393. *Further Experiments on the Mechanism of the Baker–Venkataraman Transformation.*

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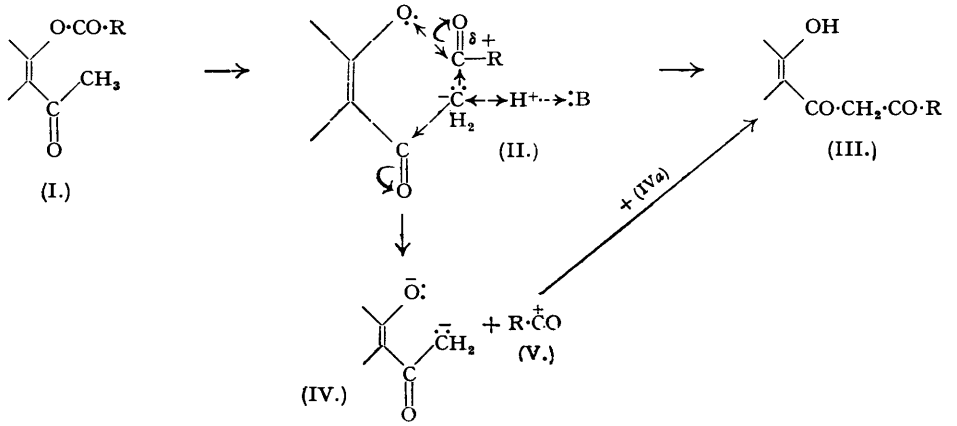
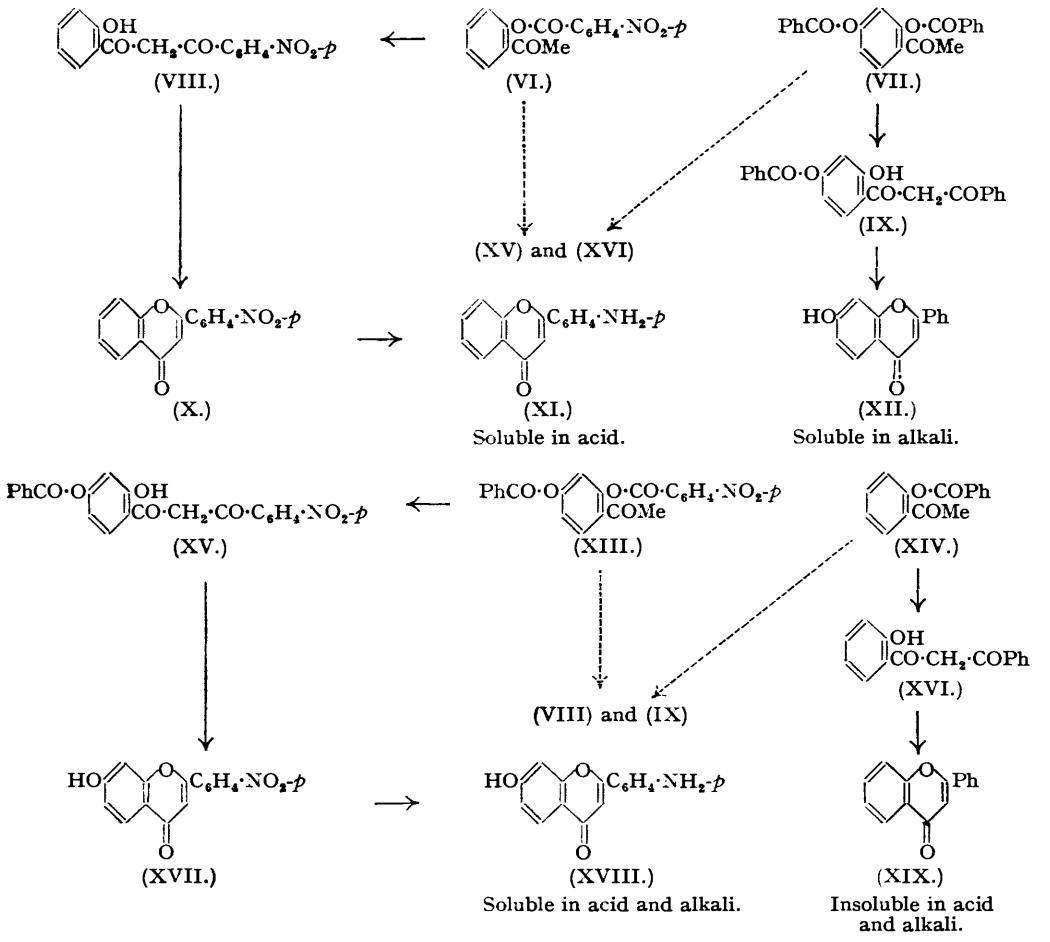
" Crossed " products were not isolated when a mixture of two *o*-aroyloxyacetoarones was transformed in the same solution by the Baker–Venkataraman method into *o*-hydroxydiaroylmethanes. The absence of these products indicates that the reaction is intra- and not intermolecular.

Doyle, Gógan, Gowan, Keane, and Wheeler (*Proc. Roy. Dublin Soc.*, 1948, **24**, 291) showed that the Baker–Venkataraman transformation of *o*-aroyloxyacetoarones (I) into *o*-hydroxydiaroylmethanes (III) (Baker, *J.*, 1933, 1381; Mahal and Venkataraman, *J.*, 1934, 1767) is probably a base-catalysed intramolecular Claisen condensation involving the transition compound (II). The nature of the catalysis is scarcely in doubt since a variety of bases ranging from the triphenylmethyl ion to the benzoate ion is effective in producing the rearrangement. There is a possibility, however, that the reaction may be intermolecular, involving the dissociation of (II) into the anion (IV) and the aroyl cation (V), which latter condenses with an anion (IVa) similar to (IV), to form (III).



This paper describes experiments, the results of which indicate that the reaction is intramolecular and (V) is never free during rearrangement. The method employed is that used by Ingold and Kidd (*J.*, **1933**, 984) in an investigation of the mechanism of the benzidine change. A mixture of *o*-(*p*-nitrobenzoyloxy)acetophenone (VI) and of 2 : 4-dibenzoyloxyacetophenone (VII) was transformed in pyridine solution by using powdered potassium hydroxide. The resulting diketone mixture was cyclized to the corresponding flavones with concentrated sulphuric acid which simultaneously hydrolyses any aroyloxy-groups present (Baker, *loc. cit.*), and the product was treated with stannous chloride in hydrochloric acid to convert any nitro-flavone formed into the corresponding amino-flavone.

If the reaction is intramolecular, (VI) will give (XI) with intermediate formation of (VIII) and (X), and (VII) will yield similarly (IX) and thence (XII). On the other hand, if aroyl ions become free during the transformation, (XV) and (XVI) will also be formed. Compound (XV) will produce (XVII) and thence (XVIII), and (XVI) will give (XIX). The four flavones (XI), (XII), (XVIII), and (XIX) can be separated by suitable treatment with acid and alkali; this was confirmed by starting with a mixture of (X), (XII), (XVII), and (XIX) which was reduced and separated. As shown in the Experimental section, a mixture of (VI) and (VII) gave (XI) and (XII) only, and a mixture of (XIII) and (XIV) yielded exclusively (XVIII) and (XIX). The fact that each mixture gave " straight " as opposed to " crossed " products indicates that the formation of (VIII) and (IX) only from (VI) and (VII) is not due to the complete instability



Full lines show intramolecular reactions. *Dotted lines show intermolecular reactions.*

of (XV) and (XVI); and similarly for the formation of (XV) and (XVI) from (XIII) and (XIV). The identity of the various flavones was confirmed by mixed-melting-point determinations with

authentic specimens. In the synthesis of these specimens no striking difference was observed in the rate of transformation of the four esters (VI, VII, XIII, and XIV) involved. If one ester of a pair in a mixture transformed much more rapidly than the other, it might be that all the corresponding free aroyl ion (IV), if formed, would have recombined to form the straight diketone before the slow transformation of the second ester would have sensibly progressed (see Ingold and Kidd, *loc. cit.*).

As there is a loss in the various stages of transformation, cyclization and reduction, and, as the control experiments show, in the separation of the flavones produced, it is not possible to assert that no intermolecular exchange occurs. The evidence, however, is in favour of intramolecular reaction, and it is probable that the transformation proceeds exclusively in this way.

Experimental.

4-Benzoyloxy-2-(p-nitrobenzoyloxy)acetophenone (XIII) separated when a mixture of 2-hydroxy-4-benzoyloxyacetophenone (10·8 g.) (Baker, *J.*, 1933, 1381), *p*-nitrobenzoyl chloride (8·8 g.), and pyridine (30 ml.), which had been heated for 3 hours at 100°, was poured into excess of 10% hydrochloric acid. The *ester* which was recovered after the product had been kept overnight at 0° yielded on extraction with boiling methyl alcohol (4 × 150 ml.) white needles (12·8 g., 75%) which melted at 110—112° (Found: C, 64·7; H, 3·8; N, 3·4. $C_{22}H_{15}O_7N$ requires C, 65·2; H, 3·7; N, 3·5%).

4'-Nitro-2-hydroxy-4-benzoyloxydibenzoylmethane (XV).—A mixture of 4-benzoyloxy-2-(*p*-nitrobenzoyloxy)acetophenone (2 g.), pyridine (20 ml.), and potassium hydroxide (1 g.), previously powdered in a hot mortar, was heated for 15 minutes under reflux, a copious precipitate of the yellow potassium salt of 4'-nitro-2-hydroxy-4-benzoyloxydibenzoylmethane being obtained. The product was poured into excess of 10% acetic acid and the resulting *phenol* (1·3 g., 65%) was twice crystallized from acetone–dioxan (charcoal). It separated in yellow crystals, m. p. 198—200° (Found: C, 65·4; H, 3·7; N, 3·5. $C_{22}H_{15}O_7N$ requires C, 65·2; H, 3·7; N, 3·5%).

2-Hydroxy-4-benzoyloxydibenzoylmethane (IX) was similarly prepared (50% yield) from 2 : 4-dibenzoyloxyacetophenone (VII) (Baker, *loc. cit.*), and 4'-nitro-2-hydroxydibenzoylmethane (VIII) (90% yield) from *o*-(*p*-nitrobenzoyloxy)acetophenone (VI) (Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291).

Preparation of Authentic Specimens of Flavones.—4'-Nitro-2-hydroxy-4-benzoyloxydibenzoylmethane was dissolved in concentrated sulphuric acid (cf. Baker, *loc. cit.*) and after 4 hours the solution was poured with cooling into excess of water. The resulting precipitate of 4'-nitro-7-hydroxyflavone (XVII) separated from glacial acetic acid in light yellow crystals (92%) which melted at 308—310°. Anand and Venkataraman (*Proc. Indian Acad. Sci.*, 1947, **26**, 279) give m. p. 310—311°.

7-Hydroxyflavone (XII) was similarly obtained (96% yield) from 2-hydroxy-4-benzoyloxydibenzoylmethane and was conveniently purified through the acetyl derivative (Emilewicz and Kostanecki, *Ber.*, 1898, **31**, 704). 4'-Nitroflavone (X) was prepared (91% yield) from 4'-nitro-2-hydroxydibenzoylmethane by using acetic acid containing a trace of mineral acid as described by Doyle *et al.* (*loc. cit.*). Flavone (XIX) was synthesized by the Baker–Venkataraman method from *o*-benzoyloxyacetophenone in over 70% yield (see Dunne *et al.*, *J.*, 1950, 1252).

4'-Amino-7-hydroxyflavone (XVIII).—A mixture of 4'-nitro-7-hydroxyflavone (0·3 g.), stannous chloride (1·5 g.), and concentrated hydrochloric acid (10 ml.) was heated for 30 minutes under reflux. The precipitate obtained on keeping the product for some hours at 0° was dissolved in methyl alcohol, and the solution was made strongly alkaline by the drop-wise addition of aqueous ammonia (*d* 0·880) and concentrated at 100°. The yellow crystals (0·1 g., 37%) which separated melted at 337—338° after crystallization from methyl alcohol. Anand and Venkataraman (*loc. cit.*) give m. p. 338—340°.

4'-Aminoflavone (XI) was similarly obtained from 4'-nitroflavone by using 20% sodium hydroxide solution to precipitate the base from the solution of the hydrochloride (cf. Doyle *et al.*, *loc. cit.*, p. 304). The product separated from alcohol in yellow needles (86%) which melted at 233—234°. Bogert and Marcus (*J. Amer. Chem. Soc.*, 1919, **41**, 92) give m. p. 234—236°.

Test of Technique for Separation of Flavones.—A mixture of flavone, 4'-nitroflavone, 7-hydroxyflavone and 4'-nitro-7-hydroxyflavone (0·5 g. of each flavone) was heated intermittently for 15 minutes under reflux with stannous chloride (5 g.) in concentrated hydrochloric acid (15 ml.) and then kept overnight at 0°. The solid (*A*) formed was separated and treated with concentrated aqueous ammonia, with water, and then with 10% aqueous sodium hydroxide (2 × 100 ml.). On acidification of the alkaline solution beyond pH 1, 7-hydroxyflavone (0·39 g.) separated (*B*). It was acetylated by treatment for 15 minutes at 100° with acetic anhydride (10 parts) and pyridine (10 parts). The product was poured into excess of 10% hydrochloric acid. The resulting precipitate after crystallization from methyl alcohol melted at 129—130° and did not depress the m. p. of an authentic specimen of 7-acetoxyflavone.

The acid mother-liquor (*B*) did not yield any further solid when kept overnight at 0°. It was neutralized to Congo-red with concentrated aqueous ammonia and kept overnight at 0°, a yellow precipitate (0·12 g.) separating. After 2 crystallizations from methyl alcohol this precipitate melted at 330—335°; 4'-amino-7-hydroxyflavone melts at 338—340° (Anand and Venkataraman, *loc. cit.*).

The portion of (*A*) (see above), which was insoluble in 10% aqueous sodium hydroxide, was extracted with 5% hydrochloric acid (2 × 100 ml.). The combined extracts when rendered alkaline deposited a yellow solid (0·18 g.) which melted at 228—229°. 4'-Aminoflavone has m. p. 234—236° (Bogert and Marcus, *loc. cit.*). The residue (0·45 g.) of (*A*) which was insoluble in both acid and alkali yielded, when crystallized from light petroleum (b. p. 40—60°), flavone with m. p. 97° (lit., m. p. 99—100°).

Experiments on the Transformation of Mixtures.—(1) *Simultaneous transformation of* o-(p-*nitrobenzoyloxy)acetophenone* (VI) *and* 2 : 4-*dibenzoyloxyacetophenone* (VII). A mixture of *o*-(*p*-nitrobenzoyloxy)-acetophenone (1 g.), 2 : 4-dibenzoyloxyacetophenone (1 g.), powdered potassium hydroxide (1 g.), and

pyridine (25 ml.) was heated for 30 minutes under reflux, and when cool was diluted with water (250 ml.) and acidified with glacial acetic acid. The insoluble yellow solid so obtained was collected, dried, and dissolved in concentrated sulphuric acid (25 ml.). After 4 hours the solution was added with cooling to water (300 ml.). The resulting buff-coloured precipitate was dried at 100° and heated intermittently under reflux for 30 minutes with stannous chloride (5 g.) in concentrated hydrochloric acid (15 ml.). The solid which separated after the mixture had been kept overnight at 0° was treated with concentrated aqueous ammonia, washed with water, and dried. It was ground and extracted with 10% aqueous sodium hydroxide (2 × 50 ml.) (*C*) and the combined extracts acidified with concentrated hydrochloric acid (*D*). The resulting precipitate (0·27 g.) was acetylated as described above for 7-hydroxyflavone (XII). The product after crystallization from methyl alcohol melted at 129° and did not depress the m. p. of an authentic specimen of 7-acetoxyflavone.

The acid mother-liquor [see (*D*) above] was neutralized to Congo-red with concentrated aqueous ammonia but yielded no precipitate when kept overnight at 0° [absence of 4′-amino-7-hydroxyflavone (XVIII)].

The residue from the alkaline extraction [see (*C*) above] dissolved completely in 10% hydrochloric acid (50 ml.) [absence of flavone (XIX)], and this acid extract on treatment with 10% aqueous potassium hydroxide to alkalinity gave a yellow solid (0·11 g.) which after crystallization from alcohol melted at 231° and did not depress the m. p. of an authentic specimen of 4′-aminoflavone (XI).

(2) *Simultaneous transformation of* o-*benzoyloxyacetophenone* (XIV) and 4-*benzoyloxy*-2-(p-*nitrobenzoyloxy*)*acetophenone* (XIII). A mixture of *o*-benzoyloxyacetophenone (1 g.) and 4-benzoyloxy-2-(*p*-nitrobenzoyloxy)acetophenone (1 g.), potassium hydroxide (1 g.), and pyridine (25 ml.) was heated under reflux and treated as described at (1) above up to and including reduction with stannous chloride in hydrochloric acid and subsequent treatment with aqueous ammonia and with water. The dried solid product was extracted with 10% aqueous sodium hydroxide (*E*). On acidification of the extract with concentrated hydrochloric acid a transient opalescence but no permanent precipitate was obtained [absence of 7-hydroxyflavone (XII)]. The acidified extract was neutralized to Congo-red with concentrated aqueous ammonia and kept overnight at 0°. The crude yellow solid (0·09 g.) melted at 300—320° and this m. p. was raised to 323—330° by addition of an authentic sample of 4′-amino-7-hydroxyflavone, (XVIII).

The residue [see (*E*) above] which was insoluble in alkali was extracted with 10% hydrochloric acid (2 × 50 ml.), but no precipitate was obtained when this extract was rendered alkaline with 10% aqueous potassium hydroxide [absence of 4′-aminoflavone (XI)]. The solid remaining after the alkali and the acid extraction was crystallized from light petroleum (b. p. 40—60°), whereupon it melted at 97° and did not depress the m. p. of an authentic sample of flavone (XIX).

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