A NEW SYNTHESIS OF CATENARIN AND ERYTHROGLAUCIN

By K. Chandrasenan, S. Neelakantan and T. R. Seshadri, F.A.Sc.

(Department of Chemistry, University of Delhi)

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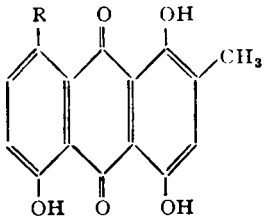
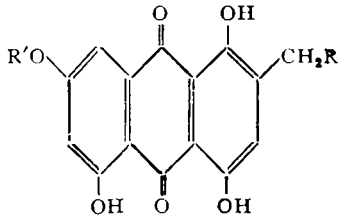
Among the naturally occurring polyhydroxy-2-methyl anthraquinones of fungal origin, islandicin (I), cynodontin (II), catenarin (III), erythroglaucin (IV) and tritisporin (V) possess a 1 : 4-dihydroxy system.



I, R=H
II, R=OH



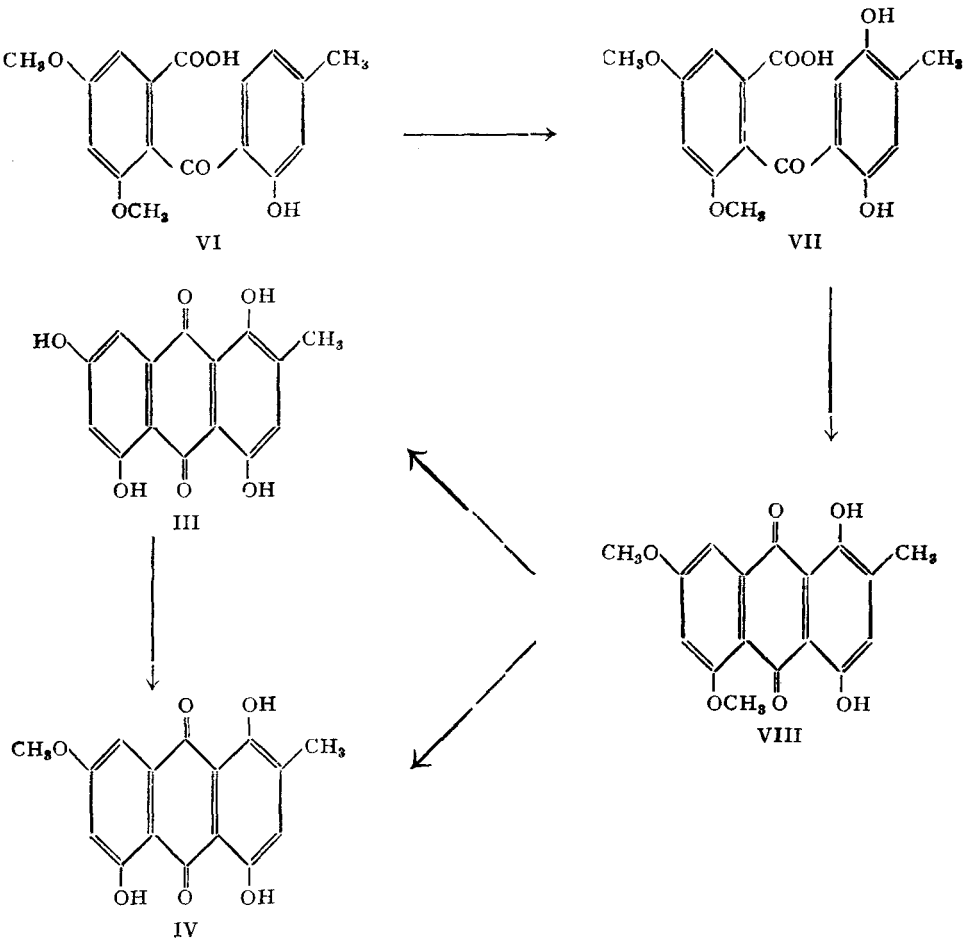
III, R=R′=H
IV, R=H; R′=CH_3
V, R=OH; R′=H

It has recently been suggested[1-2] that *para*-nuclear oxidation forms a stage in the evolution of these compounds and that this oxidation probably takes place in a preanthraquinone stage like the benzoyl benzoic acid stage. Following this suggestion a new synthesis of 2-methyl quinizarin, islandicin (I) and cynodontin (II) have recently been reported[3] using the *para*-nuclear oxidation procedure. This method has now been extended for the synthesis of catenarin (III) and erythroglaucin (IV) and is found to work very satisfactorily.

Catenarin (III) was first isolated[4] as a metabolic product of *Helminthosporium gramineum* Rabenhorst. Later, it was found[5] to be the main colouring matter of *Helminthosporium catenarium* Drechsler. Its constitution was established as (III) by Anslow and Raistrick[6] who also synthesised[7] it using a modification of the method used by Jacobson and Adams[8] for the synthesis of emodin. 3 : 5-Dimethoxy phthalic anhydride was condensed with *m*-cresol and the resulting benzoyl benzoic acid (VI) was brominated to give the bromoderivative. Ring closure was followed by demethylation and replacement of the bromine atom by hydroxyl. In the present synthesis

3: 5-dimethoxy-2 (2′-hydroxy-4′-methyl)-benzoyl benzoic acid (VI) has been subjected to *para*-nuclear oxidation with alkaline potassium persulphate and the resulting quinol derivative (VII) cyclized using concentrated sulphuric acid and boric acid when a good yield of the dimethyl ether (VIII) of catenarin is obtained. It has been completely demethylated by boiling with a mixture of constant boiling hydrobromic acid and glacial acetic acid for 20 hours when catenarin (III) is produced. Partial demethylation using the same reagent and shorter time (2 hours) gives erythroglaucin (IV).

Anslow and Raistrick[6] established the structure of erythroglaucin as 7-**O**-methyl catenarin (IV) by partial methylation of catenarin (III) using methyl iodide and sodium methoxide and heating in a sealed tube. This partial methylation could be more conveniently carried out with good yields



using restricted amount of dimethyl sulphate (1 mole) and potassium carbonate in acetone medium.

EXPERIMENTAL

3 : 5-Dimethoxy-2-(2' : 5'-dihydroxy-4'-methyl)-benzoyl benzoic acid (VII)

3 : 5-Dimethoxy-2-(2'-hydroxy-4'-methyl)-benzoyl benzoic acid[7–8] (VI, 2 g.) was dissolved in a solution of potassium hydroxide (1·3 g. in 40 c.c. of water) and the solution cooled to 15–20°. A saturated solution of potassium persulphate (1·9 g.) in water was added with stirring in the course of two hours and the mixture was kept at room temperature overnight. The dark red reaction mixture was acidified to congo red and the separated unreacted benzoyl benzoic acid was filtered ; for removing last traces, the filtrate was extracted with ether twice. To the aqueous solution were added sodium sulphite (1 g.) and concentrated hydrochloric acid (16 c.c.) and the mixture heated on a water-bath for 20 minutes. On cooling a light brown solid separated which was filtered and washed with a little water. It crystallised from dilute ethanol as clusters of light brown prisms, m.p. 234–35° ; yield, 1·7 g. (Found: C, 61·4 ; H, 4·9 ; $C_{17}H_{16}O_7$ requires C, 61·4 ; H, 4·8%). It gave a green colour with alcoholic ferric chloride which turned brown on keeping. With aqueous sodium carbonate and sodium hydroxide it gave a yellow colour changing to red.

1 : 4-Dihydroxy-5 : 7-dimethoxy-2-methyl anthraquinone (VIII)

The nuclear oxidation product (VII, 1·5 g.) was heated with a mixture of melted and powdered boric acid (1·5 g.) and concentrated sulphuric acid (25 c.c.) on a water-bath. At 70°, fuming sulphuric acid (3·8 c.c.) was added and the mixture was allowed to stand for an hour at that temperature. The deep blue solution was then poured on crushed ice and stirred well. The precipitate was coagulated by heating on a steam-bath for 15 minutes. It was cooled, filtered and washed with hot water. The red solid crystallised from acetic acid as plates. It was further purified by sublimation in vacuum at 160·65° and finally crystallised from ethanol ; red needles, m.p. 212–13° ; yield, 1·2 g. (Found: C, 64·5; H, 4·6 ; OCH_3, 18·4; $C_{17}H_{14}O_6$ requires C, 65·0 ; H, 4·5 ; 2-OCH_3, 19·7%).

It was readily soluble in chlorofrom, moderately soluble in glacial acetic acid and less soluble in alcohol. It was insoluble in aqueous sodium bicarbonate and sodium carbonate, but soluble in aqueous sodium hydroxide and potassium hydroxide giving bluish violet solutions from which a violet precipitate separated on standing. With concentrated sulphuric acid it

gave a deep blue colour and with methanolic magnesium acetate a pink colour.

Catenarin tetramethyl ether.—The above dimethoxy compound (VIII, 0·2 g.) was methylated with dimethyl sulphate (1 g.) and anhydrous potassium carbonate (2 g.) in boiling acetone solution (6 hours). The product crystallised from acetone as golden yellow leaflets, m.p. 190–91°; yield, 0·15 g. (Found: C, 66·5 ; H, 5·7 ; $C_{19}H_{18}O_6$ requires C, 66·6 ; H, 5·3%).

Catenarin (1 : 4 : 5 : 7-*tetrahydroxy-2-methylanthraquinone, III*)

The above dimethyl ether (VIII, 0·5 g.) was refluxed with glacial acetic acid (50 c.c.) and hydrobromic acid (constant boiling, *d.* 1·8 ; 75 c.c.) for 20 hours. The product was filtered hot and the filtrate cooled in ice, when a red solid separated. It was filtered and stirred with 2% aqueous sodium carbonate (75 c.c.) in which it dissolved almost completely. The filtered solution was acidified and the precipitate was filtered and crystallised repeatedly from alcohol yielding red plates, m.p. 245–46° ; yield, 0·25 g. (Found: C, 62·5 ; H, 3·7 ; $C_{15}H_{10}O_6$ requires C, 62·9 ; H, 3·5%). It agreed in all its properties with an authentic sample of catenarin ; a mixed melting-point with the latter showed no depression. Its ultraviolet spectrum in ethanol had $\lambda_{max.}$ 230 (log ϵ 4·52), 256 (log ϵ 4·23), 280 (log ϵ 4·28), 303 (log ϵ 4·05) and 490 (log ϵ 4·17) agreeing with the natural sample. In the earlier record[9] 298 mμ was reported for the natural sample in place of 303 mμ. But the natural sample we have examined gives the absorption at 303 mμ.

The acetate was prepared by treating a solution of catenarin in acetic anhydride with a drop of concentrated sulphuric acid, allowing the solution to stand for an hour and pouring it on crushed ice. The product was crystallised from ethyl acetate yielding lemon yellow rods, m.p. 234–35°, agreeing with the earlier record.

Erythroglaucin (1 : 4 : 5-*trihydroxy-7-methoxy-2-methyl anthraquinone, IV*)

(*i*) *Partial Demethylation.*—1 : 4-Dihydroxy-5 : 7-dimethoxy-2-methyl anthraquinone (VIII) (0·3 g.) was treated with glacial acetic acid (30 c.c.) and hydrobromic acid (45 c.c.) and the mixture heated under reflux for two hours. The product was filtered and the filtrate cooled in ice. The solid which had separated, was filtered and crystallised from glacial acetic acid yielding deep red plates, m.p. 205–06° ; yield, 0·2 g. (Found: C, 63·5 ; H, 4·1 ; $C_{16}H_{12}O_6$ requires C, 64·0 ; H, 4·0%). It agreed in all its properties with an authentic specimen of erythroglaucin ; a mixed melting-point

with the latter showed no depression. Its ultraviolet spectrum in chloroform had $\lambda_{max.}$ 277 (log ϵ 4·28), 305 (log ϵ 4·06), 355 (log ϵ 3·26) and 495 (log ϵ 4·18) agreeing fully with the natural sample.

(*ii*) *Partial methylation of catenarin.*—Catenarin (0·1 g.) was dissolved in boiling acetone (10 c.c.) and dimethyl sulphate (0·035 g.) and anhydrous potassium carbonate (1 g.) were added and the mixture heated under reflux for 4 hours. The mineral salts were removed by filtration and thoroughly extracted with acetone. The solvent was evaporated and the residue stirred with 2% aqueous sodium carbonate and filtered. The red solid thus obtained crystallised from glacial acetic acid as deep red plates, m.p. 205–06° ; yield, 0·08 g. The melting-point was unaffected by mixing with an authentic sample of erythroglaucin.

SUMMARY

A convenient synthesis, following suggested path of biogenesis, of catenarin and erythroglaucin has been made. It involves nuclear oxidation of the corresponding benzoyl benzoic acid. This reaction and the following ring closure give very good yields of catenarin dimethyl ether. Complete demethylation yields catenarin and partial demethylation erythroglaucin which can also be formed by the partial methylation of catenarin.

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REFERENCES

1. Aghoramurthy, K. and Seshadri, T. R. .. *J. Sci. Industr. Res., India*, 1954, **13A**, 114.
2. Neelakantan, S. and Seshadri, T. R. *Ibid.*, 1960, **19 A**, 71.
3. ———, Rajagopalan, T. R. and Seshadri, T. R. *Proc. Ind. Acad. Sci.*, 1959, **49A**, 234.
4. Charles, J. H. V., Raistrick, H., Robinson, R. and Todd, A. R. *Biochem. J.*, 1933, **27**, 449.
5. Raistrick, H., Robinson, R. and Todd, A. R. *Ibid.*, 1934, **28**, 559.
6. Anslow, W. K. and Raistrick, H. .. *Ibid.*, 1940, **34**, 1124.
7. ———— .. *Ibid.*, 1924, **35**, 1006.
8. Jacobson, R. A. and Adams, R. *J. Amer. Chem. Soc.*, 1924, **46**, 1312.
9. Birkinshaw, J. H. .. *Biochem. J.*, 1955, **59**, 485.