XXIV.—*The Reactivity of the Double Bond in Coumarins and Related αβ-Unsaturated Carbonyl Compounds. Part I. Addition of Cyanoacetamide to Coumarins.*

By TIRUVENKATA RAJENDRA SESHADRI.

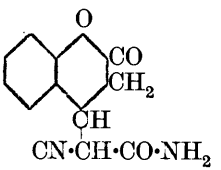
THE unsaturated centre in coumarin seems to differ greatly in reactivity from the double bond in related compounds such as cinnamic acid and ethyl cinnamate. For instance, sodium bisulphite combines readily in a few minutes with coumarin, whereas with cinnamic acid under comparable conditions the combination remains incomplete even after 12 hours. This question of the reactivity of the double

bond in coumarins in comparison with other αβ- unsaturated carbonyl compounds has not hitherto been systematically investigated.

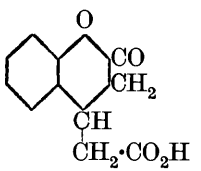
The interaction of cyanoacetamide and coumarins is of much interest from the theoretical point of view and incidentally offers a method for the preparation of a series of reduced coumarin derivatives containing asymmetric carbon atoms. When heated in alcoholic solution in the presence of piperidine, coumarin and cyanoacetamide react additively in equimolecular proportion at the double bond. The reaction is complete in about 6 hours; but in similar circumstances, although the heating was continued for 40—50 hours, cinnamic acid, ethyl cinnamate and even coumaric acid yielded no detectable quantity of additive products, the original substances being recovered unchanged. Hence it appears at first sight that the reactivity of the double bond in coumarin is greatly enhanced as the result of its situation in a ring structure.

Nevertheless, this explanation of the enhanced reactivity of coumarin as compared with ethyl cinnamate, although considered to be a part of the truth, is probably inadequate; a further important factor is doubtless connected with the degree of neutralisation of the ketonic properties of the carbonyl group by the singly bound oxygen atom. In coumarin, the aromatic nucleus makes demands of the attached oxygen, reducing the capacity of this atom for neutralising the carbonyl group. Electronic mechanisms embodying this suggestion have been put forward by Robinson. Thus coumarin should occupy a position intermediate between a typical alkyl cinnamate and a typical alkyl styryl ketone. The relative importance of the parts played by the cyclic structure and the conjugation of the oxygen atom with the nucleus could be estimated from the results of a comparative study of the reactions of alkyl and aryl cinnamates, and it is proposed to continue the investigation in this direction.

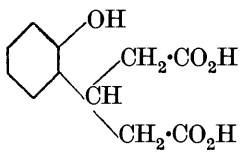
3 : 4-*Dihydrocoumarin*-4-*cyanoacetamide* (I) is readily hydrolysed by boiling concentrated hydrochloric acid or 10% caustic potash solution with the formation of 3 : 4-*dihydrocoumarin*-4-*acetic aci* (II) and β-o-*hydroxyphenylglutaric acid* (III).



(I.)



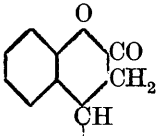
(II.)

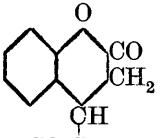


(III.)

The relationship of these acids was established by their interconversion. At its melting point, (III) decomposes with the

evolution of water and forms (II). The lactone (II) or the hydroxy-acid (III) can be obtained from an alkaline solution of either according as the solution is strongly acidified and warmed or is rendered just acid and kept cold. Intermediate stages represented by 3 : 4-*dihydrocoumarin*-4-*cyanoacetic acid* (IV) and 3 : 4-dihydrocoumarin-4-carbamylacetic acid (V) were isolated only in cases where hydrolysis in stages with cold concentrated hydrochloric acid was possible.

(IV.) 



(V.)

Alkyl and halogen substituents in the pyrone ring, as in 4 : 7-dimethylcoumarin, 3-methylcoumarin, and 3-bromocoumarin, completely inhibit the addition. But their presence in the benzene ring has not yet been found to offer any hindrance and the addition takes place with almost as much ease as in the case of coumarin. 7-Methylcoumarin yields a product which resembles in every respect dihydrocoumarincyanoacetamide and gives rise to the same series of hydrolytic products. 6-Aminocoumarin, a golden-yellow solid, forms a colourless additive compound with cyanoacetamide, whereas the product from the colourless 6-nitrocoumarin is deep yellow.

6-*Nitro*-3 : 4-*dihydrocoumarin*-4-*cyanoacetamide* was unaffected by cold concentrated hydrochloric acid and hence stepwise hydrolysis was not possible; only 6-*nitro*-3 : 4-*dihydrocoumarin*-4-*acetic acid* could be obtained in a pure condition from the products of hydrolysis. This acid is colourless and gives colourless solutions in organic solvents and in aqueous acid; on the other hand, its solutions in water, especially hot water, and in aqueous alkali are yellow. In all probability these yellow solutions contain the nitrophenolic acid $NO_2 \cdot C_6H_3(OH) \cdot CH(CH_2 \cdot CO_2H)_2$, which could only be isolated in the form of its *disilver* salt.

Experimental.

3 : 4-*Dihydrocoumarin*-4-*cyanoacetamide* (I).—A solution of coumarin (3 g.), cyanoacetamide (2 g.), and a few drops of piperidine in alcohol (30 c.c.) was kept at the point of incipient ebullition for 6 hours. The cooled liquid slowly deposited a mass of colourless crystals, which were washed with cold alcohol (yield, 4 g.; m. p. 215—216°). The substance was slightly soluble in boiling water and readily soluble in boiling alcohol, chloroform or benzene, crystallising on cooling in flat, colourless needles, m. p. 219—220°

(decomp.) (Found: C, 62·8; H, 4·4; N, 12·4. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4; N, 12·2%). It was insoluble in aqueous sodium carbonate or ammonia, but dissolved slowly in dilute aqueous sodium hydroxide with the production of ammonia.

3 : 4-*Dihydrocoumarin*-4-*cyanoacetic Acid* (IV).—A mixture of dihydrocoumarincyanoacetamide (1 g.) and cold concentrated hydrochloric acid (5 c.c.) was vigorously shaken, giving a clear solution which soon deposited a colourless, crystalline precipitate. This crystallised from much water or alcohol in colourless, hexagonal plates, m. p. 226—227° (Found: C, 62·6; H, 4·1; N, 6·1. $C_{12}H_9O_4N$ requires C, 62·3; H, 3·9; N, 6·1%).

Dihydrocoumarincyanoacetic acid underwent further hydrolysis when boiled with concentrated hydrochloric acid, dilute aqueous sodium hydroxide or even ammonia, so that when the silver salt was prepared in the usual way by means of ammonium hydroxide and silver nitrate the disilver salt of β-*o*-hydroxyphenylglutaric acid (below) was produced.

3 : 4-*Dihydrocoumarin*-4-*acetic Acid* (II).—Dihydrocoumarincyanoacetamide (1 g.) was boiled with concentrated hydrochloric acid (5 c.c.) for 5 minutes and on cooling *dihydrocoumarinacetic acid* crystallised; a further quantity of it was obtained by evaporating the mother-liquor to dryness and adding a few drops of water to dissolve the ammonium chloride (yield, 0·7 g.). Purification was effected by dissolution in aqueous sodium carbonate and reprecipitation; the acid crystallised from boiling water, alcohol, or benzene in colourless, stout prisms, m. p. 113—114° (Found: C, 64·0; H, 4·8. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). This acid was obtained also by the hydrolysis of dihydrocoumarincyanoacetamide (1 g.) with aqueous potassium hydroxide (2 g. in 10 c.c. of water) at the boiling point for a few minutes; the clear solution was acidified with hydrochloric acid and evaporated to dryness. Enough water was then added to dissolve the inorganic salts, leaving an almost pure specimen of dihydrocoumarinacetic acid (yield, 0·75 g.). The silver salt of this acid could not be obtained by the usual method, since the product was found on analysis to be the disilver salt of β-*o*-hydroxyphenylglutaric acid described below.

β-o-*Hydroxyphenylglutaric Acid* (III).—This acid was obtained whenever dihydrocoumarinacetic acid was prepared. When the mother-liquor after the separation of the acetic acid was kept for several hours, stout, colourless crystals of the glutaric acid separated. The best method of preparation is to dissolve dihydrocoumarinacetic acid in dilute aqueous sodium carbonate and then to render the solution just acid and keep it cold for several hours; colourless, stout crystals are slowly deposited. The *acid*

is sparingly soluble in ether or benzene; it is easily soluble in boiling water, alcohol, or acetone, and crystallises in colourless cubes melting at 160° with evolution of steam and formation of dihydrocoumarinacetic acid (Found : C, 59·2; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). Its aqueous solution was strongly acid to litmus and when boiled with dilute hydrochloric acid it underwent conversion into the closed-ring acetic acid. The *disilver* salt was obtained as a colourless, amorphous, bulky precipitate in the usual way by means of ammonia and silver nitrate and when dry was a colourless powder (Found : Ag, 49·0. $C_{11}H_{10}O_5Ag_2$ requires Ag, 49·3%).

7-*Methyl*-3 : 4-*dihydrocoumarin*-4-*cyanoacetamide*.—An alcoholic solution of 7-methylcoumarin (4 g.), cyanoacetamide (2 g.), and a few drops of piperidine was boiled for 15 hours, a shorter period involving admixture of the condensation product with unchanged 7-methylcoumarin. The product (about 4 g.) was fairly soluble in boiling acetone or alcohol and very readily soluble in pyridine, from which it crystallised in colourless, rectangular prisms, m. p. 245° (Found : C, 64·2; H, 5·1; N, 11·8. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·9; N, 11·5%).

7-*Methyl*-3 : 4-*dihydrocoumarin*-4-*cyanoacetic acid* was obtained from the above compound by treatment with cold concentrated hydrochloric acid. At first a clear solution was produced which soon deposited a colourless, crystalline precipitate; this crystallised from boiling water or alcohol in colourless, rhombic prisms, m. p. 230—232° (Found : N, 5·9. $C_{13}H_{11}O_4N$ requires N, 5·7%).

7-*Methyl*-3 : 4-*dihydrocoumarin*-4-*acetic acid*, which resulted from the hydrolysis of 7-methyldihydrocoumarincyanoacetamide with hot concentrated hydrochloric acid or hot aqueous potash, was easily soluble in boiling water, alcohol, acetone, or benzene and crystallised from these solvents in colourless, rectangular plates, m. p. 111—112° (Found : C, 65·3; N, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

β-p-*Methyl*-o-*hydroxyphenylglutaric acid* was obtained by dissolution of the above lactonic acid in dilute aqueous sodium carbonate and careful acidification of the solution in the cold. The colourless, rectangular prisms that were slowly deposited melted at 148—149° with formation of 7-methyldihydrocoumarinacetic acid. The phenolic acid is sparingly soluble in benzene, but dissolves readily in boiling water, alcohol, or acetone (Found : C, 60·3; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). The disilver salt, which was a colourless powder, was identical with those resulting from the cyanoacetic and acetic acids mentioned above (Found : Ag, 47·4. Calc. : Ag, 47·7%).

6-*Nitro*-3 : 4-*dihydrocoumarin*-4-*cyanoacetamide* (VI).—Golden-

yellow crystals were deposited when an alcoholic solution of 6-nitrocoumarin (3 g.), cyanoacetamide (1·5 g.), and a few drops of piperidine was gently boiled for 4 hours (yield, about 3·5 g.). The substance was sparingly soluble in benzene, acetone, or alcohol and readily soluble in boiling pyridine, from which it separated in golden-yellow plates which neither melted nor decomposed below 300° (Found: N, 15·6. $C_{12}H_9O_5N_3$ requires N, 15·3%). Nitrodihydrocoumarincyanoacetamide was only very slowly affected by cold dilute hydrochloric acid or sodium hydroxide; on boiling with the alkali, however, solution took place with the evolution of ammonia.

6-*Nitro*-3 : 4-*dihydrocoumarin*-4-*acetic Acid* (VII).—A boiling mixture of nitrodihydrocoumarincyanoacetamide (1 g.) and concentrated hydrochloric acid (10 c.c.) gradually deposited a white, crystalline precipitate. This dissolved in cold dilute aqueous sodium carbonate to a deep yellow solution, which, when rendered strongly acid, turned colourless and *nitrodihydrocoumarinacetic acid* soon separated in colourless, rhombic prisms, m. p. 205° (decomp.) (Found: N, 5·8. $C_{11}H_9O_6N$ requires N, 5·6%). The acid dissolved very sparingly in benzene or chloroform and was slightly soluble in alcohol; these solutions were perfectly colourless, even on boiling. The aqueous solution, however, was yellow and the colour deepened on boiling; introduction of a trace of any alkali rendered it deep yellow, whereas the addition of mineral acid not only removed the colour but caused the precipitation of the acid. The silver salt prepared by the usual method was obtained as a light yellow powder and on analysis was found to be the *disilver* salt of the open-chain phenolic glutaric acid (Found: Ag, 44·3. $C_{11}H_9O_7NAg_2$ requires Ag, 44·7%).

6-*Amino*-3 : 4-*dihydrocoumarin*-4-*cyanoacetamide*.—The best yield of this product was obtained by boiling an alcoholic solution of 6-aminocoumarin (2 g.), cyanoacetamide (1 g.), and a few drops of piperidine for 6 hours. Longer heating produced a resin and the yield was lowered when the period of reaction was shortened. The solid was isolated and washed with hot alcohol to remove unchanged aminocoumarin. The product was sparingly soluble in chloroform, benzene, or alcohol and crystallised from pyridine in colourless prisms, m. p. 270° (decomp.) (yield, 1·5 g.) (Found: C, 59·0; H, 4·4; N, 17·4. $C_{12}H_{11}O_3N_3$ requires C, 58·7; H, 4·5; N, 17·1%). A yellow solution in dilute aqueous sodium hydroxide is formed slowly in the cold and readily on boiling, ammonia being evolved; the substance is also readily soluble in dilute or concentrated hydrochloric acid. The formulation of this compound as an analogue of dihydrocoumarincyanoacetamide is justified by the observation

that the addition product is a primary aromatic amine. The corresponding diazonium salt couples with β-naphthol to give a scarlet-red azo-compound that dissolves in concentrated sulphuric acid to a crimson solution.

The *benzoyl* derivative was obtained by carrying out the benzoylation in the presence of dilute aqueous sodium carbonate. It was sparingly soluble in alcohol and crystallised from pyridine in colourless, flat needles, m. p. 300° (decomp.) (Found : C, 65·1; H, 4·4. $C_{19}H_{15}O_4N_3$ requires C, 65·3; H, 4·3%).

6-*Amino*-3 : 4-*dihydrocoumarin*-4-*carbamylacetic Acid*.—A solution of 6-aminodihydrocoumarincyanoacetamide (1 g.) in cold concentrated hydrochloric acid (10 c.c.) remained clear until it was heated just to boiling. Immediately precipitation started and a good yield of colourless, rectangular rods was obtained on cooling. The product was washed with cold concentrated hydrochloric acid and finally with alcohol; m. p. 225° (decomp.) (Found : C, 48·1; H, 4·4; N, 9·3; Cl, 11·9. $C_{12}H_{13}O_5N_2Cl$ requires C, 47·9; H, 4·3; N, 9·3; Cl, 11·8%). As it contained no water of crystallisation, it was evident that it was the hydrochloride of 6-aminodihydrocoumarincarbamylacetic acid. To isolate the free *acid*, the hydrochloride was dissolved in a small volume of cold water and very dilute aqueous sodium hydroxide added drop by drop till the solution was almost neutral. Colourless crystals (rectangular plates) slowly filled the liquid; they were washed with cold water and with alcohol; m. p. 170—171° (decomp.) (Found : C, 54·1; H, 4·9. $C_{12}H_{12}O_5N_2$ requires C, 54·5; H, 4·6%). The acid was insoluble in alcohol and was easily soluble in cold dilute acid or alkali and underwent decomposition when these solutions were warmed. When diazotised and coupled with β-naphthol, the hydrochloride as well as the free acid gave rise to scarlet-red azo-compounds.

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THE UNIVERSITIES OF MADRAS AND
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