INSECTICIDAL PROPERTIES AND CHEMICAL CONSTITUTION

Part V. Flavanones and Chalkones

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SINCE flavanones have a dihydropyrone ring they resemble in structure rotenone and its allies more closely than the flavones do. Consequently a study of their toxic properties will be useful. They occur fairly widely in nature mainly in the form of glycosides. Except for the capacity of hesperidin and eriodictyn to serve as vitamin-P[1] and the marked bitterness of naringin,[2] very little is known about their physiological properties. The chalkones are closely related to flavanones and also occur in nature though not so widely. The reputed anthelmintic property of kamala seems to be due to the presence of rottlerin[3] which has the chalkone structure.[4] This indicated the need for the study of the simpler chalkones also.

The method adopted for the tests using fresh-water fish (*Haplochilus panchax*) has already been indicated in our earlier publication on this subject.[5] It is desirable to use porcelain troughs for the experiments in order to minimise injury to the fish when they strike against the side in their anxiety to get away. It is also necessary to provide a glass cover for the trough since in most cases the fish attempt to jump out. The reactions of fish vary considerably under the influence of different substances. Some times an extraordinary tendency is exhibited to jump out; this is totally absent in some other cases; with some substances wriggling is prominent.

The following table gives a summary of the results using a number of flavanones and chalkones.

The chalkones and flavanones listed in the above table have been prepared following the methods described in the literature with slight modifications. The completely methylated chalkones have been obtained by the methylation of the corresponding 2-hydroxy compounds with dimethyl sulphate and potassium carbonate in anhydrous acetone medium. Derivatives of naringenin have been prepared by the partial and complete methylation of naringenin and of naringin accompanied by hydrolysis. Details will be given later in some other connection. Pedicellin required for the tests has been isolated from the leaves of *Didymocarpus pedicellata*.[13]

TABLE

(ge = gelatin added)

No.	Name of the compound	Concentration in milligrams per litre	Turning time in minutes	Remarks
1	7-Hydroxy-flavanone[6] ..	50 (ge)	16·0	Fish not recovered
		30 (ge)	27·0	
2	7-Methoxy-flavanone[7] ..	30 (ge)	4·0	
		20	6·0	
		10	12·0	
3	5-Methoxy-flavanone ..	10 (ge)	..	No effect in 2 hours
		20 (ge)	..	Turbidity developed
4	5-Hydroxy-7-methoxy-flavanone[8] ..	10 (ge)	20·5	
		20 (ge)	..	Solid separated
5	5 : 7-Dimethoxy-flavanone[7] ..	30 (ge)	3·5	
		20 (ge)	6·0	
		10 (ge)	16·0	
6	7-Hydroxy-4′-methoxy-flavanone[7] ..	40 (ge)	22·5	
		20 (ge)	120·0	
7	Naringenin (5 : 7 : 4′-trihydroxy-flavanone) ..	150	53·0	
		100	90·0	
8	Isosakuranetin(4′-methyl-ether of Naringenin)	40 (ge)	31·5	
		20 (ge)	285·0	
9	Naringenin-7 : 4′-dimethyl-ether ..	10 (ge)	17·0	Fish exhibit marked tendency to jump
		20 (ge)	..	Turbidity developed
10	5 : 7 : 4′-Trimethoxy-flavanone (Naringenin-trimethyl-ether)	20 (ge)	9·0	
		10 (ge)	29·5	
11	4′-Methylether of butin[9] ..	50 (ge)	..	No effect in 20 hours
12	Butin trimethylether[10] (7 : 3 : 4′trimethoxy-flavanone)	20	9·0	
		10	21·0	
13	5 : 7 : 3′ : 4′-tetramethoxy-flavanone[11] ..	40 (ge)	16·5	
		20	40·0	
14	2 : 4-Dihydroxy-chalkone[6] ..	60 (ge)	14·0	
		40 (ge)	19·5	
15	2-Hydroxy-4-methoxy-chalkone[12] ..	10 (ge)	..	Fish slightly affected and blackening was noticed. Solid separated after 2 hours
16	2-Hydroxy-6-methoxy-chalkone ..	20 (ge)	7·5	Recovery slow
		10 (ge)	17·0	
17	2 : 4-Dihydroxy-4′-methoxy chalkone[7] ..	30 (ge)	9·0	
		20 (ge)	15·0	
18	2-Hydroxy-4: 4′-dimethoxy-chalkone ..	20 (ge)	..	Separation of solid
		10 (ge)	..	do
19	2-Hydroxy-4 :6-dimethoxy-chalkone[7] ..	30 (ge)	12·0	
		20 (ge)	18·0	
20	2-Hydroxy-4 : 6 : 4′-trimethoxy-chalkone ..	10 (ge)	..	Solid separated. Slight toxicity. Fish exhibit tendency to jump
21	2 : 4 : 4′-Trihydroxy-3′-methoxy-chalkone ..	50	24·5	Fish blackened
		40	29·0	
22	2-Hydroxy-4 : 3′ : 4′-trimethoxy-chalkone[10] ..	10 (ge)	59·0	
		20 (ge)	..	Solid separated
23	2 : 4 : 6-Trimethoxy-chalkone ..	20 (ge)	5·0	Violent jumping
		10 (ge)	12·5	
24	2 : 4 : 6 : 4′-Tetramethoxy-chalkone ..	30 (ge)	9·5	Violent jumping
		20 (ge)	14·0	
25	Pedicellin[13] ..	30 (ge)	9·0	Slight reddening
		20 (ge)	18·0	

With regard to their toxicity, the flavanones resemble the flavones in a general way. They are definitely and markedly toxic thus supporting the presence of a toxophore in them. The simpler hydroxy and methoxy compounds are highly toxic and the toxicity falls off with increase in these groups (compare 2, 5, 10, 12 and 13). The methyl ethers are far more toxic than the corresponding hydroxy compounds. Further the presence of more than one methoxyl in the side-phenyl nucleus brings down the potency markedly (compare 10 and 13) and in some compounds the presence of a free 5-hydroxyl enhances toxicity (compare 9 and 10) but not in all cases. There is a big drop in toxicity from isosakuranetin (8) to naringenin (7); this may indicate the marked effect of a free hydroxyl in the 4′-position. Compared with the corresponding derivatives of flavones, the methyl ethers of flavanones are somewhat less toxic, whereas the hydroxy compounds are more toxic. For example, 7-methoxy-flavanone is less toxic than 7-methoxy-flavone which gives a turning time of 5 minutes for 10 mg. It approximates to the methoxy-phenyl-coumarins. On the other hand, 7-hydroxy-flavanone is considerably more toxic than 7-hydroxy-flavone and it approximates to 3-phenyl-umbelliferone. It is remarkable that 5-methoxy-flavanone has no marked toxic property whereas the isomeric 7-methoxy-compound is so powerful. Similar lowering of toxicity has already been noted in regard to 5-methoxy-flavone also (see Part IV[14]).

The chalkones are also definitely toxic and the effect of adding hydroxyl and methoxyl groups are in general the same as in the flavanones. In the case of some of the hydroxy compounds though the toxic effect was slow in coming on, the recovery of the fish when returned to fresh water was also slow and in some cases they died. Such an effect in a much more marked manner has been noticed with rottlerin[15] which is also a hydroxy-chalkone; in this case the fish do not recover at all and die immediately after turning upside down. Comparing the flavanones with the corresponding isomeric chalkones the following points emerge. Hydroxy-flavanones (1, 6 and 11) are much weaker than the isomeric chalkones (14, 17 and 21) whereas with the flavanone methyl ethers the reverse is the case (compare 2, 5, 10 and 12 with 15, 19, 20 and 22). It should be noted however as an exception that 2-hydroxy-6-methoxy chalkone (16) is markedly toxic whereas the isomeric 5-methoxy flavanone (3) has very little toxicity. A further interesting feature is that as soon as the remaining ortho-hydroxyl group in the chalkone is also methylated the fully methylated chalkones are considerably more toxic (see 23 and 24). In this connection the behaviour of the naturally occurring chalkone pedicellin (25) is interesting. Though it has five methoxyl groups it is appreciably toxic to fish.

Summary

The toxic properties of a number of simple hydroxy and methoxy flavanones and chalkones have been studied using fresh-water fish. The flavanones resemble the flavones in a general way. However the methyl ethers of the flavanones appear to be less toxic than the corresponding flavone derivatives, whereas with the hydroxy compounds the reverse seems to be the case.

With the chalkones the toxic symptoms set in more slowly but they are more persistent. The methoxy chalkones are less toxic than the isomeric flavanones whereas when a number of hydroxyl groups are present the reverse is the case. As soon as all the hydroxyl groups in chalkones are methylated the toxicity increases considerably.

References

1. Brückner and Gyorgyi .. *Nature*, 1936, **138**, 1057.
   Bentsath, Rusznyak and Gyorgyi .. *Ibid.*, 1937, **139**, 326.
2. Asahina and Inubuse .. *J. Pharm. Soc. Japan*, 1929, **49**, 128.
3. Semper .. *Arch. Exp. Path. Pharm.*, 1910, **63**, 10.
4. McGookin, Robertson and Tittenser .. *J. C. S.*, 1939, 1579.
5. Krishnaswamy and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1942, **16**, 231.
6. Ellison .. *J. C. S.*, 1927, 1720.
7. Shinoda .. *J. Pharm. Soc. Japan*, 1928, **48**, 214.
8. Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1946, **23**, 213.
9. ———— .. *Ibid.*, 1941, **14**, 29.
10. Perkin and Hummel .. *J. C. S.*, 1904, **85**, 1459.
11. Kostanecki, Lampe and Tambor .. *Ber.*, 1904, **37**, 1402.
12. Bargellini and Monti .. *Gazz. Chim. ital.*, 1914, **44 II**, 25.
13. Siddiqui .. *J. I. C. S.*, 1937, **14**, 703.
14. Murti, Row and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1948
15. Rao and Seshadri .. *Ibid.*, A, 1947.