

Solvent Effect in the Synthesis of 4-Carbamoyl-3-hydroxycoumarins

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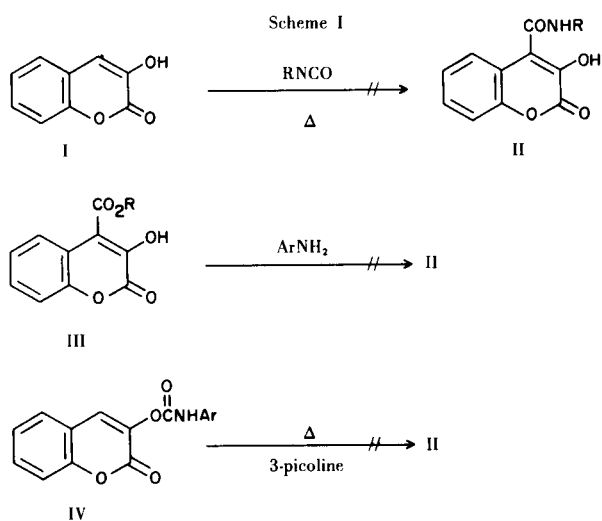
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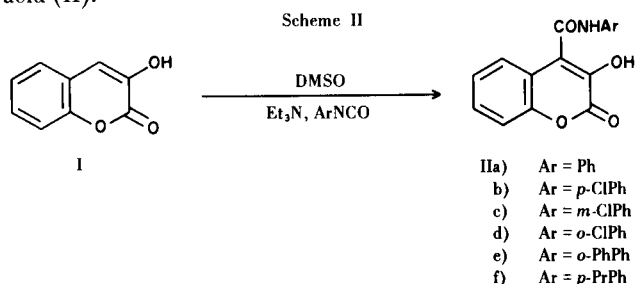
A new synthesis of 4-carbamoyl-3-hydroxycoumarin is reported. The synthesis of carbanilates of 3-hydroxycoumarin and their novel rearrangement to the carboxamides is also described.

Functionalization and derivatization of the 4-hydroxycoumarin nucleus at the 3-position is well documented (1-5), while functionalization of 3-hydroxycoumarin at the 4-position has been only slightly studied (6). We now wish to offer a novel preparation of carboxamides and urethanes of 3-hydroxycoumarin and the novel rearrangement of the urethanes to carboxamides.

All of the reported methods of functionalization of 4-hydroxycoumarin to 3-carboxamides (2-5) failed when applied to the 3-hydroxycoumarin nucleus. The thermal reaction of 3-hydroxycoumarin with isocyanates (Scheme I) yielded a gross mixture containing starting coumarin, ureas, and polymeric materials. 4-Carboethoxy-3-hydroxycoumarin (III) was prepared and when this material was heated with aryl amines (Scheme I) no carboxanilides were observed. The attempted thermal rearrangement of carbanilates of 3-hydroxycoumarin (Scheme I) gave a complex mixture of many compounds. Attempted amidation of 3-hydroxycoumarin-4-carboxylic acid with carbonyldiimidazole and anilines also failed.



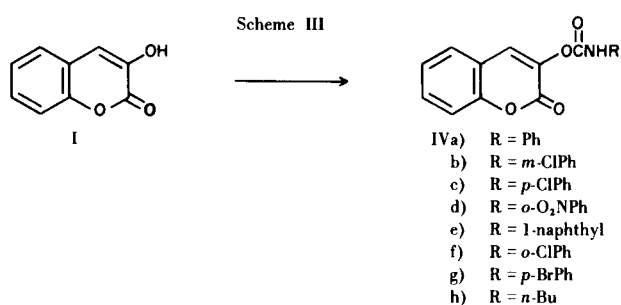
The use of DMSO as a solvent for effecting carbamoylation had been reported in other systems (7-9) and this stimulated us to examine this solvent in the 3-hydroxycoumarin system. The reaction of 3-hydroxycoumarin with aryl isocyanates (Scheme II and Table I) in DMSO in the presence of triethylamine, gave the desired new compounds, anilides of 3-hydroxycoumarin-4-carboxylic acid (II).



This reaction was essentially complete in 1-2 hours at room temperature, and the compounds obtained are all high melting. The carboxamides are characterized in the mass spectrum by the charged ions of the two major fragments, an isocyanate and hydroxycoumarin and in the ir by absorbances at 1735 and 1805 cm^{-1} . The parent ion is observed only fleetingly and in minor proportions.

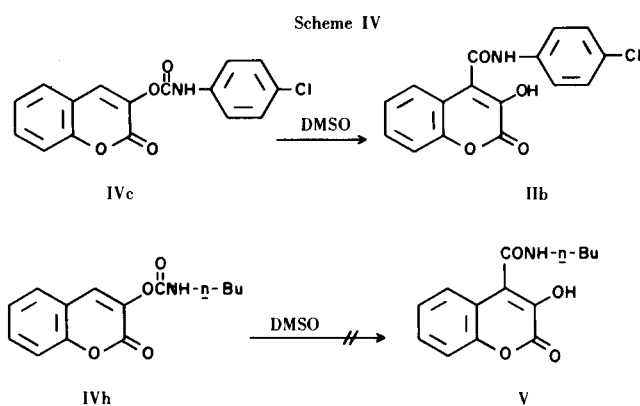
The reaction is successful only with aryl isocyanates and only with those having a relative degree of solubility at room temperature in DMSO. When alkyl isocyanates, alkyl or aryl isothiocyanates or insoluble aryl isocyanates were employed, a mixture of starting coumarin, some amide, and polymeric material is obtained, which were not characterized. The employment of DMF as a solvent gave a similar mixture.

If nitrobenzene (containing triethylamine) or pyridine is employed as a solvent with 3-hydroxycoumarin and isocyanates, the urethanes are obtained. The urethanes are characterized in the ir by absorbances at 1735 and 1760 cm^{-1} . This reaction was successful with both

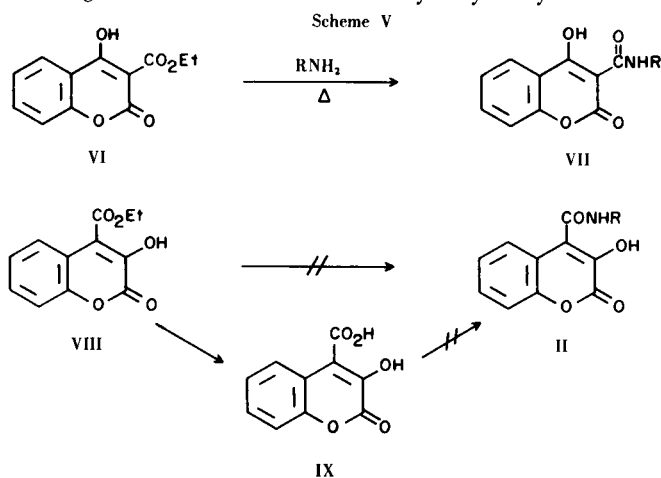


aryl and alkyl isocyanates (Scheme III and Table I).

The aryl urethanes are smoothly, cleanly, and quantitatively rearranged at room temperature in DMSO to the amides (II). This novel transformation took place in DMSO and in DMSO containing several drops of triethylamine and was essentially complete after overnight stirring. This rearrangement was successful with only aryl urethanes. When alkyl urethanes were subjected to rearrangement conditions, some coumarin and polymeric material were obtained (Scheme IV).



We attempted to prepare additional *N*-alkylamides and additional *N*-aryl amides by refluxing 4-carbethoxy-3-hydroxycoumarin (VIII) (10) with substituted amines, analogous to that with 3-carbethoxy-4-hydroxycoumarin

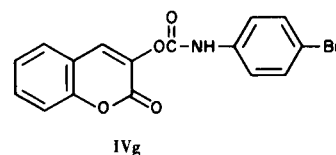


(3,4) (VI, Scheme V). This, however, was unsuccessful, yielding a gross mixture of materials.

We hydrolyzed ester VIII (10) and attempted to amidate with carbonyldiimidazole activation or with mixed anhydrides (Scheme V), but these were unsuccessful.

A curious base induced bathochromic shift was observed in the uv with both the amides and urethanes. We attributed this to ring opening, which occurs in both systems. If either material is treated with methanolic sodium hydroxide and the solvent removed, the carboxylate anion bands are evident in the ir. Treatment of the residue from the urethanes with methanolic hydrochloric acid regenerates the starting material. Similar treatment of the amide residue generates a new material, which was not characterized.

Initially, we had difficulty in determining which molecules were the urethanes and which were the carboxamides. An x-ray crystallographic analysis on IVg proved the structure to be unequivocally that shown as the urethane (IVg).



The crystals of IVg grown from acetone were found to be orthorhombic, space group $P2_12_12_1$, with unit cell parameters $a = 6.09 \text{ \AA}$, $b = 12.20 \text{ \AA}$, $c = 19.24 \text{ \AA}$. Three-dimensional data were collected on a CAD-3 diffractometer to give 1268 independent reflections, in the range $5 < \Theta < 60$, of which 916 were classed as observed with $I > 2.5 \sigma(I)$. The $\Theta - 2\Theta$ scan method was used with $\text{Cu-K}\alpha$ radiation.

The bromine position was deduced from a three-dimensional Patterson function. Thereafter the structure was solved by the heavy atom method. Initial refinement was carried out using individual isotropic temperature parameters with all atoms, except bromine, treated as carbon. After three cycles of block-diagonal, unit weight, least-squares atom types were assigned on the basis of temperature parameter values. Further anisotropic refinement using unit weights and a block diagonal approximation led to an R factor of .074. Bond distances and angles at this stage are shown below (Figure II). In a difference electron-density synthesis peaks were found corresponding to all hydrogen atoms. Inclusion of these atoms reduced R to .066.

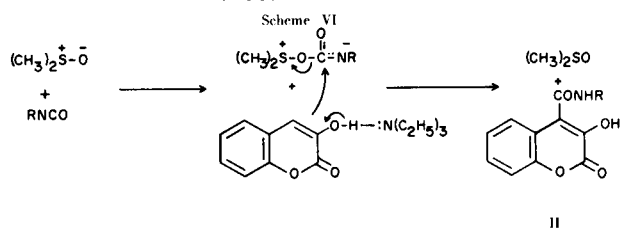
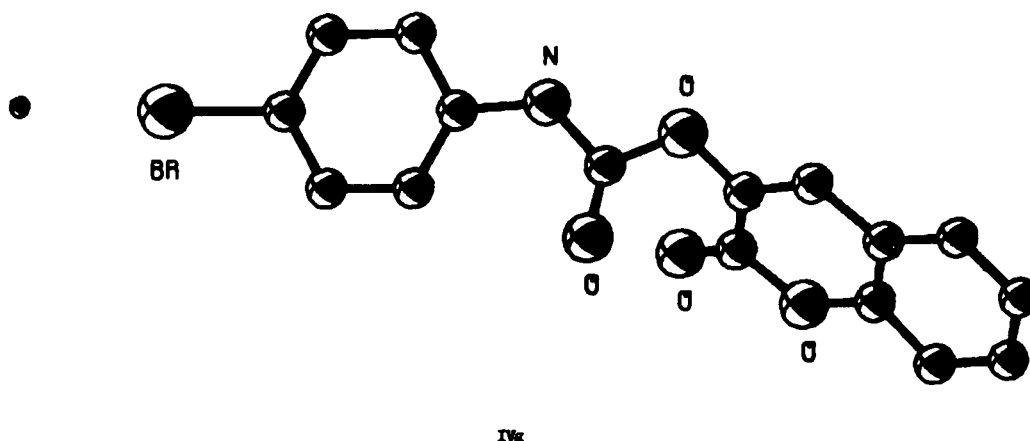
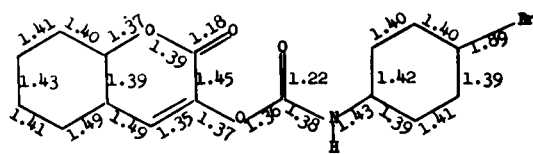
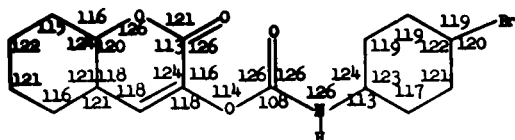


Figure I



IVg

Figure II

E.S.D. $\approx 0.03 \text{ \AA}$ E.S.D. $\approx 1.75^\circ$

IVg

A survey of the contact distances shows a close contact, probably corresponding to an N-H...O hydrogen bond, between the nitrogen atom of one molecule and the carbonyl oxygen on the coumarin ring system of a symmetry related molecule; the distance between nitrogen and oxygen is 2.79 Å (Figure III).

The mechanism and the intermediates involved in the formation of amides II and the rearrangement of urethanes IV are uncertain, but we can speculate about the pathways involved. Since, under essentially identical conditions, the amide formation from urethanes is longer on

a time basis than formation from 3-hydroxycoumarin and isocyanate, we would suggest that possibly the urethane is not an intermediate. Instead we would be tempted to postulate some complex between DMSO and the aryl isocyanate as attacking 3-hydroxycoumarin (Scheme VI).

EXPERIMENTAL

All melting points are uncorrected and were observed on a Mel-Temp[®]. Ir spectra were recorded with a Perkin-Elmer 137 and, unless noted, were recorded as a potassium bromide pellet. Nmr spectra were recorded on a Varian HA 100 and uv spectra on a Cary 14 spectrophotometer. All reagents, when commercially available, were, unless specifically noted, used without purification. All solvents were dried over molecular sieves.

General Preparation of 4-Arylcarbamoyl-3-hydroxycoumarin (II, Table I).

Equimolar portions of 3-hydroxycoumarin (11), triethylamine, and aryl isocyanate were stirred in DMSO for 3 hours. The mixture was partitioned between aqueous hydrochloric acid and ether. The solid which collected at the interface was removed by filtration, air dried, and recrystallized.

4-(Phenylcarbamoyl)-3-hydroxycoumarin (IIa).

A mixture of 3-hydroxycoumarin (1 g., 0.0061 mole), triethylamine (0.61 g., 0.0061 mole), and phenyl isocyanate in 15 ml. of DMSO was stirred at ambient temperature for 3 hours. The solution was partitioned between 1 N hydrochloric acid and ether and the solid at the interface was collected and air dried. Recrystallization from acetone-hexane (charcoal) gave a yellow powder (0.75 g., 45%), m.p. 279-282°; ir: 1800, 1835, 1666 cm^{-1} ; nmr (deuteriochloroform-DMSO- d_6): δ 6.9 (m, 2), 7.2 (m, 1), 7.4 (s, 1), 7.96 (m, 1), 7.51 (5, m).

Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{NO}_4$ (281.2): C, 68.34; H, 3.91; N, 4.98. Found: C, 68.25; H, 4.00; N, 4.86.

General Preparation A of 3-Hydroxycoumarin, Carbanilates (IV, Table I).

TABLE I

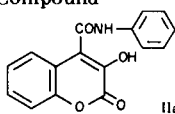
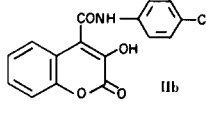
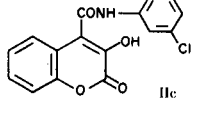
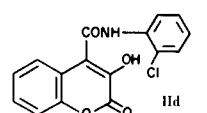
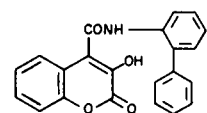
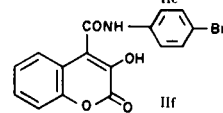
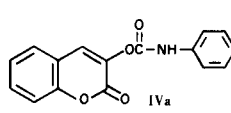
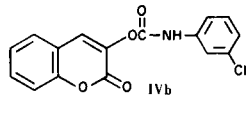
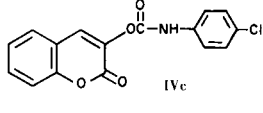
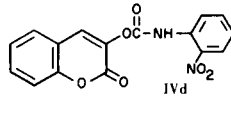
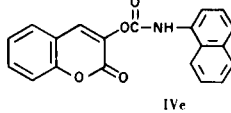
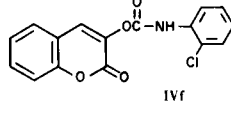
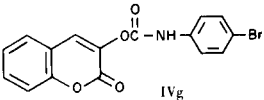
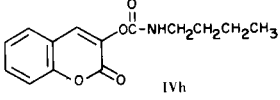
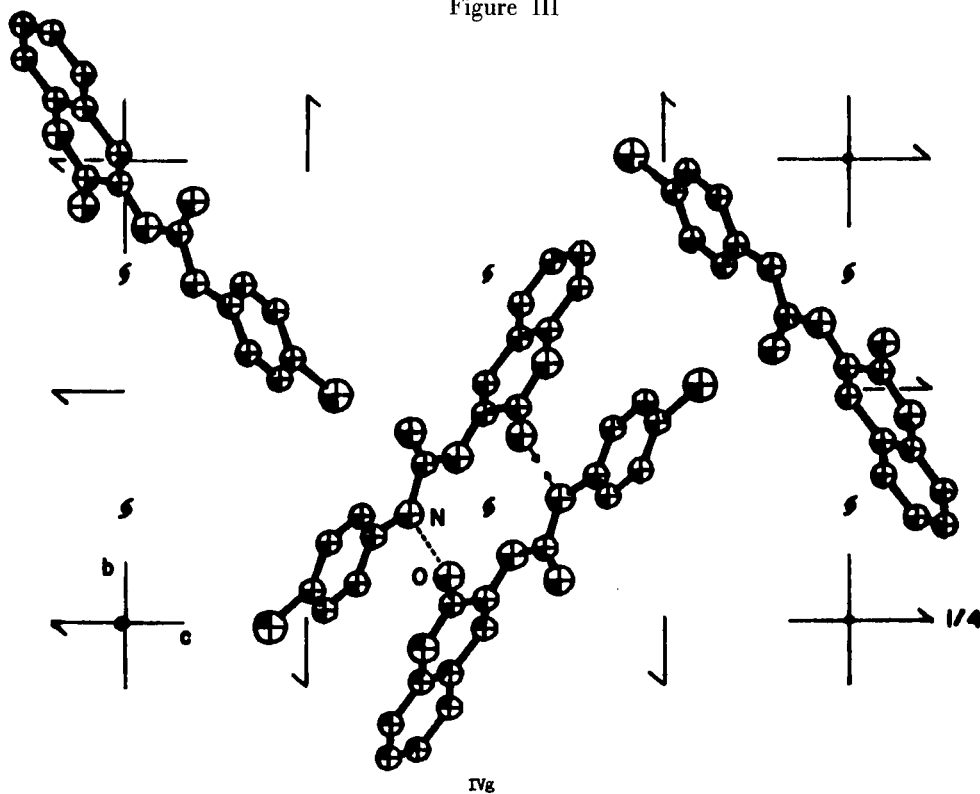
Compound	Molecular Formula	M.p., °C	Yield (a) %	Analysis	Calcd. Found
 IIa	C ₁₆ H ₁₁ NO ₄	279-282	45	C, 68.34; H, 3.91; N, 4.98. C, 68.25; H, 4.00; N, 4.86.	
 IIb	C ₁₆ H ₁₀ ClNO ₄	292-295	48	C, 60.87; H, 3.19; N, 4.44; Cl, 11.23. C, 60.69; H, 3.51; N, 4.46; Cl, 11.39.	
 IIc	C ₁₆ H ₁₀ ClNO ₄	246-249	25	C, 60.87; H, 3.19; N, 4.44; Cl, 11.23. C, 60.82; H, 3.21; N, 4.54; Cl, 11.48.	
 IIId	C ₁₆ H ₁₀ ClNO ₄	210-212	34	C, 60.87; H, 3.19; N, 4.44; Cl, 11.23. C, 60.54; H, 3.02; N, 4.48; Cl, 11.63.	
 IIe	C ₂₂ H ₁₅ NO ₄	224-227	28	M ⁺ 357	
 IIIf	C ₁₆ H ₁₀ BrNO ₄	284-287	43	C, 53.35; H, 2.80; N, 3.89; Br, 22.19. C, 53.39; H, 2.76; N, 4.15; Br, 22.54.	
 IVa	C ₁₆ H ₁₁ NO ₄	155-158	50	C, 68.34; H, 3.91; N, 4.98. C, 68.32; H, 3.89; N, 4.62.	
 IVb	C ₁₆ H ₁₀ ClNO ₄	169-172	55	C, 60.85; H, 3.19; N, 4.46; Cl, 11.23. C, 60.97; H, 3.02; N, 4.45; Cl, 11.23.	
 IVc	C ₁₆ H ₁₀ ClNO ₄	203-206	46	C, 60.85; H, 3.19; N, 4.46; Cl, 11.23. C, 61.14; H, 3.14; N, 4.52; Cl, 11.57.	
 IVd	C ₁₆ H ₁₀ N ₂ O ₆	194-197	13	C, 58.90; H, 3.09; N, 8.59. C, 58.99; H, 2.99; N, 8.43.	
 IVe	C ₂₀ H ₁₃ NO ₄	208-209.5	60	C, 72.50; H, 3.95; N, 5.23. C, 72.49; H, 4.04; N, 5.26.	
 IVf	C ₁₆ H ₁₀ ClNO ₄	175-178	48	C, 60.85; H, 3.19; N, 4.46; Cl, 11.23. C, 60.95; H, 3.21; N, 4.46; Cl, 11.58.	

TABLE I (continued)

Compound	Molecular Formula	M.p., °C	Yield (a) %	Analysis	Calcd. Found
	C ₁₆ H ₁₀ BrNO ₄	212-213	62	C, 53.35; H, 2.80; N, 3.89; Br, 22.19.	C, 53.39; H, 2.86; N, 4.05; Br, 21.84.
	C ₁₄ H ₁₅ NO ₄	187-191	55	C, 64.35; H, 5.79; N, 5.36.	C, 64.31; H, 5.96; N, 5.74.

(a) Isolated and recrystallized yields.

Figure III



3-Hydroxycoumarin (3 g., 0.0186 mole), triethylamine (0.0186 mole), and aryl isocyanate (1 equivalent) were mixed in the above order in nitrobenzene. If after 30 minutes a solid had formed, this was collected and recrystallized. If no precipitate formed, the mixture was partitioned between chloroform and 1 *N* hydrochloric acid. The organic layer was separated and dried (magnesium sulfate). Solvent removal and recrystallization followed.

3-Hydroxycoumarin, Carbanilate (IVa).

To 15 ml. of nitrobenzene were added with stirring in order, 3 g. (0.0186 mole) of 3-hydroxycoumarin, 1.86 g. (0.0186 mole) triethylamine and 2.68 g. (0.0186 mole) of phenyl isocyanate.

After several minutes, the voluminous precipitate which resulted was collected and recrystallized from chloroform-hexane (charcoal) giving a fine white fluffy solid, m.p. 155-158°. Yield 2.7 g. (50%); nmr (deuteriochloroform): δ 7.0-7.7 (m, 6), 10.0 (NH); ir: 1740 (d), 1600 cm⁻¹.

Anal. Calcd. for C₁₆H₁₁NO₄ (281.2): C, 68.34; H, 3.91; N, 4.98. Found: C, 68.32; H, 3.89; N, 4.62.

3-Hydroxycoumarin, *p*-Chlorocarbanilate (IVc).

3-Hydroxycoumarin (3 g., 0.0186 mole), triethylamine (1.86 g., 0.0186 mole), and *p*-chlorophenyl isocyanate (2.91 g., 0.0186 mole), added in the listed sequence to nitrobenzene (15 ml.)

failed, after stirring 2 hours at room temperature, to yield a precipitate. The solution was partitioned between chloroform and 1 *N* hydrochloric acid. The organic phase was separated, dried (magnesium sulfate), and the solvent removed *in vacuo* to give an oil which was recrystallized from chloroform-hexane (charcoal), giving white flakes, m.p. 203-208°, yield 2.89 g. (50%); ir: 1760, 1745 cm^{-1} ; nmr (deuteriochloroform): δ 7.03 (m, 1), 7.24 (m, 1), 7.30-7.70 (m, 6), 10.12 (1, NH).
Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{ClNO}_4$ (315.72): C, 60.85; H, 3.19; N, 4.46; Cl, 11.23. Found: C, 60.97; H, 3.02; N, 4.45; Cl, 11.23. MS, m^+ 315 (observed only in high temperature scans), 162, 153 (100%).

General Preparation B of 3-Hydroxycoumarin, Carbanilates (IV, Table I).

A solution of 3-hydroxycoumarin (1 g., 0.006 mole) and isocyanate (1 equivalent) in 10 ml. of pyridine was stirred at ambient temperature for 3 hours. The solution was poured into 50 ml. of cold 3 *N* hydrochloric acid, the solid collected, dried, and recrystallized.

3-Hydroxycoumarin, *m*-Chlorocarbanilate (IVb).

A solution of 1 g. (0.006 mole) of 3-hydroxycoumarin and 1 g. (0.006 mole) of *m*-chlorophenyl isocyanate in 10 ml. of pyridine was stirred at room temperature for 3 hours. The solution was poured into 50 ml. of cold 1 *N* hydrochloric acid, the solid was collected, air dried, and recrystallized from chloroform-hexane giving 970 mg. (75%) of a white fluffy solid, m.p. 170-172°; ir: 1755, 1745 cm^{-1} ; nmr (deuteriochloroform): δ 7.03 (m, 1), 7.24 (m, 1), 7.30-7.70 (m, 6), 10.12 (NH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{ClNO}_4$ (315.72): C, 60.85; H, 3.19; N, 4.46; Cl, 11.23. Found: C, 60.97; H, 3.02; N, 4.45; Cl, 11.23.

3-Hydroxycoumarin, *n*-Butylcarbamate (IVb).

A solution of 1 g. (0.0062 mole) of 3-hydroxycoumarin in 10 ml. of pyridine was treated with 0.6 g. of *n*-butyl isocyanate and the mixture stirred at room temperature for 3 hours. The solution was poured into 50 ml. of 1 *N* hydrochloric acid; the resultant solid was collected, air dried, and recrystallized from chloroform-hexane giving a white powder, m.p. 187-191° (750 mg., 55%); ir: 1750 (d), 1650 (d); nmr (deuteriochloroform): δ 1.9 (t, 3), 2.2-2.6 (m, 4), 3.1 (m, 2), 7.35 (s, 1), 7.2-7.8 (m, 4).

4-Bromo-3-hydroxycoumarin, Carbanilate.

A solution of 4-bromo-3-hydroxycoumarin (6) and phenyl isocyanate (300 mg., 1.1 equivalent) in 5 ml. of pyridine was stirred at room temperature for 2 hours. The mixture was poured into iced 3 *N* hydrochloric acid and the white precipitate collected and recrystallized from chloroform-hexane, m.p. 147-149°; yield 550 mg., 71%; ir: 1750 (d); nmr (deuteriochloroform-DMSO- d_6): δ 7.1 (m, 1), 7.8 (m, 1), 7.3-7.6 (m, 7), 9.8 (1, NH); m/e m^+ , 242, 240 (100%, 4-bromo-3-hydroxycoumarin $^+$), 212 (240-CO), 184 (100% - 2CO), 119 (phenylisocyanate $^+$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{BrNO}_4$ (360.17): C, 53.35; H, 2.80; N, 3.89; Br, 22.19. Found: C, 53.01; H, 2.74; N, 3.60; Br, 22.17.

Rearrangement of 3-Hydroxycoumarin, Carbanilate.

A solution of 1 g. of urethane in 10 ml. of DMSO containing several drops of triethylamine was stirred at room temperature overnight. The mixture was poured into cold 1 *N* hydrochloric acid, the solid was collected, air dried, and recrystallized from chloroform, yielding a yellow powder, m.p. 278-282°, identical to that reported earlier.

4-Carboxy-3-hydroxycoumarin (VIII).

A solution of 2,3-coumarandione (12) (5 g.) in 16 ml. of ethyl diazoacetate was stirred and cooled in an ice bath. Zinc chloride in 0.2 g. batches was added slowly until 3.5 g. had been added (until all nitrogen evolution had ceased). The suspension was partitioned between 50 ml. of ether and 50 ml. of water. After stirring for 5 minutes, the solid which collected at the interface was filtered off, refluxed with 100 ml. of 40% acetic acid and cooled. The deposited solid was collected and recrystallized from cyclohexane, m.p. 105-108°; lit. m.p. 102-104° (10).

3-Hydroxycoumarin-4-carboxylic Acid (IX).

A suspension of 600 mg. of 4-carboxy-3-hydroxycoumarin and 20 cc of 5% sodium carbonate was stirred and heated on a steam bath until solution was complete. Cooling and acidification gave dark yellow crystals, m.p. 212-215°; lit. m.p. 202-204° (10), yield 0.52 g. (94%) giving a dark blue color with ferric chloride; nmr (deuteriochloroform): δ 7.2 (3), 8.0 (1), 9-10.5 (2, exchangeable).

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