SYNTHESIS OF SOME 3-SUBSTITUTED 4-METHYL-7-HYDROXYCOUMARINS

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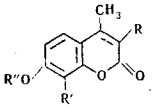
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 2, pp. 150–154, 1970

UDC 547.814.07

The Pechmann condensation reaction was used to synthesize a number of 4-methyl-7-hydroxycoumarins possessing a chain of three carbon atoms at position 3.

Derivatives of 7-hydroxycoumarin (umbelliferone) are found in plants, and attract the attention of investigators as biologically active compounds. There are reports, for example regarding the spasmolytic, vasodilator, bactericidal, and fungicidal activities of substituted umbelliferones [1, 2]. Among recent achievements we may mention the preparation of the coronary-dilator agent intensain, which is the hydrochloride of 3-(β-diethylaminoethyl)-4-methyl-7-carbethoxymethoxycoumarin [2].

In the present work some 4-methyl-7-hydroxycoumarins having a chain of three carbon atoms in position 3 (I–XV) were synthesized:



	R	R′	R″
I	$CH_2CH=CH_2$	H	H
II	$CH_2CH=CH_2$	H	CH_3CO
III	$CH_2CHOHCH_3$	H	H
IV	$CH_2(CH_3)CHOCOCH_3$	H	CH_3CO
V	$CH_2(CH_3)CHOCOCH_3$	H	H
VI	$CH_2CH_2CH_2OH$	H	H
VII	$CH_2CHClCH_3$	H	H
VIII	$CH_2CH_2CH_2Cl$	H	H
IX	$CH_2CH_2CONH_2$	H	H
X	CH_2CH_2COOH	H	H
XI	CH_2CH_2CN	H	H
XII	$CH_2CHClCH_3$		H
XIII	$CH_2CH_2CONH_2$	$CH_2N(C_2H_5)_2$	H
XIV	$CH_2CH_2CONH_2$		H
XV	CH_2CH_2CN		H

The Pechmann reaction of allylacetoacetic ester and resorcinol in 75% H_2SO_4, with standing for 2 hr, gave 3-allyl-4-methyl-7-hydroxycoumarin (I), mp 184–185° C. In the literature [3] under this name a compound has been described with mp 221–222° C (acetate: mp 152–153° C), which was prepared by the same procedure but with longer standing, the reaction mixture being left to stand until the following day. On repeating the synthesis with the longer standing time we isolated a compound having mp 219–220° C, which, however, from the analytical data and chemical composition did not correspond to I, but to 3-(β-hydroxypropyl)-4-methyl-7-hydroxycoumarin (III), not previously described. We also synthesized compound III by the reaction of allylacetoacetic ester with resorcinol in the presence of hydrobromic acid.

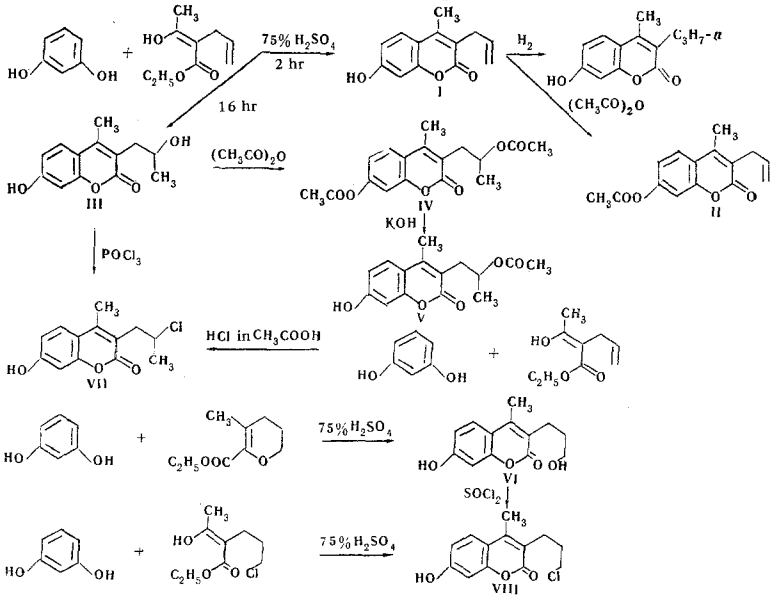
Compound I is readily hydrogenated to the known 3-propyl-4-methyl-7-hydroxycoumarin [4, 5]. The presence of a phenolic function in I was confirmed by the ability of the substance to dissolve in alkalis and by the formation of an acetate II, mp 93–94° C. The PMR spectrum of II in deuterochloroform was in agreement with this structure: 2.23 and 2.26 ppm (two overlapping singlets of the protons of the two methyl groups); 2.80 ppm (doublet $J \approx 6$ Hz, CH_2 group connected with the pyrone ring); 4.8 and 5.0 ppm (two groups of lines characteristic for a vinyl CH_2 group in an allyl radical); 5.4–6.0 ppm (complex signal of the methine proton in the same radical); 6.6–7.5 ppm (benzene ring protons).

The authors wish to thank E. P. Prokof'ev who measured the PMR spectra on an RS-60 instrument operating at a frequency of 60 MHz using deuterated solvents, the standard being hexamethyldisiloxane, δ-scale.

The alcoholic and phenolic functions of III were established by the fact that it gave a diacetate IV, mp 106–107° C, from which by partial hydrolysis with alcoholic KOH 3-(β-acetoxypropyl)-4-methyl-7-hydroxycoumarin (V) mp 164–165° C was obtained. The allylcoumarin I did not react with $POCl_3$, whereas the carbinol III yielded on reaction with $POCl_3$ the corresponding secondary chloride VII, mp 205–206° C. The structure of VII was confirmed by the PMR spectrum (in CD_3OD): doublets appear due to the protons of the methyl and methylene groups of the secondary chloropropyl radical, at 0.9 and 2.5 ppm, respectively. A 3-(Chloropropyl)-4-methyl-7-hydroxycoumarin with a melting point (200–201° C) close to that given above has been described in the literature: it was prepared from allylacetoacetic ester and resorcinol by the action of HCl in glacial CH_3COOH. The structure of this compound had not been proved. It could be the secondary, VII, or the primary, VIII, chloride. We synthesized the primary chloride VIII from γ-chloropropylacetoacetic ester and resorcinol, and found the mp 174–175° C, differing considerably from the above-mentioned value. This confirms that the compound III which we had prepared had the secondary alcohol structure. Consequently, the chloride described in the literature [3] must be considered to be the secondary compound (VII), which is in agreement with Markownikoff's rule regarding the addition of hydrogen chloride to an allyl residue. We prepared the above-mentioned γ-chloropropylacetoacetic ester by a modified method in which acetoacetic ester and 1, 3-chlorobromopropane were heated in boiling acetone in the presence of potassium carbonate. From sodioacetonacetic ester and 1, 3-chlorobromopropane we obtained 2-methyl-3-ethoxycarbonyl-5, 6-dihydropyran by a published method [6] and by condensing this with resorcinol in the presence of 75% H_2SO_4, we obtained the previously-unknown 3-(γ-hydroxypropyl)-4-methyl-7-hydroxycoumarin (VI), which by reaction with $SOCl_2$ was converted into the chloride VIII, mp 174–175° C, identical with the sample prepared as indicated above. It can by assumed that during the synthesis of VI the original 2-methyl-3-ethoxycarbonyl-5, 6-dihydropyran is hydrated with opening of the pyran ring, being converted into γ-hydroxypropylacetoacetic ester which then undergoes a Pechmann condensation with resorcinol to form VI.

The reaction of resorcinol with α-monocyanethylacetoacetic ester in H_2SO_4 was accompanied by conversion of the nitrile group into an amide group, and resulted in compound IX, which was converted by acid hydrolysis into the known acid X, obtained previously by another route [7]. It was possible to condense the same components with retention of the nitrile group to form 3-(β-cyanoethyl)-4-methyl-7-hydroxycoumarin (XI) by the action of HBr in glacial acetic acid.

The Mannich reaction of the 7-hydroxycoumarins VII, IX, XI with secondary amines and formaldehyde afforded the compounds XII–XV.



EXPERIMENTAL

3-Allyl-4-methyl-7-hydroxycoumarin (I). A mixture of 46.3 g (0.274 mole) of α-allylacetoacetic ester, 30.1 g (0.274 mole) of resorcinol and 280 ml of 75% H_2SO_4 was allowed to stand for 2 hr and after the usual working-up I was obtained, yield 14.2 g (24.3%), mp 184–185° C (from acetone). Found, %: C 72.03; H 5.76. Calculated for $C_{13}H_{12}O_3$, %: C 72.21; H 5.59.

3-Allyl-4-methyl-7-acetoxycoumarin (II). By boiling a mixture of 2 g of I with 8 ml of acetic for 1 hr, 0.89 g (37%) of II was obtained, mp 93–94° C (from ethanol). Found, %: C 69.98; H 5.62. Calculated for $C_{15}H_{14}O_4$, %: C 69.75; H 5.46.

3-n-Propyl-4-methyl-7-hydroxycoumarin. 3.9 g of I in 30 ml of ethanol was hydrogenated for 1 hr at 20° over 5 g of 5% Pd/$BaSO_4$ (2 mole-equiv of H_2 were obsorbed), 3-n-propyl-4-methyl-7-hydroxycoumarin was obtained, yield 3.28 g (83%), mp 169–170° C (from aqueous alcohol). Literature data: mp 169–171° C [4]; 171–173° C [5].

3-(β-Hydroxypropyl)-4-methyl-7-hydroxycoumarin (III). A) A reaction analogous to that for the preparation of I was carried out, but with a standing time of 24 hr, yield 13.7%, mp 219–220° C (from ethanol), Found, %: C 66.68; H 5.99. Calculated for $C_{13}H_{14}O_4$, %: C 66.66; H 6.02.

B) A mixture of 14.6 g (0.1 mole) of allylacetoacetic ester, 11 g (0.1 mole) of resorcinol, and 100 ml of 40% HBr was allowed to stand for 24 hr at 20° C; then 100 ml of a 10% solution of HBr in glacial CH_3COOH was added, the mixture was allowed to stand for 24 hr, and the III was isolated, yield 2.3 g (11%), mp 219–220° C not depressing the mp on admixture with the sample prepared as described above.

3-(β-Acetoxypropyl)-4-methyl-7-acetoxycoumarin (IV). 2.34 g (0.01 mole) of III and 10 ml of acetic anhydride were boiled for 1 hr. After the usual treatment with water and drying, 2.95 g (92%) of IV, mp 106–107° C (from ethanol) was isolated. Found, %: C 64.46; H 5.87. Calculated for $C_{17}H_{18}O_6$, %: C 64.14; H 5.70.

3-(β-Acetoxypropyl)-4-methyl-7-hydroxycoumarin (V). 1.07 g (0.03 mole) of IV and 0.18 g of KOH in 25 ml of ethanol were boiled for 1 hr, the greater part of the alcohol was evaporated in vacuum, and the residue was dissolved in water. If traces of the starting material were present in suspension, the solution was filtered, and then the filtrate was acidified, and the precipitate was washed with water and dried to give 0.59 (64%) of V, mp 164–165° C (from aqueous ethanol). Found, %: C 65.02; H 5.87. Calculated for $C_{15}H_{16}O_5$, %: C 65.21; H 5.83.

3-(γ-Hydroxypropyl)-4-methyl-7-hydroxycoumarin (VI). 6.8 g (0.04 mole) of 2-methyl-3-ethoxycarbonyl-5,6-dihydropyran and 4.4 g (0.04 mole) of resorcinol in 100 ml of 75% H_2SO_4 kept for 24 hr at 20° C, the mixture was poured into water, and the precipitate was dried and recrystallized from alcohol to give 3 g (32%) of VI, mp 175–176° C (from aqueous ethanol). Found, %: C 66.42; H 5.97. Calculated for $C_{13}H_{14}O_4$, %: C 66.66; H 6.02.

3-(β-Chloropropyl)-4-methyl-7-hydroxycoumarin (VII). A) 3.2 g of III was allowed to stand for two days with 15 ml of $POCl_3$, and then the mixture was decomposed with water and the precipitate was separated off dried, and crystallized from ethanol to give 0.92 g (25%) of VII, mp 205–206° C (dec.) (from alcohol). Found, %: C 62.02; H 5.26; Cl 14.06. Calculated for $C_{13}H_{13}ClO_3$, %: C 61.78; H 5.18; Cl 14.03.

B) 51 g (0.3 mole) of α-allylacetoacetic ester and 33 g (0.3 mole) of resorcinol dissolved in 400 ml of 6% HCl in glacial CH_3COOH was left to stand for three days at 20° C. The crystals were separated off, washed with water, and recrystallized from alcohol, mp 202–203° C; this product was boiled with benzene for 9–10 min and recrystallized: mp 205–206° C (from ethanol), yield 8 g (10%). The filtrate was poured into water and a less pure product separated. The substance did not give a depression of the melting point with the sample prepared as described above.

3-(γ-Chloropropyl)-4-methyl-7-hydroxycoumarin (VIII). A) The precursor γ-chloropropylacetoacetic ester was prepared by boiling for 6 hr 39 g (0.3 mole) of acetoacetic ester and 47.2 g (0.3 mole) of 1,3-chlorobromopropane (bp 141–143° C) in the presence of 62.1 g (0.44 mole) of dry potassium carbonate in 150 ml of acetone. Yield 11.3 g (18%), bp 116–126° C (5 mm). According to literature data [6], bp 118–119.5 (5 mm). From 11 g (0.05 mole) of this reaction product, 5.5 g (0.05 mole) of resorcinol, and 70 ml 75% H_2SO_4 kept for 24 hr at 20° C, after the usual working-up, 1.23 g (7%) of VIII, mp 174–175° C (from ethanol) was obtained. Found, %: C 62.16; H 5.15; Cl 14.22. Calculated for $C_{13}H_{13}ClO_3$, %: C 61.78; H 5.18; Cl 14.03.

B) 4.75 g (0.02 mole) of VI and 20 ml of $SOCl_2$ were allowed to stand for three days at 20° C, and the mixture was poured into water. The precipitate was separated off and dissolved in 20 ml of 10% NaOH. On acidification with HCl solution, **VIII** precipitated out, and it was recrystallized from 60% alcohol. Yield, 1.84 g (36%). The compound was identical in mp (mixed mp test) with the sample obtained as described above.

3-(β-Carbamoylethyl)-4-methyl-7-hydroxycoumarin (IX). 129 g (0.7 mole) of α-cyanoethylacetoacetic ester and 77 g (0.7 mole) of resorcinol in 700 ml of 75% H_2SO_4 were left to stand for 2 hr at 20° C, and by the usual procedure 38 g (22%) of **IX** was isolated, mp 226–227° C (from alcohol). Found, %: C 62.87; H 5.49; N 5.70. Calculated for $C_{13}H_{13}NO_4$, %: C 63.16; H 5.30; N 5.66.

3-(β-Carboxyethyl)-4-methyl-7-hydroxycoumarin (X). 25 g of **IX** in 150 ml of 40% HBr was boiled for 4 hr. The resulting precipitate was dissolved in aqueous $NaHCO_3$, and the solution was filtered and acidified with dil HCl (1:1) to give 9.05 g (36%) of **X**, mp 224–225° C; literature data: mp 224° C [7].

3-(β-Cyanoethyl)-4-methyl-7-hydroxycoumarin (XI). A mixture of 165 g (0.9 mole) of α-cyanoethylacetoacetic ester and 99 g (0.9 mole) of resorcinol in 300 ml of glacial CH_3COOH containing 10% of HBr was left to stand for 24 hr at 20° C, and was then poured into 1 *l* water, and the precipitate was separated off, washed with water, dried, and crystallized from ethanol to give 27.1 g (13%) of **XI**, mp 226–227° C. Found, %: N 5.76. Calculated for $C_{13}H_{11}NO_3$, %: N 6.11.

3-(β-Chloropropyl)-4-methyl-7-hydroxy-8-piperidinomethylcoumarin (XII). 2.1 g (8 mole) **VII**, 0.24 g (8 mM) of paraform, and 2.55 g (30 mM) of piperidine in 20 ml of ethanol were boiled for 5 hr, and by the usual working-up procedure gave 0.42 g (14%) of **XII**, mp 127–128° C (from ethanol). Found, %: N 3.91. Calculated for $C_{19}H_{24}NO_3Cl$, %: N 4.03.

3-(β-Carbamoylethyl)-4-methyl-7-hydroxy-8-diethylaminomethylcoumarin (XIII). 7.5 g (0.03 mole) of IX, 10.95 g (0.15 mole) of diethylamine, and 0.9 g (0.03 mole) of paraform in 100 ml alcohol and 20 ml of ethylene glycol were boiled for 5 hr, and 1.6 g (16%) of the hydrate of **XIII** was isolated, mp 154–155° C (from alcohol). Found, %: C 60.07; H 7.48; N 7.89. Calculated for $C_{18}H_{24}N_2O_4 \cdot 1.5\ H_2O$, %: C 60.15; H 7.57; N 7.80. After 3-hr drying at 70–80° C (3 mm), anhydrous **XIII** was obtained. Found, %: N 8.23. Calculated for $C_{18}H_{24}N_2O_4$, %: N 8.42.

3-(β-Carbamoylethyl)-4-methyl-7-hydroxy-8-piperidinomethylcoumarin (XIV). 7.5 g (0.03 mole) of **IX**, 12.8 g (0.15 mole) of piperidine, and 0.9 g (0.03 mole) of paraform in 100 ml of ethanol were boiled for 5 hr, to give 7.3 g (70%) of **XIV**, mp 210–211° C (from ethanol). Found, %: C 66.48; H 7.11; N 8.37. Calculated for $C_{19}H_{24}N_2O_4$; %: C 66.26; H 7.03; N 8.13. Hydrochloride: decomp. p). 183° C [dried at 70–80° C (3 mm) for 3 hr]. Found, %: Cl 9.33. Calculated for $C_{19}H_{24}N_2O_4 \cdot HCl$, %: Cl 9.31.

3-(β-Cyanoethyl)-4-methyl-7-hydroxy-8-piperidinomethylcoumarin (XV). 6.9 g (0.03 mole) of **XI**, 0.9 g (0.03 mole) of paraform, 10 ml of piperidine, and 50 ml of isopropyl alcohol were boiled for 30 min, the volatile material was distilled off in vacuum, and the residue was washed with water, dried, and crystallized from acetone to give 2.84 g (30%) of **XV**, mp 161–162° C (from acetone). Found, %: C 69.93; H 6.85; N 8.79. Calculated for $C_{19}H_{22}N_2O_3$, %: C 69.91; H 6.79; N 8.58.

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4 March 1968

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