The Rearrangement of 4-Hydroxycoumarin Carbamates

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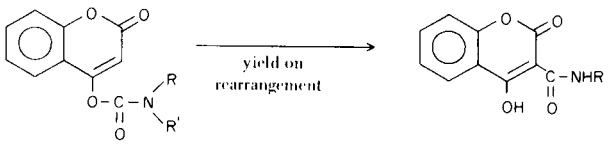
Carbamate esters of 4-hydroxycoumarin were prepared, and their base-catalyzed and thermal rearrangement to 3-(*N*-substituted carbamoyl)-4-hydroxycoumarins were studied. A mechanism for the rearrangement is proposed.

The rearrangement of 4-hydroxycoumarin esters has been the subject of several papers since Eisenhauer and Link reported their results on the reaction of 4-hydroxycoumarin (**1**) with acid chlorides (1-4). Although the rearrangement of 4-hydroxycoumarin carbamates has not been studied, it has been shown that **1** reacts with isocyanates at 160-180° to give 4-hydroxycoumarin-3-carboxamides (5). We have prepared several carbamates of **1** and have studied their thermal and base catalyzed rearrangement to the corresponding 4-hydroxycoumarin-3-carboxamides.

The carbamate esters of 4-hydroxycoumarin were prepared by treatment of **1** in dry acetone or tetrahydrofuran with the appropriate isocyanate at 22-25°. The esters (**2**, **2a**, **2b**) which were characterized by their carbonyl absorption at 5.7 μ, were obtained analytically pure in 23 to 61% yield. The authentic amides (**3**, **3a**, **3b**) were prepared in 35-87% yield by heating **1** and the appropriate isocyanate at 100° in dry pyridine or alternately by heating a pyridine solution of the esters at 100°.



2: R -CH_3; R' - H — 25% → 3: R -CH_3

2a: R -Ph; R' - H — 86% → 3a: R -Ph

2b: R -(3,4-Cl); R' H — 76% → 3b: R -(3,4-Cl)

2c: R R' -CH_3 — No reaction

The rearrangement reaction was followed by monitoring the disappearance of the ester carbonyl absorption in the infrared. It can be seen from these results that both the aliphatic and aromatic carbamate esters rearrange to the corresponding amides. These results are in contrast to the previously reported study of Eisenhauer and Link (4) which showed that only the aliphatic esters rearrange in pyridine. The benzoyl ester, however, has been rearranged to 3-benzoyl-4-hydroxycoumarin with aluminum chloride (6).

To obtain additional information on this rearrangement methyl carbamate (**2**) was heated in pyridine with an equimolar quantity of phenyl isocyanate. The carboxanilide (**3a**) was isolated in 63% yield. The remaining crude material did not contain any **2** but did have 5% **3** as determined by nmr. In a trapping experiment, the ester **2** was decomposed at 170° under a nitrogen atmosphere and the resulting gas was washed with a benzene solution of 3,4-dichloroaniline. Only, *N*-methyl-*N'*-3,4-dichlorophenylurea (27%) was isolated from this solution.

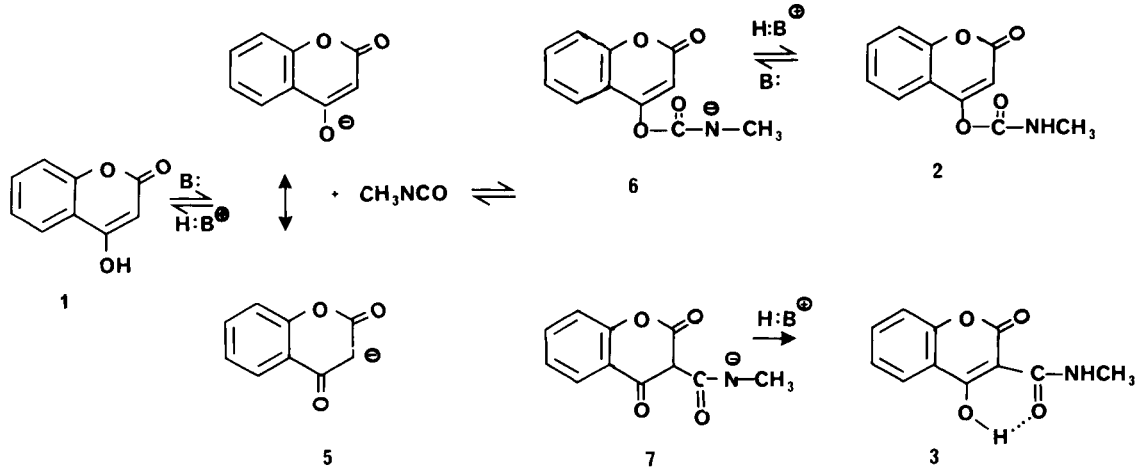
We prepared the previously reported (7) *N*,*N*-dimethylcarbamate (**2c**) which was heated in a pyridine solution at 100° for 4 days. A high yield of **2c** was recovered. The literature (8,9) indicates that *N*,*N*-disubstituted carbamates are not subject to thermal rearrangement. Thus, **2c** was reported to distill at 182-184° (0.2 mm). Likewise, enol carbamates were prepared by allowing aldehydes or ketones to react with *N*,*N*-dialkylcarbamoyl chlorides without solvent at 160°.

When stoichiometric quantities of **1** and phenyl isocyanate were reacted in pyridine at room temperature, a 41% yield of the ester **2a** was isolated after 1 day. The ir spectrum of the residue indicated the presence of a trace of **3a** (amide has characteristic bands at 9.7, 11.1, 12.5, and 14.8 μ). However, if the reaction mixture was allowed to stand for 6 days, the carboxanilide **3a** precipitated in 41% yield. No ester (**2a**) was found (ir) in the residue. The same reactants in tetrahydrofuran without catalysis gave only carbamate ester **2** in 43% yield after 6 days. The residue contained no amide (ir).

The methyl and phenyl esters (**2** and **2a**) decomposed at their melting points leaving a residue which is mostly **1**.

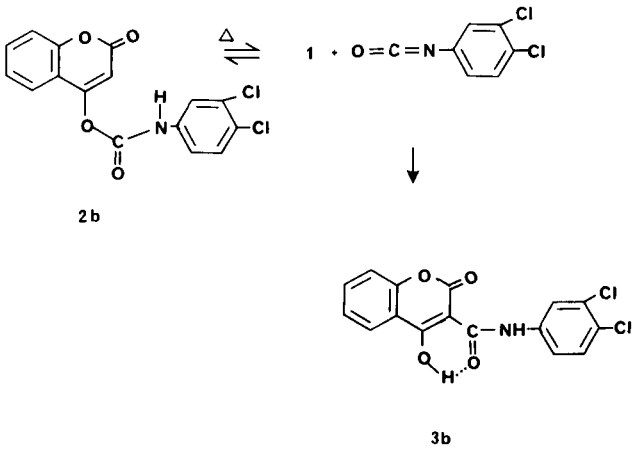
SCHEME I

Base-Catalyzed Reaction



SCHEME II

Thermal Reaction



If the methyl ester (**2**) is heated slowly, the melting point observed is 210-211°, while the melting point of **1** is 211-213° (10). If **2** is heated rapidly, the melting point is 158°; further warming at a slower rate caused resolidification with melting at 210-211°. This behavior may account for the discrepancy in the melting points of our **2** and that reported (11).

The 3,4-dichlorocarbanilic acid ester (**2b**) formed the carboxanilide (**3b**) at its melting point in a 71% isolatable yield. The lower volatility of the 3,4-dichlorophenyl isocyanate (m.p. 40-42°) apparently gave it time to react before it was volatilized.

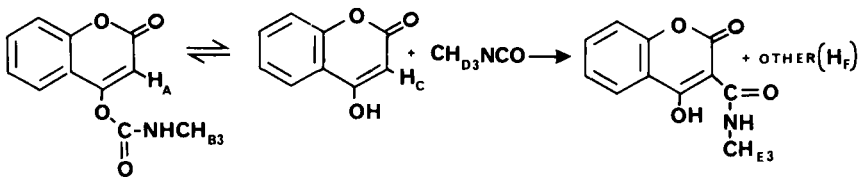
An nmr time study of the rearrangement of **2** in pyridine-d_5 was made at ambient temperature. The results (Table I) show that on dissolving ester **2** in pyridine-d_5 a very rapid decomposition occurred yielding **1** and methyl isocyanate. It further developed that these products were in equilibrium with the starting ester **2**. This was established by adding methyl isocyanate to the reaction solution after 936 hours. This resulted in an immediate decrease in **1** and an increase in **2**.

The methyl isocyanate concentration decreased more rapidly than **1** due to the formation of an unidentified material **4** (Table I, footnote b). The formation of the methyl carboxamide (3) was not observable until 24 hours had elapsed. As can be seen from Table I, the formation of **3** is slow, only a 47% yield in 936 hours. The formation of **3** is irreversible under both the conditions of the reaction (unchanged after 7 days at room temperature) and when heated at 100° in pyridine for 4 days.

The following mechanisms (Scheme I and II) are consistent with the evidence available. We have established that the carbamate ester under both base and thermal catalyzed conditions dissociates to isocyanate and **1**. It is well known that carbamates decompose under both these conditions (12). In addition, the reported (8) and our experimentally determined stability of **2c** indicates that a free N-H is necessary for the reaction to proceed. Our studies show that under basic conditions an equilibrium exists which is influenced by the irreversible formation of amide **3** (and also by formation of **4**). Reactions of a similar nature have been reported in the literature (13). It appears that the hydroxyl group in amide **3** is not reactive since we attempted to cause a

TABLE I

Nmr Time Study of the Room Temperature Rearrangement of **2** in Pyridine-d_5



2 **1** **3** **4**

Time (hours)	Moles (a) of Compounds Present from Nmr Integration				
	H_A (6.90 δ) H_B (2.97 + 2.88 δ)	H_C (5.85 δ)	H_D (2.75 δ)	H_E (2.87 + 2.79 δ)	H_F (3.33 δ) (b)
7 mins.	.53	.47	.47	--	--
3-½	.50	.45	.45	.05	--
24	.33	.37	.33	.30	.04
48	.32	.32	.27	.36	.05
100	.24	.32	.19	.44	.13
168	.22	.32	.15	.46	.17
480	.16	.37	.16	.48	.21
936	.15	.38	.15	.47	.23

(a) The nmr were run in sealed glass tubes at ambient temperature. Throughout the study the ratio of N-CH_3 protons to the remaining protons held constant at 1:2. The moles of compounds in the table were calculated from the integration of the N-CH_3 protons, assuming 1 mole **2** was initially present. The moles of 1 were calculated as the sum of H_D and H_F assuming that unknown **4** (H_F) did not contain a coumarin nucleus (**4** was not formed from the reaction of **3** with methyl isocyanate). (b) The unknown **4** (H_F) appeared in spectrum after 24 hours at 3.33 δ as an unaccountable sharp singlet. The unknown was not trimethyl isocyanurate (3.38 δ). It could be a homopolymer of methyl isocyanate [W. P. Ter Horst, U. S. Patent, 3,367,900 (*Chem. Abstr.*, **68**, 60038 (1968))].

reaction of **3** with methyl isocyanate under a variety of conditions without success. An infrared dilution study (5×10^3 mole/liter) of amide **3** in carbon tetrachloride showed that the hydrogen absorption at 3300 cm^{-1} was not affected and, therefore, suggests the above lack of reactivity may be due to internal hydrogen bonding.

The thermal rearrangement of these carbamate esters as illustrated in Scheme II by ester **2b**, affords **1** and the appropriate isocyanate.

In the case of ester **2b**, the recombination of these substances to the amide is a slower reaction but again yields a stable product. The rearrangement appears to be a case of ambident anion alkylation controlled by kinetic or thermodynamic factors.

EXPERIMENTAL

Melting points were determined with a Hoover-Thomas apparatus or on a Fisher-Johns Block, and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Nmr spectra were determined on a Varian A-60 in the solvent specified using TMS as an internal standard by Simon Research Laboratory, Elgin, Ill. C, H, and N analyses were performed in the IMC Analytical Laboratory.

Carbamate Esters of 4-Hydroxycoumarin.

The carbamate esters were prepared by the dropwise addition of 0.1 mole isocyanate over 0.25 hour to a stirred slurry of 0.1 mole 4-hydroxycoumarin in 100 ml. dry tetrahydrofuran (THF) or acetone containing *ca.* 0.8 g. of triethylamine or dibutyltin dilaurate catalyst at 22-25°. The reaction mixture was stirred overnight and then filtered to yield analytically pure carbamate ester. The ester could be recrystallized from tetrahydrofuran (THF), ethyl acetate or acetonitrile.

(a) Methyl Carbamic Acid Ester of 4-Hydroxycoumarin (**2**).

Compound **2** was prepared in 23% yield. It was recrystallized from ethyl acetate or THF to give white crystals, m.p. 158-159° dec. [Lit. (11) m.p. 180-187°]. The ir spectrum (nujol mull) showed major absorptions at 3.1 (broad), 5.7, 5.9, 6.0, 6.3, 6.6, 8.1, 8.5, 8.7, 8.9, 9.0, 10.7, 11.2, 11.7, 11.9, 13.1, and 13.4 μ. The nmr determined in DMSO-d_6 within 3 minutes after dissolving shows a doublet centered at 2.85 δ (J = 4 cps. 3H, CH_3N); a singlet at 6.5 δ (1H, vinylic-H); a broad band between 7-8.3 δ (4H, aromatic H); and a broad band between 8.1-8.6 δ (1H, N-H). An nmr spectrum (DMSO-d_6) determined 40 minutes after dissolving revealed the ester to be completely destroyed. Methyl

isocyanate and **1** could be detected in the spectrum, but no **3** was formed. The basic nature of DMSO probably accounts for the decomposition (14). A sample dissolved in pyridine-d_5 gave the results in Table I.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.31; H, 4.14; N, 6.40. Found: C, 60.23; H, 4.37; N, 6.20.

(b) Carbanilic Acid Ester with 4-Hydroxycoumarin (**2a**).

Ester **2a** was prepared in 61% yield. The crude material decomposes at 158° on rapid heating. On further heating at a slower rate it resolidified to remelt at 208-209°. The ir spectrum (nujol mull) showed major absorptions at 3.1, 5.7, 5.9, 6.2, 6.4, 7.6, 8.3, 8.4, 8.7, 9.1, 10.5, 11.8, 13.1, 13.4, 13.7, 14.0, and 14.6 μ.

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.95; N, 4.99. Found: C, 68.57; H, 3.96; N, 4.94.

(c) 3,4-Dichlorocarbanilic Acid Ester with 4-Hydroxycoumarin (**2b**).

Carbamate **2b** was prepared in 46% yield. It was recrystallized from acetonitrile to yield a white solid, m.p. 201-203°. The ir spectrum (nujol mull) showed major absorptions at 3.1, 5.7, 5.9, 6.3, 6.4, 6.5, 8.2, 8.3, 8.4, 8.8, 9.0, 10.4, 11.6, 11.8, 13.0, and 14.0 μ.

Anal. Calcd. for $C_{16}H_9Cl_2NO_4$: C, 54.88; H, 2.59; N, 4.00. Found: C, 55.09; H, 2.59; N, 4.09.

Preparation of 3-*N*-Substituted Carbamyl-4-hydroxycoumarins.

Method A: Direct Method.

A solution of 4-hydroxycoumarin (0.02 mole) and isocyanate (0.02 mole) in 20 ml. dry pyridine was heated on a steam bath overnight. (In the case of methyl isocyanate a 100% excess was used, and the reaction was run in a citrate pressure bottle). After cooling, the precipitated carboxamide was filtered from the reaction mixture and washed with a small amount of cold pyridine. Recrystallization from ethanol or THF gave the analytical sample.

Method B: Rearrangement of the Esters.

The carbamate ester (0.02 mole) was dissolved in 20 ml. dry pyridine and heated on a steam bath overnight. (A citrate pressure bottle was used for the methyl ester). The precipitated carboxamide was filtered from the cooled reaction mixture and washed with pyridine. The compounds obtained were identical to those prepared by the reaction of isocyanate with **1** in pyridine.

(a) 4-Hydroxy-3-(*N*-methylcarbamoyl)coumarin (**3**).

Amide **3** was prepared by method A in 35% yield and by method B in 25% yield. Recrystallization from ethanol gave the analytical sample, m.p. 200-202°. The ir spectrum (nujol mull) showed major absorptions at 3.1, 5.9, 6.2, 6.5, 7.8, 8.3, 8.7, 9.3, 9.7, 10.0, 11.2, 12.9, 13.3, and 14.8 μ. The nmr (deuteriochloroform) showed a doublet centered at 3.08 δ (J = 5 cps, 3H, CH_3-N); a broad band from 7.3-8.3 δ (~ 5H-aromatics + N-H); and a broad band centered at 9.6 δ (1H, OH). The nmr (deuteriotrifluoroacetic acid) showed a singlet at 3.0 δ (3H, CH_3-N); a broad multiplet between 7.1-8.1 δ (4H, aromatic H); and a broad band 12.8-13.3 (2H, exchangeable protons).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.31; H, 4.14; N, 6.40. Found: C, 60.09; H, 3.96; N, 6.31.

(b) 4-Hydroxy-3-phenylcarbamoylcoumarin (**3a**) (14).

Compound **3a** was prepared by method A in 73% yield and by method B in 86% yield. The crude compound prepared by either method had m.p. 209-211° [Lit. (13) m.p. 213.5-215°]. The ir spectrum (nujol mull) showed major absorptions at 3.2, 5.9, 6.3, 6.5, 6.7, 7.6, 8.3, 9.7, 9.8, 10.0, 11.1, 12.5, 13.2, 13.4, 14.5, and 14.8 μ.

(c) 4-Hydroxy-3-(3′,4′-dichlorophenylcarbamoyl)coumarin (**3b**).

Amide **3b** was prepared by method A in 87% yield and by method B in 76% yield. It was recrystallized from THF to yield the analytical sample, m.p. 228-230°. The ir spectrum (nujol mull) showed major absorptions at 5.9, 6.3, 6.5, 9.6, 9.8, 10.5, 10.8, 11.4, 12.3, and 13.1 μ.

Anal. Calcd. for $C_{16}H_9Cl_2NO_4$: C, 54.88; H, 2.59; N, 4.00. Found: C, 54.61; H, 2.56; N, 3.85.

Dimethylcarbamic Acid Ester of 4-Hydroxycoumarin (**2c**).

To a stirred solution of **1** (8.1 g., 0.05 mole) in 75 ml. dry dimethylacetamide protected from atmospheric moisture by a drying tube was added in small portions over 1.25 hours 57% sodium hydride in mineral oil (2.1 g., 0.05 mole). The reaction mixture was maintained at room temperature during the addition. After stirring 4 hours, dimethylcarbamoyl chloride (5.4 g., 0.05 mole) was added dropwise to the homogeneous solution over 0.25 hour with no apparent reaction. The mixture was stirred an additional 1.5 hours, and then hydrolyzed by the dropwise addition of a mixture of 15 ml. dimethylacetamide and 5 ml. water. The reaction mixture was poured onto ice and stirred to give 3.8 g. of white solid m.p. 80-90°. Recrystallization from 75 ml. 2:1 hexane-benzene (treated with charcoal) gave 2.5 g. of white crystals, m.p. 97-97.5° (a 21.6% yield) Lit. (7) m.p. 97-97.5°. The ir spectrum (nujol mull) have major absorptions at 5.7, 5.8, 6.2, 6.4, 7.8, 8.3, 8.4, 8.8, 9.2, 9.5, 10.2, 10.7, 11.5, 11.7, 12.1, 13.1, 13.2, 13.4, 13.6, 13.9, 14.5, and 15.4 μ. The nmr (deuteriochloroform) showed a doublet centered at 3.13 δ (6H, $(CH_3)_2N$), a singlet at 6.49 δ (1H vinylic H) and a broad band at 7.15-7.7 δ (4H, aromatic protons). The nmr is consistant with the ester structure assigned **2c**.

Attempted Rearrangement of **2c**.

Compound **2c** (1.15 g., 5 moles) in 5 ml. dry pyridine was heated on a steam bath for four days. The pyridine was removed under reduced pressure, and the residue stirred with 10 ml. 2:1 hexane-benzene to give 0.97 g. tan solid m.p. 93-94.5°, m.m.p. with **2c** 93-96°. A residue of 0.13 g. brown solid m.p. 80-85° was obtained. The ir of both fractions indicated only **2c**.

Trapping Experiment.

Ester **2** (2.2 g., 0.01 mole) was heated under a slow stream of nitrogen to 175° for 1 hour. The exiting gas stream was bubbled through 10 ml. benzene containing 3,4-dichloroaniline (1.6 g., 0.01 mole). The benzene solution, after standing overnight, was filtered to yield 0.6 g. of *N*-3,4-dichlorophenyl-N^1-methylurea, m.p. 154-157° [Lit. (16) m.p. 153-154°] (a 27% yield). The urea was identical to an authentic sample prepared by the reaction of methyl isocyanate with 3,4-dichloroaniline, m.p. 155-157° (27% yield). The decomposition residue appeared to be mostly **1** with a small amount of undecomposed **2** present *via* ir.

Exchange Experiment.

Carbamate **2** (4.4 g., 0.02 mole) and phenyl isocyanate (2.2 g., 0.025 mole) were dissolved in 20 ml. dry pyridine and heated on a steam bath overnight. The cooled solution was filtered to yield 3.40 g. solid (63% yield), m.p. 208-211°, which was shown to be **3a** *via* ir. Concentration of the filtrate gave 1.55 g. of orange semisolid. The nmr (deuteriochloroform) of the dry residue showed it to contain no **2** and no more than 5% **3**.

Room Temperature Reaction of **1** with Phenyl Isocyanate.

Mixtures of **1** (0.02 mole) and phenyl isocyanate (0.02 mole) in 20 ml. of dry solvent were stoppered in flasks and allowed to stand from 1 to 6 days at room temperature.

A. Pyridine.

(1) After 1 day the pyridine was stripped at room temperature with high vacuum to give a solid residue which was triturated with THF to yield 2.3 g. of **2a** (a 41% yield) m.p. 160° dec.; ir identical to an authentic sample. Concentration of the filtrate gave 2.3 g. of solid residue, m.p. 175-185°. An infrared examination of the residue indicated the absence of **3a**. Absorptions attributable to **1** and diphenylurea were present.

(2) After 6 days, 2.3 g. of **3a** (a 41% yield) precipitated, m.p. 209-211°. Concentration of the filtrate gave 2.5 g. of solid, m.p. 165-170°. An infrared examination of the residue revealed the presence of **1** and diphenylurea.

B. THF.

(1) After 1 day, concentration of the reaction mixture, gave a semisolid. The ir showed the semisolid to be mostly starting material with a small amount of **2a** present.

(2) After 6 days, 2.4 g. of **2a** (a 43% yield) m.p. *ca.* 165° was filtered from the reaction mixture. Concentration of the residue gave white solid, m.p. ~ 165°. The ir of the solid showed it to be mostly **2a** containing some **1**. No **3a** could be detected.

Thermal Decomposition of the Carbamate Esters.

Small portions of **2** or **2a** were heated to their melting points between glass plates on a Fisher-Johns melting point apparatus. The ir spectrum of the cooled residues (nujol mull) showed them to be **1**. Ester **2b** (3.5 g., 0.01 mole) was heated in a test tube to its melting point (200°) for 45 minutes. Recrystallizations of the residue from THF gave 2.5 g. of **3b**, m.p. 228-230° (71% yield).

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