X-Ray Crystallography. Crystals were received as prismatic needles; a sample showing good crystal quality under microscopic examination, with and without polarized light, was chosen from the batch. The sample was approximately 0.3 × 0.2 × 0.5 mm and was mounted with the largest dimension as the goniometer rotation axis.

Preliminary precession camera investigation showed the unit cell to be monoclinic with a choice of either $P2_1/c$ or $P2_1/n$ as the space group; because of the near-cubic geometry of the resulting unit cell, $P2_1/n$ was chosen for indexing [general positions $\pm(x,y,z;\ x + \frac{1}{2}, y - \frac{1}{2}, z + \frac{1}{2})$].

Precision lattice constants were obtained by least-squares refinement[5] of 2θ diffractometer angular settings on 18 independent reflections within the range $23 < 2\theta < 43°$ (λ 0.7107 Å, Mo Kα radiation). This calculation gave a = 14.148 (4), b = 11.432 (1), c = 11.318 (4) Å, β = 97.50 (4)°. Assuming four formula units per cell, the calculated density, ρ_{calcd}, was found to be 1.304 (6) g/cm^3, which agrees favorably with the experimental density (determined by immersion in a mixed solvent of equal density) of 1.32 g/cm^3 at room temperature.

The linear absorption coefficient, μ, for the compound is 1.04 cm^{-1} for Mo Kα radiation. An absorption correction for data collected using Mo Kα radiation was, therefore, deemed unnecessary.

Approximately 2400 independent reflections in the range $0.05 < \sin \theta/\lambda < 0.75$ were measured by the θ-2θ scanning technique using a card-controlled Picker diffractometer. With 235 parameters to be set in the final anisotropic model (excluding hydrogens), this gives approximately ten reflections per parameter to be set.

Diffracted intensities were measured at a take-off angle of about 2°; the range of each scan, at a rate of 2°/min, consisted of a reflection base width of 2° and an increment, $\Delta(2\theta) = (0.285 \tan \theta)°$, to allow for spectral dispersion. Background counts, for 30-sec duration, were taken at the limits of the scan. The intensities of three standard reflections were monitored at intervals of 50 data points as alignment checks while these three plus three others were used at roughly 12-hr intervals as decomposition checks. Through the data collection period, these monitored reflections showed no noticeable trend. The criteria for distinguishing observed from unobserved reflections was set such that, to be "observed," $F_{\text{obsd}} > 3.0\sigma_F$, where σ_F is the standard deviation on F_{rel} as computed from scan and background counts corrected for instrumental instability (estimated as 0.5%).

The structure was resolved using direct method techniques: Karle–Hauptmann statistics[6] and symbolic addition.[7] This led to determination of 288 phases with high probability of being correctly determined (approximately 11 reflections per nonhydrogen atom; 26 nonhydrogen atoms in the molecule). An E map using these phased reflections was then searched for the 26 largest peaks; 25 were easily chosen, the 26th had several possibilities and so was ignored in this first screening. The program OR-TEP-II[8] was used to "search" for a "molecule" amoung these 25 peak positions, working out from the highest one and using criteria of reasonable ranges for bond lengths;[3] each peak position was tested in each of the four possible positions allowed by the general positions of the space group. The resulting "molecule" was then drawn in stereo on a graphics display terminal[9] and studied for chemical sense.

This trial molecule was found to be entirely satisfactory in all chemical respects; the position of the 26th atom previously ignored was determined visually and found to agree with the position of a peak on the E map. Chemical considerations also readily led to the definition of atom types (C, N, or O) in all positions but the two positions occupied by C3 and N1 (refer to Figure 1) where the question of which position should be carbon and which nitrogen depended entirely on nmr data. The initial model defined the atoms in these two positions as they are shown in Figure 1.

A test of the model was made by performing two cycles of full-matrix least-squares on the nonhydrogen atoms of this model; unit weights and individual isotropic thermal parameters were used. The two cycles caused "R" to fall from an initial value of 0.24 for the raw model to 0.13; at the end of the two cycles, the model appeared quite reasonable with respect to individual atomic thermal parameters, bond lengths, and angles, and the appearance of a difference Fourier synthesis.

At this time, weights and anisotropic thermal parameters were introduced for all nonhydrogen atoms; hydrogen positions were introduced by calculation;[10] and cycles of full-matrix least-squares were continued. Hydrogen positions were recalculated at the close of each cycle according to shifts in the nonhydrogen atoms. The weighting function used was $w = 1/|\Delta F|^2$, where $|\Delta F| = A + B|F_{\text{obsd}}|$, and A and B are obtained from a plot of $|\Delta F|$ *vs.* F_{obsd} for 20 groups of reflections, each group containing about the same number of reflections. The plot was linear and gave values of 2.80 and 0.0492 for A and B, respectively. The final cycle gave a conventional R value of 0.064 and weighted R of 0.072.

A final structure factor calculation was made using σ values from counting statistics as weights. The weighted R value for this calculation did not differ significantly from the above weighted R value.

As a test of the possibility that C3 and N1 should be interchanged, two additional cycles of full-matrix least squares were made for the entire molecule with these two atoms interchanged as to atomic type. The resultant R value, changes in atomic parameters, and the appearance of a subsequent difference Fourier map were used as criteria of the correctness of this alternative structure. It was found that the R value increased to 0.076, thermal parameters for C3 (now defined as a nitrogen) became smaller while those for N1 (now defined as a carbon) became larger (atomic coordinate values for all nonhydrogen atoms did not change appreciably; thermal parameters for all nonhydrogen atoms but C3 and N1 did not change appreciably), and, on the difference Fourier, a hole was noted at the position of C3 while a peak was noted at the position N1 (all other atom positions showed neither appreciable peaks nor holes). This evidence led to the conclusion that C3 and N1 were correctly defined from the start.

A final difference Fourier synthesis, on the correct model, having a maximum electron density of 1 e/Å^3 was judged to be free of significant features. Because the goal of this structure determination was to find the molecular architecture of this compound rather than details of accurate bond lengths and thermal parameters, additional refinement cycles were deemed unnecessary. As a final observation, only five of the original 288 reflections phased by direct method techniques were found to be incorrect.

Supplementary Material Available. Tables of bond distances and bond angles (with their estimated standard deviations), and atomic coordinates, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036. Remit $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1007.

Registry No.—3, 35324-31-3; 4, 50378-65-9.

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(5) All structure refinements were done using "X-ray '70" programs from Dr. James Stewart, University of Maryland.

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(9) The Burroughs B-6700 at the University of Delaware Computing Center was employed for all programs used for this structure.

(10) Hydrogen positional parameters were calculated with ATMCAL, adapted from a general hydrogen position calculating program supplied by Dr. Lloyd D. Guggenberger, Du Pont, Wilmington, Del.

A Novel Synthesis of 4-Hydroxycoumarin-3-carboxamides

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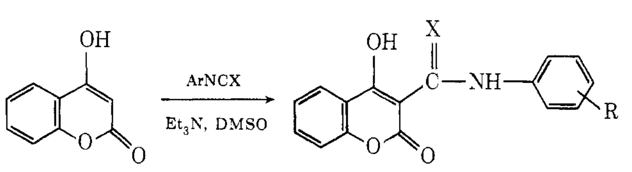
The formation of amides of 4-hydroxycoumarin-3-carboxylic acid has been well documented.[1-5] These methods

Scheme I



I

IIa, X = O; R = H
b, X = O; R = *p*-Cl
c, X = S; R = *p*-F

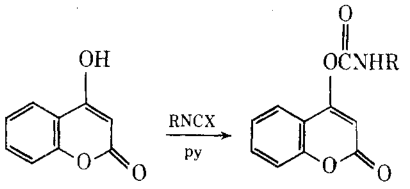
employ thermal activation in one form or another. The amides are formed by the thermal reaction of 4-hydroxycoumarin with isocyanates at 160°,[1-4] or by the reaction of 3-carbethoxy-4-hydroxycoumarin[5] in refluxing anilines.[2-4]

The room-temperature reaction of 4-hydroxycoumarin with aryl isocyanates or aryl isothiocyanates in DMSO containing triethylamine yields cleanly in one step the desired materials,[6] amides of 4-hydroxycoumarin-3-carboxylic acid. For example, 4-hydroxycoumarin and *p*-chlorophenyl isocyanate in DMSO (1 equiv of triethylamine) gave in 71% yield[7] 3-(*p*-chlorophenylcarbamoyl)-4-hydroxycoumarin (IIb, Scheme I), mp 218–220° (lit.[1,3] mp 219–221°). Similarly the reaction of 4-hydroxycoumarin with *p*-fluorophenyl isothiocyanate gave 3-(*p*-fluorophenylthiocarbamoyl)-4-hydroxycoumarin (IIc) in 82% yield[7] (Scheme I), mp 220–223°.[6]

This reaction is complete in 0.5–2 hr and is successful only with aryl isocyanates and isothiocyanates. Alkyl isocyanates and isothiocyanates yield some starting coumarin and polymeric materials. Those aryl isocyanates and isothiocyanates which have a limited solubility in DMSO (at room temperature) gave very poor yields.

The use of pyridine as a solvent yields urethanes. Thus 4-hydroxycoumarin and phenyl isocyanate in pyridine at room temperature gave 4-hydroxycoumarin, carbanilate (IIIa, Scheme II) in 60% yield, mp 210–213° (lit.[3] mp 206–209°).

Scheme II

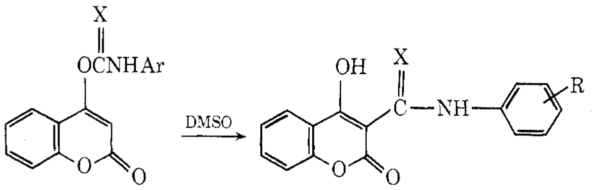


I

IIIa, R = Ph
b, R = *n*-Bu

This reaction was successful with both aryl and alkyl isocyanates and isothiocyanates. 4-Hydroxycoumarin and *n*-butyl isocyanate in pyridine gave 4-hydroxycoumarin *n*-butylcarbamate (IIIb), mp 168–171°. The aryl urethanes rearrange in DMSO (at room temperature) to the 3-carboxamides. Thus 4-hydroxycoumarin carbanilate is cleanly and quantitatively rearranged by overnight stirring in DMSO (containing several drops of triethylamine) to 3-phenylcarbamoyl-4-hydroxycoumarin (Scheme III, IIa), yield 100%, mp 215–216° (lit.[1-4] mp 219–221°). Likewise 4-hydroxycoumarin *m*-chlorocarbanilate yields 3-*m*-chlorophenylcarbamoyl-4-hydroxycoumarin (IId), yield 95%, mp 191–193° (lit.[1] mp 190–192°). Alkyl urethanes fail to give amides, instead yielding polymer-like materials.

Scheme III



III

IIa, X = O; R = H
d, X = O; R = *m*-Cl

Experimental Section

All commercial reagents were used as received and all solvents were dried over molecular sieves. Melting points are uncorrected.

3-Phenylcarbamoyl-4-hydroxycoumarin (IIa). 4-Hydroxycoumarin (5 g, 0.031 mol), triethylamine (3.1 g, 0.031 mol), and phenyl isocyanate (1 equiv), added in the listed sequence to 50 ml of dry DMSO, were stirred at room temperature for 2 hr. The solution was poured into 100 ml of 3 *N* HCl, and the solid was filtered, air dried, and recrystallized from acetone, giving 6.1 g (70%) of a white powder, mp 215–216° (lit.[1,3] mp 219–221°).

3-(*p*-Fluorophenylthiocarbamoyl)-4-hydroxycoumarin (IIc). The procedure described for IIa gave IIc in 82% yield, mp 220–223°.

Anal. Calcd for $C_{16}H_{10}FNO_3S$ (283.32): C, 60.94; H, 3.20; N, 4.44; S, 10.17; F, 6.03. Found: C, 60.69; H, 3.22; N, 4.50; S, 9.99; F, 5,80.

4-Hydroxycoumarin Carbanilate (IIIa). A solution of 5 g (0.031 mol) of 4-hydroxycoumarin in 50 ml of pyridine was treated in a dropwise fashion with 4 g (1 equiv) of phenyl isocyanate. After stirring for 3 hr at room temperature, the solution was poured into water, and the solid was collected, air dried, and recrystallized from chloroform–hexane, mp 210–212° (yield 5.6 g, 60%).

Rearrangement of Urethanes to Amides. A suspension of 250 mg of 4-hydroxycoumarin carbanilate in 5 ml of DMSO containing several drops of triethylamine was stirred overnight at room temperature. The solution was poured into 25 ml of 1 *N* HCl and the solid IIa was collected, mp 212–215° (250 mg, 100%). The spectral properties of the samples are identical with those of samples previously prepared.

Acknowledgment. We wish to acknowledge Mr. L. Brancone and staff for required microanalytical data, Mr. W. Fulmor, Mr. G. O. Morton, and coworkers for spectral information and interpretation, and Dr. G. Van Lear for his mass spectral considerations.

Registry No.—IIa, 14206-95-2; IIc, 50600-32-3; IIIa, 37982-58-4; 4-hydroxycoumarin, 1076-38-6; phenyl isocyanate, 103-71-9; *p*-fluorophenyl isothiocyanate, 1544-68-9.

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(6) All new materials had proper physical constants and correct elemental analyses.
(7) Isolated and recrystallized yields.

Product Evidence for an Enamine Mechanism in the Acid-Catalyzed Cleavage of β-Amino Alcohols. Independence of Mechanism on Nature of Acid[1]

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Two mechanisms have been suggested to explain the acid-catalyzed cleavage of α-aryl-β-amino alcohols to β-carbonyl compounds.[2-4] These mechanisms involve a gly-