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

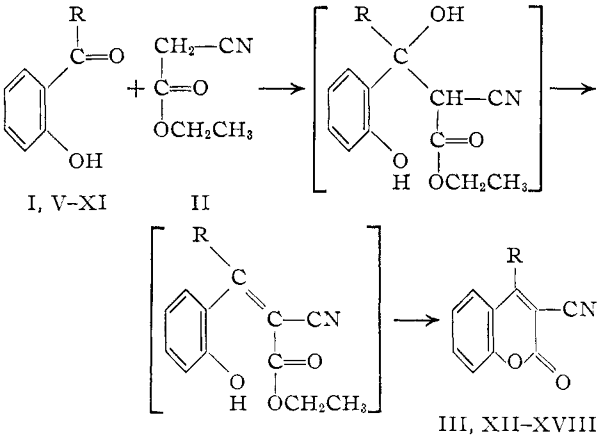
The Synthesis of Various 3-Substituted-4-alkylcoumarins[1]

BY CHARLES WIENER, COLLIN H. SCHROEDER AND KARL PAUL LINK

RECEIVED MAY 13, 1957

Some new 3-cyano-4-alkylcoumarins have been synthesized by the condensation of ethyl cyanoacetate and various *o*-hydroxyacylphenones. These 3-cyano-4-alkylcoumarins were then converted, by classical methods, to other new 3-substituted-4-alkylcoumarins.

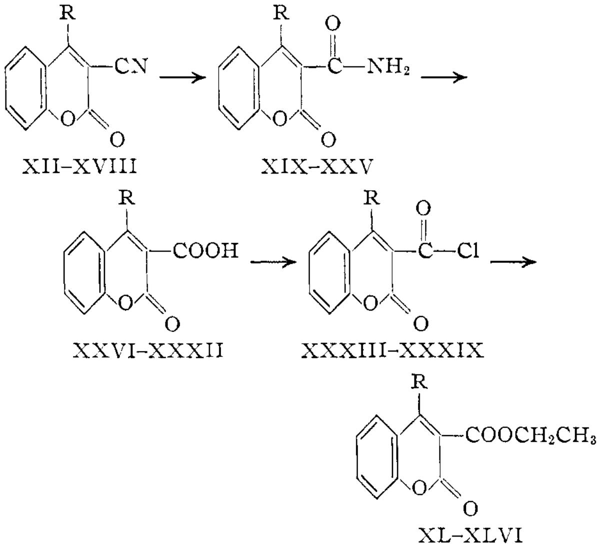
This is the second of two papers dealing with the synthesis of 3-substituted-4-alkylcoumarins. In the previous paper[2] the synthesis of 3-cyano-4-methylcoumarin and 3-substituted-4-methylcoumarins was reported. The first step of a mechanism suggested is considered to be the aldol condensation of *o*-hydroxyacetophenone (I) and ethyl cyanoacetate (II), followed by spontaneous dehydration and cyclization of the aldol condensate to give 3-cyano-4-methylcoumarin (III), as shown in the equation.



The present study was made in order to develop methods for the preparation of various substituted coumarins to be screened for hypertension activity. This paper reports the synthesis of new 3-substituted-4-alkylcoumarins and the investigation of conditions necessary for the condensation of various *o*-hydroxyacylphenones (V-XI), with ethyl cyanoacetate (II), as shown in the above equation. The investigation of the conditions for hydration of compounds XII-XVIII to the corresponding amides and the synthesis of various classical derivatives is also reported.

Attempts to condense the ketones V-XI with II in ethanol solution containing various concentrations of sodium ethoxide resulted in poor or no yields of products XII-XVIII. Variations of this procedure were tried, *i.e.*, removal of the water formed during the course of the reaction and the use of higher boiling solvents such as ethylene glycol in the hope that higher yields might be obtained. However, none of these methods proved suitable.

It was found that the condensations of the ketones V-XI with II carried out in benzene solution in the presence of acetic acid and ammonium acetate gave good yields of the desired 3-cyano-4-alkylcoumarins (XII-XVIII). The use of acetic acid–ammonium acetate catalyst for the condensation of ketones with active methylene compounds has been reported by Cope.[3]



It is to be noted that dehydration and cyclization of the intermediate aldol condensate IV occurs *in situ* and only the cyclized product was isolated. Table I lists the physical and analytical data of the 3-cyano-4-alkylcoumarins.

Although the hydrolysis of 3-cyano-4-methylcoumarin (III) to the corresponding acid proceeds readily under alkaline conditions,[2] the hydrolysis of the 3-cyano-4-alkylcoumarins XII-XVIII, reported herein, did not take place under similar conditions. Variation of the alkali concentration and/or the reaction temperature gave none of the desired carboxylic acids. The only products isolated from these reaction mixtures were the starting material and the corresponding *o*-hydroxyacylphenones. It was found, however, that compounds XII-XVIII when treated with concentrated sulfuric acid containing $1-2\%$ fuming sulfuric acid gave excellent yields of the corresponding amides. They, in turn, could be converted to the carboxylic acids in a dilute alkaline solution. An attempt was made to raise the yields of this conversion by the use of nitrous acid. This method proved practical only in the conversion of 3-carbamyl-4-octylcoumarin to the corresponding acid. The lower carbamyl analogs gave poor or no yields. The physical and analytical data for the amides are in

---

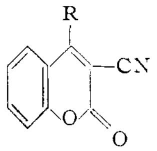
[1] Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

[2] Collin H. Schroeder and Karl Paul Link, THIS JOURNAL, **75**, 1886 (1953).

[3] A. C. Cope, *ibid.*, **59**, 2327 (1937).

TABLE I

3-CYANO-4-ALKYLCOUMARINS

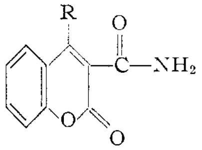


	R is	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
XII	CH_2CH_3	139–140	75	$C_{12}H_9O_2N$	72.4	72.0	4.5	4.4
XIII	$CH_2CH_2CH_3$	130–131	65	$C_{13}H_{11}O_2N$	73.3	73.1	5.1	5.3
XIV	$CH_2(CH_2)_2CH_3$	98–99	68	$C_{14}H_{13}O_2N$	74.0	74.0	5.7	6.1
XV[a]	$CH_2(CH_2)_3CH_3$	94–96	70	$C_{15}H_{15}O_2N$	74.7	74.4	6.2	6.3
XVI	$CH_2(CH_2)_4CH_3$	105–107	54	$C_{16}H_{17}O_2N$	75.3	75.3	6.6	6.7
XVII	$CH_2(CH_2)_5CH_3$	83–85	42	$C_{17}H_{19}O_2N$	75.8	75.5	7.1	7.5
XVIII	$CH_2(CH_2)_6CH_3$	91–92	40	$C_{18}H_{21}O_2N$	76.3	76.2	7.5	7.2

[a] E. J. Cragoe, Jr., C. M. Robb and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950), reported m.p. as 94–95°.

TABLE II

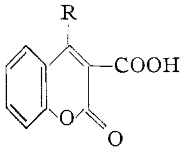
3-CARBAMYL-4-ALKYLCOUMARINS



	R is	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
XIX	CH_2CH_3	220–222	97	$C_{12}H_{11}O_3N$	66.3	66.2	5.1	5.2
XX	$CH_2CH_2CH_3$	185–186	93	$C_{13}H_{13}O_3N$	67.5	67.5	5.6	5.9
XXI	$CH_2(CH_2)_2CH_3$	165–166	98	$C_{14}H_{15}O_3N$	68.5	68.6	6.2	6.4
XXII	$CH_2(CH_2)_3CH_3$	157–158	96	$C_{15}H_{17}O_3N$	69.5	69.8	6.6	6.7
XXIII	$CH_2(CH_2)_4CH_3$	163–165	92	$C_{16}H_{19}O_3N$	70.3	70.0	7.0	7.1
XXIV	$CH_2(CH_2)_5CH_3$	148–149	95	$C_{17}H_{21}O_3N$	71.0	71.1	7.4	7.4
XXV	$CH_2(CH_2)_6CH_3$	115–116	93	$C_{18}H_{23}O_3N$	71.7	71.6	7.6	7.9

TABLE III

3-CARBOXY-4-ALKYLCOUMARINS

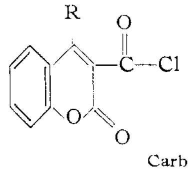


	R is	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
XXVI	CH_2CH_3	165–166	75	$C_{12}H_{10}O_4$	66.1	66.1	4.6	4.8
XXVII	$CH_2CH_2CH_3$	145–146	73	$C_{13}H_{12}O_4$	67.2	67.2	5.2	5.6
XXVIII	$CH_2(CH_2)_2CH_3$	134–135	63	$C_{14}H_{14}O_4$	68.3	68.1	5.7	6.0
XXIX	$CH_2(CH_2)_3CH_3$	93–96	85	$C_{15}H_{16}O_4$	69.2	69.2	6.1	6.0
XXX	$CH_2(CH_2)_4CH_3$	85–88	65	$C_{16}H_{18}O_4$	70.1	70.3	6.6	7.1
XXXI	$CH_2(CH_2)_5CH_3$	84–86	70	$C_{17}H_{20}O_4$	70.8	70.5	7.0	7.1
XXXII	$CH_2(CH_2)_6CH_3$	85–87	43[a]	$C_{18}H_{22}O_4$	71.5	71.0	7.3	7.4

[a] The yield for the conversion of XXV to XXXII was increased to 80% by the use of nitrous acid.

TABLE IV

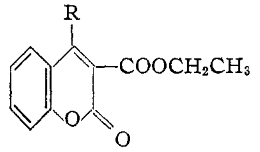
3-CHLOROFORMYL-4-ALKYLCOUMARINS



	R is	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
XXXIII	CH_2CH_3	115–116	94	$C_{12}H_9O_3Cl$	61.0	60.8	4.6	4.8
XXXIV	$CH_2CH_2CH_3$	124–126	82	$C_{13}H_{11}O_3Cl$	62.3	62.1	4.4	4.5
XXXV	$CH_2(CH_2)_2CH_3$	120–122	97	$C_{14}H_{13}O_3Cl$	63.5	63.5	4.9	5.1
XXXVI	$CH_2(CH_2)_3CH_3$	105–109	95	$C_{15}H_{15}O_3Cl$	64.6	64.4	5.4	5.5
XXXVII	$CH_2(CH_2)_4CH_3$	60–63	82	$C_{16}H_{17}O_3Cl$	65.6	65.9	5.9	6.0
XXXVIII	$CH_2(CH_2)_5CH_3$	73–74	50	$C_{17}H_{19}O_3Cl$	66.5	66.5	6.2	6.5
XXXIX	$CH_2(CH_2)_6CH_3$	55–56	61	$C_{18}H_{21}O_3Cl$	67.4	67.4	6.6	6.7

TABLE V

3-CARBETHOXY-4-ALKYLCOUMARINS



	R is	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
XL	CH_2CH_3	50–52	85	$C_{14}H_{14}O_4$	68.3	68.0	5.7	5.8
XLI	$CH_2CH_2CH_3$	61–63	71	$C_{15}H_{16}O_4$	69.2	69.3	6.1	6.2
XLII	$CH_2(CH_2)_2CH_3$	48–49	75	$C_{16}H_{18}O_4$	70.0	70.3	6.6	6.6
XLIII	$CH_2(CH_2)_3CH_3$	65–68	62	$C_{17}H_{20}O_4$	70.8	70.7	6.9	7.1
XLIV	$CH_2(CH_2)_4CH_3$	40–41	47	$C_{18}H_{22}O_4$	71.5	71.7	7.3	7.3
XLV	$CH_2(CH_2)_5CH_3$	13–14	70	$C_{19}H_{24}O_4$	72.1	72.3	7.6	7.9
XLVI	$CH_2(CH_2)_6CH_3$	8–10	85	$C_{20}H_{26}O_4$	72.7	72.9	7.9	8.0

Table II and those for the carboxylic acids in Table III.

The chloroformyl derivatives were prepared by refluxing the appropriate 3-carboxy-4-alkylcoumarin in thionyl chloride. The corresponding ethyl esters were prepared by the treatment of the chloroformyl derivatives with ethanol. Tables IV and V list the physical and analytical data for the chloroformyl derivatives and ethyl esters, respectively.

Acknowledgment.—The authors wish to express their gratitude to Professor S. M. McElvain of the Chemistry Department of this University for his helpful advice and suggestions.

Experimental

Preparation of the Ketone Intermediates V–XI.—Phenol and the appropriate acid chloride were placed in dry benzene containing magnesium metal according to Spasov[4] to form the phenol ester. The phenol ester, in turn, was rearranged to the *o*-hydroxyketone using aluminum chloride at elevated temperatures as described by Coulthard, *et al.*[5]

Preparation of 3-Cyano-4-alkylcoumarins (XII–XVIII).—The 3-cyano-4-alkylcoumarins (Table I) were all prepared according to the same general procedure. A typical example is the preparation of 3-cyano-4-ethylcoumarin (XII).

Seventy-five grams (0.5 mole) of *o*-hydroxypropiophenone (V) and 62.1 g. (0.5 mole plus 10% excess) of ethyl cyanoacetate (II) were placed in a two-necked, 500-ml. round-bottomed flask fitted with a Cope water separator. Benzene (100 ml.) containing 35 ml. of glacial acetic acid was poured into the flask and the reaction mixture was heated to reflux temperature. At this time 0.5 g. of ammonium acetate was added. The reaction was refluxed for an additional 80 hours during which time 30.8 g. of ammonium acetate was added periodically in 0.5-g. portions. The reaction mixture was then cooled and washed with an equal volume of water. The benzene layer yielded an orange paste upon vacuum concentration. Recrystallization of the orange paste from a minimum volume of boiling 95% ethanol and treatment with decolorizing charcoal (Norite) yielded 74.6 g. of the product, m.p. 139–140°.

Preparation of 3-Carbamyl-4-alkylcoumarins (XIX–XXV).—The hydration of 3-cyano-4-alkylcoumarins (Table II) to their corresponding amides was achieved readily, in all cases, as follows: forty ml. of concentrated sulfuric acid was poured slowly with stirring into a 200-ml. flask containing 10 g. of dry 3-cyano-4-alkylcoumarin. This suspension was heated to 80–90°. After the solution became clear, 0.5 ml. of fuming sulfuric acid was added and the temperature was maintained at 80–90° for one hour. The solution was cooled and poured carefully into an ice–water mixture. The solid product was filtered and recrystallized from hot aqueous ethanol.

Preparation of 3-Carboxy-4-alkylcoumarins (XXVI–XXXII). (A) **Procedure for Compounds XXVI–XXVIII.**—Five grams of the appropriate carbamyl compound (XIX–XXV) was refluxed in 150 ml. of 5% sodium hydroxide solution for one hour. The mixture was cooled, filtered and the filtrate poured into a beaker containing cracked ice. The cold solution was acidified and allowed to stand for 20 minutes. Fine needle-like crystals were collected on a filter and recrystallized from hot aqueous ethanol.

(B) **Procedure for Compounds XXIX–XXXII.**—Two grams of the appropriate carbamyl compound (XXII–XXV) was refluxed in 100 ml. of 5% sodium hydroxide solution for two hours. The mixture was then cooled, filtered and poured into a beaker containing cracked ice. This solution was acidified and the resulting oil or semi-solid was shaken with 50 ml. of ether in a separatory funnel and the two layers separated. The ether layer was treated with a small amount of Norite and filtered. The carboxylic acid (Table III) was extracted from the above ether filtrate with 100 ml. of 3% sodium bicarbonate solution in a 400-ml. separatory funnel. The aqueous sodium bicarbonate layer was separated and acidified with excess hydrochloric acid. The resulting oil was removed by ether extraction and dried one hour over anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration and the ether removed by vacuum concentration. The resulting viscous material was dissolved in 3 ml. of hot benzene and hot Skellysolve B was added to incipient turbidity. The material was allowed to crystallize for 12 hours at 0°. The thick crystalline mass was removed by filtration and again recrystallized from a benzene–Skellysolve B mixture.

Preparation of 3-Chloroformyl-4-alkylcoumarins (XXXIII–XXXIX).—One gram of the appropriate 3-carboxy-4-alkylcoumarin was refluxed for 30 minutes in 5 ml. of thionyl chloride. The thionyl chloride was removed by vacuum concentration and the residue dissolved in hot benzene. Skellysolve B was added to this solution until incipient turbidity. After cooling for two hours the solid acid chloride (Table IV) was filtered and recrystallized from benzene–Skellysolve B.

Preparation of 3-Carbethoxy-4-alkylcoumarins (XL–XLVI). (A) **Procedure for Compounds XL–XLIV.**—Two grams of the appropriate chloroformyl compound (XXXIII–XXXVII) was refluxed for 30 minutes in 15 ml. of absolute ethanol containing three drops of pyridine. The solution was then concentrated under vacuum to approximately 3 ml. and allowed to stand at 0° for 12 hours. The fine, needle-like crystals were removed by filtration and recrystallized from a benzene–Skellysolve B mixture.

(B) **Procedure for Compounds XLV and XLVI.**—Ten grams of the appropriate chloroformyl compound (XXXVIII or XXXIX) was refluxed for one hour in 75 ml. of absolute ethanol containing 0.5 ml. of pyridine. The resulting solution was concentrated under vacuum until an oil remained. This oil was distilled under diminished pressure to yield the product which is a liquid at room temperature. Compound XLV distilled at 215° (0.7 mm.). Compound XLVI distilled at 201° (0.5 mm.).

MADISON 6, WISCONSIN

---

(4) A. Spasov, *Ber.*, **75B**, 779 (1942).

(5) C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930).