CITRININ AND ITS ANALOGUES

A Thesis

submitted by

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- CONTENTS -

Part I

CITRININ AND ITS ANALOGUES

INTRODUCTION

Citrinin, a laevorotatory, yellow, phenolic carboxylic acid, was first isolated by Hetherington and Raistrick[1] from a metabolic solution of *Penicillium citrinum* Thom. From a culture in Czapek-Dox glucose medium, incubated for about 14 days at 28°, Hetherington and Raistrick obtained citrinin by acidification of the filtered solution and crystallization of the yellow precipitate. Various other organisms such as *Penicillium expansum*[2], *Aspergillus terreus*[3] and an *Aspergillus* species of the *candidus* group[4] are known to produce citrinin.

Citrinin has also been isolated in 1 to 1.2 per cent yield from dried leaves of the flowering plant, *Crotalaria crispata*[5] growing in N. Australia, India and other tropical countries.

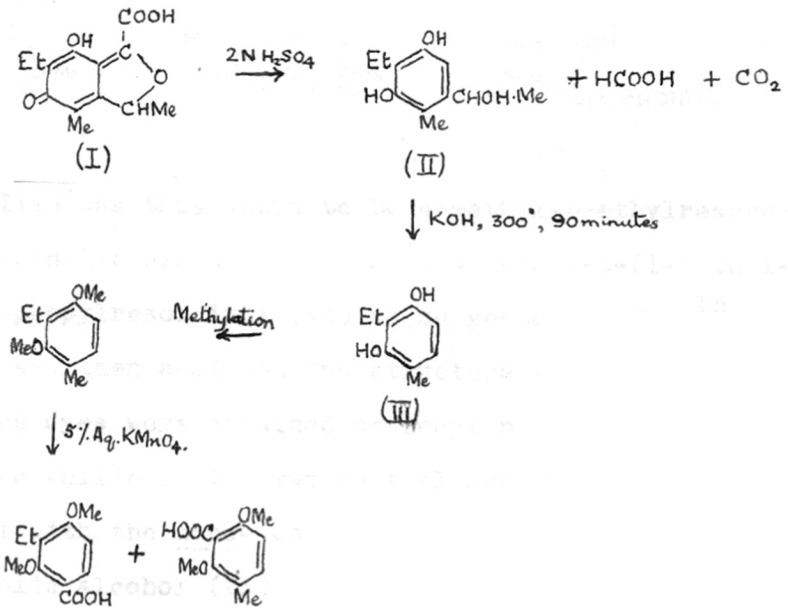
The bacteriostatic activity of citrinin has been examined by various workers (Raistrick and Smith,[6] Oxford,[7] Tauber *et al.*[8], Timonin and Rouatt,[9] Wang and Hong[10] and Wang *et al.*[11]). Wang *et al.*[11] have suggested that the antibiotic action of citrinin is chiefly due to the heterocyclic ring in the molecule. However, the phenolic hydroxyl group and the quinonoid system obviously plays a part in view of the antibacterial activity of many phenols and quinones. In spite of the ease with which citrinin can be prepared microbiologically, it has not found therapeutic application because of its high toxicity and low antibacterial action in comparison

with antibiotics such as penicillin and aureomycin. The growth of Staphylococcus aureus is inhibited by citrinin in a dilution of 1 in 60,000 and of B. subtilis in a dilution of 1 in 2,00,000.

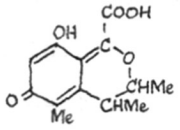
Citrinin crystallizes from alcohol in bright lemon yellow needles, m.p. 171.5° (decomp.), and is optically active; $[\alpha]$Hg green = about -42° in alcoholic solution.[1]

The constitution (I) was first assigned to citrinin by Coyne, Raistrick and Robinson[12] on the basis of the experimental results of Hetherington and Raistrick,[1] a brief outline of which is given below (Chart I).

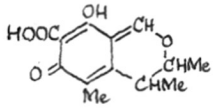
Chart I



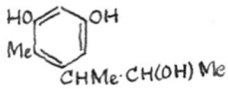
Gore et al.[13] studied the behaviour of "Notalin"[14] which was subsequently shown to be citrinin, towards diazonium salts, and disproved (I). They proposed the structure (IV) for citrinin, but finally confirmed the slightly different constitution (V) which was proposed by Robertson et al. Gore et al.[13] found that the structures assigned by Coyne et al.[12] to phenolic alcohol (II) and the dialkylresorcinol (III) obtained by alkali fusion of (II) to be untenable, since both coupled with diazonium salts to give the bisbenzeneazo derivatives. The absorption spectra, compared with those of 2:4- and 4:6-bisbenzeneazoresorcinols, indicated that the dyes from (II) and (III) belonged to the 2:4-series.



(IV)



(V)



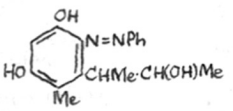
(VI)

Phenol (III) was thus shown to be 4-methyl-5-ethylresorcinol and the phenolic alcohol (II) to be 4-methyl-5-(1-methyl-2-hydroxy)-propylresorcinol (VI) as suggested by Cram.[15] Citrinin was then assigned the structure (IV).

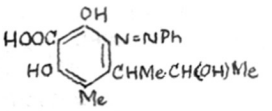
Three dyes were obtained on coupling citrinin with diazotized aniline. The two neutral dyes were shown to be identical with the mono- and bisbenzeneazo derivatives of the phenolic alcohol (VI). The third dye contained a carboxyl group. Decarboxylation yielded a dye which was identical with the monobenzeneazo derivative of the phenolic alcohol (VI), and it resembled 4-benzeneazoresorcinol in its absorption

spectrum and chromatographic behaviour.

This dye was formulated as (VII) and the azocarboxylic acid from citrinin as (VIII) in preference to (IX).



(VII)



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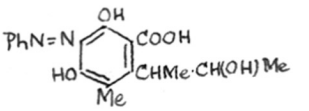


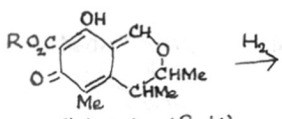
(IX)

The structure (IV) proposed for citrinin had therefore to be modified, and the alternative structure (V), which was proposed by Robertson *et al.*, proved to be more in conformity with the behaviour of citrinin towards diazonium salts.

Robertson *et al.*[16-21] have carried out extensive investigations on the degradation and synthesis of citrinin, methylcitrinin and dihydrocitrinin, and their results are summarized in Chart II.

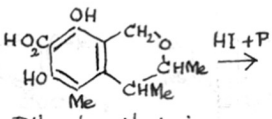
The synthesis of citrinin was achieved by Robertson *et al.*[17, 19-21] who synthesized the *p*-nitrobenzoate of the dimethyl ether of phenolic alcohol (B) and thus established the constitution of phenolic alcohol (A) and (B). The dimethyl ether of phenolic alcohol (B) was further resolved into the (+)- and (-)- forms and the latter was shown to be identical with the dimethyl ether of the phenolic alcohol (A). The synthesis of the *p*-nitrobenzoate of the dimethyl ether of phenolic alcohol (B) was carried out as follows: 3:5-Dimethoxy-2-methylbenzoic acid (X) was converted into the diazoketone (XI) *via* the acid chloride. The diazoketone (XI) was subjected to the Wolff rearrangement with ammoniacal silver nitrate which furnished the amide (XII). Dehydration of (XII) gave 3:5-dimethoxy-2-

CHART II



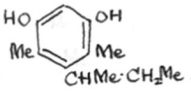
Citrinin (R=H)
(1) $C_{13}H_{14}O_5$

H_2



Dihydrocitrinin
(2) $C_{13}H_{16}O_5$

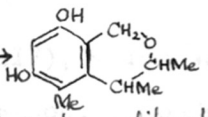
HI + P



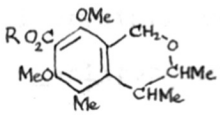
(7)

$-CO_2$

Methyl citrinin (R=Me) $\xrightarrow{H_2}$ Methyl dihydrocitrinin
$C_{12}H_{13}O_3(CO_2Me)$ $C_{12}H_{15}O_3(CO_2Me)$ (R=Me)

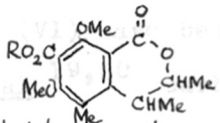


Decarboxydihydrocitrinin
(6)



2-Dimethyldihydrocitrinin methylester (R=Me) (3) → Acid (R=H)

$\downarrow CrO_3$ $C_{12}H_{13}O(OMe)_2(CO_2Me)$

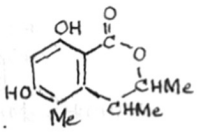


2-Dimethyldihydrocitrinone methylester (R=Me) (4) → Acid (R=H)

$C_{12}H_{11}O_2(OMe)_2(CO_2Me)$

$\downarrow HI(+P)$

heat with glycerine

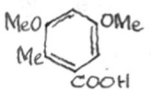


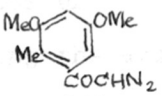
Decarboxydihydrocitrinone (5) $C_{12}H_{14}O_4$

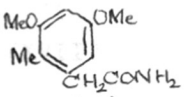
25% Aq. KOH

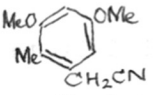
Phenolic alcohol (A) ← Decarboxydihydrocitrinone → Dimethyl ether

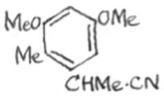
methylbenzyl cyanide (XIII). C-Methylation of the nitrile (XIII) by the interaction of the sodio-derivative with

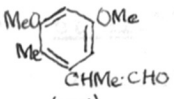

(X)

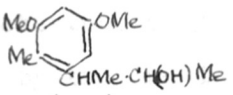

(XI)


(XII)


(XIII)

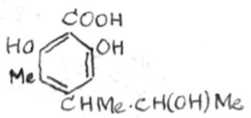

(XIV)

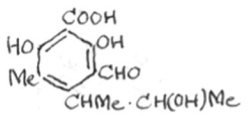

(XV)


(XVI)

dimethyl sulphate in benzene gave (XIV), which was reduced to the aldehyde (XV) by Stephen's method. Condensation of (XV) with methyl magnesium iodide yielded the alcohol (XVI). Fractional crystallization of the p-nitrobenzoate of (XVI) gave the p-nitrobenzoate of the dimethyl ether of the phenolic alcohol B which accompanies the optically active (-)-isomer (VI) when citrinin is hydrolysed.

Three partial syntheses of citrinin starting from the phenolic alcohol (VI) have been described so far. In one due to Robertson et al.[19,20] carboxylation of the phenolic alcohol (A)(VI) by means of potassium bicarbonate in glycerine at 150-55° gave the acid (XVII), from which the aldehyde (XVIII) was prepared by the Gatterman reaction.

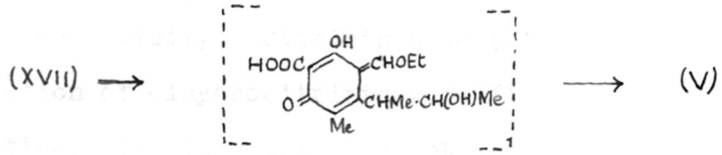

(XVII)


(XVIII)

Cold concentrated sulphuric acid effected cyclisation to citrinin which was shown to be identical with the

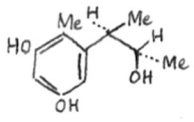
natural product. By a similar series of reactions on phenolic alcohol (B), they obtained inactive citrinin which was finally resolved into the (-)- form identical with natural citrinin by means of its brucine salt.

By heating the acid (XVII) with methylal in benzene saturated with dry hydrogen chloride in a sealed tube at 60° for 6 hours, Warren et al.[22] obtained dihydrocitrinin, which was then oxidised to citrinin by bromine in chloroform. A much simpler synthesis which has interesting possibilities in the isochroman series was achieved by Gore et al.[23] by the action of ethyl orthoformate on the acid (XVII) at room temperature and in nearly quantitative yield. The reaction probably proceeds through the ethoxymethylene derivative (XIX).

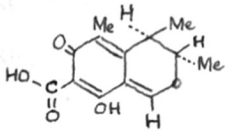


(XIX)

Cram[24] has collected evidence to represent the relative configurations about the two asymmetric carbon atoms in the phenolic alcohol (VI) and therefore in citrinin as (XX) and (XXI) respectively.



(XX)

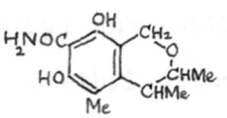


(XXI)

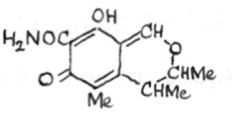
Present work

The object of the present work was to modify the structure of citrinin, and examine the toxicity and antibacterial properties of such citrinin derivatives and analogues in the hope that compounds with lower toxicity and improved antibacterial and chemotherapeutic properties may emerge. An important aspect of the investigation was the accumulation of data on the relation between constitution, toxicity and antibacterial properties in the isochroman series and in the new quinonoid type of which citrinin is an example.

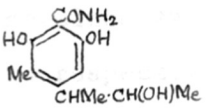
Attempts have been made to prepare derivatives of citrinin from natural citrinin or its hydrolytic products. The conversion of a carboxylic acid into its amide may be expected to decrease toxicity. Citrininamide (XXIII) was prepared by the oxidation of dihydrocitrininamide (XXII) and shown to be identical with the substance obtained by the action of ethyl orthoformate at room temperature on the amide of the acid (XXIV).



(XXII)



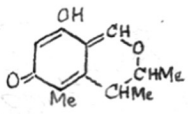
(XXIII)



(XXIV)

Dihydrocitrininamide was prepared by Schwenk *et al.*[25] from

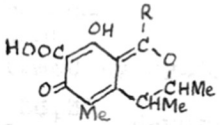
methyl dihydrocitrinin. A partial synthesis of inactive citrinin was effected by the action of ethyl orthoformate on the acid obtained by Y-carboxylation of the racemic compound produced as a by-product, together with the (-)-~~xxhx~~ form, in the acid or alkali hydrolysis of citrinin. It was observed that, whereas the acid (XVII) and its amide (XXIV) cyclised readily to citrinin and its amide on treatment with ethyl orthoformate at room temperature, the methyl ester did not cyclise under these conditions to give methyl citrinin. When the position between the two hydroxyl groups was unoccupied (VI) the ethyl orthoformate reaction gave an amorphous yellow substance, from which decarboxycitrinin (XXV) could



(XXV)

not be isolated.

With a view to study the effect of substituents in the heterocyclic ring of citrinin on its antibacterial activity, 1-alkyl derivatives of citrinin were prepared by the interaction of the acid (XVII) with appropriate ortho-esters. Thus 1-methyl and 1-ethyl citrinins (XXVI) were obtained by the use of ethyl orthoacetate and orthopropionate respectively.



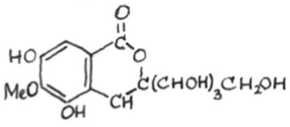
(R = Me, Et)

(XXVI)

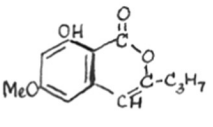
Isochromans

Isochroman and its derivatives have been stated to be useful in the preparation of medicinals and perfumes.[26] Although numerous isocoumarins[27] are known, the only isochromans apart from dihydrocitrinin that have been described in literature are the parent compounds and a few substituted isochromans.

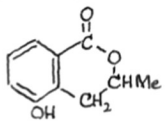
Very few isocoumarins have been reported to occur in nature. Bergenin or corylopsin[28,29] isolated from the roots of Saxifraga crassifolia and other members of the family Saxifragaceae, has been assigned the constitution (XXVII). Asahina and Nogami[30]



(XXVII)



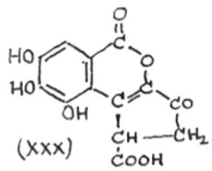
(XXVIII)



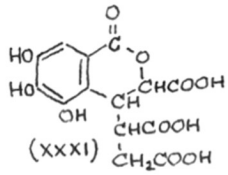
(XXIX)

isolated from Parmellia glomellifera an isocoumarin glomellin (XXVIII), the structure of which has been confirmed by synthesis.[31] Mellein or ochracin,[32,33] a mould metabolite of certain species of Aspergillus,[34] has been shown to be (XXIX) by analytical and synthetical studies.[35]

Brevifolincarboxylic acid,[36] the major crystalline component of Algarobilla tannin, has been shown to have the structure (XXX).



(XXX)



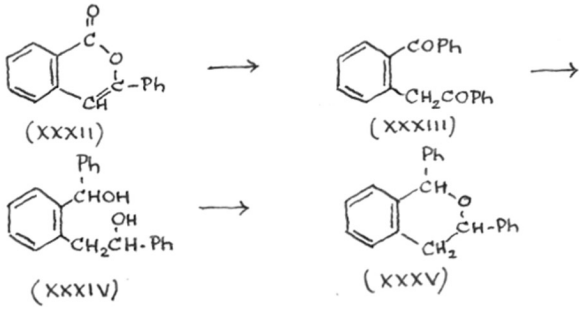
(XXXI)

of brevifolin

This has been confirmed by synthesis of O-trimethyl ether by two independent routes.[36,37] Haworth and DeSilva have shown that "split acid" (now known as chebulic acid), a hydrolysis product of chebulinic acid,[38] the crystalline constituent of the fruits of Terminalia chebula, is constituted as (XXXI).

The earliest reference to the formation of isochromans is by García Banús and Medrano[39] who found that the action of benzylmagnesium chloride on benzaldehyde gave 1:3-diphenylisochroman and 1:3-diphenylisochromene.

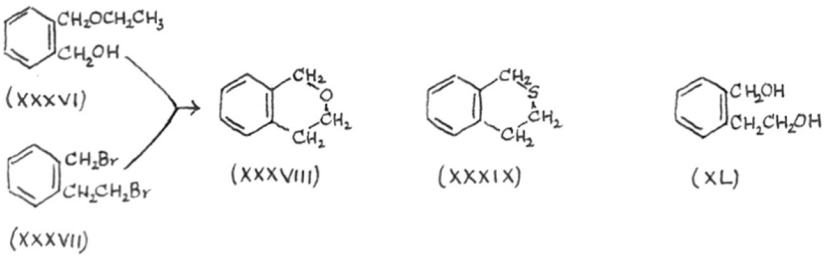
Siegel et al.[40] have recently reinvestigated the work of García Banús and have confirmed the formation of 1:3-diphenylisochroman (XXXV) by an independent synthesis. The key step in their synthesis was the addition of phenylmagnesium bromide to 3-phenylisocoumarin (XXXII) to yield 2-phenacylbenzophenone (XXXIII). The diketone (XXXIII) on



reduction with lithium aluminium hydride gave the glycol (XXXIV) which dehydrated readily to 1:3-diphenylisochroman (XXXV).

The synthesis of the parent compound (XXXVIII) is due to von Braun and Zobel,[41] who prepared it by the cyclization of β-o-ethoxymethylphenylethyl alcohol (XXXVI) with hydrobromic acid in a sealed tube at 100°. They also observed that the

two end carbon atoms in O-2-bromoethylbenzyl bromide (XXXVII) can be brought together not only through another carbon atom to



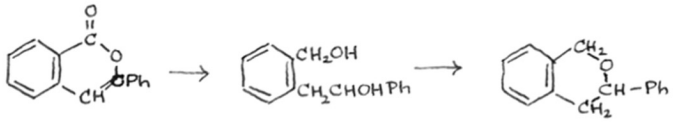
form tetralin derivatives or through a nitrogen to form tetrahydroisoquinoline derivatives, but also through oxygen or sulphur to form isochroman (XXXVIII) or thioisochroman (XXXIX).

Two German patents[26] describe the condensation of β-phenylethyl alcohol with formaldehyde or paraformaldehyde in presence of aqueous hydrochloric acid to form isochroman. With an excess of formaldehyde and hydrochloric acid, a second chloromethyl group enters the benzene ring, probably in the para position to the alcoholic group, forming a chloromethyl isochroman. The same patents also describe the preparation of methyl isochroman and chloromethyl methyl isochroman from β-tolylethyl alcohol and a nitroisochroman from β-nitrophenylethyl alcohol by the same procedure.

Siegel and Coburn[42] have reported the synthesis of isochroman by reduction of homophthalic anhydride or methyl homophthalate with lithium aluminium hydride and subsequent dehydration of the alcohol (XL) with potassium hydrogen sulphate.

Homophthalyl alcohol (XL) has been prepared in 91% yield by Anderson and Holliman[43] by lithium aluminium hydride reduction of ethyl homophthalate; when homophthalic anhydride was similarly reduced and the product distilled at 110°/25 mm., isochroman was obtained in 33% yield.

3-Phenylisochroman (XLII) has been synthesized by Siegel et al.[42] by the lithium aluminium hydride reduction of 3-phenylisocoumarin and subsequent dehydration of the glycol (XLI). Siegel, Coburn and Levering[44] describe a general

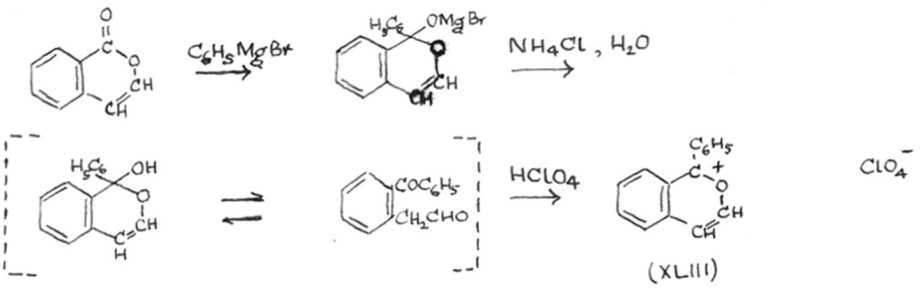


(XLI) (XLII)

method for the synthesis of 1:3-dialkyl- and 1:3-diarylisochromans by dehydration of the "abnormal products" or glycols obtained in the reaction between benzylmagnesium chloride and aldehydes. Schieler and Sprenger[45] have synthesized 6-hydroxyisochroman. m-Hydroxy-β-phenylethyl alcohol was converted into 4-hydroxy-3-(β-hydroxymethyl)-benzaldehyde, which on reduction with lithium aluminium hydride split off water spontaneously to give 6-hydroxyisochroman.

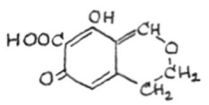
An isochromene derivative, isobenzpyrylium ferric chloride was prepared by Blount and Robinson[46] by the action of hydrogen chloride and ferric chloride on homophthaldehyde. An isobenzpyrylium salt, 1-phenylisobenzpyrylium perchlorate[47] (XLIII)

has been prepared by treating the carbinol obtained from the reaction of isocoumarin and phenylmagnesium bromide with perchloric acid.



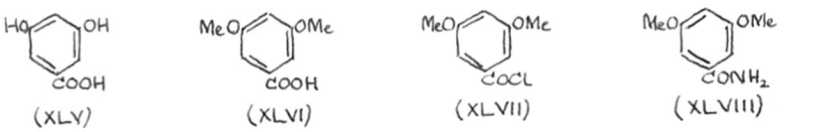
(XLIII)

The simplest analogue of citrinin is norcitrinin (XLIV) and its synthesis was attempted by several methods.



(XLIV)

β-3:5-Dimethoxyphenylethyl alcohol (LII) was prepared by two routes. The first involved the action of ethylene oxide on the Grignard reagent from 3:5-dimethoxyiodobenzene (LI) which was prepared by a series of reactions starting from α-resorcylic acid (3:5-dihydroxybenzoic acid)(XLV) via its methyl ether (XLVI), acid chloride (XLVII), amide (XLVIII) and amine (XLIX).



(XLV) (XLVI) (XLVII) (XLVIII)

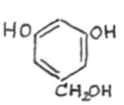
(XLIX) (L) (LI) (LII)

3:5-Dimethoxybromobenzene (L) was found to be less

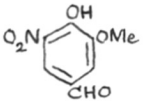
reactive than the corresponding iodo compound (LI).

In the second method 3:5-dimethoxybenzoic acid (XLVI) was reduced by lithium aluminium hydride to the benzyl alcohol (LIX), which was converted to the corresponding chloride (LX) and nitrile (LXI) following the conditions of Adams et al.[48] The nitrile on hydrolysis with caustic potash gave the acid (LXII). Birch[49] has prepared the same acid (LXII) by acid hydrolysis of the nitrile (LXI).

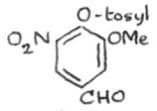
An attempt to prepare 3:5-dihydroxybenzyl alcohol (LIII) from the tosyl ester of 5-nitrovanillin (LIV) proved unsuccessful. Vanillin was nitrated with nitric acid in glacial acetic acid according to the method of Bentley[50] to give 5-nitrovanillin (LIV), which on treatment with p-toluenesulphonyl chloride gave the corresponding tosyl ester (LV). Reduction of this ester with Raney nickel in dioxan did not give the desired aminoalcohol, but an oily product which was soluble in dilute aqueous caustic soda; it contained no sulphur, and appeared to be impure 3-amino-4-hydroxy-5-methoxytoluene. The action of Raney nickel on tosyl ester of vanillin (LVI),



(LIII)

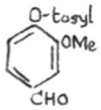


(LIV)

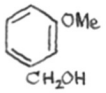


(LV)

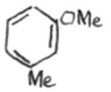
following the method of Kenner and Murray,[51] gave an 80% yield of m-methoxybenzyl alcohol (LVII).



(LVI)



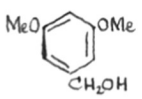
(LVII)

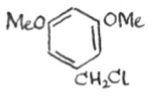


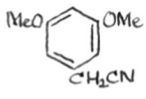
(LVIII)

The reduction of vanillin tosylate (LVI) by the Mozingo method led to m-cresol methyl ether (LVIII)[52] (60%), and a trace of a sulphur-containing oil.

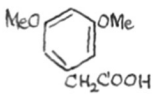
Reduction of (LXII) with lithium aluminium hydride gave β-3:5-dimethoxyphenylethyl alcohol (LII). Attempts to demethylate (LII) by various reagents, such as hydrobromic acid in acetic acid, hydriodic acid and red phosphorus, aluminium chloride and aluminium bromide in benzene, toluene, xylene and nitrobenzene and pyridine and aniline hydrochlorides were however unsuccessful. Demethylation with hydrobromic acid in

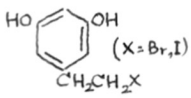

(LIX)

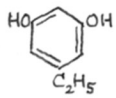

(LX)

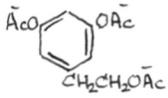

(LXI)

acetic acid and hydriodic acid and red phosphorus gave the corresponding alkyl halide (LXIII) instead of the desired phenolic alcohol. The formation of the halide was proved by its reduction with zinc and acetic acid to 5-ethylresorcinol (LXIV) and comparison with an authentic sample.[53] Attempts to replace the halogen in (LXIII) by a hydroxyl group by means of


(LXII)

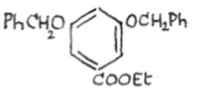

(LXIII)

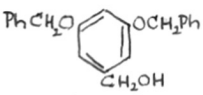

(LXIV)

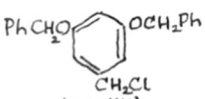

(LXV)

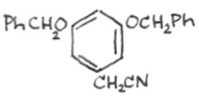
caustic alkalis were unsuccessful, intractable gummy products being formed. However, on treatment of (LXIII) with acetic anhydride and sodium acetate, the triacetate (LXV) was obtained.

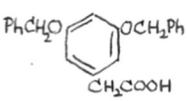
β-3:5-Dihydroxyphenylethyl alcohol (LXXV) was ultimately obtained by carrying out a similar series of reactions, starting from ethyl 3:5-bis(benzyloxy)benzoate (LXVI) instead of the dimethyl ether. It was subsequently found that β-3:5-

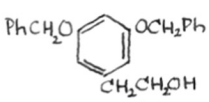

(LXVI)


(LXVII)


(LXVIII)

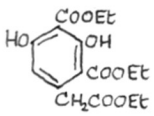

(LXIX)

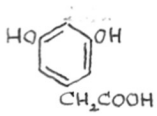

(LXX)

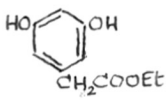

(LXXI)

bis(benzyloxy)phenylethyl alcohol (LXXI) could be more conveniently prepared from ethyl acetonedicarboxylate via the triester (LXXII) and its ethylester (LXXIV) according to Schmid and Theilacker.[54] The dibenzyl ether (LXXI) could be debenzylated

3:5-dihydroxyphenylacetic acid (LXXIII)

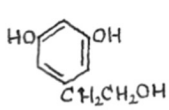

(LXXII)

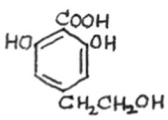

(LXXIII)

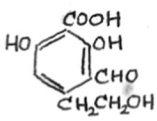

(LXXIV)

smoothly and quantitatively with palladium on charcoal to the phenol (LXXV).

Carboxylation of the phenol (LXXV) according to the method of Robertson and Robinson[55] using glycerine and potassium bicarbonate, gave the γ-acid (LXXVI) in excellent yield. The acid like the analogous intermediate (XVII) for citrinin, cyclised with ethyl orthoformate; but the product was an

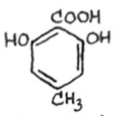

(LXXV)

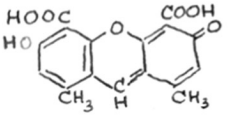

(LXXVI)


(LXXVII)

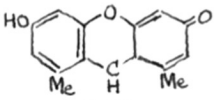
amorphous and presumably polymeric substance, and not norcitrinin (XLIV). The substance, which did not melt below 320°, behaved like a quinonecarboxylic acid, and was soluble in aqueous sodium bicarbonate; the solution exhibited a red-green fluorescence. Like citrinin it gave an iodine-brown ferric colouration.

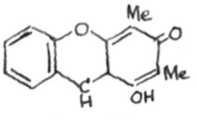
The action of ethyl orthoformate on p-orsellinic acid (LXXVIII) gave a crystalline yellowish brown substance, which decomposed at 280° and behaved like a quinone carboxylic acid. Like the ethyl orthoformate reaction product on the acid (LXXVI), it was soluble in aqueous sodium bicarbonate and


(LXXVIII)


(LXXIX)

exhibited an iodine-brown ferric reaction. Analysis agreed with the structure (LXXIX). Compounds (LXXX) and (LXXXI) have been

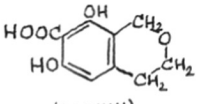

(LXXX)


(LXXXI)

recorded in literature.[56]

The acid (LXXVI) underwent the Gattermann reaction, but the resultant aldehyde (LXXVII) by also failed to cyclise to norcitrinin (XLIV) by the action of conc. sulphuric acid, as described by Robertson et al.[19,20] for the synthesis of citrinin. Robertson et al.[20] have synthesised dihydrocitrinin by the condensation of the acid (XVII) with formaldehyde in aqueous sodium hydroxide. The action of formaldehyde and aqueous

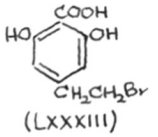
sodium hydroxide on the acid (LXXVI) failed to give dihydronorcitrinin (LXXXII); the product was an amorphous substance which had no m.p., polymerisation apparently taking place because more than one position ortho to the hydroxyl group was



(LXXXII)

unsubstituted.

The next attempt was therefore directed towards blocking one of the β-positions in the resorcinol nucleus in (LXXVI) with halogen or an alkyl group so as to eliminate the tendency for polymerisation on treatment with ethyl orthoformate, or formaldehyde and aqueous sodium hydroxide. Bromination of (LXXVI) in glacial acetic acid resulted in the formation of the alkyl bromide (LXXXIII) which failed to cyclise with

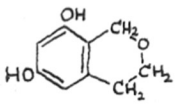


(LXXXIII)

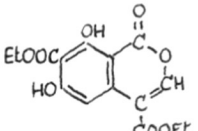
ethyl orthoformate.

The next attempt for the synthesis of norcitrinin (XLIV) was the synthesis of 6:8-dihydroxyisochroman (LXXXIV) followed by carboxylation in the γ-position. The action of ethyl orthoformate, pyridine and piperidine on the triester (LXXII) was first studied in the hope that it may yield the isocoumarin derivative (LXXXV). The product, however, was the diethyl ester (LXXXVII) of orcinol-ω-2:4-tricarboxylic acid, which was prepared by Jerdan[57] by treating ethyl acetonedicarboxylate

with magnesium and ethyl chloracetate. It was then found

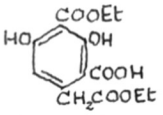


(LXXXIV)

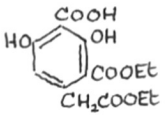


(LXXXV)

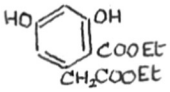
that a convenient method for the selective hydrolysis of the triester (LXXII) to the diester (LXXXVII) was to reflux the triester (LXXII) with pyridine and a little piperidine for a few hours. Jerdan had assigned the structure (LXXXVI) to the product of the interaction of ethyl acetonedicarboxylate, magnesium and ethyl chloracetate, but it was shown by Asahina and Nogami[58] that the substance was the isomeric acid (LXXXVII).



(LXXXVI)

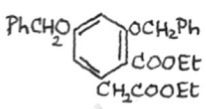


(LXXXVII)

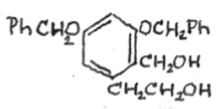


(LXXXVIII)

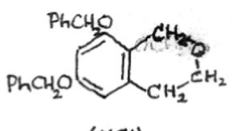
Decarboxylation of the acid (LXXXVII) to (LXXXVIII) was effected by heating with glycerine at 150°; by increasing the time of heating from 15 to 30 minutes[59] the yield was raised from 40 to 46 per cent. Treatment of (LXXXVIII) with benzyl chloride and potassium carbonate in acetone gave the dibenzyl ether (LXXXIX) as a nearly colourless viscous oil. Reduction of (LXXXIX) with an excess of lithium aluminium hydride yielded a mixture of the glycol (XC) and 6:8-bisbenzyloxy-isochroman (XCI). The glycol, on attempted debenzylation with palladium on charcoal, gave a viscous glassy product, which



(LXXXIX)



(XC)

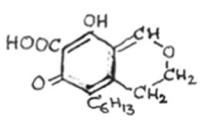


(XCI)

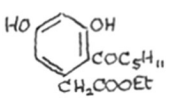
could not be purified further. Debenzylation of (XCI) with

palladinized carbon gave an almost quantitative yield of 6:8-dihydroxyisochroman (LXXXIV). Attempts to carboxylate (LXXXIV) by the glycerine-potassium bicarbonate method to dihydronorcitrinin (LXXXII) were unsuccessful.

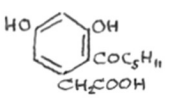
The preparation of 2-n-hexyl-β-3:5-dihydroxyphenylethyl alcohol (XCIX) was undertaken, because it was anticipated that the Y-acid (C) would cyclise readily to 5-n-hexylnorcitrinin (XCII), and that this hexylresorcinol derivative on analogy of hexylresorcinol itself in comparison with resorcinol and other alkylresorcinols may be more potent as an antibacterial agent and less toxic than citrinin.



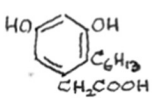
(XCII)



(XCIII)



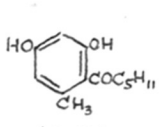
(XCIV)

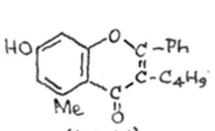


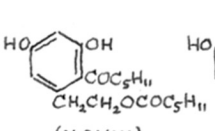
(XCV)

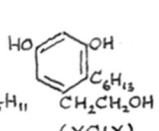
Ethyl 2-caproyl-3:5-dihydroxyphenylacetate (XCIII) was obtained by the action of boron trifluoride on n-caproic acid and ethyl 3:5-dihydroxyphenylacetate (LXXIV). That the acyl group entered one of the β-positions in the resorcinol nucleus was proved by carrying out a model experiment with orcinol (5-methylresorcinol). The ketone (XCVI) obtained by the action of boron trifluoride and n-caproic acid underwent the Allan-Robinson[60] condensation with benzoic anhydride and sodium benzoate to give in nearly quantitative yield the flavone (XCVII), which had the properties of a 7-hydroxyflavone and not a 5-hydroxyflavone. The acid (XCIV) was obtained

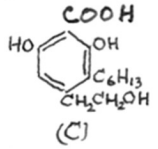
by hydrolysis of the ester (XCIII) with alcoholic caustic soda. 3:5-Dihydroxyphenylacetic acid (LXXIII) also underwent the boron trifluoride reaction with n-caproic acid to give the ketone (XCIV), but in comparatively poor yield. The ketone (XCIV) could not be reduced to the alkyl derivative (XCV) with Raney nickel according to the method of Mozingo.[61] The Clemmensen method gave an extremely poor yield of (XCV).


(XCVI)


(XCVII)

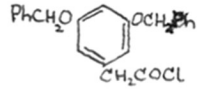

(XCVIII)

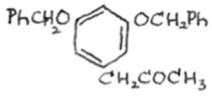

(XCIX)

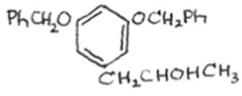

(C)

2-n-Hexyl-β-3:5-dihydroxyphenylethyl alcohol (XCIX) was obtained by the action of boron trifluoride on n-caproic acid and β-3:5-dihydroxyphenylethyl alcohol (LXXV), followed by Clemmensen's method of reduction. The condensation of (LXXV) with n-caproic acid and boron trifluoride gave the ester-ketone (XCVIII) which during reduction underwent hydrolysis. Attempts to carboxylate (XCIX) in glycerine proved unsuccessful.

The secondary alcoholic group in (XVII) may be associated with its ready cyclization to citrinin by the action of ethyl orthoformate at room temperature and in the absence of any

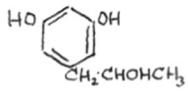

(CI)


(CII)

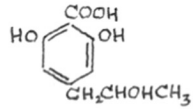

(CIII)

condensing agent. Attempts were therefore made to prepare the γ-acid (CV) from the secondary alcohol (CIV) and study the ethyl orthoformate reaction. The interaction of 3:5-bis(benzyloxy)benzyl cyanide (LXIX) with an excess of methylmagnesium iodide in warm ether

gave the ketone (CII). The same ketone was also obtained by the action of zinc-methyl iodide on 3:5-bis(benzyloxy)phenyl acetyl chloride (CI). Reduction of the ketone (CII) with lithium aluminium hydride gave an almost quantitative yield of the carbinol (CIII). Debenzylation of (CIII) in 95% methanol



(CIV)



(CV)

using palladinized carbon led to the phenol (CIV) as an almost colourless glass which could not be induced to crystallize; it gave a pale bluish violet colour with ferric chloride and was soluble in aqueous caustic soda and sodium carbonate forming a pink solution. The Y-acid (CV) was obtained by carboxylation in glycerine. The acid (CV) gave the characteristic intense blue colouration with ferric chloride, but failed to undergo cyclisation with ethyl orthoformate.

The antibacterial activity of citrinin, its degradation products and derivatives, determined by Dr. D. V. Tamhane, is recorded in Table I.

Table I

Antibacterial activity of citrinin, its degradation products and derivatives.

Compound	Antibacterial action in peptone medium
Citrinin	1:66,667 - 1:80,000 against *S. aureus* F.D.A. 209.
Optically inactive citrinin	1:17,000 - 1:20,000 against *S. aureus*.
Phenolic alcohol (A)	Not active against *S. aureus*, *S. haemolyticus*, *D.pneumoniae*, *E. coli*, *S. typhosa*. Slight inhibition against *V. cholerae*.
Phenolic alcohol (A)-carboxylic acid	No action against *S. aureus* and *E. coli*.
Dihydrocitrinin	Inactive. Results similar to phenolic alcohol (A).
Citrininamide	1:2,000 - 1:3,000 against *S.aureus* F.D.A. 209 ~~by agar streak method~~. 1:6900 - 1:10,000 against *S.albus*.
1-Methyl citrinin	Not active against *S. aureus* F.D.A. 209 and *E. coli* up to 1:3,000.

The toxicity of citrinin and its derivatives, determined by Dr. D. V. Tamhane, is recorded in Table II.

Toxicity of citrinin and its derivatives. Table II.

Compound	Method of administration	Dose g./kg.body wt.	% mortality	Remarks
Citrinin	Oral (as solution in saline citrate)	0.03-0.26 g.	No mortality	No loss of activity
		0.33 g. in one dose	-Do-	Sluggishness for 24 hours.
		0.297 in 3 doses		
	Intraperitoneal	0.066 g.	-Do-	-Do-
		0.132 g.	50% death	Extensive haemorrhage in liver, kidney and spleen.
Citrinin as salts:				
Sodium salt	Subcutaneous	0.100 g.	100% mortality	No injury to liver, kidney and spleen.
		0.133 g.	-Do-	-Do-
		0.067 g.	No death	Sluggish for 24 hours.
Ammonium salt	-Do-	0.100 g.	100% death in 24 hrs.	No signs of injury to liver, kidney and spleen.
		0.067 g.	No death	Sluggish for 24 hours.
Lithium salt	-Do-	0.100 g.	100% death	No injury to liver, kidney and spleen
		0.067 g.	No death	All mice active.
Citrinin sulphadiazine mixture (1:1)	-Do-	0.067 g.	No death	All mice active.
		0.100 g.	33% death	Other mice active.

.... contd .....

Table II (contd.)

Dihydrocitrinin (neutral solution)	Intraperitoneal	0.100 g. 0.200 g.	No death No death	All mice active Slightly sluggish for 24 hours.
Citrininamide (as solution in 66% propylene glycol)	-Do-	0.160 g. 0.400 g.	No death 100% death in 1/2 hr.	Sluggish for 24 hours. Autopsy showed no visible injury to liver, lung or spleen.

The antibacterial and antifungal activity of certain resorcinol derivatives, determined by Mrs. S. R. Shah, is recorded in Table III.

Table III - Antibacterial and antifungal activity of certain resorcinol derivatives.

Compound	Staphylococcus aureus	Bacillus typhosus	Trichophyton rubrum	Trichophyton gypseum	Aspergillus niger	Epidermophyton floccussum
3:5-Dihydroxybenzyl alcohol	1:10,000	1:10,000	1:20,000	(-ve)	1:20,000	(-ve)
4-Carboxy-3:5-dihydroxybenzyl alcohol	(-ve)	(-ve)	1:25,000	1:25,000	1:20,000	1:25,000
β-3:5-Dihydroxyphenylethyl alcohol	-Do-	-Do-	1:25,000	1:25,000	1:25,000	1:25,000
4-Carboxy-3:5-dihydroxy-β-phenylethyl alcohol	-Do-	-Do-	1:25,000	1:25,000	1:25,000	1:25,000
2-n-Hexyl-3:5-dihydroxyphenylacetic acid	-Do-	-Do-	1:20,000	1:20,000	(-ve)	1:20,000
6:8-Dihydroxyisochroman	-Do-	-Do-	1:20,000	(-ve)	-Do-	1:20,000
Ethyl orthoformate reaction product on 4-carboxy-3:5-dihydroxy-β-phenyl ethyl alcohol	-Do-	-Do-	1:20,000	1:20,000	1:20,000	1:20,000
6-Dimethylaminomethyl-5-methylresorcinol-2-carboxylic acid	1:20,000	1:20,000	1:40,000	1:40,000	1:40,000	1:40,000
4-Carboxy-3:5-dihydroxystilbene	(-ve)	(-ve)	1:15,000	1:15,000	1:7,500	1:15,000

EXPERIMENTAL

4-Methyl-5-(1-methyl-2-hydroxy)-propylresorcinol:

Phenolic alcohols (A) and (B)(VI) :

Citrinin was hydrolysed according to the method of Robertson et al.[17] by refluxing with 10% aqueous caustic soda in an atmosphere of nitrogen. The phenolic alcohol (A) crystallized from chloroform as colourless needles melting at 129-30° (Robertson et al. mention 127-28°). Phenolic alcohol (B) crystallized from ethyl acetate in colourless prisms, m.p. 169-70° (Robertson et al. mention m.p. 169-70°).

laevo-2-Carboxy-4-methyl-5-(1-methyl-2-hydroxy)-propyl resorcinol (XVII):

The acid (XVII) was obtained by carboxylation of (VI) following the method of Robertson and Robinson.[55] The product crystallized from water as colourless prisms, m.p. 171-72° (dec.) (Robertson et al.[20] mention 185°,(dec.). Warren et al.[22], m.p. 178·5 - 79·8 (dec.)) An aqueous solution of the acid gives an intense blue colouration with ferric chloride.

dl-2-Carboxy-4-methyl-5-(1-methyl-2-hydroxy)-propylresorcinol (XVII):

The acid (XVII) was prepared from the phenolic alcohol (B)(VI) following the same conditions as above. The acid crystallized from benzene as colourless prisms,

m.p. 172° (dec.). An aqueous solution of the acid gives an intense blue colouration with ferric chloride. The carboxylic acid of the phenolic alcohol (A)(XVII) was also obtained from the alcoholic mother liquor after crystallization of citrinin. The mother liquor on concentration to a small volume under diminished pressure gave a resinous residue which on keeping for 3-4 days in an open dish formed a dark brown viscous mass. The mass (about 15 g.) was extracted with a saturated solution of sodium bicarbonate (300 ml.) and the orange-yellow solution filtered. The filtrate and the washings on acidification with dilute hydrochloric acid gave a small amount of resinous precipitate which was filtered off. The clear filtrate after saturation with ammonium sulphate was ether extracted. Evaporation of ether left a solid (1.8 g.) which crystallized from water in small colourless needles, m.p. 171° (dec.). Mixed m.p. with an authentic sample of the acid (XVII) showed no depression.

Optically inactive citrinin (V):

The optically inactive acid (XVII)(0.1 g.) was weighed out in a dry test-tube and ethyl orthoformate (1 ml.) was added to it at room temperature (28°). The reaction mixture immediately turned yellow and a bright yellow crystalline solid separated. Crushed-ice was added after 10 minutes and the yellow crystalline product collected, washed and dried (0.09 g.). Crystallization from alcohol gave lemon yellow needles of inactive citrinin, m.p. 171.5° (dec.), undepressed by admixture

with a sample of natural citrinin (Found: C, 62.3; H, 5.6; $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.6%). The synthetic product exhibits the typical iodine-brown colouration in alcoholic solution with ferric chloride.

Dihydrocitrinin:

Citrinin was hydrogenated to dihydrocitrinin after the method of Robertson et al.[18] The product crystallized from benzene-acetone mixture in colourless prisms, m.p. 172° (dec.) (Robertson et al., 171°,(dec.) . An aqueous and alcoholic solution of the substance gives a blue colouration with ferric chloride.

The dihydro compound was also obtained by hydrogenating citrinin (1 g.) in alcohol (20 ml.) in presence of Raney nickel (0.2 g.) at 40 lbs./sq.inch in the course of 2 hours. After filtration of the catalyst and removal of the solvent, the residue crystallized from benzene---acetone mixture in small colourless prisms, m.p. 171-72° (dec.), identical with the product obtained in the above experiment.

Methyl ester of dihydrocitrinin:

The methyl ester of dihydrocitrinin was prepared following the method of Robertson et al.[20] The product crystallized from light petroleum (40-60°) in colourless prisms, m.p. 60° (Robertson et al. mention m.p. 60°).

Dihydrocitrinin amide (XXII):

The methyl ester of dihydrocitrinin (2.5 g.) was dissolved in dry methanol (100 ml.) and saturated with dry ammonia. The mixture was allowed to stand at room temperature (28-29°) for 24 hours. On evaporating off the ammonia and methanol, a nearly colourless mass of crystals separated (2.1 g.). Crystallization from dilute methanol gave colourless needles, m.p. 201-202° (Found: C, 62.5; H, 6.5; N, 5.5. $C_{13}H_{17}O_4N$ requires C, 62.1; H, 6.8; N, 5.6%) (Schwenk et al.[25] quote m.p. 202-203°).

Oxidation of dihydrocitrinin amide (XXII) to citrinin amide (XXIII):

Dihydrocitrinin amide (XXII)(0.1 g.) in dioxan (10 ml.) and selenium dioxide (0.2 g.) was heated on a steam bath for 1 1/2 hours. The nearly colourless reaction mixture turned bright yellow. The mixture was filtered and the filtrate concentrated under diminished pressure, when a yellow oil separated which solidified gradually (0.085 g.). Two crystallizations from dilute dioxan gave bright yellow needles, m.p. 114-15°, unchanged on admixture with citrininamide (XXIII) obtained by the action of ethyl orthoformate on (XXIV) (Found: C, 62.6; H, 6.1; N, 5.6. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.1; N, 5.6%).

2-Carbomethoxy-4-methyl-5-(1-methyl-2-hydroxy)propylresorcinol:

A solution of the acid (XVII)(8 g.) in either (100 ml.) and absolute methanol (50 ml.) was treated with more than one molecular proportion of diazomethane [from

nitrosomethylurea (6 g.) in ether (80 ml.). The reaction mixture was allowed to stand at 10° for 24 hours. The ether after filtration was washed with aqueous sodium bicarbonate, water and dried over anhydrous sodium sulphate. Evaporation of the ethereal solution gave a brown oil (6 g.), which on distillation under reduced pressure (b.p. 165-68°/0.1 mm.) gave a nearly colourless oil (5.4 g.) (Robertson et al.[20] mention b.p. 164-66°/0.1 mm.).

2-Carboxamide-4-methyl-5-(1-methyl-2-hydroxy)propylresorcinol (XXIV):

The above ester (5 g.) was dissolved in dry methanol (100 ml.) and saturated with dry ammonia at 0°. The mixture was allowed to stand at room temperature (28-29°) for 24 hours. On evaporating off the excess ammonia and methanol, a pinkish crystalline mass separated (4.6 g.). Crystallization from dilute methanol gave pale yellow plates, m.p. 194-95° (Found: C, 60.5; H, 7.3; N, 5.6. $C_{12}H_{17}NO_4$ requires C, 60.2; H, 7.2; N, 5.8%).

Citrinin amide (XXIII):

The above amide (XXIV) (0.3 g.), ethyl orthoformate (3 ml.) and acetic anhydride (2 drops) were warmed on a water-bath at 50° for 1 hour when a bright yellow solution resulted. On pouring into crushed ice and acidifying with dilute hydrochloric acid a bright yellow sticky solid separated (0.2 g.) which solidified on triturating with methanol. Crystallization from dilute dioxan gave

shining yellow needles, m.p. 114-15°, undepressed on admixture with the dehydrogenation product of dihydrocitrininamide (XXII) (Found: C, 62.3; H, 6.0; N, 5.6. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.1; N, 5.6%).

Attempted synthesis of decarboxycitrinin (XXV):

Phenolic alcohol (A)(VI) (0.2 g.) and ethyl orthoformate (1 ml.) were mixed together, acetic anhydride (2 drops) was added and the mixture warmed on a water-bath at 60° for 1 hour. The bright yellow reaction mixture was decomposed with crushed-ice and dil. hydrochloric acid and extracted with ether. Evaporation of ether gave a yellow product which could not be crystallized or sublimed but separated as an amorphous yellow solid from a mixture of benzene and n-hexane, m.p. 216-18° (Found: C, 68.2; H, 7.0. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%). An alcoholic solution of the substance gives a dirty brown ferric reaction.

1-Methylcitrinin (XXVI; R=Me):

The acid (XVII) (0.1 g.) ethyl orthoacetate (2 ml.) were mixed together and warmed on a water bath at 50° for 15 minutes when the acid went completely in solution. The greenish-brown reaction mixture was kept at room temperature (30°) for 1/2 hour. Crushed-ice and a trace of hydrochloric acid were added when a greenish-yellow crystalline solid separated which was filtered, washed and dried (0.095 g.). Crystallization from dilute

alcohol gave pale greenish yellow plates, m.p. 245° (dec.) (Found: C, 63.5; H, 6.0. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%). An alcoholic solution of the product gives an iodine-brown colouration with ferric chloride.

1-Ethylcitrinin (XXVI; R=Et)

The action of ethyl orthopropionate on the acid (XVII) gave 1-ethylcitrinin (XXVI; R=Et) in nearly quantitative yield, m.p. 137-38° (dec.) (Found: C, 64.6; H, 6.2. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%). An alcoholic solution of the substance gives an iodine-brown colouration with ferric chloride.

3:5-Dihydroxybenzoic acid: (α-resorcylic acid) (XLV):

Benzoic acid was sulphonated with 30% oleum following the method given in Organic Syntheses.[62] The barium salt was fused with a mixture of equal weights of sodium and potassium hydroxides to give a 65-66% yield of the dihydroxy acid. The product crystallized from acetic acid in nearly colourless needles, m.p. 230-31° (dec.).

3:5-Dimethoxybenzoic acid (XLVI):

For the methylation, the method of Suter and Weston[63] was employed. The product crystallized from water in colourless needles, m.p. 183-84° (Suter and Weston, 184°).

3:5-Dimethoxybenzamide (XLVIII):

The amide (XLVIII) was prepared following the method of Suter and Weston.[63] The amide crystallized from benzene (norit) as silky colourless needles, m.p. 146° (Mauthner,[64] 148-149°; Seka and Fuchs,[65] 148-149°; Suter and Weston[63] 146°).

3:5-Dimethoxyaniline (XLIX):

To an alkaline solution of sodium hypochlorite prepared by passing chlorine (0.412 g. for each g. of amide) into a mixture of cracked ice (100 g.) and a cold solution of sodium hydroxide (27 g.) in water (165 ml.) was added 3:5-dimethoxybenzamide (XLVIII)(19.5 g.) in one lot, and the mixture warmed slowly in a waterbath with mechanical stirring. The material darkened in colour

and at 50-55° (internal temperature) oily droplets began to separate. The temperature was raised to 70° and maintained at this point for 1 hour. A solution of sodium hydroxide (40 g.) in water (40 ml.) was added slowly and the temperature increased to 80° for an additional hour. Upon cooling a brown oily layer of the amine separated, which was taken up in benzene. The aqueous alkaline liquors was extracted with benzene. The benzene after washing with water was distilled off, the residual dark brown amine was distilled under reduced pressure and the fraction distilling at 170-75°/10 mm. collected (11.7 g.). The distillate solidified on cooling, m.p. 46° (Seka and Fuchs[65] mention 46°).

3:5-Dimethoxy bromobenzene (L)(A) Sandmeyer's method:

3:5-Dimethoxyaniline (XLIX)(2 g.) was diazotized by means of 46% hydrobromic acid (10 ml.) and sodium nitrite (1 g.) in water (4 ml.) and the clear yellowish brown diazonium solution was added gradually to cuprous bromide [prepared from copper sulphate (4 g.), potassium bromide (2.7 g.) and sodium sulphite (1 g.)], in hydrobromic acid (20 ml.) at 75-80° with stirring for 1 hour. The reaction mixture was cooled and extracted with benzene. The benzene layer was washed with aqueous caustic soda, dilute hydrochloric acid and water. Removal of the solvent gave a reddish oil which on distillation under reduced pressure gave a colourless oil, 110-20°/2 mm., which solidified immediately to a colourless mass

of crystals (0.8 g.), m.p. 57-58°. Recrystallization from dilute alcohol gave shining colourless plates, m.p. 60° (Found: C, 44.0; H, 4.6. $C_8H_9O_2Br$ requires C, 44.2; H, 4.1%).

(B) Schwechten's method:[66]

The amine (XLIX)(7.6 g.) was emulsified with warm water (50 ml.) and conc. hydrochloric acid (18 ml.) added. The amine hydrochloride was then diazotized at 0° with 20% aqueous sodium nitrite (3.8 g.). A solution of mercuric bromide complex[(prepared by adding a saturated solution of potassium bromide (18 g.) to mercuric nitrate (12 g.) in water (36 ml.)] was added when a reddish brown precipitate separated. After stirring for 1 hour the precipitate was collected, washed with water till the washings were colourless, and then with acetone and ether and dried in a desiccator. The complex of the diazonium compound was then intimately mixed with potassium bromide (44 g.) and heated in a thin layer in a flask provided with an air-condenser. The decomposition product was extracted with benzene. The benzene after washing with dilute alkali, hydrochloric acid and water was desolvated when a light reddish brown oil resulted which on distillation under reduced pressure gave a colourless mass of crystals (3.55 g.), m.p. 59-60°, identical with the product obtained in the previous experiment.

3:5-Dimethoxyiodobenzene (LI):

3:5-Dimethoxyaniline (XLIX)(1.5 g.) was dissolved by warming with conc. sulphuric acid (2 ml.) in water (10 ml.). The amine sulphate that separated on cooling was diazotized with sodium nitrite (0.8 g.) ~~with~~ in water (10 ml.). Potassium iodide (3 g.) was added to the clear orange-red diazonium solution and the reaction mixture stirred at ~~ø~~ 0° for 30 minutes. The temperature was then gradually raised to 60° and maintained at this point for 1 hour, cooled and extracted with ether. The ether extract was washed with dilute alkali, acid and water. Evaporation of the dried ethereal extract gave a red oil which on distillation under reduced pressure gave a colourless oil (0.6 g.), b.p. 140-50°/1-2 mm. which solidified to a mass of colourless crystals, m.p. 68-70°. Crystallization from dilute alcohol gave colourless needles, m.p. 70° (Found: C, 36.0; H, 3.1; I, 48.1. $C_8H_9O_2I$ requires C, 36.3; H, 3.4; I, 48.1%).

β-3:5-Dimethoxyphenylethyl alcohol (LII):

A solution of 3:5-dimethoxyiodobenzene (LI)(5 g.), ethyl bromide ~~xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx~~ (2.2 g.) in anhydrous ether (50 ml.) was added gradually to magnesium turnings (1 g.) suspended in anhydrous ether (50 ml.) in a three-neck flask equipped with a condenser, a dropping funnel and a mercury-seal stirrer. After complete addition (30 minutes) and when the initial vigour of the reaction had

subsided, the reaction mixture was stirred and refluxed for 2 hours. The Grignard reagent was then cooled to 0° and ethylene oxide (4 g.) in dry benzene (25 ml.) was added when a vigorous reaction took place. After standing for two hours at 0°, the mixture was left for 12 hours at room temperature (30°) and then refluxed for 4 hours. The contents of the flask were cooled again to 5° and more ethylene oxide (1 g.) in benzene (15 ml.) was added. After stirring at 0° for one hour, the mixture was again refluxed for two hours, cooled and hydrolysed with ice and dilute sulphuric acid and extracted with ether. The ethereal extract was washed with aqueous sodium bisulphite, caustic soda and water. Evaporation of the solvent gave a brown oil, which on fractionation under reduced pressure gave a forerun up to 120°/1 mm. which was discarded and the main fraction from 175-80°/1 mm. collected (2.2 g.) (Found: C, 65.4; H, 7.3. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%).

The dinitrobenzoate of (LII) crystallized from dilute alcohol in orange-yellow needles, m.p. 142° (Found: N, 7.2 . $C_{17}H_{16}O_8N_2$ requires N, 7.4%).

3:5-Dimethoxybenzyl alcohol (LIX):

3:5-Dimethoxybenzyl alcohol (LIX) was prepared from 3:5-dimethoxy benzoic acid (XLVI) by lithium aluminium hydride reduction following the method of Adams et al.[48] in 92% yield. The product distilled under reduced pressure, b.p. 170-74°/0.6-0.8 mm., m.p. 45-46° (Adams et al. mention 46°).

3:5-Dimethoxybenzyl chloride (LX) and 3:5-dimethoxybenzyl cyanide (LXI):

The alcohol (LIX) was converted into the corresponding chloride by the action of thionyl chloride in ether, in 95% yield, m.p. 46° (Adams et al.[48] mention 46°). The chloride was converted into the nitrile in 94-95% yield, m.p. 53° following the same conditions as Adams et al.[48] (Adams et al., mention 53-54°).

3:5-Dimethoxyphenylacetic acid (LXII):

3:5-Dimethoxybenzyl cyanide (LXI)(10 g.) was refluxed for 4 hours with ethylene glycol (250 ml.), caustic potash (10 g.) and water (10 ml.). The colour of the reaction mixture changed from blue to brown. After dilution with water and saturating with ammonium sulphate the solution was ether extracted to remove the unconverted nitrile. The aqueous alkaline portion was acidified with dilute hydrochloric acid and reextracted with ether. Desolvation of the dried ethereal extracts gave a solid which on crystallization from water gave colourless needles (6 g.),

m.p. 102° (Found: C, 61.5; H, 6.3. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.2%) (Birch[49] mentions m.p. 99-100°).

5-Nitrovanillin (LIV):

5-Nitrovanillin (LIV) was prepared following the conditions of Bentley.[50] The product crystallized from acetic acid in pale yellow needles, m.p. 176° (Bentley, m.p. 176°).

Tosylation of 5-nitrovanillin (XX):

5-Nitrovanillin (LIV)(5 g.) was suspended in water (300 ml.), tosyl chloride (5.5 g.) was added and the mixture stirred vigorously. Potassium carbonate (10 g.) was added in small lots and the solution maintained alkaline. After 6 hours the product was filtered, washed and dried. Crystallization from 95% alcohol gave colourless plates (2.2 g.), m.p. 145°. The aqueous alkaline filtrate on acidification gave back unreacted nitrovanillin (3.5 g.) (Found: N, 4.1; S, 9.4. $C_{15}H_{13}O_7N_5$ requires N, 4.0; S, 9.1%).

Tosylation of vanillin (XX):

Vanillin (10 g.) was dissolved in water (80 ml.) containing potassium hydroxide (4 g.), tosyl chloride (13 g.) added and agitated for 3 hours. The mixture was filtered and the residue washed with water. The product crystallized from alcohol in needles (16 g.), m.p. 127°

(Found: C, 58.6; H, 4.7. $C_{15}H_{14}O_5S$ requires C, 58.8; H, 4.6%).

D.R.P. 80,498 describes the compound as needles, m.p. about 115°.

Reduction of tosyl vanillin (LVI):

Tosyl vanillin (LVI)(5 g.) was dissolved in 95% alcohol (700 ml.), freshly prepared Raney nickel (50 g.) added and the slurry agitated for 5 hours while a steady stream of hydrogen was led in at room temperature (≯ 30°). The catalyst was filtered off, washed with warm alcohol and the filtrate concentrated. A tan-coloured oil (2.18 g.) was obtained which was taken up in ether, washed with aqueous 1% caustic soda, water and dried. The dried ethereal extracts on evaporation gave an oil which on fractional distillation under reduced pressure gave two products: a nearly colourless oil (1.92 g.), b.p. 115-20°/2 mm. (A), and a second fraction as a pale yellow viscous oil, b.p. 140-150°/2 mm. (B) which solidified gradually.

Fraction (A) was identified as m-methoxybenzylalcohol (LVII)(Found: C, 69.6; H, 7.4. Calc. for $C_8H_{10}O_2$: C, 69.6; H, 7.2%). The dinitrobenzoate of (A)(LVII) crystallized from alcohol in very pale yellow needles, m.p. 124° (Wilson and Read[67]; m.p. 124.) (Found: N, 8.4. Calc. for $C_{15}H_{12}O_7N_2$: N, 8.4%). Fraction (B) was identified as unreacted tosyl vanillin m.p. and mixed m.p. 125°. The alkaline washings on

acidification and reextraction with ether gave a crystalline solid (0.052 g.), which was identified as vanillin, m.p. and mixed m.p. 80°.

The nickel residue gave no product.

β-3:5-Dimethoxyphenylethyl alcohol (LII):

A solution of 3:5-dimethoxyphenylacetic acid (LXII) (6 g.) in dry ether (25 ml.) was added as rapidly as possible to a vigorously refluxing solution of lithium aluminium hydride (1.4 g.) in anhydrous ether (50 ml.) in a flask equipped with a stirrer, a condenser and a separating funnel. The reaction mixture was refluxed for 1.5 hours after the addition was completed, cooled and cold water (20ml.) followed by iced 10% sulphuric acid (20 ml.) added cautiously. The ethereal layer was separated, washed with sodium bicarbonate, water and after drying oven anhydrous magnesium sulphate evaporated. The tan-coloured oil obtained was distilled under diminished presence when nearly all the product distilled at 182-85°/0.8-1 mm. as a colourless oil (4.8 g.) (Found: C, 65.5; H, 7.4. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%).

The dinitrobenzoate of (LII) crystallized in orange-yellow needles, m.p. 142°. The melting point by admixture with the product obtained by the action of ethylene oxide on 3:5-dimethoxyiodobenzene (L) was not depressed (Found: N, 7.3. $C_{17}H_{16}O_8N_2$ requires N, 7.4%).

β-3:5-Dihydroxyphenylethyl bromide (LXIII; X=Br):

β-3:5-Dimethoxyphenylethyl alcohol (LII) (0.5g) was refluxed for 3 hours with glacial acetic acid (3 ml.) and aqueous hydrobromic acid (5 ml., 48%), cooled and treated with water containing sodium bisulphite and ether extracted. The ether extract was washed with aqueous caustic soda. The alkaline washings were acidified with dilute hydrochloric acid and reextracted with ether. The ether after washing with water was dried and desolvated when a brownish oil separated (0.14 g.) Crystallization from water (norit) gave nearly colourless needles, m.p. 55-56° (Found: Br, 36.3. $C_8H_9O_2Br$ requires Br, 36.8). An alcoholic solution of the substance gives a faint bluish colouration with ferric chloride.

β-3:5-Dihydroxyphenylethyl iodide (LXIII: X=I):

β-3:5-Dimethoxyphenylethyl alcohol (LII)(1 g.) acetic anhydride (10 ml.), red phosphorus (1 g.) and hydriodic acid (15 ml.)(d,1.7) were gently refluxed for 1.5 hours. The dark brown reaction mixture was filtered and the filtrate diluted with water containing sodium bisulphite and ether extracted. The ether was washed with aqueous sodium hydroxide and the alkaline extracts after acidification with dil. hydrochloric acid were reextracted with ether. The ether was washed with water, dried and evaporated when a brownish crystalline

solid separated. Crystallization from water (norit) gave nearly colourless plates (0.65 g.), m.p. 80° (Found: C, 36.3; H, 3.4; I, 48.1. $C_8H_9O_2I$ requires C, 36.0; H, 3.8; I, 48.4%). An alcoholic solution of the product gives a faint bluish colouration with ferric chloride.

5-Ethylresorcinol (LXIV):

A solution of β-3:5-dihydroxyphenylethyl iodide (LXIII) (0.3 g.) in glacial acetic acid (8 ml.) and zinc dust (0.3 g.) was gently refluxed together for 4 hours. A further quantity of zinc dust (0.2 g.) was added and the refluxing continued for a further period of 2 hours. The reaction mixture was cooled, filtered and the filtrate after neutralizing with sodium hydrogen carbonate was extracted with ether. The ether after washing and drying, gave on evaporation a brown sticky solid which crystallized from benzene (norit) in nearly colourless needles (0.18 g.), m.p. 94°, undepressed on amixture with a sample of authentic 5-ethylresorcinol (Found: C, 69.3; H, 7.0. Cald. for $C_8H_{10}O_2$ C, 69.5; H, 7.2%) (Asahina et al.[53], 93°).

β-3:5-Diacetoxyphenylethylacetate (LXV):

β-3:5-Dihydroxyphenylethyl iodide (LXIII)(0.3 g.) acetic anhydride (5 ml.) and fused sodium acetate (2 g.) were heated to 160°-70° for 8 hours. The acetic anhydride was removed under reduced pressure and the residue after pouring over crushed ice was ether extracted. The ether

layer was washed with water, dried and evaporated when a dark brown oil separated. Distillation under reduced pressure gave a very pale yellow oil (0.19 g.), b.p. 170-75°/0.2 mm. (Found: C, 60.1; H, 5.7. $C_{14}H_{18}O_6$ requires C, 60.0; H, 5.7%).

Ethyl 3:5-Dihydroxybenzoate:

3:5-Dihydroxybenzoic acid (XLV) (25 g.) was dissolved in absolute alcohol (250 ml.) and conc. sulphuric acid (25 ml.) was added, and the reaction mixture refluxed on a water-bath for 12 hours. Benzene (25 ml.) was added and the mixture distilled slowly until the distillate amounted to 100 ml. The residue was poured in water and taken up in ether, washed with aqueous sodium bicarbonate, water and dried over sodium sulphate. Removal of the ether gave a viscous oil (32.5 g.) which solidified immediately. Crystallization from water gave colourless needles, m.p. 80° (Suter and Weston[63] m.p. 80°). An aqueous solution gives a transient violet colouration with ferric chloride.

Ethyl 3:5-bis(benzyloxy)benzoate (LXVI):

Ethyl 3:5-dihydroxybenzoate (20 g.), anhydrous potassium carbonate (50 g.) and acetone were gently refluxed on a water-bath. Benzyl chloride (42 ml.) was then added drop by drop and the refluxing continued for 16 hours. The potassium carbonate was filtered off, washed twice with dry acetone and the filtrate concentrated

to a small volume. The unreacted benzyl chloride was removed by steam distillation and the residue was ether extracted. The ethereal layer was washed with aqueous sodium hydroxide, water and then dried over anhydrous sodium sulphate. Desolvation gave a dark brown solid (27.7 g.) which crystallized from absolute alcohol (norit) in colourless needles, m.p. 62-63°(Found: C, 76.5; H, 6.5. $C_{28}H_{22}O_4$ requires C, 76.2; H, 6.1%).

3:5-Bis(benzyloxy)benzyl alcohol (LXVII):

Ethyl 3:5-bis(benzyloxy)benzoate (LXVI)(16 g.) was dissolved in dry ether (350 ml.) and the solution added gradually to a vigorously refluxing solution of lithium aluminium hydride (3.4 g.) in ether (350 ml.). The reaction mixture was further refluxed for 2 hours, cooled to 0° and the excess hydride decomposed carefully by adding ice water (100 ml.) and cold dilute sulphuric acid (30 ml., 10%). The ether layer was separated, washed with aqueous sodium bicarbonate, water and dried over anhydrous sodium sulphate. Evaporation of the dried ethereal extracts gave a tan-coloured solid (14.6 g.), which crystallized from absolute alcohol (norit) in colourless needles, m.p. 78° (Found: C, 79.0; H, 6.3. $C_{21}H_{20}O_3$ requires C, 78.7; H, 6.3%).

The p-nitrobenzoate of (LXVII) crystallized from dilute alcohol in yellow needles, m.p. 115° (Found: N, 3.1. $C_{28}H_{23}O_6N$ requires N, 3.0%).

3:5-Bis(benzyloxy)benzyl chloride (LXVIII):

A solution of thionyl chloride (21 g.) in dry ether (250 ml.) was added gradually to a solution of 3:5-bis(benzyloxy)benzyl alcohol (LXVII)(14 g.) in dry ether (250 ml.) and pyridine (3 ml.) at 20°. After complete addition the reaction mixture was stirred at room temperature (30°) for 30 minutes and then poured over cracked ice (500 g.). The ether layer was separated, washed with aqueous sodium bicarbonate, water and then dried over anhydrous sodium sulphate. Desolvation gave a pale yellow crystalline solid (16.8 g.), which crystallized from 95% alcohol (norit) in colourless needles, m.p. 82°(Found: C, 74.5; H, 5.7; Cl, 10.3. $C_{21}H_{18}O_2Cl$ requires C, 74.6; H, 5.3; Cl, 10.5%).

3:5-Bis(benzyloxy)benzyl cyanide (LXIX):

Sodium cyanide (35 g., 90% purity) dissolved in water (70 ml.) was added to a solution of 3:5-bis(benzyloxy)benzyl chloride (LXVIII)(15 g.) in 95% alcohol (350 ml.). The reaction mixture was refluxed for 6 hours on a steam-bath, the alcohol removed by distillation and the residue diluted with water. A pale yellow oily product separated which solidified on cooling. The solid was filtered off, washed with water and dried in a desiccator (11 g.). Crystallization from petroleum ether (60-80°) gave colourless needles, m.p. 80-81° (Found: C, 80.7; H, 6.0; N, 4.4. $C_{22}H_{19}O_2N$ requires C, 80.2; H, 5.8; N, 4.3%).

3:5-Bis(benzyloxy)phenylacetic acid (LXX):

Ethylene glycol (150 ml.), potassium hydroxide (20 g.) in water (10 ml.) and 3:5-bis(benzyloxy)benzyl cyanide (LXIX)(10 g.) were refluxed together for 4 hours. The colour of the reaction mixture which was initially pale yellow changed to violet. Cooled and treated with ice-water (250 ml.) and ether extracted to remove the unsaponified nitrile. The aqueous alkaline portion on acidification with dilute hydrochloric acid gave a flocculent white precipitate which was filtered, washed and dried at 60° (6.4 g.). Crystallization from chloroform-petroleum ether mixture gave colourless needles, m.p. 106° (Found: C, 75.3; H, 5.4. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%).

β-3:5-Bis(benzyloxy)phenylethyl alcohol (LXXI):

3:5-Bis(benzyloxy)phenylacetic acid (LXX)(6 g.) was dissolved in anhydrous ether (50 ml.) and the solution added gradually to a vigorously refluxing solution of lithium aluminium hydride (1.5 g.) in dry ether (100 ml.). A vigorous reaction ensued. Refluxing and stirring were continued for 2 hours after which the reaction mixture was cooled to 0° and the excess hydride carefully decomposed with ice water (20 ml.) and cold dilute sulphuric acid (30 ml., 10%). The ethereal layer was separated, washed with aqueous sodium bicarbonate, water and then dried over anhydrous sodium sulphate. Evaporation of the ether gave a solid (5.5 g.) which crystallized from chloroform-

petroleum ether mixture in colourless needles, m.p. 81-82° (Found: C, 79.3; H, 6.7. $C_{22}H_{22}O_3$ requires C, 79.0; H, 6.6%).

Ethyl acetonedicarboxylate:

Ethyl acetonedicarboxylate was prepared according to the method given in Organic Syntheses.[68]

Ethyl 3:5-dihydroxy-2:4-dicarboethoxyphenyl-acetate (LXXII) and ethyl 3:5-dihydroxy-4-carboxyphenyl-acetate (LXXXVII): were prepared according to the method of Theilacker and Schmid,[54] the yields were 45-46% and 11-12% as against 53% and 5% respectively obtained by the earlier workers.

3:5-Dihydroxyphenyl-acetic acid (LXXIII) and ethyl 3:5-dihydroxyphenyl-acetate (LXXIV) were also obtained following the method of Theilacker and Schmid.[54] The ester (LXXIV) crystallized from a carbon tetrachloride-cholroform mixture in colourless plates, m.p. 128° (Theilacker and Schmid, m.p. 127-128°).

Ethyl 3:5-Bis(benzyloxy)phenyl acetate:

A mixture of ethyl 3:5-dihydroxyphenyl-acetate (LXXIV)(16 g.) in acetone (250 ml.), anhydrous potassium carbonate (250 ml.) and benzyl chloride (25 g.) was refluxed on a water-bath for 16 hours. The reaction mixture was filtered hot and the potassium carbonate washed with acetone. The filtrate and washings were concentrated and the excess benzyl chloride was removed by steam distillation. The residue was ether extracted. The

ethereal layer was washed with dilute caustic soda and with water and dried. Evaporation of the solvent gave a pale yellow oil, which on distillation under reduced pressure gave a colourless oil, b.p. 190-200°/0.01 mm. (14.8 g.) (Found: C, 76.3; H, 6.4. $C_{24}H_{24}O_4$ requires C, 76.8; H, 6.4%).

β-3:5-Bis(benzyloxy)phenylethyl alcohol (LXXI):

Ethyl 3:5-bis(benzyloxy)phenylacetate (14 g.) was dissolved in anhydrous ether (50 ml.) and added to a refluxing solution of lithium aluminium hydride (3.5 g., excess) in anhydrous ether (100 ml.). The mixture was refluxed for 3 hours and worked up as usual. An overall yield of 92% of the alcohol (LXXI) was obtained, m.p. 81°. Mixed m.p. with the product obtained by reduction of 3:5-(bisbenzyloxy)phenylacetic acid (LXX) showed no depression.

β-3:5-Dihydroxyphenylethyl alcohol (LXXV):

β-3:5-Bis(benzyloxy)phenylethyl alcohol (LXXI)(5 g.) was dissolved in 95% methanol (50 ml.), palladized carbon (10%, 1 g.) was added and the reaction mixture agitated at room temperature (30°) in an atmosphere of hydrogen till two moles were absorbed. The carbon was filtered off, washed twice with warm methanol and the filtrate concentrated under vacuum to dryness. A pink crystalline solid (2·4 g.) separated which crystallized from ethylacetate in colourless prisms, m.p. 169-70° (Found: C, 62.1; H, 6.4. $C_8H_{10}O_3$ requires C, 62.3; H, 6.5%).

An aqueous alcoholic solution gives a pale bluish-violet colouration with ferric chloride.

4-Carboxy-3:5-dihydroxy-β-phenylethyl alcohol (LXXVI):

An intimate mixture of β-3:5-dihydroxyphenyl-ethyl alcohol (LXXV)(2 g.), potassium hydrogen carbonate (10 g.) and glycerol (25 ml.) was heated in an atmosphere of dry carbon dioxide at 135° for 8 hours, cooled, treated with water (100 ml.), saturated with ammonium sulphate and extracted with ether to remove the unchanged phenol. The aqueous portion was acidified with dilute hydrochloric acid and the acid isolated by extraction with ether. Evaporation of the dried ethereal extracts gave a colourless crystalline solid (1.3 g.), which on crystallization from a mixture of ethyl-acetate-benzene gave colourless prisms, m.p. 175° (dec.)(Found: in a specimen dried in vacuum at 60° for 2 hours: C, 54.9; H, 5.2. $C_9H_{10}O_5$ requires C, 54.5; H, 5.1%).

An alcoholic solution of the acid gives an intense blue colouration with ferric chloride.

Attempted cyclization of 4-carboxy-3:5-dihydroxy-β-phenylethyl alcohol (LXXVI) with ethyl orthoformate to norcitrinin (XLIV):

(i) The acid (LXXVI)(0.1 g.) was weighed out in a dry test-tube and ethyl orthoformate (freshly distilled)(0.5 ml.) was added to it at room temperature (29-30°). The acid went into solution immediately and the reaction mixture

turned yellow and finally dark brown exhibiting a greenish fluorescence. The colour deepened on keeping for 12 hrs at room temperature. Crushed-ice containing a trace of hydrochloric acid was added when a reddish-brown amorphous solid was thrown down. It was filtered, washed and dried in a vacuum desiccator. The product could not be crystallized but precipitated as an amorphous solid on dilution of an alcoholic solution with water. It did not melt up to 300° but an alcoholic solution exhibited an iodine brown colouration with ferric chloride characteric of citrinin (Found: C, 59.2; H, 4.6. $C_{10}H_8O_5$ requires C, 57.7; H, 3.8%).

(ii) The acid (LXXVI)(0.1 g.) and ethyl orthoformate (0.5 ml.) were kept at room temperature (30°) for 1/2 hour and the deeply coloured reaction mixture decomposed and worked up as before. A pinkish solid (0.09 g.) separated which was identified as the starting material by m.p. and mixed m.p. and the characteristic deep blue colouration with ferric chloride.

(iii) Using acetic anhydride and zinc chloride: The acid (LXXVI)(0.1 g.), acetic anhydride (0.1 ml.), ethyl orthoformate (0.5 ml.) and a trace of zinc chloride were warmed on a water bath at 50° for 1 hour. The reaction mixture turned deep brownish red exhibiting a greenish fluorescence. Cooled, decomposed with crushed-ice when a reddish-brown solid separate, which was filtered, washed and dried (0.06 g.), m.p. $>$ 300°. The product exhibits an intense greenish-yellow fluorescence in alcohol, ether, benzene and

chloroform. An alcoholic solution gives the characteristic iodine-brown colouration with ferric chloride.

Action of ethyl orthoformate on p-orsellinic acid (LXXVIII)

Freshly distilled ethyl orthoformate (10 ml.) was added to p-orsellinic acid (LXXVIII)(1 g.) at room temperature (30°). The acid went into solution completely and the mixture turned yellowish brown within 10 minutes. On keeping for 1/2 hour, a yellowish brown crystalline solid separated which was filtered, washed with ether followed by warm ethanol. The product (0.8 g.) which decomposes at 280° (but does not melt to a clear liquid) crystallized from glacial acetic acid in yellowish brown needles (Found: C, 61.7; H, 3.4. $C_{17}H_{12}O_7$ requires C, 62.2; H, 3.7%). The product was soluble in aqueous sodium bicarbonate and exhibited an iodine-brown ferric colour in alcoholic solution. The substance behaved like a quinone-carboxylic acid.

2-Aldehydo-4-carboxy-3:5-dihydroxy-β-phenylethyl alcohol: (LXXVII) and attempted cyclisation to norcitrinin:

A solution of the acid (LXXVI)(0.5 g.) in dry ether (75 ml.), anhydrous hydrocyanic acid (4 ml.), zinc cyanide (1 g.) and fused zinc chloride (0.5 g.) was saturated at 0° with dry hydrogen chloride gas, and 48 hours later the reddish crystalline mass together with a reddish oil was collected, washed well with fresh dry ether, and dissolved in cold water (40 ml.). The solution after just neutralizing with ammonium hydroxide was warmed to

80° for 45 minutes, cooled and extracted with ether. The acidic product was separated from the ethereal extracts by means of aqueous sodium bicarbonate, and after acidification of the latter, reextracted with ether. Evaporation of the dried ethereal extracts gave a honey coloured oil (0.19 g.), which did not solidify and exhibited a bluish green ferric reaction in alcohol. A solution of this aldehyde in cold concentrated sulphuric acid (1.5 ml.) was kept at 20° for 15 minutes and then poured over crushed ice (25 g.) when a yellowish brown semi-solid separated (0.09 g.). The product after filtration and washing turned sticky and dark brown in colour and could not be crystallized. An alcoholic solution exhibited an iodine-brown colouration with ferric chloride characteristic of citrinin.

Attempted cyclisation of 4-carboxy-3:5-dihydroxy-β-phenylethyl alcohol (LXXVI) with formaldehyde and aqueous caustic soda to dihydronorcitrinin (LXXXII):

A solution of the acid (LXXVI)(0.1 g.) in cold 2N aqueous caustic soda (1 ml.) was treated with 40% formalin (1 ml.). The reaction mixture which turned orange-red was left at 20° for 24 hours, acidified with dilute hydrochloric acid when a buff coloured precipitate separated which was filtered and washed (0.09 g.), m.p. $>$ 320°. The product could not be crystallized and was insoluble in ether, benzene, chloroform, but soluble in methanol and ethanol from which it separated as an amorphous solid on dilution with water. An alcoholic

solution of the product gives no ferric reaction.

4-Carboxy-3:5-dihydroxy-β-phenylethyl bromide (LXXXIII):

To a solution of 4-carboxy-3:5-dihydroxy-β-phenylethyl alcohol (LXXVI)(0.1 g.) in glacial acetic acid (2 ml.), bromine (0.09 g.) in glacial acetic acid (1 ml.) was added, and the reaction mixture was warmed at 40° for 30 minutes. A colourless crystalline product separated on cooling to 20°, filtered and washed (0.11 g.). Crystallization from dilute acetic acid gave colourless prisms, m.p. 177-78°(dec.)(Found: C, 41.8; H, 4.0. $C_9H_9O_4Br$ requires C, 41.3; H, 3.5%).

An alcoholic solution gives a blue colouration with ferric chloride.

Ethyl 3:5-dihydroxy-2-carboethoxy-4-carboxyphenylacetate (LXXXVII): The triester (LXXII) (10 g.) was gently refluxed with pyridine (50 ml.) and piperidine (10 drops) for 6 hours. The initial pale yellow colour gradually deepened to wine-red. The reaction mixture was poured into crushed-ice and hydrochloric acid, when a thick yellow curdy precipitate separated, which was collected and washed with ice-water. Crystallization from benzene (norit) gave colourless needles (7.2 g.), m.p. 141° (Schmid and Theilacker,[54] 141°) (Found: C, 53.5; H, 5.0. Cald. for $C_{14}H_{16}O_8$ C, 53.8; H, 5.2%).

An alcoholic solution of the acid gives an intense blue colouration with ferric chloride.

Ethyl 3:5-dihydroxy-2-carboethoxyphenylacetate (LXXXVIII): Ethyl 3:5-dihydroxy-2-carboethoxy-4-carboxyphenylacetate (LXXXVII) (7 g.) and glycerol (150 ml.) were heated at 150° for 30 minutes under stirring. The mixture was then cooled and treated with water (150 ml.). A flocculent dirty white precipitate separated, which was filtered, washed and dried. Crystallization from benzene-petroleum ether gave colourless needles (3.8 g.), m.p. 109° (Robertson et al.,[59] 109°) (Found: C, 58.0; H, 6.0. Cald. for $C_{13}H_{16}O_6$ C, 58.2; H, 6.0%).

An alcoholic solution of the substance gives a wine-red colouration with ferric chloride.

Ethyl 3:5-bis(benzyloxy)-2-carboethoxyphenylacetate (LXXXIX): A mixture of ethyl 3:5-dihydroxy-2-carboethoxyphenylacetate (LXXXVIII) (3 g.), acetone (30 ml.), anhydrous potassium carbonate (10 g.) and benzyl chloride (3.5 ml.) was refluxed on a water-bath for 16 hours. The reaction mixture was filtered hot, and the potassium carbonate washed with acetone. The filtrate and washings were concentrated, and excess benzyl chloride was removed by steam distillation. The residue was ether extracted. The ethereal layer was washed with dilute caustic soda and with water and dried. Evaporation of the solvent gave a pale yellow oil, which was purified by distillation under vacuum . A colourless oil was obtained at 210-25°/0.3 mm (2.6 g.) (Found: C, 71.8; H, 6.0. $C_{27}H_{28}O_6$ requires C, 72.3; H, 6.3%).

3:5-Bis(benzyloxy)-2-hydroxymethyl-β-phenylethyl alcohol (XC): Ethyl 3:5-bis(benzyloxy)-2-carboethoxyphenylacetate (LXXXIX) (2.5 g.) was dissolved in anhydrous ether (20 ml.) and added as rapidly as possible to a vigorously refluxing solutions of lithium aluminium hydride (1 g., excess) in anhydrous ether (25 ml.). The mixture was refluxed for 2 hours, cooled, and decomposed with water (50 ml.) and an ice-cold solution of concentrated sulphuric acid (1.5 ml.) in water (20 ml.). The ethereal layer was separated, washed with aqueous sodium bicarbonate and with water, and dried over magnesium sulphate. Removal of the solvent gave a viscous pale yellow oil (2.2 g.), which partly crystallized

in needles on keeping in contact with petroleum ether (60-80°) for several weeks. The crystalline material (0.7 g.) was separated from the oil (A), and recrystallized from petroleum ether (60-80°); the colourless needles had m.p. 78° (Found: C, 75.3; H, 6.2. $C_{23}H_{24}O_4$ requires C, 75.8; H, 6.6%).

3:5-Dihydroxy-2-hydroxymethyl-β-phenylethyl alcohol: 3:5-Bis(benzyloxy)-2-hydroxymethyl-β-phenylethyl alcohol (XC) (0.5 g.), palladinized carbon (10%; 0.25 g.) and methanol (20 ml.) were agitated in a current of hydrogen at room temp-erature (30°) till two moles of hydrogen were absorbed. The absorption was complete in 50 minutes. The carbon was filtered off and washed with warm methanol. The filtrate on concentration yielded a pale yellow viscous oil (0.22 g.) which could not be purified further. The oil dissolved in cold aqueous caustic soda to a pink solution, but gave no ferric colour in alcoholic or aqueous solution. The oil decomposed and did not distill up to 240°/5x10^{-5} mm.

6:8-Bis(benzyloxy)isochroman (XCI): The viscous pale yellow oil (A) left after separation of crystalline 3:5-bis-(benzyloxy)-2-hydroxymethyl-β-phenylethyl alcohol was distilled under high vacuum, when a nearly colourless glassy oil (0.7 g.) distilled at 180-90°/5x10^{-5} mm. (Found: C, 79.5; H, 6.2. $C_{23}H_{22}O_3$ requires C, 79.7; H, 6.4%). An initial fraction (about 20 mg.) at 140-50°/5x10^{-5} mm. was discarded. The residue which did not distill up to 240°/5x10^{-5} mm was not further examined.

6:8-Dihydroxyisochroman (LXXXIV): 6:8-Bis(benzyloxy)isochroman (XCI) (0.65 g.), palladized carbon (10%; 0.4 g.), and glacial acetic acid (20 ml.) were agitated at room temperature (28°) till two moles of hydrogen were absorbed (1 hour). The carbon was filtered off and washed with warm acetic acid, and the filtrate and washings taken to dryness under vacuum, when a pale yellow viscous oil separated. It solidified on keeping in contact with benzene overnight. Crystallization from the same solvent gave nearly colourless needles (0.15 g.), m.p. 168° (Found: C, 65.0; H, 5.8: $C_9H_{10}O_3$ requires C, 65.1; H, 6.1%). An alcoholic or aqueous solution gives a transient violet colouration with ferric chloride.

Attempted carboxylation of 6:8-dihydroxyisochroman (LXXXIV): An intimate mixture of 6:8-dihydroxyisochroman (LXXXIV) (50 mg.) anhydrous potassium bicarbonate (0.5 g.) and glycerol (3 ml.) was heated together in a current of dry carbon dioxide for 8 hours at 135°. After cooling, the mixture was treated with water (10 ml.), saturated with ammonium sulphate and exhaustively extracted with ether to remove the unconverted isochroman. The aqueous liquor on acidification with dilute hydrochloric acid gave a pale yellow precipitate which was filtered washed and dried (35 mg.), m.p. $>$ 300°. The product was insoluble in ether and benzene, but soluble in alcohol. The substance could not be crystallized, but an amorphous solid separated on dilution of an alcoholic solution with water. An alcoholic

solution gives no colouration with ferric chloride.

Ethyl 2-caproyl-3:5-dihydroxyphenylacetate (XCIII):

The ester (LXXIV) (1 g.) was suspended in dry carbon tetrachloride (25 ml.), n-caproic acid (2 ml., excess) was added and the reaction mixture saturated with boron trifluoride gas at room temperature (30°). The temperature was gradually raised to 70° and the gas passed for another hour. A deep orange layer of the complex separated and the mixture was left at room temperature for 12 hours, treated with ice-water and extracted with ether. ~~The ether layer was washed with~~ ~~water.~~ The ether layer was washed with aqueous sodium bicarbonate and water and dried. Evaporation of the solvent gave a dark brown oil (0.82 g.), which on fractional distillation under vacuum gave a forerun of the unreacted ester 140°/0.01 mm. which solidified and an orange coloured oil (0.42 g.) 180-90°/0.01 mm. (Found: C, 64.8; H, 7.6: $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.5%).

An alcoholic solution of this product gives a brownish colouration with ferric chloride.

The bicarbonate extracts after acidification with dilute hydrochloric acid was steam distilled to remove the excess fatty acid. The residue on cooling gave a pale yellow crystalline solid (XCIV) (0.1 g.). Crystallization from water (norit) gave very pale yellow needles, m.p. 179-80° (Found: C, 63.5; H, 6.8. $C_{14}H_{18}O_5$ requires C, 63.1; H, 6.8%).

An alcoholic solution of the product gives a dirty brown colouration with ferric chloride.

2:4-Dihydroxy-6-methylcaprophenone (XCVI): Orcinol (1.24 g.) was suspended in dry carbon tetrachloride (20 ml.), n-caproic acid (2 ml.) was added and the reaction mixture saturated at room temperature (30°) with boron trifluoride gas. The temperature was gradually raised to 70° and the gas passed for another hour. A brown layer of the complex separated and the mixture was left overnight at room temperature, treated with ice-water and extracted with ether. The ether was washed with aqueous sodium bicarbonate, water and dried. Evaporation of the solvent gave an oil (1.6 g.) which solidified immediately. Crystallization from water gave fine fluffy needles, m.p. 72° (Found: C, 70.5; H, 8.5. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%).

An alcoholic solution of the ketone gives a brown colour with ferric chloride.

3-n-Butyl-7-hydroxy-5-methylflavone (XCVII): The above ketone (XCVI) (1 g.), anhydrous sodium benzoate (1.6 g.) and benzoic anhydride (16 g.) were thoroughly ground and added with stirring into a hard glass test-tube at 100°. The temperature of the mixture was then raised to 200° and maintained for 8 hours. Cooled and extracted with 95% alcohol (100 ml.) containing caustic potash (10 g.). The alcoholic solution was refluxed on a water-bath for 2 hours. On cooling the crystalline benzoate separated which was filtered off and the alcoholic filtrate concentrated under vacuum. The two residues were taken up in water (200 ml.) and saturated with carbon dioxide when a semi-solid separated

which was filtered, washed and dried (0.82 g.), crystallization from 95% methanol gave nearly colourless needles, m.p. 208° (Found: C, 78.1; H, 6.5. $C_{20}H_{20}O_3$ requires C, 77.9; H, 6.5%).

An alcoholic solution of the substance gives no colouration with ferric chloride.

(a) 2-Caproyl-3:5-dihydroxyphenylacetic acid (XCIV): Ethyl 2-caproyl-3:5-dihydroxyphenylacetate (XCIII) (0.3 g.) was refluxed with alcoholic caustic soda (10 ml.) for 1 hour and the mixture diluted with water (25 ml.) and acidified with hydrochloric acid. A pale yellow solid together with a small amount of resinous product separated, which was filtered, washed and dried (0.16 g.). Crystallization from water gave pale yellow needles, m.p. and mixed m.p. 179-80°.

(b) 2-Caproyl-3:5-dihydroxyphenylacetic acid (XCIV): Crude 3:5-dihydroxyphenylacetic acid (LXXIII) (0.5 g.) dry carbon tetrachloride (10 ml.) and n-caproic acid (1 ml., excess) was saturated with boron trifluoride gas at room temperature (30°). The temperature was gradually raised to 70° and the gas passed for another hour; 12 hours later, the mixture was treated with water and steam distilled to remove the excess fatty acid. The residue on cooling gave pale yellow needles together with a small amount of tarry material which was filtered, washed and dried (0.21 g.). Crystallization from water gave very pale yellow needles, m.p. 179-80°, undepressed on admixture with the sample of the acid (XCIV)

obtained in the previous experiment.

(i) 2-n-Hexyl-3:5-dihydroxyphenylacetic acid (XCV): Ethyl 2-caproyl-3:5-dihydroxyphenylacetate (XCIII) (0.3 g.) was dissolved in 95% alcohol (10 ml.), zinc amalgam (3 gm.) and concentrated hydrochloric acid (1 ml.) were added. The reaction mixture was gently refluxed for a period of 14 hours when the initial pale yellow colour changed to a practically colourless solution. The alcohol was distilled off and the residue taken up in ether. The ether solution was washed with aqueous sodium bicarbonate, water and dried. Evaporation of the ether gave a negligible amount of an oily product which could not be examined further. The bicarbonate extract after acidification with dilute hydrochloric acid was re-extracted with ether. Desolvation gave a light brown solid which crystallized from water in nearly colourless needles (0.08 g.) m.p. 131° (Found: C, 66.8; H, 8.5. $C_{14}H_{20}O_4$ requires C, 66.6; H, 8.0%).

An alcoholic solution gives a transient bluish violet colouration with ferric chloride.

(ii) Reduction of 2-caproyl 3:5-dihydroxyphenylacetic acid (XCIV) under similar condition gave an identical product but in extremely poor yield (8-9% theory).

2-Caproyl-3:5-dihydroxy-β-phenylethylcaproate (XCVIII): β-3:5-Dihydroxyphenylethyl alcohol (LXXV) (1 g.) was suspended in dry carbon tetrachloride (25 ml.), n-caproic acid (2 ml., excess) was added and the reaction mixture saturated with boron trifluoride gas first at room temperature (30°) for

1 hour and at 70° for another hour. An orange-yellow layer of the complex separated which was left for 12 hours. The reaction mixture was then treated with water and extracted with ether. The ether layer was washed with aqueous sodium bicarbonate, water and dried over magnesium sulphate. Desolvation gave a viscous orange yellow liquid which partly solidified. Crystallization from petroleum ether (60-80°) gave pale yellow needles (0.65 g.), m.p. 71-72° (Found: C, 68.5; H, 8.5. $C_{20}H_{30}O_5$ requires C, 68.5; H, 8.6%).

An alcoholic solution of the ketone gives a dirty brown ferric reaction.

2-n-Hexyl-β-3:5-dihydroxyphenylethyl alcohol (XCIX): The above ketone (XCVIII) (0.5 g.) was dissolved in 50% alcohol (20 ml.), amalgamated zinc (3 g.) and concentrated hydrochloric acid added (1 ml.) and the mixture refluxed for 16 hours, cooled and treated with water (50 ml.) and extracted with ether. The ether after washing with aqueous sodium bicarbonate and water was dried and evaporated. A viscous brown oil (0.26 g.) was obtained which solidified gradually. The product crystallized from a mixture petroleum ether (60-80°) and benzene in nearly colourless needles, m.p. 69-70° (Found: C, 71.1; H, 9.6. $C_{14}H_{22}O_3$ requires C, 70.6; H, 9.3%).

An alcoholic solution of the product gives a faint blue colouration with ferric chloride.

3:5-Bis(benzyloxy)phenylacetone (CII):

Method I: A solution of 3:5-bis(benzyloxy)benzyl

cyanide (LXIX) (3.3 g.) in anhydrous ether (50 ml.) was added to the Grignard reagent prepared from methyl iodide (14.2 g.), magnesium turnings (2.5 g.) and dry ether (150 ml.) during the course of 30 minutes. After refluxing for 48 hours, the reaction mixture was poured into water (400 ml.) containing cracked ice (100 g.) and concentrated hydrochloric acid (20 ml.). The ethereal solution was separated and washed twice with cold 4N hydrochloric acid (25 ml.), and the aqueous layer combined and heated on a steam cone for 6 hours. The ethereal solution was washed with aqueous sodium bicarbonate water and dried over magnesium sulphate. The aqueous acidic layer after hydrolysis of the "ketimine fraction" was extracted with ether. The combined ethereal extracts on desolvation gave a viscous brown oil (2.4 g.) which on distillation under reduced pressure, 170-80°/0.01 mm., gave a nearly colourless viscous liquid (Found: C, 79.2; H, 6.2. $C_{23}H_{22}O_3$ requires C, 79.7; H, 6.4%).

The dinitrophenylhydrozone of (CII) crystallized from alcohol in orange-yellow needles, m.p. 121° (Found: N, 10.6. $C_{29}H_{26}O_6N_4$ requires N, 10.6%).

Method II: Thionyl chloride (5 ml.) was added gradually to dry powdered 3:5-bis(benzyloxy)phenylacetic acid (LXX) (1.75 g.). After the initial vigour of the reaction had subsided, the excess thionyl chloride was distilled off at room temperature under vacuum. Dry benzene (15 ml.) was added and distilled off. Methylmagnesium iodide (0.02 mol.) was added to a mixture of freshly fused zinc

chloride (2.72 g.; 0.02 mol.) in ether (25 ml.). A vigorous reaction ensued and the mixture was refluxed for 2 hours. A solution of the foregoing acid chloride (CI) in dry benzene (50 ml.) was added with stirring during 15-20 minutes; more benzene (20 ml.) was added and the resulting mixture heated to boiling for 5 hours, after which 2N hydrochloric acid (25 ml.) was added. The mixture was refluxed again for 30 minutes on a steam-cone, cooled and the benzene layer separated, washed with aqueous 10% caustic soda and water. Evaporation of the benzene extract gave a light brown viscous oil (0.6 g.) which on distillation under reduced pressure gave a nearly colourless oil, b.p. 170-80°/0.01 mm. (Found: C, 79.6; H, 6.1. $C_{23}H_{22}O_3$ requires C, 79.7; H, 6.4%).

1-(3:5-Bisbenzyloxy)phenylpropan-2-ol (CIII): A solution of the above ketone (CII) (2.5 g.) in dry ether (25 ml.) was added during the course of 20-25 minutes to a vigorously refluxing solution of lithium aluminium hydride (1 g.; excess) in dry ether (40 ml.). The mixture was refluxed for 2 hours after which the excess hydride was carefully decomposed with water. Ice-cold sulphuric acid (20%; 20 ml.) was added and the ethereal layer separated, washed with aqueous sodium bicarbonate, water and dried over anhydrous magnesium sulphate. Desolvation gave a viscous tan coloured liquid (2.3 g.) which on distillation under diminished pressure, b.p. 195-205°/0.01 mm. gave a nearly colourless oil (Found: C, 79.5; H, 7.0. $C_{23}H_{24}O_3$ requires C, 79.3; H, 6.9%).

The dinitrobenzoate of (CIII) crystallized in orange coloured

needles, m.p. 108° (Found: N, 5.3. $C_{30}H_{26}O_8N_2$ requires N, 5.2%).

1-(3':5'-Dihydroxy)phenylpropan-2-ol (CIV): The above alcohol (CIII) (2 g.) was dissolved in 95% methanol (25 ml.), palladized carbon (0.5 g., 10%) was added and the mixture agitated in an atmosphere of hydrogen at room temperature (29-30°) till two moles of hydrogen were absorbed (2.5 hours). The carbon was filtered off, washed with warm methanol, and the filtrate and washings taken to dryness under vacuum when a nearly colourless glass (1.1 g.) separated which could not be induced to solidify. Distillation under reduced pressure gave a colourless glass, b.p. 165-70°/0.01 mm. (Found: C, 67.3; H, 8.1. $C_9H_{12}O_3$ requires C, 64.3; H, 7.2%).

An alcoholic solution gives a pale violet colouration with ferric chloride.

1-(4'-Carboxy-3':5'-dihydroxy)phenylpropan-2-ol (CV): An intimate mixture of the above phenol (CIV) (1 g.), dry potassium bicarbonate (5 g.) and anhydrous glycerol (10 ml.) was heated at 125-30° in a current of dry carbon dioxide for 8 hours. The mixture was cooled, treated with water (50 ml.) and after saturating with ammonium sulphate was exhaustively ether extracted to remove the unconverted phenol. The aqueous liquor was acidified with dilute hydrochloric acid and reextracted with ether. Evaporation of the dried ethereal extracts gave a solid (0.45 g.) which crystallized from a

mixture of ether and light petroleum ether (40-60°) in colourless needles, m.p. 166° (dec.) (Found: C, 58.3; H, 6.2. $C_{10}H_{12}O_5$ requires C, 56.6; H, 5.7%).

An alcoholic solution of the substance gives an intense blue ferric colouration.

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Part II

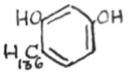
HEXYLRESORCINOL AND ITS DERIVATIVES

Derivatives of 4-n-hexylresorcinol

4-n-Hexylresorcinol (I) possesses marked antibacterial and anthelminthic properties, and is probably one of the safest drugs for ascariasis, hookworm and pinworm infections (oxyuriasis). It combines with low toxicity an adequate activity against most nematodes and tapeworms.[1] It is also useful as a urinary antiseptic.

It was thought that by the introduction of a hexylresorcinol nucleus in the citrinin molecule the antibacterial activity may be increased and the toxicity diminished. The biosynthesis of citrinin analogues by the use of hexylresorcinol and its derivatives as precursors in the fermentation was first attempted but without success.[2]

Hexylresorcinol (I) is usually prepared by Clemmensen reduction of the ketone which is obtained by the condensation of resorcinol with n-caproic acid in presence of zinc chloride (Nencki reaction).

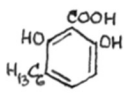


(I)

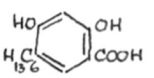
Robertson and Robinson[3] obtained p-orsellinic acid in excellent yield by carboxylating orcinol by potassium bicarbonate in glycerine in an atmosphere of carbon dioxide at 135°. Although the excellent yield is due to the fact that in 5-substituted resorcinols the Y- or 2-position is activated, carboxylation of 4-n-hexylresorcinol (I) by this method has now been investigated.

The preparation and properties of 4-n-hexylresorcinol-2- and 6-carboxylic acids are not described in the literature. However, the action of the sodium salt of hexyl and heptyl resorcinol carboxylic acids on bacteria and tissue cell has been described by Bleyer.[4] Sabalitschka and Tietz[5] have reported the antimicrobial action of certain di- and trihydroxy and alkyloxybenzoic acids and esters; the values, expressed as ratios of the minimum concentration of phenol inhibiting fermentation of glucose by yeast to the minimum concentration of the substance preventing fermentation, were as follows: hexylresorcinol (72.2); 5-hexyl 2:4-dihydroxybenzoic acid (88.6 in presence of glycerine); methyl 5-hexyl-2:4-dihydroxybenzoate (357 in presence of glycerine).

When hexylresorcinol was heated with potassium bicarbonate and glycerine at 135° in a stream of carbon dioxide, a mixture of the 2-carboxylic acid (II) and 6-carboxylic acid (III) was obtained. Repeated crystallization from benzene gave a material melting at 171-72° (dec.), which was the β-acid (III) as shown by the violet colouration with alcoholic ferric



(II)

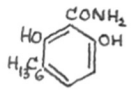


(III)

chloride, yield 25-27 per cent. The βγ-acid (II), characterized by the blue ferric colour, was obtained from the mother liquors after crystallization of (III), and it crystallized from petroleum ether in nearly colourless needles,

m.p. 114-15° (dec.), yield 14-15 per cent.

Aqueous carboxylation of hexylresorcinol gave a higher yield (32-34 per cent) of the β-acid (III). Esterification of the acids (II) and (III) was effected by diazomethane in ether and by dimethyl sulphate and anhydrous sodium bicarbonate in acetone. Treatment of the esters with boiling alcoholic caustic potash gave back the acids (II) and (III) but in poor yield, because of decarboxylation. When the ester of the acid (II) was heated under reflux with pyridine and a drop of piperidine, hydrolysis took place smoothly and the acid was obtained in nearly quantitative yield.[6] It has been found that this method of hydrolysis of esters is useful in general when the corresponding acid is liable to decomposition by alkali. The conversion of an acid into an amide may be expected to decrease toxicity. The amide (IV) of hexylresorcinol-2-carboxylic acid (II) was obtained in quantitative yield when the corresponding ester was treated with dry ammonia in absolute methanol. The ester of β-acid (III) failed to give the amide. This difference in the behaviour



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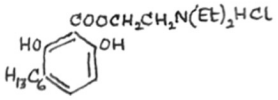

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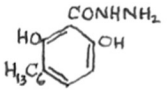

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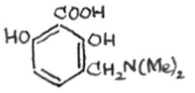

(VII)

of the two esters provide a method for the separation and purification of the two acids; hydrolysis of the amide (IV) with 10% alcoholic caustic potash gave the acid (II), but only in a yield of 9-10 per cent. The introduction of a dialkylaminoalkyl group, for instance as ethers or esters, is

a simple method for imparting basic character and acid solubility to organic compounds. Many dialkylaminoalkyl derivatives also have interesting and useful physiological properties. The attachment of a dialkylaminoalkyl group to a nitrogen atom is a common device in synthetic antimalarial agents, and well-known examples are chloroquine, pamaquine and quinacrine. Several compounds containing an $-N.CH_2CH_2NMe_2$ group are antihistamines (e.g. antergan, phenergan). Esters of dialkylaminoalkalanols are widely employed as anaesthetics and have also proved to be of interest as spasmolytic agents. The diethylaminoethyl ester of benzylpenicillin has a pronounced affinity for lung tissue, and is used clinically in the form of the hydriodide[7] (Leocillin; Estopen). Very recently dialkylaminoalkyl ester of N-methylnipecotic and N-methylisonipecotic acids have been prepared for examination as hypotensive, ganglionic blocking agents.[8] Dialkylaminoalkyl ethers of benzhydrol have antispasmodic and antihistamine activity.[9] The diethylaminoethyl ether of hexylresorcinol has high *in vitro* antitubercular acitivity.[10] The diethylaminoalkyl ester (V) of hexylresorcinol-2-carboxylic acid (II), which may have useful chemotherapeutic properties, has now been prepared. Under a variety of conditions it has not yet been possible to prepare the diethylaminoethyl ester of the β-acid (III).

The current interest in hydrazides as antitubercular agents prompted the preparation of the hydrazide (VI) of hexylresorcinol-2-carboxylic acid (II) by the usual method of

treating the ester with hydrazine hydrate. The ester of the β-acid (III) failed to give the hydrazide.

The condensation of hexylresorcinol-2-carboxylic acid (II) with dimethylamine and aqueous formaldehyde resulted in the formation of the Maninch base (VII). The antibacterial properties of these compounds are under investigation.

The antibacterial activity of hexylresorcinol and its derivatives determined by Dr. D. V. Tamhane, is recorded in Table I.

Table I

Antibacterial activity of hexylresorcinol and its derivatives.

Compound	Antibacterial activity
4-n-Hexylresorcinol	1:44,444 against S. aureus F.D.A. 209. 1:40,000 against E. coli.
4-n-Hexylresorcinol-2-carboxylic acid (γ-acid)	1:22,222 - 1:26,666 against S. aureus F.D.A. 209. 1:20,000 - 1:22,222 against E.coli. 1:3,000 against V. cholarae.
4-n-Hexylresorcinol-6-carboxylic acid (β-acid)	1:40,000 against S. aureus. F.D.A. 209. 1:28,570 against E. coli.
6-Aldehydo-4-n-hexyl-resorcinol	Compound highly insoluble and precipitated quantitatively in the medium.
γ-Acid ester with $(Et)_2NCH_2CH_2Cl$	1:13,890 - 1:16,666 against S. aureus F.D.A. 209.
Amide of γ-acid	1:50,000 - 1:66,667 against S. aureus F.D.A. 209.

The toxicity of hexylresorcinol and its derivatives, determined by Dr. D. V. Tamhane, is recorded in Table II.

Table II

Toxicity of hexylresorcinol and its derivatives.

Compound	Route of administration.	Dose g./kg. body wt.	Effect of toxicity
4-n-Hexylresorcinol (in 33% glycerine)	Subcutaneous	0.50	No death, all mice active
		1.00	-Do-
		1.50	(Lesions of skin where
		2.00	(compound injected, mice (active even after 48 hrs.
4-n-Hexylresorcinol-2-carboxylic acid (Y-acid)	Oral	1.50	Paralysis in hind legs, all died in half an hour.
		1.00	100% death in 3 hours.
		0.75	Slight irritation, 40% death.
	Subcutaneous	0.25	No death in 24 hours, mice active.
		0.50	(66% death, lesions of skin
		1.00	(where compound was (injected.
Chronic toxicity (Y-acid)	Oral	0.24	All died between 2-6 days
	Subcutaneous	0.30	All died between 5-8 days
4-n-Hexylresorcinol-6-carboxylic acid (β-acid)	Subcutaneous	1.00	All mice active, no death.
Amide of 4-n-hexylresorcinol-2-carboxylic acid (as suspension in gum acacia)	Intraperitoneal	0.50	(No death, all mice were
		1.00	(active. No lesions of
		1.40	(skin as observed with
		1.80	(hexylresorcinol and its 2-carboxylic acid.

EXPERIMENTAL

Carboxylation of 4-n-hexylresorcinol and separation of 4n-hexylresorcinol-2-carboxylic acid (II) and 4-n-hexylresorcinol-6-carboxylic acid (III):

An intimate mixture of 4-n-hexylresorcinol (I)(20 g.), dry potassium bicarbonate (50 g.) and glycerol (100 ml.) was heated at 140-45° for 6 hours in an atmosphere of carbon dioxide. After the initial vigorous frothing, the reaction mixture turned pinkish. Cooled and treated with ice-water (250 ml.). The solution after saturation with ammonium sulphate was extracted with ether to remove the unreacted phenol. The aqueous liquor was acidified with dilute hydrochloric acid when an oily product separated which solidified on cooling. The solid was filtered, washed with water and dried in a desiccator (16 g.). Repeated crystallisation from benzene gave a product (6.3 g.), m.p. 171-72° (dec.), giving a violet colouration with ferric chloride (Found: C, 65.5; H, 7.2; $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%). This was 4-n-hexylresorcinol-6-carboxylic acid (III) as the m.p. by admixture with the sample of the acid obtained by carboxylating hexylresorcinol with aqueous potassium bicarbonate and melting at 171-72°(dec.) was not depressed.

The mother liquors on evaporation of benzene gave a solid which on thrice crystallizing from petroleum ether (60-80°) gave the acid (3.7 g.), m.p. 114-15° (dec.). An alcoholic solution of this acid gives an intense blue colouration with ferric chloride. The

acid thus was 4-n-hexylresorcinol-2-carboxylic acid (II) (Found: C, 66.0; H, 7.7. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%). Equivalent: Found, 242; calculated for $C_{12}H_{17}O_2 \cdot COOH$, 238).

Carboxylation of 4-n-hexylresorcinol with aqueous potassium bicarbonate:

4-n-Hexylresorcinol (I)(5 g.) and potassium bicarbonate (15 g.) was placed in a 500 ml. three-neck flask provided with a gas inlet, a condenser and a stirrer. Water (100 ml.) was added and the reaction mixture gently refluxed on a sand-bath, while a current of carbon dioxide was passed for 6 hours, cooled, filtered and the clear filtrate acidified with dilute hydrochloric acid. The acidified solution was ether extracted, and the ether layer washed with aqueous sodium bicarbonate. Acidification of the bicarbonate extracts gave a flocculent white precipitate which after chilling was filtered, washed with ice-water and dried in a desiccator (2.1 g.). Thrice crystallizing the product from benzene gave the acid, m.p. 171-72° (dec.). The mixed m.p. of this acid with that obtained in the above experiment showed no depression (Equivalent: Found: 243, calculated for $C_{12}H_{17}O_2.COOH$; 238).

An alcoholic solution of the acid gives a violet ferric reaction.

Methyl ester of 4-n-hexylresorcinol-2-carboxylic acid (II)

Method (1):- 4-n-Hexylresorcinol-2-carboxylic acid (II) (1 g.), anhydrous sodium bicarbonate (1.2 g.), methyl sulphate (1.1 ml.) and acetone (50 ml.) were refluxed together on a water bath for 5 hours. The reaction mixture was filtered hot, and the filtrate concentrated to a small volume. The residue after diluting with water was ether extracted. The ether solution was washed with aqueous sodium bicarbonate, water and dried. Desolvation gave a viscous brown oil which on distillation under reduced pressure gave nearly colourless liquid (0.6 g.), b.p. 150-55°/1 mm. (Found: C, 66.3; H, 8.0; $C_{14}H_{20}O_4$ requires C, 66.6; H, 8.0%).

Method (2) : A solution of 4-n-hexylresorcinol-2-carboxylic acid (III)(10 g.) in absolute methanol (5 ml.) and ether (40 ml.) was treated with an ethereal solution of diazomethane (40 ml.) [from nitrosomethylurea (6 g.)] The reaction mixture was kept for 24 hours at 10°. The ether after filtration was extracted with aqueous sodium bicarbonate to remove the free acid, washed with water and dried over anhydrous sodium sulphate. Evaporation of the ether gave a dark brown viscous oil which on distillation under reduced pressure gave a colourless liquid, (8.2 g) [b.p. 150-55°/1 mm. An alcoholic solution of the ester gives a bluish-violet colouration with ferric chloride.

Methyl ester of 4-n-hexylresorcinol-6-carboxylic acid (III):

Method I - 4-n-Hexylresorcinol-6-carboxylic acid (III), (1 g.), dry sodium bicarbonate (1.2 g.), methyl sulphate (1.1 cc.) and acetone (50 ml.) were refluxed for 4 hours on a water-bath. The reaction mixture was filtered and the acetone partly removed. The residue after dilution with water was extracted with ether. The ethereal layer was washed with aqueous sodium bicarbonate, water and dried. Evaporation of the ether gave the ester which crystallized from dilute methanol in nearly colourless needles (0.5 g.), m.p. 106-7° (Found: C, 66.4; H, 8.1. $C_{14}H_{20}O_4$ requires C, 66.6; H, 8.0%).

Method II - A solution of the acid (III)(5 g.) in absolute methanol (5 ml.) and ether (40 ml.) was heated with an ethereal solution of diazomethane (40 ml.) [from nitrosomethylurea (3.2 g.)]. The reaction mixture was left for 24 hours at 10°. It was then filtered, extracted with aqueous sodium bicarbonate, water and dried over sodium sulphate. The crystalline product (4.2 g.) was crystallized from dilute methanol in colourless needles, m.p. and mixed m.p. 106-7°. An alcoholic solution of the ester gives a violet colouration with ferric chloride.

Hydrolysis of methyl-4-n-hexylresorcinol-2-carboxylate:

Method I - On heating the ester (0.5 g.) with 5% alcoholic caustic potash (10 ml.) for 2 hours at 50° and acidifying with dilute hydrochloric acid, the reaction mixture was extracted with ether, the ethereal layer washed with aqueous

sodium bicarbonate. The alkaline extracts on acidification and reextraction with ether gave a product (0.1 g.) which on crystallization from benzene gave colourless needles, m.p. 114-15° (dec.) undepressed on admixture with an authentic sample of the acid (II).

Method II - On heating the ester (0.5 g.) with pyridine (5 ml.) and a drop of piperidine for 3 hours the reaction mixture was worked up as above. The acid obtained (0.4 g.) on crystallization from benzene gave colourless needles, m.p. and mixed m.p. 114-15° (dec.)

Hydrolysis of methyl 4-n-hexylresorcinol-6-carboxylate :

The ester (0.5 g.) was warmed with 5% alcoholic caustic potash (10 ml.) for 2 hours at 50°. After cooling and acidifying with dilute hydrochloric acid, the solution was ether extracted. The ether layer was washed with aqueous sodium bicarbonate which on reacidification with dilute hydrochloric acid gave a flocculent white precipitate (0.2 g.). Crystallization from benzene gave colourless needles, m.p. 171-72° (dec.) undepressed by admixture with an authentic sample of the acid (III). The ester however could not be hydrolysed by the pyridine-piperidine method.

Amide of 4-n-hexylresorcinol-2-carboxylic acid (IV):

A solution of methyl 4-n-hexylresorcinol-2-carboxylate (10 g.) in absolute methanol (100 ml.) was saturated with dry ammonia at 0°. The reaction mixture was allowed to stand at room temperature for 24 hours. The excess ammonia and methanol were removed on a warm water-bath and the residue

treated with water till precipitation just took place. The solution was refluxed (norit) and filtered. On cooling shining needles with a greenish tinge separated (4.5 g.), m.p. 160° (Found: C, 66.0; H, 7.9 ; N, 5.6. $C_{13}H_{19}O_3N$ requires C, 65.8; H, 8.1; N, 5.9%).

Hydrolysis of the amide of 4-n-hexylresorcinol-2-carboxylic acid (IV):

The amide (IV)(0.5 g.) was refluxed with 10% alcoholic caustic potash (10 ml.) for 6 hours. The reaction mixture was diluted with water and after acidification with dilute hydrochloric acid was ether extracted. The ethereal layer was washed with aqueous sodium bicarbonate, acidified and reextracted with ether. Evaporation of the dried ethereal solution gave the acid which crystallized from benzene in colourless needles (0.09 g.), m.p. and mixed m.p. 114-15° (dec.).

Diethylaminoethyl ester of 4-n-hexylresorcinol-2-carboxylic acid (V):

The acid (II) (1 g.) was neutralized with aqueous caustic potash (0.25 g. in water 5 ml.). Absolute alcohol (50 ml.) and benzene (20 ml.) were added and the moisture removed by distillation. On adding diethylaminoethyl chloride (1 g.) in ether (10 ml.) a crystalline product separated. Dry benzene (50 ml.) was added and the reaction mixture refluxed for 3 hours and left for 2 days. A white sticky product separated on removal of benzene. On adding alcoholic hydrochloric acid a thick white product separated

which was filtered. Crystallization from alcohol gave the hydrochloride as colourless needles (0.2 g.), m.p. 120° (Found: N, 4.2. $C_{19}H_{32}ClNO_4$ requires N, 3.8%).

Hydrazide of 4-n-hexylresorcinol-2-carboxylic acid (XX):

Methyl 4-n-hexylresorcinol-2-carboxylate (2 g.) methanol (40 ml.) and hydrazine hydrate (80%, 2 ml.) were refluxed together on a water-bath for 6 hours. On removing the alcohol, a sticky solid separated (2 g.). Crystallization from dilute acetic acid gave colourless needles, m.p. 160° (Found: N, 11.4; $C_{13}H_{20}N_2O_3$ requires N, 11.1%). An alcoholic solution of the hydrazide gives a red violet colouration with ferric chloride.

6-Dimethylaminomethyl-4-n-hexylresorcinol-2-carboxylic acid (VII):

A solution of the acid (II)(0.2 g.) in aqueous dimethylamine (2ml., 30%) was cooled to 10° and aqueous formalin (0.2 ml., 38%) added. The mixture was left for 12 hrs. at 10° when a pink crystalline solid separated, which was filtered washed and dried in a desiccator (0.22 g.). Crystallization from alcohol gave pink prisms, m.p. 172° (dec.) (Found: C, 65.1; H, 8.1; N, 4.5. $C_{16}H_{25}O_4N$ requires C, 65.1; H, 8.4; N, 4.7%). An alcoholic solution of the substance gives a blue violet colouration with ferric chloride.

6-Aldehydo-4-n-hexylresorcinol:

To a solution of 4-n-hexylresorcinol (I)(5 g.) in dry ether (60 ml.) was added powdered anhydrous zinc cyanide (6 g.) and fused zinc chloride (1.5 g.). Dry hydrogen chloride was bubbled at 0° till saturation and the reaction mixture left aside at 0° in an ice-chest for 24 hours. Ether was decanted off and the sticky aldimine hydrochloride washed twice with dry ether (50 ml.), and then treated with water (100 ml.) at 90-95° for 2 hours. On cooling, pinkish flakes of the aldehyde separated, which were filtered washed and recyrstallized from benzene (norit) when colourless flakes were obtained (2.9 g.), m.p. 112-13° (Fujikawa et al.[11],109°). An alcoholic solution of the aldehyde gives a violet colouration with ferric chloride.

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Part III

ATTEMPTED SYNTHESIS OF 4-AMINO-2-HYDROXY-1-NAPHTHOIC ACID (A NAPHTHALENE ANALOGUE OF PAS)

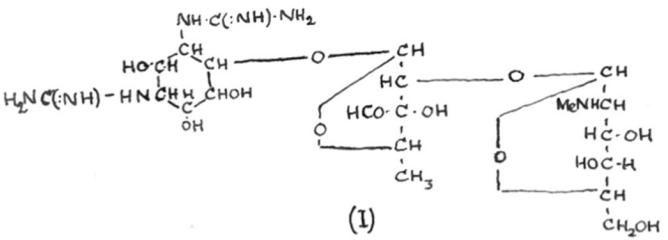
Attempted synthesis of 4-amino-2-hydroxy-1-naphthoic acid: a naphthalene analogue of 4-aminosalicylic acid.

In 1932 Wells and Long gathered the then existing knowledge of the chemotherapy of tuberculosis and concluded:[1] "A specific chemotherapy of tuberculosis has not been found and it may be a long time in coming because of the inherent difficulties of the problem, but it is not a closed chapter. We have some definite facts to go on, and some glimpses of light have been seen. Probably some new success with some other bacterial infection will be needed to stimulate a new attack on the more difficult problem offered by tuberculosis".

During the last few years numerous compounds of various types have been examined for their potential antitubercular properties. These include a wide range of naturally occurring substances and synthetic organic compounds. Although many of these compounds in high dilutions have been found to inhibit the growth of virulent stains of Myco. tuberculosis in various media, the activity is often reduced considerably when the medium of growth is enriched by blood and serum. Among the compounds which have high antitubercular activity in vitro very few have been shown to retain their activity in experimental animals. Several established animal tests are in use, such as those with guinea-pigs, mice or hamsters, the last two in an attempt to reduce the time factor.

The antitubercular drugs which are regarded at the present

time as the most promising are the naturally occurring antibiotics streptomycin[2] (I), neomycin, terramycin and viomycin, diaminodiphenylsulphone (II) and its derivatives, p-aminosalicylic acid[3] (III), p-aminobenzaldehyde thiosemicarbazone (IV) and other thiosemicarbazones, isonicotinic acid hydrazide[4] (V), verazide[5] (1-isonicotinoyl-2-veratylidene hydrazine) (VI) and cyanacetic acid hydrazide[6] (cyanazide) (VII). These substances exhibit no obvious relationship, the only common structural feature being that they all contain one or more basic nitrogenous groups. From a consideration of the structure and properties of these compounds, no generalization can be made regarding the relation between the chemical constitution, physical properties and antitubercular activity.



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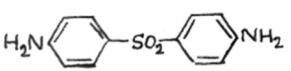

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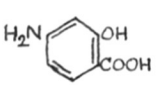

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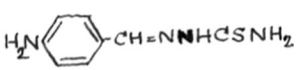

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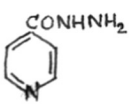

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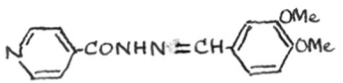

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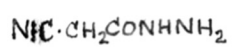

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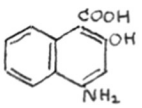
The synthesis of 4-amino-2-hydroxy-1-naphthoic acid (I), a naphthalene analogue of p-aminosalicylic acid, was undertaken in view of the antiseptic and anthelminthic properties of β-naphthol. Although the aminonaphtholsulphonic acids are largely used as intermediates for dyes, the analogous aminohydroxynaphthoic acids described in literature are very few. Beech and Legg[7] have described the synthesis of 6-amino-4-hydroxy-2-naphthoic acid ("carboxy-Y-acid") and have also recorded their failure to synthesize 7-amino-4-hydroxy-2-naphthoic acid ("carboxy J-acid"). Bhate[8] has described attempts to prepare



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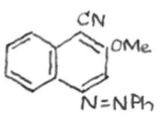
(I) by various methods: Direct carboxylation of 4-amino-2-naphthol by (a) refluxing with aqueous sodium bicarbonate, (b) by heating with potassium bicarbonate in dry glycerine in a stream of carbon dioxide, and (c) by heating with aqueous potassium bicarbonate at 100° under a carbon dioxide pressure of 30 atmospheres, was unsuccessful. Bhate[8] has also reported failure in hydrolysing 4-benzeneazo-2-methoxy-1-naphthonitrile (II) and 4-benzeneazo-2-methoxy-1-naphthamide (III), prepared by a series of reactions starting from 1-nitro-2-methoxy-



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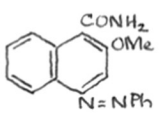
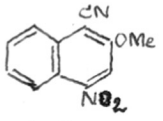


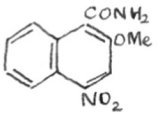
(III)

naphthalene, to the corresponding acid. 2-Methoxy-4-nitro-1-naphthonitrile (IV) and 2-methoxy-4-nitro-1-naphthamide (V)

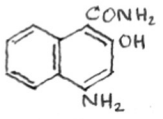
also resisted hydrolysis to the corresponding naphthoic acid. However, the naphthamide (V) on demethylation and subsequent reduction gave 4-amino-2-hydroxy-1-naphthamide (VI), which has



(IV)

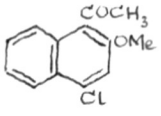


(V)

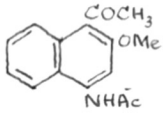


(VI)

been shown to possess slight <u>in vitro</u> activity against tubercule bacilli (1:10,000). The other routes to (I) investigated by Bhate were attempts to oxidise 1-acetyl-4-chloro-2-methoxynaphthalene (VII) and 1-acetyl-4-acetamido-2-methoxynaphthalene (VIII), which proved unsuccessful. The action of paraformal-

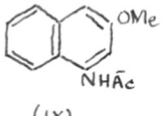


(VII)

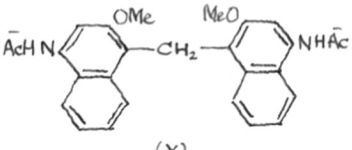


(VIII)

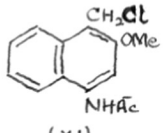
dehyde and hydrochloric acid on 4-acetamido-2-methoxynaphthalene (IX) gave 4:4'-diacetamido-2:2'-dimethoxydinaphthylmethane (X) instead of 4-acetamido-2-methoxy-1-chloromethylnaphthalene (XI).



(IX)



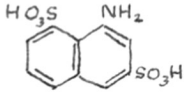
(X)



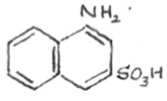
(XI)

PAS is manufactured by the direct carboxylation of <u>m</u>-aminophenol. Numerous patents[9] have been taken for the manufacture of PAS from <u>m</u>-aminophenol. The method in general consists of heating <u>m</u>-aminophenol, aqueous potassium bicarbonate and carbon dioxide under pressure. Carboxylation of 1-amino-3-naphthol (XIV) under various conditions was therefore tried in the present work, although the earlier attempts made by Bhate[8]

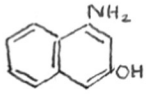
in this laboratory were unsuccessful. 1-Amino-3-naphthol (XIV) was prepared according to the method of Friedlaender[10,11] with certain modifications. Friedlaender reduced α-naphthylamine 3:8-disulphonic acid (XII) to α-naphthylamine-3-sulphonic acid (XIII) by sodium amalgam in aqueous caustic soda. This partial desulphonation proceeds in about 88% yield if Raney alloy in



(XII)



(XIII)



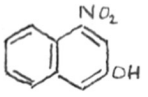
(XIV)

aqueous sodium carbonate at 100° is employed. Reduction of (XII) by the Papa method,[12] using Raney alloy and aqueous caustic soda, gave α-naphthylamine. The caustic fusion of (XIII) to 1-amino-3-naphthol (XIV) had to be carried out under careful controlled conditions of time and temperature and in an atmosphere of inert gas. Although the yield of the crude aminonaphthol was 45-47%, the yield of the pure compound was only 20-22%. Friedlaender[10,11] did not state the yields in the two steps. The aminonaphthol crystallized from toluene in light brown needles, which darkened on exposure, m.p. 202-203° (dec.) [(Friedlaender,[10] m.p. 185° (dec.); Challenor and Ingold[13] 198° (dec.)]. Morgan and Evens[14] obtained 1-amino-3-naphthol by reduction of 1-nitro-3-naphthol with tin and hydrochloric acid or with zinc dust and ammonium chloride in 50% alcohol, but the yields were not mentioned. In agreement with Friedlaender, Morgan and Evens observed that prolonged digestion with reducing agents led to the hydrolysis of the amino group and the formation of 1:3-dihydroxynaphthalene. Challenor and Ingold[13] found that the reduction of 1-nitro-3-naphthol with aluminium amalgam in moist ether led to the complete elimination of the amino

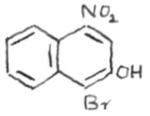
group; further reduction to naphthalene also took place. They therefore prepared the tosyl ~~derivative~~ ate of 1-nitro-3-naphthol, reduced it with aluminium amalgam and then removed the tosyl group by hydrolysis. ~~Bhate[8] has shown that~~ 1-Nitro-3-naphthol can be smoothly reduced in alcoholic solution to 1-amino-3-naphthol (XIV) by Raney nickel and hydrogen at 40 lbs. pressure in excellent yield (92-93%). Degerholm and Liljegren[15] have claimed to have synthesised (I) by direct carboxylation of the potassium salt of 1-amino-3-naphthol (XIV) by heating in an autoclave at 140-50° under a pressure of carbon dioxide at 9 atmospheres. They also claim to have prepared (I) by heating the naphthol (XIV) in toluene in presence of sodium sand and dry carbon dioxide. However, attempts to repeat the experiments using the same as well as modified conditions of time, temperature and pressure failed to give the acid (I).

Since large quantities of the aminonaphthol were needed for this investigation, the caustic fusion of α-naphthylamine-3-sulphonic acid (XIII) proved tedious. 1-Nitro-3-naphthol (XV) obtained by the procedure of Morgan and Evens,[14] as modified by Hodgson and Birtwell,[16] was hence used as the starting material. The nitration of acet-α-naphthalide gave only a 30% yield of 2:4-dinitro-α-naphthalide. However, the nitration of p-toluenesulphon-α-naphthalide proceeded smoothly and in nearly quantitative yield following the conditions of Hodgson et al.[17] 1-Nitro-3-naphthol (XV) was brominated by means of bromine in acetic acid to 4-bromo-1-nitro-3-naphthol

(XVI). Halogen-metal interaction with n-butylithium followed

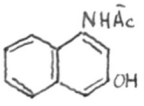


(XV)

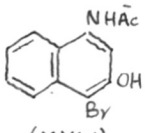


(XVI)

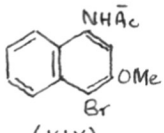
by carbonation with dry ice proved unsuccessful. Metallation of 1-amino-3-naphthol (XIV) and 1-acetamido-3-naphthol (XVII) with n-butyllithium and subsequent carbonation with solid



(XVII)



(XVIII)

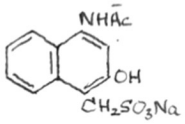


(XIX)

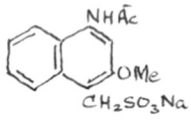
carbon dioxide failed to give the desired acid. 1-Acetamido-3-naphthol (XVII) on bromination in acetic acid gave 1-acetamido-4-bromo-3-naphthol (XVIII) in good yield. Methylation of the bromonaphthol (XVIII) with dimethyl sulphate in acetone in presence of anhydrous potassium carbonate gave 1-acetamido-4-bromo-3-methoxynaphthalene (XIX). Both the naphthol (XVIII) and the ether (XIX) failed to undergo halogen-metal interaction with n-butyllithium in diethyl ether and di-n-butyl ether, both in the cold and at reflux temperatures. As model experiments, the halogen-metal interaction of 1-acetamido-4-bromonaphthalene and 1-amino-4-bromonaphthalene was studied. In both the cases, carbonation proceeded smoothly and the naphthoic acids were obtained in excellent yield. The same acids have been prepared by the reduction[18,19] of 1-nitro-4-naphthoic acid and by the hydrolysis[19] of 1-amino-4-naphthonitrile and 1-amino-4-naphthamide. Gilman and Sunthankar[20] have prepared 2-hydroxy-1-naphthoic acid from 1-bromo-2-

naphthol by successive treatment with n-butyllithium and carbon dioxide.

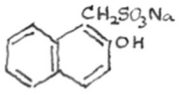
Other routes to (I) were then examined. 1-Acetamido-3-naphthol (XVII) was sulphomethylated with sodium sulphite and aqueous formaldehyde to give sodium 1-acetamido-3-hydroxy-4-methylnaphthalene-ω-sulphonate (XX). Methylation of (XX)



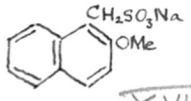
(XX)



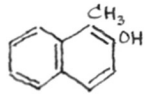
(XXI)



(XXII)



(XXIII)



(XXIV)

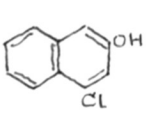
with dimethylsulphate in aqueous sodium carbonate gave the methyl ether (XXI). Oxidation of (XXI) with aqueous potassium permanganate and permanganate in acetone were unsuccessful.

β-Naphthol on sulphomethylation[21] and subsequent methylation gave (XXIII) Oxidation of (XXIII) with aqueous permanganate did not give the acid, but only traces of β-naphthol methyl ether. The Kenner-Murray reduction[22] of (XXII) with Raney nickel in presence of hydrogen gave 1-methyl-β-naphthol (XXIV).

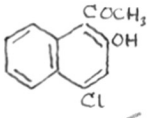
Another route starting from 4-chloro-2-naphthol (XXV) was next explored. 4-Chloro-2-naphthol (XXV) was obtained by reduction of 1:4-dichloro-2-naphthol with stannous chloride in acetic acid saturated with hydrogen chloride under pressure according to Burton.[23] Since the method involved

prolonged heating at 100° under pressure and a suitable type of autoclave was not available, the dechlorination of 1:4-dichloro-2-naphthol to 4-chloro-2-naphthol (XXV) by treatment with catalytic amounts of Raney nickel and hydrogen in aqueous alkali was attempted, but the product was β-naphthol.

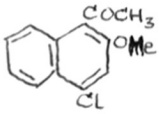
Replacement of the chlorine atom by the amino group by condensing ~~with benzylamine and~~ p-toluenesulphonamide proved unsuccessful, the naphthol being recovered. ~~The~~ condensation ~~of (XXV)~~ with benzylamine in presence of copper bronze gave β-naphthol and benzaldehyde. 1-Acetyl-4-chloro-2-naphthol (XXVI) ~~has~~ was



(XXV)

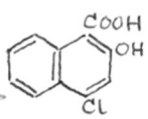


~~(XXVI)~~ (XVIII)

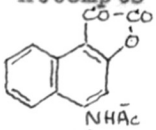


(XXVII)

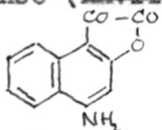
~~been~~ prepared ~~by Bhate~~[8] by the Fries migration of 4-chloro-2-naphthyl acetate in carbon disulphide in 52-54% yield. It was ~~has now been~~ subsequently found that 4-chloro-2-naphthol (XXV) reacts with excess of glacial acetic acid-boron trifluoride complex, giving a quantitative yield of the ketone (~~XXVI~~ XVIII). Methylation ~~of (XXVI) in acetone with dimethyl sulphate in presence of anhydrous potassium carbonate~~ gave 1-acetyl-4-chloro-2-methoxynaphthalene (XXVII), which Oxidation of ~~(XXVII)~~ with sodium hypochlorite ~~in alkaline solution~~ was unsuccessful. Oxidation ~~of (XXVI)~~ with iodine in pyridine according to the method of King et al.[24,25] gave 4-chloro-2-hydroxy-1-naphthoic acid (~~XXVIII~~ XIX) in poor yield. Attempts to condense (~~XXVIII~~ XIX)



~~(XXVIII)~~ XIX



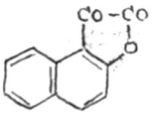
(XXIX)



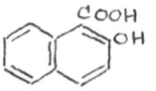
(XXX)

with benzylamine and p-toluenesulphonamide were unsuccessful.

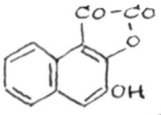
The possibility of introducing a carboxyl group in the 4-position in 1-acetamido-3-naphthol (XVII) via the coumarandione (XXIX) was next investigated. 1-Acetamido-3-naphthol (XVII) was condensed with cyanoformic ester in presence of zinc chloride and hydrogen chloride to 6-acetamido-4:5-benzocoumaron-2:3-dione (XXIX) in 20-22 per cent yield. The low yield was partly due to partial hydrolysis of the product to 6-amino-4:5-benzocoumaran-2:3-dione (XXX) which has been isolated and identified (6-8%). Passerini[26-27] has reported that benzocoumaran-2:3-dione (XXXI) obtained by the action of cyanoformic ester on β-naphthol could be oxidised to the



(XXXI)



(XXXII)

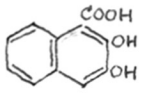


(XXXIII)

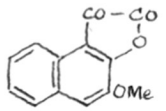
corresponding 2-hydroxy-1-naphthoic acid (XXXII) in 60-65 per cent yield with hydrogen peroxide in acetic acid at 60°. It has now been found that the oxidation of (XXXI) with silver nitrate and caustic potash gave the acid (XXXII) in satisfactory yield (62-65%). However, oxidation of (XXIX) under the same conditions did not give the corresponding carboxylic acid, the lactone being recovered. Oxidation with hydrogen peroxide in cold aqueous alkali gave phthalic acid. Hunsberger and Amstutz[28] have reported that 1:5-dimethoxy-4-naphthylglyoxylic acid and 2:7-dimethoxy-1-naphthylglyoxylic acid could be oxidised to the corresponding naphthoic acids by oxidation with potassium permanganate in 40% acetic acid. In model exploratory experiments, 2:3-dihydroxynaphthalene underwent the

cyanoformic ester condensation to give the lactone (~~XXXIII~~ XX).

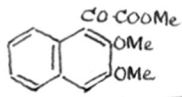
Attempted oxidation of (XXXIII) with silver nitrate and alkali and with hydrogen peroxide in acetic acid did not give the naphthoic acid (XXXIV)



(XXXIV)

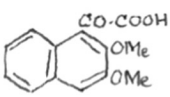


(XXXV)

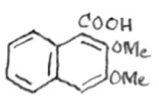


~~(XXXVI)~~ XXII

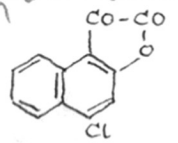
The lactone (~~XXXIII~~ XXI) on methylation with dimethyl sulphate and aqueous ~~caustic soda~~ sodium hydroxide gave (~~XXXV~~) the monomethyl ether; but methylation with dimethyl sulphate in acetone in presence of anhydrous potassium carbonate gave the ether-ester (~~XXXVI~~ XXII). Hydrolysis of (~~XXXVI~~) the ester (XXII) with ~~alcoholic caustic soda~~ alkaline gave the free glyoxylic acid (~~XXXVII~~), which on oxidation with permanganate in 40% acetic acid furnished 2:3-dimethoxy-1-naphthoic acid (~~XXXVIII~~).



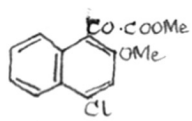
(XXXVII)



(XXXVIII)



(XXXIX)

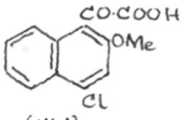


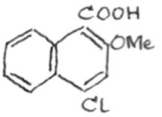
(XL)

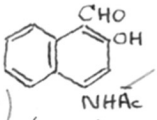
Attempts to prepare the unknown 2:3-dihydroxy-1-naphthoic acid (XXXIV) by heating 2:3-dihydroxynaphthalene with aqueous sodium bicarbonate under nitrogen pressure of 400 lbs./□" at 110-20°, and by heating a solution of 2:3-dihydroxynaphthalene in toluene in presence of sodium sand in a vigorous stream of dry carbon dioxide, were both unsuccessful.

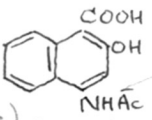
Another route starting from 4-chloro-2-naphthol (XXV) was next attempted. 4-Chloro-3-naphthol (~~XXV~~) underwent the Hoesch reaction with cyanoformic ester to give 6-chloro-4:5-benzocoumaran-2:3-dione (~~XXXIX~~). The lactone (~~XXXIX~~) was oxidised with silver ~~nitrate in alkali~~ oxide to 4-chloro-2-hydroxy-

acid
1-naphthoic (XXVIII), identical with the acid obtained earlier by the oxidation of 1-acetyl-4-chloro-2-naphthol (XXVI) with iodine


(XLI)

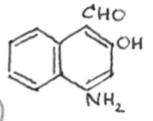

(XLII)

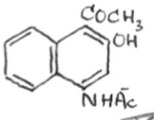

(XLIII)

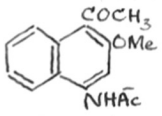

(XLIV)

and pyridine. 4-Chloro-2-methoxy-1-naphthoic acid (XLII) was obtained from (XXXIX) via (XL) and (XLI). Replacement of chlorine in (XXXIX) and (XLII) by an amino group was unsuccessful.

1-Acetamido-3-naphthol (XVII) underwent the Gattermann aldehyde synthesis to give 4-acetamido-2-hydroxy-1-naphthaldehyde (XLIII) in 45-48% yield. Bhate prepared the same aldehyde (XLIII) in very poor yield (2-3%) by treating the naphthol (XVII) with phosphorus oxychloride and N-methylformanilide. Pearl[30] has reported the smooth oxidation of vanillin to vanillic acid by silver oxide and alkali. The oxidation of (XLIII)


(XLV)


(XLVI)


(XLVII)

with silver oxide in aqueous alkali or sodium carbonate did not furnish (XLV) or (I), but gave only the deacetylated product (XLV).

1-Acetyl-4-acetamido-2-naphthol (XLVI) was obtained in excellent yield by the action of an excess of glacial acetic acid-boron trifluoride complex at 100° on (XVII). The same ketone (XLVI) was obtained by Bhate[8] by the Friedel-Crafts reaction on 1-acetamido-3-methoxynaphthalene with acetyl

(1) 1:2:5. Trihydroxy Anr. trimethyl. ether.
(1) $H_{14}O_5$ m.p. 203-4°c; blue solns in H_2SO_4. P.a.s. 582

(2) 6-Methyl-1:2:5-trihydroxyanthraquinone trimethyl ether. m.p. 229°c.; deep blue soln in H_2SO_4

(3) 7-methyl-1:2:5:6-trihydroxyanthraquinone. Trimethyl ether $C_{18}H_{18}O_5$ m.p. 214°
Violet brown in H_2SO_4.

(4) 7-methyl-1:4:5-trihydroxy anr.
1:4-dimethyl ether m.p. 172°c
blue-red in H_2SO_4.

(5) 5-methyl-1:4:6-trihydroxyaa.
6-methyl ether - blue violet in H_2SO_4.

(6) 1:2:5:8-tetrahydroxy Anr. 1:2 dimethyl ether m.p. 225-30° Blue in H_2SO_4.

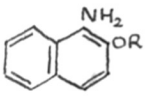
(7) 1:2:6:7) Tetrahydroxy Anr. trimethyl ether m.p. 228° violet red in H_2SO_4

(8) 1:4:5:8-Tetrahydroxy Anr. Tetra methyl ether m.p. 319°c. Greenish blue in H_2SO_4.

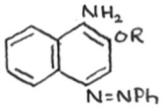
(9) 2:3:6:7-Tetrahydroxy Anr. Tetra methyl ether green soln in H_2SO_4

chloride in carbon disulphide, demethylation taking place at the same time. The naphthol (XLVI) was then methylated to the ether (XLVII) by the general method. The ketone (XLVII) could not be oxidized with sodium hypochlorite to the corresponding acid.

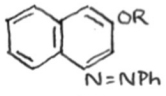
1-Amino-2-methoxynaphthalene and 1-amino-2-ethoxynaphthalene (XLVIII) coupled with diazotized aniline and pyridine to yield the azo dyes: 1-amino-4-benzeneazo-2-methoxynaphthalene and 1-amino-4-benzeneazo-2-ethoxynaphthalene (XLIX). The azo dyes were also obtained in good



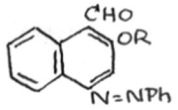
(XLVIII)



(XLIX)



(L)



(LI) (R=Me,Et)

yield and in the crystalline state, when equimolecular quantities of amine (XLVIII) and diazoaminobenzene in alcoholic solution were mixed and kept for two days. The diazonium salt of (XLVIII), on treatment with alcohol, was deaminated to 4-benzeneazo-2-methoxynaphthalene and 4-benzeneazo-2-ethoxynaphthalene (XLIX) in very poor yield (7-8%). Difficulty was experienced in diazotizing the amine, and the pure deaminated products were obtained only after chromatography on alumina. Formylation of the azo derivative (L) with dimethylformamide and phosphorous oxychloride under a variety of conditions did not give the desired aldehyde (LI).

EXPERIMENTAL

α-Naphthylamine-3-sulphonic acid (XIII):

α-Naphthylamine-3:8-disulphonic acid (XII)(50 g.) was dissolved in aqueous sodium carbonate (650 ml., 20%). The reaction mixture was heated on a steam-bath, and Raney alloy (50 g.) was added in small lots with vigorous stirring. After complete addition (1.5 hours), the mixture was further heated for 1 hour, cooled and filtered. The nickel was washed with aqueous sodium carbonate (50 ml.) and water. The alkaline filtrate on acidification gave a white flocculent precipitate which was filtered washed and dried at 100° (29.0 g.). Yield, 88%. Crystallization from water gave pink needles (Found in a sample dried at 100°/0.2 mm: N, 6.0; S, 14.2. $C_{10}H_9NO_3S$ requires N, 6.2; S, 14.3%). Partial reduction of α-naphthylamine-3:8-disulphonic acid (XII) with sodium amalgam in aqueous caustic soda according to the method of Friedlaender gave a yield of 75% of α-naphthylamine-3-sulphonic acid (XIII) (Friedlaender[10,11] did not state the yield).

1-Amino-3-naphthol (XIV):

α-Naphthylamine-3-sulphonic acid (XIII)(15 g.) was added all at once to well stirred, molten potassium hydroxide (75 g.) at 180-190° in an atmosphere of nitrogen. The temperature was gradually raised to 260-70° and maintained for 25-30 minutes. The reaction commenced at 260° with vigorous frothing. The melt was gradually cooled under stirring, and at 170° poured on to cracked-ice (300 g.) and acidified with concentrated hydrochloric acid

under cooling, when a black tarry product separated. The solution was filtered and the filtrate on neutralization with solid sodium bicarbonate gave a bright yellow flocculent precipitate, which was rapidly filtered and dried in a desiccator (5 g.). Crystallization from toluene gave light brown needles (2.1 g.), m.p. 202-203° (dec.) (Found: N, 8.6. $C_{10}H_9NO$ requires N, 8.6%) [(Friedlaender[11], m.p. 185° (dec.)(Challenor and Ingold,[13] m.p. 198° dec.)].

The naphthol (XIV) was also obtained in nearly 92% yield by the Raney nickel reduction of an alcoholic solution of 4-nitro-2-naphthol (XV) in presence of hydrogen at 40 lbs. pressure following the method of Bhate.[8] The product crystallized in light brown needles from toluene, m.p. 202-203° (dec.).

1-Acetamido-3-naphthol (XVII):

Acetic anhydride (3 ml.) was added gradually to dry 1-amino-3-naphthol (XIV)(5 g.) with cooling. The mixture was left at room temperature for 1/2 hour and poured into cracked ice. A brown oily product separated which solidified to a purple crystalline mass. The product was filtered, washed and dried. Crystallization from dilute alcohol gave nearly colourless needles (4.6 g.), m.p. 179° (Friedlaender[31], 179°).

4-Bromo-1-nitro-3-naphthol(XVI):

To a solution of 1-nitro-3-naphthol (XV)(7.5 g.) in glacial acetic acid (75 ml.) was added gradually a solution of bromine (1.8 ml.) in glacial acetic acid (18 ml.) under stirring. The reaction mixture was left overnight at room temperature (28°). On dilution with water (200 ml.) and cooling, a yellow crystalline product separated which was filtered, washed and dried (9.4 g.). Crystallization from alcohol gave yellow needles, m.p. 154° (Found: C, 44.9; H, 2.2; N, 5.6; Br, 29.8. $C_{10}H_6NO_3Br$ requires C, 44.8; H, 2.2; N, 5.2; Br, 29.8%).

1-Acetamido-4-bromo-3-naphthol (XVIII):

To a solution of 1-acetamido-3-naphthol (XVII)(1.2 g.) in glacial acetic acid (12 ml.) was added gradually a solution of bromine (0.96 g.) in glacial acetic acid (5 ml.). The mixture was left for 12 hours at room temperature and diluted with ice-water (20 ml.), when a purple crystalline product separated which was filtered, washed and dried (1.49 g.). Crystallization from dilute acetic acid (norit) gave nearly colourless needles, m.p. 198-99° (Found: C, 51.9; H, 3.9; Br, 28.4. $C_{12}H_{10}O_2NBr$ requires C, 51.4; H, 3.5; Br, 28.6%).

1-Acetamido-4-bromo-3-methoxynaphthalene (XIX):

A mixture of 1-acetamido-4-bromo-3-naphthol (XVIII) (1 g.), dry acetone (30 ml.), dimethyl sulphate (2 ml.) and anhydrous potassium carbonate (3 g.) was refluxed on

a water bath for 12 hours. After partly removing the acetone, the reaction mixture was diluted with ice-water. The product that separated was filtered, washed and dried (1.2 g.). Crystallization from dilute acetic acid gave colourless needles, m.p. 169-70° (Found: C, 52.5; H, 4.4. $C_{12}H_{12}O_2NBr$ requires C, 53.0; H, 4.1%).

1-Acetamido-4-bromonaphthalene:

1-Acetamido-4-bromonaphthalene was prepared in 95% yield following the method of Hodgson et al. The product crystallized from alcohol in colourless needles, m.p. 193° (Hodgson et al.,[16] m.p. 193°).

1-Amino-4-bromonaphthalene:

The above naphthalide (5 g.) was refluxed with hydrochloric acid (25 ml., d,1.16) and glacial acetic acid (75 ml.) for 90 minutes. The amine hydrochloride which separated on cooling was treated with ice-water (100 ml.) and filtered. The product was basified and the free amine collected, washed and dried (3.9 g.). Crystallization from petroleum ether gave colourless needles, m.p. 102° (Sergievskya[32] mentions m.p. 102°).

1-Amino-4-naphthoic acid:

Method (I) : A solution of n-butylithium (0.02 mole) was added during the course of 20-25 minutes to a well stirred solution of 1-acetamido-4-bromonaphthalene (2.6 g., 0.01 mole) in ether (50 ml.). After stirring for 2 hours, the reaction mixture was poured on to crushed solid carbon dioxide and ether. After evaporation of the carbon

dioxide, water was added. The ethereal layer was washed with aqueous sodium bicarbonate and acidified with dilute hydrochloric acid when a white solid separated (1.3 g.). The crude acid was hydrolysed with warm 5% aqueous caustic potash (15 ml.) for 4 hours at 80°, cooled and acidified with dil. acetic acid when a brownish yellow solid separated (0.8 g.). Crystallization from water gave faint brownish needles, m.p. 176-77° (Found: C, 70.1; H, 4.3; N, 7.6. $C_{11}H_9O_2N$ requires C, 70.6; H, 4.9; N, 7.5%)(Friedlaender and Weisberg[18] mention m.p. 177°, Sergievskya,[19] 176-77°).

Method (II): A solution of n-butyllithium (0.04 mol.) was added with stirring during a period of 10-15 minutes to a solution of 1-amino-4-bromonaphthalene (2.2 g. 0.01 mole.) in warm ether (50 ml.). After stirring for 3 hours at room temp., (28°), the mixture was poured into a slurry of dry ice in ether. After evaporation of the carbon dioxide the mixture was treated with water. The ether layer was separated, washed with aqueous sodium bicarbonate and acidified with dilute acetic acid, when a brownish yellow solid precipitated, which was filtered, washed and dried (1.1 g.) Crystallization from water (norit) gave faint brown needles, m.p. 176-77°, undepressed on admixture with the acid obtained by the above method.

Sodium 1-acetamido-3-hydroxy-4-methylnaphthalene-ω-sulphonate (XX):

1-Acetamido-3-naphthol (XVII)(1 g.) was suspended in water (25 ml.), sodium sulphite (1.3 g.) and aqueous formaldehyde (0.5 ml., 40%) added, when the reaction mixture turned

light brown. On heating for 4 hrs. on a steam-bath the mixture turned dark brown. Cooled, filtered and filtrate neutralized with 2N sulphuric acid when a light brown gelatinous precipitate separated which was filtered (< 10 mg.). The clear filtrate was concentrated to 1/4th its volume, when a crystalline solid separated, which was filtered, washed with ice-water and dried (0.6 g.). Crystallization from 95% alcohol gave colourless needles. The product had no m.p. (Found in a sample dried over phosphoric acid at 100°/0.2 mm.: C, 49.2; H, 3.5; N, 4.7; S, 10.6. $C_{13}H_{12}O_5NSNa$ requires C, 49.2; H, 3.8; N, 4.4; S, 10.1%).

Sodium 1-acetamido-3-methoxy-4-methylnaphthalene-ω-sulphonate (XXI):

The above sulphomethyl compound (XX)(0.2 g.) was dissolved in aqueous sodium carbonate (10 ml., 20%), dimethyl sulphate (0.4 ml., excess) was added drop by drop and the mixture agitated at room temperature (28°) for 12 hours. The clear solution was then neutralized with dilute sulphuric acid and concentrated to near dryness when a sticky light brown product separated. Crystallization from 50% alcohol (norit) gave nearly colourless needles (0.14 g.). The substance had no m.p. (Found: S, 9.2; $C_{14}H_{14}O_5NSNa$ requires S, 9.6%).

Sodium-2-hydroxy-1-naphth methylnaphthalene-ω-sulphonate (XXII) and sodium 2-methoxy-1-methylnaphthalene-ω-sulphonate (XXIII):

β-Naphthol was sulphomethylated according to the method of Suter et al.[21] The sulphomethyl derivative (XXII)

crystallized from 50% ethanol as platelets.

The methyl ether (XXIII) was prepared following the procedure of Clutterbuck and Cohen[21A] and crystallized from dilute alcohol in colourless plates.

Oxidation of sodium 2-methoxy-1-methylnaphthalene-ω-sulphonate (XXIII):

The ether (XXIII) (1 g.) was dissolved in water (20 ml.), finely powdered potassium permanganate (0.58 g.) was added under stirring. The mixture was agitated at room temp. for 4 hours, cooled and the precipitated manganese dioxide dissolved out by passing sulphur dioxide. The clear pale yellow solution was ether extracted. Desolvation gave a crystalline solid (0.09 g.). Crystallization from dilute alcohol gave colourless needles, m.p. 72°. Mixed m.p. with an authentic sample of 2-methoxynaphthalene was not depressed.

1-Methyl-2-naphthol (XXIV):

The sulphomethyl derivative (XXII)(5 g.) was dissolved in 30% alcohol (500 ml.), Raney nickel (50 g.) added and the mixture agitated for 5 hours at room temperature (2 g.) in a steady stream of hydrogen. The catalyst was filtered off and the filtrate concentrated under vacuum to 1/4th its volume and extracted with ether, after acidification with dilute hydrochloric acid. On removal of the solvent, a pale yellow oil was obtained which solidified immediately (0.8 g.). Crystallization from water (norit) gave nearly

colourless needles, m.p. 110°. The nickel residue, after deactivation with hydrochloric acid and extraction with ether, gave a further quantity of the same material (0.3 g.). Total yield 1.1 g. (36%). (Found: C, 83.4; H, 6.6. $C_{11}H_{10}O$ requires C, 83.6; H, 6.3%) (Cornforth et al.[33] mention m.p. 109-111°).

1-Acetyl-4-chloro-2-naphthol (XXVI):

4-Chloro-2-naphthol (XXV)(2 g.) and glacial acetic acid-boron trifluoride complex (12 ml.) were mixed and heated on a steam-bath for 4 hours. After keeping overnight at room temperature, the mixture was added to crushed ice, and the precipitated crystalline product filtered, washed and dried (2.3 g.). Crystallization from petroleum ether gave yellow prisms, m.p. 56-57°(Found: C, 65.1; H, 4.3 $C_{12}H_9O_2Cl$ requires C, 65.3; H, 4.3%)(Bhate[8] mentions 53-54°). The dinitrophenylhydrazone of (XXVI) crystallized from alcohol in orange needles, m.p. 208-09° (Found: N, 13.6; $C_{18}H_{13}O_5N_4Cl$ requires N, 14.0%).

4-Chloro-2-hydroxy-1-naphthoic acid (XXVIII):

The above ketone (XXVI)(0.44 g.), iodine (0.51 g.) and dry pyridine (3 ml.) were heated for 1 1/2 hours on a steam-bath. The dark brown mixture started depositing a crystalline product after half an hour. The mixture was left at room temperature for 12 hours, the excess pyridine was distilled off under vacuum and the residue treated with cold dry ether to remove the unreacted ketone and then

leached with water. The residual brown semi-solid of pyridinium iodide was dissolved in 95% alcohol (20 ml.) containing sodium hydroxide (1 g.) and heated for one hour on steam-bath. The alkaline solution was noritted and filtered. The clear brown filtrate on acidification with dilute hydrochloric acid gave a flocculent yellowish brown precipitate, which was filtered, washed and dried (0.12 g.), Crystallization from benzene gave pale yellow prisms, m.p. 139-40° (dec.) (Found: C, 59.9; H, 3.0. $C_{11}H_7O_3Cl$ requires C, 59.3; H, 3.1%).

1-Acetyl-4-chloro-2-methoxynaphthalene (XXVII):

A mixture of 1-acetyl-4-chloro-2-naphthol (XXVI)(2 g.) acetone (25 ml.) anhydrous potassium carbonate (5 g.) and dimethyl sulphate (2 ml.) was refluxed gently for 12 hours on a water-bath. After removing acetone partly, water (50 ml.) was added and the precipitated product filtered, washed and dried (2.1 g.). Crystallization from petroleum ether (40-60°) gave colourless prisms, m.p. 78-79° (Found: C, 67.0; H, 4.7; Cl, 14.7. $C_{13}H_{11}O_2Cl$ requires C, 66.5; H, 4.7; Cl, 15.1%) (Bhate[8] mentions 78°).

6-Acetamido-4:5-benzocoumaran-2:3-dione (XXIX):

1-Acetamido-3-naphthol (XVII)(1.5 g.) was suspended in dry ether (100 ml.) fused zinc chloride (1 g.) and freshly distilled cyanoformic ester (1 g.) were added and the mixture saturated with dry hydrogen chloride at 0° under mechanical stirring. The reaction mixture turned

deep red and was left aside for 24 hours in an ice-chest. A red oil together with a small amount of a reddish solid separated. The mixture was resaturated with hydrogen chloride and kept for another 24 hours. The ether was decanted off, the residue washed twice with dry ether (20 ml.). Crushed-ice and water were added and the solution warmed on a water-bath at 60-70° for 1/2 hour when a bright orange precipitate separated. Cooled, filtered, washed and dried in a desiccator (0.4 g.). Crystallization from acetone gave bright orange needles, m.p. 236°(dec.)(Found: C, 66.1; H, 3.6; N, 5.3. $C_{14}H_9O_4N$ requires C, 65.9; H, 3.5; N, 5.5%).

The acidic filtrate on neutralizing gave a bright red product (0.18 g.), which crystallized from ethyl acetate in bright red needles, m.p. 254-55° (dec.) and was identified as 6-amino-4:5-benzocoumaran-2:3-dione (XXX) (Found: C, 67.4; H, 3.2; N, 6.1. $C_{12}H_7O_3N$ requires C, 67.7; H, 3.2; N, 6.5%).

Oxidation of 6-acetamido-4:5-benzocoumaran-2:3-dione (XXIX) with hydrogen peroxide in aqueous caustic soda:

The lactone (XXIX)(0.2 g.) was dissolved in aqueous caustic soda (5 ml., 3%), hydrogen peroxide (1 ml. 10%) was added at 10° with cooling. The initial orange-red colour of the mixture gradually disappeared and after 12 hours a clear pale yellow solution resulted. The alkaline solution was acidified with dilute hydrochloric acid and ether

extracted. Desolvation gave a crystalline product (0.09 g.) which crystallized from benzene in nearly colourless needles, m.p. 206° (dec.). Mixed m.p. with an authentic sample of phthalic acid does not depress the melting point.

Oxidation of benzocoumaron-2:3-dione (XXXI) with silver nitrate and alkali:

Potassium hydroxide (0.55 g.) in water (3 ml.) was added to a solution of the lactone (XXXI)(0.5 g.) in alcohol (5 ml., 50%). Silver nitrate (1.2 g.) was added and the mixture heated on a steam-bath for 1 hour. The deep green solution deposited a silver mirror, cooled and filtered. The filtrate on acidification with dilute hydrochloric acid gave a flocculent pale yellow precipitate, which was filtered, washed and dried (0.30 g.). Crystallization from dilute acetic acid gave nearly colourless prisms, m.p. 154° (dec.). Mixed m.p. with an authentic sample of 2-hydroxy-1-naphthoic acid (XXXII) does not depress the melting point.

7-Hydroxy-4:5-benzocoumaran-2:3-dione:(XXXIII):

2:3-Dihydroxynaphthalene (16 g.) was dissolved in dry ether (100 ml.), fused zinc chloride (2 g.) and cyanoformic ester (10 ml.) were added, and the reaction mixture saturated with dry hydrogen chloride at 0° under mechanical stirring. A brick-red solid separated together with a small amount of a dark red oil. The mixture was left for 24 hours in an ice chest, the ether decanted off and the residue washed twice with fresh dry ether (50 ml.). Water

(100 ml.) was added and the solution warmed on a water-bath at 80° for 1 hour, cooled and the red solid filtered, washed and dried (13 g.). Crystallization from a mixture of benzene-ethylacetate gave brick red prisms, m.p. 200° (dec.) (Found: C, 67.3; H, 2.8. $C_{12}H_6O_4$ requires C, 67.5; H, 2.7%).

From the mother liquor, a colourless solid (0.18 g.) was obtained which on repeated crystallization from dilute alcohol gave colourless needles, m.p. 238-40° (Found: C, 68.1; H, 3.6%). The product however could not be identified.

7-Methoxy-4:5-benzocoumaran-2:3-dione (XXXV):

The above lactone (XXXIII)(0.2 g.) was dissolved in aqueous sodium hydroxide (10 ml., 5%), dimethyl sulphate (1 ml.) was added and the mixture heated on a steam bath for 2 hours. A further quantity of aqueous sodium hydroxide (2 ml.) was added, cooled and the mixture left for 12 hours at room temperature. Acidification with dilute hydrochloric acid gave an orange yellow precipitate, which was filtered, washed and dried (0.19 g.). Crystallization from benzene-ethylacetate mixture gave orange yellow-needles, m.p. 233-34° (Found: C, 68.6; H, 3.7. $C_{13}H_8O_4$ requires C, 68.4; H, 3.5%).

Methyl-2:3-dimethoxy-1-naphthylglyoxylate (XXXVI):

The lactone (XXXIII)(2 g.), dry acetone (30 ml.), anhydrous potassium carbonate (5 g.) and dimethyl sulphate (5 ml., excess) were refluxed together for 12 hours on a water bath. The acetone was distilled off, and the residue treated with ice-water (50 ml.). A pale yellow oil separated which was

taken up in ether, washed with water and dried. Evaporation of the dried ethereal extracts gave an oil (2.2 g.), which on distillation under reduced pressure gave a very pale yellow oil (165-170°/0.3 mm.)(Found: C, 66.0; H, 5.0; $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.2%).

2:3-Dimethoxy-1-naphthylglyoxylic acid (XXXVII):

The above ether-ester (XXXVI)(3.5 g.) was suspended in water (20 ml.), sodium hydroxide (2 g.) dissolved in water (10 ml.) was added, and the mixture heated on a steam-bath for 2 hours. The oil gradually went into solution and on cooling the sodium salt of the acid crystallized. The solution on acidification with dilute hydrochloric acid gave a pale yellow curdy precipitate, which was filtered, washed and dried (3 g.). Crystallization from benzene gave rhombic pale yellow prisms, m.pt. 126° (Found: C, 64.8; H, 5.0. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.7%).

2:3-Dimethoxy-1-naphthoic acid (XXXVIII):

A solution of 2:3-dimethoxy-1-naphthylglyoxylic acid (XXXVII)(0.2 g.) in 40% acetic acid (5 ml.) was treated with potassium permanganate (0.051 g.) dissolved in 40% acetic acid (5 ml.). The mixture was gently refluxed for 1/2 hour, cooled and the precipitated manganese dioxide, dissolved out by sulphur dioxide. A brown solid separated which was filtered, washed and dried (0.13 g.). Crystallization from benzene-petroleum ether (60-80°) gave nearly colourless, prisms,

m.p. 150-51° (Found: C, 67.4; H, 5.4. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%).

6-Chloro-4:5-benzocoumaran-2:3-dione (XXXIX):

Dry 4-chloro-2-naphthol (XXV)(4 g.) was dissolved in dry ether (75 ml.), fused zinc chloride (1 g.) and cyanoformic ester (4 ml., excess) added and the mixture saturated with dry hydrogen chloride at 0°. An orange-red oily material separated which solidified on keeping for 24 hours in an ice-chest. The ether was decanted off and the imine hydrochloride washed twice with dry ether (25 ml.). Water (30 ml.) was added and the mixture warmed on a water-bath for 1/2 hour at 70-80°. Cooled and the yellow solid filtered, washed and dried (4.8 g.). Crystallization from petroleum ether (80-100°) gave bright yellow prisms, m.p. 168°(dec.)(Found: C, 61.3; H, 2.8. $C_{12}H_5O_3Cl$ requires C, 61.9; H, 2.2%).

4-Chloro-2-hydroxy-1-naphthoic acid (XXVIII):

The above lactone (XXXIX)(0.2 g.) was suspended in water (4 ml.), silver nitrate (0.51 g.), potassium hydroxide (0.25 g.) and alcohol (4 ml., 95%) added and the mixture heated on a steam-bath for 1 1/2 hours, cooled, noritted and filtered. The clear greenish brown solution was acidified with dilute hydrochloric acid when a brownish yellow flocculent precipitate separated, which was filtered, washed and dried (0.07 g.). Crystallization from benzene gave pale yellow prisms, m.p. 139° (dec.) . Mixed m.p. with the acid obtained

by the pyridine-iodine oxidation of (XXVI) showed no depression.

Methyl 4-chloro-2-methoxy-1-naphthylglyoxylate (XL):

A mixture of 6-chloro-4:5-benzocoumaran-2:3-dione (XXXIX) (1 g.) in dry acetone (25 ml.), anhydrous potassium carbonate (4 g.) and dimethyl sulphate (3 g.) was refluxed on a water-bath for 16 hours. The acetone was distilled off, and the residue treated with ice-water (50 ml.) when a pale yellow oil separated which solidified on cooling. Filtered, washed and dried (1.2 g.). Crystallization from petroleum ether (60-80°) gave pale yellow needles, m.p. 78° (Found: C, 60.8; H, 3.8. $C_{14}H_{11}O_4Cl$ requires C, 60.3; H, 3.9%).

4-Chloro-2-methoxy-1-naphthylglyoxylic acid (XLI):

The above ether-ester (XL)(0.5 g.) was dissolved in alcoholic caustic potash (15 ml., 20%) and gently refluxed on a steam-bath for two hours. On cooling the sodium salt of the acid separated. The mixture was acidified with dilute hydrochloric acid, when a bright yellow flocculent precipitate separated, which was filtered, washed and dried (0.38 g.). Crystallization from benzene gave very pale yellow needles, m.p. 138-39° (Found: C, 59.2; H, 3.8. $C_{13}H_9O_4Cl$ requires C, 59.0; H, 3.4%).

4-Chloro-2-methoxy-1-naphthoic acid (XLII):

A solution of 4-chloro-2-methoxy-1-naphthylglyoxylic acid (XLI)(0.53 g.) dissolved in 50% acetic acid (10 ml.) was treated with potassium permanganate (0.24 g.) in 50% acetic

acid (10 ml.). The mixture was refluxed for 15 minutes, cooled and the precipitated manganese dioxide dissolved out with sulphur dioxide. A brownish yellow solid separated, which was filtered, washed and dried (0.11 g.). Crystallization from a mixture of benzene-petroleum ether (60-80°) gave nearly colourless needles, m.p. 108° (Found: C, 60.0; H, 3.6. $C_{12}H_9O_3Cl$ requires C, 60.8; H, 3.4%).

4-Acetamido-2-hydroxy-1-naphthaldehyde (XLIII):

A suspension of 1-acetamido-3-naphthol (XVII)(3.5 g.) in dry ether (150 ml.), anhydrous hydrocyanic acid (10 ml.) fused zinc chloride (1 g.) and zinc cyanide (3 g.) was saturated with dry hydrogen chloride at 0° under mechanical stirring. A viscous black semi-solid separated. The mixture was left at 0° in an ice-chest; 48 hours later, the sticky solid was collected, washed with dry ether and treated with water (50 ml.). A purple solid separated which immediately turned red. The solution was made slightly alkaline with 1% aqueous sodium hydroxide and left at room temp. (30°) for 24 hours, filtered and the filtrate acidified with dilute hydrochloric acid. A flocculent buff coloured precipitate separated, which was filtered, washed and dried (1.8 g.). Crystallization from dilute acetic acid gave pale yellowish brown felty needles of the aldehyde, m.p. 208° (Found: C, 68.1; H, 4.9; N, 6.5. $C_{13}H_{11}O_3N$ requires C, 68.1; H, 4.8; N, 6.4%). An alcoholic solution of the substance gives a dark brown ferric colouration (Bhate[8], m.p. 208°).

Silver oxide oxidation of 4-acetamido-2-hydroxy-1-naphthaldehyde (XLIII):

To a vigorously stirring suspension of silver oxide [(prepared from silver nitrate, (0.17 g.), and sodium hydroxide (0.04 g.)] in water (50 ml.) was added solid sodium hydroxide (0.4 g.) and the aldehyde (XLIII)(0.2 g.), all at once. The mixture was gradually warmed to 50°, when silver started depositing. The temperature was raised to 75-80° and maintained for 1 hour. Cooled and the precipitated silver filtered off and washed with water. The combined filtrate and washings were neutralized with carbon dioxide, when a light brown crystalline solid separated, which was collected, washed and dried (0.18 g.). Crystallization from benzene gave light brown plates, m.p. 215° (dec.) (Found: C, 70.6; H, 4.9; N, 7.9. $C_{11}H_9O_2N$ requires C, 70.6; H, 4.8; N, 7.5%).

The product gave a dinitrophenylhydrazone which however could not be crystallized.

1-Acetyl-4-acetamido-2-naphthol (XLVI):

A mixture of 1-acetamido-3-naphthol (XVII)(0.5 g.) and glacial acetic acid-boron trifluoride complex (5 ml.) was heated on a steam-bath for 4 hours. The mixture was cooled and poured over crushed-ice when a bright yellow solid separated, which was filtered and washed free of acid. The product was boiled for 5-10 minutes with water, cooled and filtered (0.42 g.). The brownish yellow solid on crystallization from dilute acetic acid gave pale yellow needles, m.p. 254-55° (Found: C, 68.9; H, 5.4; N, 5.1. $C_{14}H_{13}O_3N$ requires

C, 69.1; H, 5.4; N, 5.8%) (Bhate[8] mentions m.p. 254-55°).

1-Acetyl-4-acetamido-2-methoxynaphthalene (XLVII):

A mixture of above ketone (XLVI)(0.3 g.), acetone (20 ml.) anhydrous potassium carbonate (0.5 g.) and dimethyl sulphate (0.5 ml.) was refluxed for 12 hours in a water-bath. After distilling off the acetone, the residue was treated with water when a yellow solid separated. Filtered, washed and dried (0.31 g.). Crystallization from dilute acetic acid gave pale yellow needles, m.p. 186-87° (Found: C, 69.8; H, 6.1; N, 5.1. $C_{15}H_{15}O_3N$ requires C, 70.1; H, 5.8; N, 5.5%).

4-Benzeneazo-2-methoxy-α-naphthylamine (XLIX; R=Me) :

Method I: To a solution of 1-amino-2-methoxynaphthalene (XLVIII)(2.4 g.) in pyridine (60 ml.) was added neutralized diazonium solution of aniline (1.6 ml.) under stirring and cooling. The mixture was agitated for 3 hours, water (300 ml.) was added and the precipitated dye filtered, washed and dried (3 g.). Crystallization from dilute alcohol gave orange-red needles, m.p. 108° (Found: N, 14.9. $C_{17}H_{15}N_3O$ requires N, 15.2%).

Method II - To a warm solution of 1-amino-2-methoxynaphthalene (XLVIII)(17.3 g.) in 95% alcohol (40 ml.) was added a warm solution of diazoaminobenzene (20 g.) in 95% alcohol (100 ml.). The mixture was kept at room temp. (30°) for 2 days, when a red crystalline product separated (15.5 g.). The mother liquor on dilution gave a further crop of the dye (1.2 g.). Crystallization from dilute alcohol gave orange

red needles, m.p. and mixed m.p. 108°.

4-Benzeneazo-2-ethoxy-α-naphthylamine (XLIX; R=Et): was prepared by above methods from 1-amino-2-ethoxynaphthalene (XLVIII) in 85% yield. The dye crystallized from benzene-petroleum ether mixture in bright red needles, m.p. 128° (Found: N, 14.2. $C_{18}H_{17}N_3O$ requires N, 14.4%).

4-Benzeneazo-2-methoxynaphthalene (L; R=Me):

Finely powdered 4-benzeneazo-2-methoxy-α-naphthylamine (XLIX)(3.5 g.) was suspended in water (30 ml.) containing conc. hydrochloric acid (8 ml.), and diazotized with sodium nitrite (1.6 g.), in water (10 ml.) under ice cooling and stirring. The diazonium solution was stirred for 8 hours at 0-5° and then added gradually to 95% alcohol (50 ml.) The bright red solution, which turned brownish on warming was refluxed for 1 hour on a steam-bath. Cooled and diluted with water when a black tarry product separated which was extracted with benzene. The benzene extract was washed successively with dilute hydrochloric acid, aqueous caustic soda and water. On distilling off the solvent, a black pasty mass separated which was extracted with petroleum ether (60-80°) and chromatographed on alumina. The major orange band which separated was eluted with the same solvent. Desolvation gave an orange yellow crystalline solid (0.36 g.) which crystallized from dilute alcohol, m.p. 100° (Found: C, 77.8; H, 5.6; N, 10.5. $C_{17}H_{14}N_2O$

requires C, 77.8; H, 5.4; N, 10.7%).

4-Benzeneazo-2-ethoxynaphthalene (L; R=Et):

Was obtained by deaminating 4-benzeneazo-2-ethoxy-α-naphthylamine (XLIX). The pure product was obtained only after chromatography on alumina. Crystallization from dilute alcohol gave orange needles, m.p. 84° (Found: C, 77.9; H, 5.6; N, 10.5. $C_{18}H_{16}N_2O$ requires C, 78.2; H, 5.8; N, 10.1%).

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SUMMARY

PART I : CITRININ AND ITS ANALOGUES :

The present work was undertaken with the object of synthesizing compounds similar in structure to citrinin and of modifying the structure of citrinin in the hope that compounds with lower toxicity and improved antibacterial properties may emerge.

Attempts have been made to prepare derivatives of citrinin from natural citrinin or its hydrolytic products. Thus, citrininamide and dihydrocitrininamide were prepared. A partial synthesis of optically inactive citrinin was effected by the action of ethyl orthoformate on the acid obtained by the γ-carboxylation of the racemic phenolic alcohol (B). 1-Alkyl derivatives of citrinin were prepared by the interaction of the acid with the appropriate ortho-esters. Attempts to prepare decarboxycitrinin by decarboxylation of citrinin and by the action of ethyl orthoformate on phenolic alcohol (A) were unsuccessful.

The simplest analogue of citrinin is norcitrinin and its synthesis was attempted by several methods. β-3:5-Dimethoxyphenylethyl alcohol was prepared by two routes: (a) by the action of ethylene oxide on the Grignard reagent from 3:5-dimethoxyiodobenzene and (b) from 3:5-dihydroxybenzoic acid. Attempts to demethylate the above alcohol were unsuccessful. The corresponding benzyl ethers were therefore prepared. β-3:5-Bis(benzyloxy)phenylethyl alcohol could be debenzylated with palladium on charcoal to the dihydroxy-

phenylethyl alcohol, which on carboxylation in glycerine gave the γ-acid. Cyclization with ethyl orthoformate gave an amorphous and presumably polymeric product, and not norcitrinin. The γ-acid also underwent the Gattermann reaction, but the resultant aldehyde failed to cyclize to norcitrinin by the action of concentrated sulphuric acid. The action of aqueous formaldehyde and caustic soda on the acid failed to give dihydronorcitrinin.

The next attempt was therefore directed towards blocking one of the β-positions in 3:5-dihydroxy-4-carboxyphenylethyl alcohol with a halogen atom, so as to reduce the tendency for polymerization on treatment with ethyl orthoformate. Bromination however resulted in the formation of the alkyl bromide instead of nuclear bromination.

Another attempt for the synthesis of norcitrinin was the synthesis of 6:8-dihydroxyisochroman followed by carboxylation in the γ-position. 6:8-Dihydroxyisochroman was synthesized by the following route: Ethyl 2:4-dicarbethoxy-3:5-dihydroxyphenylacetate was selectively deesterified to the 4-carboxylic acid by heating with pyridine and piperidine. Decarboxylation gave ethyl 2-carbethoxy-3:5-dihydroxyphenylacetate which on benzylation and subsequent reduction with lithium aluminium hydride gave 6:8-dibenzyloxyisochroman. Debenzylation with palladized carbon gave an almost quantitative yield of 6:8-dihydroxyisochroman, which however could not be carboxylated by the usual method to dihydronorcitrinin.

The preparation of 2-n-hexyl-3:5-dihydroxyphenylethyl alcohol was undertaken, because it was anticipated that the Y-acid derived from it would readily cyclize to 5-n-hexyl-norcitrinin with ethyl orthoformate. Ethyl 2-caproyl-3:5-dihydroxyphenylacetate was obtained by the action of boron trifluoride on n-caproic acid and ethyl 3:5-dihydroxyphenyl-acetate. The ketone was submitted to Clemmensen reduction; a small amount of 2-n-hexyl-3:5-dihydroxyphenylacetic acid was obtained, but the main product was insoluble in aqueous sodium bicarboate, indicating that the acid treatment led to decarboxylation. 3:5-Dihydroxyphenylethyl alcohol was then condensed with n-caproic acid in presence of boron trifluoride to give the corresponding ketone, which on reduction by the Clemmensen method furnished 2-n-hexyl-3:5-dihydroxyphenyl-ethyl alcohol. Attempts to carboxylate this resorcinol derivative proved unsuccessful.

Attempts were next made to prepare the Y-acid from the secondary alcohol, 1-(3':5'-dihydroxy)phenylpropan-2-ol, since it was thought that the secondary alcoholic group may be associated with ready cyclization to the citrinin type by the action of ethyl orthoformate at room temperature. The scheme failed at the carboxylation stage.

PART II : HEXYLRESORCINOL AND ITS DERIVATIVES :

The biosynthesis of citrinin and its analogues by the use of appropriate precursors in the fermentation has been studied in this laboratory by Dr. D. V. Tamhane, and for

this purpose certain 4-n-hexylresorcinol derivatives were prepared by the present author. 4-n-Hexylresorcinol on carboxylation gave a mixture of β- and γ-acids which were separated. An interesting method of separation depends on the fact that, if a mixture of the methyl esters of the two acids is heated with pyridine and piperidine, the γ-ester alone undergoes hydrolysis to the acid. The amide, hydrazide and diethylaminoethyl ester of the γ-acid were prepared; it was observed that the β-acid and ester were not amenable to the reactions for the formation of these derivatives. The γ-acid reacted readily with formaldehyde and dimethylamine to yield the Mannich base, which represents a type of compound with distinct possibilities as antibacterial and chemotherapeutic agents. The antibacterial activity and toxicity of the above substances have been examined.

PART III : ATTEMPTED SYNTHESIS OF 4-AMINO-2-HYDROXY-1-NAPHTHOIC ACID, A NAPHTHALENE ANALOGUE OF 4-AMINOSALICYLIC ACID

Experiments concerning the synthesis of 4-amino-2-hydroxy-1-naphthoic acid (I), a naphthalene analogue of p-aminosalicylic acid, are described. Degerholm and Liljegren (Swedish Patent 134,386) have claimed to have synthesized (I) by direct carboxylation of the potassium salt of 1-amino-3-naphthol by heating in an autoclave at 140-50° with carbon dioxide at 9 atmospheres pressure. They also claim to have synthesized (I) by heating the aminonaphthol in toluene in presence of sodium sand and dry carbon dioxide. However, attempts to

repeat the experiments using the same as well as modified conditions of time, temperature and pressure failed to give the acid (I).

Halogen-metal interaction or metallation with n-butyllithium followed by carbonation with dry ice on 4-bromo-1-nitro-3-naphthol, 1-acetamido-4-bromo-3-naphthol and its methyl ether, 1-amino-3-naphthol and 1-acetamido-3-naphthol, were unsuccessful.

Sodium 1-acetamido-3-hydroxy-4-methylnaphthalene-ω-sulphonate and its methyl ether were prepared by the action of formaldehyde and sodium sulphte on 1-acetamido-3-naphthol and subsequent methylation. Attempts to oxidize the sulphomethyl derivative to the corresponding carboxylic acid failed.

Another route starting from 4-chloro-2-naphthol was next attempted. 1-Acetyl-4-chloro-2-naphthol was obtained by the action of boron trifluoride-acetic acid complex on 4-chloro-2-naphthol. Oxidation with iodine in pyridine gave 4-chloro-2-hydroxy-1-naphthoic acid. Attempts to condense the naphthoic acid with benzylamine and p-toluenesulphonamide were unsuccessful. Methylation of 1-acetyl-4-chloro-2-naphthol gave the methyl ether which resisted oxidation with sodium hypochlorite in alkaline solution to the corresponding acid.

6-Acetamido-4:5-benzocoumaran-2:3-dione, prepared by the condensation of cyanoformic ester with 1-acetamido-3-naphthol, could not be oxidized with hydrogen peroxide in acetic acid to the N-acetyl derivative of the desired acid.

6-Chloro-4:5-benzocoumaran-2:3-dione was prepared by condensing cyanoformic ester with 4-chloro-2-naphthol. Methyl 4-chloro-2-methoxynaphthyl-glyoxylate and the corresponding glyoxylic and naphthoic acids have been synthesized by a series of reactions starting from the chlorolactone. Replacement of the chlorine atom by the amino group proved unsuccessful.

4-Acetamido-3-naphthol was formylated by the Gattermann method but the aldehyde could not be oxidized to the N-acetyl derivative of (I). 4-Acetamido-3-naphthol on treatment with boron trifluoride-acetic acid complex gave 1-acetyl-4-acetamido-3-naphthol. Methylation yielded 1-acetyl-4-acetamido-3-methoxynaphthalene, which could not be oxidized to the corresponding acid.

Starting from 1-amino-2-methoxynaphthalene, 1-amino-4-benzeneazo-2-methoxynaphthalene was obtained by coupling with diazotized aniline in pyridine or with diazoaminobenzene in alcoholic solution. The dye was deaminated to 4-benzeneazo-2-methoxynaphthalene, which failed to undergo formylation with dimethyl-formamide and phosphorus oxychloride.

Attempts to prepare the unknown 2:3-dihydroxy-1-naphthoic acid are described. Although a synthesis of the acid has not been realized, a few derivatives of 2:3-dihydroxynaphthalene have been prepared.

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