Synthesis of Substituted Coumarins

References and Notes

7. Polythene bonded sugars have been described in: (a) B. Helferich and H. J. Hofmann, Chem. Ber., 85, 175 (1952); (b) B. Helferich and K.-H. Jung, Hoppe-Seyler's Z. Physiol. Chem., 311, 54 (1956).

References and Notes


Substituted Coumarins and Azacoumarins. Synthesis and Fluorescent Properties

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A number of new substituted 7-amino- and 8-aza-7-amino coumarins have been synthesized. Substituent effects on fluorescence properties (maxima and quantum yields) are reported. Substitution by fluorine in the 4-methyl position gives pronounced red shifts.

Recent synthesis programs in this laboratory have resulted in the preparation of a large number of substituted coumarins and azacoumarins for use as emission sources for dye laser applications. The effects of substituents on the lasing characteristics of these compounds have been reported. This report describes the synthesis of several new laser dyes and the effects of substituents on their fluorescence maxima and fluorescence quantum yields.

The new coumarin dyes prepared in the present work are shown below. Results are summarized in Table I. The syntheses led to several new results of chemical interest.

**Synthesis.** The preparation of 8-aza-7-hydroxy-4-methylcoumarin (3c) by the method of von Pechmann and ethyl acetoacetate gave in addition to the desired product small amounts of the bis addition product 10-aza-2,8-dioxo-4,6-dimethyl-2H,8H-benzo[1,2-b:5,4-b]dipyran (5) (detected by mass spectroscopy; M+ ion at m/e 249). Merchant and co-workers also noted the formation of trace amounts of a similar bis addition product in the reaction of ethyl acetoacetate with resorcinol. When the condensation of 2,6-dihydroxyprydine (4) is carried out in

![Chemical Structures](image-url)

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the presence of excess ethyl 4,4,4-trifluoroacetoacetate, 10-aza-2,8-dioxo-4,6-bis(trifluoromethyl)-5H,8H-benz[1,2-b;3,4-b]dipyran, (6), the bis addition compound, is the principal product (50% yield).

In the preparation of 7-amino-4-methylcoumarin (7) from ethyl acetoacetate and m-aminophenol, a second strongly fluorescing coumarin was isolated. This material had also been prepared by von Pechmann and was reported to be 2-keto-4,6,6,8-tetramethyl-6,7-dihydro-2H-pyrano[3,2-g]quinoline (10). This assignment is incorrect. The product exhibits a sharp absorption in the IR at 3310 cm⁻¹ indicative of the secondary amine moiety. The ¹H-NMR spectrum (see Experimental Section) which eliminates 10 does not allow a definitive choice between 8 and 9. NMR analysis employing the shift reagent Eu(fod)₃ which associates with the carbonyl oxygen made possible the assignment of all proton absorptions. However,
**Table II. Reaction of β-Ketoesters with m-Aminophenol and 6-Amino-2-pyridinol**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>X</th>
<th>R</th>
<th>R'</th>
<th>Reaction conditions</th>
<th>Coumarin (A) No. (%)</th>
<th>Quinolone (B) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>C</td>
<td>CH₃</td>
<td>CH₃</td>
<td>Neat</td>
<td>11 (46)</td>
<td>12 (trace)</td>
</tr>
<tr>
<td>(2)</td>
<td>C</td>
<td>CH₃</td>
<td>H</td>
<td>Neat</td>
<td>7 (trace)</td>
<td>13 (60)</td>
</tr>
<tr>
<td>(3)</td>
<td>C</td>
<td>CF₃</td>
<td>H</td>
<td>Neat</td>
<td>14 (major)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>(4)</td>
<td>C</td>
<td>CH₂</td>
<td>H</td>
<td>ZnCl₂/EtOH</td>
<td>7 (16)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>(5)</td>
<td>C</td>
<td>CF₂</td>
<td>H</td>
<td>ZnCl₂/EtOH</td>
<td>14 (42)</td>
<td>15 (trace)</td>
</tr>
<tr>
<td>(6)</td>
<td>N</td>
<td>CF₃</td>
<td>H</td>
<td>Neat</td>
<td>16 (61)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>(7)</td>
<td>N</td>
<td>CH₃</td>
<td>CH₃</td>
<td>Neat</td>
<td>18 (major)</td>
<td>19 (20)</td>
</tr>
</tbody>
</table>

a choice between 8 and 9 still could not be made since the geminal dimethyl group and vinylmethyl (the 6-methyl in 8 or the 8-methyl in 9) are essentially equidistant from the site of Eu(fod)₃ association.

Measurement of the nuclear Overhauser effect enhancements of the ring protons proved definitive. Saturation of the geminal dimethyl resonance resulted in the enhancement of the N–H integral and the dihydro ring vinyl proton integrals. Saturation of the 4-methyl absorption revealed enhancement of H-3 and H-5, while saturation of the dihydro ring vinyl methyl absorption resulted in observation of enhanced absorption of H-5 and the dihydro ring vinyl hydrogen. These data are consistent only with structure 8.

Product 8 is most likely formed by the Michael-type addition of the intermediate 7-amino-4-methylcoumarin (7) to mesityl oxide. The mesityl oxide most likely is formed under the reaction conditions employed from acetone (the acetone derived by retrogression from ethyl acetoacetate). Knoevenagel has reported a similar 1,4-Michael addition of aniline to mesityl oxide (formed in situ from acetone) giving 1,2-dihydro-2,2,4-trimethylquinoline. This mechanistic path is further supported by the reaction of mesityl oxide with 7 to yield 8.

A convenient method for preparation of coumarins and quinolones is to omit catalyst and solvent and simply heat the precursor aminophenol with the β-keto ester. This method, however, can lead to mixtures of coumarins and quinolones. While the reaction is regiospecific in that ring formation is ortho to the reacting functional group and para to the second giving 7-substituted products, no 5-substituted products are obtained, it is noneselective with respect to the functional groups.

Several examples illustrate this reaction feature (Table II). When m-aminophenol is heated in the presence of ethyl 2-methylacetoacetate, Table II, reaction 1, the major product is 7-amino-2,3-dimethylcoumarin (11) formed in 46% yield. A trace amount of the isomeric 7-hydroxy-2,3-dimethylquinolone (12) was isolated from the base-soluble extract of the reaction mixture. However, when m-aminophenol is heated in the presence of an equimolar amount of ethyl acetocetate, the only isolable addition product is 7-hydroxy-4-methylquinolone (13). Only a trace amount of coumarin 7 (detected by TLC analysis of the reaction mixture) was formed.

When the condensation of m-aminophenol and ethyl 4,4,4-trifluoroacetoacetate is carried out in absolute ethanol at reflux in the presence of anhydrous zinc chloride (von Pechmann conditions) the addition occurs at the hydroxyl group giving 14. Only a trace of quinolone is observed (Table II, reaction 5). Evidently the zinc chloride complexes with the amino group and thus facilitates condensation via the hydroxyl group. However, when the condensation of m-aminophenol with ethyl 4,4,4-trifluoroacetoacetate is carried out in the absence of solvent (Table II, reaction 3), the major product is the coumarin 14. A 10% yield of quinolone 15 was recovered from the base-soluble extract.

Similar results are obtained with 6-amino-2-pyridinol (20). When 20 is heated in the presence of ethyl 4,4,4-trifluoroacetoacetate a 76% yield of addition products is obtained giving approximately a 4:1 ratio of quinolone to coumarin. Table II, reaction 6. A similar product distribution is realized when 20 is allowed to react with ethyl 2-methylacetoacetate, Table II, reaction 7.

Since reaction of 20 with β-keto esters gives mixtures of quinolones and coumarins, it was necessary to modify the reaction sequence in order to obtain pure 7-aminocoumarins in good yields. This was accomplished by first deactivating the amino substituent through formation of its urethane derivative. Reaction of this intermediate gives exclusively the coumarin derivative (Scheme I). The free amino compound is then liberated by mild acid hydrolysis.

While urethane derivative 21 gave reasonable yields of coumarin upon reaction with β-keto esters, 6-acetamido-2-

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**Figure:**

![Chemical structure](attachment:image.png)

**Reaction Conditions:**

- Neat
- ZnCl₂/EtOH
- Hático/EtOH
- Reaction Conditions 1
- Reaction Conditions 2
- Reaction Conditions 3

**Yield:**

- 11 (46%)
- 7 (trace)
- 14 (major)
- 7 (16)
- 14 (42)
- 16 (61)
- 18 (major)
pyridinol (23) fails to give the desired product. Prolonged heating of 2b in the presence of excess methyl acetocetate resulted in the recovery of starting material.

A convenient procedure for the methylation of functional groups (amino, hydroxyl, amide) in these systems has been developed. Where other procedures such as reductive methylation with sodium cyanoborohydride or hydrogen (platinum catalyst) failed, simply heating the precursor in the presence of dimethyl sulfate in 2b. Similar shifts are observed in other pairs, Le., la-b, 1978. Fluorescence maxima at 537 nm. The alkylation seems to give a predictable pattern. Compounds 2b and 2d for example both exhibit large shifts in these compounds and do not seem to follow a predictable pattern. The fluorinated bis adduct lc-d. The red shift is not of the same magnitude in the azacoumarin series the quantum yields are less than in the carbon series, diminished quantum yield of fluorescence. In the azacoumarin coumarins all exhibit pronounced hypsochromic shifts when substitution by fluorine at the 4-methyl position results in a red shift of 53 nm is obtained with 3d compared to 2a. X = N. R = CH,

Varying the substituent in the 7 position does not result in large shifts in these compounds and does not seem to follow a predictable pattern. Compounds 2b and 2d for example both have fluorescence maxima at 537 nm. The alkylation seemingly has no effect. However, compound 1a exhibits a red shift of 8 nm upon methylation of the nitrogen to give 1e, and methylation of 2a results in a 13-nm red shift in 2b. The azacoumarins all exhibit pronounced hyposchromic shifts when compared to their carbon analogues.

The quantum yields of fluorescence are generally high for the substituted 7-amino-4-methylcoumarins. In all cases substitution by fluorine at the 4-methyl position results in a diminished quantum yield of fluorescence. In the azacoumarin series the quantum yields are less than in the carbon series, and again substitution of fluorine in the 4-methyl group lowers the quantum yield still further, i.e., compounds 3e and 3d.

These factors work in concert in the 4-trifluoromethyl-8-azacoumarins and these compounds exhibit low quantum yields of fluorescence. The fluorinated bis adduct 6 shows very poor fluorescence and at liquid nitrogen temperature in absolute ethanol exhibits strong phosphorescence. To the contrary, the pseudo-bis adduct 8 fluoresces strongly at 470 nm with high stability and exhibits lasing action over a 25-30 range (455-480 nm). Surprisingly, 8 also shows strong phosphorescence in ethanol at liquid nitrogen temperature indicating efficient intersystem crossing to the triplet state, a process generally regarded to be highly deleterious to laser.

Experimental Section

Proton and 13C-NMR spectra were obtained with a Varian XL-100 FT spectrometer and are referenced to tetramethylsilane as an internal standard. IR spectra (KBr discs) were obtained with a Perkin-Elmer 157 spectrometer. UV absorbance data were measured on a Cary-14 spectrophotometer. Fluorescence spectra and quantum yields were determined using a Turner Model 210 spectrophotofluorometer utilizing quinine sulfate as a quantum yield standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

7-Hydroxynolyquinoline (23). This compound was prepared from m-aminophenol via the Skraup quinoline synthesis using the procedure of Bradford et al. 16

7-Hydroxy-1,2,3,4-tetrahydroquinoline (24). 7-Hydroxyquinoline (4.0 g, 27.6 mmol) and Pd(O)2 (0.3 g) were suspended in 150 mL of 95% ethanol containing 1 mL of concentrated HCl. Hydrogenation over a palladium apparatus, room temperature, 50 lb H2 pressure, 14-16 h until the theoretical amount of H2 was absorbed (4 h). Filtration and concentration gave 5.04 g of red oil. Water (50 mL) was added and the resulting suspension was made basic (dilute NH4OH). Extraction with ether (4 x 75 mL), drying (CaCl2), and concentration gave 3.5 g of oil (90%) which solidified upon standing (mp 78-80 °C). NMR (CDCl3) δ 1.8-2.4 (m, 2H, CH2-CH2), 2.76 (t, 2, J = 7 Hz, NCH2CH3), 3.38 (t, 2, J = 6 Hz, CH2CH2Ar), 4.8 (bs, 2, OH and NH), 6.16 (d, Jpara = 2 Hz, H-6), 6.35 (d of d, 1, Jpara = 2 Hz, Jortho = 8 Hz, H-5), 7.05 (d, Jpara = 2 Hz, Jortho = 8 Hz, H-6). In subsequent preparations the HCI was omitted. While the hydrogenation generally took two or three times longer, the product (obtained in quantitative yield) was of sufficient purity for use without further purification.

2-Keto-4-methyl-6,7,8,9-tetrahydro-2H-pyrano[3,2-g]quinoline (la). Ethyl acetocetate (7.78 g, 60 mmol), 24 (7.9 g, 53 mmol), and anhydrous zinc chloride (11 g, 80 mmol) were added to absolute ethanol (410 mL). The resulting mixture was heated at reflux 14 h. A yellow solid had precipitated. More solid was deposited upon cooling to room temperature. Filtration gave 5.62 g. Pouring the mother liquors into ice water (100 mL) yielded an additional 0.75 g of yellow solid. The crude yield was 55%. Two recrystallizations from ethanol gave yellow needles, mp 236-238 °C; NMR (MeSO-d6): 6 2.78 (m, 2, CH2-CH2), 2.30 (t, 3, 4-Me), 2.23 (t, 2, J = 6.2 Hz, CH2-CH2Ar), 3.23 (t, 2, J = 6 Hz, CH2-CH2Ar), 4.8 (bs, 2, OH and NH), 6.16 (d, Jpara = 2 Hz, H-6), 6.35 (d of d, 1, Jpar = 2 Hz, Jortho = 8 Hz, H-5), 7.05 (d, Jpara = 2 Hz, Jortho = 8 Hz, H-6). In subsequent preparations the HCl was omitted. While the hydrogenation generally took two or three times longer, the product (obtained in quantitative yield) was of sufficient purity for use without further purification.

2-Keto-4,9-dimethyl-6,7,8,9-tetrahydro-2H-pyrano[3,2-g]quinoline (1e). Trichloromethane (1.0 g, 71 mmol) and 1a (1.0 g, 4.65 mmol) were heated in an oil bath at 200 °C for 30 min. The resulting dark oil set to a solid mass upon standing (mp 197-198 °C): NMR (CDCl3) δ 1.64-1.88 (m, 2, CH2-CH2Ar), 2.62 (t, 2, J = 6 Hz, CH2CH2Ar), 3.23 (t, 2, J = 6 Hz, NCH2CH3), 6.23 (bs, 2, C-5 and C-8), 7.06 (bs, 1, H-3), 8.15 (s, 1, H-5), 6.81 (bs, 1, N-H), 7.21 (s, 1, H-10): IR: 3125 cm-1 (N-H); 1710 cm-1 (C=O) (CDCl3).

2-Keto-4,9-dimethyl-6,7,8,9-tetrahydro-2H-pyrano[3,2-g]quinoline (1e). Trichloromethane (1.0 g, 71 mmol) and 1a (1.0 g, 4.65 mmol) were heated in an oil bath at 200 °C for 30 min. The resulting dark oil set to a solid mass upon standing (mp 197-198 °C): NMR (CDCl3) δ 1.64-1.88 (m, 2, CH2-CH2Ar), 2.62 (t, 2, J = 6 Hz, CH2CH2Ar), 3.23 (t, 2, J = 6 Hz, NCH2CH3), 6.23 (bs, 2, C-5 and C-8), 7.06 (bs, 1, H-3), 8.15 (s, 1, H-5), 6.81 (bs, 1, N-H), 7.21 (s, 1, H-10): IR: 3125 cm-1 (N-H); 1710 cm-1 (C=O) (CDCl3).
Synthesis of Substituted Coumarins


taining 6 mL of concentrated HCl was hydrogenated in the presence of PtO (0.5 g) in a Parr apparatus (room temperature, 50 lb H2) until the theoretical amount of Hz was absorbed. Filtration and concentration gave a dark oil. Water (100 mL) was added and the resulting solution was neutralized by addition of 1 N NaOH (70 mL). The solution was made basic with ether (25 mL). Filtration and concentration gave 5 g of a brown oily solid. The brown solid was washed with CHCl3 (100 mL) and dried to give 4.8 g of a tan solid (mp 110–12°C; IR 3180 cm⁻¹ (N-H), NMR (CDCl3) δ 6.92 (m, 2, CH2-CH2), 2.65 (6, 2, J = 7 Hz, NCH2CH2), 3.08 (t, 2, J = 7.5 Hz, CH2-CH2), 4.76 (m, 2, CH2-CH2), 5.60 (s, 1, J = 9 Hz, H-5), 7.53 (m, 2, CH2-CH2), 6.78 (d, 1, J = 8 Hz, H-7); Anal. Calcd for C13H13N04: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.95; H, 5.29; N, 5.65.

7-Amino-4-methylcoumarin (7). 7-Butyryloxycarbonyl-4-methylcoumarin (7, 7.0 g, 28 mmol) was heated at reflux 4 h in 25 g of concentrated H2SO4 to decolorize and dry (0.2 g) precipitate was deposited. The mixture was poured into 100 mL of ice water and let stand overnight. The resulting suspension was made slightly basic with 50% NaOH with cooling by addition of ice chips. The yellow precipitate was filtered, washed, and dried to give 7.5 g of a yellow solid (mp 250–252°C (lit.38 mp 223°C).

2-Chloro-4-hydroxy-3-dimethylamino-6-methylcoumarin (2a). Ethyl chloroacetate (6.63 g, 36 mmol), 23 (6.36 g, 36 mmol), and absolute ethanol (75 mL) were heated at reflux for 20 h (dry Na2SO4). The cooled solution was concentrated, taken up in 75 mL of CHCl3, washed with 1 N NaOH (2 × 50 mL) and water (50 mL), and dried (MgSO4). Filtration and concentration gave 4.0 g of yellow solid, mp 157–160°C; IR 3310 (NH), 1710 cm⁻¹ (C=O); NMR (CDCl3) δ 2.33 (s, 3, Me2), 6.12 (d, 1, J = 9 Hz, H-6), 7.38 (d, 1, J = 9 Hz, H-5), 7.48 (s, 1, J = 9 Hz, H-3); MS (FAB) m/z 281 (M+); IR NH absent.

2-Thiophene-2-carboxaldehyde (26). Ethyl chloroacetate (6.63 g, 36 mmol) was added and evaporated to dryness. The residue was treated with 1 N NaOH (2 × 50 mL) and water (50 mL) and dried (MgSO4). Filtration and concentration gave 4.0 g of yellow solid, mp 157–160°C; IR 3310 (NH), 1710 cm⁻¹ (C=O); NMR (CDCl3) δ 2.33 (s, 3, Me2), 6.12 (d, 1, J = 9 Hz, H-6), 7.38 (d, 1, J = 9 Hz, H-5), 7.48 (s, 1, J = 9 Hz, H-3); MS (FAB) m/z 281 (M+); IR NH absent.

2-Azido-4-hydroxy-3-dimethylamino-6-methylcoumarin (3c). Ethyl chloroacetate (4.55 g, 27.5 mmol) and 26 (5.0 g, 27.5 mmol) were mixed and heated at 130°C for 1 h in 400 mL of diethyl ether. The hydrochloride was dissolved in 400 mL of dry tetrahydrofuran containing 10 g (100 mmol) of triethylamine. Filtration of the reaction mixture gave 12.5 g of a grey solid which was identified as a mixture of triethylamine hydrochloride and unreacted 2-amino-6-hydroxy-3-carbonylpyridine by TLC. Evaporation of the mother liquors gave 7.5 g (73%) of small colorless needles (mp 70–72°C) which darkened appreciably upon exposure to light: IR 3436 (NH), 1724 cm⁻¹ (C=O); NMR (CDCl3) δ 2.04 (m, 2, CH2-CH2), 2.92 (t, 2, J = 7 Hz, NCH2CH2), 3.22 (t, 2, J = 7 Hz, NCH2CH2), 6.44 (s, 1, J = 9 Hz, H-5), 7.38 (s, 1, J = 9 Hz, H-3); MS (FAB) m/z 281 (M+); IR NH absent.
Table III. NOE Enhancement Factors

<table>
<thead>
<tr>
<th>Saturated group</th>
<th>H-5</th>
<th>N-H</th>
<th>H-10</th>
<th>H-3</th>
<th>H-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geminal dimethyl</td>
<td>1.00</td>
<td>1.16</td>
<td>1.00</td>
<td>0.95</td>
<td>1.23</td>
</tr>
<tr>
<td>6-Me</td>
<td>1.19</td>
<td>1.04</td>
<td>0.92</td>
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<tr>
<td>4-Me</td>
<td>1.34</td>
<td>0.97</td>
<td>0.97</td>
<td>1.54</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* The enhancement ratio was determined from the ratio of the integral obtained with the secondary irradiation frequency on to the integral obtained with the secondary irradiation frequency off, both values being the average value obtained for at least five integrations.

8-Aza-4-methyl-7-morpholinocoumarin (3c). Ethyl acetocacetate (5.1 g, 40 mmol) and 27 (2.0 g, 11 mmol) were mixed and heated at 170 °C (oil bath) for 16 h. The pyridinol hadStarting from 6-amino-2-pyridinol.

6-Acetamido-2-pyridinol (30).

2,6-Dihydroxypyridine (4). 2,6-Dihydroxypyridine hydrochloride (31).

10-Aza-2,8-dioxo-4,6-bis(trifluoromethyl)-2'H,8'H-benzo-1,2,6-triazine (4).

10-Aza-2,8-dioxo-4,6-bis(trifluoromethyl)-2'H,8'H-benzo-

References and Notes

12. Experiment was performed by Dr. R. A. Henry of this Laboratory. Details are available in the Naval Weapons Center Technical Publications 5768, Part 1, September 1973.