# SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

## Part IV. Synthesis of 6- and 7-Halo Coumarins by Direct Condensation Procedures

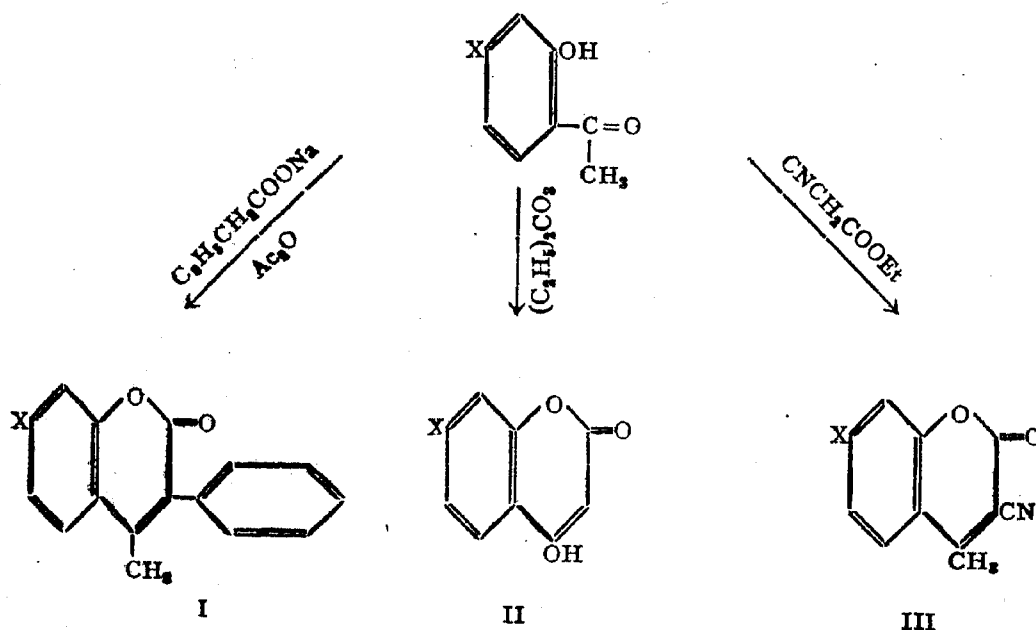By N. V. Subba Rao, F.A.Sc. and V. Sundaramurthy

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In earlier publications[1,2] from this laboratory the synthesis of 7-halo-4-methyl and 7-halo-4-methyl-3-phenyl coumarins by replacement of the amino group of the corresponding 7-amino coumarins adopting diazotisation followed by Sandmeyer reaction has been reported. These have now been synthesised by direct condensation procedures and have been shown to be identical with the compounds obtained by the diazo reaction. In addition, a number of 7-halo coumarins with different substituents in 3- and 4-positions have also been prepared by direct condensation for the study of their physiological properties.

Clayton[3] prepared 7-chloro and 7-chloro-4-methyl coumarins by the Pechmann condensation of *m*-chloro phenol. Buu-Hoi and co-workers[4] synthesised 7-bromo-3-aryl coumarins by the hydrolysis and cyclisation of the corresponding β-*o*-methoxyphenyl-α-phenylacrylonitriles using pyridine hydrochloride. In the present case, by the Pechmann condensation of *m*-bromo phenol, 7-bromo and 7-bromo-4-methyl coumarins have been prepared. 4-Halo-2-hydroxy acetophenones have been condensed with sodium phenylacetate and acetic anhydride adopting the procedure of Bargellini improved by Seshadri and co-workers,[5] with ethyl carbonate following Robertson's procedure[6] and with cyanoacetic ester adopting the procedure of Link and co-workers,[7] resulting in the formation of the corresponding 7-halo-4-methyl-3-phenyl (I) 7-halo-4-hydroxy (II) and 7-halo-4-methyl-3-cyano (III) coumarins respectively. The yields of 7-halo coumarins obtained by Pechmann condensation are comparatively poorer than those obtained by the diazotisation procedure, while the yields in the case of direct condensations making use of *o*-hydroxy acetophenones are comparatively better.

6-Bromo-4-methyl-3-phenyl coumarin has also been prepared by the condensation of 5-bromo-2-hydroxy acetophenone adopting Bargellini's procedure.

A5

X—[benzene ring]—OH
—C=O
|
CH₃

$C_6H_5CH_2COONa$ / $Ac_2O$     $(C_2H_5)_2CO_3$     $CNCH_2COOEt$

I                II                III

In tests using fish, the 7-bromo-4-methyl-3-phenyl coumarin is the most active among the compounds tested. The corresponding 6-bromo compound has less toxicity. The introduction of a hydroxyl in 4-position of 7-halo coumarins or a cyano group in 3-position of 7-halo-4-methyl coumarins does not seem to improve the toxicity but on the other hand appears to have a retarding effect.

Details of the fish toxicity data will be published elsewhere.

EXPERIMENTAL

1. 7-*Bromo coumarin.*—*m*-Bromo phenol (5 g.), malic acid (5 g.) and concentrated sulphuric acid (13 ml.) were heated in an oil-bath at 120–30° C. till the evolution of carbon monoxide ceased. The reaction mixture was allowed to stand for two hours and then poured on crushed ice with stirring. The pasty mass that separated was repeatedly extracted with petroleum ether and the product obtained on removing the solvent was recrystallised from aqueous alcohol in colourless needles (0·15 g.), m.p. 105° C. (Found: C, 48·2; H, 2·3; Br, 35·2; $C_9H_5O_2Br$ requires C, 48·0; H, 2·2; Br, 35·5%).

2. 7-*Bromo*-4-*methyl coumarin.*—*m*-Bromo phenol (5 g.) was condensed with ethyl acetoacetate (5 g.) in the presence of concentrated sulphuric acid (12 ml.). After 24 hours, the reaction mixture was poured on crushed ice and the solid that separated was filtered, washed free from acid and recrystallised from aqueous alcohol as colourless needles (0·5 g.), m.p. 138° C. Its mixed melting point with 7-bromo-4-methyl coumarin obtained earlier by the diazotisation procedure[2] was not depressed.

3. *7-Chloro-4-methyl-3-phenyl* *coumarin.*—4-Chloro-2-hydroxy aceto-phenone[8] (4 ml.), sodium phenylacetate (8 g.) and acetic anhydride (50 ml.) were heated at 120° C. for half an hour and then at 180° C. for four hours in an oil-bath. The reaction mixture was then poured in cold water and allowed to stand overnight when a pasty mass separated. The water was decanted off and the pasty mass treated with cold alcohol. The solid obtained on filtration and recrystallisation from aqueous alcohol deposited colourless needles (4 g.), m.p. 140° C. Mixed melting point of the substance with the compound prepared earlier by the diazotisation procedure[1] was not depressed.

4. *7-Bromo-4-methyl-3-phenyl* *coumarin.*—4-Bromo-2-hydroxy aceto-phenone was prepared adopting a procedure similar to the one in the pre-paration of 4-chloro-2-hydroxy acetophenone.[8] The bromo acetophenone (4 ml.) was condensed with sodium phenylacetate (8 g.) and acetic anhydride (50 ml.) as above and 7-bromo-4-methyl-3-phenyl coumarin (3 g.) was ob-tained as pale yellow needles from aqueous alcohol, m.p. 129° C. Its mixed melting point with the substance prepared earlier by diazotisation procedure[1] was not depressed.

5. *7-Iodo-4-methyl-3-phenyl* *coumarin.*—4-Iodo-2-hydroxy acetophenone (0·1 g.) was condensed with sodium phenylacetate and acetic anhydride as in 3, and the product obtained (0·03 g.) on recrystallisation from aqueous alcohol gave greyish plates, m.p. 142° C. Its mixed melting point with the product obtained by diazotisation was not depressed.

6. *7-Chloro-4-methyl-3-cyano* *coumarin.*—A mixture of 4-chloro-2-hydroxy acetophenone (2 ml.), ethyl cyanoacetate (2 g.) and sodium ethoxide (0·1 g. in 20 ml. absolute alcohol) was refluxed for about two hours when crystals began to appear. The mixture was cooled and the product sepa-rated was filtered. It was washed with small quantities of alcohol and re-crystallised from acetone-water mixture as pale-yellow needles (1·4 g.), m.p. 204° C. (Found: C, 60·5; H, 3·2; Cl, 16·3; N, 5·9; $C_{11}H_6NO_2Cl$ requires C, 60·3; H, 3·4; Cl, 16·2; N, 6·3%).

7. *7-Bromo-4-methyl-3-cyano* *coumarin.*—Starting from 4-bromo-2-hydroxy acetophenone (2 ml.) and adopting the procedure described above, 7-bromo-4-methyl-3-cyano coumarin was prepared as pale-yellow needles (1·2 g.), m.p. 210° C. (Found: C, 50·2; H, 2·8; N, 5·1; Br, 30·0; $C_{11}H_6NO_2Br$ requires C, 50·0; H, 2·3; N, 5·3; Br, 30·3%).

8. *7-Chloro-4-hydroxy* *coumarin.*—4-Chloro-2-hydroxy acetophenone (1·5 ml.) was mixed with ethyl carbonate (10 ml.) in the presence of sodium

The first case we shall consider is that in which the Mg atoms and O atoms oscillate as groups along the $x$-axis. The equations of motion are then

$$m_1 \frac{d^2\xi_1}{dt^2} = -K_0(\xi_1 - \xi_2)$$

$$m_2 \frac{d^2\xi_2}{dt^2} = -K_0(\xi_2 - \xi_1)$$

where $K_0$ is an abbreviation for $(2\alpha + 4\beta)$. Proceeding as already indicated, we obtain a quadratic equation for $\omega_1^2$, the solutions of which are

$$\omega_1^2 = \frac{K_0}{\mu}, \quad \omega_{10}^2 = 0 \tag{1}$$

where $\mu$ is the reduced mass given by the formula $1/\mu = 1/m_1 + 1/m_2$. The first solution represents mode I in Table II above, while the zero frequency represents the translations appearing at the foot of that table.

The next case is that of the tangential oscillation of the cubic layers of atoms which are parallel to the $yz$ plane along the $y$-axis. The alternate layers oscillate in opposite phases. The equations of motion are:

$$m_1 \frac{d^2\eta_1}{dt^2} = -K_0\eta_1 + 2\alpha\eta_2$$

$$m_2 \frac{d^2\eta_2}{dt^2} = 2\alpha\eta_1 - K_0\eta_2.$$

The solutions of these equations are:

$$\omega^2_{2,\,9} = \frac{\frac{1}{2}K_0}{\mu} \pm \left[\frac{K_0^2}{4\mu^2} - \frac{(K_0^2 - 4\alpha^2)}{m_1 m_2}\right]^{\frac{1}{2}}. \tag{2}$$

The alternative signs appearing in formula (2) give the frequencies of vibration $\omega_2$ and $\omega_9$ respectively. The higher frequency $\omega_2$ refers to the case in which the Mg and O atoms appearing in the same $yz$ planes move in opposite phases. The lower frequency $\omega_9$ represents the case in which the Mg and O atoms appearing in the same $yz$ planes move in the same phase. $\omega_2$ and $\omega_9$ refer respectively to the modes listed as II and IX in Table II. From formula (2) it is evident that

$$\omega_9^2 = \omega_1^2 - \omega_2^2.$$

The third case we shall consider is that in which the cubic layers of atoms in the crystal lying in the $yz$ planes oscillate normally to themselves along the $x$ axis; the alternate layers being in opposite phases. The equations of motion are: