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CLAISEN REARRANGEMENTS—XI

SYNTHESIS OF THE COUMARINS, OBLIQUETOL, OBLIQUETIN AND NIESHOUTIN

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Abstract—Obliquetol **5** has been synthesised for the first time using improved conditions for prenyloxycoumarin Claisen rearrangements. Efficient syntheses of obliquetin **6** and the related dihydrofurano-coumarin, nieshoutin **13** are also reported. The structure assigned to the natural coumarin, celerin, requires revision.

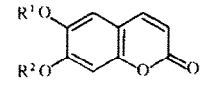
The heartwood of sneezewood, *Ptaeroxylon obliquum*, has been found to contain a fascinating array of coumarins[2-7] and chromones.[2,3,8] Apart from the 5,6,7-trioxygenated coumarin, nieshoutol,[7] the remaining eight coumarins are all derivatives of 6,7-dihydroxycoumarin **1**. Three of these contain an additional five-carbon substituent at C-8. In obliquetol[4] **5** and its 6-monomethyl ether, obliquetin **6**, this is present as a 1,1-dimethylallyl group, *ortho* in both cases to a phenol at C-7 but found as the corresponding 2,3,3-trimethyldihydrofuran in nieshoutin[3] (cycloobliquetin[4] **13**). Previously we showed[5] that obliquetin could be obtained, by Claisen rearrangement at 195°, from another of the *P.obliquum* coumarins, 7-prenyloxy-6-methoxycoumarin **4**. The yield of this *ortho*-rearrangement product from vacuum pyrolysis was however only 9%. Three other coumarins were obtained; the corresponding cyclised derivative, nieshoutin **13** (21%), scopoletin **2** (30%) from the anticipated prenyl ether cleavage[9] and the unexpected product **15** (14%) of a triple rearrangement to C-3. An attempt was made to obtain obliquetol **5** by similar vacuum pyrolysis of 7-prenyloxy-6-hydroxycoumarin **3**. The complex mixture obtained was however completely devoid of the desired *ortho*-rearrangement product, obliquetol, although the corresponding dihydrofuran **12** (10%), triple rearrangement product **14** (10%) and prenyl ether cleavage product **1** (19%) were identified.

A key step in our synthesis[1] of hortiolone required rearrangement of a prenyloxycoumarin to the *o*-(1,1-dimethylallyl)hydroxycoumarin. The convenient solution of trapping the first-formed rearrangement product as its acetate thereby preventing incursion of an abnormal Claisen rearrangement prompted us to reinvestigate the pyrolyses of **3** and **4**.

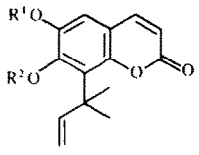
When 7-prenyloxy-6-methoxycoumarin[5] **4** was heated in refluxing acetic anhydride containing sodium acetate for 24 hr, the normal rearrangement product, obliquetin, was trapped quantitatively as its acetate **7**. The natural coumarin **6** was liberated by overnight treatment with 2% methanolic NaOH at room temperature in 91% yield. Although cyclisation of **6** to nieshoutin is a facile process, no trace of the dihydrofuran nor indeed of any cleavage or other product could be detected in the rearrangement. Conversely when acetic anhydride was omitted and an intimate mixture of **4** and sodium acetate was heated at 190° for 30 min, nieshoutin **13** became the sole product, isolated in 96% yield.

It was of interest to determine whether the above two-step method could be used for the synthesis of obliquetol. Accordingly, 7-prenyloxy-6-hydroxycoumarin[5] **3** was heated in refluxing acetic anhydride containing sodium acetate. The only product was shown to be obliquetol diacetate **8** from its ^{1}H NMR spectrum which disclosed a 1,1-dimethylallyl substituent at C-8.[5] Obliquetol **5** was obtained in 92% overall yield by hydrolysis of **8** with 2% methanolic NaOH for 5 min or by treatment with Zn dust in MeOH overnight. The latter deacetylation procedure,[10] albeit slower, is more selective, obliquetin acetate **7** being recovered intact even after prolonged treatment.

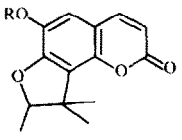
A new coumarin, celerin, has recently been isolated[11] from *Apium graveolens* seeds and structure **9** proposed from its spectra and those of its methylation and demethylation products. Celerin and obliquetin thus represent the two possible monomethyl ethers of obliquetol. Consequently if partial methylation of obliquetol could be achieved then



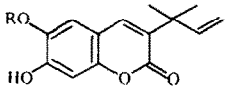
1 $R^1=R^2=H$
2 $R^1=Me$, $R^2=H$
3 $R^1=H$, $R^2=CH_2CH=CMe_2$
4 $R^1=Me$, $R^2=CH_2CH=CMe_2$



5 $R^1=R^2=H$
6 $R^1=Me$, $R^2=H$
7 $R^1=Me$, $R^2=Ac$
8 $R^1=R^2=Ac$
9 $R^1=H$, $R^2=Me$
10 $R^1=Ac$, $R^2=Me$
11 $R^1=R^2=Me$



12 R=H
13 R=Me



14 R=H
15 R=Me

either obliquetin or the structure assigned to celerin must be obtained. Bearing in mind that *O*-alkylation of 6,7-dihydroxycoumarin proceeds preferentially at the 7-position[5,6,12] and that greater selectivity in dihydroxycoumarin alkylations has been achieved by using the corresponding diacetoxycoumarin as substrate,[13] we anticipated that treatment of obliquetol diacetate **8** with one equivalent of methyl iodide in refluxing acetone containing K_2CO_3 should give celerin acetate. It was appreciated however that extended exposure of an acetoxycoumarin to these slightly alkaline reaction conditions might eventually lead to complete deacetylation.[13] After 20 hr, no starting material remained but four products were obtained, none of which contained an acetoxyl group; trace amounts of obliquetin **6** and obliquetol dimethyl ether **11** detectable only by TLC, mainly obliquetol **5** (48%) and a new diol monomethyl ether (28%), m.p. 206–208°, isomeric with obliquetin. The ^{1}H NMR spectrum of this ether is in complete accord with that expected for structure **9** but differs substantially from that reported for celerin, m.p. 154–156°. The structure assigned to celerin is clearly incorrect. In particular, the marked low-field chemical shift (δ 8.28) found for H-4 of celerin requires one of the three benzenoid substituents to be located at C-5.[14] Attempts to ascertain the correct structure of celerin are in hand.

EXPERIMENTAL

For general experimental see preceding communication.

Synthesis of obliquetin **6**

Compound[5] **4** (70 mg), NaOAc (80 mg) and Ac_2O (2 ml) were refluxed for 24 hr with stirring (oil bath 160°). The cooled mixture was partitioned between dil HCl and EtOAc, the organic layer washed with dil HCl, sat $NaHCO_3$ aq, brine, dried and evaporated to give *7-acetoxy-6-methoxy-8-(1,1-dimethylallyl)coumarin* **7** (82 mg, 100%) needles, m.p. 119–121° (from ether–hexane) (Found: C, 67.5; H, 5.7. $C_{17}H_{18}O_5$ requires: C, 67.55; H, 6.0%); ν_{max}($CHCl_3$) 1765, 1720, 1565 and 1450 cm^{-1}; NMR signals at δ 1.62 (6H, s), 2.21 (3H, s), 3.82 (3H, s), 4.92 (1H, d, J = 10 Hz), 4.97 (1H, d, J = 17.5 Hz), 6.30 (1H, dd, J = 17.5 and 10 Hz), 6.34 (1H, d, J = 9.5 Hz), 6.86 (1H, s) and 7.69 (1H, d, J = 9.5 Hz).

A soln of **7** (51 mg) in MeOH (15 ml) and methanolic NaOH (3 ml, 2% w/v) was kept overnight. The solvent was carefully evaporated under reduced pressure, the residue dissolved in a mixture of dil HCl and EtOAc and the organic layer washed with brine, dried and evaporated to give **6** (40 mg, 94%), pale yellow needles, m.p. and mixed m.p. 138–139° (lit.[4] 138–139°) (from EtOAc); NMR signals at δ 1.69 (6H, s) 3.95 (3H, s), 4.99 (1H, d, J = 10 Hz), 5.04 (1H, d, J = 17.5 Hz), 6.21 (1H, d, J = 9.5Hz), 6.39 (1H, dd, J = 17.5 and 10 Hz), 6.65 (1 H, s, O*H*), 6.74 (1 H, s) and 7.54 (1H, d, J = 9.5 Hz) identical (TLC, IR and NMR) with an authentic sample. When **7** (60 mg) was heated with K_2CO_3 (500 mg) in refluxing acetone (30 ml) for 24 h, work up gave recovered **7** (57 mg).

Synthesis of nieshoutin **13**

A mixture of **4** (44 mg) and NaOAc (70 mg) was heated for 30 min (oil bath 190°). The cooled mixture was partitioned between dil HCl and EtOAc and the organic layer washed with dil HCl, sat $NaHCO_3$ aq, brine, dried and evaporated to give **13** (42 mg, 98%), pale yellow needles, m.p. and mixed m.p. 124–125° (lit.[3] 124–125°) (from ether–hexane) identical (TLC, IR and NMR) with an authentic sample.

Synthesis of obliquetol **5**

6-Hydroxy-7-prenyloxycoumarin[5] (83 mg) and NaOAc (80 mg) were heated with stirring with refluxing Ac_2O (2 ml) for 20 hr (oil bath 160°). Work up as above gave *6,7-diacetoxy-8-(1,1-dimethylallyl)coumarin* **8** (110 mg, 99%), colourless plates, m.p. 104–106° (from ether–hexane) (Found: C, 65.35; H, 5.45. $C_{18}H_{18}O_6$ requires: C, 65.45; H, 5.5%); ν_{max}($CHCl_3$) 1770, 1730, 1610, 1565 and 1420 cm^{-1}; NMR signals at δ 1.62 (6H, s), 2.21 (3H, s), 2.26 (3H, s), 4.93 (1H, d, J = 10 Hz), 4.99 (1H, d, J = 17.5 Hz), 6.30 (1H, dd, J = 17.5 and 10 Hz), 6.37 (1H, d, J = 9.5 Hz), 7.22 (1H, s) and 7.58 (1H, d, J = 9.5 Hz).

(i) A soln of obliquetol diacetate **8** (19 mg) in MeOH (5 ml) and 2% methanolic NaOH (1 ml) was kept for 5 min. Work up as above gave **5** (14 mg, 99%) tan yellow needles, m.p. and mixed m.p. 208–212° (lit.[4] 217–218°) (from EtOAc–hexane) (Found: C, 68.1; H, 5.5. Calc. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.75%); ν_{max}(KBr) 3450, 3000(b), 1680(b), 1610 and 1575 cm^{-1}; NMR signals (acetone-d_6) at δ 1.70 (6H, s), 4.91 (1H, dd, J = 9.5 and 1.5 Hz), 4.98 (1H, dd, J = 18 and 1.5 Hz), 6.10 (1H, d, J = 9.5 Hz), 6.40 (1H, dd, J = 18 and 9.5 Hz), 6.97 (1H, s), 7.70 (1H, d, J = 9.5 Hz) and 8.30 (2H, bs, 2 × O*H*), identical (TLC and IR) with an authentic sample.

(ii) A soln of **8** (40 mg) in MeOH (5 ml) was stirred with activated Zn[10] (300 mg) at room temp for 18 hr. The mixture was filtered through celite and washed with MeOH. The filtrate was evaporated and the residue partitioned between dil HCl and EtOAc, the organic layer washed with dil HCl, brine, dried and evaporated to give obliquetol (27 mg, 93%).

Partial methylation of obliquetol diacetate

K_2CO_3 (490 mg) and a soln of MeI in acetone (0.02M, 2.5 ml, 0.5 mmole) were added to a soln of **8** (145 mg, 0.44 mmole) and the mixture refluxed for 20 hr. The cooled mixture was filtered and the filtrate evaporated. The residue was dissolved in a mixture of dil HCl and EtOAc and the organic layer washed with brine, dried and evaporated. TLC of the crude product revealed mainly **5** and **9** with traces of **6** and **11**. Column chromatography of the crude product on silica and elution with EtOAc–light petroleum (2:3) gave (i) *6-Hydroxy-7-methoxy-8-(1,1-dimethylallyl)coumarin* **9** (31 mg, 28%), colourless needles, m.p. 206–208° (from EtOAc–hexane) (Found: C, 68.95; H, 6.1. $C_{15}H_{16}O_4$ requires: C, 69.2; H, 6.2%); ν_{max}(KBr) 3420(b), 3160(b), 1680, 1600 and 1560 cm^{-1}; NMR signals (acetone-d_6) at δ 1.65 (6H, s), 3.74 (3H, s), 4.85 (1H, d, J = 10 Hz), 4.94 (1H, d, J = 17.5 Hz), 6.25 (1H, d, J = 9.5 Hz), 6.41 (1H, dd, J = 17.5 and 10 Hz), 7.03 (1H, s), 7.88 (1H, d, J = 9.5 Hz) and 8.20 (1H, bs, O*H*), and (ii) Obliquetol **5** (52 mg, 48%).

Obliquetol dimethyl ether **11**

K_2CO_3 (200 mg) and MeI (1 ml) were added to a soln of obliquetol (29 mg) in acetone (10 ml) and the mixture refluxed for 2.5 hr. Work up as above gave *obliquetin dimethyl ether* **11** (30 mg, 98%), plates, m.p. 78–82° (Found: M^+ 274. $C_{16}H_{18}O_4$ requires M^+ 274); NMR signals at δ 1.67 (6H, s), 3.76 (3H, s), 3.90 (3H, s), 4.91 (1H, d, J = 10 Hz), 4.95 (1H, d, J = 18.5 Hz), 6.30 (1H, d, J = 9.5 Hz), 6.40 (1H, dd, J = 18.5 and 10 Hz), 6.81 (1H, s) and 7.58 (1H, d, J = 9.5 Hz); mass spectral peaks at m/z 274 (100%), 259 (56), 243 (62), 231 (25), 228 (18), 217 (21), 189 (17) and 115 (32).

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