THE STRUCTURE OF MELLEIN AND STUDIES ON PHTHALIDES AND PHTHALALDEHYDIC ACIDS

BLAIR.

AUGUST. 1955.

THESIS

submitted to

THE UNIVERSITY OF GLASGOW.

in fulfilment of the
requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

by

JOHN BLAIR.

August, 1955.

ACKNOWLEDGEMENTS.

The author wishes to record his sincerest thanks to Dr. G. T. Newbold for his inspired guidance and supervision in all aspects of the work. He is also grateful to Professor F. S. Spring, F.R.S. for the opportunity to carry out this work and for his interest and support. The author would also thank Dr. J. J. Brown for his collaboration in the section entitled 'A new method for the conversion of phthalides into phthalaldehydic acids', to Dr. H. S. Burton for a generous sample of mellein and to Messrs. T. and H. Smith Ltd., for gifts of chemicals.

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The Structure of Mellein.

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PART I

The Structure of Mellein (ochracin).

SUMMARY.

The constitution of mellein (ochracin), a mould product of A. melleus Yukawa, is discussed and its structure shown to be (-)-3:4-dihydro-8-hydroxy-3-methylisocoumarin by the synthesis of its (±)-methyl ether. Two new syntheses of isoochracin confirm its structure as 3-ethyl-7-hydroxyphthalide.

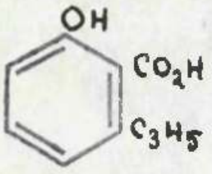
Introduction.

Nishikawa (1) and Burton (2) showed that a metabolite, mellein was produced when the mould *Aspergillus melleus* Yukawa was grown on a medium containing sucrose or maltose, respectively. Its identity with ochracin, a metabolic product of *Aspergillus ochraceus* has been established by Yabuta and Sumiki (3).

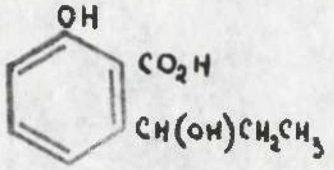
Mellein, m.p. 58°, $[\alpha]_D^{12}$ - 108.15° was obtained by Nishikawa (1) in a yield of 0.3 g./l. of culture fluid and had a molecular formula of $C_{10}H_{10}O_3$. It was soluble in organic solvents and gave a violet colour with ferric chloride solution; a monoacetate was formed but no -OMe groups were present.

When fused with potassium hydroxide at 200° an optically inactive acid, melleic acid, was produced; this compound also formed a monoacetate, and on hydrogenation, absorbed one mol. of hydrogen. If the fusion was conducted at 300°, 6-hydroxy-2-methylbenzoic acid was obtained, an acid previously isolated as a metabolic product of *Penicillium griseofulvum* Dierckx by Anslow and Raistrick (4).

From his evidence, Nishikawa (5) concluded that a provisional structure (I) could be written for melleic acid and that mellein itself must be the lactone of 6-[α(or β)-hydroxypropyl] salicylic acid (II or III)



(I)



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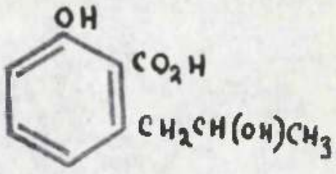
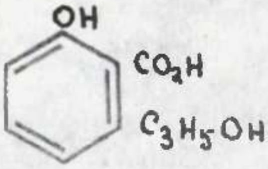


(III)

Contemporaneously with the work of Nishikawa, Yabuta and Sumiki (6) investigating the culture fluid from Aspergillus ochraceus, isolated a product which they named ochracin and which they later proved identical with mellein (3).

The analytical and degradative work of Yabuta and Sumiki (3, 6) on ochracin, produced similar evidence to that obtained by Nishikawa (1, 5) in his degradative studies on mellein. They also obtained 6-hydroxy-2-methylbenzoic acid by alkali fusion of ochracin, and, methylochracin when oxidised with potassium permanganate yielded 3-methoxyphthalic acid.

On their evidence, Yabuta and Sumiki (6) postulated the existence in ochracin of a hydroxyl-group in position 6, and strongly favoured the possibility of a lactonisation between the carboxyl-group in position 1 and the hydroxyl of the side chain in position 2.

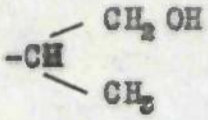


The side chain C_3H_6OH has five possible forms:

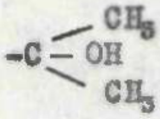
$-CH_2-CH_2-CH_2OH$

$-CH_2-CH(OH)-CH_3$

$-CH(OH)-CH_2-CH_3$

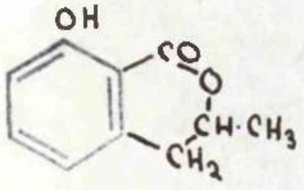


$$-CH\begin{matrix}\diagup CH_2OH \\ \diagdown CH_3\end{matrix}$$

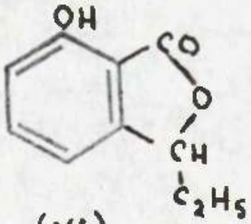


$$-C\begin{matrix}\diagup CH_3 \\ - OH \\ \diagdown CH_3\end{matrix}$$

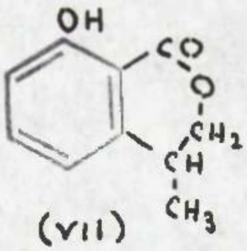
The corresponding structures for ochracin were therefore as shown (V) - (IX).



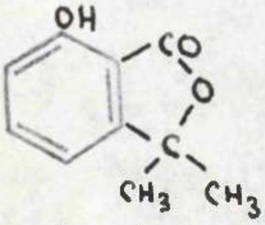
(V)



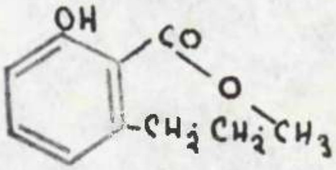
(VI)



(VII)



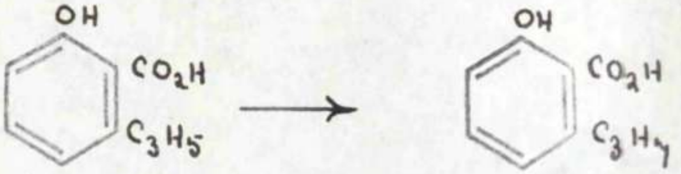
(VIII)



(IX)

Ochracin being optically active, structures (VIII) and (IX) were eliminated.

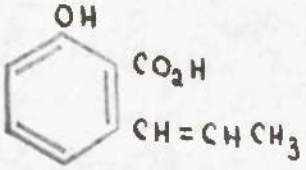
Melleic acid, the unsaturated acid obtained by the alkali fusion of ochracin was easily hydrogenated to dihydromelleic acid, and oxidation of methylmelleic acid



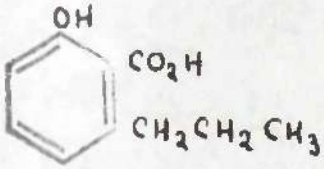
yielded acetaldehyde and 6-methoxyphthalaldehydic acid (X).

(X)

The melleic acid side chain was thus proved to be $-CH = CH - CH_3$ and not $-CH_2 - CH = CH_2$ or $-C\begin{matrix} - CH_3 \\ = CH_2 \end{matrix}$ and the acid therefore assigned the structure (XI), with dihydromelleic acid consequently having the structure (XII).

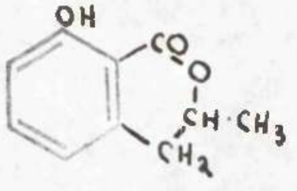


(XI)

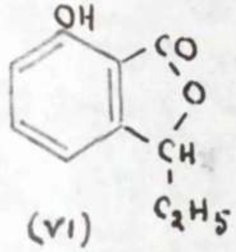


(XII)

Since the side chain in melleic acid was of the n-propenyl form it could then be deduced that of the remaining possible structures (V), (VI) and (VII) for ochracin, only two (V) and (VI) were still feasible.

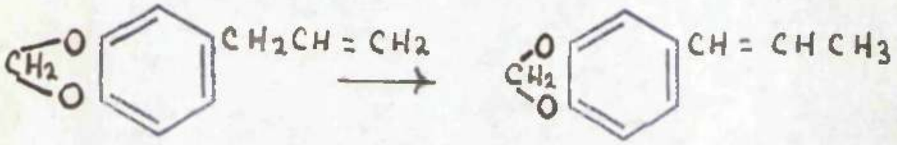


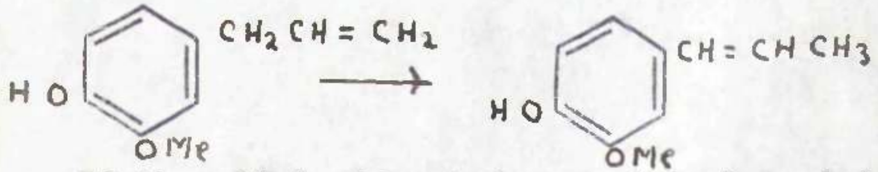
(V)



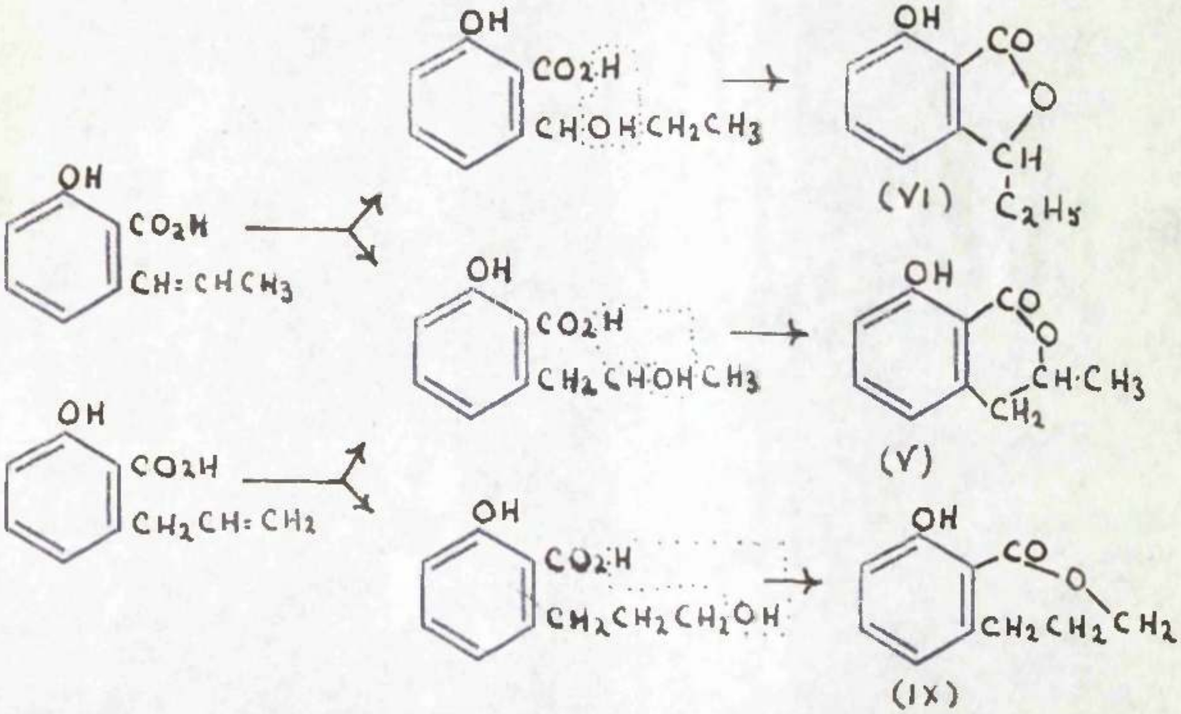
(VI)

Yabuta and Sumiki (3) suggested that, although the side chain in melleic acid (XI) was proved to be of the *n*-propenyl form, the formation of such a side chain could have been accomplished by a rearrangement of an allyl side chain such as occurred in the saffrole to *iso*saffrole and eugenol to *iso*eugenol rearrangements by alkali.





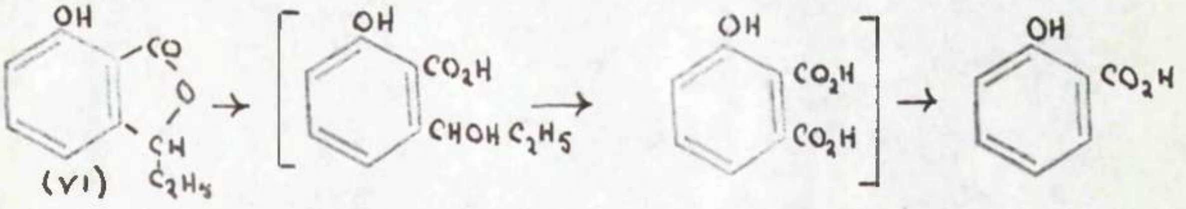
If the allyl side chain was indeed an intermediate in the melleic acid formation, it was apparent from the scheme below that ochracin must have had structure (V), structure (IX) already having been ruled out.



isoOchracin.

When melleic acid was treated with hot dilute sulphuric acid, a compound isomeric with ochracin was produced (6). It was an optically inactive lactone with one phenolic hydroxyl-group and fusion with potassium hydroxide gave salicylic acid, an acid also formed from 3-hydroxyphthalic acid by the same alkali process.

Yabuta and Sumiki (6) argued that since salicylic acid and not 6-methylsalicylic acid was formed in this alkali fusion, the lactone must necessarily be in the nature of a substituted phthalide.



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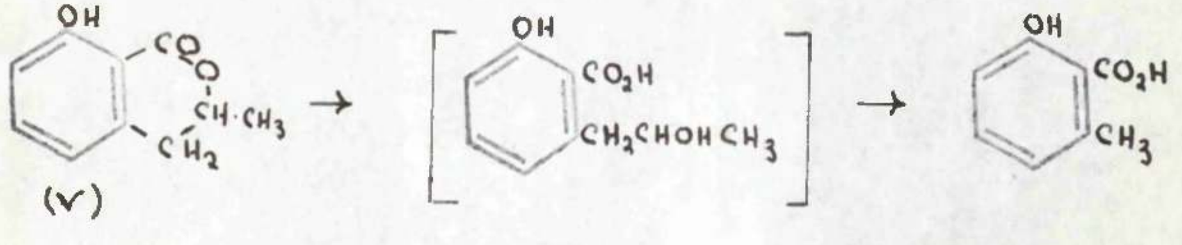


(V)

They therefore proposed that ochracin (mellein) had structure (V) and *iso*ochracin structure (VI).

It is of interest to note at this point that Chemical Abstracts (25) are in error here, having attributed structure (VI) to ochracin and (V) to *iso*ochracin.

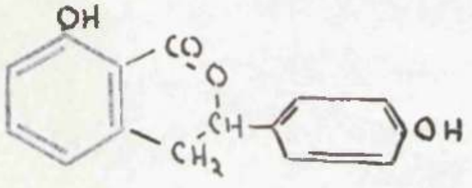
Tamura (7) has claimed a synthesis of 3-ethyl-7-hydroxyphthalide (VI) and has reported it to be identical with _iso_ochracin. His synthesis, however, was equivocal and was entirely dependent upon the degradative work on natural mellein for its structural assignment. This synthesis will be discussed in more detail later.

Mellein itself has been given the phthalide (or related hydroxy-acid formulation) in two recent reviews on mould products, by Raistrick (8), and by Aghoramurthy and Seshadri (9) respectively, and more recently, Birch and Donovan (10), discussing their 'acetate hypothesis', have stated that although they were aware of the fact that in the literature a definite decision had not been made between (V) and (VI), they did "consider the chemical evidence to favour (V) decisively" and believed their hypotheses also indicated (V) as being the more probable structure for mellein.

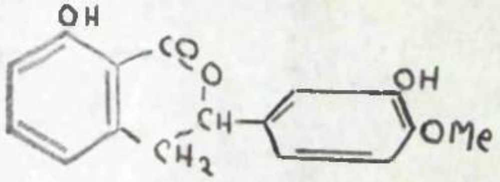
Couzi and Werner (11) have tested the culture filtrates of _Aspergillus ochraceus_ for antibiotic activity and found them active against typhoid fever in guinea pigs, the animals being completely healed. Ultra-violet irradiation of the cultures increased the activity of the antibiotic one to three times.

Hydrangenol.

A naturally occurring *isocoumarin* derivative bearing a strong structural resemblance to mellein, was hydrangenol (XIII) which occurred as a glucoside in the flowers of the garden hydrangea (*Hydrangea opuloides*)



(XIII)

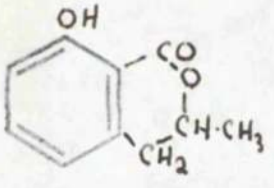


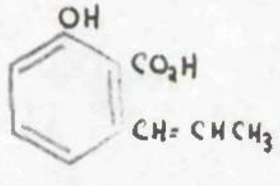
(XIV)

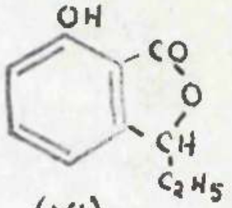
Its hydroxy-methyl ether phyllodulcin (XIV) occurred in the leaves of the same plant. The constitutions of both aglycones were established by Asahina and Asano (12).

THEORETICAL.

In view of the obvious confusion which existed in the literature as to the structure of mellein, it was considered that an unambiguous synthesis of 3:4-dihydro-8-hydroxy-3-methyl*iso*coumarin (V), and 3-ethyl-7-hydroxyphthalide (VI), should be undertaken and comparisons made with natural mellein and *iso*ochracin, the product formed when melleic acid (XI) was treated with hot mineral acid.

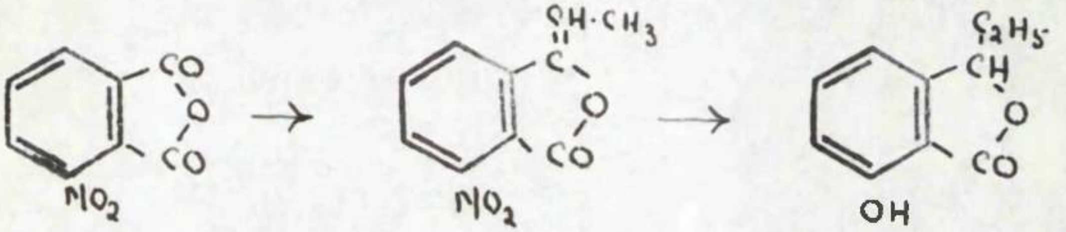

(V)


(XI)

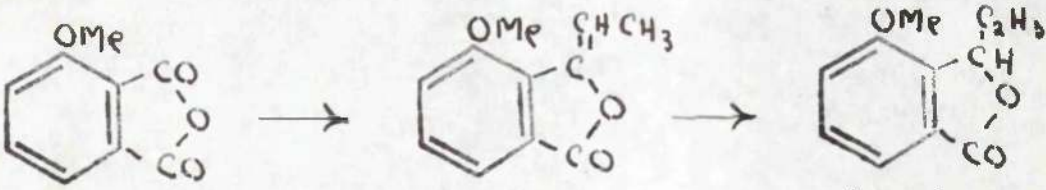

(VI)

Tamura (7) has claimed to have synthesised 3-ethyl-7-hydroxyphthalide (VI) and proved it identical with *iso*ochracin. In actual fact, however, Tamura synthesised a 3-substituted phthalide by a condensation reaction, which could have given him, either 3-ethyl-4-hydroxyphthalide, or 3-ethyl-7-hydroxyphthalide, and it was only by direct comparison of his product with *iso*ochracin, obtained from natural mellein and known by degradative studies to have a hydroxyl-group in the 7-position, that Tamura was able to state that his compound was in fact, 3-ethyl-7-hydroxyphthalide (VI). His claim to an unequivocal synthesis of *iso*ochracin cannot be maintained.

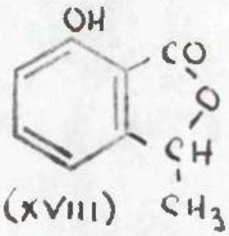
Further, his experience in having obtained this latter compound (VI), starting from a sodium propionate-propionic anhydride condensation on 3-nitrophthalic anhydride (XV) by the sequence of reactions shown, and also 3-ethyl-4-methoxyphthalide (XVII) from a similar condensation reaction starting with 3-methoxyphthalic anhydride (XVI), runs contrary to recent evidence in the literature relating to the synthesis of a degradation product of the antibiotic 'terramycin', 7-hydroxy-3-methylphthalide (XVIII). The structure of this product rested rigidly on chemical and infra-red evidence (13, 14).



(XV) (VI)

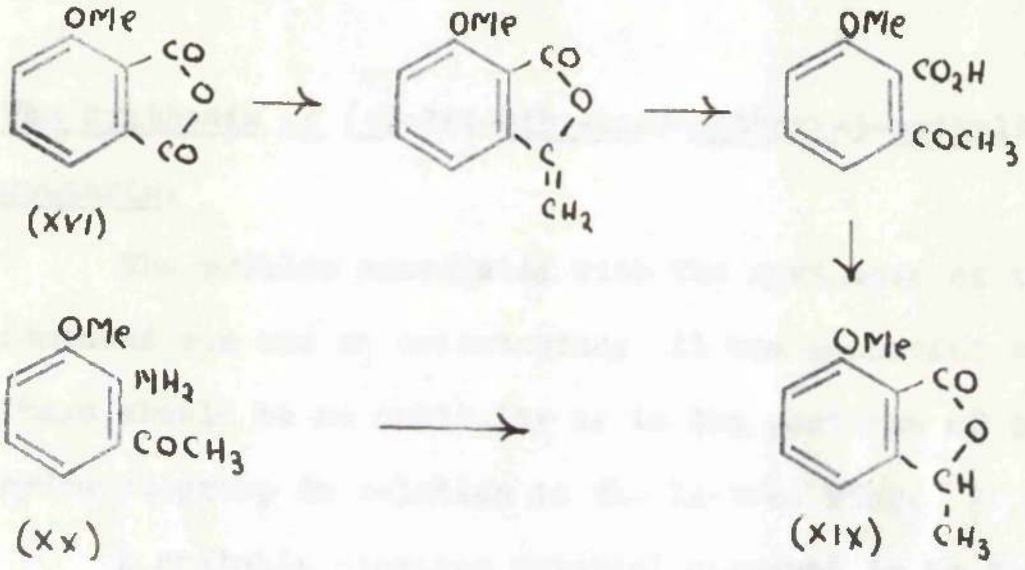


(XVI) (XVII)



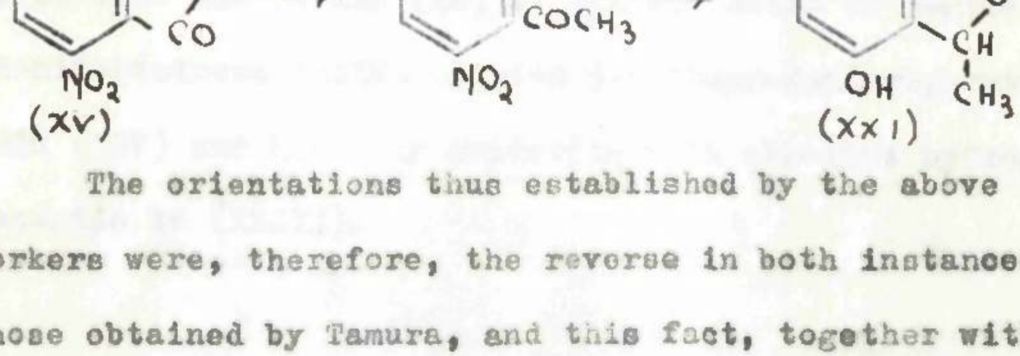
(XVIII)

Kuhn and Dury (13), and Hochstein and Pasternack (14) in submitting 3-methoxyphthalic anhydride (XVI) to a Doebner reaction and proceeding as shown, obtained 7-methoxy-3-methylphthalide (XIX), identical with the methyl ether of the above degradation product.



This methyl ether (XIX) has also been synthesised by Kushner, Morton, Boothe and Williams (16) starting from 2-amino-3-methoxyacetophenone (XX) (17).

In addition, Hochstein and Pasternack (14) have obtained 4-hydroxy-3-methylphthalide (XXI) starting with either a Doebner or Gabriel condensation on 3-nitrophthalic anhydride (XV).



The orientations thus established by the above workers were, therefore, the reverse in both instances of those obtained by Tamura, and this fact, together with the failure of several workers in this laboratory to repeat the latter's work, made the need for an unambiguous synthesis of not only 3-ethyl-7-hydroxyphthalide (VI), but 3:4-dihydro-8-hydroxy-3-methyl*iso*coumarin (V) essential.

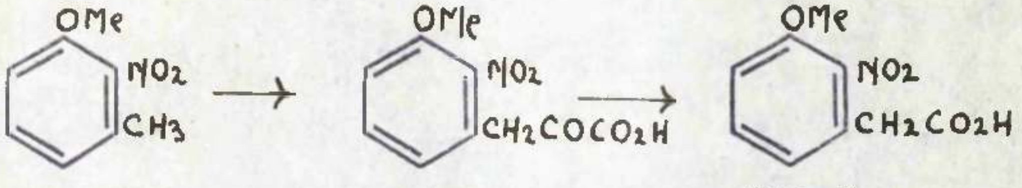
The synthesis of (±)-3:4-dihydro-8-methoxy-3-methyl*iso*coumarin.

The problem associated with the synthesis of this compound was one of orientation; it was essential that there should be no ambiguity as to the position of the hydroxyl-group in relation to the lactone ring.

A suitable starting material appeared to be 3-methoxy-2-nitrobenzoic acid (XXII), obtained by Ewins (19) from the nitration of *m*-methoxybenzoic acid, and conveniently converted by an Arndt-Eistert reaction to 3-methoxy-2-nitrophenylacetic acid (XXIII).

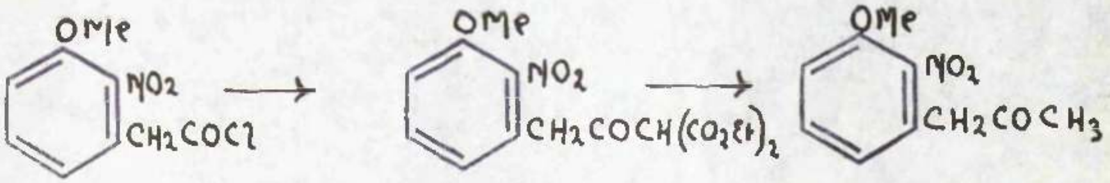
(XXII) (XXIII)

The latter compound (XXIII) has also been prepared by Blaikie and Perkin (18) by the oxalation of 3-methoxy-2-nitrotoluene (XXIV) to give 3-methoxy-2-nitropyruvic acid (XXV) and hence by oxidation with alkaline hydrogen peroxide to (XXIII).



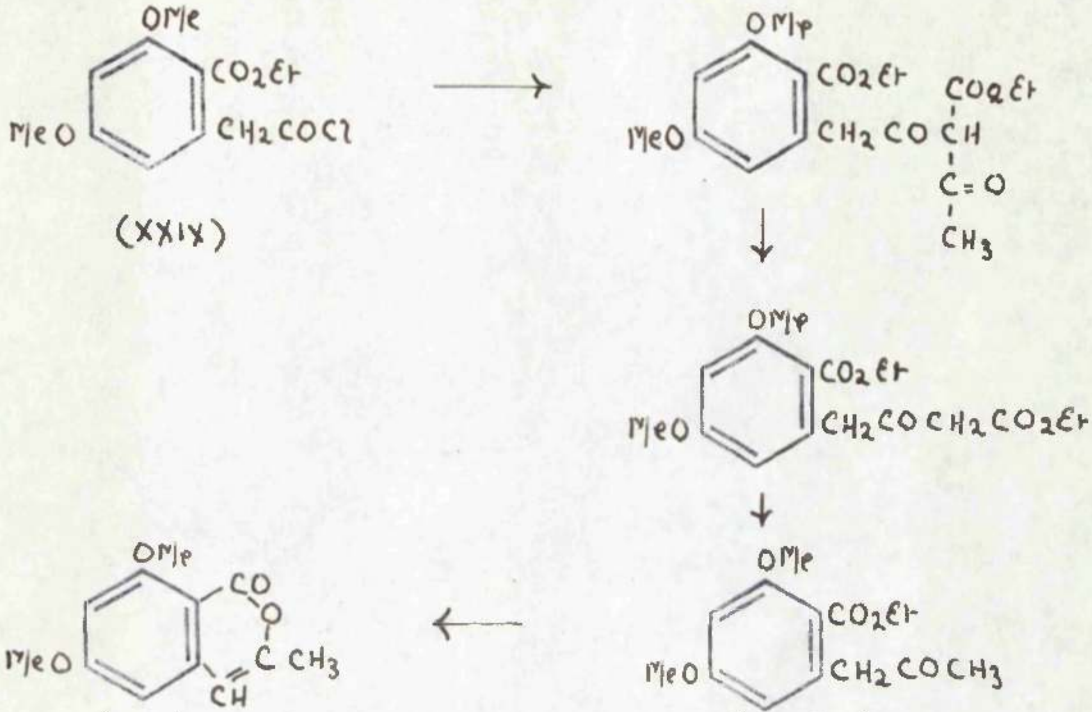
(XXIV) (XXV) (XXIII)

The acid chloride of (XXIII) was obtained, as described by Barger and Schlittler (20) and transformed readily by the ethoxymagnesiomalonate method of Walker and Hauser (21) *via* the intermediate ethyl 3-methoxy-2-nitrophenylacetylmalonate (XXVI) to 3-methoxy-2-nitrophenylacetone (XXVII).



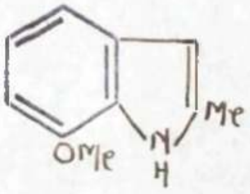
(XXVI) (XXVII)

An interesting comparison with the latter procedure was Nogami's (15) preparation of the corresponding phenylacetone (XXVIII) from 2-carbethoxy-3:5-dimethoxyphenylacetyl chloride (XXIX) by reaction with ethyl acetoacetate. Treatment of (XXVIII) with formic acid gave 3-methyl-6:8-dimethoxy*iso*coumarin (XXX).



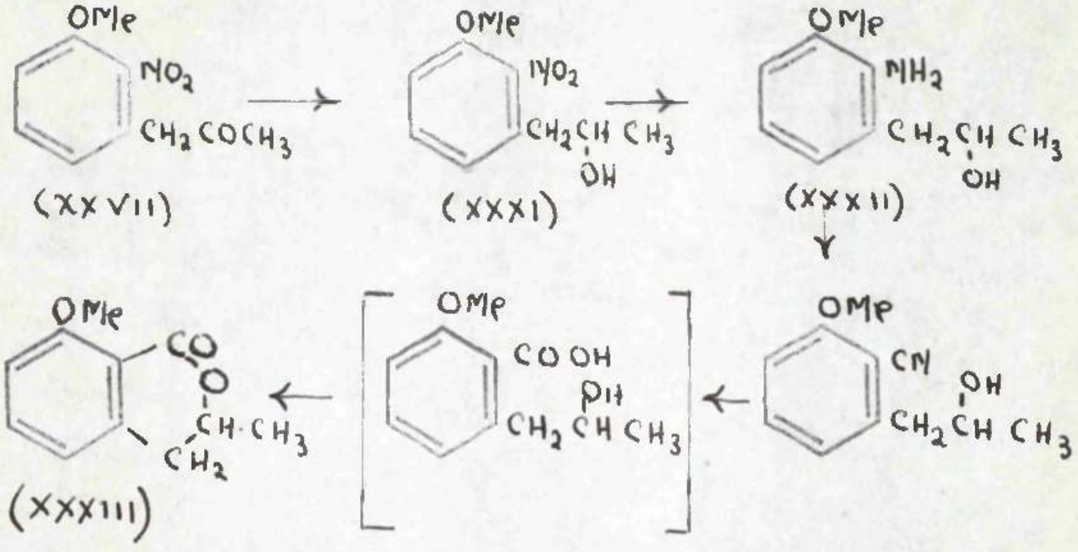
(XXIX) (XXX) (XXVIII)

When 3-methoxy-2-nitrophenylacetone (XXVII) was hydrogenated over nickel, a product m.p. 83-85° and analysing for $C_{10}H_{11}ON$ was obtained. It was soluble in warm 5 N-hydrochloric acid, being recovered on basification, formed a red picrate and had an ultra-violet absorption spectrum of 2200 (ε = 50,000) and 2650 Å. (ε = 9,000), thus showing very high intensity in the first band. A violet-red colour was produced in the Ehrlich reaction for indoles, being indistinguishable from the colour given by 2-methylindole. We considered therefore, the compound, m.p. 83-85° was 7-methoxy-2-methylindole (XXXIV).



(XXXIV)

The nitro-ketone (XXVII) on reduction with sodium borohydride gave 3-methoxy-2-nitrobenzylmethylcarbinol (XXXI) in high yield, which on hydrogenation over nickel afforded 2-amino-3-methoxybenzylmethylcarbinol (XXXII). Diazotisation of this amine with its conversion into the nitrile, which was not purified, and subsequent alkaline hydrolysis of the nitrile, gave (±)-3:4-dihydro-8-methoxy-3-methyl*iso*coumarin (XXIII) m.p. 68-67°.



The compound gave an intermediate m.p. on mixing with (-)-mellein methyl ether, m.p. 89° and the ultra-violet and infra-red absorption spectra of both compounds (the latter in carbon tetrachloride solution) were identical. The carbonyl stretching frequencies of both compounds, in solution (1741 cm.$^{-1}$), and in the solid state (1716 cm.$^{-1}$) when compared with those of 7-methoxyphthalide in the same solvent (1782 cm.$^{-1}$) and in the solid state (1748 cm.$^{-1}$), were consistent with the existence of a six-membered ring in

(XXXIII). We are indebted to Mr. J. F. Grove, Imperial Chemical Industries Ltd. for these determinations.

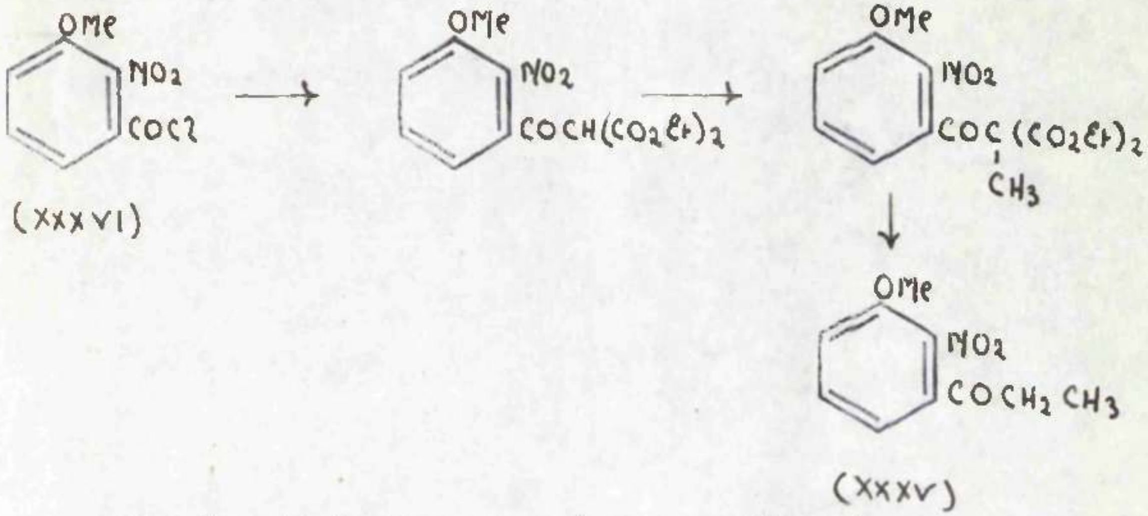
(-)-Mellein methyl ether was recovered after boiling with aqueous alkali, no appreciable racemization having been detected.

Having thus established that mellein is (-)-3:4-dihydro-8-hydroxy-3-methyl*iso*coumarin (V), attention was then directed to *iso*ochracin which must be 3-ethyl-7-hydroxyphthalide (VI).

The Synthesis of 3-Ethyl-7-hydroxyphthalide (isoOchracin).

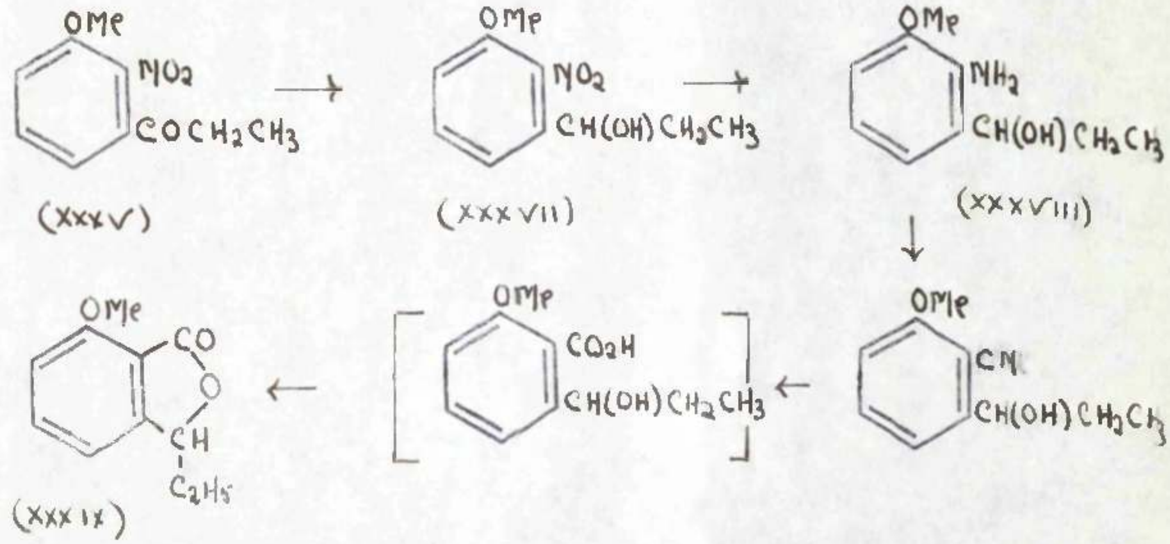
As has been mentioned previously, Kushner, Morton, Boothe and Williams (16) have synthesised 7-methoxy-3-methylphthalide (XIX) starting from 2-amino-3-methoxyacetophenone (XX) (17). An obvious analogy with the above, was the use of the propiophenone for the preparation of the corresponding 3-ethyl substituted phthalide.

Attempts to obtain 3-methoxy-2-nitropropiophenone (XXXV) by nitrating *m*-methoxypropiophenone were unsuccessful, the reaction often taking place with explosive violence. (XXXV), However, was obtained from 3-methoxy-2-nitrobenzoylchloride (XXXVI)by application of the ethoxymagnesiomalonate method to give ethyl 3-methoxy-2-nitrobenzoylmalonate which was not isolated, but C-methylated directly and the product hydrolysed and decarboxylated to give the required 3-methoxy-2-nitropropiophenone (XXXV).



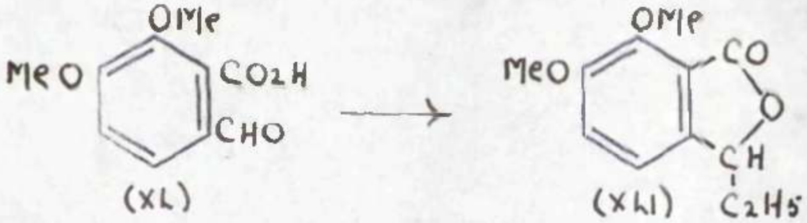
The C-methylation procedure was therefore a useful extension of the Walker and Hauser (21) reaction.

3-Methoxy-2-nitropropiophenone (XXXV) was reduced by sodium borohydride to the corresponding nitro-carbinol (XXXVII) which was hydrogenated to the amino-carbinol (XXXVIII) and the latter, by successive diazotisation, nickel potassium cyanide treatment and alkaline hydrolysis, converted to 3-ethyl-7-methoxyphthalide (XXXIX)



All these compounds were uncrystallisable; the last was chromatographed but remained a viscous oil. Demethylation of the methoxy-compound with aqueous boiling hydrobromic acid gave 3-ethyl-7-hydroxyphthalide (VI) which was identical with *iso*ochracin.

The second method for the synthesis of *iso*ochracin was based on the reaction of a phthalaldehydic acid with excess of an alkyl magnesium halide to give a 3-alkylphthalide (22)



Mermod and Simonis (22) claimed an 86% yield of 3-ethylmeconin (XLI) from opianic acid (XL) by this method; in our hands a very low yield was obtained but a high proportion of the starting material was recovered. The failure was attributed to the low solubility of opianic acid in ether, and in order to circumvent this practical difficulty an ether soluble derivative of the phthalalehydic acid was sought. Such a compound was an intermediate in the method of Blair, Brown and Newbold*(23) for the conversion of a phthalide into a phthalaldehydic acid in which the phthalide was treated with dimethylamine to give an *o*-hydroxymethyl-NN-dimethylbenzamide, and the latter oxidised

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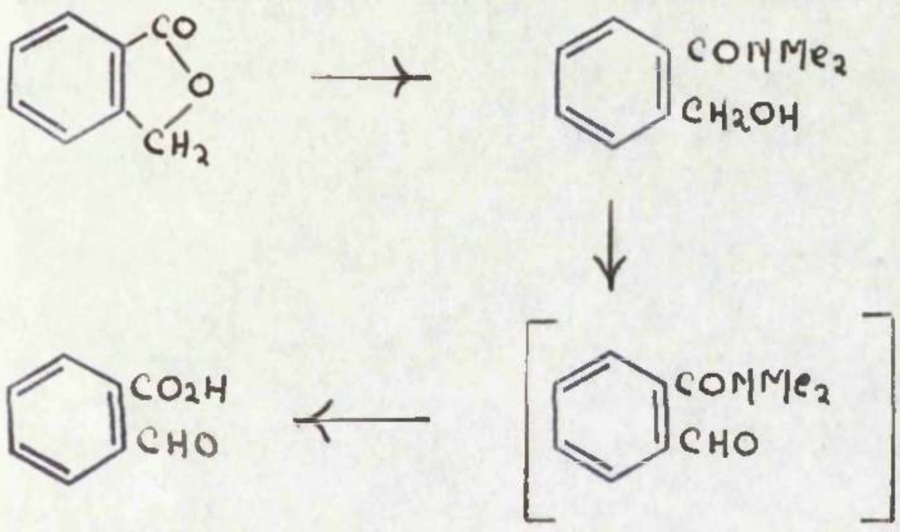
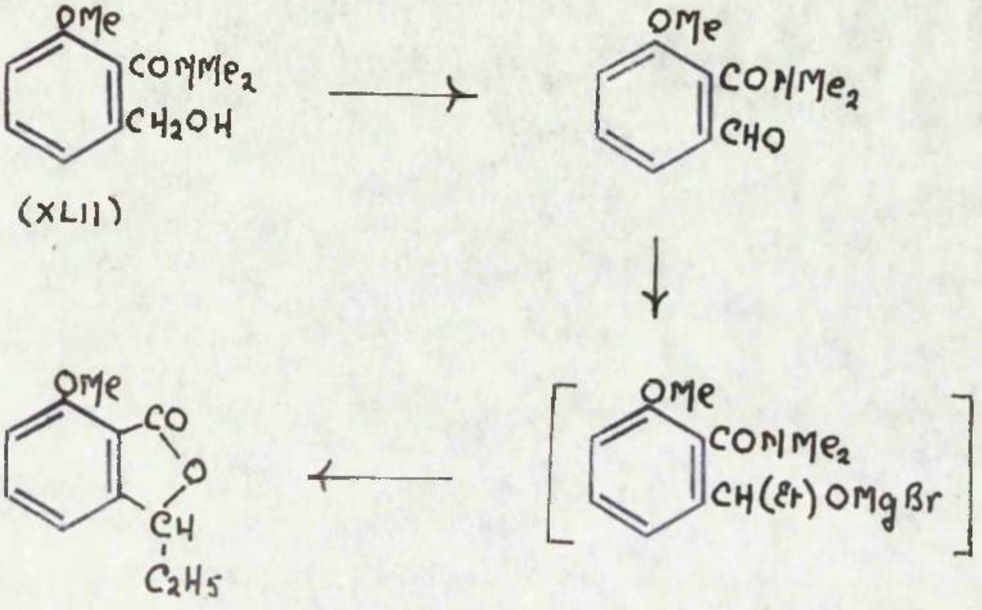
* See page 76

with chromic acid to the o-formyl-NN-dimethylbenzamide, which on heating with dilute acid gave the phthalaldehydic acid.



6-Formyl-2:3-dimethoxy-NN-dimethylbenzamide, the intermediate in the preparation of opianic acid (XL) by the foregoing method was not isolated in the pure state, but the crude material on reaction with an excess of the appropriate Grignard reagent, followed by treatment of the product with hot dilute acid, gave 3-methyl and 3-ethylmeconin in high yields.

Application of this method starting from 6-hydroxymethyl-2-methoxy-NN-dimethylbenzamide (XLII) (23) resulted in good yield 3-ethyl-7-methoxyphthalide (XXXIX) which on demethylation gave 3-ethyl-7-hydroxyphthalide (VI) (isoochracin).



(XLII)

(XXXIX)

A comparison between the ultra-violet absorption spectrum above 2,200 A. of mellein with those of certain 7-hydroxyphthalides is given below:

Compound.	Solvent.	max. Å.	Max.	max. Å.	Max.
Mellein.	EtOH	2,460	6,500	3,140	4,100
*iso*ochracin	EtOH	2,340	7,000	3,000	4,600
* 7-hydroxy-3-methylphthalide.	MeOH	2,320	7,500	2,980	4,700
7-hydroxyphthalide.	EtOH	2,320	8,700	2,990	4,600

The strong bathochromic shift of the maxima in mellein compared with the positions of those in the phthalides is noteworthy and might be of diagnostic use in deciding between isomeric 3:4-dihydro*iso*coumarin and phthalide structures.

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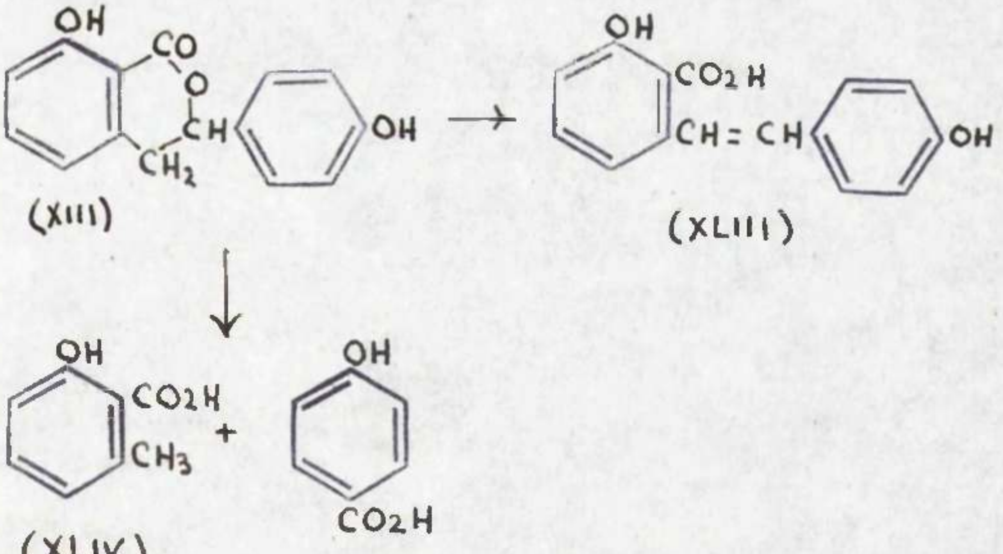
* Hochstein and Pasternack (14)

The Constitution and Synthesis of Hydrangenol.

The elucidation of the structure of hydrangenol (XIII) and its proof by synthesis was due to Asahina and Asano (12).

Alkali treatment of hydrangenol provided an unsaturated acid, hydrangeic acid (XLIII), analogous to melleic acid (XI) obtained as an alkali fission product from mellein. More drastic alkali treatment of hydrangenol (12) and mellein (3) resulted in the same product, 6-methylsalicyclic acid (XLIV)

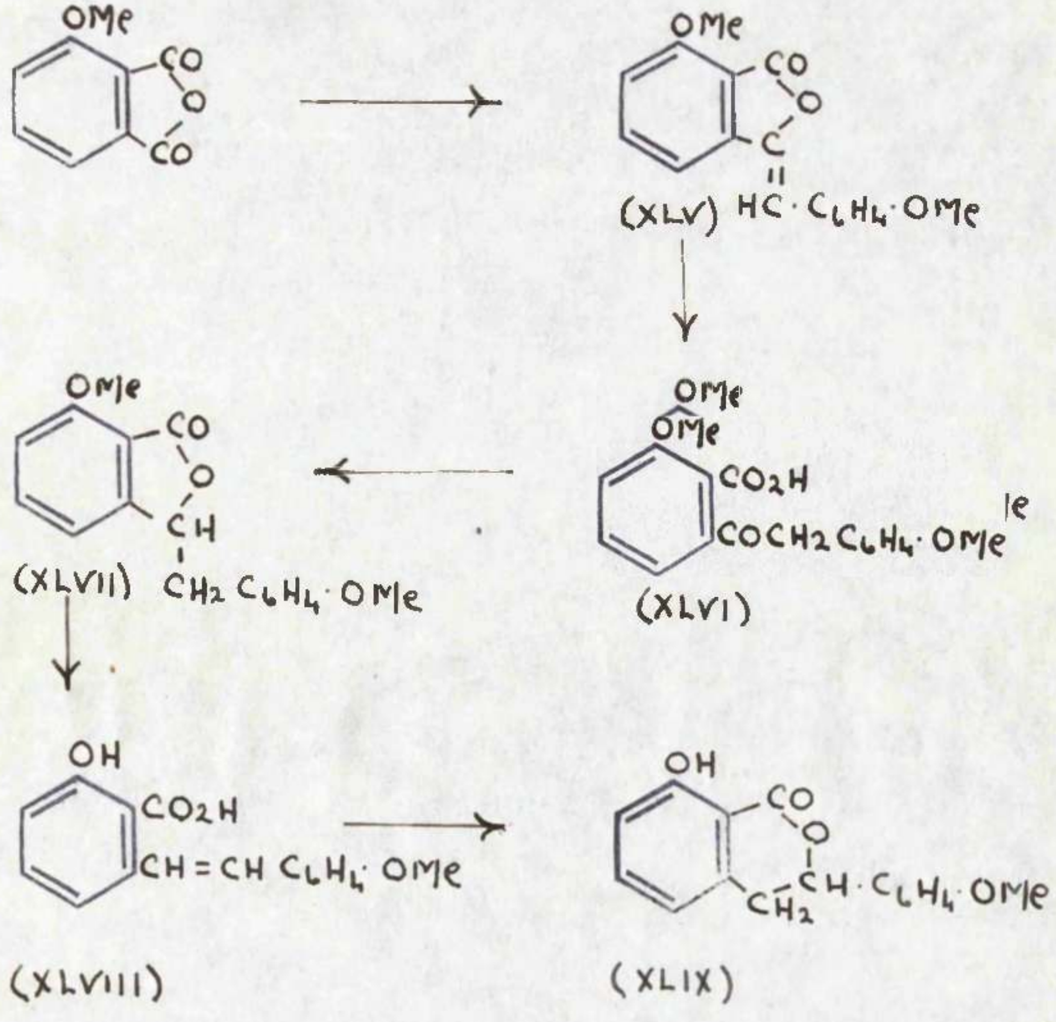


(XIII)

(XLIII)

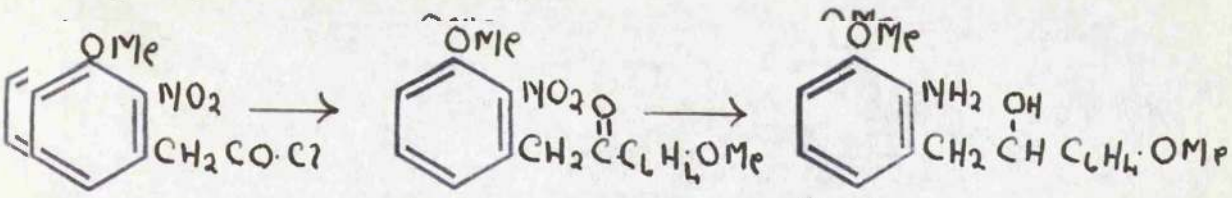
(XLIV)

Asahina and Asano (12) heated 3-methoxyphthalic anhydride with sodium acetate and p-methoxyphenylacetic acid according to the method of Gabriel (24) and obtained in poor yield, 7,4'-dimethoxybenzalphthalide (XLV). Ring opening of this compound to the ketone (XLVI) and subsequent reduction of the ketone to the secondary alcohol followed by acidification produced 7:4'-dimethoxybenzylphthalide (XLVII). This phthalide was not identical with hydrangenol dimethyl ether. When (XLVII) was evaporated to dryness with methanolic potassium hydroxide and then heated *in vacuo* at 200°, -CH$_3$ and CO$_2$ was lost and methylhydrangeic acid formed (XLVIII). The acid was easily converted into 3:4-dihydro-8-hydroxy-4'-methoxy-3-phenyl*iso*coumarin (XLIX), identical with the methyl ether of hydrangenol.



It seemed that a more elegant and less ambiguous route to hydrangenol would be one analogous to that already described for (±)-3:4-dihydro-8-methoxy-3-methyl*iso*coumarin.

If 3-methoxy-2-nitrophenylacetylchloride (L) could be made to react with anisole under Friedel-Crafts conditions, then the same sequence of reactions could be applied to the product as was applied to 3-methoxy-2-nitrophenylacetone (XXVII).



(L) (LI) (LII)

The Friedel-Crafts reaction was tried under various experimental conditions with carbon disulphide as solvent, but the required product, 3':4-dimethoxy-2'-nitrodeoxybenzoin (LI) was obtained in best yield using anisole itself as solvent. Reduction of (LI) to the nitro-alcohol with sodium borohydride followed by catalytic hydrogenation of the nitro-group, gave 2-amino-3-methoxybenzyl-*p*-anisylcarbinol (LII) in good yield. Subsequent conversion of the amine to nitrile and hydrolysis of the nitrile yielded only a small amount of solid which crystallised as short prisms from light petroleum, m.p. 150°-154°. The literature m.p. for hydrangenol dimethyl ether was 151°; the (±)-dimethyl ether was not reported by Asahino and Asano (12).

Ultra-violet spectra were determined in EtOH unless otherwise stated.

3-Methoxybenzoic acid.- (cf. Perkin and Weizmann, J., 1906, 89, 1649) 3-Hydroxybenzoic acid (20 g.), dissolved in aqueous KOH (24 g. in 80 c.c. H_2O) was stirred vigorously with dimethylsulphate (30 c.c.) for 30 mins., during which the methyl ester of 3-methoxybenzoic acid separated as an oil. Potassium hydroxide (8 g.) was added, and mixture refluxed for 1 hr.

The solution was cooled, acidified (HCl; d,1.16) and the 3-methoxybenzoic acid which separated was filtered off, and crystallised from aqueous ethanol as needles, m.p. 107° (17 g.)

3-Methoxy-2-nitrobenzoic acid. - (Ewins, J., 1912, 101, 544) Finely divided 3-methoxybenzoic acid (15 g.) was suspended in nitric acid (60 c.c.; d,1.42), the temperature raised to 35° to start reaction and then kept below 40° with water cooling. As the starting material dissolved, the products separated. After standing 3 hrs. at room temperature, the reaction mixture was diluted with water (300 c.c.), and the precipitate filtered off, washed with water, and then boiling ethanol (50 c.c.). The colourless solid remaining was crystallised from ethanol to give blades (3.5 g.), m.p. 254-256°.

3-Methoxy-2-nitrobenzoyl Chloride. - 3-Methoxy-2-nitrobenzoic acid (9.0 g.) was refluxed with redistilled thionyl chloride (60 c.c.) for 2 hrs. Excess of reagent was removed under reduced pressure, benzene added to the residue and this likewise removed, both operations conducted at bath temperature 40°. The solid residue was kept in vacuo overnight over sodium hydroxide pellets the crude product being used directly for the next stage. A specimen crystallised from anhydrous ether gave 3-methoxy-2-nitrobenzoyl chloride as needles, m.p. 85°

Found: C,44.7; H,2.55

$C_8H_6O_4NCl$ requires: C,44.6; H,2.8%

The acid chloride decomposes on keeping.

3-Methoxy-2-nitrophenyl diazomethyl ketone. - A solution of diazomethane in ether (250 c.c.) from nitrosomethylurea (33 g.) was treated with a solution of 3-methoxy-2-nitrobenzoyl chloride (9.0 g.) in dioxan (30 c.c.) with agitation at 0° and kept overnight at room temperature. Removal of the solvent under reduced pressure gave the diazoketone (9.0 g.). Crystallisation from dioxan gave 3-methoxy-2-nitrophenyl diazomethyl ketone as prisms, m.p. 144° (decomp).

Found: C,49.2; H,3.45

$C_9H_7O_4N_3$ requires: C,48.9; H,3.2%

Light absorption: Max. at 2160 (ε = 24,000), 2480 (ε = 18,400) and 2980 Å. (ε = 10,400).

3-*Methoxy*-2-*nitrophenylacetic acid*. - A solution of the foregoing diazoketone (9.0 g.) in warm dioxan (75 c.c.) was added in portions over 20 minutes to a stirred mixture of freshly prepared silver oxide (4.0 g.) in distilled water (150 c.c.) in which sodium thiosulphate (3.0 g.) and anhydrous sodium carbonate (5.0 g.) had been dissolved, the temperature being kept at 50-60°. After a further hour at 50-60° the temperature was raised to 90-95° for ½ hour and then the reaction mixture was filtered, the filtrate diluted with water (200 c.c.), acidified with dilute nitric acid and extracted with chloroform (3 x 200 c.c.). The combined chloroform extracts were washed with water (50 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave a tarry solid which was extracted with boiling water (2 x 100 c.c.). Concentration of the combined extracts followed by cooling gave 3-*methoxy*-2-*nitrophenylacetic acid* (6.05 g.) which separated from water (charcoal) as needles, m.p. 136-137°

Found: C,51.2; H,4.2

Calc. for $C_9H_9O_5N$: C,51.2; H,4.3%

Light absorption: Max. at 2090 (ϵ = 13,000), 2540-2600 (ϵ = 2,800) and 3000 A. (ϵ = 1,800). The preparation of this acid, m.p. 137-138° from 3-methoxy-2-nitrotoluene has been described by Blaikie and Perkin (*loc. cit.*).

Ethyl-3-Methoxy-2-nitrophenylacetylmalonate. - 3-Methoxy-2-nitrophenylacetic acid (4.22 g.) was converted into the acid chloride as described by Barger and Schlittler (*loc. cit.*) and a solution of the latter compound in ether (25 c.c.) added over 10 minutes to refluxing ethereal ethyl ethoxymagnesiomalonate, prepared from ethyl malonate (3.52 g.), as prescribed in *Org. Synth.* *30*, 70. A thick viscous oil formed and heating was continued for ½ hr. until stirring became difficult. The cooled reaction mixture was shaken with dilute sulphuric acid (2.5 g. in 20 c.c. water) until the oily magnesium complex had dissolved. The ethereal phase was separated, washed with water, dried (Na_2SO_4) and evaporated to give the crude product (6.0 g.) which solidified. A specimen crystallised from aqueous ethanol gave *ethyl 3-methoxy-2-nitrophenylacetylmalonate* as fine needles, m.p. 85-86°

Found: C,54.4; H,5.2

$C_{16}H_{19}O_8N$ requires: C,54.4; H,5.4%

Light absorption: Max. at 2060 (ϵ = 16,000) and 2500 Å. (ϵ = 7,250).

3-Methoxy-2-nitrophenylacetone. - Crude ethyl 3-methoxy-2-nitrophenylacetylmalonate (5.7 g.) in glacial acetic acid (12 c.c.), sulphuric acid (1.5 c.c.; d,1.84) and water (8 c.c.) was refluxed for 6 hours when evolution of carbon dioxide was no longer apparent. The cooled solution was made alkaline with 5N sodium hydroxide and extracted with ether (3 x 50 c.c.). The combined ethereal extract was washed with water, dried (Na_2SO_4) and evaporated to give an oil which rapidly solidified. Crystallisation from aqueous ethanol gave 3-methoxy-2-nitrophenylacetone (2.0 g.) as long needles, m.p. 61-62°.

Found: C,57.6; H,5.15

$C_{10}H_{11}O_4N$ requires : C,57.4; H,5.3%

Light absorption: Max. at 2060 (ϵ = 15,800), 2650 (ϵ = 1,500) and 2900-3060 Å. (ϵ = 1,200).

7-Methoxy-2-methylindole. - 3-Methoxy-2-nitrophenylacetone (1.2 g.) in ethyl acetate (100 c.c.) was shaken at room temperature and atmospheric pressure in hydrogen in the presence of Raney nickel (1 g.; W6, Org. Synth. 29, 25). Absorption was rapid and complete after ½ hr. The filtered solution was evaporated under reduced pressure and the residue crystallised from light petroleum (b.p. 40-60°) to give 7-methoxy-2-methylindole (900 mg.) as long needles, m.p. 83-85°.

Found: C,74.6; H,6.4

$C_{10}H_{11}ON$ requires: C,74.5; H,6.8%.

Light absorption: Max. at 2200 (ε = 50,000) and 2650 Å. (ε = 9000).

The picrate separated from aqueous methanol as fine red needles, m.p. 153°.

Found: C,48.85; H,3.42

$C_{16}H_{14}O_8N_4$ requires: C,49.2; H,3.6%.

Light absorption: Max. at 2220 (ε = 45,000), 2380-2420 (ε = 13,400) and 3570 Å. (ε = 16,200).

7-Methoxy-2-methylindole dissolves in warm 5N hydrochloric acid being recovered by basification of the solution; in benzene solution on treatment with aqueous ethanolic p-dimethylaminobenzaldehyde hydrochloride it gives a violet-red colour, indistinguishable from that given by 2-methylindole (Ehrlich's reaction).

3-Methoxy-2-nitrobenzylmethylcarbinol.- A solution of 3-methoxy-2-nitrophenylacetone (1.0 g.) in ethanol (30 c.c.) and water (10 c.c.) was kept at room temperature for 2 hrs. with sodium borohydride (750 mg.) then diluted with water (100 c.c.) and extracted with chloroform (3 x 50 c.c.). The dried (Na_2SO_4) extract was evaporated and the residue crystallised from benzene-light petroleum (b.p. 60-80°) to give 3-methoxy-2-nitrobenzylmethylcarbinol

(900 mg.) as needles, m.p. 82-83° subliming at 70° 0.001 mm.

Found: C,56.8; H,6.4.

$C_{10}H_{13}O_4N$ requires: C,56.9; H,6.2%.

Light absorption: Max. at 2140 (ϵ = 11,600), 2720 (ϵ = 1,550) and inflexion at 2360-2460 Å. (ϵ = 1700).

2-Amino-3-methoxybenzylmethylcarbinol. - 3-Methoxy-2-nitrobenzylmethylcarbinol (500 mg.) in ethyl acetate (50 c.c.) was shaken at room temperature and atmospheric pressure in hydrogen with the Raney nickel catalyst above (0.5 g.) until absorption was complete (5 min. with fresh catalyst). The filtered solution was evaporated under reduced pressure and the residue crystallised from light petroleum (b.p. 40-60°) to give 2-amino-3-methoxybenzylmethylcarbinol (400 mg.) as needles, m.p. 69° subliming at 60°/0.001 mm.

Found: C,66.4; H,8.6.

$C_{10}H_{15}O_2N$ requires: C,66.3; H,8.3%.

Light absorption: Max. at 2120 (ϵ= 21,000), 2380 (ϵ = 6,600) and 2860 Å. (ϵ = 2,500).

(±) 3:4-Dihydro-8-methoxy-3-methylisocoumarin. - A solution of the foregoing amino-alcohol (300 mg.) in hydrochloric acid (0.43 c.c.; d,1.16) and water (9 c.c.) was diazotised with a solution of sodium nitrite (120 mg.) in water (1 c.c.) at 0°. After neutralisation with sodium carbonate the diazonium solution was added to a solution of potassium cyanide (380 mg.), nickel chloride (300 mg.) and anhydrous sodium carbonate (100 mg.) in water (10 c.c.) at 15° with stirring, kept 2 hours and heated at 70° for 15 minutes. The cooled reaction solution was extracted with ether (3 x 20 c.c.) and the combined, dried (Na_2SO_4) extract evaporated to give a gum which was treated with aqueous potassium hydroxide (20 c.c.; 10%) and refluxed for 3 hrs. The solution was acidified (Congo red) and extracted with chloroform (3 x 25 c.c.); evaporation of the dried (Na_2SO_4) extract gave a gum which slowly solidified. Crystallisation from light petroleum (b.p. 40-60°) gave 3:4-dihydro-8-methoxy-3-methylisocoumarin (60 mg.) as prisms, m.p. 66-67°.

Found: C,68.7; H,6.6.

$C_{11}H_{12}O_3$ requires: C,68.7; H,6.3%.

Light absorption: Max. at 2120 (ϵ = 28,000), 2440 (ϵ = 7,400) and 3050 Å. (ϵ = 4,700).

Mellein Methyl Ether. - Mellein (26 mg.), m.p. 56-57° (lit.m.p. 58°), having light absorption: Max. at 2120 (ϵ = 20,000), 2460 (ϵ:6,500) and 3140 Å. (ϵ = 4,100), was kept in excess ethereal diazomethane at room temperature for 3 days. The solution was evaporated and the residual

gum taken up in benzene (5 c.c.) and the solution filtered through a column of Grade II alumina (3 x 1 cm.) and the column washed with benzene (200 c.c.). Evaporation of the combined eluates and crystallisation of the solute from light petroleum (b.p. 60-80°) gave mellein methyl ether (18mg.) as prisms, m.p. 88-89° (lit. 88-89°), $[\alpha]_D^{18°}$ - 245°, -250° (c,1.1, 0.5 in $CHCl_3$). A mixture with the synthetic lactone had intermediate m.p.
Light absorption: Max. at 2130 (ε = 27,000) 2430 (ε = 7,200) and 3050 Å. (ε = 4,500).

Attempted racemization. - Mellein methyl ether (11 mg.) was refluxed for 6 hrs. with 3N sodium hydroxide (5 c.c.). Acidification and isolation using chloroform followed by crystallisation from light petroleum (b.p. 60-80°) gave starting material (8 mg.) as prisms, m.p. and mixed m.p. 86-88°, $[\alpha]_D^{18°}$ - 240° (c,0.4 in $CHCl_3$).

3-Methylmeconin. - 6-Hydroxymethyl-2:3-dimethoxy-NN-dimethylbenzamide (2.0 g.) was prepared and oxidised with chromic acid as described by Blair, Brown and Newbold (loc. cit.) and the resulting crude aldehyde in ether (10 c.c.) treated at 15° with the Grignard reagent prepared from methyl iodide (1.42 g.) and magnesium (250 mg.) in ether (10 c.c.), the mixture refluxed for 1 hr. cooled, treated with hydrochloric acid (100 c.c.; 3N) and refluxed for 1½ hrs. Extraction with ether and washing with aqueous sodium hydrogen carbonate gave a product which was crystallised from benzene-light petroleum (b.p. 60-80°) as 3-methylmeconin (60%) in prismatic needles, m.p. 101° subliming at 100° 0.001 mm. and not depressed on mixing with a specimen prepared in 5% yield using the method of Simonis, Marben and Mermod (*loc. cit.*)

Found: C,63.0; H,6.0

Calc. for $C_{11}H_{12}O_4$: C,63.45; H,5.8%.

Light absorption: Max. at 2150 (ε = 29,000) and 3060 Å. (ε = 4,300). Using ethylmagnesium bromide, 3-ethylmeconin was prepared in 70% yield; it separated from aqueous ethanol as short prisms, m.p. 98°(lit. m.p. 98°).

Found: C,65.1; H,6.3

Calc. for $C_{12}H_{14}O_4$: C,64.85; H,6.35%.

Light absorption: Max. at 2140 (ε = 27,500) and 3060 Å. (ε = 4,000).

3-Methoxy-2-nitropropiophenone.- Using the technique described above for the preparation of diethyl 3-methoxy-2-nitrophenylacetylmalonate, 3-methoxy-2-nitrobenzoyl chloride (4.4 g.) was converted into crude ethyl 3-methoxy-2-nitrobenzoylmalonate (5.5 g.). This semi-solid was dissolved in ethanolic sodium ethoxide from sodium (0.5 g.) and ethanol (10 c.c.), methyl iodide (2 c.c.) was added and the solution refluxed for 3 hours during which methyl iodide (2 c.c.) was added in four portions. The cooled solution was diluted with water and extracted with ether (3 x 15 c.c.)

and the combined ethereal extract washed with water and dried (Na_2SO_4). Removal of the ether gave a gum which was treated as described in the above preparation of 3-methoxy-2-nitrophenylacetone to give 3-methoxy-2-nitropropiophenone (1.1 g.) which separated from aqueous ethanol as small needles, m.p. 96° subliming at 80°/0.001 mm.

Found: C,57.3; H,5.1.

$C_{10}H_{11}O_4N$ requires: C,57.4; H,5.3%.

Light absorption: Max. at 2120 (ϵ = 22,000), 2340-2400 (ϵ = 5,800) and 3080 Å. (ϵ = 2,500).

3-Ethyl-7-hydroxyphthalide. - (a) 6- Hydroxymethyl-2-methoxy-NN-dimethylbenzamide (290 mg.) was oxidised as described by Blair, Brown and Newbold (loc. cit.) and the resulting crude aldehyde in ether (20 c.c.) treated with ethereal ethylmagnesium bromide prepared from ethyl bromide (0.54 g.) and magnesium (0.12 g.) in ether (6 c.c.). A precipitate formed immediately and the mixture was refluxed for 10 minutes, cooled, treated with 3N hydrochloric acid (40 c.c.), the ether distilled off and the aqueous solution refluxed for ½ hr. The cooled solution was extracted with chloroform (3 x 50 c.c.), the combined extracts washed with water (25 c.c.), dried (Na_2SO_4) and evaporated to give a viscous oil, which could not be crystallised even after filtration in benzene solution through a column of Grade II alumina. The gum was refluxed with aqueous hydrobromic acid (20 c.c.; d,1.46) in a stream of coal gas for 1 hr. The cooled solution was diluted with water (20 c.c.) and extracted with chloroform (4 x 50 c.c.), and the combined dried (Na_2SO_4) extract evaporated to give a brown resin. The latter was extracted with boiling light petroleum (b.p. 60-80°) (4 x 50 c.c.) and the combined extracts concentrated to *ca.* 2 c.c. and kept at 0°. The resulting solid was recrystallised from light petroleum (b.p. 40-60°) to give 3-ethyl-7-hydroxyphthalide (75 mg.) as needles, m.p. 78° subliming at 75°/0.001 mm.

Found: C,67.2; H,6.1.

Calc. for $C_{10}H_{10}O_3$: C,67.4; H,5.7%.

The compound was undepressed on mixing with a specimen of *iso*ochracin m.p. 78° (*lit.* 78-79°) prepared from mellein according to Yabuta and Sumiki (*J. Agric. Chem. Soc.*, 1934, *10*, 703). It gives a violet colour with ferric chloride in aqueous ethanol.

Light absorption: Max. at 2140 (ε = 18,400), 2340 (ε = 7,000) and 3000 Å. (ε = 4,600).

(b) Using the method described above for the preparation of 3-methoxy-2-nitrobenzylmethylcarbinol, 3-methoxy-2-nitropropiophenone (700 mg.) was reduced to the corresponding alcohol, a viscous oil which was hydrogenated as given for 3-methoxy-2-aminobenzylmethylcarbinol. The product a viscous oil, was converted into the oily 3-ethyl-7-methoxyphthalide by the method described above for the formation of 3:4-dihydro-8-methoxy-3-methyl*iso*coumarin. The crude methoxy-phthalide was demethylated with boiling aqueous hydrobromic acid as in (a) to give 3-ethyl-7-hydroxyphthalide (20 mg.) which separated from light petroleum (b.p. 40-80°) as needles, m.p. 77-78° alone or mixed with preparation (a).

3':4-*Dimethoxy*-2'-*nitrodeoxybenzoin*. - To a stirred mixture of 3-methoxy-2-nitrophenylacetylchloride (600 mg.) and anisole (15 c.c.) was added anhydrous aluminium chloride (850 mg.) at 0° and the temperature then allowed to rise to room temperature. After 2 hrs. the mixture was steam-distilled to remove excess of anisole and the product extracted with ether. The ether extracts were washed with aqueous sodium hydrogen carbonate to remove any acidic material and after washing and drying (Na_2SO_4) the solvent was removed under reduced pressure to leave red oil (840 mg.). The addition of a little light-petroleum (b.p. 40-60°) and mechanical working with a glass rod induced the oil to solidify, but the best method of obtaining a pure crystalline material was by chromatography. The oil was dissolved in benzene (20 c.c.) and introduced into a small column which was then washed through with benzene (300 c.c.).

(300 c.c.). Evaporation of the benzene gave a light yellow oil (400 mg.) which rapidly solidified. Crystallisation from benzene-petrol produced needles m.p. 98° of 3':4-dimethoxy-2'-nitrodeoxybenzoin (350 mg.)

Found: C,63.84; H,4.6.

$C_{16}H_{15}O_5N$ requires: C,63.78; H,5.0%

Light absorption: Max. at 2080 (ϵ = 23,000), 2780 (ϵ = 18,800) and inflexion at 2090-2140 Å. (ϵ = 22,200).

The product gave a 2:4-dinitrophenyhydrazone on warming with Brady's reagent and then cooling.

3-Methoxy-2-nitrobenzyl-p-anisylcarbinol (not isolated).

The nitro-ketone (400 mg.) in ethanol (30 c.c.) and water(30 c.c.) was allowed to stand for 2 hrs. with sodium borohydride (200 mg.) and the solution the extracted with chloroform(3 x 20 c.c.). Evaporation of the solvent gave a gum (385 mg.) which failed to give a precipitate with Brady's reagent and would not solidify.

2-Amino-3-methoxybenzyl-p-anisylcarbinol.

The above gum (385 mg.) in ethyl acetate (150 c.c.) was shaken with Raney nickel in an atmosphere of hydrogen for 2 hrs. when absorption was complete. Filtration of the solution to remove nickel and evaporation of solvent left a solid (350 mg.) which crystallised from light petroleum (b.p. 60-80°) to give 2-amino-3-methoxybenzy-p-anisylcarbinol as needles m.p. 94°.

Found: C,71.0; H,6.5,

$C_{16}H_{19}O_3N$ requires: C,70.31; H,7.0%.

Light absorption: Max. at 2130 (ε = 24,500), 2270 (ε = 21,100) 2830 (ε = 4,250) and inflexion at 2760-2800 Å. (ε = 4,000).

(±)-3:4-Dihydro-4':8-dimethoxy-3-phenylisocoumarin. - The above amine alcohol (250 mg.) dissolved in hydrochloric acid (3 c.c.; d,1.16) was diluted with water (6 c.c.) and diazotised with a saturated solution of sodium nitrite until starch-iodide paper turned blue instantly. The solution was then neutralised with sodium carbonate and added in the cold to a mixture of potassium cyanide (600 mg.) and copper sulphate (530 mg.) in water (10 c.c.) which previously had been boiled for 5 minutes in order to convert the cupric copper to cuprous. The reaction was left overnight at room temperature (ca. 15°) and then extracted with ether. Evaporation of the solvent left a reddish brown oil and to this was added potassium hydroxide (15 c.c.; 10%) and the solution refluxed for 4 hrs. During this hydrolysis, ammonia gas was detected in the condenser. On acidification of the solution a small amount of solid was precipitated and this was collected, washed and dried. Extraction of the solid with light-petroleum (60-80°) and evaporation of the petroleum to small bulk produced crystals (needles), m.p. 150-154°.

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PART II

Phthalides, Phthalaldehydic acids and Related Products.

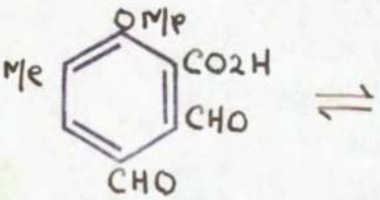
SUMMARY.

1. Two new vicinal carboxy-o-phthalaldehydes, 3-formyl-4-methylphthalaldehydic acid and 3-formyl-4-methoxyphthalaldehydic acid, analogous to the mould acid gladiolic acid, have been synthesised and their fungistatic activity evaluated.
2. The conversion of 4-hydroxymethylphthalides into the corresponding isomeric phthalan carboxylic acids by means of aqueous sodium carbonate and other reagents is described and the mechanism of the reaction discussed.
3. Two new o-phthalaldehydes, 4:5-methylenedioxyphthalaldehyde and its 3-methoxy analogue have been prepared starting from cotarnine a degradation product of the alkaloid narcotine.
4. The value of N-bromosuccinimide as a reagent in the preparation of phthalaldehydic acids and o-phthalaldehydes has been further demonstrated by the preparation of opianic acid and 3-bromopianic acid from meconin and 4-bromomeconin respectively, and 4:5-dimethoxyphthalaldehyde from 4:5-dimethoxyphthalyl alcohol.
5. The existence of the o-diformyl grouping in 3-formylopianic acid has been proved by the preparation of an isonapthazarin derivative.
6. A new oxidation method for the conversion of phthalides into phthalaldehydic acids is reported and a new synthesis of 7-methoxyphthalide given.

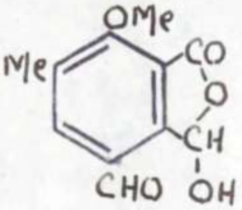
Introduction.

Considerable interest has been aroused recently by the elucidation of the structures of the metabolic mould products, gladiolic (I) (1, 2) and cyclopaldic (II) (3) acids from *Penicillium gladioli* Machacek and *Penicillium cyclopium* Westling, respectively. The vicinal carboxy-*o*-phthalaldehyde system hitherto unknown, presented new problems of synthesis in which Brown and Newbold became chiefly interested. Their synthesis of gladiolic acid (I) confirmed its structure (4).

Both acids, gladiolic and cyclopaldic, were found to be strongly antifungal, and weakly antibacterial substances which existed in tautomeric keto-lactol forms (Ia, Ib; II).

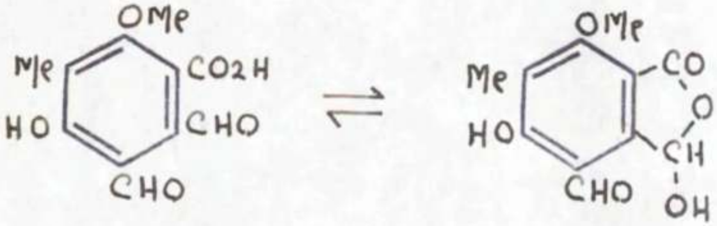


(Ia)



(Ib)

(Ic; R = OH)
(Id; R: O⁻)



(II)

By ultra-violet and infra-red spectroscopic investigation Grove (5) established that the lactol form (Ib) was present in the solid state, but in aqueous solution an equilibrium between the lactol form and the open chain form (Ia) existed, the pH being the controlling factor. In aqueous solutions of low pH, the lactol form was predominant, but on increasing the pH of the solution more and more of the hydrated open chain form (dihydroxyphthalan) (Ic and Id) was produced; thus, in the transition from a pH of 2.2 to a pH of 9, a change from 100% lactol form to 100% of open chain form was accomplished.

Various attempts have been made to correlate the effect of the pH of the external medium and the fungistatic activity of the compound and, Brian *et al*. (6) has suggested that the activity, as in the case of gladiolic acid, could be explained on the assumption that only the undissociated molecules penetrated the plasma membrane of the spore, but Grove (5) did not wholly agree with this. He believed that although the most effective penetrating species was indeed the undissociated molecule, this was also the inactive principle, while the hydrated open chain anion (Id) which had the greater difficulty in effecting penetration, was the species primarily responsible for the fungistatic activity.

As a result of a great number of tests on derivatives of gladiolic acid, simple model compounds and o-phthalaldehyde, Grove (5) was able to confirm that the fungistatic activity was conferred by the presence of the two formyl-groups in the ortho-position of the benzene nucleous. Phthalyl alcohol, o-formylbenzyl alcohol, phthalaldehydic acid and dimethyl phthalate, all compounds closely related to o-phthalaldehyde, differing only in the degree of oxidation or reduction, were inactive. The introduction of a carboxyl--group in an adjacent position to the o-diformyl-groups, enhanced greatly the specificity of the molecule. This is attributed to the fact that, near the pK value of an acid such as gladiolic acid, small changes in pH would not only produce relatively large changes in the ratio of undissociated molecules to ions, but the carboxyl substituent would confer on the molecule the penetrating power given to any weak acid. Furthermore, being situated next to one of the formyl-groups and participating in the tautomeric system (I) it would limit the proportion of fungistatic molecules and make it dependent upon pH.

During the past fifty years the o-phthalaldehyde system has created only a moderate interest; consequently, of the preparative methods that do exist (7-20), many are of very limited application being based upon the oxidation of o-xylene to o-phthalaldehyde itself. Recently however, mainly due to the efforts of Weygand and his co-workers (11, 18), who utilized the oxidation of various o-phthalyl alcohols by various reagents, and of Brown and Newbold, a few preparative methods of a more general application are now available.

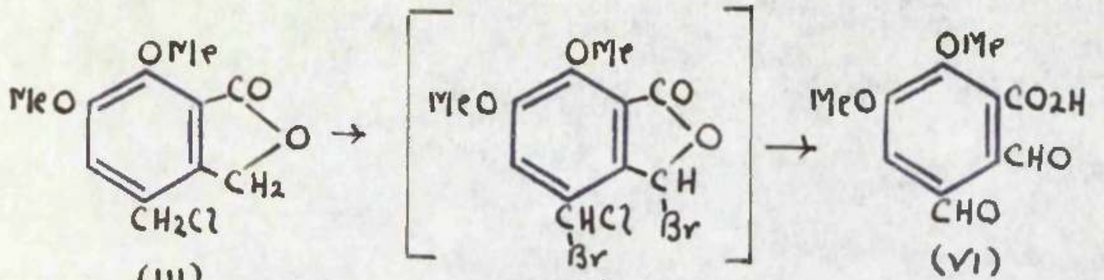
The preparation of 3-Formylopianic and Gladiolic acids.

The initial exploratory work of Brown and Newbold (21) on the synthesis of gladiolic acid (I) led them first to a synthesis of an analogous compound, namely 3-formylopianic acid (VI), from the readily available meconin (6:7-dimethoxyphthalide) (IV). As a result of this work a successful synthesis of the mould acid itself was evolved.

4-Chloromethylmeconin (III), the starting material in the synthesis of 3-formylopianic acid (VI), was obtained by the direct chloromethylation of meconin using the method of Edwards, Perkin and Stoyle (22).

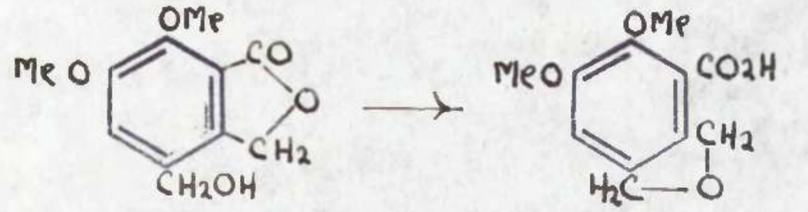
(IV) (III)

Treatment of (III) with three molecular proportions of N-bromosuccinimide in carbon tetrachloride, followed by hydrolysis of the intermediate (V) with hot water, gave 3-formylopianic acid (VI).



(III) (V) (VI)

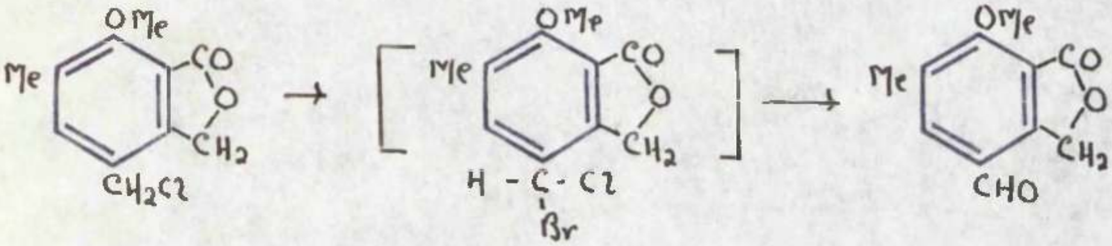
An alternative route to 3-formylopianic acid appeared to be the direct oxidation of 4-hydroxymethylmeconin (VII), the sodium carbonate hydrolysis product of 4-chloromethylmeconin. Oppenauer oxidation, with benzophenone as a hydrogen acceptor, of (VII) gave, not 3-formylopianic acid, but another acid which was shown to be 5:6-dimethoxyphthalan-4-carboxylic acid (VIII).



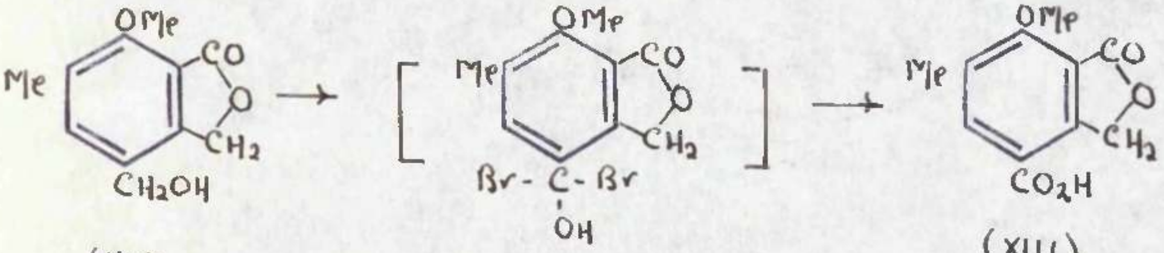
(VII) (VIII)

Oxidation of (VIII) using 2 molecular proportions of N-bromosuccinimide, gave the required 3-formylopianic acid (VI).

It appeared to Brown and Newbold (23) that by analogy, the synthesis of gladiolic acid (I) was now feasible by a route similar to that employed for 3-formylopianic acid. Treatment of 4-chloromethyl-7-methoxy-6-methylphthalide (X) with N-bromosuccinimide followed by hydrolysis of the intermediate however, did not give gladiolic acid but 4-formyl-7-methoxy-6-methylphthalide (XI) (deoxygladiolic acid).

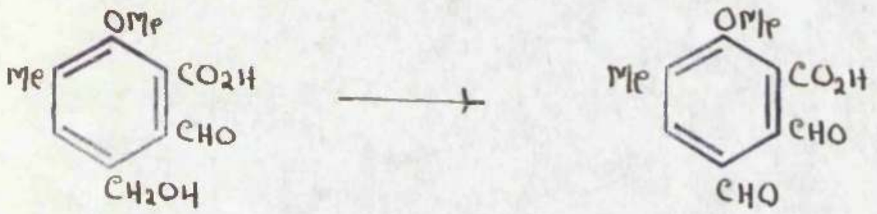

(X) (IX) (XI)

Oxidation of 4-hydroxymethyl-7-methoxy-6-methylphthalide (XII) with three molecular proportions of N-bromosuccinimide proved equally unsuccessful, 7-methoxy-6-methylphthalide-4--carboxylic acid (XIII) being the product; one molecular proportion of reagent gave 4-formyl-7-methoxy-6-methylphthalide (XI)


(XII) (XIII)

It was therefore apparent that the methylene group no longer under the influence of a more powerful electron releasing methoxyl-group in the p-position, was now impregnable towards attack by N-bromosuccinimide, an electrophilic reagent.

Raistrick and Ross (2) however had shown that dihydrogladiolic acid (XIV) could be oxidised to gladiolic acid with sodium periodate in sulphuric acid. In effect a phthalaldehyde had been produced from an o-hydroxymethylbenzaldehyde.



(XIV) (I)

Applying this latter procedure to their deoxygladiolic acid (XI) Brown and Newbold (4) obtained gladiolic acid itself in small yield.

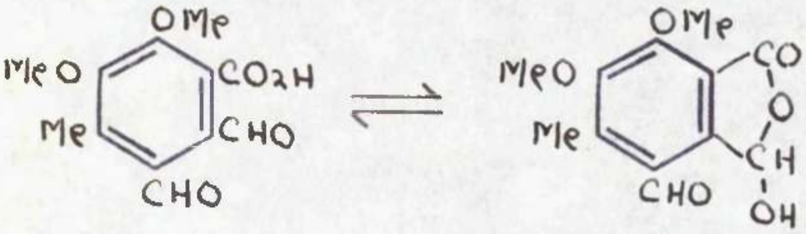
(XI) (I)

THEORETICAL.

The work described in this part of the thesis represents a continuation of the synthetic studies of Brown and Newbold (4, 21, 23, 24) on vicinal carboxy-*o*-phthalaldehydes, *o*-phthalaldehydes and related compounds, and also an attempt to supply further evidence for Groves' theory (5) concerning the relationship between structure and fungistatic activity, by the preparation of compounds suitable for biological testing within the scope of the theory.

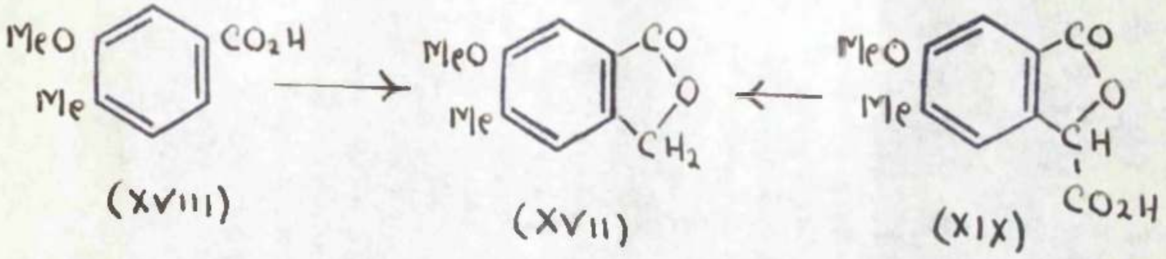
The Preparation of 3-Formyl-4-methylopianic Acid.

The synthetic route envisaged for 3-formyl-4-methylopianic acid (XV), tautomeric with (XVI), was one broadly resembling that for 3-formylopianic acid or gladiolic acid. A suitable starting material therefore appeared to be the 6-methoxy-5-methylphthalide (XVII) as prepared by Charlesworth, Rennie, Sinder and Yan (25) by the action of hydrochloric



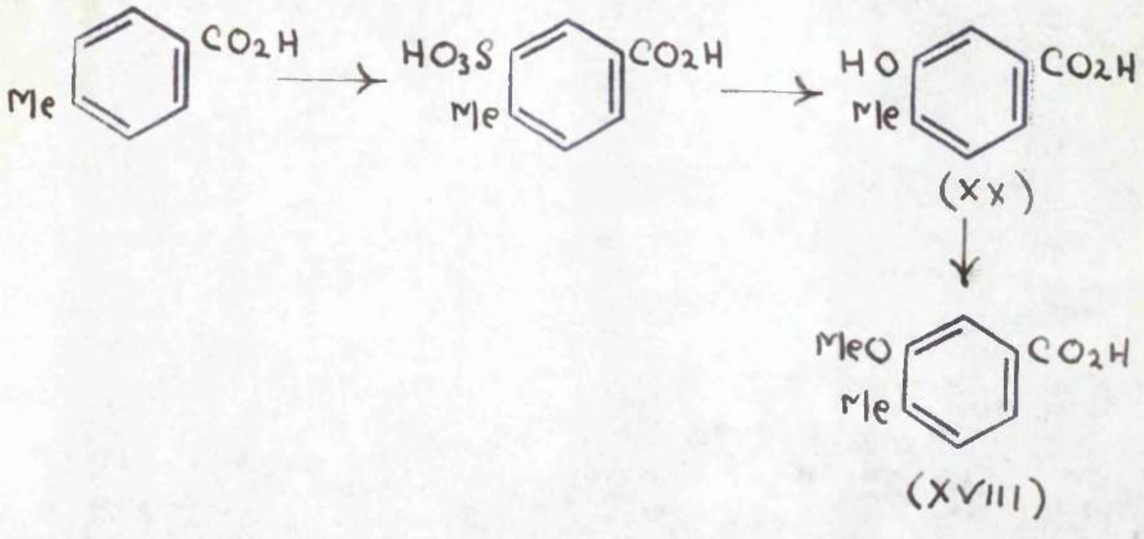
(XV) (XVI)

acid and formaldehyde on 2-methoxy-*p*-toluic acid (XVIII)

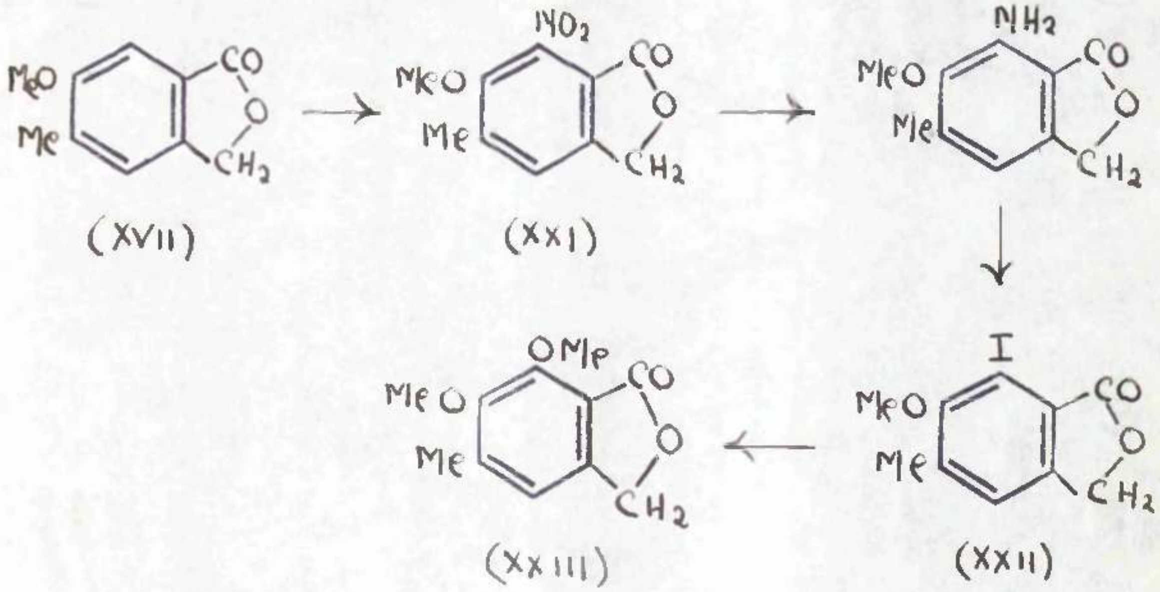


The orientation of this phthalide (XVII) was confirmed by the preparation of the same compound by the decarboxylation of 6-methoxy-5-methylphthalide-3-carboxylic acid (XIX), the orientation of which had been rigidly established by Meldrum and Kapadia (26).

2-Methoxy-p-toluic acid (XVIII) was readily obtained by the sulphonation of p-toluic acid followed by the replacement of the sulphonic-group with a hydroxyl-group according to the conditions of Meldrum and Perkin (27); methylation of the 2-hydroxy-p-toluic acid (XX) with dimethyl sulphate gave 2-methoxy-p-toluic acid in good yield.

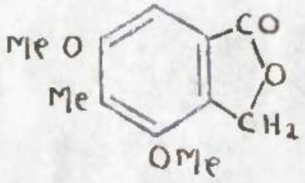


Nitration of 6-methoxy-5-methylphthalide (XVII) yielded 6-methoxy-5-methyl-7-nitrophthalide (XXI) and not the 4-nitro isomer, the proof of which became apparent from subsequent reactions. The nitro-group was replaced by a methoxyl-group by a process which involved the catalytic hydrogenation of nitro to amino, diazotisation of the amine and introduction of an iodo-group by a Sandmeyer reaction to give (XXII), and finally, elimination of the iodine and its replacement with methoxyl using the method of McRae, Van Order, Griffiths and Habgood (28). The product 5-methylmeconin (XXIII) had a m.p. of 82.5°,



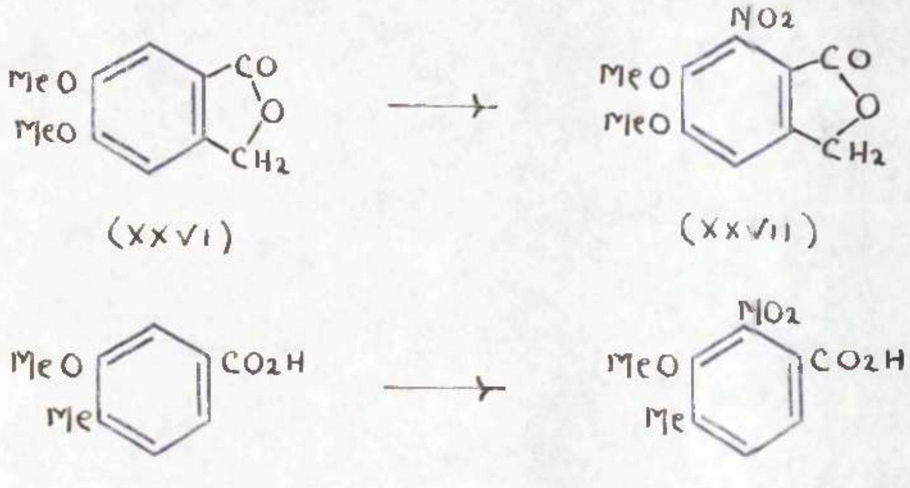
and had nitration taken place in the 4-position, the resulting methoxy-derivative would have been 4:6-dimethoxy-5-methylphthalide (XXV) a compound which has been prepared independently by Charlesworth and Robinson (29) who gave a m.p. 158°

and by Asahina and Hayashi (30) who gave a m.p. 155°.



(XXV)

Thus the nitration of 6-methoxy-5-methylphthalide (XVII) was comparable to nitration of *m*-meconin (5:6-dimethoxyphthalide) (XXVI) to 7-nitro-*m*-meconin (XXVII), (29, 35) and 2-methoxy-*p*-toluic acid to 2-methoxy-3-nitro-*p*-toluic acid (XXVIII) (31)



(XXVI) (XXVII)

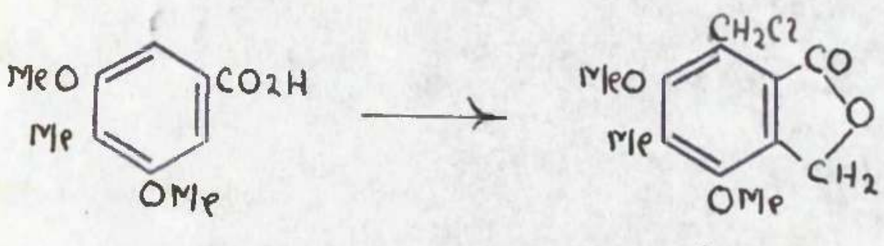
(XXVIII)

The nitration in the three cases therefore agreed with the hypothesis of Jones and Robinson (32) who believed, that if two identical groups, such as alkoxy, co-existed in a molecule and directed substituents to different positions, the influence of the one which was in the o- or p- position to a negative group (e.g. nitro or carboxyl) was weakened so that the other alkoxy group, or similar group, controlled the direction of the reaction. Ingold (33) classified this directive influence into the vicinal position, by the methoxy-group, m-substituted to a carboxyl, as an example of the general behaviour expected when a group of the + E type was substituted in the m-position to one of the -I -M type.

Chloromethylation of 5-methylmeconin (XXIII) gave 4-chloromethyl-5-methylmeconin (XXIX) m.p. 118-121° different from the product, 7-chloromethyl-4:6-dimethoxy-5-methylphthalide (XXX) m.p. 130-131° obtained by Charlesworth et al. (25) by the action of formaldehyde and hydrochloric acid on 3:5-dimethoxy-p-toluic acid.

(XXIII)

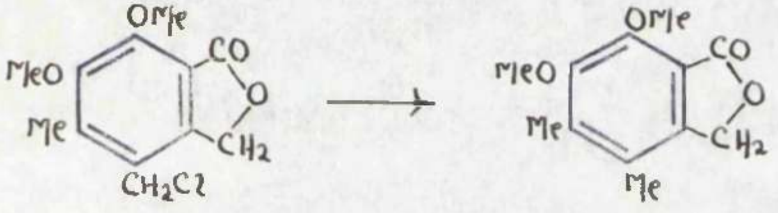
(XXIX)



(XXX)

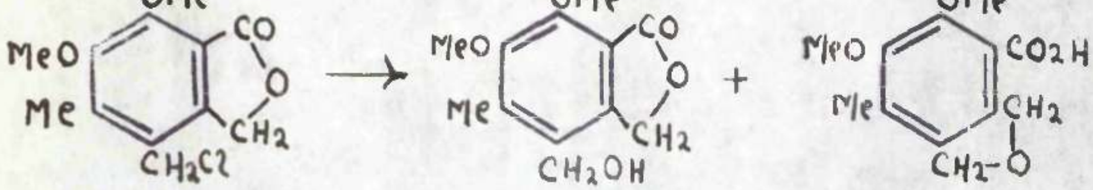
This was further evidence for the correctness of the orientation of the nitro-group in 6-methoxy-5-methyl-7--nitrophthalide (XXI).

The chloromethyl-compound (XXIX) on reduction with zinc dust and hydrochloric acid gave 4:5-dimethylmeconin (XXXI).



(XXIX) (XXXI)

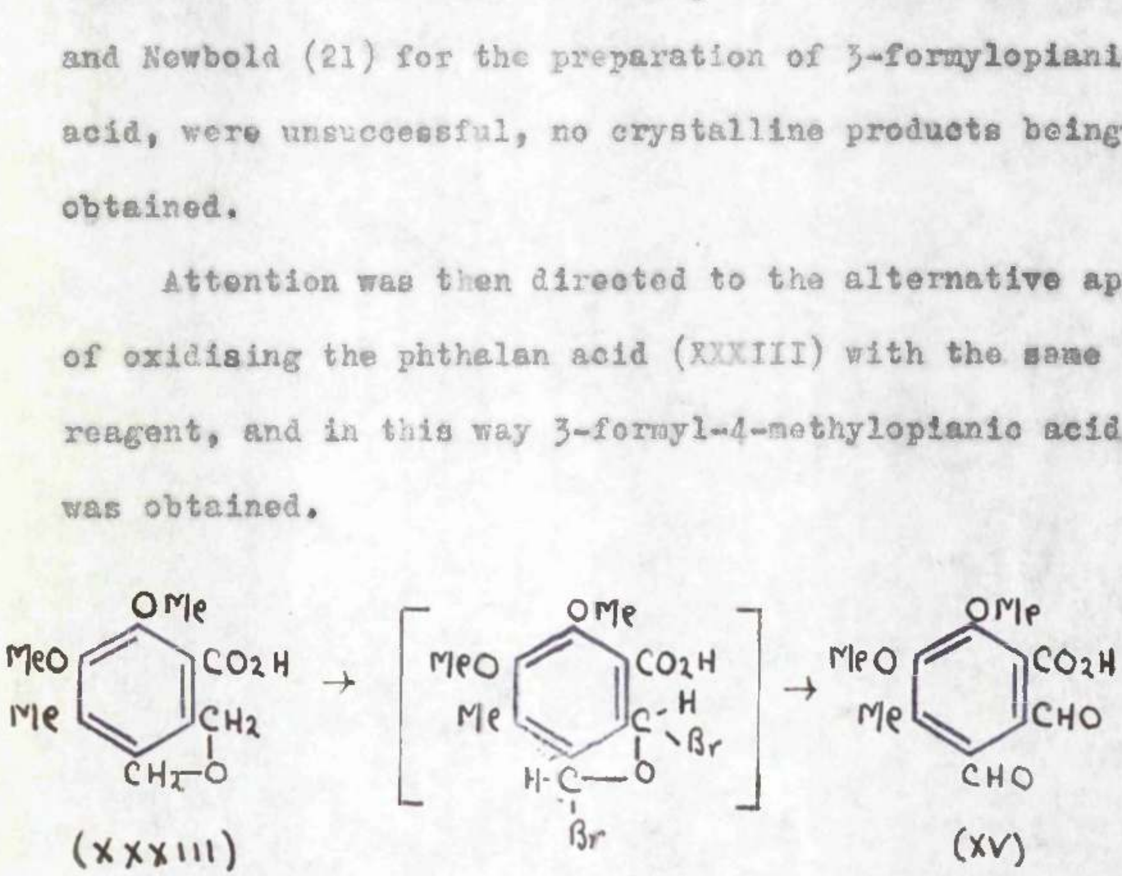
Brown and Newbold (21) have shown that 4-chloromethylmeconin (III) when heated with aqueous sodium carbonate yielded 4-hydroxymethylmeconin (VII) which then underwent an novel isomerisation to the carboxy-phthalan (VIII) on heating with aluminium-*t*-butoxide (see p.45). When 4-chloromethyl-5-methylmeconin (XXXIX) was hydrolysed with aqueous sodium carbonate, 5:6-dimethoxy-7-methylphthalan--4-carboxylic acid (XXXIII) was unexpectedly obtained as the major product_with 4-hydroxy-5-methylmeconin (XXXII), the yield of the former being increased on prolonging the reaction time.


(XXIX) (XXXII) (XXXIII)

The phthalan acid (XXXIII) was converted quantitatively into (XXXII) on heating with mineral acid. The mechanism of the reaction will be discussed later.

Attempts to convert 4-chloromethyl-5-methylmeconin (XXIX) into 3-formyl-4-methylopianic acid (XV) by oxidation with N-bromosuccinimide according to the method of Brown and Newbold (21) for the preparation of 3-formylopianic acid, were unsuccessful, no crystalline products being obtained.

Attention was then directed to the alternative approach of oxidising the phthalan acid (XXXIII) with the same reagent, and in this way 3-formyl-4-methylopianic acid was obtained.


(XXXIII) (XV)

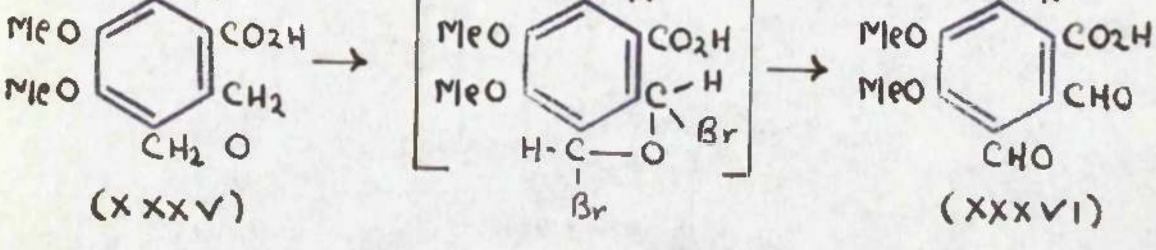
It has been shown by Grove (1) that when gladiolic acid was heated with aqueous sodium hydroxide a rearrangement took place and the product was formulated as 7-methoxy-6-methylphthalide-4-carboxylic acid (XIII) (_iso_gladiolic acid).

In a similar manner 3-formyl-4-methylopianic acid underwent this rearrangement to give 5-methylmeconin-4-carboxylic acid (XXXIV).

The same acid (XXXIV), was also obtained from the oxidation of the phthalan acid (XXXIII) in the cold with chromium trioxide in acetic acid.

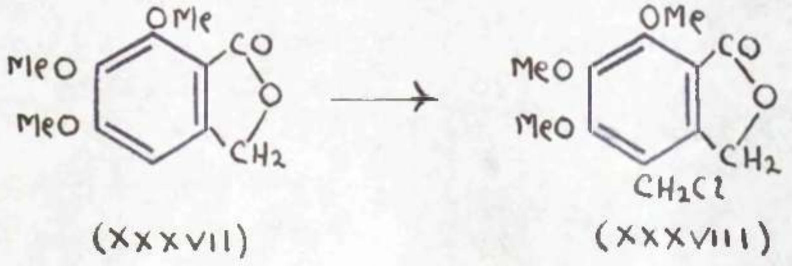
<u>Preparation of 3-Formyl-4-methoxyopianic Acid.</u>

Like its 4-methyl analogue, 3-formyl-4-methoxyopianic acid (XXXVI) was prepared by the N-bromosuccinimide oxidation of the corresponding phthalan acid (XXXV)



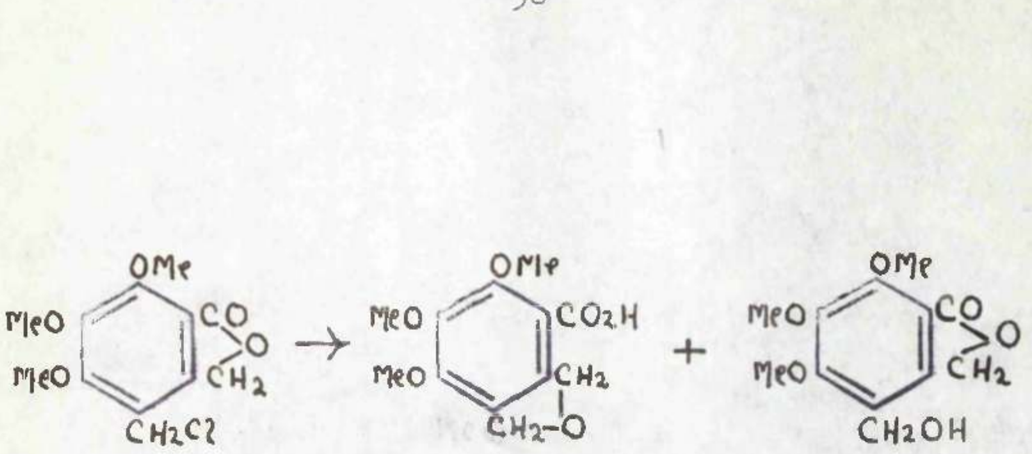
The starting material was 7-nitro-m-meconin (XXVII) (29, 35) and this was converted into 5:6:7-trimethoxyphthalide (XXXVII) using the method of McRae, Van Order, Griffiths and Habgood (28) which has been already described for the preparation of 5-methylmeconin (XXIII).

With the chloromethylation conditions of Edwards, Perkin and Stoyle (22), no crystalline material was obtained with 5:6:7-trimethoxyphthalide, but with the modified conditions employed by Wilson, Zirkle, Anderson, Stehle and Ullyot (34) for the preparation of meconin from o-veratric acid (2:3-dimethoxybenzoic acid), 5:6:7-trimethoxyphthalide was readily converted into 4-chloromethyl-5:6:7-trimethoxyphthalide (XXXVIII).



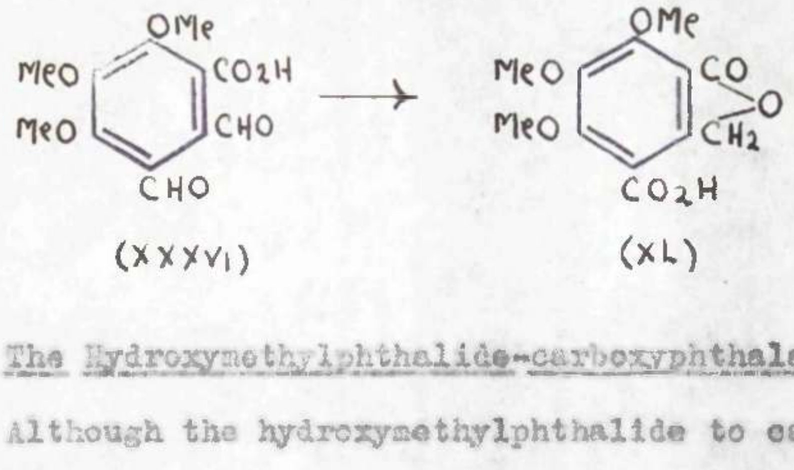
(XXXVII) (XXXVIII)

Attempted oxidations with N-bromosuccinimide on this latter compound failed as was the case with its 5-methyl analogue, but sodium carbonate hydrolysis again produced a mixture of phthalan acid (XXXV) and hydroxymethylphthalide (XXXIX).



(XXXVIII) (XXXV) (XXXIX)

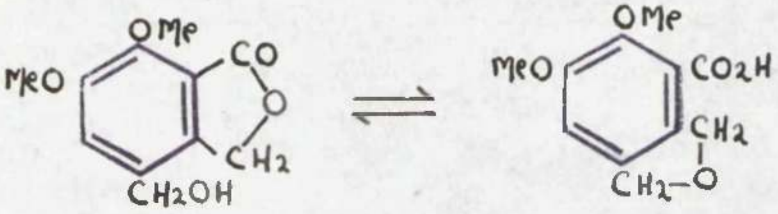
Treatment of the phthalan acid (XXXV) with two molecular proportions of N-bromosuccinimide followed by hydrolysis of the intermediate afforded the required 3-formyl-4-methoxyopianic acid (XXXVI) and the latter compound on heating with aqueous sodium hydroxide underwent the characteristic rearrangement of the carboxy-*o*-dialdehyde system to give 5:6:7-trimethoxyphthalide -4-carboxylic acid (XL).



(XXXVI) (XL)

The Hydroxymethylphthalide-carboxyphthalan Rearrangement.

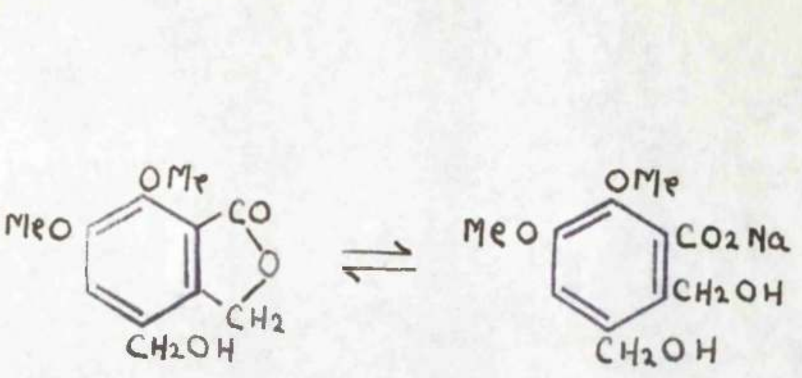
Although the hydroxymethylphthalide to carboxyphthalan rearrangement had been accomplisehd using aluminium-*t*-butoxide (21) as catalyst, the conversion by means of aqueous sodium carbonate was without precedent, and in order to gain information of the nature and mechanism of the reaction, it was decided to study the behaviour of 4-hydroxymethylmeconin (VII) with various bases.



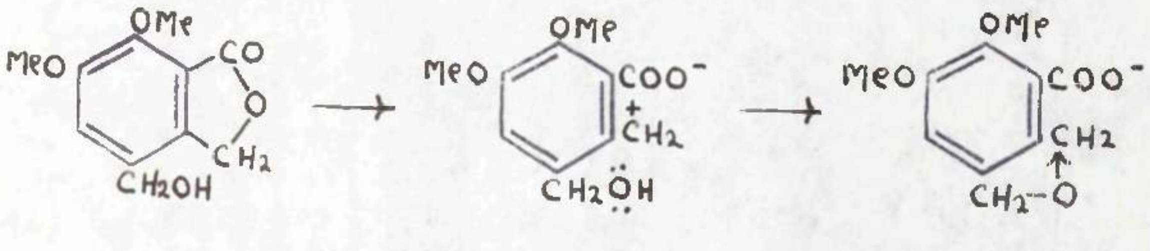
(VII) (VIII)

It was found that the isomerisation to 5:6-dimethoxyphthalan-4-carboxylic acid (VIII) was achieved in 8% yield by heating with aqueous sodium hydroxide, in 31% yield by prolonged heating with sodium carbonate, in 39% yield by heating with sodium methoxide in benzene, in 60% yield by heating with aluminium-t-butoxide in benzene (21) and in quantitative yield by using sodium methoxide in methanol.

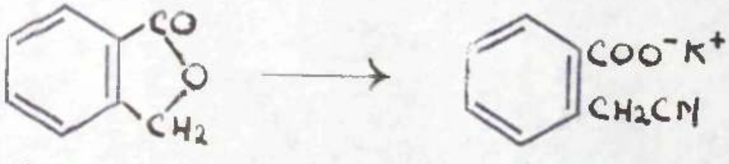
The low degree of conversion with aqueous sodium hydroxide would appear to be significant. In strong alkaline media the molecule undoubtedly would have existed in the ring opened form (VIIa), a condition which would have been most favourable towards a mechanism which involved the elimination of water from the adjacent hydroxymethyl-groups. The conversion in low yield to phthalan acid however, at once discredited such a mechanism.


(VII) (VIIa)

It was a remarkable fact that when sodium methoxide in methanol was used as a catalyst, the reaction should have gone quantitatively towards the phthalan acid without any ester formation whatsoever, and it was therefore proposed that the course of the rearrangement began by a cleavage of the lactone ring between the methylene group and the adjacent oxygen atom, giving a sodium salt bearing an intermediate carbonium ion.

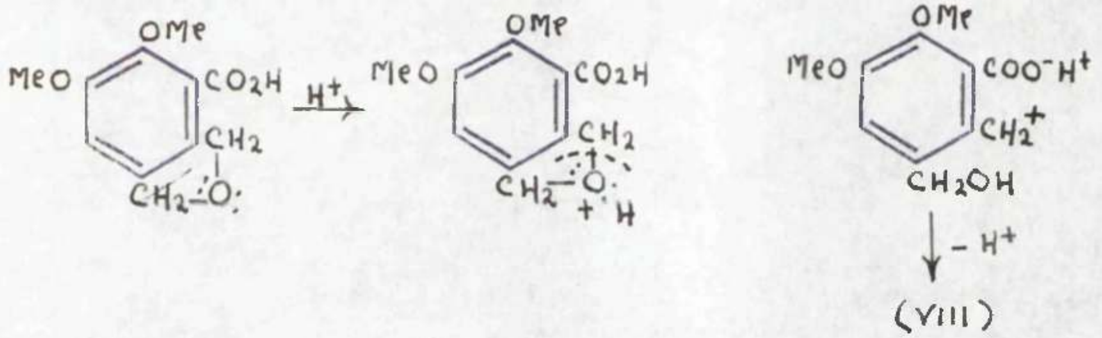


Evidence for such a mode of ring opening was found in the reaction of phthalide with potassium cyanide, in which the potassium salt of o-carboxyphenylacetonitrile was formed (XLII)(66).


(XLI) (XLII)

The interaction of the carbonium ion and the hydroxymethyl group with loss of a proton would result in the formation of the phthalan ring.

The reverse reaction of phthalan acid to hydroxymethylphthalide, in acid solution, was again readily explained by the mechanism in which the intermediate carbonium ion participated.



Clear evidence that the phthalan ring did in fact open in this manner was gained from an experiment in which the phthalan acid was treated with dry hydrogen chloride. Hydroxymethylphthalide (VII) was formed in small yield but no chloromethylmeconin was obtained.

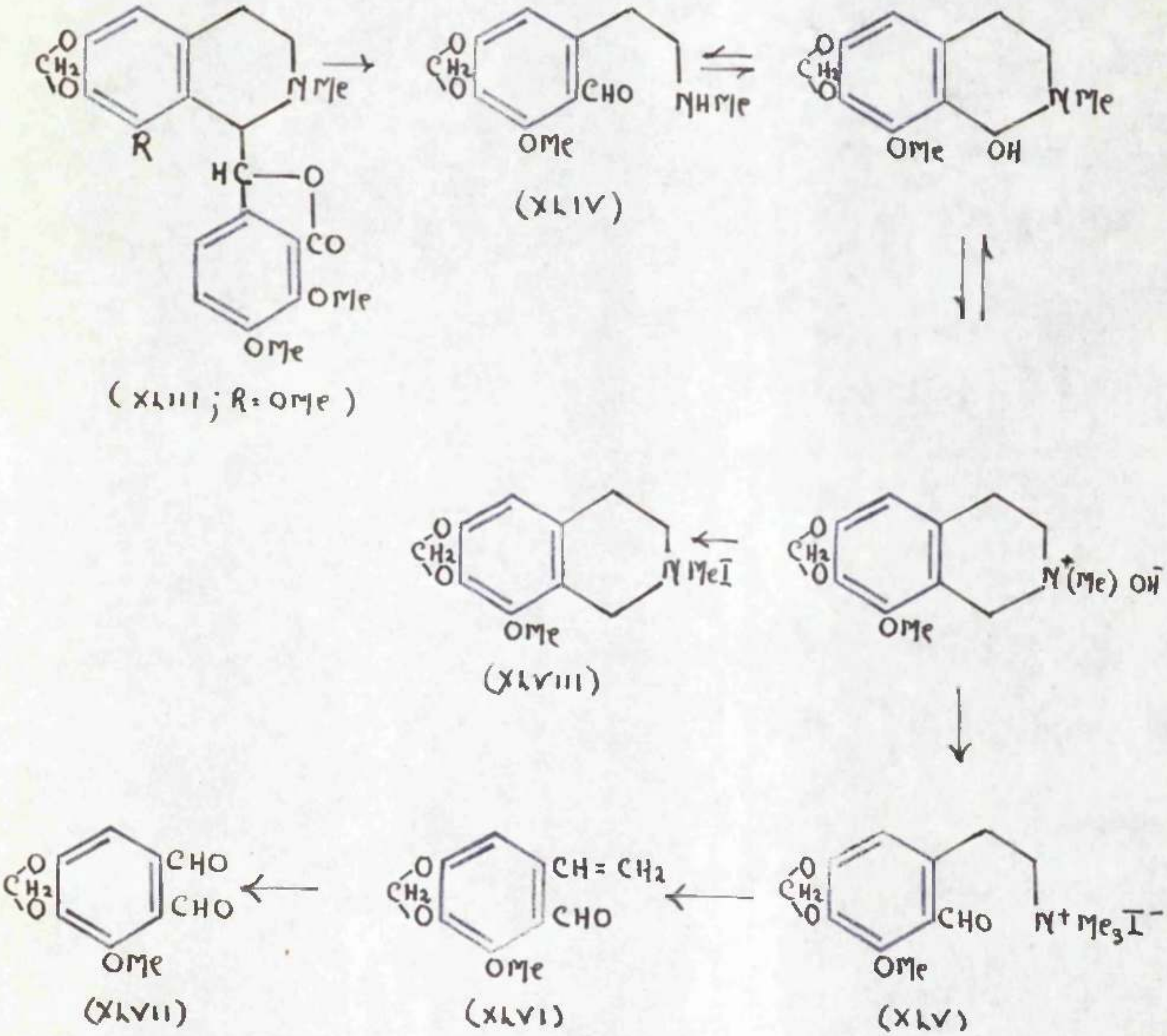
In a repeat experiment of the sodium carbonate hydrolysis by Brown and Newbold (21) of 4-chloromethylmeconin, it was found that a 20% conversion to phthalan acid had occurred on refluxing for ½ hr, and it was of interest to compare this figure with the 33 and 30% conversions respectively, under similar hydrolysis conditions for 4-chloromethyl-5-methyl and 4-chloromethyl-5-methoxyphthalides. From an examination of these figures it would appear anomalous that these substituents, methyl and methoxy in the meta-position to where carbonium ion formation occurred, and one having a + I and the other a - I effect, should both have influenced the course of the isomerisation in such a way as to account for almost the same degree of conversion to phthalan acid.

The dissociation constants of the phthalan acids discussed have been measured, and as expected the 7- substituents by increasing the electron availability in the para-position, caused a weakening of the acids. Thus, 5:6-dimethoxyphthalan-4-carboxylic acid (VIII) (pK_a 3.5) was a stronger acid than either 5:6:7-trimethoxyphthalan-4-carboxylic acid (XXXV) (pK 3.73) or 5:6-dimethoxy-7-methylphthalan-4-carboxylic acid (XXXIII) (pK_a 3.75).

The Preparation of 3-Methoxy-4:5-methylenedioxyphthalaldehyde and 4:5-methylenedioxyphthalaldehyde.

Cotarnine (XLIV), one of the oxidation products of the opium alkaloid Narcotine (XLIII; R = OMe), can be degraded to give the nitrogen free o-vinylbenzaldehyde, cotarnone (XLVI), a compound which proved suitable as a starting material for the preparation of 3-methoxy-4:5-methylenedioxyphthalaldehyde (XLVII).

With methyl iodide, cotarnine (XLIV) behaved as a secondary amine forming two products, cotarninemethine methiodide (XLV), and the water soluble cotarnine hydriodide (XLVIII). Following the usual course of exhaustive methylation, cotarninemethine methiodide (XLV) decomposed further on heating with alkali (36), with the elimination of trimethylamine to give cotarnone(XLVI).



(XLIII; R=OMe)

(XLIV)

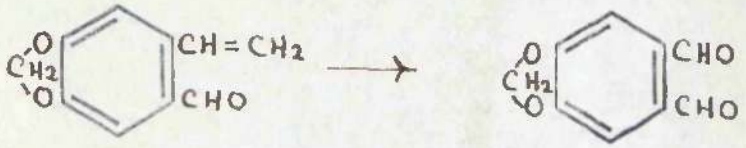
(XLVIII)

(XLVII)

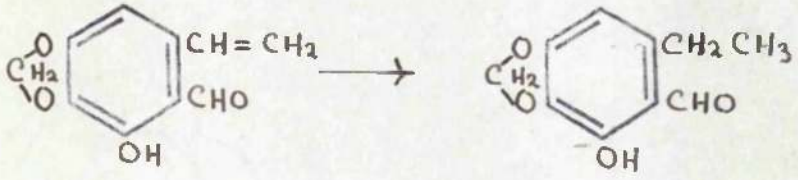
(XLVI)

(XLV)

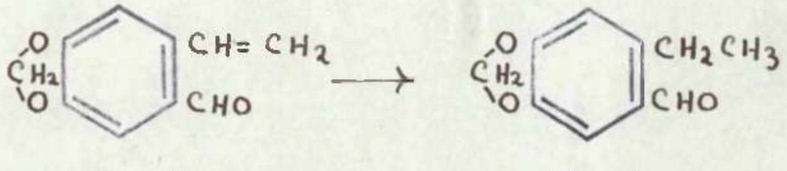
Hydrastal (XLIX), the corresponding starting material for the preparation of 4:5-methylenedioxyphthalaldehyde (L) has been obtained by a similar degradation of the alkaloid hydrastinine (XLIII; R = H), which differed from narcotine in the 8-position, having no methoxyl-group (37). Hydrastinine however, was not available to us, and hydrastal (XLIX) was prepared from cotarnine by the Brown and Newbold (40) modification of the method of Dormeyer and Freund (38), and Pyman and Remfry (39).


(XLIX) (L)

Spath, Schmid and Sternberg(41) have shown the presence of a vinyl group in norcotarnone (LI), a degradation product of Narcotine, by reduction of the group to ethyl (LII), and the presence of a vinyl group

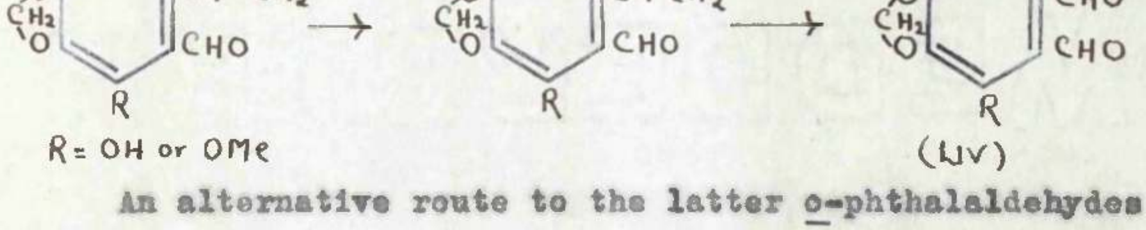

(LI) (LII)

in hydrastal was likewise shown by Brown and Newbold (40) who reduced the compound, over palladium, and obtained 6-ethylpiperonal (LIII) which they isolated as the 2:4-dinitrophenylhydrazone.


(XLIX) (LIII)

Additional evidence for the existence of the o-vinylbenzaldehyde system in hydrastal and cotarnone, was supplied by our synthesis from the latter compounds, of 4:5-methylenedioxyphthalaldehyde (L) and its 3-methoxy analogue, respectively

Using osmium tetroxide in benzene with a trace of pyridine, the double bonds of hydrastal (XLIX) and cotarnone (XLIV) were hydroxylated to the diols. Oxidation of the diols with periodate brought about the normal bond cleavage between the hydroxylated carbon atoms and produced 4:5-methylenedioxyphthalaldehyde (LIV; R = H) and 3-methoxy-4:5-methylenedioxyphthalaldehyde (LIV; R = OMe) respectively.


R = OH or OMe

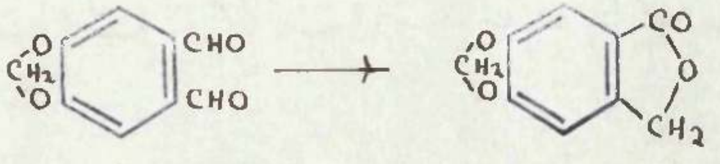
(LIV)

An alternative route to the latter o-phthalaldehydes not involving the use of the costly osmium tetroxide was sought, and it was found that cotarnone (XLIV) could be converted very smoothly to 3-methoxy-4:5-methylenedioxyphthalaldehyde by low temperature ozonolysis. The preservation of the CHO group under these conditions was noteworthy. Extreme care had to be exercised to ensure all solvents, especially chloroform, were free from mineral acid since a trace was sufficient to destroy the phthalaldehyde as it formed. Consequently, the ozonide was best decomposed by heating the solvent containing it cautiously, with water alone.

A similar ozonolysis of hydrastal yielded an amorphous powder, m.p. 120°, but ozonolysis of norcotarnone (LI) (43) gave a good yield of a crystalline material m.p. 110°, different from starting material (m.p. 89°). The Thiele (42) test indicated the presence of an o-phthalaldehyde system but a satisfactory analysis consistent with the structure (LIV; R = OH) was not obtained.

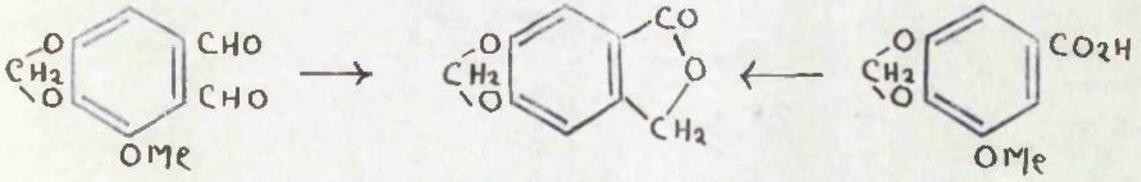
Alkali Treatment of 4:5-Methylenedioxyphthalaldehyde and 3-methoxy-4:5-methylenedioxyphthalaldehyde.

When 4:5-methylenedioxyphthalaldehyde (L) was heated on a steam-bath with alkali, a Cannizzaro reaction took place, and 5:6-methylenedioxyphthalide (LV) was produced. (The latter compound was undepressed on admixture with a sample of 5:6-methylenedioxyphthalide as prepared by Stevens (44) and Stevens and Robertson (45)).



(L) (LV)

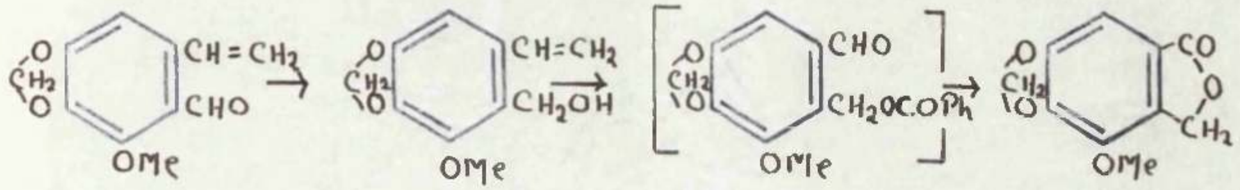
The 3-methoxy-4:5-methylenedioxyphthalaldehyde (XLVII) when heated with concentrated alkali, gave 4-methoxy-5:6-methylenedioxyphthalide (LVI), previously obtained by Spath, Schmid and Sternberg (41) by the action of formaldehyde and hydrochloric acid on myristicinic acid (LVII).



(XLVII) (LVI) (LVII)

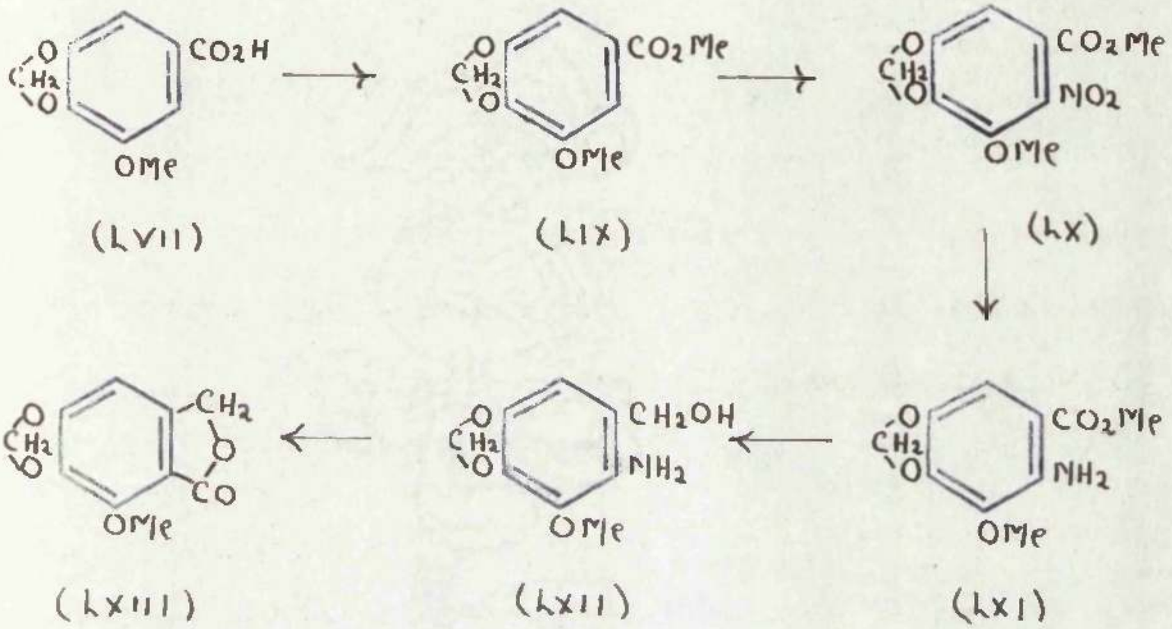
Since the isomeric phthalide 7-methoxy-5:6-methylenedioxyphthalide (LXIII) could also have been formed in the Cannizzaro reaction, and the preparation of Spath *et al.* was not completely unequivocal, (a mixture of phthalides was obtained from which they isolated (LVI)), it was decided to prepare 4-methoxy-5:6-methylenedioxyphthalide (LVI) by another route.

Reduction of cotarnone with sodium borohydride gave 2-hydroxymethyl-3-methoxy-4:5-methylenedioxystyrene (LVIII); this compound was benzoylated and submitted to low-temperature ozonolysis, and the product, not isolated, treated with concentrated alkali, whereupon 4-methoxy-5:6-methylenedioxyphthalide (LVI) was readily obtained.

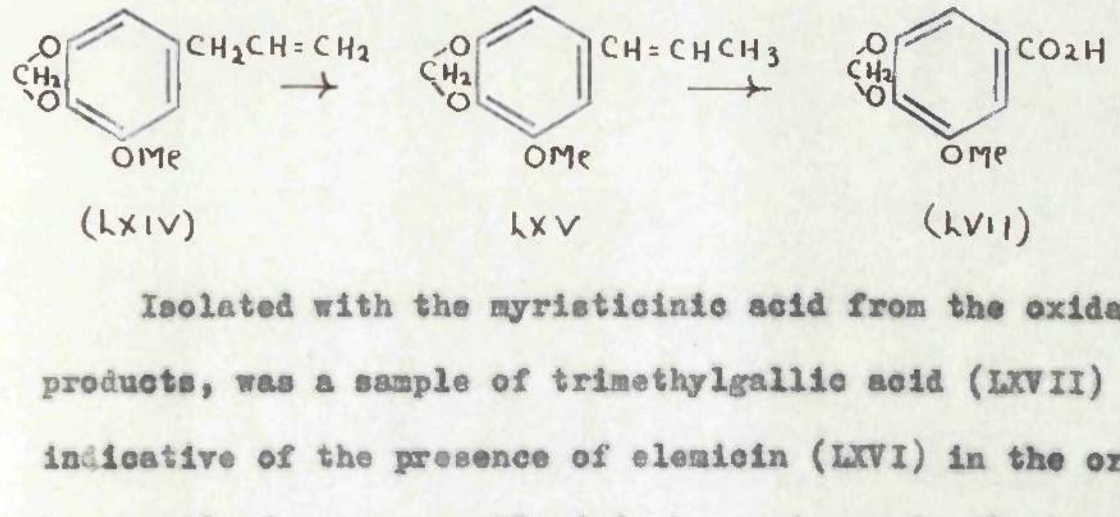


(XLVI) (LVIII) (LVI)

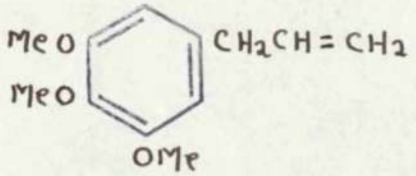
An attempt was made to prepare the isomeric phthalide, 7-methoxy-5:6-methylenedioxyphthalide (LXIII). Myristicinic acid (LVIII) was converted into methyl myristicinate (LIX) nitration of which proceeded smoothly to give, methyl 3-methoxy-4:5-methylenedioxy-2-nitrobenzoate (LX), the orientation of the entering nitro-group being inferred from the nitration of ethyl myristicinate (46). Catalytic hydrogenation of (LX) afforded methyl 2-amino-3-methoxy-4:5-methylenedioxybenzoate (LXI), and this was reduced with lithium aluminium hydride to the corresponding alcohol (LXII). Attempts to convert this amino-alcohol by the Sandmeyer reaction into the nitrile and hence to the lactone (LXIII) were unsuccessful.



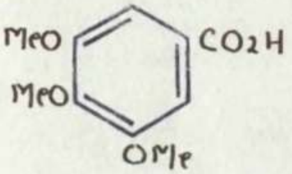
The myristicinic acid used in the above synthesis was prepared from myristicin (LXIV), a constituent of the heavy oil of nutmeg (47). Isomerisation of the myristicin to isomyristicin (LXV) with alkali, and permanganate oxidation of the latter compound provided myristicinic acid (LVII).



Isolated with the myristicinic acid from the oxidation products, was a sample of trimethylgallic acid (LXVII) indicative of the presence of elemicin (LXVI) in the original heavy oil of nutmeg. Elemicin has not previously been reported as a constituent of this oil.



(LXVI)



(LXVII)

Biological Tests.

According to Grove (5), most simple aromatic compounds, with functional groups, have fungistatic activity ranging from 10^{-3}-10^{-5} M provided the pH of the external medium is adjusted in order to reduce to a minimum the ionisation of the basic or acidic material. Considering that salicylanilide is a commercially important fungicide which inhibited (at pH 3.5) the germination of Botrytis allii at 2.9×10^{-4} M. (62.5 μg/ml.), gladiolic acid and o-phthalaldehyde, inhibiting the germination of the same species at much lower concentrations, namely 2.8×10^{-5} (6.25 μg/ml.) and 4.8×10^{-5} (6.5 μg/ml.) respectively, must be classified as strong antifungal agents.

The evaluation of fungistatic activity of 3-methoxy-4:5-methylenedioxyphthalaldehyde (XLVII) 3-formyl-4-methoxy and 3-formyl-4-methylopianic acids (XXXVI and XV) was carried out by Mr. J. F. Grove of the Akers Research Laboratories, I.C.I. Ltd., and to him we are indebted for both the determinations and interpretations of results (48)

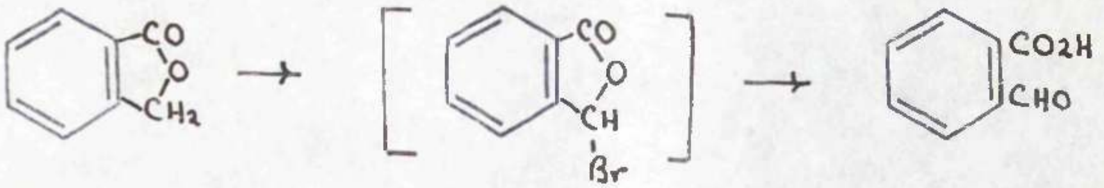
3-Methoxy-4:5-methylenedioxyphthalaldehyde inhibited the growth of *Botrytis allii* at pH 3.0, at only 25 µg/ml. (12 x 10^{-6}M) although it produced stunting down to 6.25 µg/ml. This figure for inhibition therefore showed that the compound was less than half as active as *o*-phthalaldehyde, and rather more than twice as active as salicylanilide. It was the least active *o*-phthalaldehyde tested, but otherwise, behaved similarly to *o*-phthalaldehyde itself in that its activity was largely unaffected by change in pH, and it was non-specific, in hibiting growth of nine different fungii in the concentration range 6.25-25 µg/ml.

3-Formyl-4-methylopianic acid presented a difficult problem of interpretation owing to its slight solubility in water at low pH's. The solutions had to be made up at a pH7 and then adjusted. Carrying out the tests in that way, it was inactive at pH3 and 25 µg/ml. against *Botrytis allii*. 3-Formyl-4-methoxyopianic acid behaved similarly, and this Grove believed accorded with theory, since both acids were even stronger acids than 3-formylopianic acid (pK 4.3) which was only beginning to show fungistatic powers at pH3. Gladiolic acid had pK (4.4).

The pKa values of 3-formyl-4-methylopianic acid and 3-formyl-4-methoxyopianic acid were measured by ourselves and were 3.5 and 3.8 respectively.

Further Examples of the use of N-bromosuccinimide in the Preparation of phthalaldehydic acids.

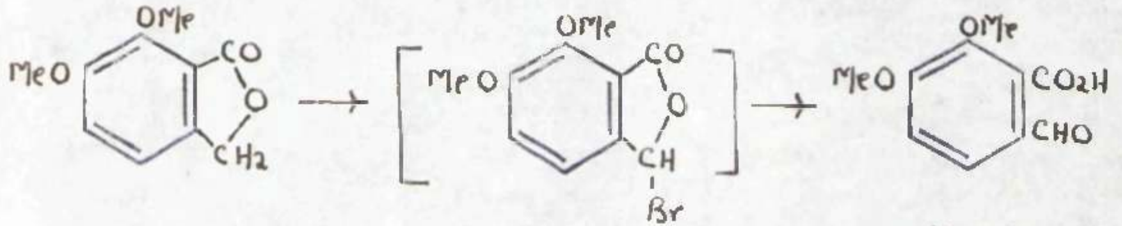
The value of N-bromosuccinimide in synthetic organic chemistry is well known and has been the subject of an excellent review (49). It was not however, until Hirshberg, Lavie and Bergmann (50) showed that phthalide (XLI) could be converted readily to phthalaldehydic acid (LXIX) *via* the intermediate 3-bromophthalide (LXVIII), by means of N-bromosuccinimide, that its potential value as a reagent for the general preparation of phthalaldehydic acids from phthalides, was realised. Brown and Newbold (40) have been chiefly responsible for the development and exploitation of the method in their preparations of *m*-opianic acid, 4:5-methylenedioxyphthalaldehydic acid, in addition to the preparations of the dialacids, 3-formylopianic and gladiolic, already described in this section.



(XLI) (LXVIII) (LXIX)

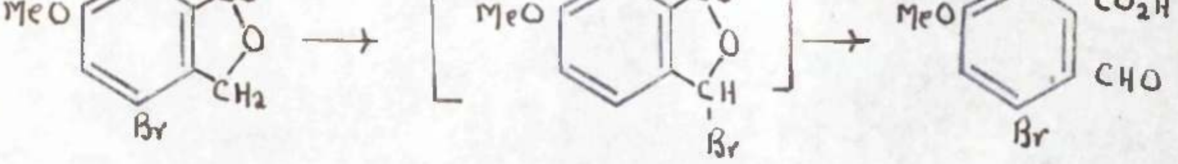
Using the same technique we have synthesised a number of other phthalaldehydic acids and one *o*-phthalaldehyde.

Of especial interest was the preparation of opianic acid (5:6-dimethoxyphthalaldehydic acid) (LXX) from meconin (IV) where it was thought that the method would be more difficult to apply due to the presence of an easily substituted nuclear position. The oxidation however, was accomplished satisfactorily.



(IV) (LXX)

4-Bromomeconin (LXXI) the product obtained when meconin was treated in glacial acetic acid with bromine (51) was also converted by N-bromosuccinimide to the corresponding 3-bromopianic acid (LXXII). Sodium borohydride reduction of (LXXXII) gave back 4-bromomeconin.

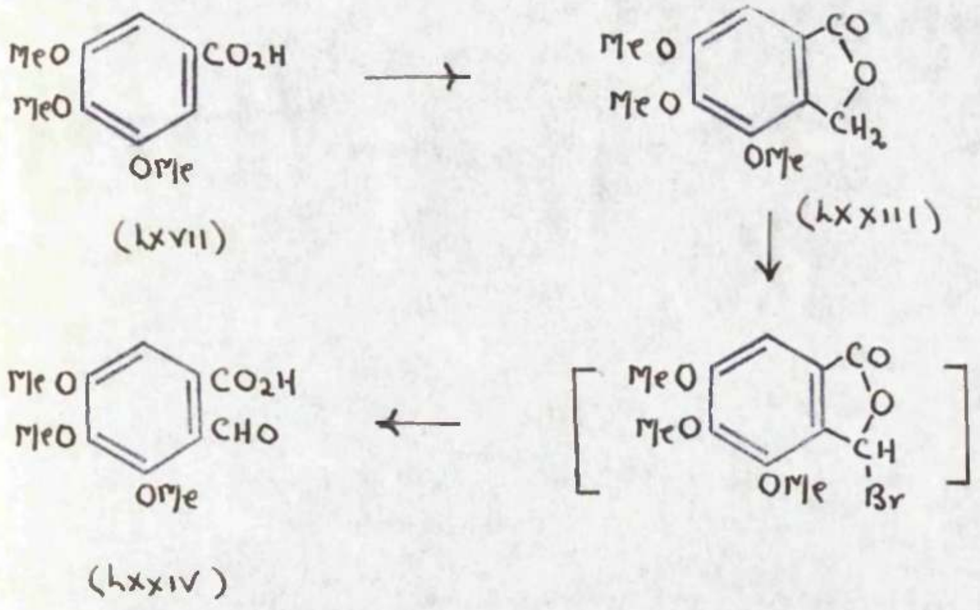


(LXXI) (LXXII)

The starting material meconin, was very conveniently prepared in excellent yield by the crossed Cannizzaro method of Rodionov and Federova (52) on opianic acid (LXX), the latter compound being obtained from the oxidation of narcotine (XLIII, R = OMe) (53).

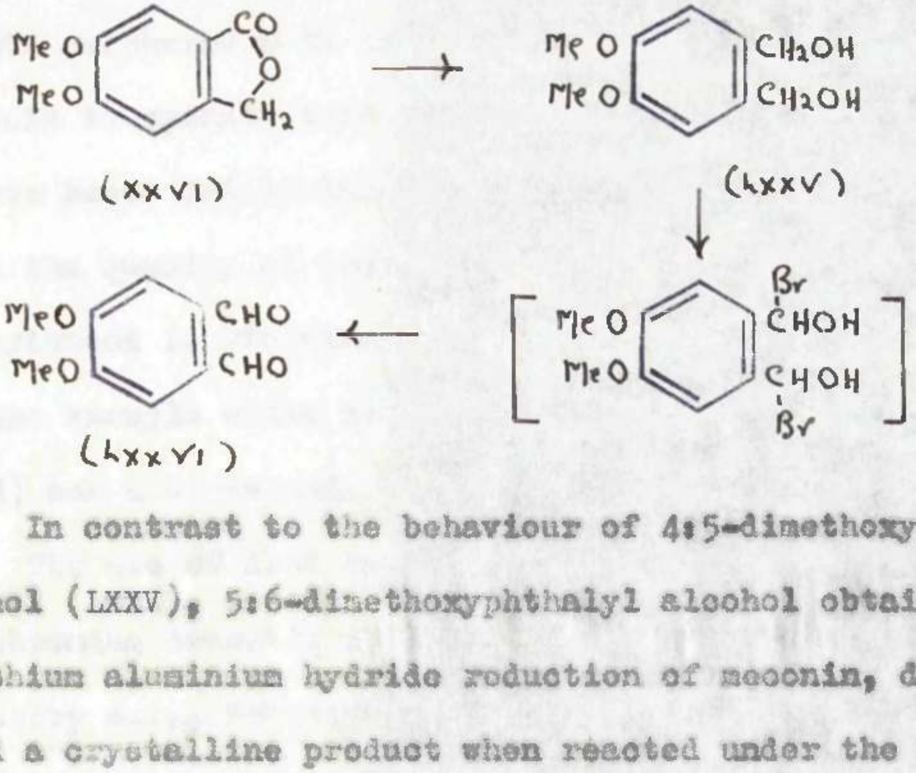
The older method of reducing opianic acid with sodium amalgam proved satisfactory and gave good yields of meconin but was much more laborious (21).

4:5:6-Trimethoxyphthalide (LXXIII) as prepared by King and King (54) from trimethylgallic acid (LXVII), also oxidised readily to 3:4:5-trimethoxyphthaldehydic acid (LXXIV) with N-bromosuccinimide when irradiated with ultra-violet light; no evidence of any nuclear substitution was apparent.



It seemed that the use of N-bromosuccinimide, under favourable conditions, might be extended towards the preparation of *o*-phthalaldehydes from the corresponding phthalyl alcohols. Two oxidations were attempted; one was successful.

m-Meconin (XXVI) with lithium aluminium hydride was reduced to 4:5-dimethoxyphthalyl alcohol (LXXV) and oxidation with N-bromoxuccinimide following the usual procedure, gave in good yield 4:5-dimethoxyphthalaldehyde (LXXVI). The characteristic '*iso*napthazarin' derivative was obtained for the latter compound and its preparation will be referred to later.



In contrast to the behaviour of 4:5-dimethoxyphthalyl alcohol (LXXV), 5:6-dimethoxyphthalyl alcohol obtained from a lithium aluminium hydride reduction of meconin, did not yield a crystalline product when reacted under the same conditions with N-bromosuccinimide. That oxidation took place is certain, since the product, a gum and probably a mixture, gave a 2:4-dinitrophenylhydrazone. Nuclear substitution in this case however, could have been expected.

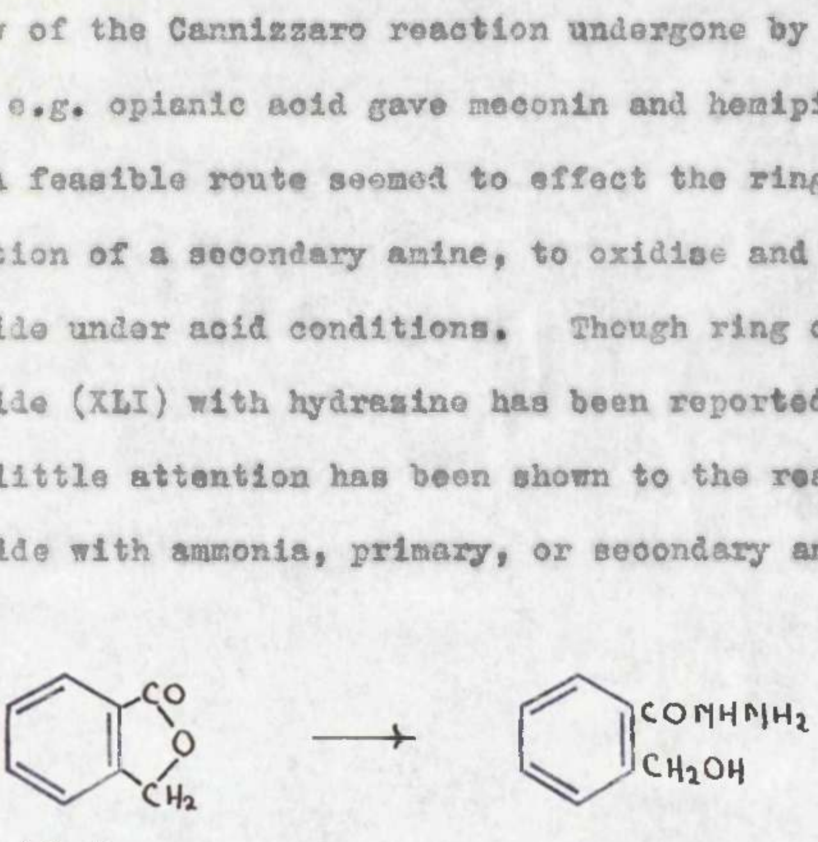
A New Method for the Conversion of Phthalides into Phthalaldehydic Acids.

Although N-bromosuccinimide has proved most useful as an oxidising agent in the conversion of phthalides to phthalaldehydic acids, its limitations had to be recognised. There would be cases where, either due to lack of activation of the methylene group, or, where an easily substituted nuclear position existed, the reagent might be ineffective, or not specific enough. The use of manganese dioxide in dilute sulphuric acid as employed for the oxidation of meconin to opianic acid by Edwards, Perkin and Stoyle (22), in our hands led to inconsistent results. Much depended upon the quality of the reagent and difficulty was often experienced in stopping the reaction at the required stage; in the example cited, hemipinic acid (3:4-dimethoxyphthalic acid) was also formed.

The use of lead dioxide in sulphuric or acetic acids, or chromium trioxide in acetic acid also appeared unsatisfactory e.g., Stevens and Robertson (45) have reported their failure to oxidise 5:6-methylenedioxyphthalide to 4:5-methylenedioxyphthalaldehydic acid by these methods

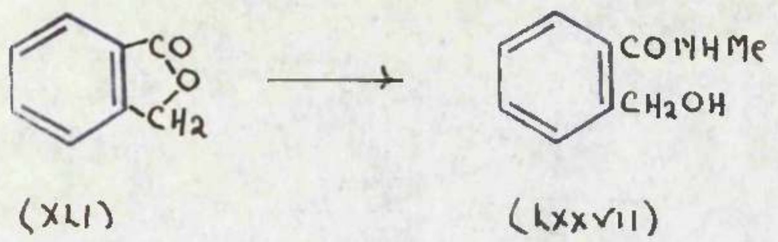
Recognising the need for another method an endeavour was made to find one that would be efficient and at the same time employ mild conditions. The oxidation of a ring opened phthalide bearing a free hydroxymethyl group was desired and while such derivatives are formed in strongly alkaline solution, the use of such a media was undesirable in view of the Cannizzaro reaction undergone by phthalaldehydic acids, e.g. opianic acid gave meconin and hemipinic acid (55).

A feasible route seemed to effect the ring opening by the action of a secondary amine, to oxidise and then hydrolyse the amide under acid conditions. Though ring opening of phthalide (XLI) with hydrazine has been reported by Teppema (56), little attention has been shown to the reaction of phthalide with ammonia, primary, or secondary amine.

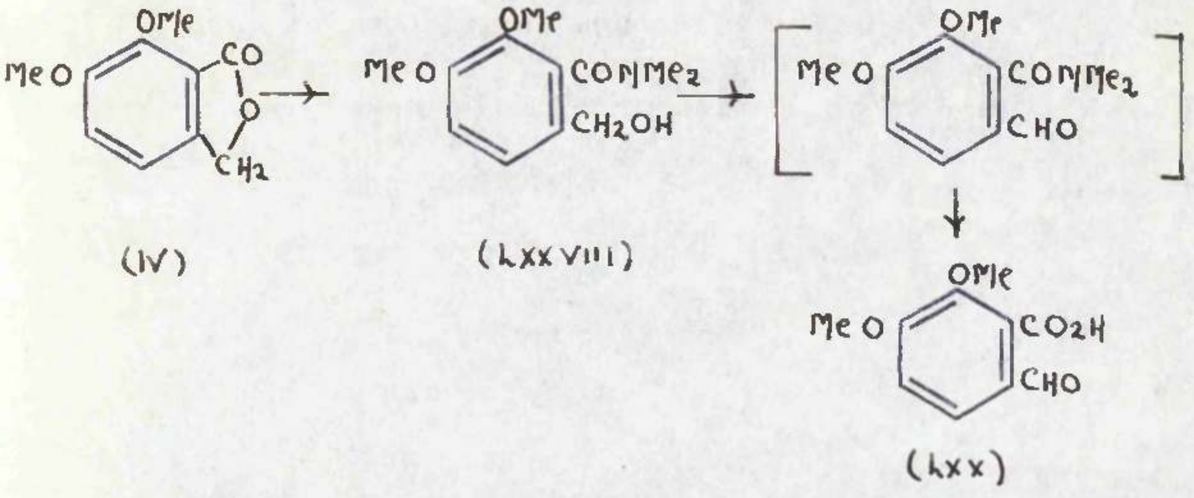


While phthalide was reported to yield 2-hydroxymethylbenzoic acid on keeping in aqueous ammonia (57), heating the lactone in an ammonia stream gave phthalimidine (58).

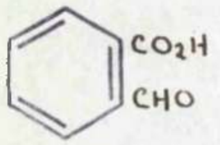
Recently Theilacker and Kalenda (59) showed that phthalide gave 2-hydroxymethyl-N-methylbenzamide (LXXVII) with aqueous methylamine.



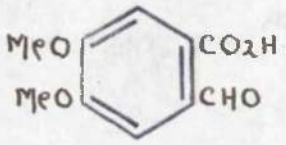
Treatment of meconin with ethanolic dimethylamine at room temperature gave 6-hydroxymethyl-2:3-dimethoxy-NN-dimethylbenzamide (LXXVIII). The dimethylamide was readily hydrolysed by heating with dilute hydrochloric acid or sodium hydroxide giving back meconin; on heating alone, the dimethylamide decomposed at <u>ca.</u>, 170° evolving dimethylamine and again giving meconin. On brief oxidation of the dimethylamide with chromium trioxide in acetic acid in the cold, followed by heating the oxidation product, not isolated in the solid state, with dilute hydrochloric acid, opianic acid (LXX) was formed in 41% overall yield from meconin. Under identical oxidation conditions, meconin was unaffected. In addition to the example just discussed, the



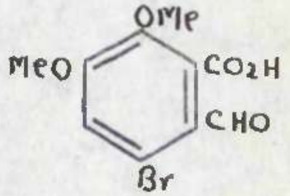
method has been employed for the preparation of, phthalaldehydic acid (LXIX), m-opianic acid (LXXIX), 3-bromopianic acid (LXXII),



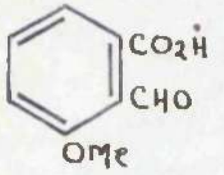
(LXIX)



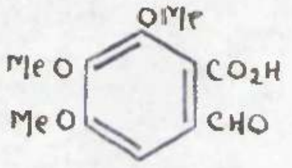
(LXXIX)



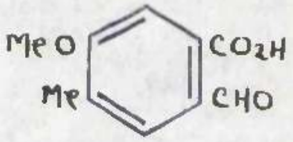
(LXXII)



(LXXX)



(LXXXI)



(LXXXII)

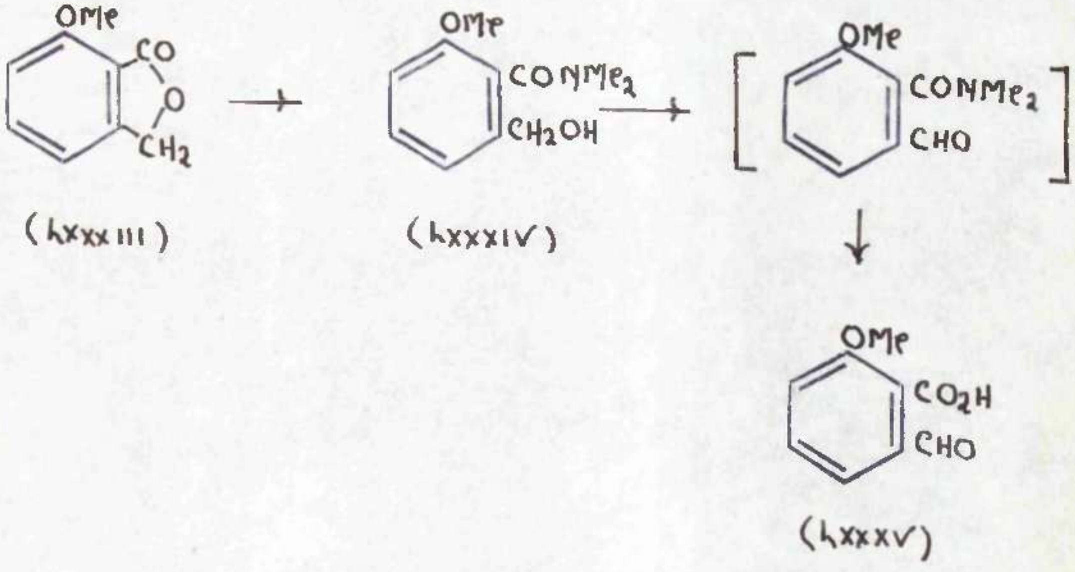
3-methoxy-(LXXX), 4:5:6-trimethoxy-(LXXXI) and 5-methoxy-4-methylphthalaldehydic (LXXXII) acids from their corresponding phthalides without isolation of the intermediate dimethylamides.

The reaction of the phthalide with dimethylamine was carried out in ethanol in the cold followed by the oxidation and hydrolysis; if the phthalide was recovered unchanged the initial dimethylamine treatment was carried out at an elevated temperature in an autoclave and the process repeated.

The action of ethanolic ammonia in the cold, on phthalide and meconin, have been examined; 2-hydroxymethylbenzamide and 6-hydroxymethyl-2:3-dimethoxybenzamide were formed respectively in good yield. It was of interest that on oxidation with chromium trioxide by the standard procedure, each amide gave the corresponding imide of the dicarboxylic acid.

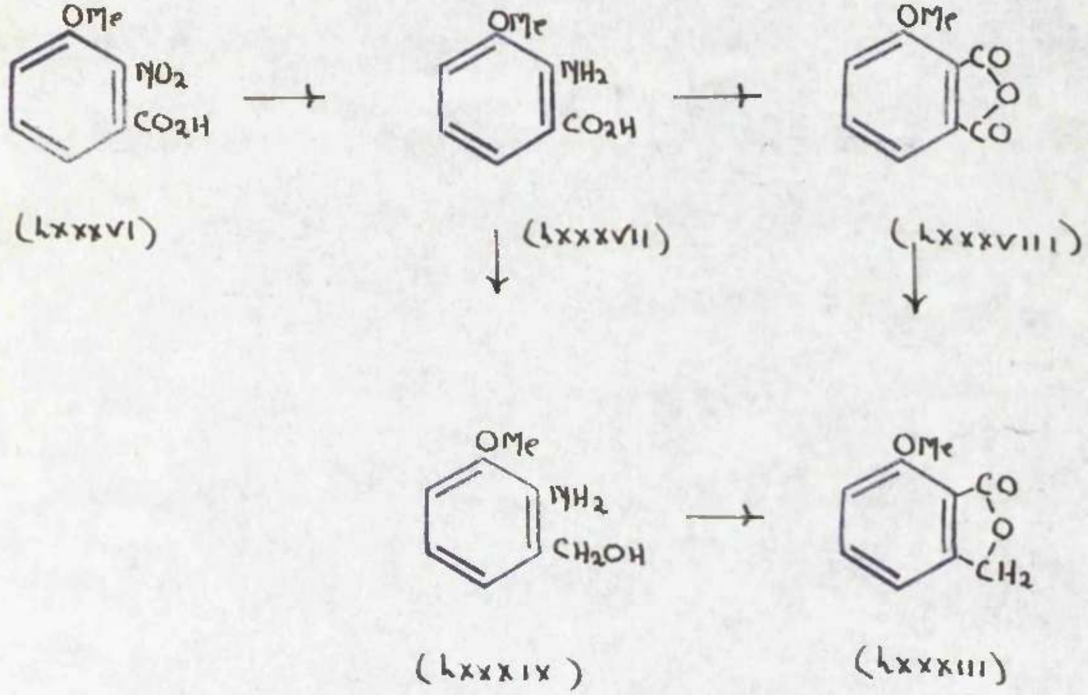
Preparation of 6-methoxyphthalaldehydic acid.

6-Methoxyphthalaldehydic acid (LXXXV) has been reported as a degradation product of mellein (see p.4) and a synthesis of this acid has been achieved by treatment of 7-methoxyphthalide (LXXXIII) with dimethylamine to give 2-methoxy-6-hydroxymethyl-NN-dimethylbenzamide (LXXXIV) followed by oxidation and hydrolysis of the product.



(LXXXIII) (LXXXIV) (LXXXV)

A convenient route to 7-methoxyphthalide (LXXXIII) has been developed starting from 3-methoxy-2-nitrobenzoic acid (LXXXVI)(60) which was reduced to the amino-acid with sodium dithionite and then transformed to 3-methoxyphthalic anhydride. 3-Methoxyphthalic anhydride (LXXXVIII) was then converted to 7-methoxyphthalide by a modification of the procedure of Duncanson, Grove and Zealley (61).

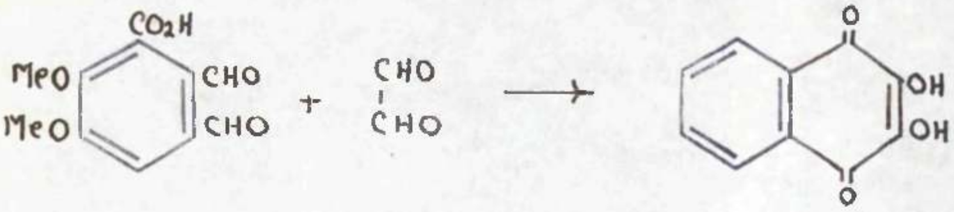


The same phthalide (LXXXIII) has been obtained in small yield, but by an unambiguous route from 2-amino-3-methoxybenzoic acid (LXXXVII) by a series of reactions used by Brown and Newbold for the synthesis of 7-methoxy-6-methylphthalide (24). The synthesis involved the reduction of the carboxyl-group with lithium aluminium hydride to (LXXXIX) and the transformation of the amino-group to a carboxyl-group by the usual Sandmeyer technique.

isoNapthazarins derived from 3-Formylopianic acid and 4:5-Dimethoxyphthalaldehyde.

It was discussed earlier (see p. 41) how compounds, such as gladiolic and 3-formylopianic acids containing the vicinal carboxy-o-phthalaldehyde system, existed in the tautomeric keto-lactol forms. Although many derivatives of the lactol form have been prepared (1, 62) no simple derivative of the open chain form had ever been reported.

Weygand (11, 63, 64) discovered a new method of preparing isonapthazarins by a condensation of glyoxal and o-phthalaldehydes in alkaline solution in the presence of cyanide ion, and employing this reaction we have demonstrated the presence of the o-diformyl-group in 3-formylopianic acid. The resulting isonapthazarin was 2:3-dihydroxy-6:7-dimethoxy-naptha-1:4-quinone-5-carboxylic acid (XC).



(XC)

The corresponding isonapthazarin derivative from gladiolic acid has been prepared independently by Weygand, Weber and Grove (65).

When 4:5-dimethoxyphthalaldehyde (LXXVI) was reacted with glyoxal under the above conditions 2:3-dihydroxy-6:7-dimethoxy-napthaquinone (XCI) was obtained.

(LXXVI)

(XCI)

EXPERIMENTAL.

Ultra-violet spectra were determined in ethanol solution unless otherwise stated.

2-Sulpho-p-toluic acid. (cf. Meldrum and Perkin J., 1908, 1419) - p-Toluic acid (68 g.) was heated with fuming sulphuric acid (170 c.c.; 100%) in a strong-necked flask and electric heating mantle at 150°C for 8 hrs. After cooling, the dark solution was added to water (220 c.c.) whereupon much heat was evolved. The acid which crystallised out on cooling was collected by filtration, and washed with a little ice-cold water (ca. 30 c.c.) yield (crude acid) 75 g. (69%).

2-Hydroxy-p-toluic acid. - Potassium hydroxide (300 g.) moistened with a little water, was heated in a large fusion pot to 200°C and 2-sulpho-p-toluic acid (75 g.) added slowly in small portions while allowing the temperature to rise to 260° C. This temperature was maintained until fusion was complete.

The cooled fusion mixture was extracted with water, and neutralised with 5N-hydrochloric acid (when the hydroxy-acid was precipitated). Crystallisation, and recrystallisation from water, gave needles m.p. 210°. Yield 36 g. (48%).

2-*Methoxy*-p-*toluic acid*. (*cf*. Perkin and Weizmann, *J*., 1906, *89*, 1649). - To an aqueous solution of potassium hydroxide (42 g.; 360 c.c. water) and 2-hydroxy-*p*-toluic acid (36 g.) was added slowly, with vigorous stirring, dimethyl sulphate (54 c.c.) over a period of 30 minutes. A further portion of aqueous potassium hydroxide (42 g.; 360 c.c. water) was then added and the whole refluxed for 1 hr. On acidification of the reaction mixture with concentrated hydrochloric acid, the methoxy-acid separated out. This was collected, washed with water and crystallised from aqueous acetic acid (30%) to give white plates, m.p. 166°. Yield 23.5 g. (61%).

6-*Methoxy*-5-*methylphthalide*. (*cf*. Charlesworth *et al*. *Canad*. *J*. *Res*., 1945, *23B*,17). - 2-Methoxy-*p*-toluic acid (6 g.), formaldehyde solution (13 c.c.; 40%) and hydrochloric acid (19 c.c.; d,1.16) were heated on a water bath for 4 hrs. On cooling, well formed prisms separated and these were crystallised from alcohol to give 5-methoxy-4-methylphthalide as glistening white needles m.p. 144°. Yield 5 g. (77%).

6-*Methoxy*-5-*methyl*-7-*nitrophthalide*. - Finely divided 6-methoxy-5-methylphthalide (5 g.) was added during 5 minutes to a stirred mixture of nitric acid (16 c.c.; d,1.5) and acetic anhydride (24 g.) at 0°. When all the phthalide had dissolved, the solution was poured on ice, and the solid separated, washed with water and crystallised from ethanol, to give 6-*methoxy*-5-*methyl*-7-*nitrophthalide* (4.5 g., 73%) as needles, m.p. 146°.

Found: C,54.2; H,4.1

$C_{10}H_9O_5N$ requires: C,53.8; H,4.1%.

Light absorption: Max. at 2060 (ϵ = 28,800) and 2890 (ϵ = 2,650); inflexion at 2410 Å. (ϵ = 6,800)

7-*Amino*-6-*methoxy*-5-*methylphthalide*. - A solution of 6-methoxy-5-methyl-7-nitrophthalide (2 g.) in ethyl acetate (200 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of freshly prepared Raney nickel (1.2 g.; W.6, *Org. Synth.*, 29, 24). When absorption was complete (*ca.* 15 min.) the mixture was filtered, the filtrate evaporated to dryness under reduced pressure, and the residual solid crystallised from benzene-light petroleum (b.p. 60-80°) from which 7-*amino*-6-*methoxy*-5-*methylphthalide* (1.7 g.) separated as needles, m.p. 109-110°

Found: C,62.5; H,5.65.

$C_{10}H_{11}O_3N$ requires: C,62.2; H,5.7%.

Light absorption: Max. at 2340 (ϵ = 34,700), 2500 (ϵ = 7,800) and 3280 Å. (ϵ = 5,700).

7-*Iodo*-6-*methoxy*-5-*methylphthalide*. - The foregoing aminophthalide (4 g.) in sulphuric acid (3 c.c.; d,1.84) and water (20 c.c.) was diazotised at 0° with sodium nitrite

(2 g.). After the addition of urea, a solution of potassium iodide (4 g.) in water (15 c.c.) was added and the mixture kept at room temperature for 3 hrs. and then heated on the steam-bath for 10 minutes. After cooling, the solid was separated and crystallised from ethanol (charcoal), to give 7-iodo-6-methoxy-5-methylphthalide (3.4 g.) as needles, m.p. 117-118°.

Found: C,39.3; H,3.1.

$C_{10}H_9O_3I$ requires: C,39.5; H,3.0%.

Light absorption: Max. at 2220 (ϵ = 28,000), 2460 (ϵ = 9,000) and 3020 Å. (ϵ = 4,700).

5-Methylmeconin. - The iodo-compound (3.2 g.) and copper bronze (100 mg.) were added to a solution of potassium methoxide from potassium (0.9 g.) and dry methanol (50 c.c.) and the mixture was refluxed for 24 hrs. The filtered solution was diluted with water (25 c.c.), made acid (congo-red) with 5N-hydrochloric acid, and extracted with ether (3 x 50 c.c.). The combined ethereal extract was washed with water, dried (Na_2SO_4), and evaporated, and the residue crystallised from light-petroleum (b.p. 40-60°), to yield 5-methylmeconin (1.6 g.) as felted needles, m.p. 82.5°.

Found: C,63.1; H,5.85.

$C_{11}H_{12}O_4$ requires: C,63.45; H,5.8%.

Light absorption: Max. at 2130 (ϵ = 29,600) 2460 (ϵ = 8,300) and 2960 Å. (ϵ = 3,000)

4-Chloromethyl-5-methylmeconin.- 5-methylmeconin (400 mg.), hydrochloric acid (5 c.c.; d,1.16), and aqueous formaldehyde (3 c.c.; 40%) were heated under reflux for 30 minutes. The cooled mixture was diluted with water (10 c.c.) and extracted with chloroform (3 x 10 c.c.). The combined chloroform extracts were washed with aqueous sodium hydrogen carbonate, then water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from benzene-light petroleum (b.p. 60-80°) gave 4-chloromethyl-5-methylmeconin (250 mg.) as needles m.p. 118-121°.

Found: C,56.4; H,5.3.

$C_{12}H_{13}O_4Cl$ requires: C,56.15; H,5.1%.

Light absorption: Max. at 2190 (ε = 40,100) and 3050 (ε = 3,800); inflexion at 2420-2480 Å. (ε = 9,700).

4:5-Dimethylmeconin. - 4-Chloromethyl-5-methylphthalide (200 mg.) in ethanol (5 c.c. 95%) was heated under reflux with zinc dust (250 mg.) and treated with hydrochloric acid (2.5 c.c.; d,1.16) added in portions during 2 hrs. The mixture was evaporated under reduced pressure; water was added and the product isolated by means of ether. Removal of the ether and crystallisation of the residue from hexane gave 4:5-dimethylmeconin (100 mg.) as prisms, m.p. 110°.

Found: C,65.2; H,6.5.

$C_{12}H_{14}O_4$ requires: C,64.85; H,6.35%.

Light absorption: Max. at 2160 (ε = 28,800), 2480 (ε = 11,000) and 3000 Å. (ε = 3,900).

5:6-*Dimethoxy*-7-*methylphthalan*-4-*carboxylic acid*. - 4-Chloromethyl-5-methylmeconin (100 mg.) was heated under reflux with a solution of anhydrous sodium carbonate (400 mg.) in water (6 c.c.) for 1½ hrs. The cooled solution was made acid to Congo-red with 3N-hydrochloric acid and extracted with chloroform (3 x 10 c.c.). The combined, dried (Na_2SO_4) extracts were evaporated and the residue was crystallised from aqueous ethanol to give 5:6-*dimethoxy*-7-*methylphthalan*-4-*carboxylic acid* (75 mg.) as plates, m.p. 156-157°.

Found: C,60.7; H,5.9%; equiv., 232.

$C_{12}H_{14}O_5$ requires: C,60.5; H,5.9%; equiv., 238.

The compound sublimed unchanged at 120° 10^{-4}mm. and showed light absorption: Max. at 2120 (ε = 29,000), 2420 (ε = 7,400) and 2960 Å. (ε = 2,800).

Under the same conditions save that heating was carried out for ½ hr. 4-chloromethyl-5-methylmeconin (400 mg.) gave 5:6-dimethoxy-7-methylphthalan-4-carboxylic acid (130 mg.) and 4-hydroxymethyl-5-methylmeconin (70 mg.), the separation being achieved by use of chloroform and aqueous sodium hydrogen carbonate.

4-Hydroxymethyl-5-methylmeconin. - The foregoing phthalan acid (100 mg.) was heated under reflux with 5N-hydrochloric acid (40 c.c.) for 1 hr. The cooled solution was extracted with chloroform (3 x 10 c.c.), the combined extracts were dried (Na_2SO_4) and evaporated, and the residue crystallised from benzene-light petroleum (b.p. 60-80°) to give 4-hydroxymethyl-5-methylmeconin (60 mg.) as needles, m.p. 101-102°.

Found: C,60.6; H,5.7.

$C_{12}H_{14}O_5$ requires: C,60.5; H,5.9%.

Light absorption: Max. at 2140 (ε = 41,000), 2470 (ε = 9,100) and 2990 Å. (ε = 3,600).

3-Formyl-4-methylopianic acid. - A solution of 5:6-dimethoxy-7-methylphthalan-4-carboxylic acid (200 mg.) in dry benzene (12 c.c.) and dry carbon tetrachloride (12 c.c.) was refluxed with N-bromosuccinimide (2.25 mols.) for 15 minutes with irradiation from a 60 watt lamp. The cold mixture was filtered, the filtrate evaporated under reduced pressure, and the remaining oil heated with water (10 c.c.) on the steam bath while being stirred for 1½ hrs. Isolation by use of chloroform gave an acid fraction which crystallised from benzene, to yield 3-formyl-4-methylopianic acid (77 mg.) as needles, m.p. 145-146°.

Found: C,57.0; H,5.0%; equiv., 247.

$C_{12}H_{12}O_6$ requires: C,57.1; H,4.8%; equiv., 252.

Light absorption in water: Max. at 2070 (ε = 29,600) and 2,800 Å. (ε = 2,000).

3-Formyl-4-methylopianic acid dissolves in concentrated sulphuric acid, giving a yellow brown solution; on exposure to ammonia vapour the solid becomes brown and resinifies, and on exposure to light it first turns pink and then brown.

5-Methylmeconin-4-carboxylic acid. - (a) A solution of 5:6-dimethoxy-7-methylphthalan-4-carboxylic acid (200 mg.) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (200 mg.) in glacial acetic acid (5 c.c.) during 1 minute with stirring. After 5 minutes the mixture was diluted with water (10 c.c.) and extracted with chloroform (3 x 15 c.c.). The combined extracts were washed with sodium hydrogen carbonate (30 c.c.; 10%); acidification of this extract with 5N-hydrochloric acid and isolation with chloroform gave 5-*methylmeconin*-4-*carboxylic acid* (100 mg.) which separated from aqueous ethanol as needles, m.p. 195-196.5°.

Found: C,57.3; H,4.9.

$C_{12}H_{12}O_6$ requires: C,57.1; H,4.8%.

Light absorption: Max. at 2200 (ε = 31,200) and 3000 Å. (ε = 3,200).

(b) 3-Formyl-4-methylopianic acid (25 mg.) in 3N-sodium hydroxide (10 c.c.) was refluxed for 30 minutes. The cooled mixture was extracted with chloroform; no neutral fraction was obtained from the extract. Acidification of the alkaline solution (Congo-red) with 5N-hydrochloric acid gave 5-methylmeconin-4-carboxylic acid (12 mg.) which crystallised from aqueous ethanol as needles, m.p. and mixed m.p. 195-196.5°.

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. 11, 619. A hot solution of potassium permanganate (34 g.) in water (500 c.c.) was added over 1hr. 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 with hydrochloric acid (Congo-red). The veratric acid which separated was collected and washed, m.p. 177° [lit., m.p. 179°].

m-Meconin. - (cf. Edwards, Perkin and Stoyle, J., 1925, 127, 195). Veratric acid (75 g.), formaldehyde (84 c.c.; 40%) and hydrochloric acid (300 c.c.; d,1.16) were heated on a steam-bath for 12 hrs. during which time a certain amount of charring occurred. The solution was cooled and diluted with water (300 c.c.), and shaken vigorously until the dark gummy material adhered to the walls of the flask. After a quick filtration, m-meconin slowly separated on standing as a dark brown powder, m.p. 155° (lit., m.p. 155-157°).

7-Nitro-m-meconin.- (cf. Ray and Robinson, J., 1925, 1621). Ray and Robinson used nitric acid (d,1.4), but in our hands m-meconin did not nitrate satisfactorily unless fuming nitric acid (d,1.5) was used.

m-Meconin (10 g.) was gradually added with stirring to nitric acid (20 c.c.; d,1.5) at 0°. After standing 2 hrs. the solution was thrown into water when 7-nitro-m-meconin was precipitated. This was collected washed with water followed by boiling alcohol (8.0 c.c.). The residue was crystallised from acetic acid to give colourless needles (9 g.), m.p. 183-184° (lit., 182-182.5°).
Light absorption: Max. at 2140 (ϵ = 27,400) 2520 (ϵ = 10,500) and 2920 A. (ϵ =4,150).

7-Amino-m-meconin. - (cf. McRae et al. Canad. J. Res., 1951, 29, 482). The above nitro-compound (9 g.) was added slowly to a hot solution of stannous chloride (30 g.) in hydrochloric acid (60 c.c.; d,1.16) when a clear solution resulted. The reaction was completed by heating 45 minutes on a steam-bath, water (200 c.c.) then added and the precipitate collected, washed with water, sodium hydrogen carbonate, water and finally crystallised from aqueous ethanol, m.p. 160°, (lit. m.p. 168°)

7-Iodo-m-meconin.- 7-Amino-m-meconin (6 g.) in sulphuric acid (5 c.c., d,1.84) and water (30 c.c.) was diazotised at 0° with sodium nitrite (2.2 g.) and the excess nitrous acid destroyed with urea. A solution of potassium iodide (6 g.) in water (15 c.c.) was added and the mixture allowed to stand until the reaction was complete. By the addition of a solution of potassium bisulphite any free iodine present was removed and the orange precipitate was collected by filtration and crystallised from glacial acetic acid to give pale yellow needles, m.p. 169-170° (lit. 169-170°). Yield 70% .

5:6:7-Trimethoxyphthalide. - (McRae, et al., Canad. J. Chem., 1951, 29, 482). Potassium (0.8 g.) dissolved in dry methanol (50 c.c.) mixed with 7-iodo-m-meconin (3.2 g.) and copper bronze (100 mg.) and heated under reflux for 12 hrs. The copper bronze was removed and the filtrate acidified with hydrochloric acid when the product was precipitated. This was crystallised from water to give needles, m.p. 136° (lit. m.p. 136.5-137°).

4-*Chloromethyl*-5:6:7-*trimethoxyphthalide*. - A suspension of 5:6:7-trimethoxyphthalide (1.0 g.) in hydrochloric acid (2 c.c.; d,1.16) and aqueous formaldehyde (1 c.c.; 40%) was treated with gaseous hydrogen chloride at 0° until solution was complete (*ca.* 10 minutes). After being kept overnight at room temperature the solution was diluted with water and the product isolated by means of chloroform. Crystallisation from light petroleum (b.p. 60-80°) gave 4-*chloromethyl*-5:6:7-*trimethoxyphthalide* (1.1 g.) as needles, m.p. 82.5°.

Found: C,52.7; H,4.9.

$C_{12}H_{13}O_5Cl$ requires: C,52.85; H,4.8%.

Light absorption: Max. at 2240 (ϵ = 39,200) and 2970 (ϵ = 29,000); inflexion at 2420-2520 Å. (ϵ =8,300).

Sodium Carbonate Treatment of 4-*Chloromethyl*-5:6:7-*trimethoxyphthalide*. - A solution of sodium carbonate (500 mg.) in water (10 c.c.) was refluxed for ½ hr. with 4-chloromethyl-5:6:7-trimethoxyphthalide (200 mg.). After acidification and extraction with chloroform (3 x 10 c.c.) the combined extracts were separated into acid and neutral fractions by using sodium hydrogen carbonate solution. The former fraction crystallised from benzene-light petroleum (b.p. 60-80°) to give 5:6:7-*trimethoxyphthalan*-4-*carboxylic acid* (60 mg.) as prisms, m.p. 125-126°.

Found: C,57.0; H,5.8%; equiv., 254.

$C_{12}H_{14}O_6$ requires: C,56.7; H,5.55% equiv., 254.

Light absorption: Max. at 2160 (ε = 31,200), 2530 (ε = 9,800), and 2940 Å. (ε = 2,700).

The neutral fraction separated from the same solvents to give 4-<u>hydroxymethyl</u>-5:6:7-<u>trimethoxyphthalide</u> (80 mg.) as needles, m.p. 73°.

Found: C,56.3; H,5.8.

$C_{12}H_{14}O_6$ requires: C,56.7; H,5.55%.

Light absorption: Max. at 2180 (ε = 36,400), 2520 (ε = 9,950) and 2960 Å. (ε = 3,000).

When 4-chloromethyl-5:6:7-trimethoxyphthalide (500 mg.) was refluxed for 2 hrs. with sodium carbonate (1.0 g.) in water (15 c.c.) and the products isolated as above, 5:6:7-trimethoxyphthalan-4-carboxylic acid (340 mg.) and 4-hydroxymethyl-5:6:7-trimethoxyphthalide (110 mg.) were obtained. The latter compound (140 mg.), when refluxed for ½ hr. with sodium carbonate (500 mg.) in water (10 c.c.), gave the corresponding carboxyphthalan (60 mg.) the remainder being unchanged. 5:6:7-Trimethoxyphthalan-4-carboxylic acid (100 mg.) was refluxed with hydrochloric acid (40 c.c.; 3N) for 2 hrs. and 4-hydroxymethyl-5:6:7-trimethoxyphthalide (55 mg.), m.p. and mixed m.p. 73°, isolated in the usual way.

3-Formyl-4-methoxyopianic acid. - 5:6:7-Trimethoxyphthalan-4-carboxylic acid (250 mg.) in benzene (12 c.c.) and carbon tetrachloride (12 c.c.) was refluxed for 20 minutes with N-bromosuccinimide (2.2 mols.) with irradiation from a 60 watt lamp. Further treatment as described for 3-formyl-4-methylopianic acid gave 3-formyl-4-methoxyopianic acid (130 mg.) which separated from benzene as needles, m.p. 146°.

Found: C, 53.55; H, 4.7%; equiv., 262.

$C_{12}H_{12}O_7$ requires: C, 53.7; H, 4.5%; equiv., 268.

Light absorption in water: Max. at 2080 (ϵ = 32,400); inflexion at 2,700-2750 Å. (ϵ = 2,100).

The compound dissolved in concentrated sulphuric acid giving a yellow solution; on exposure to ammonia vapour the solid becam brown and resinified.

5-Methoxymeconin-4-carboxylic Acid. - 3-Formyl-4-methoxyopianic acid (100 mg.) was refluxed in 3N-sodium hydroxide (30 c.c.) for 30 minutes. Isolation by means of chloroform gave 5-methoxymeconin-4-carboxylic acid (70 mg.) which separated as needles, m.p. 176°

Found: C, 53.9; H, 4.6.

$C_{12}H_{12}O_7$ requires: C, 53.7; H, 4.5%.

Light absorption: Max. at 2270 (ϵ = 36,000) and 3000 (ϵ = 3,300); inflexion at 2530-2560 Å. (ϵ = 10,400)

5:6-Dimethoxyphthalan-4-carboxylic Acid. - (a) 4-hydroxymethylmeconin (0.5 g.) was heated under reflux for 7½ hrs. with a solution of sodium methoxide in anhydrous methanol, from sodium (0.25 g.) and methanol (11 c.c.). The solution was diluted with water, made acid to Congo-red with dilute hydrochloric acid, and extracted with chloroform. The chloroform extracts were washed with aqueous sodium hydrogen carbonate, then water, dried (Na_2SO_4), and evaporated, giving no residue. Acidification of the alkaline washings and isolation of the product using chloroform gave 5:6-dimethoxyphthalan-4-carboxylic acid (0.5 g.), which separated from water as needles, m.p. 148-149° alone or mixed with Brown and Newbold's sample (J., 1952, 4878).

(b) 4-Hydroxymethylmeconin (0.5 g.) in dry benzene (10c.c.) was heated under reflux for 18 hours with sodium methoxide (0.5 g.). Isolation in the usual way gave 4-hydroxymethylmeconin (264 mg.), m.p. and mixed m.p. 126-128° and 5:6-dimethoxyphthalan-4-carboxylic acid (194 mg., 39%), m.p. and mixed m.p. 148-149°.

(c) 4-Hydroxymethylmeconin (1.0 g.) was heated on the steam-bath for 7½ hrs. in 3N-sodium hydroxide (15 c.c.). Isolation gave unchanged material (840 mg.) and 5:6-dimethoxyphthalan-4-carboxylic acid (110 mg., 8%) m.p. and mixed m.p. 146-148°. Brown and Newbold (loc. cit.) reported that 4-hydroxymethylmeconin was unchanged after 2 hrs. boiling with 3N-sodium hydroxide.

(d) 4-Hydroxymethylmeconin (1.0 g.) was heated under reflux for 7½ hrs. with a solution of anhydrous sodium carbonate (2.5 g.) in water (25 c.c.). Isolation gave starting material (700 mg.) and 5:6-dimethoxyphthalan-4-carboxylic acid (300 mg., 31%), m.p. and mixed m.p. 145-147°.

Preparation of Hydrastal from Cotarnine. - Hydrocotarnine. (cf. Brown and Newbold, J., 1952, 4397). Freund and Dormeyer's procedure (Ber., 1891, 24, 2730) for the reduction of hydrastinine lacked detail; the following method proved satisfactory.

A solution of cotarnine chloride (50 g.) in water (250 c.c.) was stirred vigorously for 6 hrs. with sodium amalgam (450 g.; 8%), 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 in 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 hrs. 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. - The oxidation of hydrohydrastinine by potassium dichromate and dilute sulphuric acid, as recommended by Freund and Will (Ber., 1887, 20, 2797), proved unsatisfactory (Brown and Newbold, loc. cit.). 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 hr. 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 (hydrosulphite) (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 methyliodide (40 c.c.) for 1 hr. The excess of 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 hydrioxide (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 = 8,600), 2480 (ε = 27,700), 3,000 (ε = 6,700), and 3280 Å. (ε = 6,700). The 2:4-dinitrophenylhydrazone separated from benzene as red prisms m.p. 227-228° (decomp.).

4:5-Methylenedioxyphthalaldehyde. - A solution of hydrastal (176 mg.) in dry benzene (25 c.c.) containing pyridine (0.16 c.c.) was treated with osmic acid (260 mg.), and the solution which darkened and soon began to deposit brown crystals was kept overnight at ca. 15°. The osmic acid-pyridine complex (450 mg.) was separated and heated under reflux in ethanol (30 c.c.) with sodium sulphite (5 g.) in water (20 c.c.) for 1 hr. Ethanol (150 c.c.) was added, the mixture filtered, and the solid extracted with boiling ethanol (2 x 30 c.c.). The combined ethanolic extracts were evaporated under reduced pressure, the residue was extracted with boiling methanol (2 x 50 c.c.) and the combined extracts were evaporated to a yellow gum. This was dissolved in pure methanol (3 c.c.), water (30 c.c.) and potassium periodate (1.0 g.) were added, the mixture was kept overnight, with occasional shaking, and extracted with ether (2 x 25 c.c.). The combined ethereal extracts were washed with water (25 c.c.) and dried (Na_2SO_4). Evaporation of the ether and crystallisation of the solid from benzene (charcoal) and benzene-light petroleum (b.p. 60-80°) gave 4:5-methylenedioxyphthalaldehyde (70 mg.) as pale yellow needles m.p. 149°-150°.

Found: C,60.8; H,3.6.

$C_9H_6O_4$ requires: C,60.7; H,3.4%.

Light absorption: Max. at 2500 (ε = 26,200) and 3220 Å. (ε = 5,300). The compound, suspended in aqueous ammonia (10%) and acidified with acetic acid, gave a violet solution (Thiele test, Annalen, 1900, 311, 360).

5:6-Methylenedioxyphthalide. - 4:5-Methylenedioxyphthalaldehyde (50 mg.) was heated on the steam-bath with potassium hydroxide (2 c.c.; 50%) for 15 minutes. The filtered solution was acidified (Congo-red) with 3N-hydrochloric acid, and the precipitate was separated and crystallised from aqueous ethanol, to give 5:6-methylenedioxyphthalide (20 mg.) as needles m.p. 187-188° alone or mixed with a specimen prepared by Brown and Newbold (loc. cit.).

Found: C,60.5; H,3.6.

Calc. for $C_9H_6O_4$: C,60.7; H,3.4%.

Light absorption: Max. at 2210 (ε = 23,000), 2560 (ε = 5,700) and 3000 Å. (ε = 7,300).

Cotarnine from Cotarnine chloride. - Cotarnine chloride (50 g.) was dissolved in water and sodium hydroxide (10%; 150 c.c.) run in slowly with vigorous stirring. The precipitated cotarnine was filtered off, any lumps being broken up and the mass washed well with water. After drying in vacuo over phosphorus pentoxide it was crystallised from a large volume of benzene, m.p. 130° (lit., 132-133°).

Cotarninemethine Methiodide. - Cotarnine (4.0 g.) and methyl iodide (30 c.c.) were heated under reflux for 1 hr. and the excess of reagent was removed by distillation. Crystallisation of the residue from water gave cotarninemethine methiodide (70%) as needles, m.p. 217-218°.

Found: C,43.1; H,5.3.

Calc. for $C_{14}H_{20}O_4NI$: C,42.8; H,5.1%.

Light absorption: Max: at 2180 (= 26,600), 2420 (= 22,100), and 2920 A. (= 10,600). Roser (Annalen, 1888, 249, 156) prepared the compound but gave no constants though he gave an analysis, and Rodionow (Bull. Soc. Chim., 1926, 39, 305) gave m.p. 219-220° but no analysis.

Cotarnone. - Roser (loc. cit.) gave insufficient details for the preparation of this compound. It is essential that the procedure below should be followed exactly. Pure cotarninemethine methiodide (15.0 g.) was rapidly heated with aqueous sodium hydroxide (250 c.c.; 10%) to the b.p., refluxed for 5 minutes, and then cooled. The oily phase rapidly solidified and was broken up, separated, washed with water, dried, and crystallised from light petroleum (b.p. 40-60°), to give cotarnone (6.2 g.) as plates, m.p. 78° (lit., 78°), giving a blue colour with acetic acid-sulphuric acid. Cotarnone had light absorption max. at 2500 (ϵ = 19,200) and 3020 Å. (ϵ = 6,200).

3-Methoxy-4:5-methylenedioxyphthalaldehyde. - (a) A solution of cotarnone (810 mg.) in benzene (50 c.c.) containing pyridine (0.625 c.c.) was treated with osmic acid (1.0 g.) as given above for hydrastal, the complex was split, and the product oxidised with potassium periodate in aqueous methanol. 3-Methoxy-4:5-methylenedioxyphthalaldehyde (500 mg.), isolated by means of acid-free chloroform, separated from benzene as needles, m.p. 179°.

Found: C,57.5; H,4.1.

$C_{10}H_8O_5$ requires: C,57.7; H,3.9%.

Light absorption: Max. at 2560 (ϵ = 26,900) and 3200 Å. (ϵ = 5,900). The compound becomes brown on prolonged exposure to light.

(b) A solution of cotarnone (0.5 g.) in chloroform (200 c.c.) at -40° was treated with a stream of ozonised oxygen until 1 mol. of ozone had been absorbed. Water (10 c.c.) was added and the mixture heated to the b.p., with shaking, during 10 minutes and refluxed for 15 minutes. The chloroform layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure to a solid which after two crystallisations from benzene gave 3-methoxy-4:5-methylenedioxyphthalaldehyde (250 mg.) as needles, m.p. and mixed m.p. with preparation (a) 179°

Found: C,58.1; H,4.2%.

2-Hydroxymethyl-3-methoxy-4:5-methylenedioxystyrene. - A solutinn of cotarnone (200 mg.) in ethanol (10 c.c.) and water (25 c.c.) was treated with sodium borohydride (500 mg.) and kept at ca. 15° overnight. The solution was extracted with chloroform (3 x 25 c.c.), and the combined extracts were washed with water (20 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave an oil which was distilled in a short-path still at 200°. (bath-temp.) 0.5 mm. The distillate, which rapidly solidified, crystallised from light petroleum (b.p. 40-60°) to give 2-hydroxymethyl-3-methoxy-4:5-methylenedioxystyrene (150 mg.) as needles m.p. 47°.

Found: C,63.7; H,6.1.

$C_{11}H_{12}O_4$ requires: C,63.45; H,5.8%.

Light absorption: Max. at 2220 (ϵ = 27,000) and 2700 Å. (ϵ = 9,700). A solution of the compound in glacial acetic acid gave a red-brown colour on addition of sulphuric acid (d, 1.84).

4-Methoxy-5:6-methylenedioxyphthalide. - (a) 3-Methoxy-4:5-methylenedioxyphthalaldehyde (300 mg.) was heated on the steam-bath with aqueous potassium hydroxide (30 c.c.; 40%) for 1 hr. The cooled solution was extracted with ether (2 x 20 c.c.) evaporation of the combined, dried (Na_2SO_4) extracts gave a negligible residue. Acidification (Congo-red) of the aqueous phase with 3N-hydrochloric acid was followed by extraction with chloroform (3 x 35 c.c.). The combined chloroform extracts were washed with 10% aqueous sodium hydrogen carbonate and with water, dried (Na_2SO_4), and evaporated. The residue was twice crystallised from aqueous ethanol to give needles (171 mg.), m.p. 138-139° not rising on subsequent crystallisation. This material was heated at 100°/10^{-4} mm., partial sublimation taking place. Four crystallisations of the residue from aqueous ethanol gave 4-methoxy-5:6-methylenedioxyphthalide (50 mg.) as needles m.p. 150-150.5°.

Found: C, 58.05; H, 4.2.

Calc. for $C_{10}H_8O_5$: C, 57.7; H, 3.9%.

Light absorption max. at 2220 (ϵ = 26,600) and 2730 (ϵ = 7,000) and inflexion at 2900-3000 A. (ϵ = 4,200). Spath, Schmid, and Sternberg (*Ber.*, 1934, 67, 2095) give m.p. 150-151°.

(b) 2-Hydroxymethyl-3-methoxy-4:5-methylenedioxystyrene (600 mg.) was heated on the steam-bath for ¾ hr. with benzoyl chloride (3 c.c.) and pyridine (5 c.c.), and the product was isolated by means of ether. Evaporation of the dried (Na_2SO_4) ethereal extract gave a viscous oil which was further purified by dissolving it in benzene (10 c.c.), adsorbing it on an alumina column (5 x 1.5 cm.), washing the column with benzene (200 c.c.), and evaporating the eluate to a colourless gum. The gum was dissolved in chloroform (150 c.c.) and treated at -30° with oxonised oxygen (1.1 mols. of ozone) and worked up as for the previous ozonolysis, the aqueous phase giving the formaldehyde-dimedone compound, m.p. and mixed m.p. 190°. Removal of the chloroform gave a gum (which gave a precipitate, rapidly with Brady's reagent) which was heated on the steam-bath with aqueous potassium hydroxide (30 c.c.; 40%) for ¾ hr., cooled, and extracted with ether. The aqueous phase was acidified (Congo-red) with 5N-hydrochloric acid, and the phthalide isolated by means of ether. Crystallisation from aqueous ethanol gave 4-methoxy-5:6-methylenedioxyphthalide (130 mg.) as needles, m.p. 151° alone or mixed with preparation (a)

Found: C,57.6; H,4.2%

Light absorption: Max. at 2230 (ε = 26,500) and 2710 (ε = 6,600), inflexion at 2900-3000 Å. (ε = 4,200).

Isolation of Myristicin from heavy oil of Nutmeg. - (cf. Power and Salway J., 1907, 91, 2054). Heavy oil of nutmeg (1 kilo.) was fractionally distilled through a 1 foot column packed with glass helices and the following fractions obtained.

1st Fraction	b.p. 60-110° /2 mm.	N^{20}_{D} 1.4822
2nd Fraction	b.p. 110-120°/2 mm.	N^{20}_{D} 1.5115
Residue		N^{20}_{D} = 15428

The second fraction (51.5 g.) was refractionated and the fraction which distilled at 118-120° 2mm. proved to be almost pure myristicin (20 g.).

isoMyristicin. - (cf. McLang, Chem. Trad. J., 1926, 24, 359; Power and Salway (loc. cit.) and Pickles, J., 1912, 101, 1435).

Myristicin (13.5 g.) in alcohol (39 g.) and potassium hydroxide (16 c.c.) moistened with water (1 c.c.) were heated under reflux for 22hrs. and then ether extracted. Evaporation of solvent left an oil which was fractionally distilled and the fraction b.p. 117-120°/1$\frac{1}{2}$ mm. collected, N^{20}_{D} = 15648. This oil (11.2 g.) was oxidised as described below to give myristicinic acid.

Myristicinic Acid. - (cf. Power and Salway (loc. cit.) isoMyristicin (5 g.) was shaken into an emulsion with water (50 c.c.) and heated on a steam-bath. With stirring a solution of potassium permanganate (13.4 g.; 4%) was added slowly and when the reaction was complete the manganese dioxide was filtered off and the filtrate acidified to give a flocculent precipitate of myristicinic acid. This was crystallised from methanol as needles (3 g.), m.p. 210-212°.

Elemicin as a constituent of Nutmeg Oil. - A second batch of heavy oil of nutmeg (1 kilo.) was distilled as above and the fraction (40 g.) b.p. 110-120°/2 mm. (N^{20}_{D} = 1.5134) collected and this oil isomerised with caustic potash and the resulting propenyl ethers (N^{20}_{D} = 1.5560) oxidised with permanganate exactly as has been described. The resulting acidic material had an indeterminate melting point 137-150° and was obviously a mixture which was then separated into its constituents according to the method of Pickles (*loc. cit.*).

The mixed acids were dissolved in the smallest possible quantity of ammonium hydroxide solution and an aqueous solution of calcium chloride added. After a short time a precipitate separated but part remained in solution in the form of a soluble calcium salt.

The insoluble salt was suspended in water and acidified with dilute hydrochloric acid and solution ether extracted. Evaporation of ether yielded a solid which crystallised from aqueous methanol to give myristicinic acid (10 g.), m.p. 211°.

The aqueous solution containing the soluble calcium salts was acidified and the precipitate collected and washed with water. Crystallisation from water gave needles (2.5 g.)

m.p. 167-168° which were undepressed on mixing with an authentic sample of trimethylgallic acid.

The identity of the acid was confirmed by forming its methyl ester which crystallised in prismatic needles m.p. 83°.

Found: C,58.22; H,6.15

$C_{11}H_{14}O_5$ requires: C,58.40; H,6.24%.

The presence of trimethylgallic acid in the oxidation products of the propenyl ethers is therefore an indication of the presence of elemicin in the original heavy oil of nutmeg.

Methyl Myristicinate. - Myristicinic acid (1.7 g.) in dry methanol (100 c.c.) containing sulphuric acid (4 c.c.; d,1.84) was heated under reflux for 2½ hrs. The solution was concentrated to one-third of its volume under reduced pressure, then diluted with water, and the ester was isolated by means of chloroform. Methyl myristicinate (1.5 g.) separated from methanol as needles, m.p. 91°.

Found: C,57.1; H,5.0.

$C_{10}H_{10}O_5$ requires: C,57.1; H,4.8%.

Light absorption: Max. at 2230 (ε = 19,900) and 2790 (ε = 8,100)

Methyl 3-Methoxy-4:5-methylenedioxy-2-nitrobenzoate. - Methyl myristicinate (1.13 g.) was added in portions of nitric acid (12 c.c.; d,1.42) cooled in ice at such a rate that the temperature did not rise above 10°. After 30 minutes at 0°, water (30 c.c.) was added, and the precipitate filtered off, washed with water, and crystallised from ethanol to give *methyl* 3-*methoxy*-4:5-*methylenedioxy*-2-*nitrobenzoate* (1.0 g.) as needles, m.p. 127°.

Found: C,47.3; H,3.85.

$C_{10}H_9O_7N$ requires: C,47.1; H,3.6%.

Light absorption: Max. at 2230 (ε = 28,000) and 2720 Å. (ε = 6,300).

Methyl 2-*Amino*-3-*methoxy*-4:5-*methylenedioxybenzoate*. - The foregoing nitro-ester (960 mg.) in ethyl acetate (150 c.c.) was shaken with hydrogen in the presence of Raney nickel (0.4 g.), (prepared according to *Org*. *Synth*. *29*, 25), until absorption ceased (2 hrs.). The filtered solution was evaporated under reduced pressure and the residue crystallised from light-petroleum (b.p. 60-80°) to give *methyl* 2-*amino*-3-*methoxy*-4:5-*methylene*-dioxybenzoate (720 mg.) as needles m.p. 89.5°.

Found: C,53.4; H,4.7.

$C_{10}H_{11}O_5N$ requires: C,53.3; H,4.9%.

Light absorption: Max. at 2260 (ε = 23,000), 2690 (ε = 5,700), and 3660 Å. (ε = 6,400).

2-*Amino*-3-*methoxy*-4:5-*methylenedioxybenzyl* *Alcohol*. - A solution of the amino-ester (610 mg.) in dry ether (10 c.c.) was added during 15 minutes to a refluxing partial solution of lithium aluminium hydride (1.0 g.) in dry ether (40 c.c.). After 3 hours refluxing the cooled mixture was treated with ice and made strongly alkaline with sodium hydroxide, and the ethereal phase was separated. After further extraction of the aqueous phase with ether (2 x 100 c.c.) the combined extracts were dried (Na_2SO_4) and evaporated to an oil which solidified rapidly. Crystallisation from benzene-light petroleum (b.p. 60-80°) gave *2-amino-3-methoxy-4:5-methylenedioxybenzyl alcohol* (470 mg.) as needles, m.p. 99°.

Found: C,55.0; H,5.8.

$C_9H_{11}O_4N$ requires: C,54.8; H,5.6%.

Light absorption: Max. at 2130 (ϵ = 31,000) and 3,000 (ϵ = 3,100); inflexion at 2420 Å. (ϵ = 5,000). The compound sublimes rapidly at 80°/10^{-4}mm.

Attempted Syntheses of 7-methoxy-5:6-methylenedioxyphthalide.

The above amino-alcohol (400 mg.) in hydrochloric acid (3 c.c.; d,1.19) and water (10 c.c.) was cooled to 0° and diazotised with sodium nitrite (400 mg.) in water (5 c.c.). After the addition of urea, the filtered solution was added with mechanical stirring to a solution of potassium cyanide (1.6 g.) and copper sulphate (1.4 g.) at 90°. The complex which formed re-dissolved on heating at this temperature for ½ hr. The solution was extracted with ether, washed, dried (Na_2SO_4) and evaporated under reduced pressure to give the nitrile as a red brown oil. The oil was then refluxed for 5 hrs. with potassium hydroxide solution (10 c.c.; 10%) and acidified with dilute hydrochloric acid. Extraction of this solution with ether and subsequent evaporation of solvent gave only a trace of material.

Preparation of Norcotarnone. - (cf. Freund and Becker, Ber. 36, 1528, 1903.

Cotarnine-Anil. - Molecular quantities of cotarnine and aniline were rubbed together in a mortar with a little water. Very soon the oily mass set to a hard crystalline solid which was broken up, washed with water and filtered. Crystallisation of the solid from benzene-petrol gave cotarnine-anil, m.p. 119-120° (lit., m.p. 124°).

Norcotarnone. - The method of Freund and Becker lacked detail and proved unsatisfactory. The method described below gave good results.

Cotarnine - anil (20 g.) and methyl iodide (20 g.) were mixed intimately until vigorous reaction commenced. When this showed signs of subsiding gentle heat was applied and then the whole was refluxed for ½ hr. on the steam-bath. Removal of the condenser and further heating on steam-bath for 1½ hrs produced a reddish brown viscous material to which dil. hydrochloric acid was added and heating resumed in order to decompose the anil. When the solution had cooled the norcotarninemethine methiodide (11 g.) was filtered off, washed and dried in vacuo m.p. 162°. An inky blue colouration was produced by a trace of the solid in ferric chloride solution.

The methiodide in 30% sodium hydroxide (17 c.c.) was boiled until contents of the flask became solid and trimethylamine ceased to be evolved. The solid was filtered off and dissolved in hot water, the solution filtered cooled and dilute hydrochloric acid added to precipitate the norcotarnone (3 g.). Crystallisation from ethanol gave plates m.p. 89° (lit., m.p. 89°). A dark blue colour was produced with acetic-sulphuric acid mixture.

<u>Ozonolysis</u> <u>of</u> <u>Norcotarnone</u>. - Norcotarnone (1 g.) in chloroform (100 c.c.) was treated with ozonised oxygen exactly as has been described for cotarnone. A solid (600 mg.) was obtained which crystallised from ethanol as needles, m.p. 110° and gave a maroon colour with acetic-sulphuric acid.

Found: C,59.67; H,4.18.

$C_9H_8O_5$ requires: C,55.68; H,3.12%.

2:3-<u>Dihydroxy</u>-6:7-<u>dimethoxynaptha</u>-1:4-<u>quinone</u>-5-<u>carboxylic</u> <u>Acid</u>. - A mixture of 3-formylopianic acid (250 mg.), glyoxal sodium bisulphite (300 mg.), and potassium cyanide (50 mg.) was treated with 2N-sodium carbonate (7 c.c.), and the mixture kept for 1 hr. at room temperature with frequent shaking and free access of air. The deep purple solution was made acid (Congo-red) with 3N-hydrochloric acid, and the red solution kept at 0° for 2 days. 2:3-<u>Dihydroxy</u>-6:7-<u>dimethoxynaptha</u>-1:4-<u>quinone</u>-5-<u>carboxylic</u> <u>acid</u> which separated crystallised from water as small red needles (100 mg.), m.p. 249-253°

(decomp.).

Found (after drying at 110° for 5 hrs): C,53.0; H,3.7

$C_{13}H_{10}O_8$ requires: C,53.1; H,3.4%.

The compound is very soluble in methanol and ethanol, slightly soluble in ether, benzene, and chloroform, and insoluble in light petroleum. It dissolves in aqueous sodium hydroxide giving a blue solution.

Light absorption: in water, Max. at 2700 (ε = 13,600) 2940 (ε = 5,700) and 4400 Å. (ε = 280); in 0.05N-NaOH, max. at 2160 (= 34,000) and 5450 (= 370), inflexion at 2450-2500 Å. (= 12,000).

Opianic Acid. - (*cf.* Wegsheider, *Monatsh.* 1882, *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 acid) and when reaction had subsided, the hot reaction mixture was filtered. On cooling, opianic acid separated and was crystallised from water (charcoal) as needles (15 g.), m.p. 143-146° (lit., m.p. 145°). If freshly precipitated manganese dioxide is used the reaction becomes too vigorous resulting in the formation of tars with subsequent low yields of opianic acid.

Meconin. - (a) (*cf.* Brown and Newbold *J.*, 1952, 4878) Opianic Acid (65 g.) in 2N-sodium hydroxide (150 c.c.) was stirred for 3 hrs. 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 (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. 101-102°.

(b) (cf. Rodionov and Fedorova, J. Gen. Chem., U.S.S.R., 1937, 7, 947). - To a suspension of opianic acid (28 g.) in a mixture of formaldehyde (33 c.c.; 40%) and water (50 c.c.) was added 50% aqueous potassium hydroxide (45 c.c.). The reaction was kept at room temperature for 10-12 hrs., 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°.

Preparation of N-Bromosuccinimide. - (cf. Zeigler et al. Ann. 1942, 551, 80). To a solution of sodium hydroxide (16 g.) in water (100 c.c.) cooled to 0°C, and containing crushed ice (75 g.) succinimide (40 g.) was added with vigorous stirring. When all the succinimide had dissolved, bromine (21.5 c.c.) was added. The bromine was rapidly taken up and a white solid was precipitated. Two minutes after the addition of bromine stirring was stopped and the solid filtered off, washed with water (ca. 2 l.) and sucked dry. After preliminary drying over calcium chloride under reduced pressure for 1 hr. the product was dried at 95° over phosphoric anhydride at 2 m.m. for 8 hrs. (Yield 50 g.). The purity of the N-bromosuccinimide was estimated by addition of excess of potassium iodide solution to a weighed sample with a little dilute hydrochloric acid and titrating liberated iodine with sodium thiosulphate.

1 ml. $\frac{N}{10}$ Sodium thiosulphate ≡ .0089 g. N-bromosuccinimide.

Oxidation of Meconin to Opianic Acid. - Meconin (500 mg.) in benzene (12 c.c.) and carbon tetrachloride (12 c.c.) was refluxed for 1 hr. with N-bromosuccinimide (1.5 mols.) with irradiation from a 60 w. lamp. The solvent was evaporated off under reduced pressure at a temperature 50°. The residual gum was treated with water (50 c.c.) and heated on the steam-bath with stirring for ¾ hr. and cooled when the precipitated solid was filtered off. Crystallisation from water gave needles (250 mg.) m.p. 145-147° undepressed by an authentic sample of opianic acid. Equivalent weight, 215 (Calc. 210).

Preparation of 4-Bromomeconin. - (cf. Perkin and Robinson, J., 1911 (I), 783). Meconin (10 g.) was dissolved in warm glacial acetic acid (25 c.c.) and gradually mixed with bromine (8.5 g.). The solution was allowed to stand until it became pale yellow and then mixed with ¼ of its volume with water. Crystallisation of precipitated solid from alcohol gave needles (7.5 g.) m.p. 176°

3-Bromopianic Acid. - 4-Bromomeconin (500 mg.) in benzene (12 c.c.) and carbon tetrachloride (12 c.c.) was treated with N-bromosuccinimide (1.5 mols.) and the product hydrolysed exactly as has been described above. The filtered solid crystallised as needles (280 mg.) from water, m.p. 200-201° which were undepressed on mixing with a sample of 3-bromopianic acid as prepared by Wegscheider, Monat. 4, 267.

Conversion of 3-bromopianic acid to 4-bromomeconin. - 3-Bromopianic acid (100 mg.) was stood overnight with sodium borohydride (100 mg.) in saturated sodium hydrogen carbonate solution (10 c.c.). On acidification of the solution 4-bromomeconin (90 mg.) was precipitated, m.p. and mixed m.p. 176°.

Trimethylgallic Acid. - (cf. Bogert and Coyne, J.Amer. Chem. Soc. 1929, 569). A 5 l. flask containing gallic acid (200 g.) suspended in 1 l. of water was fitted with a 3-holed rubber stopper carrying a thermometer, a stopcock funnel and a guard tube containing sodium hyposulphite. The acid was dissolved by the addition of sodium hydroxide (320 g.) and a small amount of sodium metabisulphite (to prevent oxidation) in 1 litre of water, and dimethyl sulphate (356 g.) was added and the temperature allowed to rise to 45° after which it was refluxed for 2 hrs. Sodium hydroxide (80 g.) was added to saponify the excess of dimethyl sulphate and refluxing continued for a further 2 hrs., the solution cooled, acidified with hydrochloric acid and the precipitate collected, washed and crystallised from a large volume of water. The product had a m.p. 168° (lit. 168°) Yield 160 g.

7-Chloromethyl-4:5:6-trimethoxyphthalide. -(cf. King and King, J., 1942, 726). A mixture of trimethylgallic acid (16 g.), aqueous formaldehyde (40 c.c.; 40%) and hydrochloric acid (d,1.16) (64 c.c.) was refluxed 20 minutes in an oil bath at 140°. On cooling and on the addition of water the oily product solidified; recrystallisation from alcohol gave the chloromethylphthalide (10 g.) as colourless needles m.p. 85° (lit. 85°).

7-Hydroxymethyl-4:5:6-trimethoxyphthalide. - 7-Chloromethyl-4:5:6-trimethylphthalide (1 g.) was heated under reflux with a solution of sodium carbonate (1 g. in 10 c.c. water) and then acidified with dilute hydrochloric acid and extracted with chloroform. Removal of the chloroform gave a solid which crystallised from benzene to give 7-hydroxymethyl-4:5:6-trimethoxyphthalide m.p. 90-91° (lit., m.p. 92°).

Attempted Synthesis of 6-formyl-3:4:5-trimethoxyphthalaldehydic Acid. - (a) A solution of 7-chloromethyl-4:5:6-trimethoxyphthalide (2 g.) in carbon tetrachloride (100 c.c.) was heated under reflux for 1½ hrs. with N-bromosuccinimide (3.94 g.) with irradiation from a 60 watt lamp.

The solid was filtered off, solvent removed, and the residual gum heated with water (150 c.c.) on the steam-bath for 2 hrs. The solid material was filtered off and crystallised from benzene m.p. 92° undepressed on mixing with a sample of 7-hydroxymethyl-4:5:6-trimethoxyphthalide.

(b) The above experiment was repeated irradiating with ultra-violet light and continuing refluxing for 7½ hrs. Benzoyl peroxide (25 mg.) was also added to reaction mixture. A solid product was obtained crystallising as needles (950 mg.) from benzene-petrol, m.p. 129.5 and giving a 2:4-dinitrophenylhydrazone. No analysis was obtained from which a satisfactory empirical formula could be determined.

4:5:6-<u>Trimethoxyphthalide</u>. - (<u>cf</u>. King and King <u>loc. cit</u>.). Method of preparation exactly as for chloromethyl compound but using following quantities: trimethylgallic acid (10 g.), hydrochloric acid (10-12 c.c.; d,1.16) and formaldehyde solution (25 c.c.; 40%). Prisms (5 g.) were obtained on crystallisation from ethanol (charcoal) m.p. 134-135°.

<u>Standard Chromium Trioxide Oxidation Procedure</u>. - A solution of the amide derivative (1 part) or if not isolated as a solid that derived from the phthalide (1 part) in glacial acetic acid (20 parts) was stirred at room temperature and treated with a solution of chromic acid (1 part) in water (1 part) and glacial acetic acid (20 parts) added in

one portion and stirred for 5 minutes. Water (100 parts) was then added and the mixture extracted with chloroform (3 x 50 parts), the combined extracts washed with water, 10% aqueous sodium hydrogen carbonate, water and dried (Na_2SO_4).

2:3-Dimethoxy-6-hydroxymethyl-NN-dimethylbenzamide. - Dimethylamine (50 c.c.) was added to a solution of meconin (2 g.) in ethanol (120 c.c.) and the mixture allowed to stand at room temperature for 2 days. After removal of solvent under reduced pressure the residual yellow gum slowly solidified on keeping; crystallisation from ethyl acetate-light petroleum (b.p. 60-80°) gave the dimethylamide (2.2 g.; 89%) as plates, m.p. 93-95°.

Found: C,60.2; H,6.8

$C_{12}H_{17}O_4N$ requires: C,60.2; H,7.2%

The compound gave a 20° depression on mixed m.p. with meconin. Light absorption: Max. at 2080 (ε = 29,400) and 2800 (ε = 2300) and inflexion at 2260 Å. (ε = 11,500). The acetate prepared in good yield by the action of acetic anhydride-pyridine at room temperature overnight separated from light petroleum (b.p. 40-60°) as prisms, m.p. 63-64°.

Found: C,60.2; H,6.6.

$C_{14}H_{19}O_5N$ requires: C,59.8; H,6.8%.

Light absorption: Max. at 2080 (ε = 32,600), 2800 (ε = 2400) and inflexion at 2260 Å. (ε = 12,500). On heating 2:3-dimethoxy-6-hydroxymethyl-NN-dimethyl benzamide to 170° (bath temp.) decomposition commenced; after ½ hr. at 170-180° the residue was cooled and crystallised from ethanol to give meconin (85% yield) as needles, m.p. and mixed m.p. 101-102°. Hydrolysis of the dimethylamide was slow on boiling with water; on boiling with 3N hydrochloric acid for ½ hr. an almost quantitative yield of meconin was obtained. Boiling with 3N sodium hydroxide also gave meconin in good yield.

Opianic Acid. - 2:3-Dimethoxy-6-hydroxymethyl-NN-dimethylbenzamide (1 g.) was oxidised according to the standard procedure and the product isolated using chloroform Removal of the chloroform under reduced pressure gave a gum (700 mg.) which was refluxed with hydrochloric acid (10 c.c.; 3N) for 2 hrs. On cooling opianic acid (400 mg.; 46%) separated from the reaction mixture; it crystallised from water as needles, m.p. and mixed m.p. 145-146°.

Found: C,57.0; H,5.0.

Calc. for $C_{10}H_{10}O_5$: C,57.1; H,4.8%.

Light absorption: Max. at 2150 (ε = 20,700) and 2840 Å. (ε = 6500). Edwards, Perkin and Stoyle *J.*, 1925, *127*, 195 give m.p. 146°.

Phthalaldehydic Acid. - Phthalide (2 g.) in ethanol (10 c.c.) was heated with anhydrous dimethylamine (20 c.c.) in an autoclave at 130° for 4 hrs. and then oxidised and the product hydrolysed as in the previous cases. Phthalaldehydic acid was obtained in 20% yield; it separated from benzene-light petroleum (b.p. 60-80°) as rosettes of needles, m.p. and mixed m.p. 97°.

m-Opianic Acid. - m-Meconin (500 mg.) and ethanolic dimethylamine (40 c.c.; 33%) were heated in an autoclave for 5 hrs. at 140-145° and then oxidised and the product hydrolysed as in the previous cases. m-Opianic acid (40 mg.) was obtained from water as needles, m.p. 185-187° alone or mixed with an authentic specimen, m.p. 187-188° (Brown and Newbold, J., 1952, 4397).

3-Methoxyphthalaldehydic Acid. - 4-Methoxyphthalide (0.5 g.) (Beuhler, Powers and Michels, J. Amer. Chem. Soc., 1944, 66, 417) was heated to 140-150° with ethanol (10 c.c.) and dimethylamine (35 c.c.) for 4 hrs. The solution was evaporated under reduced pressure below 35° (bath temperature) and the residual gum oxidised according to the standard procedure and the product hydrolysed to give 3-methoxyphthalaldehydic acid (210 mg.) crystallising from benzene-light petroleum as needles, m.p. 155-157°.

Found: C,59.9; H,4.8%; equiv. 181.

$C_9H_8O_4$ requires: C,60.0; H,4.5%; equiv. 180.

pK 5.57. Light absorption in water: Max. at 2140 (ε = 39,300), 2680 (ε = 3100) and 3010 (ε = 3900) and inflexion at 2850-2450 Å. (ε = 6800).

5-*Methoxy*-4-*methylphthalaldehydic* *Acid*. - 6-Methoxy-5-methylphthalide (500 mg.) was heated with an ethanolic solution of dimethylamine (70 c.c.; 30%) in an autoclave at 140° for 4 hours. The reaction mixture was evaporated under reduced pressure below 40° to a gum, which was oxidised by the standard procedure, and the product isolated using chloroform. The chloroform extract was evaporated and the residual gum refluxed for 1 hr. with hydrochloric acid (20 c.c.; 3N), cooled and the acid fraction isolated using chloroform. Crystallisation from benzene gave 5-*methoxy*-4-*methylphthalaldehydic* *acid* (200 mg.) as small needles, m.p. 162-163°.

Found: C,62.1; H,5.4%; equiv. 198

$C_{10}H_{10}O_4$ requires: C,61.85; H,5.2%; equiv. 194.

Light absorption in water: Max. at 2180 (ε = 22,000) and 2900 (ε = 9700) and inflexion at 2300-2340 Å. (ε = 12,900).

4:5:6-*Trimethoxyphthalaldehydic* *Acid*. - 5:6:7-Trimethoxyphthalide (McRae, Van Order, Griffiths and Habgood, *Canad*. *J*. *Chem*., 1951, *29*, 482; 300 mg.) in ethanolic dimethylamine (50 c.c.; 33%) was heated in a sealed tube at 60° for 4 hrs. and kept at room temperature for 2 days. The reaction product, not isolated as a solid, was oxidised by the standard procedure and the oxidation product hydrolysed to give 4:5:6-trimethoxyphthalaldehydic acid (50 mg.) which separated from benzene-light petroleum (b.p. 60-80°) as needles, m.p. 137-138°, depressed on mixing with starting material.

Found: C,54.9; H,5.3

$C_{11}H_{12}O_6$ requires: C,55.0; H,5.0%.

Light absorption in water: Max. at 2230 (ε = 20,500) and 2720 (ε = 9600) and inflexion at 3120-3220 Å. (ε = 2800).

2-Amino-3-methoxybenzoic Acid. - Sodium dithionite (8 g.) was added in portions, with stirring, to 3-methoxy-2-nitrobenzoic acid (2 g.; Ewins, J., 1912, 101, 544) in a solution of potassium hydroxide (2 g.) in water (20 c.c.) the temperature being kept below 40° with water cooling. After keeping at room temperature for ½ hr. the solution was made acid (Congo red) with hydrochloric acid (d,1.16) and heated on the steam bath (fume cupboard) for 3 hrs. to remove sulphur dioxide. On cooling 2-amino-3-methoxy-benzoic acid (1.4 g.) separated. It had m.p. 164-166° (lit., m.p. 162-163°).

3-Methoxyphthalic Acid. - A suspension of 2-amino-3-methoxybenzoic acid (5 g.) in hydrochloric acid (7.5 c.c.; d,1.16) and water (25 c.c.) was diazotised at 0-5° with a solution of sodium nitrite (2 g.) in water (10 c.c.). After adding urea the filtered diazonium solution was poured into a hot solution of potassium cyanide (8 g.) and copper sulphate (7 g.) in water (100 c.c.). The mixture was heated on the steam bath for 1½ hrs., cooled and acidified (Congo red) with hydrochloric acid (d,1.16). The crude cyano-acid (4 g.) which separated was refluxed with aqueous potassium hydroxide (100 c.c.; 10%) for 4 hrs. The solution was acidified (Congo red) and evaporated to dryness under reduced pressure. The dark red residue was extracted with boiling ethyl acetate (3 x 100 c.c.); concentration of the extract to small bulk and cooling gave 3-methoxyphthalic acid (3.5 g.) as a brown solid, m.p. 162-165°. Crystallisation of a specimen from ethyl acetate-light petroleum (b.p. 60-80°) gave the acid as prisms, m.p. 169-171°; Bentley, Robinson and Weizmann (J., 1907, 91,104) give m.p. 173-174°.

Found: C,54.9; H,4.3.

Calc. for $C_9H_8O_5$: C,55.1; H,4.1%.

Light absorption: Max. at 2110 (ε = 22,500) and 3000 Å. (ε = 3400).

3-Methoxyphthalic Anhydride. - The crude acid (2 g.) was heated at 180-185° for 10 minutes at atmospheric pressure and at 160-170°/10^{-3} mm. when 3-methoxyphthalic anhydride (1.8 g.) sublimed as a crystalline mass, m.p. 155-157°.

Crystallisation from ethyl acetate-light petroleum (b.p. 60-80°) gave blades, m.p. 159-160°; Bentley et al. (loc. cit.) give m.p. 160-161°.

Found: C,60.6; H,3.5.

Calc. for $C_9H_8O_4$: C,60.7; H,3.4%.

7-Hydroxyphthalide. - 3-Methoxyphthalic anhydride (4.4 g.), glacial acetic acid (13 c.c.), hydrochloric acid (13 c.c.; d,1.16) and zinc dust (11 g.) were heated under reflux for 6 hrs. The reaction mixture was kept at room temperature overnight and the filtered solution was almost neutralised with aqueous sodium carbonate, extracted with chloroform (3 x 30 c.c.) and after washing with water (20 c.c.) the dried (Na_2SO_4) extract was evaporated under reduced pressure to give a gum (3.8 g.) which rapidly solidified. The separation of 4- and 7-methoxyphthalides by fractional crystallisation (cf. Duncanson, Grove and Zealley, J. 1953, 1331) proved impracticable. The solid was refluxed for 2½ hrs. with aqueous hydrobromic acid (100 c.c.; d,1.46-1.49) in a coal gas atmosphere. The solution was evaporated under reduced pressure to give a red gum which was dissolved in water (50 c.c.), treated with charcoal and the solution evaporated to dryness under reduced pressure. The resulting solid (2.0 g.) was heated at 130-140°/10^{-3} mm., and the sublimate (1.4 g.), m.p. 125-127° collected. Crystallisation from ethyl acetate-light petroleum (b.p. 60-80°) gave

7-hydroxyphthalide as prisms, m.p. 134-136°.

Found: C,64.25; H,4.3.

Calc. for $C_8H_6O_3$: C,64.0; H,4.0%.

Light absorption: Max. at 2120 (ε = 26,000), 2320 (ε = 8700) and 2990 Å. (ε = 4600). Eliel, Rivard and Burgstahler (*J. Org. Chem.*, 1953, *18*, 1679) give m.p. 135-136.5°. The compound gave a purple colour with ferric chloride in aqueous ethanol.

7-Methoxyphthalide. - (a) 2-amino-3-methoxybenzoic acid (5 g.) was refluxed for 3 hrs. with lithium aluminium hydride (8 g.) in ether (250 c.c.). The reaction mixture was worked up as given for the corresponding methyl derivative (Brown and Newbold, *J.*, 1953, 1285). Removal of the ether gave a light yellow partially solid material (3.5 g.) which was used without further treatment for the next stage. A solution of the crude amino-alcohol in hydrochloric acid (27 c.c.; d,1.16) and water (90 c.c.) and diazotised at 0° with a solution of sodium nitrite (2.7 g.) in water (20 c.c.). After addition of urea the filtered solution was added to a hot solution of potassium cyanide (14.4 g.) and copper sulphate (12.6 g.) in water (150 c.c.). After heating on the steam bath for 30 minutes the cooled reaction mixture was extracted with ether (3 x 50 c.c.), the combined extract washed with water, dried (Na_2SO_4) and evaporated to give a red oil (700 mg.). The oil was heated under reflux with aqueous potassium hydroxide (20 c.c.; 10%) for 2 hrs. The solution was decanted from tar, acidified (Congo red) extracted with chloroform (3 x 20 c.c.), the combined chloroform extracts washed with water (20 c.c.) and dried (Na_2SO_4). Removal of the solvent gave an orange gum which slowly solidified. Crystallisation from ethyl acetate-light petroleum (b.p. 60-80°) (charcoal) gave 7-methoxyphthalide (100 mg.) as long needles, m.p. 107-109°.

Found: C,65.6; H,5.1.

Calc. for $C_9H_8O_3$: C,65.85; H,4.9%.

Light absorption: Max. at 2090 (ε = 33,000), 2340 (ε = 8200) and 2960 Å. (ε = 4700). Duncanson, Grove and Zealley (J., 1953, 1331) give m.p. 96°; that this low m.p. was due to some residual 4-methoxyphthalide in the specimen has been shown by direct comparison of the infra-red spectra of the two substances. (We are indebted to Mr. J. F. Grove for this information).

(b) A solution of 7-hydroxyphthalide (1.3 g.) in aqueous sodium hydroxide (20 c.c.; 2N) was treated with dimethyl sulphate (2 c.c.), stirred at room temperature for 1 hr. then dimethyl sulphate (1 c.c.) added and stirring continued for a further hour. After the addition of dimethyl sulphate (2 c.c.) and aqueous sodium hydroxide (10 c.c.) the reaction mixture was heated on the steam bath for ½ hr., aqueous sodium hydroxide (10 c.c.; 2N) added and heating continued for a further ½ hr. Sodium hydroxide (1 g.) was added and heating continued for a final ½ hr. The cooled acidified solution was extracted with chloroform (3 x 25 c.c.), the combined extract dried (Na_2SO_4) and evaporated. Crystallisation from ethyl acetate-light petroleum (b.p. 60-80°) gave 7-methoxyphthalide (550 mg.) as needles, m.p. 107-109° alone or mixed with preparation (a)

Found: C,66.1; H,5.1%.

A specimen of 7-methoxyphthalide was demethylated by heating under reflux with aqueous hydrobromic acid as given for the mixed phthalides furnishing 7-hydroxyphthalide as prisms from ethyl acetate-light petroleum (b.p. 60-80°) m.p. and mixed m.p. 132-134°.

2-Methoxy-6-hydroxymethyl-NN-dimethylbenzamide. - 7-Methoxyphthalide (120 mg.) in ethanol (10 c.c.) was cooled to 0° and treated with dimethylamine (10 c.c.) and kept at room temperature for 3 days. Evaporation of the solution under reduced pressure below 35° and crystallisation of the residue from ethyl acetate-light petroleum (b.p. 60-80°) gave the *dimethylamide* (140 mg.) as blades, m.p. 120-121°

Found: C,63.1; H,6.8.

$C_{11}H_{15}O_3N$ requires: C,63.1; H,7.2%.

6-*Methoxyphthalaldehydic Acid.* - 2-Hydroxy-6-hydroxymethyl-NN-dimethylbenzamide (100 mg.) was oxidised by the standard procedure and the product, isolated using chloroform, refluxed for 1 hr. with hydrochloric acid (5 c.c.; 3N). 6-*Methoxyphthalaldehydic acid hydrate* (50 mg.) isolated by chloroform crystallised from water as needles, m.p. 151-153°.

Found: equiv. 198.

$C_9H_8O_4.H_2O$ requires: equiv. 198.

After drying at 58° 0.5 mm. for 3 hrs. the anhydrous form, m.p. 151-153° was obtained.

Found: C, 58.7; H, 4.5%; equiv. 180.5.

$C_9H_8O_4$ requires: C, 60.0; H, 4.5%; equiv. 180.

Light absorption in water: Max. at 2100 (ε = 22,000), 2500 (ε = 3900) and 3060 Å. (ε = 3200). pK_a 5.13. Yabuta and Sumiki (*J. Agric. Chem. Soc. Japan*, 1934, *10*, 703) give m.p. 152-153° for 6-methoxyphthalaldehydic acid obtained from degradation of mellein; a direct comparison of the two preparations has not been possible.

The 2:4-*dinitrophenylhydrazone* separated from ethanol as yellow needles, m.p. 250-252° (decomp.) (*lit.* 245-246° decomp.)

Found: C, 50.3; H, 3.35; N, 15.8.

$C_{15}H_{12}O_7N_4$ requires: C, 50.0; H, 3.4; N, 15.55%.

2-Hydroxymethylbenzamide. - Liquid ammonia (200 c.c.) was added to a solution of phthalide (5 g.) in ethanol (100 c.c.). The reaction solution was kept overnight at room temperature, then evaporated under reduced pressure and the residue crystallised from ethyl acetate-light petroleum (b.p. 60-80°) to give 2-hydroxymethylbenzamide (75%) as blades, m.p. 149-150°

Found: C,63.1; H,5.9.

$C_8H_9O_2N$ requires: C,63.6; H,6.0%).

Phthalimide. - 2-Hydroxymethylbenzamide (500 mg.) was oxidised according to the standard procedure. Using chloroform, phthalimide (70% yield) was isolated and separated from water as needles, m.p. and mixed m.p. 235°.

2:3-Dimethoxy-6-hydroxymethylbenzamide. - Liquid ammonia (200 c.c.) was added slowly with shaking to a solution of meconin (5 g.) in ethanol (300 c.c.) and the solution kept overnight at room temperature. The solvent was removed under reduced pressure to give a gum which solidified on keeping. The solid was triturated with hot benzene, the benzene rejected and the residue crystallised from ethyl acetate-light petroleum (b.p. 60-80°) to give 2:3-dimethoxy-6-hydroxymethylbenzamide (3.5 g.) as blades, m.p. 140-142°.

Found: C,57.0; H,5.8.

$C_{10}H_{13}O_4N$ requires: C,56.9; H,6.2%.

Light absorption: Max. at 2060 (ε = 24,700) and 2820 (ε = 2200) and inflexion at 2260 Å. (ε = 9300). *The acetate,* prepared in 80% yield by the action of acetic anhydride and pyridine at room temperature overnight followed by isolation in the usual manner using chloroform, separated from benzene-light petroleum (b.p. 60-80°) as blades, m.p. 159-160°.

Found: C,57.2; H,6.1.

$C_{12}H_{15}O_5N$ requires: C,56.9; H,6.0%).

Light absorption: Max. at 2080 (ε = 23,400), 2820 (ε = 2100) and inflexion at 2260 Å. (ε = 9250).

Hemipinimide. - Oxidation of 2:3-dimethoxy-6-hydroxymethylbenzamide (250 mg.) using the standard procedure followed by isolation using chloroform and crystallisation of the product from ethanol gave hemipinimide (100 mg.) as needles, m.p. 225-227° alone or mixed with a specimen prepared from opianic acid (Liebermann, *Ber.*, 1886, *19*, 2275; *lit.*, m.p. 228-230°)

Found: C,58.1; H,4.4.

Calc. for $C_{10}H_9O_4N$: C,58.0; H,4.4%.

Light absorption: Max. at 2260 (ε = 29,600), 3320 (ε = 5000) and inflexion at 2450 Å. (ε = 15,600).

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