

Synthesis of linear diphenyl furanocoumarins*

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ABSTRACT

The elegant and direct synthesis of linear 2'-3'-diphenyl furanocoumarins is recorded for the first time by submitting the desyl ether of hydroxycoumarins to the action of mild 0.1 N KOH. This reagent brings about aldol condensation followed by cyclisation and dehydration in the presence of acids as proposed by Macleod and Worth to give the desired linear diphenyl furanocoumarins in good yield.

1. INTRODUCTION

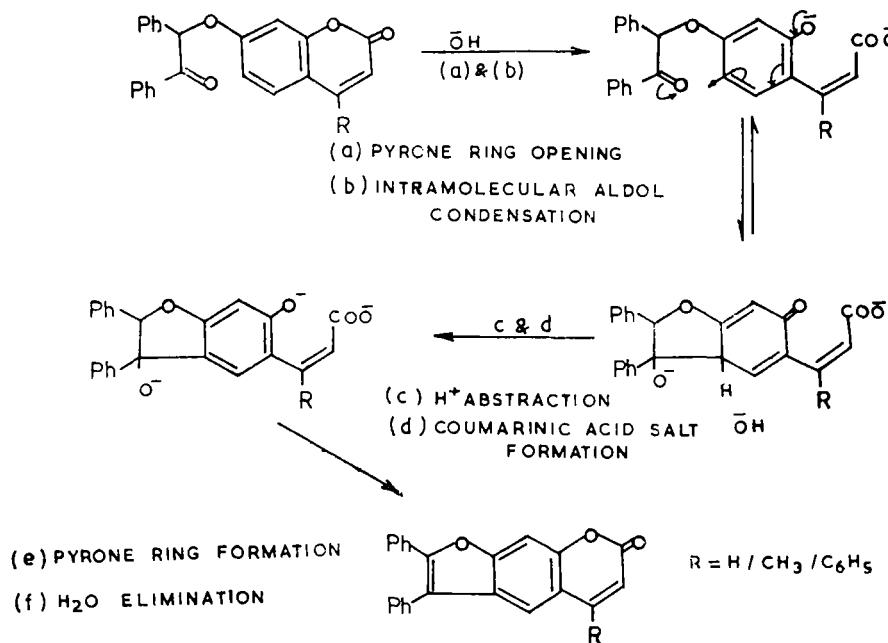
THE synthesis of 2', 3'-diphenyl furanocoumarins with the furan ring annulated in the 5, 6/7, 8 (angular) and 6, 7 (linear) positions to serve as model compounds with the cyclised triarylethylene structure so essential for anti-fertility activity has earlier been recorded.¹ These compounds could be synthesised by condensing the appropriate hydroxycoumarin with benzoin in the presence of polyphosphoric acid (PPA). It must be pointed out that for the synthesis of the linear (6, 7) isomer, however, a blocking group like the methyl group at the 8-position had to be employed so as to direct the mode of ring closure in the desired fashion. Now a direct and convenient synthesis of the linear isomer without the use of a blocking group and employing a different sequence of reactions has been worked out. This is based on the observations of Macleod and Worth² that 7-O-acetonyl/acetophenyl ether of 7-hydroxycoumarin and 7-hydroxy-4-methyl-coumarin when submitted to the action of 0.1 N KOH gives in a single step and in high yield the linear β -substituted (alkyl/aryl) furanocoumarin related to psoralen, the well known linear furanocoumarin.

Based on the above observations, attempts have now been made to synthesise linear fused 2', 3'-diphenyl furanocoumarins. As model experiments, 7-hydroxycoumarin,³ 7-hydroxy-4-methylcoumarin⁴ and 7-hydroxy-

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4-phenylcoumarin⁵ have been condensed with desyl bromide in acetone medium in presence of potassium carbonate to yield the 7-O-desyl ethers. These on heating with 0.1 N potassium hydroxide followed by acidification have yielded the linear 2', 3'-diphenyl (6, 7: 4', 5') furanocoumarins in good yields (50%). The linear structure proposed for these compounds is based on the NMR spectra as recorded in the experimental section.

This novel synthesis of the linear 2', 3'-diphenyl furano compound is visualised to proceed by the following mechanism (*vide chart*) on analogy with the one proposed by Macleod and Worth (*loc. cit.*):



(a) base hydrolysis of the pyrone ring to form the phenoxide ion; (b) intramolecular aldol condensation between the exocyclic carbonyl function and the resonance stabilized carbanion generated at the *p*-position to the phenoxide ion; (c) abstraction of a proton from the newly formed ring junction leading to the coumarinic acid salt; (d) reformation of the pyrone ring on acidification; (e) spontaneous elimination of water from the labile β -hydroxydihydrofuran to give the 2', 3'-diphenyl furan derivative.

2. EXPERIMENTAL

Melting points are uncorrected. Ultraviolet spectra were recorded on a Beckmann DU spectrophotometer and infrared spectra on a Perkin-Elmer 237 instrument. The NMR spectra were measured on a Varian A-60 spectrometer using tetramethylsilane as internal reference.

I. 7-O-DESYLCOUMARIN

7-Hydroxycoumarin (1.62 g) in acetone (150 ml) was treated with desyl bromide (2.75 g) and potassium carbonate (5 g) and the mixture refluxed for 12 hr. The inorganic salts were filtered off and the solvent distilled off from the filtrate. The crude desyl ether thus obtained crystallised from alcohol as rods, m.p. 160° C. (3.0 g, 84.5%). Found: C, 77.82; H, 4.25%. Cal. for $C_{23}H_{16}O_4$: C, 77.54; H, 4.49%. λ_{\max} (MeOH) 247 nm ($\log \epsilon = 4.25$); 295 (4.12). ν_{\max} (KBr) 1720 (lactone carbonyl), 1690 (acyl carbonyl), 1610, 1260, 1270 cm^{-1} .

II. 2, 3-DIPHENYL-7-OXO-7 H FURO (2, 3-g) (1) BENZOPYRAN

7-O-Desylcoumarin (1.0 g) was treated with KOH (0.1 N; 400 ml) and refluxed for 6 hr. The aqueous alkaline solution was filtered from the small amount of insoluble matter and then acidified. 2, 3-Diphenyl-7-oxo-7 H-furo (2, 3-g) (1) benzopyran that separated crystallised from, alcohol as shining needles, m.p. 248–49° C. (0.5 g, 52.8%). Found: C 81.45; H, 3.95. Cal. for $C_{23}H_{14}O_3$: C, 81.66; H, 4.14%. λ_{\max} (MeOH) 235 nm ($\log \epsilon = 3.33$); 285 (4.60); 344 (3.82). ν_{\max} (KBr) 1710 (lactone carbonyl) 1595, 1550, 1425, 865, 845, 830 cm^{-1} . NMR (DMSO) δ 6.29 (one-proton doublet, J 10 Hz, H 6); 8.0 (one-proton doublet, J 10 Hz, H 5) 7.71 (one-proton singlet, H 4) 7.3–7.57 (eleven-proton multiplet, 2, 3 phenyl and H 9).

III. 7-O-DESYL-4-METHYLCOUMARIN

7-Hydroxy-4-methylcoumarin (1.76 g) in acetone (150 ml) on refluxing with desyl bromide (2.75 g) and potassium carbonate (5.0 g) for 12 hrs yielded the O-desyl ether (III) as needles, m.p. 178–80° C. (3.3 g, 94.5%). Found: C, 77.83; H, 4.04. Cal. for $C_{24}H_{18}O_4$: C, 77.70; H, 4.00%. λ_{\max} (MeOH) 246 nm ($\log \epsilon = 4.24$); 295 (4.07). ν_{\max} (KBr) 1720 (lactone carbonyl), 1670 (acyl carbonyl), 1601, 1250 cm^{-1} .

IV. 2,3-DIPHENYL-5-METHYL-7-OXO-7 H FURO (2,3-g) (1) BENZOPYRAN

7-O-Desyl-4-methylcoumarin (0.8 g) was refluxed with KOH (0.1 N; 300 ml) for 6 hr and the reaction mixture worked up as in the case of 7-hydroxycoumarin. The furan compound (IV) crystallised from alcohol as needles, m.p. 225°. (0.25 g, 52%). Found: C, 82.2; H, 4.3. Cal. for $C_{24}H_{16}O_3$: C, 81.8; H, 4.6%. λ_{\max} (MeOH) 240 nm ($\log \epsilon = 4.35$); 282 (4.57). ν_{\max} (KBr) 1730 (lactone carbonyl), 1575, 1450, 1440, 1435, 865, 850, 840 cm^{-1} . NMR (CDCl_3) δ 2.45 (three-proton doublet, J 1.8 Hz, 5 methyl); 6.28 (one-proton doublet, J 1.8 Hz. H 6); 7.30 (one-proton

singlet H 9); 7.63 (one-proton singlet, H 4); 7.35-7.56 (ten-proton multiplet, 2, 3-phenyl protons).

V. 7-O-DESYL-4-PHENYLCOUMARIN

7-Hydroxy-4-phenylcoumarin (2.38 g) in acetone (130 ml), desyl bromide (2.75 g) and potassium carbonate (5.0 g) were refluxed for 12 hr. to yield 7-O-Desyl-4-phenylcoumarin. Recrystallisation from benzene yielded colourless needles melting at 186-90° C. (3.5 g, 81%) Found: C, 80.2; H, 5.0. Cal. for $C_{29}H_{20}O_4$: C, 80.6; H, 4.6%. λ_{\max} (MeOH) 234 nm ($\log \epsilon = 4.30$); 283 (4.47); 347 (4.3). ν_{\max} (Nujol) 1725 (lactone carbonyl) 1690 (acyl carbonyl), 1610 cm^{-1} .

VI. 2,3,5-TRIPHENYL-7-OXO-7 H FURO (2,3-g) (1) BENZOPYRAN

7-O-Desyl-4-phenylcoumarin (1.5 g) was refluxed with KOH (0.1 N) (aq. dioxane 3:1) 400 ml for 6 hr and the reaction mixture worked up as in the case of compounds II and IV. 2,3,5-Triphenyl-7-oxo-7 H-furo (2,3-g) (1) benzopyran thus obtained recrystallised from benzene as colourless needles melting at 244-46° C. (0.9 g, 62%). Found: C, 83.7; H, 4.6. Cal. for $C_{29}H_{18}O_3$: C, 84.0; H, 4.4%. λ_{\max} (MeOH) 233 nm ($\log \epsilon = 4.58$); 291 (4.70); 353 (4.32). ν_{\max} (Nujol) 1740 (lactone carbonyl), 1570, 1460, 1450, 1375, 1340, 885, 865, 825 cm^{-1} . NMR (CDCl) δ 6.37 (one-proton singlet, H 6); 7.35 (one-proton singlet, H 9); 7.66 (one-proton singlet, H 4); 7.38-7.55 (fifteen-proton multiplet, 2,3,5-phenyls).

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