407. *The Action of Benzoyl Chloride and Pyridine on 5-Hydroxy-6-acetyl-4-methylcoumarin and Reactions related thereto.*

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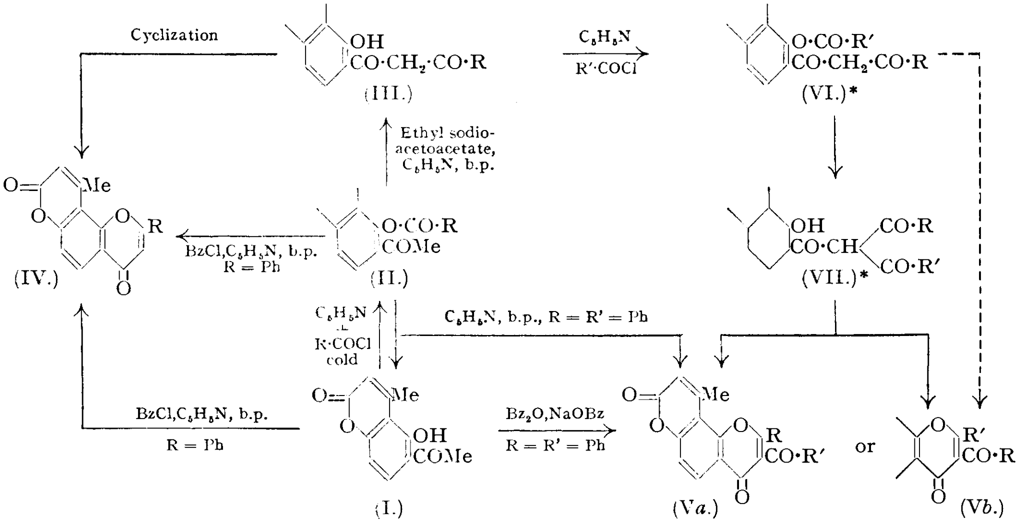
5-Hydroxy-6-acetyl-4-methylcoumarin (I) with benzoyl chloride and pyridine in the cold gives the 5-benzoate (II; R = Ph) which can be transformed into the 5-hydroxy-diketone (III; R = Ph) by an intramolecular Claisen condensation. Both these products can be cyclized to 2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (IV; R = Ph), previously (Shah and Deliwala, *Proc. Indian Acad. Sci.*, 1942, **16**, 387) obtained by the direct action of benzoyl chloride in *boiling* pyridine on (I). The 5-hydroxy-diketone is probably not an intermediate, as postulated by Shah and Deliwala, in this direct formation of (IV) from (I), since benzoyl chloride and pyridine introduce a further benzoyl group to yield 3′-benzoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (V; R = R′ = Ph). This 3′-benzoyl derivative is also formed by the action of pyridine alone on a mixture of the 5-benzoate (II) and 5-hydroxy-diketone (III).

Several analogous reactions are effected with other aroyl chlorides.

Shah and Deliwala (*Proc. Indian Acad. Sci.*, 1942, **16**, 387) found that, when 5-hydroxy-6-acetyl-4-methylcoumarin (I) was heated with benzoyl chloride and pyridine, there resulted, not the expected benzoyl derivative (II; R = Ph), but the flavone, 2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (IV; R = Ph). These authors suggested that the reaction proceeds through the ester (II; R = Ph) and the hydroxy-diketone (III; R = Ph) with subsequent cyclization to (IV; R = Ph). The transformation of *o*-aroyloxyacetoarones into *o*-hydroxydibenzoylmethanes, involved in the step (II) ⟶ (III), was first effected by Baker (*J.*, 1933, 1381) using potassium carbonate, and independently by Venkataraman and his collaborators (*Current Sci.*, 1933, **2**, 214; *J.*, 1934, 1767) using sodamide. It has been shown by Wheeler and his colleagues (Ullal and Wheeler, *Current Sci.*, 1938, **7**, 280; Wheeler, *Chem. and Ind.*, 1947, 753; Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291) that this transformation involves a base-catalysed intramolecular Claisen condensation between an ester and a methyl ketone, a wide variety of bases (alkali-metal salts of weak acids, *e.g.*, ethyl sodioacetoacetate) being effective.



* Hypothetical intermediates.

The suggestion of Shah and Deliwala in regard to the course of their reaction is supported by the fact that (I) with benzoyl chloride and pyridine under mild conditions gives the expected ester, *5-benzoyloxy-6-acetyl-4-methylcoumarin* (II; R = Ph), which with ethyl sodioacetoacetate in pyridine yields by transformation the diketone *5-hydroxy-6-benzoylacetyl-4-methylcoumarin* (III; R = Ph). The last compound is rapidly cyclized to (IV; R = Ph), *e.g.*, by hydrogen bromide in acetic acid, by anhydrous pyridine, or by a mixture of pyridine and pyridine hydrochloride such as would be formed in the benzoylation of (I) with benzoyl chloride and pyridine. Analogous *esters* (II; R = *o*-tolyl or *p*-nitrophenyl) and *diketones* (III; R = *o*-tolyl or *p*-nitrophenyl) were similarly prepared. Compound (III; R = *o*-tolyl) was cyclized to the *flavone* (IV; R = *o*-tolyl). Further, (II; R = Ph) gives (IV; R = Ph) when heated with pyridine and an excess of benzoyl chloride, the yield (30%) being better than that (a trace) obtained when (I) is used as starting substance. It may be noted that no definite compound resulted when (I) was heated with *o*-toluoyl or *p*-nitrobenzoyl chloride and pyridine.

Action of Pyridine and Aroyl Chlorides on the Diketone (III).—Although supported by the experiments just described, Shah and Deliwala's mechanism is inadequate to explain the fact that the diketone (III; R = Ph), benzoyl chloride, and pyridine, when heated at the boiling point, give a good yield of 3′-benzoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (V; R = R′ = Ph), previously synthesised by Sethna, Shah, and Shah (*J.*, 1938, 228) by aroylation of (I) with sodium benzoate and benzoic anhydride. A similar result is obtained with (III; R = *o*-tolyl) and *o*-toluoyl chloride. These observations show that (III; R = Ph) is an unlikely intermediate in Shah and Deliwala's reaction; it is more probable that (II; R = Ph), on formation from (I) by the action of benzoyl chloride and pyridine, gives (IV; R = Ph) by dehydration. Slavin (M. Sc. Thesis, University College, Dublin, 1948) found that 5-benzoyloxy-6-acetylindane is cyclized to 6-phenylindano(5′ : 6′-2 : 3)pyr-4-one by heating in glycerol.*

In the presence of pyridine (III; R = Ph) with *o*-toluoyl chloride, and (III; R = *o*-tolyl) with benzoyl chloride, give the same aroylflavone, either (V*a*) or (V*b*), and a single product is similarly obtained by both methods in the *p*-nitrophenyl series. These results are best interpreted by assuming that reaction proceeds through the ester (VI) and its transformation compound, the triketone (VII). Interchange of R and R′ in (VI) will give the same compound (VII), which presumably will cyclize in one direction only, to give either (V*a*) or (V*b*). On the other hand, direct cyclization of (VI) as indicated (broken line) would give different compounds, if R and R′ were interchanged. Baker (*loc. cit.*) postulated a similar intermediate formation of triketone in the salt–anhydride acylation of *o*-hydroxyacetophenones to 3-acylchromones. He regarded direct *C*-acylation of the methylene carbon of a diketone such as (III) to form (VII) as probable under the conditions of his experiments. Claisen *et al.* (*Ber.*, 1900, **33**, 1242, 3778; 1903, **36**, 3674; cf. Michael and Carlson, *J. Amer. Chem. Soc.*, 1935, **57**, 165; 1936, **58**, 353) found however that ethyl acetoacetate with pyridine and an acyl chloride give *O*-acyl derivatives of the enol form, so that direct *C*-benzoylation is, perhaps, unlikely in the passage from (III) to (VII) induced by pyridine and an acyl chloride; (VI) is perhaps a more likely intermediate.

It should be noted that the formation of only one form of (V) eliminates the possibility of the flavone (IV) being intermediately formed from (III) and then aroylated in the 3′-position. Further, when (IV; R = Ph) was heated under reflux with benzoyl chloride and pyridine, no trace of (V; R = R′ = Ph) was obtained. Wittig (*Annalen*, 1926, **446**, 155) also found that chromones are not acylated in the 3-position when heated with sodium acetate and acetic anhydride, though the 3-acylflavone is formed when the corresponding hydroxy-diketone is used.

Removal by alkaline hydrolysis of the 3′-aroyl group from (V), as with simpler 3-acylchromones (*e.g.*, 3-propionyl-2 : 6-dimethylchromone; Wittig, *loc. cit.*), has not been found possible (cf. Bhullar and Venkataraman, *J.*, 1931, 1165). Hence the formula of (V) is uncertain in that it may be either (V*a*) or (V*b*). This, however, does not invalidate the argument as to the course of the reaction, which requires only that different products should not be formed. Work is in progress to elucidate the structure of (V).

Action of Pyridine on the Ester (II).—While investigating the mechanism of the production of (IV; R = Ph) from (I) by the action of benzoyl chloride and pyridine, we heated the ester

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* (Added 20th April 1949.) This assumption of direct cyclization is now supported by the fact that (II; R = Ph) yields (IV; R = Ph) when heated in glycerol at 220° in a current of coal gas. This method provides a simple synthesis of flavones, details of which will be published later. It is of interest to note that Chada and Venkataraman (*J.*, 1933, 1074) found that 1-benzoyloxy-2-acetonaphthone did not cyclize under the influence of dehydrating reagents.

(II; R = Ph) with pyridine alone to determine if transformation to (III) occurred. Unexpectedly a mixture of (V; R = R′ = Ph) and (I) was obtained. The *o*-toluoyl ester (II; R = *o*-tolyl) gave a similar result. It would appear that pyridine, acting as a base, transforms part of (II) into (III) and that the aroyl group in the unchanged part of (II) wanders to the methylene carbon of (III) to give the phenol (I) and the triketone (VII), which then cyclizes to (V):

$$\text{(II)} \xrightarrow{C_5H_5N} \text{(III)} + \text{(II)} \xrightarrow{C_5H_5N} \text{(VII)} + \text{(I)} \xrightarrow{-H_2O} \text{(V)} + \text{(I)}$$

The second reaction, formation of (VII) + (I), may be regarded as involving a Claisen condensation between the diketone (III) and the ester (II), (I) being the alcohol (phenol) eliminated. The reaction mechanism is supported by the fact that heating 1 g. each of (II; R = Ph) and (III; R = Ph) with pyridine gives 0·7 g. each of (I) and (V; R = R′ = Ph); and a similar result was obtained with the *o*-tolyl derivatives.

The intermediate formation of the triketone (VII) is indicated by similar results. Compound (II; R = *o*-tolyl) with (III; R = Ph) in hot pyridine gives one form of (V; R = Ph; R′ = *o*-tolyl) and (I). The same form of (V) was similarly obtained from (II; R = Ph) and (III; R = *o*-tolyl). Further, this compound (V) was identical with that formed, as already mentioned, from (III; R = Ph) and *o*-toluoyl chloride, and from (III; R = *o*-tolyl) and benzoyl chloride.

It should be noted that the ester (II) is particularly reactive since (III; R = Ph) in the presence of pyridine gave no definite product with phenyl benzoate or *o*-benzoyloxyacetophenone. Pyridine as a solvent appears to be essential since fusion of an equimolecular mixture of (II; R = Ph) and (III; R = Ph) at 220° for 2 hours gave back (III; R = Ph) unchanged.

EXPERIMENTAL.

Esters of Hydroxycoumarins.—*5-Benzoyloxy-6-acetyl-4-methylcoumarin* (II; R = Ph) (5·2 g.) separated when a mixture of 5-hydroxy-6-acetyl-4-methylcoumarin (I) (5 g.) (Sethna, Shah, and Shah, *J.*, 1938, 228), benzoyl chloride (4 g.), and pyridine (25 ml.) which had been kept for 24 hours was poured into excess of dilute hydrochloric acid at 0°; crystallised from alcohol, it melted at 120—121° (Found: C, 70·7; H, 4·6. $C_{19}H_{14}O_5$ requires C, 70·8; H, 4·3%).

5-o-*Toluoyloxy*- (II; R = *o*-tolyl) (from ligroin), m. p. 126—127° (Found: C, 71·5; H, 5·0. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%), and *5-p-nitrobenzoyloxy-6-acetyl-4-methylcoumarin* (II; R = *p*-nitrophenyl) (from alcohol and glacial acetic acid), m. p. 159—160° (Found: C, 62·2; H, 3·6; N, 3·9. $C_{19}H_{13}O_7N$ requires C, 62·1; H, 3·5; N, 3·8%), were prepared in similar yields from (I) and *o*-toluoyl and *p*-nitrobenzoyl chloride, respectively.

The esters formed needles.

o-*Hydroxydiketones.*—*5-Hydroxy-6-benzoylacetyl-4-methylcoumarin* (III; R = Ph) (4·5 g.) (from dioxan), m. p. 240°, separated when a mixture of (II; R = Ph) (5 g.), ethyl sodioacetoacetate (5 g.), and pyridine (25 ml.), which had been heated under reflux for 20 minutes and kept at room temperature for 12 hours, was poured into excess of 10% hydrochloric acid containing ice (Found: C, 70·4; H, 4·5. $C_{19}H_{14}O_5$ requires C, 70·8; H, 4·3%).

5-Hydroxy-6-o-toluoylacetyl-4-methylcoumarin (III; R = *o*-tolyl) (from chloroform and alcohol), m. p. 176—177° (Found: C, 70·7; H, 4·9. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%), and *5-hydroxy-6-p-nitrobenzoylacetyl-4-methylcoumarin* (III; R = *p*-nitrophenyl), m. p. 300° (decomp.) (from nitrobenzene) (Found: C, 62·0; H, 3·7; N, 3·5. $C_{19}H_{13}O_7N$ requires C, 62·1; H, 3·5; N, 3·8%), were similarly prepared from (II; R = *o*-tolyl) and (II; R = *p*-nitrophenyl), respectively.

These diketones were obtained as yellow needles, yields being almost quantitative.

Chromonopyr-2-ones.—2′-Phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (IV; R = Ph) (from dioxan), m. p. 263—264°, separated in almost quantitative yield, when a solution of (III; R = Ph) in acetic acid containing 50% hydrogen bromide was diluted with water. Cyclization of (III; R = Ph) to (IV; R = Ph) was also effected by boiling with anhydrous pyridine for 4 hours with or without addition of concentrated hydrochloric acid (0·1 vol.). Compound (IV; R = Ph) (0·3 g.) also separated when a mixture of (II; R = Ph) (1 g.), benzoyl chloride (2 g.), and pyridine (2 ml.) was heated under reflux for 4 hours and then poured into excess of 10% hydrochloric acid containing ice. (Added 20.4.1949). This flavone was also prepared by heating (II; R = Ph) with glycerol (10 parts) for 4 hours at 220° in a current of coal gas; the reaction mixture was poured into water, and the yellow precipitate (yield 40%) was recrystallised several times from dioxan. The m. p. of each specimen of (IV; R = Ph) was not depressed by the addition of an authentic sample prepared from (I) by the action of benzoyl chloride and pyridine (Shah and Deliwala, *Proc. Indian Acad. Sci.*, 1942, **16**, 387) (Found: C, 74·7; H, 3·9. Calc. for $C_{19}H_{12}O_4$: C, 75·0; H, 3·9%).

2′-o-Tolyl-4-methylchromono(7′ : 8′-6 : 5)*pyr-2-one* (IV; R = *o*-tolyl) (from dioxan), m. p. 310°, separated in needles in almost quantitative yield when (III; R = *o*-tolyl) was kept in acetic acid containing 50% hydrogen bromide for 24 hours, and then diluted with water (Found: C, 74·8; H, 4·5. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%).

No useful result was obtained by heating (III; R = Ph) with benzoyl chloride under reflux for 4 hours.

Aroyl Derivatives of Chromonopyr-2-ones.—(a) *Action of pyridine and aroyl chlorides on* (III). The diketone (III) was heated under reflux with the aroyl chloride (one part) and pyridine (15—20 parts) for 4 hours, and the product (*ca.* 80% yield) separated by pouring the mixture into excess of 10% hydrochloric acid containing ice.

3′-Benzoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (V; R = R′ = Ph), prepared from (III; R = Ph) and benzoyl chloride, crystallised from glacial acetic acid, had m. p. 304—306°, not depressed by addition of an authentic specimen prepared by salt–anhydride aroylation of (I) (Sethna, Shah, and Shah, *loc. cit.*) (Found : C, 76·0; H, 3·9. Calc. for $C_{26}H_{16}O_5$: C, 76·5; H, 3·9%).

*3′-*o-*Toluoyl-2′-*o-*tolyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one* (V; R = R′ = *o*-tolyl) (from tetrahydrofurfuryl alcohol), m. p. 334—335° was prepared from (III; R = *o*-tolyl) and *o*-toluoyl chloride (Found: C, 75·9, 76·1, 75·8, 75·6, 76·1; H, 4·7, 4·7, 4·8, 4·6, 5·0. $C_{28}H_{20}O_5$ requires C, 77·0; H, 4·6; $C_{28}H_{20}O_5,0{\cdot}5H_2O$ requires C, 75·5; H, 4·7%). Flavones frequently retain water, even when heated in a high vacuum (cf. Robinson and Venkataraman, *J.*, 1929, 61; Shah, Metha, and Wheeler, *J.*, 1938, 1555). Attempts to determine combined water were unsuccessful, owing to sublimation, which occurred in a high vacuum (*ca.* 10^{-4} mm.) at the requisite temperature (220°).

*3′-Benzoyl-2′-*o-*tolyl-* or *3′-*o-*toluoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one* (V*a* or V*b*; R = *o*-tolyl; R′ = Ph) (from chloroform–alcohol), m. p. 310—312° (Found: C, 76·3; H, 4·5. $C_{27}H_{18}O_5$ requires C, 76·7; H, 4·3%), was prepared from (III; R = Ph) and *o*-toluoyl chloride, and from (III; R = *o*-tolyl) and benzoyl chloride.

*3′-Benzoyl-2′-*p-*nitrophenyl-* or *3′-*p-*nitrobenzoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one* (V*a* or V*b*; R = *p*-nitrophenyl; R′ = Ph) (from aqueous acetone), m. p. 310° (decomp.) (Found : C, 68·3; H, 3·3; N, 3·2. $C_{26}H_{15}O_7N$ requires C, 68·9; H, 3·3; N, 3·1%), was prepared from (III; R = Ph) and *p*-nitrobenzoyl chloride, and from (III; R = *p*-nitrophenyl) and benzoyl chloride.

These compounds formed needles.

(b) *Action of pyridine on* (II; R = Ph or *o*-tolyl). A solution of (II; R = Ph) (2 g.) in pyridine (20 ml.) was heated under reflux for 4 hours, poured into an excess of 10% sodium hydroxide solution, and filtered. The precipitate (0·15 g.), crystallised from glacial acetic acid, had m. p. 304—306°, not depressed by admixture with an authentic sample of (V; R = R′ = Ph) prepared according to Sethna, Shah, and Shah (*loc. cit.*). Acidification of the filtrate gave (I) (1·3 g.), the identity of which was confirmed by mixed m. p. after recrystallisation. When (II; R = *o*-tolyl) was used, the product (V; R = R′ = *o*-tolyl) was identical (mixed m. p.) with a sample obtained from (III; R = *o*-tolyl) and *o*-toluoyl chloride as described above.

(c) *Action of pyridine and esters of* (I) *on* (III). 1 G. each of (II; R = Ph) and (III; R = Ph), when treated as in (*b*), gave (mixed m. p.) 0·7 g. each of (V; R = R′ = Ph) and (I). Similarly a mixture of (II; R = *o*-tolyl) and (III; R = *o*-tolyl) gave (V; R = R′ = *o*-tolyl) and (I).

Compound (V*a*) or (V*b*) (R = *o*-tolyl; R′ = Ph), m. p. 310—312° not depressed by admixture with the product from (*a*) above, was obtained, together with (I), by heating for 4 hours with pyridine under reflux equimolecular mixtures of (II; R = *o*-tolyl) and (III; R = Ph) or of (II; R = Ph) and (III; R = *o*-tolyl). The products were formed in 70% yield and were worked up by the method described in (*b*).

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