

Reaction of Furanopyrones with Aluminium Chloride in Benzene*

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The product obtained by the reaction of angelicin (II) with aluminium chloride in benzene has been formulated as 7-hydroxy-8-(β,β -diphenylethyl)coumarin (IV). 7-Methoxy-8-(β,β -diphenylethyl) coumarin (IX) has been synthesized by the condensation of ethyl propiolate with 2-hydroxy-6-methoxy-1-(β,β -diphenylethyl)benzene (XV) in the presence of $ZnCl_2$. IX has been shown to be identical with the methyl ether of (IV). Psoralen (I) and chalepensis (V) are shown to give the furan opened benzene addition products 7-hydroxy-6-(β,β -diphenylethyl)coumarin (III) and 7-hydroxy-8-(β,β -diphenylethyl)coumarin (IV) respectively. Reaction of karanjin (XVII) with aluminium chloride in benzene gives 3,7-dihydroxy-8-(β,β -diphenylethyl)-flavone (XVIII).

IN a recent communication¹ we reported the reaction of furanocoumarins with aluminium chloride in benzene to give the benzene addition products by opening of the furan ring. Thus psoralen (I) and angelicin (II) formed (III) and (IV) respectively whereas chalepensis² (V) gave the rearrangement product (VI). Subsequent to the cleavage of the furan, the benzene addition could take place in two ways, giving hydroxy- α,β -diphenylethylcoumarin or hydroxy- β,β -diphenylethylcoumarin. In the case of (I) and (II), Krishnaswamy and Seshadri preferred to formulate the benzene addition products as (VII) and (VIII) instead of (III) and (IV) on the basis of favourable factors for the entry of the phenyl groups³. Our structure assignments (III) and (IV) were based on elemental analysis and spectral data. NMR spectra of these compounds (Table 1) were not useful in distinguishing between the alternative structures. The mass spectral fragmentations however, favoured the formulations (III) and (IV)¹. We have investigated the reaction of angelicin (II) with aluminium chloride in benzene and the product formed has been identified as 7-hydroxy-8-(β,β -diphenylethyl)coumarin (IV). 7-Methoxy-8-(β,β -diphenylethyl)coumarin (IX) has also been synthesized. It was found to be identical with the compound obtained by methylation of (IV).

Umbelliferone and its 4-methyl derivative were acylated with diphenylacetyl chloride to give (X) and (XI) respectively. Fries reaction on (X) and (XI) failed to give the rearranged phenolic ketone; instead, the deacylated compounds were obtained.

Resorcinol dimethyl ether on lithiation⁴ and reaction with diphenylacetyl chloride formed (XII), m.p. 134°, as the major product. A byproduct, m.p. 148°, obtained in this reaction has been formulated as (XIII) on the basis of elemental analysis, IR and NMR spectral data; ν_{max} 1745 (ester), 1580, 1610 cm^{-1} ($-C=C-$); NMR: δ 3.3 (6H, OMe, s), 4.95 (1H; $-CO-CH-$, s), 6.3 (*d*, $J = 7.5$ Hz; 2H; C-3, C-5) and 6.9-7.4 (21H, *m*).

Clemmensen reduction of (XII) gave β,β -diphenylethyl-2,6-dimethoxybenzene (XIV), m.p. 67° which on partial demethylation with aluminium chloride provided (XV) as a viscous oil, b.p. 150°/0.01 mm. Condensation of (XV) with ethyl propiolate in the presence of zinc chloride⁵ gave the coumarin (IX), m.p. 145°. Methylation of (IV) with diazomethane yielded a compound, m.p. 144.5° identical (m.m.p., TLC, IR and NMR) with (IX).

Krishnaswamy and Seshadri⁶ obtained α -phenyl- α,β -dihydrokaranjonol (XVI), m.p. 260-62°, by the reaction of karanjin (XVII) with aluminium chloride in benzene. In a similar reaction carried out at 25°, we obtained a compound, m.p. 233.4°, to which we ascribe the structure (XVIII). It was characterized by the formation of the dimethyl ether (XIX) and diacetate (XX). These formulations are consistent with the NMR spectra of these compounds.

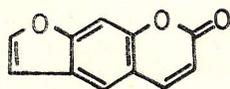
We had suggested¹ that in the formation of the benzene addition products, an initial step might be opening of the furan ring to an acetylenic intermediate. There are examples of the addition of benzene to acetylenic compounds to give diphenylethane derivatives^{7,8}. However, an alternate mechanism in which the addition of benzene to give the corresponding α -phenyldihydrofuran^{6,9} and subsequent opening of the dihydrofuran ring to give a diphenylethane derivative appears more attractive.

Experimental Procedure

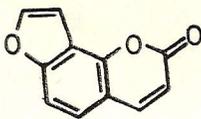
All melting points are uncorrected. UV spectra were measured in ethanol on a Beckman DK-2A spectrophotometer and IR spectra were taken on a Perkin-Elmer infracord spectrophotometer. NMR spectra were taken on a Varian A-60 instrument with tetramethylsilane as an internal standard. Mass spectra, taken on a CEC 21-110B instrument, were run at 70 eV using the direct inlet system. Metastable ions recorded are marked with an asterisk above the mass number.

3-(α,β -Dimethyl- β -phenyl)propyl-7-hydroxy-6-(β,β -diphenylethyl)ethylcoumarin (VI) — A solution of chalepensis (V; 200 mg) in benzene (10 ml) was gradually added to a suspension of anhydrous aluminium

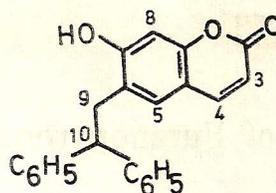
*Contribution No. 272 from CIBA Research Centre.



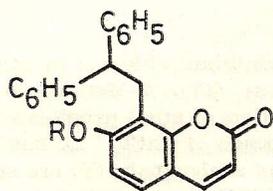
(I)



(II)

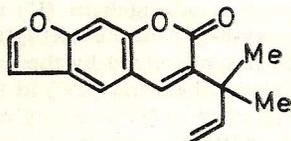


(III)

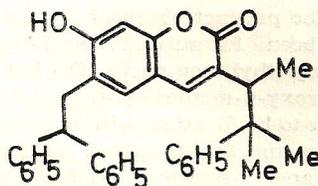


(IV) R = H

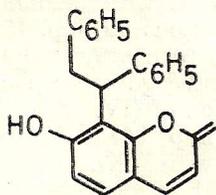
(IX) R = Me



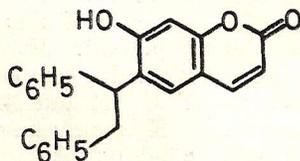
(V)



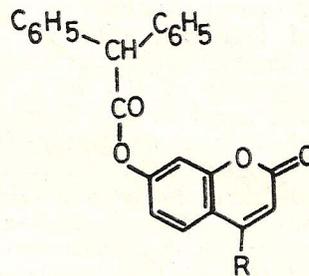
(VI)



(VII)



(VIII)



(X) R = H

(XI) R = Me

chloride (300 mg) in benzene (5 ml). The mixture was refluxed for 1 hr, poured into dil. hydrochloric acid, extracted with benzene, washed with water and the benzene extract dried (Na_2SO_4). Evaporation of the solvent gave a gum which crystallized from methylene chloride-hexane to give (VI) (150 mg), m.p. 190° ; λ_{max} 249, 260 and 338 nm ($\log \epsilon$, 3.76, 3.71 and 4.26); mass spectrum: m/e 488 (M^+) (5), 369 (100), 329 (5), 321 (5), 291 (20), 229* (20), 174 (25), 172.5* (167 (36), 165*, 150*, 119 (98), 110*, 91 (33). NMR (CD_3COCD_3): 0.92 (C-11, —Me; d , $J = 7.5$ Hz), 1.26 (6H; C-12, —Me; s), 3.45 (C-9, — CH_2 —, d , $J = 7.5$ Hz), 3.5 (C-11, —CH—Me; q , $J = 7.5$ Hz), 4.55 (C-10, —CH—; t , $J = 7.5$ Hz), 6.75-7.4 (18H, m), 9.4 (1H, s ; exchanges with D_2O) (Found: C, 83.9; H, 6.9. $\text{C}_{34}\text{H}_{32}\text{O}_3$ requires C, 83.6; H, 6.6%).

Methylation of (VI) — The coumarin VI (900 mg) was dissolved in ether (10 ml) and treated with an ethereal solution of diazomethane. After 16 hr the solvent was removed and the residual gum chromatographed over silica gel. This gave colourless crystals from ethyl acetate (600 mg), m.p. 140° ; λ_{max} 257 and 330 nm ($\log \epsilon$, 3.7 and 4.2); NMR (CDCl_3): 0.95 (3H, C-11 Me; d , $J = 7.5$ Hz), 1.29 (3H, C-12 Me; s), 1.31 (3H, C-12 Me; s), 3.35 (2H, C-9, — CH_2 —; d , $J = 8$ Hz), 3.5 (1H, C-10, —CH—; q , $J = 8$ Hz), 3.75 (3H, C-7 OMe;

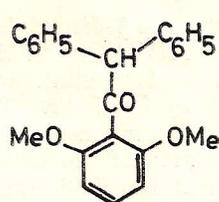
s), 4.3 (1H, C-11, —CH—; t , $J = 7.5$ Hz), 6.7-7.4 (18H, m) (Found: C, 84.0; H, 6.9. $\text{C}_{35}\text{H}_{34}\text{O}_3$ requires C, 83.6; H, 6.8%).

7-Hydroxy-6-(β,β -diphenylethyl)coumarin (III) — This was prepared from psoralen as described earlier³, m.p. 264.5° ; λ_{max} 238, 258 and 335 nm ($\log \epsilon$, 3.7, 3.6 and 4.2); mass spectrum: m/e 342 (M^+) (25), 175 (72), 167 (100), 152 (60), 147 (40), 119 (14), 115 (20), 91 (45).

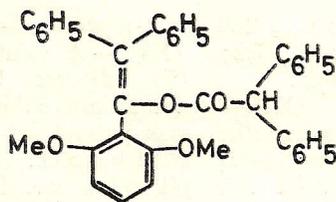
Acetylation of (III) — The compound (III; 300 mg) was refluxed with acetic anhydride (2 ml) and fused sodium acetate (0.5 g) for 1.25 hr. The mixture was poured over crushed ice, the precipitate collected and chromatographed over a column of silica gel. Elution with benzene gave the acetyl derivative which crystallized from methanol (140 mg), m.p. 138.9° (Found: C, 78.2; H, 5.5. $\text{C}_{25}\text{H}_{20}\text{O}_4$ requires C, 78.1; H, 5.2%).

7-Hydroxy-8-(β,β -diphenylethyl)coumarin (IV) — This was prepared from angelicin as described earlier³, m.p. 206° ; λ_{max} 260 and 329 nm ($\log \epsilon$, 3.73 and 4.1); mass spectrum: m/e 342 (M^+) (7), 251 (2), 175 (6), 167 (100), 165 (12), 152 (7), 147 (2), 115 (2), 91 (3).

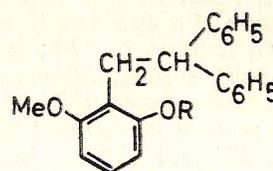
Methylation of (IV) — A solution of IV (200 mg) in ether (10 ml) and methanol (1 ml) was treated with excess of ethereal diazomethane. Removal of the solvent gave a residue which crystallized from



(XII)

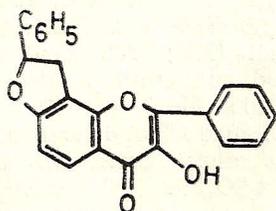


(XIII)

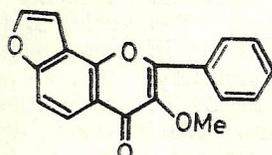


(XIV) R = Me

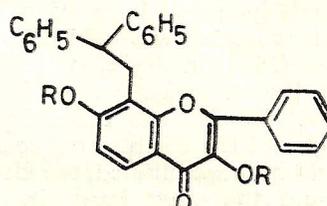
(XV) R = H



(XVI)



(XVII)



(XVIII) R = H

(XIX) R = Me

(XX) R = COMe

methanol to give IX (100 mg), m.p. 140°; λ_{max} 250, 259 and 323 nm; (log ϵ , 3.6, 3.7 and 4.1); NMR ($CDCl_3$): 3.6 (2H, C-9, $-CH_2-$; *d*, $J = 8$ Hz), 3.7 (3H, C-7 OMe; *s*), 4.45 (1H, C-10, $-CH-$; *t*, $J = 8$ Hz), 6.1 (1H, C-3, *d*, $J = 10$ Hz), 6.68 (1H, C-6; *d*, $J = 8$ Hz), 7.35 (1H, C-5; *d*, $J = 8$ Hz), 7.45 (1H, C-4; *d*, $J = 8$ Hz), 7.7.3 (10H, *m*) (Found: C, 80.6; H, 5.8. $C_{24}H_{20}O_3$ requires C, 80.9; H, 5.7%).

3,7-Dihydroxy-8-(β,β -diphenylethyl)flavone (XVIII)—A solution of karanjin (200 mg) in benzene (20 ml) was stirred with anhyd. aluminium chloride (300 mg) at 25° for 4 hr and worked up as in the case of angelicin. The residue crystallized from benzene to give (XVIII) (110 mg), m.p. 233.4°; λ_{max} 258 and 348 nm (log ϵ , 4.19 and 4.17) (Found: C, 79.9; H, 4.9. $C_{24}H_{20}O_4$ requires C, 80.2; H, 5.1%).

3,7-Dimethoxy-8-(β,β -diphenylethyl)flavone (XIX)—A solution of (XVIII; 300 mg) in dry acetone (100 ml), anhyd. potassium carbonate (3 g) and dimethyl sulphate (2 ml) were refluxed on a water-bath for 24 hr. After filtration, the solvent was removed and to the residue, water (100 ml) was added and extracted with methylene chloride. Evaporation of the solvent and crystallization from methylene chloride-hexane gave pale yellow needles of (XIX) (130 mg), m.p. 137°; λ_{max} 252 and 317 nm

(log ϵ , 4.32 and 4.26); NMR ($CDCl_3$): 3.62 (2H, $-CH_2-$; *d*, $J = 7.5$ Hz), 3.65 (3H, C-7 OMe; *s*), 3.9 (3H, C-3 OMe; *s*), 4.35 (1H, $-CH-$; *t*, $J = 7.5$ Hz), 6.85 (1H, C-6; *d*, $J = 8.5$ Hz), 8.1 (1H, C-5; *d*, $J = 8.5$ Hz), 7.0-8.0 (15H, *m*) (Found: C, 80.0; H, 6.1. $C_{31}H_{26}O_4$ requires C, 80.5; H, 5.7%).

3,7-Diacetoxy-8-(β,β -diphenylethyl)flavone (XX)—A solution of (XVIII; 150 mg) in dry pyridine (3 ml) and acetic anhydride (1.8 ml) was heated at 70° for 3 hr and left at 25° for 18 hr. It was poured over crushed ice and the residue crystallized from methylene chloride-methanol to give colourless needles of (XX) (100 mg), m.p. 185°; NMR ($CDCl_3$): 2.15 (3H, C-7 OAc; *s*), 2.32 (3H, C-3 OAc; *s*), 3.62 (2H, C-9, $-CH_2-$; *d*, $J = 7$ Hz), 4.3 (1H, C-10, $-CH-$; *t*, $J = 7$ Hz), 7.15 (1H, C-6; *d*, $J = 9$ Hz), 8.15 (1H, C-5; *d*, $J = 9$ Hz), 7.1-7.8 (15H, *m*) (Found: C, 76.6; H, 5.2. $C_{33}H_{26}O_6$ requires C, 76.4; H, 5.1%).

7-(β,β -diphenylacetoxycoumarin (X)—Diphenylacetyl chloride (10 g) was added to a solution of umbelliferone (5 g) in dry pyridine (50 ml) and the solution heated at 120° for 4 hr. Pyridine was removed under vacuum and the resulting oil poured in water and extracted with methylene chloride. Evaporation of the solvent gave a residue which

TABLE 1—NMR DATA OF COMPOUNDS III, IV AND IX

 [All signals are reported as ppm in δ values. Coupling constants are given in Hertz (Hz)]

Compound	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
III (CD_2COCD_3)	6.07 (<i>d</i> ; 9.5)	7.6 (<i>d</i> ; 9.5)	7.1 (<i>s</i>)			6.8 (<i>s</i>)	3.4 (<i>d</i> ; 7.5)	4.55 (<i>t</i> ; 7.5)
IV ($CDCl_3$)	6.0 (<i>d</i> ; 9.5)	7.45 (<i>d</i> ; 9.5)	7.38 (<i>d</i> ; 8.5)	6.8 (<i>d</i> ; 8.5)			3.55 (<i>d</i> ; 7.5)	4.6 (<i>t</i> ; 7.5)
IX ($CDCl_3$)	6.1 (<i>d</i> ; 9.5)	7.45 (<i>d</i> ; 9.5)	7.4 (<i>d</i> ; 8.5)	6.68 (<i>d</i> ; 8.5)	3.7 (<i>s</i> ; 3H)		3.58 (<i>d</i> ; 7.5)	4.45 (<i>t</i> ; 7.5)

crystallized from ethanol (7 g), m.p. 140°; λ_{\max} 280 and 310 nm (log ϵ , 4.8 and 4.6) (Found: C, 77.2; H, 4.7. $C_{23}H_{16}O_4$ requires C, 77.5; H 4.5%).

4-Methyl-7-(β,β -diphenylacetoxy)coumarin (XI)— This was prepared from 4-methyl-7-hydroxycoumarin as in (X). The product crystallized from methanol, m.p. 112°; λ_{\max} 273 and 312 nm (log ϵ 4.02 and 3.99); NMR ($CDCl_3$): 3.65 (6H, OMe, s) 5.62 (1H —CO—CH—; s) 6.45 (2H, C-3, C-5; each *d*, *J* = 7.5 Hz), 7.0-7.5 (11H, *m*) (Found: C, 77.9; H, 4.9. $C_{24}H_{18}O_4$ requires C, 77.8; H, 4.9%).

(β,β -Diphenyl)-2,6-dimethoxyacetophenone (XII) and 1-(2,6-dimethoxyphenyl)-1-diphenylacetoxy-2,2-diphenyl ethylene (XIII)— A solution of butyllithium in ether (150 ml) (prepared from 3.5 g lithium and 27 g *n*-butyl bromide) was added to resorcinol dimethyl ether (15 g) in dry ether (100 ml). The solution was heated under reflux for 24 hr in N_2 atmosphere. To this was added diphenylacetyl chloride (28 g) and the mixture refluxed for 24 hr. The reaction mixture was filtered, the filtrate washed with water and the ether layer dried (Na_2SO_4). Evaporation of the solvent gave a brown oil which was diluted with hexane and filtered. The residual solid (5 g) on crystallization from methylene chloride-hexane gave colourless cubes of (XIII), m.p. 148°; λ_{\max} 287 nm (log ϵ , 3.7) (Found: C, 81.9; H, 5.7. $C_{36}H_{30}O_4$ requires C, 82.1; H, 5.7%).

The filtrate on evaporation gave an oil. After cooling and crystallization from methylene chloride-hexane colourless needles of (XII) were obtained (10 g), m.p. 134°; λ_{\max} 260 nm (log ϵ , 3.6); NMR ($CDCl_3$): 3.65 (6H, OMe; s), 5.62 (1H, —CO—CH; s), 6.45 (2H, C-3, C-5; *d*, *J* = 7.5 Hz), 6.9-7.5 (11H, *m*) (Found: C, 79.4; H, 6.3. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.1%).

2,6-Dimethoxy-1-(β,β -diphenylethyl)benzene (XIV)— The ketone (XII, 3.3 g), ethanol (50 ml), conc. hydrochloric acid (15 ml) and amalgamated zinc (prepared for 12 g mossy zinc and 1.2 g mercuric chloride) were heated at 140° for 40 hr. The mixture was diluted with water, filtered and ethanol removed under vacuum. It was extracted with methylene chloride, chromatographed through a column of silica gel and the solid residue obtained by evaporation of the solvent crystallized from methylene chloride-hexane (3 g), m.p. 67°; λ_{\max} 297 nm (log ϵ 3.58); NMR ($CDCl_3$): 3.4 (2H, —CH₂—; *d*, *J* = 7 Hz), 3.55 (6H, OMe; s), 4.35 (1H, —CH—; *t*, *J* = 7 Hz), 6.4 (2H, C-3, C-5; each *d*, *J* = 8 Hz), 6.7-7.4 (11H, *m*) (Found: C, 82.7; H, 7.0. $C_{22}H_{22}O_2$ requires C, 83.0; H, 7.0%).

2-Hydroxy-6-methoxy-1-(β,β -diphenylethyl)benzene (XV)— A solution of XIV (1 g) in dry benzene (50 ml) was heated under reflux with anhyd. aluminium chloride (1 g) for 5 hr. The mixture was poured into dil. sulphuric acid and extracted with benzene. Evaporation of the solvent gave an oil which was distilled at 150°/0.01 mm to provide a viscous yellow liquid (300 mg); λ_{\max} 257 nm (log ϵ 3.14); NMR ($CDCl_3$): 3.5 (2H, —CH₂—; *q*, *J* = 7 Hz), 3.55 (3H, OMe, s), 4.3 (1H, —CH—; *t*, *J* = 7 Hz), 6.2 (1H, C-3; *d*, *J* = 7.5 Hz), 6.4 (1H, C-5; *d*, *J* = 7.5 Hz), 7.0-7.4 (11H, *m*), 4.3 (1H, —OH; *m*, exchanges with D_2O) (Found: C, 82.8; H, 7.0. $C_{21}H_{20}O_2$ requires C, 82.9; H, 6.6%).

7-Methoxy-8-(β,β -diphenylethyl)coumarin (IX)— The alkyl phenol (XV; 500 mg), anhyd. zinc chloride (340 mg) and ethyl propiolate (380 mg) were heated at 100° for 1 hr. The mixture was treated with dil. hydrochloric acid and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and the solvent removed. The residue was dissolved in benzene and chromatographed over silica gel. Elution with hexane-benzene (1:1) gave a solid (100 mg) which crystallized from ethanol; m.p. 145°; λ_{\max} 259 and 325 nm (log ϵ 3.3 and 3.7) (Found: C, 80.6; H, 5.9. $C_{24}H_{20}O_3$ requires C, 80.9; H, 5.7%). This was found to be identical (m.m.p., TLC, IR and NMR) with the compound obtained by methylation of (IV).

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