C O N T E N T S

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PART I

INTRODUCTION

NATURALLY OCCURRING HYDROXYANTHRAQUINONES

Among the many naturally occurring colouring matters derived from vegetable and animal origin, polyhydroxyanthraquinones form an important class of pigments. Some of the more important plant colouring matters, used since ancient times for dyeing various types of fabrics, were obtained from the roots of Rubiaceous plants such as chay root (Oldenlandia umbellata), Suranji or Morinda root (Morinda citrifolia), Munjeet (Rubia cordifolia), and the most important of all, the madder root (Rubia tinctorum). Most of these contained besides alizarin other hydroxyanthraquinones such as purpurin, xanthopurpurin, anthragallol and their derivatives. By the application of suitable mordants various shades ranging from yellow, orange, red, brown and purple were obtained. The polyhydroxyanthraquinones provide a convenient illustration of the manner in which colour is dependant not only on the number of auxochromes present, but also on their position in the molecule. A considerable amount of research has been carried out during the span of over half a century towards the elucidation of the structures of these natural pigments, which provided a direct

impetus for the synthesis in the laboratory and subsequent introduction in the market of a large number of dyes, which could compete with and excel the natural substances, in colour, light fastness and dyeing properties. A well-known example is furnished by synthetic alizarin, which was made available in the market within a few years of isolation of alizarin from madder root, with the result that madder cultivation declined in favour of synthetic alizarin, for the latter was one-fourth in cost and more effective.

Cathartic action is one of the important physiological properties of hydroxyanthraquinones, such as chrysophanol, aloe-emodin, rhein and emodin, which are 1,8-dihydroxyanthraquinones containing C-methyl, hydroxymethyl and carboxyl groups. These are present in senna, Cassia fistula pulp, cascara, rhubarb, aloes, and numerous other plants, mostly as glycosides and less frequently in the free state.[1,2] The aglycone may be of the nature of an anthrone (aloin), an anthranol (cascara) or a dianthronyl (Sennosides A and B).

Although some attempts have been made to establish a relationship between the anthraquinone content as measured by the Borntrāger reaction (see later) and the cathartic activity, no satisfactory correlation has been found to exist. The activity depends to a great extent upon the oxidation stage. Fairbairn has shown that anthracene derivatives are most highly active as anthrone glycosides, less as free anthrones and still less as free anthraquinones.[2] The free hydroxyanthraquinones themselves are active when applied directly to the large intestine, but are susceptible to metabolic destruction when orally administered. The glycosides on the other hand are unaffected, owing to the protective action of the sugar residues. Fairbairn has shown that oral doses of the anthranol of aloe-emodin are about 9 times as active as aloe-emodin, showing that the reduced form is more stable to metabolic destruction than the quinone, though not as much as the glycoside.[2]

Chrysazin (1,8-dihydroxyanthraquinone), which does not occur in nature, has been used as a mild purgative, but its use at the present time appears to be only in veterinary medicine.

2-Methylanthraquinone, purpurin, emodin, aloe-emodin, rhein and barbaloin have been reported to have antibacterial and antitubercular properties.[1]

Occurrence

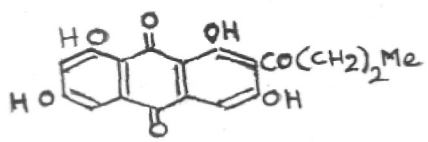
So far about 65 anthraquinone derivatives, either in the free state or as glycosides, have been isolated from natural sources. They are widely distributed in the plant kingdom, especially in the roots and barks of higher plants. A large number of them have been found to occur in lichens and fungi. In the animal kingdom their occurrence is confined to certain insects. Isolation of polyhydroxyanthraquinones from a mineral source has also been reported.[1,3] In fungi and higher plants the hydroxyanthraquinones usually occur as complex mixtures and their different oxidation stages such as carbinols, aldehydes and carboxylic acids. The corresponding reduction products such as anthrones and anthranols are also present, which are however devoid of any tinctorial properties. The fungal and lichen anthraquinones are closely related in their chemical constitution. Raistrick[4] has pointed out the close structural relation of many of the fungal anthraquinones to Frangula emodin,

though till recently emodin was not found in any mould. Recently Gatenbeck[5] has isolated emodin from Penicillium islandicum. All fungal and lichen anthraquinones (except 4-hydroxy-2-methylanthraquinone and boletol) contain two α-hydroxyl or methoxyl groups in 1,8-positions; a C-methyl, carbinol or carboxyl group, if present is invariably in the β-position.[3,6] Anthraquinones having hydroxyl or methoxyl in positions 1:2 (e.g. alizarin), or hydroxyl or other substituents in positions 1:2:3 (e.g. rubiadin, munjistin) occur in higher plants, but not in fungi, although the latter type has been found in lichens. Anthraquinones having hydroxyls in 1:4-positions (helminthosporin, islandicin, catenarin) have been isolated from some of the fungi, but not from lichens.

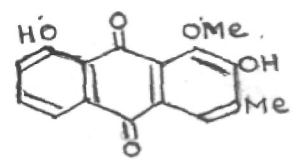
Isolation

The general methods for the isolation of plant constituents, such as carrying out series of extractions with solvents of increasing polarity, fractionation of the products from different solvents by crystallization, separation by making use of the functional groups, etc., are applicable for anthraquinone colouring matters also.

The isolation and separation of closely related anthraquinone pigments may be carried out by the use of chromatographic technique. Briggs has isolated a number of new anthraquinone pigments from the plants of Coprosma genus by using chromatography. For example, after removing the water-soluble glycosides, chromatography over calcined magnesia of the acetone extract of Coprosma lucida[7] gave eight compounds: anthragallol, its 2-methyl and 1,2-dimethyl ether, 1,6-dihydroxy-2-methylanthraquinone, rubiadin, 3-hydroxy-2-methylanthraquinone, a minute quantity of an unidentified compound, and a new trihydroxy-methylanthraquinone, lucidin (see Part III). The crinoid, Comatula pectinata,[8] consists largely of hydroxyanthraquinone pigments, which, when extracted and chromatographed over magnesium carbonate, are separated into eight zones ranging from orange to blue in colour. These pigments are formulated as the different mono- and dimethyl ethers of (I), named as rhodocomatulin. Another recent example is that of



(I)



(II)

the isolation of a new anthraquinone pigment, obtusifolin (II), from the seeds of Cassia obtusifolia.[9] The chloroform extract, when chromatographed over calcium hydrogen phosphate, gave the new pigment (II) together with the known chrysophanol and physcion.

Siddiqui et al.[28] have reported the isolation of emodin from the heartwood of Sonneratia acida Linn. and they have also described the wood as being orange in colour; but the samples of this wood supplied to us by Mr. K. P. Karamchandani, Forest Utilization Officer, Bombay State, and by Mr. V. S. Rao, Conservator General of Forests, West Bengal, were colourless and devoid of any anthraquinone pigments.

Colour Reactions

The fact that the hydroxyanthraquinones give distinct colour reactions with alkali and concentrated sulphuric acid, can be used to get an idea of the arrangement of the substituents in the anthraquinone nucleus. The Bornträger test[2] is a useful test for detecting hydroxyanthraquinones in plant extracts.

In this test the crude extract is heated with dilute mineral acid to hydrolyse the glycosides and the liberated aglycones are extracted with organic solvents such as benzene. The benzene extract is then shaken with aqueous alkali, when a beautiful rose-pink to cherry red colour is produced in the alkaline layer. Ferric chloride colouration is not characteristic for polyhydroxyanthraquinones.[6] When zirconium nitrate in dilute hydrochloric acid is added to an acetone solution of alizarin, a bluish violet colouration is obtained.[10] This is a characteristic test for all polyhydroxy-anthraquinones having two adjacent hydroxyls. Alizarin derivatives can also be judged from the shades obtained on mordanted wool. Anthraquinone derivatives having hydroxyls in 1,4-positions show fluorescence in acetic acid solution.[6] With the exception of purpurin all polyhydroxyanthraquinones having hydroxyl groups in <u>para</u>- positions are oxidized by lead tetracetate to coloured diquinoid compounds. In the case of purpurin the colour disappears rapidly, as it is very easily oxidized. This observation is useful in locating the hydroxyls in 1,2,4-positions.[11] A solution of anthragallol in aqueous sodium hydroxide rapidly changes colour

from green to brown on exposure to air.[3] Anthragallol also gives a flocculant greenish precipitate with sodium amalgam in ethanolic solution (Bargellini test) which shows the presence of hydroxyls in 1,2,3-positions.[12] According to Shibata[6] hydroxyanthraquinones having at least one α-hydroxyl group give characteristic colouration with magnesium acetate in alcoholic solution, which is bluish violet for 1,2-dihydroxy derivatives, orange to orange-red for 1,3- and 1,8-dihydroxy derivatives such as emodin and chrysophanic acid, and purple for 1,4-dihydroxy derivatives such as quinizarin and islandicin.

Constitution

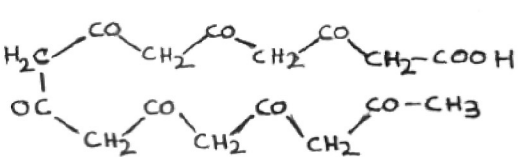
Zinc dust distillation of polyhydroxyanthraquinones gives the anthracene or the corresponding alkylanthracene. Polyhydroxyanthraquinones with one hydroxyl in the β-position are soluble in aqueous sodium carbonate, and there are examples of polyhydroxyanthraquinones with more than one β-hydroxyl groups, which are soluble in aqueous sodium bicarbonate (e.g. asperthecin). The hydroxyl in the α-position does not undergo methylation easily with ethereal diazomethane, but

can be methylated with dimethyl sulphate and alkali; whereas the methylation of β-hydroxyls can be easily carried out. The presence of two hydroxyls in 1,3-positions and absence of any substituent in the 2-position in the polyhydroxyanthraquinones, erythrolaccin and alaternin, was shown by a novel method, by treating the anthraquinone derivatives with formaldehyde and aqueous alkali to give the 2-hydroxymethyl derivative[12] (see Part III). By a careful study of these reactions, together with the colour reactions mentioned above and the infrared and ultraviolet absorption spectra, the positions of the substituents in the anthraquinone nucleus can be determined. Ultraviolet and infrared spectra are of obvious value in determining the constitution of anthraquinone derivatives, and some applications are discussed in Parts IV, V and VI. The exact constitution of the polyhydroxyanthraquinone has to be confirmed by synthesis.

Biogenesis

With the establishment of the chemical structures of many natural products during the last few decades,

and the observation of the close structural relationships of many of them, the attention of the organic chemist was diverted in recent years towards their biosynthesis. The generalizations based on biosynthesis are not of speculative interest only, because with their help it is possible to know the unsuspected relations between the classes of substances, limit the number of formulae while determining the structures and even suggest laboratory methods of synthesis.[13] Robinson[14] has shown that many natural products including quinones can arise from polyacetic acid precursors. For example heptaketopalmitic acid (III), formed from eight acetic acid units, can give the anthrone (IV) from which endocrocin (V) and emodin (VI) can be obtained. He has also pointed out that the anthrone (IV) is correctly oriented to function as the precursor of hypericin (VII), the photodynamic constituent of <u>Hypericum perforatum</u>. About half a century ago Collie[15] had advanced a similar view that diacetylacetone could be cyclised to form a benzene derivative. The acetate



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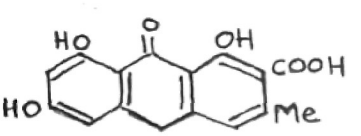

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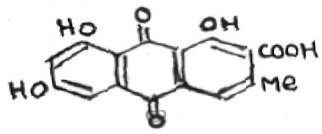

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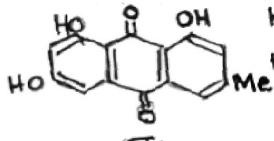

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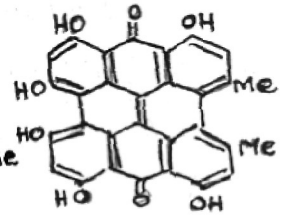
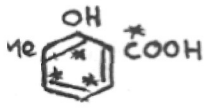


(VII)

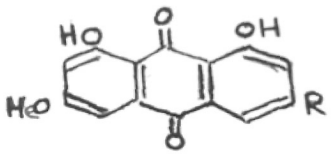
hypothesis was further extended by Birch[13] and his coworkers to demonstrate that head-to-tail linkages of acetate units could lead to phenolic substances in several ways. They showed that like the isoprene rule, the acetate hypothesis could be used, provided that proper allowance is made for nuclear oxidation and reduction reactions, in favourable cases to lessen the labour in structure determination by indicating the more probable of the alternative structures. Gatenbeck[16] successfully incorporated radioactive carbon in emodin by growing Penicillium islandicum on carboxy labelled sodium acetate and thus clearly indicated that emodin involves head-to-tail condensation of acetate units. The validity of the acetate hypothesis was earlier demonstrated by Birch[17] by showing that 6-methylsalicylic acid obtained from

Penicillium griseofulvum Dierckx grown on $CH_3{}^{14}COOH$ has the structure (VIII).



* ^{14}C

(VIII)



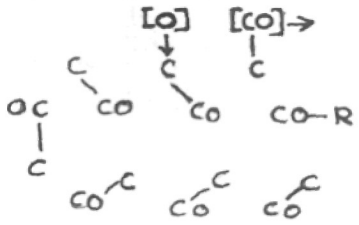
$R = -CH_2-CH_2-CH_2OH$

or

$-CH_2-CH(Me)-OH$

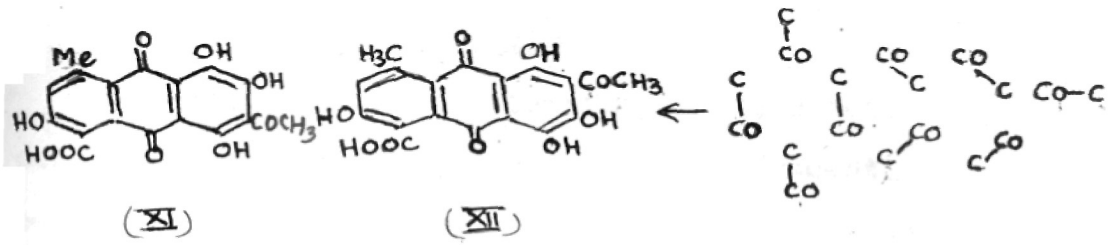
or

$-CH(Me)-CH_2OH$ (IX)



(X)

With the aid of this hypothesis Birch[18] predicted the correct structure of nalgiovensin, which was shown by Raistrick[19] to be (IX). The position of the oxygen atoms attached to the nucleus strongly suggests an acetic acid origin (X), and if the side chain is similarly derived, the most probable formula for nalgiovensin will be (IX), where R = CH_2-CHOH-CH_3. Nalgiolaxin (4- or 5-chloronalgiovensin) is unique in that it is the only naturally occurring anthraquinone containing chlorine. Kermesic acid was shown to have structures (XI) or (XII) from purely chemical evidence,[20] the latter being more probable from colour reactions. The acetate



(XI) (XII)

hypothesis also favours the latter.[21]* The acetate origin can be suspected in all cases where two hydroxyl groups are in meta-positions to each other. Many anthraquinones from higher plants contain catechol or pyrogallol rather than resorcinol structures, which must have formed from different reaction sequences.[3]

Another scheme of biogenesis based on C_8 units such as orcellinic acid and 3,5-dihydroxyphthalic acid, which occur in natural sources, was put forward by Seshadri,[22] and was extended to explain the biosynthesis of anthraquinones having catechol structures.[23]

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*However, work in progress in this laboratory indicates the need for a complete re-examination of the structures of laccaic, carminic and kermesic acids.

Classification

A systematic classification of the naturally occurring anthraquinone derivatives has recently been made by Venkataraman.[1] The hydroxyanthraquinones which have been isolated after the publication of this review are listed below:

(i) Digitoluteins (3-hydroxy-4-methoxy-2-methylanthraquinone) from *Digitalis purpurea*.[3]

(ii) Obtusifolin (3,5-dihydroxy-4-methoxy-2-methylanthraquinone) from *Cassia obtusifolia*.[9]

(iii) 1,4,7,8-Tetrahydroxy-2-methylanthraquinone from *Penicillium islandicum*.[11]

(iv) Erythrolaccin (3,4,6,8-tetrahydroxy-2-methylanthraquinone) from stick lac.[12]

(v) Rhodocomatulin (I) from *Comatula pectinata*.[8]

(vi) Damnacanthol (1-methoxy-2-hydroxymethyl-3-hydroxyanthraquinone) from *Damnacanthus major*.[24]

In addition to these, derivatives of anthraquinone-2-aldehyde have been isolated from natural sources in recent years. They are listed in Table 1.

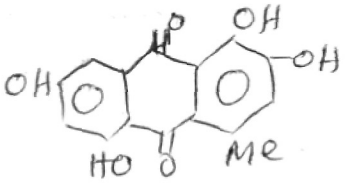

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Table 1

No.	Name	Substitution in anthraquinone-2-aldehyde	Occurrence	Reference: Isolation	Reference: Synthesis
1.	Nordamnacanthal	1,3-$(OH)_2$	*Morinda tinctoria*	23	26
2.	Damnacanthal	3-OH-1-OMe	*Damnacanthus major*	24	27
3.	Juzunal	Hydroxy damnacanthal	"	24	-
4.	Fallacinal	4,5-$(OH)_2$-7-OMe	*Xanthoria fallax*	25	25

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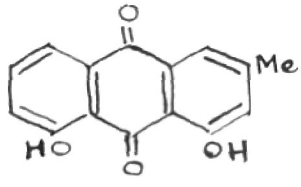
PART II

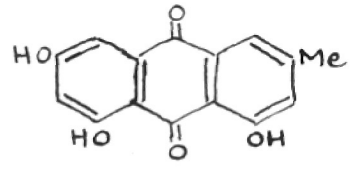
A NEW SYNTHESIS OF CHRYSOPHANOL, EMODIN AND PHYSCION AND A SYNTHESIS OF 2,3,6-TRIHYDROXYANTHRAQUINONE

23

Chrysophanol (chrysophanic acid, I) was first synthesized by Eder and Widmer[1] by condensation of 3-nitrophthalic anhydride with m-cresol. When the condensation was carried out with boric acid as the condensing agent instead of aluminium chloride, two isomeric nitro-keto-acids (III and IV) were obtained.

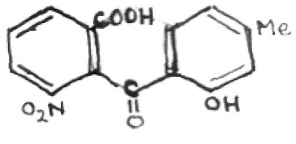


I

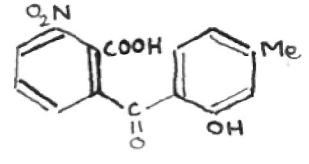


II

When the condensation was effected by means of aluminium chloride using excess of m-cresol as solvent, only (III) was formed and in good yield. Use of a solvent such as tetrachloroethane



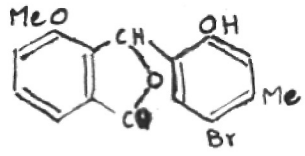
III



IV

gave very poor yields of (III). Reduction of (III) to the amine, cyclization, and final conversion of the amino group to hydroxyl yielded chrysophanol (I). Because they considered this method of synthesis to be ambiguous, the constitution of chrysophanol was

established by Naylor and Gardner[2] by a synthesis in which 3-methoxyphthalaldehydic acid was condensed with p-bromo-m-cresol to give the substituted phthalide (V) exclusively. Reduction of (V) to the corresponding benzylbenzoic acid gave an anthrone, which on oxidation and demethylation gave chrysophanol (I). Eder and Widmer[3] synthesized emodin (II) by condensing 3,5-dinitrophthalic anhydride and m-cresol following the reactions used in the synthesis of chrysophanol. Here also the constitution of the intermediates was not proved. Another disadvantage of the Eder and Widmer method is that the cyclization of the benzoylbenzoic acid to the anthraquinone involves an attack on a site which is meta to both the hydroxyl and methyl groups. Several modifications of the Eder-Widmer synthesis were reported later. Jacobson and Adams[4] condensed 3,5-dimethoxyphthalic anhydride with m-cresol and introduced a bromine atom para to the hydroxyl group before cyclization. Mühlemann[5,6] achieved an unambiguous synthesis of emodin (II) which was based on a scheme of biogenesis and involved the



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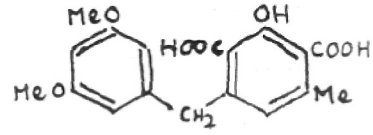
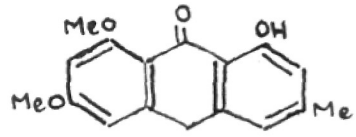


VI



VII

cyclization and simultaneous decarboxylation of (VI) to the anthrone (VII) by fusing with anhydrous zinc chloride containing sulphuric acid; (VII) was finally oxidized and demethylated.

Methods of synthesis of chrysophanol (I), emodin (II) and other hydroxyanthraquinones, which were based on the condensation of nitro- and methoxy-phthalic anhydrides with phenols, required relatively inaccessible intermediates. A new approach to the synthesis of chrysophanol (I) and emodin (II), starting from the common dye intermediate, 2-methylanthraquinone, is now described; and with appropriate modifications it can be used for the synthesis of other naturally occurring polyhydroxy-2-methylanthraquinones. Halogenation of

aminoanthraquinones, deamination *via* the diazonium salts, and the replacement of halogen by hydroxyl or methoxyl followed by demethylation has been explored earlier as a general method for the synthesis of hydroxyanthraquinones.[7,8]

Nitration of 2-methylanthraquinone to the dinitro stage gives a mixture of 1,5-dinitro- and 1,8-dinitro-2-methylanthraquinones (VIII and IX) which can be separated easily on account of their different solubilities in concentrated sulphuric acid and organic solvents such as acetone and acetic acid.[9] A series of subsequent reactions are involved, but in general they proceed smoothly and in good yield.

For the synthesis of chrysophanol (I), 1,5-dinitro-2-methylanthraquinone (VIII) is the suitable starting material. Partial reduction of (VIII) by short boiling with dimethylaniline, a reaction applied earlier to the partial reductions of 1,5- and 1,8-dinitroanthraquinones[10] gave 1-nitro-2-methyl-5-aminoanthraquinone (X) in 60-65 per cent yield; the monoamine (X) separating from

the dimethylaniline solution was crystalline and required no further purification before proceeding to the next stage. The constitution of (X) was confirmed by deamination to 1-nitro-2-methylanthraquinone. Diazotization of (X) and hydrolysis with boiling 40 per cent sulphuric acid gave 1-nitro-2-methyl-5-hydroxyanthraquinone (XI). Reduction of (XI) with sodium sulphide gave 1-amino-2-methyl-5-hydroxyanthraquinone (XII). When (XII) was treated with bromine in glacial acetic acid at 20°, the hydroxylated ring was unaffected and the sole product was the 4-bromo compound (XIII), which was deaminated to 2-methyl-4-bromo-5-hydroxyanthraquinone (XIV) by boiling the diazonium salt solution with ethanol; (XIII) is also a useful intermediate for the synthesis of islandicin (1,4,5-trihydroxyanthraquinone),[11] the red colouring matter of Penicillium islandicum. Chrysophanol (I) was obtained by the replacement of the halogen atom in (XIV) by hydroxyl by heating with aqueous lime and copper bronze in an autoclave at 200° for 24 hr.

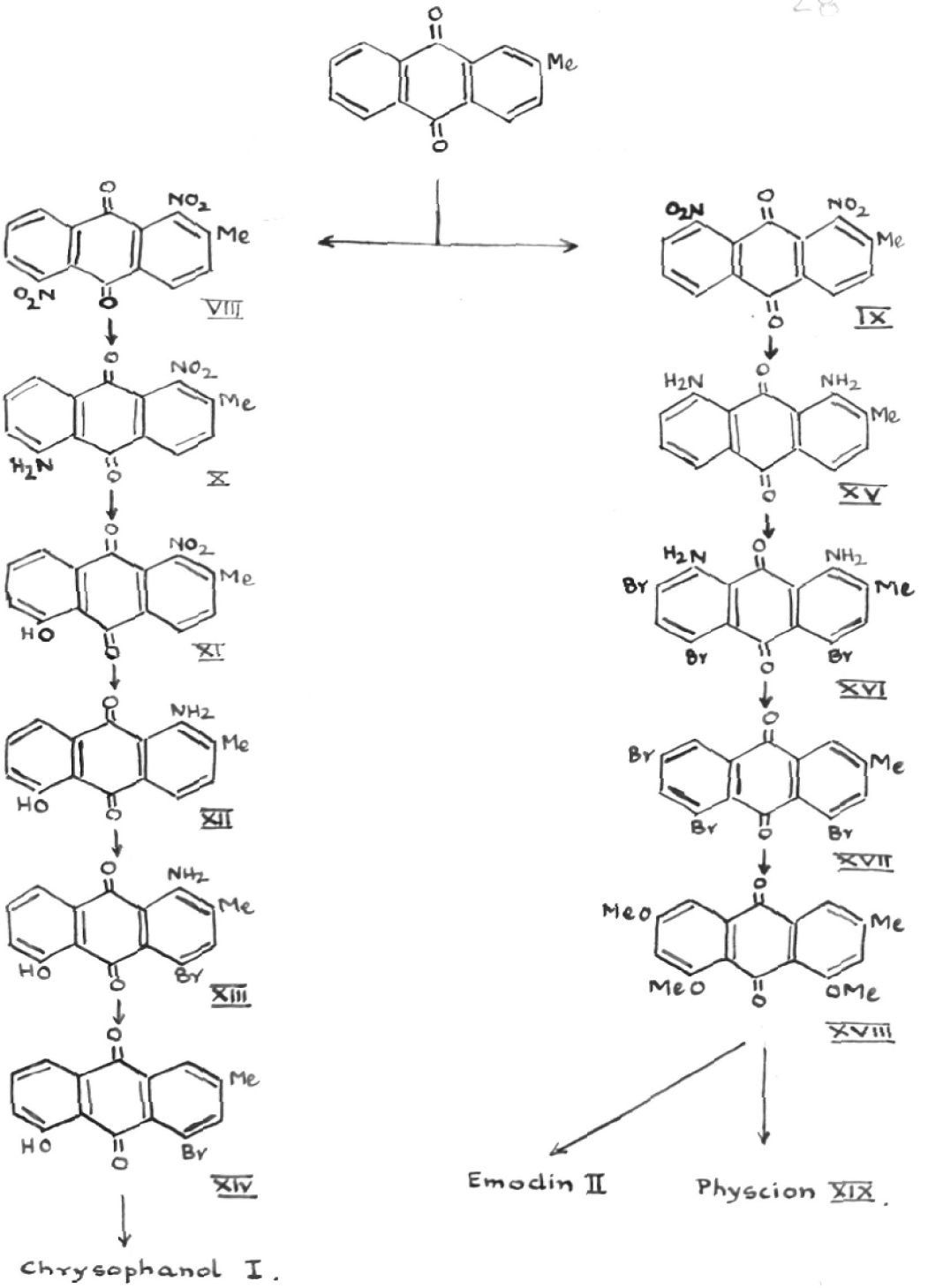
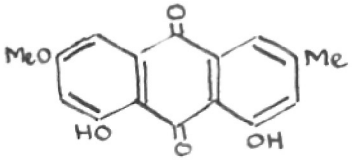
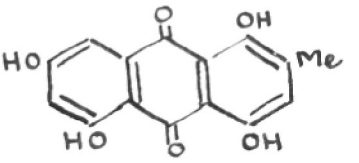

Me
VIII
X
XI
XII
XIII
XIV
Chrysophanol I.
IX
XV
XVI
XVII
XVIII
Emodin II
Physcion XIX.

CHART 1.

1,8-Diamino-2-methylanthraquinone (XV) was used as the starting material for the synthesis of emodin (II) and physcion (XIX). Bromination of (XV) with



XIX

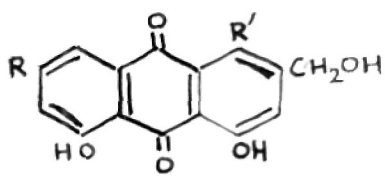


XX

excess of bromine in glacial acetic acid at 100° gave the tribromo compound (XVI), which was deaminated through the diazonium salt to give 4,5,7-tribromo-2-methylanthraquinone (XVII). Prolonged refluxing of (XVII) with sodium methoxide and methanol in presence of copper oxide gave emodin trimethyl ether (XVIII) in about 60 per cent yield; methoxylation could also be effected by heating in a sealed tube at 160-170° for 6-12 hr, but the yield was somewhat lower. Complete demethylation of emodin trimethyl ether (XVIII) to emodin (II) was best effected by treatment for a few minutes with a melt of aluminium chloride-sodium chloride at 140-150°. Selective demethylation of the α-methoxyl groups in (XVIII) by refluxing with hydrobromic acid and glacial acetic acid for one hr yielded physcion (XIX). Physcion was synthesized earlier by the partial methylation of

emodin (II) with methyl iodide and sodium methoxide in methanol[12] or with potassium acetate and dimethyl sulphate.[13]

Although N-bromosuccinimide (NBS) has been used extensively for the bromination of methylene and methoxyl groups including the side-chain bromination of aromatic hydrocarbons,[14] probably the first application to an anthraquinone derivative was the bromination of rubiadin diacetate to the corresponding 2-bromomethylanthraquinone which then led to lucidin[15] (see Part III). This method was later used for the synthesis of aloe-emodin[16] (XXI), citreorosein[16] (XXII), teloschistin[17] or fallacinol[18] (XXIII) and tritisporin[19] (XXIV) from the acetyl derivatives of chrysophanol (I), emodin (II), physcion (XIX) and catenarin (XX) respectively.



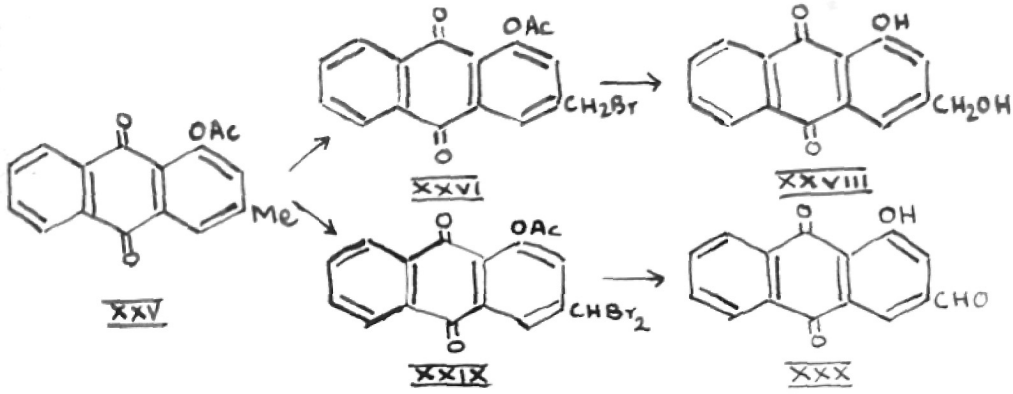
XXI, R = H; R' = H
XXII, R = OH; R' = H
XXIII, R = OMe; R' = H

XXIV, R = OH; R' = OH

In these cases the importance of the molar proportion of the brominating agent was not realised; and the bromomethyl derivatives were usually not isolated in

the pure form but were used as such for further reaction. Bhavsar, Tilak and Venkataraman[20] have shown that 2-methylanthraquinone and 1-bromo-2-methylanthraquinone gave a mixture of the corresponding 2-bromomethyl and 2-dibromomethyl derivatives, when more than one mole of the brominating agent was used. Thus in the NBS method of bromination of 2-methylanthraquinones not containing acetoxyl groups in both the adjacent positions as in rubiadin diacetate which readily yields 1,3-diacetoxy-2-bromomethylanthraquinone[15] (even when nearly twice the molar proportion of NBS was used), the molar proportion of the brominating agent is important. This has been shown by the present work carried out on 1-acetoxy-3-methylanthraquinone (XXV), which is a simpler analogue of the acetyl derivatives of chrysophanol (I), emodin (II), physcion (XIX) and catenarin (XX). When two moles of NBS were used for one of 1-acetoxy-3-methylanthraquinone (XXV), the product was 1-acetoxy-3-dibromomethylanthraquinone (XXIX), which was hydrolysed by sulphuric acid to 1-hydroxyanthraquinone-3-aldehyde (XXX), characterized as the

2,4-dinitrophenylhydrazone. On the other hand, the use of exactly one mole of NBS for one of 1-acetoxy-3-methylanthraquinone (XXV) gave the pure monobromo-compound (XXVI), which with sodium acetate and acetic anhydride gave 1-acetoxy-3-acetoxymethylanthraquinone



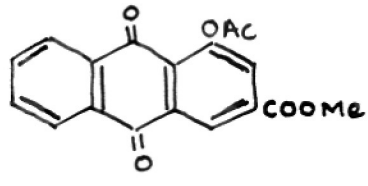
(XXVII). Hydrolysis of (XXVII) by refluxing with methanol containing a little sulphuric acid yielded 1-hydroxy-3-hydroxymethylanthraquinone (XXVIII). Aloe-emodin (XXI) was similarly prepared from chrysophanol diacetate using exactly one mole of the brominating agent.

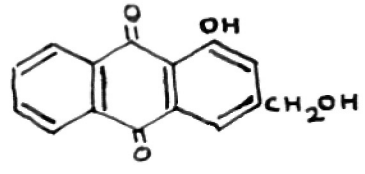
Teloschistin isolated by Seshadri[17] from the Indian lichen *Teloschistes flavicans*, and fallacinol, isolated by Murakami[18] from Japanese lichen *Xanthoria fallax*, have been assigned the same structure (XXIII); but different melting points were quoted for teloschistin (245-7°) and fallacinol

(236-7°). By the partial methylation of ω-hydroxyemodin (citreorosein, XXII) a monomethyl ether, m.p. 229-231°, was obtained;[21] the first reports on teloschistin stated that it melted at 229-230°, and that the melting point was undepressed by mixing with the 7-monomethyl ether of ω-hydroxyemodin. Both Seshadri and Murakami have described the synthesis of (XXIII), possessing the same m.p. as natural teloschistin and fallacinol respectively, by treatment of 4,5-diacetoxy-7-methoxy-2-bromomethylanthraquinone (XXXI) with silver acetate or sodium acetate. Murakami found that fallacinol was accompanied by the corresponding aldehyde, fallacinal (4,5-dihydroxy-7-methoxyanthraquinone-2-aldehyde), which was subsequently isolated also from teloschistes flavicans.[17] In the synthesis of teloschistin[17] (XXIII), 1.55 moles of NBS per mole of physcion diacetate were used by Seshadri; (XXXI) was obtained as a "sticky solid," which was used directly for the further conversion into teloschistin tetracetate. It appears probable that the compound believed to be (XXXI) consisted of, or contained a substantial amount of the corresponding ω-dibromo

derivative; and the ultimate product was th_ aldehyde, fallacinal, rather than the alcohol (XXIII). Murakami[18] used only one mole of NBS for the bromination of physcion diacetate; he too did not isolate the bromo compound (XXXI) in the pure state, but treated the crude product with sodium acetate and acetic anhydride, hydrolysed with aqueous sodium hydroxide and chromatographed a benzene solution on calcium hydrogen phosphate pretreated with phosphoric acid. Eight bands separated and fallacinol (XXIII) was recovered from the top band.

Methyl anthraquinone-2-carboxylate and methyl-1-acetoxyanthraquinone-3-carboxylate have been reduced in the present work by lithium aluminium hydride to 2-hydroxymethylanthraquinone and 1-hydroxy-3-hydroxymethylanthraquinone (XXVIII) respectively. Thus this can be used as a convenient method for the synthesis of hydroxyanthraquinones containing alcohol groups.





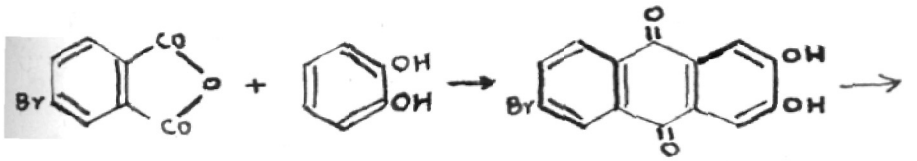
XXVIII

Although the methods described above for the synthesis of polyhydroxyanthraquinones, starting from suitably substituted anthraquinones are generally preferable to the methods which use substituted phthalic anhydride and substituted phenols, there are examples of polyhydroxyanthraquinones for which the older procedures may be employed. One is 2,3,6-trihydroxyanthraquinone, the synthesis of which is now described. Of the fourteen possible trihydroxyanthraquinones only two are unknown: 2,3,6-trihydroxyanthraquinone (XXXII) and 1,3,6-trihydroxyanthraquinone. The synthesis of 1,3,5- and 1,3,7-trihydroxyanthraquinone and a new improved synthesis of 1,3,8-trihydroxy derivative have been reported from this laboratory.[7,8] The dye intermediate, 1-amino-5-benzamidoanthraquinone, was used as the starting material. Suitably halogenated derivatives were prepared from which the trihydroxyanthraquinones were obtained by reacting with sodium methoxide and subsequent demethylation.

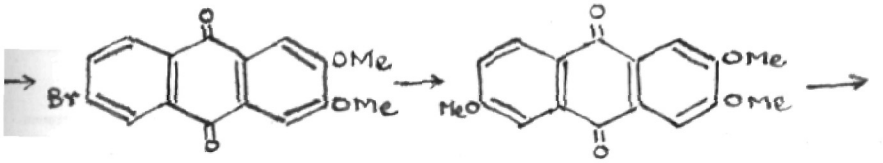
2,3,6-Trihydroxyanthraquinone (XXXII) has now been synthesized from 4-bromophthalic anhydride[22]

and pyrocatechol by the indicated series of reactions (Chart 2).

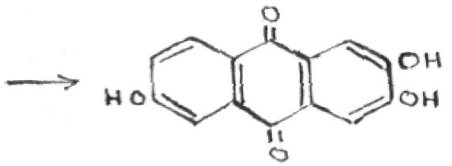
Chart 2



XXXIII



XXXIV



XXXII

4-Bromophthalic anhydride was condensed with pyrocatechol by heating the mixture with aluminium chloride-sodium chloride at 200-220° for about 20 min. The resulting 2,3-dihydroxy-6-bromoanthraquinone (XXXIII) was methylated by the acetone-potassium carbonate method, and then refluxed with sodium methoxide in methanol for 24 hr to give the trimethoxy derivative (XXXIV), which was then demethylated by heating with aluminium chloride-sodium chloride melt

at 140-150° for a few minutes to give the trihydroxy compound (XXXII). The condensation of 4-bromophthalic anhydride with catechol can take two alternative courses, but from a comparison of the melting points of the trimethyl ether and the triacetyl derivative of (XXXII) with those of the corresponding derivatives of 1,2,6- and 1,2,7-trihydroxyanthraquinone,[23] it was obvious that (XXXII) had the structure assigned to it.

Compound	Melting point
XXXII	above 360°
1,2,6-trihydroxyanthraquinone	above 330°
1,2,7-trihydroxyanthraquinone	369°
XXXIV	238°
1,2,6-trimethoxyanthraquinone	225°
1,2,7-trimethoxyanthraquinone	201°
Triacetyl derivative of XXXII	193°
1,2,6-triacetoxyanthraquinone	202-203°
1,2,7-trimethoxyanthraquinone	225-227°

The structure of (XXXII) has also been confirmed by the infrared spectrum, in which only the unchelated carbonyl band (1664 cm^{-1}) was observed. There was no absorption

in the region 1620 - 1630 cm^{-1} (chelated carbonyl), thus ruling out any possibility of the presence of a hydroxyl group in the α-position of the anthraquinone nucleus.[24]

E X P E R I M E N T A L

1,5-Dinitro-2-methylanthraquinone (VIII) (30-35% yield; m.p. 346°) and 1,8-dinitro-2-methylanthraquinone (IX) (10-12% yield; m.p. 293°) were prepared by nitrating 2-methylanthraquinone and separating the two isomers.[9]

1-Nitro-2-methyl-5-aminoanthraquinone (X) - A mixture of 1,5-dinitro-2-methylanthraquinone (5 g) and freshly distilled dimethylaniline (50 ml) was stirred in a round bottom flask fitted with a reflux condenser. The mixture was heated gently with vigorous stirring to the boiling point. The suspension of the nitro compound goes into solution with a red colour. The reaction is continued for 20 min from the start and allowed to cool overnight. The separated crystalline product was collected, washed with ether and dried (2.8 g). The product is pure enough for further reactions. Crystallization from chlorobenzene gave garnet red needles, m.p. 300°. (Found: C, 63.7; H, 3.6; N, 9.9. $C_{15}H_{10}O_4N_2$ requires: C, 63.8; H, 3.5; N, 9.9%).

1-Nitro-2-methylanthraquinone - 1-Nitro-2-methyl-5-aminoanthraquinone (X) (0.75 g) was dissolved in conc. H_2SO_4 (20 ml), cooled in ice-bath to 5°,

and diazotized with sodium nitrite (0.7 g) in conc. H_2SO_4 (10 ml) for 1 hr. Glacial acetic acid (2 ml) was added, and after 15 min the mixture was poured over crushed ice (30 g). The diazonium salt solution was added to ethanol (75 ml) and the mixture was gradually heated to boil, and then refluxed for 30 min. The yellow product was collected, washed free of acid and dried (0.7 g). Crystallization from glacial acetic acid gave yellow needles, m.p. 270-1°, undepressed when mixed with an authentic sample of 1-nitro-2-methylanthraquinone.

1-Nitro-2-methyl-5-hydroxyanthraquinone (XI) - 1-Nitro-2-methyl-5-aminoanthraquinone (X) (5 g) in conc. H_2SO_4 (100 ml) was cooled to 5° and diazotized with a mixture of sodium nitrite (5 g) and conc. H_2SO_4 (25 ml). The diazonium solution was poured over crushed ice (150 g) and then added to 50% H_2SO_4 solution (300 ml) at the boil. The mixture was heated at 140° for 1 hr and diluted with water (300 ml). The crystalline yellow product was collected, washed and dried (4.6 g). Crystallization from glacial acetic acid gave yellow needles, m.p.

275°. (Found: 63.7; H, 2.7; N, 4.8. $C_{15}H_9O_5N$ requires: C, 63.6; H, 3.2; N, 4.9%).

1-Amino-2-methyl-5-hydroxyanthraquinone (XII) - 1-Nitro-2-methyl-5-aminoanthraquinone (4 g) was made into a paste in a round bottom flask with sodium sulphide (15 g). The mixture was diluted with water (90 ml) and heated gradually on a water-bath at 100° with vigorous stirring for 1 hr. The red crystalline mass was collected, washed and dried (3.5 g). Crystallization from toluene gave red needles, m.p. 192°. (Found: C, 71.4; H, 4.3; N, 5.3. $C_{15}H_{11}O_3N$ requires: C, 71.2; H, 4.3; N, 5.5%).

1-Amino-2-methyl-4-bromo-5-hydroxyanthraquinone (XIII) - A suspension of 1-amino-2-methyl-5-hydroxyanthraquinone (XII) (3 g) in glacial acetic acid (50 ml) was stirred with bromine (1.1 ml) at 15-20° for 8 hr and left overnight. The scarlet product was collected, washed with 5% sodium bisulphite solution and with water and dried (3.78 g). Crystallization from toluene gave brownish red needles, m.p. 242°. (Found: C, 53.7; H, 3.2; N, 4.3; Br, 24.2. $C_{15}H_{10}O_3NBr$ requires: C, 54.2; H, 3.2; N, 4.2; Br, 24.1%).

2-Methyl-4-bromo-5-hydroxyanthraquinone (XIV) - A solution of 1-amino-2-methyl-4-bromo-5-hydroxyanthraquinone (XIII) (3.3 g) in conc. H_2SO_4 (50 ml) was cooled in an ice-bath to 5°, and diazotized with sodium nitrite (2 g) dissolved in conc. H_2SO_4 (20 ml). After an hr glacial acetic acid (20 ml) was added, and after 15 min the mixture was poured over crushed ice (80 g). The solution of the diazonium salt was added to ethanol (150 ml), and the mixture was gradually heated to the boil and then refluxed for 30 min. The yellow crystalline product was collected, washed free of acid and dried (3 g). Crystallization from glacial acid gave yellow needles, m.p. 203°. (Found: C, 56.9; H, 3.2. $C_{15}H_9O_3Br$ requires: C, 56.8; H, 2.8%).

Chrysophanic acid (I) - To a thin slurry made from slaked lime (12.5 g) in water (50 ml), 2-methyl-4-bromo-5-hydroxyanthraquinone (2.5 g) and copper bronze (1 g) were added. The mixture was heated in an autoclave at 200° for 24 hr. The red reaction mixture was acidified and the yellow precipitate collected, washed free of acid and dried (1.9 g). Crystallization from alcohol gave yellow plate

lets, m.p. 196° (Eder, Widmer,[1] 196°). (Found: C, 70.8; H, 4.2. $C_{15}H_{10}O_4$ requires: C, 70.9; H, 3.9%).

The acetyl derivative crystallized from alcohol as yellow needles, m.p. 208° (Eder[26], 208°).

1,8-Diamino-2-methylanthraquinone (XV), m.p. 206°, was prepared by the reduction of 1,8-dinitro-2-methylanthraquinone[9] with sodium sulphide.

1,8-Diamino-4,5,7-tribromo-2-methylanthraquinone (XVI) - A mechanically agitated solution of 1,8-diamino-2-methylanthraquinone (17.5 g) in glacial acetic acid (1750 ml) was treated at 100° with bromine in glacial acetic acid (20 ml in 250 ml) for 8 hr. On cooling to room temp. overnight, the crystalline product was collected, washed with sodium bisulphite solution and water, and dried. (25 g) crystallization from chlorobenzene or glacial acetic acid gave dark red needles, m.p. 246°. (Found: C, 37.1; H, 1.8; N, 6.0; Br, 48.6. $C_{15}H_9O_2N_2Br_3$ requires: C, 36.8; H, 1.8; N, 5.7; Br, 49.0%).

4,5,7-Tribromo-2-methylanthraquinone (XVII) - A solution of 1,8-diamino-4,5,7-tribromo-2-methylanthraquinone (10 g) in conc. H_2SO_4 (300 ml), cooled to 5°, was diazotized with sodium nitrite (5 g) in conc. H_2SO_4 (40 ml) for 1 hr. Glacial acetic acid (40 ml) was added and the mixture poured over crushed ice (2 kg). The diazonium solution thus obtained was refluxed with ethanol (1.5 l) for 1 hr. On cooling the product was collected, washed and dried (9 g). Crystallization from glacial acetic acid gave pale brownish yellow needles, m.p. 200°. (Found: C, 39.5; H, 1.9; Br, 51.9. $C_{15}H_7O_2Br_3$ requires: C, 39.3; H, 1.5; Br, 52.3%).

Emodin trimethyl ether (XVIII) - Sodium metal (12.5 g) was dissolved in absolute methanol (250 ml). 4,5,7-Tribromo-2-methylanthraquinone (5 g) and copper oxide (2 g) were added, and the mixture refluxed for 72 hr under anhydrous conditions. Dilution with water (1 l) gave a product, which was collected, washed, dried and dissolved in benzene. The solution was passed through a short column of alumina, the percolate evaporated, and the residue, which gave a negative test for halogen (1.77 g) was crystallized

from alcohol in yellow plates, m.p. 226° (Oesterle and Tisza,[27] 225°). (Found: C, 68.9; H, 5.1; OMe, 29.3. $C_{18}H_{16}O_5$ requires: C, 69.2; H, 5.1; OMe, 29.8%).

Emodin (II) - To a melt prepared from anhydrous aluminium chloride (7.5 g) and dry sodium chloride (1.5 g), emodin trimethyl ether (1.5 g) was added and the mixture stirred at 140° for 5 min. On cooling and adding 2% HCl (150 ml), the orange yellow product was collected, dissolved in 5% aqueous sodium carbonate (75 ml), filtered and the filtrate acidified. The precipitate (1.1 g) crystallized from alcohol in orange needles, m.p. 256° (Oesterle, Johann,[28] 255°). (Found: C, 66.5; H, 3.9. $C_{15}H_{10}O_5$ requires: C, 66.7; H, 3.7%). The substance gives a cherry red colour with aqueous alkali, alkali carbonate and ammonia, and a red colour with conc. H_2SO_4. In the ultraviolet and visible region (VI) exhibits the following maxima: 254, 287, and 445 m ; log max 4.42, 4.38 and 4.13 respectively.

The triacetyl derivative crystallized from alcohol as yellow needles, m.p. 197° (Oesterle, Johann,[28] 197).

Physcion (XIX) - Emodin trimethyl ether (0.5 g) was refluxed with 48% hydrobromic acid (12 ml) and

glacial acetic acid (80 ml) for 1 hr. The yellow crystalline product which separated on cooling crystallized from glacial acetic acid in golden yellow leaflets (0.3 g), m.p. 207° (Hesse,[29] 207°). (Found: C, 67.2; H, 4.4. $C_{16}H_{12}O_5$ requires: C, 67.6; H, 4.2%). The product gives a red colour in conc. H_2SO_4 and cherry red colour in aqueous sodium hydroxide. It is insoluble in cold aqueous sodium carbonate or ammonia. The properties agree with those described for natural physcion.

The diacetyl derivative was crystallized from alcohol in greenish yellow needles, m.p. 189°. (Found: C, 65.0; H, 4.3. $C_{20}H_{16}O_7$ requires: C, 65.2; H, 4.3%).

1-Acetoxy-3-bromomethylanthraquinone (XXVI)- 1-Acetoxy-3-methylanthraquinone (1.17 g), N-bromosuccinimide (0.75 g, 1 mole), benzoyl peroxide (0,05 g) and carbon tetrachloride (117 ml) were refluxed for 24 hr. The solvent was distilled off, the residue washed with hot water and dried (1.25 g). Crystallization from carbon tetrachloride gave yellow prisms, m.p. 176-7°. (Found: C, 56.6; H, 3.0. $C_{17}H_{11}O_4Br$ requires: C, 56.8; H, 3.1%). On heating a solution of

the substance in pyridine an insoluble pyridinium salt separates.

1-Acetoxy-3-acetoxymethylanthraquinone (XXVII) - 1-Acetoxy-3-bromomethylanthraquinone (X) (0.32 g) was refluxed with fused sodium acetate (0.32 g) in acetic anhydride (10 ml) for 1 hr. The mixture was cooled and poured into crushed ice. The pale yellow product was collected, washed and dried (0.26 g). Crystallization from alcohol gave pale yellow needles, m.p. 162°. (Found: C, 67.6; H, 4.4. $C_{19}H_{14}O_6$ requires: C, 67.5; H, 4.1%).

1-Hydroxy-3-hydroxymethylanthraquinone (XXVIII) - 1-Acetoxy-3-acetoxymethylanthraquinone (0.2 g) was dissolved in methanol (20 ml) by warming. Conc. H_2SO_4 (0.5 ml) was added and the solution refluxed for 30 min. The methanol was removed under vacuum, water added and the yellow product was collected, washed and dried (0.1 g). Crystallization from toluene gave yellow needles, m.p. 205-6° (Mitter et al.[25] quote m.p. 197-9°). (Found: C, 70.6; H, 3.8. $C_{15}H_{10}O_4$ requires: C, 70.9; H, 3.9%).

1-Acetoxy-3-dibromomethylanthraquinone (XXIX) - 1-Acetoxy-3-methylanthraquinone (1.8 g), N-bromosuccinimide (2.4 g; 2 moles), benzoyl peroxide (0.05 g)

and carbon tetrachloride (180 ml) were refluxed for 24 hr. The solvent was distilled off, the residue washed with hot water and dried (2.05 g). Crystallization from carbon tetrachloride gave pale yellow platelets, m.p. 192-3°. (Found: C, 46.4; H, 2.5. $C_{17}H_{10}O_4Br_2$ requires: C, 46.5; H, 2.3%).

1-Hydroxyanthraquinone-3-aldehyde (XXX) - 1-Acetoxy-3-dibromomethylanthraquinone (0.2 g) was dissolved in conc. H_2SO_4 (5 ml) and heated on a water bath for 7 hr. The mixture was poured into crushed ice. The yellow product was collected, washed and dried. Crystallization from acetic acid gave orange needles, m.p. 212-3° (Mitter et al.[25] quote m.p. 214°).

The 2,4-dinitrophenylhydrazone was crystallized from nitrobenzene as orange-red needles, m.p. 324-5°. (Found: N, 12.0; $C_{21}H_{12}O_7N_4$ requires: N, 12.8%).

1,8-Diacetoxy-3-bromomethylanthraquinone - Chrysophanol diacetate (0.5 g), N-bromosuccinimide (0.27 g, 1 mole), benzoylperoxide (0.05 g) and carbon tetrachloride (175 ml) were refluxed for 24 hr. The solvent was distilled off and the residue washed with hot water and dried (0.58 g). Crystallization from carbon tetrachloride gave pale yellow platelets, m.p. 212°.

(Found: C, 54.4; H, 3.1; Br, 18.9. $C_{19}H_{13}O_6Br$ requires: C, 54.7; H, 3.1; Br, 19.1%).

Aloe-emodin triacetate - 1,8-Diacetoxy-3-bromo methylanthraquinone (0.2 g) was refluxed with fused sodium acetate (0.2 g) and acetic anhydride (7.5 ml) for 1½ hr, poured into water and the residue was collected, washed and dried (0.15 g). Crystallization from alcohol gave pale yellow needles m.p. 176-7°. (Found: C, 63.2, H, 3.8. $C_{21}H_{16}O_8$ requires: C, 63.6; H, 4.1%).

Aloe-emodin (XXI) - 1,8-Diacetoxy-3-acetoxymethyl-anthraquinone (0.09 g) was refluxed with methanol (10 ml) containing a drop of conc. H_2SO_4 for 20 min. The methanol was removed under vacuum and the residue washed with water. Crystallization from toluene gave orange yellow needles, m.p. 224°, undepressed when mixed with an authentic sample. (Found: C, 66.5; H, 3.5. $C_{15}H_{10}O_5$ requires: C, 66.7; H, 3.7%).

2-Hydroxymethylanthraquinone - Lithium aluminium hydride (0.5 g) was dissolved in dry ether (300 ml) under unhydrous condition with mechanical stirring.

Methylanthraquinone-2-carboxylate (0.5 g), dissolved in dry ether (200 ml) was added gradually and stirred for 8 hr with gentle reflux. After keeping the reaction mixture overnight the complex was broken with 10% HCl (50 ml) in cold with stirring for 1 hr. The ether was distilled off and the separated yellow product was collected, washed and suspended in 1% NaOH solution (25 ml). After aeration the product was collected, washed and dried (0.33 g). Crystallization from alcohol gave pale yellow needles, m.p. 192°, undepressed when mixed with an authentic sample. (Found: C, 75.5; H, 4.3. $C_{15}H_{10}O_3$ requires: C, 75.6; H, 4.2%).

1-Hydroxy-3-hydroxymethylanthraquinone (XII) - Lithium aluminium hydride (0.5 g) was dissolved in dry ether (300 ml). Methyl-1-acetoxyanthraquinone-3-carboxylate, m.p. 173°. (Found: C, 67.2; H, 3.5. $C_{18}H_{12}O_6$ requires: C, 66.7; H, 3.7%). (0.5 g) in dry ether (250 ml) was added gradually with continuous stirring. Stirred for 8 hr under gentle reflux. The complex was decomposed by adding moist ethyl acetate (15 ml). 10% HCl (50 ml) was added and the ether

was distilled off. The residue was collected, washed and treated with 1% NaOH solution (20 ml), aerated for 10 min and acidified. The clean yellow product was collected, washed and dried (0.27 g). Crystallization from benzene gave yellow needles, m.p. 205°, undepressed when mixed with an authentic sample.

4-Bromophthalic anhydride was obtained by the distillation of 4-bromophthalic acid.[22]

2,3-Dihydroxy-6-bromoanthraquinone (XXXIII) - To a melt prepared from anhydrous aluminium chloride (30 g) and dry sodium chloride (6 g) a mixture of 4-bromophthalic anhydride (5.5 g) and pyrocatechol (2.2 g) was added carefully and the mixture stirred at 200-220° with stirring for 25 min. The melt was poured in 2% HCl (100 ml) and the separated brown product collected, washed free of acid, dissolved in 2% NaOH solution (50 ml), filtered and the filtrate acidified. The precipitate (5 g) was sublimed into orange yellow needles, m.p. above 330°. (Found: C, 52.2; H, 2.2; Br, 24.8. $C_{14}H_7O_4Br$ requires: C, 52.7; H, 2.2; Br, 25.0%).

2,3-Dimethoxy-6-bromoanthraquinone - A mixture of 2,3-dihydroxy-6-bromoanthraquinone (1.0 g), anhydrous potassium carbonate (10 g), dimethyl sulphate (1 ml) and acetone (300 ml) was refluxed on a water-bath for 24 hr. After removal of the acetone and dilution of the mixture with water, a greyish yellow product was obtained which crystallized from glacial acetic acid as yellow needles (0.8 g), m.p. 222°. (Found: C, 55.5; H, 3.0; OMe, 17.2. $C_{16}H_{11}O_4Br$ requires: C, 55.3; H, 3.2; OMe, 17.8%).

2,3,6-Trimethoxyanthraquinone (XXXIV) - 2,3-dimethoxy-6-bromoanthraquinone (0.7 g) and copper oxide (0.3 g) were refluxed for 24 hr with sodium methoxide solution prepared by reacting sodium (1.8 g) with dry methanol (30 ml). The mixture was then poured into water (150 ml) and the yellow product was collected, washed and dried (0.54 g). It crystallized from ethanol in yellow needles, m.p. 238°. (Found: C, 68.8; H, 4.7; OMe, 30.6. $C_{17}H_{14}O_5$ requires C, 68.8; H, 4.8; OMe, 31.2%). The compound gives reddish violet colouration with H_2SO_4 which appears greenish violet in thin layers.

2,3,6-Trihydroxyanthraquinone (XXXII) - To a melt prepared from anhydrous aluminium chloride (3 g) and dry sodium chloride (0.6 g), 2,3,6-trimethoxyanthraquinone (0.4 g) was added and the mixture stirred at 140° for 5-10 min. On cooling and adding 2% HCl (40 ml), the brown product was collected, washed and dried (0.3 g). Sublimation at 330° gave orange needles, m.p. above 360°. (Found: C, 65.2; H, 3.1. $C_{14}H_8O_5$ requires: C, 65.6; H, 3.1%). The substance gives green colour with aqueous alkali, brownish green in alkali carbonate and ammonia, and a brown-red colour with conc. H_2SO_4. The infrared spectrum (Nujol) shows maxima at 3270, 1664, 1579, 1517, 1342, 1327, 1290, 1241, 1196, 1163, 1116, 1099, 1076, 1042, 1022, 936, 912, 895, 886, 876, 857, 837, 815, 800, 793, 750, and 742 cm^{-1}.

The triacetyl derivative crystallized from glacial acetic acid in pale yellow needles, m.p. 193°. (Found: C, 63.0; H, 4.0. $C_{20}H_{14}O_8$ requires: C, 62.8; H, 3.7%).

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PART III

A SIMPLE SYNTHESIS OF LUCIDIN AND MUNJISTIN

AND

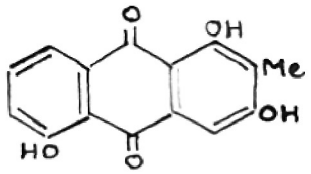
A SYNTHESIS OF NORDAMNACANTHAL, DAMNACANTHOL AND DAMNACANTHAL

From the dried bark of Coprosma lucida Briggs and Nicholls[1] isolated a new anthraquinone colouring matter to which the name lucidin was proposed. After removing the water-soluble glycosides, chromatography over calcined magnesia of the acetone extract of Coprosma lucida gave eight compounds: anthragallol, its 2-methyl and 2,3-dimethyl ether, 1,6-dihydroxy-2-methylanthraquinone, rubiadin, 3-hydroxy-2-methyl-anthraquinone, a minute quantity of an unidentified compound, and lucidin. Lucidin could be separated from the other hydroxyanthraquinones on account of its low solubility in organic solvents. Lucidin was also isolated from Coprosma acerosa.[2] Briggs and Nicholls[1] found that lucidin had the molecular formula $C_{15}H_{10}O_5$. It was soluble in sodium hydroxide, sodium carbonate and ammonium hydroxide solutions giving a red colour; and in conc. sulphuric acid with an orange-red colour. With alcoholic ferric chloride it gave a brown colouration. The lack of dyeing properties showed that an α- and a β-hydroxyl group were not in adjacent positions; lucidin was not a derivative of alizarin. Lucidin did not show fluorescence in glacial acetic acid solution which

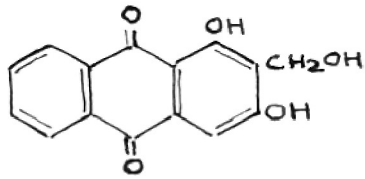
ruled out the possibility of two α-hydroxyls in 1,4-positions. The absorption spectra of lucidin and rubiadin (IV) were similar. Lucidin gave a triacetate, m.p. 175-6°, a tribenzoate, m.p. 204-5°, and a "trimethyl ether," m.p. 173°. Kuhn-Roth determination gave a C-methyl value of 4.7 per cent (theory 10 per cent). The low value was supposed to be due to the poor solubility of lucidin in the oxidizing mixture. This appeared to indicate the presence of one C-methyl group placed in a β-position in view of the formation of 2-methylanthracene by zinc dust distillation. On these grounds Briggs and Nicholls[1] ascribed to lucidin the structure 1,3,5-trihydroxy-2-methylanthraquinone (I). The 1,3,8-trihydroxy structure was ruled out on phytochemical grounds since no 1,8-dihydroxy compounds were isolated from the members of the Rubiaceae.*

*The weakness of such arguments is shown by the fact that R. G. Cooke (private communication, see Part V) has isolated 1,3,8-trihydroxy-2-hydroxymethylanthraquinone from Coelospermum reticulatum.

Subsequently they found that the repetition of the C-methyl determination gave negative results, and the "trimethyl ether," m.p. 173°, gave a methoxyl value which was much closer to that of a dimethyl ether and was probably the 1,3-dimethyl ether.[3] Infrared and ultraviolet absorption spectra indicated

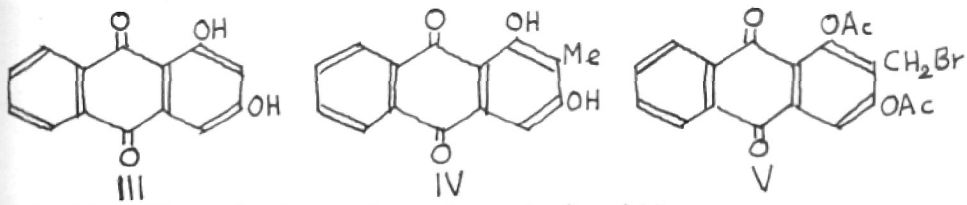


I



II

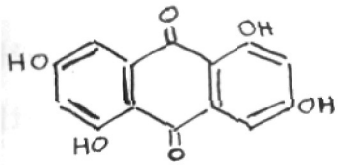
the presence of only one α-hydroxyl group. The structure of lucidin was therefore revised to 1,3-dihydroxy-2-hydroxymethylanthraquinone (II), which was confirmed by an unambiguous synthesis in this laboratory by Joshi, Parkash and Venkataraman.[4] The leuco derivative of xanthopurpurin-3-methyl ether (3-methyl ether of III) was treated with formaldehyde to give rubiadin-3-methyl ether (3-methyl ether of IV). This novel method of C-alkylation of hydroxyanthraquinones is due to Marschalk *et al.*[5] Rubiadin-3-methyl ether was demethylated to rubiadin (IV) by means of boiling hydrobromic acid and glacial acetic acid.



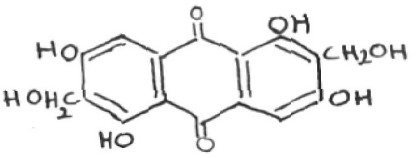
Rubiadin diacetate, when treated with N-bromosuccinimide (NBS) in boiling carbon tetrachloride, gave the ω-bromo derivative (V), which on further treatment with sodium acetate in acetic anhydride gave the triacetyl derivative of (II), identical in all its properties with the triacetyl derivative of natural lucidin. Lucidin was obtained by refluxing the triacetyl derivative with methanol containing 3 per cent by volume of conc. sulphuric acid. This synthesis involved several stages starting from xanthopurpurin (III). A much simpler synthesis of lucidin is now described.

According to a German patent[6] anthrachrysone (VI) in alkaline solution reacts readily with formaldehyde at room temperature to give a product which analyses for $C_{16}H_{12}O_8$ which would probably

have the structure (VII). By using similar



VI

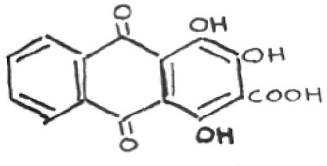


VII

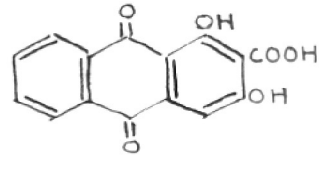
conditions xanthopurpurin (III) was directly hydroxymethylated to give lucidin (II) in excellent yield. The product was identical in all its properties with natural lucidin, and the triacetyl derivative had m.p. 175°, not depressed by mixing with the triacetate of natural lucidin kindly supplied by Dr. L. H. Briggs. The tribenzoate of the synthetic sample gave yellow prisms m.p. 205° (Tribenzoate of lucidin m.p. 204-5°[1]). It has been shown recently that this reaction is a useful diagnostic test for the presence of two hydroxyl groups in 1,3-positions and the absence of any substituent in the 2-position.[7]

The presence of munjistin (mungistin; munjisthin), a xanthopurpurin carboxylic acid, in crude purpurin isolated from madder (the ground root of Rubia tinctorum) was shown by Shunk and Römer.[8] Munjistin was earlier isolated by Stenhouse,[9] who found it,

along with purpurin in munjeet, the root of Rubia cordifolia Linn. or Rubia munjista Roxb. Munjistin also occurs in Rubia sikkimensis Kurz.[10] Munjistin crystallized from acetic acid in golden yellow leaflets, m.p. 231°, dissolving in aqueous alkali with a red colour. It dyed material mordanted with aluminium an orange shade. Munjistin decarboxylated to xanthopurpurin (III) on heating above its melting point or boiling an alkali solution. Bromination of munjistin also displaced the carboxyl group giving 2,4-dibromoxanthopurpurin. It appeared likely that as in pseudopurpurin (purpurin-3-carboxylic acid, XIII) the carboxyl group in munjistin was sandwiched between the hydroxyl groups and hence munjistin is xanthopurpurin-2-carboxylic acid (IX).



VIII



IX

Several attempts to synthesize munjistin (IX) were made by Mitter and Biswas.[11,12] Thus they were

unable to oxidize rubiadin (IV) to munjistin (IX), or to oxidize 2-(2',4'-dimethoxy-3'-methyl)-benzoyl benzoic acid to the corresponding dicarboxylic acid which might then be cyclized to 1,3-dimethoxyanthraquinone-2-carboxylic acid. Ultimately they were successful in obtaining a minute quantity of a substance, m.p. 231°, which was insufficient for analysis, but which did not depress the melting point of natural munjistin, by the following series of reactions:[13,14] The difficultly obtainable 2-chloro-6-methoxytoluene was condensed with phthalic anhydride using aluminium chloride, and the resultant 2-(2'-chloro-3'-methyl-4'-methoxy)-benzoylbenzoic acid was cyclized to 1-chloro-2-methyl-3-methoxyanthraquinone. Demethylation with aluminium chloride and oxidation with sodium nitrite and sulphuric acid in presence of boric acid at 150° yielded a product which could not be obtained chlorine-free even after repeated crystallizations, but it had all the properties of natural munjistin. A second route to a trace of munjistin was from 3-methyl alizarin by chlorination in the 4-position. Oxidation of 4-chloro-3-methyl alizarin gave impure

pseudopurpurin (containing chlorine) from which munjistin was obtained by reduction with sodium hydrosulphite in cold ammoniacal solution. This product was free of chlorine, but the yield was so poor that material was not sufficient for analysis. A similar synthesis of munjistin by the reduction of pseudopurpurin (VIII) has been reported by Oschmann.[15] Pseudopurpurin was prepared by the oxidation of 2-methylanthraquinone with sodium nitrite and sulphuric acid in the presence of mercury and arsenic trioxide, and also by oxidizing 2-methylquinizarin with sodium nitrite and sulphuric acid in presence of selenium and boric acid. No details of the oxidation and reduction procedures used by Oschmann are available, but it is obvious that his synthesis represents no improvement on the Mitter, Biswas synthesis.

A smooth conversion of lucidin (II) to munjistin (IX), which therefore constitutes an unambiguous and practicable synthesis of munjistin is now described. By the oxidation with silver oxide and aqueous caustic soda lucidin yielded munjistin in

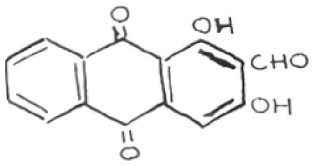
a yield of 35-40 per cent. Pearl oxidized vanillin to vanillic acid in a yield of over 92 per cent by means of silver oxide and aqueous caustic soda.[16] Only half a mole of silver oxide was necessary, and the use of one mole led to a low yield of vanillic acid together with much resinous material. These results were explained by assuming that a Cannizaro reaction catalyzed by silver or silver oxide was involved.

$$2R\text{-}CHO \xrightarrow{NaOH} R\text{-}CH_2OH + R\text{-}COONa \text{---------(1)}$$

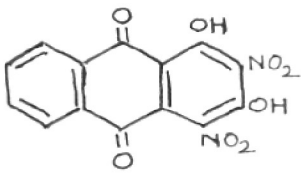
$$R\text{-}CH_2OH + Ag_2O + NaOH \longrightarrow R\text{-}COONa + 2Ag + H_2 + H_2O \text{---(2)}$$

Equation (2) was confirmed by the fact vanillyl alcohol underwent oxidation to vanillic acid in a yield of 93 per cent by treatment with aqueous caustic soda and one mole of silver oxide. The relatively low yield in the oxidation of lucidin to munjistin was apparently due to the tendency of the latter to undergo decarboxylation under the conditions of the reaction, confirmed by the isolation of xanthopurpurin from the reaction mixture after removing munjistin (IX) by extraction with aqueous sodium bicarbonate.

Lucidin (II) was readily oxidized to 1,3-dihydroxyanthraquinone-2-aldehyde (X), m.p. 220°, by treatment with manganese dioxide in boiling benzene.[17] The aldehyde (X) was characterized as 2,4-dinitrophenylhydrazone m.p. 355-6°. Pearl obtained equally good yields of vanillic acid from vanillin and vanillyl alcohol, but the aldehyde (X) gave much poorer yield of munjistin (IX) than lucidin.



X



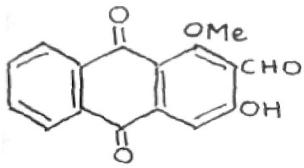
XI

Several substituted benzyl alcohols not containing nuclear hydroxyl groups have been oxidized to the corresponding aromatic aldehydes by means of dinitrogen tetroxide at 0° in chloroform or carbon tetrachloride.[18] Under these conditions lucidin, as anticipated, was nitrated in the 4-position, but simultaneous oxidation to an aldehyde did not take place; the primary alcoholic group was replaced by a nitro group, and the product was

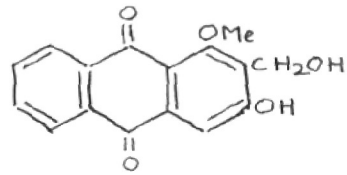
2,4-dinitroxanthopurpurin (XI), prepared earlier by Plath by treatment of xanthopurpurin with cold nitric acid or with nitrous gases in conc. sulphuric acid and described as x,x-dinitroxanthopurpurin.[19]

From the roots of the Japanese Rubiaceae Damnacanthus major Sieb and Zucc., D. major Sieb and Zucc. var. parvifolius Koidz., and D. indicus Gaertner fil. var. microphyllus Makino, Nonomura[20] isolated several closely related new anthraquinone pigments, which were designated as (a) damnacanthal, m.p. 208°, (b) damnacanthol, m.p. 288°, (c) juzunal, m.p. 248°, (d) damnidin, m.p. 180°, and (e) a neutral substance, m.p. 160°. Nonomura has pointed out the close similarity between damnacanthal and the compound $C_{16}H_{10}O_5$, m.p. 208°, isolated by Perkin and Hummel[21] from Morinda umbellata Linn. The free β-hydroxyl group in damnacanthal was shown by the formation of a monomethyl ether (with diazomethane) and a monoacetate. The presence of an α-methoxyl group was shown by the acid or alkaline hydrolysis of damnacanthal to give a compound called nordamnacanthal, $C_{15}H_8O_5$, m.p. 218°. Boiling damnacanthal with 50 per cent potassium hydroxide in an atmosphere of

hydrogen yielded some xanthopurpurin (III), which established the relative positions of the hydroxyl and methoxyl groups. The presence of an aldehyde group was shown by the formation of an oxime, hydrazone and an anil; and since the Perkin reaction gave a coumarin and a triacetate, the aldehyde group must be located next to the hydroxyl group. Oxidation of damnacanthal with alkaline hydrogen peroxide yielded damnacanthic acid, which was demethylated with sulphuric acid to give nordamnacanthic acid, bromination of which gave 2,4-dibromoxanthopurpurin. Nordamnacanthic acid was shown to be identical with munjistin (IX). On these grounds the position of the aldehyde group in damnacanthal was shown to be sandwiched between methoxyl and hydroxyl groups; and hence Nonomura ascribed to damnacanthal the structure 1-methoxy-3-hydroxyanthraquinone-2-aldehyde (XII). Damnacanthol was assumed to be 1-methoxy-2-hydroxymethyl-3-hydroxyanthraquinone (XIII). Nordamnacanthal was found to be identical with the aldehyde (X) which was



XII



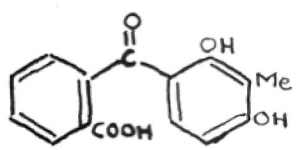
XIII

synthesized earlier by me by the oxidation of lucidin (*II*) with manganese dioxide in boiling benzene. Nordamnacanthal has been recently isolated by Seshadri et al.[22] from the heartwood of Morinda tinctoria Roxb. along with damnacanthal (XII) and morindone (1,5,6-trihydroxy-2-methylanthraquinone). They characterized nordamnacanthal as a 2,4-dinitrophenylhydrazone, m.p. 355° (2,4-dinitrophenylhydrazone of IX, m.p. 355-6°). As mentioned earlier, lucidin has become readily available by the direct hydroxymethylation of xanthopurpurin, and the preparation of damnacanthol (XIII) and damnacanthal (XII) is now described.

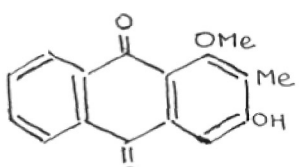
Lucidin-2,3-diacetate (XIV) was prepared by heating a mixture of lucidin, boroacetic anhydride and acetic anhydride and treating the diboro-acetate thus formed with water; (XIV) could also be

obtained by acetylating lucidin with acetic anhydride and potassium acetate at 15-20°. Methylation of (XIV) with diazomethane to 1-methoxy-2-acetoxymethyl-3-acetoxyanthraquinone (XV) and subsequent hydrolysis with methanolic potassium hydroxide gave damnacanthol (XIII), m.p. 295° (dec.). The alcohol (XIII) on oxidation with manganese dioxide in boiling benzene gave the aldehyde (XII), m.p. 211°, undepressed on admixture with a sample of natural damnacanthal kindly supplied by Professor Nonomura. The identity of the aldehyde (XII) and natural damnacanthal was also shown by the ultraviolet and infrared spectra.

While the present work was in progress, Hirose[23] reported the synthesis of (XII) and (XIII), starting from the very difficultly accessible resorcinol derivative (XVI). The keto-acid (XVI) was cyclized



XVI



XVII

to rubiadin (IV) from which the 1-methyl ether (XVII)

was prepared and submitted to the action of N-bromosuccinimide following the route for the synthesis of lucidin from rubiadin.[4]

E X P E R I M E N T A L

Lucidin (1,3-dihydroxy-2-hydroxymethylanthraquinone; II) - Xanthopurpurin (III; 5.0 g) was dissolved in 5% aqueous caustic soda (50 ml), and cooled to 20-25°. Formaldehyde (35-37%; 3 ml) was added slowly with occasional shaking, and the mixture kept at this temperature for 12 hr. A red crystalline sodium salt began to separate after about 4 hr. The product was collected, washed with cold water, and sucked dry. The sodium salt was decomposed by dissolving in warm water (200 ml) and acidifying with 5% hydrochloric acid. The bright yellow precipitate (4.6 g) crystallized from dioxane in yellow microscopic needles, which did not melt below 330°. (Found: C, 66.4; H, 3.9. $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%). The substance dissolves in conc. H_2SO_4 with an orange-red colour, and in aqueous caustic soda, sodium carbonate, and ammonia with a red colour. An alcoholic solution gives with ferric chloride a brown colouration. These properties are in agreement with those of natural lucidin and lucidin synthesized earlier by Joshi, Parkash and Venkataraman.[4]

Q-Triacetyl lucidin - 1,3-Dihydroxy-2-hydroxymethylanthraquinone (II) was acetylated by means of acetic anhydride and pyridine in the usual manner. The product crystallized from alcohol in pale yellow needles, m.p. 175°, not depressed by mixing with the triacetate of natural lucidin. (Found: C, 63.3; H, 3.7. $C_{21}H_{16}O_8$ requires C, 63.6; H, 4.0%).

Q-Tribenzoyl lucidin - 1,3-Dihydroxy-2-hydroxymethylanthraquinone (II; 0.1 g) was heated in a boiling water-bath with benzoyl chloride (1 ml) and pyridine (4 ml) for 1 hr. On cooling and pouring the solution into crushed ice, the aqueous layer was decanted off, and the thick oily product was shaken with methanol (2 ml), when a white solid separated. It crystallized from glacial acetic acid in pale yellow prisms, m.p. 205° (reference 1 cites m.p. 204-5°). (Found: C, 74.2; H, 3.9. $C_{36}H_{12}O_8$ requires C, 74.2; H, 3.8%).

1,3-Dihydroxyanthraquinone-2-carboxylic acid (munjistin; IX) - Silver nitrate (1.36 g) in water (10 ml) was treated with caustic soda (0.34 g) in water (10 ml). The separated silver oxide was

filtered, washed free from nitrate, and transferred to a beaker containing 20 ml water. With vigorous stirring NaOH (1.36 g) was added. The temperature of the mixture was maintained at 75°, and lucidin (II; 1 g) was introduced. Stirring was continued for an hour, and the mixture filtered hot. The residue of silver was washed thoroughly with warm water. The filtrate and washings were acidified, and the yellow precipitate was dissolved in 5% aqueous sodium bicarbonate. Acidification of the filtered solution and crystallization of the precipitate (0.45 g) from aqueous acetic acid gave bright golden yellow plates, m.p. 232°, after shrinking at 228° (literature m.p. 231°). (Found: C, 63.6; H, 2.9. $C_{15}H_8O_6$ requires C, 63.4; H, 2.8%). The residue (0.2 g) insoluble in $NaHCO_3$ crystallized from acetic acid as brownish yellow needles, m.p. 265-7°, undepressed when mixed with xanthopurpurin. The substance dissolves in conc. H_2SO_4 with a deep yellow colour and in aqueous $NaHCO_3$ with a deep brownish red colour. The alcoholic solution turns cherry red with ferric chloride.

1,3-Dihydroxyanthraquinone-2-aldehyde (nordamnacanthal, X) - Synthetic lucidin (1.7 g) and active manganese dioxide[17] (3.5 g) were refluxed with benzene (300 ml) for 16 hr. The solution was filtered hot, and the manganese dioxide residue washed several times with hot benzene. Removal of the solvent and crystallization of the residue from glacial acetic acid gave yellow needles (0.9 g), m.p. 220°. (Found: C, 67.6; H, 3.1. $C_{15}H_8O_5$ requires: C, 67.2; H, 3.0%). This aldehyde is soluble in warm caustic soda solution with a pink colour, and gives an intense yellowish orange colour with conc. H_2SO_4.

The 2,4-dinitrophenylhydrazone crystallized from nitrobenzene in golden yellow needles, m.p. 355-56°. (Found: C, 55.8; H, 2.6; N, 12.6. $C_{21}H_{12}N_4O_8$ requires: C, 56.2; H, 2.7; N, 12.5%).

2,4-Dinitroxanthopurpurin (XI) - To a suspension of synthetic lucidin (0.2 g) in chloroform (15 ml), cooled to 0°, dinitrogen tetroxide (0.8 ml) was added. The mixture was shaken at 0° for 15 min and kept overnight at room temperature. The small

yellow needles of lucidin had changed to long bright orange-red needles (0.13 g), which had m.p. 251°, remaining unchanged by recrystallization from glacial acetic acid (Plath[19] quotes m.p. 249-50°). Found: C, 51.5; H, 2.0; N, 8.5. $C_{14}H_6O_8N_2$ requires: C, 50.9; H, 1.8; N, 8.5%). A further quantity (0.075 g) of the same substance was recovered from the chloroform solution.

Lucidin-2,3-diacetate (XIV) - (a) Lucidin (2 g) was refluxed with a mixture of boroacetic anhydride (5 g) and acetic anhydride (25 ml) for 5 min. The crystalline diboroacetate which separated was filtered, washed with ice-cold acetic anhydride containing boroacetic anhydride and finally with ether. The diboroacetate was suspended in water (100 ml) for 12 hr at room temp. The product (2 g) gave on crystallization from ethanol yellow needles, m.p. 152°. (Found: C, 64.4; H, 3.9. $C_{19}H_{14}O_7$ requires: C, 64.2; H, 3.9%). An ethanolic solution of (XIV) gives a brown colour with alcoholic ferric chloride.

(b) A mixture of lucidin (1.5 g), acetic anhydride (10 ml) and potassium acetate (1 g) was agitated at 15-20° for one hr and kept overnight. It was then poured into ice-cold water (100 ml) and the product (1.6 g) collected. Crystallization from ethanol gave yellow needles, m.p. 152°, identical with the diacetate obtained by method (a).

3-Acetoxy-2-acetoxymethyl-1-methoxyanthraquinone (XV) - To a solution of lucidin-2,3-diacetate (XIV) (3 g) in tetrachloroethane (40 ml) excess of ethereal diazomethane was added under stirring. After 48 hr excess of diazomethane was destroyed by acetic acid, ether distilled off, and tetrachloroethane removed by steam distillation; the residue crystallized from ethanol in yellow needles (1.5 g), m.p. 156-157°. (Found: C, 65.3; H, 4.5; OMe, 8.1. $C_{20}H_{16}O_7$ requires: C, 65.2; H, 4.3; OMe, 8.4%).

Lucidin-1-methylether (Damnacanthol; XIII) - A solution of (XIII) (1.5 g) in 5% methanolic potassium hydroxide (50 ml) was maintained at 25° for 24 hr. Acidification with acetic acid gave a bright yellow crystalline product (0.75 g) which

crystallized from ethanol in yellow needles, m.p. 295° (with darkening). Found: C, 67.5; H, 4.2; OMe, 11.1. $C_{16}H_{12}O_5$ requires: C, 67.5; H, 4.2; OMe, 10.9%).

3-Hydroxy-1-methoxyanthraquinone-2-aldehyde (Damnacanthal; XII) - Lucidin-1-methyl ether (0.5 g) was refluxed with manganese dioxide[17] and benzene (40 ml) for 24 hr, and the solution filtered hot. The manganese dioxide residue was washed several times with hot benzene. After removal of the benzene, the residue (0.3 g) crystallized from ethanol in orange-yellow needles, m.p. 211°, undepressed on admixture with a sample of natural damnacanthal kindly supplied by Prof. Nonomura. (Found: C, 68.4; H, 3.6; $C_{16}H_{10}O_5$ requires: C, 68.1; H, 3.6%). The infrared spectra of damnacanthal and the compound (XII) in carbon tetrachloride show maxima at 2935, 1965, 1876, 1754, 1670, 1610, 1570, 1510, 1468, 1382, 1354, 1270, 1220, 1194, 1064, 1030 and 982 cm^{-1}. In the ultraviolet and vizible regions both damnacanthal and (XII) exhibit the following maxima: 2500, 2810, 3800 and 6150 Å; $\log \epsilon_{max}$ 4.40, 4.37, 3.60 and 3.20 respectively.

The 2,4-dinitrophenylhydrazone of (XII) crystallized from nitrobenzene in golden yellow needles, m.p. 300°. (Found: N, 12.3. $C_{21}H_{12}O_8N_4$ requires: N, 12.1%).

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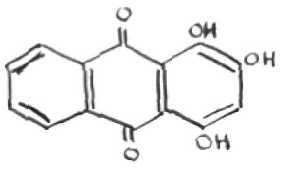
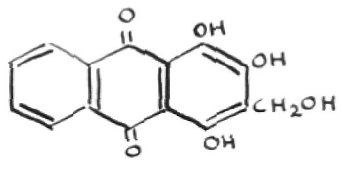
PART IV

3-HYDROXYMETHYLPURPURIN

In connection with the constitution of galiosin, considered to be a primveroside of pseudopurpurin (purpurin-3-carboxylic acid), Hill and Richter[1] described the preparation of 3-hydroxymethylpurpurin (II), orange-red needles, m.p. above 300°, by the condensation of an excess of formaldehyde with purpurin (I) in conc. sulphuric acid. The duration of the reaction between purpurin (I) and formaldehyde was not mentioned, but "the mixture was kept at 20° until on spectroscopic examination the bands of purpurin were seen to have disappeared and a strongly marked band at 5250 A had developed."



(I)



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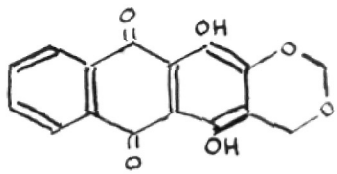


(III)

The product was isolated by precipitation with water

and crystallized from pyridine with which it formed a complex. The complex was decomposed with dilute hydrochloric acid and the product was recrystallized successively from alcohol and chloroform. Hill and Richter also stated that 3-hydroxymethylpurpurin formed with aqueous sodium hydroxide an insoluble violet sodium salt, and in sulphuric acid it showed absorption bands at 5250 and 4900 A. Repetition of this reaction did not give (II) as reported, but led to a different product, m.p. 239-240° (dec.), which analysed for $C_{16}H_{10}O_6$ and had the properties of the 1,3-dioxan (III). It was insoluble in aqueous sodium hydroxide and its solution in glacial acetic acid showed a strong orange fluorescence like quinizarin. It formed a diacetate with acetic anhydride and pyridine, and a dimethyl ether with dimethyl sulphate, potassium carbonate and acetone. The infrared spectrum of the compound (III) shows only one carbonyl band at 1620 cm^{-1} (chelated carbonyl). The absorption bands at 1068 and 1048 cm^{-1} can be attributed to the ether linkage (C-O-C-O-C) of the dioxane ring.[2] The absence of an absorption band

In this test the crude extract is heated with dilute mineral acid to hydrolyse the glycosides and the liberated aglycones are extracted with organic solvents such as benzene. The benzene extract is then shaken with aqueous alkali, when a beautiful rose-pink to cherry red colour is produced in the alkaline layer. Ferric chloride colouration is not characteristic for polyhydroxyanthraquinones.[6] When zirconium nitrate in dilute hydrochloric acid is added to an acetone solution of alizarin, a bluish violet colouration is obtained.[10] This is a characteristic test for all polyhydroxy-anthraquinones having two adjacent hydroxyls. Alizarin derivatives can also be judged from the shades obtained on mordanted wool. Anthraquinone derivatives having hydroxyls in 1,4-positions show fluorescence in acetic acid solution.[6] With the exception of purpurin all polyhydroxyanthraquinones having hydroxyl groups in <u>para</u>- positions are oxidized by lead tetracetate to coloured diquinoid compounds. In the case of purpurin the colour disappears rapidly, as it is very easily oxidized. This observation is useful in locating the hydroxyls in 1,2,4-positions.[11] A solution of anthragallol in aqueous sodium hydroxide rapidly changes colour

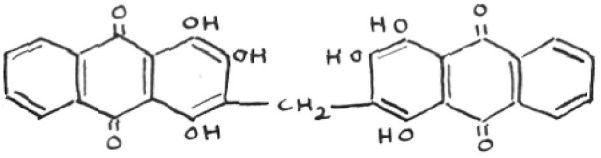
around 3300 cm^{-1} showed the absence of a β-hydroxyl or a hydroxymethyl group. In the frequency range above 1600 cm^{-1}, 2-hydroxymethylanthraquinone absorbs at 3330 cm^{-1} (free alcoholic hydroxyl group) and 1672 cm^{-1} (unchelated carbonyl groups).

If 3-hydroxymethylpurpurin (II) was readily obtainable, it would have provided another convenient route to lucidin (see Part III).

The action of formaldehyde and caustic soda on purpurin (I) under the conditions which hydroxymethylated xanthopurpurin to lucidin (see Part III) did not yield 3-hydroxymethylpurpurin (II), but a substance which was probably the hexahydroxydianthraquinonylmethane (IV). This is a case similar to one reported by Marschalk *et al.*,[3] who obtained bis(1,4-dihydroxy-2-anthraquinonyl)-methane by the action of formaldehyde and aqueous caustic soda on leucoquinizarin, in the absence of sodium hydrosulphite.

Authentic 3-hydroxymethylpurpurin (II) has now been prepared by the ω-bromination method described in Part II. 3-Methylpurpurin triacetate (V) was ω-brominated with N-bromosuccinimide to give the ω-bromo derivative (VI), which with sodium acetate and acetic anhydride gave the tetracetate (VII). Hydrolysis of (VII) by refluxing with methanol containing 3 per cent by volume of sulphuric acid gave 3-hydroxymethylpurpurin (II). It is interesting to note that 3-hydroxymethylpurpurin prepared by this method formed a clear pink solution in aqueous sodium carbonate and sodium hydroxide, and in contrast with the observation of Hill and Richter.

3-Methylpurpurin was readily obtainable according to the method of Zahn and Ochwat[4] from 2-methylquinizarin (VIII) by the Thiele acetylation of the corresponding diquinone (IX). 2-Methylquinizarin (VIII) was obtained in the present work by the action of aqueous lime on 1-hydroxy-2-methyl-4-bromoanthraquinone at 200° under pressure in an autoclave. 2-Methylquinizarin (VIII) was prepared earlier by various methods,[3,5] but the



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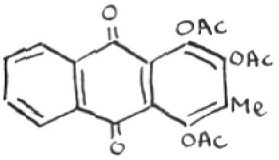

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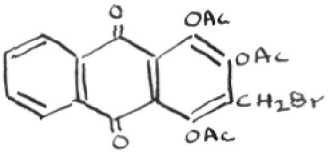

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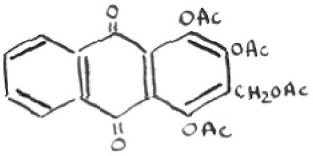

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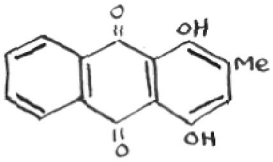

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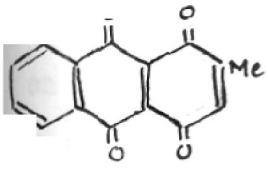
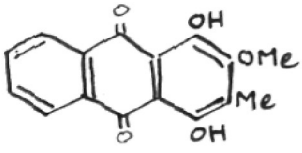
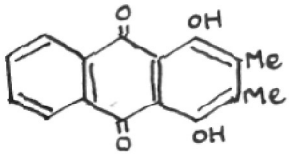


IX



X



XI

method described above was found to be more convenient.

When the synthesis of 3-methylpurpurin was attempted by the action of formaldehyde on purpurin-2-methyl ether in presence of aqueous sodium hydroxide and sodium hydrosulphite, following the method used for the synthesis of rubiadin (1,3-dihydroxy-2-methylanthraquinone),[6] the compound obtained was not 3-methylpurpurin-2-methyl ether (X) as expected, but 2,3-dimethyl-quinizarin (XI), the identity of which was established by the direct comparison with an authentic sample prepared by the method of Marschalk et al.[3] The mechanism of the reaction apparently involves two steps: (a) reductive removal of the methoxyl group to form leucoquinizarin and (b) the Marschalk reaction[3] on leucoquinizarin by the subsequent action of formaldehyde, caustic soda and sodium hydrosulphite, followed by oxidation to 2,3-dimethylquinizarin. Purpurin-2-methyl ether by the treatment of aqueous sodium hydroxide and sodium hydrosulphite alone at 95° for 1 hr, followed by aeration gave quinizarin. This interesting replacement of methoxyl by

hydrogen in 2-methoxyquinizarin has not been recorded in the literature.

Purpurin-2-methyl ether is obtained in good yields (over 80 per cent) by the methylation of purpurin with one mole of dimethylsulphate using acetone-potassium carbonate method.[7]

The electronic absorption spectra of (I), (II) and (III) are given in Fig. 1.

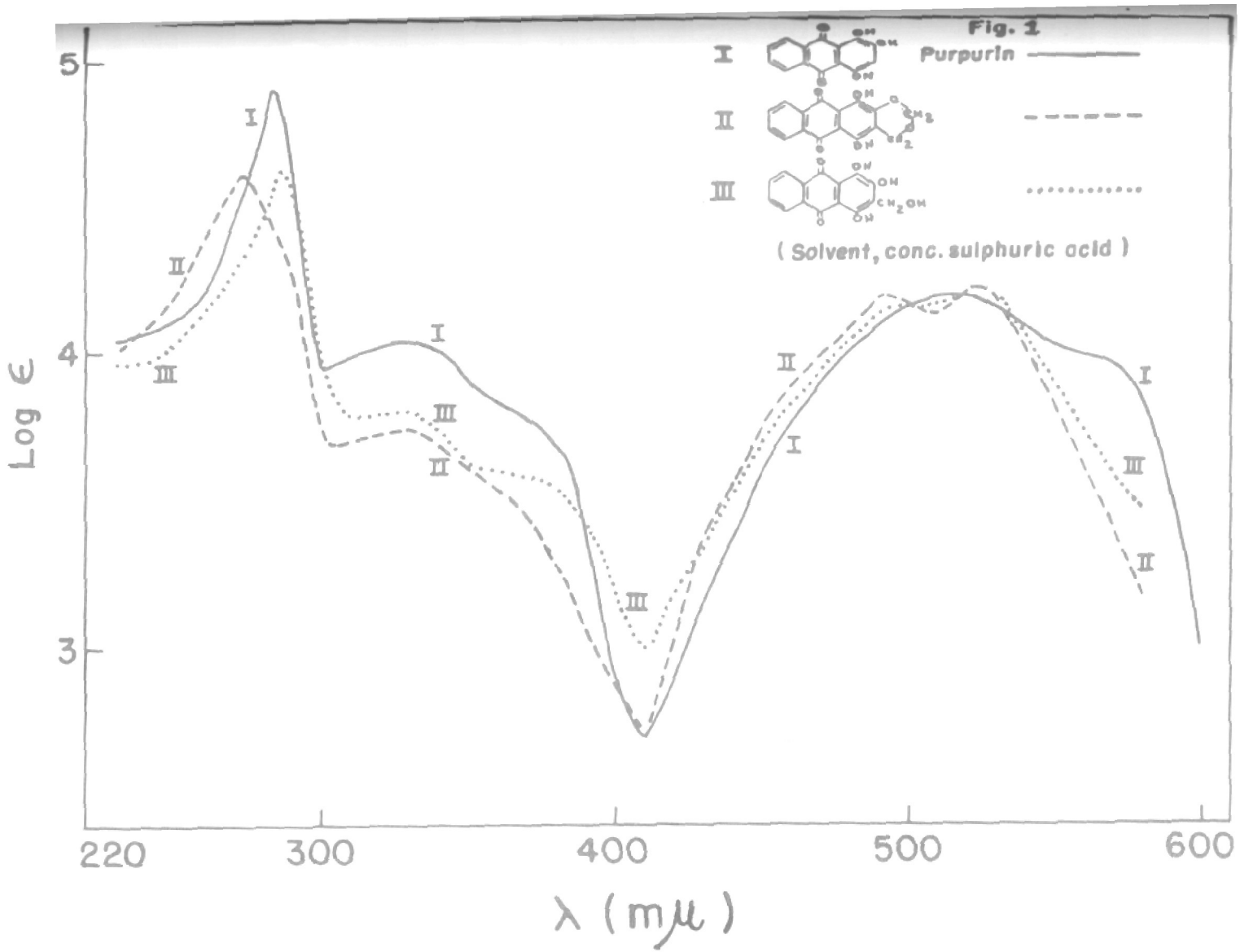


Fig. 1
I
Purpurin
II
III
(Solvent, conc. sulphuric acid)
Log ε
5
4
3
220
300
400
500
600
λ (mμ)

EXPERIMENTAL

1,3-Dioxan derivative (III) - 35-37% Formaldehyde solution (20 ml) was added to a solution of purpurin (I) (5 g) in conc H_2SO_4 (200 ml) keeping the temp at 20°, and allowed to stand at that temp. for 24 hr. Spectroscopic examination (on a Beckmann spectrophotometer) of a small portion of the reaction mixture showed strongly marked bands at 5250 and 4900 Å. The mixture was poured into crushed ice (500 g), and the separated product collected, washed free of acid and dried. Crystallization from pyridine gave a dark-red crystalline product, which was collected and treated with 5% HCl (50 ml). The resulting red product was collected, washed and dried. Crystallization from glacial acetic acid gave orange-red needles, m.p. 239-240° (dec.). (Found: C, 64.2; H, 3.7; Mol. wt. 294, 302. $C_{16}H_{10}O_6$ requires: C, 64.4; H, 3.4%; Mol. wt. 298. $C_{15}H_{10}O_6$ requires: C, 62.9; H, 3.5%; Mol. wt. 286). The substance is insoluble in aqueous Na_2CO_3 and insoluble in aqueous NaOH, but gives insoluble violet salt. With conc H_2SO_4 it gives a red solution. Its solution in glacial acetic acid shows strong orange fluorescence. With methanolic magnesium

acetate, it gives a fluorescent pink colouration. The infrared spectrum of the compound (III) in nujol shows maxima at 1620, 1582, 1545, 1377, 1273, 1239, 1181, 1068, 1045, 1024, 991, 954, 937, 897, 824, 815, 788, 756, 751, 730 and 686 cm^{-1}. The infrared spectrum of 2-hydroxymethylanthraquinone shows maxima at 3330, 2940, 1672, 1595, 1476, 1440, 1362, 1322, 1289, 1266, 1202, 1163, 1046, 970, 931, 897, 843, 814, 802, 790 and 706 cm^{-1}.

The acetyl derivative of (III), prepared in the usual manner with acetic anhydride and pyridine, crystallized from glacial acetic acid in yellow plates, m.p. 262° (dec.). (Found: C, 63.1; H, 3.4. $C_{20}H_{14}O_8$ requires: C, 62.8; H, 3.6%).

Methyl ether of (III) - A mixture of (III) (0.25 g), anhydrous potassium carbonate (3 g), dimethylsulphate (1.5 ml) and acetone (50 ml) was refluxed on a water-bath for 24 hr. After removal of the acetone and dilution of the mixture with water, a yellow product was obtained, which crystallized from alcohol as yellow needles (0.2 g),

m.p. 180°. (Found: C, 66.4; H, 4.4; OMe, 18.7. $C_{18}H_{14}O_6$ requires: C, 66.3; H, 4.3; OMe, 19.0%). The product gives no colouration with alcoholic ferric chloride or ammonia.

1,2,4,1',2',4'-Hexahydroxy-3,3'-dianthraquinonylmethane (IV) - Purpurin (I; 1g) was dissolved in 5% aqueous caustic soda (40 ml), and cooled to 20°. Formaldehyde (35-37%; 0.5 ml) was added slowly with occasional shaking, and the mixture kept at this temp for 16 hr. The separated violet sodium salt was collected, washed with little cold water and dried under suction. Decomposition of the salt with 5% HCl gave a red fluffy precipitate which was collected, washed and dried (0.4 g). The product was insoluble in most of the organic solvents such as glacial acetic acid, alcohol, chloroform, etc. Crystallization from o-dichlorobenzene gave red shining needles, m.p. above 360°. (Found: C, 66.3; H, 3.1. $C_{29}H_{16}O_{10}$ requires: C, 66.4; H, 3.1%. $C_{15}H_{10}O_6$ requires: C, 62.9; H, 3.5%).

The hexacetyl derivative prepared in the usual manner by refluxing with acetic anhydride and pyridine for 3 hr gave a yellow product which crystallized from glacial acetic acid or ethyl acetate in yellow needles, m.p. 211-212°. (Found: C, 64.0; H, 3.5. $C_{41}H_{28}O_{16}$ requires: C, 63.4; H, 3.6%).

2-Methylquinizarin (VIII) - To a thin slurry made from slaked lime (75 g) in water (300 ml), 1-hydroxy-2-methyl-4-bromoanthraquinone (15 g) and copper bronze (5 g) were added. The mixture was heated in an autoclave at 200° for 24 hr. The violet-red reaction mixture was acidified, and the precipitate was collected, washed and dried (10.5 g). Crystallization from alcohol gave red needles, m.p. 177°.

2-Methyl-1,4,9,10-anthradiquinone (IX), m.p. 195° (sintering) was prepared according to the method of Zahn and Ochwat[4], by the oxidation of 2-methylquinizarin with lead tetracetate.

3-Methylpurpurin triacetate (V) was prepared according to the method of Zahn and Ochwat.[4] Acetic anhydride (250 ml), (IX) (8 g) and perchloric acid (10 ml) were mechanically agitated together at 10-20° for 6 hr, poured into crushed ice and the pale yellow crystalline product was collected, washed and dried. Crystallization from glacial acetic acid gave pale yellow needles, m.p. 207-208° (Zahn and Ochwat[4], 207-208°).

3-Methylpurpurin - 3-Methylpurpurin triacetate (0.5 g) was dissolved in methanol (50 ml) by warming. Conc H_2SO_4 (1.5 ml) was added and the solution refluxed for 1 hr. On dilution with water the red product was collected, washed and dried (0.22 g). Crystallization from toluene gave red needles, m.p. 267° (Zahn and Ochwat[4], 265-67°; Raistrick, Robinson, Todd[8], 268°; Eder and Manaukian[9], 231-232°; Mitter and Pal[10], 231°). (Found: C, 67.1; H, 4.0. $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%).

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1,2,4-Triacetoxy-3-bromomethylanthraquinone (VI) - 3-Methylpurpurin triacetate (V) (2 g) N-bromosuccinimide (1 g), benzoyl peroxide (0.1 g) and carbon tetrachloride (200 ml) were refluxed for 24 hr. The solvent was distilled off, the residue washed with hot water and dried (2.1 g). Crystallization from carbon tetrachloride gave pale yellow needles, m.p. 189°. (Found: C, 53.7; H, 3.3. $C_{21}H_{15}O_8Br$ requires: C, 53.1; H, 3.2%).

1,2,4-Triacetoxy-3-acetoxymethylanthraquinone (VII) - 1,2,4-Triacetoxy-3-bromomethylanthraquinone (1 g) was refluxed with fused sodium acetate (1 g) and acetic anhydride (25 ml) for 1 hr. The mixture was cooled and poured into crushed ice. The pale yellow product was collected, washed and dried (0.8 g). Crystallization from acetic acid gave pale yellow needles, m.p. 180°. (Found: C, 60.8; H, 4.1. $C_{23}H_{18}O_{10}$ requires: C, 60.8; H, 4.0%).

3-Hydroxymethylpurpurin (II) - 1,2,4-Triacetoxy-3-acetoxymethylanthraquinone (0.5 g) was

refluxed with methanol (50 ml) containing conc H_2SO_4 (1.5 ml) for 30 min. On dilution with water the red product was collected, washed and dried (0.45 g). Crystallization from chloroform gave red needles, m.p. above 300° (dec.). (Found: C, 63.0; H, 3.5. $C_{15}H_{10}O_6$ requires: C, 62.9; H, 3.7%). The substance gives pink solution in sodium carbonate and sodium hydroxide solutions and a red solution in H_2SO_4. With methanolic magnesium acetate it gives a pink-red colouration.

1,4-Dihydroxy-2,3-dimethylanthraquinone - Purpurin-2-methyl ether (1 g) was stirred with 2% sodium hydroxide (100 ml) containing sodium hydrosulphite (1.5 g) under the atmosphere of nitrogen. At 40-45° formaldehyde (35-36%, 1 ml) was added, the temperature raised to 95° and heating continued for 1½ hr. The mixture was cooled and air-oxidized. The orange-red product was collected, washed and dried (0.72 g). Crystallization from glacial acetic acid gave red needles, m.p. 252-253° (Marschalk et al.[3] quote 253°), undepressed when mixed with a sample of 1,4-dihydroxy-2,3-dimethyl-anthraquinone prepared by the action of alkali

and sodium hydrosulphite on leucoquinizarin. (Found: C, 71.7; H, 4.2. $C_{16}H_{12}O_4$ requires: C, 71.6; H, 4.5%).

The diacetyl derivative, prepared in the usual manner, crystallized from acetic acid as pale yellow needles, m.p. 225°, undepressed when mixed with 1,4-diacetoxy-2,3-dimethylanthraquinone. (Found: C, 68.2; H, 4.8. $C_{20}H_{16}O_6$ requires: C, 68.2; H, 4.6%).

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PART V

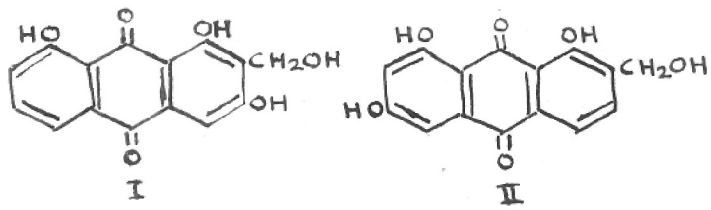
VERSICOLORIN AND COELULATIN : SYNTHESIS OF 1,3,8-TRIHYDROXY-2-HYDROXYMETHYLANTHRAQUINONE AND 1,3,8-TRIHYDROXY-7-HYDROXYMETHYLANTHRAQUINONE

From the mycelium of Aspergillus versicolor (Vuillemin) Tiraboschi, cultured on a malt extract medium containing glucose and peptone, Hatsuda and Kuyama[1] isolated two colouring matters, versicolorin, yellow-orange needles, m.p. 282°, and sterigmatocystin, yellow needles, m.p. 243°. Hatsuda et al.[2] ascribed to sterigmatocystin the molecular formula $C_{15}H_{12}O_5$ and a structure derived from xanthhydrol. This pigment was isolated later from the same organism by Davies et al.[3] and by Birkinshaw and Hammady.[4] The latter authors found the molecular formula of sterigmatocystin to be $C_{18}H_{12}O_6$, which excluded both the molecular and structural formulae proposed by Hatsuda. Birkinshaw and Hammady also obtained a second optically active pigment which crystallized from chloroform in long orange needles, m.p. 233-234°. Although colour reactions and ultraviolet absorption spectra indicated it to be a polyhydroxyanthraquinone, the H : C ratio was too high. The colouring matter was not identical with versicolorin which had a different melting point and for which no optical activity was reported.

Versicolorin has been isolated from A.versicolor

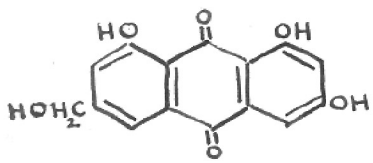
only by the Japanese workers, and they have assigned the molecular formula $C_{15}H_{10}O_6$ and the structure I or II. Evidence for the hydroxyanthraquinone structure was a red-violet colour in aqueous sodium hydroxide, which disappeared on heating with zinc dust and was restored by air oxidation. With alcoholic magnesium acetate versicolorin gave an orange solution, indicating that two hydroxyl groups were probably located meta to each other[5] (cf. Table 1). The formation of a tetra-acetate and a trimethyl ether by heating with dimethyl sulphate, potassium carbonate and acetone showed the presence of one alcoholic and three phenolic hydroxyl groups. By analogy with other fungal anthraquinones two hydroxyls were placed in 1,8-positions, the three phenolic hydroxyls therefore being in the 1,3,8-positions. The 6-position for the hydroxymethyl group was ruled out, since versicolorin would then be identical with citreorosein (III:ω-hydroxyemodin). On the assumption that the hydroxymethyl group was in a β-position, based on the fact that no naturally occurring anthraquinone colouring matter with a hydroxymethyl

group in an α-position has so far been encountered, it followed that versicolorin was constituted as I or II.



I

II



III

1,3,8-Trihydroxy-2-hydroxymethylanthraquinone (I) has now been synthesized by an unambiguous method, and several of its properties are different from those described for versicolorin, a sample of which was kindly supplied by Professor Hatsuda. Versicolorin therefore does not have the structure I. It has been shown earlier that lucidin (2-hydroxymethyl-xanthopurpurin) can be readily synthesised by the condensation of xanthopurpurin (1,3-dihydroxyanthra-quinone) with formaldehyde and sodium hydroxide solution (see Part III). Likewise, hydroxymethylation of 1,3,8-trihydroxyanthraquinone (IV) gave an

excellent yield of I, which darkens and decomposes at 295°; the m.p. quoted for versicolorin is 282°. The tetra-acetates of I and versicolorin melt at 205° and 225° respectively and their mixed melting point is depressed. The tetrabenzoate of I melts at 198°, whereas versicolorin gave a tribenzoyl derivative, m.p. 224-225°.[1]

Versicolorin and the synthetic compound I differ in their absorption spectra in the ultraviolet and visible regions (Fig.1; lucidin and 1,3,8-trihydroxy-anthraquinone are included for comparison). The infrared spectrum of I (KBr pellet) shows absorption bands at 3436 cm^{-1} (alcoholic and β-hydroxyl groups, which are not distinguishable[6]), 1670 cm^{-1} (unchelated carbonyl) and 1617 cm^{-1} (chelated carbonyl). In the region above 1600 cm^{-1} the following maxima have been recorded[7] for lucidin (1,3-dihydroxy-2-hydroxymethylanthraquinone): 3448, 3367, 1667 and 1621 cm^{-1}. Versicolorin shows absorption bands at 3330 cm^{-1}, 1673 cm^{-1} (very weak band seen as an inflexion or shoulder), and 1620 cm^{-1}. Reviewing Hatsuda's work on versicolorin, Thomson[8]

has stated that "as there appears to be only one carbonyl band in the infrared spectrum these (structures I and II) must be accepted with reserve," but there are two carbonyl bands in the infrared spectrum of the sample of versicolorin sent to us by Professor Hatsuda. When the infrared spectra were determined in Nujol, the chelated carbonyl band of both I and versicolorin was overlapped by the phenyl band and a strong absorption band was observed around 1604-1606 cm^{-1}. This type of overlapping of the phenyl and chelated carbonyl bands has been observed in the infrared spectra of 1,5- and 1,8-dihydroxyanthraquinones determined by the Nujol mull technique.[9]

Oxidation of I with manganese dioxide in boiling benzene gave the corresponding aldehyde V, which is of interest on account of the occurrence of other hydroxyanthraquinone aldehydes, damnacanthal (see below) and fallacinal,[10] in nature. Two molecules of the aldehyde (V) reacted with hydrazine to give the compound (VI), establishing that the aldehyde group in V occupies a β-position and that IV

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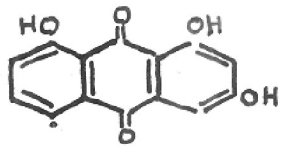
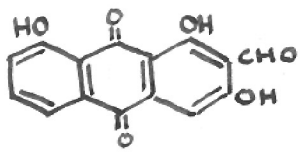
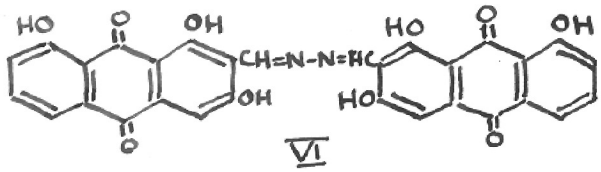
therefore had undergone hydroxymethylation in the 2-position yielding I. If IV had undergone hydroxymethylation in the 4-position, the corresponding aldehyde would have reacted only with one molecule of hydrazine to form a pyridazine derivative.



IV



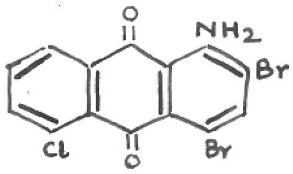
V



VI

A synthesis of 1,3,8-trihydroxyanthraquinone (IV) starting from 1-amino-6,8-dichloroanthraquinone was reported earlier,[11] but the following route is more convenient. Bromination of 1-amino-5-chloroanthraquinone gave 1-amino-2,4-dibromo-5-chloroanthraquinone (VII). Deamination of VII by diazotization and boiling with ethanol gave the trihalogenoanthraquinone (VIII), which was converted to 1,3,8-trimethoxyanthraquinone by refluxing with sodium methoxide and copper oxide in methanol. The replacement of both the α- and β-halogens by methoxyl groups was

facilitated by the use of copper oxide. When VIII was heated with calcium hydroxide and copper bronze under pressure, only the α-halogens were replaced by hydroxyl groups, and the product was 1,8-dihydroxy-3-bromoanthraquinone, confirmed by the absence of an absorption band at about 3330 cm^{-1} in the infrared spectrum.[7] Demethylation of the trimethyl ether by means of aluminium chloride-sodium chloride at 145-150° then yielded 1,3,8-trihydroxyanthraquinone (IV).



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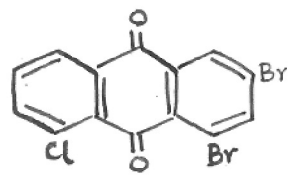
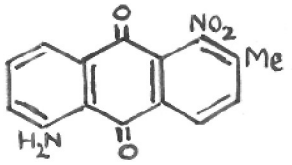


VIII

R. G. Cooke[12] isolated a new pigment, coelulatin, from Coelospermum reticulatum and deduced its structure as a trihydroxyanthraquinone-carbinol, which was different from versicolorin. The identity of 1,3,8-trihydroxy-2-hydroxymethylanthraquinone with coelulatin was established by the direct comparison of the two compounds and their tetracetyl derivatives. In a private communication Dr. Cooke has stated that a point of interest in the constitution of coelulatin is that it occurs in a

plant belonging to the family Rubiaceae and "the rule against the occurrence of 1,8-dihydroxy-anthraquinones in this family will now have to be stated in a different form."

For the synthesis of the alternative structure (II), proposed for versicolorin, 1-nitro-2-methyl-5-aminoanthraquinone (IX), an intermediate in the synthesis of chrysophanol (see Part II) served as a useful starting material. Bromination of (IX) with excess of bromine in glacial acetic acid at 100° gave the dibromo compound (X), which was deaminated through the diazonium salt to give 1-nitro-2-methyl-6,8-dibromoanthraquinone (XI). Reduction of (XI) with sodium sulphide gave the amine (XII). Diazotisation of (XII) and hydrolysis with boiling 40 per cent sulphuric acid gave 1-hydroxy-2-methyl-6,8-dibromoanthraquinone (XIII). Prolonged refluxing of the corresponding methoxy derivative (XIV) with sodium methoxide and methanol in presence of copper oxide gave 1,3,8-trimethoxy-7-methylanthraquinone (XV). Complete demethylation of (XV) to the new 1,3,8-trihydroxy-7-methyl-anthraquinone (XVI) was effected by treatment for a



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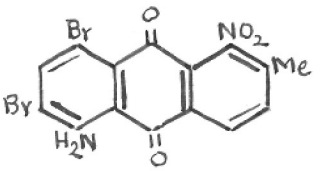

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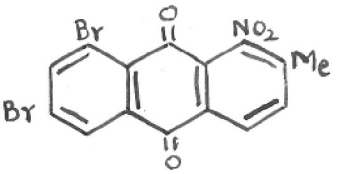

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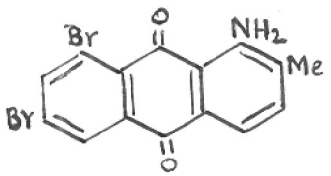

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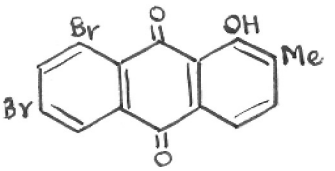

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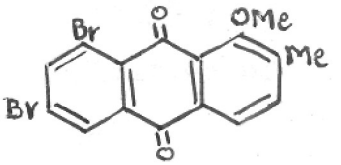

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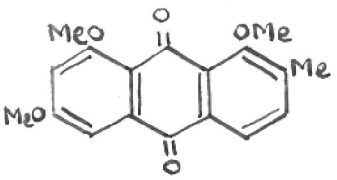

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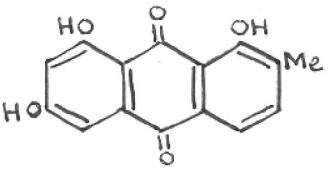
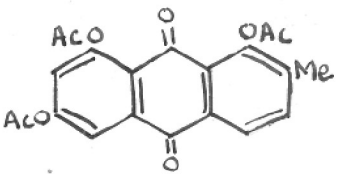


XVI



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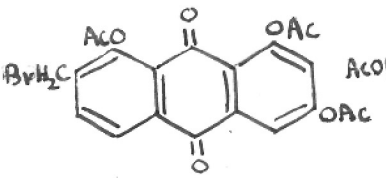
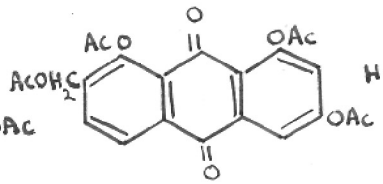
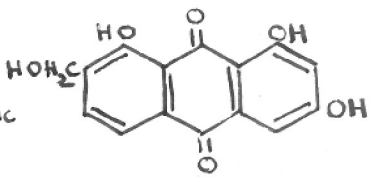


XVIII



XIX



II

min with a melt of aluminium chloride-sodium chloride at 140-150°. ω-Bromination of the triacetyl derivative (XVII), using a molar proportion of N-bromosuccinimide gave 1,3,8-triacetoxy-7-bromomethylanthraquinone (XVIII), which with sodium acetate and acetic anhydride gave the tetracetyl derivative (XIX), m.p. 183-185°, depressed when mixed with the acetyl derivative of versicolorin (mixed melting point 170-176°). Hydrolysis of (XIX) with methanolic potassium hydroxide gave 1,3,8-trihydroxy-7-hydroxymethyl-anthraquinone (II), which was purified by sublimation at 200°/0.1 mm. The compound melted at 248-250°(dec.); but the quantity was insufficient for analysis, and the synthesis is being repeated on a larger scale.

A comparison of the absorption spectra of the synthetic compound (II) and versicolorin indicates definite structural differences (see Fig. 2; 1,3,8-trihydroxy-7-methylanthraquinone is included for comparison). The synthetic compound shows the following maxima: 250, 265 (inflexion), 292 and 445 mμ; $\log \epsilon_{max}$ 4.45, 4.4, 4.4 and 4.14 respectively.

Versicolorin shows maxima at 290, 325 and 445 mμ; log ϵ_{max} 4.45, 3.88 and 3.98 respectively. The infrared spectrum of the compound (II) in Nujol shows absorption bands at 3290 cm^{-1} (alcoholic and β-hydroxyl groups), 1666 cm^{-1} (unchelated carbonyl) and 1613 cm^{-1} (chelated carbonyl); whereas in the region above 1600 cm^{-1} versicolorin in Nujol shows absorption bands at 3280, 1673 and 1604 cm^{-1} (see Table 2). However the infrared spectrum of the compound (II) shows no agreement with that of versicolorin in the region between 1600 and 700 cm^{-1}.

Reconsideration of some of the properties of versicolorin disclosed the following discrepancies:-

(i) Sulphuric acid colouration. - Versicolorin is reported to give a violet colouration with conc. sulphuric acid. 1,3,8-Trihydroxyanthraquinone, (I), (II), (XVI), emodin (see Part II) and ω-hydroxyemodin (III) give red to red-brown colourations. A violet colouration in sulphuric acid is given by 1,2,5-, 1,2,6-, 1,4,5-trihydroxyanthraquinones and also by 1,2,4,6-, 1,2,5,6-, 1,2,5,8- and 1,2,6,7-tetrahydroxy-anthraquinones.

(ii) Colouration in aqueous sodium hydroxide. - Versicolorin is reported to give a red-violet colouration with aqueous sodium hydroxide. It is found that 1,3,8-trihydroxyanthraquinone and its 2-hydroxymethyl and 7-hydroxymethyl derivatives give red colourations. A red-violet or violet colouration is given by 1,4-dihydroxy-, 1,2,5-, 1,2,7-, 1,2,8-, 1,4,5- and 1,4,6-trihydroxyanthraquinones and 1,2,5,6-, 1,2,5,8-, and 1,2,6,7-tetrahydroxyanthraquinones.

(iii) Benzoyl derivative. - Versicolorin is reported to give a tribenzoyl derivative by treatment with benzoyl chloride and pyridine at room temperature for 4 days.[1] Versicolorin, which has an alcoholic hydroxyl and three phenolic hydroxyl groups should be completely benzoylated under these conditions. In the case of lucidin (see Part III) and 1,3,8-trihydroxy-2-hydroxymethylanthraquinone (I) it has been observed that tri- and tetra-O-benzoyl derivatives are formed as expected.

The synthetic evidence and the chemical properties of the natural product indicate that the structure of versicolorin needs further investigation.

TABLE 1. COLOUR OF HYDROXYANTHRAQUINONES WITH METHANOLIC MAGNESIUM ACETATE

No	Position of substituents in anthraquinone	Colour with methanolic magnesium acetate
1	1,2-Dihydroxy	Violet
2	1,3-Dihydroxy	Orange
3	1,4-Dihydroxy	Pink
4	1,2,4-Trihydroxy	Red
5	1,2,5-Trihydroxy	Bluish violet
6	1,3,5-Trihydroxy	Orange
7	1,3,8-Trihydroxy	Reddish orange
8	1,3,8-Trihydroxy-6-methyl (emodin)	Reddish orange
9	1,3,8-Trihydroxy-6-hydroxy-methyl (citreorosein)	Reddish orange
10	1,3,8-Trihydroxy-2-hydroxymethyl (I)	Reddish orange
11	1,3,8-Trihydroxy-7-hydroxymethyl (II)	Reddish orange
12	1,3,8-Trihydroxy-7-methyl (XVI)	Reddish orange
13	Versicolorin	Orange

TABLE 2. INFRARED SPECTRA OF SUBSTITUTED ANTHRAQUINONES

Compound	Principal absorption bands in cm^{-1}					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
1,3-Dihydroxy-2-hydroxymethylanthraquinone (Lucidin) (KBr pellet)	3436 S 2940 S 2762 W 2660 W	1670 MS 1617 VS 1595 VS 1572 MS 1552 M 1530 W	1438 S 1416 S 1382 M 1338 S 1309 S	1287 S 1241 M 1212 M 1196 M 1163 W	1006 VS 987 VS 901 M	889 M 878 M 824 S 813 M 757 M 718 S
1,3,8-Trihydroxyanthraquinone (IV) (KBr pellet)	3330 S 2940 M	1670 MS 1617 VS 1582 VS 1552 M 1530 W	1480 VS 1454 VS 1416 S 1368 S 1338 S 1309 S	1280 VS 1230 VS 1163 M	1056 M 1020 M 913 W	863 M 831 M 821 M 807 M 778 VS 759 VS
Versicolorin (KBr pellet)	3330 S 2940 M	1670 W 1620 VS 1582 MS 1552 W 1530 W	1484 M 1449 M 1382 S 1313 S	1284 S 1236 M 1218 M 1182 M 1163 M	996 M 970 M 940 M 904 M	874 M 857 M 824 S 781 S 742 BS
(Nujol mull)	3280 M	1673 W 1604 VS	1449 S 1373 S 1307 M	1279 S 1231 W 1215 W 1184 W	1058 W 1040 W 1027 W 995 M 971 M 937 MS 902 M	858 S 825 S 782 MS 743 MS 723 BS 700 M

TABLE 2 (Contd.)

Compound	Principal absorption bands in cm^{-1}					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
1,3,8-Trihydroxy-2-hydroxymethylanthraquinone (I) (KBr pellet)	3436 S 2940 S 2762 W 2660 W	1670 MS 1617 VS 1572 MS 1552 W 1530 W	1480 VS 1454 VS 1416 S 1368 S 1338 S 1309 S	1280 S 1254 M 1218 M 1196 M 1163 M	1039 VS 996 VS 974 M 916 M	897 M 877 M 838 S 807 M 793 VS 765 VS 730 M
1,3,8-Trihydroxy-7-hydroxymethyl-anthraquinone (II) (Nujol mull)	3290 S	1666 MS 1613 VS 1563 MS	1403 MS 1338 M	1290 S 1245 S 1205 S 1172 S	1076 S 1040 MS 1021 M	871 S 817 M 755 S
1,3,8-Trihydroxy-6-hydroxymethylanthraquinone (Citreorosein) (KBr pellet)	3436 VS 2940 S 2762 W 2660 W	1672 MS 1617 VS 1572 MS	1465 VS 1432 W 1353 VS	1252 VS 1212 VS 1165 S	1046 VS 1022 VS 981 M 911 M	873 S 860 S 778 S 760 S

V - Very
S - Strong
M - Medium
W - Weak
B - Broad

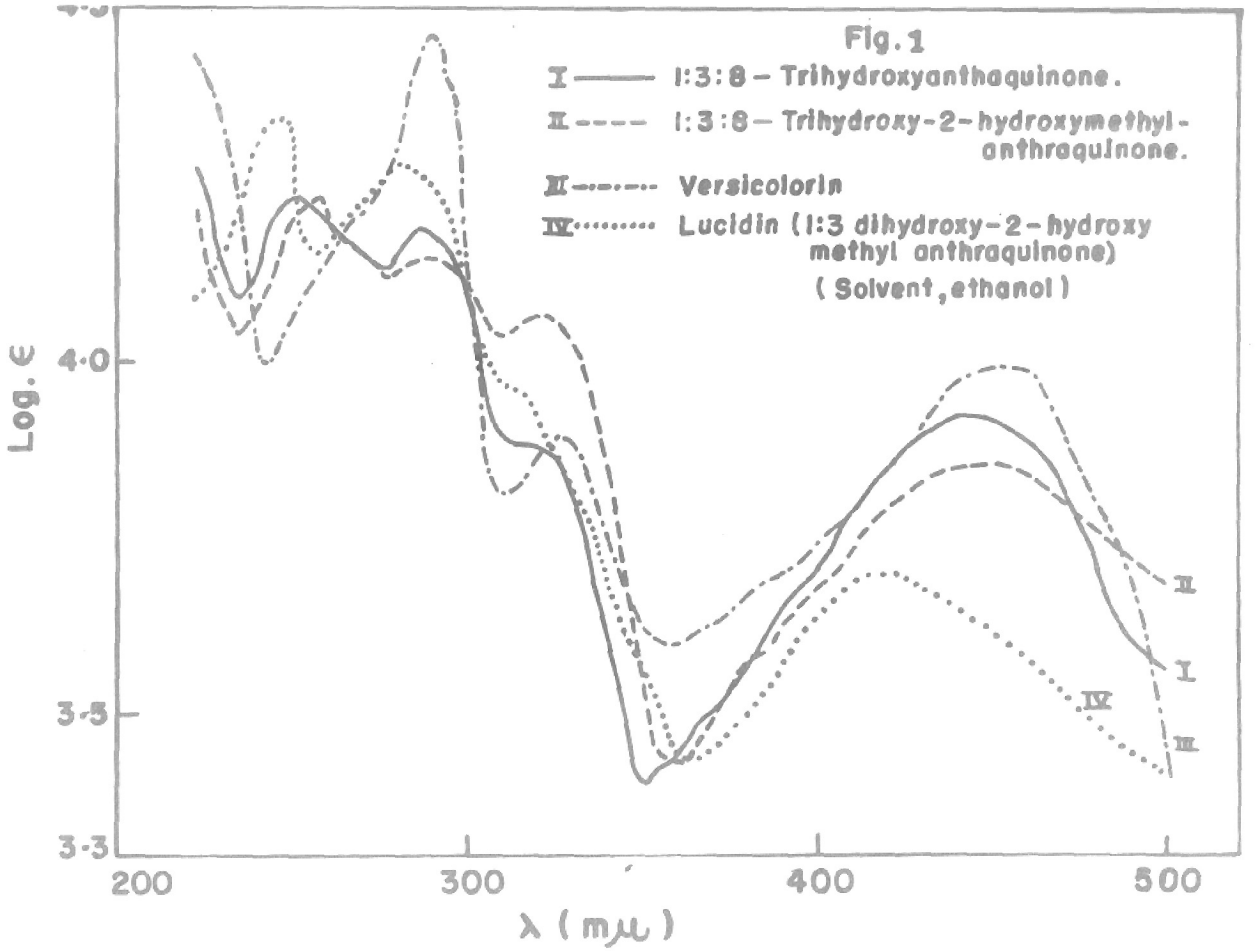


Fig. 1
I —— 1:3:8 – Trihydroxyanthaquinone.
II ---- 1:3:8 – Trihydroxy-2-hydroxymethyl-anthraquinone.
III -·-·-·- Versicolorin
IV ····· Lucidin (1:3 dihydroxy-2-hydroxy methyl anthraquinone)
(Solvent, ethanol)
Log. ε
4·0
3·5
3·3
200
300
400
500
λ (mμ)
II
I
IV
III

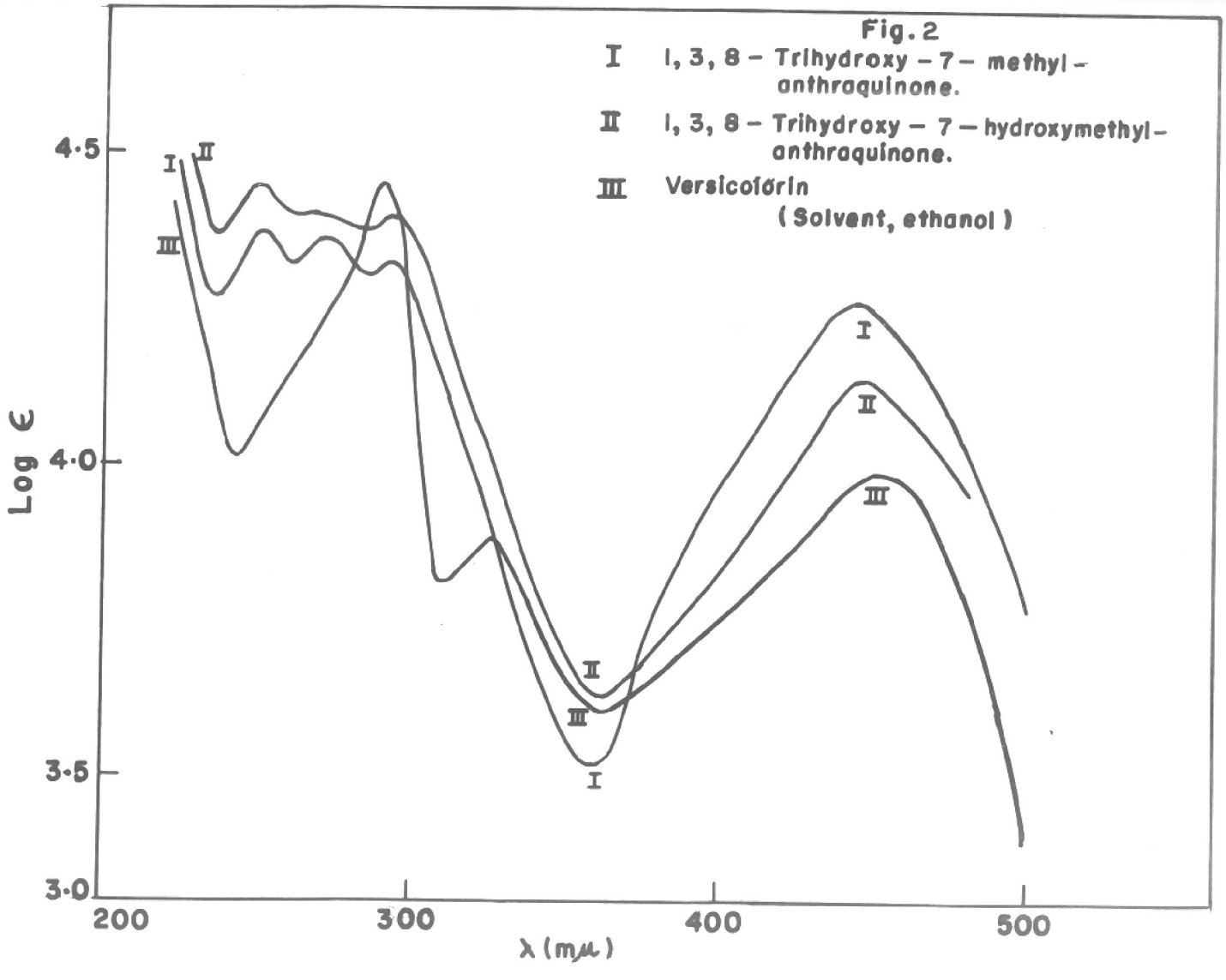


Fig. 2
I 1, 3, 8 – Trihydroxy – 7 – methyl – anthraquinone.
II 1, 3, 8 – Trihydroxy – 7 – hydroxymethyl – anthraquinone.
III Versicolorin
(Solvent, ethanol)
Log ε
4·5
4·0
3·5
3·0
200
300
400
500
λ (mμ)
I
II
III

EXPERIMENTAL

1-Amino-2,4-dibromo-5-chloroanthraquinone (VII) - To a stirred mixture of 1-amino-5-chloroanthraquinone (20 g) and glacial acetic acid (800 ml) at 100°, bromine (20 ml) in glacial acetic acid (40 ml) was added drop by drop in 2 hr. Agitation was continued at 100°, for 5 hr, and the dark red product was then collected, washed with 2% sodium bisulphite solution and water, and dried (26 g). Crystallization from chlorobenzene gave dark red needles, m.p. 250°. (Found: C, 40.5; H, 1.9; N, 3.3; Cl, 8.7; Br, 39.0. $C_{14}H_6O_2Br_2ClN$ requires: C, 40.5; H, 1.5; N, 3.4; Cl, 8.4; Br, 38.6%).

1,3-Dibromo-8-chloroanthraquinone (VIII) - 1-Amino-2,4-dibromo-5-chloroanthraquinone (25 g) was dissolved in conc. H_2SO_4 (250 ml), cooled in an ice-bath to 5°, and diazotized with sodium nitrite (20 g) in conc H_2SO_4 (100 ml) for 1 hr. Glacial acetic acid (50 ml) was added, and after 15 min, the mixture was poured over crushed ice (1 kg). The solution of the diazonium salt was added to ethanol (1 l.) and the mixture was gradually heated to the boil and then refluxed for 30 min. The greyish yellow product was collected,

washed free of acid and dried (22 g). Crystallization from glacial acetic acid gave greyish yellow needles, m.p. 245°. (Found: C, 41.6; H, 1.2. $C_{14}H_5O_2Br_2Cl$ requires: C, 42.0; H, 1.3%).

3-Bromo-1,8-dihydroxyanthraquinone - A mixture of 1,3-dibromo-8-chloroanthraquinone (VIII; 5 g), calcium hydroxide (30 g), copper bronze (2 g) and water (100 ml) was heated in a rocking autoclave at 230° and 27 atmospheres pressure for 24 hr. The violet calcium salt was acidified with 5% HCl, the brown product collected, washed, and extracted with 5% NaOH, and the extract acidified. The precipitate was collected, washed free of acid and dried (2.6 g). On extraction with petroleum ether, an orange yellow product (2 g) was obtained, which on crystallization from glacial acetic acid gave orange-yellow needles, m.p. 210°. (Found: C, 53.2; H, 2.1; Br, 25.1. $C_{14}H_7O_4Br$ requires: C, 52.7; H, 2.2; Br, 25.1%). The infrared spectrum (Nujol) shows maxima at 1687, 1634, 1571, 1470, 1402, 1384, 1360, 1278, 1207, 1158, 1051, 992, 927, 911, 869, 840, 805 and 757 cm^{-1}.

The diacetyl derivative crystallized from glacial acetic acid in pale yellow needles, m.p. 192°. (Found: C, 53.7; H, 2.4; Br, 20.2. $C_{18}H_{11}O_6Br$ requires: C, 53.6; H, 2.7; Br, 19.8%).

1,3,8-Trimethoxyanthraquinone - 1,3-Dibromo-8-chloroanthraquinone (3 g) and copper oxide (1 g) were refluxed for 24 hr with sodium methoxide solution prepared by reacting sodium 7.5 g) with dry methanol (150 ml). The mixture was then poured into water (500 ml), and the yellow product was collected, washed and dried (1.95 g). It crystallized from ethanol in yellow platelets, m.p. 196°.[11] (Found: C, 68.8; H, 4.8; OMe, 29.9. $C_{17}H_{14}O_5$ requires: C, 68.5; H, 4.8; OMe, 31.2%).

1,3,8-Trihydroxyanthraquinone (IV) - 1,3,8-Trimethoxyanthraquinone (1.7 g) was added to a melt of anhydrous aluminium chloride (8 g) and sodium chloride (1.5 g) at 145-150°. The mixture was stirred at 150° for 5 min and then poured into 5% HCl (150 ml). The brown-red precipitate was coagulated by heating for a few min, collected (1.5 g), and crystallized from ethyl acetate;

the brown plates melted at 287°.[11] (Found: C, 65.5; H, 3.1. $C_{14}H_8O_5$ requires: C, 65.6; H, 3.1%). The substance dissolves in conc H_2SO_4 with a reddish orange colour and gives a red solution in aqueous caustic soda and sodium carbonate. These properties are in agreement with those described.[11]

1,3,8-Trihydroxy-2-hydroxymethylanthraquinone (I) - A solution of 1,3,8-trihydroxyanthraquinone (1.5 g) in 5% NaOH (20 ml) was cooled to 20-25°, and treated with formalin (37-40%; 0.6 ml) under stirring. After 30 min agitation at 20-25°, the mixture was allowed to stand for 16 hr, then acidified, and the golden yellow precipitate collected, washed and dried (1.5 g). The product, which was very sparingly soluble in ethyl acetate and ethanol, crystallized from dioxan in orange yellow microscopic needles, darkening and decomposing above 295°. (Found: C, 62.8; H, 3.8. $C_{15}H_{10}O_6$ requires: C, 62.9; H, 3.7%). The substance gives a red solution in sodium carbonate and sodium hydroxide solutions and a brown solution in H_2SO_4. Versicolorin gives a violet solution in sodium carbonate and sodium hydroxide solutions and a bright

violet solution in H_2SO_4.

The tetracetyl derivative, prepared in the usual manner by means of acetic anhydride and pyridine, crystallized from ethanol in pale yellow needles, m.p. 205°. (Found: C, 60.4; H, 4.0. $C_{23}H_{18}O_{10}$ requires: C, 60.8; H, 4.0%).

O-Tetrabenzoyl derivative of (I) was prepared by heating (I) (0.1 g) on a boiling water-bath with benzoyl chloride (1.5 ml) and pyridine (5 ml) for 1 hr. On cooling and pouring the solution into crushed ice, the aqueous layer was decanted off and the thick oily product was shaken with methanol (2 ml), when a white solid separated, which crystallized from glacial acetic acid in pale yellow needles, m.p. 198°. (Found: C, 73.4; H, 3.9. $C_{43}H_{26}O_{10}$ requires: C, 73.5; H, 3.7%).

1,3,8-Trimethoxy-2-hydroxymethylanthraquinone - A mixture of 1,3,8-trihydroxy-2-hydroxymethylanthraquinone (0.14 g), anhydrous potassium carbonate (3 g), dimethyl sulphate (0.25 ml), and acetone (100 ml) was refluxed on a water-bath for 24 hr. After removal of the acetone and dilution of the mixture

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with water, a yellow product was obtained, which crystallized from ethanol in shining yellow needles, m.p. 220°. (Found: C, 65.9; H, 4.7. $C_{18}H_{16}O_6$ requires: C, 65.9; H, 4.9%).

1,3,8-Trihydroxyanthraquinone-2-aldehyde (V) - 1,3,8-Trihydroxy-2-hydroxymethylanthraquinone (I), (0.4 g) and activated manganese dioxide[16] (0.8 g) were refluxed with benzene (150 ml) for 16 hr. The mixture was filtered hot, and the manganese dioxide residue washed several times with hot benzene. Evaporation of the solvent and crystallization of the residue from glacial acetic acid gave brownish yellow needles (0.25 g), m.p.223°. (Found: C, 63.4; H, 3.0. $C_{15}H_8O_6$ requires: C, 63.4; H, 2.8%). The aldehyde dissolves in warm sodium hydroxide solution with a red-violet colour, and in conc H_2SO_4 with an orange-red colour. The azine (VI) was prepared by treating a warm solution of V (0.01 g) in glacial acetic acid (5 ml) with excess of hydrazine hydrate solution. Immediately a flocculent yellow crystalline precipitate separated. Crystallization from nitrobenzene gave yellow needles, m.p. 360°. (Found: N, 5.0. $C_{30}H_{16}O_{10}N_2$ requires: N, 5.0%).

1-Nitro-2-methyl-5-amino-6,8-dibromoanthraquinone (X) - A mechanically agitated solution of 1-nitro-2-methyl-5-aminoanthraquinone (see Part II) (17.4 g) in glacial acetic acid (525 ml) was treated at 100° with bromine (15 ml) in glacial acetic acid (130 ml) for 7 hr. On cooling to room temp. overnight, the red crystalline product was collected, washed with 5% sodium bisulphite solution and water, and dried (18.9 g). Crystallization from benzyl alcohol or chlorobenzene gave red needles, m.p. 250°. (Found: Br, 36.1; N, 6.3. $C_{15}H_8O_4N_2Br_2$ requires: Br, 36.4; N, 6.4%).

1-Nitro-2-methyl-6,8-dibromoanthraquinone (XI) - A solution of (X) (12.5 g) in conc H_2SO_4 (125 ml), cooled to 5°, was diazotized with sodium nitrite (6 g) in conc H_2SO_4 (40 ml) for 1 hr. Glacial acetic acid (30 ml) was added and the mixture poured over crushed ice (800 g). The diazonium solution thus obtained was refluxed with 95% alcohol (1 l.) for 1 hr. On cooling the product was collected, washed and dried (11 g). Crystallization from chlorobenzene or glacial acetic acid gave yellow needles, m.p. 300°. (Found: C, 42.4; H, 1.8.

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$C_{15}H_7O_4NBr_2$ requires: C, 42.4; H, 1.6%).

1-Amino-2-methyl-6,8-dibromoanthraquinone (XII) - 1-Nitro-2-methyl-6,8-dibromoanthraquinone (10 g) was made into a paste with sodium sulphide (40 g) and little water. The paste was diluted with water (300 ml) and stirred at 100° for 2 hr. The red crystalline product was collected, washed and dried (8.5 g). Crystallization from chlorobenzene gave red needles, m.p. 273°. (Found: C, 45.2; H, 2.0; Br, 41.0. $C_{15}H_9O_2NBr_2$ requires: C, 45.6; H, 2.3; Br, 40.5%).

1-Hydroxy-2-methyl-6,8-dibromoanthraquinone (XIII) - A solution of 1-amino-2-methyl-6,8-dibromoanthraquinone (8 g) in conc H_2SO_4 (80 ml) was cooled in an ice-bath to 5°, and diazotized with sodium nitrite (4 g), dissolved in conc H_2SO_4 (20 ml). After an hour, glacial acetic acid (10 ml) was added and after 15 min the mixture was poured over crushed ice (400 g). The diazonium solution, thus obtained, was gradually added to a boiling 40% H_2SO_4 solution (400 ml) and the mixture heated at 140° for 30 min. The yellow crystalline

product was collected, washed and dried (7.8 g). Crystallization from glacial acetic acid gave yellow needles, m.p. 215°. (Found: C, 45.0; H, 2.1; Br, 40.3. $C_{15}H_8O_3Br_2$ requires: C, 45.4; H, 2.2; Br, 40.4%).

1-Methoxy-2-methyl-6,8-dibromoanthraquinone (XIV) - A mixture of 1-hydroxy-2-methyl-6,8-dibromoanthraquinone (4.5 g), anhydrous potassium carbonate (45 g), dimethylsulphate (4.5 ml) and acetone (900 ml) was refluxed on a water-bath for 24 hr. After removal of the acetone and dilution of the mixture with water, a yellow product was obtained which was collected, washed and dried (4.5 g). Crystallization from glacial acetic acid gave yellow needles, m.p. 180°. (Found: C, 47.1, H, 2.5; Br, 39.1; OMe, 7.9. $C_{16}H_{10}O_3Br_2$ requires: C, 46.8; H, 2.4; Br, 39.0; OMe, 7.6%).

1,3,8-Trimethoxy-7-methylanthraquinone (XV) - 1-Methoxy-2-methyl-6,8-dibromoanthraquinone (3 g) and copper oxide (1 g) were added to a solution of sodium methoxide in methanol, prepared by dissolving sodium metal (7.5 g) in absolute methanol

(150 ml), and the mixture was refluxed for 72 hr under anhydrous conditions. Dilution with water (1 l.) gave a product which was collected, washed, dried and dissolved in benzene. The solution was passed through a short column of alumina, the percolate evaporated and the residue, which gave a negative test for halogen, was crystallized from alcohol as pale yellow needles, (0.92 g), m.p. 160°. (Found: C, 68.7; H, 5.1; OMe, 29.0. $C_{18}H_{16}O_5$ requires: C, 69.2; H, 5.1; OMe, 29.8%).

1,3,8-Trihydroxy-7-methylanthraquinone (XVI) - To a melt prepared from anhydrous aluminium chloride (2.5 g) and dry sodium chloride (0.5 g), 1,3,8-trimethoxy-7-methylanthraquinone (0.5 g) was added and the mixture stirred at 140° for 5 min. On cooling and adding 2% HCl (50 ml), the orange yellow product was collected, dissolved in 5% aqueous sodium carbonate (25 ml), filtered and the filtrate acidified. The precipitate (0.35 g) crystallized from alcohol in orange needles, m.p. 283-284°. (Found: C, 66.6; H, 4.0. $C_{15}H_{10}O_5$ requires: C, 66.7; H, 3.7%). The substance gives a red solution in sodium carbonate and sodium

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hydroxide solutions and a violet-red solution in H_2SO_4. It gives an orange colouration with alcoholic magnesium acetate.

The triacetyl derivative (XVII) prepared in the usual manner by means of acetic anhydride and pyridine crystallised from alcohol in pale yellow needles, m.p. 204°. (Found: C, 63.7; H, 4.1. $C_{21}H_{16}O_8$ requires: C, 63.6; H, 4.0%).

1,3,8-Triacetoxy-7-bromomethylanthraquinone (XVIII) - 1,3,8-Triacetoxy-7-methylanthraquinone (0.158 g), N-bromosuccinimide (0.08 g), benzoyl peroxide (0.02 g) and carbon tetrachloride (25 ml) were refluxed for 24 hr. The solvent was distilled off, the residue washed with hot water and dried(0.18 g). Crystallization from carbon tetrachloride gave pale yellow needles, m.p. 214°. (Found: C, 53.3; H, 2.8. $C_{21}H_{15}O_8Br$ requires: C, 53.1; H, 3.2%).

1,3,8-Triacetoxy-7-acetoxymethylanthraquinone (XIX) - 1,3,8-Triacetoxy-7-bromomethylanthraquinone (0.08 g) was refluxed with fused sodium acetate (0.1 g) and acetic anhydride (5 ml) for 1 hr. The mixture was cooled and poured into crushed ice. The pale

yellow product collected, washed and dried (0.065 g). Crystallization from alcohol gave pale yellow needles, m.p. 183-185°. The melting point depressed when mixed with versicolorin triacetate (170-176°). (Found: C, 61.4; H, 3.8. $C_{23}H_{18}O_{10}$ requires: C, 60.8; H, 4.0%).

1,3,8-Trihydroxy-7-hydroxymethylanthraquinone (II) - A solution of the tetracetyl derivative (XIX) (0.03 g) in 5% methanolic potassium hydroxide (10 ml) was agitated for 24 hr. Acidification gave an orange product which was sublimed at 200-220°/0.1 mm of Hg in orange micro needles, m.p. 248-250° (dec.). The product was not sufficient for analysis. The substance gives a red solution in sodium carbonate and sodium hydroxide, and a deep-red solution in H_2SO_4.

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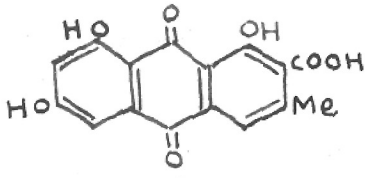
PART VI

EXPLORATORY WORK FOR THE SYNTHESIS OF ENDOCROCIN : A SYNTHESIS OF 1-HYDROXY-3-METHYLANTHRAQUINONE-2-CARBOXYLIC ACID

Endocrocin, an orange yellow colouring matter, was first isolated by Asahina and Fuzikawa[1] from the Japanese leafy lichen, Nephromopsis endocrocea, in which it is also accompanied by the closely related hydroxyanthraquinone, physcion (see Part II). The Japanese workers assigned to endocrocin the structure (I) on the basis of degradation studies,



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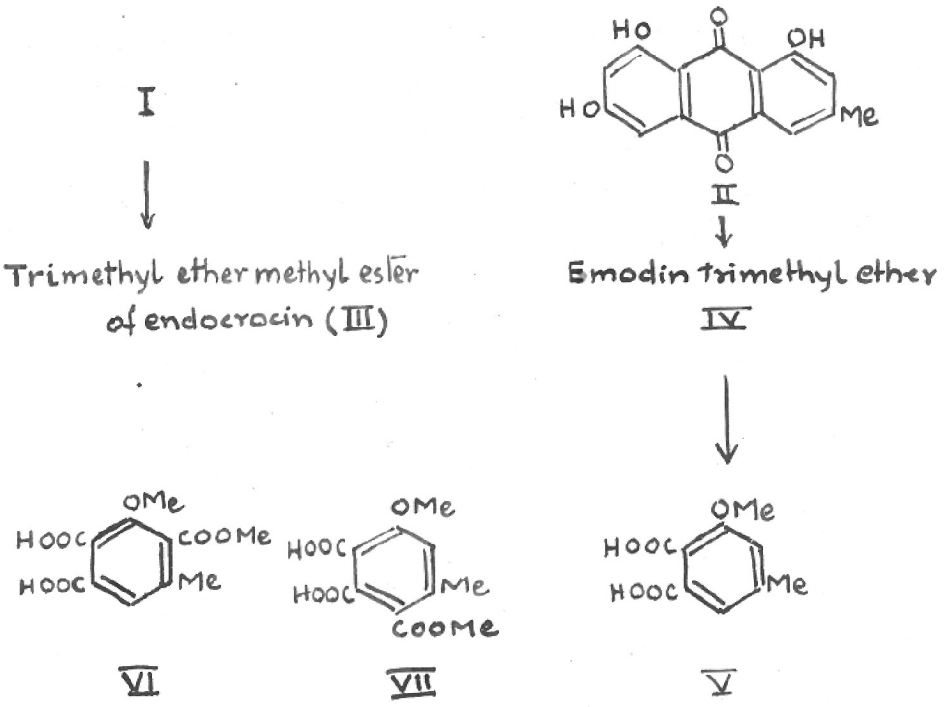
and they also indicated the close similarity between endocrocin and the hydroxyanthraquinone, "Origmaea säure" isolated by Zopf[2] from "Sticta origmaea." Endocrocin was later isolated by Shibata and Natori[3] from the mould, Aspergillus amstelodami, along with catenarin (1,4,5,7-tetrahydroxy-2-methylanthraquinone). Very recently Franck and Reschke[4,5] have isolated from the ergot fungus Claviceps purpurea, two anthraquinone colouring matters, clavonibin and clavoxanthin; the latter has been shown to be identical with endocrocin isolated

by Asahina and Fuzikawa.[1] Endocrocin has also been found to occur in the ultraviolet mutant of Penicillium islandicum,[6] from which emodin (see Part II), catenarin and islandicin (1,4,5-trihydroxy-2-methylanthraquinone) were isolated earlier.

Endocrocin has the molecular formula $C_{16}H_{10}O_7$. Its solubility in aqueous sodium bicarbonate with a brown red colour indicates the presence of a carboxyl group. Endocrocin gives with alcoholic ferric chloride, a reddish brown colouration, with conc. sulphuric acid a red colouration and with methanolic magnesium acetate an orange red colouration.

Asahina and Fuzikawa[1] showed that the thermal decomposition of endocrocin yielded emodin and that the ultraviolet absorption curves of endocrocin and emodin overlapped each other. These observations showed that endocrocin is an emodin carboxylic acid. The position of the carboxyl group as shown in (I) was assigned on the basis of degradative experiments on endocrocin as well as emodin trimethyl ether.[1]

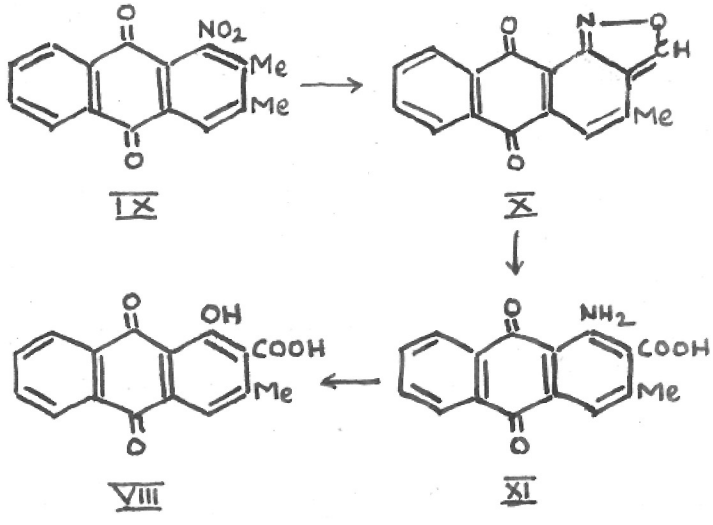
Emodin trimethyl ether (IV) on chromic acid oxidation yielded γ-coccinic acid methyl ether (V), whereas the



fully methylated endocrocin (III) yielded a mono-ester of a tricarboxylic acid, which was a carbomethoxy derivative of (V), showing thereby that the methyl and carbomethoxy groups of fully methylated endocrocin (III) were present in the same ring. The oxidation product was therefore regarded as (VI) or (VII). The acid (VII) incidentally is stated to be a degradation

product of kermesic acid,[7] and its non-identity with the oxidation product obtained from (III) led Asahina and Fuzikawa to assign the structure (VI) for this oxidation product, from which followed the structure (I) for endocrocin.

Although the structure of endocrocin (I) is based on weighty evidence, its confirmation by synthesis seemed desirable. In order to devise a suitable method for introducing the carboxyl group in the desired position of the anthraquinone nucleus, the synthesis of the unknown 1-hydroxy-3-methyl-anthraquinone-2-carboxylic acid (VIII) was undertaken as an exploratory work.

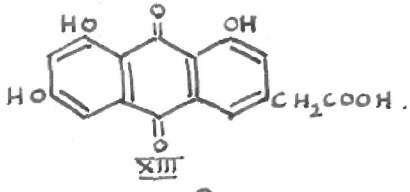


A (1-Nitro-2,3-dimethylanthraquinone (IX) was prepared by the nitration of 2,3-dimethylanthraquinone with dry potassium nitrate in sulphuric acid at 0°. Marschalk *et al.*[8] had prepared 1-nitro-2,3-dimethylanthraquinone by the nitration of 2,3-dimethylanthraquinone with a mixture of nitric acid and sulphuric acid in sulphuric acid solution at -10°. They did not isolate or characterize the nitro compound, but reduced it directly to 1-amino-2,3-dimethylanthraquinone. The direct conversion of 1-nitro-2,3-dimethylanthraquinone to the amino-acid (XI) by alkali treatment was not feasible. (*O*-Nitrotoluene gives anthranilic acid when treated with alcoholic alkali.[9]) The isoxazole (X) was prepared by the known method of heating with aluminium chloride at 150-160°.[10] Addition of sodium chloride helped the reaction to proceed smoothly. Reductive hydrolysis of the isoxazole (X) to 1-amino-3-methylanthraquinone-2-aldehyde (XII) was carried out, following German patents,[10] with the object of further oxidation to the amino-acid (XI); but the yield of the aldehyde (XII) was not satisfactory. The isoxazole (X) was however found

to be hydrolysable to the acid (XI) in 50-60 per cent yield by refluxing with alcoholic potassium hydroxide. The amino-acid (XI) was converted into 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (VIII) by the usual method of diazotization and subsequent hydrolysis by boiling with 40 per cent sulphuric acid. The electronic absorption spectra of 1-hydroxy-3-methylanthraquinone and 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (VIII) (see Fig. 1) are very similar.

The infrared spectrum of (VIII) (Nujol mull) shows absorption bands at 2660 cm^{-1} (OH stretching vibrations of carboxyl group), 1670 cm^{-1} (unchelated carbonyl and C=O vibration of aryl carboxyl group, which are not distinguishable), and 1633 cm^{-1} (chelated carbonyl) of the quinone group. In the region above 1600 cm^{-1}, endocrocin shows the following maxima:[5] 3380 (β-hydroxyl group), 1720, 1665 and 1612 cm^{-1}. From the data[11] available on the infrared spectra of carboxylic acids it will be seen that the carbonyl frequency of aryl carboxylic acids is in the region 1700-1680 cm^{-1}, whereas saturated aliphatic carboxylic acids absorb between 1725 and

1700 cm^{-1}. We therefore examined in this laboratory the infrared spectrum of 1-hydroxyanthraquinonyl-2-acetic acid[8] and found that in the region above 1600 cm^{-1} the following maxima were present: 2660, 1729, 1668 and 1639 cm^{-1}. The 1729 cm^{-1} band is close to the 1725-1700 cm^{-1} region observed in saturated aliphatic carboxylic acids. The absorption band at 1720 cm^{-1} in the case of endocrocin is not in conformity with the structure (I) assigned to endocrocin, but suggests an alternative structure (XIII) having a saturated aliphatic carboxyl group.



XIII

Marschalk et al.[8] have shown that the thermal decomposition of 1-hydroxyanthraquinonyl-2-acetic acid gives 1-hydroxy-2-methylanthraquinone. Thus (XIII), when heated above its melting point, should decarboxylate to give emodin. Gatenbeck[6] obtained emodin by the thermal decomposition of endocrocin, isolated from Penicillium islandicum. The degradative experiments carried out on endocrocin trimethyl

ether methyl ester (III) by Asahina and Fuzikawa[1] do not rule out the possibility of the structure (XIII) for endocrocin. A Kuhn-Roth determination gave a value of 5.6[5] (theory, 4.8), which appeared to indicate the presence of one C-methyl group; but any interpretations based on Kuhn-Roth oxidation method for C-methyl estimation should be done with caution.

The synthesis of both (I) and (XIII) is in progress in this laboratory.)

TABLE 1. INFRARED SPECTRA OF SUBSTITUTED ANTHRAQUINONES

Compound	Principal absorption bands in cm^{-1}					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
Endocrocin[5]	3380 S	1720 S 1665 M 1612 VS 1570 M	1475 S 1400 M 1364 M	1252 S 1207 S 1152 S 1100 MS	1065 MS 1021 M 972 W 931 S	842 W 868 M 826 W 798 W 777 M 763 S 725 M 692 W
1-Hydroxy-3-methyl-anthraquinone-2-carboxylic acid (Nujol mull)	2660 W	1670 S 1633 S 1583 VS	1357 VS	1297 S 1261 S 1215 W 1190 W 1167 MS	1077 MS 1050 M 1035 W 997 S	898 M 885 W 867 W 827 W 824 W 802 M 795 W 785 W 754 M 735 M 713 MS

TABLE 1 (Contd.)

Compound	Principal absorption bands in cm^{-1}					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
Anthraquinone-2-carboxylic acid (Nujol mull)	2650 W	1685 VS 1589 VS	1484 W 1415 W 1313 W	1287 MS 1255 W 1174 S 1152 M 1131 M 1128 W	1086 M 992 M 974 S 969 W 949 W 937 VS	893 W 869 S 796 VS 769 S 700 S
1-Hydroxyanthraquinonyl-2-acetic acid (Nujol mull)	2660 W	1729 VS 1668 M 1639 M 1589 S	1396 W 1341 W 1329 W	1297 M 1286 M 1262 W 1228 M 1195 M 1186 W 1181 W	1043 W 1032 M 1001 M 988 W 938 W	893 M 862 M 837 M 819 W 790 W 775 M 755 S 717 MS

V - Very M - Medium

S - Strong W - Weak

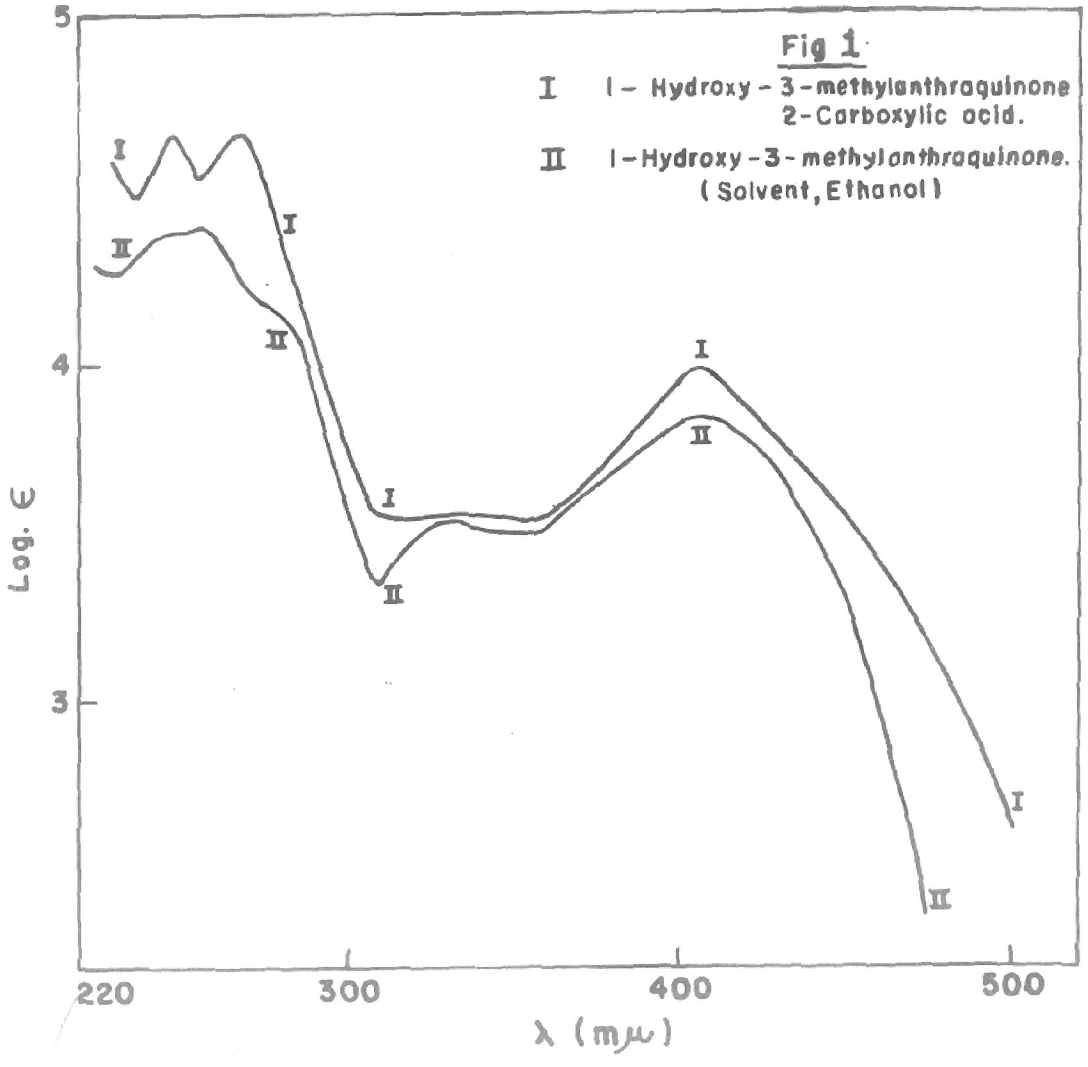


Fig 1
I 1- Hydroxy-3-methylanthraquinone 2-Carboxylic acid.
II 1-Hydroxy-3-methylanthraquinone. (Solvent, Ethanol)
5
4
3
Log. ε
220
300
400
500
λ (mμ)

EXPERIMENTAL

2,3-Dimethylanthraquinone (m.p. 208°) was prepared by condensing phthalic anhydride and o-xylene in presence of aluminium chloride at 70°, cyclizing the resulting keto-acid and separating the 1,2- and 2,3-dimethylanthraquinones taking advantage of their differential solubilities in glacial acetic acid.[12]

1-Nitro-2,3-dimethylanthraquinone (VII) - 2,3-Dimethylanthraquinone (20 g) were dissolved in conc H_2SO_4 (d. 1.84; 180 g) with stirring and cooled to 0° in an ice-bath. Finely powdered potassium nitrate (10 g) were then added in small portions with vigorous stirring and maintaining the temperature at 0°. The nitro compound starts separating out after 15 min. The stirring was continued at 0° for 12 hr more and the resulting thick mixture was poured over crushed ice (1 kg). The pale yellow product was collected, washed free of acid and dried (22 g). Crystallization from glacial acetic acid gave pale yellow needles, m.p. 252°. (Found: C, 68.3; H, 3.8; N, 5.0. $C_{16}H_{11}O_4N$ requires: C, 68.4; H, 3.9; N, 5.0%).

1-Amino-2,3-dimethylanthraquinone - 1-Nitro-2,3-dimethylanthraquinone (2 g) was made into a paste with sodium sulphide (6 g), diluted with water (100 ml) and heated on a water-bath with stirring at 100° for 1 hr. The red crystalline amino compound was collected, washed thoroughly and dried (1.5 g). Crystallization from toluene gave red needles, m.p. 209°. (Found: C, 76.3; H, 4.9; N, 5.7. $C_{16}H_{13}O_2N$ requires: C, 76.5; H, 5.2; N, 5.5%).

3-Methylanthraquinone-1,2-isoxazole (VIII) - 1-Nitro-2,3-dimethylanthraquinone (3 g) was mixed thoroughly with powdered anhydrous aluminium chloride (15 g) and sodium chloride (0.5 g). The mixture was heated at 160° for 1 hr, cooled and the product was drowned in ice water (100 ml) containing conc HCl (10 ml). The resulting brown product was collected, washed and dried (2.3 g). The product was purified by dissolving in hot xylene, from which it separated in amorphous, though pure form. The substance did not exhibit a sharp m.p. but decomposed at 250°. (Found: C, 72.7; H, 3.4; N, 5.4. $C_{16}H_9NO_3$ requires: C, 73.0; H, 3.4; N, 5.3%).

1-Amino-3-methylanthraquinone-2-aldehyde (X) - 3-Methylanthraquinone-1,2-isoxazole (2 g) was boiled with 40% H_2SO_4 (50 ml) and ferrous sulphate (2 g) for 2 hr. The separated red product was collected, washed and dried. The purification of the product was done by dissolving in benzene, passing through a short column of alumina and concentrating the eluted benzene from which red needles were obtained (0.6 g), m.p. 231°. (Found: C, 72.7; H, 4.1; N, 5.4. $C_{16}H_{11}O_3N$ requires: C, 72.5; H, 4.1; N, 5.3%).

1-Amino-3-methylanthraquinone-2-carboxylic acid (IX) - 3-Methylanthraquinone-1,2-isoxazole (2 g) was refluxed with methanolic potassium hydroxide (30%, 30 ml) for 2 hr, filtered and the filtrate acidified with HCl. The separated red product was digested on a water-bath for 15 min and collected, washed and dried (1.1 g). Crystallization from nitrobenzene gave brownish red needles, m.p. 261°. (Found: C, 67.9; H, 4.1; N, 5.2. $C_{16}H_{11}O_4N$ requires: C, 68.3; H, 3.9; N, 5.0%). The product is soluble in aqueous ammonia and aqueous sodium carbonate with a red colour.

1-Hydroxy-3-methylanthraquinone-2-carboxylic acid (VI) - 1-Amino-3-methyl-2-carboxylic acid (1 g) in conc H_2SO_4 (20 ml) was cooled to 5° and diazotized with a mixture of sodium nitrite (0.25 g) and conc H_2SO_4 (10 ml). The diazonium salt solution was poured over crushed ice (30 g) and then added to 40% H_2SO_4 solution at the boil. The mixture was gently boiled for ½ hr and diluted with water (60 ml). The crystalline yellow precipitate was collected, washed and dried (0.65 g). Crystallization from benzene gave yellow needles, m.p. 276°. (Found: C, 67.9; H, 3.4. $C_{16}H_{10}O_5$ requires: C, 68.0; H, 3.5%). The compound dissolves in aqueous sodium carbonate and sodium hydroxide giving orange-red colour and in conc H_2SO_4 yellow-brown colouration.

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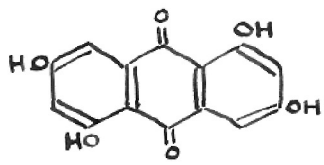
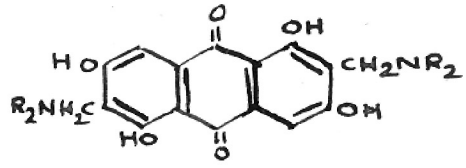
PART VII

MANNICH BASE REACTION ON XANTHOPURPURIN AND PURPURIN

According to a German patent[1], anthrachrysone (I) reacts with formaldehyde in aqueous alkylamine solutions to give Mannich type bases having the formula (II). Under similar conditions, xanthopurpurin and purpurin readily undergo the Mannich base reaction with



(I



II

formaldehyde and dialkylamines at room temperature giving (III) and (IV) respectively. The present work describes the synthesis of the following Mannich bases:

a) 2-dimethylaminomethylxanthopurpurin (V)

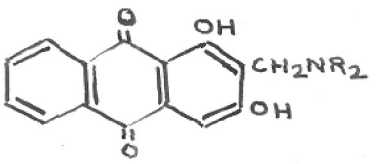
b) 3-dimethylaminomethylpurpurin (VI)

c) 3-diethanolaminomethylpurpurin (VII) and

d) 1,2,4-trihydroxy-3-anthraquinonylmethylamine-N,N-diacetic acid (VIII).

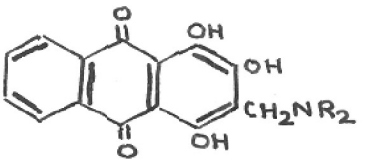
Such basic derivatives of anthraquinone may have interest from several points of view, because of their physical and chemical properties. Dimethylaminomethyl-xanthopurpurin (V) was kindly tested for antitubercular activity by Dr. V. C. Barry, Director of Laboratories,

Trinity College, Dublin, who reported that it partially inhibited M. tuberculosis (H 37 Rv, Proskauer and Beck medium containing 5 per cent human serum) at a dilution of 100,000; the anthraquinone ring in this case has probably little significance, since a similar Mannich base from Orcinol-8-carboxylic acid[2] exhibited activity of the same order. However the observations of Knox[3], Winder[4], and Maher et al[5] that isonicotinic acid hydrazide killed tubercle bacilli through the intracellular accumulation of hydrogen peroxide, and the observation of Manchot and Herzog[6] in 1901 that hydrogen peroxide is formed when anthrahydroquinone (9,10-dihydroanthracene) absorbs oxygen, appear to justify further work on the potential antitubercular activity of anthraquinone derivatives. Purpurin condenses smoothly with formaldehyde and diethanolamine to form 3-diethanolaminomethylpurpurin (VII), from which (IX) can be prepared, which may be of some interest in cancer studies as a biological alkylating agent and as a quinone with a metal chelating properties. Both dimethylaminomethylpurpurin (VI) and diethanolamino-

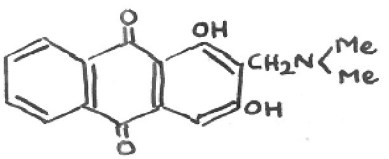


III

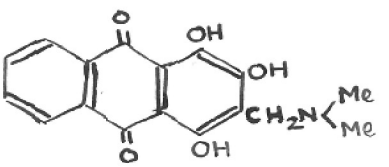
R = Alkyl



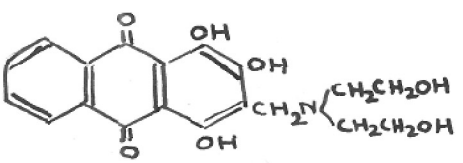
IV



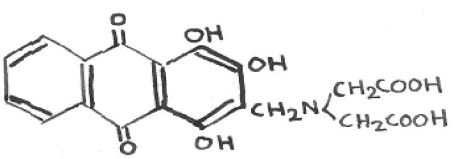
V



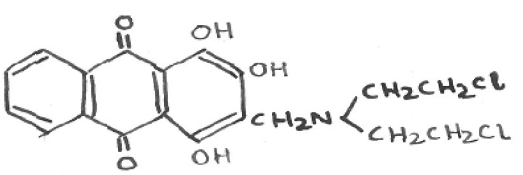
VI



VII



VIII



IX

methylpurpurin (VII) have been sent for testing to Dr. Barry.

The only reference in the literature to the Mannich base condensation in the anthraquinone series, other than the cited patent[1], is the preparation of Mannich base from formaldehyde, iminodiacetic acid and alizarin, 1,2,5-, 1,2,6- and 1,2,7-trihydroxyanthraquinones and quinalizarin by Belcher, Leonard and West[7]. These authors reported that "very little nitrogenous product was obtained from the corresponding reaction with 2-hydroxy, 1,4-, 1,5- or 1,8-dihydroxy-, or 1,2,3- or 1,2,4-trihydroxyanthraquinone or with a mixture of the 5 or 8-sulphonic acids derived from 1,2-dihydroxyanthraquinone." The reaction was carried out at 75° for 14 hr. using excess of aldehyde and the acid (as the disodium salt) in presence of aqueous sodium hydroxide, and the products (obtained as yellow or orange-brown powders in 13 per cent yield from alizarin and unspecified yield in other cases) were examined as complexometric indicators in EDTA titrations[7]. It has been found in the present work that purpurin, which was found by Belcher, Leonard

and West to be unreactive, reacts readily with formaldehyde and aqueous iminodiacetic acid (disodium salt) at room temperature yielding (VIII) as red needles, in good yield. 1,2,4-Trihydroxy-3-anthraquinonylmethylamine-N,N-diacetic acid (VIII) and similar compounds are being examined as indicators for EDTA titration in this Laboratory by Dr. J. Gupta and Dr. Subbaraman of the Inorganic Division.

E X P E R I M E N T A L

2-Dimethylaminomethylxanthopurpurin (V) -

Xanthopurpurin (2.4 g) was dissolved in 25 per cent dimethylamine solution (10 ml); and 35-7 per cent formaldehyde solution (1 ml, 1 mole) was added dropwise with agitation at 20°. After shaking for 15 min. the mixture was left overnight. The separated brown crystalline product was collected, washed with little cold water and dissolved in 5 per cent hydrochloric acid (100 ml) from which the hydrochloride separates out on cooling. The hydrochloride was collected, and the free base was liberated by adding saturated solution of sodium bicarbonate dropwise. The free base was collected, washed and dried (2.2 g). Crystallization from dioxane gave brown needles, m.p. 202° (Found: C, 68.6; H, 5.2; N, 4.4. $C_{17}H_{15}O_4N$ requires C, 68.6; H, 5.0; N, 4.7%).

3-Dimethylaminomethylpurpurin (VI) - Purpurin (2.56 g) was dissolved in 25 per cent dimethylamine solution (13 ml) and 35-7 per cent formaldehyde (1 ml, 1 mole) was added at 20°. After working up as in the case of (V), the free base was collected, washed and dried (2.3 g). Crystallization from 75%

alcohol gave red needles, m.p. 208-9° (Found: C, 64.7; H, 5.0; N, 4.6. $C_{17}H_{15}O_5N$ requires: C, 65.2; H, 4.8; N, 4.5%).

3-Diethanolaminomethylpurpurin (VII) - Purpurin (2.56 g) was dissolved in 25 per cent diethanolamine solution (15 ml) and at 20°, 35-37 per cent formaldehyde (1 ml) was added with agitation. After shaking for 15-20 min. the mixture was left overnight. The separated crystalline violet-red product was collected, washed with water and dried (2.7 g). Crystallization from cyclohexanol gave dark red needles, m.p. 240-3° (dec.). (Found: N, 3.1; $C_{19}H_{19}O_7N$ requires: N, 3.7%)

1,2,4-Trihydroxy-3-anthraquinonylmethylamino-N,N-diacetic acid (VIII) - Purpurin (2.56 g), 30 per cent iminodiacetic acid solution (25 ml) and 35-7 per cent formaldehyde (1 ml; 1 mole) were agitated together at 20-25°. The purpurin, which is in suspension partially at the beginning of the reaction, goes into solution as the reaction proceeds. After 24 hr. the reaction mixture was filtered and the filtrate acidified with acetic acid.

The separated red product was collected, washed with little cold water and dried (3.1 g.) Crystallization from glacial acetic acid gave red needles, m.p. above 300°(dec). (Found: N, 3.5; $C_{19}H_{15}O_9N$ requires: C, 3.5%). The compound dissolves in aqueous sodium bicarbonate with red colour.

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SUMMARY

PART I

A brief review is made of the hydroxyanthraquinones occurring in nature with special reference to their physiological properties, occurrence, isolation, colour reactions, constitution, biogenesis and classification. Synthetic methods are described in parts II, III, IV, V and VI.

PART II

The earlier methods of synthesis of hydroxyanthraquinones, such as chrysophanol (I) and emodin (II), were based on the condensation of nitro- or methoxyphthalic anhydrides with phenols or phenolic ethers, requiring relatively inaccessible intermediates. A new approach to their synthesis, starting from the common dye intermediate, 2-methylanthraquinone, is now described. 1,5-Dinitro-2-methylanthraquinone (VIII) served as the starting material for the synthesis of chrysophanol (I). Partial reduction of (VIII) gave 1-nitro-2-methyl-5-aminoanthraquinone (X). A series of subsequent reactions, shown in Chart 1, are involved, but they proceed smoothly and in good yield. 1,8-Dinitro-2-methylanthraquinone was used as the starting material

for the synthesis of emodin (II) and physcion (XIX). The series of reactions involved are shown in Chart 1.

The importance of the molar proportion of N-bromosuccinimide (NBS) used for the ω-bromination of 2-methylanthraquinones containing acetoxyl groups has been demonstrated in the present work on 1-acetoxy-3-methylanthraquinone (XXV) and the diacetate of chrysophanol (I). When two moles of NBS were used for one of (XXV), the product was 1-acetoxy-3-dibromomethyl-anthraquinone (XXIX), which could be hydrolysed to 1-hydroxyanthraquinone-3-aldehyde (XXX). The use of exactly one mole of NBS for one of (XXV) gave 1-acetoxy--3-bromomethylanthraquinone (XXVI), from which 1-hydrox$-3-hydroxymethylanthraquinone was obtained. Aloe-emodin (XXI) was similarly obtained from chrysophanol diacetate.

It has also been shown in the present work that methyl anthraquinone-2-carboxylate and its 4-acetoxy derivative can be reduced to the corresponding hydroxy-methyl compounds with lithium aluminium hydride.

For the synthesis of the unknown 2,3,6-trihydroxy anthraquinone the other method of the condensation of a phthalic anhydride derivative with a phenol has been found to be useful (see Chart 2).

PART III

An unambiguous synthesis of lucidin (II) from xanthopurpurin (III), following a series of reactions was reported earlier from this Laboratory. A much simpler, one-step synthesis of lucidin is now described. Treatment of xanthopurpurin (III) with formaldehyde and aqueous sodium hydroxide gave lucidin (II) in excellent yield. Oxidation of lucidin (II) with silver oxide and sodium hydroxide gave munjistin (IX), a colouring matter of Rubia munjista and Rubia sikkimensis. These reactions constitute the first unambiguous and practicable synthesis of munjistin. Oxidation of lucidin (II) with manganese dioxide in boiling benzene gave 1,3-dihydroxyanthraquinone-2-aldehyde (X), which agreed in its properties with nordamnacanthal, obtained by Nonomura, by the demethylation of damnacanthal (XII), a colouring matter of Damnacanthus major and Damnacanthus indicus. Nordamnacanthal has been isolated more recently by Seshadri from the heartwood of Morinda tinctoria. The synthesis of damnacanthol (XIII) and and damnacanthal (XII) is also described in the present work. Methylation of lucidin-2,3-diacetate, followed by deacetylation gave damnacanthol (XIII), which was oxidised with manganese dioxide in boiling benzene to

damnacanthal (XII).

PART IV

In connection with the constitution of galiosin, a primeveroside of purpurin-3-carboxylic acid, Hill and Richter reported the preparation of 3-hydroxymethylpurpurin (II) by the condensation of purpurin with formaldehyde in conc. sulphuric acid at room temperature. Repetition of the reaction however gave a different product, m.p. 239-40°, having the properties of the 1,3-dioxan derivative (III). When the hydroxymethylation of purpurin was attempted with formaldehyde and caustic soda at room temperature, the dimer (IV) was obtained instead of 3-hydroxymethylpurpurin (II). 3-Hydroxymethylpurpurin (II) was then synthesised from 3-methylpurpurin by ω-bromination with NBS and subsequent hydrolysis.

An interesting observation made in the course of this work is the replacement of a methoxyl group in 2-methoxyquinizarin by hydrogen by the action of sodium hydroxide and hydrosulphite. When the synthesis of 3-methylpurpurin-2-methyl ether was attempted by the action of formaldehyde, sodium hydroxide and sodium hydrosulphite on 2-methoxy-quinizarin, the product was 2,3-dimethylquinizarin.

PART V

1,3,8-Trihydroxy-2-hydroxymethylanthraquinone (I) and 1,3,8-trihydroxy-7-hydroxymethylanthraquinone (II), the two alternative structures proposed for versicolorin, a colouring matter of Aspergillus versicolor, have been synthesised and shown to be non-identical with versicolorin. Direct hydroxymethylation of 1,3,8-trihydroxyanthraquinone with formaldehyde and caustic soda gave 1,3,8-trihydroxy-2-hydroxymethylanthraquinone (I) in good yield. Oxidation of (I) with manganese dioxide in boiling benzene gave the corresponding aldehyde (V), which is of interest on account of the occurrence of other hydroxyanthraquinone-aldehydes in nature. 1-Amino-5-chloroanthraquinone is a convenient starting material for the synthesis of 1,3,8-trihydroxyanthraquinone. 1,3,8-Trihydroxy-7-hydroxymethylanthraquinone (II) was prepared by the ω-bromination of 1,3,8-triacetoxy-7-methylanthraquinone and subsequent hydrolysis. The new 1,3,8-trihydroxy-7-methylanthraquinone has been prepared from 1-nitro-2-methyl-5-aminoanthraquinone described in Part II. Bromination, deamination and reduction of the nitro group gave 1-amino-2-methyl-6,8-dibromoanthraquinone (XII). The diazonium salt of (XII), when hydrolysed with

boiling 40 per cent sulphuric acid, gave the hydroxy derivative (XIII), which was methylated and refluxed with sodium methoxide and methanol to give the trimethoxy derivative (XV). Demethylation of (XV) with aluminium chloride-sodium chloride melt gave 1,3,8-trihydroxy-7-methylanthraquinone (XVI).

PART VI

Although the structure of endocrocin (I), the colouring matter of Nephromopsis endocrocea, is based on weighty evidence, its confirmation by synthesis seemed desirable. As an exploratory work the synthesis of the unknown 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (VIII) was carried out. Mononitration of 2,3-dimethylanthraquinone gave 1-nitro-2,3-dimethylanthraquinone (IX), which was treated with aluminium chloride-sodium chloride melt to give the isoxazole (X). Boiling (X) with 40 per cent potassium hydroxide solution gave the amino-acid (XI), from which 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (VIII) was obtained. From the comparison of the infrared spectra of (VIII) and 1-hydroxyanthraquinonyl-2-acetic acid with the infrared spectrum of endocrocin it appears probable

that the structure of endocrocin must be revised to 1,6,8-trihydroxyanthraquinonyl-3-acetic acid (XIII).

PART VII

The synthesis of the following Mannich bases have been described: (a) 2-dimethylaminomethyl-xanthopurpurin (V), (b) 3-dimethylaminomethyl-purpurin (VI), (c) 3-diethanolaminomethylpurpurin (VII) and (d) 1,2,4-trihydroxy-3-anthraquinonyl-methylamino-N,N-diacetic acid (VIII). Such basic derivatives of anthraquinone are of interest because of their physical and chemical properties. The compound (V) has been tested for antitubercular activity; and the compound (VIII) is being examined as a complexometric indicator for EDTA titration.

A C K N O W L E D G M E N T

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