

SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

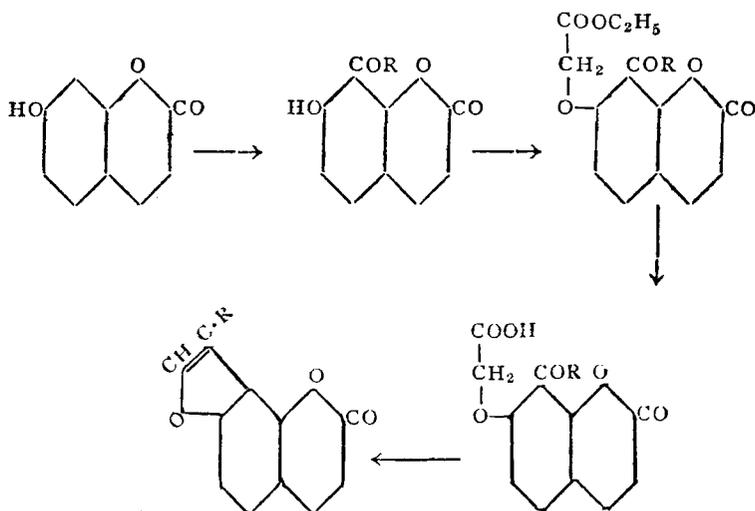
Part II. Synthesis of Flavono- and Coumarino-7:8-Furan- β -ones and Their Derivatives

BY L. RAMACHANDRA ROW AND T. R. SESHADRI

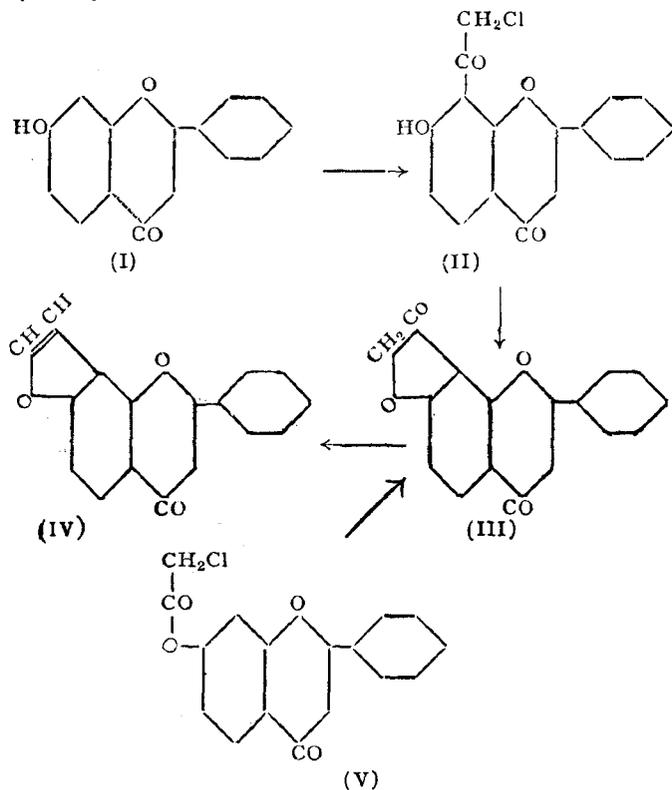
(From the Department of Chemistry, Andhra University, Waltair)

Received January 27, 1940

FOR the building up of a fresh furan ring fused to the benzene nucleus of a coumarin structure two methods have been adopted successfully by Spaeth and Pailer^{1, 2} with particular reference to the synthesis of angelicin. First the sodium derivative of umbelliferone was heated with bromo-acetal in a sealed tube. A very poor yield of angelicin was obtained along with the ethyl ether of umbelliferone. Condensation of bromo- or iodo-acetic ester with the sodium compound of umbelliferone-8-aldehyde offered a better method though here also, the yields were very poor. The second method was employed earlier by Limaye *et al*³ using hydroxy ketone to produce better yields of a methyl derivative of angelicin. An application of this procedure to 7-hydroxy-3-methoxy flavone in an attempt to prepare Karanjin was described in Part I.⁴ Besides poor yields other difficulties also came in, particularly with reference to the flavone compounds. Hence possibilities of other methods of introducing the furan nucleus for the synthesis of coumarino-furans and chromono-furans had to be examined.



In this communication are described experiments relating to an alternative method of preparing such compounds, which has not been till now explored. It consists in introducing a chloro-acetyl group in a hydroxy-benzo-pyrone, closing up the furanone ring and subsequently converting it into a furan. The scheme can be represented as below with particular reference to 7-hydroxyflavone.



The simplest procedure would be to obtain (II) by the action of ClCH_2CN on (I) under the conditions of Hoesch's reaction. This, however, could not be achieved. 7-Hydroxy-flavones and 7-hydroxy-coumarins did not undergo condensations with aceto-nitrile or chloroacetonitrile under various conditions that were employed. This may be attributed to the fact that the eighth position is not so easily accessible except under more drastic conditions. For example for the preparation of 7-hydroxy-coumarin-8-aldehyde the use of hexamine and acetic acid and higher temperatures are necessary. An alternative course was therefore attempted and found to be quite successful. The chloroacetates were obtained in satisfactory yields by the action of excess of chloroacetyl chloride on the hydroxy compounds and these underwent

the Fries migration smoothly when heated with anhydrous aluminium chloride. It was, however, noticed that the resulting products were free from halogen, obviously due to simultaneous ring closure (V to III). The intermediate stage (II) could not be isolated. Further when methoxy groups were present as in the case of 7-hydroxy-3-methoxy-flavone, demethylation also took place. The formation of the furanones was further confirmed by the preparation of their benzylidene derivatives by the action of benzaldehyde and acetyl derivatives by the action of acetic anhydride and acetyl chloride. Furanones and their derivatives from the following have been prepared and characterised.

1. 4-Methyl-7-hydroxy coumarin.
2. 7-Hydroxy coumarin (umbelliferone).
3. 3-Methoxy-7-hydroxy-flavone.
4. 7-Hydroxy flavone.

Experimental

7-Chloracetoxy-4-methyl-coumarin.—A mixture of 4-methyl-7-hydroxy coumarin (1 g.) and chloracetyl chloride (10 to 12 c.c.) was refluxed at 120° in an oil-bath. The contents rapidly assumed a cherry red colour and hydrogen chloride was evolved briskly. After heating for about 2 hours, most of the excess of the chloracetyl chloride was recovered by distillation, and the remaining quantity was decomposed by pouring the residual mixture into ice-cold water with stirring. The precipitated solid was filtered, washed with water and recrystallised from alcohol, when 7-chloracetoxy-4-methyl coumarin was obtained as colourless fibrous needles (yield 85%) melting at 181–82°. (Found: C, 57.4; H, 3.6; Cl, 14.5; $C_{12}H_9O_4Cl$ requires C, 57.0; H, 3.2; Cl, 14.1%.) An alternative method using equimolecular quantities of chloroacetyl chloride and 4-methyl umbelliferone and dry pyridine as the condensing agent was not so successful either from the point of view of yield or purity of the product.

4-Methyl-coumarino-7 : 8-furan- β -one.—An intimate mixture of 4-methyl-7-chloracetoxy-coumarin (0.5 g.) and anhydrous aluminium chloride (2.5 g.) was heated in an oil-bath at 175° for about 2 hours. The contents of the flask were then cooled and treated with concentrated hydrochloric acid (10 c.c.). After about 15 minutes, the mixture was diluted to about 50 c.c. with water and filtered. The residue was crystallised twice from glacial acetic acid and thereby 4-methyl-coumarino-7 : 8-furan- β -one was obtained in the form of yellow rhombic prisms melting at 254–56° in an yield of 30%. It gave no test for the presence of chlorine and did not give any colour with ferric

chloride indicating the absence of a phenolic hydroxyl in the 7th position. (Found: C, 66.1; H, 4.0; $C_{12}H_8O_4$ requires C, 66.7; H, 3.7%.)

The benzyldine derivative.—To a solution of the above furanone (0.5 g.) in glacial acetic acid benzaldehyde (0.5 c.c.) was added. A current of dry hydrogen chloride was then passed through the solution at the laboratory temperature. The original yellow colour of the solution deepened and gradually turned out into a dark red colour. Soon after the saturation of the solution with hydrogen chloride gas, crystals of the benzyldine derivative began to separate copiously. The current of hydrogen chloride was continued for one hour more and then the flask was corked tight, paraffined and left overnight. The crystalline solid was then filtered and washed first with dilute acetic acid and then with water. The crystals which were dark brown in colour, crumbled into a deep greenish yellow powder on pressing upon the tile. On recrystallising from hot glacial acetic acid, fine needles of yellow colour were obtained melting at 194–96°. (Found: C, 74.5; H 4.2; $C_{16}H_{12}O_4$ requires C, 75.0; H, 3.9%.)

The acetyl derivative.—Acetylation of the furanone was first carried out using sodium acetate and acetic anhydride. The mixture was kept gently boiling for about 4 to 6 hours and after cooling poured into water. The solid that separated was crystallised from alcohol. In this case crystallisation was particularly difficult owing to the resinification of the material during acetylation. The yield was poor and the product impure. Hence the following procedure was adopted. The methyl coumarino-furanone (1 g.) was heated for an hour with freshly distilled acetic anhydride (30 c.c.) and acetyl chloride (1 c.c.) on a boiling water-bath. The excess of acetic anhydride was then distilled under reduced pressure and the residue was treated with water. The solid that separated was crystallised from alcohol when it yielded 0.8 g. of fine yellow needles melting at 172–3°. (Found: C, 64.4; H, 4.4; $C_{14}H_{10}O_5$ requires C, 65.1 and H, 3.9%.)

7-Chloracetoxy-coumarin.—Umbelliferone was obtained in good yield by adopting the improved method of Bridge, Crocker, Cubin and Robertson.⁵ By the action of excess of chloracetyl chloride, the chloracetoxy coumarin was easily obtained. It crystallised from alcohol (charcoal) in clusters of colourless fibrous needles melting at 163–4°. The yield was 90%. (Found: C, 55.6; H, 3.4; Cl, 14.6; $C_{11}H_7O_4Cl$ requires C, 55.4; H, 2.9; Cl, 14.9%.)

Coumarino-7:8-furan- β -one was obtained by heating a mixture of 7-chloracetoxy-coumarin and anhydrous aluminium chloride at 160° for about two hours. The product was crystallised from a mixture of glacial acetic acid and water and was obtained in the form of yellow rectangular plates

melting at 252–3°. The yield was 25%. (Found: C, 64.8; H, 3.5; $C_{11}H_6O_4$ requires C, 65.3; H, 3.0%.)

The benzylidene derivative was obtained as orange red needles melting at 284–6°. The acetyl derivative crystallised from alcohol in the form of fine yellow needles melting at 152–3°. (Found: C, 63.9; H, 3.8; $C_{13}H_8O_5$ requires C, 63.9; H, 3.3%.)

7-Chloracetoxy-3-methoxy flavone was obtained in good yield (90%) by heating a mixture of 7-hydroxy-3-methoxy flavone and chloracetyl chloride. It crystallised from alcohol in colourless fibrous crystals melting at 169°. (Found: C, 62.6; H, 4.2, Cl, 10.7; $C_{18}H_{13}O_5Cl$ requires C, 62.7; H, 3.8, Cl, 10.4%.)

3-Hydroxy-flavono-7:8-furan- β -one was prepared by heating a mixture of anhydrous aluminium chloride and the above chloro-compound at its melting point. The product crystallised from glacial acetic acid in the form of small rhombic prisms melting at 284–6°. The yield was 25%. The substance contained no methoxyl and gave a brownish pink colour with ferric chloride. (Found: C, 66.0; H, 4.2; $C_{17}H_{10}O_5$, H_2O requires C, 65.4; H, 3.8%.) The benzylidene derivative, which was obtained from glacial acetic acid as tiny plates, melted at 274°. The acetyl derivative readily crystallised from alcohol in the form of rhombic prisms of light yellow colour and melted at 192°. (Found: C, 66.7; H, 4.1; $C_{21}H_{14}O_7$ requires C, 66.7; H, 3.8%.)

7-Chloracetoxy-flavone was obtained in the form of colourless, long fibrous needles melting at 138–39° when crystallised from alcohol. It exhibited a greenish tinge which was difficult to remove. (Found: C, 64.8; H, 4.0; Cl, 11.4; $C_{17}H_{11}O_4Cl$ requires C, 64.9; H, 3.5; Cl, 11.3%.)

Flavono-7:8-furan- β -one was prepared by subjecting 7-chloracetoxy flavone to Fries migration using anhydrous aluminium chloride. The product was crystallised from alcohol (yield 25%) in the form of tiny yellow needles melting at 206–7°. (Found: C, 71.3; H, 4.3; $C_{17}H_{10}O_4$, $\frac{1}{2} H_2O$ requires C, 71.1; H, 4.0%.) The benzylidene derivative crystallised in the form of rectangular needles of light green colour melting at 224–5°. (Found: C, 71.3; H, 4.6; $C_{24}H_{14}O_4$, $2 H_2O$ requires C, 71.6; H 4.5%.) The acetyl derivative was obtained in the form of tiny needles collecting as stars and melting at 260–61°.

Summary

Starting from 7-hydroxy-coumarins and flavones the chloracetoxy compounds have been prepared and these have been converted into

coumarino-7 : 8-furanones and flavono-7 : 8-furanones by means of the Fries reaction. Their properties have been studied and their benzylidene and acetyl derivatives obtained.

REFERENCES

1. Spaeth and Pailer .. *Ber.*, 1934, 1212.
2. ————— .. *Ibid.*, 1935, 940.
3. Limaye .. *Ibid.*, 1932, 375.
4. Rangaswami and Seshadri .. *Proc. Ind. Acad. Sci.*, (A), 1939, 9, 7 and 259.
5. Bridge, Crocker, Cubin and Robertson .. *J.C.S.*, 1937, 1533.