SYNTHESIS OF CITREOROSEIN AND ALŒ-EMODIN

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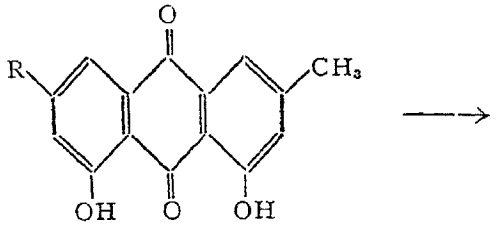
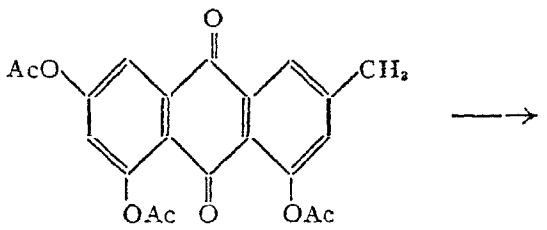
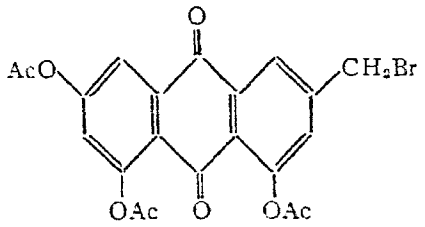
In continuation of the earlier work on the synthesis of teloschistin,[1] the synthesis of citreorosein has now been accomplished. The starting substance is frangula-emodin (I) the synthesis of which has already been recorded by Eder and Widmer[2] and also by Jacobson and Adams.[3] Its triacetate (III) undergoes smooth reaction with N-bromosuccinimide yielding the ω-bromo derivative (IV) which on treatment with silver acetate and acetic anhydride forms the tetra-acetate of citreorosein (V). Hydrolysis with methanolic sulphuric acid produces a good yield of citreorosein (VI) which agrees in every respect with the natural samples obtained from (i) *Penicillium cyclopium* Westling by Anslow, Breen and Raistrick[4] and from (ii) *Penicillium citreoroseum* Dierckx by Posternak and Jacob[5] and the mixed melting points are undepressed.



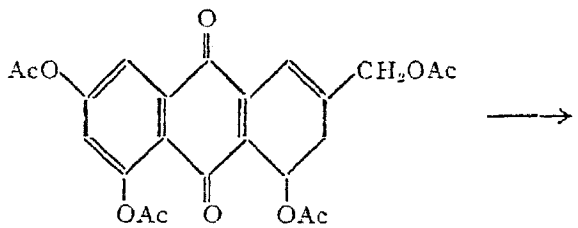
I, R=OH
II, R=H



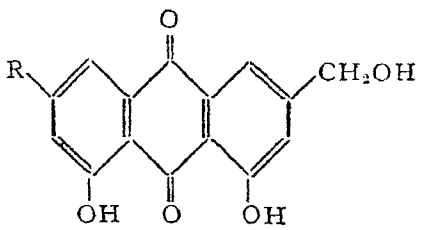
III



IV

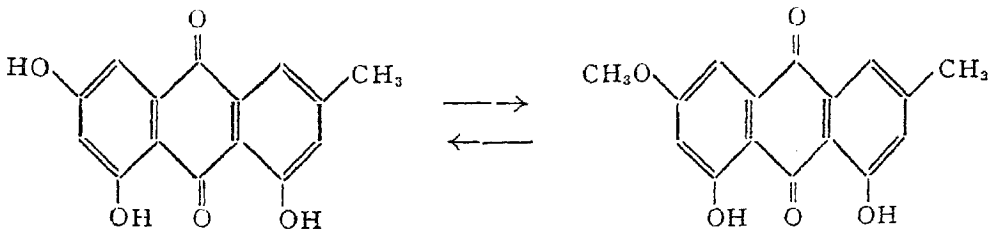


V



VI, R=OH
VII, R=H

In the course of this study, it has been observed that emodin (I) can be conveniently methylated using dimethyl sulphate and potassium carbonate to yield physcion (VIII) and the reverse conversion from physcion to emodin can be brought about by boiling with hydrobromic acid for a long period.



I VIII

As a piece of exploratory work a simpler case has been examined. Starting from chrysophanol (II), alœ-emodin (VII) has been prepared and the method using N-bromosuccinimide works quite satisfactorily and is far more convenient as compared with the earlier method of synthesis using rhein and effecting reduction to the carbinol in two stages.[6]

Experimental Procedure

Synthesis of citreorosein

(i) *Bromination of emodin triacetate to the ω-bromo derivative.*—Emodin triacetate was prepared by suspending emodin (0·9 g.) in acetic anhydride (17 c.c.) containing concentrated sulphuric acid (2 drops) and refluxing the mixture for a few minutes. The mixture was allowed to cool to the room temperature and after two hours it was poured on crushed ice and the yellow solid separated was filtered, washed with water and dried. It was crystallised from ethyl acetate yielding long yellow needles melting at 196–98° C. Yield, 0·85 g.

To a solution of emodin triacetate (0·5 g.) in dry carbon tetrachloride (150 c.c.) were added freshly crystallised and dried N-bromosuccinimide (0·4 g.) and benzoyl peroxide (0·02 g.) and the mixture refluxed on a water-bath for 24 hours. The solution was then filtered hot to remove the separated succinimide and the filtrate cooled in ice, when a pale yellow crystalline solid separated. It was filtered and washed with cold water and then with boiling water to remove succinimide and unreacted bromosuccinimide. The solid was dried in a vacuum desiccator and crystallised thrice from dry ethyl acetate yielding ω-bromo-emodin triacetate as pale yellow long needles, melting at 232–34° C. Yield, 0·35 g. (Found: C, 53·2; H, 3·4; Br, 16·8%. $C_{21}H_{15}O_8Br$ requires C, 53·1; H, 3·2; Br, 16·9%).

(ii) *Conversion of the bromo derivative into citreorosein tetra-acetate.*—The above bromo compound (0·2 g.) was suspended in acetic anhydride (15 c.c.) and silver acetate (0·6 g.) added and the mixture refluxed for 6 hours. It was then poured on crushed ice and stirred. The brownish yellow solid was filtered, washed well with water and dried. The solid was repeatedly boiled with benzene (5 × 25 c.c.) and filtered to leave behind the silver bromide. The filtrate on evaporation yielded a pale yellow solid, which was crystallised from dry benzene to yield pale yellow needles of the tetra-acetate of citreorosein melting at 190–91°. Yield, 0·15 g. (Anslow *et al.*, 190–91°).

(iii) *Hydrolysis of the acetate to citreorosein.*—The acetate (0·1 g.) was suspended in methanol (50 c.c.), concentrated sulphuric acid (2 c.c.) added carefully and the mixture refluxed on a water-bath for an hour. Methanol was then removed under reduced pressure and the solution poured on crushed ice. The gelatinous precipitate was coagulated by boiling for an hour, and the orange solid was filtered. It was crystallised from methanol (norite) to yield dull orange needles of citreorosein, melting at 288–89°. Yield, 0·07 g. (Anslow *et al.*, 288°). Mixed melting points with the natural samples of citreorosein kindly supplied by Professor H. Raistrick and Professor T. Posternak were undepressed. (Found: C, 62·6; H, 3·8%. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%).

It was insoluble in cold 2% aqueous sodium bicarbonate but dissolved in aqueous sodium carbonate and sodium hydroxide giving red solution in each case. It gave a reddish orange colour with concentrated sulphuric acid and reddish brown colour with alcoholic ferric chloride.

Demethylation of Physcion

To a suspension of physcion (1 g.) in glacial acetic acid (150 c.c.) was added hydrobromic acid (d.1.8; 120 c.c.) and the mixture was refluxed for 12 hours at the end of which the solution became clear. Glacial acetic acid was distilled off under reduced pressure and the residue poured on crushed ice. The separated brown solid was filtered and dissolved in aqueous sodium carbonate (5%, 200 c.c.). The carbonate solution was filtered from suspended impurities and acidified with ice-cold dilute hydrochloric acid. The precipitate was filtered and on crystallisation from dilute alcohol, it yielded emodin as orange red needles, melting at 253–55°. Yield, 0·9 g. Mixed melting point with an authentic sample of emodin was undepressed.

Partial methylation of emodin to physcion

To a solution of emodin (1 g.) in dry acetone (100 c.c.) were added dimethyl sulphate (0·4 c.c.; 1·1 moles) and dry potassium carbonate (3 g.).

The mixture which was deep red in colour was refluxed for 4 hours, filtered off and the potassium salts repeatedly washed with hot acetone. The solvent was distilled off from the filtrate and the residue was dissolved in chloroform. The chloroform solution was extracted with aqueous sodium carbonate (5%; 50 c.c.) to remove the unreacted emodin (0·3 g.). After washing the chloroform layer with water, it was dried over anhydrous sodium sulphate and then distilled, when an orange-red solid was left behind, which crystallised from glacial acetic acid as orange-yellow rectangular plates melting at 206–07°. Yield, 0·5 g. It was insoluble in aqueous sodium carbonate (5%) but dissolved easily in sodium hydroxide and potassium hydroxide producing purple red solutions from which pink precipitates separated soon. With alcoholic ferric chloride, it gave a reddish brown colour. Mixed melting point with an authentic sample of physcion was undepressed.

Synthesis of alœ-emodin

Chrysophanol diacetate (60 mg.), carbon tetrachloride (15 c.c.), N-bromosuccinimide (50 mg.) and benzoyl peroxide (20 mg.) were employed and the reaction carried out as described in the case of emodin triacetate. The crude bromo compound, melting at 212–15° with earlier sintering, was directly used for further stages. It was refluxed with silver acetate (50 mg.) and acetic anhydride (3 c.c.) for 6 hours. On working up and crystallising the product from benzene, alœ-emodin triacetate was obtained as yellow needles melting at 175-77°. Hydrolysis with methanolic sulphuric acid yielded alœ-emodin as pale brown orange needles, m.p. 221–23°, undepressed by admixture with the natural sample of alœ-emodin, kindly supplied by Prof. Shibata (m.p. 222–24°).

SUMMARY

Starting from chrysophanol and frangula-emodin the corresponding ω-hydroxy compounds, alœ-emodin and citreorosein have been prepared adopting the N-bromosuccinimide method. Partial methylation of frangula-emodin to physcion is effected most conveniently by the methyl sulphate-potassium carbonate method. Physcion can be demethylated directly to frangula-emodin by long boiling with hydrobromic acid.

ACKNOWLEDGMENTS

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