# THE REACTIVITY OF THE DOUBLE BOND IN COUMARINS AND RELATED UNSATURATED CARBONYL COMPOUNDS

## Part VIII. Addition of Cyanoacetamide to Umbelliferone and its Methyl Ether

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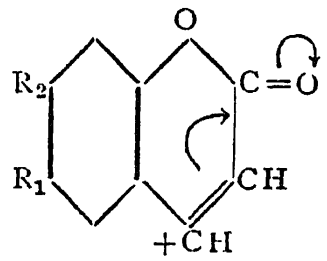
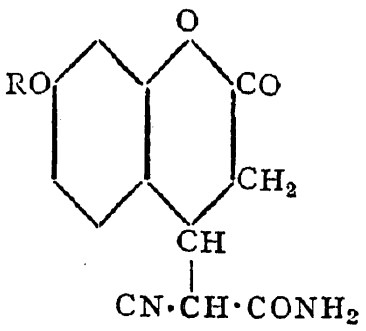
FROM the results presented in Part I,[1] certain conclusions could be arrived at regarding the influence of substituents on the addition of cyanoacetamide to the double bond in coumarins. Substituents in the pyrone ring completely prevent addition; but their presence in the benzene ring does not produce such great influence. Nevertheless, they seem to effect some control over the reaction. For example, it was noticed that a nitro group in the 6th position speeds up the addition considerably, whereas a methyl group in the 7th position slows it markedly. These findings are in accordance with expectations, since the kationoid reactivity of the carbon atom in position 4 arises according to the mechanism given below (I) and it is the reactive centre promoting the addition of cyanoacetamide. A nitro group in the 6th position as in nitro coumarin (I, $R_1 = NO_2$, $R_2 = H$), can increase the kationoid activity both by its direct effect on the carbon atom in position 4 and also indirectly by influencing the oxygen atom which is linked to the phenyl ring. Groups that can act as electron sources such as methyl when present in the 7th position as in 7-methyl-coumarin (I, $R_1 = H$, $R_2 = CH_3$) produce the opposite effect and consequently reduce the reactivity of the pyrone double bond. This conclusion is now further supported by the experiments on 7-methoxy and 7-hydroxy coumarins described in this paper. They react very slowly producing about 90% yield, the time taken being 50 hours for the methoxy compound, and 120 hours for the hydroxy compound. Larger quantities of the catalyst (1 c.c.) are also required. On the hydrolysis of the methoxy compound (II), both the dihydro-coumarin cyanoacetic acid (III) and the dihydro-coumarin acetic acid (IV) derivatives could be obtained, whereas only the latter could be isolated from the hydroxy compound. The methoxy and hydroxy-dihydro-coumarin acetic acids have also been prepared by the reduction of 7-methoxy and 7-hydroxy

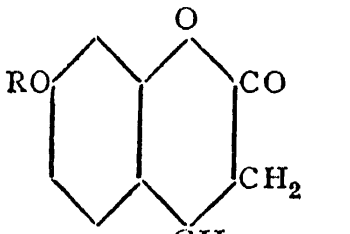
coumarin 4-acetic acids (V) using sodium amalgam. There is thus independent confirmation for the addition of cyanoacetamide to the pyrone double bond in coumarins.



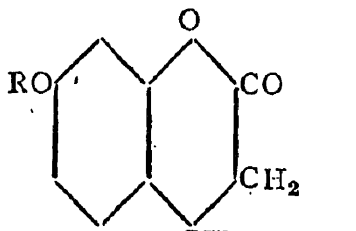

I



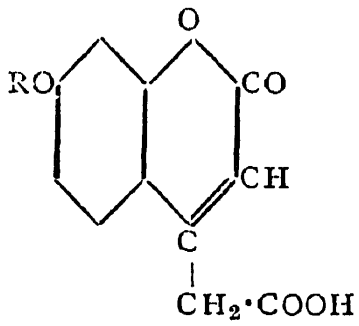

II




III




IV




V

R = $CH_3$ or H.

The above compounds form a series of dihydro-coumarin derivatives useful for the study of fluorescence in relation to chemical constitution which is in progress in these laboratories.

## *Experimental*

*7-Methoxy-3 : 4-dihydro-coumarin-4-cyanoacetamide (II).*—

A solution of 7-methoxy coumarin (2·0 g.), cyanoacetamide (1·2 g.) and piperidine (1·0 c.c.) in alcohol (30 c.c.) was kept boiling for 50 hours. After the end of about 25 hours an insoluble solid began to separate out and the yield of the product was only 0·7 g. The boiling was continued for a further 25 hours when the total yield of the product amounted to 2·7 g. (about 90%). Boiling for longer hours did not improve the yield to any considerable extent. The solid was filtered from the mother-liquor, and washed with hot alcohol to remove unchanged 7-methoxy coumarin. It was insoluble in alcohol, benzene or chloroform and was crystallised from aqueous

pyridine when it came out as lustrous rectangular plates melting at 262–63°. (Found: C, 57·8; H, 5·1; $C_{13}H_{12}O_4N_2$, $\frac{1}{2}$ $H_2O$ requires C, 58·0; H, 4·8%.) The substance dissolves in dilute sodium hydroxide slowly in the cold and readily on boiling to form a yellow solution without fluorescence. It does not exhibit any fluorescence in concentrated sulphuric acid.

*7-Methoxy*-3 : 4-*dihydro-coumarin*-4-*cyanoacetic acid* (*III*).—

A mixture of 7-methoxy -3 :4-dihydro-coumarin-4-cyanoacetamide (1·0 g.) and cold concentrated hydrochloric acid (6 c.c.) was vigorously shaken, giving a clear solution which soon deposited a colourless crystalline precipitate. It crystallised from much water or aqueous alcohol in long colourless rectangular plates, melting at 247–49°. (Found: C, 59·8; H, 4·2; $C_{13}H_{11}O_5N$ requires C, 59·8; H, 4·4%.) It gives a colourless solution in concentrated sulphuric acid, alcohol or aqueous sodium hydroxide and exhibits no fluorescence in any of the above solutions.

*7-Methoxy*-3 : 4-*dihydro-coumarin*-4-*acetic acid* (*IV*, $R = CH_3$).—

(*a*) *By hydrolysis.*—This can be obtained by further hydrolysing the above compound with hydrochloric acid. 7-Methoxy-3 : 4-dihydro-coumarin-4-cyanoacetamide (1·0 g.) was boiled with 10 c.c. of concentrated hydrochloric acid for five minutes and the clear solution was evaporated to dryness on a water-bath. The residue was treated with a few drops of water to dissolve the ammonium chloride and the viscous liquid left behind, was allowed to solidify during the course of 2 days. The solid product was crystallised from hot water, using a little animal charcoal, when it came out in long colourless rectangular plates melting at 122–23°. (Found: C, 61·2; H, 5·2; $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). The substance dissolves easily in sodium carbonate or sodium hydroxide, and the solution which is at first colourless changes to yellow on standing. The solutions in concentrated sulphuric acid, alcohol, or in dilute aqueous alkali give no fluorescence.

(*b*) *By reduction of 7-methoxy-coumarin*-4-*acetic acid.*—7-Methoxy-coumarin-4-acetic acid prepared according to the method of Dey and Row[2, 4] was dissolved in absolute alcohol, treated with sodium amalgam (2·5%, 25 g.) and the mixture was kept at a temperature of 50–60° for a period of about three days. Disappearance of fluorescence of the alcoholic solution on dilution with water indicated complete reduction of the compound. The mercury was then separated and the solution was concentrated to a small volume under reduced pressure. Finally it was acidified with dilute sulphuric acid, filtered, and the clear solution was repeatedly extracted with ether. A liquid was obtained on the evaporation of the ether and it solidified in the

course of 4 days. The solid was repeatedly recrystallised from boiling water using a little animal charcoal, when it came out in the form of long colourless rectangular plates melting at 122–23°. It agreed in all properties with the sample obtained by the method of hydrolysis and did not exhibit any fluorescence in concentrated sulphuric acid, alcohol or in dilute aqueous alkali. The mixed melting point was undepressed.

*7-Hydroxy-3 : 4-dihydro-coumarin-4-cyanoacetamide (II, R = H).*—

A solution of 7-hydroxy-coumarin (2·0 g.), cyanoacetamide (1·2 g.) and piperidine (1·0 c.c.) in alcohol (30 c.c.) was kept boiling for about 120 hours. A good yield of the product could be obtained only on boiling for a very long time, the yield being 6% in 25 hours, 20% in 50 hours, 55% in 100 hours and finally 90% in 120 hours. The solid was filtered and washed with plenty of hot alcohol to remove unreacted umbelliferone (m.p. 254-57°). It was finally crystallised from aqueous pyridine when it came out as small rectangular plates which neither melted nor decomposed below 300°. (Found: C, 56·2; H, 4·0; $C_{12}H_{10}O_4N_2$, $\frac{1}{2}$ $H_2O$ requires C, 56·5; H, 4·3%.) The product was insoluble in alcohol, chloroform or benzene. A reddish-brown solution is formed in dilute aqueous sodium hydroxide slowly in the cold and readily on heating, ammonia being evolved.

*7-Hydroxy-3 : 4-dihydro-coumarin-4-acetic-acid (IV, R = H).*—

(*a*) *By hydrolysis.*—7-Hydroxy-3 : 4-dihydro-coumarin-4-cyanoacetamide (1·0 g.) was treated with concentrated hydrochloric acid (10 c.c.) and heated on a water-bath till a clear solution was obtained (about 3 minutes). When the solution was evaporated to dryness, it left a crystalline product which was treated with a few drops of water to dissolve the ammonium chloride formed. The remaining solid was crystallised from hot water using a little animal charcoal when it came out in the form of colourless hexagonal tablets, melting at 180–81°. (Found: C, 58·9; H, 4·8; $C_{11}H_{10}O_5$ requires C, 59·4; H, 4·5%.) The substance did not exhibit any fluorescence in concentrated sulphuric acid, alcohol or dilute aqueous alkali.

(*b*) *By reduction of 7-Hydroxy-coumarin-4-acetic-acid.*—7-Hydroxy-coumarin-4-acetic acid prepared according to the method of Dey and Row,[2, 3] was reduced in the manner described in the case of the 7-methoxy compound. The reduction took about five days, the absence of any fluorescence on dilution of the alcoholic solution with water being taken as completion of the reaction in this case also. The compound (m.p. 180–81°) was similar in all its properties with the sample obtained by hydrolysis and the mixed melting point was undepressed.

*Summary*

The addition of cyanoacetamide to the double bond of 7-methoxy and 7-hydroxycoumarins is very slow and it is attributed to the influence of the substituents which act as electron sources. On hydrolysis, the products yield the corresponding cyanoacetic acid and acetic acid derivatives the latter of which could also be obtained by the reduction of methoxy and hydroxy coumarin-4-acetic acids using sodium amalgam. These compounds do not fluoresce in solution.

REFERENCES

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2. Dey and Row .. *J. I. C. S.*, 1924, 111–12.
3. Burton and Pechmann .. *Ann.*, 1891, **261**, 167.
4. Dey .. *J. C. S.*, 1915, **107**, 1633.