688. *The Course of the Perkin Coumarin Synthesis. Part I.*

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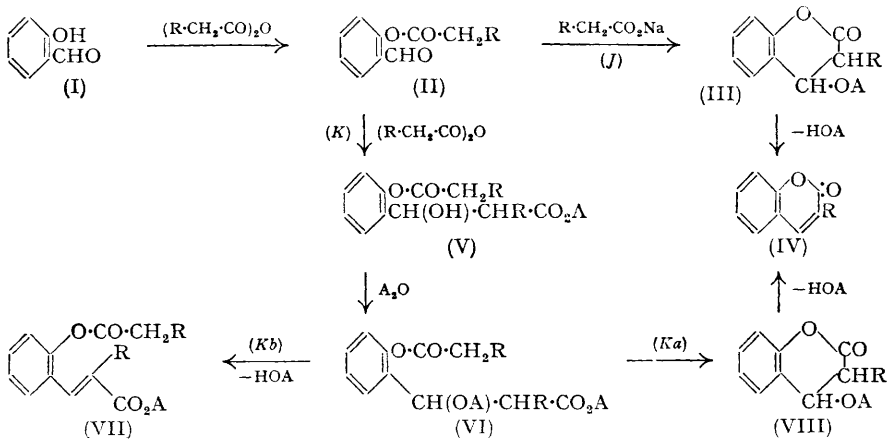
The condensation of salicylaldehyde and its derivatives with acid anhydrides and the corresponding sodium salts can take place both intramolecularly and intermolecularly to give the same coumarin, in the latter case frequently accompanied by the corresponding *o*-coumaric acid. A novel method of converting *o*-coumaric acid into coumarin in good yield is described.

In the Perkin synthesis of coumarin from salicylaldehyde, acetic anhydride, and sodium acetate, *o*-hydroxycinnamic acid is unlikely to be an intermediate. Its *trans*-isomer, *o*-coumaric acid, does not lactonise under the conditions of the reaction. The *cis*-isomer, *o*-coumarinic acid, lactonises very readily, but the formation of *cis*-acids in the Perkin reaction is met with rarely and then only in small amount (cf., *e.g.*, Bakunin, *Gazzetta*, 1895, **25**, 137; Breslow and Hauser, *J. Amer. Chem. Soc.*, 1939, **61**, 786). The following scheme is now suggested as providing a satisfactory reaction mechanism. There are three distinct reaction sequences, all found to occur. As double-bond formation takes place last in each case, no stereochemical difficulties arise.

Course *J* (intramolecular condensation) consists of (*a*) acylation, (I) ⟶ (II), (*b*) intramolecular condensation, (II) ⟶ (III) (A = H or acyl), and (*c*) double-bond formation by elimination (III) ⟶ (IV).

Course *Ka* (intermolecular condensation) consists of (*a*) acylation, (I) ⟶ (II), (*b*) intermolecular condensation, (II) ⟶ (V), and further acylation, (V) ⟶ (VI) (A = acyl), (*c*) cyclisation (lactonisation), (VI) ⟶ (VIII), and (*d*) double-bond formation by elimination, (VIII) ⟶ (IV).

Course *Kb* (intermolecular condensation leading to the *trans*-acid) consists of (*a*) and (*b*) as in course *Ka*, then (*c*) double-bond formation by elimination, (VI) ⟶ (VII).

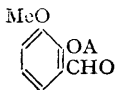


Intramolecular Condensation.—Course *J* is similar to that suggested by Heilbron, Hey, and Lythgoe (*J.*, 1936, 295) for the formation of 6-methoxy-4-methyl-3-phenylcoumarin from 2-hydroxy-4-methoxyacetophenone by the Kostanecki reaction using sodium phenylacetate and phenylacetic anhydride, except that an *o*-hydroxyarylaldehyde is substituted for an *o*-hydroxyaryl ketone. Salicylaldehyde reacts similarly with sodium phenylacetate and acetic anhydride to produce 3-phenylcoumarin. This is Oglialoro's modification (*Gazzetta*, 1878, **8**, 429) of the Perkin reaction. In it phenylacetic anhydride is the essential reactant. If acetylsalicylaldehyde (II; R = H) is used, 3-phenylcoumarin is formed in good yield in the absence of acetic anhydride. Trans-esterification, converting (II; R = H) into (II; R = Ph), occurs, as a mixture of acetylsalicylaldehyde, benzaldehyde, and sodium phenylacetate gives, on heating, 3-phenylcoumarin and not α-phenylcinnamic acid. Phenylacetylsalicylaldehyde (II; R = Ph), when heated with sodium acetate, or better phenylacetate, gives 3-phenylcoumarin in good yield, thus confirming the reaction sequence. Strong heating of phenylacetylsalicylaldehyde alone gives only very little 3-phenylcoumarin. When these esters are heated with sodium phenylacetate intermolecular condensation is excluded. The rather lower yields obtained indicate that in the presence of anhydride some intermolecular condensation occurs. This is substantiated by the high yield given when acetylsalicylaldehyde, acetic anhydride, and sodium phenylacetate are heated together.

Intermolecular Condensation.—Intramolecular condensation does not occur in the reaction between salicylaldehyde, acetic anhydride, and sodium acetate, as acetylsalicylaldehyde gives not more than a trace of coumarin when heated with sodium acetate even on addition of various salts, bases, solvents, or dehydrating agents (see Experimental section). Acetic anhydride addition, however, leads to ready coumarin formation, although a mixture of benzoic anhydride and sodium benzoate is ineffective. The function of the acetic anhydride is, therefore, not merely that of solvent or dehydrating agent but of reactant. Since acylation is already complete the only alternative is for the anhydride to condense, leading to compounds (V) and (VI) (R = H, A = Ac). Two possibilities now appear: (*a*) cyclisation giving (VIII; R = H, A = Ac), followed by elimination and double-bond formation, yielding coumarin (IV; R = H); and (*b*) loss of acetic acid from

(VI), *i.e.*, elimination instead of cyclisation, to give (VII; R = H, A = Ac). This compound has the *trans*-configuration and has been formed by the normal Perkin reaction sequence. It cannot give rise to coumarin but yields instead a substituted cinnamic acid.

The Formation of trans-*Acid.*—*trans*-Acids are frequent by-products in coumarin syntheses. When the hydroxyl group of salicylaldehyde is methylated or replaced by almost any other group, including H, the *trans*-acid is the sole product because the cyclisation *Ka* cannot occur. The ordinary Perkin reaction is thus a special case (*Kb*) of a more general reaction which with appropriately substituted aldehydes can take three different courses, *J*, *Ka*, or *Kb*. 3-Methoxysalicylaldehyde (IX; A = H), in the coumarin synthesis, gives 8-methoxycoumarin (X; R = H) and a much larger amount of 2-acetoxy-3-methoxycinnamic acid (XI; R = H, A = Ac) according to Mauthner (*J. pr. Chem.*, 1939, **152**, 23) and Dey and Kutti (*Proc. Nat. Inst. Sci., India*, 1940, **6**, 641). This has been confirmed. With acetic anhydride and sodium phenylacetate the main product is 8-methoxy-3-phenylcoumarin (X; R = Ph) accompanied by some 2-acetoxy-3-methoxy-α-phenylcinnamic acid (XI; R = Ph, A = Ac), an acetyl derivative which on hydrolysis



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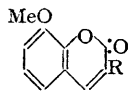

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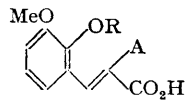
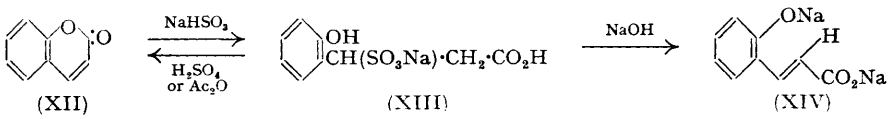


(XI)

gives the free hydroxy-acid (XI; R = Ph, A = H). The much lower yield of *trans*-acid is due to the predominance of intramolecular condensation. This is proved by heating 2-acetoxy-3-methoxybenzaldehyde (IX; A = Ac) with sodium phenylacetate in absence of anhydride. Only the coumarin is formed and no *trans*-acid, since intermolecular condensation is eliminated. All three reaction sequences thus occur in the condensation of 3-methoxysalicylaldehyde with phenylacetic anhydride. The appreciable yields of *trans*-acid in the condensations of this aldehyde are probably due to steric interference of the *o*-methoxy-group with cyclisation *Ka*. The alternative mechanism *Kb*, which is not affected, consequently supplants it.

Further Remarks on Intermolecular Condensation.—The following observations have some bearing on intermolecular condensation. When coumarin (XII) is heated with sodium sulphite or hydrogen sulphite solution a compound (XIII) is obtained (Dey and Row, *J.*, 1924, 554; Dodge, *J. Amer. Chem. Soc.*, 1916, **38**, 446), resembling the aldol intermediate in the Perkin reaction. Treated with sodium hydroxide solution (XIII) loses $NaHSO_3$ and gives (XIV). The action of sulphuric acid or acetic anhydride, however, on (XIII) causes cylisation first, and then elimination, to give coumarin (XII). As in stages *Ka* and *Kb* the *trans*-acid is formed if elimination is first, but coumarin if cyclisation precedes it.



(XII) (XIII) (XIV)

Heating *o*-coumaric acid with acetic anhydride and sodium acetate merely acetylates it. Tiemann and Herzfeld (*Ber.*, 1877, **10**, 283) heated the solid acetyl derivative above its melting point, causing decomposition with evolution of acetic acid and formation of coumarin. Thus isomerisation does take place under forced conditions. It has now been noted that *o*-coumaric acid, when heated with acetic anhydride or, better, butyric anhydride and a very little iodine readily gives coumarin in good yield. Iodine in acetic or butyric acid is ineffective. The reaction does not depend, therefore, on iodine addition, or on acylation since ethylcoumarin is not obtained when butyric anhydride is used. More probably the addition of some entity, acetylium iodide, iodine acetate, or an ion of one of these, gives a free-rotation phase, thus reversing stage *Kb*, so leading through ring closure *Ka* to coumarin.

Acetylsalicylaldehyde with butyric anhydride and sodium butyrate gives 3-ethyl-

coumarin, which is not conclusive proof of intermolecular condensation owing to the ease of trans-esterification, *e.g.*, acetylsalicylaldehyde with benzoic anhydride and sodium benzoate yields only benzoylsalicylaldehyde. Trans-esterification occurs, the liberated acetyl group passing into sodium acetate rather than acetic anhydride as no coumarin is formed.

The Yield of Coumarin.—The overall equation for the synthesis of coumarin is:

$$HO{\cdot}C_6H_4{\cdot}CHO + 2(CH_3{\cdot}CO)_2O = \text{Coumarin} + 3CH_3{\cdot}CO_2H$$

The quantities usually recommended (*e.g.*, Cohen, "Practical Organic Chemistry," Macmillan, London, 1924, p. 221) are one mol. of salicylaldehyde to 1·6 mol. of acetic anhydride. According to Yanagisawa and Kondô (*J. Pharm. Soc. Japan*, 1921, 472, 498; *A*, 1921, i, 682) such quantities give a 27% yield. The optimum yield (45·8%) is now found to be obtained by using two mols. of the anhydride.

Experimental

Action of Acetic Anhydride and Sodium Acetate on o-*Coumaric Acid.*—*o*-Coumaric acid (4 g.) was heated with acetic anhydride (10 ml.) and sodium acetate (4 g.) for 6 hr. at 180°. The mixture was poured into sodium carbonate solution and extracted with ether. No coumarin was found in the ether but acidification of the carbonate solution gave a precipitate having, after crystallisation from aqueous alcohol, m. p. 145°, which is identical with that of *o*-acetoxycinnamic acid.

Perkin–Oglialoro Condensation of Salicylaldehyde.—Salicylaldehyde (5 g.), acetic anhydride (9 g.), and sodium phenylacetate (12 g.) were heated together for 2 hr. at 180°. The cooled product was warmed with water, cooled, and filtered off. The resulting yellow solid gave pale yellow needles (from alcohol) of 3-phenylcoumarin (6·3 g., 69%), m. p. 142°.

Action of Sodium Phenylacetate on Acetylsalicylaldehyde.—A mixture of the two substances (12 and 5 g. respectively) was heated for 2 hr. at 170°. The brown solid product on decolorisation and crystallisation from alcohol gave 3-phenylcoumarin (3·5 g., 52%), m. p. 141—142°.

Acetylsalicylaldehyde, Benzaldehyde, and Sodium Phenylacetate.—A mixture of the three substances (5, 8, and 12 g., respectively) was heated for 2 hr. at 170°. From the product benzaldehyde, phenylacetic acid, and 3-phenylcoumarin, but no α-phenylcinnamic acid, were recovered.

Phenylacetylsalicylaldehyde.—Phenylacetyl chloride (5 g.) was added to a suspension of the sodium salt of salicylaldehyde (4·5 g.) in dry ether (20 ml.) and the whole heated under reflux for 1 hr. Next morning the sodium chloride formed was filtered off. After removal of the ether the yellow oil remaining was distilled, giving a fraction, b. p. 130—170°/0·7 mm., which solidified. After washing of its ethereal solution with sodium carbonate the *phenylacetylsalicylaldehyde* was finally obtained as fine needles (from aqueous alcohol), m. p. 52°, having a pleasant odour (Found: C 74·2; H, 5·0. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). The yield was poor. Its *semicarbazone* crystallised from alcohol in fine needles m. p. 176° (Found: C, 64·3; H, 5·4; N, 14·2. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·1; N, 14·1%).

Action of Sodium Acetate on Phenylacetylsalicylaldehyde.—The two substances (0·2 g. each) were heated together at 170—180° for 2 hr., but did not become completely molten. 3-Phenylcoumarin (27%), m. p. 141—142°, was obtained.

Action of Sodium Phenylacetate on Phenylacetylsalicylaldehyde.—The two substances (0·6 and 0·3 g. respectively) were heated similarly; the mixture melted completely. The yield of 3-phenylcoumarin was 53·5%.

Action of Heat on Phenylacetylsalicylaldehyde.—Phenylacetylsalicylaldehyde (0·2 g.) was heated at 210—220° for 2 hr. The product was dissolved in hot alcohol, which on cooling deposited a small amount (⩾0·02 g.) of 3-phenylcoumarin, m. p. 141—142°.

Action of Acetic Anhydride and Sodium Acetate on 3-*Methoxysalicylaldehyde.*—The three substances (30, 15, and 10 g., respectively) were heated at 180° for 6 hr. The product was shaken with sodium hydroxide solution and extracted with ether. From the ethereal extract was obtained 8-methoxycoumarin (1·2 g., 10·5%), m. p. 87—89° (from water). Acidification of the alkaline layer gave 2-hydroxy-3-methoxycinnamic acid (3·1 g., 24%), m. p. 175—176° (from aqueous alcohol).

Perkin–Oglialoro Condensation of 3-*Methoxysalicylaldehyde.*—3-Methoxysalicylaldehyde (10 g.) acetic anhydride (25 g.), and sodium phenylacetate (25 g.) were heated at 180° for 6 hr. The

product was treated with sodium carbonate solution. The insoluble portion on recrystallisation from alcohol gave 8-*methoxy*-3-*phenylcoumarin* (8·1 g., 51%), pale yellow needles, m. p. 162° (Found: C, 75·9; H, 4·8. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%). The alkaline filtrate on acidification gave a mixture of acids which was extracted with hot water to remove phenylacetic acid. The residue separated from alcohol in colourless needles, m. p. 225°, of 2-*acetoxy*-3-*methoxy*-α-*phenylcinnamic acid* (1·1 g., 5·3%) (Found: C, 69·5; H, 5·1. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). A portion of this acid was hydrolysed by hot 10% sodium hydroxide solution for 5 hr. 2-*Hydroxy*-3-*methoxy*-α-*phenylcinnamic acid* was obtained as colourless needles, m. p. 198°, from aqueous alcohol (Found: C, 71·5; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

Action of Sodium Phenylacetate on 2-Acetoxy-3-methoxybenzaldehyde.—The two substances (8 and 5 g. respectively) were heated together for 2 hr. at 180°. The aqueous extract of the product on acidification gave only phenylacetic acid. The aqueous sodium carbonate extract of the residue on acidification gave no precipitate. The residue separated from alcohol in long pale yellow needles of 8-methoxy-3-phenylcoumarin, m. p. 162° (2·6 g., 40%).

Action of Acetic Anhydride and Sodium Phenylacetate on Acetylsalicylaldehyde.—The three reactants (6·5 g., 12 g. and 5 g. respectively) were heated at 170° for 2 hr. The product was poured into warm water, cooled and filtered. The residue, crystallised from alcohol, gave 3-phenylcoumarin, m. p. 141—142° (4·5 g., 66·5%).

Attempts to Convert Acetylsalicylaldehyde into Coumarin without Use of Acetic Anhydride.—Acetylsalicylaldehyde (4 g.) was heated at 180° or under reflux for 2—5 hr. as follows: (1) with sodium acetate (4 g.), (2) with potassium acetate and formate (5 g. each), (3) with pyridine (10 ml.) and a trace of piperidine, (4) with sodium acetate (4 g.), acetic acid (4 g.), and pyridine (excess), (5) with sodium acetate (4 g.) and xylene (50 ml.) in a Dean and Stark flask (no water was formed), (6) with sodium acetate (4 g.) and quinoline (10 ml.), (7) with sodium acetate (4 g.) and acetamide (10 g.), (8) with sodium acetate (4 g.) and pyridine (10 ml.), (9) with sodium acetate (4 g.) and ethylene glycol (10 ml.), (10) with sodium acetate (4 g.) and acetic acid (excess) which was allowed to distil over during the heating, and (11) with zinc chloride (2 g.). The reaction product in each case was poured into water, and the mixture extracted with ether. In no instance was more than a trace of coumarin obtained.

Action of Benzoic Anhydride and Sodium Benzoate on Acetylsalicylaldehyde.—The three reactants (14, 8, and 5 g., respectively) were heated at 180° for 4 hr. and the product poured into warm water. An ethereal extract, when washed with sodium carbonate solution and evaporated, yielded an oil. This was benzoylsalicylaldehyde and gave benzoic acid on hydrolysis.

Action of Butyric Anhydride and Sodium Butyrate on Acetylsalicylaldehyde.—The three reactants (20, 13·5, and 10 g., respectively) were heated for 2 hr. at 180°. An ethereal extract of the product was washed, dried, and distilled, finally under reduced pressure, giving an oil (b. p. 160°/14 mm.) which solidified to crystals of 3-ethylcoumarin (2·85 g., 26%), m. p. 74°, which depressed the m. p. of coumarin.

Conversion of o-Coumaric Acid into Coumarin.—A mixture of *o*-coumaric acid (5 g.), iodine (0·1 g.), and acetic anhydride (10 ml.) was heated at 180° for 2 hr. The product was poured into warm water. An ethereal extract was washed with sodium carbonate solution and dried, and the ether removed. The residue on crystallisation from light petroleum (b. p. 60—80°) gave coumarin (2·4 g., 54·5%).

Similarly, *o*-coumaric acid (4 g.), iodine (0·1 g.), and butyric anhydride (15 ml.) yielded a product (2·1 g., 60%) which did not depress the m. p. of a sample of coumarin.

When the anhydride was replaced by acetic acid (15 ml.) or butyric acid (15 ml.), only unchanged *o*-coumaric acid was recovered.

Effect of the Proportion of Acetic Anhydride on the Yield of Coumarin.—Salicylaldehyde (10 g., 1 mol.), sodium acetate (2·5 mols.), and acetic anhydride (8·36—25·08 g., 1—3 mol.) were heated for 5 hr. at 180°. The product was poured into warm water. An ethereal extract was shaken with sodium hydrogen sulphite solution, washed, and dried, and the ether removed. The resulting solid was dissolved in alkali, and the solution was boiled with charcoal, filtered, and acidified. The precipitated coumarin was crystallised from light petroleum (60—80°), yields being:

Ac_2O (mol.)	1	2	3
Yield (%)	19	45·8	40

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