SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part VII. Synthesis of Halo and Nitro Coumarones

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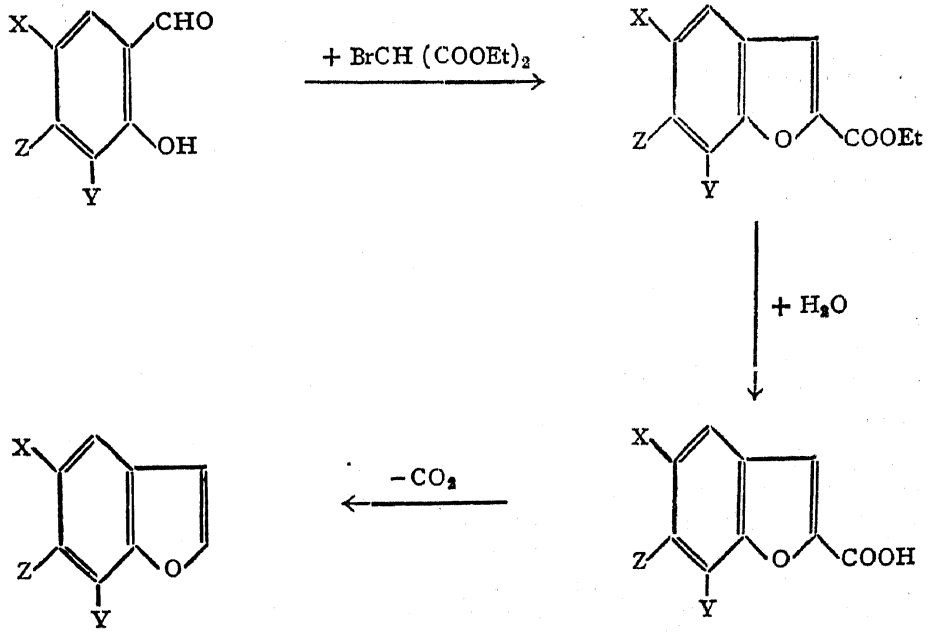
NATURALLY occurring furano-compounds such as rotenone, khellin, usnic acid, and karanjin have marked physiological activity. In recent years, coumarone derivatives have been synthesised as potential anti-tubercular agents.[1-2] Läuger, Martin and Müller[3] investigated the toxicity of furano-coumarins and coumarones to insects and found them fairly toxic. Coleman and Rigternik[4] patented the preparation of chloro- and polychloro-2-methyl coumarones as parasiticides, especially against the house-fly.

For the preparation of halo and nitro coumarones substituted in the benzene ring direct halogenation or nitration of coumarones is not feasible since it gives rise to substitution in the furan ring. Other methods of synthesis have therefore been explored. The important methods used in the past for this purpose are (*a*) elimination of hydrogen halide from *o*-hydroxy-β-halo ethyl or ethylene benzene,[5] (*b*) condensing *o*-hydroxy benzaldehyde or arylketone with halogen-substituted ethyl acetate or an aliphatic ketone,[6-9] (*c*) ring closure of an α-phenoxy carbonyl compound or corresponding acetal.[10] Of these (*a*) and (*c*) are not suitable, owing to the starting materials being difficultly accessible and the procedures involved being tedious. Sanae Tanaka's method of condensing[11] substituted *o*-hydroxy benzaldehyde with bromo-malonic ester, which is a modification of method (*b*), is preferred because of the reported good yields.

5-Halo salicylaldehydes on condensation with bromo-malonic ester following the above procedure yielded 5-halo-2-carbethoxy coumarones. Hydrolysis of these esters with alcoholic potash gave 5-halo-2-carboxy coumarones which on subsequent decarboxylation, using copper-quinoline method resulted in 5-halo coumarones. These compounds have been found to possess the properties reported earlier by Stoermer,[10] using a different method. Simonis and Wenzel[12] obtained 5: 7-dibromo coumarone from 6: 8-dibromo coumarin dibromide adopting method (*a*). The preparation of

5-chloro coumarone by Andrisano and Duro[13] adopting the method of Sanae Tanaka has come to our notice, after the work on this was completed. From 3: 5-dihalo salicylaldehydes[14,15] 5: 7-dihalo coumarones have been synthesised in a similar manner. 5-Chloro, 5-bromo[16] and 5-nitro-4-methoxy salicylaldehydes[17] gave on condensation the corresponding 5-substituted-6-methoxy coumarones. 3-Chloro, 3-bromo[18] and 3-nitro[18]-5-methoxy salicylaldehydes gave rise to the corresponding 7-chloro, 7-bromo, and 7-nitro-5-methoxy coumarones. 5-Chloro-4-methoxy and 3-chloro-5-methoxy salicylaldehydes required for the above condensation have been prepared by chlorination of the respective methoxy salicylaldehydes using sulphuryl chloride in the presence of fused sodium acetate in acetic acid.



I. 5-Halo coumarones: $Z = Y = H$; $X = Cl$ or Br.

II. (*a*) 5: 7-Dihalo coumarones: $Z = H$; $X = Y = Cl$ or Br.

(*b*) 5-Methoxy-7-halo or nitro coumarones; $Z = H$; $X = -OCH_3$; $Y = Cl$, Br, or NO_2.

(*c*) 6-Methoxy-5-halo or nitro coumarones: $Y = H$; $Z = -OCH_3$; $X = Cl$, Br, or NO_2.

The physiological activity of the coumarones synthesised has been evaluated on fish adopting the procedure of Krishnaswamy and Seshadri[19] taking the turning time as criterion. 5: 7-Dibromo, 5: 7-dichloro, 5-bromo-6-methoxy coumarones have been found to possess appreciably high toxicity to fish among the series of the compounds tested, exhibiting an activity equal

to five times that of Karanjin and one-sixth of rotenone. The carbethoxy and simple coumarones are found to possess physiological activity, whereas the corresponding acids showed no activity. Details of the results of toxicity experiments will be published elsewhere.

EXPERIMENTAL

I. 5-Chloro Coumarone

(*a*) *5-Chloro-2-carbethoxy coumarone.*—A mixture of 5-chlorosalicylaldehyde[14] (2 g.), bromoethyl malonate [20] (2 g.), anhydrous potassium carbonate (2·5 g.), and methyl ethyl ketone (30 ml.) was refluxed on a water-bath for seven hours. The solvent was removed and the residue diluted with water. The product was filtered (1·5 g.) and crystallised from ethyl alcohol, needles, m.p. 65° C. (Found: C, 58·8; H, 4·5; $C_{11}H_9O_3Cl$ requires C, 58·8; H, 4·0%).

(*b*) *5-Chloro-2-carboxy coumarone.*—The above ester (1 g.) was hydrolysed with 10% alcoholic potash (30 ml.) by heating on steam-bath for half-an-hour. The alcohol was distilled off and then diluted with water. Acidification with dilute sulphuric acid gave crude 5-chloro-2-carboxy coumarone (0·7 g.) which crystallised from benzene in needles, m.p. 258° C. (Stoermer,[10] and Simonis and Wenzel[12] reported 258° C., while Andrisano and Duro[13] reported 266° C.).

(*c*) *5-Chloro coumarone.*—The above acid (0·5 g.) with a small amount of copper was refluxed in quinoline (10 ml.) for half-an-hour. The quinoline solution was diluted with ether, filtered free from copper and washed with dilute hydrochloric acid (2N). It was finally washed with water and dried over anhydrous sodium sulphate. On evaporation of ether, 5-chloro coumarone (0·2 g.), b.p. 216° C. was obtained. (Stoermer,[10] and Simonis and Wenzel[12] reported b.p. 216° C. and Andrisano and Duro[13] obtained 216-17° C.).

II. 5-Bromo Coumarone

Condensation of 5-bromo salicylaldehyde[21] (2 g.) and bromo ethyl malonate (2 g.) as in I (*a*) gave 5-bromo-2-carbethoxy coumarone (1·7 g.), prismatic rods from alcohol, m.p. 90° C. (Found: C, 48·9; H, 3·2; $C_{11}H_9O_3Br$ requires C, 49·1; H, 3·4%). Hydrolysis of the ester (1 g.) as in I (*b*) yielded the corresponding acid (0·7 g.) needles from benzene, m.p. 253° C. (Stoermer,[10] and Simonis and Wenzel[12] reported m.p. 253° C.). The acid (0·5 g.) on decarboxylation with copper-quinoline as in I (*c*) resulted in 5-bromo

coumarone, an oily liquid (0·2 g.), b.p. 226° C. (Stoermer,[10] and Simonis and Wenzel[12] reported b.p. 226° C.).

III. 5: 7-*Dichloro Coumarone*

3: 5-Dichloro-salicylaldehyde[14] (3 g.) was condensed with bromoethyl malonate (2 g.). 5: 7-Dichloro-2-carbethoxy coumarone (2·5 g.) thus obtained was crystallised from ethyl alcohol, clusters of needles, m.p. 123–24°C. (Found: C, 50·5; H, 2·9; $C_{11}H_8O_3Cl_2$ requires C, 50·9; H, 3·1%). The ester (2 g.) on hydrolysis gave the corresponding acid (1·0 g.) which crystallised from benzene as tiny needles, m.p. 260° C. (Found: C, 46·4; H, 1·9; $C_9H_4O_3Cl_2$ requires C, 46·7; H, 1·7%). Decarboxylation of the acid (0·1 g.) yielded 5: 7-dichloro coumarone (0·06 g.), needles from methyl alcohol, m.p. 60° C. (Found: C, 51·6; H, 2·4; $C_8H_4OCl_2$ requires C, 51·4; H, 2·1%).

IV. 5: 7-*Dibromo Coumarone*

Condensation of 3: 5-dibromo salicylaldehyde[15] (3 g.) with bromoethyl malonate (2·5 g.) gave 5: 7-dibromo-2-carbethoxy coumarone (2·3 g.), needles from ethyl alcohol, m.p. 102–03° C. (Found: C, 38·3; H, 2·6; $C_{11}H_8O_3Br_2$ requires C, 37·8; H, 2·3%). The ester (2 g.) on hydrolysis gave the corresponding acid (1·8 g.), needles from benzene, m.p. 275° C. (Simonis and Wenzel[12] reported 276° C.). The acid was decarboxylated as described in I (*c*). 5: 7-Dibromo coumarone thus obtained (0·06 g.) crystallised from methyl alcohol in needles, m.p. 57° C. (Simonis and Wenzel[12] reported 57·5° C.).

V. 5-*Chloro*-6-*Methoxy Coumarone*

(*a*) 5-*Chloro*-2-*hydroxy*-4-*methoxy benzaldehyde.*—To a solution of 2-hydroxy-4-methoxy benzaldehyde[22] (5 g.) in acetic acid (15 ml.) was added a solution of sulphuryl chloride (4 ml.) in acetic acid (10 ml.) in the course of half-an-hour in the presence of fused sodium acetate. The mixture was stirred for one hour and diluted with water and the product (3·5 g.) thus obtained was crystallised from alcohol, clusters of needles, m.p. 102° C. The compound gave violet colouration with ferric chloride solution (Found: C, 51·5; H, 3·8; $C_8H_7O_3Cl$ requires C, 51·4; H, 3·7%).

(*b*) 5-*Chloro*-6-*methoxy coumarone.*—5-Chloro-2-hydroxy-4-methoxy-benzaldehyde (2 g.) and bromoethyl malonate (1·5 g.) on condensation gave 5-chloro-6-methoxy-2-carbethoxy coumarone (1·5 g.) which crystallised from methyl alcohol as needles, m.p. 104° C. The substance did not give colouration with ferric chloride (Found: C, 56·4; H, 4·6; $C_{12}H_{11}O_4Cl$ requires

C, 56·6; H, 4·3%). The ester (1 g.) on hydrolysis yielded the corresponding acid (0·3 g.), rectangular plates from methyl alcohol, m.p. 280° C. (Found C, 53·2; H, 2·8; $C_{10}H_7O_4Cl$ requires C, 52·9; H, 3·1%). The acid (0·1 g.) on decarboxylation gave 5-chloro-6-methoxy coumarone (0·06 g.), rectangular plates from methyl alcohol, m.p. 59–60° C. (Found: C, 59·7; H, 4·2; $C_9H_7O_2Cl$ requires C, 59·3; H, 3·8%).

VI. 5-*Bromo*-6-*Methoxy Coumarone*

5-Bromo-2-hydroxy-4-methoxy benzaldehyde[16] (2 g.) was condensed with bromoethyl malonate (2·5 g.) and 5-bromo-6-methoxy-2-carbethoxy coumarone (1·5 g.) thus obtained was crystallised from ethyl alcohol in bushy needles, m.p. 101° C. (Found: C, 48·1; H, 3·8; $C_{12}H_{11}O_4Br$ requires C, 48·2; H, 3·7%). The ester (1 g.) on hydrolysis gave the acid (0·8 g.) which crystallised from methyl alcohol as tiny needles, m.p. 230° C. (Found: C, 44·1; H, 2·8; $C_{10}H_7O_4Br$ requires C, 44·3; H, 2·6%). The acid (0·1 g.) gave on decarboxylation 5-bromo-6-methoxy coumarone (0·05 g.), needles from methyl alcohol, m.p. 51–52° C. (Found: C, 47·7; H, 3·1; $C_9H_7O_2Br$ requires C, 47·6; H, 3·2%).

VII. 5-*Nitro*-6-*Methoxy Coumarone*

5-Nitro-2-hydroxy-4-methoxy benzaldehyde[17] (2 g.) on condensation with bromoethyl malonate (1·5 g.) gave 5-nitro-6-methoxy-2-carbethoxy coumarone (1·5 g.) which crystallised from methyl alcohol as needles, m.p. 140° C. (Found: C, 54·2; H, 4·0; $C_{12}H_{11}O_6N$ requires C, 54·5; H, 4·2%). The ester (1 g.) on hydrolysis gave the acid (0·8 g.), rectangular plates from methyl alcohol, m.p. 300° C. (Found: C, 51·0; H, 3·4; $C_{10}H_7O_6N$ requires C, 50·6; H, 2·9%). The acid (0·2 g.) on decarboxylation gave 5-nitro-6-methoxy coumarone (0·15 g.), needles from methyl alcohol, m.p. 96° C. (Found: C, 56·4: H, 4·1; $C_9H_7O_4N$ requires C, 56·9; H, 3·6%).

VIII. 7-*Chloro*-5-*Methoxy Coumarone*

(*a*) 3-*Chloro*-2-*hydroxy*-5-*methoxy benzaldehyde*.—2-Hydroxy-5-methoxy-benzaldehyde[18] (9·5 g.) was chlorinated with sulphuryl chloride (4 ml.) in glacial acetic acid (20 ml.) as in V (*a*). The chloroaldehyde (4·5 g.) thus obtained was crystallised from ethyl alcohol as yellow needles, m.p. 80° C. (Found: C, 51·5; H, 3·8; $C_5H_7O_3Cl$ requires C, 51·4; H, 3·7%).

(*b*) 7-*Chloro*-5-*methoxy coumarone*.—Condensation of the chloro-aldehyde (2 g.) with bromoethyl malonate (1·8 g.) gave 7-chloro-5-methoxy-2-carbethoxy coumarone (1·5 g.), needles from methyl alcohol, m.p. 87° C.

(Found: C, 56·9; H, 3·8; $C_{12}H_{11}O_4Cl$ requires C, 56·6; H, 4·3%). The ester (0·3 g.) on hydrolysis gave the acid (0·22 g.), needles from methanol, m.p. 241° C. (Found: C, 52·6; H, 3·5; $C_{10}H_7O_4Cl$ requires C, 52·9; H, 3·1%). The acid (0·17 g.) on decarboxylation gave 7-chloro-5-methoxy coumarone (0·07 g.) needles from methanol, m.p. 100° C. (Found: C, 59·2; H, 3·8; $C_9H_7O_2Cl$ requires C, 59·2; H, 3·8%).

IX. 7-Bromo-5-Methoxy Coumarone

3-Bromo-2-hydroxy-5-methoxy benzaldehyde[18] (2 g.) on condensation with bromoethyl malonate (1·8 g.) yielded 7-bromo-5-methoxy-2-carbethoxy coumarone (1·5 g.) which crystallised from methyl alcohol as needles, m.p, 104–05° C. (Found: C, 48·6; H, 3·6; $C_{12}H_{11}O_4Br$ requires C, 48·2; H, 3·7%). The ester (1 g.) on hydrolysis gave the acid (0·8 g.), that crystallised from methyl alcohol as tiny needles, m.p. 210° C. (Found: C, 44·6; H, 2·9; $C_{10}H_7O_4Br$ requires C, 44·3; H, 2·6%). The acid (0·1 g.) was decarboxylated to 7-bromo-5-methoxy coumarone (0·05 g.), needles from methanol, m.p. 68° C. (Found: C, 48·0; H, 2·9; $C_9H_7O_2Br$ requires C, 47·6; H, 3·1%).

X. 7-Nitro-5-Methoxy Coumarone

Condensation of 3-nitro-2-hydroxy-5-methoxy benzaldehyde[18] (1·8 g.) with bromoethyl malonate (1·8 g.) yielded 7-nitro-5-methoxy-2-carbethoxy coumarone (1·5 g.), needles from acetone, m.p. 128° C. (Found: C, 54·6; H, 4·5; $C_{12}H_{11}O_6N$ requires C, 54·4; H, 4·2%). The ester (1 g.) on hydrolysis gave the acid (0·7 g.), needles from aqueous alcohol, m.p. 210° C. (Found: C, 50·8; H, 3·2; $C_{10}H_7O_6N$ requires C, 50·6; H, 2·9%). The acid (0·1 g.) on decarboxylation resulted in 7-nitro-5-methoxy coumarone (0·06 g.), needles from methanol m.p. 128° C. (Found: C, 56·4; H, 4·0; $C_9H_7O_4N$ requires C, 55·9; H, 3·6%).

SUMMARY

5- and 5:7-dihalo, 5-methoxy-7-halo and 5-methoxy-7-nitro, 5-halo-6-methoxy and 5-nitro-6-methoxy coumarones have been synthesised by condensing the appropriately substituted salicylaldehydes with bromomalonic ester.

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