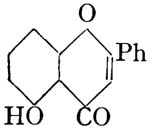
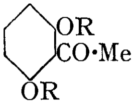
319. *The Synthesis of 5-Hydroxyflavone.*

By SHIGEHIKO SUGASAWA.

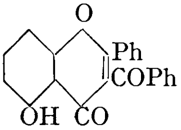
5-HYDROXYFLAVONE (I) has been prepared by the general method of Allan and Robinson (J., 1924, **125**, 2192; 1925, **127**, 181, *et seq.*) from 2 : 6-dihydroxyacetophenone (II), which is a possible intermediate in the synthesis of primetin (Sugasawa, J., 1933, 1621). The hydroxy-ketone (II) was prepared (i) by demethylation of 2 : 6-dimethoxyacetophenone (III), itself obtained from 2 : 6-dimethoxybenzonitrile and methylmagnesium iodide (Mauthner, *J. pr. Chem.*, 1934, **139**, 290), and (ii) more conveniently by Limaye's process (*Ber.*, 1934, **67**, 12) from 4-methylumbelliferone acetate *via* 8-acetyl-4-methylumbelliferone. Fusion of 2 : 6-dihydroxyacetophenone with benzoic anhydride and sodium benzoate at 205—210° gave mainly *5-hydroxy-3-benzoylflavone* (IV), but fusion at 180—190° gave a small yield of *5-hydroxyflavone*, which was purified through its *acetyl* derivative.



(I.)



(II, R = H; III, R = Me.)



(IV.)

EXPERIMENTAL.

2 : 6-*Dimethoxyacetophenone* (III).—2 : 6-Dimethoxybenzonitrile (10 g.) in pure anisole (100 c.c.) was added with continuous shaking to the Grignard reagent prepared from 10 g. of methyl iodide, 2 g. of magnesium, and 100 c.c. of pure ether. The product was treated according to Robertson's method (J., 1933, 1164), but the addition of xylene was unnecessary. The crude ketone (6—6·5 g.), on distillation, afforded 5—5·5 g. of pure substance, b. p. 135—136°/2 mm., m. p. 68—69°; colourless needles from ethyl acetate–light petroleum, m. p. 68—69° (Found : C, 66·4; H, 6·5. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%).

2 : 6-*Dihydroxyacetophenone* (II).—(i) The foregoing ketone (10 g.), aluminium chloride (15 g.), and dry toluene (5 c.c.) were heated at 120° for about ½ hour, and afterwards treated as usual. 2 G. of the crude hydroxy-ketone were obtained; yellow needles from hot water, m. p. 156—157° (Mauthner, *loc. cit.*, obtained a better yield).

(ii) 8-Acetyl-4-methylumbelliferone (20 g.), prepared by Limaye's method (*Ber.*, 1932, **65**, 375) but not purified by the semicarbazone, was boiled with aqueous sodium hydroxide (20 g. in 100 c.c. of water) for an hour. The dark brown solution was acidified with hydrochloric acid, and the yellow precipitate crystallised from hot water (charcoal); yellow needles, m. p. 153°, sintering from about 147°; yield 11·5 g. of crude substance (Found : C, 62·8; H, 4·9. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·2%).

When this substance was methylated with excess of methyl sulphate and alkali, a yellow crystalline substance was obtained, insoluble in alkali and giving no coloration with alcoholic ferric chloride. This was collected, dried, and distilled, b. p. 135—136°/2 mm., and then melted at 68—69° alone or admixed with 2 : 6-dimethoxyacetophenone (Found : C, 67·0; H, 6·7%).

5-*Hydroxyflavone* (I).—An intimate mixture of 2 : 6-dihydroxyacetophenone (2 g.), sodium benzoate (5 g.), and benzoic anhydride (20 g.) was heated (oil-bath at 180—190°) for 5 hours. Alcohol (80 c.c.) was added, and the whole was refluxed for 2 hours; then a solution of potassium hydroxide (15 g.) in water (20 c.c.) was added and the mixture was boiled for 30 minutes, and then evaporated under diminished pressure. Addition of water to the residue caused turbidity, from which a yellow amorphous substance was deposited after some time (0·5 g.); this was boiled with acetic anhydride and a drop of pyridine for 1 hour, and then poured on ice. The white amorphous solid (0·5 g.) was crystallised from alcohol and then from ethyl acetate, 5-*acetoxyflavone* being obtained as colourless, long, hairy needles, m. p. 145° (Found : C, 73·2; H, 4·5. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%).

The acetate, on hydrolysis by alcoholic potash (2%), afforded a yellow solid, which was crystallised from alcohol, and then, for analysis, from ethyl acetate; long, thin, yellow needles, m. p. 156—157°, giving a dark purple coloration with ferric chloride (Found : * C, 75·6; H, 4·4. $C_{15}H_{10}O_3$ requires C, 75·6; H, 4·2%).

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* Microanalysis by Mr. Kasahara.

In an attempt to improve the yield, the fusion was carried out at 205—210° for 5 hours; but after being worked up as before, the product gave mainly 3-*benzoyl*-5-*acetoxyflavone*, which crystallised from much ethyl acetate as colourless, microscopic prisms, m. p. 189—190° (Found : C, 74·8; H, 4·4. $C_{24}H_{16}O_5$ requires C, 75·0; H, 4·2%). On hydrolysis, this gave 5-*hydroxy*-3-*benzoylflavone* (IV), long yellow pillars from ethyl acetate, m. p. 173—174° (Found : C, 76·7; H, 4·4. $C_{22}H_{14}O_4$ requires C, 77·2; H, 4·1%).

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