

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

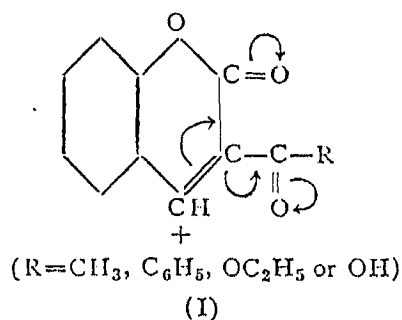
Part IX. Addition of Cyanoacetamide to Coumarins with Electron-attracting Groups in the 3-Position

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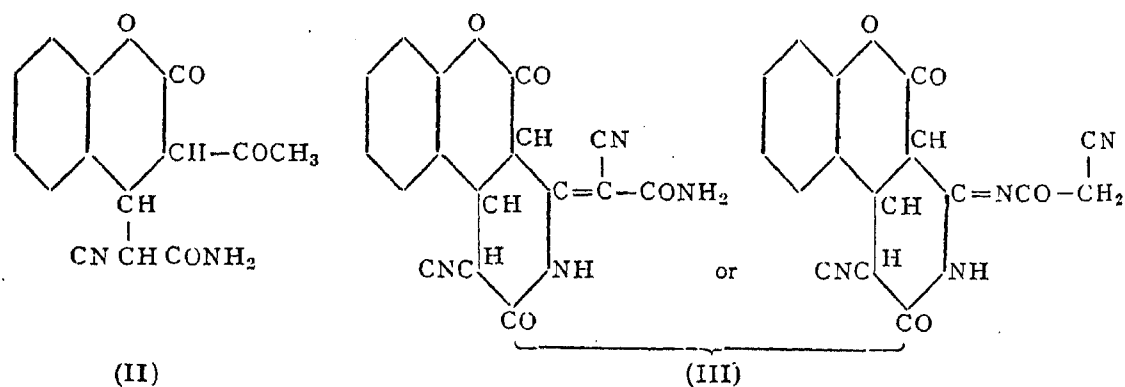
IN previous publications on this subject¹ it was shown that amongst compounds having reactive methylene groups only cyano-acetamide adds to the double bond of coumarins, that the addition is considerably accelerated by a nitro-group in the 6th position and that it is retarded by hydroxy and methoxy groups in the 7th position. The reaction is prevented by the presence of alkyl and bromo substituents in the pyrone ring. The results of a few typical experiments on the influence of electron-attracting groups such as the carbonyl, cyano and phenyl, when present in the 3-position, on this addition, are now reported. They could be expected to enhance the reactivity of the coumarin double bond by increasing the cationoid activity of the carbon atom in the 4th position as shown below (I) :



3-Acetyl coumarin reacts fast with cyano-acetamide but the yield of the product (II) is not high owing to the existence of side reactions and the removal of the catalyst (piperidine) involved in partial deacetylation of the acetyl compound. This is supported by the observation that a second addition of piperidine gives increased yields. 3-Benzoyl coumarin is similar though the addition is comparatively much slower. With 3-carbomethoxy coumarin the reaction goes further, ring formation taking place and a second molecule of the amide also taking part. From the analytical values formula (III) is suggested for the product and it finds support in the

fact that the compound is devoid of an ethoxyl group. A good portion of piperidine is used up for the formation of the piperidide of coumarin-3-carboxylic acid. Coumarin-3-carboxylic acid behaves like coumarin, forming dihydro-coumarin-cyanoacetamide. This is obviously due to decarboxylation taking place in the course of the reaction. In a similar reaction of this carboxylic acid using cyanoacetic ester no addition takes place, but still de-carboxylation proceeds resulting in coumarin. It is interesting to note that 3-cyanocoumarin reacts much faster and gives much better yields of the addition product than the others. This reaction seems also to be free from complications. 3-Phenylcoumarin does not react to any appreciable extent even when boiled for 60 hours. Though the phenyl group is capable of acting both as an electron donor and as an acceptor, as far as the present reaction is concerned, it resembles alkyl groups and does not seem to be functioning as an electron sink.

Special mention should be made of the reactions taking place when cyanoacetic ester, malonic ester and acetoacetic ester are employed in the place of cyano-acetamide. 3-Acetyl-coumarin undergoes complex change. No addition product could be obtained, but a sparingly soluble compound is formed which answers to the requirements of dihydro-dicoumarinyl



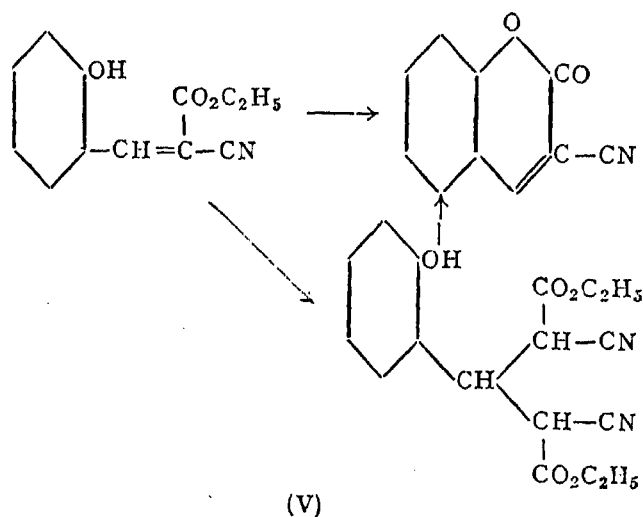
(formula IV). It may arise due to the condensation between themselves of two molecules of the acetyl-coumarin with the subsequent elimination of acetyl groups. This explanation is supported by the observation that the same reaction takes place in the presence of piperidine even when there is no outside additive agent. Such a reaction has not been noticed in the case of other coumarins. 3-Cyanocoumarin, being the most reactive, forms an addition product with cyano-acetic ester and not with others. The rest of the coumarins studied do not form addition products with these esters.

Experimental

Preparation of the required coumarins

3-Acetyl-coumarin,² 3-benzoyl-coumarin,³ and 3-carbethoxy-coumarin,⁴ were easily prepared by Knoevenagel's method using salicylaldehyde and the appropriate ketonic ester. Coumarin-3-carboxylic acid⁴ was obtained by hydrolysing the ester with aqueous alkali. For the preparation of small quantities of the acid this method seems to be the most convenient.

3-Cyanocoumarin was first prepared by adopting the indirect method of Bechert⁵ in which salicylidine-bis-cyanoacetic ester is treated in warm alcoholic solution with hot alcoholic potash and the resulting potassium salt is decomposed with dilute sulphuric acid. Knoevenagel and Arnot³ reported the formation of salicylidine-bis-cyanoacetic ester melting at 139°–40° by the combination of salicylaldehyde and cyanoacetic ester in equimolecular proportions in the presence of piperidine as catalyst, the condensation taking place at room temperature. On repeating this reaction at the laboratory temperature of Waltair (about 28°), as given below, a 25–30% yield of cyanocoumarin could be obtained. When the reaction was carried out at 10–15° which may approximate to Knoevenagel's conditions



the bis-cyanoacetic ester was formed as the main product. The course of the reaction may be represented as below (V) :

To a mixture of salicylaldehyde (2 c.c.) and cyanoacetic ester (2 c.c.) were added 5 drops of piperidine. The resulting mixture became quite warm and red in colour. After cooling under the tap the reaction was allowed to proceed at the room temperature for four to five hours by which time the mixture set to a solid mass. It was then treated with a small volume of alcohol and thoroughly stirred. The resulting solid was filtered and washed successively with a small volume of alcohol, a small quantity of water and finally with alcohol. It then melted at 182–84°. After recrystallisation from alcohol it appeared as rectangular prisms and prismatic needles and the melting point rose to 185–86°. The yield was 30% of the theoretical. [Found : C, 70.7; H, 3.2; $C_{10}H_5O_2N$ requires C, 70.2; H, 2.9%.]

When, however, two molecular proportions of cyanoacetic ester were employed for one of the aldehyde and the reaction carried out at the laboratory temperature the product was entirely the *bis*-compound which when recrystallised from alcohol melted at 140–41° (yield 60%).

3-Phenyl-coumarin^{6,7} was made using salicylaldehyde, sodium phenylacetate and acetic anhydride (Perkin's reaction), or the ethyl ester of phenyl-acetic acid and piperidine (Knoevenagel's method). For the preparation of small quantities, the second method is quite satisfactory though the yield is poor.

Addition of Cyanoacetamide

3-Acetyl-dihydro-coumarin-4-cyanoacetamide (II).—As a typical example of the general addition reaction the one involving acetyl-coumarin and cyano-acetamide is given below in detail.

3-Acetyl-coumarin (4 g.) and cyano-acetamide (2 g.) were dissolved in alcohol (50 c.c.) and a few drops of piperidine were added and the solution kept just boiling. A bulky yellow crystalline precipitate was formed; the reaction seemed almost complete in $\frac{1}{2}$ hour. The precipitate was filtered off and washed thoroughly with water and hot alcohol (yield 1.2 g.). On further boiling of the mother-liquor for 4 hours a small additional quantity of a deeper coloured product was obtained. If, however, a few drops of piperidine were added before the second boiling, the yield of the product was practically doubled. The substance was sparingly soluble in most organic solvents and moderately soluble in pyridine from which it crystallised out as colourless elongated rectangular plates. It began to turn dark pink at about 240° and shrink at 290° and it finally decomposed at 295°.

A sample which was crystallised from pyridine and washed well with water and hot alcohol and dried *in vacuo* at 120° gave the following analytical figures : C, 61.3; H, 4.4; N, 10.8; $C_{14}H_{12}O_4N_2$ requires C, 61.8; H, 4.4; N, 10.3%.

3-Benzoyl-dihydro-coumarin-4-cyanoacetamide

3-Benzoyl-coumarin yielded an yellow coloured product in about the same yield as above after boiling for 6 hours. There was no rapid precipitation as in the case of acetyl-coumarin. Only after leaving overnight a collection of hard yellow crystals was obtained and they were sparingly soluble in alcohol, ether, benzene and acetone. From boiling pyridine the substance crystallised as light yellow rhombic prisms. It sintered at 308° and finally melted with decomposition at 315° [Found: C, 68.8; H, 4.3; N, 8.8; $C_{19}H_{14}O_4N_2$ requires C, 68.3; H, 4.2; N, 8.4%.]

Compound (III) from 3-carbethoxycoumarin

The product from 3-carbethoxy-coumarin was obtained in the form of rhombic plates and needles on crystallising from pyridine and it did not melt below 360°. Regarding its solubility in organic solvents it resembled the other compounds described above. Yield, about 15%. [Found: C, 59.1; H, 2.8; N, 17.0; $C_{16}H_{10}O_4N_4$ requires C, 59.6; H, 3.1; N, 17.4%.]

When tested for the presence of (OC_2H_5) group by the micro-Zeisel method, the compound did not respond.

In the case of this ester the poorness of the yield may partly be accounted for, by the formation of the piperidide, thereby the catalyst being removed. When an alcoholic solution of the ester is treated with a few drops of piperidine only and boiled, no dihydrodicoumarinyl is produced; but a small amount of the piperidide could be isolated. This piperidide which is useful as a drug can be readily made in good yield by the following procedure, though previous workers employed the less easily available acid chloride for the purpose. The compound is irritant and bitter but not pungent to the taste (compare piperidide of cinnamic acid).

Equimolecular quantities of coumarin-3-carboxylic ester (2 g.) and dry piperidine (1 c.c.) were dissolved in 30 c.c. of toluene and the resulting solution refluxed for 3 hours. On cooling the piperidide crystallised out. M. P. 179°; yield, 1 gm. (*cf.* Merck's *Jahrberichte*, 1936, p. 98).

3-Cyano-dihydro-coumarin-4-cyano-acetamide

3-Cyano-coumarin added on cyano-acetamide producing an almost quantitative yield. The product crystallised out as colourless flat needles

from pyridine, being sparingly soluble in other organic solvents. It did not melt below 360° . [Found : C, 60.7 ; H, 3.5 ; N, 17.0 ; $C_{13}H_9O_3N_3$ requires C, 61.2 ; H, 3.5 ; N, 16.5%.]

Other reactions

Formation of Dihydro-dicoumarinyl (IV).—3-Acetyl-coumarin (1 g.) was dissolved in alcohol and piperidine (3 drops) added. When the resulting solution was refluxed for 3 hours, a pale yellow product separated out which was filtered, washed with a little water and finally with alcohol and recrystallised from pyridine. The substance crystallised as colourless narrow rectangular plates melting at 293° (decomp.). Yield 0.5 g. It is not soluble in ether and alcohol and is moderately soluble in hot pyridine, nitrobenzene and glacial acetic acid. It does not contain nitrogen and does not give a phenylhydrazone. It is insoluble in cold aqueous potash but dissolves on boiling. From this solution it could be recovered by acidification. [Found : C, 74.0 ; 74.3 ; H, 4.0 ; 3.9 ; $C_{18}H_{12}O_4$ requires C, 74.0 ; H, 4.1%.]

When pyridine was used instead of piperidine in the above reaction, there was no condensation. Also when malonic, acetoacetic and cyanoacetic esters were used in conjunction with piperidine the same-dihydro-dicoumarinyl was obtained.

3-Cyano-dihydro-coumarin-4-cyano-acetic ester

3-Cyano-coumarin (0.6 g.) was dissolved in alcohol, cyanoacetic ester (0.3 c. c.) added along with three drops of piperidine and the whole refluxed for 4 to 5 hours when a yellowish crystalline precipitate was obtained. It was filtered off ; a further quantity of the same substance could be obtained when the mother-liquor was left overnight (yield 0.6 g.). The crude product which was washed well with water and a small quantity of alcohol, was crystallised from alcohol in which it was moderately soluble. It came out as colourless needles melting at $247-48^{\circ}$. [Found : C, 63.1 ; H, 3.9 ; N, 10.4 ; $C_{15}H_{12}O_4N_2$ requires C, 63.4 ; H, 4.2 ; N, 9.9%.]

The same compound was obtained when a solution of salicylidene-bis-cyanoacetic ester in alcohol was treated with three drops of piperidine and refluxed on the water-bath for 5 to 6 hours.

Summary

Addition of cyanoacetamide to coumarins having substituents in the 3-position, such as the carbonyl, cyano and phenyl which are electron-attracting, has been studied. Unlike alkyl groups and bromine atoms they do not in general inhibit addition. The following coumarins have been

employed : (1) 3-acetyl-coumarin, (2) 3-benzoyl-coumarin, (3) 3-carbetoxy-coumarin, (4) coumarin-3-carboxylic acid, (5) 3-cyano-coumarin, and (6) 3-phenyl-coumarin. The speed of the reaction and the yield of the product depend upon (a) the activating capacity of the substituent group and (b) the readiness with which it can be eliminated under the experimental conditions. Compounds (1) and (2) give poor yields of the products; (3) combines with 2 molecules of cyano-acetamide; (4) resembles coumarin due to ready decarboxylation; (5) reacts without complications; (6) does not react. Among other additive compounds tested cyanoacetic ester reacts satisfactorily with 3-cyano-coumarin. 3-Acetyl-coumarin seems to undergo polymerisation and deacetylation to form dihydro-dicoumarinyl in the presence of piperdine.

Convenient methods for the preparation of 3-cyanocoumarin, coumarin-3-carboxylic acid and its piperidide have been investigated.

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