[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

The Synthesis of Some 3-Substituted-4-methylcoumarins[1]

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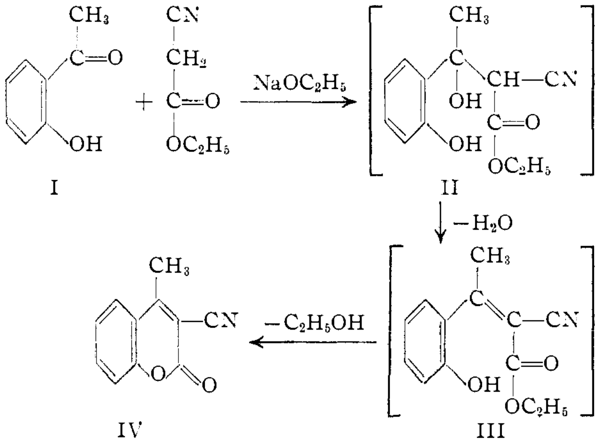
3-Cyano-4-methylcoumarin (IV) and several other 4-methylcoumarins have been synthesized. Sodium ethoxide catalyzed the aldol condensation of *o*-hydroxyacetophenone (I) and ethyl cyanoacetate to IV better than pyridine and piperidine. An attempt at condensation of I with diethyl malonate failed. Compound IV was converted to 3-carboxy-4-methylcoumarin (VII) by alkaline hydrolysis. Ease of acid hydrolysis was used to compare the stability of some of the intermediates formed in the alkaline hydrolysis of IV. The acid chloride (VIII), prepared from VII by conventional procedures, gave the corresponding 3-substituted-4-methylcoumarins with ammonia, ethanol and 4-hydroxycoumarin. A Rosenmund reduction of VIII gave 3-formyl-4-methylcoumarin (XII). The acid anhydride of VII was made from the acid chloride.



Studies on 4-methylcoumarins having a methyl group or chlorine atom in the three position have been reported. Chakravarti and Majumdar,[2] and Chakravarti and Dutta,[3] using the Reformatsky reaction with *o*-hydroxyacetophenone and ethyl α-bromopropionate, obtained 3,4-dimethylcoumarin. Chakravarti[4] also cyclized certain substituted phenols with ethyl α-chloroacetoacetate to obtain 3-chloro-4-methylcoumarins having substituents on the benzene ring. This paper describes the synthesis of 3-cyano-4-methylcoumarin and the preparation of several other 3-substituted-4-methylcoumarins.

o-Hydroxyacetophenone (I), in the presence of sodium ethylate, was shown to undergo condensation with the active methylene group of ethyl cyanoacetate to form 3-cyano-4-methylcoumarin (IV).

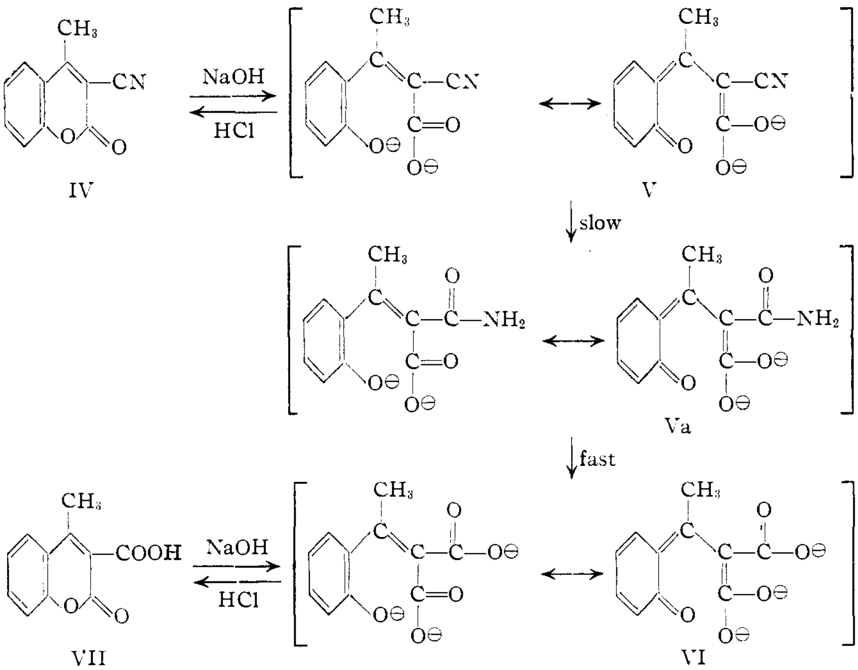
The reaction is conveniently carried out in one operation. It is suggested that it proceeds with the formation of an aldol condensate (II). Dehydration of II forms the intermediate (III) which by intramolecular Claisen condensation yields 3-cyano-4-methylcoumarin (IV).

The reaction proceeded rapidly and smoothly in ethanol solution. The product (IV) crystallized from the refluxing solution as it was formed.

Other catalysts such as pyridine and piperidine were also used, but comparatively lower yields were obtained.

The initial action of alkali on coumarin is to open the pyrone ring forming a salt of coumarinic acid.[5] This has been assigned the orthoquinoid structure since the salt of the corresponding 4-methyl derivative is colorless.[6] Upon acidification, coumarin is regenerated.

Attempts to prepare 3-carbethoxy-4-methylcoumarin by condensing I with diethyl malonate under similar conditions were unsuccessful. Hydrolysis of 3-cyano-4-methylcoumarin (IV) to 3-carboxy-4-methylcoumarin (VII) was accomplished by shaking IV with dilute alkali at room temperature. *o*-Hydroxyacetophenone was isolated from reaction mixtures when stronger alkali or higher temperatures were used.



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[1] Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

[2] D. Chakravarti and B. Majumdar. *J. Indian Chem. Soc.*, **15**, 136 (1935).

[3] D. Chakravarti and N. Dutta, *ibid.*, **17**, 65 (1940).

[4] D. Chakravarti, *ibid.*, **8**, 407 (1931).

[5] H. Bleibtreu, *Ann.*, **59**, 177 (1848).

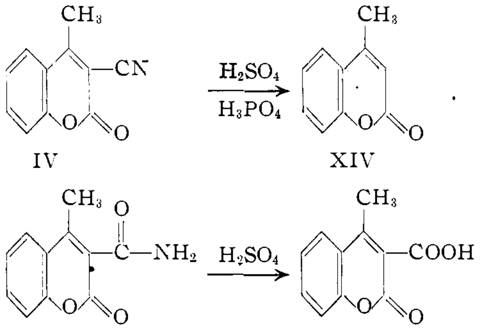
[6] L. A. Jordan and J. F. Thorpe. *J. Chem. Soc.*, **107**, 387 (1915).

TABLE I

3-SUBSTITUTED-4-METHYLCOUMARINS

Compound	3-Substituent	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
IV	$—C\equiv N$	79	$C_{11}H_7NO_2$	71.4	71.6	3.78	3.81
VII	—COOH	78	$C_{11}H_8O_4$	64.8	64.7	3.93	4.13
VIII	—COCl	93	$C_{11}H_7O_3Cl$	59.4	59.2	3.26	3.14
IX	$—COOCH_2CH_3$	91	$C_{13}H_{12}O_4$	67.2	67.2	5.18	5.25
X	$—CONH_2$	94	$C_{11}H_9O_3N$	65.1	64.9	4.44	4.14
XI	$—COOC_9H_5O_2$	76	$C_{20}H_{12}O_6$	69.3	69.6	3.43	3.71
XII	—CHO	40	$C_{11}H_8O_3$	70.2	70.2	4.25	4.45
XIII	—CH=NNH—*m*-di-NO_2—C_6H_3	99	$C_{17}H_{12}N_4O_6$	55.4	55.2	3.26	3.46
XV	$—C_{11}H_7O_4$	69	$C_{22}H_{14}O_7$	67.8	67.9	3.59	3.85

The presence of the orthoquinoid structures V, Va and VI formed by alkaline scission of the pyrone ring was indicated by the bright yellow color of the solution. Upon acidification with 6 *N* hydrochloric acid, two compounds identified as 3-cyano-4-methylcoumarin (IV) and 3-carboxy-4-methylcoumarin (VII) were recovered. Compounds IV and VII are colorless. It is postulated that this reaction occurred in several steps: the opening of the pyrone ring (V), hydration to the amide (Va), hydrolysis to the sodium salt (VI) of the acid and finally the closure of the pyrone ring by acidification, forming the acid (VII). Attempts to isolate 3-carbamyl-4-methylcoumarin (X) from the reaction mixture failed. It is thought that the hydrolysis of Va proceeds very rapidly.

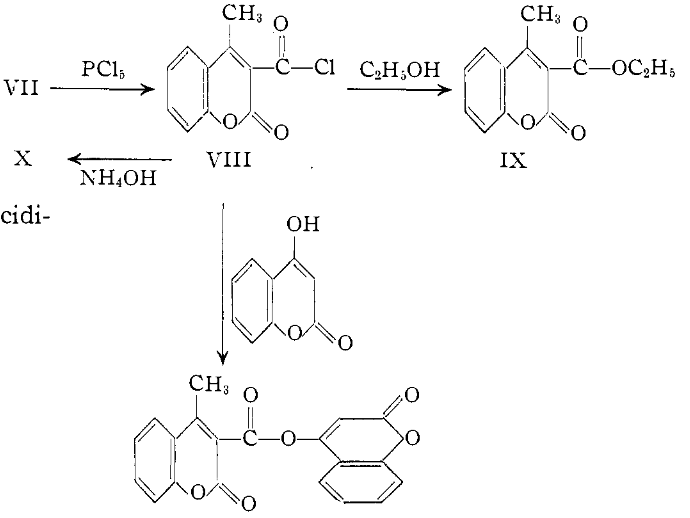


X VII

Using 6 *N* sulfuric acid, X was readily hydrolyzed to VII. In contrast, 4 parts 85% phosphoric acid and 1 part 85% sulfuric acid were required to hydrolyze IV. This reaction was accompanied by decarboxylation and only 4-methylcoumarin was isolated. It would appear that the conditions necessary for the hydration of the nitrile (IV) in alkaline solution caused rapid hydrolysis of Va to VI. This would account for the failure to isolate X from the reaction mixture.

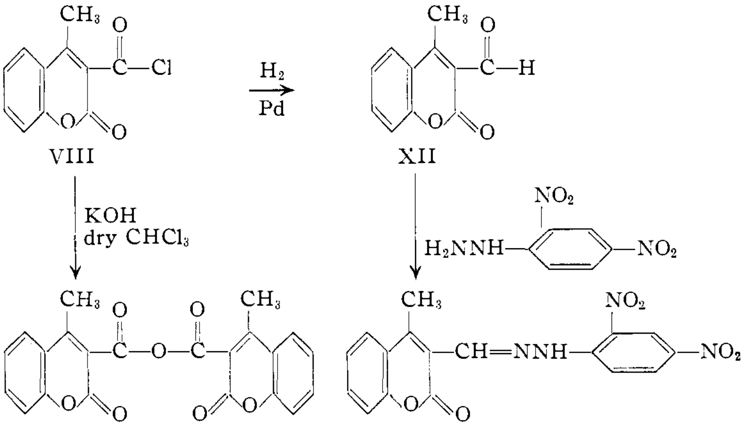
Derivatives of 4-methylcoumarin, having substituent groups on carbon 3, were obtained from 3-carboxy-4-methylcoumarin (VII). Treatment of VII with phosphorus pentachloride gave the expected product, 3-(4-methylcoumarinyl)-formyl chloride (VIII).

The highly reactive acid chloride (VIII) readily underwent esterification, ammonolysis and reduction. Reaction of VIII with ethanol gave 3-carbethoxy-4-methylcoumarin (IX).



XI

Similarly, treatment of VIII with 4-hydroxycoumarin in pyridine[7] gave 4-hydroxycoumarin ester of 3-carboxy-4-methylcoumarin (XI). When VIII was heated with concentrated ammonium hydroxide, 3-carbamyl-4-methylcoumarin (X) was obtained. Reduction of VIII with hydrogen using palladium-on-barium sulfate as the catalyst (Rosenmund procedure) produced 3-formyl-4-me-



XV XIII

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[7] M. A. Stahmann, L. H. Graf, C. F. Huebner, S. Roseman and K. P. Link, THIS JOURNAL, **66**, 900 (1944).

thylcoumarin (XII), which readily formed the 2,4-dinitrophenylhydrazone (XIII). Treatment of VIII with dry potassium hydroxide in dry chloroform yields the acid anhydride (XV).

Experimental

3-Cyano-4-methylcoumarin (IV).—A mixture of 20 g. of *o*-hydroxyacetophenone (I), 25 g. of ethyl cyanoacetate and 1 g. of sodium ethoxide in 200 ml. of absolute ethanol was refluxed for two hours after the appearance of needle-shaped crystals. The mixture was cooled and the crystals removed by filtration. They were washed with a small amount of cold ethanol to remove the yellow color. Recrystallization from acetone–water gave 26 g. of IV, yield 79%, m.p. 191–192°.

3-Carboxy-4-methylcoumarin (VII).—A mixture of 13 g. of IV and 0.13 g. of pyridine[8] was shaken with 200 ml. of 4% sodium hydroxide solution at room temperature. Agitation was continued for 24 hours after complete solution. The resulting yellow solution was acidified to *p*H 2 with 6 *N* hydrochloric acid whereupon the color disappeared. The crude material remaining after filtration was extracted with two 25-ml. portions of 10% sodium bicarbonate solution. The combined extracts were acidified with 12 *N* hydrochloric acid and the product was collected on a filter. Recrystallization from dilute acetone gave 11.2 g. of needle-shaped crystals (VII), yield 78%, m.p. 161–162°.

3-(4-Methylcoumarinyl)-formyl Chloride (VIII).—A mixture of 5.0 g. of VII and 6.0 g. of phosphorus pentachloride in 70 ml. of dry benzene was placed in a dry 200-ml. round-bottom flask fitted with a condenser. The mixture was warmed to about 40° to initiate the reaction which is moderately exothermic. The evolution of hydrogen chloride ceased after about 15 minutes. Skellysolve B was then added to the clear solution until it remained permanently turbid. After standing for 12 hours at 5°, the product crystallized. It was collected on a filter and washed with Skellysolve B. The product, recrystallized from benzene–Skellysolve B, yielded 5.1 g. of VIII, 93%, m.p. 91–92°. The alternative procedure of using thionyl chloride proceeded equally well.

3-Carbethoxy-4-methylcoumarin (IX).—One gram of VIII in 10 ml. of ethanol was refluxed for 30 minutes. The excess ethanol was removed under reduced pressure. The crude product was recrystallized from dilute ethanol; yield 0.9 g. (91%), m.p. 95–96°.

3-Carbamyl-4-methylcoumarin (X).—One-half gram of VIII was heated with 10 ml. of concentrated ammonium hydroxide until complete solution occurred. Crystals of X separated upon cooling. Additional quantities were recovered after concentration of the mother liquor. The crude product was recrystallized from water; yield 0.43 g. (93%), m.p. 151–152°.

4-Hydroxycoumarin Ester of 3-Carboxy-4-methylcoumarin (XI).—One gram of VIII was added with vigorous stirring to a solution of 0.5 g. of 4-hydroxycoumarin in 5 ml. of dry pyridine at 0°. After about 10 minutes, crystals appeared and stirring was continued for two hours at room temperature. The crude product was filtered and washed with cold ethanol to remove the pyridine. Recrystallization from xylene–Skellysolve B gave 1.2 g. of a very flocculent product (XI), yield 76%, m.p. 196–198°. The product tended to form gels during recrystallization.

Acid Hydrolysis of 3-Carbamyl-4-methylcoumarin (X).—One-tenth gram of X was heated at about 70° in 1 ml. of 6 *N* sulfuric acid for 10 minutes. One ml. of water was added, and the product was allowed to crystallize. After filtering, recrystallization from acetone–water gave 0.08 g. of VII, m.p. 161–162°.

Acid Hydrolysis of 3-Cyano-4-methylcoumarin (IV).—One gram of IV was heated at about 160° for one hour in 20 ml. of 85% phosphoric acid and 5 ml. of 85% sulfuric acid. The solution was then diluted with 100 ml. of water. Crystals separated upon cooling. Recrystallizations from water gave 0.8 g. of needles, m.p. 81–83°. This product was identified as 4-methylcoumarin, m.p. 81–83°, undepressed on admixture with an authentic specimen. The acid (VII) was not isolated. It is likely that the hydrolysis of IV produced the acid (VII), but the strong conditions caused its rapid decarboxylation to 4-methylcoumarin.

3-Formyl-4-methylcoumarin (XII) by the Rosenmund Method.—A small 3-necked flask, fitted with a reflux condenser, mercury-sealed stirrer, and a gas inlet was charged with 20 ml. of dry xylene and 0.5 g. of palladium-on-barium sulfate. Two grams of VIII was added, hydrogen flow was started and the mixture was refluxed. To follow the reaction, the hydrogen chloride issuing from the flask through the condenser was passed into a water solution containing phenolphthalein and a known amount of sodium hydroxide. The reaction was continued for three hours and then filtered through Filter-cel while hot. The mixture was concentrated and Skellysolve B was added until the solution became turbid. After filtering the crystals, formed on cooling, they were dissolved in ethanol, and the solution treated with Darco G-60. After several recrystallizations from dilute ethanol solution the product melted at 139–141°.

3-Formyl-4-methylcoumarin 2,4-Dinitrophenylhydrazone (XIII).—To an alcohol solution of 0.15 g. of XII was added an excess of 2,4-dinitrophenylhydrazine reagent. The mixture was heated 0.5 hour at about 78°. Filtration gave 0.1 g. of XIII after cooling to room temperature. Recrystallization from 95% ethanol gave orange crystals melting at 276–280°

3-Carboxy-4-methylcoumarin Anhydride (XV).—To a solution of 1 g. of finely divided dry potassium hydroxide in 20 ml. of dry chloroform was added 1.0 g. of acid chloride (VIII) at room temperature. After three hours the mixture was filtered and the chloroform removed from the filtrate under reduced pressure. After the crude material was recrystallized twice from dry benzene 0.6 g. of XV, m.p. 180–182°, was obtained.

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[8] The use of pyridine raised the yield from about 30% to 79%.