93. The Synthesis of 5-Hydroxyflavone.

By Shigehiko Sugasawa.

Pharmaceutical Institute, Imperial University, Tokyo.

(Comm. by Y. Asahina, M.I.A., June 12, 1934.)

The attempt of synthesising primetin, 5:6-dihydroxyflavone (I), had failed, the isomeric 5:8-dihydroxyflavone (II) being produced. 1) This time 2:6-dihydroxyacetophenone (IV) was prepared as one of the starting materials in the above work, which is also a suitable intermediate in the synthesis of 5-hydroxyflavone (III) by the general method of Allan and Robinson. 2) The project was successful and thus 5-hydroxyflavone was synthesised for the first time.

2:6-Dihydroxyacetophenone and its dimethylether (V) were not yet known when this work was started, and they were prepared in two different days.

1) 2:6-Dimethoxybenzonitrile (VI) (10 g.) in pure anisole (100 cc.) was added with continuous shaking to the Grignard's solution (from 10 g. of methyliodide and 2 g. of magnesium). After treating the reaction-product properly (chiefly according to Robertson, 3) who prepared 2:6-dimethoxyisovalerophenone from 2:6-dimethoxybenzonitrile and isobutylmagnesium bromide, about 6 g. of 2:6-dimethoxyacetophenone were obtained, which was conveniently purified by distilling in vacuum, b.p. 135-136°C/2 mm. Colourless crystals melting at 68-69°C. (Found: C, 66.4; H, 6.5: Calc. for C₁₀H₁₂O₃: C, 66.7; H, 6.7%).

When the foregoing ketone was demethylated by means of aluminium chloride in dry toluene, 2:6-dihydroxyacetophenone was obtained, forming yellow needles from hot water, m.p. 156-157°C.

This method is, therefore, essentially the same with that of Mauthner, 4) which was published while I was working at the condensation of the dihydroxyketone, sodium benzoate and benzoic anhydride. His method for demethylation, using chlorobenzene as solvent, however, is preferable to that of mine, because it gives better yield of the dihydroxyketone.

2) By Nidhon-process. According to Limaye\textsuperscript{1}) 4-methylumbelliferone benzoate yields 4-methyl-8-benzoylumbelliferone, when it undergoes the Fries-transformation, because the latter substance, when boiled with aqueous sodium hydroxide, gives rise to a benzoylresorcin, which is different from the well known 4-benzoylresorcin and therefore must be 2-benzoyl derivative.

This method, which the author called Nidhon-process, was applied upon 4-methylumbelliferone acetate (VII), yielding 2:6-dihydroxyacetophenone (IV) in good yield. Though the purified substance, yellow needles, melted at 153° after sintering at about 147°, i.e. a few degrees lower than the specimen prepared by the first method, their identity was proved by converting the former into its dimethylether, which, after purification, melted at 68–69° alone or admixed with the authentic specimen of 2:6-dimethoxyacetophenone. (Found: C, 67.0; H, 6.7. Calc. for C\textsubscript{8}H\textsubscript{6}O(OCH\textsubscript{3})\textsubscript{2}: C, 66.7; H, 6.7%; Found: C, 62.8; H, 4.9. Calc. for C\textsubscript{8}H\textsubscript{6}O(OH)\textsubscript{2}: C, 63.2; H, 5.2%).

For the preparation of 2:6-dihydroxyacetophenone in larger quantity, the second method is rather preferable, though by the first method purer substance can be obtained.

The intimate mixture of 2:6-dihydroxyacetophenone, sodium benzoate and an excess of benzoic anhydride was heated at 180–190° for 5 hours. By treating the reaction-product as usual 5-hydroxyflavone was obtained, which was purified through its acetate.

5-Hydroxyflavone crystallizes from ethyl acetate, forming yellow needles melting at 156–157°, while its acetate forms colourless long hairy needles melting sharply at 145°. (Found: C, 75.6; H, 4.4. Calc. for C\textsubscript{15}H\textsubscript{9}O\textsubscript{2}(OH): C, 75.6; 4.2%; Found: C, 73.2; H, 4.5. Calc. for C\textsubscript{15}H\textsubscript{9}O\textsubscript{2}(OCOCH\textsubscript{3}): C, 72.9; H, 4.3%).

When the above condensation was carried out at higher temperature, 205–210°, 2-benzoyl-5-hydroxyflavone (VIII) was the main product, which was also purified through its acetate.

2-Benzoyl-5-hydroxyflavone: long, yellow pillars form ethyl acetate, m.p. 173–174°. (Found: C, 76.7; H, 4.4. Calc. for C\textsubscript{22}H\textsubscript{14}O\textsubscript{4}: C, 77.2; H, 4.1%).

2-Benzoyl-5-acetoxyflavone: colourless microscopic prisms from ethyl acetate, m.p. 189–190°. (Found: C, 74.8; H, 4.4. Calc. for C\textsubscript{24}H\textsubscript{16}O\textsubscript{5}: C, 75.0; H, 4.2%).

(I) \[ \text{HO} \text{CO}_2 \text{C}_6\text{H}_5 \text{HO} \]

(II) \[ \text{HO} \text{CO}_2 \text{C}_6\text{H}_5 \text{HO} \]

(III) \[ \text{HO} \text{CO}_2 \text{C}_6\text{H}_5 \text{OR} \]

(IV) \[ \text{R}=\text{H}, \text{V) } \text{R}=\text{CH}_3 \]

(VI) \[ \text{CH}_3 \text{O} \text{C}_6\text{H}_5 \text{CN} \]

(VII) \[ \text{CH}_3 \text{CO} \text{O} \text{C}_6\text{H}_5 \]

(VIII) \[ \text{HO} \text{CO}_2 \text{C}_6\text{H}_5 \text{CO-C}_6\text{H}_5 \]