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THE EXTRACTIVES OF *PISCIDIA ERYTHRINA* L.—I

THE CONSTITUTION OF ICHTHYNONE

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Abstract—Ichthynone isolated from Jamaican Dogwood, *Piscidia erythrina L.*, is shown to be the isoflavone (VII).

THE Jamaican Dogwood, *Piscidia erythrina* L.,* has been the subject of a large number of investigations concerned with the variety of physiological effects attributed to this plant and the numerous attempts to isolate the active principles responsible for these unusual claims have been reviewed.[1] More recent studies include the determination of the structures of piscidic acid[2] and jamaicin,[3] and two further examinations[4,5] of the extractives of *Piscidia erythrina* L. have led to the isolation of several new natural products. The determination of the structures of several of these, including lisetin, is in progress.[6] It may be noted that previous investigators have not always isolated the same natural products from what is described as the same plant source, and it is possible that *Piscidia erythrina* L. exists in various varietal forms or that its constituents vary with the conditions of growth.

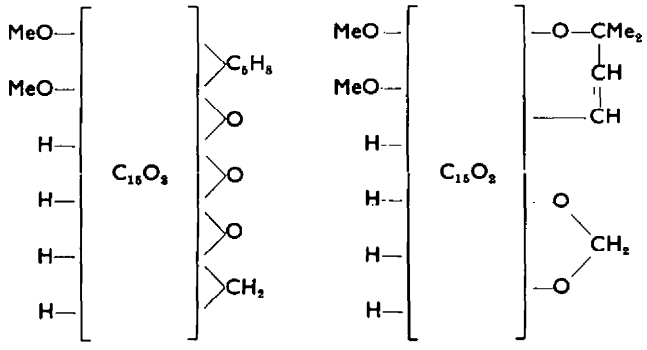
The root bark of Jamaican Dogwood has been used extensively throughout Central and South America as a fish narcotic and Russell and Kaczka[7] isolated from this source two substances which were both toxic to fish. One was identified as rotenone and the other was called ichthynone. The first structural investigation[7] of ichthynone was only exploratory. The molecular formula $C_{21}H_{14}O_5(OMe)_2$ was proposed and on the basis of a few reactions a relation between ichthynone and the rotenoids was suspected.

The study of ichthynone now reported was initiated by three of us (W.D.O., E.A.K., and L.M.J.) on the original sample[7] of ichthynone, but later it was discovered that a more extensive investigation (by J.S.P.S. and A.I.C.) was also being carried out simultaneously. The results of the two groups were complementary and defined the structure of ichthynone, so it was agreed to publish the results jointly.

* On several occasions the names *Ichthyomethia piscipula* L., A. Hitch. and *Piscidia piscipula* have been used for this plant, but according to *Index Kewensis* these names are not correct and *Piscidia erythrina* L. should be used.

[1] E. G. Auxence, *Economic Botany* **7**, 270 (1953).
[2] W. Bridge, F. Coleman and A. Robertson, *J. Chem. Soc.* 257 (1958).
[3] O. A. Stamm, H. Schmid and J. Büchi, *Helv. Chim. Acta* **41**, 2006 (1958).
[4] J. A. Moore and S. Eng, *J. Amer. Chem. Soc.* **78**, 395 (1956).
[5] A. L. Kapoor, A. Aebi and J. Büchi, *Helv. Chim. Acta* **40**, 1574 (1957).
[6] C. P. Falshaw, J. A. Moore and W. D. Ollis, unpublished results.
[7] A. Russell and E. A. Kaczka, *J. Amer. Chem. Soc.* **66**, 548 (1944).

On biosynthetic grounds the molecular formula $C_{21}H_{14}O_5(OMe)_2$ for ichthynone was possibly compatible with the presence of a $C_{15}O_2$-nucleus of the flavonoid or isoflavonoid type in association with an isoprenoid C_5-residue.[8] Absorption in the hydroxyl region of the IR spectrum of ichthynone was absent and the fact that its UV spectrum was unchanged in the presence of base suggested that phenolic hydroxyl groups were absent. This led to the consideration of the partial formula (I) for ichthynone, which immediately indicated that the remaining carbon atom in the ichthynone structure might well be present as a methylenedioxy group. This was supported by the observation that ichthynone gave a pronounced green coloration with concentrated sulphuric acid and ethanolic gallic acid.[9]



The nature of the groups present in the ichthynone structure were indicated by its NMR spectrum (Table 1) and the high field singlets could be assigned to two methoxyl groups (τ 6·06 and 6·28) and one methylenedioxy group[10–12] (τ 4·07). The doublets (τ 3·21 and 4·29; J = 10 c/sec) each equivalent to one proton, and the singlet (τ 8·44) equivalent to six protons are highly characteristic of the *cis*-olefinic and *gem*-dimethyl groups of a 2,2-dimethylchromene structure.[13] The 2,2-dimethylchromene and the methylenedioxy groups are indicated in the partial formula (II) and in this formula the four separately indicated protons must be uncoupled as they give rise to singlets (τ 2·11, 2·47, 3·20 and 3·39).

The IR spectrum of ichthynone showed features characteristic of the 2,2-dimethylchromene system[13] with bands at 1375 and 1360 cm^{-1} attributable to the *gem*-dimethyl group and a band at 1590 cm^{-1} to be expected for the styrenoid carbon-carbon double bond. Bands present at 1040 and 940 cm^{-1} are to be expected for the methoxyl and methylenedioxy groups.[14] Ichthynone showed a carbonyl band at 1640 cm^{-1} as do chromones or 5-hydroxychromanones, but the latter could be excluded on several grounds. Ichthynone gave no coloration with ethanolic ferric chloride, its

[8] W. D. Ollis and I. O. Sutherland, *Chemistry of Natural Phenolic Compounds* (Edited by W. D. Ollis) p. 74. Pergamon, London (1961).
[9] J. A. Labat, *Bull. Soc. Chim. Biol.* **15**, 1344 (1933).
[10] S. Goodwin, J. N. Shoolery and L. F. Johnson, *Proc. Chem. Soc.* 306 (1958); I. R. C. Bick, J. Harley-Mason, N. Sheppard and M. J. Vernengo, *J. Chem. Soc.* 1896 (1961).
[11] L. Crombie and J. W. Lown, *J. Chem. Soc.* 775 (1962).
[12] L. Crombie and D. A. Whiting, *J. Chem. Soc.* 1569 (1963).
[13] B. F. Burrows, W. D. Ollis and L. M. Jackman, *Proc. Chem. Soc.* 177 (1960).
[14] L. H. Briggs, L. Colebrook, H. Fales and W. C. Wildman, *Analyt. Chem.* **29**, 904 (1957).

UV spectrum is unchanged by base, and the function of the oxygen atoms of ichthynone, as defined by its NMR spectrum, also precluded the presence of a hydroxyl group. It appeared therefore that ichthynone as a chromone derivative could be either a flavone or an isoflavone. As discussed in the following paper,[15] the UV spectrum of ichthynone was initially misleading because it was so unlike that normally associated with isoflavones.[16] However, the isoflavonoid nature of ichthynone was fully established by the following transformations of dihydroichthynone.

Catalytic reduction of ichthynone has been previously recorded[7] as yielding a tetrahydro-derivative, but re-investigation of this compound shows that it is in fact dihydroichthynone. Comparison of the NMR spectra (Table 1) of ichthynone and dihydroichthynone shows that the environment of the four low field protons has not changed and clearly the 2,2-dimethylchromene has been reduced to a 2,2-dimethylchroman. This is fully supported by the triplet character of the signals to be associated with the benzylic methylene group (τ 7·10; J = 7 c/sec) and the adjacent aliphatic methylene group (τ 8·12; J = 7 c/sec). The chemical shift of the high field methylene triplet (τ 8·12) is consistent with its deshielding by the oxygen atom and the aromatic ring. In addition, the *gem*-dimethyl groups in ichthynone (τ 8·44) and dihydroichthynone (τ 8·55) differ in a way consistent with the change in their environment on reduction of an allylically placed carbon-carbon double bond.

Mild alkaline hydrolysis of dihydroichthynone, $C_{21}H_{16}O_5(OMe)_2$, gave a phenol, $C_{20}H_{18}O_5(OMe)_2$, called dihydroichthynol, which was an *o*-hydroxyketone. It gave a strong coloration with ethanolic ferric chloride and its IR spectrum indicated a chelated aromatic ketone (ν_{max} 1625 cm^{-1}). The chelated nature of this phenol was shown by its easy extraction by ether from a strongly basic solution and the very low field position (τ −2·82) of the phenolic proton resonance in the NMR spectrum of dihydroichthynol (Table 1). This spectrum also showed a singlet (τ 5·91) due to the two protons of the newly formed methylene group. It was therefore concluded that dihydroichthynol was a deoxybenzoin corresponding to an isoflavone, dihydroichthynone. Dihydroichthynone was smoothly reformed from dihydroichthynol by heating it with ethyl orthoformate, pyridine and piperidine.[17]

These reactions established that ichthynone was an isoflavone with a 2,2-dimethylchromene residue, and when this was suspected initially, an attempt was made to effect the alkaline hydrolysis of ichthynone directly. Even under fairly mild conditions this resulted in a complex mixture of at least five products, which is to be associated with the known lability of 2,2-dimethylchromenes to alkali if they bear hydroxyl substituents at positions 5 or 7.[18] This instability to alkali of the derived deoxybenzoin suggested that the 2,2-dimethylchromene ring in ichthynone was more likely to be associated with ring A (see III), particularly as mundulone,[19] an isoflavone with a 2,2-dimethylchromene residue on ring B, is smoothly hydrolysed to the corresponding

[15] S. F. Dyke, W. D. Ollis, M. Sainsbury and J. S. Paul Schwarz, *Tetrahedron* **20**, 1331 (1964).

[16] W. K. Warburton, *Quart. Revs.* **8**, 67 (1954); K. Venkataraman, *Fortsch. Chem. org. Nat.* **17**, 1 (1959); W. D. Ollis, *The Chemistry of Flavonoid Compounds*, ed. T. A. Geissman, Pergamon, Oxford, 1961, p. 353.

[17] V. R. Sathe and K. Venkataraman, *Current Sci. (India)* **18**, 373 (1949).

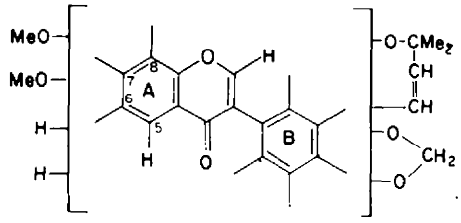
[18a] W. Bridge, R. G. Hayes and A. Robertson, *J. Chem. Soc.* 279 (1937).

[b] J. Polonsky, *Bull. Soc. Chim.* **22**, 541 (1955); **23**, 914 (1956); **25**, 929 (1958).

[c] Ref. 8, p. 94.

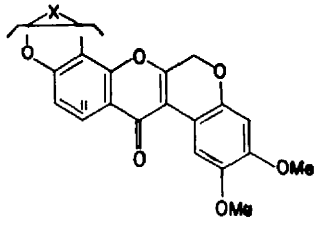
[19] B. F. Burrows, N. Finch, W. D. Ollis and I. O. Sutherland, *Proc. Chem. Soc.* 150 (1959).

deoxybenzoin. An informative alkaline degradation of ichthynone was, however, achieved by heating it with an ethanolic solution of potassium hydroxide in the presence of zinc dust. This reaction yielded a mixture of two isomeric compounds, $C_{20}H_{16}O_5(OMe)_2$, named ichthynol and piscidol, and these were easily separated when an ethereal solution of their mixture was shaken with 5 % aqueous potassium hydroxide. Like dihydroichthynol, ichthynol was not extracted and this, and its NMR spectrum (Table 1), showed that ichthynol was the deoxybenzoin corresponding to ichthynone with a chelated phenolic hydroxyl group. The other hydrolysis product, piscidol, was extracted by alkali and its constitution is discussed later.



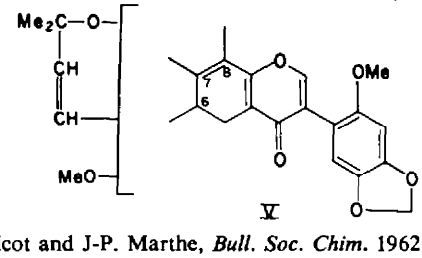
III

When it was established that ichthynone was an isoflavone (III), then the lowest field singlets in the NMR spectra of ichthynone (τ 2·11) and dihydroichthynone (τ 2·10) could be firmly assigned to the protons in position 2.[20] The singlets in the spectra of ichthynone (τ 2·47) and dihydroichthynone (τ 2·53) can be assigned to protons in position 5 (see III) which are specifically deshielded by the adjacent carbonyl group. This situation corresponds to the 11-proton of $6_a,12_a$-dehydrorotenoids (IV) which show a considerable paramagnetic shift[11] in the cases of $6_a,12_a$-dehydrodeguelin (IVa; τ 2·04) and $6_a,12_a$-dehydroisorotenone (IVb; τ 2·07). The

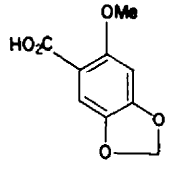


IVa X = $Me_2C{-}CH{=}CH$

IVb X = $Me_2CH{-}C{=}CH$



V

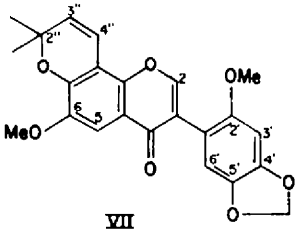


VI

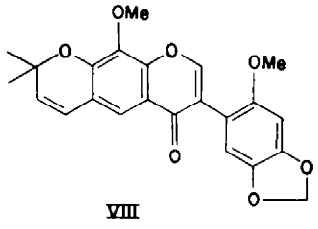
[20] J. Massicot and J-P. Marthe, *Bull. Soc. Chim.* 1962 (1962); W. D. Ollis and R. E. Wheeler, unpublished observations; C. S. Barnes, J. L. Occolowitz, N. L. Dutta, P. M. Nair, P. S. Phadke and K. Venkataraman, *Tetrahedron Letters* No. 5, 281 (1963). S. F. Dyke, W. D. Ollis and M. Sainsbury, *Proc. Chem. Soc.* 179 (1963).

differences between the chemical shifts for the protons in position 5 in ichthynone (τ 2·47) and dihydroichthynone (τ 2·53), as compared with the corresponding situation for $6_a,12_a$-dehydrorotenoids (IVa; τ 2·04 and IVb; τ 2·07), require that ichthynone (III) must be oxygenated either at position 6 or at position 8. A proton is, of course, excluded from position 6 in ichthynone (III) because the proton in position 5 gives rise to a singlet.

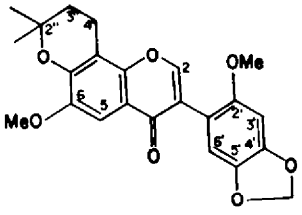
Oxidation of ichthynone with alkaline hydrogen peroxide gave 6-methoxypiperonylic acid (VI)[3] and a carboxylic acid, $C_{12}H_{11}O_4(OMe)$; dihydroichthynone similarly gave the acid (VI) and a carboxylic acid, $C_{12}H_{13}O_4(OMe)$. Thus the partial structure (V) can be developed for ichthynone which, with the additional condition that either position 6 or position 8 is oxygenated, gives four possible structures. In two of these position 7 is oxygenated, whereas in the other two structures it is not. The latter situation is much less likely since all the known isoflavones[16] are oxygenated in position 7, so on biogenetic grounds the two structures VII or VIII were favoured for ichthynone.



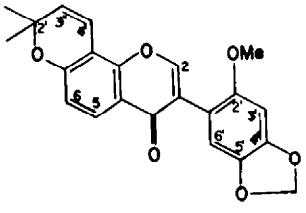
VII



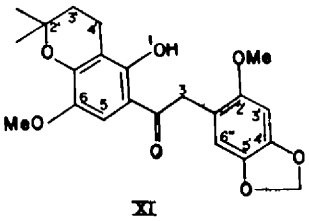
VIII



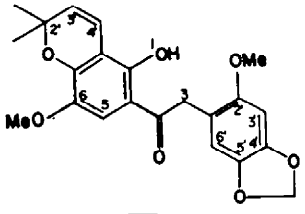
IX



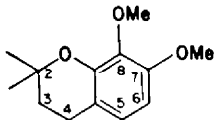
X



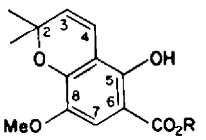
XI



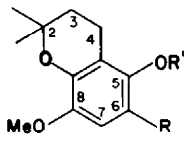
XII



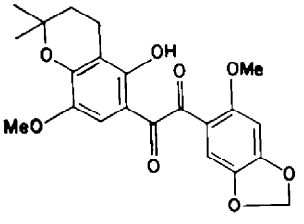
XIII



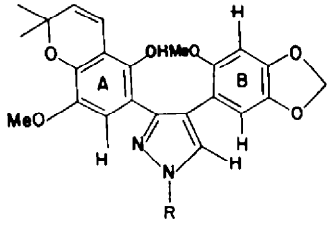
XIV a R=H
XIV b R=Me



XV a $R=CO_2H$, $R'=H$
XV b $R=CO_2Me$, $R'=H$
XV c $R=R'=H$
XV d R=H, $R'=Me$



XVI



XVII a (R=Ph)
XVII b (R=H)

A decision against one of these favoured structures (VII or VIII) for ichthynone was possible on the following grounds. Thermal decarboxylation of the carboxylic acid, $C_{12}H_{13}O_4(OMe)$, obtained by oxidation (see above) of dihydroichthynone gave a phenol, $C_{11}H_{13}O_2(OMe)$, which was characterized as its methyl ether, $C_{11}H_{12}O(OMe)_2$. If ichthynone had the structure VIII, then this methyl ether, $C_{11}H_{12}O(OMe)_2$, would have had the structure XIII. Direct comparison between the degradation product, $C_{11}H_{12}O(OMe)_2$ from ichthynone and the compound XIII showed that they were different, and this demonstrated that ichthynone could not be represented by structure VIII. The compound XIII was synthesized by a Clemmensen reduction of the known 7,8-dimethoxy-2,2-dimethylchroman-4-one.[21]

The exclusion of structure VIII for ichthynone rendered the alternative VII most probable, and this choice was obviously supported by the UV spectrum of the dimethyl ether, $C_{11}H_{12}O(OMe)_2$, which clearly indicated the presence of a 1,2,4-trioxygenated benzene chromophore. Thus the spectrum of the dimethyl ether, λ_{max} 285 mμ (ε 3,180), was very similar to that of 1,2,4-trimethoxybenzene,[22] λ_{max} 285 mμ (ε 3,900), and significantly different from the spectra[23] of 1,2,3-trimethoxybenzene, λ_{max} 267 mμ (ε 655), and 1,3,5-trimethoxybenzene, λ_{max} 265 mμ (ε 482). On these grounds the dimethyl ether, $C_{11}H_{12}O(OMe)_2$, was most probably 5,8-dimethoxy-2,2-dimethylchroman (XVd); this certainly indicated that ichthynone had the structure VII. Final proof that this structure (VII) for ichthynone is correct is provided by the synthetic evidence discussed in the following paper.[15] Ichthynone (VII) is clearly

[21] J. H. Richards, A. Robertson and J. Ward, *J. Chem. Soc.* 1610 (1948).

[22] F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *J. Amer. Chem. Soc.* **75**, 5462 (1953); R. C. Shah, A. B. Kulkarni and V. M. Thakore, *J. Chem. Soc.* 2515 (1955).

[23] T. W. Campbell and G. M. Coppinger, *J. Amer. Chem. Soc.* **73**, 2708 (1951).

biogenetically related to jamaicin (X), also isolated[3-5] from *Piscidia erythrina* L., and their NMR spectra (Table 1) are also very similar and provide strong support for their structural relationship. The major difference between the NMR spectra (Table 1) of ichthynone (VII) and jamaicin (X) is that in jamaicin the protons in positons 5 and 6 are coupled, giving an AB system (τ 1·97 and 3·15; J = 8·5 c/sec), whereas in ichthynone the singlet due to the proton in position 5 is shifted to higher field (τ 2·47) due to the adjacent methoxyl group. It follows that dihydroichthynone (IX) and the deoxybenzoins, ichthynol (XII) and dihydroichthynol (XI), have the indicated structures in accord with their NMR spectra (Table 1), and this was confirmed by the catalytic reduction of ichthynol (XII) to dihydroichthynol (XI).

It is now possible to rationalize the formation and properties of the degradation products of ichthynone in terms of its structure (VII). Oxidation of dihydroichthynone (IX) with alkaline hydrogen peroxide gave a phenol and a mixture of two carboxylic acids. The phenol, $C_{20}H_{16}O_6(OMe)_2$, was yellow and its formulation as a benzil (XVI) was supported by its NMR spectrum (see Table 1). The similar formation of benzils during the alkaline degradation of afromosin[24] and tlatlancuayin[25] has been observed. The mixture of carboxylic acids which accompanied the benzil (XVI) as oxidation products of dihydroichthynone was treated for a short time with diazomethane and then separated into phenolic and neutral fractions by rapid extraction with cold sodium hydroxide. The neutral fraction yielded the methyl ester of 6-methoxypiperonylic acid (VI). The phenolic fraction gave the methyl ester (XIVb) which clearly contained a chelated ester grouping. It showed an ester carbonyl band at 1660 cm^{-1} and its NMR spectrum was fully compatible with the structure XVb, in particular the hydroxyl proton appeared at very low field (τ −0·83) due to internal hydrogen bonding. Alkaline hydrolysis of this ester (XVb) gave the acid (XVa), which was clearly a salicylic acid. Its IR and NMR spectra indicated a chelated carboxyl group (ν_{CO} 1642 cm^{-1}) and a hydrogen bonded proton (τ −0·60). The aromatic proton in the acid (XVa; τ 2·84) and in the ester (XVb; τ 2·96) are clearly deshielded by the *ortho*-carbonyl functions.

The shielding influence of the 8-methoxyl group upon the aromatic proton in position 7 in this acid (XVa; τ 2·84) is clearly indicated by comparison with the chemical shift of the corresponding proton in β-tubaic acid (τ 2·28) and dihydro-β-tubaic acid (τ 2·33) (Table 2). Thermal decarboxylation of the salicylic acid (XVa) gives the phenol (XVc) whose NMR spectrum (Table 2) indicates an AB system (τ 3·38 and 3·72, J = 9 c/sec) to be associated with *ortho*-related protons. The NMR spectrum of the methyl ether (XVd) is quite different from that of the isomer (XIII). It also follows that the alkaline hydrogen peroxide oxidation of ichthynone gave the 2,2-dimethylchromene-carboxylic acid (XIVa) which was characterized as its methyl ester (XIVb).

The compounds previously described[7] as "ichthynone hydrazone" and "ichthynone phenylhydrazone" were recognized as probably being incorrectly formulated, since it has been established[26] that reaction of chromones with hydrazine or phenylhydrazine gives pyrazoles rather than the simple hydrazones. A re-examination of "ichthynone hydrazone" and "ichthynone phenylhydrazone" suggested that they were

[24] T. B. H. McMurry and C. Y. Theng, *J. Chem. Soc.* 1491 (1960).
[25] P. Crabbé, *Bull. Soc. Chim. Belg.* **70**, 189 (1961).
[26] W. Baker, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.* 1303 (1952).

TABLE 1. CHEMICAL SHIFTS (τ) FOR THE INDICATED PROTONS IN THE NMR SPECTRA OF ICHTHYNONE AND RELATED COMPOUNDS

Location of protons or substituents	2-H	5-H	6-H	3′-H	6′-H	2″-*gem*-Me_2	3″-H	4″-H	3′–4′ CH_2O_2	2′-OMe	6-OMe	1-OH*	3-H_2*	7-OH*
Ichthynone (VII)	2·11	2·47		3·39	3·20	8·44	4·29 (d, J = 10)	3·21 (d, J = 10)	4·07	6·28	6·06			
Jamaicin (X)	2·08	1·97 (d, J = 8·5)	3·15 (d, J = 8·5)	3·38	3·15	8·51	4·28 (d, J = 10)	3·20 (d, J = 10)	4·05	6·28				
Ichthynol (XII)*		2·75		3·45	3·30	8·50	4·40 (d, J = 10)	3·32 (d, J = 10)	4·11	6·23	6·19	−2·72*	5·90*	
Piscidol (XVIII)*		2·69		3·46	3·31	8·52	4·31 (d, J = 10)	3·31 (d, J = 10)	4·12	6·29	6·17		5·75	3·76* Broad
Dihydroichthynone (IX)	2·10	2·53		3·40	3·19	8·55	8·12 (t, J = 7)	7·10 (t, J = 7)	4·08	6·29	6·07			
Dihydroichthynol (XI)*		2·84		3·47	3·31	8·61	8·20 (t, J = 7)	7·30 (t, J = 7)	4·13	6·25	6·21	−2·82*	5·91*	
Dihydroichthynolone (XVI)*		3·36		3·50	2·58	8·57	8·13 (t, J = 6·7)	7·24 (t, J = 6·7)	3·96	6·30 or 6·40	6·40 or 6·30	−1·91*		
6-Methoxypiperonylic acid (VI)*				3·41*	2·44*				3·97*	5·98*				

* For ease of comparison of the chemical shifts of corresponding protons, the formulae of ichthynol (XII), piscidol (XVIII), dihydroichthynol (XI), and dihydroichthynolone (XVI) have been numbered to correspond with the isoflavones (VII, IX, and X). Similarly the chemical shifts of 6-methoxypiperonylic acid (VI) have been recorded without regard to its systematic numbering.

TABLE 2. CHEMICAL SHIFTS (τ) FOR INDICATED PROTONS IN THE NMR SPECTRA OF ICHTHYNONE DEGRADATION PRODUCTS AND RELATED COMPOUNDS

Location of protons or substituents	2-gem-Me_2	3-H	4-H	5-H	5-OH	5-OMe	6-H	6-CO_2Me	7-H	7-OMe	8-H	8-OMe
(XIVb)	8·51	4·39 (d, J = 10)	3·26 (d, J = 10)		−0·89			6·09	2·82			6·18
(XVa)	8·59	8·17 (t, J = 7)	7·27 (t, J = 7)		−0·60				2·84			6·18
(XVb)	8·62	8·20 (t, J = 7)	7·30 (t, J = 7)		−0·83			6·14	2·96			6·23
(XVc)	8·63	8·20 (t, J = 7)	7·31 (t, J = 7)		4·92		3·72 (d, J = 9)		3·38 (d, J = 9)			6·22
(XVd)	8·63	8·23 (t, J = 7)	7·34 (t, J = 7)			6·21	3·71 (d, J = 9)		3·37 (d, J = 9)			6·23
(XIII)	8·63	8·21 (t, J = 7)	7·26 (t, J = 7)	3·24 (d, J = 9)			3·57 (d, J = 9)			6·17		6·17
7,8-Dimethoxy-2,2-dimethyl chroman-4-one (cf. XIII)	8·50	7·30		2·35 (d, J = 9)			3·38 (d, J = 9)			6·08		6·13
β-Tubaic acid[13] (cf. XIVa; 8-OMe = H)	8·54	4·43 (d, J = 10)	3·30 (d, J = 10)						2·28 (d, J = 8)		3·65 (d, J = 8)	
Dihydro-β-tubaic acid (cf. XVa; 8-OMe = H)	8·65	8·22 (t, J = 7)	7·23 (t, J = 7)		−0·95				2·33 (d, J = 9)		3·62 (d, J = 9)	

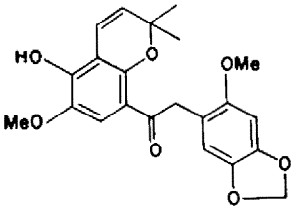
The spectra recorded in Tables 1 and 2 were determined in deuterochloroform solution with tetramethylsilane as an internal standard on a Varian A 60 spectrometer.

Proton counts. All signals have the appropriate integrated intensities.

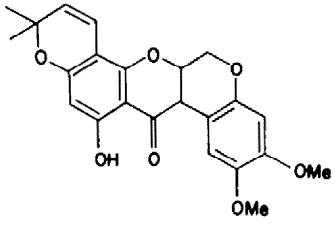
Multiplicity of signals. Unless otherwise indicated, all signals are singlets. For other cases d = doublet, t = triplet, and the coupling constant J is given in c/sec.

both phenolic since they gave positive ferric chloride colorations. Furthermore, the NMR spectrum of "ichthynone phenylhydrazone" shows signals with the indicated intensities and chemical shifts characteristic of the 2,2-dimethylchromene [τ 8·49 (6); τ 4·36, d, J = 10 c/sec (1); τ 3·15, d, J = 10 c/sec (1)], two methoxyl groups [τ 6·06 (3), τ 6·18 (3)], one methylenedioxy group [τ 4·14 (2)], one A-ring proton (τ 3·15), two *para*-related B-ring protons (τ 3·41 and 3·36), the pyrazole proton (τ 2·03), the phenyl group [$\sim\tau$ 2·74, 2·83, 3·08 (multiplet) (5)] and an internally chelated hydroxyl group (τ −2·88). This spectrum is fully compatible with the pyrazole structure (XVIIa), and the corresponding structure (XVIIb or a tautomer) may be proposed for "ichthynone hydrazone".

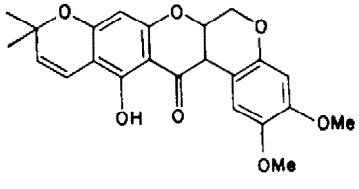
The formation of two isomeric compounds, ichthynol and piscidol, by treatment of ichthynone with ethanolic sodium hydroxide and zinc dust was unexpected. As already discussed, ichthynol is clearly the expected deoxybenzoin (XII) and the NMR spectrum of piscidol (Table 1) shows many striking similarities to the spectrum of ichthynol (XII). It is clear that ichthynol and piscidol differ only in the orientation of the 2,2-dimethylchromene ring and the structure XVIII may be proposed for piscidol, this structure is fully supported by the NMR and IR spectra of piscidol which shows in particular an unbonded phenolic hydroxyl group (ν_{max} 3530 cm^{-1}; τ 3·76 broad) and an unbonded conjugated carbonyl (ν_{max} 1660 cm^{-1}).



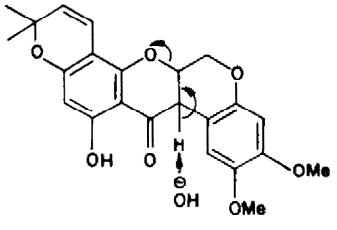
XVIII



XIX



XX

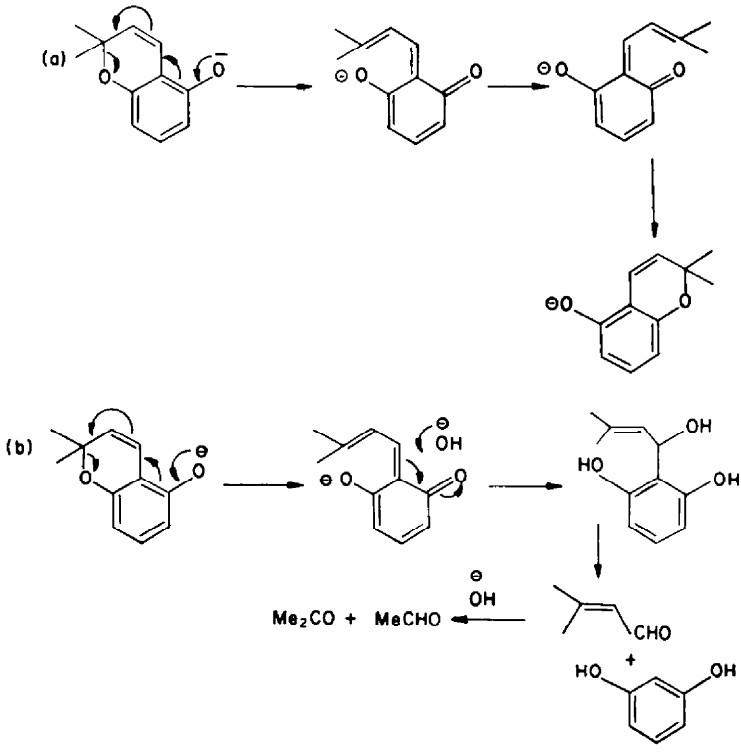


XXI

The formation of piscidol (XVIII) necessarily involves a base-catalysed isomerization of ichthynol (XII) and such a rearrangement of a 2,2-dimethylchromene has not been detected previously. Although it is formally similar to the base-catalysed rearrangement of α-toxicarol (XIX) to β-toxicarol (XX),[27] the two rearrangements differ mechanistically in that the toxicarol rearrangement (XIX → XX) involves a

[27] R. S. Cahn, R. F. Phipers and J. J. Boam, *J. Chem. Soc.* 513 (1938).

base-catalysed β-elimination (XXI).[28] On the other hand, the ichthynol-piscidol transformation (XII → XVIII) involves a cleavage of the 2,2-dimethylchromene ring as represented by mechanism (a). Mechanism (a) is similar in form to mechanism (b), which is now proposed to account for the base-catalysed hydrolysis of phenolic 2,2-dimethylchromenes[18] to give acetone, acetaldehyde and a phenol; mechanism (b) replaces the mechanism previously proposed[8] for this alkaline cleavage reaction.



EXPERIMENTAL

M.ps were taken by the capillary tube method (designated e.c. if evacuated) and are uncorrected. IR spectra were determined on a Perkin-Elmer 21 Spectrophotometer and significant (OH, CO, and C=C) bands are recorded. UV spectra were determined on a Cary 14 Spectrophotometer. All analyses were performed at the Microanalytical Laboratory of the Squibb Institute for Medical Research.

Extraction of the root wood of Piscidia erythrina L.

Isolation of ichthynone (VII) *and rotenone.* The ground root wood (720 g) was divided into 5 batches and separately extracted with hot n-hexane for 7 hr. Evaporation of the combined extracts under diminished pressure yielded a partially crystalline residue (5·78 g, 0·80%) which was triturated several times with cold ether until the washings were colourless. This yielded virtually pure ichthynone (1·78 g, 0·25%), m.p. (e.c.) 199–201° which was recrystallized from ethanol giving colourless rodlets, m.p. (e.c.) 202·5–203·5° (lit. m.p. 203–204°),[7] λ_{max} (95% ethanol) 232 mμ (ε 33,600), 262 mμ (ε 24,300), 309 mμ (ε 14,100), 331 mμ (ε 11,000), 345 mμ (9,400). ν_{max} (nujol) 1622–1652, 1595, 1515 cm^{-1}. (Found: C, 67·70; H, 4·93; OMe, 15·13. Calc. for $C_{21}H_{14}O_6(OMe)_2$: C, 67·64; H, 4·94; OMe, 15·13%).

[28] L. Crombie, P. J. Godin, D. A. Whiting and K. S. Siddalingaiah, *J. Chem. Soc.* 2876 (1961) and references therein.

The ethereal washings were concentrated (ca. 125 ml), then refrigerated for 2 hr, and the crystalline precipitate collected (344 mg; m.p. 153–155°). Further concentration (ca. 20 ml) gave a second fraction (552 mg; m.p. 150–154°). These fractions were combined and recrystallized from ethanol giving rotenone, m.p. 164–165° (410 mg; 0·057%) identical with an authentic specimen.

Dihydroichthynone (IX). Ichthynone (500 mg) in ethyl acetate (100 ml) was hydrogenated using Adams' platinic oxide catalyst (150 mg, Englehard Industries) at room temp and 1 atm. Absorption of hydrogen was completed after 75 min and the product had precipitated. This was dissolved by heating and the solution after filtration yielded *dihydroichthynone* (439 mg, 88%) as colourless needles, m.p. (e.c.), 236–238°, λ_{max} (95% ethanol) 220 mμ sh (ε, 33,300), 233 mμ sh (ε 24,400), 256 mμ sh (ε 15,700), 312 mμ (ε 18,700); [ν_{max} (nujol) 1648, 1626, 1603, 1504 cm^{-1}.] (Found: C, 67·12; H, 5·93; OMe, 15·13. $C_{21}H_{16}O_5(OMe)_2$ requires: C, 67·31; H, 5·40; OMe, 15·12%).

The identity of dihydroichthynone with the compound previously described[7] as "tetrahydroichthynone" was established by direct comparison with the original sample. They had the same m.p. and mixed m.p. and identical IR and UV spectra.

Alkaline hydrolysis of ichthynone (VII) *to ichthynol* (XII) *and piscidol* (XVIII)

A mixture of ichthynone (1 g), zinc dust (2 g), and potassium hydroxide (1 g) in ethanol (110 ml) was heated under reflux for 5 hr, then diluted with water (500 ml), acidified with dil. H_2SO_4 and extracted with ether. The ethereal extract was shaken with 5% KOH aq. and the alkaline extract was examined separately. The ethereal extract yielded ichthynol (XII) as pale yellow needles, m.p. 134–136°, from ethanol; it gave an olive-green coloration with ethanolic ferric chloride (ν_{max} 1650 cm^{-1}). (Found: C, 66·57; H, 5·76. $C_{22}H_{22}O_7$ requires: C, 66·32; H, 5·57%).

The alkaline extract was acidified and extracted with ether yielding piscidol (XVIII) as colourless plates, m.p. 129°, from aqueous ethanol (ν_{max} 3530, 1660 cm^{-1}). (Found: C, 66·34; H, 5·75. $C_{24}H_{24}O_7$ requires: C, 66·32; H, 5·57%).

Alkaline hydrolysis of dihydroichthynone (IX) *to dihydroichthynol* (XI)

(a) Dihydroichthynone (82 mg) and 2N ethanolic potassium hydroxide (20 ml) were heated under reflux (N_2 atm.) for 2 hr and the ethanol removed under diminished pressure. Water was added and the alkaline solution extracted directly with ether yielding *dihydroichthynol* (XI, 67 mg) which gave light yellow crystals (31 mg, 39%), m.p. (e.c.) 161·5–162°, from either ethyl acetate–n-hexane or benzene–n-hexane mixtures, λ_{max} (95% ethanol), 216 mμ sh (ε 22,400), 237 mμ (14,700), 294 mμ (ε 16,000), 348 mμ (ε 8,800); [ν_{max} (nujol) 1625, 1612, 1506 cm^{-1}]. (Found: C, 66·14; H, 5·80; OMe, 15·38; m.wt., 367 (Rast). $C_{20}H_{18}O_5(OMe)_2$ requires: C, 65·99; H, 6·04; OMe, 15·52%. m.wt., 400).

Effect of base upon UV spectrum: λ_{max} (95% EtOH–2·5% KOH) 226 mμ sh (ε 86,400), 289 mμ (ε 17,000), 371 mμ (ε 11,600).

(b) Dihydroichthynone (100 mg), KOH (3 g), and water (1 ml) were heated (N_2 atm.) at 220° for 45 min, cooled, water added, and the solid (85 mg) collected. Crystallization from benzene–n-hexane gave the same ketone (XI, 61 mg, 63%) with an identical IR spectrum.

Catalytic reduction of ichthynol. Ichthynol (42 mg) and platinum black catalyst (50 mg) (18 ml) was reduced with hydrogen (1 atm) and after 2·5 hr the uptake of hydrogen ceased. The filtrate yielded dihydroichthynol, m.p. 161°, identical with the hydrolysis product of dihydroichthynone (see above).

Transformation of dihydroichthynol (XI) *to dihydroichthynone* (IX). Dihydroichthynol (XI, 50 mg), ethyl *ortho*-formate (0·2 ml), pyridine (1 ml), and piperidine (2 drops) were heated under reflux (N_2 atm.) for 6 hr, cooled, and 2N HCl (6 ml) added. The precipitate was collected, dissolved in hot ethyl acetate (7 ml), and the solution decolorized with Norite-A. This yielded dihydroichthynone (32 mg, 62%), m.p. (e.c.) 238·5–239°, identical (mixed m.p., UV and IR spectra) with an authentic specimen.

Oxidation of dihydroichthynone with alkaline hydrogen peroxide.

Formation of the diketone (XVI), *6-carbomethoxy-5-hydroxy-8-methoxy-2,2-dimethylchroman* (XIVb) *and 6-methoxypiperonylic acid methyl ester* (*cf.* VI). Dihydroichthynone (713 mg) was added to a 5% solution (70 ml) KOH in aqueous ethanol (80% EtOH) and the stirred solution was warmed at 42·5–45° during 1 hr and at 48–52° for a further hour. During the 2 hr period, sufficient 30% H_2O_2 was added at 15 min intervals to maintain gentle evolution of oxygen. The resulting deep

yellow solution was concentrated under diminished pressure, water was added, and the solution extracted with ether. This extract yielded a yellow oil (18 mg) which was not examined further.

Carbon dioxide was then passed through the alkaline solution and the precipitate was extracted into chloroform. This yielded the *diketone* (XVI, 247 mg) as yellow crystals, m.p. 137·5–138·5° (180 mg, 25%) from ethanol [ν_{max} (nujol) 1650, 1603–1620, 1504 cm^{-1}]. (Found: C, 63·82; H, 5·41, OMe, 15·26. $C_{30}H_{16}O_6(OMe)_2$ requires: C, 63·76; H, 5·35; OMe, 14·98%).

After extracting the diketone (XV), the aqueous bicarbonate solution was acidified (pH 2) and extracted with chloroform. This extract yielded a mixture of acids which was treated with ethereal diazomethane for 1 min and then separated into neutral and phenolic fractions by *rapid* extraction with ice-cold 2N KOH aq. Carbon dioxide was passed rapidly into the alkaline extract and chloroform extraction yielded a crude phenolic methyl ester (160 mg) which was purified by sublimation (90°, 4×10^{-3} mm) followed by crystallization from n-hexane yielding 6-carbomethoxy-5-hydroxy-8-methoxy-2,2-dimethylchroman (74 mg), m.p. 112–113·5°. The crystallization mother liquors gave material which was separated on chromatoplates (Woelm alumina-A5; 1:1 benzene–n-hexane as mobile phase). The ultraviolet blue-fluorscent material was crystallized from n-hexane giving a further quantity (60 mg, total yield 29%) of the phenolic ester. Recrystallization from methanol gave *6-carbomethoxy-5-hydroxy-8-methoxy-2,2-dimethylchroman* (XVb) as colourless needles, m.p. 111·5–113°, λ_{max} (95% ethanol) 212 mμ (ε 24,900), 228 mμ (ε 14,900), 270 mμ (ε 12,900), 320 mμ (ε 7,100); [ν_{max} ($CDCl_3$) 1660 and 1620 cm^{-1}]. (Found: C, 63·14; H, 6·83; OMe, 23·27. $C_{12}H_{12}O_3(OMe)_2$ requires: C, 63·14; H, 6·81; OMe, 23·31%).

The alkali-insoluble, non-phenolic ester fraction (157 mg) was sublimed (90°, 5×10^{-3} mm) and the sublimate (143 mg) was hydrolysed by heating it under reflux with 2N KOH aq. (2 ml) and 95% ethanol (10 ml). The ethanol was removed under diminished pressure and the residual solution was acidified and extracted with chloroform. Crystallization from ether gave 6-methoxypiperonylic acid (65 mg, 19%), m.p. 149–149·5°, whereas crystallization from ethanol or ether–n-hexane gave a polymorphic form, m.p. 135–136° (the existence of polymorphic forms of this acid, m.p. 136–137° and 151–151·5°, have been previously described[8]). This acid was identical (mixed m.p. and IR spectra) with an authentic specimen.*

Oxidation of ichthynone with alkaline hydrogen peroxide

Formation of 6-carbomethoxy-5-hydroxy-8-methoxy-2,2-dimethylchromene (XIVb). Ichthynone (300 mg) was added to a 5% solution (30 ml) KOH in 95% ethanol and the stirred solution was maintained at 49–51° during the portionwise addition of 30% H_2O_2 during 1 hr. Sufficient H_2O_2 was added to maintain a gentle evolution of oxygen and after standing for a further hour at room temp excess H_2O_2 was removed by boiling and the mixture was worked up as in the preceding experiment; the isolation of 6-methoxypiperonylic acid methyl ester was not duplicated. The crude phenolic-ester fraction (150 mg) was chromatographed on alumina (10 g, Woelm neutral-AV), and elution with 50% n-hexane–chloroform mixture followed by crystallization from n-hexane gave *6-carbomethoxy-5-hydroxy-8-methoxy-2,2-dimethylchromene* (77 mg, 40%) as colourless needles, m.p. 113–114°, [ν_{max} ($CDCl_3$) 3000–3200, 1666, 1615 cm^{-1}]. (Found: C, 64·14; H, 5·93. $C_{14}H_{16}O_5$ requires: C, 63·62; H, 6·10%).

5-Hydroxy-8-methoxy-2,2-dimethylchroman-6-carboxylic acid (XVa). 6-Carbomethoxy-5-hydroxy-8-methoxy-2,2-dimethylchroman (105 mg), 2N NaOH (2 ml), and 95% ethanol (2 ml) were heated under reflux for 30 min, acidified with conc. HCl, and the product, m.p. (e.c.) 203–204° (92 mg, 88%) collected after standing. Crystallization from aqueous ethanol gave the *acid* m.p. (e.c.) 203–204° with decarboxylation, [ν_{max} ($CDCl_3$) 1642 and 1620 cm^{-1}]. (Found: C, 62·09; H, 6·56; OMe, 12·07. $C_{12}H_{12}O_4(OMe)$ requires: C, 61·89; H, 6·39; OMe, 12·30%).

5-Hydroxy-8-methoxy-2,2-dimethylchroman (XVc). The preceding acid (92 mg) was heated for 30 min in an evacuated tube which was completely submerged in a Wood's metal bath at 200°. The product was crystallized from benzene–n-hexane giving 5-hydroxy-8-methoxy-2,2-dimethylchroman (57 mg; 75%), m.p. 155–156°, λ_{max} (95% ethanol) 286 mμ (ε 3,700), [ν_{max} (CCl_4) 3600 cm^{-1}; ν_{max} ($CDCl_3$) 3570 3410, 1612 (sh), 1600 cm^{-1}]. (Found: C, 68·98; H, 7·59. $C_{12}H_{16}O_3$ requires: C, 69·21; H, 7·74%).

Effect of base upon UV spectrum: λ_{max} (95% ethanol—2·5% KOH 297 mμ (ε 4,390).

* Kindly supplied by Professor H. Schmid.

5,8-*Dimethoxy*-2,2-*dimethylchroman* (XVd). 5-Hydroxy-7-methoxy-2,2-dimethylchroman (45 mg), anhydrous potassium carbonate (200 mg), and acetone (5 ml) were heated under reflux for 3 hr while methyl iodide (three 0·3 ml portions) was added at one-hourly intervals. The mixture was filtered, and solid well washed with acetone, and the combined filtrates were evaporated giving a residue which was dissolved in ether and shaken with 2N KOH solution. The ethereal solution was evaporated and distillation (100°, 10^{-1} mm), followed by chromatography on alumina (Woelm, neutral A-1) elution with ethyl acetate, and redistillation, gave 5,8-*dimethoxy*-2,2-*dimethylchroman* as a solid, m.p. 59·5–61°, λ_{max} (95% ethanol) 285 mμ (ε 3,180) [ν_{max} (KBr) 1610–1596, 1490 cm^{-1}]. (Found: C, 70·21; H, 8·13. $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·16%).

7,8-*Dimethoxy*-2,2-*dimethylchroman* (XIII). A mixture of 7,8-dimethoxy-2,2-dimethylchromanone[21] (112 mg), 95% ethanol (2 ml), conc. HCl (2 ml), water (3 ml) and amalgamated zinc (4 g) was heated under reflux for 75 min, when the disappearance of the carbonyl band in its IR spectrum was completed. Chloroform extraction gave a crude product (103 mg) which was purified by separation on chromatoplates (Woelm neutral alumina-AV; solvent 1:1 n-hexane–chloroform) followed by distillation (65–70°, 5×10^{-2} mm) gave 7,8-dimethoxy-2,2-dimethylchroman (23 mg, 22%) as a colourless oil, λ_{max} (95% ethanol) broad band 274–283 mμ (ε 1,100): [ν_{max} ($CDCl_3$) 1610, 1575, 1496 cm^{-1}]. (Found: C, 69·74; H, 8·09; OMe, 27·85. $C_{11}H_{12}O(OMe)_2$ requires: C, 70·24; H, 8·16; OMe, 27·92%).