. 166–167° (corrected), lit.[6] m.p. 162–163°. (Found: C, 70·05; H, 6·45. Calc. for $C_{16}H_{18}O_4$: C, 70·05; H, 6·6%); ν_{max} 1736, 1622 and 1598 cm^{-1}; λ_{max} 223, 254, 261 and 328 nm (log ε 4·09, 3·96, 3·98 and 4·15); NMR signals at τ 8·34 (6H, s), 6·15 (3H, s), 6·07 (3H, s), 5·15 (1H, d, J = 10 Hz), 5·14 (1H, d, J = 18 Hz), 3·87 (1H, d, J = 9·5 Hz), 3·71 (1H, dd, J = 10 and 18 Hz), 3·67 (1H, s) and 2·03 (1H, d, J = 9·5 Hz); mass spectral peaks at *m/e* 275, 274 (M^+), 260, 259, 231 and 219 (relative abundance 12, 63, 17, 100, 35 and 29%). This compound was found to be identical with an authentic sample of pinnarin by TLC behaviour, mp, mmp, and solution IR.

Acknowledgements—One of us (MMB) is grateful to the S.R.C. for a maintenance award.

REFERENCES

[1] P. H. McCabe, R. McCrindle and R. D. H. Murray, *J. Chem. Soc.* (C), 145 (1967).

[2] R. D. H. Murray and M. M. Ballantyne, *Tetrahedron Letters* 4031 (1969); R. D. H. Murray and M. M. Ballantyne, *Tetrahedron* **26**, 4473 (1970)

[3] M. M. Ballantyne, R. D. H. Murray and A. B. Penrose, *Tetrahedron Letters* 4155 (1968)
[4] R. D. H. Murray, M. M. Ballantyne and K. P. Mathai, *Ibid.* 243 (1970)
[5] Private communications with Professor A. G. González, Universidad de la Laguna, Tenerife
[6] R. E. Reyes and A. G. González, *Anales real Soc. Espan. Fis. Quim.* **65**, 91 (1969); R. E. Reyes and A. G. González, *Phytochemistry* **9**, 833 (1970)
[7] V. K. Ahluwalia, T. R. Seshadri and P. Venkateswarlu, *Indian J. Chem.* **7**, 115 (1969)
[8] A. Jefferson and F. Scheinmann, *J. Chem. Soc.* (C), 243 (1969)
[9] T. R. Seshadri and M. S. Sood, *Indian J. Chem.* **3**, 354 (1965; K. D. Kaufmann, *J. Org. Chem.* **26**, 117 (1961)
[10] J. Hlubucek, E. Ritchie and W. C. Taylor, *Chem. & Ind.* 1780 (1969)
[11] B. Chaudhury, S. K. Saha and A. Chatterjee, *J. Indian Chem. Soc.* **39**, 783 (1962)
[12] A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.* **81**, 4524 (1959)
[13] R. D. H. Murray and P. H. McCabe, *Tetrahedron* **25**, 5819 (1969) and refs cited.
[14] One of the products of pyrolysis of 7-O-(3,3-dimethylallyl)-4-methylumbelliferone; R. D. H. Murray and M. M. Ballantyne, unpublished results.