

SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

Part VI. Action of Aluminium Chloride on Angelicin, Psoralen and Related Compounds

BY B. KRISHNASWAMY AND T. R. SESHADRI

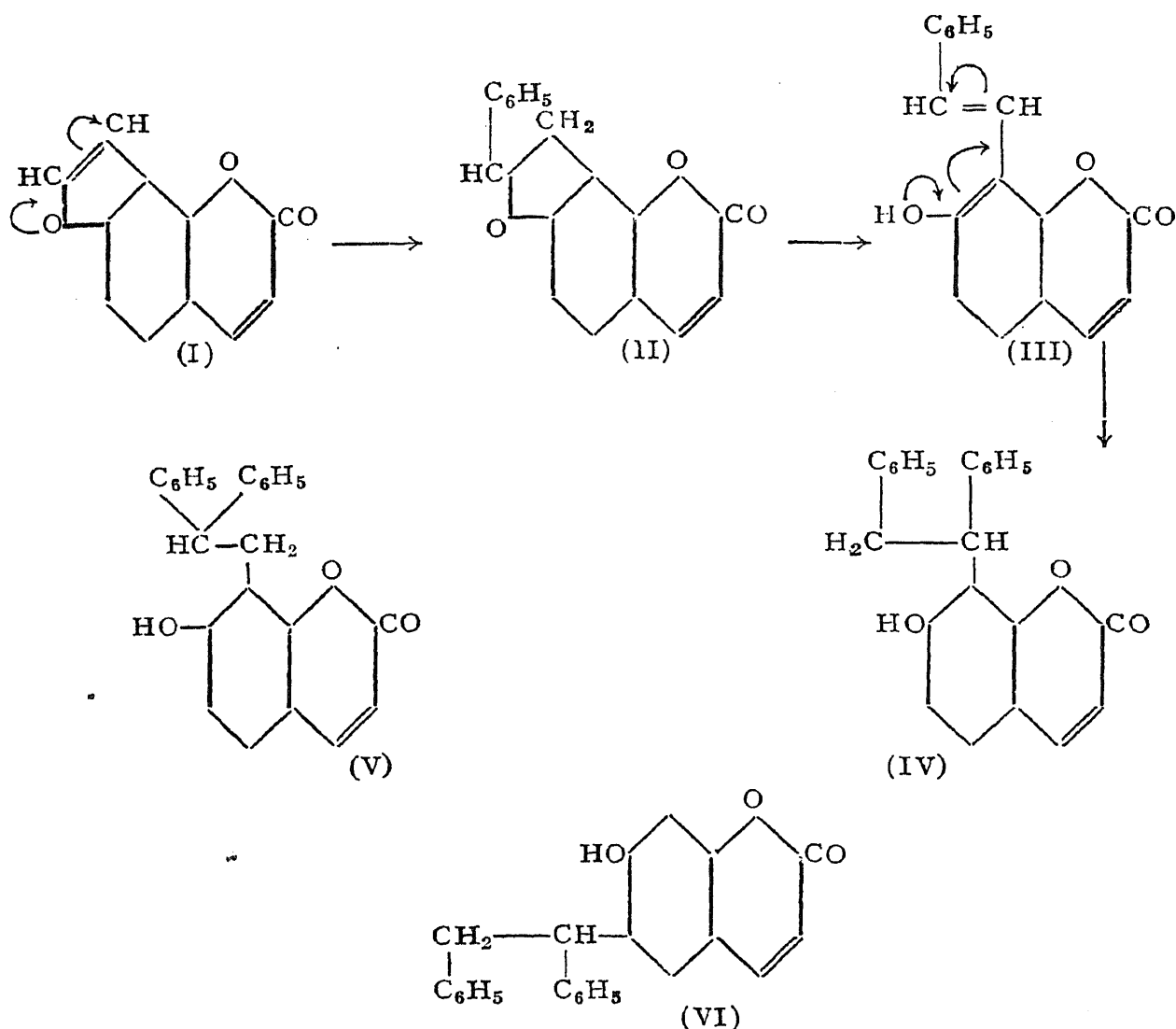
(From the Department of Chemistry, Andhra University, Waltair)

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IN a previous publication¹ it was shown that karanjin adds on a molecule of benzene or toluene in the presence of aluminium chloride, the addition taking place at the double-bond of the furan ring. Simpler flavones related to karanjin do not undergo this addition. Only demethylation of methoxyl groups takes place. If this observation could be proved to be general for all furan compounds, it will be useful for the synthesis of complex organic compounds and also for the purpose of diagnosing the presence of furan ring in such structures. The work has therefore been extended now to coumarin analogues.

Angelicin also called *iso*-psoralen (I) which has the constitution of coumarino-7:8-furan reacts very vigorously with aluminium chloride and benzene even in the cold. The crystalline product obtained is soluble in dilute alkali exhibiting fluorescence, characteristic of umbelliferone derivatives. This is sufficient indication that the furan ring has reacted and has opened out to produce a hydroxyl group at the 7-position, and that the pyrone ring has remained unaffected. From the results of analysis of this product it is concluded that 2 molecules of benzene have taken part in the reaction and that the furan ring has been broken open. The constitution of the new substance, 8-diphenylethyl umbelliferone can be either IV or V and the former is preferred since the influence of the structural factors will favour the entry of the phenyl groups in this manner. The details are represented in the following formulæ.

Psoralen which has the constitution of coumarino-6:7-furan gives a definite crystalline product more easily on treatment with benzene and aluminium chloride. It is readily soluble in dilute alkali. Its solutions exhibit fluorescence and it forms a methyl ether. From these properties and from the results of analysis of this product and also of the methyl ether, it is concluded that as in the case of angelicin two molecules of benzene



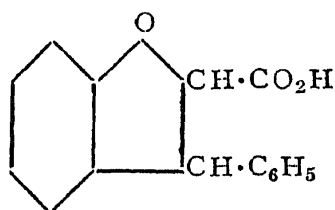
have taken part in the reaction and that the furan ring has been broken open so as to form 6-diphenylethylumbelliferone. Of two possible alternatives, constitution VI appears preferable for this product for the same reason as given in the case of the angelicin derivative.

Though toluene also reacts very vigorously with both psoralen and *iso*-psoralen, resulting amorphous sticky products could not be purified and crystallised.

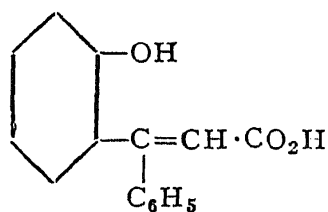
In order to obtain further evidence that the α -pyrone ring is not involved in the above reactions, simpler coumarins were next studied. Coumarin itself undergoes no change. Obviously the pyrone double-bond is not sufficiently anionoid to enter into the reaction. It seems to be strongly cationoid with the carbon atom in position 4 exhibiting cationoid activity. As could be expected 6-nitrocoumarin also undergoes no change. Since a hydroxyl or a methoxyl in the 7-position could reduce this cationoid activity, 7-methoxy-coumarin and 7-methoxy-4-methylcoumarin were carefully studied. Even in these cases no addition took place. In benzene and

toluene solution there was demethylation by aluminium chloride, the corresponding hydroxy-coumarins being formed. Even this did not take place when nitrobenzene was employed as solvent. In this respect there is resemblance to 7-methoxy-flavones.

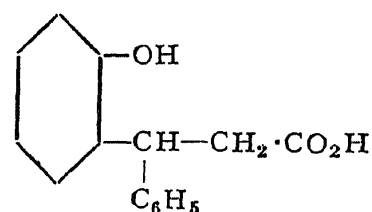
It is therefore obvious that the pyrone ring does not undergo this addition with benzene or toluene. With a view to obtain more positive evidence that the furan ring is involved, simple coumarones have next been investigated. Coumarone itself undergoes rapid change into a solid resin in benzene or toluene. The same phenomenon is noticed in nitrobenzene. They seem to be products of polymerisation and such resins obtained by the action of dehydrating agents are well known. In this case polymerisation is so fast that the addition reaction seems to have little chance of taking place. Coumarilic acid should be much better owing to the modifying action of the carboxyl group. According to expectation it reacts with benzene smoothly to form 3-phenyl-dihydro-coumarilic acid (VII). The properties of this compound support this conclusion and differentiate it from the isomeric β -phenyl-coumaric acid (VIII) that may be produced if the dihydrofuran ring opened out.



(VII)



(VIII)



(IX)

It is interesting to record that coumaric acid undergoes addition of benzene satisfactorily to form β -phenyldihydrocoumaric acid (IX) and is thus sharply distinguished from coumarin. Similar difference in reactivity was also noted in their reaction with cyanoacetamide.² In this reaction with benzene coumaric acid closely resembles coumarilic acid.

Experimental

Addition of benzene to angelicin (iso-psoralen): 8- α : β -diphenylethyl-umbelliferone.

Iso-psoralen (0.2 g.) was dissolved in benzene (20 c.c.), powdered aluminium chloride (0.5 g.) added and the conical flask was well stoppered and shaken for about 4 hours at room temperature. Dilute hydrochloric acid (1:1) was then added and the benzene was removed by steam distillation. The viscous liquid product in the distilling flask set to a solid on cooling. On repeated crystallisation from alcohol or acetone, it gave

glistening micaceous plates, melting at $205-6^{\circ}$. (Found: C, 80.4; H, 5.6; mol.wt. by Rast's Method 337. $C_{11}H_6O_3 + 2C_6H_6$ requires C, 80.7; H, 5.3%; mol.wt., 342. $C_{11}H_6O_3 + C_6H_6$ requires C, 77.3; H, 4.5%; mol.wt., 264. It dissolved in dilute alkali and the solution exhibited a blue fluorescence. The solution in concentrated sulphuric acid emitted a bright violet fluorescence.

Addition of benzene to psoralen: 6- α : β -diphenylethyl-umbelliferone.

Psoralen (0.5 g.) was dissolved in benzene (25 c.c.), powdered anhydrous aluminium chloride (1.0 g.) added and the mixture refluxed for 35-40 minutes. It was then cooled, the solvent decanted into another flask and evaporated to dryness. After treatment with dilute hydrochloric acid the product from both the flasks was collected on one filter and recrystallised from alcohol. Colourless rectangular plates, melting at $259-60^{\circ}$ were thus obtained. Yield 0.2 g. Its solution in dilute alkali gave a bright blue fluorescence and in concentrated sulphuric acid a bright violet fluorescence. (Found: C, 80.6; H, 5.8; mol.wt. by Rast's method 333. $C_{11}H_6O_3 + 2C_6H_6$ requires C, 80.7; H, 5.3%; mol.wt., 342). The above compound was methylated by treating with methyl iodide and anhydrous potassium carbonate in acetone solution and refluxing for 6 hours. The methyl ether was obtained after recrystallisation from alcohol in the form of soft fibres melting at $172-73^{\circ}$. It was insoluble in dilute alkali but dissolved in concentrated sulphuric acid exhibiting violet fluorescence as in the case of the unmethylated compound. (Found: C, 80.7; H, 5.9; OCH_3 , 8.9; $C_{24}H_{20}O_3$ requires C, 80.9; H, 5.6; OCH_3 , 8.7%.)

To Coumarilic acid: 3-phenyl-dihydrocoumarilic acid.—A suspension of coumarilic acid (0.5 g.) in benzene (15 c.c.) was treated with aluminium chloride (1.0 g.) and refluxed for about 45 minutes, when the acid gradually went into solution. Finally the mixture was cooled, treated with dilute hydrochloric acid and the benzene removed by steam distillation. The solid product thus isolated crystallised from alcohol in needles melting at $143-4^{\circ}$. Yield 0.5 g. It gave no colour with ferric chloride. It did not decolourise a solution of bromine in acetic acid thus showing that there was no unsaturation and that the ring had not been opened. (Found: C, 75.0; H, 4.6; mol. wt., 245. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0; mol. wt., 240.)

To Coumaric acid: β -phenyl-dihydrocoumaric acid.

Coumaric acid (0.5 g.) with the same treatment as above gave a product which crystallised from alcohol in rectangular plates. It melted at $152-53^{\circ}$,

and the mixed melting point with the coumarilic acid-benzene compound was lower than that of the two. It did not decolourise a solution of bromine in acetic acid and gave no colour with ferric chloride. Yield almost quantitative. (Found: C, 74.9; H, 6.2; mol. wt., 230; $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%; mol. wt., 242.)

Demethylation of 7-methoxy-4-methyl-coumarin.

(i) *In benzene solution.*—7-Methoxy-4-methyl-coumarin (0.5 g.) was dissolved in dry benzene (20 c.c.), powdered anhydrous aluminium chloride (1 g.) added and heated gently under reflux on a water-bath (70–75°) for about 30 minutes. It was then cooled, the solution decanted into another flask and evaporated to dryness. .10 c.c. of dilute hydrochloric acid (1:1) was added to each of the two flasks to decompose the aluminium chloride and the resulting precipitates were collected together on the same filter. On recrystallisation, the product yielded long plates melting at 185°. The mixed melting point with a sample of 4-methyl-umbelliferone was unaltered. Yield 0.4 g.

(ii) *In toluene solution.*—The procedure was similar to the above except that since in place of benzene, toluene (20 c.c.) was used, it was finally removed by steam distillation. The product was recrystallised from alcohol and found to be identical with 4-methyl umbelliferone.

The behaviour of 7-methoxy-coumarin was the same as that of the 4-methyl compound under the above conditions.

Polymerisation of Coumarone

(i) *In benzene solution.*—Coumarone (10 drops) was dissolved in benzene (10 c.c.) and powdered aluminium chloride (1 g.) added. The mixture was shaken for about 2 hours, when the solution gradually turned to a deep purple colour and deposited a solid. It was filtered, digested with hydrochloric acid to remove any aluminium chloride and again filtered. The product was a white amorphous solid insoluble in all ordinary organic solvents.

(ii) *In nitrobenzene solution.*—The above experiment was repeated using nitrobenzene instead of benzene. Here also the solution gradually turned deep purple but no solid was deposited in two hours as in the above experiment. On keeping overnight, however, the whole solution set to a jelly. This was treated with hydrochloric acid and steam-distilled to remove nitrobenzene. A brown amorphous solid insoluble in the common organic solvents was thus obtained.

Summary

Angelicin and psoralen combine with benzene in the presence of aluminium chloride to form 8 or 6- α : β -diphenyl-ethylumbelliferone. Two molecules of benzene add on and the furan ring is opened out. That the coumarin ring is not involved and that the furan ring is the active centre are confirmed by the following observations: (1) Coumarin and 6-nitro-coumarin are unaffected; (2) umbelliferone and 4-methyl-umbelliferone methyl ether undergo simple demethylation; (3) coumarone undergoes polymerisation too vigorously to condense with benzene; (4) coumarilic acid undergoes addition with one molecule of benzene smoothly. Coumaric acid resembles coumarilic acid in regard to this reaction (addition) and differs from coumarin.

REFERENCES

1. Krishnaswamy and Seshadri .. *Proc. Ind. Acad. Sci. (A)*, 1942, **15**, 437.
2. Seshadri .. *J.C.S.*, 1928, 166.