INSECTICIDAL PROPERTIES AND CHEMICAL CONSTITUTION

Part II. Coumarins

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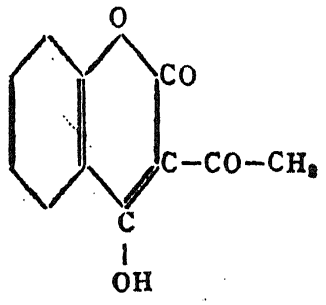
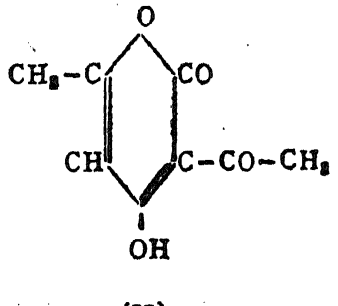
IN Part I[1] it was shown that the methyl ethers of some of the simpler flavones are markedly toxic to fish. They have in them the characteristic toxophore $-CO-C=C-O-$ also found in rotenone. Results recorded by previous workers relating to the simpler coumarins having the toxophore $-C=C-CO-O-$ suggest that they are comparatively feeble. Späth[2] found that 175·5 mg. of 4-methyl umbelliferone and 63·7 mg. of 7-ethoxy coumarin per litre of water were necessary for causing death of fish in 8 hours. The more potent among the compounds studied by him contain also furan rings and other complications. Later Mahal[3] noted that 4-methyl umbelliferone does not possess appreciable anthelmintic properties. Again Läuger *et al.*[4], though they have not presented details, have reported that the simpler coumarins have only weak insecticidal properties. They observed very good strength only in the case of 4-hydroxy coumarins with a carbonyl substituent in the 3-position (I). This discovery was based on the similarity in structure between those compounds and dehydracetic acid (II) which has also very good insecticidal properties.



(I)

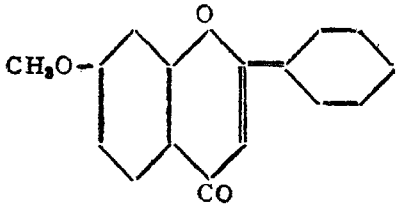


(II)

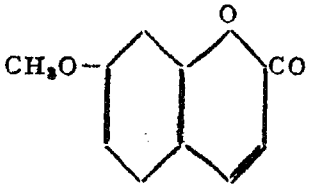
It appeared to be necessary to study the cause of this marked difference in toxicity between the simple coumarins and the simple flavones. An examination of a number of simple coumarin derivatives employing fish and the 'turning time' as a measure of toxicity has now established that they have weak toxic properties. For example, 7-hydroxy flavone takes

about 12 hours to show toxic symptoms in a concentration of 20 mg. per litre whereas for umbelliferone a concentration of more than 200 mg. per litre is found to be necessary; 7-methoxy flavone (III) in a concentration of 10 mg. per litre has a 'turning time' of 5·5 minutes while 7-methoxy coumarin (IV) is required in a concentration of 100 mg. per litre to produce the toxic effect in about 7 minutes.

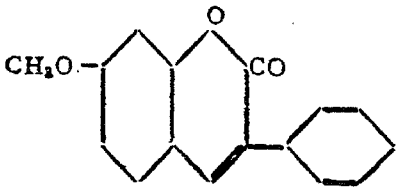
It appeared to be possible that the above difference may not all be due to the difference in the toxophores, but due to the absence of a side phenyl nucleus in the coumarins studied. Consequently, 3-phenyl and 4-phenyl umbelliferones and their methyl ethers (V and VI) were tested. These compounds are considerably more toxic and compare favourably with the isomeric flavone derivatives. 3-Phenyl umbelliferone seems to be even better than 7-hydroxy flavone. The methyl ethers are somewhat weaker than 7-methoxy flavone; however, they seem to have the same order of toxicity. Isomerism in the methyl ethers of the phenyl coumarins does not seem to make much difference in toxicity though in the case of the hydroxy compounds difference in the position of the side phenyl nucleus seems to have a marked effect.



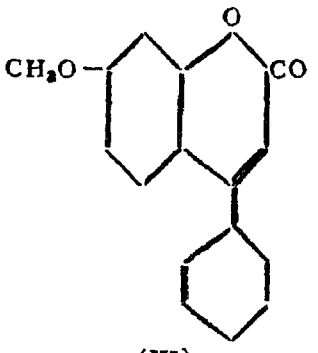
(III)



(IV)



(V)



(VI)

The data obtained in the experiments carried out with a large number of coumarin derivatives are given in the accompanying table. One important point that emerges from these results relates to the marked effect of concentration in many of the compounds of the weak type. Below what might be considered as the critical concentration, the effect seems to drop off very markedly; on the other hand above that concentrations the rise in toxicity is also marked.

(ge.)=gelatin added

Name of the Compound	Concentration, milligrams per litre	Turning time
1. 7-Methoxy flavone ..	10	5·5 min.
2. Umbelliferone ..	200	12 hrs.
	100	No effect in 24 hrs.
3. 7-Methoxy coumarin ..	150	3·0 min.
	100	6·5 ,,
	20 and 50	No effect in 5 hrs.
4. 3-Phenyl umbelliferone ..	100 ge.	3·5 min.
	30 ,,	15·0 ,,
	20 ,,	29·0 ,,
5. 3-Phenyl-7-methoxy coumarin ..	10 ,,	9·0 ,,
	5 ,,	28·5 ,,
6. 4-Phenyl umbelliferone ..	100 ,,	5·0 ,,
	80 ,,	35·5 ,,
7. 4-Phenyl-7-methoxy coumarin ..	20 ,,	5·0 ,,
	10 ,,	11·5 ,,
	5 ,,	31·0 ,,
8. 7-Hydroxy-5-methyl-3-phenyl coumarin ..	40 ,,	10·0 ,,
	20 ,,	16·5 ,,
9. 7-Methoxy-5-methyl-3-phenyl coumarin ..	10 ,,	18·0 ,,
10. 3-Acetyl-umbelliferone ..	200 ,,	29·5 ,,
11. 3-Acetyl-7-methoxy coumarin ..	20 ,,	No effect in 3 hrs.
12. 3-Benzoyl-7-methoxy coumarin ..	20 ,,	do
13. 3-Carbethoxy-7-methoxy coumarin ..	50 ,,	13·0 min.
	30 ,,	25·0 ,,
	20 ,,	42·0 ,,
14. 4-Methyl umbelliferone ..	200	34·5 ,,
	150	58·0 ,,
	100	No effect in 20 hrs.
15. 4-Methyl-7-methoxy coumarin ..	100 ge.	6·0 min.
	67 ,,	11·0 ,,
	50 ,,	25·5 ,,
	33 ,,	About 15 hours
16. 5-Methoxy-4 methyl coumarin ..	30	3·0 min.
	20	5·0 ,,
	10	No effect in 18 hrs.
17. 5-Hydroxy-4:7-dimethyl coumarin ..	200 ge.	39·5 min.
18. 5-Methoxy-4:7-dimethyl coumarin ..	40 ,,	7·0 ,,
	20 ,,	12·5 ,,
19. 6-Hydroxy-4-methyl coumarin ..	200	11·5 ,,
20. 6-Methoxy-4-methyl coumarin ..	100 g.	25·0 ,,
21. 7-Hydroxy-5-methyl coumarin ..	200 ,,	27·0 ,,
	100 ,,	No effect in 24 hrs.
22. 5:7-Dihydroxy-4-methyl coumarin ..	200 ,,	do
23. 5:7-Dimethoxy-4-methyl coumarin ..	20 ,,	14·5 min.
	10	34·0 ,,
24. 7:8-Dihydroxy-4-methyl coumarin ..	200	No effect in 12 hrs.
25. 7:8-Dimethoxy-4-methyl coumarin ..	50 ge.	19·0 min.
	30 ,,	No effect in 4 hrs.
26. 5:7-Dihydroxy-3-phenyl coumarin ..	30 ,,	No effect in 16 hrs.
27. 5:7-Dimethoxy-3-phenyl coumarin ..	10 ,,	No effect in 5 hrs.

In the case of a number of compounds in which the solubility in water is inadequate for the purpose of the experiments, it has been found that the concentration could be considerably increased by the preliminary addition of gelatin; ordinarily about one gram per litre of water is found

to be adequate. That gelatin has no effect on the toxic properties under these conditions has been proved by means of blank and comparative experiments.

Amongst the number of the coumarin derivatives examined the 5-methoxy compounds appear to show some promise though they are more difficult to prepare. A more detailed study of this type of compounds will be described later. A methyl group situated in the 4-position seems to have a favourable influence. But a further addition of this group in the 7-position decreases the effect. An interesting point relates to the comparative effect of an acetyl, carbethoxyl, and phenyl groups in the 3-position of the umbelliferones and their methyl ethers. The results suggest that as given above they are in the rising order of toxicity, whereas Lauger *et al.* using compounds devoid of the hydroxyl and methoxyl groups found that 3-acetyl (as in 3-acetyl coumarin) is somewhat more powerful than the phenyl or carbethoxyl.

Summary

The simpler coumarins are considerably less toxic as compared with the simpler flavones. This could be attributed to the lack of a side-phenyl nucleus in the former. 3-Phenyl and 4-phenyl umbelliferones and their methyl ethers are found to be highly toxic and compare favourably with 7-hydroxy and 7-methoxy-flavones. A large number of related coumarin derivatives have been studied for their toxicity towards fish.

References

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2. Späth and Kuffner .. *Monatsh*, 1936, **69**, 75.
3. Mahal .. *Proc. Ind. Acad. Sci.*, B, 1937, **5**, 186.
4. Läuger, Martin and Müller .. *Helv. Chim. Acta.*, 1944, **27**, 925.