

GEOMETRICAL INVERSION IN THE ACIDS DERIVED FROM THE COUMARINS

Part VII. The Behaviour of Acetyl Coumaric Acids

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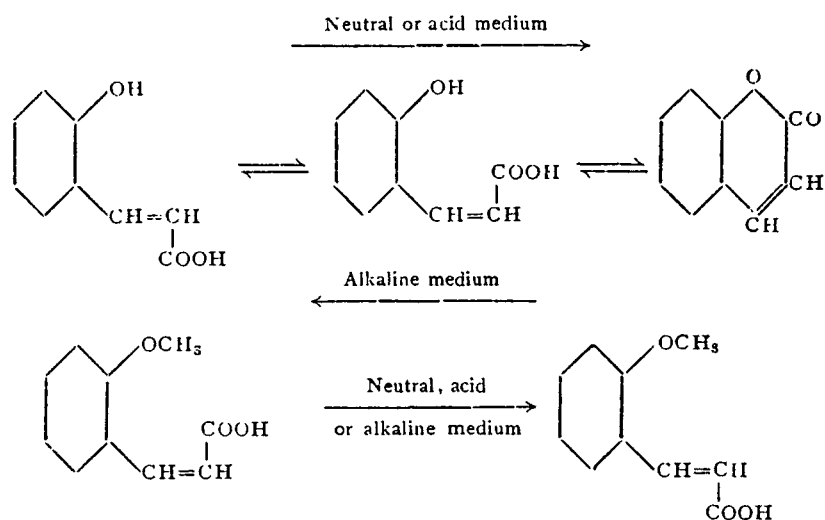
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It was originally noticed by Seshadri,¹ and Seshadri and Rao^{2,3} that in the case of the acids derived from the coumarins the *cis* to *trans* inversion takes place in an alkaline medium, whereas the reverse happens under neutral or acid conditions. More recently, however, Rangaswami and Seshadri⁴ observed that, since normally the *trans* is the stabler form, *cis* to *trans* inversion always takes place irrespective of the nature of the medium, provided the tendency of the unstable coumarinic acids to change into the stable coumarins through ring closure is precluded by the protection of the phenolic hydroxyl group through methylation. Even here, when the chance for the hydrolysis of the methyl ether group exists as with sulphuric acid, coumarins are formed.



Methoxyl or alkoxyl groups in general are quite stable and do not undergo change except under drastic conditions. Acyl groups such as the

acetyl are, on the other hand, mild in their protective effect. The part played by such mild protective groups seems to have a bearing on the problem of the biogenesis of coumarins. In regard to the origin and occurrence of coumarins in plants, all available evidence seems to indicate that coumaric acids are the immediate precursors and they slowly undergo change under the influence of light or other causes to produce coumarins. Coumarin itself occurs in nature along with coumaric and melilotic acids and a glucoside of coumaric acid has been isolated from plant sources.

A study of the behaviour of acetyl coumaric acids has, therefore, been undertaken with a view to understand the degree of protection which mild groups can give and the facility with which these compounds can undergo change. We have now investigated the action of light, heat and mercuric chloride in neutral medium on the acetyl derivatives of the following *trans* acids:—(1) Coumaric acid, (2) 4-methylcoumaric acid, (3) 5-nitrocoumaric acid, (4) psoralic acid, and (5) isopsoralic acid. All these acids are readily obtained from the corresponding coumarins by treatment with mercuric oxide and sodium hydroxide according to the method of Seshadri and Rao.^{2,5}

Acetyl coumaric acid was originally prepared by Tiemann and Herzfeld⁶ as a bye-product in the preparation of coumarin from salicylaldehyde. The same acid was obtained by Stoermer⁷ by the direct acetylation of coumaric acid with anhydrous sodium acetate and acetic anhydride at the boiling point of the anhydride. It has now been more conveniently produced with better yields by acetylating coumaric acid at the temperature of the steam-bath (100°). The other acids also undergo smooth acetylation by adopting this modification. If they are acetylated at the boiling temperature of the acetic anhydride, they undergo conversion considerably into the corresponding coumarins.

From the experiments on acetylation it could be concluded that the acetyl derivatives that are first produced undergo further change into the coumarins to more or less extent depending upon the conditions. At 100° the change is very small in all cases, whereas at about 150° (the temperature required for keeping acetic anhydride boiling in the reaction mixture) the conversion is very little with acetyl coumaric acid and very large with acetyl nitrocoumaric acid, the others coming in between.

The action of ultra-violet light on acetyl coumaric acid in alcohol or benzene solutions was originally studied by Stoermer (*loc. cit.*) and acetyl coumarinic acid in a considerable amount and a small quantity of coumarin were stated to have been produced.

Under the influence of sunlight which has been shown by Dey, Rao and Seshadri⁸ to be an effective and convenient substitute for ultra-violet light, the acetyl coumaric acids in general undergo very slow transformation. In most cases very little change is noticed within 48 hours when alcoholic solutions are employed, and after prolonged exposure for 200 hours considerable yields of coumarins are obtained. Acetyl coumarinic acids could not be isolated amongst the products. The acetyl derivative of 5-nitrocoumaric acid is somewhat different in its behaviour. A change of about 40 per cent. is observed even within 48 hours. This difference may be due to some extent to the influence of the nitro-group in facilitating geometrical inversion. It has been already shown that nitrocoumaric acid and its methyl and ethyl esters undergo change in the presence of sunlight more vigorously than those that do not have the nitro-group. This effect of the nitro-group cannot however be the major factor because ordinary coumaric acids and their esters undergo considerable change into coumarins within 24 hours. The more important factor, therefore, seems to be the facility with which the pyrone ring closes up by eliminating a molecule of acetic acid. A nitro-group in the *para*-position obviously makes the acetoxy group more reactive and favours this change. A similar explanation holds good in regard to the behaviour of these acetyl acids under the influence of heat.

TABLE I

Acetyl derivative of	Percentage conversion under the influence of light		
	After 24 hours	After 48 hours	After 200 hours
1. Coumaric acid ..	Nil	Negligible	85 to 90%
2. 4-Methylcoumaric acid	Nil	Negligible	80 to 85%
3. 5-Nitrocoumaric acid ..	5%	40%	95 to 100%
4. Psoralic acid ..	Nil
5. Isopsoralic acid ..	Nil

When the acetyl compounds are heated to temperatures above their melting points considerable conversion into the corresponding coumarins takes place. This is, however, accompanied by the production of some resinous products also. As volatile products, along with acetic acid, some carbon dioxide is also evolved. It is therefore clear that two simultaneous reactions take place, one involving ring closure with the removal of one

molecule of acetic acid and the other involving elimination of carbon dioxide producing resinous products (see formulæ given below). In this respect the acetyl coumaric acids fall midway between coumaric acids which undergo almost completely decarboxylation on heating and the methyl and ethyl esters of coumaric acids which produce coumarins as the main product. The resinous matter obtained in the above reactions with acetyl compounds is probably produced as the result of polymerisation of the styrenes that have been formed by decarboxylation.

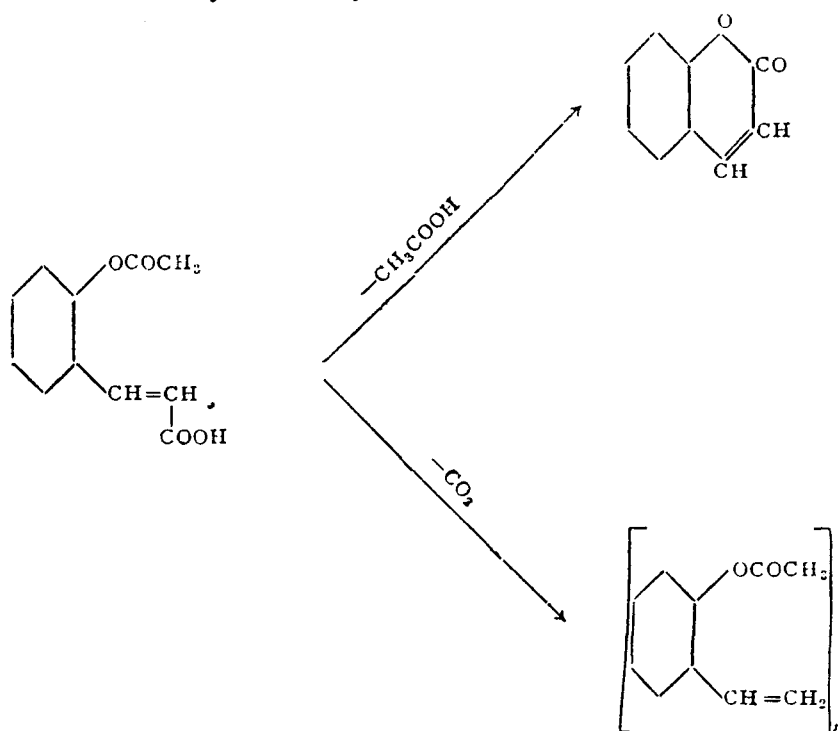


TABLE II

No.	Acetyl derivative of	Percentage conversion under the influence of heat
		%
1	Coumaric acid ..	60
2	4-Methylcoumaric acid	70
3	5-Nitrocoumaric acid ..	75
4	Psoralic acid	75
5	Isopsoralic acid ..	80

On boiling with mercuric chloride in alcoholic or aqueous solutions, the acetyl coumaric acids readily undergo complete conversion into the coumarins.

Experimental

Preparation of Acetyl Coumaric Acids—

Acetyl Coumaric Acid.—Coumaric acid (2 g.), anhydrous sodium acetate (5 g.) and acetic anhydride (20 c.c.) were heated for six hours by immersing in a boiling water-bath. The reaction mixture was then cooled and poured into 100 c.c. of ice-cold water. After leaving overnight, the acetyl derivative that separated out was purified by dissolution in aqueous sodium bicarbonate at 0° and subsequent reprecipitation from the clear filtrate with dilute hydrochloric acid. During this process the temperature should not be allowed to rise above 0° as otherwise the acetyl derivative undergoes some hydrolysis. The precipitated solid was then crystallised from benzene, when it came out as rectangular plates melting at 154–55°. (Tiemann and Herzfeld⁶ gave the crystal structure as needles and the melting point as 146°; Roth and Stoermer⁹ reported the melting point to be 154–55°.) The yield of the pure acetyl coumaric acid was 2.2 g. When the acetylation was carried out at a higher temperature by keeping the acetic anhydride boiling, the yield was lower (2.0 g.).

Acetyl 4-Methylcoumaric Acid.—The same procedure as in the previous case was adopted to acetylate 4-methylcoumaric acid. After purification, the substance crystallised from alcohol as fibrous needles melting at 155°. The yield was almost theoretical. (Found: C, 64.9; H, 5.0; $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.4%.) The boiling temperature of acetic anhydride was not suitable for the reaction, since conversion into 7-methylcoumarin took place to a considerable extent.

Acetyl 5-Nitrocoumaric Acid.—This substance was conveniently prepared by acetylating 5-nitrocoumaric acid at 100° as in the previous cases. The crude product obtained by the treatment of the reaction mixture with water did not readily dissolve in bicarbonate solution, unless it had been well triturated first with a small quantity of the bicarbonate. Practically the whole of the solid went into solution by this treatment. It was subsequently reprecipitated and crystallised from benzene when it was obtained in the form of colourless rectangular rods, m.p. 217°. The yield of the pure product was 5.5 g. from 5 g. of nitrocoumaric acid. The substance was not easily soluble in alcohol. (Found: C, 52.3; H, 3.3; N, 5.7; $C_{11}H_9O_6N$ requires C, 52.6; H, 3.6; N, 5.6%.) At the boiling point of acetic anhydride the reaction yielded very little of the acetyl derivative, the product being mainly nitrocoumarin.

Acetyl Psoralic Acid.—Psoralic acid could be acetylated at the boiling point of the anhydride, provided the reaction mixture was gently refluxed only for 3 hours on an oil-bath at a temperature of 150°. Purification was effected as in the previous cases, and the yield was about 80%. It crystallised from alcohol as clusters of needles and rectangular prisms melting at 180–81°. The experiment was more conveniently carried out using a boiling water-bath for 6 hours and the yield was also found to be better. (Found: C, 62.9; H, 4.4; $C_{13}H_{10}O_5$ requires C, 63.4; H, 4.1%.)

Acetyl Isopsoralic Acid.—The procedure was just the same as in the case of the acetyl psoralic acid, and the yield was almost theoretical. It crystallised from alcohol in the form of needles melting at 210–11°. (Found: C, 63.5; H, 4.4; $C_{13}H_{10}O_5$ requires C, 63.4; H, 4.1%.)

Action of Sunlight on Acetyl Coumaric Acids.—Acetyl coumaric acid (1 g.) was dissolved in anhydrous ethyl alcohol (25 c.c.) contained in a quartz flask. The solution was then exposed to direct sunlight for 24 hours (8 hours a day). When the exposure was over, all the alcohol was distilled off and the product was treated with sufficient quantity of sodium bicarbonate solution. All the solid dissolved, indicating that no conversion of the acetyl coumaric acid into the pyrone had taken place. The bicarbonate solution on acidification yielded the original acid, which, after recrystallisation from benzene, melted at 154°.

The experiment was repeated increasing the period of exposure. Even after 48 hours there was very little change and no detectable amount of coumarin was formed. However exposure for 200 hours brought about almost complete conversion. The residue obtained after distilling off the alcohol did not dissolve in sodium bicarbonate solution. It was then crystallised from alcohol and was found to be identical with coumarin melting at 69°. Yield was about 90%.

Acetyl 4-methylcoumaric acid resembled closely the acetyl coumaric acid in its behaviour under the influence of light. As in the previous case, only prolonged exposure (200 hours) brought about inversion to an extent of 80 to 85%.

Acetyl 5-nitrocoumaric acid yielded 5% of 6-nitrocoumarin, even when the period of exposure was only 24 hours. It produced 40% yield of nitrocoumarin after 48 hours and underwent complete conversion (95–100%), when the exposure was for 200 hours.

Acetyl psoralic and isopsoralic acids did not produce any psoralen and isopsoralen, when exposed to sunlight for 24 hours. For want of sufficient material, their behaviour on longer exposures could not be further studied.

In all the above experiments relating to the action of light on the acetyl coumaric acids it was noticed that small quantities of amorphous sparingly soluble complex products were produced along with the coumarins. These were probably due to polymerisation which is known to take place with coumaric acids in the presence of sunlight.

Action of Heat.—Acetyl coumaric acid (1.5 g.) was taken into a clean dry test-tube and heated for half an hour in an oil-bath at a temperature 40–50° above the melting point of the acid with frequent stirring. A beautiful crystalline substance sublimed on to the cooler parts of the test-tube. Carbon dioxide was evolved during the heating and acetic acid could be distinctly smelt. After the decomposition was over, the test-tube was cooled, when the molten mass changed into an amorphous solid. The crystalline sublimate was carefully scraped off and after recrystallisation from alcohol was found to be identical with coumarin melting at 69°. The solid mass remaining in the test-tube was not soluble either in sodium carbonate, alcohol or ether. It was resinous and no definite compound could be isolated from it. The yield of coumarin was 60%.

Acetyl 4-methylcoumaric acid was heated at 210° as described above. Its behaviour was just the same as that of acetyl coumaric acid. There was 70% conversion into 7-methylcoumarin in this case. As regards acetyl 5-nitrocoumaric acid, the temperature was maintained at 255°, though 6-nitrocoumarin began to form even at a much lower temperature and the yield was 75%. Acetyl psoralic and isopsoralic acids were heated at 230° and 240° respectively. A conversion of about 75% in the case of the former acid and about 80% in the case of the latter was noticed.

Action of Mercuric Chloride.—Acetyl coumaric acid (1 g.) was dissolved in 25 c.c. of rectified spirit and an equimolecular quantity of mercuric chloride was added. The resulting clear solution was refluxed on a water-bath for 3 hours. It was then diluted and allowed to stand, when coumarin mercuric chloride was deposited with its characteristic crystalline structure. After leaving overnight, the crystals were filtered and recrystallised from water. They came down as colourless needles melting at 164°. Mixed melting point with an authentic sample was not depressed. When boiled for about 5 minutes with dilute hydrochloric acid, the substance decomposed into coumarin melting at 70°. The yield was theoretical.

The result was similar when the experiment was repeated using water instead of alcohol as the solvent.

The other acetyl coumaric acids produced the corresponding coumarins in almost theoretical yields, when they were boiled with alcoholic or aqueous

solutions containing equimolecular quantities of mercuric chloride and subsequently treated with hydrochloric acid in order to decompose completely the mercuric chloride addition compounds.

Summary

The acetyl derivatives of coumaric, 4-methylcoumaric, 5-nitrocoumaric, psoralic and isopsoralic acids have been prepared and their behaviour studied under conditions which bring about *trans* to *cis* inversion. Under the influence of sunlight, the first three acids produce the corresponding coumarins on prolonged exposure. When heated to above their respective melting points all the acetyl compounds undergo inversion to an extent of 60–80%. Along with the pyrones, highly polymerised resinous compounds are also produced on heating. Treatment with equimolecular amounts of mercuric chloride in aqueous or aqueous alcoholic medium brings about inversion in all the cases with almost theoretical yields.

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