SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XVIII. Synthesis of 6- and 7-Halo-2-Alkylchromones

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A NUMBER of 2-alkylchromones, *viz.*, Khellin and Visnagin, acquired importance because of their physiological activity.[1,2] Seshadri and co-workers investigated the fish-toxicity of 7-alkoxy-2-methyl-chromones and found that 7-methoxy and 7-allyloxy-2-methylchromones were highly toxic.[3] The fish-toxicity of halocoumarins synthesised in our laboratories showed that a halo group in 7-position is more effective than a methoxy group in the same position, 7-bromo-3-phenyl-4-methylcoumarin exhibiting appreciable toxicity to fish.[4] It has been found that among chromones, 2-methylchromones were found to be physiologically active and those that lack the 2-methyl group are devoid of any activity, suggesting that an alkyl group in 2-position is essential for chromones to exhibit any physiological activity.[5,6] In the present investigation, different alkyl chains were introduced at 2-position in 6- and 7-halochromones and changes brought about in thier insecticidal activity have been studied.

The synthesis of 6- and 7-halo-2-alkylchromones has been achieved by conducting diazotization and Sandmeyer reaction on the corresponding amino-2-alkylchromones. The synthesis of halocoumarins from amino coumarins[4] and halo-2 : 3-dimethylchromones from amino-2 : 3-dimethyl chromones[7] is known by diazotization and Sandmeyer reaction.

The 6- and 7-amino-2-alkylchromones were prepared by adopting unambiguous method, *viz.*, by the Claisen condensation of 5- and 4-acetamido-2-hydroxyacetophenones with ethylacetate, ethyl-propionate and ethyl-*n*-butyrate in the presence of sodium as catalyst and subsequent hydrolysis with alcoholic hydrochloric acid. In these condensations it was observed that with ethylacetate, 2-methylchromones were obtained directly whereas with the other two esters, liquids which could not be induced to crystallisation were obtained. These were formulated as β-diketones on the basis of their (*a*) deep ferric colour; (*b*) by the presence of two distinct absorptions in their I.R. spectra in the region around 1661 cm.$^{-1}$ and 1665 cm.$^{-1}$

assignable to carbonyl frequency; and (*c*) by their ability to undergo dehydrative cyclisation in the presence of concentrated sulphuric acid to give 6- and 7-acetamido-2-ethyl- and 2-*n*-propylchromones respectively.

To authenticate 6- and 7-halo-2-alkylchromones thus obtained, they have been prepared from the corresponding halo-2-hydroxyacetophenones, adopting Claisen condensation with those three esters in the presence of sodium. In these condensations also it is observed that with ethylacetate, 2-methyl-chromones are obtained directly whereas with the other two esters, liquids which were diagnosed as β-diketones by their positive response to the three tests outlined above have been obtained 6- and 7-halo-2-alkylchromones obtained by the direct condensation are found to be identical with those by the diazotization method.

The contrasting behaviour exhibited by the β-diketones obtained from ethylacetate and those obtained from the other two, *viz.*, ethylpropionate and ethyl-*n*-butyrate in their power of cyclisation clearly indicates that with the increase in the length of the alkyl chain in ω-acyl group of β--diketones, their power of spontaneous cyclisation is inhibited. These steric effects dwindle rapidly in the presence of strong protonating acids, like concentrated sulphuric acid, undergo smooth cyclisation even at 0° C. and furnished 6- and 7-acetamido or halo-2-alkylchromones in good yields. Further, it is also noticed that the synthesis of 6- and 7-halo-2-alkylchromones by

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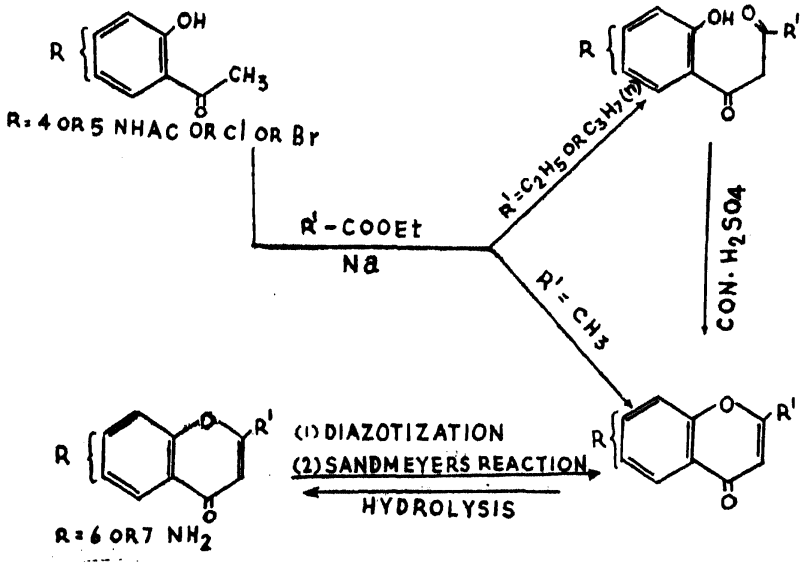

the diazotization method from the corresponding amino-2-alkylchromones is preferable to the direct condensation method from the respective halo-2-hydroxyacetophenones, considering their overall yields.

U.V. and I.R. Spectra.—The U.V. data of 6- and 7-halo-2-alkyl-chromones in ethanol reveal two distinct absorptions, one in the region 230 to 240 mμ (Band II), and the other in the region 310 to 340 mμ (Band I). The intensity of Band I is always higher than Band II in all the cases, consistent with the reported observation that 2-alkylchromones in general exhibit an absorption maximum around 250 mμ and a slightly more intense absorption around 259 to 300 mμ.[2]

The I.R. spectra of 6- and 7-acetamido-2-alkyl-chromones reveal two distinct absorptions one around 1700 $cm.^{-1}$ and the other around 1635 $cm.^{-1}$. The former may be assigned to the carbonyl in the acetamido group, while the latter to the chromone carbonyl. It is reported that chromone, in general, absorbs at 1660 $cm.^{-1}$ due to the carbonyl.[8]

Fish-toxicity.—The method of Krishnaswamy and Seshadri[9] was adopted for evaluating fish-toxicity of these compounds using freshwater fish, *Barbus ticto*. It is found that all the 2-alkylchromones in both 6- and 7-series exhibited very feeble toxicity even at 40 ppm. However, it is observed that 2-methylchromones are more toxic than the corresponding 2-ethyl- and 2-*n*-propylchromones, suggesting that the increase in the length of the alkyl chain at 2-position is not favourable to enhancing the fish-toxicity. 7-Bromo-2-methylchromone is found to possess the maximum activity among 6- and 7-halo-2-alkylchromones.

EXPERIMENTAL

(*a*) *General procedure for the synthesis of* 6- *and* 7-*amino-2-alkyl-chromones.*—In general, 5- and 4-acetamido-2-hydroxyacetophenone[10] (2 g.) was suspended in ethyl esters of acetic, propionic and *n*-butyric acids (25 ml.) and powdered sodium (5 g.) was gradually added cooling the reaction mixture in crushed ice. When the vigorous reaction subsided, the reaction was completed on a steam-bath for one more hour. The excess of sodium, invariably present, was destroyed by the slow addition of methanol. The sodium salt obtained after removing methanol was suspended in water (50 ml.) and an acid mixture containing glacial acetic acid (10 ml.) and concentrated hydrochloric acid (1 ml.) was added. The solid product obtained was purified by crystallisation from the appropriate solvent (Table I), while the liquids were extracted with ether (5 × 50 ml.) and the dried liquid

TABLE I

Sl. No.	Chromone	M.P. °C.	Shape of crystals	Molecular formula	Analytical data					
					Required			Found		
					C%	H%	N%	C%	H%	N%
1	2	3	4	5	6	7	8	9	10	11
1	6-Chloro-2-methyl ..	115[11]	..	..	..	..	..	..	..	..
2	6-Bromo-2-methyl ..	171	Square plates	$C_{10}H_7O_2Br$	50·2	3·0	..	50·1	2·9	..
3	6-Acetamido-2-ethyl ..	205[5]	..	..	..	..	..	..	..	..
4	6-Amino-2-ethyl ..	161[5]	..	..	..	..	..	..	..	..
5	6-Chloro-2-ethyl ..	138[11]	..	..	..	..	..	..	..	..
6	6-Bromo-2-ethyl ..	185	Rectangular rods	$C_{11}H_9O_2Br$	52·1	3·5	..	52·2	3·6	..
7	6-Acetamido-2-*n*-propyl ..	232	Square plates	$C_{14}H_{15}O_3N$	68·5	6·1	5·7	68·6	6·5	5·9
8	6-Amino-2-*n*-propyl ..	187	Square plates	$C_{12}H_{13}O_2N$	71·3	6·4	6·8	71·1	6·5	6·9
9	6-Chloro-2-*n*-propyl ..	125	Rectangular rods	$C_{12}H_{11}O_2Cl$	64·7	4·9	..	64·8	5·0	..
10	6-Bromo-2-*n*-propyl ..	186	Yellow square plates	$C_{12}H_{11}O_2Br$	53·9	4·1	..	54·0	4·2	..
11	7-Acetamido-2-methyl ..	248	Yellow rectangular rods	$C_{12}H_{11}O_3N$	66·3	5·0	6·4	66·4	5·4	6·5
12	7-Amino-2-methyl ..	180	Brown square plates	$C_{10}H_9O_2N$	68·5	5·1	8·0	68·4	5·2	8·2
13	7-Chloro-2-methyl ..	128	Square plates	$C_{10}H_7O_2Cl$	61·7	3·6	..	61·6	3·4	..
14	7-Bromo-2-methyl ..	141	Yellow prisms	$C_{10}H_7O_2Br$	50·2	2·9	..	50·3	2·8	..
15	7-Acetamido-2-ethyl ..	211	Square plates	$C_{13}H_{13}O_3N$	67·5	5·6	6·0	67·6	5·8	6·0
16	7-Amino-2-ethyl ..	174	Brown square plates	$C_{11}H_{11}O_2N$	69·8	5·8	7·0	69·8	5·9	7·0
17	7-Chloro-2-ethyl ..	181	Square plates	$C_{11}H_9O_2Cl$	63·3	4·3	..	63·2	4·4	..
	7-Bromo-2-ethyl ..	191	Clusters of needles	$C_{11}H_9O_2Br$	52·1	3·5	..	52·2	3·5	..
	7-Acetamido-2-*n*-propyl ..	242	Square plates	$C_{14}H_{13}O_3N$	68·7	6·1	5·7	68·6	6·3	2·8
	7-Amino-2-*n*-propyl ..	202	Square plates	$C_{12}H_{13}O_2N$	71·3	6·4	6·9	71·2	6·4	6·9
	7-Chloro-2-*n*-propyl ..	174	Rectangular rods	$C_{12}H_{11}O_2Cl$	64·7	4·9	..	64·7	5·1	..
	7-Bromo-2-*n*-propyl ..	192	Square plates	$C_{12}H_{11}O_2Br$	53·9	4·1	..	54·0	4·1	..

Unless otherwise stated, ethanol was used as the solvent for crystallisation.

was cyclised in dry chloroform (50 ml.) with concentrated sulphuric acid (10 ml.) at 0° C. The chloroform layer was washed with water, dried and the solvent removed. The solid product obtained was crystallised from the appropriate solvent. The 6- and 7-acetamido-2-alkylchromones were hydrolysed with alcoholic hydrochloric acid (100 ml.) and the product was precipitated by the addition of ammonia.

(*b*) *Diazotization and Sandmeyer reaction.*—6- and 7-amino-2-alkylchromones (200 mg.) were dissolved in concentrated sulphuric acid (5 ml.) and cooled to 0° C. Well-cooled sodium nitrite (1 g. in 1 ml. of water) was slowly added over a period of half an hour. After keeping the reaction mixture for one hour more the excess of nitrous acid was destroyed by the addition of a dilute solution of urea. A solution of cuprous chloride (1·5 g. in 5 ml. of concentrated hydrochloric acid) or cuprous bromide (1·5 g. in 5 ml. of 45% hydrobromic acid) were added to the diazotized solution. When the vigorous reaction subsided, the reaction was completed by heating on a water-bath kept at 50° C. On dilution, the halo-2-alkylchromone was precipitated and purified by crystallisation from the appropriate solvent.

(*c*) *Direct synthesis of* 6- *and* 7-*halo*-2-*alkylchromones.*—In general, 5-chloro,[11] 5-bromo,[12] 4-chloro[13] and 4-bromo[14]-2-hydroxyacetophenones (3 g.) were condensed separately with ethylacetate, ethyl-propionate or ethyl-*n*-butyrate (25 ml.), in the presence of sodium (5 g.) and the reaction mixture was worked out in the same way as outlined in the case of 6- and 7-acetamido-2-hydroxyacetophenones. The products isolated were crystallised from the appropriate solvents mentioned in Table I.

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