# CHEMICAL INVESTIGATION OF INDIAN LICHENS

## Part II. Synthetic Uses of Some Lichen Acids

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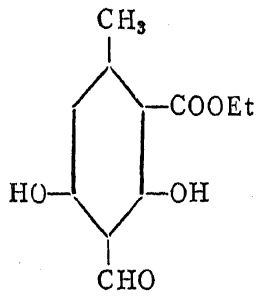
Received October 21, 1940

Simple 5-hydroxy-pyrones do not occur in nature and their preparation is beset with difficulties. It was only during recent years that 5-hydroxy-flavone (Sugasawa[1]) and 5-hydroxy-coumarin (Shah and Shah[2]) have been obtained. For the syntheses of the simpler 5-hydroxy-coumarin derivatives orcinol seems to be capable of serving as the starting material to some extent. Pechmann[3] condensed orcinol with malic acid in the presence of concentrated sulphuric acid and reported the formation of 7-hydroxy-5-methyl-coumarin. Using orcinol and acetoacetic ester he claimed to have obtained 7-hydroxy-4: 5-dimethyl-coumarin. But this has been conclusively proved by Dey[4] to be 5-hydroxy-4: 7-dimethyl-coumarin. Following this analogy even the first compound has been assumed to be 5-hydroxy-7-methyl-coumarin (Sen and Chakravarti[5]). But in the course of the work recorded in this paper a compound answering to the formula 5-hydroxy-7-methyl-coumarin has been for the first time prepared by unambiguous methods, and it is found that Pechmann's compound is the 7-hydroxy-isomer. Consequently it has to be noted that orcinol is capable of reacting in two different ways, (1) in the $\beta$-position with malic acid and (2) in the $\gamma$-position with ethyl aceto-acetate.

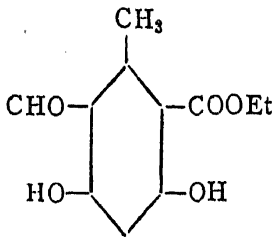
A large number of lichen acids and their simple degradation products are derivatives of orcinol and these seem to offer greater possibilities for preparing 5-hydroxy-coumarins definitely. Atranorin and lecanoric acid can be isolated in very good yield from the Indian lichen *Parmelia abessinica*. By easy hydrolysis they give rise to ethyl hæmatommate and ethyl orsellinate respectively. Possibilities of utilising all the four compounds for the synthesis of 5-hydroxy-coumarins have been explored and the results are recorded in this paper.

Since the yield of ethyl hæmatommate (I *a*) by the hydrolysis of atranorin (Curd *et al.*)[6] was poor it was synthesised by an improved method starting from ethyl orsellinate (II). Pfau[7] obtained it synthetically from ethyl

orsellinate by the Gattermann reaction in the presence of zinc chloride with ether as diluent. But it was contaminated with a larger amount of the isomeric iso-hæmatommate (1 *b*) which had to be separated by steam distillation. The yield by this method also was therefore poor. By a slight modification in the procedure and adding anhydrous aluminium chloride as a condensing agent according to the method of Shah and Laiwalla[8] it is now found that a good yield (80%) of ethyl hæmatommate uncontaminated by its isomer can be produced. This is obviously due to the fact that the presence of aluminium chloride enhances the reactivity of the $\gamma$-position in ethyl orsellinate.



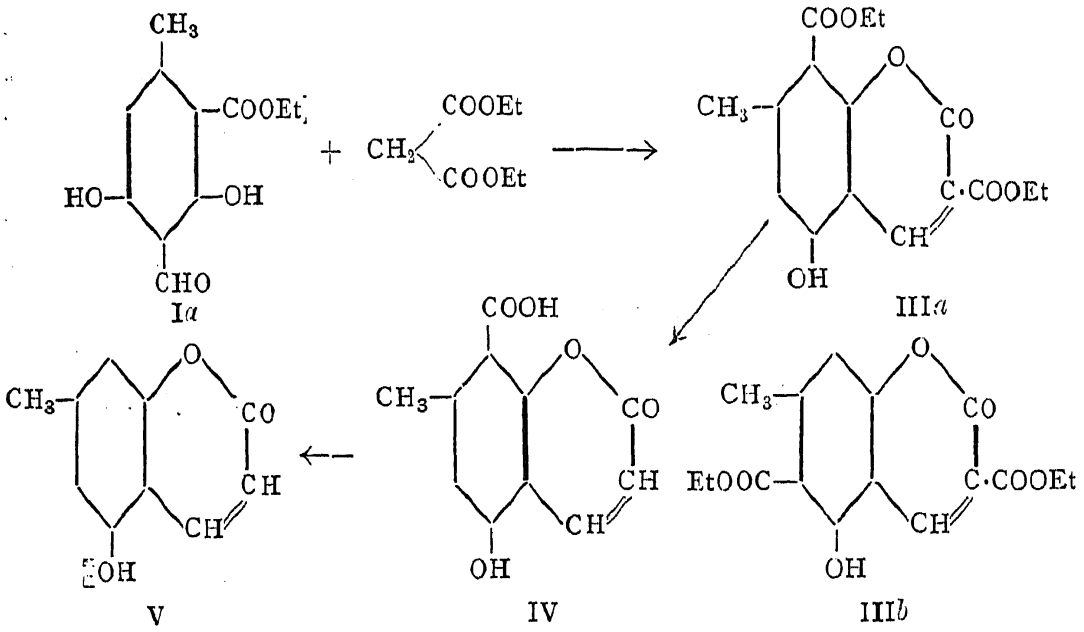

Ia




Ib

The presence of an aldehyde group in the $\gamma$-position of the atranol residue of both atranorin and ethyl hæmatommate suggested the possibility of synthesising 5-hydroxy-coumarin derivatives from them. However both Perkin's[9] and Knoevenagel's[10] reactions failed to take place satisfactorily with atranorin. The first reaction was not successful even in the case of ethyl hæmatommate. There was considerable resinification probably due to the high temperature that has to be employed for the reaction.

Ethyl hæmatommate condenses with diethyl malonate when piperidine is employed as a condensing agent. The reaction could take place in one of two ways yielding either the 8-carbethoxy compound (III *a*) or the 6-carbethoxy compound (III *b*). Since it did not give any colouration with alcoholic ferric chloride thereby indicating the absence of the carbethoxy group in a position ortho to the hydroxyl it has been given the constitution (III *a*). The ester could be hydrolysed to the corresponding monocarboxylic acid (IV) which underwent decarboxylation to yield 5-hydroxy-7-methyl-coumarin (V). This constitutes the first unequivocal synthesis of 5-hydroxy-7-methyl coumarin. It may be mentioned here that this compound and its derivatives do not exhibit any fluorescence. This seems to be a characteristic of 5-hydroxy coumarins easily distinguishing them from the corresponding 7-hydroxy compounds which exhibit bright fluorescence. Further, the 5-hydroxy compounds produce deep yellow colour in alkaline solutions whereas the 7-hydroxy compounds are devoid of this property.

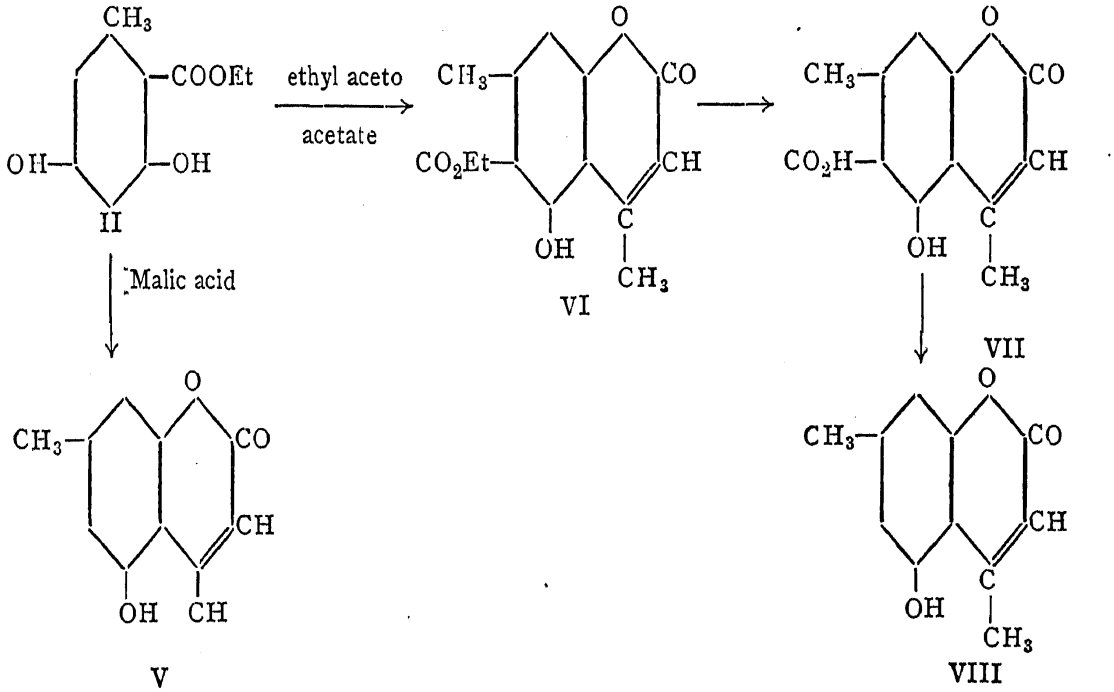



When the condensation between ethyl hæmatommate and diethyl malonate is effected by means of concentrated sulphuric acid 5-hydroxy-7-methyl-coumarin is obtained directly without any intermediate stages though the final yield is not better than by the previous method.

In regard to the condensation of ethyl orsellinate with ethyl acetoacetate or malic acid in the presence of concentrated sulphuric acid as a condensing agent (Pechmann's method) only 5-hydroxy-coumarin derivatives have been obtained indicating thereby that the $\gamma$-position between the two phenolic hydroxyl groups is the reactive one in the molecule of ethyl orsellinate. When this substance was condensed with ethyl acetoacetate in the presence of concentrated sulphuric acid in the cold (freezing mixture) the product was an ester giving a violet colour with alcoholic ferric chloride and it corresponded with the constitution (VI). This is further supported by the fact that the corresponding acid (VII) obtained by hydrolysis of the ester undergoes decarboxylation to yield the 5-hydroxy-4: 7-dimethyl-coumarin (VIII). This condensation could also be effected satisfactorily in dry nitrobenzene solution in the presence of anhydrous aluminium chloride, using the temperature range 120–30° (Sethna, Shah and Shah[11]). When the conditions were however modified using sulphuric acid and the temperature range of 90–5°, 5-hydroxy-4: 7-dimethyl-coumarin was obtained as the only product, obviously due to the loss of the carbethoxy group by hydrolysis and decarboxylation. In regard to the condensation with ethyl acetoacetate therefore ethyl orsellinate behaves very similar to orcinol.

Ethyl-orsellinate and malic acid undergo condensation in the presence of concentrated sulphuric acid to yield 5-hydroxy-7-methyl-coumarin which was identical with the product obtained from ethyl hæmatommate as the

starting material. Herein we have an easy method for the preparation of this coumarin. The condensation of orcinol with malic acid effected by Pechmann seems to produce an isomeric compound capable of fluorescence and hence has probably the constitution of a 7-hydroxy-coumarin. It may be presumed therefore that in the reaction with ethyl orsellinate the coumarin condensation takes place completely prior to the removal of the carbethoxy group, as otherwise, if orcinol were produced to any extent and subsequent condensation occurred, at least some quantity of 5-methyl-umbelliferone would be found in the product and easily detected by its fluorescence.




In regard to the preparation of 5-hydroxy-7-methyl-coumarin a very useful observation was made that lecanoric acid could be conveniently substituted for ethyl orsellinate in the above condensation and the yield is extremely satisfactory. This eliminates the need for the preparation of ethyl orsellinate as an intermediate stage. Further, lecanoric acid is a convenient starting material since it occurs to the extent of 3·3% in *Parmelia abessinica* and can be easily extracted.

## *Experimental*

Atranorin was obtained in 1·1% yield by extracting the lichen *Parmelia abessinica* (Kremp.) with petroleum ether.

*Preparation of Ethyl Hæmatommate.*—The method of hydrolysis of atranorin employed by Curd *et al.*, was adopted. Thereby colourless silky needles of ethyl hæmatommate were obtained melting at 112–13°. The yield was poor being 0·1 g. from 0·5 g. of atranorin. It could, however, be obtained in satisfactory yield from ethyl orsellinate by the modified Gattermann reaction using anhydrous aluminium chloride.

To a solution of ethyl orsellinate in dry ether (100 c.c.) contained in a three-necked flask, fitted with a mercury seal and mechanical stirrer and cooled in a bath of freezing mixture, zinc cyanide (6·0 g.) was added followed by a solution of anhydrous aluminium chloride (3·4 g.) in 50 c.c. of dry ether. Dry hydrogen chloride was then passed through the cooled mixture with continuous stirring. Zinc cyanide gradually disappeared, the solution turned brown and a pasty mass separated. The flask was stoppered air-tight, sealed and left in the ice-chest overnight. The ether layer was then decanted off and the solid washed with more of the dry solvent. It was subsequently dissolved in 50 c.c. of water and heated on a water-bath for half an hour in a fume chamber. After cooling, the product was filtered at the pump. It was then dissolved in a slight excess of rectified spirit, boiled with animal charcoal and quickly filtered while hot. The filtrate was concentrated by distilling off the alcohol and the solid allowed to crystallise slowly. The crystals were filtered at the pump and the mother liquor pressed out. By this method a fairly pure sample of ethyl hæmatommate was obtained in the form of long needles. This was then recrystallised from hot alcohol when a very pure sample melting at 113–14° alone or mixed with a specimen obtained from atranorin was obtained. The yield was 3·2 g. (80%). (Found: C, 59·3; H, 5·3; $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%.)

Evaporation of the ethereal filtrate and washings from the aldimine hydrochloride gave some unchanged ethyl orsellinate melting at 132° (1·0 g.).

*Condensation of Ethyl Hæmatommate with Diethyl Malonate*—

*Ethyl-5-hydroxy-7-methyl-coumarin-3 : 8-dicarboxylate.*—To a mixture of a dry sample of ethyl hæmatommate (0·5 g.) and diethyl malonate (0·6 g.) which was cooled in a bath of freezing mixture, piperidine (4 drops) was added. It was allowed to stand at the laboratory temperature overnight and then treated with dilute hydrochloric acid when a pale yellow solid was obtained which crystallised from alcohol in colourless short fibrous needles melting at 141–2° (yield 0·4 g.). (Found: C, 59·8; H, 5·2; OEt, 26·7; $C_{16}H_{16}O_7$ requires C, 60·0; H, 5·0; OEt, 28·1%.) The substance was soluble in ether and acetone and insoluble in chloroform and benzene. It did not give any colour with alcoholic ferric chloride and dissolved in sodium hydroxide yielding a deep yellow solution without fluorescence—characteristic property of 5-hydroxy-coumarins. It dissolved in concentrated sulphuric acid yielding a red solution without any blue fluorescence and it was insoluble in sodium bicarbonate solution.

*5-Hydroxy-7-methyl-coumarin-8-carboxylic acid.*—A solution of the above ester (0·3 g.) in 5% potash (5 c.c.) was kept overnight at the room temperature. The clear brown solution was acidified with dilute hydrochloric acid

and the precipitated solid was filtered, washed and dissolved in aqueous sodium bicarbonate. The resulting solution was filtered and the filtrate acidified with dilute hydrochloric acid when a pale yellow solid separated out. It crystallised in tiny yellow prismatic needles (yield 0·2 g.) from aqueous alcohol and melted at 270–71° with decomposition. (Found: C, 57·8; H, 4·2; $C_{11}H_8O_5$, $\frac{1}{2}H_2O$ requires C, 57·6; H, 3·9%.)

This gave all the reactions of the previous ester and did not give a colour with alcoholic ferric chloride.

5-*Hydroxy-7-methyl-coumarin.*—The above acid (0·2 g.) was heated with quinoline (2–3 c.c.) and copper bronze (0·1 g.) for $\frac{3}{4}$ hour at 150-60° in an oil-bath. Care was taken not to allow the temperature of the bath to exceed 160°. The solution was then dissolved in an excess of ether and filtered to remove the copper bronze. The ether was then distilled over, the residue mixed with an excess of dilute hydrochloric acid and repeatedly extracted with ether. The ether extract was then washed with dilute sodium bicarbonate solution to free it from acid and then evaporated. The resulting brown product was washed with a little benzene to remove resinous matter and then crystallised from alcohol. 5-Hydroxy-7-methyl-coumarin was thus obtained as pale yellow needles melting at 215–16° (decomp.). The yield was 0·05 g. (Found: C, 64·7; H, 4·9; loss on drying at 120°, 4·93; $C_{10}H_8O_3$, $\frac{1}{2}H_2O$ requires C, 64·9; H, 4·9, and loss on drying 4·9%.)

5-Hydroxy-7-methyl-coumarin was obtained in a slightly better yield and more readily by condensing ethyl hæmatommate with diethyl malonate employing cold concentrated sulphuric acid as the condensing agent.

Ethyl hæmatommate (0·2 g.) was mixed with malonic ester (0·5 g.), cooled in a bath of freezing mixture, concentrated sulphuric acid (2 c.c.) added and the mixture kept overnight at room temperature. It was then poured into ice water (50 c.c.) when a yellow solid melting at about 175° was obtained. On crystallisation from alcohol the melting point was raised to about 201°. Further crystallisation from acetone yielded the pure substance melting with decomposition at 215–16° (yield 50 mg.). The mixed melting point with the 5-hydroxy-7-methyl-coumarin obtained above was not depressed. The two samples gave identical reactions.

*Ethyl Orsellinate from Lecanoric Acid.*—Lecanoric acid could be obtained in an yield of 3·3% from *Permelia abessinica.* It is also found in *Roccella montagnei* but the yield in this case is neither good nor consistent. Ethyl orsellinate was prepared from the acid by the method of Schunck,[12] the yield being 6·2 g. from 10 g. of lecanoric acid. It was condensed with ethyl acetoacetate under various conditions using concentrated sulphuric

acid as the condensing agent. The reaction was carried out in the cold and at 90° and in a separate experiment anhydrous aluminium chloride was employed in nitrobenzene medium. The products that were obtained are described below.

(*a*) *Ethyl-5-hydroxy-4: 7-dimethyl-coumarin-6-carboxylate.*—To a mixture of ethyl orsellinate (0·5 g.) and ethyl acetoacetate (2 c.c.) cooled in a bath of freezing mixture, concentrated sulphuric acid (1 c.c.) was added and the mixture kept overnight at the laboratory temperature. The product was poured over crushed ice when a colourless solid separated out. It was filtered and crystallised from alcohol and thus was obtained as colourless needles melting at 179–80° (yield 0·4 g.). The substance was sparingly soluble in cold alcohol. It dissolved in dilute sodium hydroxide solution with yellow colour and did not exhibit any fluorescence with concentrated sulphuric acid. It gave a violet red colour with alcoholic ferric chloride solution. (Found: C, 64·5; H, 5·6; OEt, 16·4; $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3; OEt, 17·2%.)

The above ester was obtained in a lesser yield from ethyl orsellinate and ethyl acetoacetate using anhydrous aluminium chloride as a condensing agent in nitrobenzene solution. Anhydrous ethyl orsellinate (0·5 g.) and ethyl acetoacetate (0·5 g.) were dissolved in hot dry nitrobenzene (1·5 c.c.), a solution of anhydrous aluminium chloride (2 g.) in hot nitrobenzene (3 c.c.) added and the mixture heated at 120–30° for about an hour. The evolution of hydrogen chloride at the end of this period was negligible. The product was then cooled in ice and 4 N hydrochloric acid (2 c.c.) added, and the nitrobenzene distilled in steam. The residual brown mass crystallised from rectified spirit in colourless needles melting at 179–80° (yield, 0·2 g.). The mixed melting point with a sample of ethyl-5-hydroxy-4: 7-dimethyl-coumarin described above was not depressed.

5-*Hydroxy*-4: 7-*dimethyl-coumarin-6-carboxylic acid.*—The above ester (0·3 g.) was dissolved in 10% aqueous potash (5 c.c.) and set aside for 32 hours. At the end of this period the solution was neutralised with cold dilute hydrochloric acid and the resulting product filtered. It was crystallised from hot rectified spirit when pale-brown needles melting at 247° with a decomposition were obtained in an yield of 0·25 g. (Found: C, 61·4; H, 4·5; $C_{12}H_{10}O_5$ requires C, 61·6; H, 4·3%.) The substance gave a violet colour with alcoholic ferric chloride solution. It was soluble in dilute alkali and concentrated sulphuric acid with an yellow colour.

5-*Hydroxy*-4: 7-*dimethyl-coumarin.*—The above acid was dissolved in quinoline (2 c.c.) and heated with copper bronze (0·1 g.) for about an hour

170° in an oil-bath. The product was dissolved in an excess of ether d rapidly filtered. Ether was then removed and the residue treated with ute hydrochloric acid. The insoluble portion was filtered, washed free m acid and crystallised from rectified spirit. It was obtained in the m of colourless needles melting at 258°. The product was soluble in ohol and acetone. It gave with alkali a deep yellow colour without any orescence. It did not give any colour with alcoholic ferric chloride solun. The mixed melting point with a sample of 5-hydroxy-4: 7-dimethyl-umarin obtained from orcinol and acetoacetic ester (Dey[4]) was not pressed. (Found: C, 69·2; H, 5·5; $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%.)

The above condensation was carried out with the modification that the nperature of 90–95° was employed and the condensation completed in out an hour. When the mixture was treated with ice-water a product elting at about 235° was obtained. It was washed with sodium bicarbone solution and the insoluble residue crystallised twice from acetone when lourless needles melting at 258° were obtained. It was identical with ıydroxy-4: 7-dimethyl-coumarin in all respects (yield 0·35 g.).

*ndensation of Ethyl Orsellinate and Lecanoric Acid with Malic Acid—* 5-*hydroxy-7-methyl-coumarin.*—To a mixture of ethyl orsellinate (0·5 g.) d malic acid (0·75 g.) concentrated sulphuric acid (3 c.c.) was added in the ld and heated at 90–95° on a water-bath for half an hour. The solution ıs allowed to cool and poured over crushed ice with stirring. The resulting oduct was filtered and washed. After drying, it was dissolved in ether and e ethereal solution was shaken with aqueous sodium bicarbonate. The dium bicarbonate layer was separated from the ether layer and the ether aporated. A yellow product was thus obtained which when crystallised om alcohol yielded pale yellow needles melting at 215–16°; the mixed elting point with an authentic sample already described showed no pression (yield 0·3 g.).

A mixture of lecanoric acid (0·5 g.), malic acid (1·5 g.) and concentrated lphuric acid (5 c.c.) was heated at 90–95° on a water-bath for about an ur. The solution was then cooled and poured over crushed ice. The llow product that separated was filtered, washed and crystallised from cohol. It was finally crystallised from acetone when pale yellow crystalline edles melting at 215–16° separated out. It was identical with the hydroxy-7-methyl-coumarin in every respect (yield 0·4 g.).

## *Summary*

The lichen acids, atranorin and lecanoric acid obtained from *Parmelia essinica* have been made the starting points for the preparation of

5-hydroxy-coumarin derivatives. 5-Hydroxy-7-methyl-coumarin has been synthesised for the first time from ethyl hæmatommate and has been shown to be different from the compound prepared by Pechmann by the action of malic acid on orcinol. The above coumarin can also be readily obtained from ethyl orsellinate and lecanoric acid. Some of its derivatives along with those of 5-hydroxy-4: 7-dimethyl-coumarin have been obtained and characterised. An improved method for the synthesis of ethyl hæmatommate is described.

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