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By the action of 2-aminothiazole, 2-aminopyridines, and 2-aminopyrimidines, respectively, on 4-chloro-3-nitrocoumarin (**3**) the corresponding 4-heteroarylamino-3-nitrocoumarins **5-7** have been isolated in very good yields. Reactions of coumarins **6** and **7** with either aqueous tetrabutylammonium bisulfate/sodium hydroxide in a two phase system or 5% aqueous sodium hydroxide have been studied.

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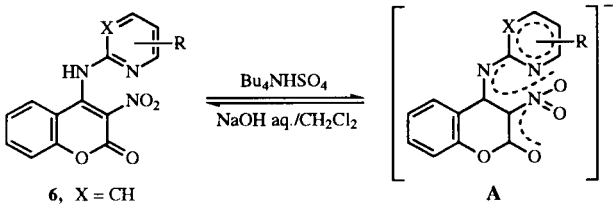
In continuation of our work on the chemistry of 3,4-disubstituted coumarins and the derived coumarins annelated in the 3,4-position [1] we decided to prepare some 4-heteroarylamino-3-nitrocoumarins and to investigate the possibilities of their intramolecular cyclization.

By nitration of 4-hydroxycoumarin (**1**) we have prepared 4-hydroxy-3-nitrocoumarin (**2**) [2], which was converted to 4-chloro-3-nitrocoumarin (**3**) [3] and to 3-nitro-4-tosyloxycoumarin (**4**). Nucleophylic substitution of **3** and **4** by 2-aminothiazole, 2-aminopyridines, and 2-aminopyrimidines, respectively, has given the corresponding 4-heteroarylamino-3-nitrocoumarins **5-7** in good yields.

In one of our previous papers [4] alkylation of a number of 4-arylaminocoumarins in aqueous sodium hydroxide solution and quaternary ammonium salts as catalysts has been described. In spite of the ambident nature of the intermediate anions in these phase transfer catalyzed reactions [5] exclusively 3-alkylation was observed.

Having in mind these results we supposed that the action of 25% aqueous sodium hydroxide and tertrabutylammonium bisulphate on solutions of coumarins **6** and **7** in dichloromethane should give the similar anions **A**, additionally stabilized by the resonance effects of the nitro group and the ring nitrogen atoms.

Scheme 1



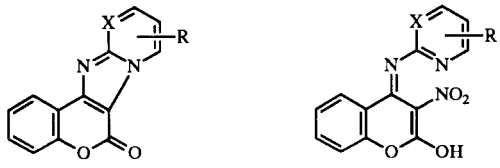

**6**, X = CH
**7**, X = N

**A**

The acidity of the amino group of aniline is strongly increased by the influence of an *o*-nitro group [p$K_a$, aniline = 27; p$K_a$ *o*-nitroaniline ≈ 19]. Anions thus formed could then be transformed in an intramolecular nucleophilic process into the desired systems **B**.

However, instead of the expected annelation in the experiments described, we have obtained compounds which gave combustion analyses similar to the starting products. On the basis of spectral analysis one can suppose that aqueous tetrabutylammonium bisulfate/sodium hydroxide promoted partial tautomerization of coumarins **6** and **7** to the corresponding chromenes **8** and **9**, respectively. The ir spectra of the starting coumarins contained strong stretching vibrations of the NH group in the 3220-3315 region and only weak absorptions at 3410-3440 $cm^{-1}$. The compounds obtained are characterized by broad ir bands at 3400-3460 $cm^{-1}$ (ν OH) and very weak ν NH bands indicating chromene structures. As one can expects the $^1H$ nmr spectra of both types of compounds are similar with the exception of the chemical shifts corresponding to the H-5 protons which are influenced differently by the neighboring amino and imino groups. The chromene structure of these compounds is also confirmed by conversion of **8e** to its methoxyl derivative **10**, whose $^1H$ nmr spectrum contained a sharp singlet at δ 3.90 corresponding to the protons of the methoxyl group.

Scheme 2




**B**

**8**, X = CH
**9**, X = N

To complete our findings about this tautomerization, coumarins⇌ chromenes by aqueous tetrabutylammonium bisulfate/sodium hydroxide in a two phase system, we have explored the reaction of the compounds investigated with 5% aqueous sodium hydroxide. It is known from the literature [6] that 4-hydroxy-3-nitrocoumarin (**2**) in alkaline medium hydrolyzes and decarboxylates giving 2-hydroxy-ω-nitroacetophenone (**11**). The same compound was isolated in reactions of either coumarins **6**, **7** or chromenes **8**, **9** with 5% sodium hydroxide at room temperature for 5 minutes. 4-Hydroxycoumarin and 3-amino-4-hydroxycoumarin [7] are stable even by heating in alkaline medium. Apparently, the nitro group at position 3 influenced this decomposition. The hydrolysis

Table 1

Physical and Analytical Data of Compounds **6** and **8**

| Compound | R | Yield (%) | Mp (°C) | Formula (MW) | Analysis Calcd./Found (%) C | H | N |
|---|---|---|---|---|---|---|---|
| **6a** | H | 78 | 224-225 | $C_{14}H_9N_3O_4$ | 59.37 | 3.20 | 14.83 |
| | | | | (283.2) | 59.39 | 3.18 | 15.07 |
| **6b** | 3'-$CH_3$ | 76 | 227-229 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 60.32 | 3.59 | 14.19 |
| **6c** | 4'-$CH_3$ | 84 | 243-244 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 60.67 | 3.87 | 14.20 |
| **6d** | 5'-$CH_3$ | 76 | 225-226 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 61.00 | 3.81 | 14.09 |
| **6e** | 6'-$CH_3$ | 92 | 250-252 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 60.58 | 3.57 | 14.08 |
| **8b** | 3'-$CH_3$ | — | 245-246 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 60.37 | 3.91 | 13.98 |
| **8c** | 4'-$CH_3$ | — | 250-252 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 60.90 | 3.91 | 14.32 |
| **8d** | 5'-$CH_3$ | — | 233-234 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 61.12 | 3.91 | 13.91 |
| **8e** | 6'-$CH_3$ | — | 274-275 | $C_{15}H_{11}N_3O_4$ | 60.60 | 3.73 | 14.14 |
| | | | | (297.3) | 60.87 | 3.85 | 14.22 |

Table 2

IR and $^1H$ NMR Data of Compounds **6** and **8**

| Compound | IR ($cm^{-1}$) ν OH | ν NH | ν $CH_3$ | ν C=O (ν C=N) | ν C=C | $^1H$ NMR (δ) H-5 | H-6' | H-7 | H-4' | H-6 | H-8 | H-3' | H-5' | $CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **6a** | — | 3280 s | — | 1685 s | 1590 s | 8.40.....8.12 (m, 2) | | 7.87.....7.66 (m, 2) | | 4.50.....7.28 (m, 2) | | 7.27.....6.96 (m, 2) | | — |
| **6b** | 3420 sh | 3260 s | 2920 w | 1665 s | 1590 s | 8.35 (d, 1) | 8.03 (d, 1) | 7.93 (m,2) | 7.56 | 7.44 (t,2) | | — | 7.13 (t, 1) | 2.29 (s, 3) |
| **6c** | 3410 sh | 3290 s | 2920 w | 1692 s | 1595 s | 8.31 (dd, 1) | 8.02 (d, 1) | 7.71 (m, 1) | — | 7.47 (t, 2) | | 6.99 (s, 1) | 6.94 (d, 1) | 2.33 (s, 3) |
| **6d** | 3410 sh | 3260 s | 3910 w | 1680 s | 1600 s | 8.31 (dd, 1) | 8.00 (s, 1) | 7.26 (td, 2) | | 7.53 (t, 2) | | 7.16 (d, 1) | — | 2.26 (s, 3) |
| **6e** | 3440 sh | 3300 s | 2920 w | 1690 s | 1605 s | 8.36 (d, 1) | — | 7.77 (t, 2) | | 7.48 (t, 2) | | 7.00 (t, 2) | | 2.35 (s, 3) |
| **8b** | 3460 b | 3200 sh | 2950 w | 1665 b | 1600 s | 8.26 (dd, 1) | 7.81 (dd, 1) | 8.25.....7.35 (m, 2) | | 7.14 (t, 2) | | — | 6.62 (m, 1) | 2.15 (s, 3) |
| **8c** | 3410 b | 3300 w | 2960 w | 1675 b | 1600 s | 8.22 (dd, 1) | 7.99 (d, 1) | 7.73 (td, 1) | — | 7.43 (tt, 2) | | 6.94 (dd, 2) | | 2.33 (s, 3) |
| **8d** | 3400 b | 3300 sh | 2920 w | 1655 b | 1600 s | 8.21 (dd, 1) | 7.85 (d, 1) | 7.45.....7.35 (m, 2) | | 7.15 (t, 2) | | 6.64 (d, 1) | — | 2.16 (s, 3) |
| **8e** | 3410 b | 3310 w | 2940 s | 1665 s | 1596 s | 8.24 (dd, 1) | — | 7.53 (m, 2) | 7.30 | 7.15 (t, 2) | | 6.53 (d, 2) | | 2.21 (s, 3) |

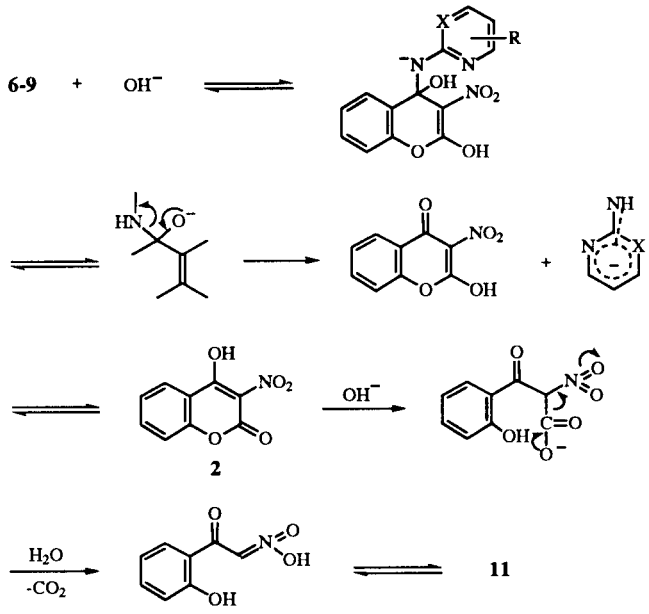
Table 3

Antimicrobial Activity of Coumarins **6** and **7** (inhibition zones/mm)

| Microorganism | *Staphylococcus aureus* 4487 | | | *Escherichia coli* 15 | | | *Candida albicans* 4088 | | | *Candida albicans* 4079 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound (No./μg) | 50 | 100 | 150 | 50 | 100 | 150 | 50 | 100 | 150 | 50 | 100 | 150 |
| **6a** | 0 | 9.8 | 9.9 | 0 | 16.1 | 20.0 | 10.9 | 12.7 | 18.3 | 13.8 | 15.9 | 23.4 |
| **6c** | 0 | 8.3 | 12.9 | 0 | 18.9 | 20.2 | 0 | 0 | 14.0 | 0 | 0 | 18.1 |
| **6d** | 0 | 0 | 0 | 0 | 18.6 | 19.1 | 14.2 | 18.4 | 23.8 | 11.9 | 17.3 | 23.5 |
| **6e** | 0 | 0 | 0 | 0 | 12.0 | 20.2 | 0 | 9.8 | 18.8 | 0 | 0 | 19.9 |
| **7a** | 0 | 0 | 0 | 0 | 14.3 | 18.7 | 0 | 0 | 15.8 | 0 | 10.7 | 19.9 |

of enamines in either alkaline or acidic medium proceeds *via* imines [8]. One can suppose a similar mechanism for the conversions described in which the imino group of the chromenes (generated in the coumarin-chromene equilibrium) has been attacked by an hydroxide anion giving the addition product, which by liberation of the resonance stabilized 2-pyridyl- and 2-pyrimidinylamido ions was converted to 4-hydroxy-3-nitrocoumarin (**2**). This intermediate can be easily hydrolyzed and decarboxylated by participation of the nitro group to the acetophenone **11**.

Scheme 3



An alternative mechanism in which the pyran ring of **6-9** has been cleaved first and thereafter the intermediate Schiff base hydrolyzed to **11** can be proposed.

It has been demonstrated that some of the coumarins **6** and **7** exhibited antimicrobial activity.

## EXPERIMENTAL

General Information.

The melting points were determined on a Reichert Thermovar BT 11 apparatus and are uncorrected. The ir spectra (ν/cm$^{-1}$) were recorded as potassium bromide pellets on a Perkin-Elmer 257 Grating Infrared Spectrophotometer. The $^1$H nmr spectra (δ values; DMSO-$d_6$ solutions) were recorded on a JEOL FT 90Q Spectrometer with tetramethylsilane as the internal standard. Mass spectra were determined on a Shimadzu GCNS-QP 1000 spectrometer (70 eV).

4-Hydroxycoumarin (**1**) has been nitrated to give 84% of 4-hydroxy-3-nitrocoumarin (**2**) [2], which was converted by the action of phosphorus oxychloride to 4-chloro-3-nitrocoumarin (**3**) (97%) [3]. Compound **2** was converted to 3-nitro-4-tosyloxycoumarin (**4**) (96%), mp (ethanol) 132-133°.

3-Nitro-4-(2-thiazolylaminocoumarin) (**5**).

Procedure A.

A solution of 1.00 g (0.044 mole) of 4-chloro-3-nitrocoumarin (**3**) and 0.44 g (0.044 mole) of 2-aminothiazole in 30 ml of absolute ethanol under argon was mechanically stirred over a period of 25 minutes, and thereafter 1 ml of triethylamine was added. The reaction mixture was refluxed for 6 hours. Yellow crystals separated. The precipitate was filtered, washed with ethanol and crystallized from aqueous ethanol (1:1 v/v) to yield 1.00 g (78%) of **5**, mp 200-202°; ir: 3340 s, 3270 s (ν NH), 1690 vs (ν C=O), 1620 s cm$^{-1}$ (ν C=C); $^1$H nmr: δ 8.82 (b, 1, NH), 8.01 (dd, 1, H-5), 7.63 (td, 1, H-7), 7.31 (m, 3, H-6, H-8, H-4'), 7.03 (m, 1, H-3').

*Anal.* Calcd. for $C_{12}H_7N_3O_4S$: C, 49.83; H, 2.44; N, 14.53. Found: C, 50.01; H, 2.62; N, 14.20.

Procedure B.

A solution of equimolar amounts of **4** and 2-aminothiazole in dimethyl sulfoxide was heated at 60° for 4-5 hours. The reaction mixture was cooled and poured into ice water. The crystals which separated were filtered and crystallized from aqueous ethanol giving 75% of coumarin **5** exhibiting the same mp and ir spectrum as sample prepared under procedure A.

General Procedure for Preparation of 3-Nitro-4-(2-pyridylamino)coumarins **6a-6e**.

A solution of 1.00 g (0.044 mole) of 4-chloro-3-nitrocoumarin (**3**) and 0.044 mole of the appropriate 2-aminopyridine in 25-30 ml of acetonitrile with 1 ml of triethylamine was refluxed over a period of 3-4 hours. The precipitate which separated was filtered from the hot reaction mixture, washed with acetonitrile, dried in air and crystallized from *N,N*-dimethylformamide (Tables 1 and 2); ms: m/z (relative intensity) **6b**: 251 (M-$NO_2$, 23.8), 236 (5.9), 223 (12.6), 195 (6.2), 185 (6.2), 142 (100.0); **6d**: 251 (M-$NO_2$, 26.0), 236 (5.7), 223 (28.3), 211 (5.7), 195 (10.0), 185 (6.4), 142 (100.0).

3-Nitro-4-(2-pyrimidinylamino)coumarin (**7a**) and 3-Nitro-4-(4,6-dimethyl-2-pyrimidinylamino)coumarin (**7b**).

In a similar manner as described for preparation of compounds **6** reaction of equimolar amounts of 4-chloro-3-nitrocoumarin (**3**) and either 2-aminopyrimidine or 4,6-dimethyl-2-aminopyrimidine with a catalytic amount of triethylamine after refluxing for 6-10 hours gave compounds **7**.

Compound **7a** had mp 178-180° (ethanol, 64%); ir: 3420 w (ν OH assoc), 3220 w (ν NH), 1720 s (ν C=O), 1600 s cm$^{-1}$ (ν C=C); $^1$H nmr: δ 8.64 (d, 2, H-4', H-6'), 8.34 (dd, 1, H-5), 7.80 (m, 1, H-7), 7.50 (m, 2, H-6, H-8), 7.14 (t, 1, H-5').

*Anal.* Calcd. for $C_{13}H_8N_4O_4$: C, 54.92; H, 2.84; N, 19.71. Found: C, 54.79; H, 2.90; N, 19.34.

Compound **7b** had mp 243-245° (ethanol, 62%); ir: 3415 w (ν OH assoc), 3315 (ν NH), 2920 w (ν C-H, $CH_3$), 1755 s (ν C=O), 1595 s cm$^{-1}$ (ν C=C); $^1$H nmr: δ 8.38 (dd, 1, H-5), 7.79 (td, 1, H-7), 7.44 (tt, 2, H-6, H-8), 6.90 (s, 1, H-5'), 2.36 (s, 6, $CH_3$).

*Anal.* Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.68; H, 3.88; N, 17.94. Found: C, 57.43; H, 4.02; N, 17.89.

2-Hydroxy-3-nitro-4-(2-pyridylimino)-4*H*-chromenes **8b-8e**.

To a solution of 0.016 mole of 3-nitro-4-(2-pyridylamino)coumarin **8b-8e** in 30 ml of dichloromethane, 25 ml of 25% aqueous sodium hydroxide and 0.1 g of tetrabutylammonium

bisulphate were added. The reaction mixture was mechanically stirred vigorously for 2-3 hours at 25-40°. After cooling, the organic layer was separated, dried over magnesium sulphate and evaporated to dryness (Tables 1 and 2); ms: m/z (relative intensity) **8b**: 251 (M-$NO_2$, 100), 236 (2.4), 223 (10.0), 206 (10.6), 195 (9.9), 193 (19.6); **8d**: 251 (M-$NO_2$, 100), 236 (3.0), 223 (13.7), 206 (6.9), 195 (13.5).

2-Hydroxy-3-nitro-4-(2-pyrimidinylimino)-4*H*-chromene (**9a**) and 2-Hydroxy-3-nitro-4-(4,6-dimethyl-2-pyrimidinylimino)-4*H*-chromene (**9b**).

In a similar manner to that described for the preparation of compounds **8** by the action of 25% sodium hydroxide and tetrabutylammonium bisulphate in dichloromethane solution of either **7a** or **7b** chromenes **9a** and **9b** were obtained.

Compound **9a** had mp 80-82° (93%); ir: 3420 b (ν OH assoc), 3250 sh (ν NH), 1730 s (ν C=O), 1592 s $cm^{-1}$ (ν C=C); $^1H$ nmr: δ 8.37 (d, 2, H-4', H-6'), 8.25 (dd, 1, H-5), 7.41 (td, 1, H-7), 7.18 (td, 2, H-6, H-8), 6.69 (t, 1, H-5'), 11.35 (m, 1, OH).

*Anal.* Calcd.for $C_{13}H_8N_4O_4$: C, 54.93; H, 2.84; N, 19.71. Found: C, 55.22; H, 3.01; N, 19.53.

Compound **9b** had mp 103-105° (96%); ir: 3405 b (ν OH assoc), 3260 sh (ν NH), 2950 s (ν C-H, $CH_3$), 1735 s (ν C=O), 1595 s $cm^{-1}$ (ν C=C); $^1H$ nmr: δ 8.23 (dd, 1, H-5), 7.48 (td, 1, H-7), 7.18 (t, 2, H-6, H-8) 6.47 (s, 1, H-5'), 2.19 (s, 6, $CH_3$), 11.51 (m, 1, OH).

*Anal.* Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.68; H, 3.88; N, 17.94. Found: C, 57.91; H, 3.91; N, 18.15.

2-Methoxy-3-nitro-4-(6-methyl-2-pyridylimino)-4*H*-chromene (**10**).

To a suspension of 60 mg (0.2 mmole) of 2-hydroxy-3-nitro-4-(6-methyl-2-pyridylimino)-4*H*-chromene (**6e**) an excess of an ethereal solution of diazomethane was added with external ice cooling. After standing for 24 hours the clear reaction mixture was evaporated to dryness. The product obtained was purified by thin layer chromatography on silica gel (Merck, Kieselgel 60 $HF_{254}$) using a mixture of benzene: ethanol (30/1) as eluent, 55 mg (88%) yellow crystals, mp 245-246; ir: 3910 m (ν C-H, $CH_3$), 1630 s (ν C=N), 1605 s $cm^{-1}$ (ν C=C); $^1H$ nmr: δ 8.22 (d, 1, H-5), 7.73 (t, 2, H-7, H-4'), 7.41 (t, 2, H-6, H-8), 6.92 (t, 2, H-3', H-5'), 3.90 (s, 3, $OCH_3$), 2.66 (s, 3, $CH_3$).

*Anal.* Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.94; H, 4.32; N, 13.64.

2-Hydroxy-ω-nitroacetophenone (**11**).

A solution of 1 mmole of compounds **6** or **8** in 10 ml of 5% aqueous sodium hydroxide has been either allowed to stand over a period of 1 hour at room temperature or heated by means of oil bath at 90-95°. After addition of some crushed ice the reaction mixture was acidified with aqueous hydrochloric acid. The precipitated product was filtered off, washed with water and dried over phosphorus pentoxide yielding 70-90% of **11** (ethanol, mp 96-97°) [6]; ir: 3400 b (ν OH), 3080 b (ν OH, chelat.), 1645 s (ν C=O), 1610 s $cm^{-1}$ (ν C=C); $^1H$ nmr: 11.41 (bs, 1, phenolic OH), 7.87 (dd, 1, H-6), 7.64 (td, 1, H-4), 7.18 (q, 2, H-3, H-5), 6.28 (s, 2, $CH_2$).

*Anal.* Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.74. Found: C, 52.94; H, 4.18; N, 7.72.

Antimicrobial Activity of Compounds **6** and **7**.

Examination of the antimicrobial activity of coumarins **6** and **7** has been performed in Petri dishes with Mueller-Hinton's agar, on which either bacteria or fungi were inoculated. On the so prepared agars the 6 mm diameter wells have been cut, in which DMF solutions of the samples examined (50, 100 and 150 μg, respectively) were applied. Subsequently, the dishes have been incubated at 37° during a period of 24 hours for bacteria or 48 hours for fungi, respectively, and the inhibition zones were measured (Table 3).

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