

ANTHRAQUINONE AND ANTHRONE SERIES

Part VII. A Synthesis of Islandicin

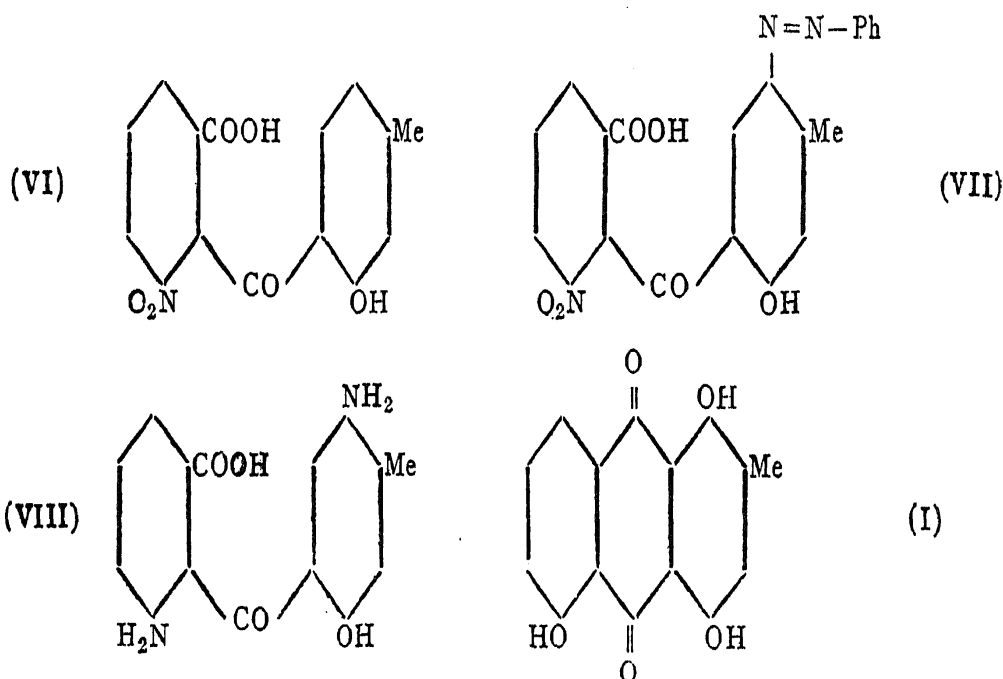
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HOWARD AND RAISTRICK¹ have recently isolated a new coloring matter from the dried mycelium of five different strains of *Penicillium islandicum* Sopp. The compound was a trihydroxy-2-methylantraquinone, which was converted by oxidation to the known 1:4:5:8-tetrahydroxy-2-methylantraquinone (cynodontin). It followed, therefore, that the coloring matter must be one of the following four possible trihydroxy-2-methylantraquinones: 1:4:5- (I), 1:4:8- (II), 4:5:8- (helminthosporin; III) and 1:5:8-trihydroxy-2-methylantraquinones (IV). Of these, (III) and (IV) are known compounds which were different from the coloring matter of *Penicillium islandicum*. Reduction of the latter gave an anthranol which on oxidation gave the known 4:5-dihydroxy-2-methylantraquinone (chrysophanic acid; V); of the two compounds (I) and (II), only the former could give (V). Howard and Raistrick therefore assigned to the coloring matter from *P. islandicum* the structure 1:4:5-trihydroxy-2-methyl-antraquinone (I) and later² gave it the trivial name "islandicin". The constitution of islandicin has now been confirmed by an unambiguous synthesis.

3-Nitro-2-(2'-hydroxy-4'-methyl)-benzoylbenzoic acid (VI), obtained by the condensation of 3-nitrophthalic anhydride with *m*-cresol,³ was coupled



with diazotized aniline in alkaline solution, and the azo dye (VII) was reduced by sodium hydrosulphite in dioxane to 3-amino-2-(5'-amino-2'-hydroxy-4'-methyl)-benzoylbenzoic acid (VIII). The diamine was tetrazotized and the solution poured into concentrated sulphuric acid at 150°, when simultaneous replacement of the amino by hydroxyl groups and cyclization of the benzoylbenzoic acid resulted, yielding 1:4:5-trihydroxy-2-methylantraquinone (I), which crystallized from chloroform in dark red lustrous plates, m.p. 218°. The trimethyl ether (IX) crystallized from alcohol in orange-yellow needles, m.p. 161°. The properties of (I) and (IX) were identical with those for islandicin and its trimethyl ether described by Howard and Raistrick.¹

EXPERIMENTAL

3-Nitro-2-(5'-benzeneazo-2'-hydroxy-4'-methyl)-benzoylbenzoic acid (VII).—Aniline (1.84 c.c.; 0.02 mole), hydrochloric acid (4.8 c.c.) and water (4.8 c.c.) were cooled to 0° and a solution of sodium nitrite (1.0 g.) in water (4 c.c.) was added. The diazonium salt solution was added to a solution of 3-nitro-2-(2'-hydroxy-4'-methyl)-benzoylbenzoic acid (VI)³ (6.0 g.; 0.02 mole) in 2% sodium hydroxide solution (120 c.c.) during 15 minutes and the mixture stirred below 5° for about one hour. The red solution was acidified with hydrochloric acid. The red-brown dye which separated was filtered (8.0 g.) and crystallized twice from glacial acetic acid when it was obtained as red-brown plates, m.p. 252° (dec.) (Found: N, 10.0. C₂₁H₁₅N₃O₆ requires N, 10.3%).

3-Amino-2-(5'-amino-2'-hydroxy-4'-methyl)-benzoylbenzoic acid (VIII).—Sodium hydrosulphite (12.0 g.) was added to a boiling solution of the pure dye (VII; 2.0 g.) in dioxane (30 c.c.) and water (25 c.c.) and the mixture refluxed for 7 hours, during which the color of the mixture changed from red to orange-yellow. The mixture was extracted several times with benzene, the extract concentrated to a small bulk and diluted with ether. The diamino-benzoylbenzoic acid, which separated as a yellow microcrystalline precipitate (2.2 g.), was crystallized from chlorobenzene. The pale yellow plates had m.p. 218° (dec.) (Found: C, 62.4; H, 4.9; N, 9.8. C₁₅H₁₄N₂O₄ requires C, 62.9; H, 4.9; N, 9.8%). The diamine (VIII) after diazotization and coupling with an alkaline solution of β-naphthol, gave a red dye, was soluble in ammonia, and gave a hydrochloride with concentrated hydrochloric acid.

1:4:5-Trihydroxy-2-methylantraquinone (Islandicin; I).—The above acid (VIII), (0.6 g.) was dissolved in ammonia and reprecipitated with hydrochloric acid (9 c.c.). Aqueous sodium nitrite (0.3 g. in 12 c.c. water) was added to the ice-cold suspension of the acid and the solution kept for 30

minutes below 5°. The solution was gradually poured in concentrated sulphuric acid (35 c.c.) at 150° and the mixture further heated for 15 minutes. After cooling, the purple-red solution was added to crushed ice. The brown-red precipitate (0.4 g.), after two crystallizations from chloroform, gave lustrous dark red plates, m.p. 218° (Found: C, 66.6; H, 4.1. $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%). The substance is insoluble in 10% sodium bicarbonate, sodium carbonate and ammonia solutions, dissolves in 10% sodium hydroxide solution giving a violet solution, and gives a yellowish orange solution in glacial acetic acid which has a green fluorescence. A solution in concentrated sulphuric acid is bright purple-red in bulk and bluish red in thin layers with a fiery red fluorescence. All these properties have been described by Howard and Raistrick for islandicin.

1:4:5-Triacetoxy-2-methylantraquinone.—A solution of 1:4:5-trihydroxy-2-methylantraquinone (0.09 g.) in acetic anhydride (1 c.c.) and 2 drops of pyridine was refluxed for one hour and poured in ice containing a little hydrochloric acid. The brownish yellow precipitate was crystallized twice from alcohol and once from glacial acetic acid; the pale yellow needles had m.p. 208° (Found: C, 63.6; H, 4.3. $C_{21}H_{16}O_8$ requires C, 63.6; H, 4.1%).

The melting points of synthetic 1:4:5-trihydroxy-2-methylantraquinone and its triacetyl derivative were undepressed when mixed with natural islandicin and its triacetyl derivative.

1:4:5-Trimethoxy-2-methylantraquinone (IX).—1:4:5-Trihydroxy-2-methylantraquinone (84 mg.), boiling dry acetone (10 c.c.), dimethyl sulphate (0.4 c.c.) and anhydrous potassium carbonate (0.4 g.) were refluxed for 10 hours. The yellow solution was filtered and the residue extracted with hot acetone. The residue obtained after removal of the solvent under reduced pressure, crystallized from alcohol in orange-yellow needles, m.p. 161° (Howard and Raistrick, 161°) (Found: C, 69.2; H, 5.2. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.2%). The trimethoxy derivative is insoluble in 10% sodium hydroxide, dissolves in concentrated sulphuric acid, giving a blue solution with a faint purple fluorescence.

SUMMARY

The constitution (I), assigned by Howard and Raistrick¹ to islandicin, the coloring matter from the dried mycelium of *Penicillium islandicum* Sopp., has now been confirmed by unambiguous synthesis.

3-Nitro-2-(5'-benzeneazo-2'-hydroxy-4'-methyl)-benzoylbenzoic acid (VII), obtained by coupling 3-nitro-2-(2'-hydroxy-4'-methyl)-benzoylbenzoic acid

(VI) with diazotized aniline, gave on reduction 3-amino-2-(5'-amino-2'-hydroxy-4'-methyl)-benzoylbenzoic acid (VIII). The latter was converted in one step to 1:4:5-trihydroxy-2-methylanthraquinone (I) by tetrazotization and treatment with hot sulphuric acid. The properties of (I), its triacetate and its trimethyl ether are identical with those of islandicin, its triacetate and its trimethyl ether described by Howard and Raistrick.

We are greatly indebted to Prof. H. Raistrick, F.R.S., for sending us specimens of natural islandicin and its triacetyl derivative.

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REFERENCES

1. .. *Biochem. J.*, 1949, **44**, 227.
2. .. *Ibid.*, 1950, **46**, 49.
3. Eder and Widmer .. *Helv. Chim. Acta.*, 1923, **6**, 419.