# A NEW SYNTHESIS OF ISLANDICIN AND CYNODONTIN

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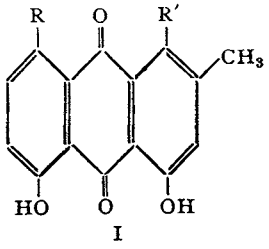
Abstract

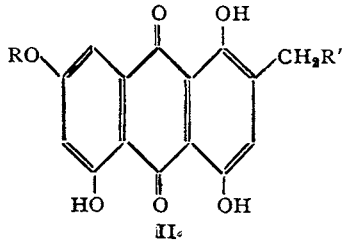
2-Methylanthraquinones with the 1 : 4-dihydroxy system are conveniently prepared by the persulphate oxidation of the intermediate benzoylbenzoic acids and subsequent ring closure. 2-Methylquinizarin, islandicin and cynodontin have been prepared by this method as typical examples.

Among the naturally occurring polyhydroxyanthraquinones of fungal origin,[1] the following have 1 : 4-dihydroxy system: helminthosporin (I *a*), islandicin (I *b*), cynodontin (I *c*), catenarin (II *a*), erythroglaucin (II *b*) and tritisporin (II *c*). For the synthesis of these compounds, a number of methods[2–4] have been used in the past but none of them follows any possible path of biogenesis.




I

(*a*) R=OH; R′=H
(*b*) R=H; R′=OH
(*c*) R=R′=OH




II

(*a*) R=R′=H
(*b*) R=CH3; R′=H
(*c*) R=H; R′=OH

A possible scheme of evolution of lichen and mould anthraquinones has been recently outlined.[5] It is based on their origin from $C_8$-unit (orsellinic unit) and its modifications. Two such units are involved in the formation of mould anthraquinones. The above-mentioned compounds having the 1 : 4-dihydroxy system are considered to be related to simpler compounds and involve an extra stage of *para* nuclear oxidation. Based on this idea, the anthraquinones, catenarin (II *a*), erythroglaucin (II *b*) and tritisporin (II *c*) are related to *frangula*-emodin, physcion and ω-hydroxyemodin respectively Similarly, helminthosporin (I *a*) and islandicin (I *b*)

may be related to the common precursor, chrysophanol. Though they do not occur together, this biogenetical relationship between chrysophanol and islandicin is supported by the occurrence of the former in the place of the latter as a metabolic product of one of the strains (N.R.R.L. 1175) of *Penicillium islandicum* Sopp., examined by Howard and Raistrick.[6] Cynodontin (I *c*) then involves an extra stage of nuclear oxidation as compared with helminthosporin (I *a*) or islandicin (I *b*) and this view is supported by the occurrence of helminthosporin (I *a*) and cynodontin (I *c*) together in the metabolic product of *Helminthosporium cynodontis* Marignoni.[7]

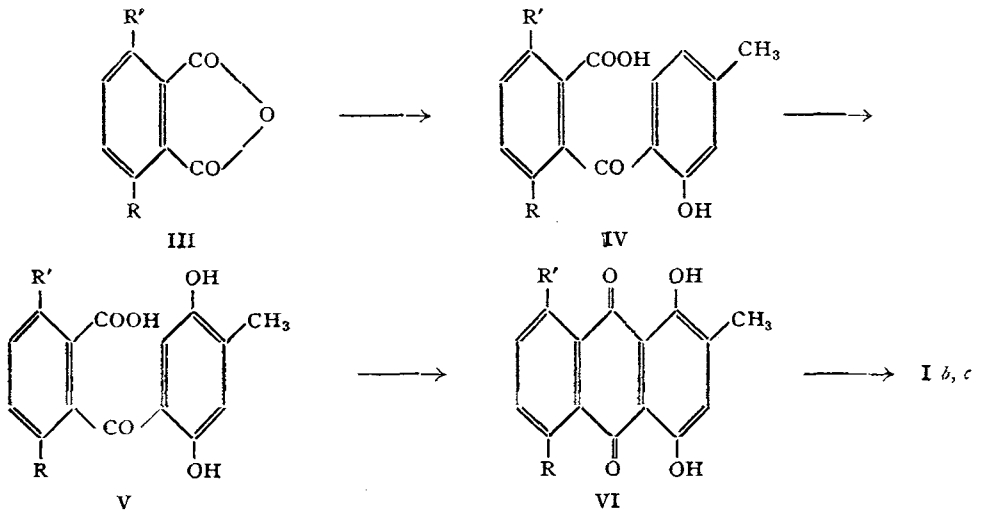
Experiments carried out in the past for the direct nuclear oxidation of hydroxyanthraquinones under mild conditions using persulphate have not been successful.[8-9] It could be inferred that in Nature too, this oxidation is not feasible. This result could be attributed to lack of adequate reactivity of the nuclear positions. Consequently, the alternative possibility of oxidation in an earlier stage such as the benzoylbenzoic acid stage or even at the $C_8$-unit stage had to be considered. The feasibility of the *para* oxidation of the hydroxybenzoylbenzoic acids has now been investigated using simpler examples.

The simplest example of this series would be 2-methylquinizarin though it has not, so far, been found to occur in Nature. 2-(2′-Hydroxy-4′-methyl) benzoylbenzoic acid (IV *a*), obtained by the condensation of phthalic anhydride (III *a*) and *m*-cresol, has now been subjected to oxidation with potassium persulphate in alkaline medium. The resulting quinol derivative (V *a*) has been cyclised with concentrated sulphuric acid when 2-methylquinizarin (VI *a*) is obtained. This was earlier prepared by Ullmann and Schmidt[10] by a different method.

A more complex member is islandicin (I *b*). For its synthesis, 3-methoxyphthalic anhydride (III *b*) is condensed with *m*-cresol to yield 3-methoxy-2-(2′-hydroxy-4′-methyl) benzoylbenzoic acid (IV *b*) which undergoes smooth oxidation to yield the quinol derivative (V *b*). Subsequent ring closure could be effected using fuming sulphuric acid and melted boric acid at 70° yielding 1 : 4-dihydroxy-5-methoxy-2-methylanthraquinone (VI *b*). Demethylation of this substance with hydrobromic acid-acetic acid mixture gives islandicin (I *b*) which is found to be identical with the natural sample.[11] The use of sulphuric acid alone at a higher temperature produces ring closure as well as demethylation but the yield is found to be poor.

The mould product, cynodontin (I *c*) has a hydroxyl group more than islandicin (I *b*). Its synthesis has now been carried out using 3 : 6-dimethoxyphthalic anhydride, prepared by a modification of the method of Graves

and Adams.[12] A parallel series of experiments yielded the benzoylbenzoic acid (IV *c*) which gave the corresponding quinol derivative (V *c*) by oxidation. Ring closure to the corresponding dihydroxy-dimethoxy-anthraquinone (VI *c*) and subsequent demethylation yielded 1 : 4 : 5 : 8-tetrahydroxy-2-methylanthraquinone (I *c*) which is identical with a sample of cynodontin, isolated by Raistrick *et al.*[7] as a metabolic product of *H. cynodontis* Marignoni.




(*a*) R=R'=H
(*b*) R=$OCH_3$; R'=H
(*c*) R=R'=$OCH_3$

## EXPERIMENTAL

2-(2' : 5'-*Dihydroxy-4'-methyl*) *benzoylbenzoic acid* (*V* a).—To a continuously stirred solution of 2-(2'-hydroxy-4'-methyl) benzoylbenzoic acid[10] (2·5 g.) in aqueous potassium hydroxide (3 g. in 30 c.c.) was added, dropwise in the course of 2 hrs., a saturated solution of potassium persulphate (3 g.) in water (18–20°). The deep brown solution was kept overnight at laboratory temperature and then acidified (Congo red) and the unreacted acid (0·5 g.) was extracted with ether. Concentrated hydrochloric acid (20 c.c.) and sodium sulphite (3 g.) were added to the aqueous solution, and the mixture heated on a boiling water-bath for half an hour and then cooled in the refrigerator when a crystalline solid separated. It was filtered and crystallised from water when the dihydroxy acid was obtained as orange-yellow prisms, m.p. 161–62.° Yield, 0·5 g. (Found: C, 65·7; H, 4·1; $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%). It gave a red solution with aqueous sodium hydroxide and a green colour with alcoholic ferric chloride changing to brown with excess of the reagent.

1 : 4-*Dihydroxy-2-methylanthraquinone* (*2-methylquinizarin*) (*VI* a).—The above oxidation product (0·5 g.) was heated with concentrated sulphuric acid (3 c.c.) in an oil-bath at 150° for ½ hr., and the deeply coloured solution carefully diluted with water when a scarlet-red precipitate separated. It was extracted with chloroform and the chloroform solution dried over anhydrous sodium sulphate. On removal of the solvent and crystallisation of the residue from methanol or dioxan containing a little water, 2-methylquinizarin was obtained as scarlet needles, m.p. 176–77°. Yield, 0·3 g. It gave a greenish brown colour with alcoholic ferric chloride and a violet colour with aqueous sodium hydroxide. Its solution with concentrated sulphuric acid was pink-violet and the solution in organic solvents was red with a green fluorescence. With methanolic magnesium acetate it gave a purple colour. Ullmann and Schmidt[10] also reported the same m.p. for 2-methylquinizarin.

Its acetate was prepared using acetic anhydride and concentrated sulphuric acid and it crystallised from ethyl acetate as yellow prisms, m.p. 208–10° (Found: C, 67·0; H, 4·5; $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·2%). It did not give any colour with alcoholic ferric chloride. Nietzki[13] reported 185° as the m.p. of the acetate of 2-methylquinizarin.

3-*Methoxy-2-(2′-hydroxy-4′-methyl) benzoylbenzoic acid* (*IV* b).—3-Methoxyphthalic anhydride[14] (III *b*) (5 g.) was dissolved in warm *m*-cresol (30 c.c.) and to the cooled solution, powdered anhydrous aluminium chloride (10 g.) was added in small lots. The reaction mixture was kept overnight at room temperature and then heated at 70° for 6 hrs. with mechanical stirring. The dark red reaction mixture was allowed to stand overnight and then treated with ice and concentrated hydrochloric acid (10 c.c.). The excess of cresol was steam distilled and the supernatant aqueous layer decanted when the residual oil quickly solidified. It was dissolved in 1 *N* sodium hydroxide (150 c.c.) and the solution saturated with carbon dioxide. The dull yellow phthalein by-product, which separated, was filtered and washed with water. The filtrate was acidified with ice-cold hydrochloric acid when the benzoylbenzoic acid separated as a brown solid. It was crystallised from methanol when the acid was obtained as colourless prisms, m.p. 210–12°. It gave a red colour with alcoholic ferric chloride and was soluble in aqueous sodium bicarbonate. Yield, 1·2 g. (Found: C, 66·9; H, 4·8; $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%).

3-*Methoxy-2-(2′: 5′-dihydroxy-4′-methyl) benzoylbenzoic acid* (*V* b).—A solution of the above benzoylbenzoic acid (IV *b*) (1 g.) in aqueous potassium hydroxide (1·1 g. in 25 c.c. water) was treated with a solution of potassium

persulphate (1·2 g.) and was worked up as described earlier. The nuclear oxidation product crystallised from methanol as pale yellow tiny prisms, m.p. 228–31° (decomp.). Yield, 0·5 g. (Found: C, 63·1; H, 4·9; $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·7%). It gave a green colour with alcoholic ferric chloride which changed to brown on shaking in air or with excess of the reagent. It was soluble in aqueous sodium bicarbonate.

1 : 4-*Dihydroxy*-5-*methoxy*-2-*methylanthraquinone* (*VI* b).—The above acid (V *b*) (0·2 g.) was heated with a mixture of melted and finely powdered boric acid (0·2 g.) and sulphuric acid monohydrate (3 c.c.) on a water-bath. At 70°, fuming sulphuric acid (0·5 c.c.) was added and the mixture allowed to stand for an hour at that temperature. The deep reddish blue solution was then poured on crushed ice and stirred well. After a few hours, the precipitate was coagulated by heating on a boiling water-bath. The red solid was filtered, washed with hot water and dried. It crystallised from chloroform-methanol mixture as long bright red needles, m.p. 197–99°. Yield, 0·15 g. (Found: $OCH_3$, 10·1; $C_{16}H_{12}O_5$ requires 1 $OCH_3$, 10·9%).

It was insoluble in aqueous sodium bicarbonate and sodium carbonate but readily soluble in aqueous sodium hydroxide giving a deep violet solution from which a violet precipitate separated on standing. It gave a purple colour with methanolic magnesium acetate. It was soluble in glacial acetic acid giving an orange-yellow solution with a green fluorescence. With concentrated sulphuric acid, it gave a purple-red colour in bulk and bluish red in thin layers with a fiery red fluorescence.

1 : 4 : 5-*Trihydroxy*-2-*methylanthraquinone* (*islandicin*) (*I* b).—The above methyl ether (VI *b*) (0·1 g.) was refluxed with a mixture of glacial acetic acid (10 c.c.) and hydrobromic acid (constant boiling; 15 c.c.) for 5 hrs. The hot reaction mixture was filtered and cooled in ice, when glistening red plates separated which were filtered and washed well with water. The solid was dried and crystallised from either chloroform or dioxan when islandicin was obtained as dark red lustrous large plates or leaflets, m.p. 216–18°. Yield, 0·085 g. (Found: C, 67·1; H, 3·8; $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

It was insoluble in aqueous sodium bicarbonate and carbonate but readily soluble in aqueous sodium hydroxide giving a violet solution the colour of which faded to pale yellow after a few hours' exposure to air. With cold concentrated sulphuric acid, it gave a bright purple-red colour in bulk and bluish red in thin layers with a fiery red fluorescence. Its solution in glacial acetic acid was yellow-orange in colour with a green fluorescence.

With methanolic magnesium acetate, it gave a purple colour with a violet fluorescence. Mixed m.p. with the natural sample[11] was undepressed.

The above synthetic sample of islandicin was acetylated using acetic anhydride containing a drop of concentrated sulphuric acid. The acetate crystallised from methanol as pale yellow needles, m.p. 206–08° alone or when mixed with the acetate prepared from the natural sample of islandicin.

The methyl ether, prepared by the dimethyl sulphate-acetone-potassium carbonate method, crystallised from aqueous methanol as orange-yellow prisms, m.p. 159–60° (lit.,[11] m.p. 161°).

2 : 3-*Dicyanohydroquinone dimethyl ether.*—The following method was found to be more convenient than the earlier methods.[12, 15]

2 : 3-Dicyanohydroquinone[16] (20 g.), dissolved in dry acetone (400 c.c.), was refluxed with potassium carbonate (80 g.) and dimethyl sulphate (18 c.c., 3 moles.) for 4 hrs. The methyl ether began to separate in about 15 minutes. The reaction mixture was filtered and the residue containing the methyl ether and the potassium salts was treated with water to dissolve the latter. The insoluble solid was filtered and washed with water and then with a little acetone. It crystallised from glacial acetic acid as colourless needles, m.p. 280–81°. Yield, 21 g. (lit.,[12] m.p. 275°).

3 : 6-*Dimethoxy*-2-(2′ : 5′-*dihydroxy*-4′-*methyl*) *benzoylbenzoic acid* (*V* c).—3 : 6-Dimethoxyphthalic anhydride required for this was obtained by the hydrolysis of the above dimethyl ether.[12]

A solution of 3 : 6-dimethoxy-2-(2′-hydroxy-4′-methyl) benzoylbenzoic acid[12] (IV *c*) (0·9 g.) in potassium hydroxide (0·7 g. in 17 c.c. of water) was treated with a saturated solution of potassium persulphate (1 g.) and worked up as described earlier. The quinol derivative crystallised from aqueous methanol as clusters of yellow prisms, m.p. 227–29° (decomp.). Yield, 0·4 g. (Found: C, 60·9; H, 5·1; $C_{17}H_{16}O_7$ requires C, 61·4; H, 4·9%). It gave a green colour with alcoholic ferric chloride which turned brown on keeping or on addition of excess of the reagent. Mixed m.p. with the starting material (m.p. 231–33°) was depressed (216–20°).

1 : 4-*Dihydroxy*-5 : 8-*dimethoxy*-2-*methylanthraquinone* (*VI* c).—The above benzoylbenzoic acid (0·25 g.) was cyclised with boric acid (0·25 g.), sulphuric acid monohydrate (7 c.c.) and fuming sulphuric acid (0·3 c.c.) as in the case of islandicin. The anthraquinone derivative crystallised from chloroform-methanol mixture as red needles, m.p. 222–24°. Yield, 0·15 g. (Found: C, 64·6; H, 4·8; $OCH_3$, 18·8; $C_{17}H_{14}O_6$ requires C, 64·9; H, 4·5; 2 $OCH_3$, 19·7%).

It was insoluble in aqueous sodium bicarbonate and carbonate solutions, but soluble in alkali giving a blue-violet solution. With concentrated sulphuric acid, it gave a deep blue colour and with methanolic magnesium acetate a bluish violet colour.

1 : 4 : 5 : 8-*Tetrahydroxy-2-methylanthraquinone* (*cynodontin*) (*I* c).—The above methyl ether (0·12 g.) was demethylated using glacial acetic acid (10 c.c.) and hydrobromic acid (constant boiling; 20 c.c.) as described earlier. Cynodontin crystallised from chloroform as brown leaflets with a bronze lustre, m.p. 258–60° alone or when mixed with the natural sample.[7] Yield, 0·05 g. (Found: C, 63·0; H, 4·0; $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%). It was identical in properties and colour reactions with the natural sample of cynodontin. It gave a blue colour with methanolic magnesium acetate.

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## REFERENCES


1. Raistrick, H. — *Proc. Roy. Soc.*, 1949, **199 A,** 156; *Acta Chem. fenn*, 1950, **110 A,** 237.
2. ———, Robinson, R. and Todd, A. R. — *J. Chem. Soc.*, 1933, 488.
3. Anslow, W. K. and Raistrick, H. — *Biochem. J.*, 1940, **34,** 1546; 1941, **35,** 1006.
4. Joshi, B. S., Tilak, B. D. and Venkataraman, K. — *Proc. Ind. Acad. Sci.*, 1950, **32 A,** 348.
5. Aghoramurthy, K. and Seshadri, T. R. — *J. Sci. Industr. Res., India*, 1954, **13 A,** 114.
6. Howard, B. H. and Raistrick, H. — *Biochem. J.*, 1950, **46,** 49.
7. Raistrick, H., Robinson, R. and Todd, A. R. — *Ibid.*, 1933, **27,** 1170.
8. Bruce, D. B. and Thomson, R. H. — *J. Chem. Soc.*, 1955, 1090.
9. Jain, A. C. and Seshadri, T. R. — *J. Sci. Industr. Res., India*, 1956, **15 B,** 61.
10. Ullmann, F. and Schmidt, W. — *Ber. Dtsch. Chem. Ges.*, 1919, **52,** 2098.
11. Howard, B. H. and Raistrick, H. — *Biochem. J.*, 1949, **44,** 227.
12. Graves, G. D. and Adams, R. .. — *J. Amer. Chem. Soc.*, 1923, **45,** 2439.
13. Nietzki, R. .. — *Ber. Dtsch. Chem. Ges.*, 1877, **10,** 2011.
14. Kenner, J. and Mathews, A. M. — *J. Chem. Soc.*, 1914, **105,** 2477.
15. Cruickshank, J. H., Raistrick, H. and Robinson, R. — *Ibid.*, 1938, 2063.
16. Pai, V. N. and Guha, P. C. .. — *J. Indian. Chem. Soc.*, 1934, **11,** 234.