A

SYNTHESIS AND CONSTITUTION OF SOME COLOURING MATTERS DERIVED FROM ANTHRAQUINONE

A thesis submitted by

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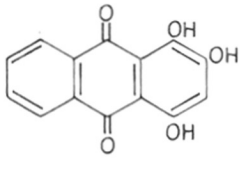
PART I

INTRODUCTION

NATURALLY OCCURRING HYDROXYANTHRAQUINONES

Polyhydroxyanthraquinones, which form an important class of pigments among the naturally occurring colouring matters of animal and vegetable origin, are no longer of any interest as colouring matters, but their physiological properties seem to encourage further study. Hydroxyanthraquinones containing C-methyl, hydroxymethyl, carboxyl and glycosidic groups have been known to be present in cathartic drugs, such as rhubarb, senna, cascara and aloes, from some of which anthrones and anthranols have been isolated. Stoll[1] showed that the active cathartic constituents of senna, sennoside A and B, are derivatives of 10,10'-dianthronyl. Hydroxyanthraquinones reported to be having antitubercular and antibacterial properties[2] are 2-methylanthraquinone, purpurin (I), emodin (II), aloe-emodin (III), rhein (IV) and barbaloin.



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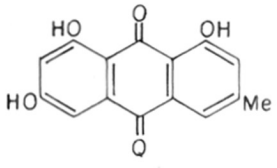

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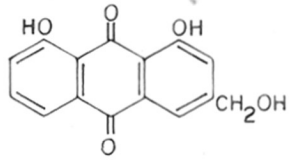

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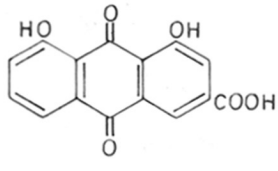


IV

Attempts to correlate the anthraquinone content of plant extracts, measured by the Borntrāger reaction[3] with

the cathartic activity, did not give satisfactory results. The activity depends to a great extent on the oxidation stage and Fairbairn showed that anthracene derivatives are highly active as "anthrone" glycosides, less as free anthrones and still less as free anthraquinones.[4] The free anthraquinones are active when applied directly to the large intestine, but undergo metabolic destruction when administered orally. However, as glycosides they are not destroyed because of the protective action of sugar residues.

Sugiura found that a dose of 225 mg/kg of hydrogen peroxide had a moderate inhibitory effect on sarcoma 180 ascites tumour in rats.[5] The physiological properties of anthraquinone derivatives gained additional interest because of the observation made by Manchot and Herzog in 1901[6] that hydrogen peroxide is formed when 9,10-dihydroxy-anthracene absorbs oxygen.

Occurrence

Derivatives of anthraquinone and anthrone occur widely in nature and have been isolated from minerals, fungi, lichens, plants and insects.[7] In fungi and higher plants

the hydroxyanthraquinones occur usually as complex mixtures in their different oxidation stages, such as carbinols, aldehydes and carboxylic acids. The fungal and lichen anthraquinones are closely related in their chemical constitution. Raistrick[8] has observed the close structural relation of many of the fungal anthraquinones to Frangula emodin, and Gatenbeck[9] isolated recently 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.[7] Anthraquinones having hydroxyl or methoxyl in 1,2-positions (e. g. alizarin), or hydroxyl or other substituents in 1,2,3-positions (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 and catenarin) have been isolated from some of the fungi, but not from lichens.

Isolation

The naturally occurring anthraquinones are isolated by the usual general methods, such as a series of

extractions with solvents of increasing polarity, fractionation of the products from different solvents by crystallization, separation by taking advantage of the functional groups, etc. Lately the chromatographic technique has been successfully employed for the separation of closely related anthraquinone pigments. Thus, for example, Briggs isolated a number of new anthraquinone pigments by chromatography of the acetone extract of Coprosma lucida[10] over calcined magnesia. Magnesium carbonate chromatography was used for the separation of anthraquinone pigments (the mono and dimethyl ethers of rhodocomatulin) from Comatula pectinata.[11] By chromatography over calcium hydrogen phosphate, Takido isolated from the seeds of Cassia obtusifolia, apart from chrysophanol, physcion and obtusifolin, three new colouring matters, obtusin, chrysoobtusin and aurantioobtusin.[12a,b]

Colour Reactions

Distinct colour reactions of hydroxyanthraquinones with alkali, conc sulphuric acid, etc., reveal to a certain extent the arrangement of the substituents in the anthraquinone nucleus. The Borntrāger test[3] is useful

for detecting hydroxyanthraquinones in plant extracts. This test consists of heating the crude extract with a dilute mineral acid to hydrolyse the glycosides, extracting the liberated aglycones with organic solvents like benzene, shaking the benzene extract with aqueous alkali; a beautiful rose-pink to cherry-red colour in the aqueous alkaline layer is characteristic of hydroxy-anthraquinones. Ferric chloride colouration is not characteristic of polyhydroxyanthraquinones. Polyhydroxy-anthraquinones having adjacent hydroxyls give a bluish violet colouration in acetone with zirconium nitrate solution in dilute hydrochloric acid. Alizarin derivatives can be judged by the shades on mordanted wool. Anthraquinone derivatives having hydroxyls in 1,4-positions show fluorescence in acetic acid solution. With the exception of purpurin all polyhydroxyanthraquinones having hydroxyl groups in <u>para</u>-positions are oxidized by lead tetracetate to the corresponding coloured diquinonoid compounds. In the case of purpurin it is very easily degraded to phthalic acid and hence the colour disappears rapidly. This observation is useful for locating hydroxyl groups in 1,2,4-positions.[13] The well-known reduction of purpurin to xanthopurpurin by treatment with alkaline dithionite and reoxidation of the leuco

compound can also be used to locate hydroxyls in 1,2,4-positions. Anthragallol gives a flocculent greenish precipitate with sodium amalgam in ethanolic solution (Bargellini test) which shows the presence of hydroxyls in 1,2,3-positions.[14] Also, a solution of anthragallol in aqueous sodium hydroxide rapidly changes colour from green to brown on exposure to air.[7] Hydroxyanthraquinones, having at least one α-hydroxyl group, give characteristic colourations with magnesium acetate in alcoholic solution,[15] which are violet for 1,2-dihydroxy-derivatives, orange 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

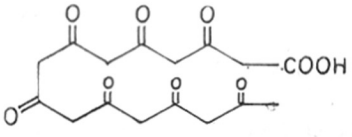
Polyhydroxyanthraquinones with one hydroxyl in the β-position are soluble in cold aqueous sodium carbonate. There are a few instances of polyhydroxyanthraquinones dissolving in bicarbonate because of the presence of more than one β-hydroxyl group (e. g. asperthecin). Zinc-dust distillation of hydroxyanthraquinones gives the anthracene or the corresponding alkyl anthracene.

The hydroxyl in α-position does not undergo methylation easily with diazomethane in ether, but can be methylated with dimethyl sulphate and alkali. The hydroxyl in β-position can be methylated easily. The presence of two hydroxyls in 1,3-positions and absence of any substituent in the 2-position in the polyhydroxyanthraquinones, erythrolaccin and alaternin, were shown by a novel method by treating the anthraquinone derivatives with formaldehyde and aqueous alkali to give the 2-hydroxymethyl derivative.[14] Ultraviolet and infrared spectra are obviously of great value in determining the constitution of anthraquinone derivatives, and some of their applications are discussed in Parts II and III. However, the exact constitution of polyhydroxyanthraquinones has to be confirmed by synthesis, and the syntheses of a few of them based on the new methods developed in this laboratory[16] are described in the present work (Parts II and III).

Biogenesis

With the establishment of chemical structures of a number of natural products in the last few decades the organic chemist has diverted his attention towards biosynthesis. The generalizations based on biosynthesis

are not of speculative interest only, because with their help it is possible (a) to know the unsuspected relations between classes of substances, (b) to limit the number of formulae while determining the structures, and (c) even to suggest laboratory methods of synthesis.[17] Robinson[18] suggested that many natural products including quinones can arise from polyacetic acid precursors. For example, heptaketopalmitic acid (V), formed from eight acetic acid units, can give rise to the anthrone (VI), which in turn can give endocrocin (VII) and emodin (II).



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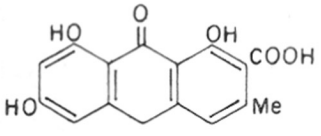

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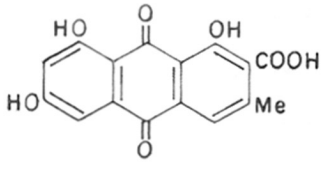

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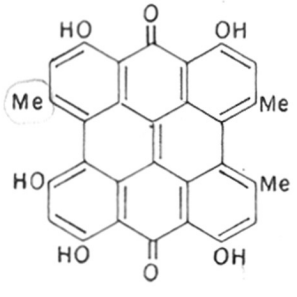
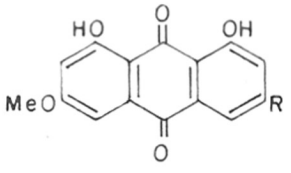
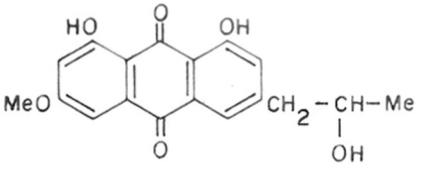


VIII

Robinson has also pointed out that the anthrone (VI) is correctly oriented to function as the precursor of hypericin (VIII), the photodynamic constituent constituent of Hypericum perforatum. Collie[19] had advanced in 1901 a similar view that diacetylacetone could be cyclized to form a benzene derivative. Birch[17] and his coworkers extended the acetate hypothesis further to demonstrate that head-to-tail linkages of acetate units could lead to phenolic substances in many 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 possible of the alternative structures. Gatenbeck[20] incorporated radioactive carbon in emodin by growing Penicillium islandicum on carboxy labelled sodium acetate and clearly indicated that emodin involves head-to-tail condensation of acetate units. Nalgiovensin was shown by Raistrick[21] to have one of the structures (IX), in which R = $CH_2CH_2CH_2OH$; CH_2-CHOH-Me or CHMe-CH_2OH.



IX



X

Birch[22] predicted the correct structure of nalgiovensin to be (X) on the basis of the acetic acid theory of biosynthesis. Very recently Birch[23] has confirmed (X) by synthesizing 4,5,7-trimethoxy-2-propyl-anthraquinone, which was identical with the product obtained from nalgiovensin by reduction, oxidation and methylation.

The acetate origin can be suspected in cases where two hydroxyl groups are in meta-positions to each other. Many anthraquinones from higher plants contain catechol or pyrogallol structures which must have formed from a different type of reaction sequence, or by mechanisms involving the removal and/or addition of hydroxyl groups.

Seshadri[24] put forward another scheme of biogenesis based on C_8 units, such as orsellinic acid and 3,5-dihydroxyphthalic acid, which occur in natural sources. This scheme was extended to explain the biosynthesis of anthraquinones having catechol structures.[25]

Classification

A systematic classification of the naturally occurring anthraquinone derivatives has been made by Venkataraman.[2] After the publication of this review a

number of hydroxyanthraquinones have been isolated and are listed in Table 1. Some of these have been mentioned by Joshi[26] in a recent publication.

TABLE 1

No.	Name	Substitution in anthraquinone	Occurrence	Reference: Isolation and structure	Reference: Synthesis
1.	Digitolutein	3-OH-4-OMe-2-Me	Digitalis purpurea	27, 28	29
2.	Obtusifolin	3,5-$(OH)_2$-4-OMe-2-Me	Cassia obtusifolia	12a	30*
3.	Obtusin	3,5-$(OH)_2$-4,6,7-$(OMe)_3$-2-Me	-do-	12b	-
4.	Chrysoobtusin	3-OH-4,5,6,7-$(OMe)_4$-2-Me	-do-	12b	-
5.	Aurantio-obtusin	3,5,7-$(OH)_3$-4,6-$(OMe)_2$-2-Me	-do-	12b	-
6.	Rhodocomatulin	1,3,6,8-$(OH)_4$-2-$CO(CH_2)_2Me$	Comatula pectinata	11	-
7.	Damnacanthol	1-OMe-2-CH_2OH-3-OH	Damnacanthus major	31	38, 32
8.	Damnacanthal	3-OH-1-OMe-2-CHO	-do-	31	38, 32

TABLE 1 (Contd.)

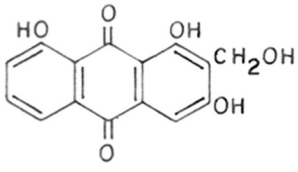
1.	2.	3.	4.	5.	6.
9.	*nor*-Damnacanthal	1,3-$(OH)_2$-2-CHO	*Morinda tinctoria*	39	38
10.	Juzunol	2,8-$(OH)_2$-4-OMe-3-CH_2OH	*Damnacanthus* sp.	31, 32	32*
11.	Juzunal	2,8-$(OH)_2$-4-OMe-3-CHO	-do-	31, 32	32*
12.	Coelulatin	1,3,8-$(OH)_3$-2-CH_2OH	*Coelospermum reticulatum*	33	34
13.	Macrosporin	5,7-$(OH)_2$-3-OMe-2-Me	*Macrosporium porri*	35, 36	37*
14.	Fallacinal	4,5-$(OH)_2$-7-OMe-2-CHO	*Xanthoria fallax*	40	40
15.	Colucidin	1,3,6-$(OH)_3$-2-Me	*Coprosma* genus	54	-
16.	-	1,4,7,8-$(OH)_4$-2-Me	*Penicillium islandicum*	13	13
17.	-	2-CH_2OH	*Tectona grandis*	41	43
18.	-	2-CHO	-do-	41	44
19.	-	3-OH-2-Me	-do-	42	45

*In these cases only the syntheses of the corresponding "nor" compounds have been reported.

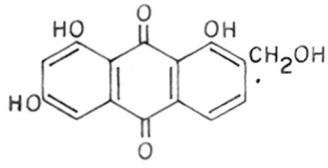
Recently structural studies have been done on alaternin

(isolated from Rhamnus alaternus[46]), erythrolaccin (from stick-lac[47]), dermocybin (from Dermocybe sanguinea[48]), and versicolorin (from Aspergillus versicolor[49]).

Alaternin has been shown to be 1,2,6,8-tetrahydroxy-2-methylanthraquinone.[50] The structure of erythrolaccin has been formulated as 3,4,6,8-tetrahydroxy-2-methylanthraquinone.[14] Dermocybin was proved to be either 4,5,7,8-tetrahydroxy-6-methoxy-2-methylanthraquinone or 4,5,6,8-tetrahydroxy-7-methoxy-2-methylanthraquinone.[51] Ayyangar[34] synthesized the two alternative structures (XI) and (XII) proposed for versicolorin and found that neither corresponded to the natural pigment.



XI



XII

Naturally Occurring Hydroxyanthraquinone Carboxylic Acids

The naturally occurring anthraquinone carboxylic acids, which are of immediate interest in the present work, are listed in Table 2.

TABLE 2

No.	Name	Substitution in anthraquinone	Occurrence	Reference: Isolation	Reference: Synthesis
1.	Munjistin	1,3-$(OH)_2$-2-COOH	*Rubia* sp.	7g	7g, 52
2.	Rhein	4,5-$(OH)_2$-2-COOH	*Rheum officinale*	7g	7g
3.	Pseudopurpurin	1,2,4-$(OH)_3$-3-COOH	*Rubia tinctorum*	7g	7g
4.	Emodic acid	4,5,7-$(OH)_3$-2-COOH	*Penicillium cyclopium*	7g	7g
5.	Boletol	1,2,4-$(OH)_3$-5- or 8-COOH	*Boletus* sp.	7g	7g
6.	Endocrocin	1,6,8-$(OH)_3$-3-Me-2-COOH	*Nephromopsis endocrocea*; *Aspergillus amstelodami*; *Penicillium islandicum*; *Claviceps purpurea*	53	Part III of this Thesis
7.	Rhodocladonic acid	1,3,6,8-$(OH)_4$-2-CH_2OH-7-COOMe	*Cladonia* sp.	7f, 7g	-
8.	Carminic acid	1,2,4,7-$(OH)_4$-3-$C_6H_{11}O_5$-5-Me-8-COOH	*Coccus cacti*	7g	-
9.	Kermesic acid	1,2,4,7-$(OH)_4$-3-Ac-5-Me-8-COOH	*Coccus ilici*	7g	-
10.	Laccaic acid	1,4,6-$(OH)_3$-2-Ac-3-Et-7,8-$(COOH)_2$	*Coccus laccae*	7g	-

The structures of rhodocladonic acid and laccaic acids are in need of further investigation. Thus Dimroth's laccaic acid

has been shown to contain 1-2 per cent nitrogen and to be a mixture of several pigments.[30] Also the evidence in favour of the structures of carminic acid and kermesic acid, the essential colouring matters of cochineal and kermes, is extensive but by no means conclusive. The structure of munjistin was assigned as xanthopurpurin-2- or 4-carboxylic acid on the basis of the following evidence. Munjistin, on heating above its m.p., lost carbon dioxide and gave xanthopurpurin, and on bromination yielded 2,4-dibromoxanthopurpurin, the carboxyl group being replaced by bromine. The structure was proved to be xanthopurpurin-2-carboxylic acid by synthesis. Mitter and Biswas[55,56] obtained a minute amount of a substance which was insufficient for analysis, but did not depress the m.p. of natural munjistin by the following series of reactions. 2-Chloro-6-methoxytoluene was condensed with phthalic anhydride and aluminium chloride and the 2-(2'-chloro-3'-methyl-4'-methoxy)-benzoylbenzoic acid was cyclized to 1-chloro-2-methyl-3-methoxyanthraquinone. Demethylation followed by oxidation yielded a product which could not be obtained chlorine-free after repeated crystallizations but had all the properties of munjistin. Another method which yielded again a trace of munjistin started with chlorination of

3-methylalizarin. Oxidation of the 4-chloro derivative to pseudopurpurin and reduction of pseudopurpurin with sodium hydrosulphite and ammonia gave munjistin. Oschmann[57] reported a synthesis of munjistin which was obtained by the reduction of pseudopurpurin, prepared by the oxidation of 2-methylanthraquinone or 2-methylquinizarin. However the first unambiguous and practicable synthesis of munjistin reported[58] is by the oxidation of lucidin with silver oxide in aqueous caustic soda.

Rhein, 1,8-dihydroxyanthraquinone-3-carboxylic acid, was assigned this structure since it could be obtained by the oxidation of chrysophanic acid and aloe-emodin. Starting from the common dye-intermediate 1-amino-5-chloroanthraquinone, the synthesis of rhein has recently been reported.[59] 1-Amino-5-chloroanthraquinone was converted to the corresponding 2-methyl derivative, following Marschalk's method, and this on bromination yielded 1-amino-2-methyl-4-bromo-5-chloroanthraquinone. Deamination and oxidation followed by replacement of the halogen atoms by hydroxyls, using lime under pressure, yielded rhein.

The structure of emodic acid was confirmed to be 1,6,8-trihydroxyanthraquinone-2-carboxylic acid by getting the same by the oxidation of triacetyl-emodin

and deacetylation of the acid obtained.[60]

Pseudopurpurin gave purpurin on decarboxylation, and munjistin on vatting and reoxidation. Hence it was constituted as 1,2,4-trihydroxyanthraquinone-3-carboxylic acid. Oxidation of 1,2- or 1,4-dihydroxyanthraquinone with manganese dioxide yielded pseudopurpurin.[61]

Boletol, another naturally occurring anthraquinone carboxylic acid, was found to be 1,2,4-trihydroxy-anthraquinone-5- or 8-carboxylic acid since it gave purpurin on decarboxylation, and hemimellitic acid on oxidation with alkaline hydrogen peroxide.[62,63] Kogl and Deijs[62,63] attempted the synthesis by two ambiguous routes. One synthesis started with hemimellitic anhydride which was condensed with 1,2,4-trimethoxybenzene. They obtained the mixed anthraquinones from the condensation product and isolated from this mixture one product identical with boletol. In the other synthesis condensation of hemi-mellitic anhydride and quinol gave quinizarin-5-carboxylic acid. Oxidation of this with lead tetraacetate yielded the diquinone, which on Thiele acetylation and hydrolysis gave a mixture of 1,2,4-trihydroxyanthraquinone-5- and 8-carboxylic acids. The two were separated chromatographically and one of them was identical with the natural pigment. Thus the structure of boletol was left still

unconfirmed.

Among the unsynthesized naturally occurring hydroxyanthraquinone carboxylic acids (in Table 2) endocrocin occupies an important position since its constitution is taken into consideration as an example for the validity of the biogenetic acetate hypothesis. An examination of the structure proposed for it and confirmation of the correct structure by synthesis are reported in Parts II and III.

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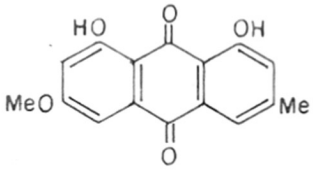
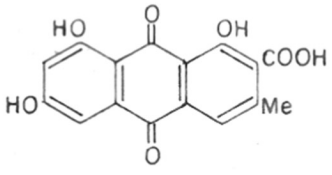
PART II

THE CONSTITUTION OF ENDOCROCIN

Endocrocin (orange-red crystals from dilute acetone or copper-red leaflets from acetic acid; m.p. 318° decomp) was first isolated by Asahina and Fuzikawa[1] by acetone extraction of the dried thalli of the Japanese leafy lichen Nephromopsis endocrocea, in which it is accompanied by the closely-related hydroxyanthraquinone, physcion (I).



I



II

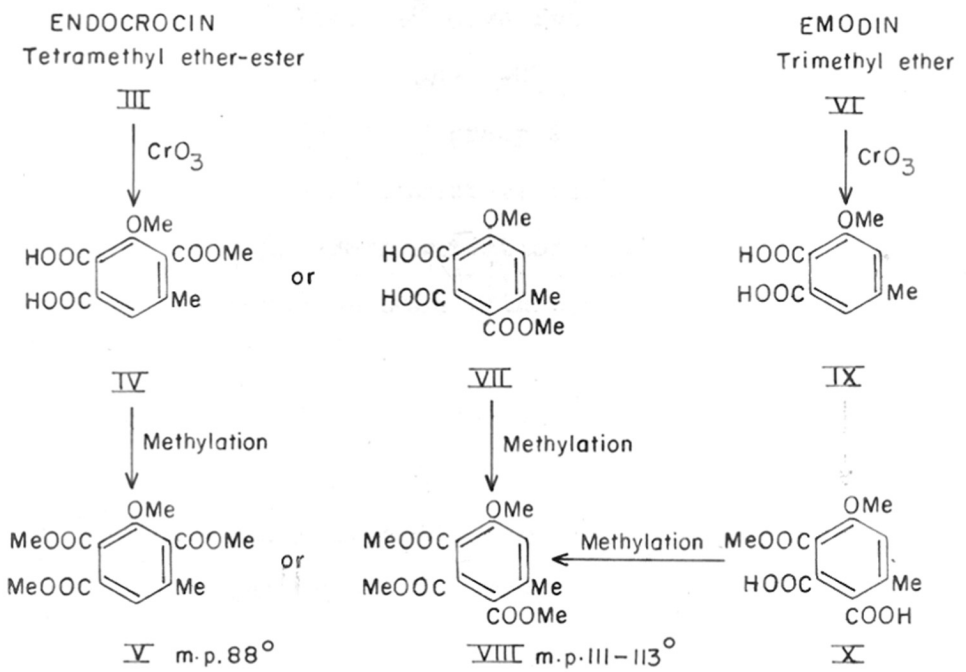
The Japanese workers assigned to endocrocin the structure 1,6,8-trihydroxy-3-methylanthraquinone-2-carboxylic acid (II) on the basis of degradation studies and also indicated the close similarity between endocrocin and the hydroxyanthraquinone "Origmaea säure" isolated by Zopf[2] from Sticta origmaea. Later, from the mould Aspergillus amstelodami, Shibata and Natori[3] isolated endocrocin together 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 colouring matters, clavorubin and clavoxanthin; the latter pigment (m.p. 340° decomp) has been shown to be identical with

endocrocin. A colouring matter (m.p. 290-320° decomp) identical with endocrocin has also been found to occur in an ultraviolet mutant of Penicillium islandicum[6] from which emodin, catenarin and islandicin were isolated earlier.

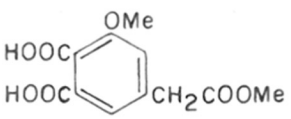
Asahina and Fuzikawa showed that endocrocin has the molecular formula $C_{16}H_{10}O_7$. It gave a red colour in sodium bicarbonate, a violet-red colour in sodium carbonate and sodium hydroxide, a purple colouration in conc sulphuric acid, and a red brown colouration with alcoholic ferric chloride.[1] Asahina and Fuzikawa also noted that endocrocin gave emodin on thermal decomposition and that absorption spectra of endocrocin and emodin, in the ultraviolet and visible regions overlapped each other. These observations showed that endocrocin is an emodin carboxylic acid. The position of the carboxyl group as shown in (II) was assigned on the basis of degradative experiments carried out on the trimethyl ether methyl ester and the trimethyl ether of endocrocin and emodin.

Emodin trimethyl ether (VI) on chromic acid oxidation gave γ-coccinic acid methyl ether (IX). Fully methylated endocrocin (III) yielded on oxidation a compound $C_{12}H_{12}O_7$, which was found to be a

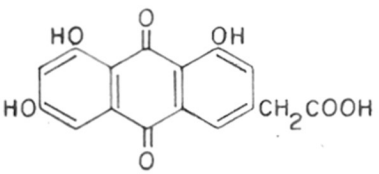
carbomethoxy derivative of (IX), showing thereby that the methyl and carbomethoxy groups of fully methylated endocrocin were in the same ring. Hence the oxidation product $C_{12}H_{12}O_7$ from (III) was regarded as either the methyl ether monomethyl ester of isocochenillic (IV) or cochenillic (VII) acid. The acid (X) had been reported earlier by Dimroth[7] to be a degradation product of kermesic acid and the dimethyl ester of (X), indicated as (VIII), had m.p. 111-113°. The oxidation product $C_{12}H_{12}O_7$ on complete methylation gave a compound melting at 88°. It followed therefore that the oxidation product from (III) should be constituted as (IV) and endocrocin as (II).



Asahina and Fuzikawa[1] did not consider a third possible structure (XI) for the oxidation product $C_{12}H_{12}O_7$ from (III). The structure (XI), which fits in with the degradation results of Asahina and Fuzikawa, leads to the possibility of an alternative structure (XII) for endocrocin. The compound (XII) can also give emodin on thermal decarboxylation; 1-hydroxyanthraquinonyl-2-acetic acid gave 1-hydroxy-2-methylanthraquinone on heating above its m.p.[8]



XI

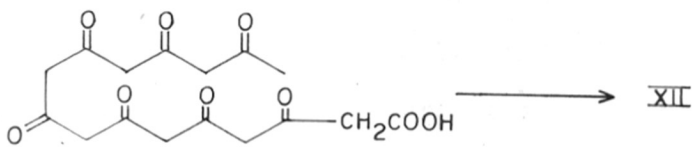


XII

Franck and Reschke[5] have recorded a C-methyl value of 5.6 (calculated for one C-CH_3: 4.8%), indicating the presence of one C-methyl group in endocrocin. Although this is in favour of structure (II), any interpretation based on the Kuhn-Roth oxidation method for C-methyl estimation should be done with caution in the anthraquinone series.

Among the naturally occurring anthraquinone pigments endocrocin is of special interest as a likely intermediate in the biogenesis of emodin and other hydroxy-2-methylanthraquinones. Robinson[9] has drawn attention to

the possibility of its derivation from 8 molecules of acetic acid through the heptaketopalmitic acid (XIII). The alternative structure (XII) is also derivable from the heptaketopalmitic acid (XIII).



XIII → XII

The infrared spectrum of endocrocin (in nujol) showed absorption bands at 1615, 1666 and 1718 cm^{-1} in the carbonyl region. Franck and Reschke[5] have taken the infrared spectrum of endocrocin (KBr pellet) and have recorded the same frequencies for the bands in the carbonyl region. The first two bands are obviously assignable to chelated and unchelated carbonyl groups in the anthraquinone nucleus. The band at 1718 cm^{-1} in the case of endocrocin appears to be at too high a frequency for a carboxyl group attached to an aromatic nucleus and again suggested the possibility of structure (XII) for endocrocin.

Infrared spectra in paraffin mull are considered in the present discussion; thus benzoic acid has a carbonyl frequency at 1685 $\pm$ 5 cm^{-1} and salicylic acid at 1665 $\pm$5 cm^{-1}; phenylacetic acid shows a CO frequency

at 1697 ± 3 cm^{-1} and acetic acid at 1712 ± 5 cm^{-1}. The lowering of the carbonyl frequency in the case of salicylic acid is due to intramolecular hydrogen bonding. Flett found that generally aromatic carboxylic acids absorbed below 1700 cm^{-1} and aliphatic acids above 1700 cm^{-1} in the region near 1700 cm^{-1}.[10] These correlations of Flett were based on a study of the infrared spectra of a number of acids, including aliphatic, benzene and naphthalene carboxylic acids.

In the present work the infrared spectra of a series of anthraquinone carboxylic acids, including a few anthraquinonylacetic acids, have been examined and are reported in Table 1.

The carbonyl stretching vibrations of some of the anthraquinone carboxylic acids examined are separately given in Table 2, and the following discussion is restricted to the carbonyl region.

Infrared absorption in the carbonyl region

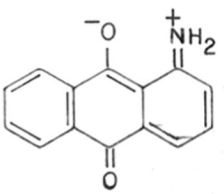
Anthraquinone-1- and 2-carboxylic acids showed only one sharp band arising from both the carbonyls of the anthraquinone nucleus and the carbonyl of the carboxyl group (Figs. 1 and 2). Anthraquinone-1,2-dicarboxylic acid resembled the monocarboxylic acids in its carbonyl frequencies (Fig. 3).

TABLE 2

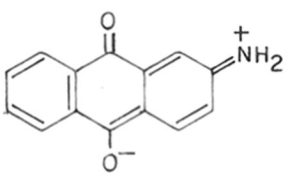
Sr. No.	Substitution in anthraquinone	CO frequencies in cm^{-1}
1.	None	1675
2.	1-COOH	1668
3.	2-COOH	1685
4.	1,2-$(COOH)_2$	1701, 1672
5.	1,8-$(OH)_2$-3-COOH (Rhein)	1692, 1634, 1617
6.	1,3-$(OH)_2$-2-COOH (Munjistin)	1669, 1620
7.	1-OH-3-Me-2-COOH	1670, 1633
8.	1,6,8-$(OH)_3$-3-COOH (Emodic acid)	1704, 1616
9.	1-OH-5-COOH	1672, 1630
10.	1-OH-2,4$(NO_2)_2$-5-COOH	1708, 1680, 1645
11.	1-NH_2-2-COOH	1667, 1623
12.	1-NH_2-4-Br-2-COOH	1695, 1669, 1631
13.	3-NO_2-1-COOH	1709, 1672
14.	6-NO_2-1-COOH	1718, 1672
15.	1-Cl-2-COOH	1695, 1669
16.	6-Cl-1-COOH	1692, 1667
17.	Endocrocin	1718, 1666, 1615
18.	2-CH_2COOH	1708, 1680
19.	1-OH-2-CH_2COOH	1729, 1668, 1639

In general it was found that all the few hydroxyanthraquinone carboxylic acids examined, which had at least one chelated carbonyl in the anthraquinone nucleus, the CO band of the carboxyl group and the CO band of the unchelated

carbonyl in the anthraquinone nucleus overlapped each other; but endocrocin and 1-hydroxy-2,4-dinitroanthraquinone-5-carboxylic acid, which exhibited three bands in the CO region, were exceptions. Rhein and emodic acid having one carbonyl function in the anthraquinone nucleus doubly hydrogen bonded owing to the presence of hydroxyls in 1,8-positions, showed an increased frequency for the carbonyl of the carboxyl group as compared with the other hydroxyanthraquinone carboxylic acids examined. Thus emodic acid gave rise to two bands: one at 1704 cm^{-1} (carbonyl of the carboxyl group and unchelated carbonyl of the anthraquinone nucleus) and at 1616 cm^{-1} (chelated carbonyl of the anthraquinone nucleus). In rhein the frequency at 1692 cm^{-1} represents both the carbonyl of the carboxyl group and unchelated carbonyl of the nucleus; the 1617 cm^{-1} band is to be assigned to the chelated carbonyl, since in other 1,8-dihydroxyanthraquinone derivatives it appears between 1615 and 1630 cm^{-1};[13] the origin of the medium strong band at 1634 cm^{-1} is not clear (Fig. 4).



XIV



XV

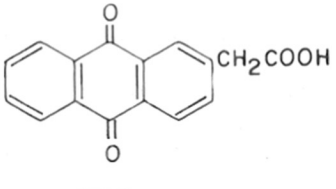
Although this discussion is primarily concerned with the unique character of the endocrocin spectrum in the carbonyl region, a few aminoanthraquinones and other anthraquinone carboxylic acids are considered in view of a general programme of work in progress in this laboratory on the application of infrared spectra to structural problems in the anthraquinone field. 1-Aminoanthraquinone exhibits carbonyl frequencies at 1665 and 1612 cm^{-1};[11] the lowering of the frequency of one carbonyl group is the result of the contribution made by the ionic structure (XIV) and not to hydrogen bonding with the amino group, because NH frequencies are at 3420 and 3300 cm^{-1}. This is confirmed by the very similar CO and NH frequencies of 2-aminoanthraquinone (1676; 1625; 3470; 3330; 3220 cm^{-1}), in which no hydrogen bonding is possible, but the ionic structure (XV) can contribute to the resonance of the molecule. 1-Aminoanthraquinone-2-carboxylic acid shows a band at 1667 cm^{-1} assignable to carbonyl of the anthraquinone nucleus as well as the CO of the carboxyl group and a shoulder at 1623 cm^{-1} because of the perturbed carbonyl group (Fig. 5). 1-Amino-4-bromoanthraquinone-2-carboxylic acid shows bands at 1695 cm^{-1} (carbonyl of the carboxyl group) and 1669 cm^{-1} (the free carbonyl in the anthraquinone nucleus) and a shoulder at 1631 cm^{-1}

(the perturbed carbonyl in the anthraquinone nucleus) (Fig. 6). The reason for a very low absorption for the perturbed carbonyl in both these cases may be owing to hydrogen bonding between NH_2 and CO of the carboxyl group or zwitterion formation between NH_2 and COOH, although the latter is unlikely because anthranilic acid shows normal amine and carboxyl absorption bands slightly modified by an intramolecular hydrogen bond.[12] The NH stretching frequencies (3448, 3333 cm^{-1}) are identical for both 1-amino-anthraquinone-2-carboxylic acid and the 4-bromo derivative.

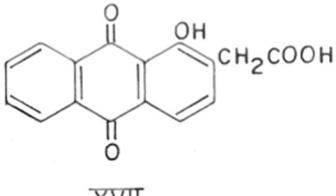
The carbonyl frequency of the carboxyl in the case of most of the anthraquinone carboxylic acids lies below 1700 cm^{-1} except for emodic acid and nitroanthraquinone carboxylic acids. The three nitroanthraquinone carboxylic acids examined show CO frequency of the carboxyl group above 1700 cm^{-1}. No simple explanation can be found for this effect of the nitro group, because in two of the three nitroanthraquinone carboxylic acids examined the nitro and carboxyl groups are in different benzene rings which are largely insulated by the two carbonyl groups (Figs. 7 and 8). The electron-attracting effect of the nitro groups is probably responsible for the slight shift to higher frequency (1690 $\pm$ 5 cm^{-1}) in m- and p-nitrobenzoic acids as compared with benzoic acid

(1685 ± 5 cm^{-1}); the frequency of 1700 ± 3 cm^{-1} for o-nitrobenzoic acid[10] indicates an additional steric effect.

1-Chloro- and 2-chloroanthraquinones have nearly the same frequency (1678 cm^{-1}) as anthraquinone itself (1675 cm^{-1}). 1-Chloroanthraquinone-2-carboxylic acid shows bands at 1695 cm^{-1} (carbonyl of the carboxyl group) and at 1669 cm^{-1} (carbonyls of the anthraquinone nucleus) (Fig. 9). The increase in the carbonyl frequency of the the carboxyl group as compared to anthraquinone-2-carboxylic acid (1668 cm^{-1}) must therefore be related to the adjacent positions of the halogen atom and carboxyl group. Ortho and para chlorobenzoic acids exhibit the following frequencies: o - 1690 ± 2 cm^{-1}; p - 1685 ± 5 cm^{-1}; the higher frequency for the o acid may be ascribed to a steric or a field effect. Flett has recorded 1710 cm^{-1} ("value uncertain owing to other CO group in molecule") for 4-bromo-1-chloroanthraquinone-2-carboxylic acid.[10] The high frequency (1692 cm^{-1}) for 6-chloroanthraquinone-1-carboxylic acid (Fig. 10) is difficult to explain.



XVI

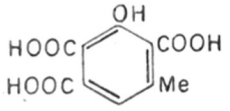


XVII

To study the carbonyl frequency of an aliphatic carboxyl group in a side chain attached to an anthraquinone nucleus the infrared spectra of anthraquinonyl-2-acetic acid (XVI) and 1-hydroxyanthraquinonyl-2-acetic acid (XVII), prepared by the Marschalk reaction on 1-hydroxyanthraquinone and glyoxylic acid, were examined. Anthraquinonyl-2-acetic acid had absorption bands at 1708 cm^{-1} (CO of the aliphatic carboxyl group) and 1680 cm^{-1} (carbonyls of the anthraquinone nucleus). 1-Hydroxyanthraquinonyl-2-acetic acid showed bands at 1729 cm^{-1} (CO of the aliphatic carboxyl group), 1668 cm^{-1} (unchelated carbonyl of the anthraquinone nucleus) and 1639 cm^{-1} (chelated carbonyl of the anthraquinone nucleus) (Fig. 12). The spectrum of (XVII) thus showed three distinct bands for the three carbonyls in contrast with the hydroxyanthraquinone carboxylic acids examined (with the carboxyl group attached to the nucleus), except endocrocin.

Thus the high carbonyl frequency of the carboxyl groups at 1718 cm^{-1} in the case of endocrocin, though not ruling out the structure (II) for it, went more in favour of an aliphatic carboxylic acid structure (XII). Shibata[14] has mentioned that the shift of the carboxyl band to a higher frequency is unique in the case of endocrocin. However, he found that isocochenillic acid (XVIII)

absorbed at 1724, 1698 and 1675 cm^{-1} and its monomethyl ether at 1720 and 1697-1710 cm^{-1}. For 6-methylsalicylic acid the CO frequency (KBr disc) has been recorded as 1653 cm^{-1}, identical with the value for salicylic acid.[15]



XVIII

Franck[16] ascribed the high carbonyl frequency of the carboxyl group in the case of endocrocin to the fact that the steric interaction of the carboxyl group with the neighbouring hydroxyl and methyl groups shifts it out of the plane of the aromatic ring, and the carboxyl group in endocrocin therefore exhibits the CO frequency of an aliphatic carboxylic acid. Franck's explanation is untenable because 1-hydroxy-3-methyl-anthraquinone-2-carboxylic acid, the synthesis of which is reported in Part III, having the same orientation of substituents as structure (II) for endocrocin in the ring carrying the carboxyl group, has a frequency only at 1670 cm^{-1} for the carbonyl of the carboxyl group (Fig.13).

Hence it was found necessary to confirm the constitution of endocrocin as either (II) or (XII) by synthesis. The synthesis of (XII) was taken up first because it is also a useful intermediate for the synthesis of nalgiovensin.

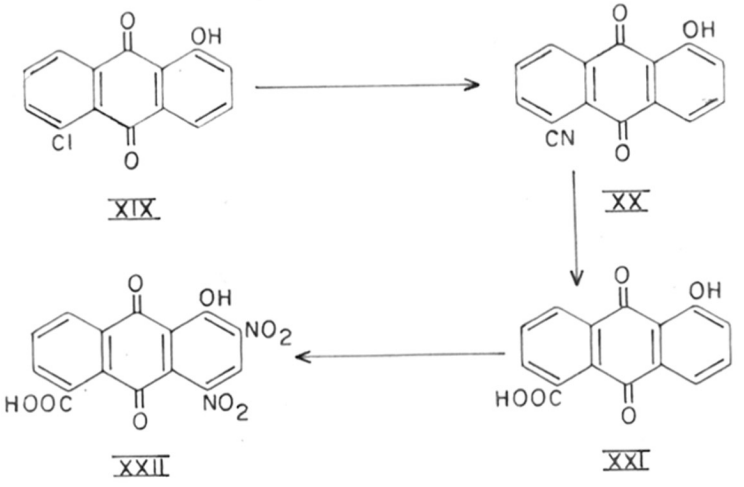
Infrared absorption in other regions

All the carboxylic acids derived from anthraquinone, except anthraquinonyl-2-acetic acid, munjistin and 3-nitroanthraquinone-2-carboxylic acid, have a weak band in the region 2500-3000 cm^{-1}, which is assignable to the OH stretching vibration of the carboxyl group and which Flett[10] observed in other carboxylic acids. A band near 1400 cm^{-1}, observed by Flett in 45 out of 60 carboxylic acids examined by him, is not characteristic of the anthraquinone carboxylic acids. Like all the acids studied by Flett, the anthraquinone carboxylic acids showed weak or medium bands between 1230 and 1280 cm^{-1}. Out of the eighteen acids examined only eleven showed bands at 935 $\pm$ 15 cm^{-1}, which were assigned by Hadzi and Sheppard[17] to the OH out-of-plane deformation mode of carboxyl groups. The β-hydroxyl group in emodic acid shows a band at 3413 cm^{-1}. In munjistin a band owing to a β-hydroxyl group in this region is absent probably because of chelation with the neighbouring carboxylic acid group. The three nitroanthraquinone carboxylic acids examined showed nitro bands in the expected regions near 1538 cm^{-1} and 1350 cm^{-1}.

Compounds included in the infrared study

Most of the compounds included in Table 2 were

prepared and purified by known literature methods and the infrared spectra were determined on analytically pure samples. A few of the anthraquinone carboxylic acids were specially synthesized for examining their infrared spectra and also for establishing feasible routes for the synthesis of (XII) and (II). The synthesis of 1-hydroxy-3-methyl-anthraquinone-2-carboxylic acid and anthraquinonyl-2-acetic acid are described in relevant portions dealing with the syntheses of (XII) and (II) in this Part and in Part III.

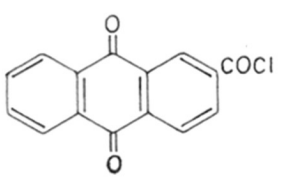


1-Hydroxyanthraquinone-5-carboxylic acid was synthesized starting from 1-hydroxy-5-chloroanthraquinone (XIX). The compound (XIX)[18] on refluxing with cuprous cyanide in dimethylformamide gave the corresponding cyano compound (XX) which was hydrolyzed to 1-hydroxy-anthraquinone-5-carboxylic acid (XXI). The dinitration of (XXI) at 0^{o}, using fuming nitric acid yielded (XXII) and

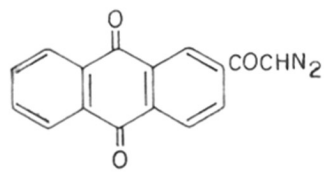
this structure was confirmed by getting 1-hydroxy-2,4-dinitroanthraquinone on decarboxylation. Reduction of (XXII) to the corresponding diamino compound was also done by hydrogenation over palladium charcoal at atmospheric pressure.

The synthesis of 1,6,8-trimethoxyanthraquinonyl-3-acetic acid methyl ester and its non-identity with endocrocin tetramethyl ether-ester

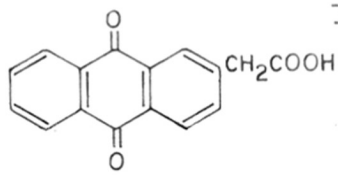
Since it was found that anthraquinonyl-2-acetic acid (XVI) was unknown, although the 1-hydroxy derivative (XVII) had been prepared by the Marschalk reaction,[8] the preparation of (XVI) was first undertaken so that the conditions for the conversion of emodic acid trimethyl ether to the corresponding anthraquinonylacetic acid (XXVIII) and its ester (XXIX) could be standardized. Anthraquinone-2-carboxyl chloride (XXIII) was prepared following the usual method by treatment of anthraquinone-2-carboxylic acid with thionyl chloride.



XXIII



XXIV



XVI

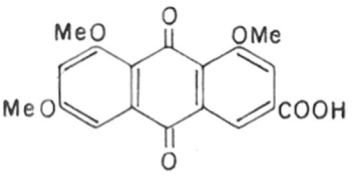
Arndt-Eistert reaction[19] provides a means of lengthening an acid chain: R-COOH → R-CH_2COOH. The initial step in the Arndt-Eistert reaction is condensation of an acid chloride with diazomethane to form a diazoketone. The diazoketone on heating with water in the presence of silver oxide as catalyst gets rearranged (called Wolff-rearrangement)[20] to give a higher homologous acid. The corresponding methyl ester can be prepared by conducting the Wolff-rearrangement in methanol in presence of silver oxide (R-COCHN_2 → R-CH_2COOMe). Arndt and Eistert prepared anthraquinonyl-2-diazoketone (XXIV) from anthraquinone-2-carboxyl chloride (XXIII) in connection with the preparation of the corresponding anilide.[19] They had not characterized the diazoketone (XXIV), but used it directly for the next stage. Now, the diazoketone (XXIV) has again been prepared from (XXIII) by reacting with diazomethane and characterized. Wolff-rearrangement[20] in dioxan and water, using silver oxide as catalyst, gave anthraquinonyl-2-acetic acid (XVI).

Newman and Beal found that the Wolff-rearrangement of α-diazoketones in methanol to the corresponding esters by the normal method, using silver oxide, gave different yields when repeated on the same compound for no apparent reason.[21] Hence, they developed an improved method to conduct the Wolff-rearrangement in a

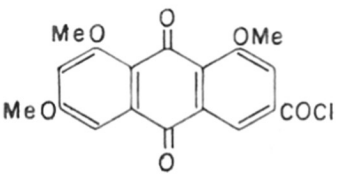
homogeneous medium. This consisted of treating the diazoketone in methanol with silver benzoate in triethylamine. In the present work the conversion of anthraquinonyl-2-diazoketone (XXIV) to anthraquinonyl-2-acetic acid methyl ester was done by both methods, and in this case the method of Newman and Beal was found not to offer any special advantage over the normal method.

For the synthesis of the tetramethyl ether-ester of 1,6,8-trihydroxyanthraquinonyl-3-acetic acid (XXIX) emodin was the starting material and it was obtained starting from 1,8-dinitro-2-methylanthraquinone following a method reported from this laboratory[22] and also from chrysarobin. Chrysarobin is a product obtained from Araroba or Goa powder (a deposit found in the wood of Andira Araroba Aguiar) by extraction with solvents and it has been found that it contains chrysophanol, physcion and emodin accompanied by other products.[23] A method reported for the isolation of emodin from chrysarobin consists of reduction, demethylation and acetylation of chrysarobin, followed by dissolution of the acetylated product in a specified quantity of acetic acid and cooling when chrysophanic acid-9-anthranol triacetate separated. This was filtered and the filtrate after dilution gave a precipitate which was oxidized with chromic acid

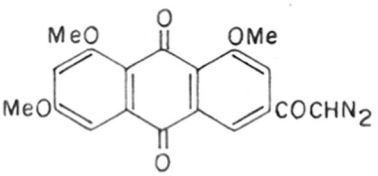
(0.34 g/gm of precipitate) in acetic acid. The resulting triacetyl emodin was deacetylated with ethanolic KOH to get emodin.[24]



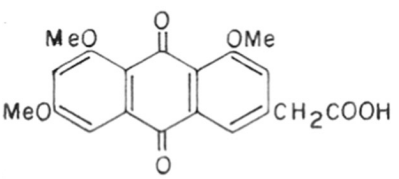
XXV



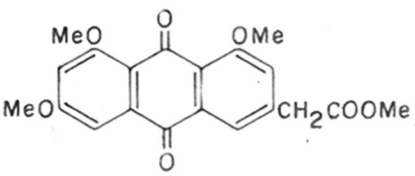
XXVI



XXVII



XXVIII



XXIX

Now a method less tedious than the above method and the other methods recorded has been adopted for the isolation of emodin. Chrysarobin was oxidized with chromic acid in acetic acid to convert all the anthranols to the corresponding quinones. The oxidized product was treated with a melt of sodium chloride and aluminium chloride at 160° for 10 min to get the hydroxy compounds from the corresponding methyl ethers.

Extraction with cold 10 per cent sodium carbonate solution removed only emodin from the mixture. The emodin so obtained was acetylated and oxidized with chromic acid in acetic acid and acetic anhydride at 55-60° to get emodic acid. This on methylation with dimethyl sulphate in acetone containing anhydrous potassium carbonate gave the so far unreported tetramethyl ether-ester of emodic acid, which was saponified with alcoholic KOH to give (XXV). Treatment of (XXV) with thionyl chloride gave the corresponding acid chloride (XXVI) which on condensation with diazomethane yielded 1,6,8-trimethoxyanthraquinonyl-3-diazoketone (XXVII). Wolff-rearrangement on this diazoketone, using silver oxide as catalyst, gave 1,6,8-trimethoxyanthraquinonyl-3-acetic acid (XXVIII). By conducting the Wolff-rearrangement of the diazoketone (XXVII) in methanol the ether-ester (XXIX) was obtained, m.p. 228-230°, and it depressed the m.p. of the tetramethyl ether-ester of natural endocrocin, m.p. 225-226° (kindly supplied by Professor Shibata) to 208-210°.

While this work was in progress, Shibata[14] reported further evidence in support of structure (II) for endocrocin in a private communication to K. Venkataraman. He obtained an authentic sample of the methyl ether of isocochenillic acid from Mühlemann[26] and proved its

identity with the ether obtained as a degradation product from endocrocin.

Later Franck[16] also found additional evidence in support of structure (II) by measuring the proton resonance spectrum and the pK_a value (in 70 per cent methanol) of endocrocin. The proton resonance spectrum of endocrocin showed three methyl protons and three aromatic protons. The pK_a value (at 20°) of endocrocin in 70 per cent methanol was found to be 4.2 for the carboxyl group and 7.6 for the hydroxyl groups. Under the same conditions the pK_a values of phenylacetic, salicylic (for the carboxyl group) and benzoic acids were found to be 5.6, 3.9 and 5.5 respectively.

No satisfactory explanation for the high carbonyl frequency of the carboxyl group in endocrocin seems to be possible at this stage.

The synthesis of the structure (II) is described in Part III of the thesis.

TABLE 1. INFRARED SPECTRA OF SOME ANTHRAQUINONE CARBOXYLIC ACIDS, ACETIC ACIDS AND THEIR DERIVATIVES IN NUJOL

Substitution in anthraquinone	Principal absorption bands in cm-1					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
None		1675S 1570M	1333S 1300W	1284S 1209W 1160M	1098W 970M 940S	812S 690W
1-COOH	2640W 2550W	1668VS 1571S	1372S 1326S	1280S 1246W 1193W 1179W 1163MS 1149S	1079W 978S 948W 940W 920MS	837M 809S 784M 742M 707S 695M
2-COOH	2650W	1685VS 1589VS	1484W 1415W 1313W	1287MS 1255W 1174S 1152M 1131M 1128W	1086M 992M 974S 969W 948W 937VS	893W 869S 796VS 769S 700S
1,2-$(COOH)_2$	(3534M)	1701M 1672M 1585VS	1312W	1271S 1232M 1176W 1156W	1031W 990W 970W 961W	806M 775M 736M 714S
1-OH-3-Me-2-COOH	2660W	1670S 1633S 1583VS	1357VS	1297S 1261S 1215W 1190W 1167MS	1077MS 1050M 1035W 997S	898M 885W 867W 827W 824W 802M 795W 785W 754M 735M 713MS
1,3-$(OH)_2$-2-COOH (Munjistin)		1669W 1620M 1570S	1410W 1337M	1287VS 1230W 1205W 1163MS 1101W	1096M 1079S 1061W 1033M 1009W 983S 917S	874W 827W 815W 786W 746S 717S

TABLE 1 (Contd.)

Substitution in anthraquinone	Principal absorption bands in cm^{-1}					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
1,8-$(OH)_2$-3-COOH (Rhein)	2667W	1692VS 1634MS 1617S 1590S	1307VS	1266W 1190W 1156W	1098W 1075S 1053M 1004S 943W 900M	847S 820M 813M 781W 769W 752M 735M 709W
1,6,8-$(OH)_3$-3-COOH (Emodic acid)	3340 3180 2360W	1704S 1616S 1561W 1542W	1348W 1329	1266S 1209S 1169S 1152W 1103M	1025M 999W 914M 899M 884M	772W 757M
1-OH-5-COOH	2645W 2550W	1672M 1630M 1575MS	1335W	1273MS 1240W 1200M	1085W 1030W 990W	890M 772W 710M 697W
1-OH-2,4-$(NO_2)_2$-5-COOH	3078W 2627W 2400M	1705M 1680W 1645M 1588W 1530S	1410W 1357W	1267MS 1240M 1187M 1150S	1095S 1052S 1005S 918W	897MS 872W 845W 802S 784MS 760W 730M 708W
1-OAc-3-COOH	2695W	1770VS 1695MS 1672M 1613M 1587VS	1323S	1295VS 1266W 1206S 1163W 1100W	1091W 1053M 1031S 1005M 976M 940W 934S 915S	869M 847M 826MS 800S 775W 756W 740S 714VS 704W

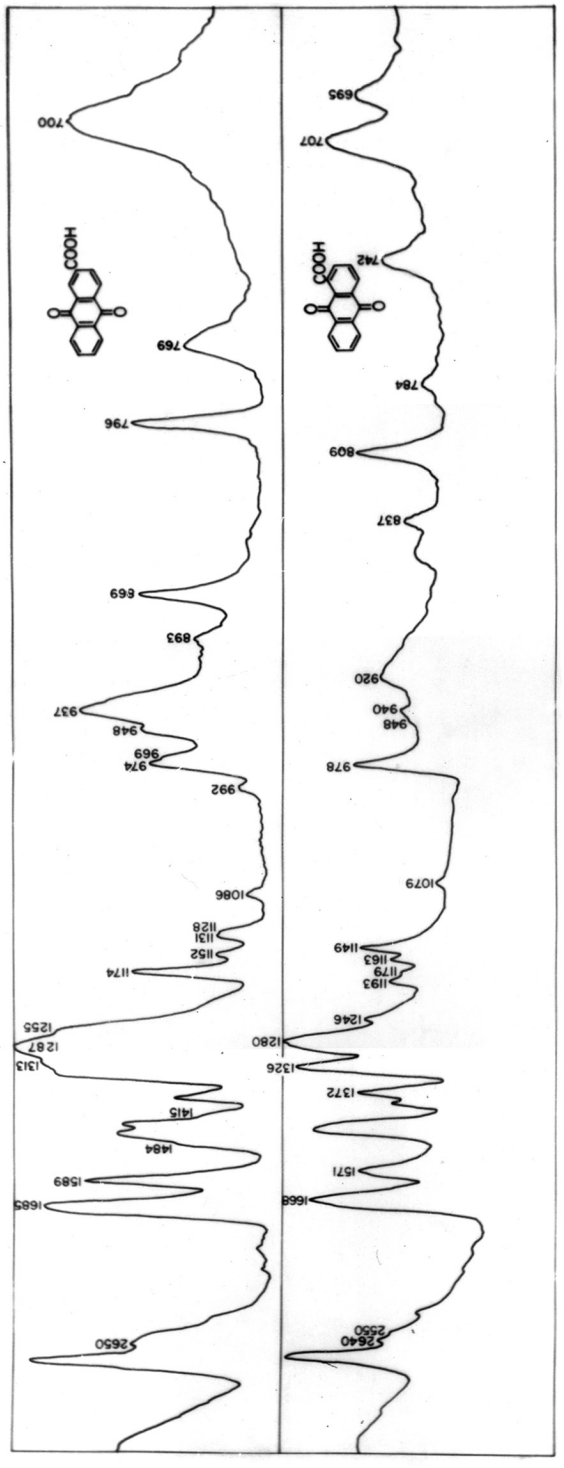
TABLE 1 (Contd.)

Substitution in anthraquinone	Principal absorption bands in cm^{-1}					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
1-NH_2-2-COOH	3448S 3333S 2703W	1667VS 1623VW 1587S 1563W 1543W	1316W	1266M 1163W 1143M	1042W 1026W 980W 954M 900M	854MS 793W 769W 740M 714S
1-NH_2-4-Br-2-COOH	3448M 3333W 2667W	1695W 1669W 1631VW 1587W 1538S	1333M	1232M 1149MS	1093M 1042M 1020M 961W 901S	854W 826W 793S 763W 740W 719M 699W
1-Cl-2-COOH	2632W	1695M 1669W 1587VS	1312W	1282M 1250W 1170VS 1149W 1124W	1085W 990W 970M 952W 943S	892W 806W 800VS 769W 699VS
6-Cl-1-COOH	2695W	1692W 1667VS 1575S	1316MS	1282W 1235W 1189M 1170W 1156W 1149M 1111W	1075M 1000MS 970W 934MS 909S	869W 854MS 840VS 800W 769W 740S 714VS
3-NO_2-1-COOH		1709W 1669VS 1608W 1575S 1538S	1348W 1319M	1276MS 1182W 1163W	1042W 1000S 950W 934M 909MS	806W 790W 740W 709MS 694W 680W
6-NO_2-1-COOH	3534MS 2646W	1718VS 1672VS 1605S 1567S 1534VS	1351W 1330S	1282M 1235M 1190W 1176M 1163M 1143W 1124W	1075W 1000W 961W 934M	877M 840MS 800M 781M 763W 740M 714S 684W

TABLE 1 (Contd.)

Substitution in anthraquinone	Principal absorption bands in cm^{-1}					
	3500-2000	2000-1500	1500-1300	1300-1100	1100-900	900-650
2-CH_2COOH		1708M 1680S 1570S 1540M	1327S	1290S 1240W 1155W	988M 967W 929S	838W 815W 793W
1-OH-2-CH_2COOH	2660W	1729VS 1668M 1639M 1589S	1396W 1341W 1329W	1297M 1286M 1262W 1228M 1195M 1186W 1181W	1043W 1032M 1001M 988W 938W	893M 862M 837M 819W 790W 775M 755S 717MS
1,6,8-$(OMe)_3$-3-COOMe (Emodic acid methyl ether-ester)	2325W	1711S 1660S 1589S 1561W	1334S	1240W 1225W 1190W 1172M 1150W 1104S	1071S 1042W 1009S 980S 956M 923W 903M	883W 871S 840S 775M 750S 722W
1,6,8-$(OMe)_2$-3-Me-2-COOMe (Endocrocin methyl ether-ester)	2895M	1726M 1660M 1591S	1453M 1406M 1327S	1298W 1254S 1172S 1146M 1120W	1089S 1039M 994M 948M	899W 847W 835W
2-CH_2COOMe	2645W	1732VS 1675VS 1587VS	1345M 1321S	1294S 1265M 1220S 1180S 1156W	1015S 993M 956S 923W 915M	889W 874S 856W 845W 824S 791W 778W 758W 741W 726M
2,2'-Dianthraquinonyl-1,1'-$(COOH)_2$	2703W	1667VS 1587VS 1550	1325W 1302M	1269M 1212W 1159VS 1111S	1020W 1016W 975S 925W	877S 833W 806M 763M 722VS 689W

V = Very. S = Strong. M = Medium. W = Weak.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796
669
893
937
948
969
974
992
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1128
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1287
1313
1415
1484
1589
1685
2650
COOH
695
707
742
784
809
837
920
940
948
978
1079
1149
1163
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1193
1246
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1326
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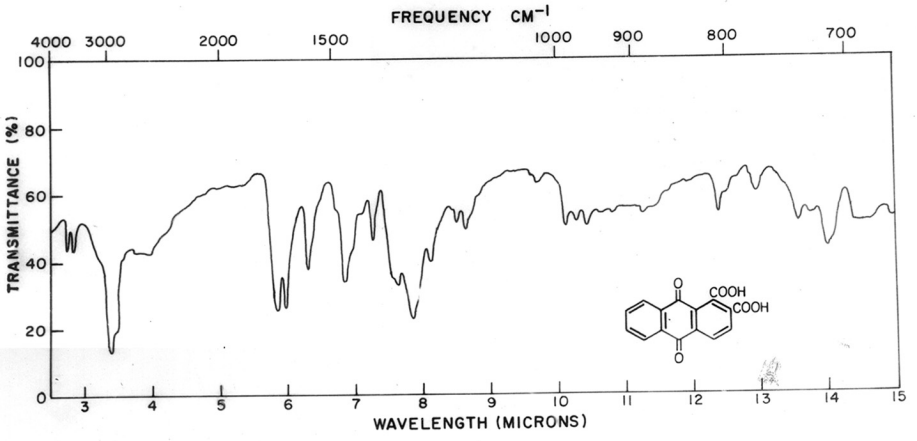
1571
1668
2550
2640

Fig.1

Fig.2

Fig.3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80
60
40
20
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TRANSMITTANCE (%)
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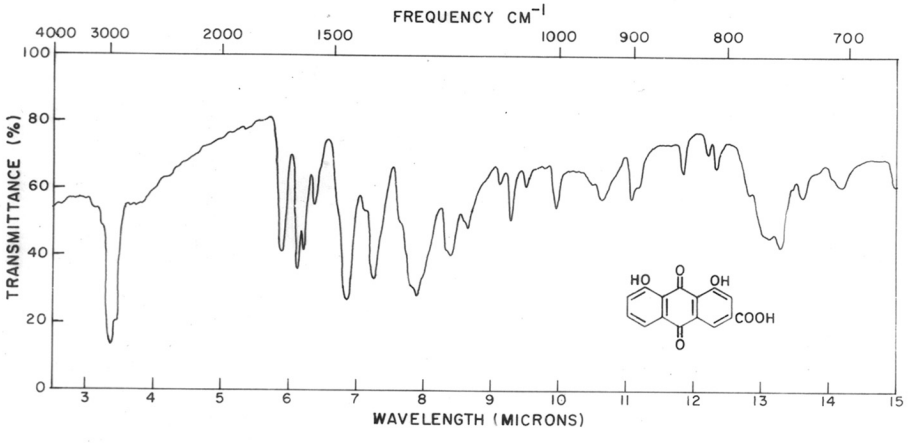
WAVELENGTH (MICRONS)
O
COOH
COOH
O

Fig.4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80
60
40
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TRANSMITTANCE (%)
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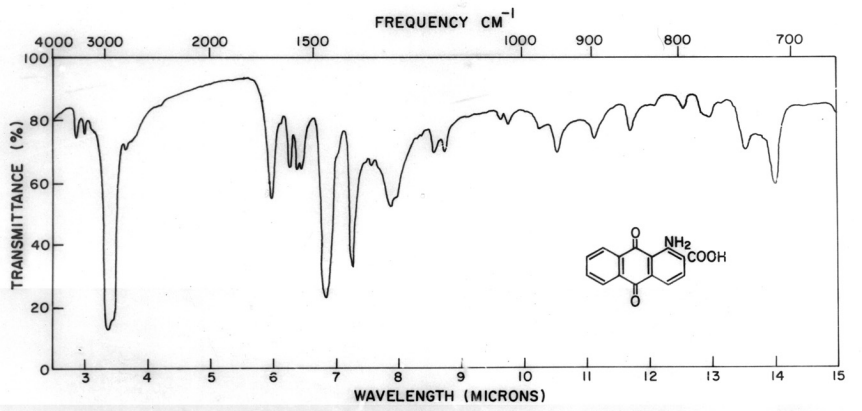
WAVELENGTH (MICRONS)
HO
O
OH
COOH
O

Fig. 5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100
80
60
40
20
0
TRANSMITTANCE (%)
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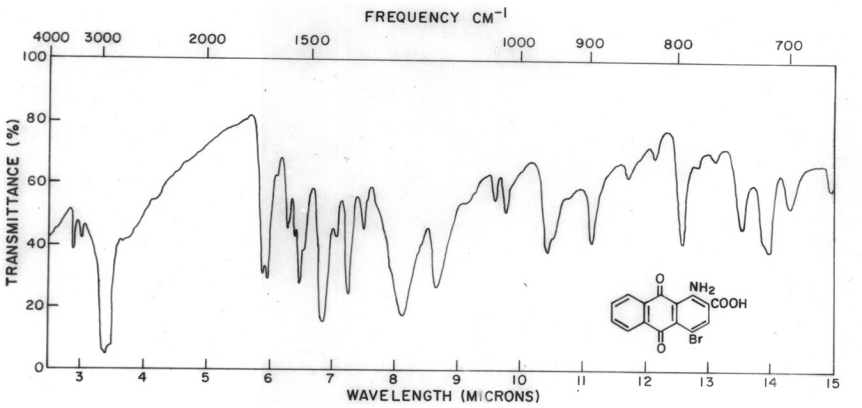
WAVELENGTH (MICRONS)
O
NH2
COOH
O

Fig. 6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80
60
40
20
0
TRANSMITTANCE (%)
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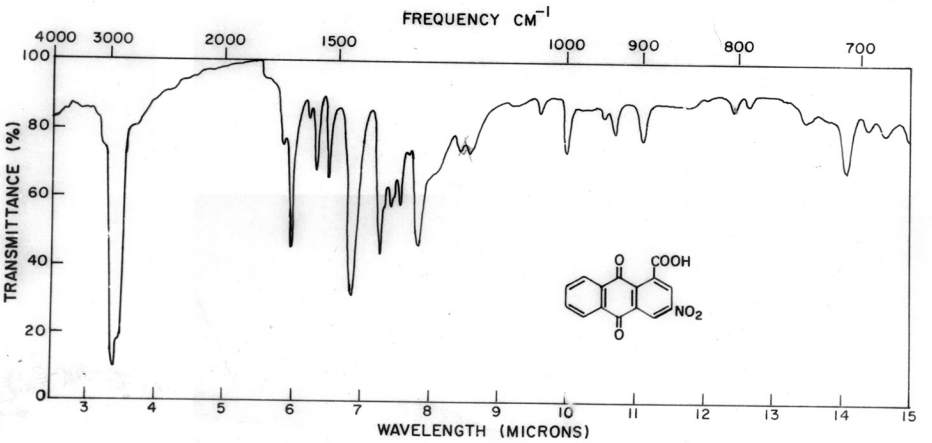
WAVELENGTH (MICRONS)
O
NH2
COOH
Br
O

Fig.7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TRANSMITTANCE (%)
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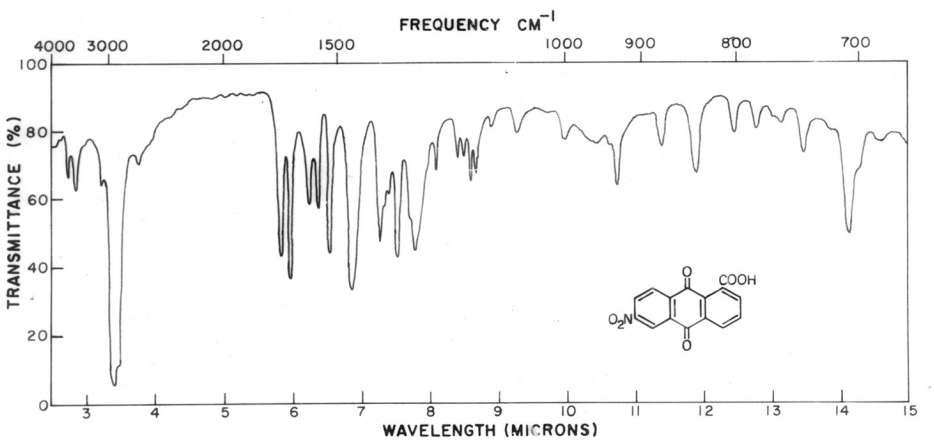
WAVELENGTH (MICRONS)
COOH
NO2
O
O

Fig.8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TRANSMITTANCE (%)
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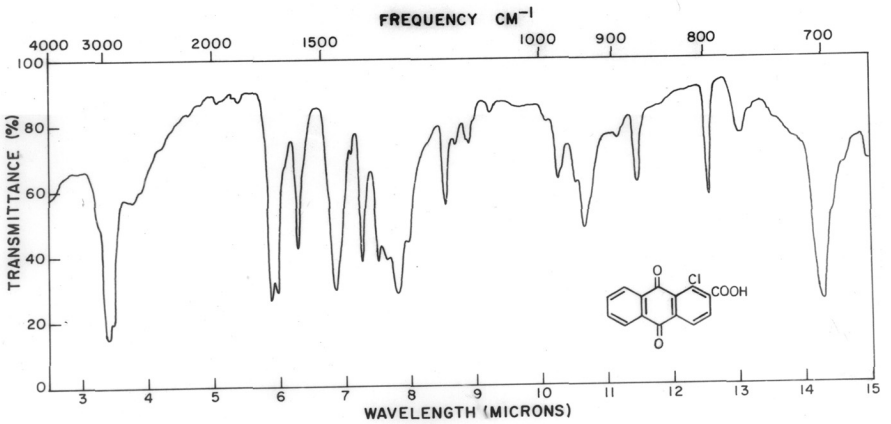
WAVELENGTH (MICRONS)
COOH
O2N
O
O

Fig. 9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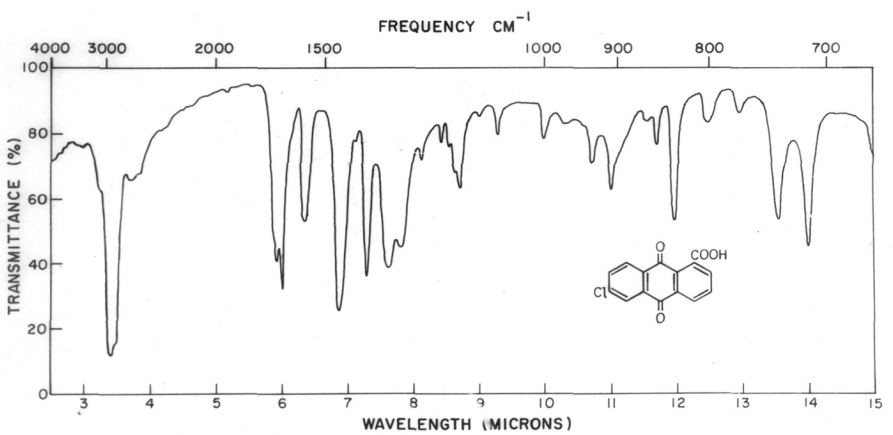
WAVELENGTH (MICRONS)
O
Cl
COOH
O

Fig. 10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TRANSMITTANCE (%)
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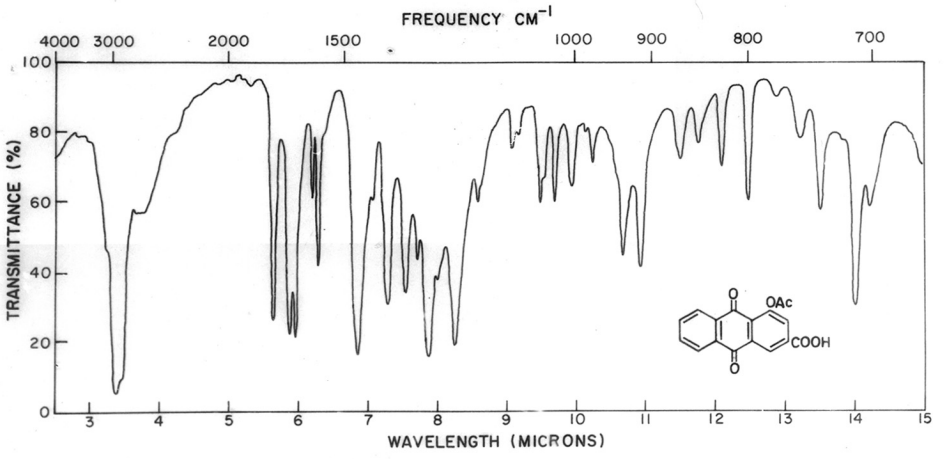
WAVELENGTH (MICRONS)
O
COOH
Cl
O

Fig. 11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TRANSMITTANCE (%)
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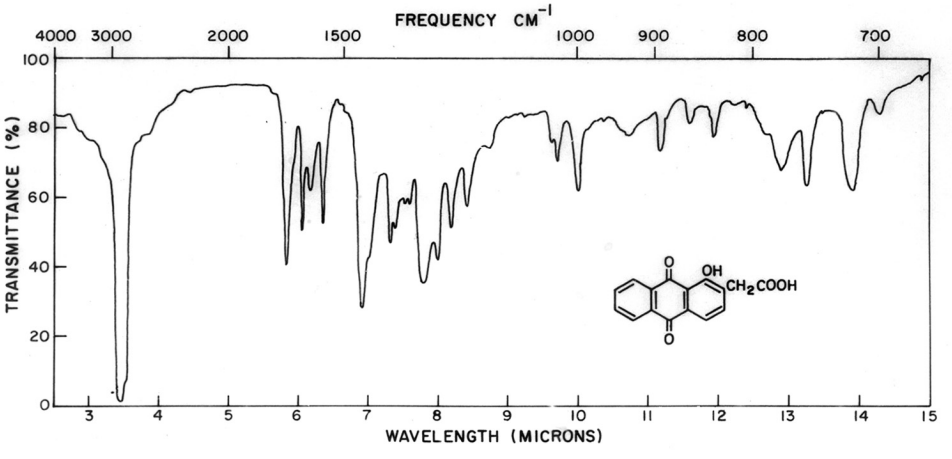
WAVELENGTH (MICRONS)
OAc
COOH

Fig. 12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TRANSMITTANCE (%)
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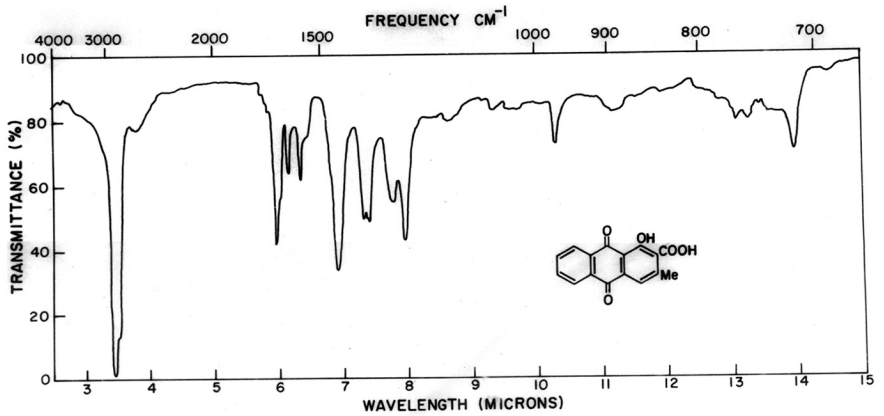
WAVELENGTH (MICRONS)
OH
CH2COOH

Fig. 13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60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
OH
COOH
Me
O

Experimental

Infrared investigations

The infrared spectra of anthraquinone carboxylic acids recorded were done on Perkin-Elmer 137 infracord spectrophotometer and Grubb-Parsons double beam infrared spectrophotometer, fitted with NaCl prism. Because of the poor solubility of the anthraquinone carboxylic acids in the usual solvents, they were examined as paraffin mulls. All the compounds examined were analytically pure.

1-Hydroxy-5-chloroanthraquinone (XIX)

This was prepared by the diazotization of 1-amino-5-chloroanthraquinone and boiling the diazonium salt solution with sulphuric acid at 130-140°, m.p. 221-222° (lit.[18] m.p. 221-222°).

1-Hydroxy-5-cyanoanthraquinone (XX)

1-Hydroxy-5-chloroanthraquinone (1 g) and dry cuprous cyanide (0.42 g; 1.2 mole) in dimethylformamide (30 ml) were refluxed for 4 hr, after which the product was cooled and poured into water (60 ml). Hydrated ferric chloride (1.2 g) and conc HCl (5 ml) were added and kept at 60-70° for 20 min. The product was then filtered, washed and dried (0.8 g). Crystallization

from gl acetic acid gave grey crystals, m.p. 286-288°. (Found: C, 72.5; H, 3.0; N, 5.6. $C_{15}H_7O_3N$ requires: C, 72.3; H, 2.8; N, 5.6%).

1-Hydroxyanthraquinone-5-carboxylic acid (XXI)

1-Hydroxy-5-cyanoanthraquinone (0.7 g) was dissolved in sulphuric acid (7.2 ml) and water (2.4 ml) was added under stirring. The mixture was refluxed for 5 min and cooled, and water (15 ml) was added. The separated product was filtered, washed and extracted with a 5% solution of sodium bicarbonate, filtered and washed. The filtrate and the washings were acidified with HCl and the separated carboxylic acid was filtered, washed neutral and dried (0.5 g). Crystallization from gl acetic acid gave yellow needles, m.p. 255-258° (decomp). (Found: C, 67.1; H, 2.8. $C_{15}H_8O_5$ requires: C, 67.2; H, 3.0%). The product dissolved in sodium bicarbonate with a brown colour.

1-Hydroxy-2,4-dinitroanthraquinone-5-carboxylic acid (XXII)

1-Hydroxyanthraquinone-5-carboxylic acid (0.4 g) was dissolved in conc H_2SO_4 (10 ml) and cooled to 0-5°. Fuming nitric acid (1.1 ml) was added under stirring when the yellow dinitro compound started separating.

After $\frac{1}{2}$ hr under the same conditions, the product was poured over crushed ice, filtered, washed neutral and dried (0.45 g). Crystallization from gl acetic acid gave yellow shining needles, m.p. 278-280°. (Found: C, 50.8; H, 1.5; N, 7.5. $C_{15}H_6O_9N_2$ requires: C, 50.3; H, 1.7; N, 7.8%).

1-Hydroxy-2,4-dinitroanthraquinone

1-Hydroxy-2,4-dinitroanthraquinone-5-carboxylic acid (0.05 g) was heated above its m.p. in a dry test-tube on a metal-bath until no more yellow sublimate collected on the top sides of the test-tube. The sublimate was washed down with gl acetic acid from which it was crystallized as yellow needles, m.p. 245-246° (lit.[29] m.p. 246-248°). The mixed m.p. with an authentic sample prepared from 1-hydroxyanthraquinone was undepressed.

1-Hydroxy-2,4-diaminoanthraquinone-5-carboxylic acid

1-Hydroxy-2,4-dinitroanthraquinone (0.2 g) was dissolved in pure dioxan (20 ml) and hydrogenated at 28° at atm pressure under stirring with 6 moles of hydrogen, using palladium charcoal (0.02 g) as catalyst. The first 3 moles were taken up in $2\frac{1}{2}$ hr and the remaining 3 moles in $4\frac{1}{2}$ hr. When the hydrogenation

was over, the violet solution was filtered and the catalyst washed repeatedly with dioxan. The solvent was removed and the residue (0.12 g) crystallized from gl acetic acid as dark violet needles, m.p. above 360°. (Found: C, 60.2; H, 3.5; N, 9.2. $C_{15}H_{10}O_5N_2$ requires: C, 60.4; H, 3.4; N, 9.4%).

Anthraquinonyl-2-diazoketone (XXIV)

Anthraquinone-2-carboxylic acid-chloride (6 g) was dissolved in sodium dry dioxan (20 ml), dry ether (20 ml) added and cooled to 0°. The acid chloride solution was added to diazomethane (5.1 g) in ether (80 ml) under stirring in 10 min when a yellow precipitate of the diazoketone started separating. The reaction was kept overnight at 0° and then for 3 hr at room temp. Gl acetic acid (8 ml) was added dropwise to destroy the excess diazomethane and the yellow precipitate was collected and washed with ether (5.5 g), m.p. 165°(decomp). The product crystallized from benzene-petrol (1:1) mixture in pale yellow needles (5.2 g), m.p. 177°(decomp). (Found: C, 69.7; H, 3.0; N, 10.0. $C_{16}H_8O_3N_2$ requires: C, 69.5; H, 2.8; N, 10.2%).

Anthraquinonyl-2-acetic acid (XVI)

Anthraquinonyl-2-diazoketone (0.5 g) was dissolved in dioxan (20 ml) and warmed to 50-60°. Silver oxide (0.25 g) as a slurry in a small amount of water was added slowly to the diazoketone solution at this temperature, when evolution of nitrogen took place. The temperature was then raised to 80° and maintained at this temperature for 3 hr and the mixture was filtered and residue washed with dioxan (10 ml). The filtrate and washings were poured on ice and the colourless precipitate was filtered, washed with water and sucked dry. The acid was extracted with 10% sodium carbonate solution (10 ml), filtered, and the filtrate acidified with dil HNO_3. The precipitated acid was filtered, washed free of acid, dried and crystallized from acetic acid (0.3 g), m.p. 236-237°. (Found: C, 71.8; H, 3.8. $C_{16}H_9O_4$ requires: C, 72.2; H, 3.8%).

Anthraquinonyl-2-acetic acid methyl ester

(a) By the normal method. Anthraquinonyl-2-diazoketone (0.2 g) was dissolved in methanol (50 ml). Silver oxide (0.1 g) was made into a slurry in methanol (4 ml) and this slurry was added to the diazoketone solution under stirring in the course of 10 min at 55-60°. After the addition the mixture was refluxed for $\frac{1}{2}$ hr, filtered off, and the residue washed repeatedly with

methanol. The filtrate and the washings were distilled off to dryness and the residue on crystallization from ethanol gave colourless needles (0.12 g), m.p. 160°. (Found: C, 72.4; H, 4.4. $C_{17}H_{12}O_4$ requires: C, 72.8; H, 4.3%).

(b) By the method of Newman and Beal.[21] Anthraquinonyl-2-diazoketone (0.2 g) was dissolved in methanol (20 ml) and silver benzoate (0.05 g) in triethylamine (2 g) was added to it at room temp (silver benzoate was prepared by mixing equivalent solutions of silver nitrate and sodium benzoate), when the mixture became black with evolution of nitrogen. As soon as the evolution of nitrogen slackened, fresh addition of silver benzoate solution was made and a total of 0.1 g of silver benzoate was added in 2 hr. The mixture was then heated under reflux for a few minutes, norit added and filtered. The solvent was removed and the product on crystallization from ethanol gave colourless needles (0.12 g), m.p. 160°, and the mixed m.p. with the ester by the previous method was not depressed.

Emodin from chrysarobin

Chrysarobin (20 g) was taken in a round-bottom flask fitted with a condenser and chromium trioxide (10 g)

in gl acetic acid (150 ml) and water (15 ml) was added, keeping the temperature of the mixture below 20° during addition. When the addition was over, the mixture was heated on a steam-bath for 3 hr, after which it was cooled and poured into water. The product which separated out was filtered, washed and dried (19 g).

This product (19 g) was added to anhydrous aluminium chloride:sodium chloride (95 g: 19 g) melt and kept at 160° under stirring for 10 min. The product was cooled and treated with ice, water and hydrochloric acid, when a greenish yellow product separated. This was filtered, washed and the cake was taken in cold 10% sodium carbonate solution (250 ml). After stirring for a few min, the extract was filtered. The residue was washed with water and the filtrate and washings were acidified with dil hydrochloric acid. The separated brown precipitate was filtered, washed and dried (2 g). Crystallization from acetic acid gave orange needles, m.p. 254-256° (Oesterle, Johann[27] 255°). Mixed m.p. with authentic sample of emodin was undepressed.

Emodic acid

Triacetyl-emodin was prepared by the acetylation of emodin (1.5 g) with acetic anhydride and a few drops of perchloric acid and crystallized from benzene, m.p.

196-197° (Oesterle, Johann[27] 197°). Oxidation of triacetyl-emodin following the reported method[25] gave triacetyl-emodic acid, crystallized from acetic acid, m.p. 208-210° (lit.[25] m.p. 210-211°). Deacetylation with ethanolic 5% KOH gave emodic acid, crystallized from acetic acid, m.p. 357° (lit.[28] m.p. 360°).

Emodic acid trimethyl ether methyl ester

Emodic acid (2.0 g) in dry acetone was refluxed with anhydrous potassium carbonate (10 g) and dimethyl sulphate (5 ml) for 20 hr. The mixture was filtered and the potassium carbonate was washed with hot acetone (100 ml). The filtrate and the washings were distilled off to dryness and the residue on crystallization from benzene gave yellow needles (2.0 g), m.p. 256°. (Found: C, 64.4; H, 5.0. $C_{19}H_{16}O_7$ requires: C, 64.0; H, 4.5%). The de-esterification was done by taking this product in 5% ethanolic potassium hydroxide (50 ml) and heating on a water-bath for 4 hr. On acidification emodic acid trimethyl ether separated, which was filtered, washed and dried (1.7 g). Crystallization from gl acetic acid gave pale yellow microscopic needles, m.p. 267° (lit.[28] m.p. 270°).

Emodic acid-chloride-trimethyl ether (XXVI)

Trimethyl ether of emodic acid (1.5 g) was dissolved in thionyl chloride (20 ml) and the solution was refluxed for 2 hr. The thionyl chloride was removed under vacuum and the yellow crystalline product on recrystallization from benzene-pet ether (40-60° (1:1) gave pale yellow needles (1.1 g), m.p. 188°. (Found: C, 60.2; H, 3.3. $C_{18}H_{13}O_6Cl$ requires: C, 60.0; H, 3.6%).

1,6,8-Trimethoxyanthraquinonyl-3-diazoketone (XXVII)

Trimethyl ether of emodic acid chloride (1 g) was dissolved in dry dioxan (15 ml), ether (20 ml) and cooled to 0°. To this solution was added dropwise at 0° a solution of diazomethane (1.1 g) in ether (20 ml) during 10 min, when a yellow precipitate of the diazoketone started separating out. The reaction mixture was allowed to stand overnight at 0° and then at room temp for 3 hr. The precipitate was filtered, washed with ether and sucked dry (0.5 g). It crystallized from benzene as yellow needles (0.4 g), m.p. 208°. (Found: C, 62.6; H, 3.2; N, 7.6. $C_{19}H_{14}O_6N_2$ requires: C, 62.3; H, 3.8; N, 7.6%).

1,6,8-Trimethoxyanthraquinonyl-3-acetic acid methyl ester (XXIX)

1,6,8-Trimethoxyanthraquinonyl-3-diazoketone (0.1 g) was dissolved in methanol (25 ml). Silver oxide (0.05 g) was added to methanol (4 ml) and this was added to the diazoketone solution in methanol in the course of 10 min at 55-60°. After the addition, the mixture was refluxed for $\frac{1}{2}$ hr, filtered, and the residue washed thoroughly with methanol. The filtrate and the washings were distilled off to dryness and the residue crystallized from benzene as greenish-yellow needles (0.04 g), m.p. 228-230°. (Found: C, 64.5; H, 4.5. $C_{20}H_{18}O_7$ requires: C, 64.9; H, 4.9%). Mixed m.p. with a sample of natural endocrocin methyl ether ester was 208-210°.

1,6,8-Trimethoxyanthraquinonyl-3-acetic acid (XXVIII)

1,6,8-Trimethoxyanthraquinonyl-3-diazoketone (0.1 g) was dissolved in dioxan (10 ml) and silver oxide (0.05 g) as a slurry in a small amount of water was added at 55-60° under stirring. After addition in about 30 min the temperature was raised to 98° and maintained for 4 hr. The mixture was filtered, the dioxan removed under vacuum, and the residue extracted with benzene. After removal of the benzene, the residue was crystallized from methanol as yellow needles (0.05 g), m.p. 243-245°. (Found: C, 63.5; H, 4.8. $C_{19}H_{16}O_7$ requires: C, 64.0; H, 4.5%).

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PART III

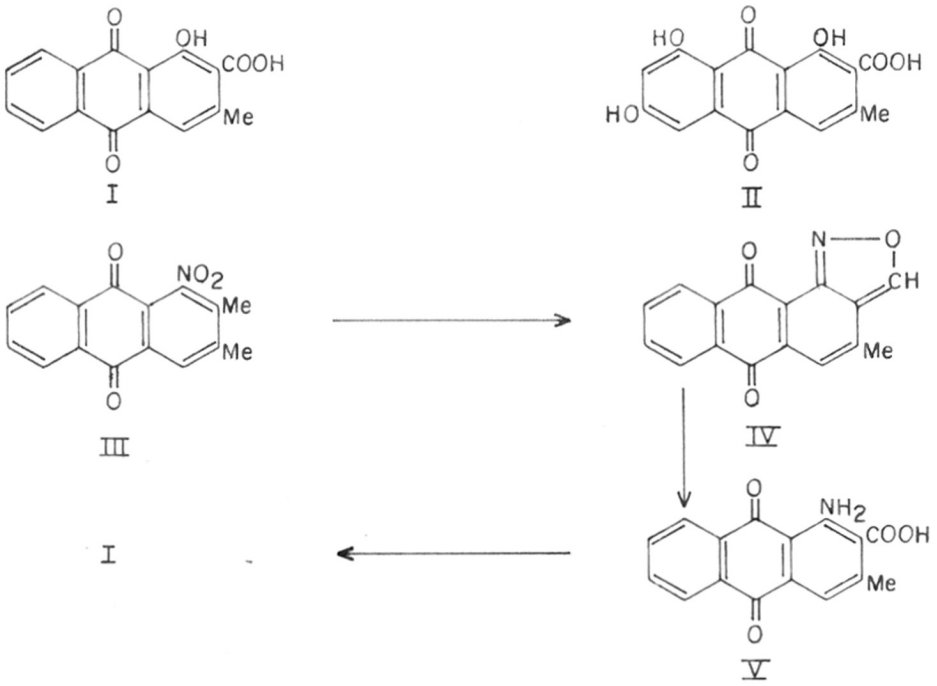
(a) EXPLORATORY WORK FOR THE SYNTHESIS OF ENDOCROCIN; A NEW SYNTHESIS OF 1-HYDROXY-3-METHYLANTHRAQUINONE-2-CARBOXYLIC ACID

and

(b) THE SYNTHESIS OF ENDOCROCIN, 1,6,8-TRIHYDROXY-3-METHYLANTHRAQUINONE-2-CARBOXYLIC ACID

(a) Exploratory Work for the Synthesis of Endocrocin; A New Synthesis of 1-Hydroxy-3-methylanthraquinone-2-carboxylic Acid

Though 1,6,8-trihydroxy-3-methylanthraquinone-2-carboxylic acid (II) was found to be the only possible structure for endocrocin, its confirmation by synthesis seemed desirable. In order to devise a suitable method for introducing a carboxyl group in the desired position in the anthraquinone nucleus, the synthesis of 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (I) was taken up as an exploratory work.



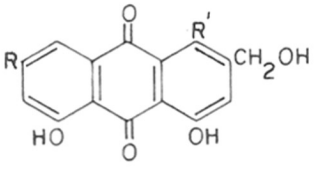
In the previous method reported for the synthesis of (I)[1] 1-nitro-2,3-dimethylanthraquinone (III) was heated with aluminium chloride-sodium chloride melt at 160° to get the corresponding isoxazole (IV). The isoxazole (IV) was hydrolyzed to the amino carboxylic acid (V) with ethanolic 40 per cent potassium hydroxide at the boil. Diazotization of (V) and boiling the diazonium salt solution with 40 per cent sulphuric acid gave 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (I).

In the present work, for the conversion of (III) to the corresponding isoxazole (IV), the use of polyphosphoric acid, anhydrous aluminium chloride in a solvent and 20 per cent oleum, has been investigated. While (III) remained unaffected with polyphosphoric acid at 170° for 4 hours, it gave a 25 per cent yield of (IV) when refluxed for 1 hour with anhydrous aluminium chloride in tetrachloroethane. Methanolic baryta at the boil was found to give the best results in the hydrolysis of the isoxazole (IV) to the amino carboxylic acid (V). This acid on diazotization and hydrolysis gave (I), m.p. 176° (lit.[1] m.p. 176°).

For the new synthesis of (I), 1-amino-2,3-dimethylanthraquinone[1] was the starting material. Replacement of the amino group by hydroxyl via the diazonium salt

gave 1-hydroxy-2,3-dimethylanthraquinone (VI), which on acetylation with acetic anhydride and a few drops of perchloric acid yielded 1-acetoxy-2,3-dimethylanthraquinone (VII).

N-Bromosuccinimide (NBS) has been used extensively for the bromination of methylene and methoxyl groups including the side-chain bromination of aromatic hydrocarbons.[2] But probably the first application to an anthraquinone derivative was the bromination of rubiadin diacetate to the corresponding 2-bromomethylanthraquinone, which then led to lucidin.[3] This method was later used for the synthesis of aloe-emodin[4] (XI), citreorosein[4] (XII), telochistin[5] or fallacinol[6] (XIII) and tritisporin[7] (XIV) from the acetyl derivatives of chrysophanol, emodin, physcion and catenarin respectively. In these cases the importance of the molar proportion of the brominating agent was not realised.



XI, R = H; R' = H

XII, R = OH; R' = H

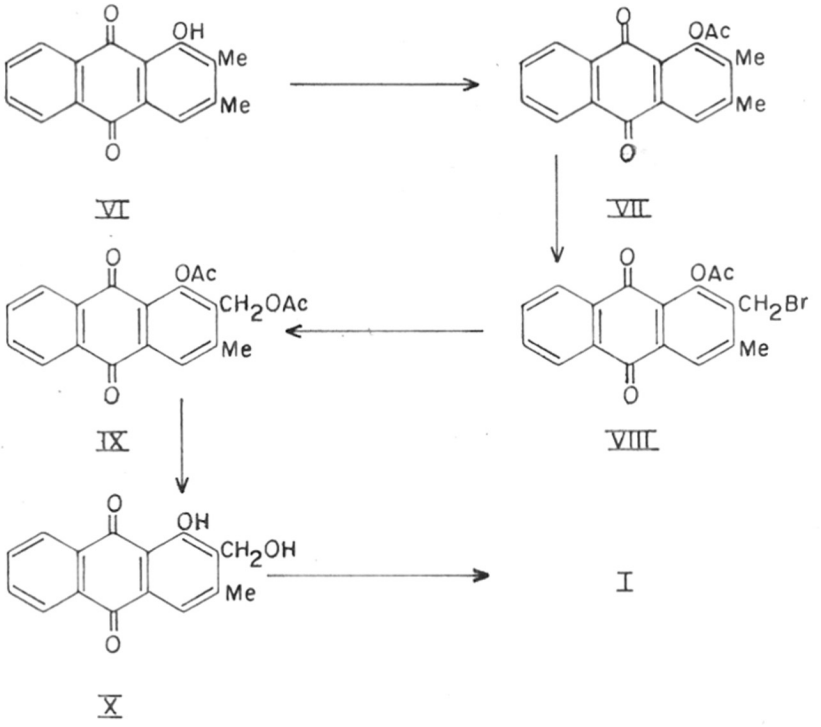
XIII, R = OMe; R' = H

XIV, R = OH; R' = OH

Ayyangar[1] has reported that for one mole of 1-acetoxy-3-methylanthraquinone, when two moles of NBS were used, the product was 1-acetoxy-3-dibromomethyl-

anthraquinone while the use of exactly one mole of NBS for one of 1-acetoxy-3-methylanthraquinone gave the pure mono bromo compound.

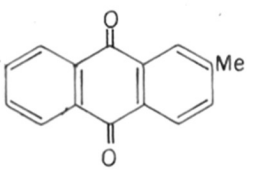
In the present work the NBS method of ω-bromination was done on 1-acetoxy-2,3-dimethylanthraquinone (VII), where a number of different ω-brominated products are possible. However the use of one mole of NBS for one mole of 1-acetoxy-2,3-dimethylanthraquinone resulted in 1-acetoxy-2-bromomethyl-3-methylanthraquinone (VIII) as the major product. This on refluxing with sodium acetate and acetic anhydride gave 1-acetoxy-2-acetoxy-methyl-3-methylanthraquinone (IX), which on hydrolysis in methanol with a few drops of sulphuric acid yielded (X). The alcohol (X) on oxidation with silver oxide gave (I), m.p. 176°, in 60 per cent yield. The mixed m.p. with the acid of authentic structure obtained by the previous method (through the isoxazole) was undepressed. This was also confirmed by the identity of their infrared spectra. The infrared spectrum of the carboxylic acid (I) (Part II; Fig. 13) showed absorption bands at 2660 cm^{-1} (OH stretching of carboxylic acid), 1670 cm^{-1} (unchelated carbonyl not distinguishable from the aromatic carboxylic acid) and 1633 cm^{-1} (chelated carbonyl). The electronic absorption spectrum of (I) is given in Fig. 1.



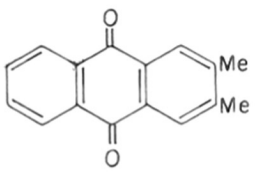
(b) The Synthesis of Endocrocin, 1,6,8-Trihydroxy-3-methylanthraquinone-2-carboxylic acid

On the basis of the exploratory work the routes that were conceived for the synthesis of endocrocin (II) could be divided into two types, viz. (1) involving at some stage the formation of an isoxazole ring between a nitro and a methyl group ortho to each other in the anthraquinone nucleus, and (2) utilizing at an intermediate step the possibility of ω-brominating preferentially the methyl group ortho to an acetoxyl group in a compound similar to 1-acetoxy-2,3-dimethylanthraquinone (VII). The structure (II) for endocrocin has now been confirmed by the synthesis of its tetramethyl ether-ester following two routes.

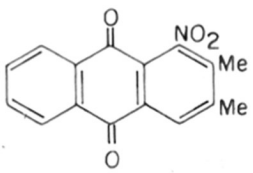
The first successful route to endocrocin, utilizing the isoxazole formation as a method to introduce the carboxyl group in the required position, started with the nitration of 2,3-dimethylanthraquinone (XV) which behaved differently from anthraquinone and 2-methylanthraquinone (XVII). The nitration of anthraquinone requires rather more drastic conditions than in the case of hydrocarbons, heating with mixed acid at 50-75° being necessary. Since the reactivities of the two benzene rings in the anthraquinone nucleus are largely independent of each other, exclusive mononitration is not possible and in fact considerable amounts of 1,5- and 1,8-dinitroanthraquinones are simultaneously formed. Pure α-nitroanthraquinone is therefore difficult to prepare, except by several crystallizations or by vacuum distillation.[8] On the other hand the mononitration of 2-methylanthraquinone (XVII) requires much milder conditions (nitration in monohydrate at 0° using potassium nitrate) and forms 82 per cent of 1-nitro-2-methylanthraquinone (XVI).[9] The mononitration of 2,3-dimethylanthraquinone (XV) gave 1-nitro-2,3-dimethylanthraquinone (III) in 85 per cent yield by doing the nitration at 0°, using potassium nitrate for nitration.[1,20]



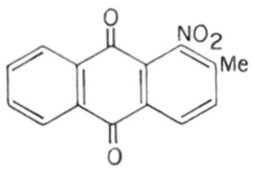
XVII



XV



III

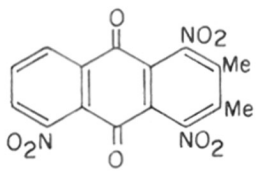


XVI

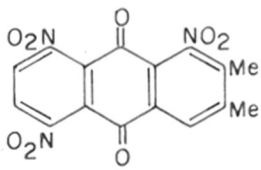
Among the mononitroanthraquinones, 1-nitroanthraquinone and (XVI) behave similarly on further nitration, which can be done by treatment with excess of fuming nitric acid. Both give the corresponding 1,5- and 1,8-dinitro compounds and they can be separated, utilizing their differential solubilities in monohydrate and glacial acetic acid.

But, when further nitration of 1-nitro-2,3-dimethyl-anthraquinone (III) was done following the same conditions as in the case of the nitration of (XVI), using excess of nitric acid (1.4 to 1.5 mole), the resulting product was found to contain a trinitrodimethylanthraquinone along with 1,5- and 1,8-dinitrodimethylanthraquinones (XXIV and XXV). This was detected by reduction of the crude nitration product with sodium sulphide and chromatographing the reduction product in toluene over alumina, when a violet

band appeared above the pink and red bands of 1,8-diamino-2,3-dimethylanthraquinone and 1,5-diamino-2,3-dimethylanthraquinone respectively. By using more than 2 moles of nitric acid for the nitration of (III) or using more than 3 moles for the nitration of (XV) it was possible to get this trinitro compound in 65-70 per cent yield. The pure trinitro-dimethylanthraquinone was got by crystallization of the crude nitrated product from nitrobenzene. Reduction with sodium sulphide gave the corresponding triamino compound.

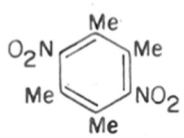


XVIII

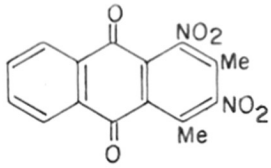


XIX

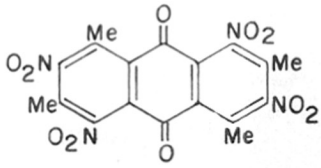
The structure of the trinitro compound has been fixed as (XVIII). Since this trinitroanthraquinone could be got in high yields by using excess of nitric acid in the nitration of (XV) or (III), and because of the well-known tendency of a nitro group to enter the α-position in the anthraquinone nucleus, the possible structures for it could be only (XVIII) or (XIX).



XX

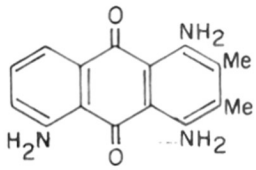


XXI



XXII

Durene gives on nitration 3,6-dinitro-1,2,4,5-tetramethylbenzene (XX),[10] the para nitration being owing to the directing effect of the methyl groups. Two nitro groups entering in the same benzene ring of the anthraquinone nucleus, meta to each other, is found in 2,4-dimethyl-1,3-dinitroanthraquinone (XXI)[11] and 2,4,6,8-tetramethyl-1,3,5,7-tetranitroanthraquinone (XXII),[12] in the anthraquinone series. Both the structures possible for the trinitrodimethylanthraquinone got in the present work, involve para nitration (probably reported for the first time in the anthraquinone series), and the structure (XVIII) has been assigned for this, considering the directing influence of the methyl group in the 3-position. The corresponding triamino compound got the structure (XXIII).



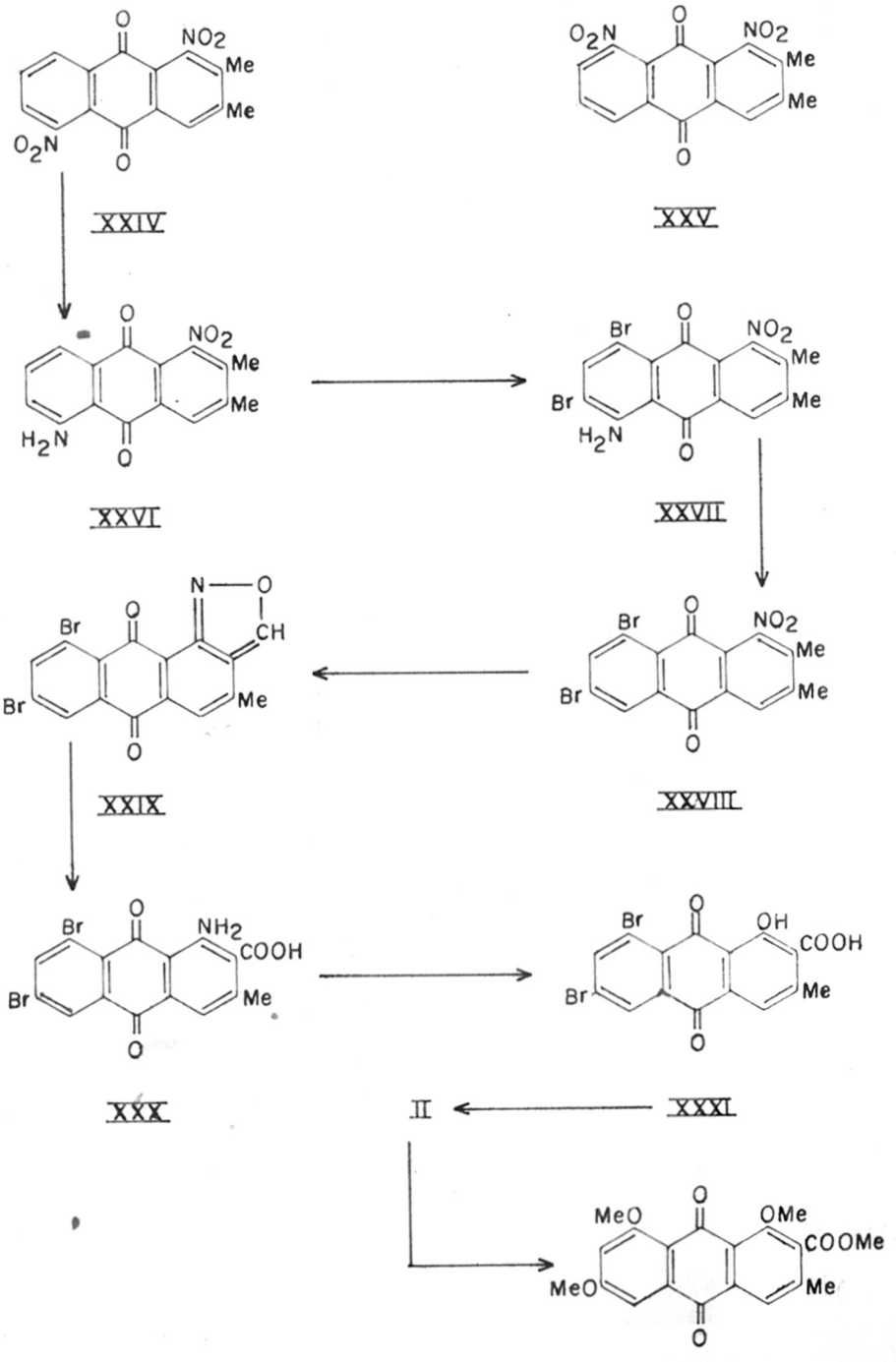
XXIII

During the course of these nitration experiments it was found that 1,5-dinitro-2,3-dimethylanthraquinone, when refluxed with benzyl alcohol for 1 hr, oxidizes benzyl alcohol to benzaldehyde. 1,5-Diamino-2,3-dimethylanthraquinone was isolated from the reaction mixture. The

suitability of dinitroanthraquinones as oxidizing agents in other oxidation reactions is under investigation.

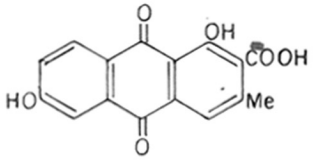
The dinitration of 2,3-dimethylanthraquinone (XV) with only 2 moles of nitric acid (d, 1.5) (to avoid the formation of XVIII) gave a mixture of 1,5-dinitro- and 1,8-dinitro-2,3-dimethylanthraquinones (XXIV and XXV) which could be separated easily by their differential solubilities in conc sulphuric acid and glacial acetic acid. Partial reduction of (XXIV) by short boiling with dimethylaniline, a reaction applied earlier to the partial reductions of 1,5- and 1,8-dinitroanthraquinones,[13] gave 1-nitro-2,3-dimethyl-5-aminoanthraquinone (XXVI) in 50 per cent yield. The monoamine (XXVI) separated out of dimethylaniline in crystalline form, and further purification was not found necessary before proceeding to the next step. The constitution (XXVI) was confirmed by deamination to 1-nitro-2,3-dimethylanthraquinone (III). Bromination of (XXVI) with excess of bromine in glacial acetic acid at 98-100° gave the dibromo compound (XXVII), which on deamination through the diazonium salt gave 1-nitro-2,3-dimethyl-6,8-dibromoanthraquinone (XXVIII). The corresponding isoxazole (XXIX) was prepared by treatment of (XXVIII) with 20 per cent oleum for 12 hours at 25-30°. The hydrolysis of the isoxazole (XXIX) was done separately

CHART I

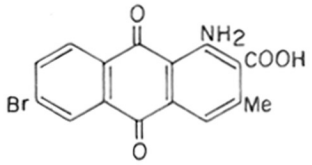

XXIV
XXV
XXVI
XXVII
XXVIII
XXIX
XXX
XXXI
II
ENDOCROCIN
Trimethyl ether methyl ester

with 40 per cent ethanolic potassium hydroxide and methanolic baryta at the reflux. In both these cases the amino carboxylic acid (XXX) was accompanied by a monobromo compound. Diazotization and hydrolysis by boiling with 40 per cent sulphuric acid yielded the corresponding ∝-hydroxy compound (XXXI), but again accompanied by a monobromo compound. When this mixture was treated with lime under pressure at 220° for 24 hours using copper powder as catalyst, the major product was 1,6-dihydroxy-3-methylanthraquinone-2-carboxylic acid (XXXII) as its infrared, ultraviolet and visible spectra were similar to 1,6-dihydroxyanthraquinone, rather than endocrocin or emodin. The presence of small amounts of endocrocin was indicated from the elementary analysis and from the colour reactions. However, when the replacement of the bromine atoms was done at 220° for 24 hours with calcium hydroxide under pressure using copper oxide as catalyst, a product was obtained which, on complete methylation and chromatography in benzene over alumina, gave an ether ester, m.p. 223-225°, which did not depress the m.p. of the ether ester of natural endocrocin, 225-226°. This methyl ether ester on demethylation with

anhydrous aluminium chloride and sodium chloride at 140° for 5 minutes gave endocrocin, m.p. 310-320° (decomp), having all the properties of the natural pigment.

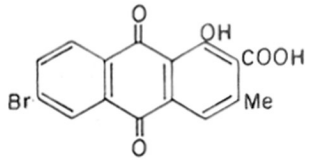


XXXII

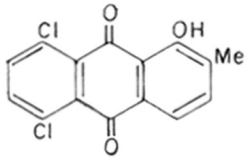


XXXIII

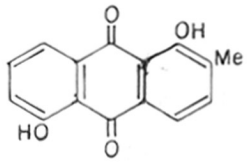
In the above synthesis of endocrocin, probably during the hydrolysis of the isoxazole (XXIX), partly the ∝-bromine got replaced by hydrogen resulting in a mixture of (XXX) and 1-amino-3-methyl-6-bromoanthraquinone-2-carboxylic acid (XXXIII). This mixture was carried over in the corresponding ∝-hydroxy compound which had the required compound (XXXI) accompanied by 1-hydroxy-3-methyl-6-bromoanthraquinone-2-carboxylic acid (XXXIV).



XXXIV



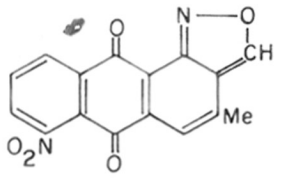
XXXV



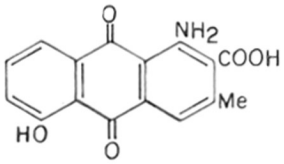
XXXVI

Marriott and Robinson,[14] after a number of experiments (with lime under pressure, baryta, etc.) on the replacement of halogen atoms in 1-hydroxy-2-methyl-5,8-dichloroanthraquinone (XXXV), found that in every case the major product was 1,5-dihydroxy-2-methylanthraquinone (XXXVI) and that only traces of 1,5,8-trihydroxy-2-methylanthraquinone were indicated. In the case of the mixture containing (XXXI) and (XXXIV), lime under pressure with copper catalyst replaced the α-bromine by hydrogen resulting in 1,6-dihydroxy-3-methylanthraquinone-2-carboxylic acid (XXXII) as the major product. However, when copper oxide was used in place of copper as catalyst in the lime under pressure reaction, probably the reduction accompanying the hydrolysis was suppressed and the major product was endocrocin (II).

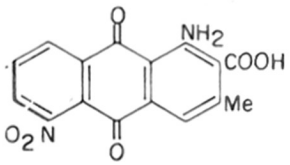
Another route which was examined for the synthesis of endocrocin started again with 1,5-dinitro-2,3-dimethylanthraquinone (XXIV). The corresponding isoxazole (XXXVII) was prepared from (XXIV) by treatment with 20 per cent oleum at 25-30°. The hydrolysis of the isoxazole with alcoholic potash gave 1-amino-3-methyl-5-hydroxyanthraquinone-2-carboxylic acid (XXXVIII) and not the required product (XXXIX). The action of methanolic baryta also did not give the desired product.



XXXVII



XXXVIII



XXXIX

The other successful route for the synthesis of endocrocin involved preferential ω-bromination as an intermediate step and 1-nitro-2,3-dimethyl-5-aminoanthraquinone (XXVI) was the starting material. The monoamine on diazotization and boiling with 40 per cent sulphuric acid gave 1-nitro-2,3-dimethyl-5-hydroxyanthraquinone (XL).

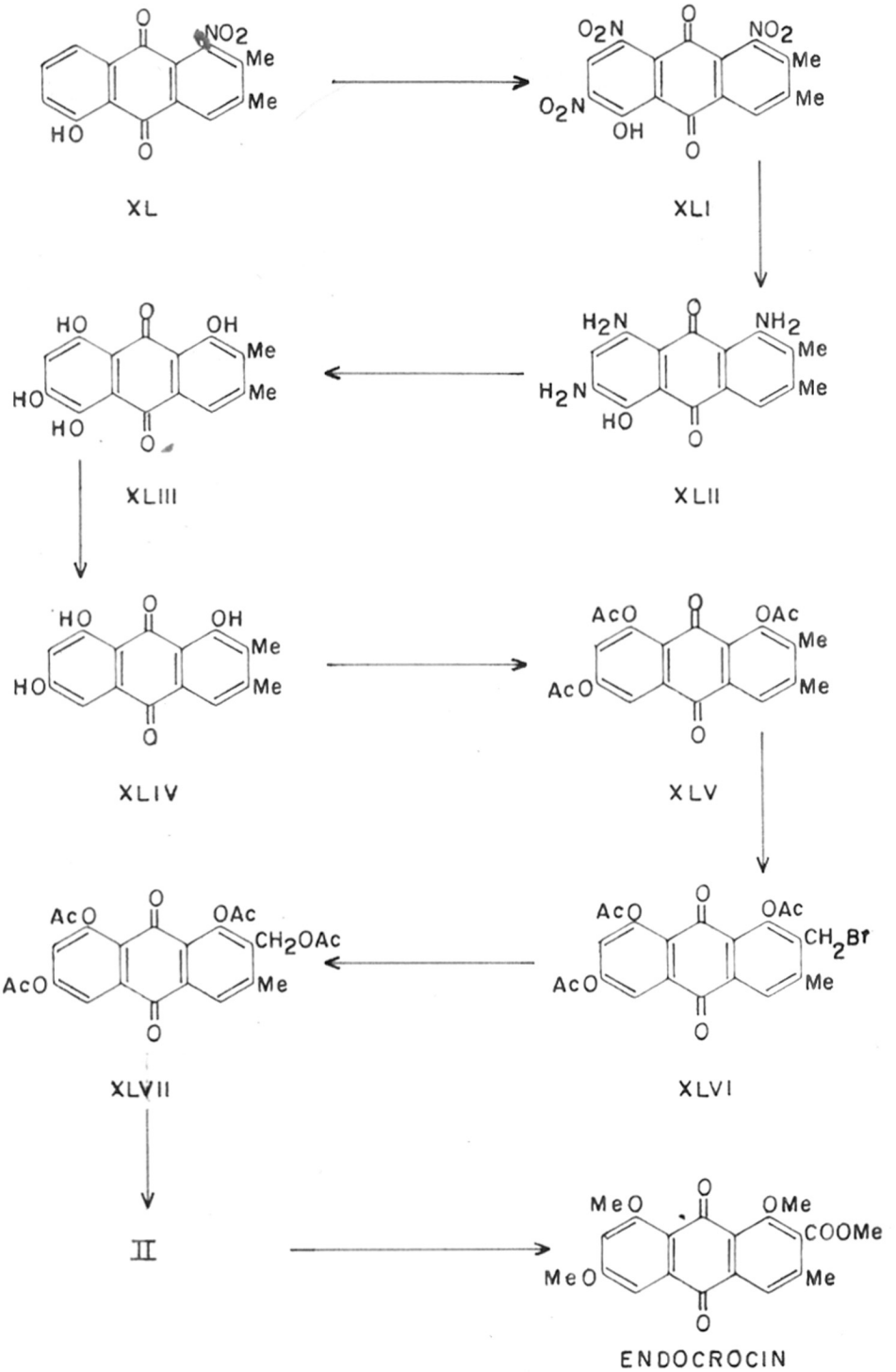
Halogenation of aminoanthraquinones, deamination via the diazonium salts and the replacement of halogen by hydroxyl or methoxyl followed by demethylation, have been explored earlier as a general method for the synthesis of hydroxyanthraquinones.[15,16] In the present work it is found that in the case of the synthesis of certain hydroxyanthraquinones having hydroxyl groups in 2,4-positions, their introduction in the anthraquinone nucleus can be

equally conveniently effected by the following general method, viz. nitration of a suitably substituted anthraquinone, reduction, replacement of the amino by hydroxyl, dinitration, reduction, hydrolysis through the corresponding bis-diazo compound, vatting and reoxidation.

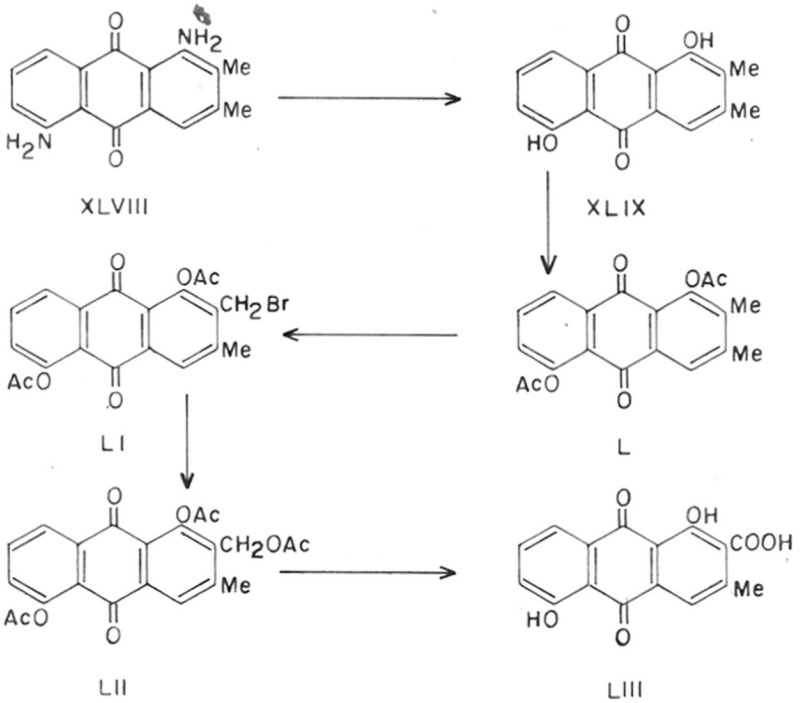
1-Hydroxy-2,4-dinitroanthraquinone[17] was prepared by nitrating 1-hydroxyanthraquinone in sulphuric acid monohydrate with fuming nitric acid. In the present work the synthesis of purpurin was undertaken to explore the suitability of the above general method in the synthesis of endocrocin. 1-Hydroxy-2,4-dinitroanthraquinone was prepared by heating 1-aminoanthraquinone with conc nitric acid following the method reported by Jayaraman.[18] Reduction with Raney nickel and hydrazine hydrate gave 1-hydroxy-2,4-diaminoanthraquinone, which on bis-diazotization and short boiling with 40 per cent sulphuric acid yielded purpurin.

1-Nitro-2,3-dimethyl-5-hydroxyanthraquinone (XL), prepared by diazotization of (XXVI) and boiling the diazonium salt with dilute sulphuric acid, was dinitrated with fuming nitric acid and the trinitro compound (XLI) was obtained. This 1,6,8-trinitro-2,3-dimethyl-5-hydroxyanthraquinone could also be prepared by heating the monoamino compound (XXVI) with conc nitric acid. Reduction of (XLI) with excess of sodium sulphide yielded the corresponding triamino compound (XLII), which

CHART II


XL
XLI
XLII
XLIII
XLIV
XLV
XLVI
XLVII
II
ENDOCROCIN
Methyl ether methyl ester

on tris-diazotization and boiling with 40 per cent sulphuric acid gave 1,5,6,8-tetrahydroxy-2,3-dimethyl-anthraquinone (XLIII). Vatting and reoxidation yielded 2-methyl emodin (XLIV). The corresponding triacetoxy compound (XLV) was ω-brominated with one mole of N-bromosuccinimide to give (XLVI) as the major product. This mixture on boiling with acetic anhydride and sodium acetate gave again a mixture containing 1,6,8-triacetoxy-2-acetoxymethyl-3-methylanthraquinone (XLVII) as the major product. This on treatment with silver oxide in alkali got deacetylated and oxidized to endocrocin (II) having all the properties of the natural compound and endocrocin prepared through the previous route. This was methylated with dimethyl sulphate and anhydrous potassium carbonate in acetone and the methyl ether ester was chromatographed in benzene over alumina and the ether ester was crystallized from benzene, m.p. 225-226°. It did not depress the m.p. of the ether ester of natural endocrocin (kindly supplied by Professor Shibata) and the ether ester of endocrocin of authentic structure prepared by the isoxazole route in Chart 1. The natural and synthetic ether esters had superposable infrared spectra (taken in nujol).



Another route examined for the synthesis of endocrocin (II) was starting from 1,5-diamino-2,3-dimethylanthraquinone (XLVIII). Diazotization and hydrolysis gave the corresponding dihydroxy compound (XLIX), which was acetylated to give (L). ω-Bromination of 1,5-diacetoxy-2,3-dimethylanthraquinone (L) with 1 mole of N-bromosuccinimide yielded 1,5-diacetoxy-2-bromomethyl-3-methylanthraquinone (LI) as the major product. This mixture on heating with sodium acetate and acetic anhydride gave (LII), which with silver oxide in alkali was converted to 1,5-dihydroxy-3-methylanthraquinone-2-carboxylic acid (LIII). Attempts to get the corresponding 6,8-dinitro compound by nitration of (LIII) with nitric acid, were unsuccessful.

FIG. I

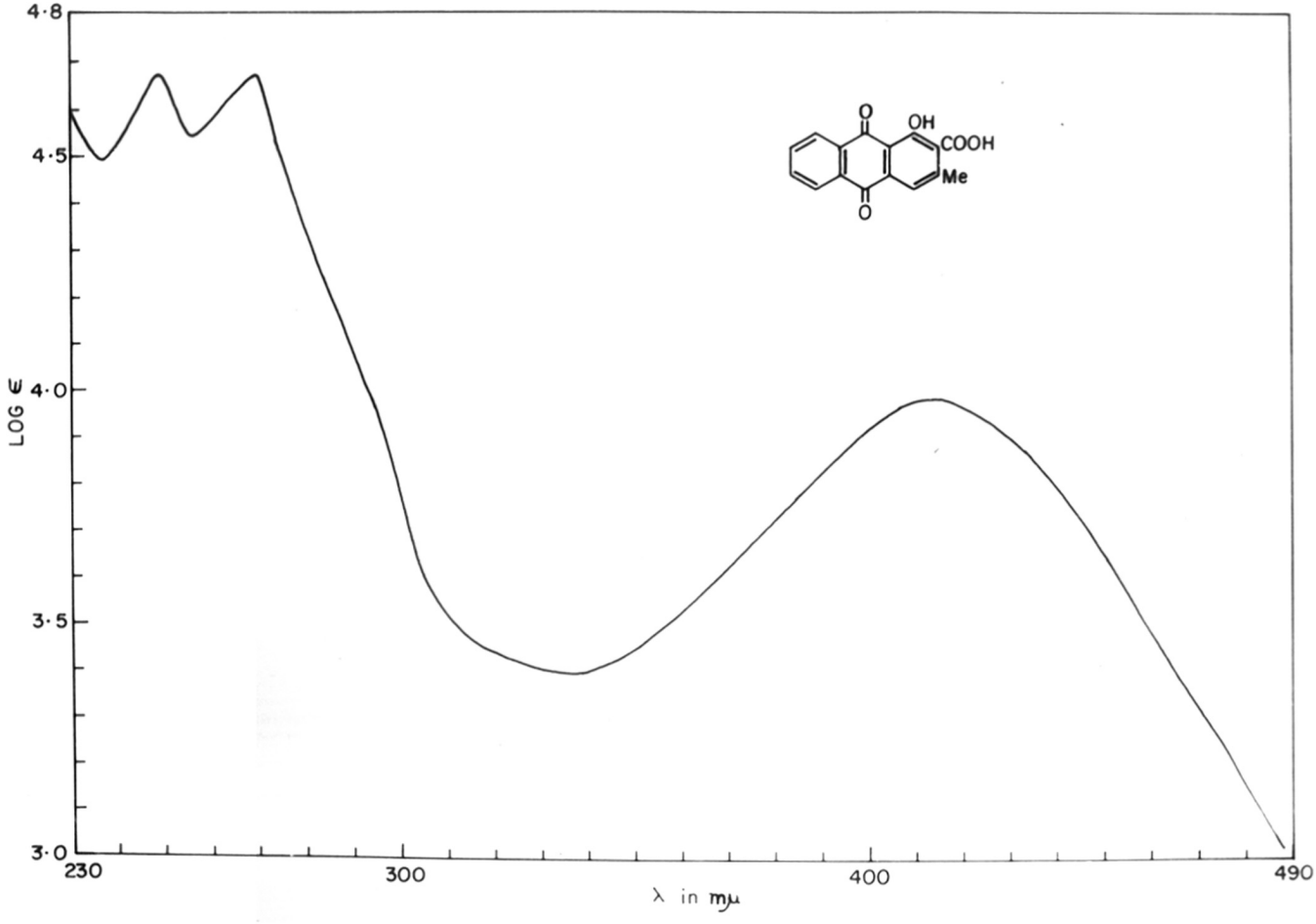
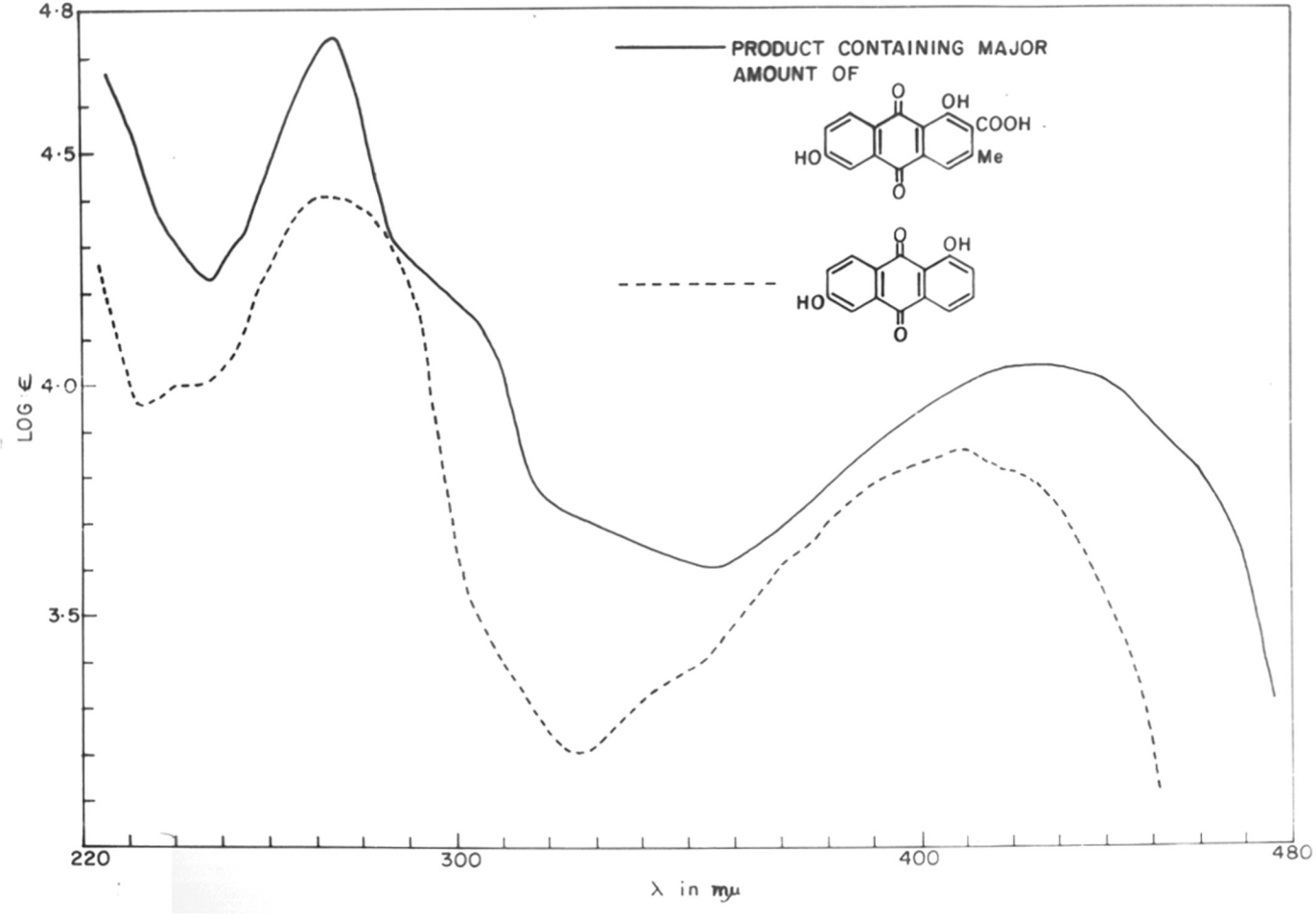
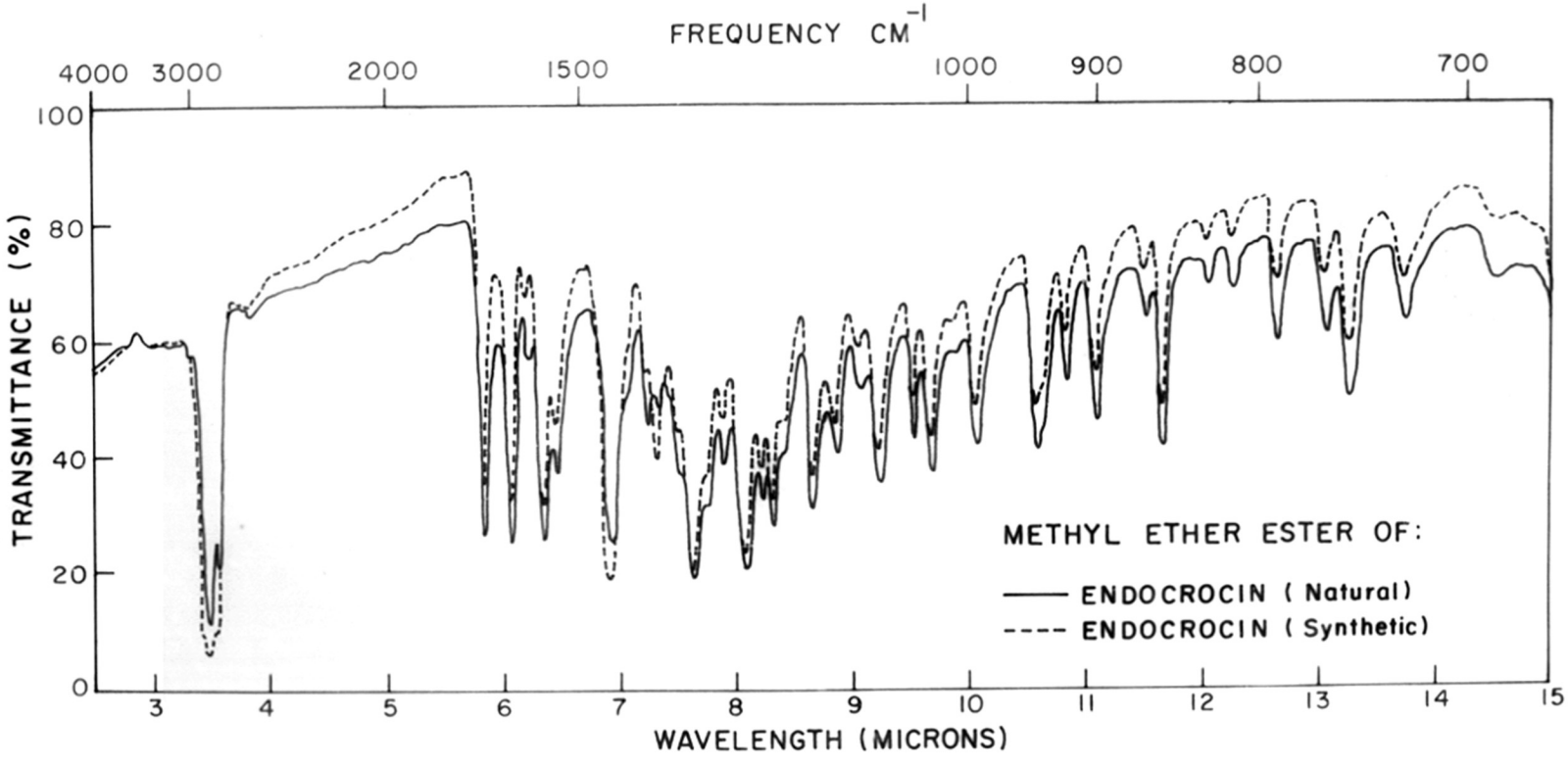


FIG. II


4·8
4·5
4·0
3·5
LOG ε
220
300
400
480
λ in mμ
PRODUCT CONTAINING MAJOR AMOUNT OF
O
OH
COOH
HO
Me
O
O
OH
HO
O


FREQUENCY CM⁻¹
4000 3000 2000 1500 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
METHYL ETHER ESTER OF:
ENDOCROCIN (Natural)
ENDOCROCIN (Synthetic)

Experimental

2,3-Dimethylanthraquinone (m.p. 208°)

This compound 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 acetic acid.[19]

1-Nitro-2,3-dimethylanthraquinone (m.p. 252°) (III)

This was prepared by nitration of 2,3-dimethylanthraquinone in sulphuric acid with potassium nitrate at 0° and crystallization of the mononitro compound from gl acetic acid.[1,20]

3-Methylanthraquinone-1,2-isoxazole (IV)

(a) Using aluminium chloride in tetrachloroethane. 1-Nitro-2,3-dimethylanthraquinone (3 g) was dissolved in dry tetrachloroethane (100 ml), and anhydrous aluminium chloride (15 g) was added in 15 min. The mixture was refluxed for 1 hr more and then the product was cooled and drowned in ice water (200 ml) containing conc

hydrochloric acid (15 ml). The tetrachloroethane was removed by steam-distillation and the product was filtered, washed and dried (2.6 g). The crude isoxazole was dissolved in hot xylene, from which it separated out in amorphous though pure form (0.4 g), m.p. 250° (decomp) (lit.[1] m.p. 250° decomp.) (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%).

(b) Using 20% oleum. 1-Nitro-2,3-dimethylanthraquinone (2 g) was added to 20% oleum (20 ml) under stirring at 25°. (It was necessary to cool the reaction mixture in ice during addition). The solution was left overnight at the same temperature, after which it was poured over crushed ice, filtered, washed free of acid and dried (1.8 g). The crude isoxazole was purified by dissolving in hot xylene from which it separated out in an amorphous though pure form (0.3 g). The substance did not exhibit a sharp m.p., but decomposed at 250° and was identical with the isoxazole prepared by method (a).

(c) Attempted preparation using polyphosphoric acid. 1-Nitro-2,3-dimethylanthraquinone (2 g) was added to polyphosphoric acid (prepared from 20 g of 80% o-phosphoric acid and 20 g of phosphorus pentoxide), kept heated on a water-bath under vigorous stirring.

After the addition was complete, the temperature was raised to 170° by heating on an oil-bath and maintained at this temperature for 3 hr. Then the reaction mixture was cooled, poured into water, filtered, washed with hot water and dried (1.92 g), m.p. 250°. The product was identical with 1-nitro-2,3-dimethylanthraquinone (mixed m.p. 250°).

1-Amino-3-methylanthraquinone-2-carboxylic acid (V)

3-Methylanthraquinone-1,2-isoxazole (0.4 g) was refluxed with methanolic baryta (10 g of baryta was suspended in 40 ml of water and 10 ml of methanol added) at the boil for 2 hr, after which the methanol was removed under vacuum and the product was filtered and washed with water. The filtrate and washings were acidified, when 1-amino-3-methylanthraquinone-2-carboxylic acid separated as a fluffy amorphous product. It was filtered, washed and dried (0.1 g). The residue, insoluble in baryta, was boiled with conc hydrochloric acid (5 ml), filtered and washed free of acid. Then it was extracted with a 5% solution of sodium bicarbonate. After filtration, the filtrate was acidified when more of 1-amino-3-methylanthraquinone-2-carboxylic acid separated. The acid was filtered, washed and dried (0.05 g). Crystallization from nitrobenzene gave brownish-red needles,

m.p. 261° (lit.[1] m.p. 261°).

1-Hydroxy-3-methylanthraquinone-2-carboxylic acid (m.p. 276°) was prepared by diazotization of the above amino acid and boiling with sulphuric acid.[1]

1-Hydroxy-2,3-dimethylanthraquinone (VI)

1-Amino-2,3-dimethylanthraquinone (4 g) in conc H_2SO_4 (80 ml) was cooled to 5° and diazotized with a mixture of sodium nitrite (2 g) and conc H_2SO_4 (40 ml). The diazonium salt solution was poured over crushed ice (120 g) and then added to 40% H_2SO_4 solution at the boil. The mixture was gently boiled for $\frac{1}{2}$ hr and diluted with water (200 ml). The yellow precipitate was collected, washed and dried (3.2 g). Crystallization from acetic acid gave yellow needles, m.p. 212°. (Found: C, 75.9; H, 4.7. $C_{16}H_{12}O_6$ requires: C, 76.2; H, 4.8%).

1-Acetoxy-2,3-dimethylanthraquinone (VII)

1-Hydroxy-2,3-dimethylanthraquinone (3 g) was dissolved in acetic anhydride (30 ml) and a few drops of perchloric acid were added and the solution allowed to stand for $\frac{1}{2}$ hr. The product was poured over crushed ice (100 g) and left for a few hours, when the pale

yellow acetyl derivative separated. This was filtered, washed and dried (3 g). Crystallization from acetic acid gave pale yellow needles, m.p. 191°. (Found: C, 73.4; H, 5.2. $C_{18}H_{14}O_4$ requires: C, 73.5; H, 4.8%).

1-Methoxy-2,3-dimethylanthraquinone

1-Hydroxy-2,3-dimethylanthraquinone (0.1 g), anhydrous potassium carbonate (2 g) and dimethyl sulphate (0.1 ml) in acetone (50 ml) were refluxed for 12 hr on a water-bath. The product was filtered and the residue washed repeatedly with acetone (100 ml). The solvent was removed, and after addition of water the precipitate was collected and dried (0.08 g). Crystallization from methanol gave greenish-yellow needles, m.p. 168°. (Found: C, 76.9; H, 5.5; OMe, 11.1. $C_{17}H_{14}O_3$ requires: C, 76.7; H, 5.3; OMe, 11.6%).

1-Acetoxy-2-bromomethyl-3-methylanthraquinone (VIII)

1-Acetoxy-2,3-dimethylanthraquinone (2.5 g), N-bromosuccinimide (1.67 g; 1.1 mole), benzoyl peroxide (0.05 g) in carbon tetrachloride (250 ml) were refluxed for 24 hr. The solvent was distilled off, the residue washed with hot water and dried (2.7 g). The product

was dissolved in benzene and chromatographed over neutral alumina. The single fraction obtained was collected and the residue crystallized thrice from carbon tetrachloride, m.p. 210-212°. (Found: C, 56.6; H, 3.7; Br, 23.8. $C_{18}H_{13}O_4Br$ requires: C, 57.9; H, 3.5; Br, 21.4%).

1-Acetoxy-2-acetoxymethyl-3-methylanthraquinone (IX)

The ω-bromo compound from the previous step (2 g) was refluxed with fused sodium acetate (2 g) and acetic anhydride (10 ml) for 1 hr. The mixture was cooled and poured over crushed ice (80 g). The pale yellow product was collected, washed and dried (1.8 g). Repeated crystallization from ethanol gave 1-acetoxy-2-acetoxymethyl-3-methylanthraquinone as yellow needles, m.p. 148°. (Found: C, 67.9; H, 4.6. $C_{20}H_{16}O_6$ requires: C, 68.2; H, 4.5%).

1-Hydroxy-2-hydroxymethyl-3-methylanthraquinone (X)

1-Acetoxy-2-acetoxymethyl-3-methylanthraquinone (1 g) was dissolved in boiling methanol (50 ml). Conc H_2SO_4 (2 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 (0.7 g). Crystallization from ethanol gave

yellow needles, m.p. 155°. (Found: C, 71.1; H, 4.6. $C_{16}H_{12}O_4$ requires: C, 71.6; H, 4.5%).

1-Hydroxy-3-methylanthraquinone-2-carboxylic acid (I)

Silver nitrate (0.68 g) in water (5 ml) was treated with caustic soda (0.17 g) in water (5 ml). The precipitated silver oxide was filtered, washed and added to sodium hydroxide (0.68 g) in water (20 ml) under vigorous stirring. The temperature of the mixture was maintained at 75°, and 1-hydroxy-2-hydroxymethyl-3-methylanthraquinone (0.6 g) was added. Stirring was continued for 1 hr and the mixture filtered hot. The residue was washed thoroughly with hot water and the filtrate and washings were acidified. The yellow precipitate was dissolved in 5% aqueous sodium bicarbonate and the filtrate acidified. The precipitate (0.4 g) crystallized from acetic acid as yellow needles, m.p. 276°. (Found: C, 68.4; H, 3.5. $C_{16}H_{10}O_5$ requires: C, 68.0; H, 3.5%). Mixed m.p. with the acid obtained by the isoxazole route was undepressed.

Nitration of 1-nitro-2,3-dimethylanthraquinone (III) with 1.5 mole of nitric acid

1-Nitro-2,3-dimethylanthraquinone (5 g) was dissolved in sulphuric acid monohydrate (50 ml) in a flask

provided with a stirrer and the solution heated to 80°. Then mixed acid containing fuming nitric acid (1.1 ml) and monohydrate (10 ml) was added dropwise and the temperature was raised to 90-95°. After $\frac{1}{2}$ hr, the product was cooled and poured over crushed ice and the nitrated dimethylanthraquinones which separated out were filtered, washed and dried (6 g).

The product (0.2 g) was pasted with sodium sulphide (2 g) and a little water. After dilution with water (20 ml), the mixture was heated at 100° for 3 hr. The reduction product was filtered, washed and dried (0.14 g). A portion of it (0.05 g) was dissolved in toluene and chromatographed over alumina, when four bands - violet, pink, red and yellow - separated. The pink, red and yellow bands indicated 1,8-diamino-, 1,5-diamino- and unconverted 1-nitro-2,3-dimethylanthraquinones respectively and the violet band showed the presence of a triamino compound.

1,4,5-Trinitro-2,3-dimethylanthraquinone (XVIII)

2,3-Dimethylanthraquinone (5 g) was dissolved in monohydrate (50 ml) and the solution was heated to 100° on a water-bath. Mixed acid containing fuming nitric acid (3.2 ml; 3.6 moles) and monohydrate (15 ml) was added drop by drop under stirring. After stirring

under the same conditions for 5 hr, the separated yellow product was filtered through a sintered glass funnel, washed with sulphuric acid first and then with water and dried (5.7 g). Crystallization from nitrobenzene gave yellow needles, m.p. > 360°. (Found: C, 52.2; H, 2.7; N, 11.3. $C_{16}H_9O_8N_3$ requires: C, 51.8; H, 2.4; N, 11.3%).

1,4,5-Triamino-2,3-dimethylanthraquinone (XXIII)

1,4,5-Trinitroanthraquinone (1 g) was pasted with sodium sulphide (10 g) and a little water. The paste was diluted with more water and heated at 100° for 3 hr. The blue triamine which separated out was filtered, washed with hot water and dried (0.52 g). Crystallization from o-dichlorobenzene gave violet needles, m.p. 289°. (Found: C, 67.8; H, 5.3; N, 14.5. $C_{16}H_{15}O_2N_3$ requires: C, 68.3; H, 5.3; N, 14.9%).

Oxidation of benzyl alcohol to benzaldehyde with 1,5-dinitro-2,3-dimethylanthraquinone

1,5-Dinitro-2,3-dimethylanthraquinone (1 g) was taken in freshly distilled benzyl alcohol (20 ml) (tested to be free from aldehyde) and refluxed for 1 hr. The reaction mixture which had turned to a brown-red colour was then steam-distilled. The distillate was treated with excess 2,4-

dinitrophenylhydrazine and a few drops of conc H_2SO_4. The dinitrophenylhydrazone which separated out was filtered, washed with ether and dried (0.4 g), m.p. 234°. Mixed m.p. with an authentic sample of the 2,4-dinitrophenylhydrazone (m.p. 237°) was undepressed.

The residue after steam-distillation was filtered, washed and dried. Crystallization from gl acetic acid gave red needles, m.p. 278°, and was identical with the same diamine got by the reduction of 1,5-dinitro-2,3-dimethylanthraquinone.

1,5-Dinitro-2,3-dimethylanthraquinone (XXIV)

2,3-Dimethylanthraquinone (25 g) was dissolved in 100% sulphuric acid (200 ml) at room temp. Then mixed acid, consisting of 100% sulphuric acid (27.5 ml) and fuming nitric acid (10.9 ml; 2.2 moles; d, 1.5), was added under stirring in $\frac{1}{2}$ hr at the same temperature. After the addition was over, the reaction mixture was heated to 85-90° on a water-bath. The 1,5-dinitro-2,3-dimethylanthraquinone started separating out as a yellow product. After 5 hr the separated 1,5-dinitro derivative was filtered off on a sintered glass funnel and washed first with conc sulphuric acid (200 ml) and then with water till the filtrate was no more acidic. The crude

1,5-dinitro-2,3-dimethylanthraquinone (25 g) was purified by boiling with gl acetic acid (10 ml/g) to remove the more soluble mononitro derivatives and the 1,8-isomer, and then was dissolved in gl acetic acid (450 ml/g), from which it came out as pale yellow needles (18.5 g), m.p. 280°. (Found: C, 59.4; H, 3.3; N, 8.3. $C_{16}H_{10}O_6N_2$ requires: C, 58.9; H, 3.1; N, 8.6%).

1,8-Dinitro-2,3-dimethylanthraquinone (XXV)

The 1,8-dinitro derivative having more solubility in sulphuric acid was obtained from the sulphuric acid filtrate and washings of the above experiment. The sulphuric acid filtrate and washings from the above experiment were poured over crushed ice and the product which separated out as yellow flocs was filtered and washed free of acid and dried. The crude product (5.5 g), m.p. 211-238°, was extracted with gl acetic acid (1 ml/g) to remove the more soluble mononitro derivatives and filtered. The residue (4.9 g), m.p. 235-242°, was repeatedly crystallized from gl acetic acid, from which it came out as pale yellow needles. After 5 crystallizations the m.p. was 262-266° and one more crystallization did not increase the m.p. of this product (2.0 g). (Found: C, 58.4; H, 2.8; N, 9.1. $C_{16}H_{10}O_6N_2$ requires: C, 58.9; H, 3.1; N, 8.6%).

1-Nitro-2,3-dimethyl-5-aminoanthraquinone (XXVI)

A mixture of 1,5-dinitro-2,3-dimethylanthraquinone (17.5 g) and freshly distilled dimethylaniline (175 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 went into solution with a red colour. The reaction was continued for 20 min from the start and allowed to cool overnight. The separated product was collected, washed with ether and dried (8.7 g). Crystallization from benzyl alcohol gave red needles, m.p. above 360°. (Found: C, 64.9; H, 4.1; N, 9.5. $C_{16}H_{12}N_2O_4$ requires: C, 65.0; H, 4.1; N, 9.5%).

1-Nitro-2,3-dimethylanthraquinone (III)

1-Nitro-2,3-dimethyl-5-aminoanthraquinone (0.75 g) was dissolved in conc H_2SO_4 (20 ml), cooled in an 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 (0.6 g).

Crystallization from gl acetic acid gave yellow needles, m.p. 252°, undepressed when mixed with an authentic sample of 1-nitro-2,3-dimethylanthraquinone.

1-Nitro-2,3-dimethyl-5-amino-6,8-dibromoanthraquinone (XXVII)

To a mechanically agitated solution of 1-nitro-2,3-dimethyl-5-aminoanthraquinone (8 g) in gl acetic acid (800 ml), bromine (8 ml) in gl acetic acid (75 ml) was added at 98-100°. After 6 hr of stirring at the same temperature, the reaction mixture was allowed to cool overnight. The crystalline red product which separated was collected, washed first with 5% sodium bisulphite solution, then with water, and dried (8.1 g). Crystallization from benzyl alcohol gave red needles, m.p. 278°. (Found: C, 42.8; H, 2.2; N, 5.8; Br, 34.7. $C_{16}H_{10}O_4N_2Br_2$ requires: C, 42.3; H, 2.2; N, 6.2; Br, 35.2%).

1-Nitro-2,3-dimethyl-6,8-dibromoanthraquinone (XXVIII)

1-Nitro-2,3-dimethyl-5-amino-6,8-dibromoanthraquinone (7.5 g) was dissolved in conc H_2SO_4 (75 ml), cooled in an ice-bath to 5° and diazotized with sodium nitrite (4 g) in conc H_2SO_4 (23 ml) for 1 hr. Gl acetic acid (15 ml) was added and after 15 min, the mixture was poured over crushed ice (400 g). The diazonium salt solution was added to ethanol (1 l.) 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 (6.6 g). Crystallization from gl acetic acid gave pale yellow needles, m.p. 313°. (Found: C, 44.0; H, 2.1; N, 3.2; Br, 35.9. $C_{16}H_9O_4NBr_2$ requires: C, 43.7; H, 2.1; N, 3.2; Br, 36.4%).

6,8-Dibromo-3-methylanthraquinone-1,2-isoxazole (XXIX)

1-Nitro-2,3-dimethyl-6,8-dibromoanthraquinone (6.5 g) was added to 20% oleum (65 ml) under stirring at 25-28°. The solution was left overnight at the same temperature and was then poured over crushed ice, filtered, washed free of acid and dried (5.9 g). The crude isoxazole was chromatographed over alumina in xylene. The xylene eluate containing the isoxazole was concentrated (10 ml) and the isoxazole came out as an amorphous powder (0.7 g), m.p. 245-260° (decomp). (Found: C, 45.1; H, 1.6; N, 3.5. $C_{16}H_7NO_3Br_2$ requires: C, 45.6; H, 1.7; N, 3.3%).

Hydrolysis of 6,8-dibromo-3-methylanthraquinone-1,2-isoxazole

(a) With alcoholic KOH. 6,8-Dibromo-3-methylanthraquinone-1,2-isoxazole (0.3 g) was refluxed with alcoholic 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, collected, washed and dried (0.2 g). Crystallization from nitrobenzene gave brownish-red needles, m.p. 284-287°.

(b) With methanolic baryta. 6,8-Dibromo-3-methyl-anthraquinone-1,2-isoxazole (0.2 g) was refluxed with methanolic baryta (10 g of baryta suspended in 40 ml of water and 10 ml of methanol added) at the boil for 3 hr, after which the methanol was removed under vacuum and the product was filtered and washed with water. The filtrate and washings were acidified when the amino carboxylic acid separated, and it was collected, washed and dried (0.12 g). The residue, insoluble in baryta, was boiled with conc HCl (2 ml), filtered, washed and extracted with a 5% solution of $NaHCO_3$. The bicarbonate solution was filtered and acidified, when more of the amino carboxylic acid separated, which was filtered, washed and dried (0.04 g). Crystallization from nitro-benzene gave brownish-red needles, m.p. 284-287°. The mixed m.p. with the acid by method (a) was not depressed. (Found: C, 47.8; H, 2.0; N, 3.6; Br, 29.2. $C_{16}H_9O_4NBr_2$ requires: C, 43.7; H, 2.1; N, 3.2; Br, 36.4. $C_{16}H_{10}O_4NBr$ requires: C, 53.3; H, 2.8; N, 3.9; Br, 22.2. $C_{16}H_{10}O_5NBr$ requires: C, 51.1; H, 2.7; N, 3.8; Br, 21.3%).

Replacement of amino by hydroxyl in the compound from the previous step

A solution of the compound from the previous step (0.3 g) with conc H_2SO_4 (4 ml) was cooled in an ice-bath to 5° and diazotized with sodium nitrite (0.15 g) dissolved in conc H_2SO_4 (2 ml). After an hr the mixture was poured over crushed ice (10 g). The diazonium solution thus obtained was gradually added to a boiling 40% H_2SO_4 solution (15 ml) and the mixture heated to 140° for 30 min. After cooling, the solution was diluted with water (15 ml) and the yellow product which separated was collected, washed and dried (0.25 g). Crystallization from gl acetic acid gave yellow needles, m.p. 278-282°. (Found: C, 47.6; H, 2.1; Br, 29.3. $C_{16}H_8O_5Br_2$ requires: C, 43.6; H, 1.8; Br, 36.4. $C_{16}H_9O_6Br$ requires: C, 50.9; H, 2.4; Br, 21.2. $C_{16}H_9O_5Br$ requires: C, 53.2; H, 2.5; Br, 22.2%).

Lime under pressure reaction on the previous compound using

(a) copper bronze as catalyst. To a thin slurry made from slaked lime (0.5 g) in water (5 ml) the compound from the previous step (0.1 g) and copper bronze (0.02 g) were added. The mixture was heated in a sealed tube at 210-220° for 24 hr. The red reaction mixture was acidified and the yellow precipitate

collected, washed and dried (0.06 g). Crystallization from gl acetic acid gave orange needles, m.p. 290-320° (decomp). (Found: C, 63.4; H, 3.6. $C_{16}H_{10}O_7$ requires: C, 61.1; H, 3.1. $C_{16}H_{10}O_6$ requires: C, 64.4; H, 3.4%).

[M.p. reported for endocrocin: 318° (decomp),[21] 290-320° (decomp)[22] and 340° (decomp)[23]].

The substance gives brown-red colouration in sodium bicarbonate, violet colour in alkali and carbonate, purple colour in sulphuric acid, and red-brown colouration with alcoholic ferric chloride. The infrared spectrum of this compound in Nujol shows maxima at 3400, 1689, 1633, 1591, 1573, 1360, 1326, 1297, 1260, 1240, 1211, 1167, 1109, 1080, 1049, 980 and 941 cm^{-1}. In the ultraviolet and visible regions it showed the following maxima: 274 and 422 mμ; log ε_{max} 4.74 and 4.3 respectively.

The methyl ether ester was prepared by refluxing the above compound (0.02 g) with anhydrous potassium carbonate (0.2 g), dimethyl sulphate (0.05 ml) and acetone (40 ml) on a water-bath for 12 hr. After removal of the acetone and dilution of the mixture with water, a yellow product separated and it was collected, washed and dried (0.02 g). The product was dissolved in benzene and chromatographed over alumina when the ether ester ran down fast as a greenish-yellow solution in benzene.

The solvent was distilled off to dryness. Crystallization from methanol gave yellow needles, m.p. 190°. (Found: C, 62.9; H, 4.6. $C_{20}H_{18}O_7$ requires: C, 64.9; H, 4.9. $C_{19}H_{16}O_6$ requires: C, 67.0; H, 4.7%).

(b) copper oxide as catalyst; 1,6,8-trihydroxy-3-methylanthraquinone-2-carboxylic acid (endocrocin) (II). To a thin slurry made from slaked lime (0.5 g) in water (5 ml), the hydroxy bromo carboxylic acid from the previous step (0.1 g) and copper oxide (0.02 g) were added and heated in a sealed tube at 210-220° for 24 hr. The reaction mixture on working up as in (a) gave a product (0.06 g). This product (0.06 g) was methylated by refluxing it in acetone (90 ml) with anhydrous potassium carbonate (0.6 g) and dimethyl sulphate (0.2 ml) for 12 hr. The acetone was removed, water added to the mixture, and the yellow product which separated was collected, washed and dried (0.06 g). The product was dissolved in benzene and chromatographed over alumina. The benzene eluate containing the ether ester was distilled to dryness. Crystallization of the product from benzene gave shining yellow needles, m.p. 223-225°. The mixed m.p. with the ether ester of natural endocrocin (m.p. 225-226°) (kindly supplied by Professor

Shibata) was undepressed. (Found: C, 64.5; H, 4.6. $C_{20}H_{18}O_7$ requires: C, 64.9; H, 4.9%).

Endocrocin

Endocrocin (II) was obtained by heating the above compound (0.01 g) with anhydrous aluminium chloride (0.1 g) and sodium chloride (0.03 g) at 140-150° for 5 min. The product was cooled, water and HCl added, filtered, washed and dried (0.006 g). Crystallization from acetic acid gave copper-red leaflets, m.p. 310-320° (decomp). The substance gave all the colour reactions reported for endocrocin, viz. brown-red in sodium bicarbonate, violet in alkali and carbonate, purple in sulphuric acid and red-brown with alcoholic ferric chloride. (Found: C, 60.9, H, 3.0. $C_{16}H_{10}O_7$ requires: C, 61.1; H, 3.1%).

3-Methyl-5-nitroanthraquinone-1,2-isoxazole (XXXVII)

1,5-Dinitro-2,3-dimethylanthraquinone (1 g) was added to 20% oleum (10 ml) under stirring at 25-28°. The solution was left overnight at the same temperature and was then poured over crushed ice, filtered, washed free of acid and dried (0.8 g). The crude isoxazole was crystallized from dimethylformamide, water mixture (2:1)

as brown microscopic needles, m.p. 240-250° (decomp). (Found: C, 61.8; H, 2.5; N, 8.9. $C_{16}H_8O_5N_2$ requires: C, 62.3; H, 2.6; N, 9.1%).

1-Amino-3-methyl-5-hydroxyanthraquinone-2-carboxylic acid (XXXVIII)

5-Nitro-3-methylanthraquinone-1,2-isoxazole (0.6 g) was refluxed with alcoholic potassium hydroxide (30%; 20 ml) for 2 hr, after which the product was filtered and the residue washed with water. The filtrate and washings were acidified and the precipitated amino carboxylic acid was digested on a water-bath for 15 min, filtered, washed and dried (0.35 g). Crystallization from benzene gave red needles, m.p. 250-252°. (Found: C, 65.1; H, 3.8; N, 5.2. $C_{16}H_{11}O_5N$ requires: C, 64.6; H, 3.7; N, 4.7%).

1-Hydroxy-2,4-diaminoanthraquinone

1-Hydroxy-2,4-dinitroanthraquinone (0.5 g) was dissolved in alcohol (100 ml) by warming, and hydrazine hydrate 99-100% (1 ml) was added under stirring. The mixture was warmed over a water-bath and a small amount of Raney nickel catalyst was added. A vigorous reaction set in. When the evolution of gas subsided after 1 hr, the reaction mass was refluxed over a steam-bath for about an hr, filtered hot, the catalyst washed with hot ethyl alcohol and the combined filtrates and washings were

evaporated to dryness. The residue was suspended in water and acidified with gl acetic acid. The product (0.3 g), on crystallization from acetic acid, gave violet needles, m.p. 292° (decomp). (Found: C, 65.8; H, 4.1; N, 10.6. $C_{14}H_{10}O_3N_2$ requires: C, 66.1; H, 3.9; N, 11.0%).

1,2,4-Trihydroxyanthraquinone; purpurin

A solution of 1-hydroxy-2,4-diaminoanthraquinone (0.2 g) in conc H_2SO_4 (3 ml) was cooled in an ice-bath to 5° and diazotized with sodium nitrite (0.2 g), dissolved in conc H_2SO_4 (3 ml). After an hr the mixture was poured over crushed ice (10 g). The solution of the diazonium salt was added to 40% sulphuric acid (10 ml) at the boil and kept at the boil for 30 min. The product was cooled, diluted with water (10 ml) and the separated product was filtered (0.1 g). The filtrate was extracted with benzene, the benzene layer separated, dried and distilled to dryness to get more of purpurin (0.02 g). Crystallization from alcohol gave red needles, m.p. 254-256° (lit.[24] m.p. 255-257°). The mixed m.p. with an authentic sample of purpurin was undepressed. This compound gave a cherry-red solution in aqueous KOH and in cold aqueous Na_2CO_3.

1-Nitro-2,3-dimethyl-5-hydroxyanthraquinone (XL)

A solution of 1-nitro-2,3-dimethyl-5-aminoanthraquinone (10 g) in conc H_2SO_4 (100 ml) was cooled in an ice-bath to 5° and diazotized with sodium nitrite (5 g), dissolved in conc H_2SO_4 (25 ml). After an hr the mixture was poured over crushed ice (500 g). The diazonium solution thus got was gradually added to a boiling 40% H_2SO_4 solution (400 ml) and the mixture heated at 140° for 30 min. The yellow product was collected, washed and dried (9.3 g). Crystallization from gl acetic acid gave yellow needles, m.p. 278-280°. (Found: C, 65.0; H, 3.8; N, 5.1. $C_{16}H_{11}O_5N$ requires: C, 64.6; H, 3.7; N, 4.7%).

1,6,8-Trinitro-2,3-dimethyl-5-hydroxyanthraquinone (XLI)

1-Nitro-2,3-dimethyl-5-hydroxyanthraquinone (7 g) was dissolved in conc H_2SO_4 (150 ml) under stirring. The flask was cooled to 0-5° and fuming nitric acid (8 ml) was added drop by drop in 5-10 min and the stirring was continued for 2 hr more. The product was then poured over crushed ice, filtered, washed just free of acid (as it is soluble in water) and dried (8.0 g). Gl acetic acid crystallization gave greenish yellow needles, m.p. 268°.

(Found: C, 49.4; H, 2.1; N, 11.2. $C_{16}H_9O_9N_3$ requires: C, 49.6; H, 2.3; N, 10.9%).

The same compound was got by the following method (reported on 1-aminoanthraquinone by Jayaraman[18]). 1-Nitro-2,3-dimethyl-5-aminoanthraquinone (1 g) was heated on a water-bath with conc HNO_3 (d, 1.42; 25 ml) for 5 hr. After that the mixture was cooled, poured into water (150 ml), and the yellow product was collected, washed and dried (0.75 g). Gl acetic acid crystallization gave greenish yellow needles, m.p. 268°. The mixed m.p. with the product by the previous method was undepressed.

1,6,8-Triamino-2,3-dimethyl-5-hydroxyanthraquinone (XLII)

1,6,8-Trinitro-2,3-dimethyl-5-hydroxyanthraquinone (7 g) was made into a paste with sodium sulphide (55 g) and a little water. The paste was diluted with water (300 ml) and stirred at 100° for 3 hr. The violet product was collected, washed with hot water and dried (4.8 g). Crystallization from o-dichlorobenzene gave violet needles, m.p. 270-285° (decomp). (Found: C, 64.9; H, 5.0; N, 13.8. $C_{16}H_{15}O_3N_3$ requires: C, 64.6; H, 5.1; N, 14.1%).

1,5,6,8-Tetrahydroxy-2,3-dimethylanthraquinone (XLIII)

A solution of 1,6,8-triamino-2,3-dimethyl-5-hydroxy anthraquinone (4 g) in conc H_2SO_4 (40 ml) was

tris-diazotized with sodium nitrite (8 g) dissolved in conc H_2SO_4 (40 ml) at room temp (28-30°). After 2 hr the mixture was poured over crushed ice (450 g). The solution thus obtained was gradually added to a boiling 40% H_2SO_4 solution (400 ml) and the mixture heated at 140° for 45 min. The orange product was collected, washed and dried (3.5 g). The product separated from hot gl acetic acid in an amorphous form, m.p. 310-325° (decomp). (Found: C, 63.5; H, 3.8. $C_{16}H_{12}O_6$ requires: C, 64.0; H, 4.0%).

1,6,8-Trihydroxy-2,3-dimethylanthraquinone (XLIV)

1,5,6,8-Tetrahydroxy-2,3-dimethylanthraquinone (3 g) was dissolved in sodium hydroxide solution (1.5%; 300 ml) in presence of sodium hydrosulphite (12 g). The temperature was maintained at 45-50° for 20 min and then the vatted solution was air-oxidized. After 3 hr, the solution was acidified with HCl, the yellow precipitate digested on a water-bath for 15 min, collected, washed and dried (2.5 g). Crystallization from alcohol gave yellow needles, m.p. 269-270°. (Found: C, 67.4; H, 4.0. $C_{16}H_{12}O_5$ requires: C, 67.6; H, 4.2%).

The triacetyl derivative (XLV) was prepared by dissolving the above compound (2 g) in acetic anhydride (100 ml) and adding a few drops of perchloric acid.

After 30 min the mixture was poured over crushed ice. After 3 hr the yellow product which separated was collected, washed and dried, m.p. 212°.

1,6,8-Triacetoxy-2-bromomethyl-3-methylanthraquinone (XLVI)

1,6,8-Triacetoxy-2,3-dimethylanthraquinone (2 g), N-bromosuccinimide (0.96 g; 1.1 mole), benzoyl peroxide (0.02 g) in carbon tetrachloride (500 ml) were refluxed for 24 hr. The solvent was removed, the residue washed with hot water, collected and dried (2.4 g). The product was dissolved in benzene and chromatographed over neutral alumina. The single fraction obtained was collected and the residue crystallized thrice from carbon tetrachloride, m.p. 222-226°. (Found: C, 52.9; H, 3.8; Br, 18.4. $C_{22}H_{17}O_8Br$ requires: C, 54.0; H, 3.5; Br, 16.4%).

1,6,8-Triacetoxy-2-acetoxymethyl-3-methylanthraquinone (XLVII)

The ω-bromo compound from the previous step (1 g) was refluxed with sodium acetate (1 g) and acetic anhydride (15 ml) for 1 hr. The mixture was cooled and poured over crushed ice (20 g). The pale yellow product was collected, washed and dried (0.8 g). Repeated crystallization from ethyl alcohol gave yellow needles, m.p. 162-165°. (Found: C, 60.8; H, 4.0. $C_{24}H_{20}O_{10}$ requires: C, 61.5; H, 4.2%).

Endocrocin, 1,6,8-trihydroxy-3-methylanthraquinone-2-carboxylic acid (II), and its ether ester

Silver nitrate (0.82 g) in water (6 ml) was treated with caustic soda (0.2 g) in water (6 ml). The separated silver oxide was filtered, washed free from nitrate and transferred to a beaker containing 12 ml of water. With vigorous stirring NaOH (1.1 g) was added. The temperature of the mixture was maintained at 75°, and 1,6,8-triacetoxy-3-methyl-2-acetoxymethyl-anthraquinone (0.6 g) was introduced. Stirring was continued for an hr, and the mixture filtered hot. The residue of silver was washed thoroughly with warm water. The filtrate and washings were acidified, and the orange precipitate was dissolved in 5% aqueous sodium bicarbonate. Acidification of the filtered solution and crystallization of the precipitate (0.22 g) from gl acetic acid gave copper-red leaflets, m.p. 310-320° (decomp). The compound gave a brown-red colour in sodium bicarbonate, a violet colour in sodium carbonate and alkali, a purple colour in conc sulphuric acid, and a red-brown colour with alcoholic ferric chloride. This product (0.05 g) was methylated by refluxing it in acetone (50 ml) with anhydrous potassium carbonate (0.5 g) and dimethyl sulphate (0.15 ml) for 12 hr. The acetone was filtered and the potassium carbonate was repeatedly washed with acetone. The filtrate and the washings

were concentrated and brought to dryness, water added and the yellow product was collected, washed and dried (0.05 g). Then it was dissolved in benzene, chromatographed over alumina and allowed to crystallize from the benzene eluate after filtration and concentration to 3 ml. The ether ester came out as yellow needles, m.p. 225-226°. The mixed m.p. with the ether ester (223-225°) by the previous isoxazole route and with the ether ester (225-226°) of natural endocrocin was undepressed.

The infrared spectra of this synthetic ether ester and natural ether ester are superposable.

1,5-Diamino-2,3-dimethylanthraquinone (XLVIII)

1,5-Dinitro-2,3-dimethylanthraquinone (10 g) was made into a paste with sodium sulphide (35 g) and a little water. The paste was diluted with water (300 ml) and stirred at 100° for 2 hr. The brownish-red crystalline product was collected, washed and dried (7.2 g). Crystallization from o-dichlorobenzene gave red needles, m.p. 278°. (Found: C, 72.6; H, 5.0; N, 10.7. $C_{16}H_{14}N_2O_2$ requires: C, 72.2; H, 5.3; N, 10.5%).

1,5-Dihydroxy-2,3-dimethylanthraquinone (XLIX)

A solution of 1,5-diamino-2,3-dimethylanthraquinone

(7 g) in conc H_2SO_4 (70 ml) was cooled in an ice-bath to 5° and diazotized with sodium nitrite (7 g) in conc H_2SO_4 (50 ml). After 1 hr, the mixture was poured over crushed ice (500 g). The diazonium solution thus obtained was gradually added to a boiling 40% H_2SO_4 solution (300 ml) and the mixture heated at 140° for 30 min. The yellow precipitate was collected, washed and dried (6.6 g), m.p. 186-187°. (Found: C, 71.2; H, 4.5. $C_{16}H_{12}O_4$ requires: C, 71.6; H, 4.5%).

1,5-Diacetoxy-2,3-dimethylanthraquinone (L)

1,5-Dihydroxy-2,3-dimethylanthraquinone (6 g) was dissolved in acetic anhydride (60 ml) and a few drops of perchloric acid were added at room temp. The solution was allowed to stand for 30 min, after which the mixture was poured over crushed ice (200 g) and left for a few hr when the pale yellow acetyl derivative separated. This was filtered, washed and dried (7.5 g). Crystallization from acetic acid gave pale yellow needles, m.p. 228°. (Found: C, 67.8; H, 4.9. $C_{20}H_{16}O_6$ requires: C, 68.2; H, 4.5%).

1,5-Diacetoxy-2-bromomethyl-3-methylanthraquinone (LI)

1,5-Diacetoxy-2,3-dimethylanthraquinone (7 g), N-bromosuccinimide (3.9 g; 1.1 mole) in carbon tetrachloride (900 ml) were refluxed for 24 hr. The solvent

was removed, the residue washed with hot water, collected and dried (8.2 g). The product was dissolved in benzene and chromatographed over alumina. The fraction containing the bromo compound was collected and the solvent removed to dryness. The residue was crystallized from carbon tetrachloride, m.p. 175-180°. (Found: C, 54.6; H, 3.2; Br, 21.0. $C_{20}H_{15}O_6Br$ requires: C, 55.7; H, 3.5; Br, 18.6%).

1,5-Diacetoxy-2-acetoxymethyl-3-methylanthraquinone (LII)

The ω-bromo compound from the previous step (8 g) was refluxed with sodium acetate (8 g) and acetic anhydride (50 ml) for 1 hr. The mixture was cooled and poured over crushed ice (200 g). The pale yellow product was collected, washed and dried (7.8 g). Crystallization four times from ethanol gave yellow needles, m.p. 167-168°. (Found: C, 63.9; H, 4.4. $C_{22}H_{18}O_8$ requires: C, 64.4; H, 4.4%).

1,5-Dihydroxy-3-methylanthraquinone-2-carboxylic acid (LIII)

Silver nitrate (6.8 g) in water (50 ml) was treated with caustic soda (1.7 g) in water (50 ml). The separated silver oxide was filtered, washed free from nitrate and transferred to a beaker containing 100 ml of water. With vigorous stirring NaOH (8.4 g) was added. The temperature of the mixture was maintained at 75°, and 1,5-diacetoxy-2-acetoxymethyl-3-methylanthraquinone (5 g)

was introduced. Stirring was continued for an hr, and the mixture filtered hot. The residue of silver was washed thoroughly with warm water. The filtrate and washings were acidified and the brownish-yellow precipitate was dissolved in 5% aqueous sodium bicarbonate. Acidification of the filtered solution and crystallization of the precipitate (2.2 g) from aqueous acetic acid gave brownish-yellow needles, m.p. 255°. (Found: C, 64.0; H, 3.2. $C_{16}H_{10}O_6$ requires: C, 64.4; H, 3.4%).

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S U M M A R Y

PART I. INTRODUCTION - NATURALLY OCCURRING HYDROXYANTHRAQUINONES

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. Since the present work is mainly on anthraquinone carboxylic acids, a separate table of the naturally occurring hydroxyanthraquinone carboxylic acids is included, followed by a brief account of the facts on which their structures are based and the routes adopted for their syntheses wherever reported.

PART II. THE CONSTITUTION OF ENDOCROCIN

Among the naturally occurring anthraquinone pigments, endocrocin (II) is of special interest as a likely intermediate in the biogenesis of emodin and other hydroxy-2-methylanthraquinones. Robinson has drawn attention to the possibility of its derivation from 8 molecules of acetic acid through the heptaketopalmitic acid (XIII). Endocrocin has been isolated from *Nephromopsis endocrocea*, *Aspergillus amstelodami*, *Penicillium islandicum* and *Claviceps purpurea*.

The structure 1,6,8-trihydroxy-3-methylanthraquinone-2-carboxylic acid (II) proposed for endocrocin by Asahina

and Fuzikawa was supported by adequate degradative evidence, which however did not rule out the possibility of the alternative structure, 1,6,8-trihydroxyanthraquinonyl-3-acetic acid (XII), which is also derivable from the heptaketopalmitic acid (XIII).

The infrared spectrum of endocrocin shows three bands in the carbonyl region at 1615, 1666 and 1718 cm^{-1}. The 1615 and 1666 cm^{-1} bands can obviously be assigned to the chelated and the unchelated carbonyls in the anthraquinone nucleus, but the 1718 cm^{-1} band appears to be at too high a frequency for an aromatic carboxylic acid. The infrared spectra of a series of anthraquinone carboxylic acids were examined, and their principal absorption bands are reported in Table 1. Except emodic acid, all the hydroxyanthraquinone carboxylic acids examined, including 1-hydroxy-3-methylanthraquinone-2-carboxylic acid which has the same orientation of substituents as structure (II) for endocrocin in the ring carrying the carboxyl group, show bands below 1700 cm^{-1} for the CO of the carboxyl group. The infrared spectra of a few anthraquinonyl acetic acids were also examined. 1-Hydroxyanthraquinonyl-2-acetic acid (XVII) shows a band at 1729 cm^{-1} for the carbonyl of the aliphatic carboxyl group. The infrared spectra of a series of amino-, nitro-, chloro- and bromo-anthraquinone

carboxylic acids are included in Table 1, and their spectra, especially in the carbonyl region, have been discussed. Among the acids included in Table 1 1-hydroxyanthraquinone-5-carboxylic acid and 1-hydroxy-2,4-dinitroanthraquinone-5-carboxylic acid are new, and their synthesis are described.

To establish feasible routes for the synthesis of the trimethyl ether and tetramethyl ether-ester of 1,6,8-trihydroxyanthraquinonyl-3-acetic acid (XXVIII) and (XXIX), the synthesis of the unknown anthraquinonyl-2-acetic acid (XVI) was first taken up. Anthraquinone-2-carboxyl-chloride was converted to the diazoketone (XXIV) by condensation with diazomethane. The diazoketone (XXIV) was converted to the acetic acid (XVI) and its methyl ester by the Wolff-rearrangement in dioxan-water and methanol respectively. The methyl ester of (XVI) was also prepared from (XXIV) following the method of Newman and Beal.

Emodic acid, the starting material for the synthesis of (XXVIII), was obtained from 1,8-dinitro-2-methyl-anthraquinone, following a method reported from this laboratory and also from emodin isolated from chrysarobin. A simple method for the extraction of emodin from chrysarobin is described. Emodic acid chloride trimethyl

ether (XXVI) was converted to the diazoketone (XXVII). The Wolff-rearrangement on (XXVII) in dioxan yielded the acetic acid (XXVIII) and in methanol gave the tetramethyl ether-ester (XXIX). The latter, m.p. 228-230°, depressed the m.p. of the tetramethyl ether-ester of natural endocrocin, 225-226°.

PART III. (a) EXPLORATORY WORK FOR THE SYNTHESIS OF ENDOCROCIN, AND
(b) THE SYNTHESIS OF ENDOCROCIN

The synthesis of 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (I) was reported by Ayyangar. Different conditions for the preparation of the isoxazole (IV) from 1-nitro-2,3-dimethylanthraquinone and its hydrolysis to the acid (V) have been investigated. The action of N-bromosuccinimide on 1-acetoxy-2,3-dimethylanthraquinone (VII) was found to give a major amount of the 2-bromomethyl derivative (VIII), and this led to a new synthesis of (I). The 2-bromomethyl compound (VIII) was converted to 1-hydroxy-2-hydroxymethyl-3-methylanthraquinone (X) through the acetoxymethyl derivative (IX). Silver oxide oxidation of (X) yielded (I).

The structure (II) for endocrocin has now been confirmed by the synthesis of its tetramethyl ether-ester

following two routes. Both involved as the first step the dinitration of 2,3-dimethylanthraquinone, separation of the 1,5-dinitro derivative and its reduction by boiling dimethylaniline to 1-nitro-2,3-dimethyl-5-aminoanthraquinone.

In the nitration of 2,3-dimethylanthraquinone it was found that the 1,5- and 1,8-dinitro derivatives were accompanied by a trinitro compound when excess of nitric acid was used for the nitration. This trinitro compound has the structure 1,4,5-trinitro-2,3-dimethylanthraquinone (XVIII), and represents the first reported **para** dinitro derivative in the anthraquinone series. Conditions are described to get this trinitro compound (XVIII) in high yield. The corresponding triamine is also described.

During the course of the nitration experiments, it was observed that 1,5-dinitro-2,3-dimethylanthraquinone (XXIV) smoothly oxidizes benzyl alcohol to benzaldehyde, and is reduced to 1,5-diamino-2,3-dimethylanthraquinone (XLVIII).

Bromination of the monoamine (XXVI) in acetic acid gave 1-nitro-5-amino-6,8-dibromo-2,3-dimethylanthraquinone (XXVII). This on deamination gave (XXVIII), which was converted to the isoxazole (XXIX) by treatment

with 20 per cent oleum. Hydrolysis of (XXIX) with ethanolic potassium hydroxide or methanolic baryta gave 1-amino-6,8-dibromo-3-methylanthraquinone-2-carboxylic acid (XXX), accompanied by a monobromo compound. Replacement of the amino group by hydroxyl and treatment of the product with lime and copper powder under pressure yielded mainly 1,6-dihydroxy-3-methylanthraquinone-2-carboxylic acid (XXXII); but when copper powder was replaced by copper oxide as catalyst, a product was obtained which on methylation gave an ether-ester that did not depress the m.p. of natural endocrocin tetramethyl ether-ester.

In another attempted route 1,5-dinitro-2,3-dimethylanthraquinone (XXIV) was converted to the corresponding isoxazole (XXXVII); this on hydrolysis with ethanolic potassium hydroxide gave (XXXVIII) instead of the required compound (XXXIX).

In the alternative route the monoamine (XXVI) was converted to 1-nitro-5-hydroxy-2,3-dimethylanthraquinone (XL), which on nitration gave the trinitro compound (XLI). Reduction diazotization and hydrolysis yielded 1,5,6,8-tetrahydroxy-2,3-dimethylanthraquinone (XLIII). When this compound was submitted to the well-known purpurin → xanthopurpurin reduction by treatment with

aqueous sodium dithionite and sodium hydroxide, atmospheric oxidation gave 2-methylemodin (XLIV). The 2-bromomethyl derivative (XLVI) was obtained as the major product by the action of N-bromosuccinimide in carbon tetrachloride on the acetate (XLV). 1,6,8-Trihydroxy-3-methylanthraquinone-2-carboxylic acid (II) was obtained from (XLVI) through the 2-acetoxymethyl derivative (XLVII), and (II) had all the properties of the natural pigment. Methylation gave an ether-ester identical with the ether-ester from natural endocrocin and also with the ether-ester obtained by the isoxazole route. By a similar procedure 1,5-dihydroxy-3-methyl-anthraquinone-2-carboxylic acid (LIII) was prepared from 1,5-diacetoxy-2,3-dimethylanthraquinone (L).

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