

INSECTICIDAL PROPERTIES AND CHEMICAL CONSTITUTION

Part VI. Some Phenyl and Halogen substituted Coumarins

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Received December 11, 1951

IN previous parts of this series¹⁻⁵ were presented results relating to the activity of pyrones and related compounds as fish poisons. Among them the coumarins are the easiest to prepare. A side phenyl nucleus in the 3- or 4-position of the coumarin molecule is essential for high toxicity.² It was also noticed that a hydroxyl group in the 5-position was more favourable than one in the 7-position.² In continuation, a few new compounds (coumarins) have been prepared embodying these features. 5-Hydroxy- and 5-methoxy-3-phenyl-4-methyl coumarins and 5-hydroxy- and 5-methoxy-4-phenyl coumarins have been synthesised. In order to test the influence of the presence of more phenyl groups, 3:4-diphenyl derivatives have also been prepared.

The presence of halogen atoms has been recognised as useful for the enhancement of toxic properties. In the preparation of compounds containing them, the influence of the position occupied by these atoms has to be taken into account. The preparation of the required chloro and bromo coumarins has already been described elsewhere.⁶⁻⁸ A careful investigation of the toxicity of bromo-compounds was first carried out in order to understand the influence of halogen atoms and based on this knowledge, select cases of chloro-derivatives have also been examined.

Originally *Haplochilus panchax*, a small fresh water fish, which is available on the eastern coast of India, was employed. But this is not found in Delhi and it was not easy to transport large numbers of the original fish and keep them at Delhi for experimental purposes. Hence a small fresh-water fish, commonly available in Delhi, has been used. This has been identified as *Barbus tetraurpepus*. In order to make comparisons with older data, it was necessary to carry out tests with some of the older compounds using the new fish. It was noticed that *Barbus tetraurpepus* is considerably more sensitive and therefore smaller quantities of substances could be used for the tests.

The preparation of new compounds used for the tests and not reported elsewhere is given in the experimental part. The results of toxicity experiments are presented in Tables I and II.

The introduction of a methyl or a phenyl group in the 4-position does not seem to enhance the toxic properties of 3-phenyl umbelliferone. However if the molecular weights are taken into consideration, mole for mole, 3:4-diphenyl-7-hydroxy coumarin is better than 3-phenyl umbelliferone. As expected, 5-hydroxy-3-phenyl-4-methyl coumarin is considerably more toxic than the isomeric 7-hydroxy compound. Similarly 5-hydroxy-4-phenyl coumarin exhibits high toxicity. The earlier observation¹⁻⁵ that the methyl ethers are more toxic than the corresponding hydroxy compounds is confirmed in these experiments.

Among the bromo compounds it can be readily seen that the 3-bromo derivative of 4-methyl umbelliferone is far superior to the nuclear brominated (6-) derivative. However in conjunction with a bromine atom in the 3-position, bromine atoms in the 6- and 8-positions enhance the toxic properties considerably (3:6- and 3:8-dibromo derivatives). 3:6:8-Tribromo-4-methyl umbelliferone is however far less toxic than either 3:6- or 3:8-dibromo compounds. Solubility considerations also play an important part. Whereas the 3-substituted compound is quite easily soluble, the nuclear brominated derivatives of coumarins (6- and 8- bromo umbelliferones) are far less soluble. Among the dibromo-compounds, those having bromine atoms in the 3-position are comparatively more soluble.

TABLE I

Past results with Haplochilus panchax (for comparison)²

No.	Substance	Conc. mgm. per litre	Turning time min.	Mol. wt. of sub- stance	Remarks
1	4-Methyl-7-hydroxy coumarin	200	34.5	176	
		150	58.0		
2	4-Methyl-7-methoxy coumarin	100	6.0	190	
		67	11.0		
		50	25.5		
3	3-Phenyl-7-hydroxy coumarin	100	3.5	238	
		30	15.0		
		20	29.0		
4	3-Phenyl-7-methoxy coumarin	10	9.0	252	
		5	28.5		

TABLE II
New Results with *Barbus tetraurpepus*

No.	Substance	Conc. mgm. per litre	Turning time min.	Mol. Wt. of substance	Remarks
1	3-Phenyl-7-hydroxy coumarin	30	3.2	238	
		20	5.9		
2	3-Phenyl-7-methoxy coumarin ..	5	10.0	252	
3	3-Phenyl-4-methyl-7-hydroxy coumarin ⁶ ..	20	7.5	252	
4	3-Phenyl-4-methyl-7-methoxy coumarin ⁶ ..	20	0.8	266	
		10	3.8		
		5	8.6		
5	3:4-Diphenyl-7-hydroxy coumarin ..	20	7.6	314	
6	3:4-Diphenyl-7-methoxy coumarin ..	10	18.6	328	
7	3-Phenyl-4-methyl-5-hydroxy coumarin ..	20	2.4	252	
		10	5.7		
8	3-Phenyl-4-methyl-5-methoxy coumarin ..	5	9.0	266	
9	4-Phenyl-5-hydroxy-coumarin ..	20	2.4	238	
		10	6.3		
10	4-Phenyl-5-methoxy coumarin ..	5	5.9	252	
11	3-Chloro-4-methyl-7-hydroxy coumarin ⁹ ..	80	4.4	210.5	Fish tried to jump out at the beginning. All the fish died within 5.5 min. after turning
		40	10.0		All the fish died immediately after turning
12	3-Chloro-4-methyl-7-methoxy coumarin ⁷ ..	20	4.8	224.5	
13	3-Chloro-4:7-dimethyl-5-hydroxy coumarin ⁹	20	57.0	224.5	
14	3-Bromo-4-methyl-7-hydroxy coumarin ¹⁰ ..	80	4.2	255	One fish died immediately
		40	9.5		All fish died immediately
15	3-Bromo-4-methyl-7-methoxy coumarin ¹¹ ..	20	6.4	269	
16	4-Bromomethyl-7-hydroxy coumarin ⁶ ..	80	27.3	255	
17	6-Bromo-4-methyl-7-hydroxy coumarin ^{12, 13}	40	..	255	No effect in 15 hours
18	6-Bromo-4-methyl-7-methoxy coumarin ¹³ ..	13	..	269	No effect in 2 hours
19	3:6-Dibromo-4-methyl-7-hydroxy coumarin ¹⁰	40	4.0	334	One fish died
20	3:8-Dibromo-4-methyl-7-hydroxy coumarin ¹⁰	40	3.0	334	The fish jumped violently
21	3:6:8-Tribromo-4-methyl-7-hydroxy coumarin ¹⁰ ..	40	18.0	413	
22	3-Bromo-4-phenyl-7-hydroxy coumarin ⁸ ..	20	9.6	317	Fish very much affected. Recovered only very slowly
		10	19.5		Two fish died
23	3-Bromo-4-phenyl-7-methoxy coumarin ⁸ ..	10	5.9	331	The fish were very restless and were affected seriously
24	3-Chloro-4-phenyl-7-methoxy coumarin ⁸ ..	10	5.3	286.5	
25	6-Bromo-3-phenyl-7-hydroxy coumarin ⁶ ..	20	5.8	317	
26	8-Bromo-3-phenyl-7-hydroxy coumarin ⁶ ..	20	7.1	317	Fish tried to jump out
27	6:8-Dibromo-3-phenyl-7-hydroxy coumarin ⁶	20	9.4	396	All the fish died immediately after turning
28	6:8-Dibromo-3-phenyl-4-methyl-7-hydroxy coumarin ⁶	20	..	410	No effect in 25 min.

The bromo derivatives of 3-phenyl umbelliferone are not more useful than the unsubstituted coumarin itself. Here again comparison of molar quantities would lead to the conclusion that bromination in this series also

enhances toxic properties slightly. The bromo derivatives of 3-phenyl-4-methyl umbelliferone and the methyl ethers of brominated 3-phenyl umbelliferones⁶ could not be tested owing to their low solubilities. Although 6:8-dibromo-3-phenyl umbelliferone is not as toxic as 3-phenyl umbelliferone, it has a greater lethal effect since all the fish employed in the experiment using it died immediately after turning.

Bromo and chloro derivatives have nearly the same toxicity and therefore substitution of chlorine atoms in place of bromine atoms does not have a marked effect. Considering molar proportions, bromo-compounds may be said to be the better of the two. But chloro-compounds should be eventually cheaper to prepare and they seem to be more soluble.

One negative substituent, a phenyl group in either the 3- or the 4-position or a halogen atom in the 3-position increases toxicity considerably, the effect of the former being far more prominent. But the effect of further substitution in these positions is not additive. 3:4-Diphenyl umbelliferone and 3-bromo-4-phenyl umbelliferone and their methyl ethers and 3-chloro-4-phenyl-7-methoxy coumarin are less toxic than the related monophenyl umbelliferones and their methyl ethers. This is in agreement with an earlier observation in the case of chromones,⁴ where it was found that 7-hydroxy-2:3-diphenyl chromone was much less toxic than 7-hydroxy-2-phenyl or 7-hydroxy-3-phenyl chromone.

3-Chloro-4:7-dimethyl-5-hydroxy coumarin seems to have an unexpectedly low toxicity, taking into consideration the high toxicity exhibited in general by 5-hydroxy coumarins. This could possibly be explained as due to the presence of a methyl group in the 7-position which could exert an effect somewhat similar to an hydroxyl group. If such is the case, the result is not unusual since 5:7-dihydroxy-4-methyl coumarin in which both the 5- and 7-positions are occupied is much inferior to either 5- or 7-hydroxy-4-methyl coumarin.²

EXPERIMENTAL

3:4-Diphenyl-7-acetoxy coumarin

Resbenzophenone¹⁵ (4 g.), sodium phenyl acetate (8 g.) and acetic anhydride (50 c.c.) were heated together at 170–80° for four hours and the mixture poured into crushed ice. A yellow semi-solid mass separated out on leaving overnight. The aqueous layer was decanted off and the semi-solid washed first with water and then with petroleum ether by decantation. The residual petroleum ether was removed on a water bath. On adding alcohol to the residue, a colourless solid separated out. It was filtered and

washed with cold alcohol. Yield 6 g. On crystallisation from alcohol, 3:4-diphenyl-7-acetoxy coumarin was obtained as colourless rectangular prisms melting at 222–23°. (Found: C, 77.3; H, 4.6; $C_{23}H_{16}O_4$ requires C, 77.5; H, 4.5%.) Bargellini¹⁴ carried out this reaction for 30 hours and obtained a poor yield of the acetate, which he describes as yellowish crystals, m.p. 220°.

3:4-Diphenyl-7-hydroxy coumarin

The above acetate (4 g.) was dissolved in aqueous alcohol (1:2; 200 c.c.) and concentrated sulphuric acid (10 c.c.) was added and the solution refluxed for 2 hours. On cooling, the 7-hydroxy compound separated. Yield 3 g. It was crystallised twice from alcohol. It was obtained in the form of stout colourless prisms melting at 286–87°. Further crystallisations did not raise the m.p. It was sparingly soluble in alcohol. Bargellini¹⁴ gives the m.p. as 290° (Found: C, 80.0; H, 4.4; $C_{21}H_{14}O_3$ requires C, 80.3; H, 4.5%).

3:4-Diphenyl-7-methoxy coumarin

3:4-Diphenyl-7-hydroxy coumarin (2.8 g.) was dissolved in dry acetone (200 c.c.) and dimethyl sulphate (0.93 c.c.) and anhydrous potassium carbonate (5 g.) were added and the mixture gently refluxed for 6 hours. The acetone solution was filtered off and the potassium salts were washed with warm acetone. The solvent was distilled off and the residue treated with water to decompose excess of dimethyl sulphate. The solid was filtered and when dry, crystallised from benzene. It separated as colourless rectangular rods, m.p. 175–77°. Yield 2.5 g. (Found: C, 80.4; H, 4.8; $C_{22}H_{16}O_3$ requires C, 80.5; H, 4.9%).

3-Phenyl-4-methyl-5-hydroxy coumarin

A mixture of 2:6-dihydroxy acetophenone¹⁶ (4 g.), fused sodium phenyl acetate (8 g.) and acetic anhydride (50 c.c.) was heated at 170–80° for 4 hours. The product was crystallised twice from alcohol when it separated as colourless stout rectangular rods melting at 150–52°. Yield 5.5 g. This acetate (5 g.) was hydrolysed with 10% alcoholic sulphuric acid (150 c.c.) by refluxing on a water-bath for one hour. The solution was diluted with water (100 c.c.) and the alcohol was distilled off. The mixture was cooled and the precipitate of 5-hydroxy-3-phenyl-4-methyl coumarin filtered off. Yield 4 g. It was crystallised twice from alcohol. Colourless rectangular prisms, m.p. 276–78°. It did not give any colour with alcoholic ferric chloride and dissolved easily in dilute aqueous sodium hydroxide and dilute aqueous sodium carbonate to give yellow solutions. These reactions show that the product is a 5-hydroxy coumarin and not a 5-hydroxy chromone (Found: C, 76.5; H, 5.2; $C_{11}H_{16}O_3$ requires C, 76.2; H, 4.8%).

3-Phenyl-4-methyl-5-methoxy coumarin

The above hydroxy coumarin (1.32 g.) was methylated with dimethyl sulphate (0.6 c.c.) and anhydrous potassium carbonate (3 g.) in dry acetone solution. 3-Phenyl-4-methyl-5-methoxy coumarin (1 g.) was crystallised twice from alcohol. It separated as colourless prisms tapering at both ends. m.p. 165–66° (Found: C, 77.1; H, 5.2; $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%).

4-Phenyl-5-acetoxy coumarin

A mixture of 2:6-dihydroxy benzophenone¹⁷ (4 g.), fused sodium acetate (10 g.) and acetic anhydride (50 c.c.) was refluxed on an oil bath at 170–80° for 24 hours, cooled and poured into crushed ice. A heavy viscous brown oil separated on leaving overnight. It was separated from the aqueous portion by decantation, was washed first with water and then thrice with petroleum ether. The traces of petroleum ether remaining were removed by heating on a water bath. Treatment of the residual oil with cold alcohol (10 c.c.) yielded a colourless solid, which was filtered and washed with alcohol. Yield 1.7 g. It crystallised from alcohol as colourless stout prisms melting at 170–71° (Found: C, 72.8; H, 4.4; $C_{17}H_{12}O_4$ requires C, 72.9; H, 4.3%).

4-Phenyl-5-hydroxy coumarin

4-Phenyl-5-acetoxy coumarin (3 g.) was refluxed with 10% alcoholic sulphuric acid (150 c.c.) for a period of two hours. The solution was diluted with water (100 c.c.) and as much of the alcohol as possible was distilled off on a water-bath. On cooling, the hydroxy coumarin separated out. Yield 2.5 g. It crystallised from alcohol as very stout prismatic crystals melting at 221–22°. It did not give any colour with ferric chloride in alcoholic solution and was soluble in aqueous sodium carbonate to give a yellow solution (Found: C, 75.2; H, 4.2; $C_{15}H_{10}O_3$ requires C, 75.6; H, 4.2%).

4-Phenyl-5-methoxy coumarin

4-Phenyl-5-hydroxy coumarin (0.7 g.) was methylated in dry acetone solution with dimethyl sulphate (0.35 c.c.) and excess of potassium carbonate. 5-Methoxy-4-phenyl coumarin crystallised from alcohol as stout rectangular prisms melting at 98–100° (Found: C, 76.1; H, 4.5; $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.8%).

SUMMARY

A number of phenyl and halogen substituted coumarins with substituents in different positions have been examined as fish poisons. The presence of a phenyl group in the 3 or 4 position or a halogen atom in the

3-position seems to be most favourable. Higher substitution does not appreciably enhance the toxic properties. In consonance with previous results, a hydroxyl group in the 5-position seems to produce greater toxicity than one in the 7-position.

Our thanks are due to Mr. N. Majumdar of the Department of Zoology, Delhi University, for his help in the collection of fish used in this work and for the identification. We are grateful to the Council of Scientific and Industrial Research for a grant-in-aid in support of this investigation.

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