Tetrahedron, 1958, Vol. 2, pp. 241-245. Pergamon Press Ltd., London

STUDIES IN HALOCHALCONES AND RELATED COMPOUNDS: SYNTHESIS OF 3′:5′-DICHLORO-2′-HYDROXYCHALCONES AND THEIR DERIVATIVES

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(*Received* 17 *July* 1957)

Abstract—The condensation of 3:5-dichloro-2-hydroxy acetophenone with various aldehydes afforded chalcones, which were converted into the corresponding 6:8-dichloroflavanones by the action of dilute ethanolic hydrochloric acid. The oxidation of chalcones by means of selenium dioxide and by alkaline hydrogen peroxide gave 6:8-dichloro-flavones and -flavonols respectively. Incidentally, some chalcones from 3:5-dichloro-2-methoxyacetophenone were also prepared.

ALTHOUGH a considerable amount of work has appeared describing the synthesis of the chalcones and related compounds containing the hydroxy and alkoxy groups in different positions, those containing other substituents have been comparatively less synthesised. Some chalcones and flavonoid compounds containing alkyl,[1] amino- and acetamino-,[2] carboxyl-,[3] nitro-[4] and mono-halo-[5] groups have been described in the literature. Chalcones containing two halo-groups in the ketonic part of the molecule seem to have been hardly studied. That such compounds may possess bacteriostatic activity adds to the interest of this work. As a part of the comprehensive study of the dihalochalcones and the related heterocyclic compounds, the synthesis of 3′:5′-dichloro-2′-hydroxychalcones and the corresponding 6:8-dichloroflavonoid derivatives have been described in this communication.

3:5-dichloro-2-hydroxyacetophenone was condensed smoothly with benzaldehyde in presence of 40% alcoholic alkali. The product obtained was identified as 3′:5′-dichloro-2′-hydroxy chalcone (I) as (a) it gave a characteristic deep-red colour with concentrated sulphuric acid and red-brown colour with alcoholic ferric chloride, (b) it dissolved in sodium hydroxide with yellow coloration and (c) it gave acetyl and benzoyl derivatives confirming the presence of the free hydroxy group.

This chalcone was cyclised to the 6:8-dichloroflavanone (II) by means of dilute ethanolic hydrochloric acid.[6] Further, it was oxidised directly by means of selenium

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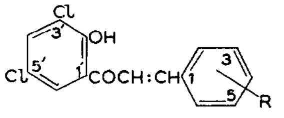
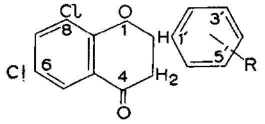
dioxide[7] in *iso*amyl alcohol to 6:8-dichloroflavone (III, R = H) and by cold alkaline hydrogen peroxide[8] to 6:8-dichloroflavonol (IV, R = —OH).

Also 3:5-dichloro-2-methoxy acetophenone (m.p. 42°) has been condensed with 2-methoxy-, 4-methoxy- and 3:4-dimethoxy- benzaldehydes by keeping the reaction mixture for 90–100 hr, and the chalcones isolated were found to be identical with the methoxy derivatives listed in Table 1 (nos. 7, 13, 24 *or* 10, 17 and 27 respectively).

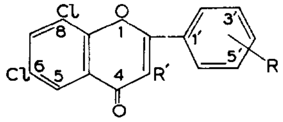
Other chalcones containing substituents in the styryl components and their flavonoid derivatives were prepared similarly. Thus, the chloro-groups in 3- and 5-positions of 2-hydroxyacetophenone nucleus do not hinder the formation of chalcones, which could also be smoothly converted into the 6:8-dichloroflavonoid compounds. This is in conformation with the other substituted chalcones studied.



(I)



(II)



(III R′ = H and OH)

EXPERIMENTAL

All melting points are uncorrected.

3:5-*Dichloro-2-hydroxyacetophenone* (m.p. 97°) was prepared by the Fries isomerisation of 2:4-dichloro phenyl acetate (1 mole) by means of anhydrous aluminium chloride (3·3 moles) at 150° for 2 hr (Yield: 55 per cent). Found: Cl, 34·21. Calc. for $C_8H_6O_2Cl_2$: Cl, 34·63.

General procedures

Chalcone (I) Caustic potash (30 ml 40 per cent) was added to a homogeneous solution of 3:5-dichloro-2-hydroxyacetophenone (2 g, 1 mole) and the aldehyde (1 mole) in ethyl alcohol (25–30 ml) with continuous shaking. The coloured reaction mixture was kept overnight at room temperature (25–30°) after heating for 5–10 min on a water-bath, when the reddish colour of the reaction mixture deepened considerably. On dilution with ice-cold water and acidifying with hydrochloric acid (1 : 1), the solid separated. It was collected, washed with dilute sodium bicarbonate solution and crystallised. In case of the chalcones, serial no. 4, 11, 21 and 24 the reaction mixture was left at room temperature for 100 hr. All chalcones gave a characteristic deep red colour with concentrated sulphuric acid.

The *benzoyl* derivative or the *acetyl* derivative was prepared by heating a mixture of the chalcone, benzoyl chloride *or* acetic anhydride and few drops of pyridine. The reaction mixture after dilution with acidulated water gave a solid which was crystallised.

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The *methoxy* derivative was prepared by refluxing at 70° a mixture of the chalcone, dimethyl sulphate, potassium carbonate (fused) and acetone (solvent) for 4–6 hr. The solid was crystallised after dilution and finally washing with acidulated water.

Flavanone (II) A hot solution of 3′:5′-dichloro-2′-hydroxy-chalcone (0·5 g) in ethanol (50 ml) was treated with hydrochloric acid (15 ml, 10 per cent) till a distinct turbidity appeared. Enough ethanol (10–15 ml) was then added to get a clear solution, which was refluxed on a water-bath for 45–50 hr. On removal of ethanol, the remaining liquid gave a solid, which crystallised from ethanol. Yield: 0·2–0·3 g. It gave a reddish colour with concentrated sulphuric acid.

TABLE 1. 3′-5′-DICHLORO-2′-HYDROXY CHALCONES (I)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
1.	Nil	Orange needles	143	$C_{15}H_{10}O_2Cl_2$	24·23	24·13
2.	Benzoyl of (1)	White plates	101	$C_{22}H_{14}O_3Cl_2$	17·88	17·70
3.	Acetyl of (1)	Yellow needles	67	$C_{17}H_{12}O_3Cl_2$	20·98	21·19
4.	2-Hydroxy	Yellowish-green shining needles (*a*)	195	$C_{15}H_{10}O_3Cl_2$	22·98	22·72
5.	Dibenzoyl of (4)	White granules (*a*)	150	$C_{29}H_{18}O_5Cl_2$	13·74	14·06
6.	Diacetyl of (4)	Yellowish prisms (*a*)	105	$C_{19}H_{14}O_5Cl_2$	18·07	17·98
7.	Dimethoxy of (4)	Discoloured granules	215	$C_{17}H_{14}O_3Cl_2$	20·11	20·31
8.	2-Methoxy	Yellow granules	143	$C_{16}H_{12}O_3Cl_2$	21·99	22·10
9.	Benzoyl of (8)	Yellow needles	81	$C_{23}H_{16}O_4Cl_2$	16·63	16·48
10.	Methoxy of (8)	Discoloured granules	215	identical	with	(7)
11.	4-Hydroxy	Shining yellow plates (*a*)	160	$C_{15}H_{10}O_3Cl_2$	22·98	22·73
12.	Dibenzoyl of (11)	White needles (*a*)	107	$C_{29}H_{18}O_5Cl_2$	13·74	13·87
13.	Dimethoxy of (11)	Golden-yellow fine needles	120	$C_{17}H_{14}O_3Cl_2$	20·11	20·00
14.	4-Methoxy	Orange needles (*a*)	165	$C_{16}H_{12}O_3Cl_2$	21·99	21·87
15.	Benzoyl of (14)	Pale-yellow granules (*a*)	105	$C_{23}H_{16}O_4Cl_2$	16·63	16·44
16.	Acetyl of (14)	Shining yellow granules	101	$C_{18}H_{14}O_4Cl_2$	19·45	19·35
17.	Methoxy of (14)	Golden-yellow small needles	120	identical	with	(13)
18.	3:4-methylenedioxy	Yellow granules (*a*)	195	$C_{16}H_{10}O_4Cl_2$	21·07	20·9
19.	Benzoyl of (18)	Shining yellow needles (*a*)	201	$C_{23}H_{14}O_5Cl_2$	15·89	16·10
20.	Acetyl of (18)	Yellow needles (*a*)	114	$C_{18}H_{12}O_5Cl_2$	18·74	18·50
21.	3-Methoxy-4-hydroxy	Deep-orange needles	195	$C_{16}H_{12}O_4Cl_2$	20·94	21·42
22.	Dibenzoyl of (21)	Yellowish-white needles	95	$C_{30}H_{20}O_6Cl_2$	12·98	12·83
23.	Diacetyl of (21)	Colourless granules (*c*)	120	$C_{20}H_{16}O_6Cl_2$	16·79	16·66
24.	Trimethoxy of (21)	Yellowish-white rectangular plates (*c*)	100	$C_{18}H_{16}O_4Cl_2$	19·35	19·11
25.	3:4-Dimethoxy	Orange needles (AcOEt)	144	$C_{17}H_{14}O_4Cl_2$	20·11	19·98
26.	Acetyl of (25)	Yellow needles	110	$C_{19}H_{16}O_5Cl_2$	17·98	17·73
27.	Methoxy of (25)	Yellowish-white rectangular plates (*c*)	100	identical	with	(24)
28.	2-Chlore	Yellow granules	137	$C_{15}H_9O_2Cl_3$	32·57	32·10
29.	Acetyl of (28)	Yellow needles (acetone)	112	$C_{17}H_{11}O_3Cl_3$	28·86	28·41
30.	Benzoyl of (28)	Yellow shining plates	115	$C_{22}H_{13}O_3Cl_3$	24·71	24·23

Flavone (III, R = H) Selenium dioxide (0·4 g) was added to 3′:5′-dichloro-2′-hydroxychalcone (0·5 g) dissolved in dry *iso*amyl alcohol (20–25 ml) and the mixture was refluxed at 150–160° for about 15 hr ($CaCl_2$ guard tube). The precipitated selenium was, then filtered and the filtrate was subjected to steam distillation to remove *iso*amyl alcohol. The brownish solid obtained on cooling the residual liquid in the flask, was crystallised as yellowish crystals. Yield: 0·2–0·3 g.

Flavonol (III, *R* = *OH*). To a solution of the chalcone (0·4 g) in ethanol (25 ml), sodium hydroxide solution (25 ml, 5 per cent) was added. The red solution was treated with hydrogen peroxide (5–7 ml, 18 per cent) after thoroughly cooling in the ice-bath and left for 3–4 hr. A solid began to separate and the colour of the solution slowly changed to yellow. The reaction mixture was then left overnight at room temperature (25–30°). On dilution with ice-cold water and acidification by dilute hydrochloric acid, a yellow solid separated which was crystallised from ethanol. Yield: 0·2–0·3 g. Flavonol was soluble in dilute sodium hydroxide giving a pale yellow solution.

TABLE 2. 6:8-DICHLORO-FLAVANONES (II)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
31.	Nil	Yellowish-white plates	115	$C_{15}H_{10}O_2Cl_2$	24·23	23·93
32.	2′-Hydroxy	Shining plates	90	$C_{15}H_{10}O_3Cl_2$	22·98	22·79
33.	2′-Methoxy	Yellow shining plates	105	$C_{16}H_{12}O_3Cl_2$	21·99	21·87
34.	4′-Hydroxy	Yellowish prismatic needles	95	$C_{15}H_{10}O_3Cl_2$	22·98	22·51
35.	4′-Methoxy	Brownish plates	118	$C_{16}H_{12}O_3Cl_2$	21·99	21·89
36.	3′:4′-methylenedioxy	Discoloured granules	255	$C_{16}H_{10}O_4Cl_2$	21·07	20·93
37.	3′-Methoxy-4′-hydroxy	Faint-yellow granules	165	$C_{16}H_{12}O_4Cl_2$	20·94	20·67
38.	3′:4′-dimethoxy	Yellowish fine needles	75	$C_{17}H_{14}O_4Cl_2$	20·11	19·67
39.	2′-Chloro	Yellowish fine needles	135	$C_{15}H_9O_2Cl_3$	32·52	32·02

TABLE 3. 6:8-DICHLORO-FLAVONES (III, R = H)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
40.	Nil	White needles	154	$C_{15}H_8O_2Cl_2$	24·40	24·05
41.	2′-Hydroxy	Discoloured granules	240	$C_{15}H_8O_3Cl_2$	23·13	22·91
42.	2′-Methoxy	Yellowish-white needles	160	$C_{16}H_{10}O_3Cl_2$	22·12	21·92
44.	4′-Hydroxy	Pale-yellow granules (*b*)	200	$C_{15}H_8O_3Cl_2$	23·13	22·96
44.	4′-Methoxy	Yellow short needles	187	$C_{16}H_{10}O_3Cl_2$	22·12	21·92
45.	3′:4′-methylenedioxy	Yellow needles	230	$C_{16}H_8O_4Cl_2$	21·19	21·09
46.	3′-methoxy-4′-hydroxy	Yellowish-white granules	147	$C_{10}H_{10}O_4Cl_2$	21·07	20·98
47.	3′:4′-Dimethoxy	Yellowish-white needles	225	$C_{17}H_{12}O_4Cl_2$	20·23	20·01
48.	2′-Chloro	White granules	190	$C_{15}H_7O_2Cl_3$	32·71	32·5

The *acetyl* derivative of flavonol was prepared by acetic anhydride–pyridine method, and was crystallised from ethanol. It is insoluble in sodium hydroxide.

All the compounds are tabulated in Tables 1–4. The solvent for crystallisation, unless otherwise mentioned, was ethanol (95 per cent) in each case. Where another solvent has been used, it is indicated in tables by letters in parenthesis along with the colour and shape of crystals (*a*, acetic acid, *b*, benzene and *c*, petrol ether b.p. 60–80°).

TABLE 4. 6:8-DICHLORO-FLAVONOLS (III, R = OH)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
49.	Nil	White shining plates	187	$C_{15}H_8O_3Cl_2$	23·13	22·95
50.	Acetyl of (49)	Yellowish needles	157	$C_{17}H_{10}O_4Cl_2$	20·3	20·18
51.	2′-Hydroxy	White needles	222	$C_{15}H_8O_4Cl_2$	21·99	21·90
52.	Acetyl of (51)	White granules	120	$C_{19}H_{12}O_6Cl_2$	17·45	17·25
53.	2′-Methoxy	Whitish-yellow needles	228	$C_{16}H_{10}O_4Cl_2$	21·07	20·97
54.	Acetyl of (53)	Yellow prismatic needles	161	$C_{18}H_{12}O_5Cl_2$	18·74	18·64
55.	4′-Hydroxy	White granules	220	$C_{15}H_8O_4Cl_2$	21·99	21·25
56.	Acetyl of (55)	White granules	145	$C_{19}H_{12}O_6Cl_2$	17·45	17·21
57.	4′-Methoxy	Orange needles	222	$C_{16}H_{10}O_4Cl_2$	21·07	20·91
58.	Acetyl of (57)	Fine yellow needles	176	$C_{18}H_{12}O_5Cl_2$	18·74	18·53
59.	3′:4′-methylene dioxy	Yellow granules	280	$C_{16}H_8O_5Cl_2$	20·33	20·00
60.	Acetyl of (59)	Yellowish needles	230	$C_{18}H_{10}O_6Cl_2$	18·07	18·09
61.	3′-Methoxy-4′-hydroxy	Yellowish-white granules	215	$C_{16}H_{10}O_5Cl_2$	20·11	19·97
62.	Acetyl of (61)	Yellowish-fine needles	136	$C_{20}H_{14}O_7Cl_2$	16·25	16·22
63.	3′:4′-dimethoxy	Yellow granules	215	$C_{17}H_{12}O_5Cl_2$	19·35	19·21
64.	Acetyl of (63)	Yellow needles	195	$C_{19}H_{14}O_6Cl_2$	17·36	17·23
65.	2′-Chloro	Clusters of white needles	194	$C_{15}H_7O_3Cl_3$	31·18	30·93
66.	Acetyl of (65)	Yellowish-white granules	182	$C_{17}H_9O_4Cl_3$	27·76	27·33