Studies on 1:2-Dihydro-1-Keto-2-Thianaphthalenes and The Synthesis of Gladiolic Acid

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JOHN JOHNSTON BROWN

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PART I

STUDIES ON 1:2-DIHYDRO-1-KETO-2-THIANAPHTHALENES

SUMMARY

1. m-Opianic acid and 4:5-methylenedioxyphthalaldehydic acid have been prepared in good yield from m-meconin and 5:6-methylenedioxyphthalide respectively.

2. A new phthalide, 4:5-methylenedioxyphthalide, has been obtained from piperonylic acid.

3. Reaction of 1:2-dihydro-1-keto-6:7-dimethoxy-2--thianaphthalene-3-carboxylic acid and 1:2-dihydro-1-keto--6:7-methylenedioxy-2-thianaphthalene-3-carboxylic acid with Raney nickel gives 5:6-dimethoxyindan-1-one and 5:6-methylenedioxyindan-1-one respectively.

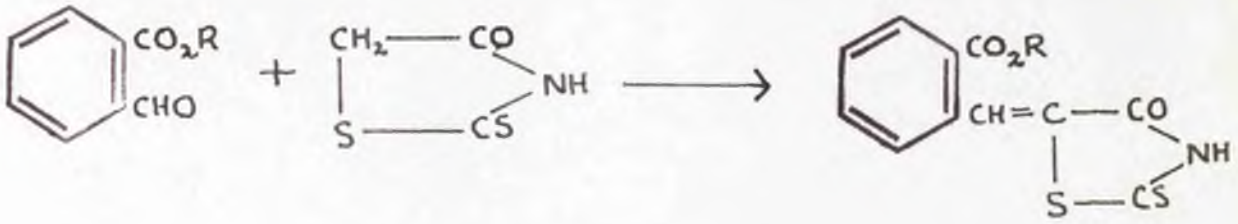
4. 5:6-Methylenedioxyindan-1-one has been obtained by the action of Raney nickel on hydrastal (6-vinylpiperonal).

5. A mechanism has been suggested for the conversion of 1:2-dihydro-1-keto-2-thianaphthalenes into indanones using Raney nickel.

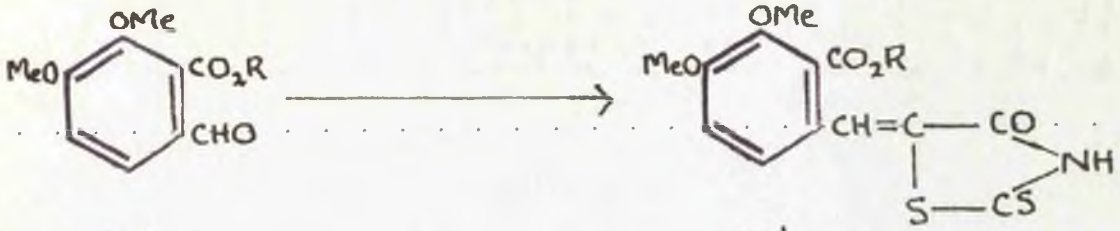
INTRODUCTION

INTRODUCTION

1:2-Dihydro-1-keto-2-thianaphthalene derivatives were first prepared from o-carboxy-derivatives of aromatic aldehydes and ketones by Dijksman and Newbold (1) who condensed the o-carbomethoxy-aromatic aldehyde or ketone with rhodanine and hydrolysed the resulting benzylidenerhodanine to form the thianaphthalene derivative. Thus, methyl phthalaldehydate (I; R=Me) and α-methyl opianate (IV; R=Me) were condensed with rhodanine (II), by refluxing in glacial acetic acid in the presence of sodium acetate, to give respectively, 5-o--carbomethoxybenzylidenerhodanine (III; R=Me) and 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)rhodanine (V; R=Me). By the same method, phthalaldehydic acid (I; R=H) and 2-carboxyacetophenone (VI) gave respectively, 5-o-carboxybenzylidenerhodanine (III; R=H) and 5-(o--carboxy-α-methylbenzylidene)rhodanine (VII).



(I) (II) (III)



(IV) (V)

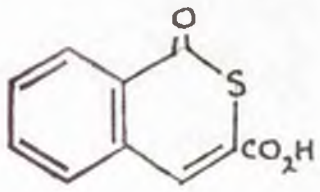
(VI) (VII)

Unlike phthalaldehydic acid (I; R=H), opianic acid (IV; R=H) did not give the corresponding o-carboxy--benzylidenerhodanine (V; R=H) on condensation with rhodanine, but gave the sodium salt of the product (V; R=Na). Dijksman (Ph.D. Thesis, 1951) suggested that this behaviour of opianic acid was due to the fact that, while phthalaldehydic acid is of comparable acidic strength to acetic acid, opianic acid is much stronger, and reaction with sodium acetate occurs along with rhodanine condensation. The dissociation constants of

the acids are shown in the table below.

Acid	Ka at 25°
Opianic	3.82×10^{-4}
Acetic	1.845×10^{-5}
Phthalaldehydic	3.6×10^{-5}

Alkaline hydrolysis of 5-o-carbomethoxybenzylidene-rhodanine (III; R=Me) or 5-o-carboxybenzylidenerhodanine (III; R=H) gave an acidic product $C_{10}H_8O_3S$ which Dijksman and Newbold formulated as 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (VIII), the product being formed by loss of water from the intermediate o-carboxy-α-thiolcinnamic acid (IX), tautomeric with the β-o-carboxyphenyl-α-thiopropionic acid (X).



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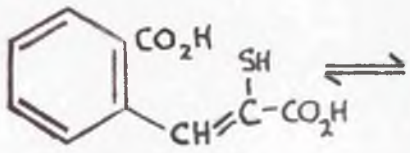
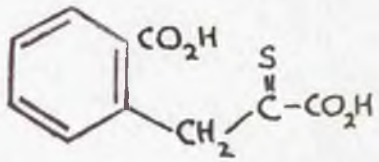


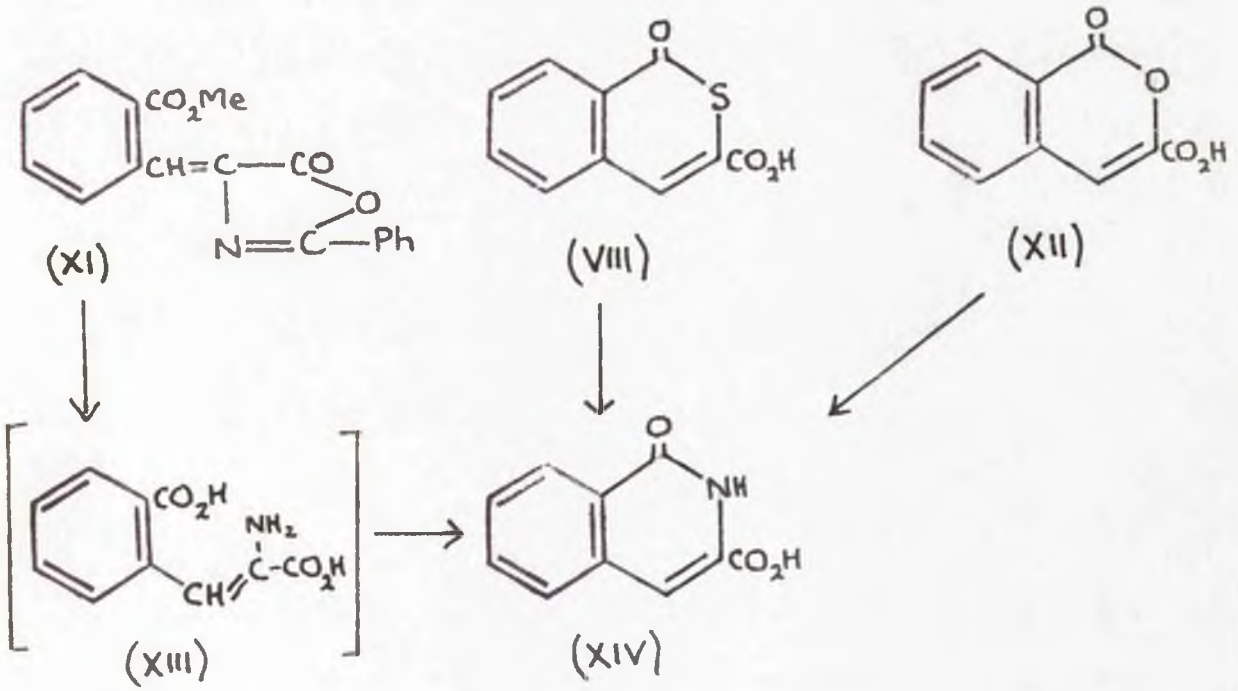
(IX)



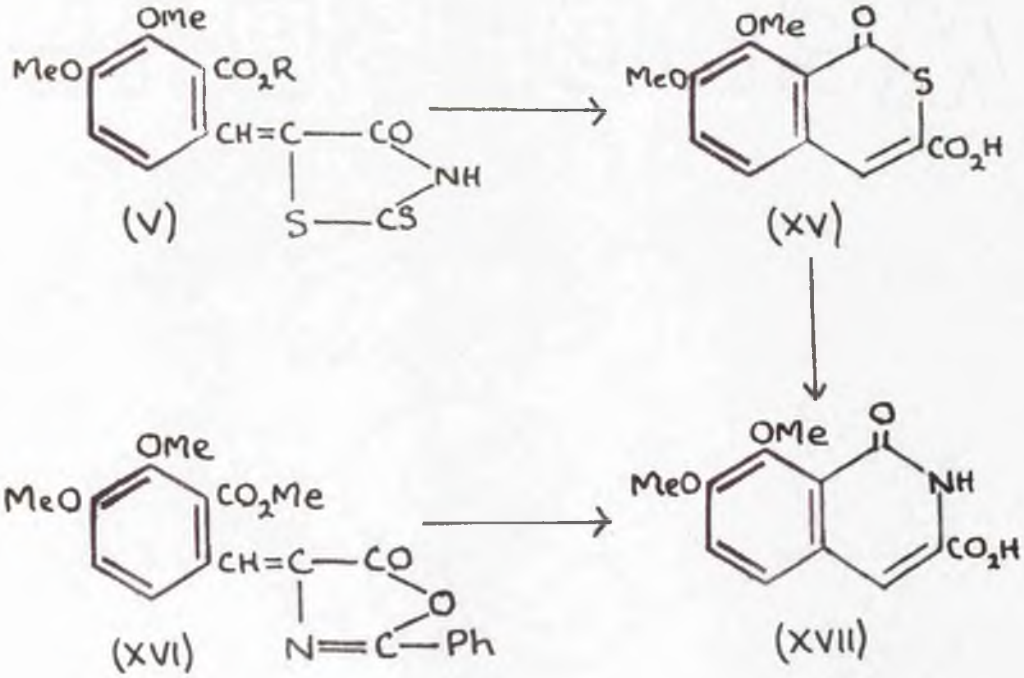
(X)

The structure of the compound $C_{10}H_8O_3S$ was supported by treating the compound with ethanolic ammonia to form

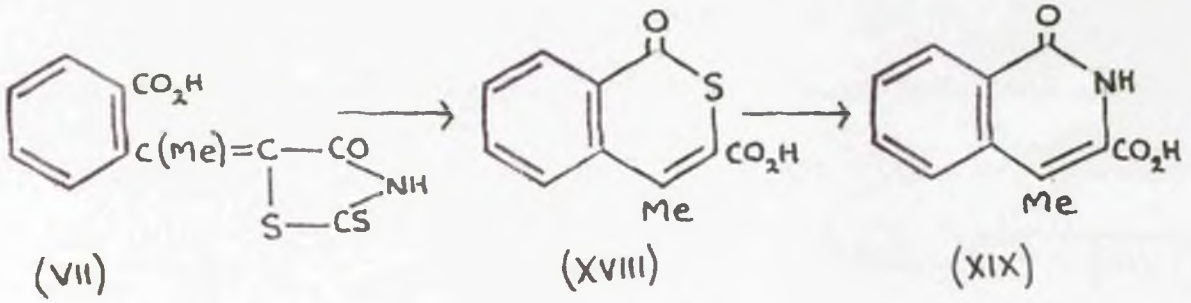
1:2-dihydro-1-keto*iso*quinoline-3-carboxylic acid (XIV). Bamberger and Kitschelt (2) obtained the acid (XIV) by the action of ammonia on *iso*coumarin-3-carboxylic acid (XII) and Bain, Perkin, and Robinson (3) prepared the same compound by alkaline hydrolysis of 5-*o*-carbomethoxy--benzylidene-2-phenyloxazol-4-one (XI). In the latter reaction, the ready cyclisation of the intermediate α-amino-*o*-carboxycinnamic acid (XIII) to the *iso*quinoline parallels the method of formation of 1:2-dihydro-1-keto--2-thianaphthalene-3-carboxylic acid.



Similarly, 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)rhodanine (V; R=Me) or 5-(2'-carboxy-3':4'-dimethoxybenzylidene)rhodanine (V; R=H) or the sodium salt of the acid (V; R=Na), on hydrolysis with aqueous sodium hydroxide, gave an acidic product, 1:2-dihydro-1-keto--7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (XV) which, with ethanolic ammonia, gave the known compound, 1:2-dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid (XVII), previously prepared by Bain, Perkin, and Robinson (3) by the alkaline hydrolysis of 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-2-phenyloxazol-4-one (XVI).



5-(o-Carboxy-α-methylbenzylidene)rhodanine (VII) was also cyclised by alkali to 1:2-dihydro-1-keto-4--methyl-2-thianaphthalene-3-carboxylic acid (XVIII) which readily formed 1:2-dihydro-1-keto-4-methylisoquinoline--3-carboxylic acid (XIX) when heated with ethanolic ammonia.



(VII) (XVIII) (XIX)

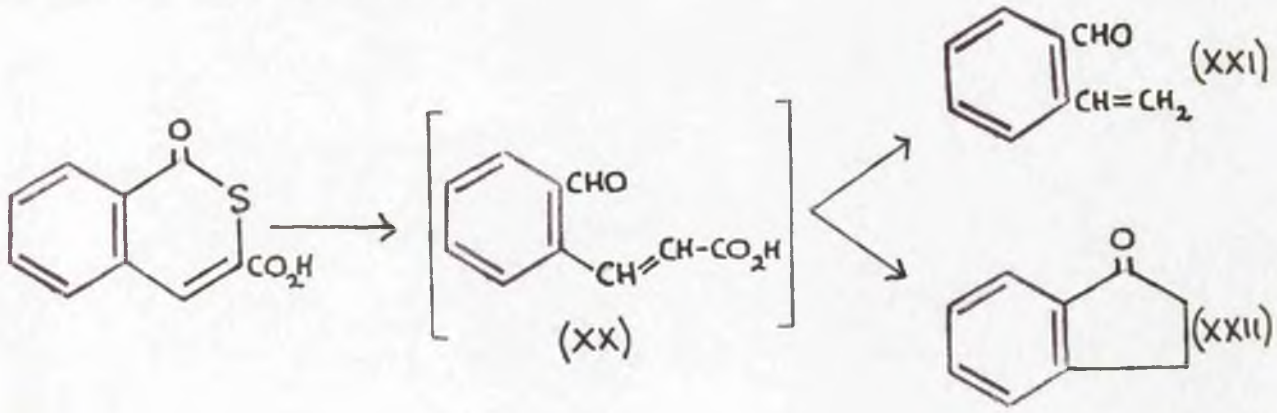
The structure of the thianaphthalenes was thus proved beyond all doubt by their conversion into the corresponding isoquinolines.

The Action of Raney Nickel on 1:2-Dihydro-1-keto-2--thianaphthalenes.

Wolfrom and Karabinos (4) showed that treatment of thiol-esters with Raney nickel led to the formation of aldehydes;

$$R.CO.SR' \longrightarrow R.CHO$$

Thus, when Dijksman and Newbold (5) refluxed 1:2-dihydro--1-keto-2-thianaphthalene-3-carboxylic acid with a suspension of Raney nickel in ethanol, the expected product would have been o-formylcinnamic acid (XX). The product obtained, however, was a neutral carbonyl compound, isolated as its semicarbazone and its 2:4-dinitrophenylhydrazone. There were two possibilities for the structure of this compound: (a) o-vinylbenzaldehyde (XXI), formed by decarboxylation of the intermediate acid (XX), and (b) indan-1-one (XXII). A comparison of the corresponding derivatives of indan-1-one (6) showed structure (XXII) to be correct.

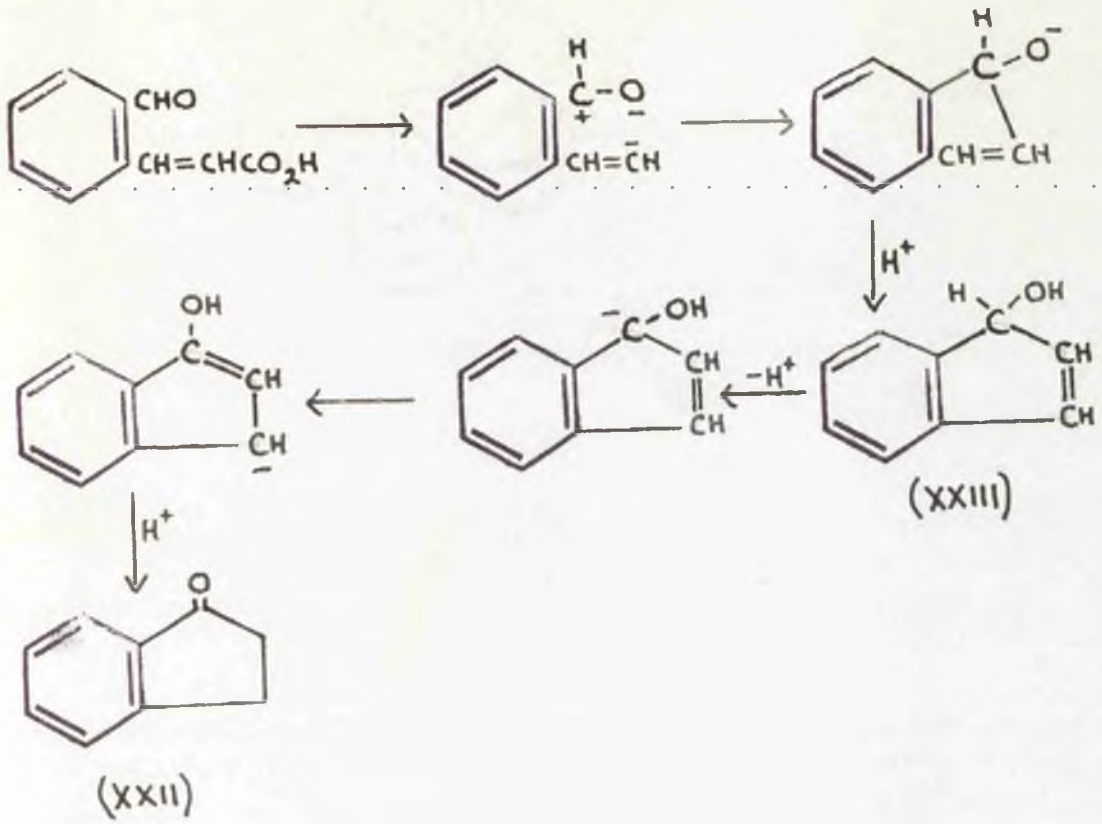


The mechanism of the decarboxylation of the intermediate o-formylcinnamic acid (XX) to give indan-1-one, was explained by Wiley and Hobson (7), who attempted the preparation of o-vinylbenzaldehyde (XXI) by decarboxylating

o-formylcinnamic acid (XX), prepared by the interaction of phthalaldehyde with malonic acid in the presence of pyridine.

(XX) (XXI)

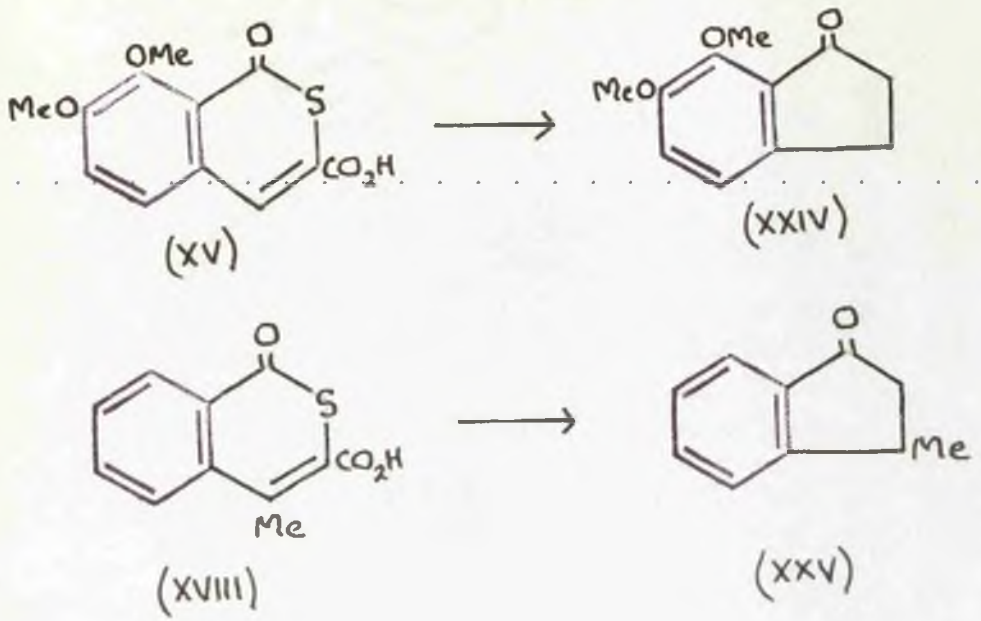
Decarboxylation of o-formylcinnamic acid occurred readily when the acid was dissolved in quinoline at room temperature, with the formation of indan-1-one (XII) and not the expected o-vinylbenzaldehyde (XXI). Wiley and Hobson postulated that the formation of indan-1-one was due to the tendency of the ion formed on decarboxylation, to combine with the carbonyl carbon rather than with the proton, followed by addition of the proton to the carbonyl oxygen to give 1-hydroxyindene (XXIII). Rearrangement of (XXIII) to indan-1-one is similar to the prototropic change of α-phenyl allyl alcohols to propiophenones, previously noted by Tiffeneau (3).



(XXIII)

(XXII)

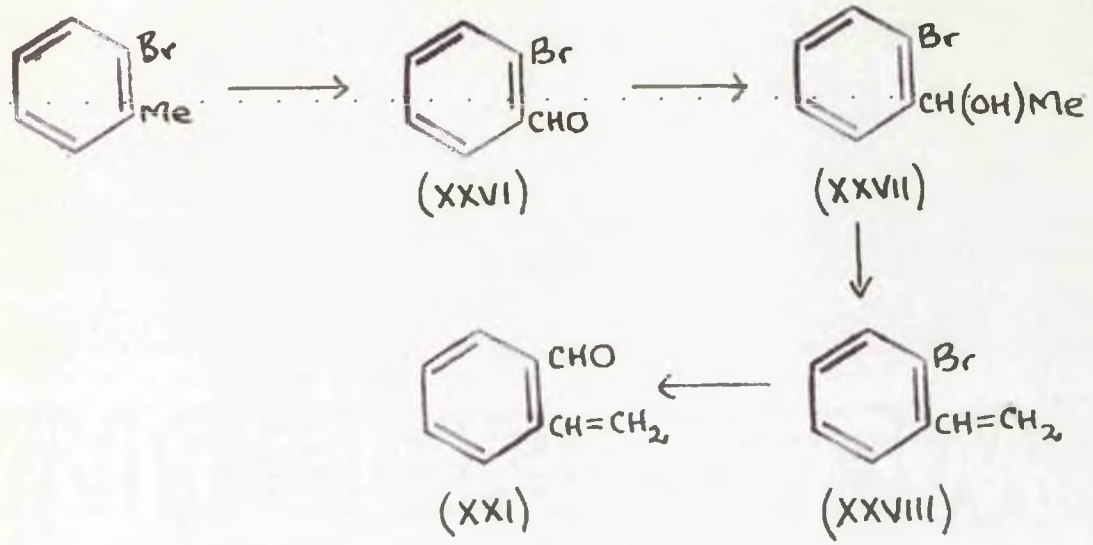
1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene--3-carboxylic acid (XV) and 1:2-dihydro-1-keto-4-methyl--2-thianaphthalene-3-carboxylic acid (XVIII), on similar treatment with Raney nickel, gave 6:7-dimethoxyindan-1--one (XXIV) and 3-methylindan-1-one (XXV) respectively, both compounds being isolated as their semicarbazones and 2:4-dinitrophenylhydrazones. Authentic derivatives of 6:7-dimethoxyindan-1-one were prepared according to Schöpf et al. (9), and of 3-methylindan-1-one, according to Koelsch, Hochmann, and Le Claire (10), for comparison.



Dijksman (Ph.D. Thesis, 1951) attempted the preparation of o-vinylbenzaldehyde by two routes, both of which were unsuccessful.

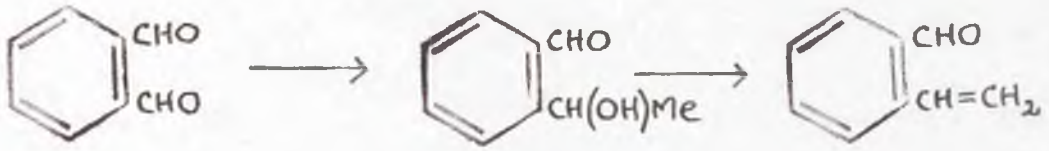
In the first, o-bromobenzaldehyde (XXVI), prepared by the Etard oxidation of o-bromotoluene (11), was reduced to o-bromophenylmethylcarbinol (XXVII) by the Grignard reaction, and dehydration of (XXVII) with sodium hydrogen sulphate gave o-vinylbromobenzene (XXVIII). Attempts to convert o-vinylbromobenzene to o-vinylbenzaldehyde (XXI) by the Grignard route failed, due to the unreactivity of the bromine atom.

The starting material for the second attempt was o-phthalaldehyde (XXIX), which, with one molecular proportion of methylmagnesiumbromide, gave o-formylphenyl-



(XXVI) (XXVII) (XXI) (XXVIII)

methylcarbinol (XXX), but the last compound failed to dehydrate using sodium hydrogen sulphate, to give the desired product (XXI).

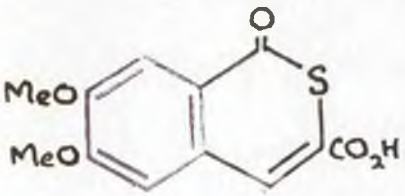


(XXIX) (XXX) (XXI)

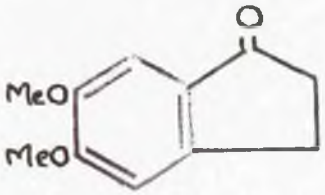
THEORETICAL

THEORETICAL

In view of the failure of Wiley and Hobson (7), and of Dijksman (Ph.D. Thesis, 1951), to prepare o-vinylbenzaldehyde, and also the fact that Raney nickel desulphurisation of 1:2-dihydro-1-keto-2-thianaphthalene--3-carboxylic acids gave indanones and not o-vinylaldehydes, it was decided to study the action of Raney nickel on 1:2-dihydro-1-keto-6:7-dimethoxy- (XXXI) and -6:7-methylenedioxy-2-thianaphthalene-3-carboxylic acid (XXXIV) in order to compare the expected products 5:6--dimethoxy- (XXXII) and 5:6-methylenedioxy-indan-1-one (XXXV) with o-vinylbenzaldehydes previously reported in the literature:- 4:5-dimethoxy-2-vinylbenzaldehyde (XXXIII), obtained by Perkin (12) as a degradation product of cryptopine (XXXVII) and hydrastal (XXXVI), obtained by Freund (13) by degradation of hydrastine (XXXVIII).



(XXXI)



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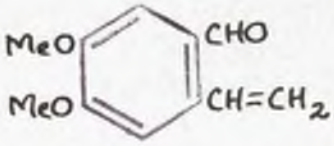
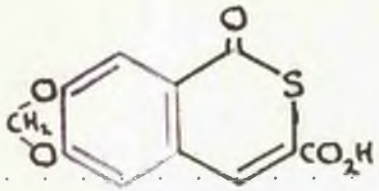
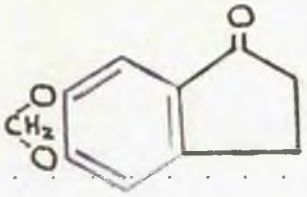


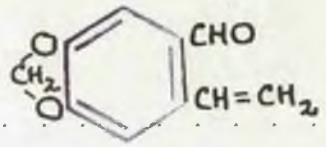
(XXXIII)



(XXXIV)



(XXXV)



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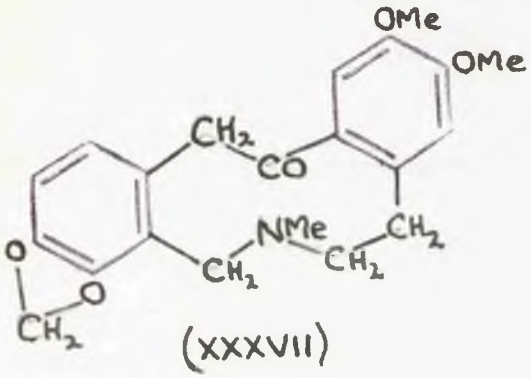
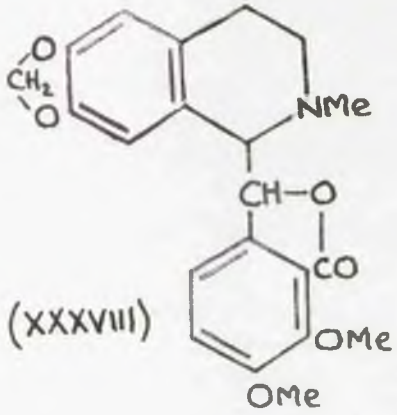


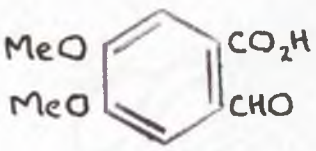
(XXXVII)



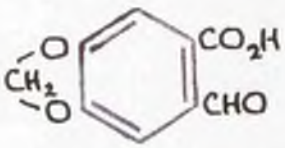
(XXXVIII)

The Preparation of m-Opianic Acid and 4:5-Methylenedioxyphthalaldehydic Acid.

The starting materials for the preparation of the required thianaphthalene acids were m-opianic acid (XXXIX) and 4:5-methylenedioxyphthalaldehydic acid (XL).

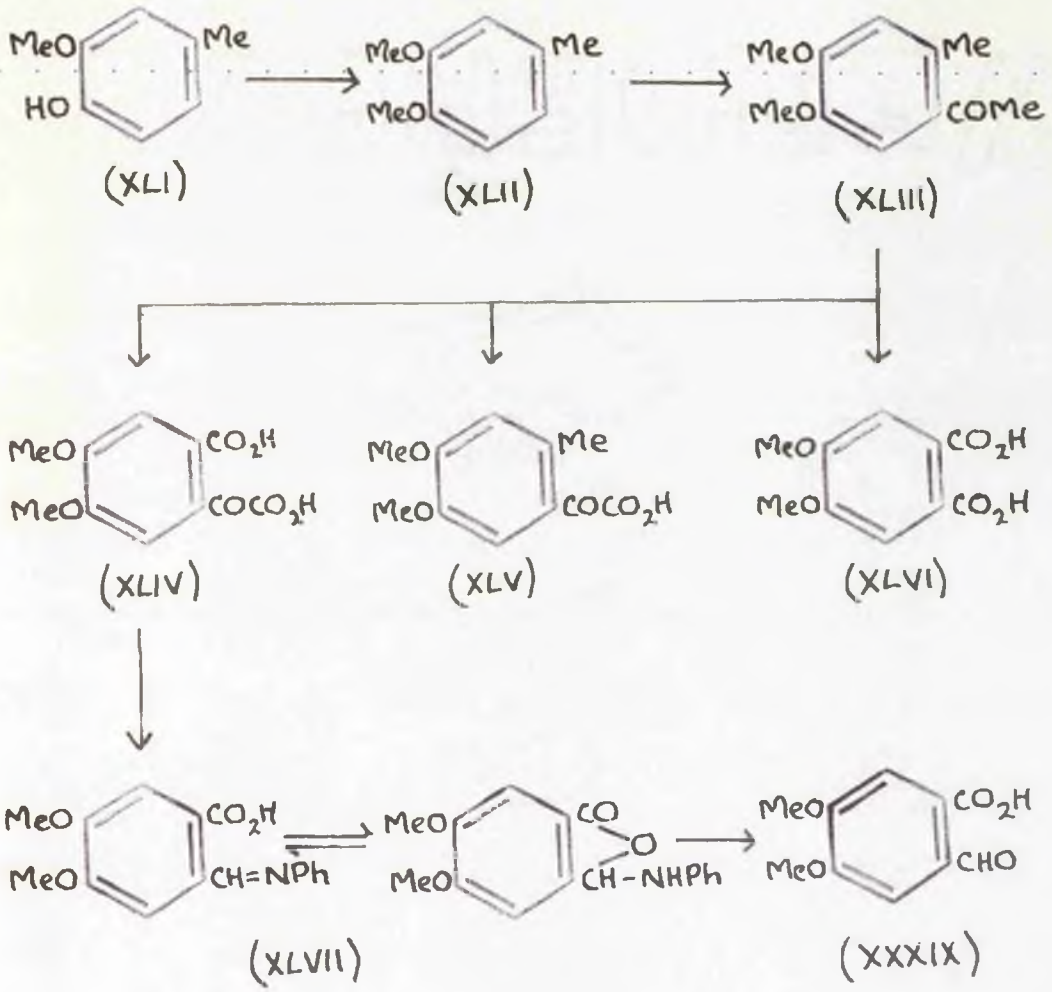


(XXXIX)

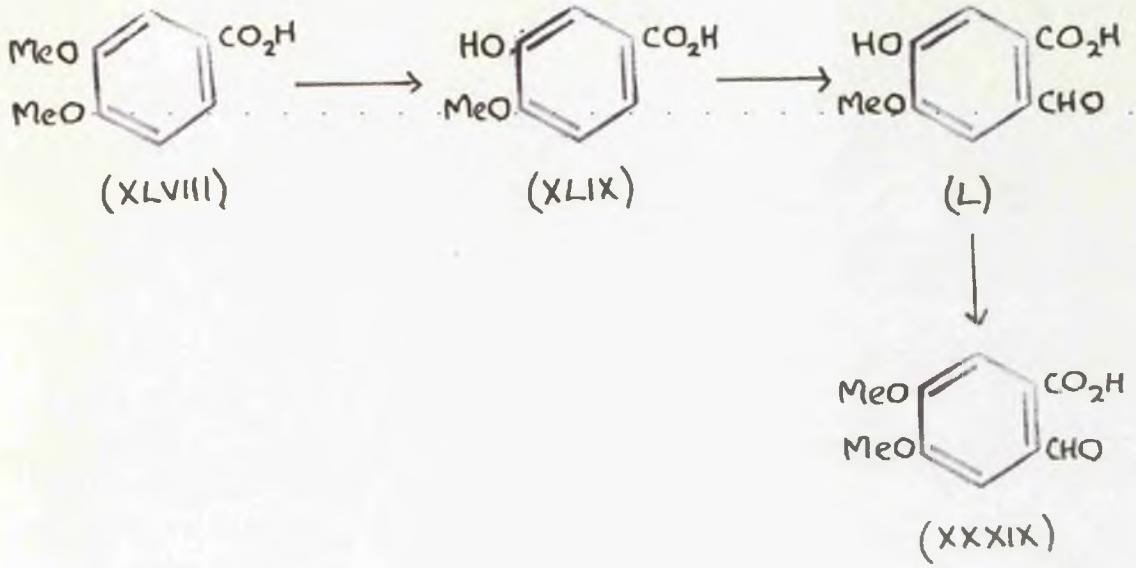


(XL)

m-Opianic acid was first obtained (12) as one of the products of the degradation of cryptopine (XXXVII) and had been synthesised by several methods, none of which was of preparative use. In the first, according to Fargher and Perkin (14), homoveratrole (XLII), obtained by methylating creosol (XLI), was converted by the Friedel-Crafts reaction into 4:5-dimethoxy-o-tolyl methyl ketone (XLIII) which gave 4:5-dimethoxyphthalmnic acid (XLIV) along with o-tolylglyoxylic acid (XLV), m-memipinic acid (XLVI) and oxalic acid when oxidised with potassium permanganate. 4:5-Dimethoxyphthalonic acid (XLIV) gave a sodium hydrogen sulphite derivative which, on heating, decomposed into carbon dioxide and the corresponding derivative of m-opianic acid, from which the free acid (XXXIX) was obtained by treatment with hydrochloric acid. The acid (XLIV) also gave the aniline salt of anilino-4:5-dimethoxyphthalonic acid which, when boiled with xylene, lost carbon dioxide to give anilino-m-opianic acid (XLVII) which was hydrolysed with hydrochloric acid to m-opianic acid (XXXIX).

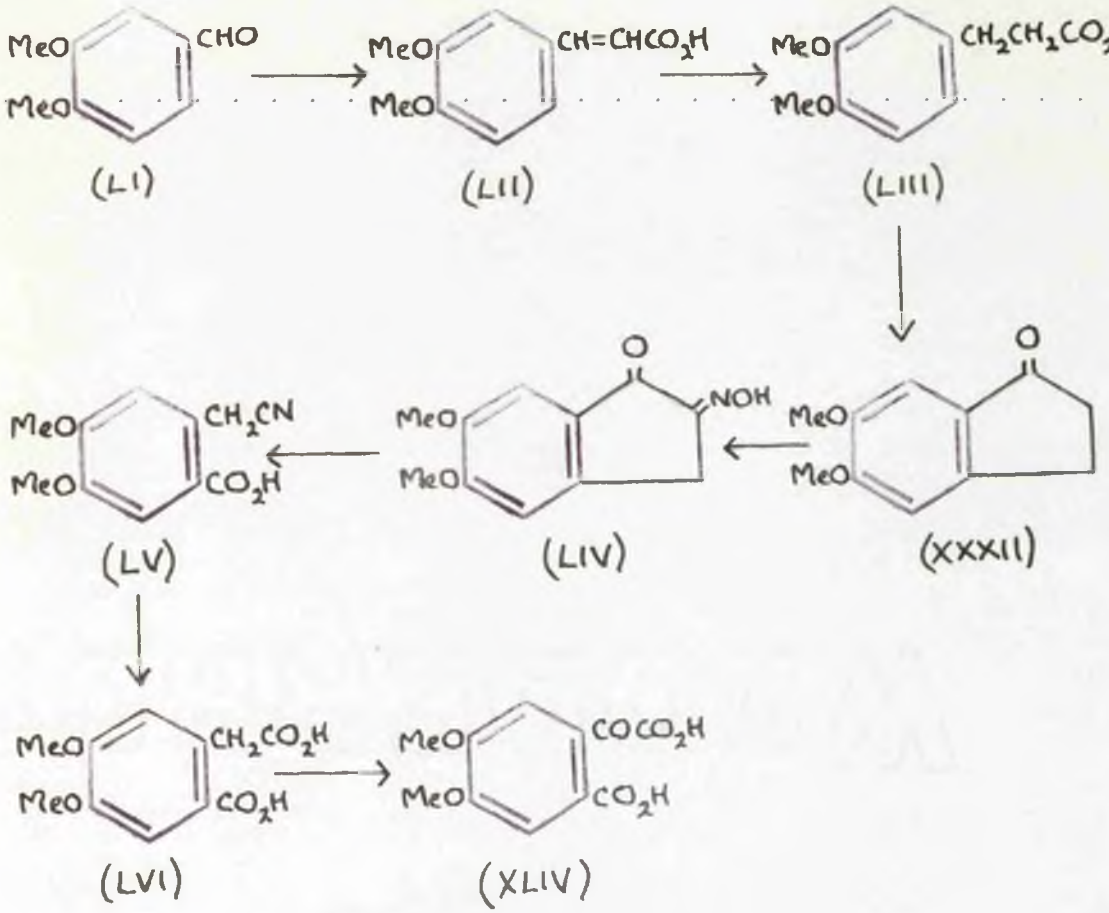


In the second, Perkin and Stoyle (15) subjected isovanillic acid (XLIX) (obtained by demethylating veratric acid (XLVIII) with hydrobromic acid) to the Reimer-Tiemann reaction, methylation of the product, 5-hydroxy-4-methoxy-phthalaldehydic acid (L), giving m-opianic acid (XXXIX).



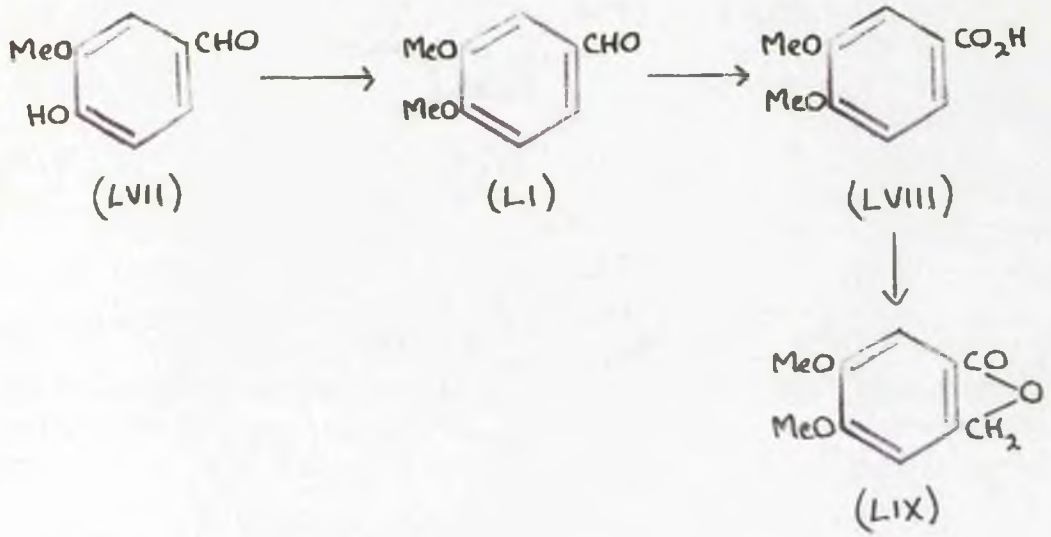
(XLVIII) (XLIX) (L) (XXXIX)

A third method was that of Chakravarti and Swaminathan (16), who oxidised 4:5-dimethoxyhomophthalic acid (LVI) to the phthalonic acid (XLIV) using selenium dioxide, and completed the synthesis after Pargher and Perkin (14). The preparation of 4:5-dimethoxyhomophthalic acid (LVI), however, required for this method, was tedious, involving the conversion of veratric aldehyde (LI) through 3:4-dimethoxycinnamic acid (LII), β-(3:4-dimethoxyphenyl)propionic acid (LIII), 5:6--dimethoxyindan-1-one (XXXII), and the 2-isonitroso-derivative (LIV) of the latter which underwent the Beckmann rearrangement, hydrolysis (17) of the product (LV) giving 4:5-dimethoxyhomophthalic acid (LVI).



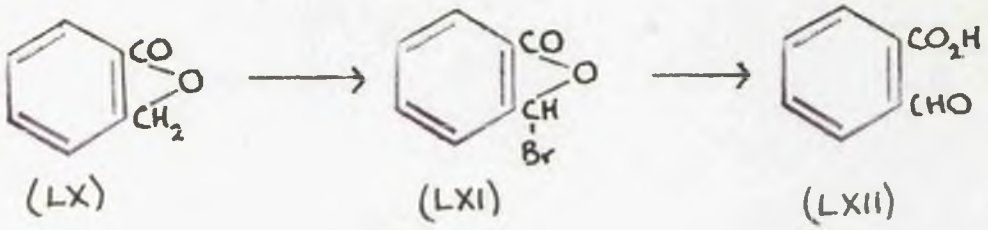
For our work, m-opianic acid was required in relatively large quantities, and since the above methods of preparation were not suitable, our attention was turned to the possibility of obtaining m-opianic acid by the oxidation of m-meconin (LIX). m-Meconin was prepared in low yield according to Edwards, Perkin, and Stoyle (18) by the action of formaldehyde in hydrochloric acid on veratric acid (LVIII), a compound readily available by methylating (19) vanillin (LVII) to veratric aldehyde (LI)

and oxidising the latter compound with potassium permanganate (18).



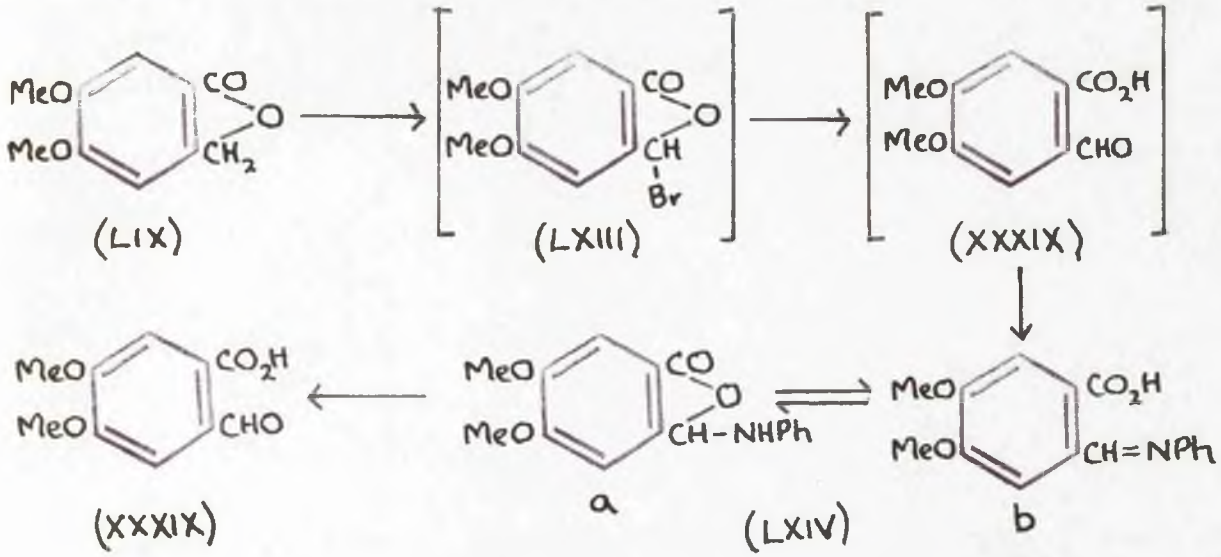
Edwards, Perkin, and Stoyle (18) attempted the oxidation of m-meconin with manganese dioxide in sulphuric acid but only traces of m-opianic acid could be obtained. Manske, McRae, and Moir (43) obtained only a very low yield of m-opianic acid on oxidising m-meconin with red lead in acetic acid. An alternative method of oxidation was therefore desirable and this was suggested by the work of Hirschberg, Lavie, and Bergmann (20) who showed that phthalide (LX) could be smoothly converted, using N-bromosuccinimide, into 3-bromophthalide (LXI), which readily gave phthalaldehydic acid (LXII)

on heating with water (21).



(LX) (LXI) (LXII)

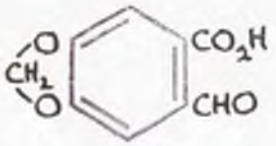
Applying the same reaction to m-meconin (LIX), it was found that bromination of m-meconin using N-bromo-succinimide, followed by hydrolysis without isolation of the intermediate bromo-compound (LXIII), gave m-opianic acid (XXXIX) in 85% yield, the acid being isolated from the hydrolysis solution by the formation of an insoluble anilino compound (LXIV a and b), treatment of which with hydrochloric acid gave the acid (XXXIX).



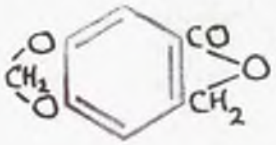
(LIX) (LXIII) (XXXIX)

(XXXIX) a (LXIV) b

The preparation of the other required aldo-acid, 4:5-methylenedioxyphthalaldehydic acid (XL), was another problem since the only method reported in the literature, that of Chakravarti, Swaminathan, and Verkataramen (22) who prepared the compound by a similar route to that described by Chakravarti and Swaminathan (16) for m-opianic acid, was of no preparative value. The most promising route was similar to that used above for m-opianic acid, i.e. starting from the phthalide, 5:6-methylenedioxyphthalide (LXV).



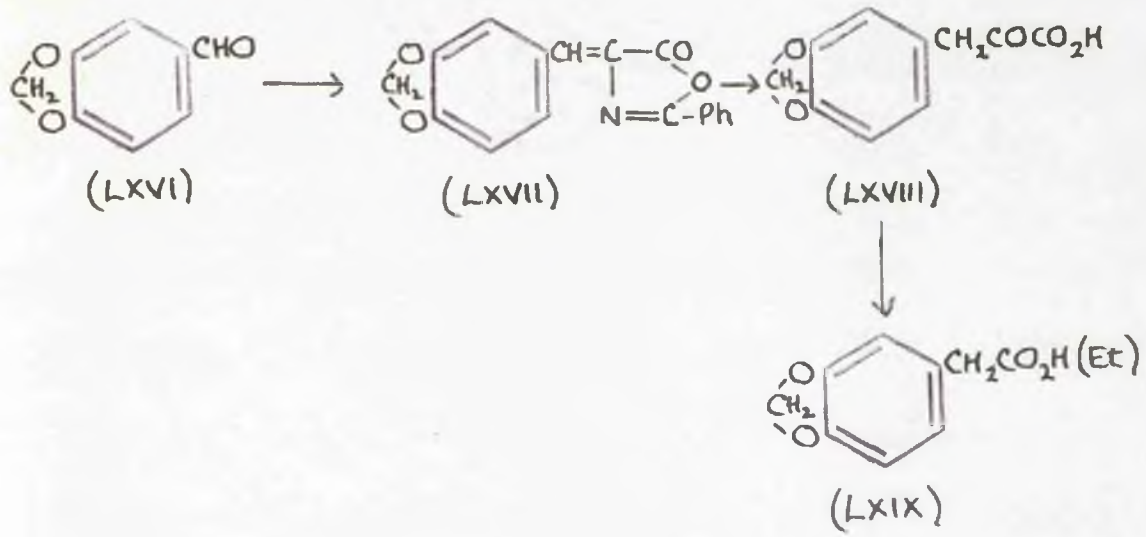
(XL)



(LXV)

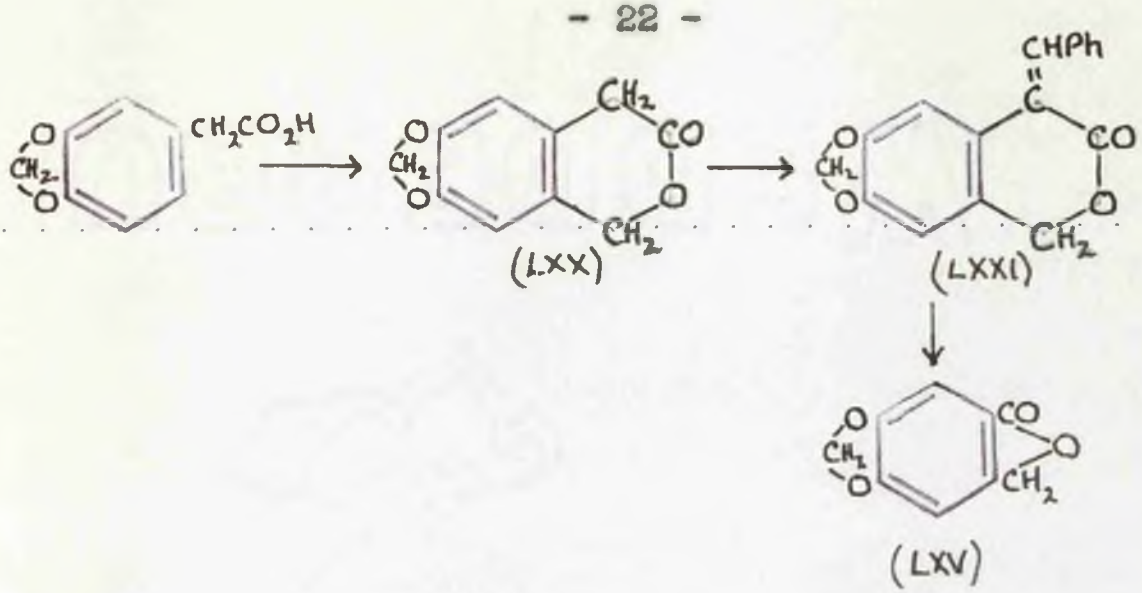
The preparation of 5:6-methylenedioxyphthalide required homopiperonylic acid (LXIX) as an intermediate. This was obtained in good yield by treating piperonal (LXVI) with hippuric acid (23) to form the azlactone, 5-(3':4'-methylenedioxybenzylidene)-2-phenyl-oxazol-4--one (LXVII), alkaline hydrolysis of which, gave

3:4-methylenedioxyphenylpyruvic acid (LXVIII), and hydrogen peroxide oxidation of this compound gave homopiperonylic acid (LXIX) isolated as its ethyl ester which was then hydrolysed (24).

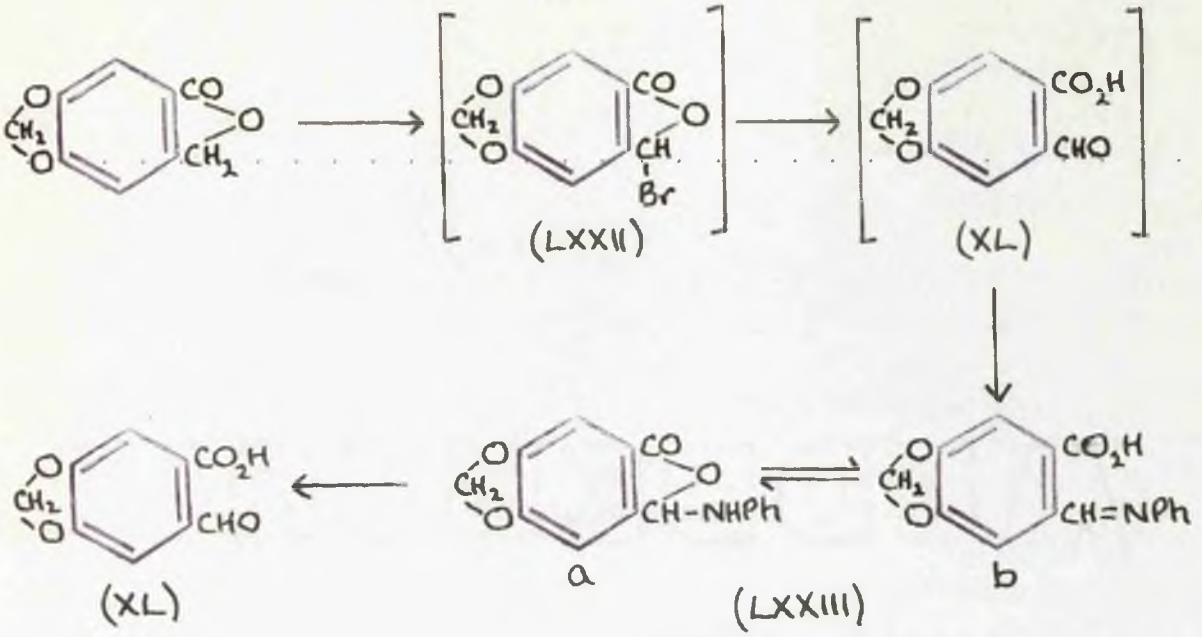


(LXVI) (LXVII) (LXVIII) (LXIX)

Treatment of homopiperonylic acid with formaldehyde in hydrochloric acetic acids after Stevens (25), gave the lactone of 6-hydroxymethylhomopiperonylic acid (LXX), which, on condensation with benzaldehyde (26), formed α-(6-hydroxymethylpiperonyl)cinnamolactone (LXXI), from which 5:6-methylenedioxyphthalide (LXV) was obtained by permanganate oxidation.

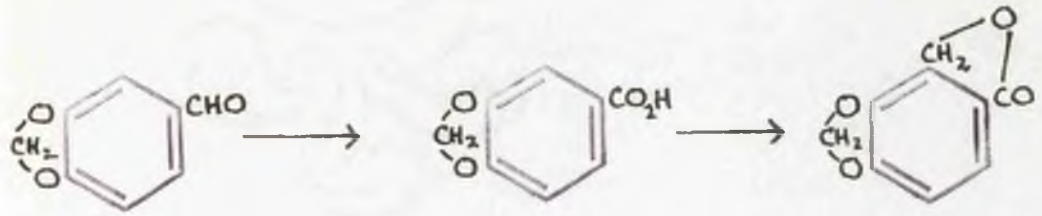


Stevens and Robertson (26) reported that 4:5--methylenedioxyphthalaldehydic acid (XL) could not be obtained from (LXV) by oxidation with manganese dioxide, or lead dioxide in sulphuric or acetic acids, or by use of chromium trioxide in acetic acid. We found that, like m-meconin, treatment of 5:6-methylenedioxyphthalide with N-bromosuccinimide followed by hydrolysis without isolation of the intermediate bromo-compound (LXXII) gave the acid (XL) in 72% yield, and, as with m-opianic acid, the acid was isolated from the hydrolysis solution by the formation of an insoluble anilino compound (LXXIII a and b), acid hydrolysis of which gave 4:5-methylenedioxy-phthalaldehydic acid (XL).



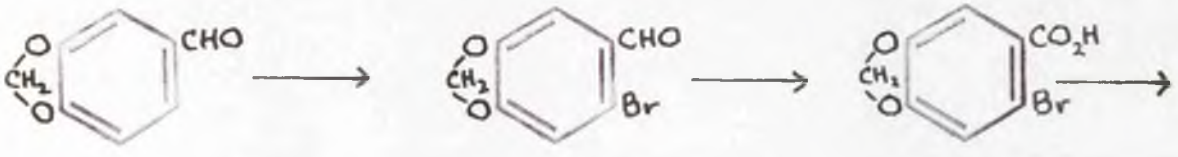
An attempt was made to prepare 5:6-methylenedioxyphthalide by the action of formaldehyde in hydrochloric acid on piperonylic acid (LXXIV), (obtained by permanganate oxidation of piperonal) though Edwards, Perkin, and Stoyle (18) reported that piperonylic acid on long boiling with formaldehyde and hydrochloric acid resulted in unchanged acid plus a small yield of an easily oxidised substance of high molecular weight. We confirmed that the bulk of piperonylic acid was recovered after the reaction but isolated a small quantity of a compound, $C_9H_6O_4$, m.p.176-178°, having the properties of a phthalide and whose ultra-violet light absorption was similar to that of 5:6-methylenedioxyphthalide. This material was

was 4:5-methylenedioxyphthalide (LXXV), a hitherto unknown compound.

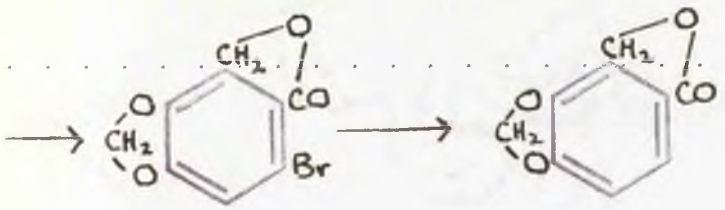


(LXXIV) (LXXV)

An attempt was made to synthesise 4:5-methylenedioxyphthalide (LXXV) by an unambiguous route by treating 6-bromopiperonylic acid (LXXVII) with formaldehyde in hydrochloric-acetic acids to form 7-bromo-4:5-methylenedioxyphthalide (LXXVIII), debromination of which would give the required phthalide (LXXV). Accordingly, 6-bromopiperonylic acid (LXXVII) was prepared by brominating piperonal (LXVI) to 6-bromopiperonal (LXXVI) after Orr, Robinson, and Williams (27) and oxidising (LXXVI) to (LXXVII) by permanganate but the conversion of (LXXVII) to the bromophthalide (LXXVIII) was unsuccessful.

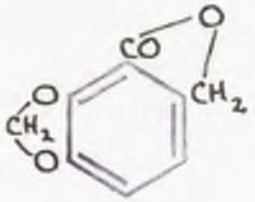


(LXVI) (LXXVI) (LXXVII)



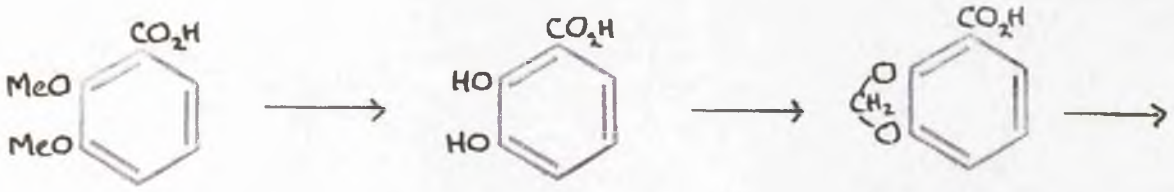
(LXXVIII) (LXXV)

The third isomer, 6:7-methylenedioxyphthalide (LXXIX) has been previously synthesised as follows:

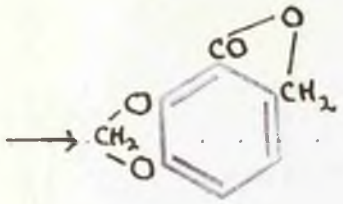


(LXXIX)

Perkin and Trikojus (28) demethylated o-veratric acid (LXXX) to 2:3-dihydroxybenzoic acid (LXXXI) and methylenated the latter to o-piperonylic acid (LXXXII) which condensed readily with formaldehyde in hydrochloric--acetic acids to yield 6:7-methylenedioxyphthalide (LXXIX).

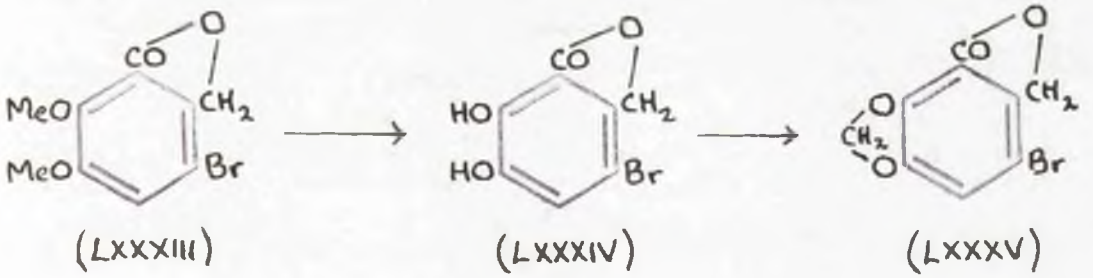


(LXXX) (LXXXI) (LXXXII)

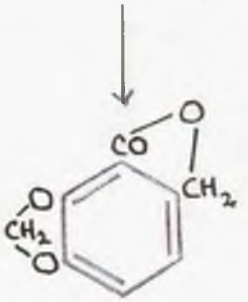


(LXXIX)

Groenewood and Robinson (29) methylenated 4-bromo--6:7-dihydroxyphthalide (LXXXIV), obtained by demethylation of 4-bromomeconin (LXXXIII), and the product (LXXXV) was debrominated to give the phthalide (LXXIX).



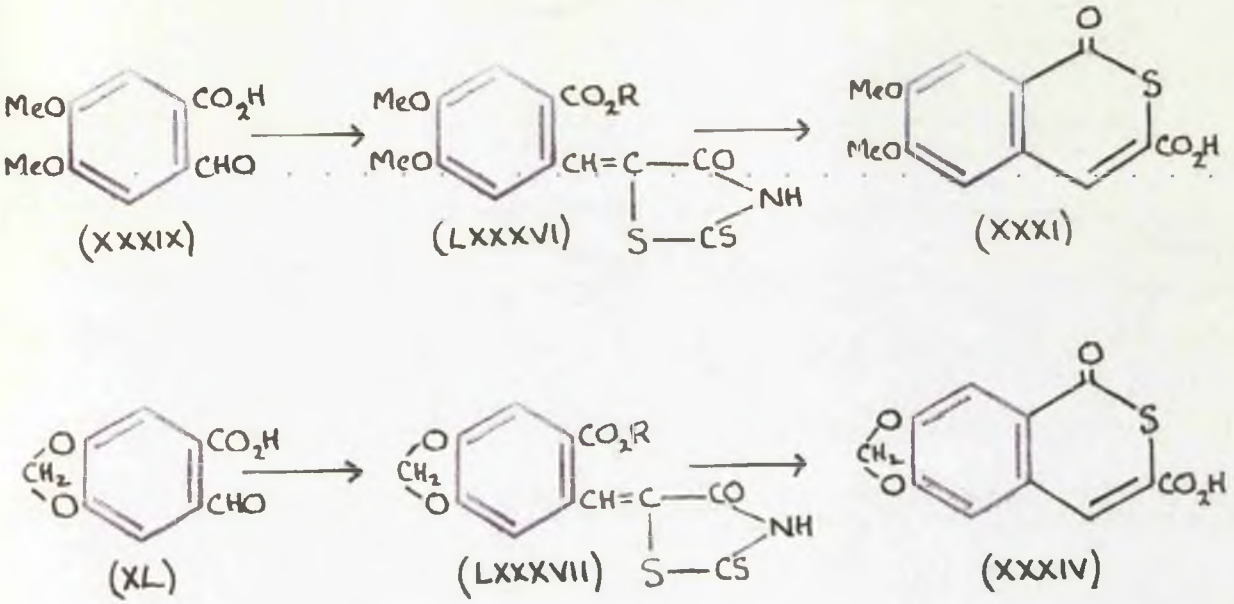
(LXXXIII) (LXXXIV) (LXXXV)



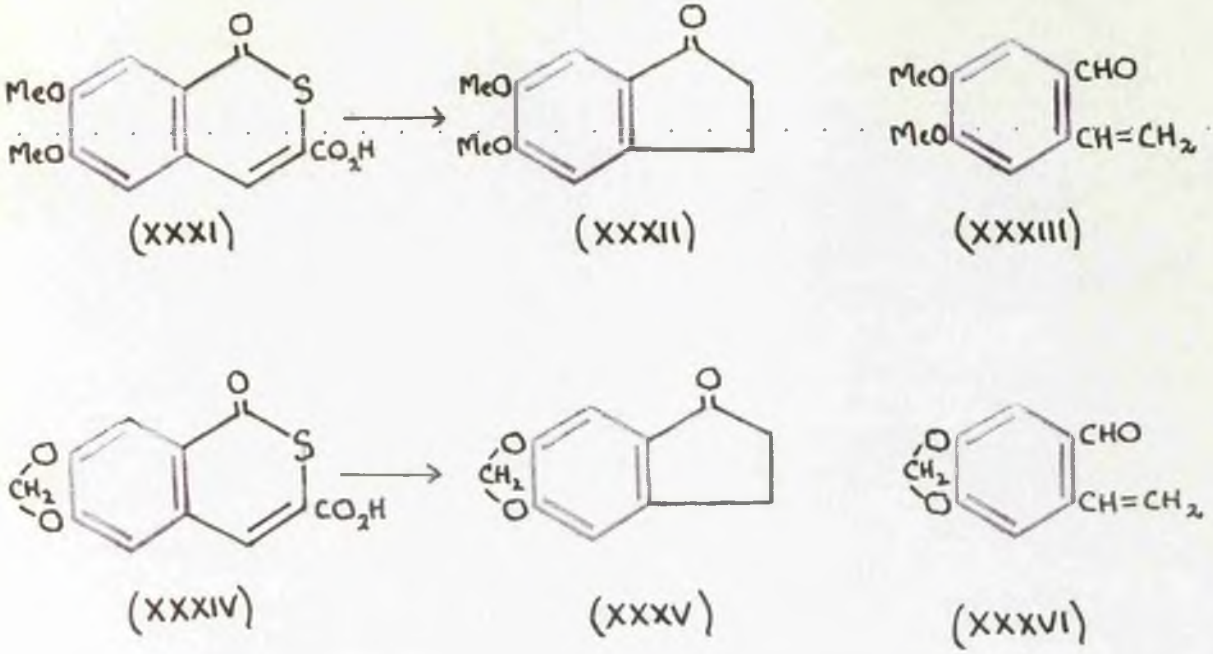
(LXXIX)

The action of Raney nickel on 1:2-dihydro-1-keto-6:7--dimethoxy-2-thianaphthalene-3-carboxylic acid and 1:2-dihydro-1-keto-6:7-methylenedioxy-2-thianaphthalene--3-carboxylic acid.

m-Opianic acid (XXXIX) and 4:5-methylenedioxyphthalaldehydic acid (XL) condensed readily with rhodanine, when refluxed in glacial acetic acid in the presence of anhydrous sodium acetate, to give the sodium salts of 5-(2-carboxy-4:5-dimethoxybenzylidene)rhodanine (LXXXVI; R=Na) and 5-(2-carboxy-4:5-methylenedioxybenzylidene)-rhodanine (LXXXVII; R=Na) respectively. The free rhodanine acids, (LXXXVI; R=H) and (LXXXVII; R=H), were liberated for characterisation by solution of the salt in aqueous sodium carbonate followed by acidification with mineral acid. Alkaline hydrolysis of these condensation products gave in the one case, 1:2-dihydro-1-keto-6:7-dimethoxy-2--thianaphthalene-3-carboxylic acid (XXXI), and in the other, 1:2-dihydro-1-keto-6:7-methylenedioxy-2-thianaphthalene-3-carboxylic acid (XXXIV), both acids being characterised by the preparation of their methyl esters.

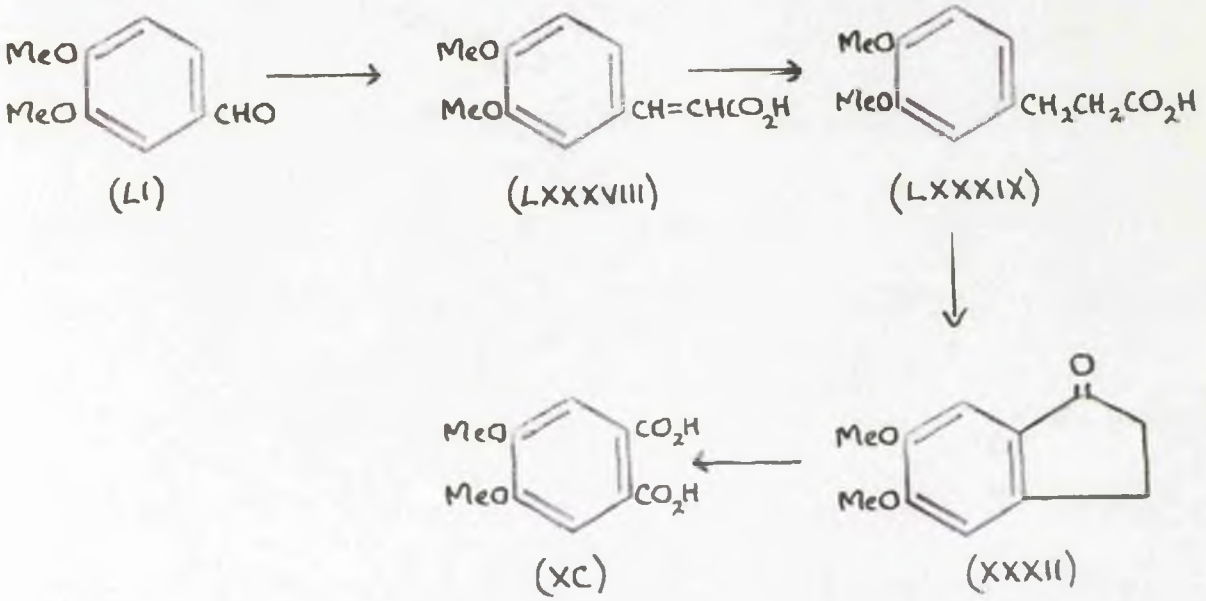


Treatment of (XXXI) and (XXXIV) in boiling ethanol with Raney nickel gave respectively 5:6-dimethoxyindan--1-one (XXXII) and 5:6-methylenedioxyindan-1-one (XXXV) and not the corresponding o-vinylaldehydes, (XXXIII) and (XXXVI), although the crude products in both cases gave a blue colour with concentrated sulphuric acid in acetic acid, a very sensitive and specific test for o-vinylaldehydes (30,31), but the intensity of the colour compared with that given by hydrastal (XXXVI), indicated the presence of only traces of such compounds, and no 4:5--dimethoxy-2-vinylbenzaldehyde (XXXIII) nor hydrastal (XXXVI) could be isolated in the two experiments.

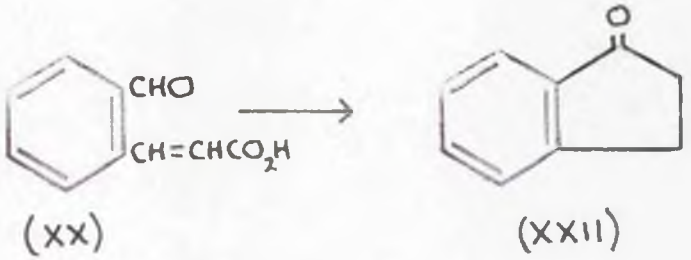


The indanones (XXXII) and (XXXV) obtained above, were compared with authentic specimens prepared according to Perkin and Robinson (32). In the dimethoxy series, 4:5-dimethoxycinnamic acid (LXXXVIII) was prepared by refluxing veratric aldehyde (LI) with malonic acid in pyridine-piperidine (33), and reduction of the acid (LXXXVIII) using sodium amalgam (32) gave β-(4:5--dimethoxyphenyl) propionic acid (LXXXIX) which, on refluxing with phosphorus pentoxide in benzene, readily cyclised to 5:6-dimethoxy-indan-1-one (XXXII), the direction of ring closure being shown by oxidation to the corresponding hemipinic acid (XC). 5:6-Methylenedioxy-

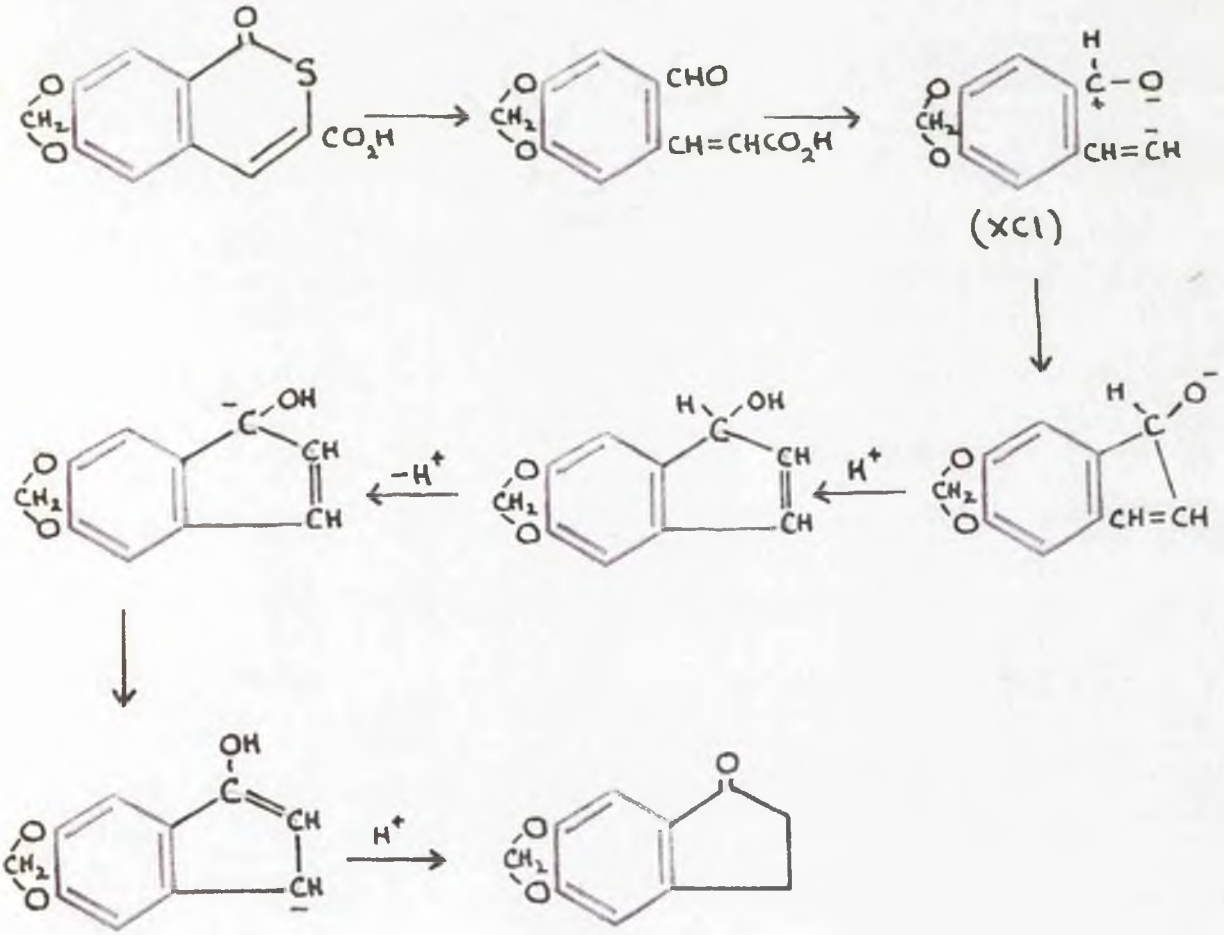
indan-1-one was prepared by a similar route starting from piperonal.



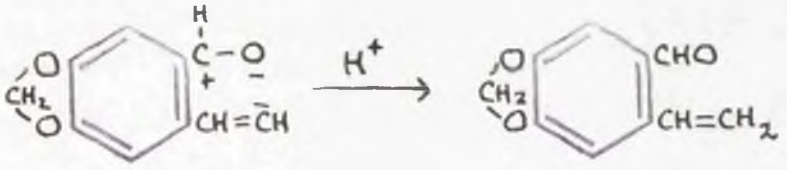
Wiley and Hobson (7) suggested a mechanism for the cyclisation of o-formylcinnamic acid (XX) to indan-1-one (XXII) (see p.7).



Applying a similar mechanism to the conversion of 1:2-dihydro-1-keto-6:7-methylenedioxy-2-thianaphthalene--3-carboxylic acid (XXXIV) into 5:6-methylenedioxyindan--1-one (XXXV) would give the following scheme:



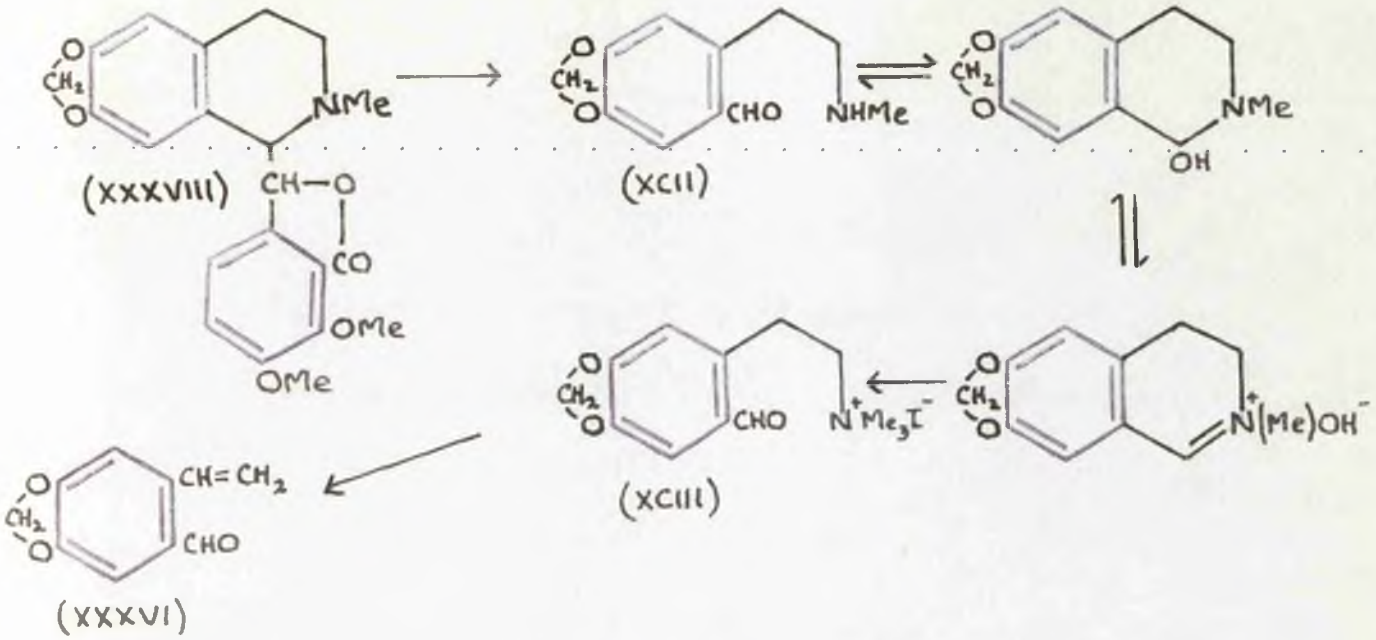
However, the colour test using sulphuric-acetic acids showed that hydrastal was formed, though only as a trace, in the Raney nickel reduction of (XXXIV). This suggests that either hydrastal (XXXVI) was formed in a side reaction from the ion (XCI) by the addition of a proton, or it was an intermediate in the formation of the indanone (XXXV).



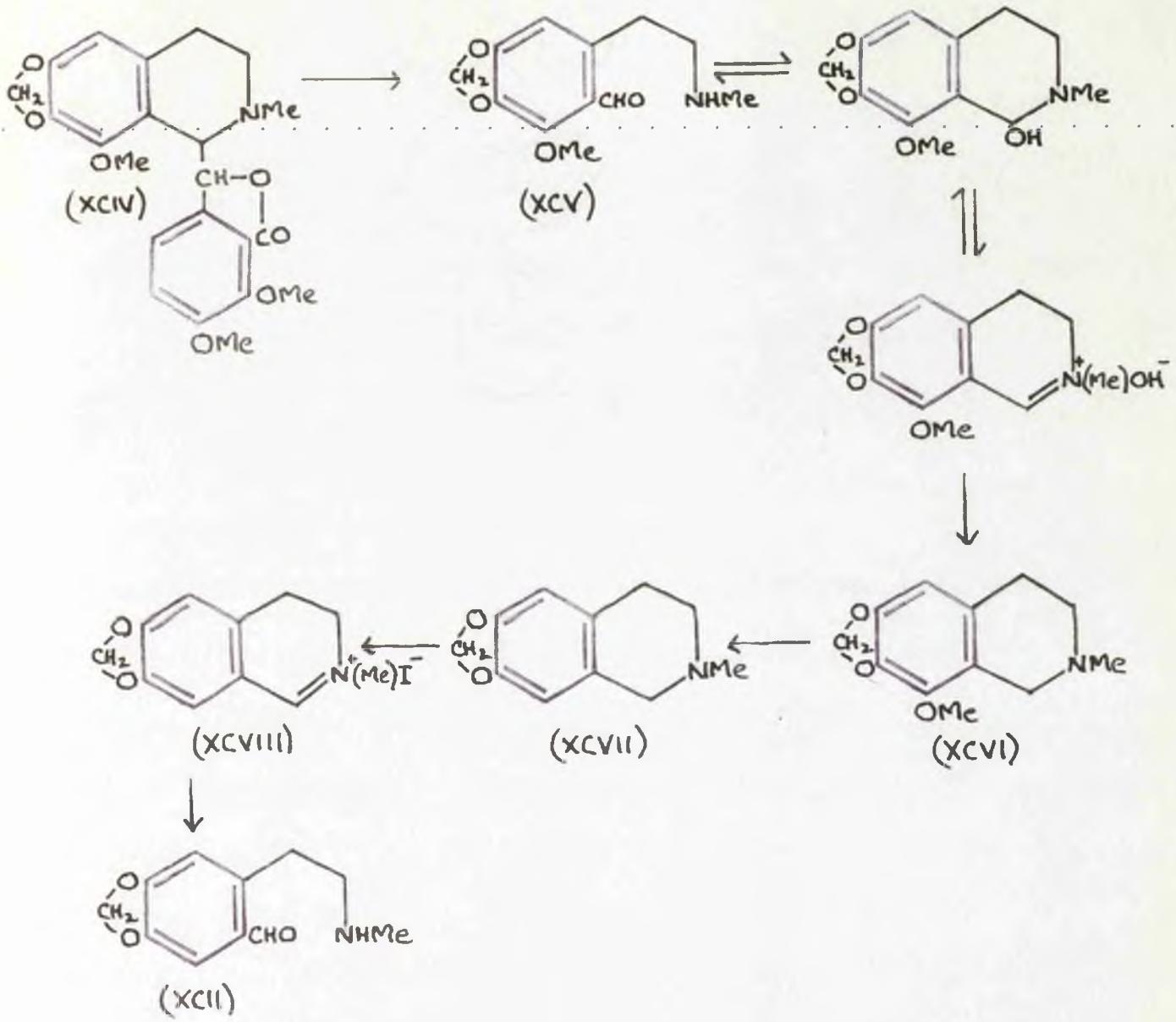
(XCI) (XXXVI)

In order to investigate these possibilities, the preparation of hydrastal was necessary.

Hydrastal was obtained by Freund (34) by the degradation of hydrastine (XXXVIII). Hydrastine on oxidation (35) with nitric acid gave hydrastinine (XCII) which readily formed hydrastinine methiodide (XCIII) on treatment with methyl iodide (34), and alkaline hydrolysis of (XCIII) yielded hydrastal (XXXVI).

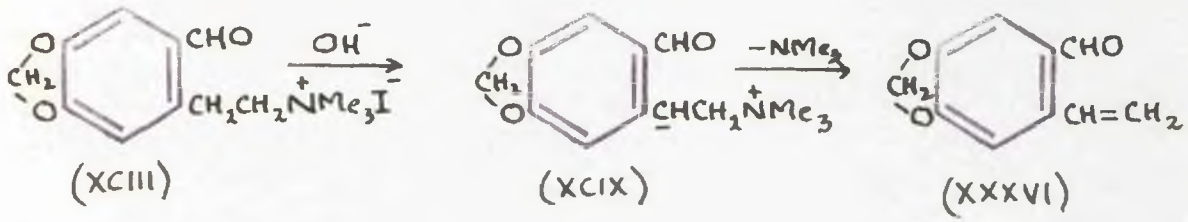


Hydrastine was not available to us, however, and it was decided to prepare hydrastal starting from cotarnine (XCV), obtained by oxidising narcotine (XCIV) with manganese dioxide in sulphuric acid (36). Cotarnine chloride was reduced to hydrocotarnine (XCVI) using sodium amalgam, a method used by Freund and Dormeyer (37) to reduce hydrastinine (XCII) to hydrohydrastinine (XCVII). Hydrocotarnine (XCVI) was converted to hydrohydrastinine (XCVII) by the method of Pyman and Remfry (38) who used sodium in amyl alcohol, and (XCVII), on oxidation with iodine after Topchiev (39), gave hydrastinine hydriodide (XCVIII), from which the free base (XCII) was readily obtained on treatment with alkali. The synthesis was then completed according to Freund (34) above.



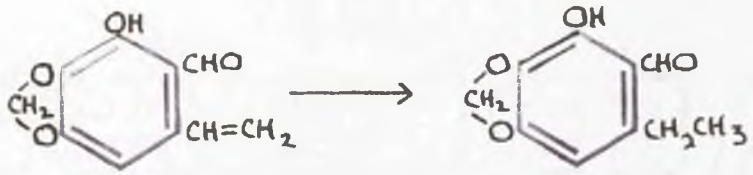
There was no possibility of indanone formation during the preparation of hydrastal by application of the Hofmann elimination reaction to hydrastinine methiodide (XCIII) since, according to current views on the Hofmann elimination reaction (40), loss of a proton

from the 'onium hydroxide from (XCIII) would give an intermediate (XCIX) which would lose trimethylamine to give hydrastal (XXXVI).



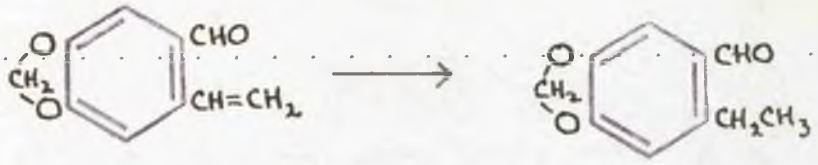
(XCIII) (XCIX) (XXXVI)

Späth, Schmid and Sternberg (41) showed the presence of a vinyl group in norcotarnone (C), a degradation product of narcotine, by reducing this group to ethyl (CI).



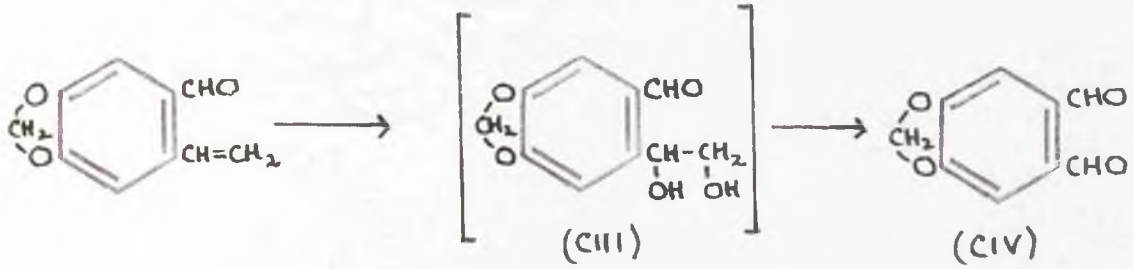
(C) (CI)

The presence of a vinyl group in hydrastal was likewise shown by us by reducing hydrastal over palladium to obtain 6-ethylpiperonal (CII), isolated as its 2:4--dinitrophenylhydrazone.



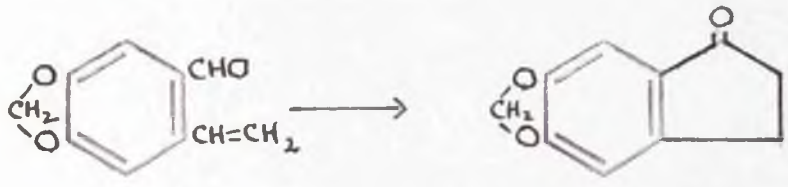
(CII)

Blair and Newbold (42) also confirmed the presence of a vinyl group in hydrastal by hydroxylating the double bond using osmium tetroxide and oxidising the diol (CIII) (not isolated) by periodate to 4:5-methylenedioxyphthalaldehyde (CIV).



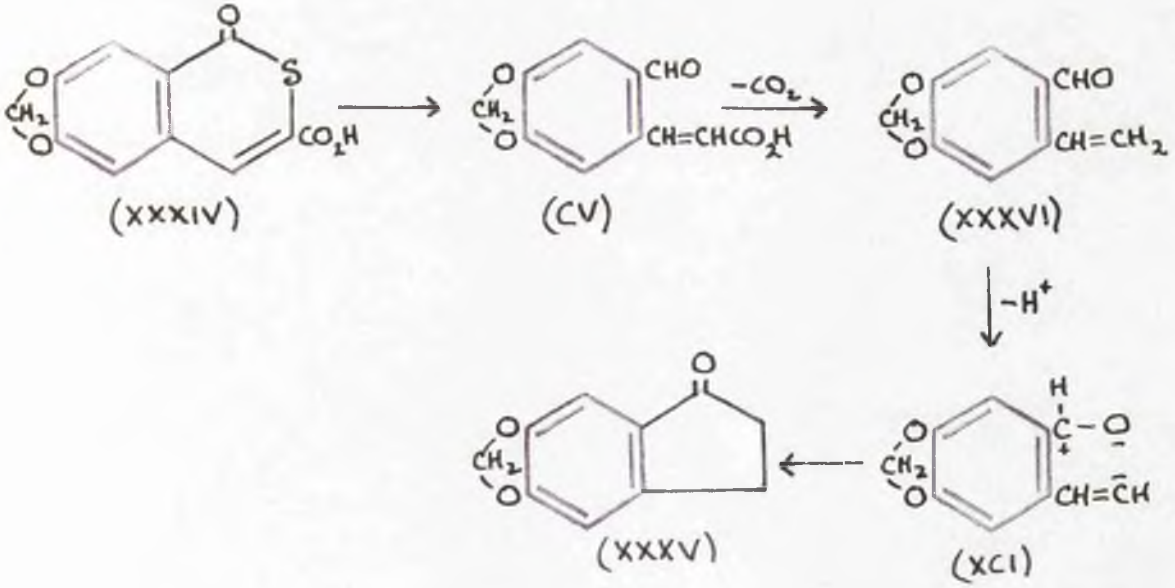
(CIII) (CIV)

It was found that when hydrastal was refluxed in ethanol in the presence of Raney nickel, it was isomerised to 5:6-methylenedioxyindan-1-one (XXXV).



(XXXV)

This reaction showed that the presence of a trace of hydrastal in the product from the Raney nickel reduction of 1:2-dihydro-1-keto-6:7-methylenedioxy-2--thianaphthalene-3-carboxylic acid (XXXIV) was not due to a side reaction involving the addition of a proton to the ion (XCI), but that hydrastal must be an intermediate in the formation of the indanone (XXXV). The mechanism of the conversion of the thianaphthalene acid (XXXIV) to the indanone (XXXV) must then be as below: (cf. p.30).



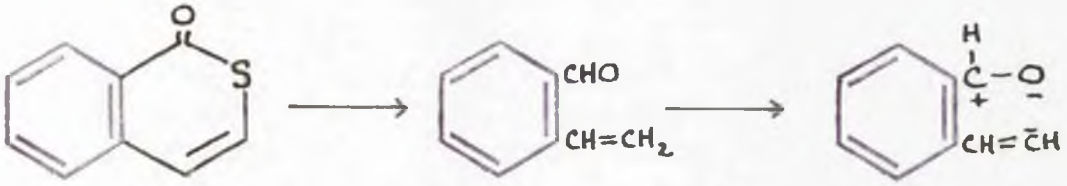
Hydrastal must have been formed by the decarboxylation of the acid (CV). Raney nickel could then effect the change (XXXVI) to the ion (XCI) by loss of a proton,

the stages from (XCI) to the indanone (XXXV) being the same as shown on p.30.

This mechanism is supported by the fact that Dijksman and Newbold (5) treated 1:2-dihydro-1-keto-2--thianaphthalene (CVI) (prepared by decarboxylation of the corresponding thianaphthalene-3-carboxylic acid) and obtained indan-1-one (XXII), isolated as its 2:4--dinitrophenylhydrazone and semicarbazone.

(CVI) (XXII)

This reaction cannot be explained by the Wiley and Hobson mechanism. Desulphurisation of the thianaphthalene (CVI) must give the intermediate o-vinylbenzaldehyde (XXI), which, under the reaction conditions, loses a proton to give the ion (CVII) and thence indan-1-one (XXII).



(CVI) (XXI) (CVII)

It is probable that Wiley and Hobson's formation of indan-1-one from o-formylcinnamic acid (see p.7) has also a similar mechanism to that above.

Thus, the direct conversion of hydrastal into 5:6-methylenedioxyindan-1-one showed that the formation of o-vinylaldehydes is an intermediate stage in the conversion of 1:2-dihydro-1-keto-2-thianaphthalenes into indanones using Raney nickel.

EXPERIMENTAL

EXPERIMENTAL

All melting points are uncorrected.

Veratric Acid. - (cf. Edwards, Perkin, and Stoyle, J.,1925,127,195). Veratric aldehyde was prepared in 60% yield from vanillin according to Org.Synth.,Coll.Vol. II,619. A hot solution of potassium permanganate (34 g.) in water (500 c.c.) was added over 1 hour to a stirred mixture of veratric aldehyde (50 g.) and water (300 c.c.) kept at 50-60°, a current of carbon dioxide being passed through the solution the whole time. After the addition was complete, the filtered solution was cooled, extracted with ether (2 x 200 c.c.) to remove any unchanged aldehyde, and acidified (Congo red) with hydrochloric acid (d, 1.16). The veratric acid (40 g.) separated as needles, m.p.177-178° (lit., m.p.179°).

m-Meconin. - (cf. Edwards, Perkin, and Stoyle, J.,1925,127,195). Veratric acid (50 g.), formaldehyde (55 c.c.; 40%) and hydrochloric acid (200 c.c.; d, 1.16) were heated on the steam-bath for 12 hours during which time considerable charring occurred. The product was cooled, diluted with water (200 c.c.), and shaken

vigorously until a dark gummy material adhered to the side of the flask. The solution was then filtered quickly and, on standing, m-meconin (10 g.) slowly separated as a dark brown crystalline powder. A specimen crystallised from aqueous ethanol as needles, m.p.158° (lit., m.p.155-157°), having light absorption in ethanol: Max. at 2200 (ϵ = 24,100), 2530 (ϵ = 9400), and 2940 (ϵ = 7200).

5-(3:4-Methylenedioxybenzylidene)-2-phenyl-oxazol--4-one. - (cf. Org.Synth.,Coll.Vol.II,55). A mixture of piperonal (160 g.), powdered, dry hippuric acid (192 g.), powdered, freshly fused sodium acetate (80 g.), and acetic anhydride (278 c.c.) was heated over an electric hot plate with constant shaking. The reaction mixture gradually solidified until at a temperature of 110° it was a solid, yellow mass. Heating was stopped and ethanol (400 c.c.) was added slowly, with external cooling, and the yellow crystalline product was filtered. The product was washed with ice-cold ethanol (2 x 200 c.c.) and then with boiling water (2 x 200 c.c.). After drying, the 5-(3:4-methylenedioxybenzylidene)-2-phenyl--oxazol-4-one weighed 285 g. (90%), m.p.196-197° (Kropp

and Decker, Ber.,1909,42,1133, give m.p.197°).

Homopiperonylic Acid. - (cf. Org.Synth.,Coll.Vol.II, 333). 5-(3:4-Methylenedioxybenzylidene)-2-phenyl-oxazol--4-one (285 g.) was refluxed with 10% sodium hydroxide solution (1 litre) for 10 hours until evolution of ammonia was complete. Sodium hydroxide solution (120 c.c.; 40%) was added, and the ice-cold solution was stirred while 30% hydrogen peroxide (105 c.c.) in water (105 c.c.) was added slowly, keeping the temperature below 15°. After standing overnight, the solution was acidified (Congo red) with hydrochloric acid (d, 1.16) and was then extracted with hot benzene (4 x 500 c.c.). The yellow residue obtained by drying ($MgSO_4$) the benzene extract and evaporating the solvent under reduced pressure, was refluxed for 6 hours with ethanol (1,250 c.c.) containing sulphuric acid (25 c.c.; d,1.84). A portion of the ethanol (500 c.c.) was evaporated and the remainder was poured into water (1 litre) when a dark brown oil separated which was extracted with benzene (3 x 500 c.c.). The combined extracts were washed with 10% sodium carbonate solution (2 x 130 c.c.), water (2 x 130 c.c.) and then dried ($MgSO_4$). The benzene was evaporated under reduced pressure

and the residual oil was distilled giving ethyl benzoate, b.p.80°/5 mm. and ethyl homopiperonylate (100 g.; 50%), b.p.130°/2 mm. (Keimatsu, J.Pharm.Soc.Japan,1933,53,1070, gives b.p.145-147° 3 mm.). Ethyl homopiperonylate (45.5 g.) was refluxed for 2 hours with 10% sodium hydroxide solution (200 c.c.). The cooled solution was poured into hydrochloric acid (30 c.c.; d, 1.16) containing ice (130 g.) and the homopiperonylic acid (33.5 g.; 95%) which separated was filtered and washed with ice-water (2 x 20 c.c.), m.p.127° (Mauthner, Annalen,1909, 370,368, gives m.p.127°).

Lactone of 6-Hydroxymethylhomopiperonylic Acid. - (cf. Stevens, J.,1927,178). To a solution of homopiperonylic acid (20 g.) in hot acetic acid (60 c.c.) was added hydrochloric acid (20 c.c.; d, 1.16) and formaldehyde (20 c.c.; 40%) and the mixture was heated on the steam-bath for 45 minutes. The mixture was poured into water (200 c.c.), extracted with chloroform (3 x 70 c.c.) and the combined extracts were washed with sodium hydrogen carbonate solution (50 c.c.; 10%), water (50 c.c.), and dried (Na_2SO_4). Evaporation of the solvent gave the lactone of 6-hydroxymethylhomopiperonylic acid as a

colourless solid which crystallised from ethanol as needles (10 g.), m.p.136-137° (lit., m.p.137°).

α-(6-Hydroxymethylpiperonyl)cinnamolactone. - (cf. Stevens and Robertson, J.,1927,2790). The lactone of 6-hydroxymethylhomopiperonylic acid (10 g.) was dissolved in benzaldehyde (15 c.c.) and, after adding 10 drops of piperidine, the mixture was heated at 120° for 2 hours. The melt was dissolved in the minimum amount of boiling acetic acid from which α-(6-hydroxymethylpiperonyl)cinnamolactone (8.0 g.) separated as yellow needles, m.p.189-191° (lit., m.p.190-192°).

5:6-Methylenedioxyphthalide. - (cf. Stevens and Robertson, loc cit.). A solution of α-(6-hydroxymethylpiperonyl)cinnamolactone (5.0 g.) in warm acetone (150 c.c.) was cooled and stirred while a warm concentrated aqueous solution of potassium permanganate (6.5 g.) and magnesium sulphate (6.5 g.) was added dropwise. The solution was brought to the boil, filtered, and on cooling 5:6-methylenedioxyphthalide (2.5 g.) separated from the filtrate as needles, m.p.138-139° (lit., m.p.138-139°). A specimen crystallised from aqueous ethanol as needles

had light absorption in ethanol: Max. at 2200 (ϵ = 21,800), 2560 (ϵ = 5,400), and 2980 Å (ϵ = 7,300).

4:5-Methylenedioxyphthalide. - Piperonylic acid (45 g.) was heated with hydrochloric acid (200 c.c.; d, 1.16) and formaldehyde (45 c.c.; 40%) on the steam-bath for 12 hours. The reaction mixture was diluted with an equal volume of water and filtered from unchanged piperonylic acid (40 g.). The filtrate gradually deposited a solid (1.0 g.), m.p. ca. 135°, which after five crystallisations from aqueous ethanol gave 4:5-methylenedioxyphthalide (100 mg.) as long fine needles, m.p. 176-178°, depressed to 145-150° on mixture with 5:6-methylenedioxyphthalide (Found: C,60.7; H,3.5; M(Rast),192. $C_9H_6O_4$ requires C,60.7; H,3.4%; M,178). Light absorption in ethanol: Max. at 2240 (ϵ = 25,100), 2700 (ϵ = 6250), and 2940 Å (ϵ = 4900). The compound is more soluble in water than the 5:6-isomer, but dissolves in 5% aqueous potassium hydroxide on warming and is precipitated from the cold solution on acidification with hydrochloric acid. It dissolves in aqueous sodium carbonate on warming, crystallising out on cooling.

6-Bromopiperonal. - (cf. Orr, Robinson, and Williams, J.,1917,111,946). A solution of bromine (8 c.c.) in acetic acid (20 c.c.) was added dropwise with cooling to a stirred solution of piperonal (25 g.) in acetic acid (50 c.c.). The reaction mixture was kept overnight when 6-bromopiperonal (9.0 g.) separated as needles, m.p.127--128° (lit., m.p.129°). The filtrate was diluted with water (100 c.c.) and the solid which separated was digested with hot concentrated aqueous sodium meta-bisulphite and filtered. 6-Bromopiperonal (6.0 g.) was precipitated from the filtrate on addition of aqueous sodium carbonate.

6-Bromopiperonylic Acid. - 6- Bromopiperonal (3.0 g.) was dissolved in acetone (100 c.c.) and the solution was stirred during the gradual addition of potassium permanganate (6.0 g.) and magnesium sulphate (6.0 g.) in warm concentrated aqueous solution. The mixture was filtered, acetone was evaporated and the aqueous solution was extracted with ether (3 x 25 c.c.) to remove unchanged aldehyde. Acidification (Congo red) of the solution with hydrochloric acid (d, 1.16) gave 6-bromopiperonylic acid (2.0 g.) as needles, m.p.204-205° (Fittig and Mielck,

Annalen, 1874, 172, 158 give m.p. 204-205°).

Attempted Preparation of 4:5-Methylenedioxyphthalide.- A mixture of 6-bromopiperonylic acid (2.0 g.), acetic acid (12 c.c.), hydrochloric acid (2 c.c.; d, 1.16) and formaldehyde (3 c.c.; 40%) was heated on the steam-bath for 45 minutes. The mixture was diluted with water (50 c.c.) and extracted with chloroform (3 x 30 c.c.). The combined chloroform extracts were washed with water (30 c.c.), sodium hydrogen carbonate solution (2 x 30 c.c.; 10%) and water (30 c.c.) and dried (Na_2SO_4). Evaporation of the solvent gave no product. The sodium hydrogen carbonate solution was acidified (Congo red) with hydrochloric acid (d, 1.16) and unchanged 6-bromopiperonylic acid (1.8 g.) separated, m.p. 204-205° alone or mixed with 6-bromopiperonylic acid.

m-Opianic Acid. - A solution of m-meconin (10 g.) in dry benzene (250 c.c.) was distilled until 50 c.c. of distillate was collected and then treated successively with dry carbon tetrachloride (200 c.c.) and N-bromosuccinimide (18.5 g.). The mixture was heated under reflux on the steam-bath for 2 hours while irradiated

with a 60-watt lamp adjacent to the flask. The cooled reaction mixture was filtered from succinimide and the filtrate evaporated under reduced pressure to give a yellow oil, which was stirred with water (250 c.c.) on the steam-bath for 1 hour. The yellow solution was decanted from tar, heated on the steam-bath, and treated with aniline, added in portions until an excess was present. Methanol (50 c.c.) was added, and the mixture allowed to cool. The aniline compound was separated, washed with methanol (20 c.c.), and dried (13.5 g.; m.p.213-214°; Fargher and Perkin, J.,1921,119,1724 give m.p.213-214°). The aniline compound was hydrolysed by heating it with hydrochloric acid (100 c.c.; 3N) on the steam-bath for 30 minutes. The crude m-opianic acid which separated on cooling was purified by digestion with saturated aqueous sodium carbonate, filtration, and acidification of the filtrate (Congo red) with 3N-hydrochloric acid, giving m-opianic acid (6.9 g.; 65%; m.p.183°). A specimen, once crystallised from water (charcoal), separated as needles, m.p.187-188° (Fargher and Perkin, loc.cit., and Chakravarti and Swaminathan, J.Indian Chem. Soc.,1934,11,715 give m.p.187-188°) (Found: C,57.4; H,5.0; equiv.,208. Calc. for $C_{10}H_{10}O_5$: C,57.15;

H,4.8%; equiv.,210). Light absorption in ethanol: Max. at 2240 (ϵ = 13,400), 2430 (ϵ = 11,100) and 2920 Å (ϵ = 7200).

4:5-Methylenedioxyphthalaldehydic Acid. - A solution of 5:6-methylenedioxyphthalide (7.0 g.) in dry benzene (350 c.c.) was distilled until 50 c.c. of distillate was collected. Carbon tetrachloride (300 c.c.) and N-bromosuccinimide (13 g.) were added and the mixture was treated as above and the product hydrolysed. The crude acid was isolated as the aniline compound (10 g.; m.p.185-186°; Chakravarti, Swaminathan, and Verkataraman, J.Indian Chem. Soc.,1940,17,264 give m.p.187°) which after treatment as described above gave 4:5-methylenedioxyphthalaldehydic acid (5.5 g., 72%; m.p.164-166°). A sample crystallised from water (charcoal) in needles, m.p.167° (idem.,ibid., give m.p.167°) (Found: C,55.9; H,3.2%; equiv.,198. Calc. for $C_9H_6O_5$: C,55.7; H,3.1%; equiv.,194). Light absorption in ethanol: Max. at 2240 (ϵ = 13,800), 2400 (ϵ = 4300), 2600 (ϵ = 4600) and 3000 Å (ϵ = 6400).

Rhodanine. - Rhodanine was prepared according to the method given in Org.Synth.,27,73.

5-(2-Carboxy-4:5-dimethoxybenzylidene)rhodanine. - m-Opianic acid (4.0 g.), rhodanine (2.6 g.), and fused sodium acetate (3.0 g.) in glacial acetic acid (50 c.c.) were heated under reflux for 30 minutes. The solution was poured into water (300 c.c.); the precipitated sodium salt (4.3 g.) was separated, and a portion dissolved in 20% aqueous sodium carbonate in the cold, filtered, and acidified (Congo red) with 3N-hydrochloric acid. Crystallisation of the precipitate from ethanol gave 5-(2-carboxy-4:5-dimethoxybenzylidene)rhodanine as yellow needles, m.p. 260° (decomp.) (Found: C, 43.0; H, 3.1. $C_{13}H_{11}O_5NS_2$ requires C, 43.6; H, 3.4%). Light absorption in ethanol: Max. at 2150 (ϵ = 13,500), 2520 (ϵ = 14,200), 2630 (ϵ = 12,900), 2900 (ϵ = 11,500) and 3360 Å (ϵ = 22,000).

5-(2-Carboxy-4:5-methylenedioxybenzylidene)rhodanine. - 4:5-Methylenedioxyphthalaldehydic acid (4.0 g.), rhodanine (2.3 g.), and fused sodium acetate (10 g.) in glacial acetic acid (50 c.c.) were heated under reflux for 30 minutes. The reaction mixture was treated as above and gave the sodium salt (4.8 g.). The free acid, 5-(2-carboxy-4:5-methylenedioxybenzylidene)rhodanine,

separated from aqueous ethanol as needles, m.p.256-257° (decomp.) (Found: C,46.6; H,2.3. $C_{12}H_7O_5NS_2$ requires C,46.6; H,2.3%). Light absorption in ethanol: Max. at 2080 (ϵ = 18,300), 2220 (ϵ = 18,500), 2530 (ϵ = 13,400), 2940 (ϵ = 14,500), and 3350 Å (ϵ = 13,400).

1:2-Dihydro-1-keto-6:7-dimethoxy-2-thianaphthalene--3-carboxylic Acid. - The sodium salt of 5-(2-carboxy-4:5--dimethoxybenzylidene)rhodanine (4.1 g.) was heated under reflux for 1 hour with 15% aqueous sodium hydroxide (60 c.c.). The cooled solution was poured into excess of 3N-hydrochloric acid, and the precipitate separated. Crystallisation from ethanol gave 1:2-dihydro-1-keto-6:7--dimethoxy-2-thianaphthalene-3-carboxylic acid (3.35 g.) as fine yellow needles, m.p.306-307° (Found: C,53.3; H,3.9; S,11.3%; equiv.,262. $C_{12}H_{10}O_5S$ requires C,54.1; H,3.8; S,12.0%; equiv.266). Light absorption in ethanol: Max. at 2320 (ϵ = 13,700), 2720 (ϵ = 36,500), 3280 (ϵ = 7600), 3500 (ϵ = 8750), and 3660 Å (ϵ = 7600). Esterification by ethereal diazomethane gave the methyl ester, which formed light yellow, felted needles, m.p.212°, from methanol (Found: C,55.9; H,4.5; S.9.8. $C_{13}H_{12}O_5S$ requires C,55.7; H,4.3; S,10.2%). Light absorption in

ethanol: Max. at 2320 (ϵ = 10,400), 2530 (ϵ = 26,400), 2760 (ϵ = 34,100), 2840 (ϵ = 30,100), 3380 (ϵ = 8950), 3520 (ϵ = 10,600), and 3630 Å (ϵ = 9650).

1:2-Dihydro-1-keto-6:7-methylenedioxy-2-thianaphthalene-3-carboxylic Acid. - The sodium salt of 5-(2-carboxy--4:5-methylenedioxybenzylidene)rhodanine (4.8 g.) was treated as above to give 1:2-dihydro-1-keto-6:7-methylenedioxy-2-thianaphthalene-3-carboyxlic acid (2.5 g.) as yellow needles, m.p.335-336° (decomp.) from ethanol (Found: C,52.7; H,2.7. $C_{11}H_6O_5S$ requires C,52.8; H,2.4%). Light absorption in ethanol: Max. at 2520 (ϵ = 27,000), 2620 (ϵ = 21,300), 2700 (ϵ = 22,800), 2740 (ϵ = 23,500), 3320 (ϵ = 5900), 3500 (ϵ = 6400) and 3640 Å (ϵ = 5200). The methyl ester was prepared by esterification with ethereal diazomethane and separated from ethanol as light yellow needles, m.p.223-229° (Found: C,54.5; H,3.2; S,11.9. $C_{12}H_8O_5S$ requires C,54.5; H,3.0; S,12.1%). Light absorption in ethanol: Max. at 2030 (ϵ = 8000), 2560 (ϵ = 32,200), 2710 (ϵ = 25,400), 2760 (ϵ = 23,200), 2830 (ϵ = 23,100), 3520 (ϵ = 9100), and 3700 Å (ϵ = 7800).

3:4-Dimethoxycinnamic Acid and 3:4-Methylenedioxycinnamic Acid. - These acids were prepared in 80% yield from veratric aldehyde and piperonal respectively by condensation with malonic acid in pyridine-piperidine according to the method given in Org. Reactions, Vol. I, p.249. 3:4-Dimethoxycinnamic acid had m.p.179-180° (Perkin and Schiess, J., 1904, 85, 159 give m.p.180°) and 3:4-methylenedioxycinnamic acid had m.p.227-229° (Slotta and Heller, Ber., 1930, 63, 3029 give m.p.232°).

β-(4:5-Dimethoxyphenyl)propionic Acid. - (cf. Perkin and Robinson, J., 1907, 91, 1073). 3:4-Dimethoxycinnamic acid (10 g.) dissolved in aqueous sodium hydroxide (200 c.c.; 2N), was stirred during the portionwise addition of sodium amalgam (200 g.; 3-4%), the solution being kept just alkaline by the frequent addition of small quantities of 3N-hydrochloric acid. After 2 hours, the aqueous phase was filtered, acidified (Congo red) with hydrochloric acid (d, 1.16), and β-(4:5-dimethoxyphenyl)propionic acid (7.5 g.) separated, m.p.97° (lit., m.p.97°).

β-(4:5-Methylenedioxyphenyl)propionic Acid. - 3:4--Methylenedioxycinnamic acid (10 g.) gave, by the method above, β-(4:5-methylenedioxyphenyl)propionic acid (8.0 g.), m.p.86-87° (lit., m.p.87-88°).

5:6-Dimethoxyindan-1-one. - (a) 1:2-Dihydro-1-keto--6:7-dimethoxy-2-thianaphthalene-3-carboxylic acid (3.0 g.) was heated under reflux for 6 hours with a suspension of Raney nickel (34 g.; W.6, prepared according to Org.Syth., 29,25) in ethanol (100 c.c.). After removal of the nickel and nickel sulphide, the filtrate and ethanol washings were evaporated to small bulk under reduced pressure, diluted with water (200 c.c.), and extracted with ether (4 x 50 c.c.). The combined ethereal extracts were washed with 2N-sodium hydroxide (2 x 50 c.c.) and water (2 x 50 c.c.) and dried (Na_2SO_4). Removal of the ether gave a colourless solid (300 mg.) which gave a blue colour in glacial acetic acid solution with concentrated sulphuric acid. Crystallisation of the solid from benzene-light petroleum (b.p.40-60°) gave 5:6-dimethoxy-indan-1-one as needles, m.p.116-177°, undepressed when mixed with a specimen prepared in (b) (Found: C,68.6; H,6.3. Calc. for $C_{11}H_{12}O_3$: C,68.7; H,6.3%). Light absorption in ethanol: Max. at 2300 (ϵ = 13,000), 2680 (ϵ = 11,700), and 3120 Å (ϵ = 10,400).

(b) (cf. Perkin and Robinson, J.,1907,91,1073). β-(4:5--Dimethoxyphenyl)propionic acid (10 g.), phosphoric anhydride (50 g.), and dry benzene 30 c.c.) were heated

under reflux on the steam-bath for 3 hours. The mixture was cooled and careful addition of ice gave a yellow solution which was extracted with ether (3 x 50 c.c.). The combined ethereal extracts were washed with aqueous sodium hydroxide (2 x 25 c.c.; 10%), water (2 x 50 c.c.), and dried (Na_2SO_4). Removal of solvent gave 5:6--dimethoxyindan-1-one (5.0 g.) which crystallised from benzene-light petroleum (b.p.40-60°) as needles, m.p.116--117° (lit., m.p.115°).

5:6-Methylenedioxyindan-1-one. - (a) 1:2-Dihydro-1--keto-6:7-methylenedioxy-2-thianaphthalene-3-carboxylic acid (3.5 g.) and Raney nickel (35 g.) in ethanol (70 c.c.) were heated under reflux for 8 hours. The reaction mixture was worked up as in the previous experiment. The solid residue (1.0 g.), after removal of ether, gave a blue colour in the sulphuric-acetic acid test. Crystallisation from benzene-light petroleum (b.p.40-60°) gave prismatic needles (300 mg.), m.p.156-158°, which on further crystallisation from the same solvent and sublimation at 120°/10^{-4} mm. gave 5:6-methylenedioxyindan-1-one, m.p.164-165° (Found: C,67.8; H,4.8. Calc. for $C_{10}H_8O_3$: C,68.1; H,4.5%). Light absorption in ethanol: Max. at

2080 (ϵ = 16,000), 2290 (ϵ = 16,500), 2650 (ϵ = 7500) and 3150 Å (ϵ = 10,000). It was undepressed on mixing with a specimen prepared in (b). The compound gave a crimson colour with concentrated sulphuric acid. The 2:4-dinitrophenylhydrazone separated from benzene as bright red needles, m.p.265-266° (decomp.) (Found: C,54.3; H,3.4; N,15.7. $C_{16}H_{12}O_8N_4$ requires C,53.9; H,3.4; N,15.7%). Light absorption in chloroform: Max. at 2460 (ϵ = 18,300), 3160 (ϵ = 7950), 3340 (ϵ = 7950), and 4040 Å (ϵ = 32,700).

(b) (*cf.* Perkin and Robinson, *J.*, 1907, **91**, 1073). Using the method given for 5:6-dimethoxyindan-1-one, β-(4:5--methylenedioxyphenyl)propionic acid (10 g.) gave 5:6--methylenedioxyindan-1-one (4.0 g.) as prismatic needles, m.p.164-165° (lit., m.p.160°) from benzene-light petroleum (40-60°) (Found: C,68.25; H,4.7%).

Preparation of Hydrastal from Cotarnine. - Hydrocotarnine. Freund and Dormeyer's procedure (*Ber.*, 1891, **24**, 2730) for the reduction of hydrastinine to hydrohydrastinine lacks detail; the following method proved satisfactory. A solution of cotarnine chloride (50 g.) in water (250 c.c.) was stirred vigorously for 6 hours with sodium amalgam (450 g.; 3%), the solution being kept

acid (Congo red) by frequent additions of 5N-sulphuric acid. The solution was made alkaline with 3N-sodium hydroxide and extracted with ether (3 x 150 c.c.), the combined extracts being washed with water (100 c.c.) and dried (Na_2SO_4). Removal of the ether gave hydrocotarnine (20.0 g.) as a dark brown oil which solidified when kept at 0° overnight. The product had m.p.55-56° (lit., m.p. 55.5-56.5°) and gave a yellow colour with concentrated sulphuric acid in the cold, becoming deep purple on warming.

Hydrohydrastinine. - (cf. Pyman and Remfry, J.,1912, 101,1595). 25 c.c. of a solution of hydrocotarnine (20 g.) in dry amyl alcohol (75 c.c.) were heated with an oil-bath (the bath temperature being maintained at 130-135°) and sodium (30 g.) was added in one portion. The sodium melted and the remainder of the hydrocotarnine solution (50 c.c.) was added over 20 minutes. Dry amyl alcohol (42 c.c.) was then added at 10 minute intervals over 2 hours. Undissolved sodium was skimmed off, the solution was cooled, water (160 c.c.) and hydrochloric acid (134 c.c.) were added, and the mixture was thoroughly shaken. The alcohol phase was separated and extracted with 5N--hydrochloric acid (3 x 100 c.c.). The combined aqueous

phase and acid extracts were made alkaline by addition of powdered sodium carbonate, extracted with chloroform (3 x 300 c.c.), and the combined chloroform extracts were washed with 2N-sodium hydroxide (2 x 200 c.c.), water (2 x 200 c.c.), and dried (Na_2SO_4). The solvent was evaporated to give crude hydrohydrastinine. A solution of the impure product in ethanol (50 c.c.) was acidified (Congo red) with hydrobromic acid (d, 1.46-1.49) and the hydrastinine hydrobromide which separated on standing, was crystallised from water, m.p.184° (6.3 g.) (lit. m.p.193°). The hydrobromide (6.0 g.), dissolved in warm water (30 c.c.) was neutralised with saturated aqueous sodium carbonate and hydrohydrastinine (3.5 g.) separated as an oil which solidified on cooling. The free base had m.p.54-55° (lit., m.p.61-62°) and gave a yellow solution with concentrated sulphuric acid in the cold, becoming dark red on warming.

Hydrastinine hydriodide. - In our hands the oxidation of hydrohydrastinine by potassium dichromate and dilute sulphuric acid, as recommended by Freund and Will (Ber., 1887,20,2797), proved very unsatisfactory. The following method, a modification of that of Topchiev (J.Applied Chem.,

U.S.S.R.,1933,6,529), was used. Hydrohydrastinine (13.5 g.) and freshly fused sodium acetate (9.5 g.) were heated under reflux in ethanol (34 c.c.) and treated with a solution of iodine (21.6 g.) in ethanol (210 c.c.), added dropwise during 1 hour. The solution was kept overnight at room temperature, and the solid (22 g.) which separated was filtered off and added in small amounts to a solution of sodium dithionite (hydrosulphute) (7.0 g.) in water (50 c.c.). The solution was warmed and filtered, hydrastinine hydriodide (15 g.) separating as yellow needles, m.p.231-233° (lit., m.p.233--234°), on cooling.

Hydrastinine Methiodide. - (cf. Freund, Ber.,1889, 22,2329). The hydriodide (16 g.) was suspended in water (20 c.c.) and shaken with a solution of potassium hydroxide (16 g.) in water (16 c.c.) in the cold. The precipitated hydrastinine (10 g.), m.p.106-107° (lit., m.p.116-117°) was separated, washed with water, and dried in vacuo over solid sodium hydroxide. Hydrastinine (8.0 g.) was heated under reflux with methyl iodide (40 c.c.) for one hour. The excess methyl iodide was removed under reduced pressure and the residue crystallised

twice from water to give hydrastinine methiodide (5.0 g.) as yellow needles, m.p. 262-264° (lit., m.p. 267°).

Hydrastal. - (cf. Freund, loc.cit.). Hydrastinine methiodide (5.0 g.) was heated on the steam-bath with 10% aqueous potassium hydroxide (90 c.c.) for 15 minutes; trimethylamine was evolved and an oil (2.7 g.) separated which solidified on cooling. Crystallisation from light petroleum (b.p. 60-80°) gave hydrastal (2.0 g.) as plates, m.p. 76-78° (Freund, loc.cit., gives m.p. 78-79°). The compound gave an intense deep blue colour in acetic acid with concentrated sulphuric acid. It showed light absorption in ethanol: Max. at 2060 (ϵ = 8600), 2480 (ϵ = 27,700), 3000 (ϵ = 6700), and 3280 Å (ϵ = 6700). The 2:4-dinitrophenylhydrazone separated from benzene as small red prisms, m.p. 227-228° (decomp.) (Found: C, 54.1; H, 3.6; N, 15.9. $C_{16}H_{12}O_6N_4$ requires C, 53.9; H, 3.3; N, 15.7%). Light absorption in chloroform: Max. at 2500 (ϵ = 22,500), 3140 (ϵ = 9000), and 3960 Å (ϵ = 47,900).

5:6-Methylenedioxyindan-1-one from Hydrastal. - A solution of hydrastal (500 mg.) in ethanol (10 c.c.) was heated under reflux with Raney nickel (4.0 g.) for 4 hours.

The filtrate and washings from the catalyst were concentrated under reduced pressure to 5 c.c. and diluted with water (50 c.c.), and the mixture was extracted with ether (3 x 25 c.c.). The dried (Na_2SO_4) ethereal extract was evaporated to give a colourless oil (450 mg.) which gave no colour with the sulphuric-acetic acid test, but gave a crimson colour with concentrated sulphuric acid. Since the product showed no signs of solidification, it was dissolved in methanol (10 c.c.) and treated with Brady's reagent, and the resulting precipitate (500 mg.) crystallised three times from benzene, to give 5:6-methylenedioxyindan-1-one 2:4-dinitrophenylhydrazone as fine red needles, m.p.266-267° (decomp.) alone or mixed with a specimen of the authentic derivative (Found: C,54.3; H,3.5. Calc. for $C_{16}H_{12}O_6N_4$: C,53.9; H,3.4%). Light absorption in chloroform: Max. at 2460 (ϵ = 17,000), 3160 (ϵ = 7800), 3320 (ϵ = 7800), and 4040 Å (ϵ = 29,400).

6-Ethylpiperonaldehyde 2:4-Dinitrophenylhydrazone. - A solution of hydrastal (500 mg.) in methanol (30 c.c.) was shaken for 15 minutes with previously reduced 3% palladium-calcium carbonate catalyst at room temperature and pressure with hydrogen, after which time 68 c.c. had

been absorbed (calc. for 1 mol.: 68 c.c.). The filtered solution was evaporated under reduced pressure to give a clear viscous oil, which gave a dark red colour rapidly assuming a green-brown hue with concentrated sulphuric acid on warming. With sulphuric-acetic acid similar behaviour was shown. A portion of the oil on treatment in methanol with Brady's reagent gave 6-ethylpiperonaldehyde 2:4-dinitrophenylhydrazone which separated from benzene as red needles, m.p.236-237° (decomp.) (Found: C,54.0; H,4.3. $C_{16}H_{14}O_6N_4$ requires C,53.6; H,4.7%). Light absorption in chloroform: Max. at 2460 (ϵ = 17,700), 3120 (ϵ = 7450), and 3830 Å (ϵ = 23,700).

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BIBLIOGRAPHY

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PART II

THE SYNTHESIS OF GLADIOLIC ACID

SUMMARY

1. 3-Formylopianic acid has been prepared from 4-chloromethylmeconin and some reactions of the former compound are discussed and compared with those of the mould product, gladiolic acid.

2. The structure of isogladiolic acid, the alkali rearrangement product of gladiolic acid, has been confirmed as 7-methoxy-6-methylphthalide-4-carboxylic acid by synthesis.

3. 3-Hydroxymethylopianic acid has been prepared from the monoacetate of 3-formylopianic acid. A comparison of the properties of the former compound shows that dihydrogladiolic acid has the structure 3-hydroxymethyl--6-methoxy-5-methylphthalaldehydic acid.

4. Gladiolic acid has been obtained by periodate oxidation of deoxygladiolic acid (4-formyl-7-methoxy-6-methylphthalide).

INTRODUCTION

INTRODUCTION

The Structures of Dihydrogladiolic Acid and Gladiolic Acid.

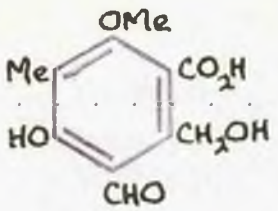
Brian et al. (1) showed that strains of Penicillium gladioli produced a strongly antifungal and weakly antibacterial substance, gladiolic acid $C_{11}H_{10}O_5$, and the structure of this acid was elucidated independently by Raistrick and Ross (2) and Grove (3).

Raistrick and Ross derived the structure of gladiolic acid from that of dihydrogladiolic acid, $C_{11}H_{12}O_5$, a mould product obtained from Penicillium gladioli, by altering the proportion of the constituents in the medium used for the production of gladiolic acid. Dihydrogladiolic acid titrated sharply as a monobasic acid using phenolphthalein as indicator, gave no colour with ferric chloride, and the presence of a reactive carbonyl group (probably -CHO) was shown by the formation of a mono-2:4-dinitrophenylhydrazone, mono-semicarbazone, and mono-anil. Acetylation of dihydrogladiolic acid gave a diacetate, $C_{15}H_{16}O_7$, which, on treatment with dilute mineral acid, formed dihydrogladiolide, $C_{11}H_{10}O_4$, a substance also produced by high vacuum sublimation of dihydrogladiolic acid. Thus

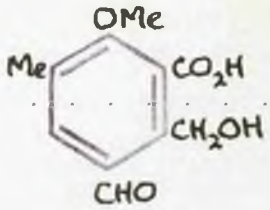
the following groups were shown to be present in the dihydrogladiolic acid molecule: one $-OCH_3$ group and one $C-CH_3$ group (estimated); one $-CHO$ group; one $-CO_2H$ group; one $-CH_2OH$ group vicinal to the $-CO_2H$ group which would account for the loss of one molecule of water in the formation of dihydrogladiolide from dihydrogladiolic acid. Dihydrogladiolide thus contained a lactone ring. Raistick and Ross attributed the formation of a diacetate to the acetylation of the $-CHO$ group and wrote the formula of dihydrogladiolic acid as a pentasubstituted benzene derivative.

$C_6.(H).(OMe).(CH_3).(CHO).(CO_2H).(CH_2OH) = C_{11}H_{12}O_5$

A similarity was noticed in the reactions of dihydrogladiolic acid and cyclopolic acid (I), a metabolic product of Penicillium cyclopium Westling, the structure of which had been determined by Birkinshaw, Raistrick, Ross, and Stickings (4). The empirical formulae of cyclopolic acid and dihydrogladiolic acid were $C_{11}H_{12}O_6$ and $C_{11}H_{12}O_5$ respectively. Since only cyclopolic acid gave a colour with ferric chloride, it seemed likely that the extra atom of oxygen in this compound was present as the phenolic group. Hence a possible structure of dihydrogladiolic acid was (II).

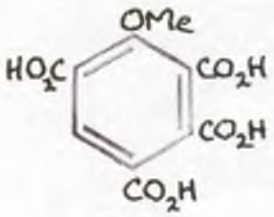


(I)

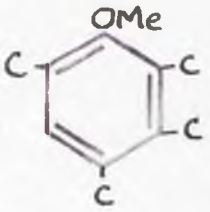


(II)

Alkaline permanganate oxidation of dihydrogladiolic acid gave 4-methoxybenzene-1:2:3:5-tetracarboxylic acid (III), shown to be similar to a synthetic specimen prepared by Grove (3). Thus dihydrogladiolic acid had the skeleton structure (IV).

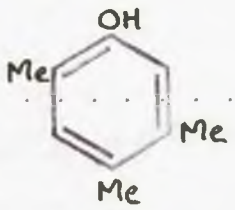


(III)



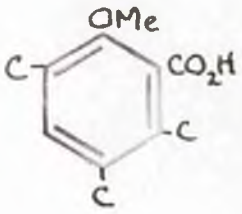
(IV)

Clemmensen reduction of dihydrogladiolic acid followed by treatment of the product, $C_{11}H_{12}O_3$, with hydriodic acid and red phosphorus gave pseudocumenol, 2:4:5-trimethylphenol (V) (identical with a synthetic specimen), simultaneous demethylation and decarboxylation having occurred.

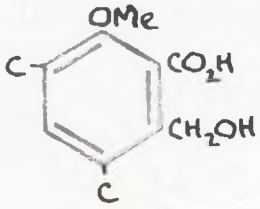


(V)

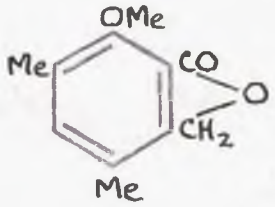
In order to conform to the structure (IV), the carboxyl group which was eliminated must have been ortho to the phenolic group and to the methoxyl group in dihydrogladiolic acid. The structure (IV) was thus expanded to (VI) and since Raistrick and Ross decided that the formation of dihydrogladiolide was due to a hydroxymethyl group ortho to the carboxyl, (VI) became (VII) giving the Clemmensen reduction product, $C_{11}H_{12}O_3$, as (VIII).



(VI)



(VII)

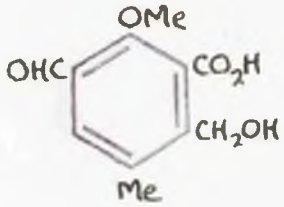


(VIII)

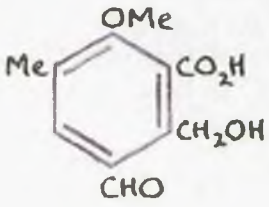
It was maintained that (VIII), on heating with hydriodic acid and red phosphorus, would be demethylated, the lactone ring would be slowly opened, and decarboxylation and reduction of the hydroxymethyl group to methyl

to give pseudocumenol (V) would take place.

As dihydrogladiolic acid contained an aldehyde and a methyl group, there were now only two possibilities, (IX) and (X), for the structure.

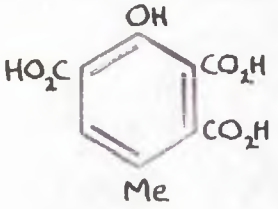


(IX)

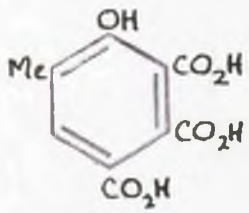


(X)

Dihydrogladiolic acid on oxidation with cold alkaline permanganate formed a tricarboxylic acid, $C_{11}H_{10}O_7$, which contained one C-CH_3 group and gave no precipitate with Brady's reagent nor colour with ferric chloride. Oxidation of dihydrogladiolic acid with potassium hydroxide at 300° in air gave a tricarboxylic acid $C_{10}H_8O_7$ which gave a colour with ferric chloride and which, on methylation, was identical with the acid from the permanganate oxidation. This acid $C_{10}H_8O_7$ was either structure (XI) derived from (IX) or structure (XII) derived from (X).

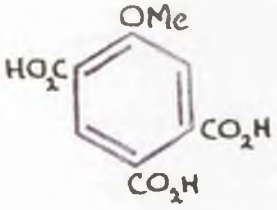


(XI)

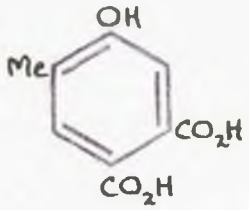


(XII)

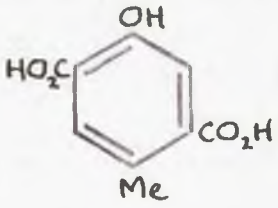
Decarboxylation of the acid $C_{10}H_8O_7$ (XI or XII) produced a dicarboxylic acid $C_9H_8O_5.H_2O$ which formed an anhydride, gave little or no colour with ferric chloride, and oxidation of its methyl ether with boiling alkaline permanganate yielded 5-methoxybenzene-1:2:4-tricarboxylic acid (XIII), identical with a synthetic specimen. The possibilities for the dicarboxylic acid were thus (XIV) or (XV).



(XIII)

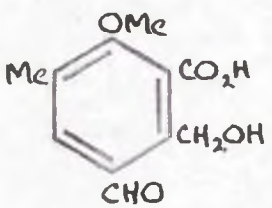


(XIV)



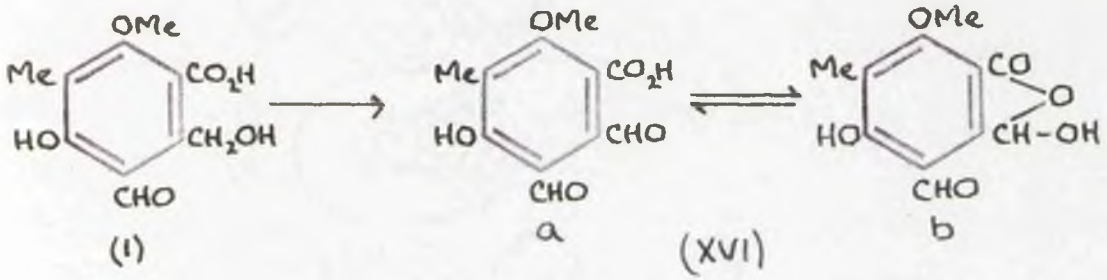
(XV)

As the structure (XV) could not form an anhydride and, like salicylic acid, would give an intense colour with ferric chloride, (XIV) was taken to be the correct structure and from this Raistrick and Ross concluded that the structure of dihydrogladiolic acid was (X), 5-formyl--6-hydroxymethyl-2-methoxy-3-methylbenzoic acid.

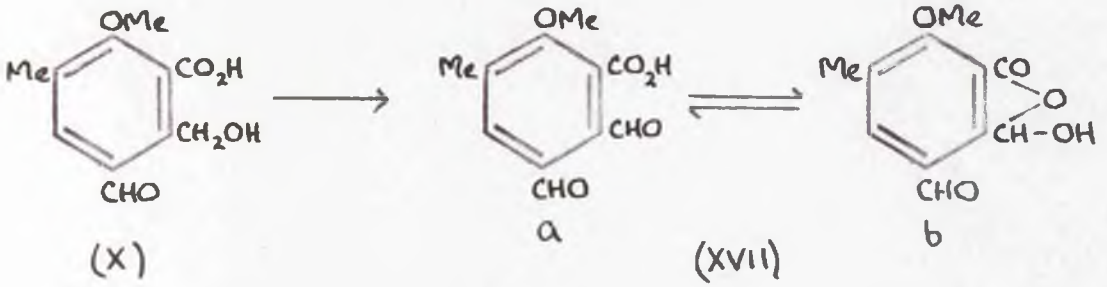


(X)

Birkinshaw et al. (4) showed that cyclopolic acid (I), on oxidation with potassium periodate in dilute sulphuric acid, formed cyclopaldic acid (XVI, a and b).



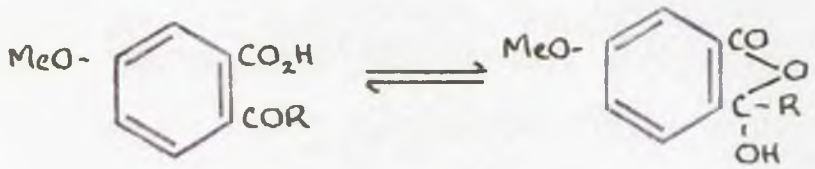
Raistrick and Ross found that similar treatment of dihydrogladiolic acid (X) yielded gladiolic acid which was identical with an authentic specimen. Thus, by analogy, they established the structure (XVII a and b) for gladiolic acid.



Unlike Raistrick and Ross (2), Grove (3) established the structure of gladiolic acid by degradative work on

the acid itself. In gladiolic acid, the presence of a benzene nucleus was indicated by the stability of the compound towards bromine and by the ultraviolet absorption spectrum. Formation of a 2:4-dinitrophenylhydrazone showed that gladiolic acid contained a carbonyl group, probably formyl (-CHO), since mild oxidation with permanganate produced a dibasic acid, substance A, $C_{11}H_{10}O_6$) and the reducing properties of gladiolic acid were eliminated. This dibasic acid showed the presence of a tautomeric system. There were six oxygen atoms in the acid; four contained in two carboxyl groups; one in a methoxyl group; one in a carbonyl group as shown by the formation of a semicarbazone which titrated as a dibasic acid. The formation of a monobasic monoacetate, $C_{13}H_{12}O_7$, on acetylation of substance A, indicated the presence of a hydroxyl group which was explained by giving substance A the partial structure (XVIII), showing keto-lactol tautomerism. Of the five oxygen atoms in gladiolic acid, four were present in the methoxyl substituted keto-acid (XVIII); the fifth was contained in a formyl group different from that involved in the tautomeric system because gladiolic acid formed a neutral acetate, $C_{13}H_{12}O_6$,

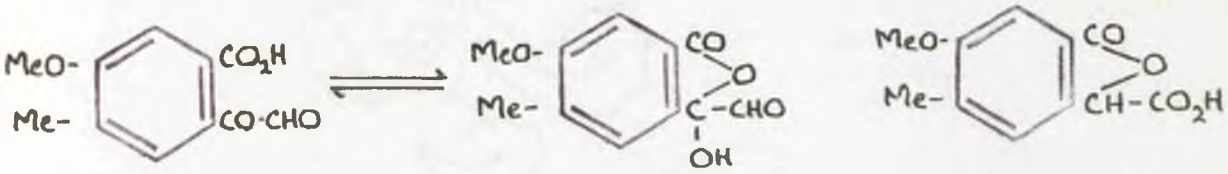
which retained the carbonyl reactivity and reducing properties of gladiolic acid.



(XVIII)

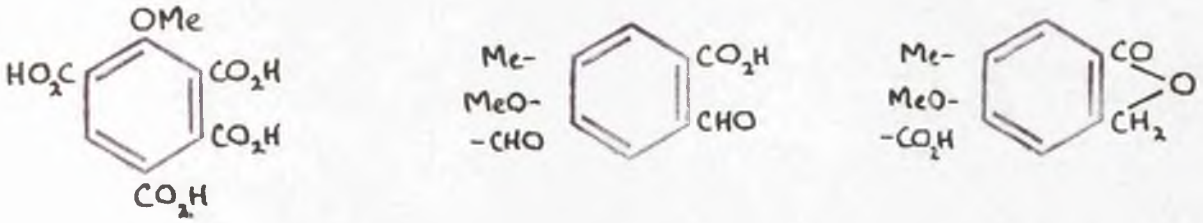
The additional nuclear substituents which had to be applied to (XVIII) were $-CH_3$, -CHO, or $-CH_3$ and -CHO depending on whether R was -CHO, $-CH_3$, or H respectively. R=CH_3 was not possible since gladiolic acid did not give the iodoform reaction or the nitroprusside test for a CH_3CO- group. Moreover, it was found (1) that oxidation of gladiolic acid with alkaline permanganate gave a methoxybenzene-tricarboxylic acid and it was concluded that gladiolic acid was a benzene ring containing a methoxyl group and three carbon side-chains. The structure of gladiolic acid was then thought to be that of a 2-carboxyphenylglyoxal (XIX) and <u>iso</u>gladiolic acid, the alkaline rearrangement product of gladiolic acid, to be (XX), formed by rearrangement of the phenylglyoxal portion of the molecule to the corresponding mandelic acid

followed by lactonization.



(XIX) (XX)

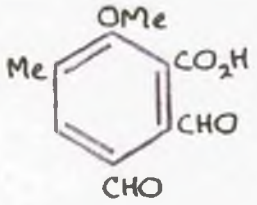
However, periodate oxidation of gladiolic acid did not yield the expected methoxy-methylphthalic acid and on repeating the permanganate oxidation on both gladiolic and isogladiolic acids, a tetracarboxylic acid was obtained, shown by synthesis to be 4-methoxybenzene--1:2:3:5-tetracarboxylic acid (XXI). Structures (XIX) and (XX) were excluded and gladiolic and isogladiolic acids were given the structures (XXII) and (XXIII) respectively.



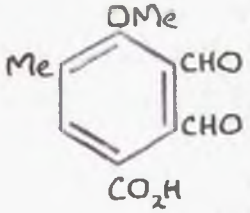
(XXI) (XXII) (XXIII)

Gladiolic acid gave a bluish-green colour with ammonia. Since this colour is also given by o-phthalaldehyde but

not iso- nor tere- phthalaldehyde, it suggested that the o-phthalaldehyde structure was present in gladiolic acid. The well-known alkaline rearrangement of o-phthalaldehyde to give phthalide gave an explanation of the formation of isogladiolic acid from gladiolic acid. Grove suggested (XXIV) and (XXV) as the most probable structures of gladiolic acid. (For simplicity only the phthalaldehyde structures are shown.)



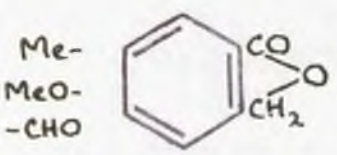
(XXIV)



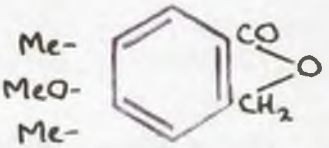
(XXV)

Reduction of gladiolic acid with iron powder and acetic acid yielded deoxygladiolic acid, $C_{11}H_{10}O_4$, which retained the carbonyl reactivity and reducing properties of gladiolic acid. It seemed likely in this reaction that gladiolic acid was reduced in the lactol form to the corresponding phthalide, giving deoxygladiolic acid the structure (XXVI). Clemmensen reduction of gladiolic acid reduced the lactol form to the phthalide and the formyl group to methyl to give the compound $C_{11}H_{12}O_3$ with

the structure (XXVII).

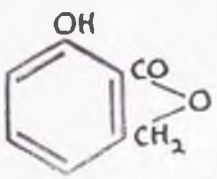


(XXVI)



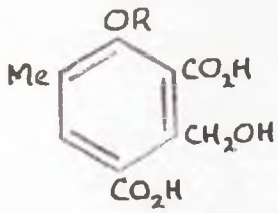
(XXVII)

Grove showed that the reactive formyl group in gladiolic acid corresponded with the carboxyl group in isogladiolic acid by permanganate oxidation of deoxy-gladiolic acid which gave isogladiolic acid. It was assumed that the lactone ring remained intact under these reaction conditions. isoGladiolic acid on demethylation formed the phenolic compound, norisogladiolic acid, which gave an intense reddish-purple colour with ferric chloride, suggesting the hydroxyl group was ortho to a carbonyl group, present either in the carboxyl group or in the lactone ring. Infra-red methods (5) showed that the latter possibility was correct and Grove formulated norisogladiolic acid as containing the partial structure (XXVIII).

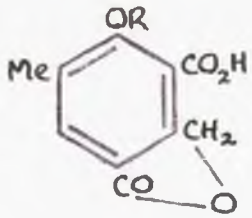


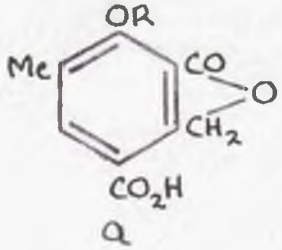
(XXVIII)

It was noted that the open structure (XXIX) must have been present as the sodium salt in alkaline solution following the rearrangement of gladiolic acid, and that on acidification this closed preferentially to give only one product. Thus, if there was no rearrangement of type (XXX) in the formation of norisogladiolic acid, then isogladiolic acid must have been 7-methoxy-6-methyl-phthalide-4-carboxylic acid (XXXa).



(XXIX)

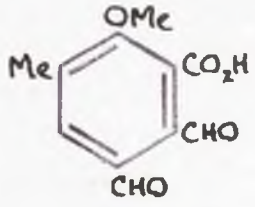




a

(XXX)

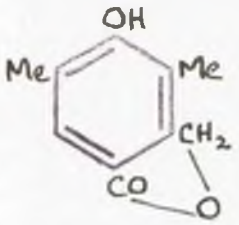
This established gladiolic acid as 3-formyl-6-methoxy--5-methylphthalaldehydic acid (XXIV).



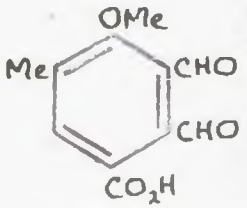
(XXIV)

Infra-red investigation of the phenol $C_{10}H_{10}O_3$, obtained by demethylation of the Clemmensen reduction product, $C_{11}H_{12}O_3$, indicated the structure to be (XXXI).

This gave gladiolic acid the structure (XXV) and it was concluded that a rearrangement of type (XXX) had taken place during the oxidation of deoxygladiolic acid to <u>iso</u>-gladiolic acid or during the demethylation of <u>iso</u>gladiolic acid.

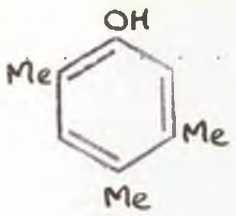


(XXXI)

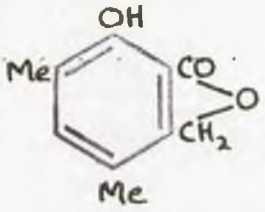


(XXV)

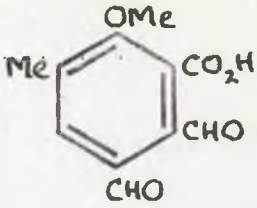
Raistrick and Ross (2), however, obtained the phenol $C_{10}H_{10}O_3$ by demethylation of the Clemmensen reduction product of dihydrogladiolic acid, and treatment of the phenol with hydriodic acid and red phosphorus yielded pseudocumenol, 2:4:5-trimethylphenol (XXXII). This established the structure of the phenol $C_{10}H_{10}O_3$ as 7--hydroxy-4:6-dimethylphthalide (XXXIII) and from this the structure of gladiolic acid could only have been (XXIV), 3-formyl-6-methoxy-5-methylphthalaldehydic acid.



(XXXII)

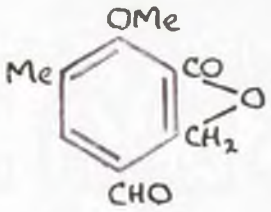


(XXXIII)

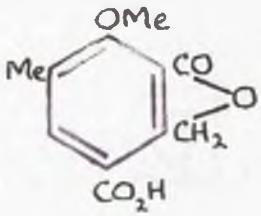


(XXIV)

It followed that deoxygladiolic acid was 4-formyl--7-methoxy-6-methylphthalide (XXXIV) and, assuming the lactone ring to remain intact during oxidation of (XXXIV), isogladiolic acid was 7-methoxy-6-methylphthalide-4--carboxylic acid (XXXV).

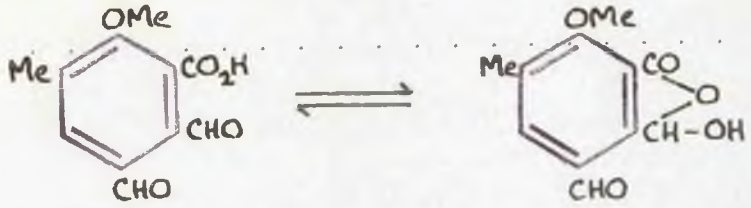


(XXXIV)



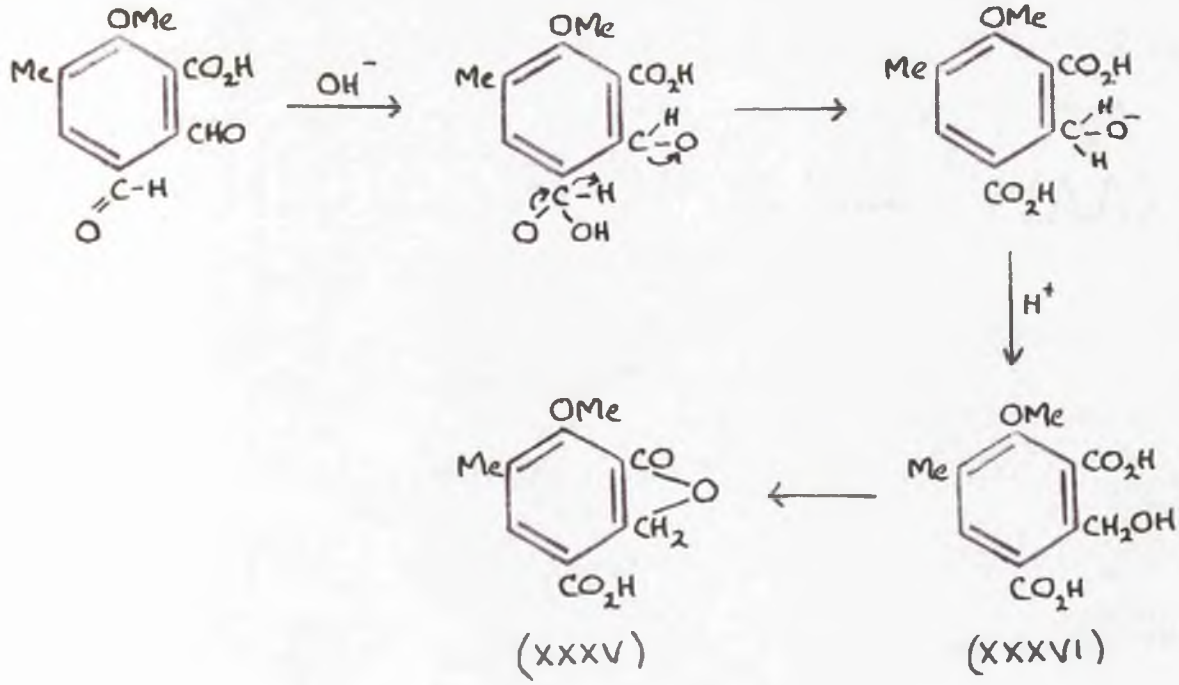
(XXXV)

Keto-lactol tautomerism in gladiolic acid (XXIV a and b) was shown by the rearrangement of the keto form (XXIVa) to isogladiolic acid and by formation of a neutral acetyl-gladiolic acid and pseudoesters derived from the lactol form (XXIVb) and by infra-red methods (5,6,7).



(XXIV)

Grove explained the formation of isogladiolic acid (XXXV) from gladiolic acid by analogy with the mechanism for the rearrangement of phenylglyoxal to mandelic acid recently advanced by Alexander (8) and Doering et al. (9). This gave the following scheme:



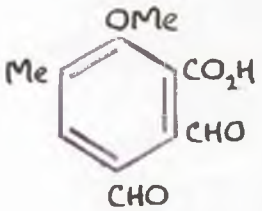
(XXXV) (XXXVI)

Grove stated that the preferential lactonization of (XXXVI) to isogladiolic acid (XXXV) was due to steric considerations arising from the presence of the methoxy substituent ortho to one of the carboxyl groups.

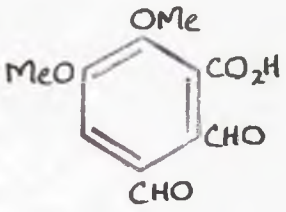
THEORETICAL

THEORETICAL

Although the elegant analytical work of Raistrick and Ross (2) and Grove (3) elucidated the structure of gladiolic acid as 3-formyl-6-methoxy-5-methylphthal-aldehydic acid (XXIV) (for simplicity, the other tautomeric form of compounds having the vicinal carboxy-o--phthalaldehyde system has been omitted), these authors did not synthesise the metabolic product or any of its derivatives. Thus final proof of the structure of gladiolic acid lay in an unambiguous synthesis of the compound. With this aim in view, it was decided to attempt the preparation of an analogous compound, 3-formylopianic acid (XXXVII), and compare its properties and derivatives with those of gladiolic acid.



(XXIV)



(XXXVII)

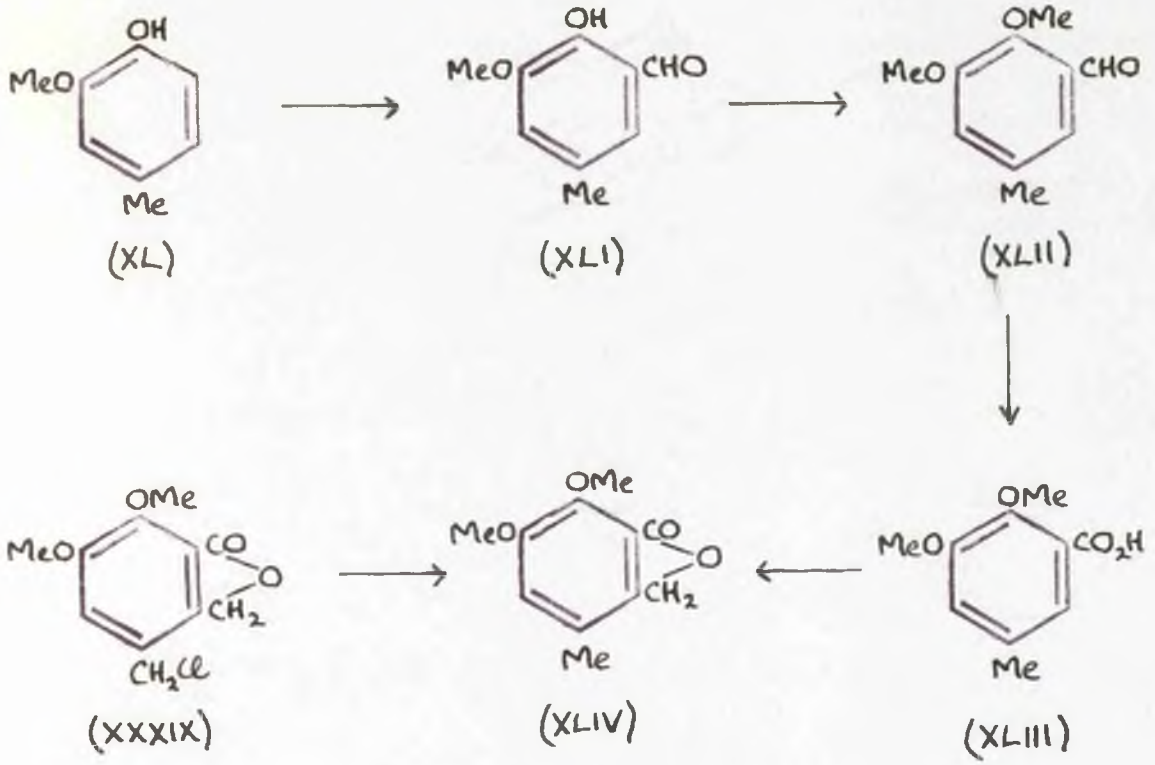
The Preparation of 3-Formylopianic Acid.

4-Chloromethylmeconin (XXXIX) was used as the starting material. This compound was described by Manske and Ledingham (10) who obtained it by the action of formaldehyde and hydrochloric acid on o-veratric acid (XXXVIII).

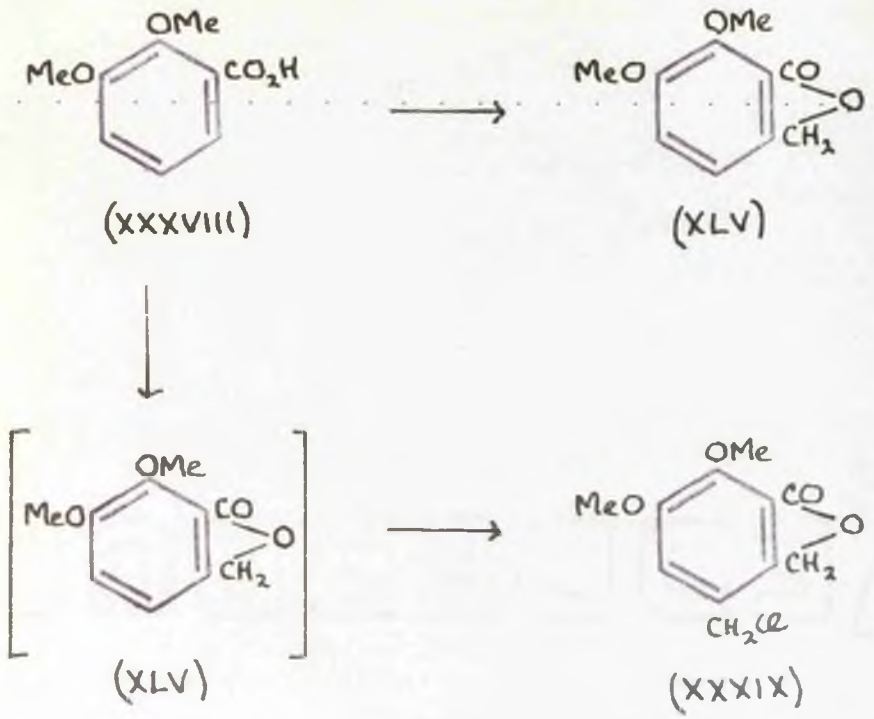
(XXXVIII) (XXXIX)

The structure (XXXIX) was proved by reduction to 4-methylmeconin (XLIV) which was synthesised by an unambiguous route starting from creosol (3-methoxy-p--cresol)(XL). Creosol was converted into 2-hydroxy-3--methoxy-5-methylbenzaldehyde (XLI) by the method of Duff (11), using hexamethylenetetramine in glycoboric acid, and hydrolysing the resulting complex with dilute sulphuric acid. Methylation of (XLI) gave (XLII) from which 2:3-dimethoxy-5-methylbenzoic acid (XLIII) was obtained on permanganate oxidation. Treatment of the

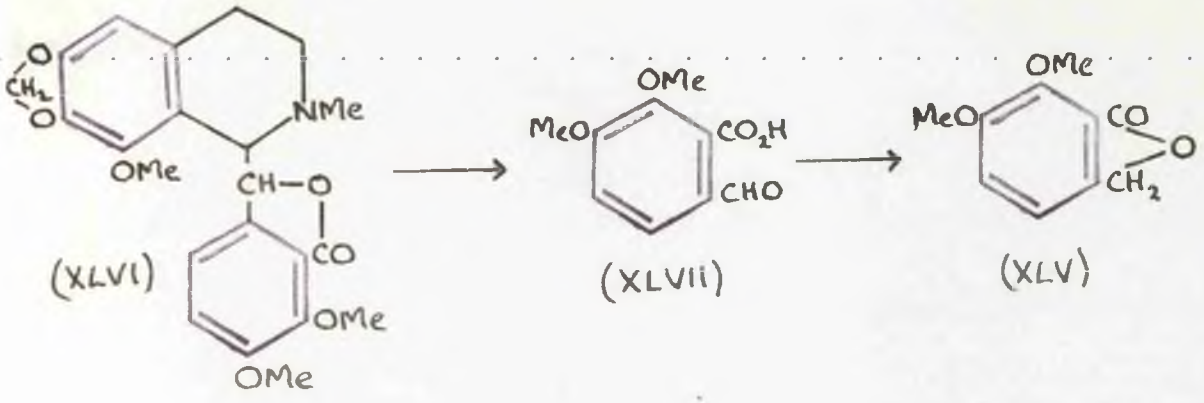
acid (XLIII) with formaldehyde and hydrochloric acid yielded 4-methylmeconin (XLIV).



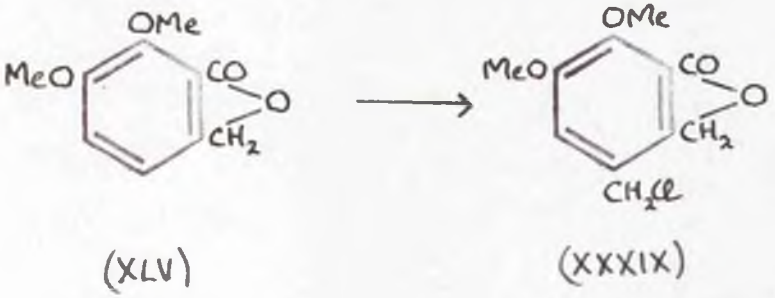
Since meconin (XLV) had been obtained by the action of formaldehyde and hydrochloric acid (12,13) on o-veratric acid (XXXVIII), it seemed likely that, in the above preparation of 4-chloromethylmeconin, meconin was an intermediate stage which reacted further to form (XXXIX).



It was, therefore, a possibility that 4-chloromethylmeconin could be prepared from meconin thus eliminating the use of o-veratric acid which was somewhat inaccessible. Meconin (XLV) was prepared in good yield by reducing opianic acid (XLVII) (obtained by the oxidation (14) of narcotine (XLVI) with manganese dioxide in dilute sulphuric acid) with sodium amalgam. A more convenient method was that of Rodionov and Federova (15) who treated opianic acid with formaldehyde and strong aqueous potassium hydroxide and obtained meconin in excellent yield on acidification of the alkaline solution

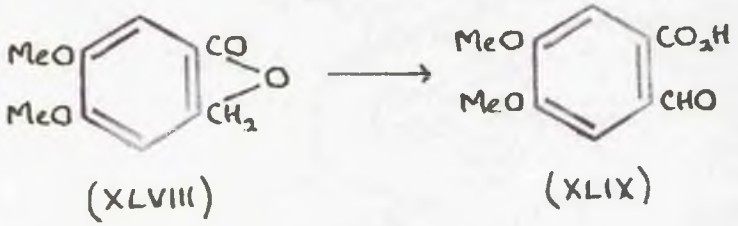


It was found that chloromethylation of meconin (XLV) proceeded in 50% yield giving 4-chloromethylmeconin (XXXIX), identical with the material prepared by the method of Manske and Ledingham (10).



It had already been shown (16) that m-opianic acid (XLIX) and 4:5-methylenedioxyphthalaldehydic acid (LI) were obtained from m-meconin (XLVIII) and 5:6-methylene-

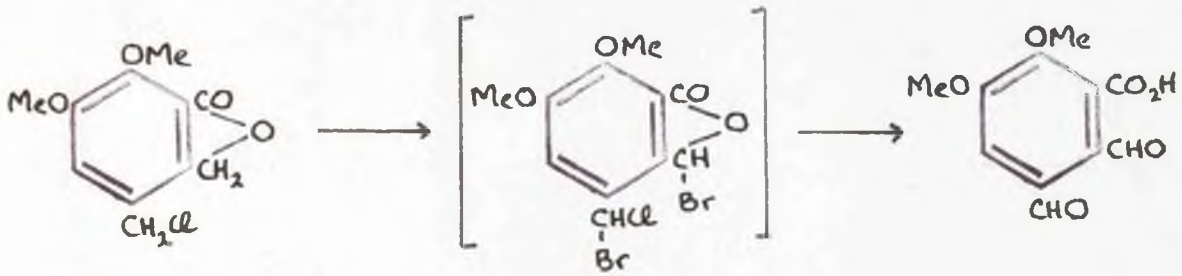
dioxyphthalide (L) respectively by use of N-bromosuccinimide.



(XLVIII) (XLIX)

(L) (LI)

Treatment of 4-chloromethylmeconin (XXXIX) with three molecular proportions of N-bromosuccinimide in carbon tetrachloride followed by hydrolysis of the intermediate (LII) with hot water gave 3-formylopianic acid (LIII).

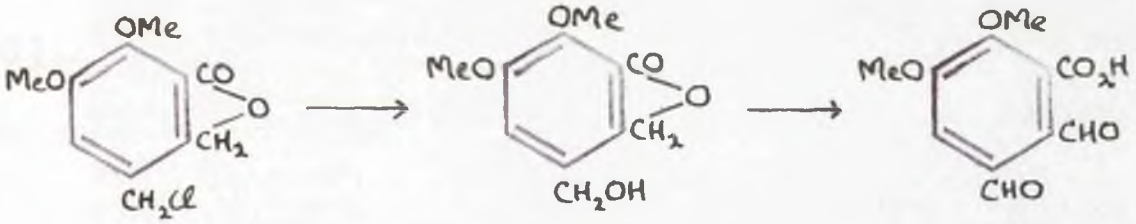


(XXXIX) (LII) (LIII)

The compound titrated as a monobasic acid, and only one of the aldehyde groups was reactive, as the compound

gave a mono-2:4-dinitrophenylhydrazone. 3-Formyl opianic acid gave a number of characteristic colour tests (see Experimental) also given by gladiolic acid (2,3).

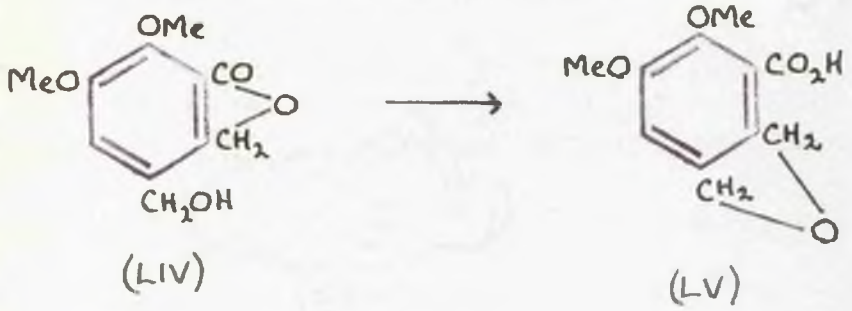
Another possible route to 3-formylopianic acid (LIII) appeared to be the direct oxidation of 4-hydroxymethylmeconin (LIV), readily obtained by hydrolysis of 4-chloromethylmeconin (XXXIX).



(XXXIX) (LIV) (LIII)

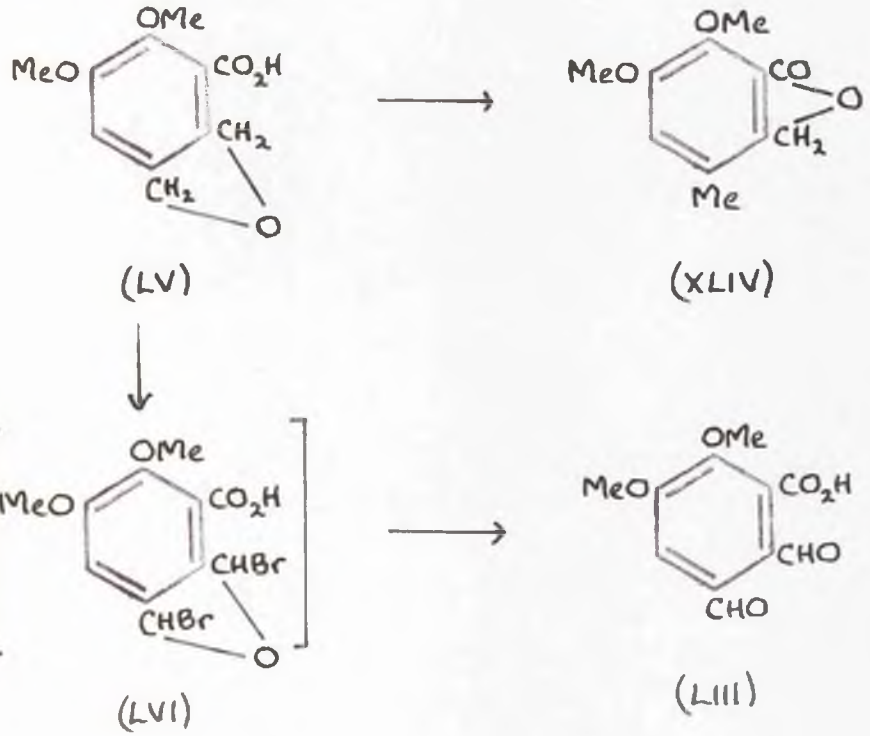
Oppenauer oxidation of (LIV) using benzophenone as hydrogen acceptor, gave an isomeric acid product $C_{11}H_{12}O_5$, subsequent examination showing that the compound could be obtained by reflux of 4-hydroxymethylmeconin in benzene with aluminium t-butoxide alone without benzophenone. The compound $C_{11}H_{12}O_5$ was formulated as 5:6-dimethoxyphthalan--4-carboxylic acid (1:3-dihydro-5:6-dimethoxybenzo[C]furan--4-carboxylic acid)(LV) since it was stable to alkali but isomerised by acid to 4-hydroxymethylmeconin, properties

which would be expected of an ether.



(LIV) (LV)

(LV) was reduced to 4-methylmeconin (XLIV), identical with a specimen prepared according to Manske and Ledingham (10), by the Clemmensen procedure. Reaction of (LV) with two molecular proportions of N-bromosuccinimide followed by hydrolysis of the intermediate (LVI) gave 3-formyl-opianic acid (LIII).

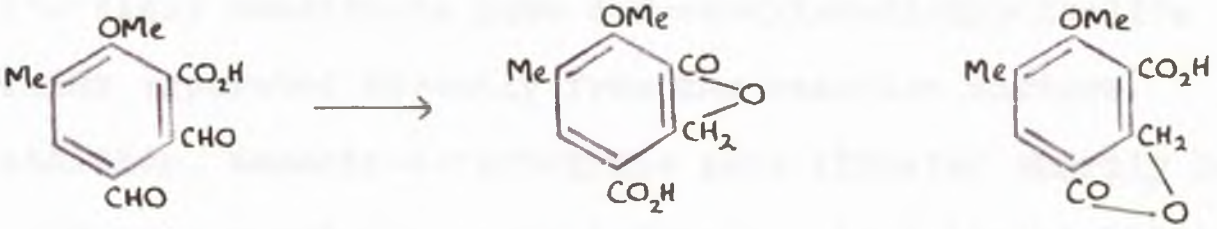


(LV) (XLIV)

(LVI) (LIII)

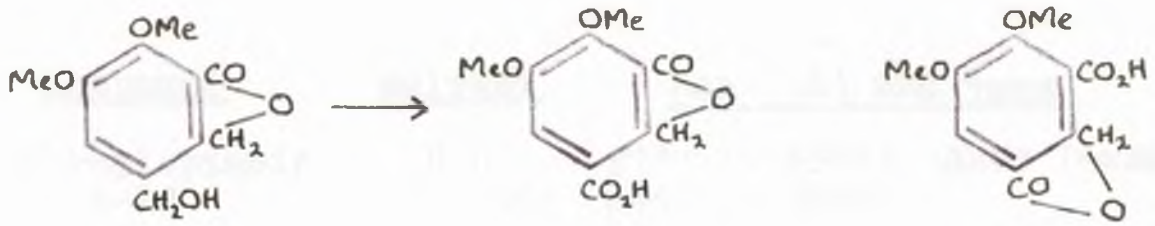
3-Formylopianic acid (LIII), on heating with aqueous sodium hydroxide, was converted into an isomeric monobasic acid which we regarded as meconin-4-carboxylic acid (LVII). Gladiolic acid (XXIV) on similar treatment gave isogladiolic acid (2,3) which was formulated by Grove as 7-methoxy-6-methylphthalide-4-carboxylic acid (XXXV) though he did not entirely discount the structure (LVIII) in which lactonization had proceeded in the alternative direction. (For mechanism see p.79).

(LIII) (LVII)



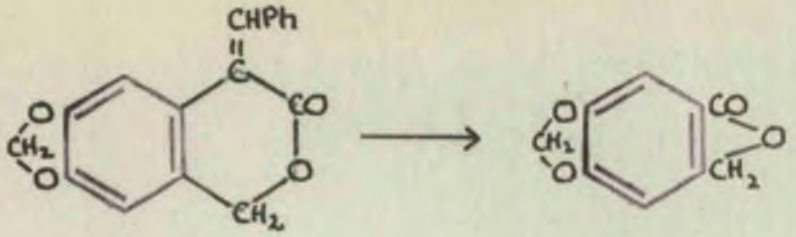
(XXIV) (XXXV) (LVIII)

Oxidation of 4-hydroxymethylmeconin (LIV) with neutral permanganate gave meconin-4-carboxylic acid (LVII), identical with the product of the alkaline rearrangement of 3-formylopianic acid, and it was thought that the formation of the alternative structure (LIX) was excluded because the alkalinity of the medium was insufficient to open the lactone ring in (LVII).



(LIV) (LVII) (LIX)

In support of this hypothesis was the observation of Stevens and Robertson (17) that the oxidation of α-(6--hydroxymethylpiperonyl)-cinnamolactone (LX) under identical conditions gave 5:6-methylenedioxyphthalide (L) which separated directly from the reaction mixture. In addition, meconin-4-carboxylic acid titrated sharply in the cold as a monobasic acid, indicating that the stability of the lactone ring had not been lessened by the proximity of the carboxyl group.

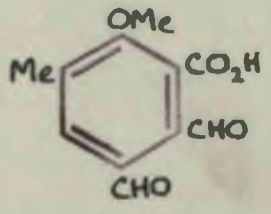


(LX) (L)

The ultra-violet absorption spectra of gladiolic acid and isogladiolic acid (3) are compared with those of 3-formylopianic acid and meconin-4-carboxylic acid in the table.

Compound	Solvent	Max. (A°) and ε max.
3-Formylopianic acid	H_2O	2730 (ε=4300), 3240 (ε=2800)
	0.1N NaOH	2340 (ε=2500)
Gladiolic acid	H_2O	2690 (ε=11,000), 3070 (ε=4500)
	0.1N NaOH	2750 (ε=3400), 343 (ε=6600)
Meconin-4-carboxylic acid	EtOH	2130 (ε=27,600), 3161 (ε=6000)
isoGladiolic acid	EtOH	2930 (ε=5350)

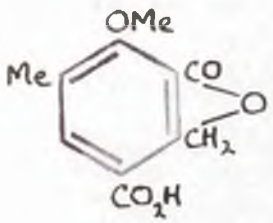
Thus the properties and reactions of 3-formylopianic acid discussed above supported the formulation of gladiolic acid by Raistrick and Ross (2) and Grove (3) as (XXIV).



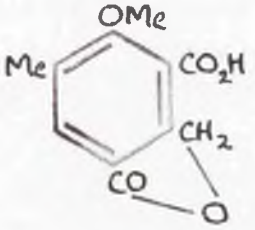
(XXIV)

The Synthesis of isoGladiolic Acid.

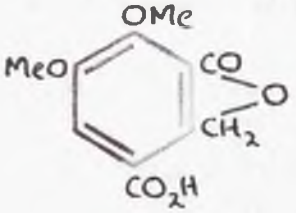
While Grove (3) formulated isogladiolic acid, the alkaline rearrangement product of gladiolic acid, as (XXXV), he considered that the structure (LVIII), in which lactonization had proceeded in the alternative direction, was a possibility. Although it had been shown (13) that the alkaline rearrangement product of 3-formylopianic acid was meconin-4-carboxylic acid (LVII) and thus, by analogy, isogladiolic acid was (XXXV), it was apparent that a synthesis of isogladiolic acid was necessary in order to decide between the possible structures (XXXV) and (LVIII).



(XXXV)

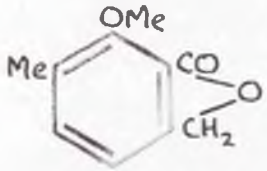


(LVIII)



(LVII)

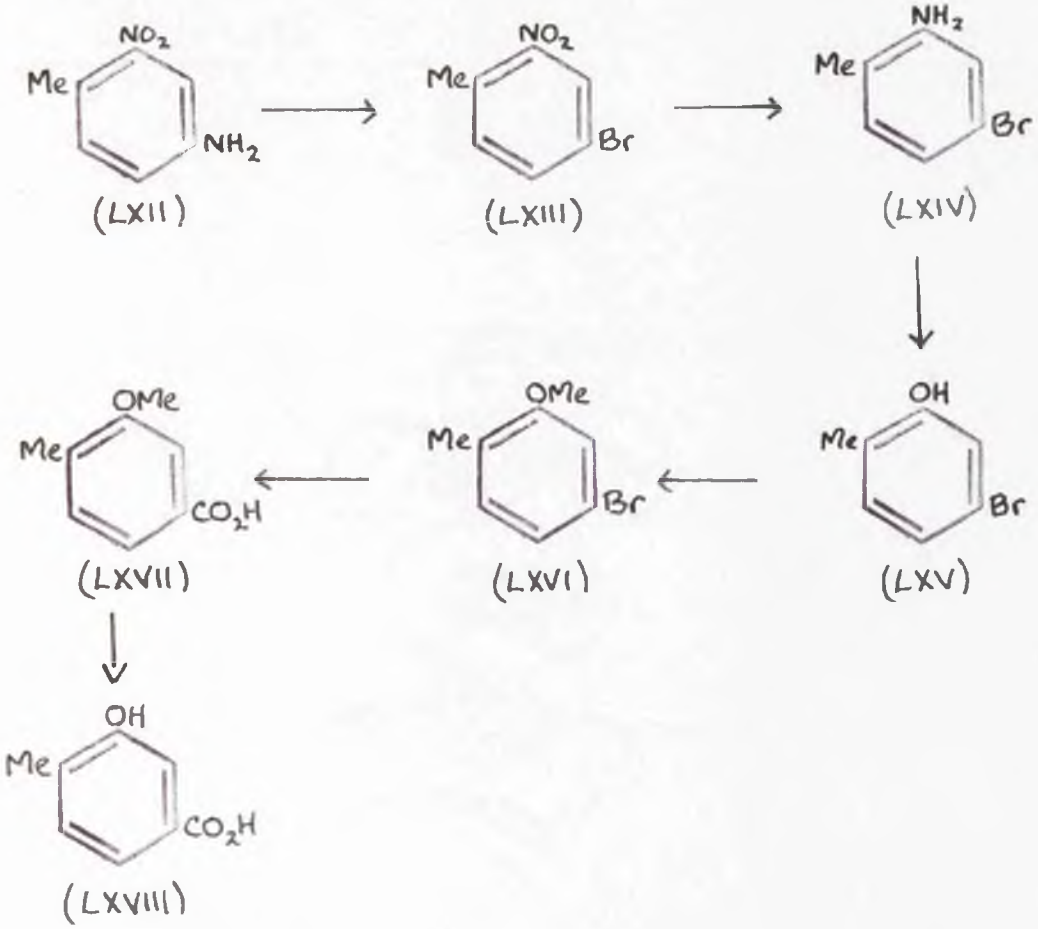
The synthetical route envisaged required the preparation of 7-methoxy-6-methylphthalide (LXI) as an intermediate.



(LXI)

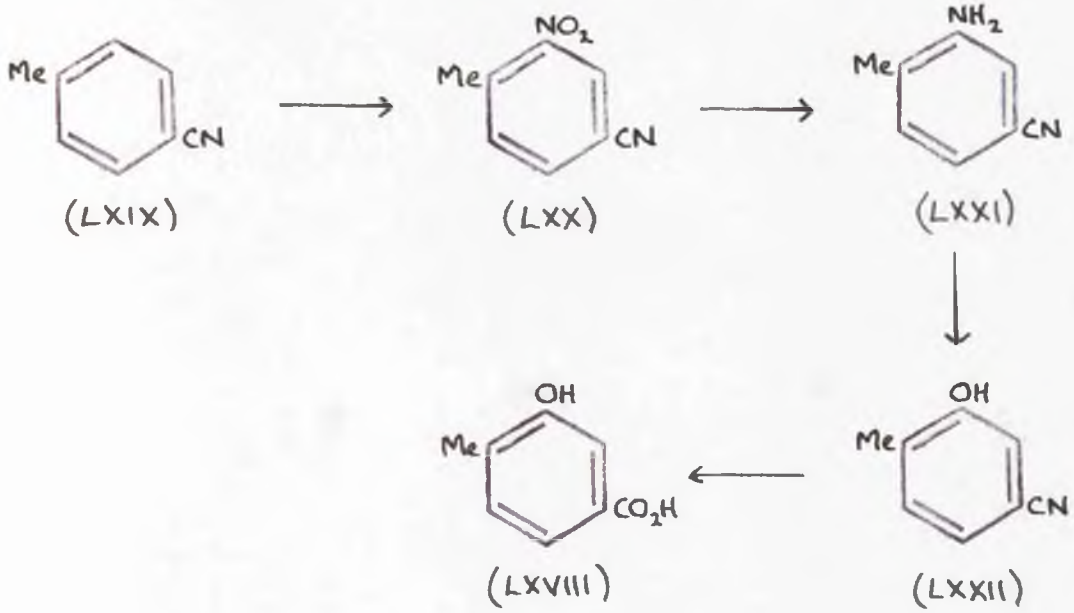
In an attempt to prepare this compound, 2-hydroxy--p-toluic acid (LXVIII) was prepared by four different routes.

In the first, 4-amino-2-nitrotoluene (LXII) was diazotised and converted into 4-bromo-2-nitrotoluene (LXIII) after Gibson and Johnson (19). Reduction of the nitrotoluene (LXIII) with sodium sulphide according to Hodgson and Moore (20) gave 2-amino-4-bromotroluene (LXIV), diazotisation of which yielded 4-bromo-o-cresol (LXV).

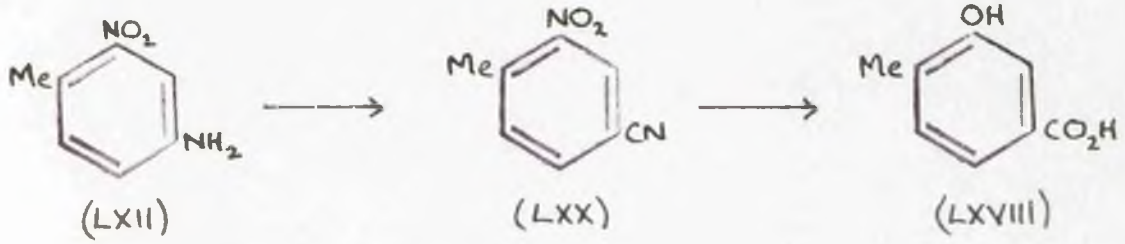


(LXV) was methylated to (LXVI) and 2-methoxy-p-toluic acid (LXVIII) was obtained from the latter compound by the Grignard method. Demethylation of (LXVII) using aluminium bromide in benzene gave 2-hydroxy-p-toluic acid (LXVIII).

Secondly, nitration of p-tolunitrile (LXIX) according to Pfeiffer (21) and reduction of the product, 2-nitro-p-tolunitrile (LXX), with stannous chloride in hydrochloric acid, gave 2-amino-p-tolunitrile (LXXI) from which 2-hydroxy-p-tolunitrile (LXXII) was obtained by the method of Borsche and Böcker (22). Alkaline hydrolysis of (LXXII) yielded the acid (LXVIII).

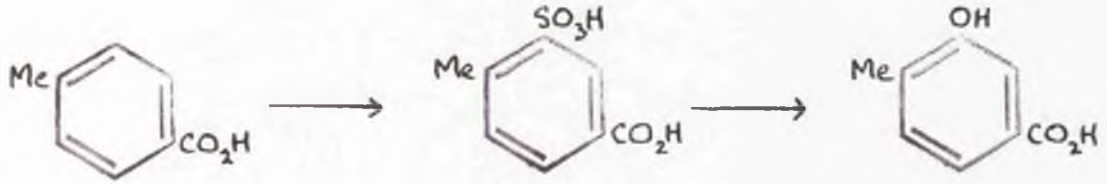


Thirdly, 4-amino-2-nitrotoluene (LXII) was diazotised and converted into 2-nitro-p-tolunitrile (LXX) by the method of Reich and Lenz (23), the synthesis of (LXVIII) being completed as above.



(LXII) (LXX) (LXVIII)

Fourthly, 2-sulpho-p-toluic acid (LXXIV) was prepared by sulphonation of p-toluic acid (LXXIII) and fused with alkali according to Meldrum and Perkin (24) to give 2-hydroxy-p-toluic acid (LXVIII).

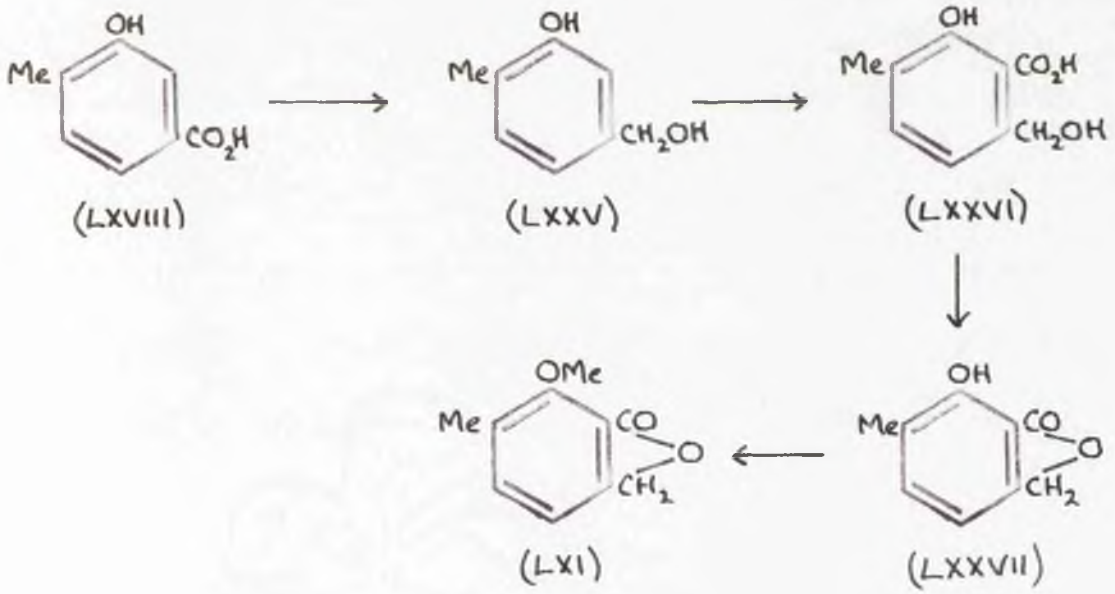


(LXXIII) (LXXIV) (LXVIII)

Of the four methods of preparation described above, that of Meldrum and Perkin (24) was most convenient.

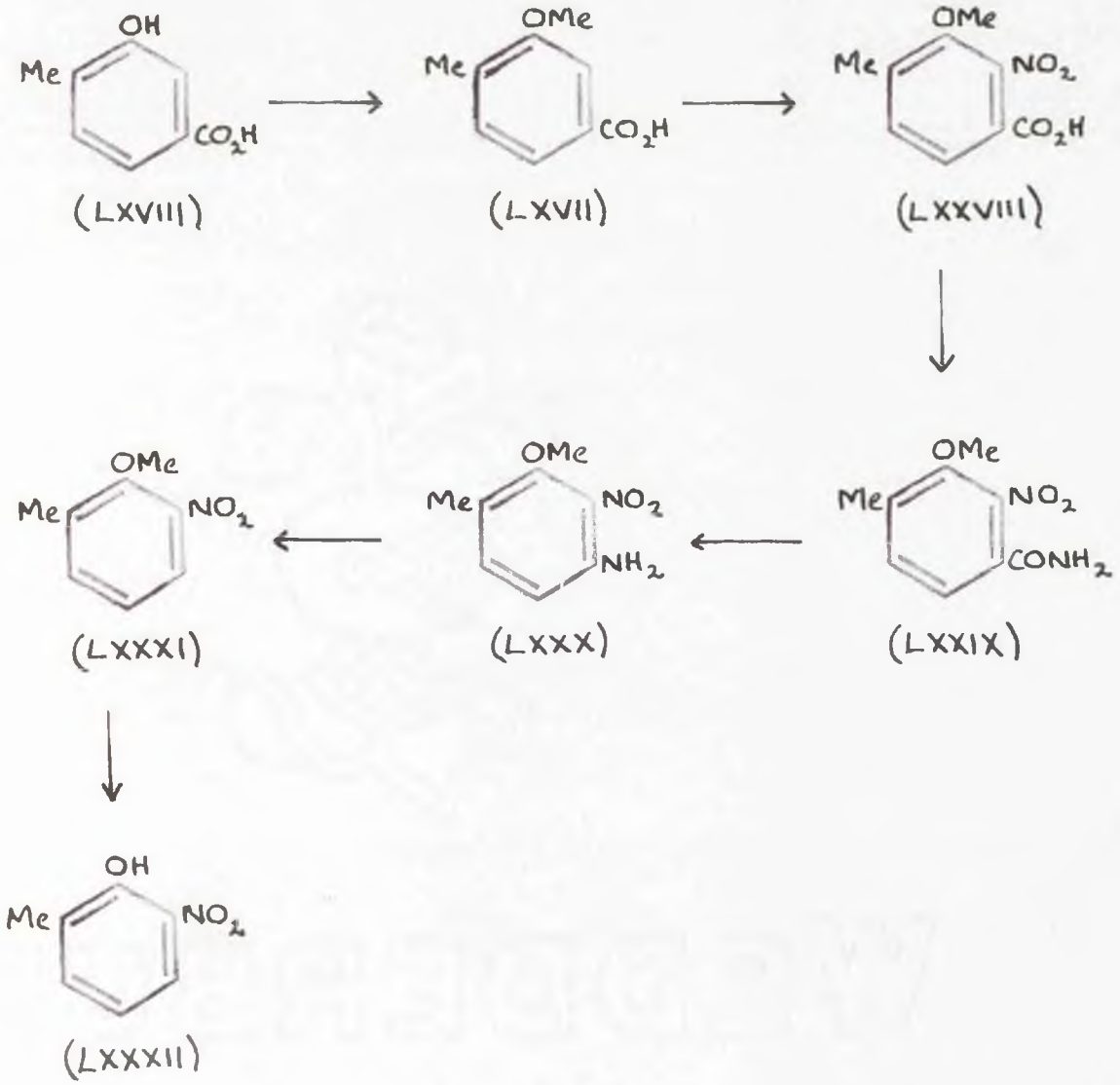
2-Hydroxy-p-toluic acid (LXVIII) was reduced by lithium aluminium hydride to 3-hydroxy-4-methylbenzyl

alcohol (LXXV); a number of variants of the Kolbe procedure were tried in order to carboxylate the latter compound to give the lactone of (LXXVI), 7-hydroxy-6--methylphthalide (LXXVII), methylation of which would have given the required phthalide (LXI), but all failed to give this product.

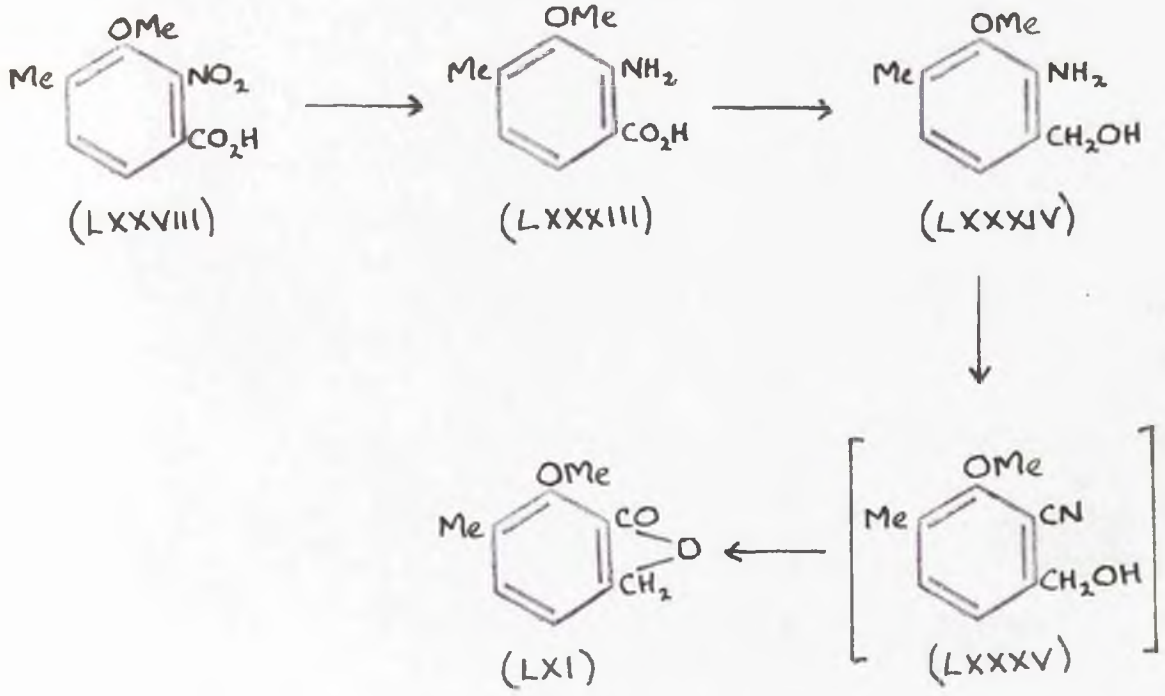


Attention was then turned to 2-methoxy-p-toluic acid (LXVII) as starting material. This compound was readily obtained by methylation (25) of 2-hydroxy-p-toluic acid (LXVIII). Simonsen and Rau (26) showed that nitration of (LXVII) gave 2-methoxy-3-nitro-p-toluic acid (LXXVIII),

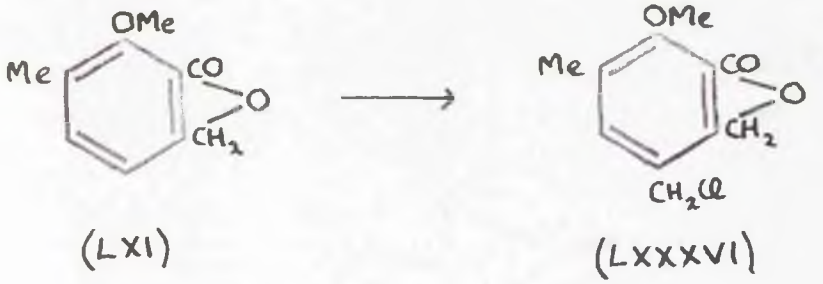
the orientation of the nitro-group being proved by forming the amide (LXXIX), subjecting it to the Hofmann procedure, and deaminating the resulting 2-methoxy-3-nitro-p-toluidine (LXXX) to give 2-methoxy-3-nitrotoluene (LXXXI) which on demethylation yielded 3-nitro-o-cresol (LXXXII).



The same authors reduced the nitro-acid (LXXVIII) to 3-amino-2-methoxy-p-toluic acid (LXXXIII) using ferrous sulphate and ammonia. We found sodium hydrosulphite (dithionite) a more satisfactory reagent for effecting this reaction. Reduction of the amino-acid (LXXXIII) with lithium aluminium hydride gave 2-amino-3--methoxy-4-methylbenzyl alcohol (LXXXIV) which was diazotised and treated with cuprous cyanide. The nitrile (LXXXV) was not isolated in the pure state; the crude product on alkaline hydrolysis gave 7-methoxy-6-methylphthalide (LXI).



Treatment of 7-methoxy-6-methylphthalide (LXI) with formaldehyde and hydrochloric acid gave a product which we formulated as 4-chloromethyl-7-methoxy-6-methyl-phthalide (LXXXVI), the position of the entering group being inferred by analogy with the chloromethylation (18) of meconin (XLV) which gave 4-chloromethylmeconin (XXXIX).

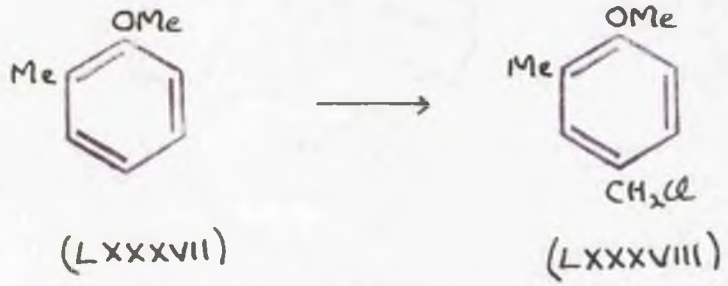


(LXI) (LXXXVI)

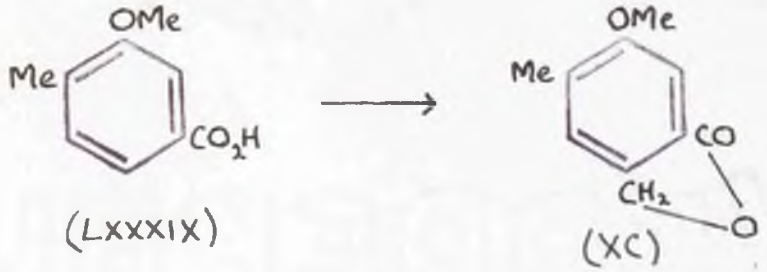
(XLV) (XXXIX)

In general, the chloromethyl group preferentially enters in the para-position to a methoxyl group if this is free and the methoxyl group exerts a much more powerful directive influence than the methyl group, e.g. the reaction of o-cresyl methyl ether (LXXXVII) to give

4-methoxy-3-methylbenzyl chloride (LXXXVIII) and the formation of 6-methoxy-5-methylphthalide (XC) from 2--methoxy-p-toluic acid (LXXXIX) carried out by Quelet and Anglade (27) and Charlesworth, Rennie, Sinder, and Yan (28) respectively.



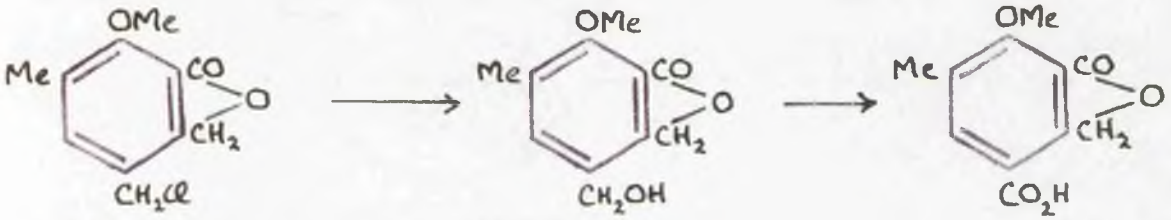
(LXXXVII) (LXXXVIII)



(LXXXIX) (XC)

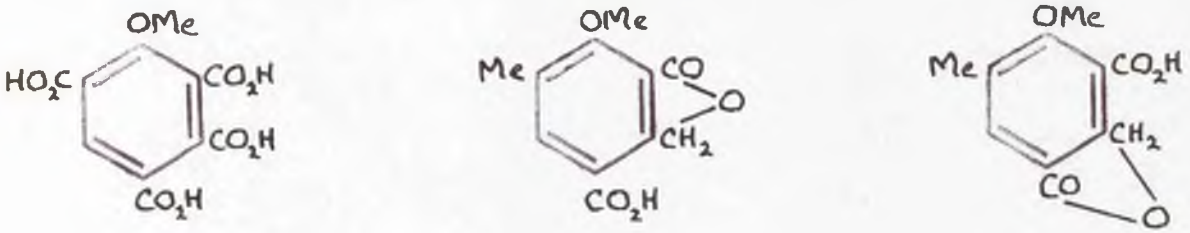
Hydrolysis of 4-chloromethyl-7-methoxy-6-methylphthalide (LXXXVI) by aqueous sodium carbonate gave 4--hydroxymethyl-7-methoxy-6-methylphthalide (XCI), and 7-methoxy-6-methylphthalide-4-carboxylic acid (XXXV), identical with isogladiolic acid, was obtained from (XCI) on oxidation with dilute, acid, potassium permanganate.

(We are indebted to Mr. J.F. Grove, Imperial Chemical Industries Ltd., Butterwick Research Laboratories, for the mixed m.p. determination and infra-red spectrum comparison of these preparations).



(LXXXVI) (XCI) (XXXV)

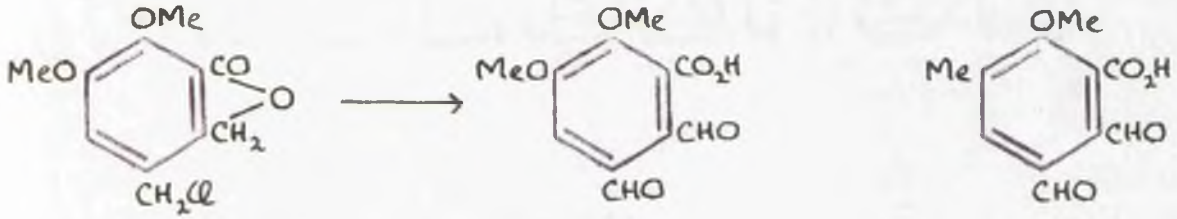
Grove (3) oxidised <u>isog</u>ladiolic acid to 4-methoxybenzene-1:2:3:5-tetracarboxylic acid (XXI) whose structure was proved by synthesis; it followed that the chloromethylation of 7-methoxy-6-methylphthalide took place in the 4-position. The structure of <u>isog</u>ladiolic acid was thus established as (XXXV) and the alternative structure (LVIII) eliminated.



(XXI) (XXXV) (LVIII)

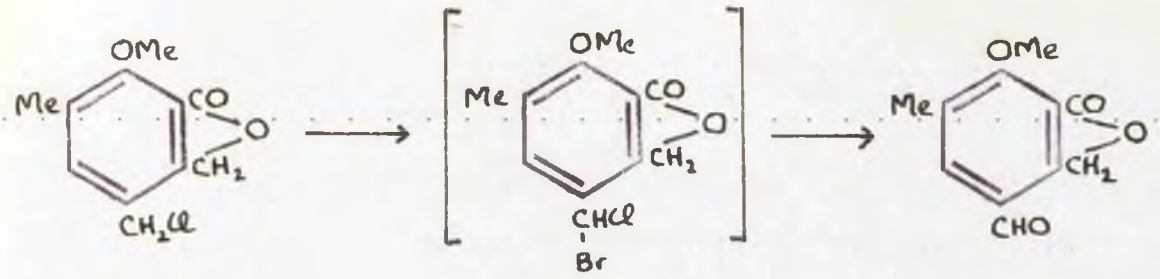
The Synthesis of Deoxygladiolic Acid.

We showed (13) that treatment of 4-chloromethyl-meconin (XXXIX) with three molecular proportions of N-bromosuccinimide gave 3-formylopianic acid (XXXVII), a compound similar in structure to gladiolic acid (XXIV).



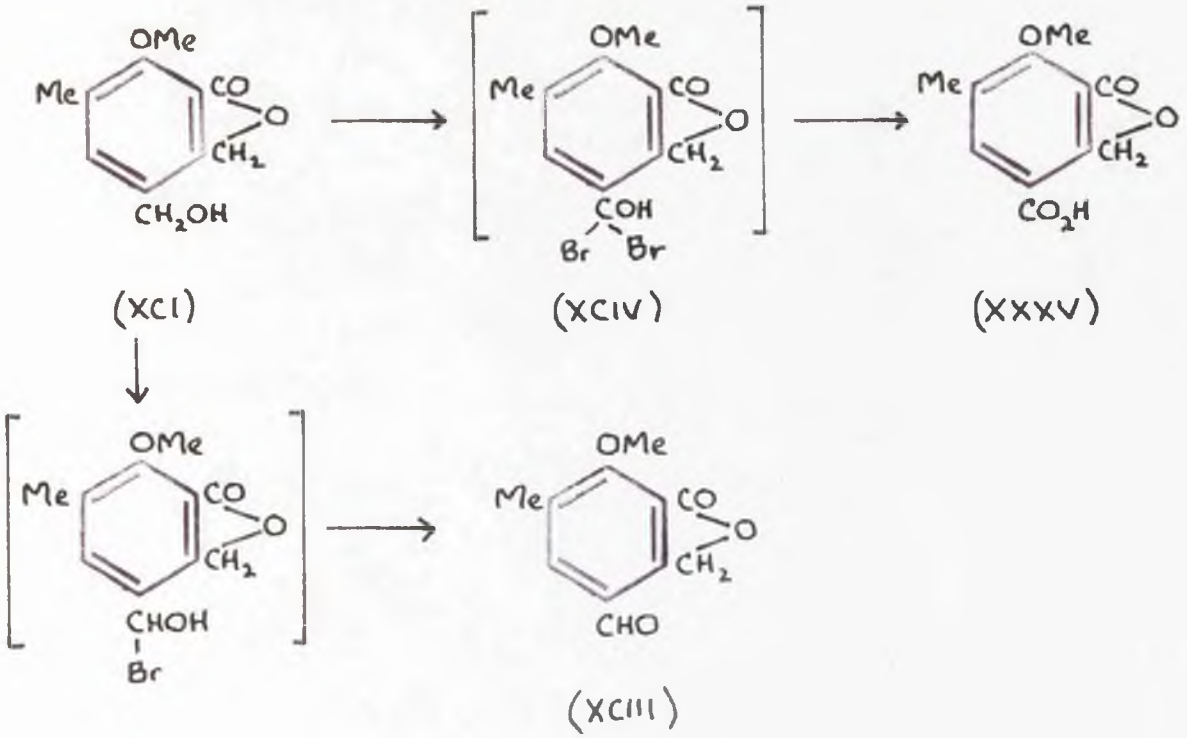
(XXXIX) (XXXVII) (XXIV)

By analogy, it was decided to attempt the synthesis of gladiolic acid by treating 4-chloromethyl-7-methoxy--6-methylphthalide (LXXXVI) with three molecular proportions of N-bromosuccinimide. Hydrolysis of the postulated intermediate bromo-compound (XCII), however, gave 4-formyl-7-methoxy-6-methylphthalide (XCIII), identical with deoxygladiolic acid obtained by Grove (3) by reduction of gladiolic acid with iron powder and acetic acid. From the crystallisation mother-liquor of the phthalide there was obtained a trace of crude material which gave a positive ammonia test - a sensitive reaction for gladiolic acid - but no modification of the reaction conditions gave an isolable quantity of this compound.



(LXXXVI) (XCII) (XCIII)

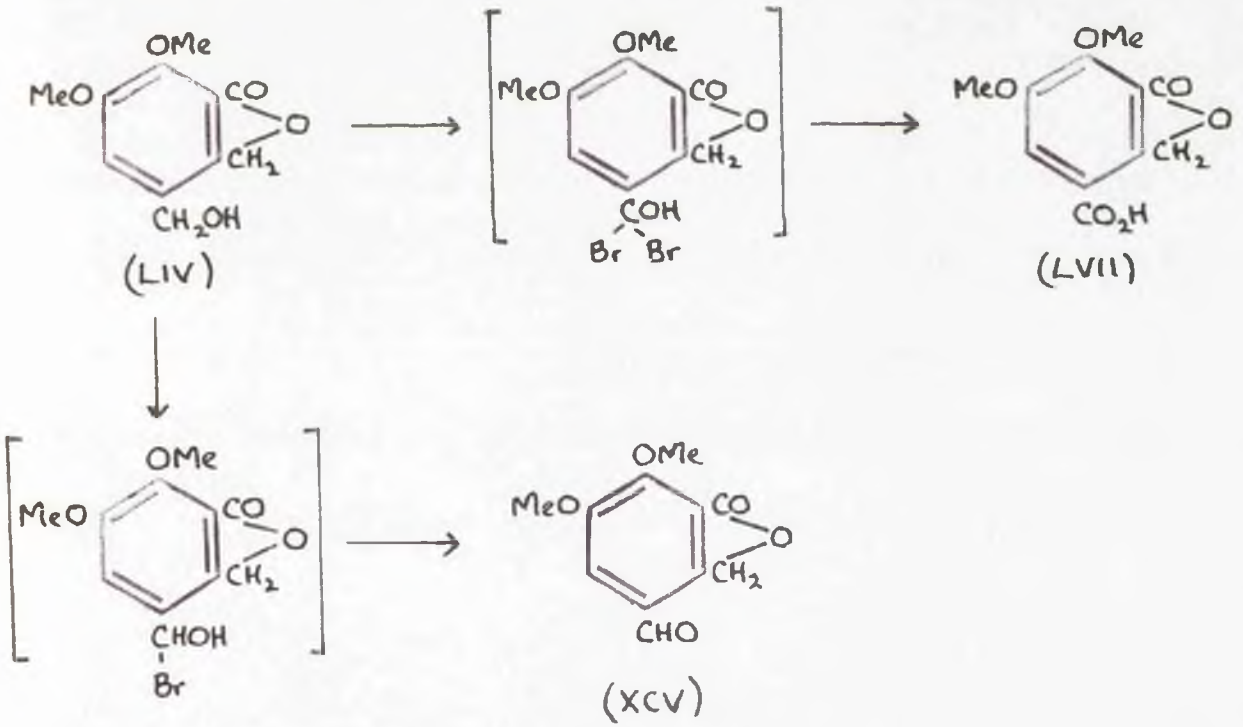
Reaction of 4-hydroxymethyl-7-methoxy-6-methyl-phthalide (XCI) with three molecular proportions of N--bromosuccinimide followed by hydrolysis of the postulated intermediate compound (XCIV) gave 7-methoxy-6-methyl-phthalide-4-carboxylic acid (XXXV); using one molecular proportion of reagent deoxygladiolic acid (XCIII) was obtained in good yield.



(XCI) (XCIV) (XXXV)

(XCIII)

In the dimethoxy-series, 4-hydroxymethylmeconin (LIV) gave 4-formylmeconin (XCV) with one molecular proportion of N-bromosuccinimide and meconin-4-carboxylic acid (LVII) with three molecular proportions. 4-Formylmeconin (XCV) was also obtained by chromic acid oxidation of 4-hydroxymethylmeconin (LIV).



4-Chloromethylmeconin gave 3-formylopianic acid in good yield on treatment with N-bromosuccinimide in contrast to the behaviour of 4-chloromethyl-7-methoxy-6--methylphthalide above. Clearly, the methylene-group in the phthalide ring in the latter compound was less reactive than that in 4-chloromethylmeconin. N-bromo-

succinimide is an electrophilic reagent and attack by it on the 3-methylene group would be facilitated by the presence of an electron releasing group para to it, i.e. in the 6-position. Since the methoxyl group is much more electron releasing than the methyl group, the lack of reactivity of the 3-methylene group in 4-chloromethyl--7-methoxy-6-methylphthalide followed.

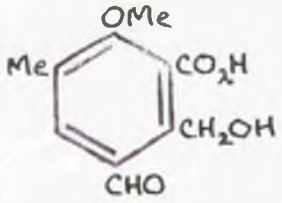
The formation of 4-formyl-7-methoxy-6-methylphthalide and not7-methoxy-6-methylphthalide-4-carboxylic acid by treatment of 4-chloromethyl-7-methoxy-6-methylphthalide with three molecular proportions of N-bromosuccinimide was probably due to steric effects in that the chloromethyl group could only accommodate one bromine atom because of the size of the chlorine atom and the close proximity of the phthalide ring. In the bromination of 4-hydroxymethyl-7-methoxy-6-methylphthalide and 4-hydroxymethylmeconin, the hydroxyl-group is very much smaller than the chlorine atom in the 4-chloromethyl group with the result that the 4-hydroxymethyl group could accommodate one or two bromine atoms giving on hydrolysis a formyl- or a carboxyl-group respectively.

The smaller yields in the bromination of 4-hydroxy-

methylmeconin were probably due to a certain amount of attack on the 3-methylene group.

The Synthesis of 3-Hydroxymethylopianic Acid.

A further problem in the chemistry of the antifungal metabolic products of Penicillium gladioli was the structure of dihydrogladiolic acid. Dihydrogladiolic acid had been formulated as (XCVI) by Raistrick and Ross (2).



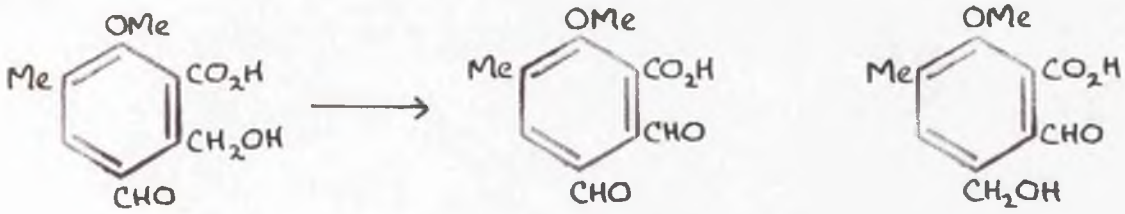
(XCVI)

This structure appeared unlikely in view of the known instability of o-hydroxymethyl benzoic acids which cyclise when their salts are acidified to give phthalides. Also, acetylation of dihydrogladiolic acid (XCVI) using acetic anhydride-pyridine gave a diacetate to which Raistrick and Ross gave the structure (XCVII).

(XCVI) (XCVII)

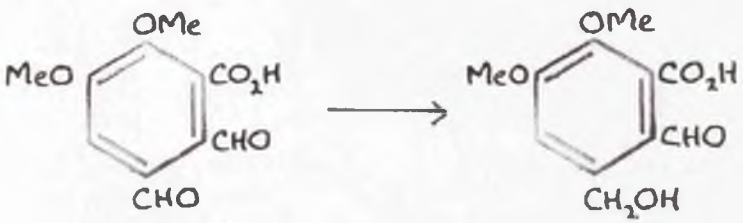
Under the acetylation conditions used, it seemed doubtful that the formyl group would form a diacetate, because, normally, more drastic conditions are required for this reaction.

Since Raistrick and Ross showed that periodate oxidation of dihydrogladiolic acid (XCVI) gave gladiolic acid (XXIV) in good yield, the only other possible structure for the former compound, which must have been gladiolic acid with one of the formyl groups reduced to hydroxymethyl, was (XCVIII).



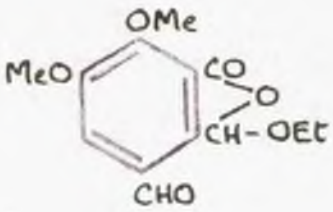
(XCVI) (XXIV) (XCVIII)

Gladiolic acid was not available in sufficient quantity, and we therefore decided to convert 3-formylopianic acid (XXXVII) into 3-hydroxymethylopianic acid (XCIX) and compare the properties of the latter with those of dihydrogladiolic acid.

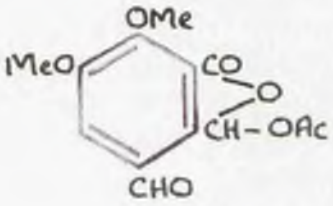


(XXXVII) (XCIX)

The starting materials envisaged were 3-ethoxy-4--formylmeconin (C) or 3-acetoxy-4-formylmeconin (CI); the latter compound was found to be more convenient to prepare in good yield.

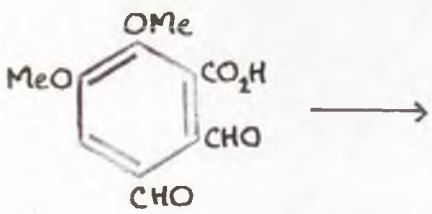


(C)

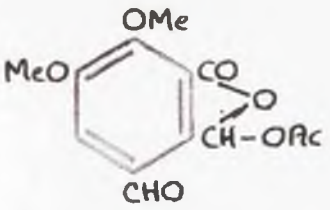


(CI)

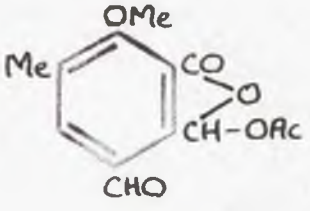
Treatment of 3-formylopianic acid (XXXVII) with acetic anhydride-acetic acid as described by Grove (3) for the formation of monoacetylgladiolic acid (CII) gave the analogous 3-acetoxy-4-formylmeconin (CI), a neutral compound readily hydrolysed to 3-formylopianic acid by boiling dilute sulphuric acid. This preparation required



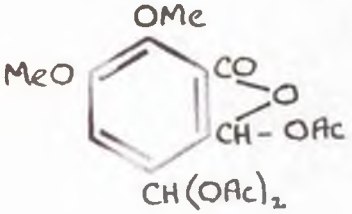
(XXXVII)



(CI)



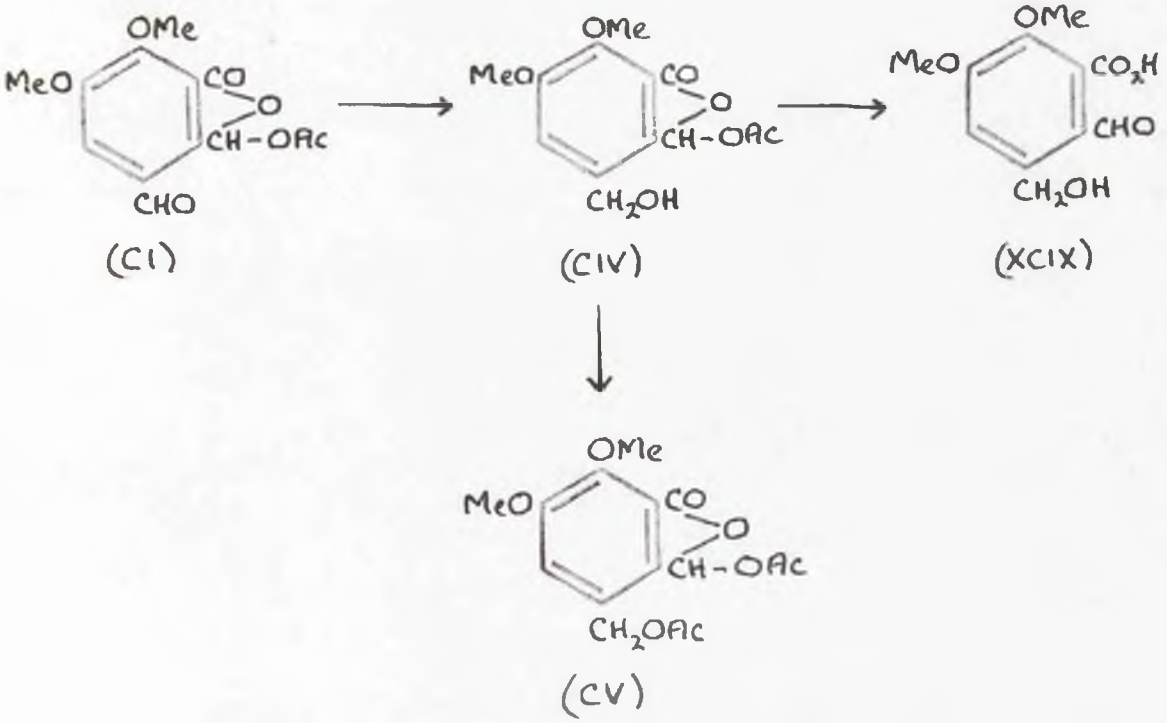
(CII)



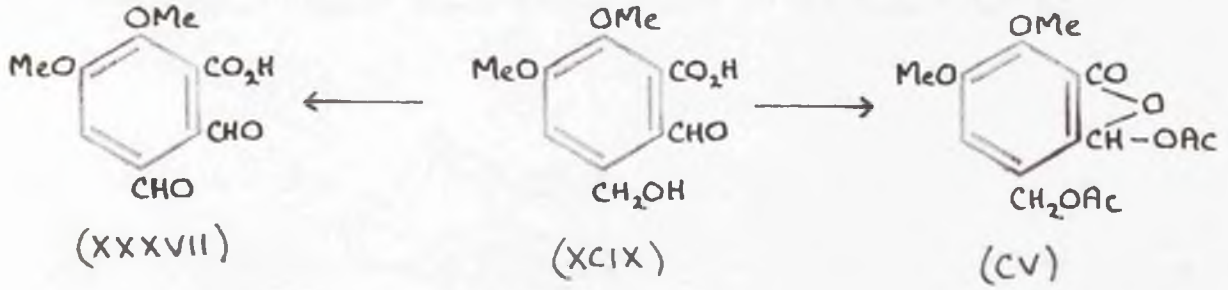
(CIII)

great care, since a trace of mineral acid was sufficient to cause the formation of a triacetate, 3-acetoxy-4--diacetoxymethylmeconin (CIII).

Catalytic hydrogenation of 3-acetoxy-4-formylmeconin (CI) in acetic acid using platinum as catalyst gave in excellent yield 3-acetoxy-4-hydroxymethylmeconin (CIV) which was characterised by the formation of its acetate, 3-acetoxy-4-acetoxymethylmeconin (CV). Hydrolysis of the monoacetate (CIV) with dilute alkali at room temperature gave on acidification 3-hydroxymethylopianic acid (XCIX).



In common with dihydrogladiolic acid, 3-hydroxymethylopianic acid dissolved in sodium hydrogen carbonate solution with effervescence, titrated sharply as a monocarboxylic acid with sodium hydroxide, formed a 2:4-dinitrophenylhydrazone, and did not reduce Schiff's reagent, Fehling's solution, nor ammoniacal silver nitrate. Oxidation of 3-hydroxymethylopianic acid (XCIX) with sodium metaperiodate in dilute sulphuric acid gave 3-formylopianic acid (XXXVII) in good yield. On acetylation the compound (XCIX) gave 3-acetoxy-4-acetoxymethylmeconin (CV).



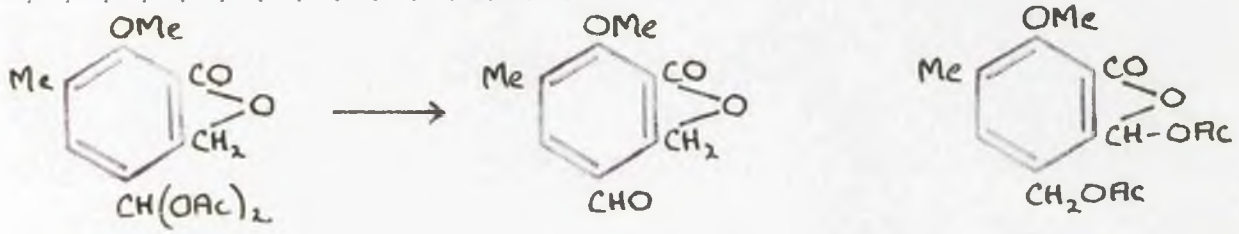
Raistrick and Ross (2) showed that sublimation of dihydrogladiolic acid (XCVI) gave 'dihydrogladiolide', deoxygladiolic acid (XCIII). Likewise, we found that 4-formylmeconin (XCV) was obtained, although in low yield, from 3-hydroxymethylopianic acid (XCIX) on sublimation.

(XCVI) (XCIII)

(XCIX) (XCV)

Raistrick and Ross also described the formation of deoxygladiolic acid from the acetylation product of dihydrogladiolic acid by reflux with mineral acid. This acetylation product described as 'dihydrogladiolide diacetate' (XCVII) must have had the structure (CVI) by analogy with the acetylation of 3-hydroxymethylopianic acid described above. Though 4-formylmeconin was obtained by heating 3-hydroxymethylopianic acid with mineral acid, the yield was very poor, much tar being formed in contrast to the conversion of the diacetate of Raistrick and Ross

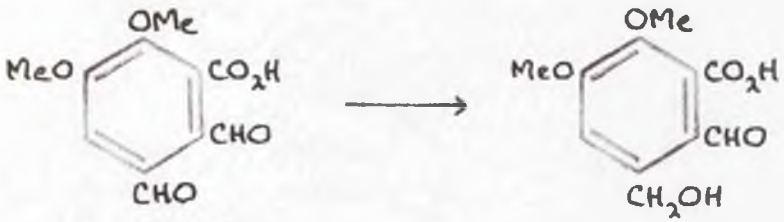
to deoxygladiolic acid (XCIII).



(XCVII) (XCIII) (CVI)

It is evident that a molecular rearrangement took place during the formation of deoxygladiolic acid from dihydrogladiolic acid and during the analogous change in the dimethoxy series.

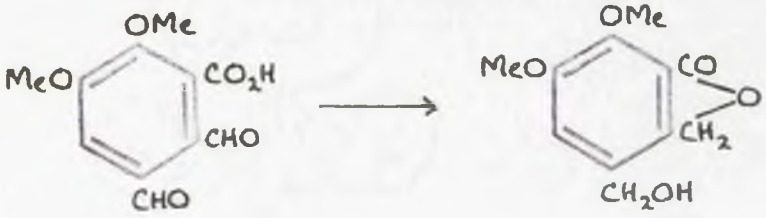
A further preparation of 3-hydroxymethylopianic acid (XCIX) was attempted by the action of sodium borohydride on 3-formylopianic acid (XXXVII). It was thought that only the more reactive formyl group, i.e. in the 3-position, would be reduced under the mild conditions used, to give the compound (XCIX).



(XXXVII) (XCIX)

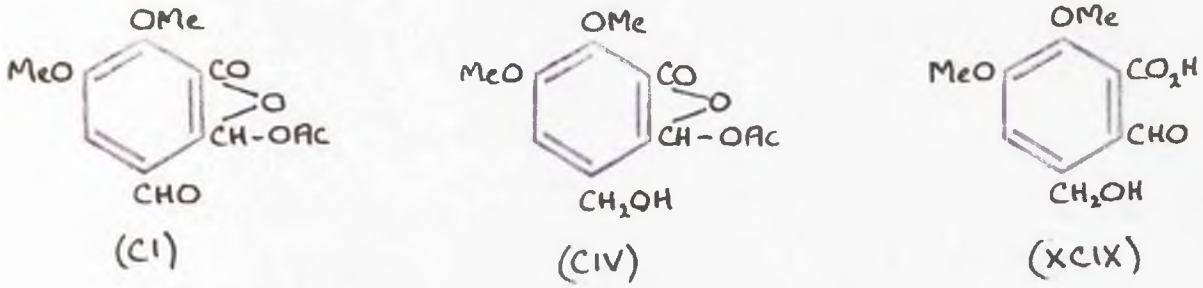
However, when 3-formylopianic acid (XXXVII) was dissolved in aqueous sodium hydrogen carbonate and treated

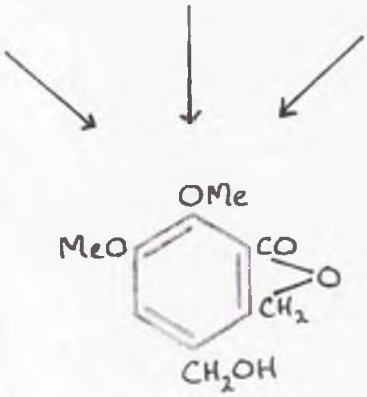
with the reagent at room temperature 4-hydroxymethyl-meconin (LIV) was obtained in good yield, both formyl groups in the acid (XXXVII) having been reduced.



(XXXVII) (LIV)

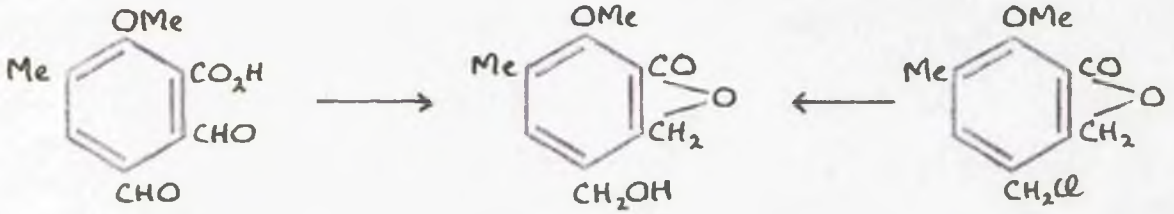
The same product (LIV) was also readily formed from 3-acetoxy-4-formylmeconin (CI), 3-acetoxy-4-hydroxymethyl-meconin (CIV), and 3-hydroxymethylopianic acid (XCIX).





(LIV)

Gladiolic acid (XXIV) on reduction with sodium borohydride gave 4-hydroxymethyl-7-methoxy-6-methylphthalide (XCI) identical with synthetic material (29) prepared by hydrolysis of 4-chloromethyl-7-methoxy-6-methylphthalide (LXXXVI).

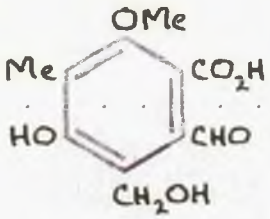


(XXIV) (XCI) (LXXXVI)

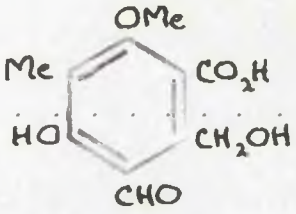
Thus reduction by sodium borohydride was found to be a simple method of preparing 4-hydroxymethylphthalides from the vicinal o-carboxyphthalaldehydes and derivatives.

From the reactions discussed above it was most likely that dihydrogladiolic acid had the structure (XCVIII) and not (XCVI) as proposed by Raistrick and Ross (2). By analogy, the closely related metabolic product of *Penicillium cyclopium*, cyclopolic acid, had probably the structure (CVII) and not (CVIII) as proposed by Birkinshaw, Raistrick, Ross, and Stickings (4).

(XCVIII) (XCVI)

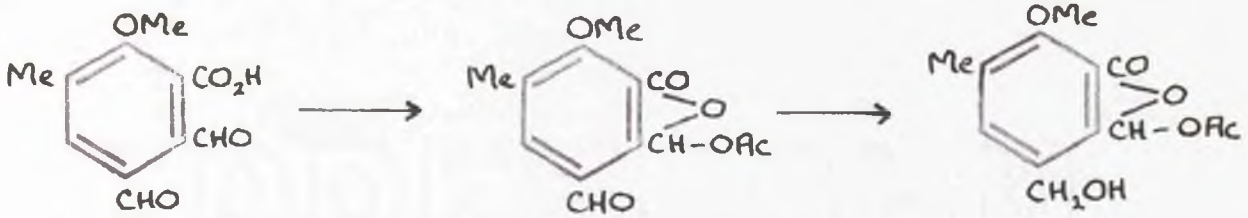


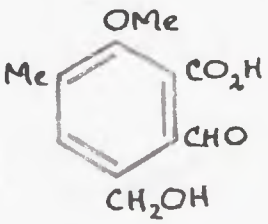
(CVII)



(CVIII)

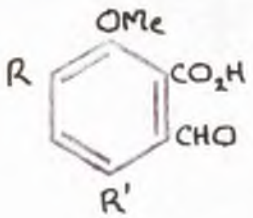
It was now decided to convert gladiolic acid into dihydrogladiolic acid by a similar scheme to that above for the preparation of 3-hydroxymethylopianic acid. On communicating with Mr. J. F. Grove, information was later received that he had already shown dihydrogladiolic acid to have the structure (XCVIII) by the scheme below and we agreed to simultaneous publication of our findings (30, 31).



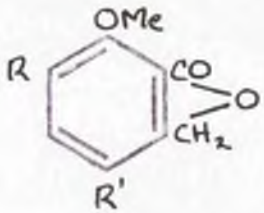


(XCVIII)

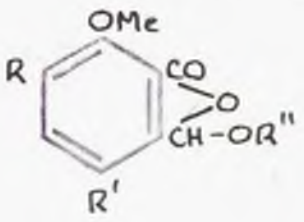
Since ultra-violet absorption data was available for a number of corresponding compounds in the dimethoxy- and methylmethoxy-series, a comparison has been made in the Table, the position of the maximum nearest the visible region being given for each compound. In each of the first twelve structures in the Table, replacement of the methyl substituent by methoxyl caused a bathochromic shift in the position of maximum absorption in ethanol solution of 16 ± 3 mu supporting the chemical evidence of structural similarity between compounds of the two series. The position of maximal absorption in ethanol for dihydrogladiolic acid, in contrast with that for 3-hydroxymethylopianic acid, was dependent on concentration (30), showing a large hypsochromic shift with dilution. Chloroform was a better solvent for the comparison of spectral absorption of the two compounds; values for 4-hydroxymethylmeconin and 4-hydroxymethyl-7-methoxy-6-methylphthalide in this solvent are included in the Table to indicate that the change of solvent caused no fundamental change in absorption maximum for normal compounds.



(I)



(II)



(III)

TABLE

(Solvent, ethanol unless otherwise indicated)

Compound	λ_{max}^{mu} (R=OMe)	λ_{max}^{mu} (R=Me)	mu
(I; R'=CHO)	320[a]	305[c]	15
(II; R'=H)	303[a]	295[b]	13
(II; R'=CH_2Cl)	315[a]	298[b]	17
(II; R'=CH_2OH)	312[a]	298[b]	14
	310[e] ($CHCl_3$)	299[e] ($CHCl_3$)	11
(II; R'=CH_2OAc)	314[d]	296[e]	18
(II; R'=CHO)	324[e]	306[c]	13
(II; R'=CO_2H)	318[a]	298[c]	18
(III; R'=CHO, R''=Et)	323[e]	305[c]	18
(III; R'=CHO, R''=Ac)	320[e]	306[c]	14
(III; R'=$CH(OAc)_2$, R''=Ac)	312[e]	297[c]	15
(III; R'=CH_2OH, R''=Ac)	314[e]	299[f]	15
(III; R'=CH_2OAc, R''=Ac)	312[3]	298[f]	14
(I; R'=CH_2OH)	310[e] (3.7×10^{-4}M)	296[f] (4.9×10^{-3}M)	14
	308[e] (3.4×10^{-5}M)	276[f] (2.2×10^{-4}M)	
	311[e] ($CHCl_3$)	299[g] ($CHCl_3$)	12

a Brown and Newbold, J., 1952, 4373.

b *Idem.*, J., 1953, 1285.

c Grove, J., 1952, 3345.

d This compound was prepared by Brown and Newbold, J.,1952,4873; for light absorption in ethanol see this thesis, p.126.

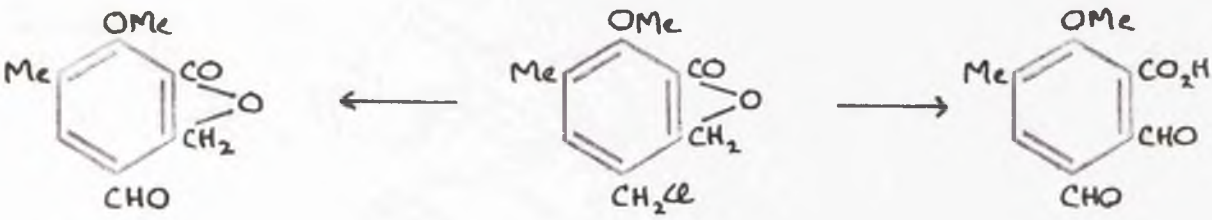
e Brown and Newbold, J.,1953,3648.

f Grove (private communication), λ_{max} values for (III; R=Me, R'=CH_2OH, R''=Ac), 2500; for (III; R=Me, R'=CH_2OAc, R''=Ac), 3000 and for (I; R=Me, R'=CH_2OH), 2050.

g Duncanson, Grove, and Zealley, J.,1953,3637.

The Synthesis of Gladiolic Acid.

Although previous work (2,3,18) had shown the structure of gladiolic acid to be (XXIV), this had still to be proved by synthesis. As shown in the previous section, an attempt to convert 4-chloromethyl-7-methoxy-6-methylphthalide (LXXXVI) into gladiolic acid (XXIV) using N-bromosuccinimide was unsuccessful, deoxygladiolic acid (XCIII) being formed with only a trace of gladiolic acid insufficient for isolation.

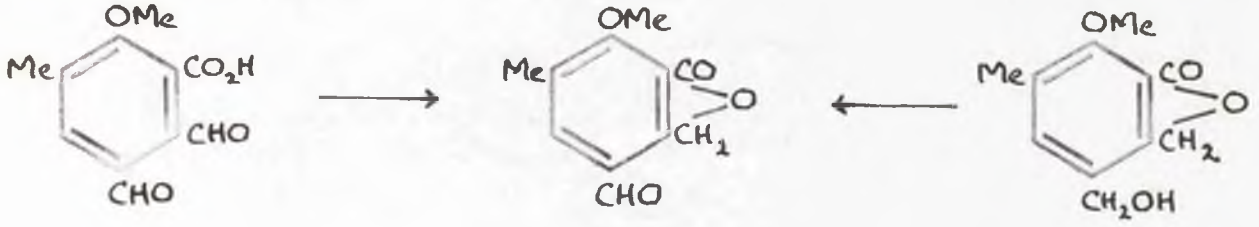


(XCIII) (LXXXVI) (XXIV)

Raistrick and Ross (2) showed that dihydrogladiolic acid (XCVIII), the structure of which was elucidated by Duncanson, Grove, and Zealley (30) and Brown and Newbold (31), was oxidised by periodate to gladiolic acid (XXIV) i.e. an o-phthalaldehyde was formed from an o-hydroxymethylbenzaldehyde.

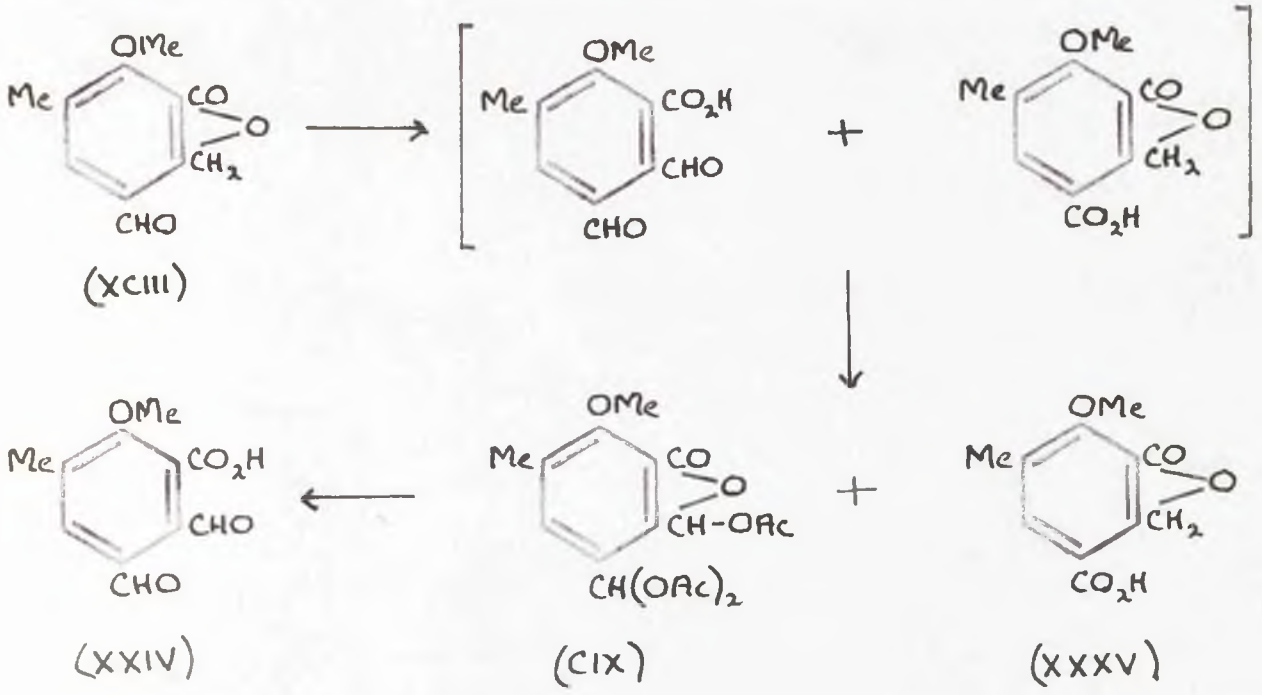
(XCVIII) (XXIV)

Since deoxygladiolic acid (XCIII), formed from gladiolic acid (XXIV) by reduction with iron powder in acetic acid (3) and by the action of N-bromosuccinimide (31) on 4-hydroxymethyl-7-methoxy-6-methylphthalide (XCI) followed by hydrolysis, had the related o-formylphthalide system, our attention was turned to periodate oxidation of this compound.



(XXIV) (XCIII) (XCI)

Prolonged oxidation of deoxygladiolic acid (XCIII) with sodium metaperiodate in boiling dilute sulphuric acid resulted in its partial conversion into gladiolic acid (XXIV) and isogladiolic acid (XXXV). Deoxygladiolic acid (73%) was recovered and the gladiolic acid was isolated by the formation of its hydrate triacetate (CIX) which was obtained in 10% yield on the deoxygladiolic acid converted. The gladiolic acid hydrate triacetate (CIX) was smoothly hydrolysed to gladiolic acid (XXIV) by heating with mineral acid. Both the latter and the triacetate (CIX) were indistinguishable from the natural material (supplied by Mr. J. F. Grove) and its derivative respectively. isoGladiolic acid was isolated in 40% yield on deoxygladiolic acid converted, from the acid fraction of the acetylation reaction mixture.



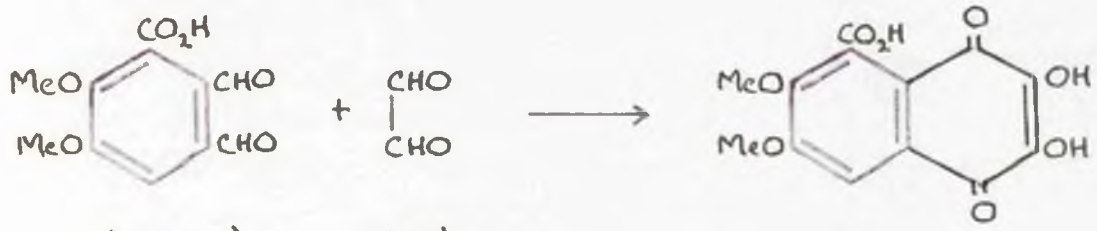
Duncanson, Grove, and Zealley (30) converted gladiolic acid (XXIV) into dihydrogladiolic acid (XCVIII) by the route shown on p.115. This synthesis of gladiolic acid was, therefore, a formal synthesis of dihydrogladiolic acid.

(XXIV) (XCVIII)

Oxidation of 4-formylmeconin (XCV) with periodate proceeded much more rapidly than that of deoxygladiolic acid; 71% of the material was recovered and 3-formylopianic acid (XXXVII) readily isolated in 40% yield on the 4-formylmeconin transformed. This further illustrated the greater reactivity of the phthalide methylene group towards an oxidising agent in the dimethoxy series than in the methylmethoxy series.

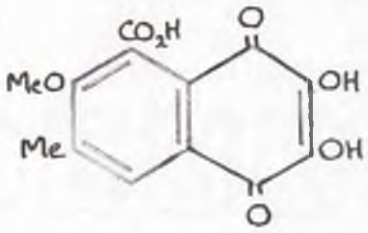
(XCV) (XXXVII)

Mr. J. Blair, B.Sc. (this laboratory) demonstrated (32) the presence of the o-phthalaldehyde system in 3--formylopianic acid (XXXVII) by reacting the latter compound with glyoxal (CX) in mildly alkaline solution in the presence of cyanide which gave 2:3-dihydroxy-6:7--dimethoxynaphtha-1:4-quinone-5-carboxylic acid (CXI).



(XXXVII) (CX) (CXI)

This reaction of o-phthalaldehydes to give iso-naphthazarin derivatives was developed by Weygand and his collaborators (33.34.35). The preparation of the corresponding isonaphthazarin derivative (CXII) from gladiolic acid was carried out independently by Weygand, Weber, and Crove (36).



(CXII)

EXPERIMENTAL

EXPERIMENTAL

All melting points are uncorrected.

Opianic Acid. - (cf. Wegscheider, Monatsh.,1382,3, 350). Manganese dioxide (30 g.; technical grade) was added rapidly, portionwise, to a solution of narcotine (40 g.) in boiling dilute sulphuric acid (600 c.c.water; 34 c.c. concentrated sulphuric acid) and when the vigorous reaction had subsided, the hot reaction mixture was filtered. On cooling, opianic acid separated which crystallised from water (charcoal) as needles (15 g.), m.p.143-146° (lit., m.p.145°). If precipitated manganese dioxide was used instead of technical grade quality, oxidation proceeded too vigorously and large amounts of tar were obtained with very low yields of opianic acid.

Meconin. - (a) No details are given by Matthiessen and Foster (J.,1863,16,342) for the preparation of this compound by sodium amalgam reduction of opianic acid. The following procedure was used: Opianic acid (65 g.) in 2N-sodium hydroxide (150 c.c.) was stirred for 3 hours with sodium amalgam (650 g.; 3½%) and left overnight. The aqueous phase was acidified (Congo red), and extracted

with chloroform (3 x 100 c.c.), and the combined extracts were washed with sodium hydrogen carbonate solution (2 x 100 c.c.; 10%), then with water (100 c.c.) and dried (Na_2SO_4). Removal of the chloroform and crystallisation from ethanol gave meconin (47 g.) as needles, m.p.101-103°. Light absorption in ethanol: Max. at 2130 (ε = 25,000) and 3080 Å (ε = 3300).

(b) (*cf.* Rodionov and Fedorova, *J.Gen.Chem.*, U.S.S.R., 1937, *7*, 947). To a suspension of opianic acid (23 g.) in a mixture of formaldehyde (33 c.c.; 40%) and water (50 c.c.) was added aqueous potassium hydroxide (45 c.c.; 50%). The reaction mixture was kept at room temperature for 10-12 hours, diluted with an equal volume of water, and acidified (Congo red) with hydrochloric acid (d, 1.16) when meconin (20 g.) separated as needles, m.p.101-102°.

4-Chloromethylmeconin. - (a) Meconin (12 g.) was heated under reflux for 45 minutes with hydrochloric acid (50 c.c.; d, 1.16) and formaldehyde solution (30 c.c.; 40%). The mixture was diluted with water (50 c.c.) and extracted with chloroform (3 x 50 c.c.). The combined chloroform extracts were washed with water (50 c.c.), sodium hydrogen carbonate solution (50 c.c.; 10%), and

water (50 c.c.) and dried (Na_2SO_4). Evaporation and crystallisation from ethanol gave 4-chloromethylmeconin (6.0 g.) as needles, m.p.104-106°, undepressed on mixing with a specimen prepared in (b) (Found: C,54.8; H,4.9. Calc. for $C_{11}H_{11}O_4Cl$: C,54.4; H,4.6%). Light absorption in ethanol: Max. at 2150 (ε = 23,000) and 3150 Å (ε = 4850).

(b) (*cf.* Manske and Ledingham, Can. J. of Research, 1944, 22, B, 115). *o*-Veratric acid was prepared according to Edwards, Perkin, and Stoyle, J., 1925, 127, 195. - 2:3-Dimethoxybenzaldehyde (5.0 g.) was heated under reflux with a solution of potassium hydrogen carbonate (6.0 g.) in water (50 c.c.) while a solution of potassium permanganate (4.0 g.) in hot water (50 c.c.) was added dropwise. The mixture was cooled, filtered, and acidified (Congo red) with hydrochloric acid (d, 1.16). *o*-Veratric acid (5.3 g.) separated as needles, m.p.119-122° (lit., m.p.120-122°).

o-Veratric acid (4.5 g.), hydrochloric acid (20 c.c.; d, 1.16) and formaldehyde (12 c.c.; 40%) were heated under reflux for 1 hour. The solution was decanted from tar, diluted with water (20 c.c.), and extracted with chloroform (3 x 25 c.c.). The combined chloroform

extracts were washed with water (20 c.c.), sodium hydrogen carbonate solution (2 x 20 c.c.; 10%), and water (20 c.c.). Evaporation of the dried (Na_2SO_4) extract and crystallisation from ethanol gave 4-chloromethylmeconin (500 mg.) as needles, m.p.104-106°.

4-Hydroxymethylmeconin. - 4-Chloromethylmeconin (1.0 g.) was heated under reflux with a solution of anhydrous sodium carbonate (1.0 g.) in water (10 c.c.) for 30 minutes. The solution was acidified (Congo red) and extracted with chloroform (3 x 15 c.c.), and the combined extracts were washed with water (15 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave 4-hydroxymethylmeconin which crystallised from benzene as needles (750 mg.), m.p.130-132° (Found: C,59.2; H,5.6. $C_{11}H_{12}O_5$ requires C,58.9; H,5.4%). The compound sublimes rapidly at 125°/10^{-3}mm. Light absorption in ethanol: Max. at 2140 (ϵ = 29,400) and 3120 Å (ϵ = 4550). 4-Hydroxymethylmeconin was quantitatively recovered after 2 hours in boiling 3N-sodium hydroxide. The acetate, prepared by using acetic anhydride-pyridine at room temperature overnight, separated from water as needles, m.p. 112-113° (Found: C,59.0; H,5.45. $C_{13}H_{14}O_6$ requires C,58.6;

H,5.3%). Light absorption in ethanol: Max. at 2130 (ϵ = 23,200), and 3140 Å (ϵ = 4300).

5:6-Dimethoxyphthalan-4-carboxylic Acid. - 4-Hydroxymethylmeconin (2.5 g.) in dry benzene (50 c.c.) was heated under reflux for 18 hours with aluminium tert.-butoxide (2.5 g.). The filtered mixture was extracted with 0.5N sodium hydroxide solution (3 x 30 c.c.), the combined extracts were acidified (Congo red), and the precipitate was extracted with chloroform (3 x 20 c.c.). After being washed with water (25 c.c.), the chloroform extract was evaporated and the solid residue crystallised from water, to give 5:6-dimethoxyphthalan-4-carboxylic acid (1.5 g.) as fine needles, m.p.143-150° (Found: C,59.2; H,5.5; C-Me,0.0%; equiv.,230. $C_{11}H_{12}O_5$ requires C,58.9; H,5.4; C-Me,6.7%; equiv.,224). Light absorption in ethanol: Max. at 2130 (ϵ = 21,000) and 3060 Å (ϵ = 3300). The compound dissolves in cold saturated sodium hydrogen carbonate solution with effervescence. It was unaffected when heated on the steam-bath with 15% aqueous sodium hydroxide but in boiling 5N-hydrochloric acid was converted in good yield into 4-hydroxymethylmeconin, m.p. and mixed m.p.130-131° (Found: C,58.3; H,5.7%). The

methyl ester, formed by ethereal diazomethane, separated from aqueous ethanol as needles, m.p.90°, which sublimed readily at 85°/10^{-3}mm. (Found: C,60.7; H,6.2. $C_{12}H_{14}O_5$ requires C,60.5; H,5.9%). Light absorption in ethanol: Max. at 2140 (ϵ = 23,000) and 3100 Å (ϵ = 4300).

4-Methylmeconin. - (a) Granulated zinc (5.0 g.) was shaken for 5 minutes with mercuric chloride (0.5 g.) in hydrochloric acid (0.25 c.c.; d,1.16) and water (5 c.c.), and the solution decanted off and rejected. Water (4 c.c.), hydrochloric acid (5 c.c.; d, 1.16), and 5:6--dimethoxyphthalan-4-carboxylic acid (130 mg.) were added and the mixture was heated under reflux for 5 hours. The solution was decanted from zinc and extracted with chloroform (3 x 20 c.c.). The combined chloroform extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residual 4-methylmeconin crystallised from aqueous ethanol as needles (150 mg.), m.p.125-127°, undepressed when mixed with a specimen prepared in (b) (Found: C,63.7; H,6.0; C-Me,7.1. Calc. for $C_{11}H_{12}O_4$: C,63.45; H,5.8; C-Me,7.2%). Light absorption in ethanol: Max. at 2140 (ϵ = 18,900) and 3100 Å (ϵ = 3300).

(b) (cf. Manske and Ledingham, Can.J.of Research,1944, 22,B,115). 4-Chloromethylmeconin (2.0 g.) was heated

under reflux with zinc dust (2.0 g.), ethanol (35 c.c.), and hydrochloric acid (3.5 c.c.; d, 1.16) for 16 hours. The filtered solution was reduced in bulk to 10 c.c. under reduced pressure, diluted with water (25 c.c.), and extracted with chloroform (3 x 25 c.c.). The combined chloroform extracts were dried (Na_2SO_4) and removal of solvent and crystallisation of the residue from aqueous ethanol gave 4-methylmeconin (1.3 g.) as needles, m.p.125--127° (lit., m.p.127°).

3-Formylopianic Acid. - (a) A solution of 4-chloromethylmeconin (2.0 g.) in carbon tetrachloride (100 c.c.) was heated under reflux with N-bromosuccinimide (4.4 g.) for 1 hour with irradiation from a 60-watt lamp placed close to the flask. Succinimide was filtered off, solvent removed under reduced pressure, and the residual oil heated with water (250 c.c.) on the steam-bath for 1 hour with stirring. After keeping overnight at room temperature, the solid (1.3 g.; m.p.163-165°) which separated was collected and crystallised twice from water (charcoal) to give 3-formylopianic acid as needles, m.p.176° (Found: C,55.2; H,4.5%; equiv.,236. $C_{11}H_{10}O_6$ requires C,55.5; H,4.2%; equiv.,238). Light absorption

in ethanol: Max. at 2120 (ϵ =18,300), 2730 (ϵ = 4200), and 3200 Å (ϵ = 3300).

(b) To a solution of 5:6-dimethoxyphthalan-4-carboxylic acid (2.0 g.) in benzene (150 c.c.) and carbon tetrachloride (150 c.c.) was added N-bromosuccinimide (3.18 g.; 2 mols.) and the mixture heated under reflux with irradiation as above for 10 minutes. The reaction mixture was then treated as in (a) to give 3-formylopianic acid (1.0 g.) as needles, m.p.175-176° from water (charcoal) (Found: C,55.6; H,4.3%). It was undepressed in m.p. on mixing with preparation (a). The compound dissolves in cold saturated aqueous sodium hydrogen carbonate with effervescence and gives a green-brown colour with aqueous ammonia (d, 0.88). It does not reduce Fehling's solution nor Schiff's reagent but reduces ammoniacal silver nitrate on heating; it gives a greenish-yellow solution in cold or warm sulphuric acid (d, 1.84) and a solution in technical benzene (but not pure benzene) gives a red colour at the interface with sulphuric acid (d, 1.84). 3-Formylopianic acid is soluble in ethanol but sparingly so in ether, chloroform, or benzene. The 2:4-dinitrophenylhydrazone separated from ethylene glycol monomethyl ether as orange needles, m.p.254-255° (decomp.) (Found: N,12.9.

$C_{17}H_{14}O_9N_4$ requires N,13.4%).

Meconin-4-carboxylic Acid. - (a) 3-Formylopianic acid (500 mg.) in 3N-sodium hydroxide solution (25 c.c.) was refluxed for 30 minutes. The solution was acidified (Congo red) with hydrochloric acid (d, 1.16) and the precipitate crystallised from aqueous ethanol to give meconin-4-carboxylic acid as needles, m.p. 219-221° (Found: C,55.7; H,4.4%; equiv.,232. $C_{11}H_{10}O_6$ requires C,55.5; H,4.2%; equiv.,238). The compound dissolved in cold saturated aqueous sodium hydrogen carbonate solution with effervescence.

(b) A solution of 4-hydroxymethylmeconin (500 mg.) in acetone (20 c.c.) at 60° was treated during 5 minutes, with shaking, with potassium permanganate (1.0 g.) and magnesium sulphate (1.0 g.) in water (20 c.c.), added in portions. The solution was rapidly heated to boiling and filtered. The filtrate was cleared using sulphur dioxide, concentrated, and extracted with chloroform (3 x 25 c.c.). The combined chloroform extracts were washed with saturated sodium hydrogen carbonate solution (3 x 20 c.c.) and the combined washings acidified (Congo red) with hydrochloric acid (d, 1.16) and the product was

isolated *via* chloroform to give meconin-4-carboxylic acid (250 mg.) which separated from aqueous ethanol as needles, m.p.220-222° alone or mixed with preparation (a) (Found: C,55.6; H,4.3%). Light absorption in ethanol: Max. at 2130 (ϵ = 27,600) and 3160 Å (ϵ = 6000).

4-*Bromo*-2-*nitroluene.* - (*cf.* Gibson and Johnson, *J.*,1929,1229). A suspension of finely divided 4-amino--2-nitrotoluene (50 g.) in hydrobromic acid (35 c.c.; d, 1.46-1.49) and water (110 c.c.) was diazotised at 0-5° with a solution of sodium nitrite (23.5 g.) in water (40 c.c.). The diazonium solution was run fairly rapidly with constant stirring and without external cooling into a solution of cuprous bromide in hydrobromic acid (130 c.c.; d, 1.46-1.49). [Cuprous bromide was prepared by passing sulphur dioxide through a solution of copper sulphate (60 g.) and potassium bromide (30 g.) in water (270 c.c.). The cuprous bromide which precipitated was washed with water by decantation.] After the vigorous reaction had subsided, the mixture was heated on the steam-bath for 30 minutes and then steam-distilled. The distillate (10 litres) was extracted with ether; the extract was washed with N-sodium hydroxide solution, water, and dried (Na_2SO_4).

Removal of solvent gave 4-bromo-2-nitrotoluene (39 g.) as a yellow oil which quickly solidified on standing, m.p.43-46° (lit., m.p.47°).

4-Bromo-o-cresol. - (cf. Hodgson and Moore, J.,1926, 2036). 4-Bromo-2-nitrotoluene (72 g.) was heated under reflux for 3 hours with a solution of sodium sulphide (216 g.) in water (200 c.c.). The mixture was steam--distilled, sulphuric acid (100 c.c.; d,1.84) was added to the distillate (3 litres) and 2-amino-4-bromotoluene sulphate (77 g.) separated.

The sulphate (40 g.) suspended in sulphuric acid (16 c.c.; d,1.84) and water (200 c.c.) was diazotised at 0-5° with a solution of sodium nitrite (10 g.) in water (20 c.c.). The diazonium solution was added to sulphuric acid (20 c.c.; d,1.84) and water (200 c.c.); the mixture was heated on the steam-bath for 1 hour and then steam--distilled. The distillate (4 litres) was extracted with ether and the dried (Na_2SO_4) extract was evaporated to give 4-bromo-o-cresol (10 g.) as a colourless oil which soon solidified, m.p.74-76° (lit., m.p.78°).

4-Bromo-2-methoxytoluene. - A solution of 4-bromo-o--cresol (6.0 g.) in sodium hydroxide solution (30 c.c.;

10%) at room temperature was treated with dimethyl sulphate (7 c.c.), stirred for 30 minutes and then slowly heated to 100° and maintained there for 30 minutes. The reaction mixture was steam-distilled until 300 c.c. of distillate had been collected. The distillate was extracted with ether (3 x 50 c.c.) and the combined ether extracts were dried (Na_2SO_4). Removal of solvent gave 4-bromo-2-methoxytoluene (52. g.; 80%) as a colourless oil, b.p.108°/15 mm., n_D^{16} 1.5632 (Found: C,43.0; H,4.7. C_8H_9OBr requires C,47.8; H,4.5%). Light absorption in ethanol: Max. at 2100 (ϵ = 13,700), 2220 (ϵ = 9000) and 2760 Å (ϵ = 13,700).

2-Methoxy-p-toluic Acid. 4-Bromo-2-methoxytoluene (10 g.) was added with a crystal of iodine to magnesium turnings (5.0 g.) covered with dry ether (50 c.c.) and the mixture stirred while heating under gentle reflux. A further 26 g. of the bromo-compound in dry ether (100 c.c.) was added dropwise over 2 hours; reflux and stirring were continued for a further 2 hours when most of the magnesium had dissolved. The reaction mixture was cooled to -10° with stirring and a stream of dry carbon dioxide gas directed on the surface at such a rate as to keep the

temperature below -2°. When the temperature dropped again, an excess of sulphuric acid (25%) was added with cooling, the ethereal layer separated and the aqueous phase extracted with ether (3 x 50 c.c.). The combined ethereal extracts were washed with sodium hydroxide solution (3 x 50 c.c.; 25%), the alkaline extract washed with ether (3 x 25 c.c.), boiled, cooled, and acidified (Congo red) with sulphuric acid (50%). The crude acid which separated was crystallised from aqueous acetic acid (30%) to give 2-methoxy-p-toluic acid as needles (57%), m.p.165-166°, undepressed by a specimen, m.p.166°, prepared below by methylation of 2-hydroxy-p-toluic acid (Found: C,65.0; H,6.1. Calc. for $C_9H_{10}O_3$: C,65.05; H,6.1%). Light absorption in ethanol: Max. at 2120 (ϵ = 55,000), 2450 (ϵ = 20,400) and 2920 Å (ϵ = 3000).

2-Nitro-p-tolunitrile. - (a) (cf. Pfeiffer, Ber., 1918,51,554). A solution of p-tolunitrile (25 g.) in sulphuric acid (100 c.c.; d,1.84) was stirred during the gradual addition of nitric acid (35 c.c.; d,1.42), the temperature being kept below 30°. When the addition was complete, the mixture was allowed to stand for $\frac{3}{4}$ hour, poured onto ice, and the white precipitate which separated

was washed with water and crystallised from ethanol to give 2-nitro-*p*-tolunitrile (20 g.) as needles, m.p.105--106° (lit., m.p.107°).

(b) (*cf.* Reich and Lenz, *Helv.Chim.Acta*,1920,3,144). A solution of 4-amino-2-nitrotoluene (45 g.) in hydrochloric acid (73 c.c.; d,1.16) and water (220 c.c.) was diazotised at 0-5° with a solution of sodium nitrite (23.5 g.) in water (50 c.c.). Cuprous cyanide solution was prepared by passing sulphur dioxide through a solution of copper sulphate (96 g.) and sodium chloride (30 g.) in water (400 c.c.). The precipitated cuprous chloride was washed by decantation, suspended in water (200 c.c.) and sodium cyanide (50 g.) was added when solution took place with evolution of heat. The diazonium solution was added in small quantities to the cuprous cyanide solution and the mixture was heated on the steam-bath for 45 minutes. 2-Nitro-*p*-tolunitrile (25 g.) separated as a chocolate-brown precipitate which was used in the next stage without further purification.

2-*Amino*-*p*-*tolunitrile*. - 2-Nitro-*p*-tolunitrile (50g.) was added in portions with stirring to a solution of stannous chloride (250 g.) in hydrochloric acid (500 c.c.;

d, 1.16), initially at 60°, keeping the temperature below 70°. The reaction mixture was made strongly alkaline with sodium hydroxide solution (20%) keeping the temperature below 40° and extracted with ether (4 x 500 c.c.). The combined ethereal extracts were washed with water (3 x 250 c.c.) and dried (Na_2SO_4); removal of the ether gave 2-amino-p-tolunitrile (37 g., 91%) m.p.77-78°, which was used directly in the next stage, [cf. reduction of 2-nitro-p-tolunitrile with tin and hydrochloric acid (Borsche and Böcker, Ber.,1903,36,4357) who claim a 50% yield].

2-Hydroxy-p-tolunitrile. - (cf. Borsche and Böcker, loc.cit.). Finely divided 2-amino-p-tolunitrile (55 g.) was dissolved in sulphuric acid (1100 c.c.; 10%) and diazotised at 0-5° with a solution of sodium nitrite (41.3 g.) in water (50 c.c.). The filtered diazonium solution was heated on the steam-bath until effervescence ceased. The hot solution was decanted from tar and on cooling, 2-hydroxy-p-tolunitrile (40 g.)separated as light yellow needles, m.p.93-96° (lit., m.p.99.5°).

2-Sulpho-p-toluic Acid. - (cf. Meldrum and Perkin, J.,1903,1416). p-Toluic acid (63 g.) was heated to 150°

for 8 hours with sulphuric acid (170 c.c.; 100%). The mixture was cooled, added cautiously to water (220 c.c.), and on cooling, crude 2-sulpho-p-toluic acid (75 g.) separated which was used for the next stage.

2-Hydroxy-p-toluic Acid. - (a) Anhydrous aluminium bromide (10 g.) in warm dry benzene (60 c.c.) was added to a solution of 2-methoxy-p-toluic acid (2.0 g.) in dry benzene (70 c.c.) and the solution refluxed for 4½ hours. Hydrochloric acid (100 c.c.; d, 1.16) was added to the cooled solution and the mixture was extracted with ether (3 x 50 c.c.). The combined ethereal extracts were washed with sodium hydroxide solution (3 x 30 c.c.; 15%) and the alkaline extract was washed with ether (2 x 25 c.c.) and acidified (Congo red) with hydrochloric acid (d, 1.16). The solution was extracted with ether (3 x 30 c.c.); the combined ethereal extracts were washed with water (2 x 20 c.c.), dried (Na_2SO_4), and removal of solvent gave 2-hydroxy-p-toluic acid which crystallised from water (charcoal) as needles (1.4 g.), m.p.207-208° undepressed by an authentic specimen prepared below (Found: C,63.3; H,5.5. Calc. for $C_8H_8O_3$: C,63.15; H,5.3%. Light absorption in ethanol: Max. at 2060 (ϵ = 46,500), 2440

(ϵ = 12,000), and 2980 Å (ϵ = 4500).

(b) 2-Hydroxy-p-tolunitrile (40 g.) was heated under reflux for 4 hours with sodium hydroxide solution (500 c.c.; 10%). The solution was acidified (Congo red) with hydrochloric acid (d, 1.16) and extracted with ether (3 x 250 c.c.). The combined ethereal extracts were washed with water (200 c.c.), dried (Na_2SO_4), and removal of solvent and crystallisation of the residue from aqueous acetic acid gave 2-hydroxy-p-toluic acid (37 g.) as needles, m.p.205-207°, undepressed by an authentic specimen.

(c) (cf. Meldrum and Perkin, J.,1903,1416). 2-Sulpho-p--toluic acid (75 g.) was added in portions to potassium hydroxide (300 g.), previously moistened with a little water, heated to 200°. During the addition the temperature increased to 260° at which it was maintained until the fusion was complete. The fusion mixture was extracted with water, acidified (Congo red) with 50% hydrochloric acid, and the 2-hydroxy-p-toluic acid which separated was crystallised from aqueous acetic acid as needles (36 g.), m.p.206° (lit., m.p.206-207°).

3-Hydroxy-4-methylbenzyl Alcohol. - Commercial lithium aluminium hydride (10 g.) was refluxed with dry ether

(200 c.c.) for 30 minutes, cooled to 15° and treated while stirring with a solution of 2-hydroxy-p-toluic acid (6.0 g.) in dry ether (200 c.c.) added dropwise over 1 hour. The reaction mixture was then refluxed for 3 hours, cooled, and poured cautiously on to ice. The mixture was acidified (Congo red) with sulphuric acid (350 c.c.; 4N), the ethereal layer separated, the aqueous phase saturated with sodium chloride, and extracted with ether (4 x 200 c.c.). The combined ethereal extracts were washed with water (2 x 50 c.c.), dried (Na_2SO_4), and the ether evaporated. The residual solid was crystallised from benzene to give 3-hydroxy-4-methylbenzyl alcohol (4.7 g.; 86%) as needles, m.p.102-103° (Found: C,69.55; H,7.5. $C_8H_{10}O_2$ requires C,69.5; H,7.3%). The compound sublimed readily at 90°/10^{-3}mm. and had light absorption in ethanol: Max. at 2200 (ϵ = 6300) and 2730 Å (ϵ = 2200).

Attempted Carboxylation of 3-Hydroxy-4-methylbenzyl Alcohol. - (a) Carbon dioxide was passed into 3-hydroxy--4-methylbenzyl alcohol (1.0 g.), potassium hydrogen carbonate (7.0 g.), and glycerol (9 c.c.) maintained at a temperature of 120-125° for 7 hours. The cooled mixture was dissolved in hot water (40 c.c.), saturated with sodium

chloride, and extracted with ether (3 x 50 c.c.). The combined ethereal extracts were washed with water (25 c.c.) and dried (Na_2SO_4). Removal of solvent and crystallisation from benzene gave needles (0.9 g.), m.p. 97-99°, alone or mixed with a specimen of starting material. Examination of the ether-extracted alkaline solution by acidification (Congo red) and ether extraction, yielded no product. Further attempts to carboxylate with the temperature 150°, 170° and 190° for 4 hours were unsuccessful; starting material was recovered at the two lower temperatures and charring occurred at the highest.
(b) 3-Hydroxy-4-methylbenzyl alcohol (2.0 g.) was recovered unchanged after heating in an autoclave with water (20 c.c.), potassium hydrogen carbonate (10 g.) and carbon dioxide (9.0 g.) at 100° for 6 hours and 130° for 24 hours.

2-Methoxy-p-toluic Acid. - (cf. Perkin and Weizmann, J.,1906,89,1649). A solution of 2-hydroxy-p-toluic acid (6.0 g.) in potassium hydroxide (7.0 g.) and water (60 c.c.) was treated with methyl sulphate (9 c.c.) and stirred vigorously for 30 minutes. A further 7.0 g. of potassium hydroxide was added and the mixture was heated under reflux for 1 hour. The solution was acidified

(Congo red) with hydrochloric acid (d, 1.16); 2-methoxy--p-toluic acid separated and was crystallised from aqueous acetic acid as needles (5.0 g.), m.p.165-166°. Vongerichten and Rössler, Ber.,1878,11,1586 give m.p.156°.

2-Methoxy-3-nitro-p-toluic Acid.- (cf. Simonsen and Rav, J.,1921,119,1339). Finely powdered 2-methoxy-p--toluic acid (11 g.) was added in portions to a cooled mixture of nitric acid (14.7 c.c.; d,1.5) and acetic anhydride (40 c.c.) below 10°. After standing for 15 minutes, the temperature was allowed to rise to 20-30° and the reaction mixture was poured on to ice. The solid which separated was collected and crystallised from aqueous acetic acid to give 2-methoxy-3-nitro-p-toluic acid as needles (8.0 g.), m.p.166-168° (lit., m.p.165-166°).

3-Amino-2-methoxy-p-toluic Acid. - (cf. Simonsen and Rau, loc.cit.). Reduction of 2-methoxy-3-nitro-p-toluic acid using ferrous sulphate and ammonia gave a low yield in our hands. The following method proved satisfactory: sodium hydrosulphite (dithionite) (40 g.) was added in portions during 20 minutes to a cooled stirred solution of 2-methoxy-3-nitro-p-toluic acid (10 g.) in a solution of potassium hydroxide (10 g.) in water (100 c.c.), keeping

the temperature below 40°. The solution was made acid (Congo red) with hydrochloric acid (d, 1.16) and stored overnight. The solid which separated was crystallised once from water giving 3-amino-2-methoxy-p-toluic acid (7.5 g.) as needles, m.p.161-162° (lit., 162°).

2-Amino-3-methoxy-4-methylbenzyl Alcohol. - Commercial lithium aluminium hydride (2.0 g.) was heated under reflux with dry ether (70 c.c.) for 30 minutes, cooled, and treated with a solution of 3-amino-2-methoxy-p-toluic acid (1.0 g.) in dry ether (70 c.c.) added dropwise over 30 minutes. The reaction mixture was refluxed for 3 hours, cooled, poured on to ice and acidified (Congo red) with sulphuric acid (90 c.c., 4N). The solution was then made strongly alkaline with sodium hydroxide and extracted with ether (3 x 50 c.c.). The combined extracts were washed with water (25 c.c.) and dried (Na_2SO_4). Removal of the ether gave a dark brown oil which was extracted with boiling light petroleum (b.p. 40-60°) 3 x 50 c.c.). Concentration of the combined extracts to 150 c.c. and storage, gave 2-amino-3-methoxy--4-methylbenzyl alcohol (400 mg.) which separated from benzene-light petroleum (b.p.40-60°) as needles, m.p.48-

-49° (Found: C,64.9; H,7.6. $C_9H_{13}O_2N$ requires C,64.65; H,7.8%). Light absorption in ethanol: Max. at 2110 (ϵ = 26,000), 2400 (ϵ = 6300) and 2890 Å (ϵ = 2100). The compound sublimed rapidly at 50°/10^{-3}mm.

7-Methoxy-6-methylphthalide. - A solution of 2-amino-3-methoxy-4-methylbenzyl alcohol (400 mg.) in hydrochloric acid (3 c.c.; d, 1.16) and water (10 c.c.) was cooled to 0° and diazotised with a solution of sodium nitrite (0.4 g.) in water (5 c.c.). After the addition of urea, the filtered solution was added to a solution of potassium cyanide (1.6 g.) and copper sulphate (1.4 g.) in water (20 c.c.) at 70°, heated on the steam-bath for 15 minutes, cooled, and extracted with ether (4 x 25 c.c.). The combined ethereal extracts were washed with water (25 c.c.), dried (Na_2SO_4) and the ether evaporated. The residual dark red oil was heated under reflux with potassium hydroxide solution (10 c.c.; 10%) for 2 hours. The solution was acidified (Congo red) with hydrochloric acid (d, 1.16) and the precipitate crystallised from water to give 7-methoxy-6-methylphthalide (200 mg.) as felted needles, m.p.120° (Found: C,67.5; H,5.8. $C_{10}H_{10}O_3$ requires C,67.4; H,5.7%). Light absorption in ethanol:

Max. at 2130 (ϵ = 26,000), 2370 (ϵ = 7500) and 2950 Å (ϵ = 2300). The compound sublimed rapidly at 80°/10^{-3}mm.

4-Chloromethyl-7-methoxy-6-methylphthalide. - 7-Methoxy--6-methylphthalide (250 mg.) was heated under reflux with hydrochloric acid (5 c.c.; d,1.16) and formaldehyde (3 c.c.; 40%) for 45 minutes. Solution was rapid and was followed by the separation of an oil. The reaction mixture was diluted with water (10 c.c.), extracted with chloroform (5 x 10 c.c.), the combined extracts washed with water (10 c.c.), saturated sodium hydrogen carbonate solution (10 c.c.), water (10 c.c.), and dried (Na_2SO_4). Removal of the chloroform gave a light yellow gum (250 mg.) which partly crystallised on standing; the solid was separated with the aid of a little methanol and crystallised from ether-light petroleum (b.p.40-60°) to give 4-chloromethyl-7-methoxy-6-methylphthalide as fine needles, m.p. 88-90° (Found: C,58.6; H,5.2. $C_{11}H_{11}O_3Cl$ requires C,58.3; H,4.9%). Light absorption in ethanol: Max. at 2160 (ϵ = 29,400) and 2930 (ϵ = 3000); inflexion at 2400 Å (ϵ = 7300).

4-Hydroxymethyl-7-methoxy-6-methylphthalide. - The crude 4-chloromethyl-7-methoxy-6-methylphthalide (200 mg.)

as obtained after evaporation of the chloroform extract in the previous experiment was heated under reflux with a solution of sodium carbonate (0.5 g.) in water (5 c.c.) for 30 minutes. The solution was made acid (Congo red) with hydrochloric acid (d, 1.16), extracted with chloroform (20 c.c.), the chloroform extract dried (Na_2SO_4) and evaporated. The solid residue crystallised from benzene to give 4-hydroxymethyl-7-methoxy-6-methylphthalide (150 mg.) as needles, m.p.119° (Found: C,63.5; H,5.9. $C_{11}H_{12}O_4$ requires C,63.45; H,5.8%). Light absorption in ethanol: Max. at 2120 (ϵ = 31,000), 2380 (ϵ = 6500) and 2980 Å (ϵ = 3000). A mixture of the compound with 7-methoxy-6-methylphthalide had m.p.105-110°.

7-Methoxy-6-methylphthalide-4-carboxylic Acid. - A solution of 4-hydroxymethyl-7-methoxy-6-methylphthalide (50 mg.) in sulphuric acid (25 c.c.; N) at 70° was treated with aqueous potassium permanganate (7 c.c.; 1%). After 10 minutes at 70°, the solution was decolorised by sulphur dioxide and kept at 0° for 1 hour. The solid was separated and crystallised from aqueous ethanol to give 7-methoxy-6-methylphthalide-4-carboxylic acid (25 mg.) as needles, m.p.230-232°, undepressed on mixing with iso-

gladiolic acid (Found: C,59.7; H,4.6. Calc. for $C_{11}H_{10}O_5$: C,59.5; H,4.5%). Light absorption in ethanol: Max. at 2160 (ϵ = 33,000), and 2930 (ϵ = 5000); inflexion at 2440 Å (ϵ = 9000).

4-Formylmeconin. - (a) A solution of 4-hydroxymethylmeconin (500 mg.) in dry carbon tetrachloride (25 c.c.) and dry benzene (25 c.c.) was refluxed with N-bromosuccinimide (430 mg.; 1 mol.) for 15 minutes with irradiation from a 60-watt lamp adjacent to the flask. The filtered reaction mixture was evaporated under reduced pressure and the residual oil heated on the steam-bath with water (50 c.c.) for 1 hour. The cooled mixture was extracted with chloroform (50 c.c.) and the extract washed with sodium hydrogen carbonate solution (2 x 25 c.c.), water (2 x 25 c.c.) and dried (Na_2SO_4). Removal of the chloroform under reduced pressure gave a solid which crystallised from methanol to give 4-formylmeconin (170 mg.) as blades, m.p.195-196° (Found: C,59.5; H,4.8. $C_{11}H_{10}O_8$ requires C,59.5; H,4.5%). The compound sublimed at 150°/10^{-3}mm. and showed light absorption in ethanol: Max. at 2270 (ϵ=20,000), 2770 (ϵ = 4600), and 3240 (ϵ = 6000); inflexion at 2400 Å (ϵ = 16,000). The 2:4-dinitrophenyl-

hydrazone prepared by the action of methanolic 2:4--dinitrophenylhydrazine sulphate and well washed with methanol formed micro-needles gradually decomposing but not melting below 350° (Found: N,13.5. $C_{17}H_{14}O_8N_4$ requires N,13.9%).

(b) 4-Hydroxymethylmeconin (500 mg.) dissolved in glacial acetic acid (10 c.c.) was treated at 15° with a solution of chromic anhydride (500 mg.) in glacial acetic acid (10 c.c.) added over 2 minutes with stirring. After 5 minutes the solution was diluted with water (20 c.c.) and extracted with chloroform (3 x 15 c.c.). The combined chloroform extracts were washed with water (15 c.c.), aqueous sodium hydrogen carbonate (3 x 15 c.c.), water (15 c.c.), and dried (Na_2SO_4). Removal of the chloroform gave 4-formylmeconin (300 mg.) separating from methanol as blades, m.p.196° (Found: C,60.0; H,4.2%).

4-Formyl-7-methoxy-6-methylphthalide. - (a) A solution of pure 4-chloromethyl-7-methoxy-6-methylphthalide (284 mg.) in dry carbon tetrachloride (25 c.c.) was heated under reflux with N-bromosuccinimide (670 mg.; 3 mols.) for 1½ hours with irradiation from a 60 watt lamp adjacent to the flask. The filtered reaction mixture was

evaporated under reduced pressure to give a yellow oil which was heated with water (25 c.c.) on the steam-bath for 1 hour. The hot solution was decanted from a little tar and on cooling deposited a solid which on crystallisation from methanol gave 4-formyl-7-methoxy-6-methylphthalide (30 mg.) as needles, m.p.173-174° alone or mixed with a specimen of deoxygladiolic acid (Found: C,64.0; H,5.1. $C_{11}H_{10}O_4$ requires C,64.1; H,4.9%). Light absorption in ethanol: Max. at 2240 (ϵ = 23,300), 2630 (ϵ = 8500), and 3060 Å (ϵ = 4550). The compound sublimed at 120°/10^{-3}mm.

(b) 4-Hydroxymethyl-7-methoxy-6-methylphthalide (500 mg.) dissolved in a mixture of benzene and carbon tetrachloride (50 c.c.; 1:1) was heated under reflux with N-bromosuccinimide (430 mg.; 1 mol.) for 15 minutes with irradiation as before. The filtered reaction mixture was evaporated under reduced pressure and the residual solid heated with water (50 c.c.) on the steam-bath for $\frac{1}{2}$ hour, cooled, and extracted with chloroform (3 x 25 c.c.). The combined chloroform extracts were washed with water (25 c.c.), aqueous sodium hydrogen carbonate (25 c.c.; 10%), and water (25 c.c.) and dried (Na_2SO_4). Removal of the chloroform and crystallisation of the solid from benzene-light

petroleum (b.p.60-80°) gave 4-formyl-7-methoxy-6-methylphthalide (350 mg.) as needles, m.p.172-173°, undepressed on mixing with preparation (a) (Found: C,64.45; H,5.0%).

Meconin-4-carboxylic Acid. - 4-Hydroxymethylmeconin (500 mg.) was refluxed with N-bromosuccinimide (1.2 g.; 3 mols.) in a mixture of carbon tetrachloride (25 c.c.) and benzene (25 c.c.) for 20 minutes with irradiation from a 60 watt lamp adjacent to the flask. The reaction mixture was hydrolysed and worked up as above to give a neutral fraction from which 4-formylmeconin (20 mg.) was obtained separating from methanol as blades, m.p.193° undepressed by the preparation above. The acidic fraction crystallised from aqueous ethanol (charcoal) to give meconin-4-carboxylic acid (150 mg.) as needles, m.p.220--221° alone or mixed with an authentic specimen (Found: C,55.7; H,4.4. Calc. for $C_{11}H_{10}O_6$: C,55.5; H,4.2%). Light absorption in ethanol: Max. at 2160 (ϵ = 28,700) and 3180 Å (ϵ = 6000).

7-Methoxy-6-methylphthalide-4-carboxylic Acid. - 4-Hydroxymethyl-7-methoxy-6-methylphthalide (250 mg.) was treated with N-bromosuccinimide (3 mols.) exactly as in

the foregoing experiment. No crystalline material was obtained from the neutral fraction. The acidic fraction gave 7-methoxy-6-methylphthalide-4-carboxylic acid (150 mg.) separating from aqueous ethanol as needles, m.p. 232-233° alone or mixed with isogladiolic acid (Found: C,59.5; H,4.3. $C_{11}H_{10}O_5$ requires C,59.5; H,4.5%). Light absorption in ethanol: Max. at 2160 (ε = 34,000), and 2980 (ε = 4800); inflexion at 2430Å (ε = 8500).

3-Acetoxy-4-formylmeconin. - 3-Formylopianic acid (500 mg.) was heated with acetic anhydride (5 c.c.) and glacial acetic acid (5 c.c.) on the steam-bath for 1¼ hours. The cooled solution was poured on ice (30 g.) and the mixture extracted with chloroform (3 x 30 c.c.). The combined chloroform extracts were washed with water (20 c.c.), sodium hydrogen carbonate solution (2 x 20 c.c.; 10%), water (20 c.c.), and dried (Na_2SO_4). Removal of the chloroform under reduced pressure followed by crystallisation from ethanol gave 3-acetoxy-4-formylmeconin (400 mg.) as needles, m.p. 177° (Found: C,55.7; H,4.5. $C_{13}H_{12}O_7$ requires C,55.7; H,4.3%). Light absorption in ethanol: Max. at 2350 (ε = 13,500), 2800 (ε = 3700), and 3200 Å (ε = 4300). It is most important that the reaction

mixture is free from mineral acid since the presence of a trace of the latter causes formation of 3-acetoxy-4--diacetoxymethylmeconin.

3-Ethoxy-4-formylmeconin. - A solution of 3-formylopianic acid (500 mg.) in dry ethanol (5 c.c.) with sulphuric acid (5 drops; d, 1.84) added, was heated under reflux for 30 minutes. The cooled solution was diluted with water (20 c.c.), extracted with ether (3 x 20 c.c.) and the combined ethereal extracts were washed with water (20 c.c.), sodium hydrogen carbonate solution (20 c.c.), water (20 c.c.) and dried (Na_2SO_4). Removal of the ether and crystallisation of the residue from benzene-light petroleum (b.p.60-80°) gave 3-ethoxy--4-formylmeconin (200 mg.) as needles, m.p.107-108° (Found: C,58.6; H,5.5. $C_{13}H_{14}O_6$ requires C,58.6; H,5.3%). Light absorption in ethanol: Max. at 2300 (ϵ = 16,800), 2780 (ϵ = 3700), and 3230 Å (ϵ = 3900).

3-Acetoxy-4-diacetoxymethylmeconin. - 3-Formylopianic acid (100 mg.) suspended in acetic anhydride (2 c.c.) was treated with sulphuric acid (1 drop) when solution took place rapidly. The solution was heated on the steam bath for 5 minutes, cooled, and poured on

ice. The precipitate was collected and crystallised from aqueous ethanol from which 3-acetoxy-4-diacetoxymethylmeconin (120 mg.) separated as needles, m.p.120--121° (Found: C,53.5; H,5.0 $C_{17}H_{18}O_{10}$ requires C,53.4; H,4.75%). Light absorption in ethanol: Max. at 2190 (ϵ = 29,400) and 3120 Å (ϵ = 4000).

3-Acetoxy-4-hydroxymethylmeconin. - 3-Acetoxy-4-formylmeconin (1.43 g.) part dissolved in glacial acetic acid (150 c.c.) was added to a suspension of freshly reduced platinum (from Adams platinum oxide; 300 mg.) in glacial acetic acid (25 c.c.) and the mixture shaken with hydrogen at room temperature when absorption (150 c.c.; calc. 135 c.c. for 1 mol.) had ceased. Removal of the catalyst and evaporation of the solvent under reduced pressure gave an oil which rapidly solidified. Crystallisation from benzene-light petroleum (b.p.60-80°) gave 3-acetoxy-4-hydroxymethylmeconin (1.1g.) as needles, m.p.136° (Found: C,55.5; H,5.2. $C_{13}H_{14}O_7$ requires C,55.3; H,5.0%). Light absorption in ethanol: Max. at 2180 (ϵ = 31,400) and 3140 Å (ϵ = 4200).

3-Hydroxymethylopianic Acid. - 3-Acetoxy-4-hydroxymethylmeconin (1.08 g.) was treated with aqueous sodium

hydroxide (60 c.c.; 0.1N) at room temperature when solution was rapid. After 2 minutes the solution was acidified (Congo red) with hydrochloric acid (d, 1.16) and stored at 0° overnight. The solid which had separated was collected, washed with water, dried over phosphoric oxide *in vacuo* and crystallised from ethyl acetate-light petroleum (b.p.60-80°) to give 3-*hydroxymethylopianic acid* (500 mg.) as fine needles, m.p.141° (Found: C,55.2; H,5.2%; equiv.,235. $C_{11}H_{12}O_6$ requires C,55.0; H,5.0%; equiv.,240). Light absorption in ethanol: Max. at 2160 (ϵ = 27,400) and 3030 Å(ϵ = 3500); in chloroform: 2460 (ϵ = 3900) and 3110 Å (ϵ = 3150). The 2:4-*dinitrophenylhydrazone* separated from ethanol as small red needles which on heating shrink at 215-220° and decompose gradually as the temperature is raised to 350° (Found: N,13.5. $C_{17}H_{16}O_9N_4$ requires N,13.3%). 3-Hydroxymethylopianic acid gave no colour with aqueous ammonia (d, 0.88), did not reduce Schiff's reagent, Fehling's solution, nor ammoniacal silver nitrate.

4-*Formylmeconin from 3-hydroxymethylopianic Acid*. - (a) The acid (140 mg.) was heated under reflux with sulphuric acid (5 c.c.; 2N) for 4½ hours. The red solution

was decanted from tar, and the solid collected, washed with sodium hydrogen carbonate solution, and water, and crystallised from methanol. 4-Formylmeconin (10 mg.) separated as blades, m.p.194-195° alone or mixed with an authentic specimen (Found: C,59.4; H,4.9. Calc. for $C_{11}H_{10}O_5$: C,59.5; H,4.5%).

(b) 3-Hydroxymethylopianic acid (100 mg.) was heated to 200° and the melt sublimed at 190°/10^{-3}mm. The small amount of sublimate was crystallised from methanol to give 4-formylmeconin (2 mg.) as blades, m.p.192-193° alone or mixed with preparation (a).

3-Acetoxy-4-acetoxymethylmeconin. - (a) 3-Acetoxy--4-hydroxymethylmeconin (40 mg.) in dry pyridine (0.2 c.c.) and acetic anhydride (0.2 c.c.) was kept at room temperature overnight. The product was precipitated by addition of water (5 c.c.), separated, and crystallised from aqueous ethanol from which 3-acetoxy--4-acetoxymethylmeconin (38 mg.) formed needles, m.p.124° (Found: C,55.7; H,5.3. $C_{15}H_{16}O_8$ requires C,55.55; H,5.0%). Light absorption in ethanol: Max. at 2130 (ε = 30,800) and 3120 Å (ε = 4000).

(b) 3-Hydroxymethylopianic acid (50 mg.) was acetylated

as in (a) giving 3-acetoxy-4-acetoxymethylmeconin (50 mg.) which separated from aqueous ethanol as needles, m.p.125° alone or mixed with preparation (a) (Found: C,55.4; H,5.3%).

4-Hydroxymethylmeconin. - (a) A solution of 3-formylopianic acid (250 mg.) in sodium hydrogen carbonate solution (15 c.c.; 10%) was treated at room temperature with sodium borohydride (250 mg.) and stored overnight. The solution was acidified (Congo red) with dilute hydrochloric acid and extracted with chloroform (3 x 20 c.c.). The combined chloroform extracts were washed with water (20 c.c.), dried (Na_2SO_4) and evaporated. Crystallisation of the residue from benzene gave 4-hydroxymethylmeconin (200 mg.) as needles, m.p.129° alone or mixed with an authentic specimen (Found: C,59.0; H,5.7. Calc. for $C_{11}H_{12}O_5$: C,58.9; H,5.4%). Light absorption in ethanol: Max. at 2120 (ϵ = 23,600) and 3120 Å (ϵ = 4100); in chloroform: Max. at 2440 (ϵ = 5750) and 3100 Å (ϵ = 4400). (b) A solution of 3-acetoxy-4-formylmeconin (150 mg.) in ethanol (30 c.c.) was added to a solution of sodium borohydride (150 mg.) in water (10 c.c.) at room temperature and kept for 5 hours. Working up as in (a) gave

4-hydroxymethylmeconin (70 mg.) which separated from benzene as needles, m.p.127° alone or mixed with preparation (a) (Found: C,59.25; H,5.55%).

(c) A suspension of 3-acetoxy-4-hydroxymethylmeconin (50 mg.) in water (10 c.c.) was shaken with sodium borohydride (250 mg.) with warming to 40° until solution was complete (5 minutes). The solution was stored overnight at room temperature and worked up as in (a) to give 4-hydroxymethylmeconin (37 mg.) separating from benzene as needles, m.p.127-128° alone or mixed with preparations (a) or (b) (Found: C,58.65; H,5.5%). 4-Hydroxymethylmeconin was similarly obtained from sodium borohydride reduction of 3-hydroxymethylopianic acid, m.p. and mixed m.p.128°. The benzoyl derivative, prepared by the action of benzoyl chloride-pyridine on 4-hydroxymethylmeconin at room temperature overnight followed by working up via ether, separated from ethanol as needles, m.p.131-132° (Found: C,66.1; H,5.2. $C_{18}H_{16}O_6$ requires C,65.85; H,4.9%).

4-Hydroxymethyl-7-methoxy-6-methylphthalide.-Gladiolic acid (100 mg.) dissolved in sodium hydrogen carbonate solution (10 c.c.; 10%) was treated with sodium borohydride

(200 mg.) added in one portion at room temperature, and the solution was stored overnight, then acidified (Congo red) with 3N-hydrochloric acid and extracted with chloroform (3 x 15 c.c.). The combined chloroform extracts were washed with water (15 c.c.), dried (Na_2SO_4), and evaporated. The residual solid was crystallised from benzene to give 4-hydroxymethyl-7-methoxy-6-methylphthalide (30 mg.) as fine needles, m.p.119° alone or mixed with an authentic specimen (Found: C,63.3; H,6.0. Calc. for $C_{11}H_{12}O_4$: C,63.45; H,5.8%). Light absorption in ethanol: Max. at 2120 (ϵ = 28,000), 2370 (ϵ = 6200) and 2980 Å (ϵ = 3000); in chloroform: Max. at 2440 (ϵ = 2250) and 2990 Å (ϵ = 3200). The <u>acetate</u>, prepared by the action of acetic anhydride and pyridine at room temperature overnight, separated from aqueous ethanol as needles, m.p.95° (Found: C,62.5; H,5.8. $C_{13}H_{14}O_5$ requires C,62.4; H,5.6%). The compound sublimed rapidly at 90°/10^{-3} mm. and showed light absorption in ethanol: Max. at 2120 (ϵ = 33,800) and 2960 (ϵ = 3500); inflexion at 2340 (ϵ = 8200).

3-<u>Formylopianic Acid.</u> - 3-Hydroxymethylopianic acid (170 mg.) was heated under reflux with a solution of

sodium metaperiodate (500 mg.) in sulphuric acid (5 c.c.; N) for 15 minutes. The cooled solution deposited a crystalline solid which proved to be a sodium salt. This was dissolved in aqueous sodium carbonate (10%) and acidified (Congo red) with 5N-hydrochloric acid. The precipitated solid was collected and crystallised from water to give 3-formylopianic acid (105 mg.) as needles, m.p.175-176° undepressed on mixing with an authentic specimen (Found: C,55.6; H,4.4. Calc. for $C_{11}H_{10}O_6$: C,55.5; H,4.2%).

Gladiolic Acid Hydrate Triacetate. - Deoxygladiolic acid (300 mg.) and sodium metaperiodate (3.0 g.) in sulphuric acid (20 c.c.; N) were refluxed for 40 hours. The cooled solution, which deposited crystals, was extracted with chloroform (3 x 25 c.c.), the combined extract washed with water (20 c.c.), aqueous sodium hydrogen carbonate (3 x 20 c.c.; 10%), water (20 c.c.) and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the residue from benzene-light petroleum (b.p.60-80°) gave deoxygladiolic acid (220 mg.) as needles, m.p. and mixed m.p.173-174°. The combined sodium hydrogen carbonate extracts were acidified (Congo

red) with 3N-hydrochloric acid, extracted with chloroform (3 x 25 c.c.) and the combined chloroform extracts washed with water (20 c.c.) and dried (Na_2SO_4). Evaporation of the chloroform gave a pale yellow solid (50 mg.) which gave a strong ammonia test for gladiolic acid. The solid was heated on the steam bath for 10 minutes with acetic anhydride (2 c.c.) and sulphuric acid (1 drop; d, 1.84) and the solution poured on to crushed ice (5.0g.) when an oil, rapidly solidifying, separated. This was extracted with chloroform (3 x 15 c.c.), the combined extracts washed with aqueous sodium hydrogen carbonate (2 x 10 c.c.; 10%) (combined to give solution A), water (10 c.c.), dried (Na_2SO_4) and the chloroform evaporated. Crystallisation of the residue from aqueous ethanol gave gladiolic acid hydrate triacetate (12 mg.) as needles, m.p.131-132° undepressed on mixing with a specimen prepared from natural gladiolic acid (Found: C,55.4; H,5.1. Calc. for $C_{17}H_{18}O_9$: C,55.7; H,4.95%). Light absorption: Max. at 2140 (ϵ = 37,000) and 2980 (ϵ = 3100); inflexion at 2340 Å (ϵ = 7000).

Gladiolic Acid. - The triacetate (19 mg.) was heated under reflux for 1 hour with sulphuric acid (2.5 c.c.; 2N).

The solid which crystallised from the cooled solution was recrystallised from water to give gladiolic acid (11 mg.) as needles, m.p.159-160° alone or mixed with a specimen of natural gladiolic acid kindly supplied by Mr. J. F. Grove (Found: C,59.7; H,4.8. Calc. for $C_{11}H_{10}O_5$: C,59.5; H,4.5%). Light absorption: Max. at 2140 (ε = 18,500), 2710 (ε = 6900) and 3040 Å (ε = 3200). The 2:4-dinitrophenylhydrazone separated from glacial acetic acid as orange needles, m.p. and mixed m.p.231-233° (decomp.).

iso<u>Gladiolic Acid.</u> - Solution A from the triacetate formation was acidified (Congo red) with 3N-hydrochloric acid and the solution extracted with chloroform (3 x 10 c.c.), the extracts washed with water (10 c.c.) and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the resulting solid from aqueous ethanol gave <u>iso</u>gladiolic acid (33 mg.) as needles, m.p. and mixed m.p.232-233° (Found: C,59.8; H,4.8. Calc. for $C_{11}H_{10}O_5$: C,59.5; H,4.5%). Light absorption: Max. at 2180 (ε = 33,000) and 3000 (ε = 4400); inflexion at 2450 Å (ε = 3600).

3-Formylopianic Acid. - 4-Formylmeconin (140 mg.) was heated under reflux for 3 hours with a solution of sodium metaperiodate (1.5 g.) in sulphuric acid (10 c.c.; N). The cooled solution was extracted with chloroform (3 x 15 c.c.) and the combined extract washed with aqueous sodium hydrogen carbonate (2 x 10 c.c.; 10%), water (10 c.c.), dried (Na_2SO_4), evaporated and the residue crystallised from methanol to give 4-formylmeconin (100 mg.) as blades, m.p. and mixed m.p.193-195°. The combined aqueous washings were acidified (Congo red) with 3N-hydrochloric acid and extracted with chloroform (3 x 20 c.c.). Evaporation of the dried (Na_2SO_4) chloroform extracts followed by crystallisation of the residue from water gave 3-formylopianic acid (17 mg.) as fine needles, m.p.173-174° undepressed on mixing with an authentic specimen (Found: C,55.6; H,4.5. Calc. for $C_{11}H_{10}O_6$: C,55.5; H,4.2%). Light absorption: Max. at 2110 (ϵ = 21,000), 2750 (ϵ = 4400) and 3190 Å (ϵ = 3900); pK_a 5.1 in aqueous ethanol; 4.3 in water.

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