REACTIVITY OF THE DOUBLE BOND IN COUMARINS AND RELATED α-β UNSATURATED CARBONYL COMPOUNDS.

Part II.* Reaction of Mercury Salts on Coumarins.

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That the double bond in coumarins is reactive has been established from the easy addition of typical reagents. Clayton[3] was the first to prepare coumarin compounds containing mercury. He found that coumarin and alkyl substituted coumarins combine with an equimolecular proportion of mercuric chloride readily in the cold to form addition products and he was of the opinion that the mercuric salt was held by the oxygen of the pyrone ring by means of residual affinity. Biilmann[2] could observe no reaction between coumarin and mercuric acetate in methyl alcoholic solution and was led to think that it did not contain an ordinary ethylenic link, since derivatives of coumarinic and coumaric acids reacted readily in the cold, the double bond being the point of attack by the reagent. Sen and Chakravarti[9] remarked that mercuric chloride and mercuric acetate failed to mercurate coumarin in aqueous, alcoholic or acetic acid solution. Therefore, they opened up the pyrone ring by dissolving the coumarins in aqueous alkali and subsequently effected mercuration of the coumarinic acids and their salts either by treatment with mercuric acetate in cold aqueous solution or by boiling with yellow mercuric oxide (see Naik and Patel[8]). With a group of coumarins as represented by 6-nitro and 6 : 8-dibromocoumarin they noticed that inversion to the coumaric acid took place and no mercuration was effected. With another group as typified by 7-hydroxy-4-methylcoumarin they found that mercuration of the benzene ring took place whereas no inversion was produced. That coumarin itself under these conditions gives coumaric and mercurated coumaric acids has been recently shown by us.[11] Recently after our work described in this paper had made considerable

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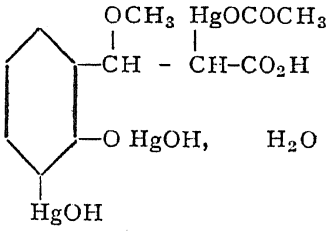
progress, a paper by K. Matejka[6] on the mercuration of cinnamic acid, safrole and coumarin appeared. This author observed mercuration of coumarin in hot alcoholic solution using mercuric acetate and claimed to have isolated two compounds of the following probable formulæ. But these rather unusual constitutions are based only on the analysis for carbon, hydrogen and mercury of specimens which were probably not pure and not on an adequate study of their properties or the preparation of known derivatives.



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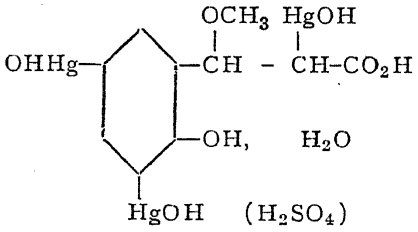
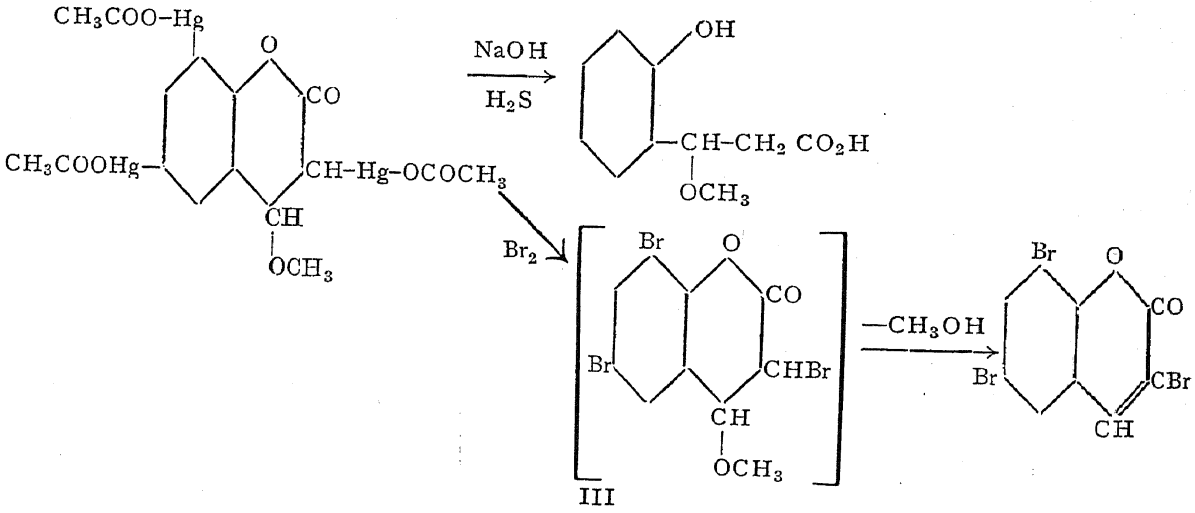


II

Contrary to previous statements it is now found that coumarin reacts slowly in the cold with mercuric acetate in methyl alcoholic solution yielding a trimercury compound. The reaction is less slow when the solution is boiled. Irrespective of the molecular proportions 1, 2 or 3 of mercuric acetate employed the same product, 3 : 6 : 8-triacetoxymercuri-4-methoxymelilotic anhydride is obtained. Though with the larger proportions the yield improves, purity suffers due to admixture with an impurity containing a higher percentage of mercury and a lower percentage of carbon, which is probably mercurous acetate. The substance cannot be crystallised from any of the ordinary organic solvents since it is sparingly soluble. It is insoluble in sodium carbonate, but dissolves in aqueous ammonia and sodium hydroxide easily in the cold and on passing hydrogen sulphide into these solutions all acetoxymercury groups are replaced by hydrogen atoms, the resulting product being β-methoxymelilotic acid (Biilmann, *loc. cit.*). The mercury compound reacts rapidly with bromine in the cold in the presence of glacial acetic acid producing mercuric bromide and 3 : 6 : 8-tribromocoumarin which is identified by comparison with an authentic specimen (Simonis and Wenzel, 1906) and by conversion into 4 : 6-dibromocoumarilic acid. From these the constitution of the mercury compound is clearly established as III and hence it has to be concluded that mercuric acetate reacts with the double bond in coumarin and also mercurates the benzene ring in 6 and 8 positions.

7-Methylcoumarin behaves similar to coumarin though the reaction with mercuric acetate is slower still. By the action of aqueous alkali and



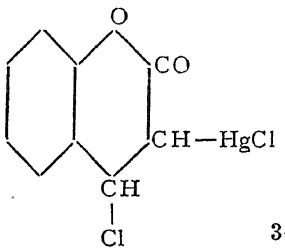
hydrogen sulphide on the trimercury compound 4-methyl-β-methoxymelilotic acid could not be isolated probably due to its instability, 4-methylcoumaric acid being obtained instead. The formation of a coumaric acid under these conditions seems to take place only when the double bond originally has been attacked by the mercuric salt. On treatment with bromine it gives a tribromo-7-methylcoumarin which from analogy is considered to be 3 : 6 : 8-tribromo-7-methylcoumarin.

6-Nitrocoumarin forms a dimercury compound which is 6-nitro-3 : 8-diacetoxymercuri-4-methoxymelilotic anhydride. With aqueous alkali and hydrogen sulphide it gives 5-nitrocoumaric acid and with bromine 3 : 8-dibromo-6-nitrocoumarin which is found to be identical with that of Dey and Row.[4] Hence with 6-nitrocoumarin besides addition at the double bond mercuration in the 8 position takes place.

Though it is now established that mercuric acetate is capable of reacting with the double bond in coumarin it has to be accepted that the reactivity is far less than in the case of coumaric and cinnamic acids and similar compounds. Just the opposite was experienced with cyanacetamide and sodium sulphite.[10] This reversal in the order of reactivity seems obviously to be due to the differences in the nature of the reagents employed, and the remarks made in Part I on the influences controlling the reactivity of the double bond in coumarins seem to hold good.

The reaction of mercuric chloride on the three coumarins mentioned above and the products obtained therefrom have now been more closely studied. Coumarin and 7-methylcoumarin react readily in the cold in the presence of any of the ordinary organic solvents and combine with only one molecule of the chloride; 6-nitrocoumarin does not react. The compound from coumarin is more stable being unaffected by boiling water

whereas the product from 7-methylcoumarin is far less stable. By the action of aqueous sodium hydroxide and hydrogen sulphide they give the corresponding coumaric acids. In view of these properties, and the work of Adams *et al*,[1] Middleton,[7] Vorlander,[13] and Wright[14] on similar compounds and the present work on the action of mercuric acetate on coumarins they have to be considered as addition products of mercuric chloride on the double bond (IV). Experiments intended to settle the constitution more precisely were not successful.



IV 3-chloromercuri-4-chloromelilotic anhydride.

Experimental.

Action of Mercuric Acetate.—

(i) *On coumarin.*—Preparation of 3 : 6 : 8-triacetoxymercuri-4-methoxymelilotic anhydride.

Mercuric acetate (4 g.) was dissolved in pure methyl alcohol (80 c.c.) containing a little acetic acid and mixed with coumarin (2 g.) in the same solvent (5 c.c.). The mixture which was quite clear in the cold was boiled on a water-bath under reflux. After about four hours it became milky and when allowed to stand overnight deposited about 0·5 g. of a colourless solid which on analysis gave too high a value for mercury and too low a value for carbon. It was probably contaminated with some mercurous acetate (*compare* Henry and Sharp)[5]. After filtering off this product, heating was continued for further 8 hours when another fraction separated out even from the hot solution. It was filtered, washed repeatedly in the cold with a very dilute solution of acetic acid and subsequently with hot methyl alcohol and dried first in air and finally in a vacuum desiccator. It was a crystalline looking powder, though under the microscope it exhibited no definite shape. (Found : Hg, 63·2 ; C, 20·4 ; $C_{16}H_{16}O_9Hg_3$ required Hg, 63·1 ; C, 20·1%.) The yield of the pure product was about 2·5 g. It turns brown at about 250° and decomposes at 270° and is very sparingly soluble in all the ordinary organic solvents. Though it is unaffected by aqueous sodium carbonate, it dissolves readily in ammonia and sodium hydroxide solutions.

When twice and three times the quantity of mercuric acetate solution was employed, the same product was obtained in greater yield, but its

formation was slower owing to the concentration of coumarin being lower and further it was less pure. If, however, the solution was made more concentrated by employing just enough alcohol to keep the reactants in solution at the beginning when hot, the condensation was faster and the yield better.[6] But the product was not found to be pure even though it was repeatedly washed with alcohol and dilute acetic acid.

The reaction was found to take place even when the solution of mercuric acetate and coumarin in alcohol was allowed to stand at the ordinary temperature of the laboratory (30°). After 2 days, the solution became turbid and in about a fortnight a white crystalline powder (0·5 g.) was obtained. It was found to be identical with the product obtained from heating.

The mercury compound was dissolved in a normal solution of sodium hydroxide, cooled to 0° C. with ice and saturated with hydrogen sulphide. The whole was allowed to stand in the cold chamber overnight, the precipitated mercuric sulphide filtered off and the filtrate acidified with a normal solution of sulphuric acid, the temperature being kept at about 0°. Hydrogen sulphide was removed by passing a current of air through the solution. β-methoxymelilotic acid was precipitated as a white crystalline solid. It was filtered, washed with a small quantity of water and finally crystallised from hot water. It appeared as rhombohedral plates, melted at 122–23°, changed to coumaric acid slowly in the presence of dilute acid or alkali, and was found to be identical with the product obtained by Biilmann's method (*loc. cit.*). The pure dry sample is quite stable and remains unchanged over long periods.

The mercury compound was suspended in glacial acetic acid and a solution of bromine in the same solvent slowly added with vigorous shaking. Bromine was rapidly used up and the addition was stopped when the bromine colour persisted. The mixture was then poured into a large volume of water and the precipitated solid which consisted of a mixture of the bromocompound and mercuric bromide was washed repeatedly with aqueous potassium bromide with a view to remove as much of the mercuric bromide as possible. It was then repeatedly crystallised from boiling glacial acetic acid and was obtained as colourless flat needles, melting at 195°. It was found to be identical with 3 : 6 : 8-tribromocoumarin prepared by direct bromination of coumarin according to the method of Simonis and Wenzel, as shown by mixed melting point, crystalline form, sparing solubility in alcohol and formation with alcoholic potash of 4 : 6-dibromocoumarilic acid.[12]

(ii) *On 7-methyl coumarin.*—Preparation of 3 : 6 : 8-triacetoxymercuri-4-methoxy-7-methyl-melilotic anhydride.

The reaction was carried out under the same conditions as with coumarin. It was much slower since it took 12 hours heating to get the first crop (0·5 g.) and a further 40 hours to get 2·5 g. more. It was purified by first washing with cold dilute acetic acid and subsequently with hot methyl alcohol. After drying in a vacuum desiccator it was found to decompose at 265° without melting. (Found : Hg, 61·7 ; $C_{17}H_{18}O_9Hg_3$ required Hg, 62·2%.) This compound resembled the coumarin derivative closely in all its properties. When hydrogen sulphide was passed into a cold solution of the substance in sodium hydroxide as usual, the corresponding β-methoxy-melilotic acid could not be obtained. On filtering off the mercuric sulphide and acidifying the filtrate, pure 4-methylcoumaric acid was obtained melting at 195° (decomp.). By treatment with bromine in glacial acetic acid a tribromocompound was isolated. It was sparingly soluble in alcohol, but dissolved easily in glacial acetic acid and crystallised in long narrow rectangular plates, melting at 207–8°. (Found : Br, 60·8 ; $C_{10}H_5O_2Br_3$ required Br, 60·4%.) By analogy with the coumarin compound this is given the constitution 3 : 6 : 8-tribromo-7-methylcoumarin. Since a compound of this formula does not seem to have been recorded in the literature, its preparation by other methods is under investigation.

(iii) *On 6-nitrocoumarin.*—Preparation of 3 : 8-diacetoxymercuri-4-methoxy-6-nitromelilotic anhydride.

Nitrocoumarin (2 g.) was dissolved in methyl alcohol (100 c.c.) and mixed with mercuric acetate (7·5 g.) in the same solvent (150 c.c.) containing a little acetic acid. After the removal of a small precipitate after heating for 4 hours, the clear solution gave 2·5 g. of a yellow crystalline product after boiling for 24 hours and some more was obtained on longer heating. It was purified as usual and dried in a vacuum desiccator. It was definitely yellow, remained unaffected below 300°, was very sparingly soluble in organic solvents and dissolved easily in sodium carbonate, ammonia and sodium hydroxide. (Found : Hg, 54·1 ; $C_{14}H_{13}O_9Hg_2$ required Hg, 54·1%.)

6-Nitro-3 : 8-diacetoxymercuri-4-methoxy-melilotic anhydride was dissolved in fairly strong sodium hydroxide (10% solution), allowed to stand for an hour and then hydrogen sulphide passed. After completely precipitating mercury it was filtered and the filtrate acidified. 5-nitrocoumaric acid was thereby obtained in good yield. If, on the other hand, dilute alkali is used and hydrogen sulphide passed immediately after solution, the resulting acid is contaminated with some amount of 6-nitrocoumarin.

By the action of bromine in glacial acetic acid, the mercury compound yielded a bromoderivative which crystallised from acetic acid in colourless prisms melting at 213–15°. It was identified as 6-nitro-3 : 8-dibromocoumarin by comparison with the compound prepared by the method of Dey and Row.[4]

Action of Mercuric Chloride.—

(i) *On coumarin.*—Preparation of 3-chloromercuri-4-chloromelilotic anhydride.

The method of Clayton (1908), using ether as a solvent, is inconvenient owing to the small solubility of mercuric chloride in it. Acetone and methyl alcohol are better. The easiest procedure is to dissolve coumarin and mercuric chloride separately in the minimum of acetone, mix the two solutions and add water to the uniform mixture. The product separates out as a mass of colourless needles, melting at 165° and identical with the compound obtained from ether. It is filtered and washed with water. It is easily recrystallised from boiling water. (Found : Hg, 47·9 ; $C_9H_6O_2Cl_2Hg$ required Hg, 48·0%.) Though the compound is stable in boiling water, it is easily decomposed by boiling 2 per cent. aqueous hydrochloric acid as shown below :

3-Chloromercuri-4-chloromelilotic anhydride (1 g.) is boiled with 2 per cent. hydrochloric acid (20 c.c.) when it quickly goes into solution. The heating is continued for ten minutes longer and the solution allowed to cool. Coumarin, that is first formed as a liquid, gradually turns into a crystalline solid melting at 70°.

When small quantities of the compound are treated with dilute aqueous alkali, coumaric acid could be easily obtained as shown below : About 0·2 g. of the compound is suspended in water, and dilute caustic soda added. There is a rapid precipitation of yellow mercuric oxide. After about 10 minutes, the solution is filtered and acidified. The crystalline solid that separates out is purified by dissolving in sodium carbonate and reprecipitating. It melts at 208–10° and is found to be pure coumaric acid. But when larger quantities are employed the resulting acid is impure melting at about 185°, and is found to contain mercury. In such cases, the alkali solution is treated with hydrogen sulphide, the precipitated mercury sulphide is filtered off and the filtrate acidified, when pure coumaric acid is obtained.

(ii) *On 7-methylcoumarin.*—Preparation of 3-chloromercuri-4-chloro-7-methylmelilotic anhydride.

The addition compound in this case is unstable in the presence of water even in the cold and heating produces considerable decomposition. It

is, therefore, necessary to avoid water in its preparation. Besides ether (Clayton, *loc. cit.*) acetone can be used. Instead of adding water the acetone mixture is simply allowed to concentrate. The product is obtained as sheaves of colourless flat needles, melting at 173–74° and identical with the compound described by Clayton. It decomposes completely in about a minute in boiling 1% hydrochloric acid giving rise to 7-methylcoumarin. 4-methylcoumaric acid can be easily obtained by the action of sodium hydroxide and hydrogen sulphide.

6-nitrocoumarin does not react with mercuric chloride in acetone solution either in the cold or on heating. Ether is not a suitable solvent owing to the insolubility of nitrocoumarin in this solvent.

Summary.

In methyl alcoholic solution coumarin reacts with mercuric acetate to form 3 : 6 : 8-triacetoxymercuri-4-methoxymelilotic anhydride. By the action of sodium hydroxide and hydrogen sulphide β-methoxymelilotic acid is obtained from it and by the action of bromine 3 : 6 : 8-tribromocoumarin. 7-methylcoumarin behaves similarly giving a trimercury compound. 6-nitrocoumarin forms 3 : 8-diacetoxymercuri-6-nitro-4-methoxymelilotic anhydride which, with alkali and hydrogen sulphide, gives 5-nitrocoumaric acid and with bromine 3 : 8-dibromo-6-nitrocoumarin. It is therefore established that mercuric acetate reacts with the double bond in these coumarins and further mercurates the benzene ring in positions 6 and 8 if they should be free. Mercuric chloride adds on to the double bond in coumarin and 7-methylcoumarin. The reactions of these addition products have been studied. 6-nitrocoumarin does not react with this reagent.

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