# SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

## Part V. Synthesis of Nitro Coumarins

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The synthesis of nitro-substituted coumarins has been undertaken as part of a general scheme of search for physiologically active compounds, in view of the fact that nitro-substituted compounds have a unique place in the attack against pathogenic micro-organisms.

The preparation of 6-nitro[1], 7-nitro[2] and 8-nitro[3] coumarins by the Perkin condensation has been reported in literature. By heating the corresponding nitro salicylaldehydes with sodium phenylacetate and acetic anhydride, the 6-nitro, 8-nitro and 6:8-dinitro-3-phenyl coumarins[4] were prepared. The condensation of 5-nitro salicylaldehyde with ethyl acetoacetate in the presence of alkali gives the 6-nitro-3-acetyl coumarin.[5] 7-nitro-4-hydroxy coumarin was prepared by Julia and Tchernoff[6] following Anschutz[7] procedure.

In the present work a number of nitro coumarins substituted with different groups in 3 and 4 positions have been prepared using the corresponding nitro-substituted salicylaldehydes and 3-nitro-2-hydroxy acetophenones.

Among the required intermediates, 3-nitro and 5-nitro salicylaldehydes have been prepared by the direct nitration of salicylaldehyde according to Diehl[8] and 6-nitro salicylaldehyde by the Reimer-Tiemann reaction on *m*-nitro phenol.[9] 4-Nitro salicylaldehyde is an abnormally substituted derivative and is difficult to prepare. This was originally synthesised by Segesser and Calvin[10] from 4-nitro-2-acetoxy toluene through photobromination and hydrolysis and later by Libermann following Thiele's oxidation procedure. In both the cases the yields were poor. The compound has now been prepared following the recent method of Goldberg and Walker[11] by the Khronke reaction on 4-nitro-2-acetoxy benzyl bromide.

The nitration of *o*-hydroxy acetophenone oxime was reported by Lindemann and Romanoff[12] whereby the 3- and 5-nitro isomers were obtained.

It was therefore considered worthwhile to investigate if the direct nitration of *o*-hydroxy acetophenone also gave the two isomers. When the nitration was carried out at 15° C. in acetic acid medium with fuming nitric acid, the bulk of the product formed was found to be the 3-nitro isomer reported by the other workers.

Starting from 6-nitro salicylaldehyde, 5-nitro coumarin was prepared by Perkin's reaction. Following Bargellini's procedure 5-nitro-3-phenyl and 7-nitro-3-phenyl coumarins could be prepared from 6-nitro and 4-nitro salicylaldehydes respectively. By the condensation of 6-nitro, 5-nitro and 3-nitro salicylaldehydes with ethyl acetoacetate the 5-nitro, 6-nitro and 8-nitro-3-acetyl coumarins respectively could be obtained. Condensation of 3-nitro-2-hydroxy acetophenone with sodium phenylacetate and acetic anhydride, cyanoacetic ester [13] and ethyl carbonate gave the 8-nitro-4-methyl-3-phenyl, 8-nitro-4-methyl-3-cyano and 8-nitro-4-hydroxy coumarins respectively.

In toxicity tests, the nitro-3-phenyl coumarins have been found to be active against bacteria and fungi of select species but are not appreciably toxic to fish.

## EXPERIMENTAL

1. *5-nitro coumarin.*—6-Nitro salicylaldehyde[9] (0·2 g.), anhydrous sodium acetate (1 g.) and acetic anhydride (10 ml.) were refluxed at 170-80° C. for about four hours in a paraffin-bath. The reaction mixture was poured on crushed ice and the solid that separated was crystallised from glacial acetic acid in yellow needles (0·2 g.), m.p. 160° C. (Found: C, 56·9; H, 2·5; N, 6·9; $C_9H_5NO_4$ requires C, 56·5; H, 2·6; N, 7·3%).

2. *5-Nitro-3-phenyl coumarin.*—6-Nitro salicylaldehyde[9] (1 g.), sodium phenylacetate (2 g.) and acetic anhydride (15 ml.) were refluxed in an oil-bath at 170–80° C. for five hours and then poured in ice-cold water. After keeping overnight, the solid that separated was filtered, washed free from acid and recrystallised from glacial acetic acid, yellow needles (0·6 g.), m.p. 140° C. (Found: C, 67·5; H, 3·7; N, 5·3; $C_{15}H_9NO_4$ requires C, 67·4; H, 3·8; N, 5·2%).

3. *7-Nitro-3-phenyl coumarin.*—Starting from 4-nitro salicylaldehyde,[11] 7-nitro-3-phenyl coumarin was prepared following the procedure described in 2. The product (0·6 g.) obtained was recrystallised from glacial acetic acid, golden yellow needles, m.p. 242° C. (Found: C, 67·2; H, 3·8; N, 5·2; $C_{15}H_9NO_4$ requires C, 67·4; H, 3·8: N, 5·2%).

4. 8-*Nitro*-3-*acetyl coumarin*.—3-Nitro salicylaldehyde[8] (1 g.) was dissolved in ethyl acetoacetate (2 ml.) after the addition of a small quantity of alcohol and heating. The hot solution was cooled to about 40° C. and three to four drops of piperidine were added. The liquid became viscous, and on cooling and scratching solidified. The solid was triturated with a small quantity of alcohol and filtered. The residue was washed with cold alcohol until free from colour and recrystallised from alcohol-acetone mixture as pale yellow needles (0·6 g.), m.p. 200° C. (Found: C, 56·7; H, 3·2; N, 6·4; $C_{11}H_7NO_5$ requires C, 56·6; H, 3·0; N, 6·0%).

5. 6-*Nitro*-3-*acetyl coumarin*.—5-Nitro salicylaldehyde[8] (1 g.) was condensed with ethyl acetoacetate (2 ml.) following the procedure described in 4. The product (0·8 g.) obtained on recrystallisation from alcohol-acetone mixture gave pale yellow needles, m.p. 192° C. (Wahlburg,[5] m.p. 193° C.).

6. 5-*Nitro*-3-*acetyl coumarin*.—This substance was prepared from 6-nitro salicylaldehyde following the procedure described above and recrystallised from glacial acetic acid as light yellow needles, m.p. 156° C. (Found C, 56·7; H, 3·0; N, 5·9; $C_{11}H_7NO_5$ requires C, 56·6; H, 3·0; N, 6·0%).

7. 8-*Nitro*-4-*methyl*-3-*phenyl coumarin*.—3-Nitro-2-hydroxy acetophenone was prepared by the direct nitration of *o*-hydroxy acetophenone at 15–20° C., m.p. 87–88° C. (Lindemann and Romanoff,[12] m.p. 88° C.).

3-Nitro-2-hydroxy acetophenone (1 g.), sodium phenylacetate (2 g.), and acetic anhydride (25 ml.) were refluxed in an oil-bath at 170–80° C. for five hours and then poured on crushed ice. The pasty mass that separated on leaving overnight was treated with cold alcohol and the solid obtained was recrystallised from glacial acetic acid as pale yellow needles (0·8 g.), m.p. 228° C. (Found: C, 68·2; H, 4·4; N, 4·6; $C_{16}H_{11}NO_4$ requires C, 68·3; H. 3·9; N, 4·9%).

8. 8-*Nitro*-4-*methyl*-3-*cyano coumarin*.—A mixture of 3-nitro-2-hydroxy acetophenone (2 g.), ethyl cyanoacetate (2 g.) and sodium ethoxide (0·1 g. in 20 ml. of absolute alcohol) was refluxed for about two hours when crystals began to appear. The mixture was cooled, the crystals that separated were filtered and washed with small amounts of cold alcohol to remove the colour. On recrystallisation from acetone-water mixture pale yellow needles were obtained (0·5 g.), m.p. 219° C. (Found: C, 57·2; H, 3·0; N, 11·9; $C_{11}H_6N_2O_4$ requires C, 57·4; H, 2·6; N, 12·2%).

9. 8-*Nitro*-4-*hydroxy coumarin*.—3-Nitro-2-hydroxy acetophenone (1·5 g.) was mixed with ethyl carbonate (10 ml.) in the presence of sodium

powder (1·5 g.). After the initial vigorous reaction had subsided, the reaction mixture was heated on a steam-bath for one hour. Alcohol was then added to destroy the excess of sodium and the excess of ethyl carbonate was removed by ether extraction. The product obtained on acidification was recrystallised from ethyl alcohol as straw yellow needles, m.p. 118° C. (Found: C, 52·5; H, 2·3; N, 6·2; $C_9H_5NO_5$ requires C, 52·6; H, 2·4; N, 6·7%).

## SUMMARY

5-Nitro, 5-nitro-3-phenyl, 7-nitro-3-phenyl, 5-nitro-3-acetyl, 6-nitro-3-acetyl, 8-nitro-3-acetyl, 8-nitro-4-methyl-3-phenyl, 8-nitro-4-methyl-3-cyano and 8-nitro-4-hydroxy coumarins have been prepared.

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