SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part 1. Synthesis of 7-Amino and 7-Halo-4-methyl-3-phenyl Coumarins

BY N. V. SUBBA RAO AND V. SUNDARAMURTHY

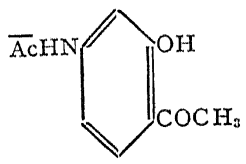
(Chemistry Department, Osmania University)

Received October 14, 1955

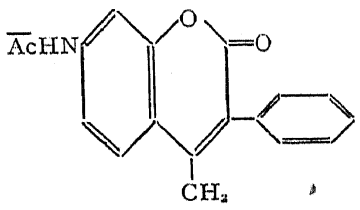
(Communicated by Prof. T. R. Seshadri, F.A.SC.)

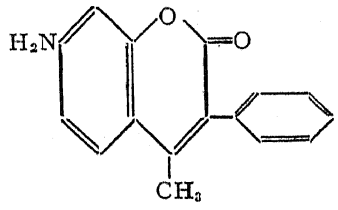
7-HYDROXY-4-methyl-3-phenyl coumarins and their methyl ethers were reported by Seshadri and Varadarajan[1] to be highly toxic to fish. The toxicity of these compounds was explained on the basis of their close resemblance to isoflavones. Recently Naito and others[2] reported 7-amino-4-methyl coumarin to be active against tubercle bacilli (1 : 64,000). It was therefore considered desirable to prepare 7-amino and 7-halo-4-methyl-3-phenyl coumarins which may possess better bactericidal and insecticidal properties. These compounds have not been prepared previously. The method of Bargellini[3] for the preparation of 3-phenyl-4-methyl umbelliferones was improved by Seshadri and Varadarajan.[4] It does not seem to have been applied for the preparation of 7-substituted coumarins other than the 7-hydroxy derivatives.

In the present case, *p*-acetamino-*o*-hydroxy acetophenone[5] (I) obtained by the Fries migration of *m*-acetamino phenyl acetate, was condensed with sodium phenyl acetate and acetic anhydride. The resulting product on hydrolysis and recrystallisation from hot alcohol gave 7-amino-4-methyl-3-phenyl coumarin (II). From it the corresponding 7-halogen substituted

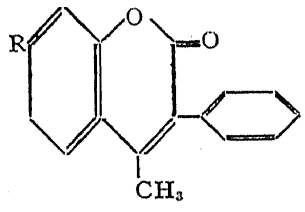


(I)





(II)



$R = \begin{Bmatrix} Cl \\ Br \\ I \end{Bmatrix}$

(III)

coumarins (III) were prepared through diazotisation and Sandmeyer reactions. This indirect method was adopted for the preparation of the halogen compounds, as direct halogenation[6–9] usually results in the 3, 6 and 8 positions being substituted in the order of availability, and other synthetic routes like the Perkin and Pechmann condensations involve preparation of difficultly accessible intermediates and generally result in poor yields.

The 7-amino compound was feebly toxic to fish whereas the 7-halogen derivatives were found to possess appreciable toxicity. Comparison of their toxicity to fish with the corresponding 7-hydroxy compound showed that the halo-compounds were far more toxic. Full details of the physiological activity of the compounds towards fish and bacteria will be reported later.

EXPERIMENTAL

(i) *7-Acetamino-4-methyl-3-phenyl coumarin*

p-Acetamino-*o*-hydroxy-acetophenone[5] (4 g.), sodium phenyl acetate (8 g.) and acetic anhydride (50 ml.) were heated at 120° C. for ½ hr. and then at 180° C. for 4 hrs. The reaction mixture was poured in water and allowed to stand overnight when a pasty mass separated. The water was decanted off and the pasty mass was treated with cold alcohol when the solid acetate separated. It was filtered, washed with cold alcohol, dried (2·5 g.) and recrystallised from glacial acetic acid; white glistening plates, m.p. 266° C. (Found: C, 73·5; H, 5·4; N, 4·7; $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1; N, 4·8%).

(ii) *7-Amino-4-methyl-3-phenyl coumarin*

The acetate (4 g.) was heated with alcoholic hydrochloric acid (2 : 1, 100 ml.) for 2 hrs. and allowed to stand overnight. The compound that separated (3 g.) on recrystallisation from hot alcohol gave pale yellow needles, m.p. 280° C. (Found: C, 76·4; H, 5·5; N, 5·7; $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

(iii) *7-Chloro-4-methyl-3-phenyl coumarin*

7-Amino-4-methyl-3-phenyl coumarin (0·5 g.) was dissolved in dil. sulphuric acid (30 ml., 5 N) by warming and diazotised with sodium nitrite (0·2 g. in 5 ml. water) at 0–5° C. After standing for 1 hr. the cold diazonium solution was added to an ice-cold solution of cuprous chloride (2 g. in 10 ml. conc. hydrochloric acid) with vigorous stirring. The reaction mixture was allowed to attain room temperature and then warmed

on the water-bath at 60° C. till the frothing subsided indicating the completion of the reaction. The 7-chloro-4-methyl-3-phenyl coumarin that separated was collected (0·4 g.) and on recrystallisation from alcohol gave colourless needles, m.p. 137° C. (Found: C, 71·0; H, 4·7; Cl, 13·1; $C_{16}H_{11}O_2Cl$ requires C, 71·0; H, 4·1; Cl, 13·1%).

(iv) *7-Bromo-4-methyl-3-phenyl coumarin*

The cold diazonium solution obtained from 7-amino-4-methyl-3-phenyl coumarin (0·5 g.) was added to a cold solution of cuprous bromide (2 g. in 10 ml. hydrobromic acid) gradually with mechanical stirring and the precipitate obtained (0·4 g.) was worked up as above. 7-Bromo-4-methyl-3-phenyl coumarin on recrystallisation from alcohol separated as lemon yellow needles, m.p. 129° C. (Found: C, 61·3; H, 3·7; Br, 24·9; $C_{16}H_{11}O_2Br$ requires C, 61·0; H, 3·5; Br, 25·4%).

(v) *7-Iodo-4-methyl-3-phenyl coumarin*

The cold diazonium solution obtained from 7-amino-4-methyl-3-phenyl coumarin (0·5 g.) was stirred with potassium iodide solution (2 g. in 10 ml. water) and the precipitate (0·5 g.) obtained was worked up as usual. The product on recrystallisation from alcohol gave greyish plates, m.p. 142° C. (Found: C, 53·6; H, 3·5; $C_{16}H_{11}O_2$ I requires C, 53·1; H, 3·1%).

Summary

7-Amino-4-methyl-3-phenyl coumarin has been prepared from 4-acetamido-*o*-hydroxy acetophenone. The corresponding halogen substituted coumarins, which are prepared through diazotisation and Sandmeyer reactions, have been found to be highly toxic to fish.

We are thankful to Mr. C. Venkata Ratnam for the microanalyses recorded in the paper.

References

1. Seshadri and Varadarajan — *Proc. Ind. Acad. Sci.*, 1952, **35 A**, 75.
2. Naito and others .. *J. Pharm. Soc. Japan*, 1951, **71**, 1343–45.
3. Bargellini .. *Chemical Abstracts*, 1926, **20**, 595.
4. Seshadri and Varadarajan .. *J. Sci. Ind. Res.*, 1952, **11 B**, 48.
5. Marc Julia and Michele .. *Bull. Soc. Chim. France*, 1952, 639–42.
6. Perkin .. *J. Chem. Soc.*, 1871, **24**, 37.
7. Simonis and Wenzel .. *Ber.*, 1900, **33**, 421, 1961, 2326.
8. Peters and Simonis .. *ibid.*, 1908, **41**, 830.
9. Seidel .. *J. Prakt. Chem.*, 1899, **59** (2), 122.