SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part II. Synthesis of 7-Amino and 7-Halo-4-Methyl Coumarins

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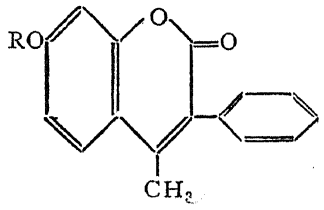
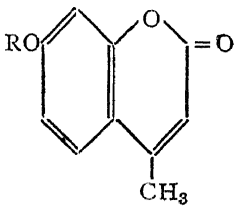
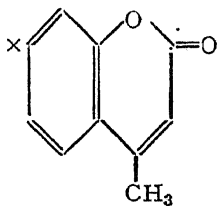
SESHADRI AND VARADARAJAN[1] reported that 3-phenyl-4-methyl umbelliferrone (I *a*) and its methyl ether (I *b*) were comparatively more toxic to fish than the corresponding 4-methyl umbelliferrone (II *a*) or its methyl ether (II *b*). Later Rao and Sundaramurthy[2] observed that the toxic properties were considerably enhanced if the hydroxyl of 3-phenyl-4-methyl umbelliferrone is replaced by halogen group. In order to verify whether this is always true in other cases and also to establish the superior toxic properties of the 3-phenyl substituent in the coumarins, it has been considered desirable to synthesise 7-halo-4-methyl coumarins (III) and compare their physiological activity with the corresponding 3-phenyl coumarins and also with the 7-hydroxy and 7-methoxy-4-methyl coumarins.



I (*a*) R=H
(*b*) R=CH_3



II (*a*) R=H
(*b*) R=CH_3



III X = { Cl, Br, I }

Clayton[3] prepared the 7-chloro-4-methyl coumarin by the Pechmann condensation of *m*-chloro phenol. But the 7-bromo and 7-iodo-4-methyl coumarins do not seem to have been prepared so far. Since the *m*-halo phenols are not easily accessible and by Pechmann condensation give very poor yields of the coumarins, the direct condensation procedures have been found to be unsuitable for the preparation of the above compounds. It was, however, found convenient to synthesise the 7-amino-4-methyl coumarin and from it the corresponding 7-halo-4-methyl coumarins following the procedure already adopted by us in the synthesis of 7-halo-4-methyl-3-phenyl coumarins.[2] As the direct condensation of *m*-amino phenol with ethyl acetoacetate in the presence of anhydrous zinc chloride, adopted by Pechmann,[4] gave rise to some difficulties in the isolation of the final product,

the condensation has been improved making use of *m*-acetamino phenol instead of amino phenol and phosphorous oxychloride as the condensing agent. The 7-acetamino-4-methyl coumarin obtained in good yield by this method was later hydrolysed to the corresponding 7-amino compound with alcoholic hydrochloric acid. From the amino compound the 7-halo-4-methyl coumarins have been prepared by diazotisation followed by Sandmeyer reaction. 7-Chloro-4-methyl coumarin obtained by this procedure has been found to be identical with that obtained by the Pechmann condensation of *m*-chloro phenol.

Though the 7-amino-4-methyl coumarin did not possess appreciable toxicity to fish, the 7-halo-4-methyl coumarins were comparatively more toxic than the corresponding methoxy compound and far weaker than the 7-halo-4-methyl-3-phenyl coumarins.

EXPERIMENTAL

(*i*) *7-Amino-4-methyl coumarin*

m-Acetamino phenol (10 g.), ethyl acetoacetate (10 ml.) and phosphorous oxychloride (2·5 ml.) were heated on a water-bath for 1 hr., kept overnight and poured in ice-cold water. The 7-acetamino-4-methyl coumarin that separated was filtered, washed with water, dried (4 g.) and on recrystallisation from alcohol gave colourless plates, m.p. 270° C., which agreed in all its properties with that prepared by Pechmann through acetylation of 7-amino-4-methyl coumarin.

The acetamino coumarin (4 g.) was refluxed with alcoholic hydrochloric acid (2 : 1, 50 ml.) for 2 hrs., cooled, diluted with water and neutralised with 5% alkali. The compound that separated (2·8 g.) was recrystallised from alcohol when cream coloured glistening needles were obtained, m.p. 226° C. (Pechmann, 219–23° C.). (Found: C, 68·3; H, 5·6; N, 7·9; $C_{10}H_9O_2N$ requires C, 68·6; H, 5·2; N, 8·0%.)

(*ii*) *7-Chloro-4-methyl coumarin*

7-Amino-4-methyl coumarin (0·2 g.) was dissolved in 4 N hydrochloric acid (20 ml.) and diazotised with sodium nitrite (0·1 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 (1 g. in 5 ml. conc. hydrochloric acid) with vigorous stirring. The reaction mixture was allowed to attain room temperature and then warmed on a water-bath at 60° C. till frothing subsided. The 7-chloro-4-methyl coumarin that separated (0·1 g.) was collected and on recrystallisation from aqueous alcohol gave colourless needles; m.p. 144° C. Mixed melting point of the substance with the one prepared

following Clayton's procedure was not depressed. (Found: C, 61·8; H, 3·8; Cl, 18·3; $C_{10}H_7O_2Cl$ requires C, 61·7; H, 3·6; Cl, 18·1%.)

(*iii*) *7-Bromo-4-methyl coumarin*

The cold diazonium solution obtained from 7-amino-4-methyl coumarin (0·2 g.) was added to a cold solution of cuprous bromide (1 g. in 5 ml. of hydrobromic acid) gradually with mechanical stirring and the precipitate obtained (0·08 g.) was worked up as above. The 7-bromo-4-methyl coumarin on recrystallisation from aqueous alcohol gave pale yellow needles; m.p. 135° C. (Found: C, 50·7; H, 3·2; Br, 31·8; $C_{10}H_7O_2Br$ requires C, 50·4; H, 2·9 ; Br, 31·1%).

(*iv*) *7-Iodo-4-methyl coumarin*

The cold diazonium solution obtained from 7-amino-4-methyl coumarin (0·2 g.) was stirred with potassium iodide solution (1 g. in 5 ml. water) and the precipitate obtained (0·1 g.) was worked up as usual. The product on recrystallisation from aqueous alcohol gave light grey needles; m.p. 157° C. (Found: C, 41·8; H, 2·8; I, 43·6; $C_{10}H_7O_2I$ requires C, 41·8; H, 2·4; I, 44·4%.)

Summary

An improved method for the preparation of 7-amino-4-methyl coumarin is described. The corresponding halo-substituted coumarins prepared from the amino compound by diazotisation and Sandmeyer reaction have been found to be more toxic to fish than the 7-methoxy-4-methyl coumarin and far less toxic than the corresponding 3-phenyl coumarins.

We thank Mr. C. V. Ratnam for the micro-analyses recorded in the paper.

References

1. Seshadri and Varadarajan .. *Proc. Ind. Acad. Sci.*, 1953, **35 A**, 75.
2. Rao and Sundaramurthy .. *Ibid.*, 1955, **42 A**, 249.
3. Clayton .. *J. Chem. Soc.*, 1908, **93**, 2021.
4. Pechmann .. *Ber.*, 1899, **32**, 3681.