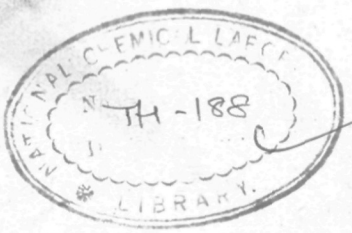

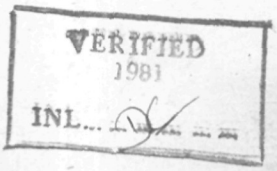

SYNTHESIS OF CITRININ AND ITS ANALOGUES

A Thesis Submitted by

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to

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for

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PART I. A TOTAL SYNTHESIS OF CITRININ

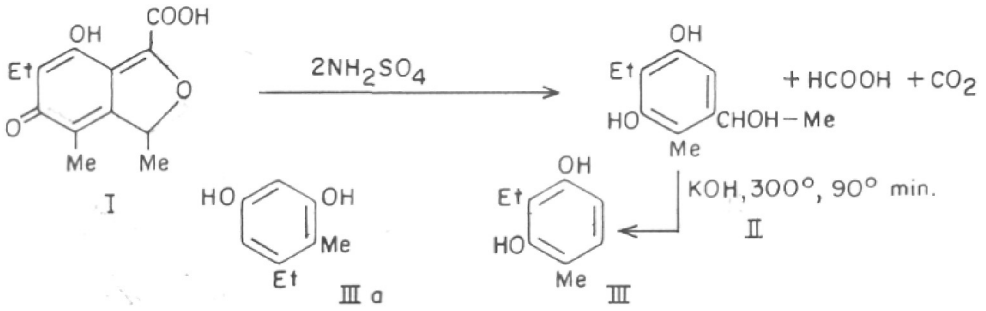
Introduction

Citrinin, a yellow metabolite of *Penicillium citrinum* Thom., was isolated by HETHERINGTON and RAISTRICK[1] in 1931. Later it was found that various other organisms, such as *Penicillium expansum*,[2] *Aspergillus terreus*[3] and an *Aspergillus* species of the *candidus* group,[4] produce citrinin. The yield of citrinin varies from 1.0 to 4.5 g per litre of the medium, depending on the organism, the medium and other factors. A reported isolation of citrinin from the leaves of *Crotalaria crispata* F. Muell[5] was not supported by adequate evidence of identification and could not be repeated in recent investigations of this plant.[6]

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

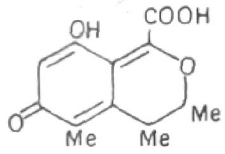
The bacteriostatic activity of citrinin has been examined by various workers,[7-12] who found that it possesses high toxicity and low antibacterial action in comparison with antibiotics, such as penicillin and aureomycin. Hence in spite of the ease with which citrinin can be prepared microbiologically, it has not found therapeutic application.

The structure of citrinin was first investigated by HETHERINGTON and RAISTRICK[1] who subjected citrinin to a series of reactions and isolated the degradation products. These results were later interpreted by COYNE, RAISTRICK and ROBINSON[13] as involving the sequence of reactions in I, II and III, and citrinin was assigned the isobenzofuran structure I.

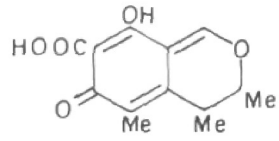


GORE et al.[14] were the first to show that structure I for citrinin was untenable because (a) citrinin coupled with diazotized aniline to give a monoazo dye containing a carboxyl group and a disazo dye free from carboxyl; and (b) the phenolic alcohol II and the phenol III obtained by the degradation of citrinin, and to which COYNE, RAISTRICK and ROBINSON[13] had assigned the indicated structures, gave disazo dyes with diazotized aniline. A resorcinol derivative substituted in the 2,4-positions, as in II and III, obviously can only give monoazo dyes. COYNE, RAISTRICK and ROBINSON[13] regarded the structure

of the phenol III, which was assigned "for good and sufficient reasons,"[2] as fundamental in their arguments for the constitution of citrinin I. On the basis of the electronic absorption spectra of a series of phenylazoresorcinols and the other data already available, but without recourse to new degradative or synthetic experiments, GORE, PANSE and VENKATARAMAN showed that the phenol III obtained by the degradation of citrinin was 5-ethyl-4-methylresorcinol (IIIa), and they proposed structure IV for citrinin, which represented the first example of a pigment derived from the isochroman and methylenequinone ring systems. The independent and simultaneous work of Robertson and collaborators[15-20] led to the slightly different structure V, which is now known



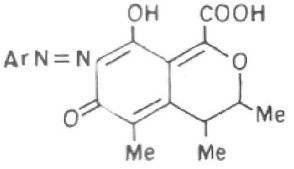
IV



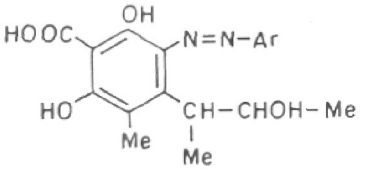
V

to be correct. The failure on the part of GORE et al.[14] to place the carboxyl group in the right position was for two reasons: (a) the characteristic blue ferric colour of Y-resorcylic acid shown by dihydrocitrinin was not noticed; and (b) the nitrogen contents of the azo dyes VI and VII were within the limits of experimental error, and the possibility of the pyran ring undergoing fission

during diazonium coupling was not anticipated. Later work[21] showed that the carboxylic acid obtained by coupling citrinin with a molar proportion of diazotized aniline had the structure VII; ROBERTSON was not able to isolate (VII), because he was not aware of the correct experimental conditions.



VI



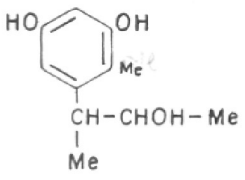
VII

The phenolic alcohol obtained by acid hydrolysis of citrinin was a mixture of optical isomers, phenolic alcohols: (A), m.p. 128°, which was laevorotatory, and the optically inactive (B), m.p. 169°, shown to be the racemate of phenolic alcohol (A). Degradation of citrinin with aqueous sodium hydroxide produced phenolic alcohol (A) only. Phenolic alcohol (A) can be racemized to phenolic alcohol (B) by boiling with dilute sulphuric acid.[15]

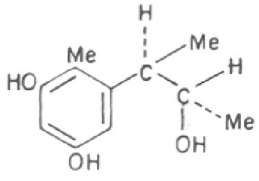
Phenolic alcohol (B) was shown by ROBERTSON *et al.*[20] to be a single racemate. After obtaining inactive citrinin from phenolic alcohol (B), as mentioned later, they resolved it into the *d* and *l* forms by means of its brucine salt.

Hydrolytic decomposition of the (+) and (-) citrinin with aqueous sodium hydroxide gave respectively (+) and (-) phenolic alcohol (A), a mixture of which furnished phenolic alcohol (B). The relationship between these two phenols was also demonstrated by resolution with brucine, of the hydrogen phthalate of dimethyl ether of phenolic alcohol (B), to give the (+) and (-) hydrogen phthalates of phenolic alcohol (A).

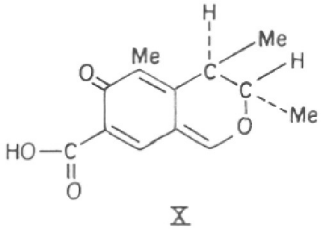
CRAM[22] deduced the structure of phenolic alcohols (A) and (B) as (VIII) and further elaborated the relative configuration of the two asymmetric carbon atoms in phenolic alcohol (A) as IX and in citrinin as X. CRAM[23] suggested that the acid catalysed racemization of the phenolic alcohol (A) to phenolic alcohol (B) with retention of configuration proceeds by way of a Wagner-Meerwein rearrangement.



VIII



IX



X

Since citrinin (V) has two asymmetric carbon atoms, there should be four optically active forms and two racemates; but only one pair of enantiomorphs (the form of which is natural citrinin) and the corresponding racemate are known.

The synthesis of the dimethyl ether of phenolic alcohol (B) (VIII) was accomplished by ROBERTSON by two methods outlined in Charts 1 and 2.[16,20]

The routes in Charts 1 and 2 led to two racemates, which were separated as their p-nitrobenzoates; one of them was identical with the p-nitrobenzoate of the dimethyl ether of phenolic alcohol (B) from citrinin. Demethylation of the dimethyl ether of phenolic alcohol (A) with hydriodic acid for 5 min gave phenolic alcohol (B) in 10 per cent yield, demethylation being accompanied by racemization. ROBERTSON did not demethylate the synthetic dimethyl ether XI (Chart 1 and 2) to phenolic alcohol VIII.

ROBERTSON[19] achieved a partial synthesis of citrinin starting from phenolic alcohol VIII (B), obtained from natural citrinin; this was carboxylated by means of potassium carbonate in glycerine at 150-155°. The resulting acid (XII) was submitted to the Gattermann-Adams reaction

Chart 1

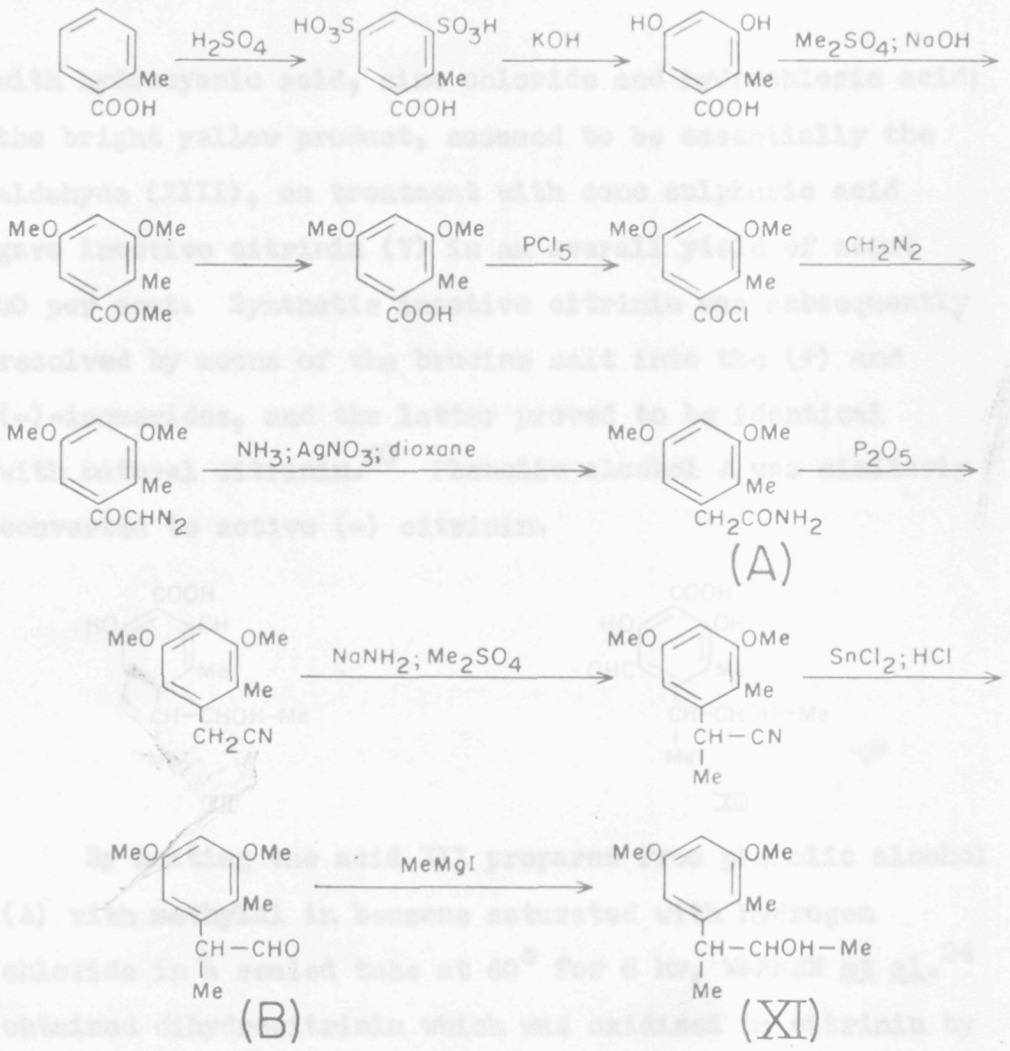
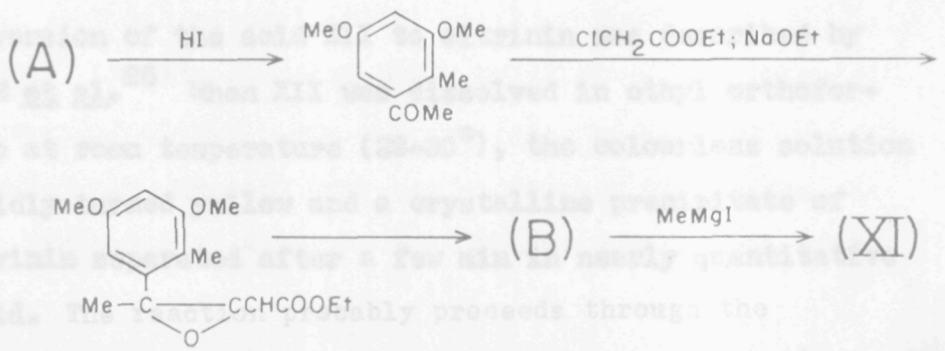
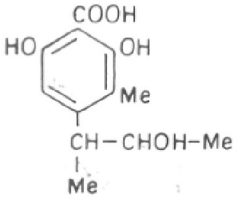


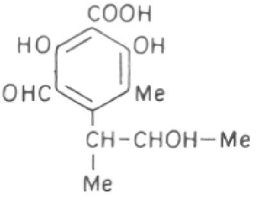
Chart 2



with hydrocyanic acid, zinc chloride and hydrochloric acid; the bright yellow product, assumed to be essentially the aldehyde (XIII), on treatment with conc sulphuric acid gave inactive citrinin (V) in an overall yield of about 30 per cent. Synthetic inactive citrinin was subsequently resolved by means of the brucine salt into the (+) and (-)-isomerides, and the latter proved to be identical with natural citrinin.[20] Phenolic alcohol A was similarly converted to active (-) citrinin.



XII

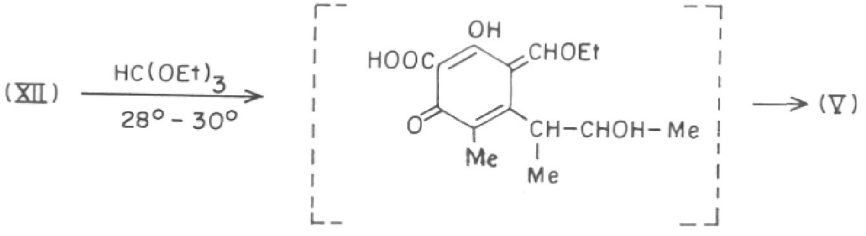


XIII

By heating the acid XII prepared from phenolic alcohol (A) with methylal in benzene saturated with hydrogen chloride in a sealed tube at 60° for 6 hr, WARREN *et al.*[24] obtained dihydrocitrinin which was oxidized to citrinin by bromine in chloroform.

A remarkably simple and interesting reaction for the conversion of the acid XII to citrinin was described by GORE *et al.*[25] When XII was dissolved in ethyl orthoformate at room temperature (28-30°), the colourless solution rapidly turned yellow and a crystalline precipitate of citrinin separated after a few min in nearly quantitative yield. The reaction probably proceeds through the

ethoxymethylene derivative XIIIa.



The biosynthesis of citrinin has been examined by BIRCH et al.[26] by feeding experiments with ^{14}C-labelled acetic and formic acids. They suggest that citrinin can arise from five acetic acid units and three formic acid units, but a better defined route will need further investigation.

The NMR spectrum of citrinin has been discussed by TERHARARA and collaborators.[27]

Present work

It is to be noted that the syntheses of citrinin reported above have been accomplished, starting from the phenolic alcohol (VIII),[19,24,25] which was obtained by the hydrolysis of citrinin itself. Although the structure of the phenolic alcohol (VIII) has been conclusively proved,[16] and its dimethyl ether synthesized, the recorded syntheses of citrinin can only be regarded as "partial" or "formal." The present work was undertaken to achieve a total synthesis of citrinin and also to develop procedures

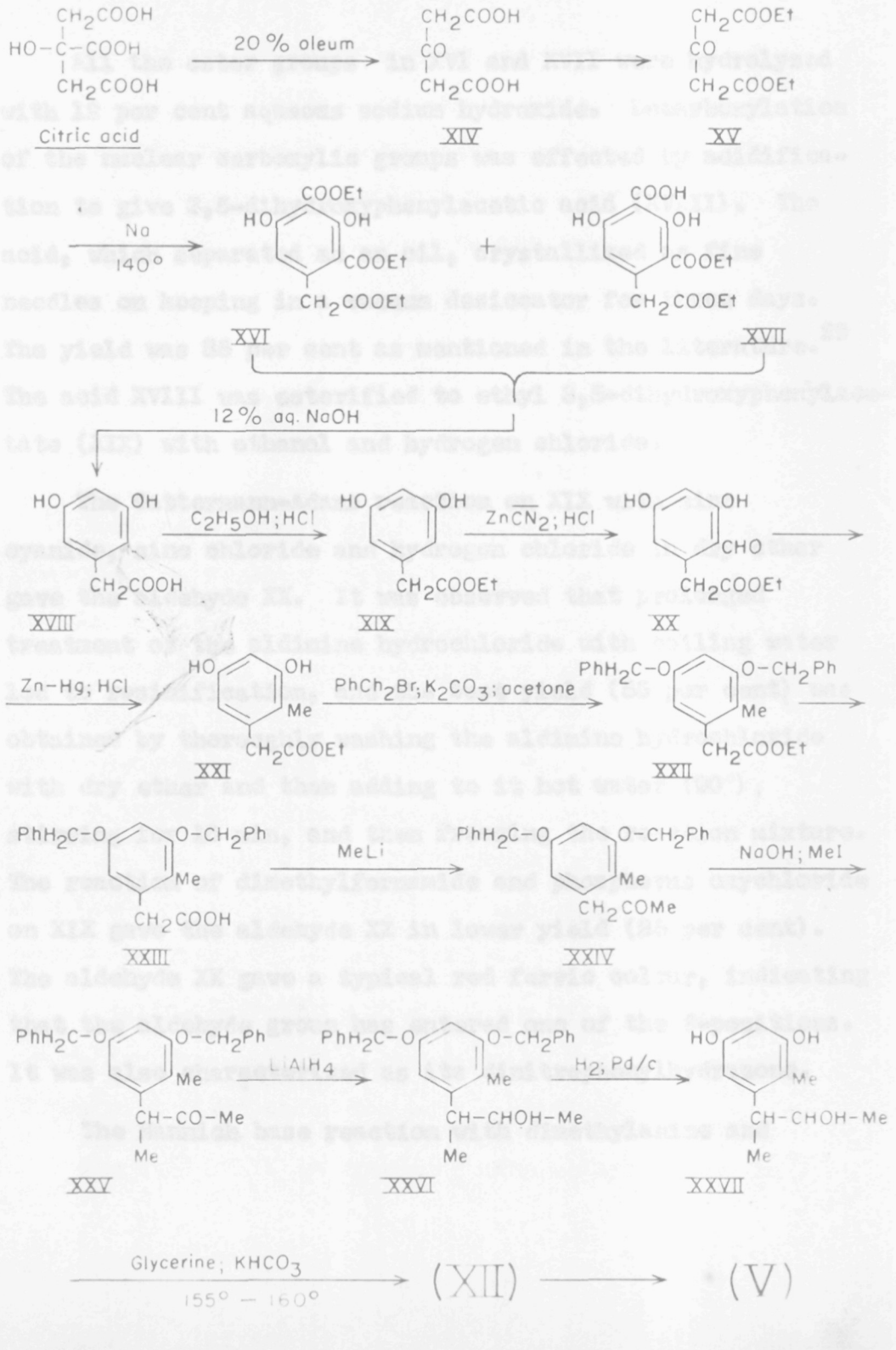
for the synthesis of analogues of citrinin, which may be less toxic and have more powerful antibacterial properties than citrinin.

This part of the thesis deals with (A) a total synthesis of citrinin starting from citric acid; and (B) a study of the stereochemistry of the synthetic phenolic alcohol (XXVII) in comparison with the phenolic alcohol obtained from natural citrinin.

The reactions involved in the synthesis of citrinin are shown in Chart 3.

(A) Citric acid was first converted to acetonedicarboxylic acid (XIV) by reaction with 20 per cent oleum in an overall yield of 85 per cent. The acid (XIV) was esterified with ethanol and hydrogen chloride; the product was fractionally distilled to give pure diethyl acetonedicarboxylate (XV).[28] DIECKMANN cyclization of XV with metallic sodium at 140° gave ethyl 3,5-dihydroxy-2,4-dicarbethoxyphenylacetate (XVI) and ethyl carbethoxy-3,5-dihydroxy-4-carboxyphenylacetate (XVII). It was observed that the yields of XVI and XVII were 45-46 per cent and 11-12 per cent respectively as against 53 and 5 per cent reported by THEILACKER and SCHMID[29].

Chart 3

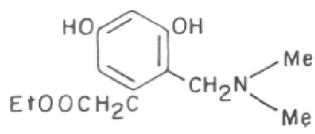

20 % oleum
Citric acid
XIV
XV
Na
140°
XVI
XVII
12 % aq. NaOH
C2H5OH; HCl
ZnCN2; HCl
XVIII
XIX
XX
Zn-Hg; HCl
PhCH2Br; K2CO3; acetone
XXI
XXII
MeLi
NaOH; MeI
XXIII
XXIV
LiAlH4
H2; Pd/c
XXV
XXVI
XXVII
Glycerine; KHCO3
155° – 160°
(XII)
(V)

All the ester groups in XVI and XVII were hydrolyzed with 12 per cent aqueous sodium hydroxide. Decarboxylation of the nuclear carboxylic groups was effected by acidification to give 3,5-dihydroxyphenylacetic acid (XVIII). The acid, which separated as an oil, crystallized as fine needles on keeping in a vacuum desiccator for three days. The yield was 85 per cent as mentioned in the literature.[29] The acid XVIII was esterified to ethyl 3,5-dihydroxyphenylacetate (XIX) with ethanol and hydrogen chloride.

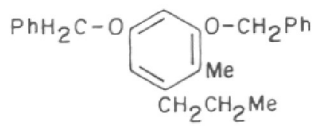
The Gattermann-Adams reaction on XIX with zinc cyanide, zinc chloride and hydrogen chloride in dry ether gave the aldehyde XX. It was observed that prolonged treatment of the aldimine hydrochloride with boiling water led to resinification, and the best yield (55 per cent) was obtained by thoroughly washing the aldimine hydrochloride with dry ether and then adding to it hot water (90°), stirring for 10 min, and then freezing the reaction mixture. The reaction of dimethylformamide and phosphorus oxychloride on XIX gave the aldehyde XX in lower yield (25 per cent). The aldehyde XX gave a typical red ferric colour, indicating that the aldehyde group has entered one of the o-positions. It was also characterized as its dinitrophenylhydrazone.

The Mannich base reaction with dimethylamine and

formaldehyde on XIX under various conditions failed to give XXVIII as a crystalline solid, which could then by hydrogenolysis with Raney nickel and hydrogen give XXI; the product was a red amorphous polymer having no melting point up to 350° and insoluble in most organic solvents.



XXVIII



XXIX

Clemmensen reduction of the aldehyde XX with freshly prepared zinc amalgam and conc hydrochloric acid in methanol led to ethyl 3,5-dihydroxy-2-tolylacetate (XXI). The ester XXI was benzylated by means of benzyl chloride and potassium carbonate in acetone to give ethyl 3,5-dibenzyloxy-2-tolylacetate (XXII). For obtaining the maximum yield of the benzylated product (85 per cent), the reaction time was 72 hr. The reaction could be completed in a much shorter time (12 hr) by employing benzyl bromide in place of benzyl chloride.

Alkaline hydrolysis of the ester XXII yielded 3,5-dibenzyloxy-2-tolylacetic acid (XXIII), but only in 70 per cent yield under the best conditions.

The acid XXIII on treatment with methyllithium in

ether led to 3,5-dibenzyloxy-*o*-tolylacetone (XXIV) in 85 per cent yield. The ketone was characterized by its 2,4-dinitrophenylhydrazone.

It was observed that when the acid XXIII was refluxed with excess methyllithium in ether for a prolonged period (40 hr), the product obtained was not the ketone XXIV, but 2,4-dibenzyloxy-6-*n*-propyltoluene (XXIX) as a result of reduction of the ketone.

C-Methylation of the ketone XXIV was effected with sodium hydroxide and methyl iodide. The product XXV, purified by distillation under reduced pressure, was a colourless viscous oil, which gave the correct elementary analysis. The 2,4-dinitrophenylhydrazone melted at 152°. No attempt was made to crystallize the ketone.

Reduction of the ketone XXV with lithium aluminium hydride gave the corresponding alcohol XXVI, methyl α-(3,5-dibenzyloxy-*o*-tolyl)-ethyl carbinol, as a colourless oil in nearly quantitative yield. The IR spectrum of this product (liquid film) (Fig. 1) (as well as CCl_4) (Fig.2) was identical with that of the dibenzyl ether of the phenolic alcohol (A) prepared from natural citrinin. Later, in the study of the stereochemistry of this synthetic alcohol an attempt was made to determine the composition of the oily product. Chromatography on alumina followed by

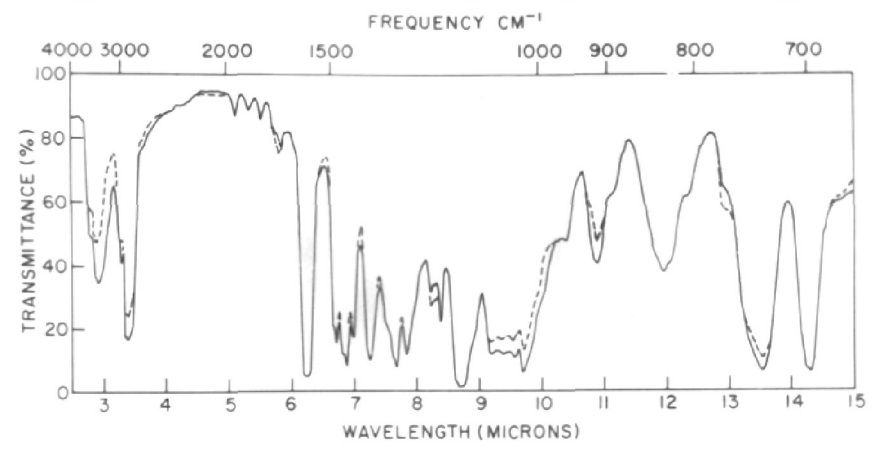


Fig. 1. IR spectra (liquid film) of the dibenzyl ether of phenolic alcohol (A) (————) and the lithium aluminium hydride reduction product of synthetic ketone XXV (------) .

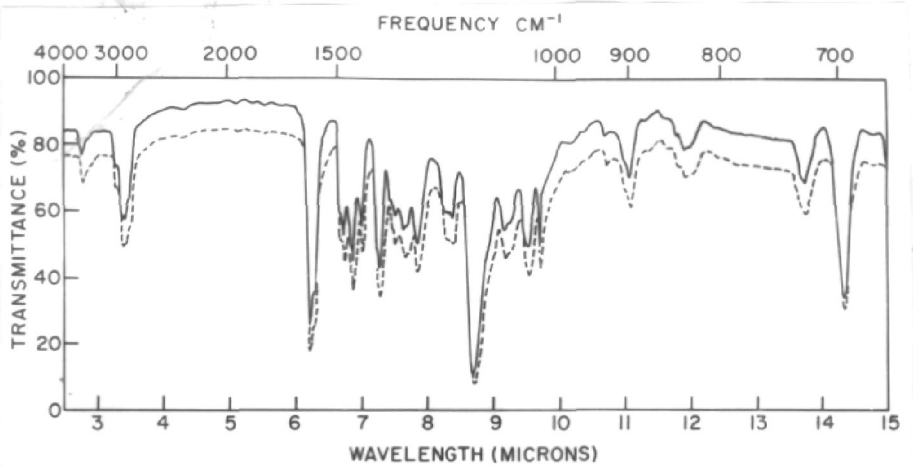


Fig. 2. IR spectra (CCl_4) of the dibenzyl ether of phenolic alcohol (A) (————) and the lithium aluminium hydride reduction product of synthetic ketone XXV (-------) .

fractional crystallization from hexane resulted in the fractionation of this oil into a crystalline solid melting at 86° and an oil, both of which analysed correctly for the alcohol with structure XXVI and had identical IR spectra in carbon tetrachloride (Fig. 3). However, the IR spectra of these two products in Nujol showed differences (Fig. 4) that may be expected from the two racemates of the alcohol.[30-32] In the present synthesis the oily product was used without resolution of the component isomers.

The hydrogenolysis of XXVI in methanol in presence of 10 per cent palladium on carbon led to methyl α-(3,5-dihydroxy-o-tolyl)-ethylcarbinol (XXVII), m.p. 125°, in 85 per cent yield. The reported melting points of the phenolic alcohols (A) and (B) are 128° and 169° respectively. The mixed m.p. of the synthetic phenolic alcohol with (A) or (B) did not show any depression below 125°. The IR spectrum of the synthetic phenolic alcohol was identical with that of phenolic alcohol (B) (Fig. 5). Further characterization of the phenol was made by the preparation of its bisphenylazo derivative, m.p. 202°.

The synthetic phenolic alcohol (XXVII), by carboxylation in glycerine at 155-60° with potassium bicarbonate in an atmosphere of carbon dioxide, gave 2,6-dihydroxy-4-methyl-5-(α-methyl-β-hydroxy-n-propyl)-benzoic acid (XIV);

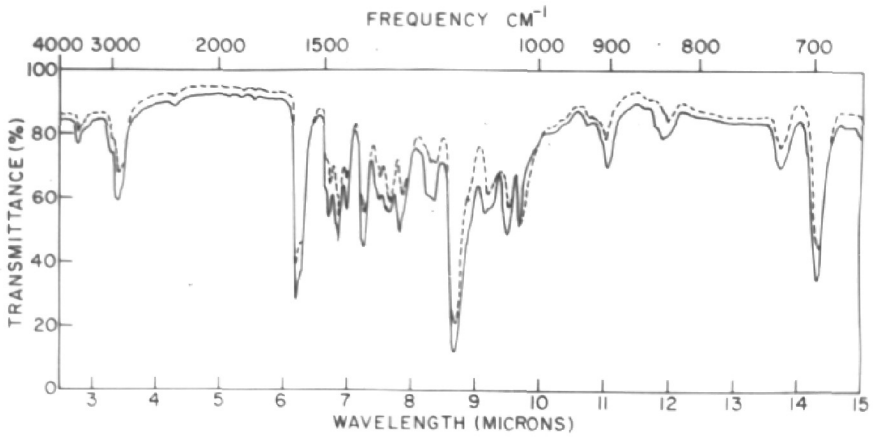


Fig. 3. IR spectra (CCl_4) of crystalline and oily fractions of synthetic XXVI. Crystals, m.p. 86° (——); oil (----).

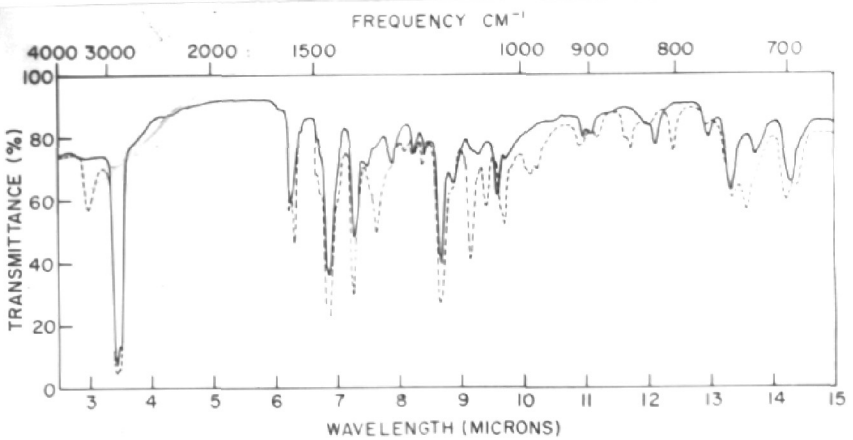


Fig. 4. IR spectra (Nujol) of crystalline and oily fractions of synthetic XXVI. Crystals, m.p. 86° (——); oil (----).

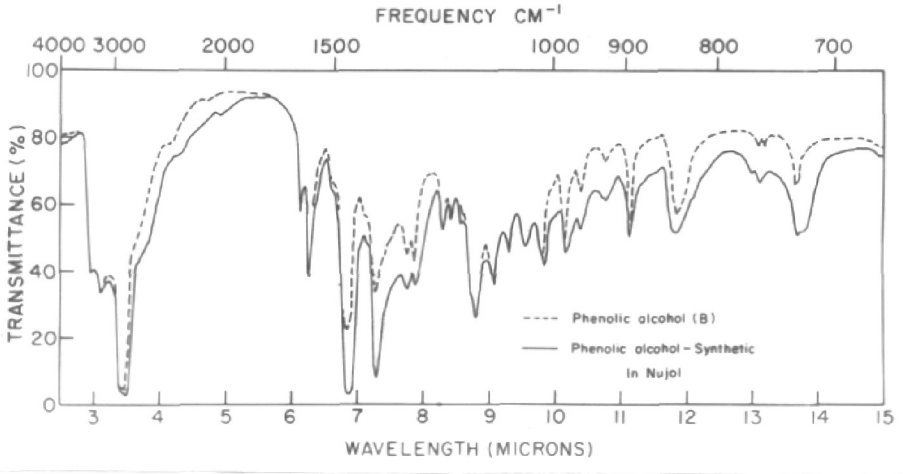


Fig. 5.

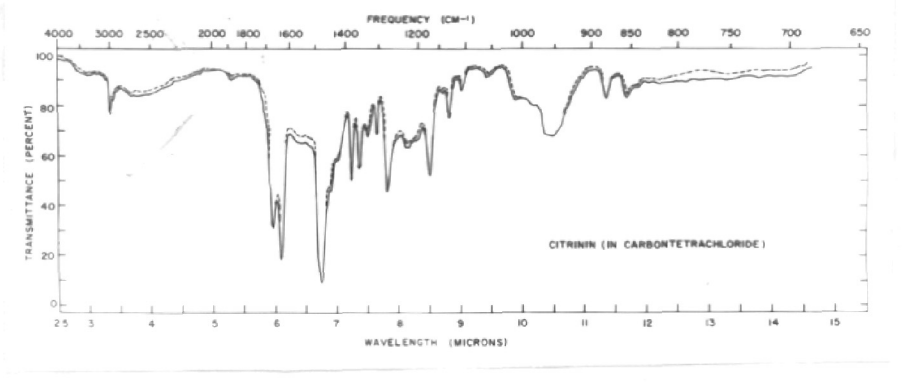


Fig. 6. IR spectra of the synthetic sample (———) and the natural sample (-----).

the yield was only 35 per cent as against 45-50 per cent claimed by ROBERTSON et al. An aqueous solution of the acid gave an intense blue ferric colouration characteristic of γ-carboxylic acids.

The acid XII, on reaction with ethyl orthoformate at room temperature,[25] gave citrinin, m.p. 171°, in 75 per cent yield. The mixed m.p. with natural citrinin, m.p. 171°, was undepressed. The synthetic citrinin was optically inactive. The IR spectra of the synthetic and natural citrinin are shown in Fig. 6. The UV absorption spectra of the two are given in Fig. 7. It will be noticed that the synthetic and natural citrinin have identical IR and UV spectra.

(B) Study of the stereochemistry of the synthetic phenolic alcohol in comparison with the phenolic alcohol obtained from citrinin

It is evident from the structures of citrinin (V), phenolic alcohol (XXVII), dibenzyl ether (XXVI) and dimethyl ether (XI) of phenolic alcohol (XXVII), all of which have two asymmetric carbon atoms, that they can exist in four optically active forms (two diastereoisomers and their enantiomers) and two racemic forms.

Starting with either the l-form (A) of the phenolic alcohol or the racemic form (B), obtained from natural citrinin, ROBERTSON et al. synthesized natural (-) citrinin

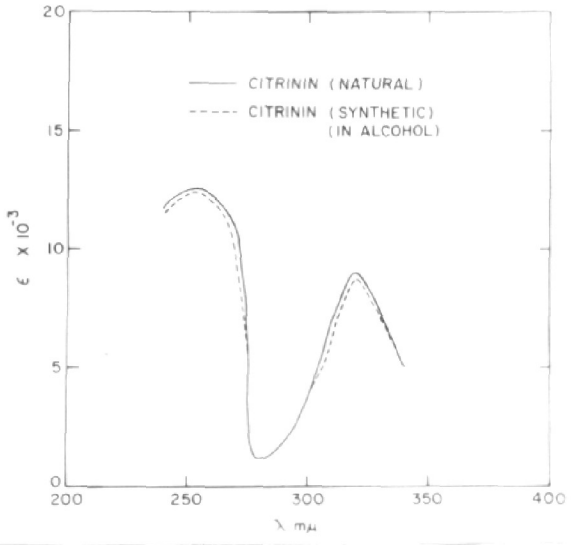


Fig. 7. UV spectra of citrinin.

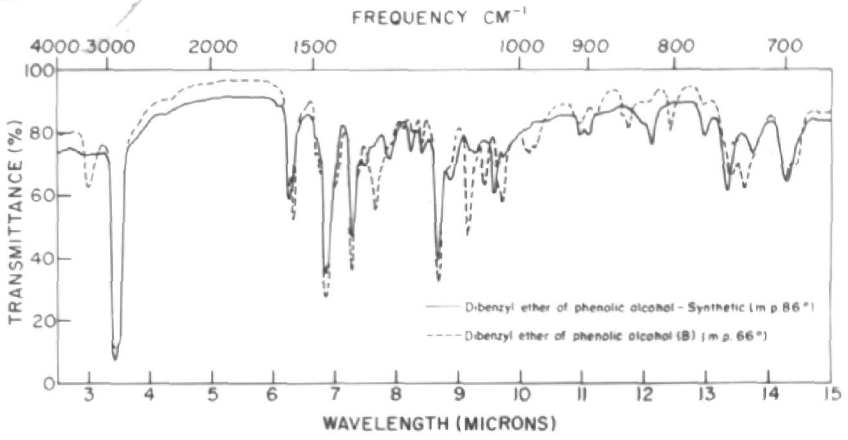


Fig. 8. IR spectra in Nujol.

or inactive citrinin respectively. Further these workers synthesized the inactive dimethyl ether (XI) of the phenolic alcohol (XXVII) and isolated from it by fractional crystallization the p-nitrobenzoate of one of the racemic forms, identical with the p-nitrobenzoate of the dimethyl ether obtained from natural citrinin. No information is so far available regarding the identity of the other racemic form of the phenolic alcohol (XXVII) and its dimethyl ether (XI). According to CRAM[23] the racemization of phenolic alcohol (A) to phenolic alcohol (B) with retention of configuration proceeds by way of Wagner-Meerwein transformation. He further elaborated on the relative configuration of the two asymmetric carbon atoms in phenolic alcohol (A), which indicated that phenol (A), and hence citrinin, possesses the threo configuration.

In the present synthetic studies it was observed that the dibenzyl ether (XXVI) of the phenolic alcohol (XXVII) was obtained as a colourless oil and analysed correctly for the structure XXVI. It was further observed that this oil had the same IR spectrum as that of the dibenzyl ether of the phenolic alcohol (A) obtained from natural citrinin, either liquid film or carbon tetrachloride (Figs. 1 and 2). However, when the synthetic oil

in hexane was chromatographed over alumina (grade II), an oil was eluted which crystallized from hexane in white needles, m.p. 86°; the mother liquor yielded an oily residue. Both the products (the crystalline solid and the oil) analysed correctly for the structure (XXVI). However, the IR of the product with m.p. 86° in Nujol showed differences when compared with that of the dibenzyl ether of phenolic alcohol (B) obtained from natural citrinin (Fig. 8).

When the product, m.p. 86°, was debenzylated with 10 per cent palladium on carbon in methanol, it gave a phenolic alcohol, m.p. 169°, which is also the m.p. of the racemic phenol (B), and it analysed correctly for the structure (XXVII). However the mixed m.p. of the synthetic and natural samples gave a lowering in the m.p. by 15°. The difference between the two samples was also brought out in their IR spectra in Nujol shown in Fig. 9. Because of the insolubility of these two phenolic alcohols in carbon tetrachloride, chloroform and carbon disulphide, it was not possible to compare their IR spectra in solution.

That the phenolic alcohol (B) is a single racemate, m.p. 169°, has already been conclusively shown by ROBERTSON *et al.*[20] It could be argued that the compound

that has been obtained by hydrogenolysis of the compound having m.p. 86° is either a single racemate other than phenolic alcohol (B) or a mixture. However, a mixture of (B) and the phenolic alcohol now obtained shows a lowering of melting point. Also, the IR spectrum of the synthetic compound (Fig. 9) shows the absence of some of the absorption peaks, for example 1640 cm^{-1}, 1190 cm^{-1}, and 970 cm^{-1}, which are present in phenolic alcohol (B). It is therefore clear that the product now obtained is not a mixture of the two possible racemates. Further evidence in this direction was obtained by degradative study of natural citrinin involving the retracing of the synthetic steps, reported earlier, and comparison of the natural and synthetic compounds.

Natural citrinin was subjected to alkaline hydrolysis to give the laevorotatory phenolic alcohol (A) (XXVII), m.p. 128°. This alcohol was benzylated with benzyl bromide and potassium carbonate in acetone; the oily dibenzyl ether was laevorotatory. Attempts to crystallize it were unsuccessful. The oil was oxidized with chromic anhydride in dimethylformamide, using sulphuric acid as catalyst.[33] The IR spectrum of the oil obtained after oxidation showed the presence of some starting material

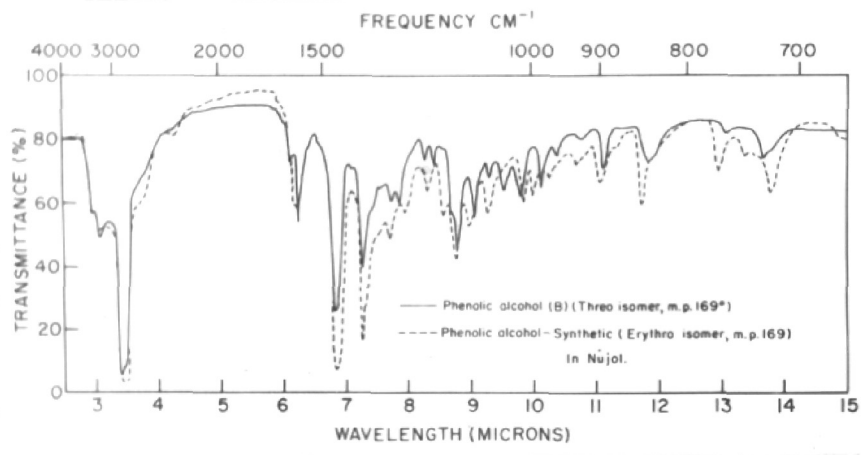


Fig. 9.

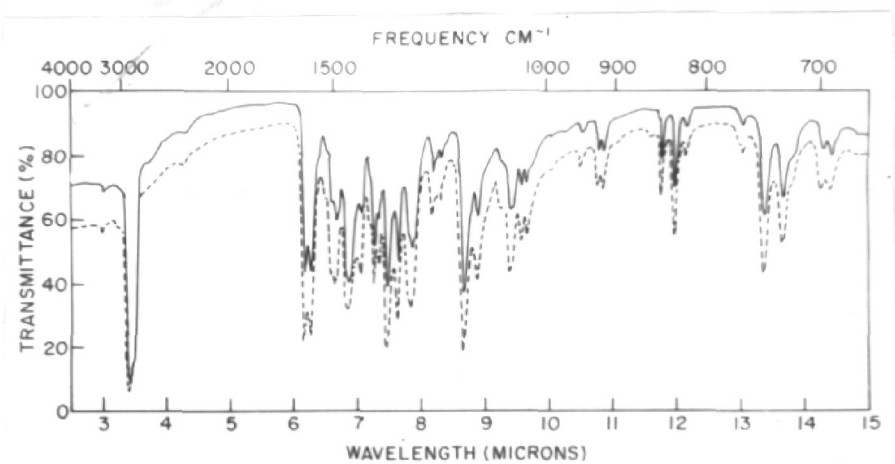


Fig. 10. IR spectra (Nujol) of the 2,4-dinitrophenylhydrazone of ketone XXV:
(——) ketone, synthetic;
(----) ketone obtained from phenolic alcohol (A).

(hydroxyl peak at 3350 cm^{-1}); it was therefore chromatographed over alumina with hexane. The eluent obtained after distillation under reduced pressure gave the pure dibenzyl ether of the ketone XXV, and its IR spectrum showed absence of the OH peak at 3350 cm^{-1} and CO absorption at 1708 cm^{-1}. This ketone was racemized by refluxing with ethanolic potassium hydroxide for 8 hr. The 2,4-dinitrophenylhydrazone of this inactive ketone had m.p. 153°, undepressed by mixing with the dinitrophenylhydrazone of the synthetic ketone XXV. The IR spectra of the two dinitrophenylhydrazones in Nujol were superposable (Fig.10).

The above ketone (prepared from natural citrinin) was subjected to lithium aluminium hydride reduction and an oily product was obtained. The IR spectrum of this oil was completely identical with that of the product XXVI obtained synthetically (Fig. 11). However, when this oil was given the same treatment of chromatography and crystallization as was given to the oil in XXVI, it was found that about 55 per cent of the total material could be crystallized out by seeding mother liquors with the crystals. The crystals melted at 66°, undepressed by mixing with the benzyl ether of phenolic alcohol (B), showing that a single racemate has been obtained. Further attempts to crystallize the oil were unsuccessful.

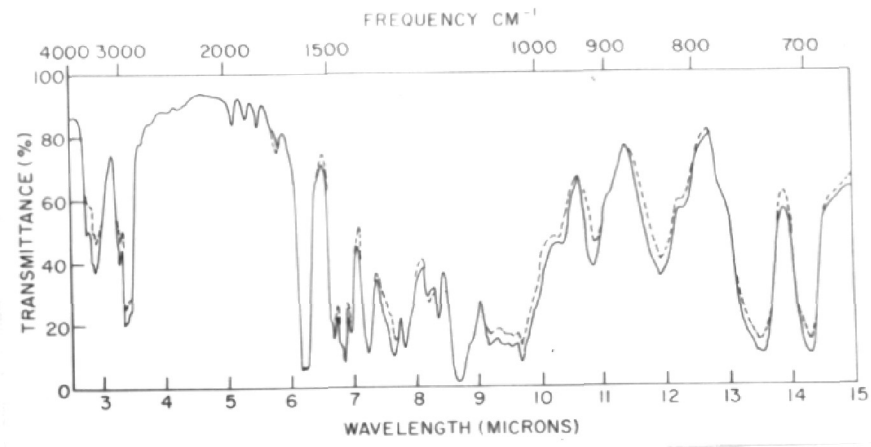


Fig. 11. IR spectra (liquid film) of XXVI: (——) from phenolic alcohol (A) after benzylation, chromic anhydride oxidation and lithium aluminium hydride reduction; (----) from synthetic ketone XXV after lithium aluminium hydride reduction.

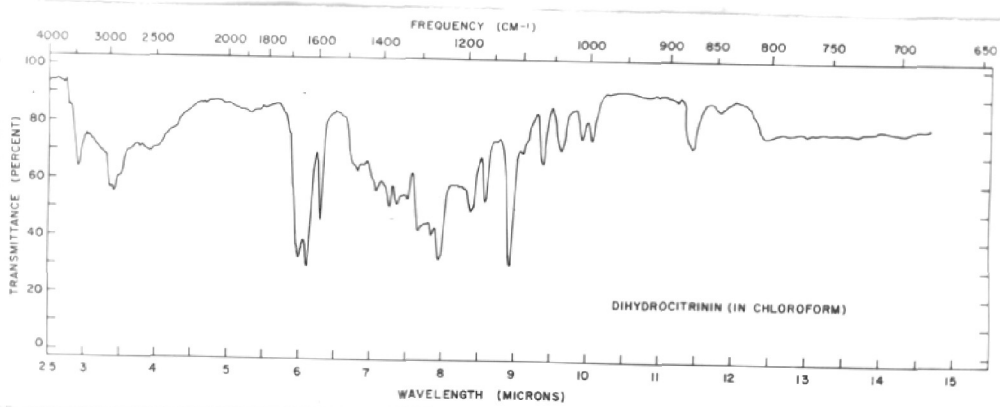
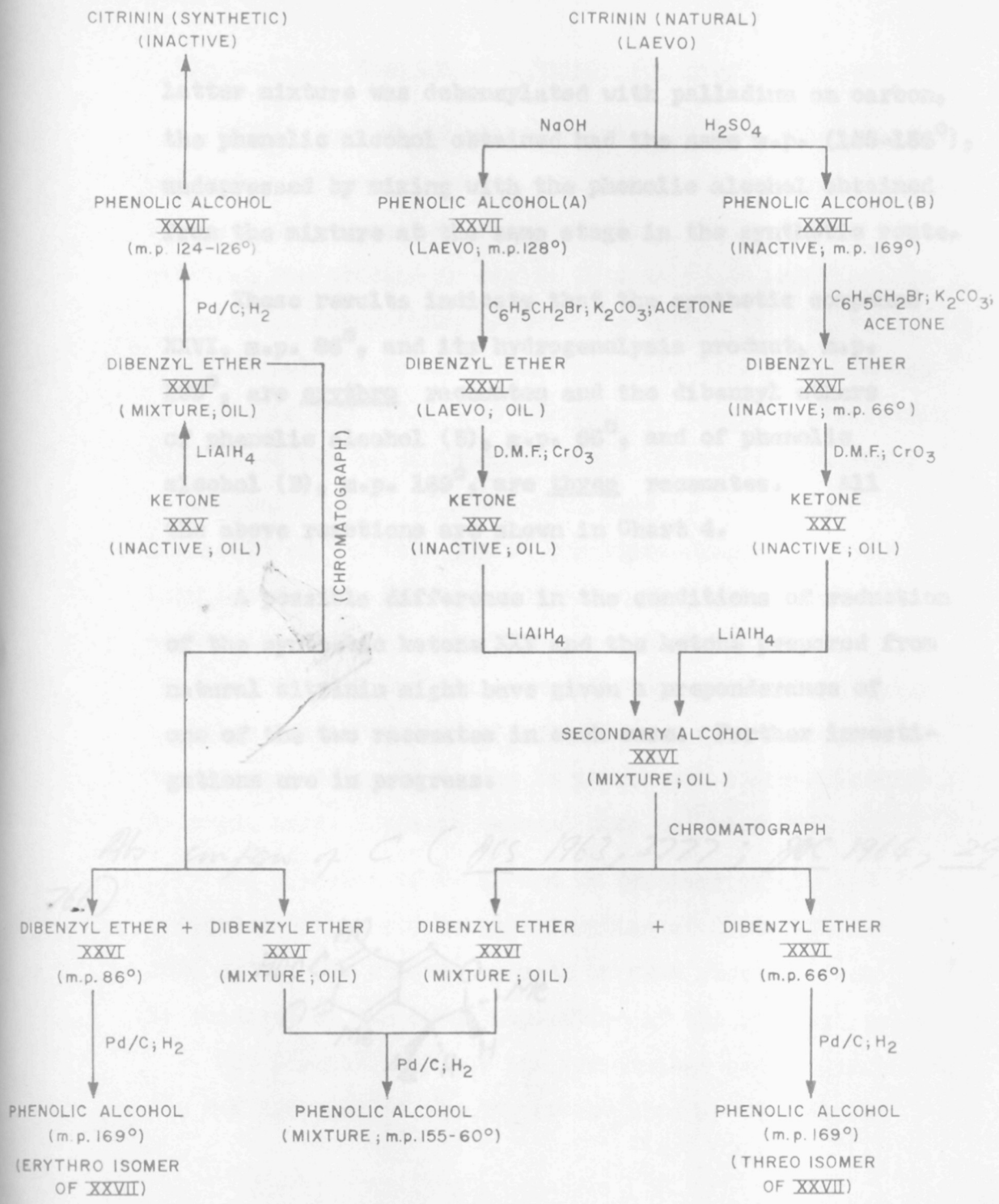


Fig. 12.

The IR spectrum of this oil was identical with that of the mixture (after removing the crystalline solid, m.p. 86°) obtained by the completely synthetic route. The oil on debenzylation with palladized carbon in methanol gave a phenol having a m.p. over a range of 155-160°. Debenzylation of the original mixture from the synthetic route gave the phenol having m.p. 155-160° and their mixed m.p. was undepressed.

The whole series of reactions as in the case of phenolic alcohol (A) mentioned above was repeated with phenolic alcohol (B), obtained by the sulphuric acid hydrolysis of natural citrinin. Phenolic alcohol (B) was benzylated and the racemic dibenzyl ether had m.p. 66°. This alcohol was oxidized to the ketone with chromic anhydride in dimethylformamide, and an oil was obtained which was subjected to chromatography to obtain the pure ketone. This ketone on reduction with lithium aluminium hydride gave an oil having the same IR spectrum (Figs. 1 and 2) as that of the synthetic compound XXVI. When the oily secondary alcohol was subjected to further purification by chromatography through alumina and fractional crystallization, identical products as in the route followed for phenol (A), were obtained: a crystalline compound, m.p. 66°, plus a liquid mixture. When the

Chart 4

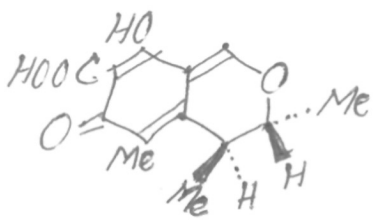

CITRININ (SYNTHETIC)
(INACTIVE)
CITRININ (NATURAL)
(LAEVO)
NaOH
H_2SO_4
PHENOLIC ALCOHOL
XXVII
(m.p. 124-126°)
PHENOLIC ALCOHOL(A)
XXVII
(LAEVO; m.p.128°)
PHENOLIC ALCOHOL(B)
XXVII
(INACTIVE; m.p. 169°)
Pd/C; H_2
$C_6H_5CH_2Br$; K_2CO_3; ACETONE
$C_6H_5CH_2Br$; K_2CO_3; ACETONE
DIBENZYL ETHER
XXVI
(MIXTURE; OIL)
DIBENZYL ETHER
XXVI
(LAEVO; OIL)
DIBENZYL ETHER
XXVI
(INACTIVE; m.p. 66°)
$LiAlH_4$
D.M.F.; CrO_3
D.M.F.; CrO_3
KETONE
XXV
(INACTIVE; OIL)
KETONE
XXV
(INACTIVE; OIL)
KETONE
XXV
(INACTIVE; OIL)
(CHROMATOGRAPH)
$LiAlH_4$
$LiAlH_4$
SECONDARY ALCOHOL
XXVI
(MIXTURE; OIL)
CHROMATOGRAPH
DIBENZYL ETHER + DIBENZYL ETHER
XXVI
(m.p. 86°)
(MIXTURE; OIL)
DIBENZYL ETHER + DIBENZYL ETHER
XXVI
(MIXTURE; OIL)
XXVI
(m.p. 66°)
Pd/C; H_2
Pd/C; H_2
Pd/C; H_2
PHENOLIC ALCOHOL
(m.p. 169°)
(ERYTHRO ISOMER OF XXVII)
PHENOLIC ALCOHOL
(MIXTURE; m.p. 155-60°)
PHENOLIC ALCOHOL
(m.p. 169°)
(THREO ISOMER OF XXVII)

latter mixture was debenzylated with palladium on carbon, the phenolic alcohol obtained had the same m.p. (155-156°), undepressed by mixing with the phenolic alcohol obtained from the mixture at the same stage in the synthetic route.

These results indicate that the synthetic compound XXVI, m.p. 86°, and its hydrogenolysis product, m.p. 169°, are erythro racemates and the dibenzyl ethers of phenolic alcohol (B), m.p. 66°, and of phenolic alcohol (B), m.p. 169°, are threo racemates. All the above reactions are shown in Chart 4.

A possible difference in the conditions of reduction of the synthetic ketone XXV and the ketone prepared from natural citrinin might have given a preponderance of one of the two racemates in each case. Further investigations are in progress.

Abs. confign of C (JCS 1963, 3777; JOC 1964, 29, 766).



The infrared spectra of citrinin and dihydrocitrinin

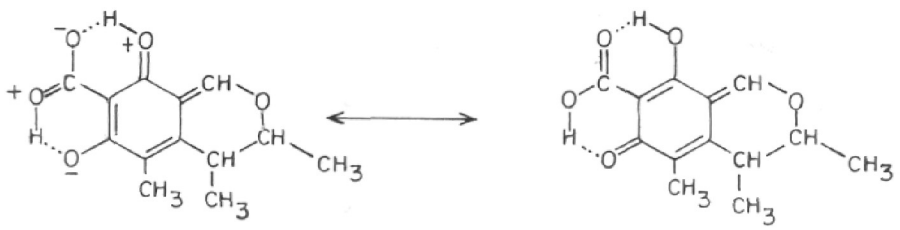
The IR spectra of citrinin (Fig. 7) and dihydrocitrinin (Fig. 12) were taken on a Perkin-Elmer 221 IR spectrophotometer with sodium chloride prism. The spectrum of citrinin was studied in carbon tetrachloride and dihydrocitrinin in chloroform, because the latter did not have adequate solubility in carbon tetrachloride. The spectrum of citrinin indicates that there is no specific absorption band which can be assigned to a free hydroxyl stretching vibration. The broad absorption band in the region 3500-3000 cm^{-1} arises out of the intramolecular hydrogen bond between the hydroxyl group and the carbonyl of the carboxylic acid. The broader absorption band in the region 2800-2300 cm^{-1} is presumably due to intermolecular hydrogen bonds. Salicylic acid shows a similar behaviour,[34] the corresponding bands due to intra- and inter-molecular hydrogen bonds appearing around 3200 cm^{-1} and 3000 cm^{-1}.

The presence of $C-CH_3$ and CH tertiary groups are indicated by the stretching vibration at 2982, 2940 and 2874 cm^{-1}. The stretching mode of =C-H above 3000 cm^{-1} is obscured by the broad absorption of the hydroxyl group.

The asymmetrical and the symmetrical bending modes of the C-H linkages of the CH_3 groups show up at 1480 and

and 1380 cm^{-1}.

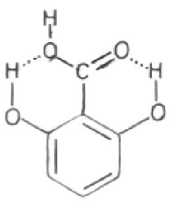
In the carbonyl region two strong absorption bands were observed at 1675 and 1638 cm^{-1}, with a faint shoulder at 1682 cm^{-1}. The absorption band at 1675 cm^{-1} is due to the carbonyl of the carboxylic acid, forming a strong chelate bond with the hydroxyl group situated in the ortho position. The absorption band at 1638 cm^{-1} may be assigned to the quinonoid carbonyl of the compound. Hydrogen bonding with the hydroxyl group of the carboxylic acid is probably involved in bringing the absorption frequency down to the observed value. 1-Hydroxyanthraquinone[35] shows a carbonyl at 1637 cm^{-1} due to strong intramolecular hydrogen bonding and is conspicuous by the absence of a strong absorption in the hydroxyl stretching region of the spectrum. The bonding in citrinin may be represented by the following structures.



Further the frequency of the C=C stretching vibrations is reduced from its normal value of 1660-1670 cm^{-1} to a lower value by conjugation and is masked by the carbonyl which appears as a strong band at 1638 cm^{-1}. The

deformation vibration of the hydroxyl group of the carboxylic acid appears at 950 cm^{-1} due to hydrogen bonding with the adjacent carbonyl as a band of medium strength.

The spectrum of dihydrocitrinin in chloroform solution shows a weak shoulder at 3580 cm^{-1}, a strong band at 3425 cm^{-1} and weak bands at 2550 and 2450 cm^{-1} in the hydroxyl stretching region attributable to a free hydroxyl intramolecularly and intermolecularly bonded hydroxyl groups respectively. Y-Resorcylic acid forms intramolecular hydrogen bonds in the solid state and in bromoform solution, and the corresponding bands are observed at 3472 and 3300 cm^{-1}.[36] The structure given is



In dihydrocitrinin the Y-resorcylic acid part is fully substituted and the intramolecular bonds are probably of equal lengths, giving rise to a single band at 3425 cm^{-1}. The spectrum of salicylic acid in the solid state shows a broad absorption band in the region around 2564 cm^{-1} attributable to strong intermolecular hydrogen bonding. The spectrum of dihydrocitrinin indicates that intermolecular hydrogen bonds similar to those in salicylic acid

are involved.

In the C-H stretching region the absorption bands at 2985, 2933 and 2887 cm^{-1}, similar to those of citrinin but with reduced intensities, are observed.

A strong absorption band at 1667 cm^{-1} due to the carbonyl of the carboxylic acid, bonded to the hydroxyl, is observed. The reduction from 1675 cm^{-1} to 1667 cm^{-1}, as compared to citrinin, is due to the change of the solvent.[37] The strong bands at 1634 and 1590 cm^{-1} may be assigned to the C=C stretching vibrations of the aromatic ring and are also shown in the spectrum of Y-resorcylic acid.

Characteristic vibrations of the carboxylic acid are shown at 1421 and 1278 cm^{-1} in citrinin and at 1410, 1305 and 1275 cm^{-1} in dihydrocitrinin. When this work was complete, IR spectrum of citrinin was reported.[38]

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

Acetonedicarboxylic acid (XIV)

Citric acid was converted to acetonedicarboxylic acid by reaction with 20% oleum according to the method described in Org. Syntheses.[28]

Diethylacetonedicarboxylate (XV)

The acid XIV was esterified with ethanol and dry hydrogen chloride gas. The product of esterification was fractionally distilled to give pure diethylacetonedicarboxylate.[28]

Ethyl 3,5-dihydroxy-2,4-dicarbethoxyphenylacetate (XVI) and ethyl 3,5-dihydroxy-4-carboxyphenylacetate (XVII)

These were prepared according to the method of THEILACKER and SCHMID.[29] The yields were 45-46% and 11-12% as against 53% and 5% respectively.

3,5-Dihydroxyphenylacetic acid (XVIII) and ethyl 3,5-dihydroxyphenylacetate (XIX)

The acid XVIII and its ester XIX were also obtained, following the method of THEILACKER and SCHMID.[29] The ester XIX was crystallized from a mixture of carbon tetrachloride-chloroform in colourless plates, m.p. 128° (lit. 127-128°).[29]

Ethyl 2-aldehydo-3,5-dihydroxyphenylacetic acid (XX)

(a) To a solution of (XIX; 8.5 g) in dry ether (150 ml),

powdered zinc cyanide (20 g) and fused zinc chloride (5 g) were added. Dry hydrogen chloride was passed at 0° under stirring till it was saturated, and the reaction mixture allowed to stand in a refrigerator for 48 hr. The ether layer was decanted off and the viscous tan coloured aldimine hydrochloride thoroughly washed with dry ether (4 x 50 ml) and then hot water (150 ml; 90°) was added to it. The reaction mixture was then stirred vigorously at room temp for 10 min. The aldehyde which separated out on cooling the aqueous solution with ice-salt mixture, crystallized from dil methanol (norit) in long colourless needles (4.1 g), m.p. 117°. (Found: C, 58.8; H, 5.1. $C_{11}H_{12}O_5$ requires: C, 58.8; H, 5.3%).

An ethanolic solution of the aldehyde gave a red colour with ferric chloride. The dinitrophenylhydrazone crystallized from ethanol in long fibrous violet needles, m.p. 261° (dec). (Found: C, 50.5; H, 3.7; N, 13.8. $C_{17}H_{16}O_8N_4$ requires: C, 50.4; H, 3.7; N, 13.8%).

(b) Phosphorus oxychloride (3 ml) was added gradually to a cooled solution of dimethylformamide (20 ml) over a period of 10 min. (The solution acquired a pink colour). To this complex was added ethyl 3,5-dihydroxyphenylacetate (6 g) under vigorous stirring and the reaction mixture left at room temp for 12 hr. It was then poured over a

saturated solution of sodium acetate (150 ml), and extracted with ether. The ether extract was washed first with water and then with a solution of bicarbonate, and dried over sodium sulphate. Complete removal of ether gave a solid, which crystallized from dil methanol as colourless needles (1.9 g), m.p. 117°. Mixed m.p. with the compound obtained from the previous experiment remained undepressed.

Ethyl 3,5-dihydroxy-o-tolylacetate (XXI)

A solution of the aldehyde (XX; 5 g) in methanol (250 ml) was added to a freshly prepared zinc amalgam (50 g) in conc hydrochloric acid (50 ml) during 15 min. The reaction mixture was refluxed for 30 min, cooled, filtered, and the solvent was removed under vacuum. The residue was diluted with water and extracted with ether. The ether extract was washed with sodium bicarbonate solution, and then with water, and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil (3 g), which solidified on cooling and crystallized from benzene-hexane in colourless prisms, m.p. 125-126°. (Found: C, 62.5; H, 6.3. $C_{11}H_{14}O_4$ requires: C, 62.8; H, 6.7%).

Ethyl 3,5-dibenzyloxy-o-tolylacetate (XXII)

The ester (XXI; 3 g), anhydrous potassium carbonate (30 g),

benzyl chloride (7 g) and dry acetone (300 ml) were refluxed for 72 hr. The reaction mixture was filtered and the residue washed with acetone. The filtrate and washings were concentrated and the excess of benzyl chloride was removed by steam distillation. The brown viscous oil was ether extracted and the ether solution washed with water and dried. Evaporation of the solvent gave a light-brown viscous oil (5 g), which crystallized from pet ether (60-80°) in colourless needles, m.p. 42-43°. (Found: C, 76.6; H, 6.6. $C_{25}H_{26}O_4$ requires: C, 76.9; H, 6.7%).

3,5-Dibenzyloxy-o-tolylacetic acid (XXIII)

The above ester (XXII; 5 g) was refluxed with 2% ethanolic potassium hydroxide (200 ml) for 4 hr. The ethanol was removed under reduced pressure and the reaction mixture cooled, diluted with water and ether extracted to remove the unconverted ester. The aqueous alkaline layer on acidification gave a pale yellow precipitate which was filtered, washed and dried (2.9 g). Crystallization from dil ethanol gave colourless needles, m.p. 144°. (Found: C, 76.2; H, 6.8. $C_{23}H_{22}O_4$ requires: C, 76.2; H, 7.1%).

3,5-Dibenzyloxy-o-tolylacetone (XXIV)

To a solution of methyllithium (prepared from 4.8 g of lithium and 48 g of methyl iodide in 250 ml of dry ether at

0°) a solution of the acid (XXIII; 3 g) in dry ether (80 ml) was added slowly during 30 min. The reaction mixture was stirred vigorously at this temp for 2 hr and then refluxed for 30 min, cooled and decomposed with water. The ethereal layer was separated, washed with aqueous sodium carbonate and dried over sodium sulphate. Evaporation of the ether gave an oil (2.1 g), which solidified on addition of pet ether and crystallized from pet ether (60-80°) in colourless needles, m.p. 85°. (Found: C, 80.0; H, 6.9. $C_{24}H_{24}O_3$ requires: C, 80.0; H, 6.7%).

The 2,4-dinitrophenylhydrazone crystallized from ethanol in yellow needles, m.p. 132° (dec). (Found: N, 10.0. $C_{30}H_{28}O_6N_4$ requires: N, 10.4%).

Methyl α-(3,5-dibenzyloxy-o-tolyl)-ethyl ketone (XXV)

An intimate mixture of powdered sodium hydroxide (2.4 g) and the ketone (XXIV; 1.2 g) was warmed on a water-bath at 70° for 30 min. After cooling to 30°, methyl iodide (3.6 g) was added. The reaction mixture was maintained at 30° for 2 hr, gently refluxed for 3 hr, and finally heated at 100° for 2 hr. After decomposition with water, the product was extracted with ether. Removal of the ether gave a pale-yellow oil (0.9 g) which distilled at 185-190° (air-bath

temp)/10^{-3} mm. (Found: C, 80.2; H, 7.0. $C_{25}H_{26}O_3$ requires: C, 80.2; H, 7.0%).

The 2,4-dinitrophenylhydrazone crystallized from benzene-hexane in brownish-yellow plates, m.p. 152-153°. (Found: N, 10.3. $C_{31}H_{30}O_6N_4$ requires: N, 10.1%).

Methyl α-(3,5-dibenzyloxy-o-tolyl)-ethylcarbinol (XXVI)

A solution of the ketone (XXV; 2.2 g) in dry ether (50 ml) was added in 40 min to a refluxing solution of lithium aluminium hydride (2 g) in dry ether (150 ml). The mixture was refluxed for 4 hr, decomposed by moist ether and cold 20% sulphuric acid (30 ml). The ether layer was separated and the aqueous layer was extracted with ether (3 x 100 ml). The ether extract was washed with aqueous sodium bicarbonate and dried over sodium sulphate. Distillation of the ether gave a light-brown oil (2.0 g) which distilled at 190-195°/4.83 x 10^{-4} mm. (Found: C, 79.8; H, 7.1. $C_{25}H_{28}O_3$ requires: C, 79.7; H, 7.4%).

Methyl α-(3,5-dihydroxy-o-tolyl)-ethylcarbinol (XXVII)

The alcohol (XXVI; 1 g), 10% palladized carbon (0.4 g) and methanol (60 ml) were agitated in an atmosphere of hydrogen at room temp till 2 moles of hydrogen were absorbed (4 hr). The carbon was filtered off and washed with

warm methanol (60 ml); the filtrate and washings were taken to dryness under vacuum, when an almost colourless oil was obtained. Crystallization from ethyl acetate gave colourless prisms (0.42 g), m.p. 124-126°. (Found: C, 67.1; H, 8.0. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.1%). The mixed m.p. with phenol (A), m.p. 128°, or phenol (B) prepared from citrinin was not depressed.

The bisphenylazo derivative, obtained by coupling with diazotized aniline, crystallized from ethanol in bright needles, m.p. 202°. (Found: N, 14.2. Calc. for $C_{23}H_{24}O_3N$: N, 13.8%).

2,6-Dihydroxy-4-methyl-5-(α-methyl-β-hydroxy-n-propyl)-benzoic acid (XII)

Carbon dioxide was bubbled through a mixture of the phenol (XXVII; 0.8 g), potassium bicarbonate (7.5 g) and glycerine (60 ml) at 150-155° for 7 hr. The reaction mixture was cooled, diluted with water (50 ml), saturated with ammonium sulphate, and extracted with ether to recover unconverted phenol. The aqueous phase was acidified with dil hydrochloric acid and extracted with ether. The product crystallized from benzene in colourless prisms, m.p. 172° (dec) (0.3 g). (Found: C, 59.6; H, 6.6. Calc. for $C_{12}H_{16}O_5$: C, 60.0; H, 6.7%). An aqueous solution of the acid gives an intense blue colouration with ferric chloride.

Optically inactive citrinin (V)

The above acid (XII; 0.2 g) was treated with ethyl orthoformate (15 drops) at room temp. The solution rapidly turned yellow and a bright yellow crystalline solid separated. Crushed ice was added after 10 min, and the yellow crystalline product collected, washed and dried (0.13 g). Crystallization from ethanol gave lemon-yellow needles of inactive citrinin, m.p. 171° (dec), undepressed on admixture with a sample of natural citrinin, m.p. 171°. (Found: C, 62.3; H, 5.6. $C_{13}H_{14}O_5$ requires: C, 62.4; H, 5.6%). An ethanolic solution exhibits the typical iodine brown colouration with ferric chloride.

2,4-Dibenzyloxy-6-n-propyltoluene (XXIX)

To a solution of methyllithium (from 1.6 g of lithium and 28.4 g of methyl iodide) at 0° was added a solution of the acid (XXIII; 1 g) in ether (100 ml) as rapidly as possible. The reaction mixture was gradually heated to 25° and finally refluxed for 40 hr, cooled again to 0°, decomposed with ice, and extracted with ether. The ethereal extract was washed with water and dried. Removal of the solvent gave a brown oil (0.85 g), which on distillation at 160-165°/10^{-4} mm was obtained as a very pale yellow liquid. (Found: C, 82.8; H, 7.7. $C_{24}H_{26}O_2$ requires: C, 83.2; H, 7.6%).

Separation of methyl α-(3,5-dibenzyloxy-2-tolyl)-ethylcarbinol (XXVI)

The oil (XXVI; 1 g) in benzene (5 ml) was adsorbed over an alumina column (25 x 2.5 cm) and eluted with hexane (10 l.), then with benzene-hexane mixture (10%; 3 l.), and finally with benzene (1 l.). The hexane eluate on distillation gave an oil A (0.15 g). The benzene-hexane eluate on distillation did not yield any product. The benzene eluate on distillation gave an oil B (0.75 g).

The oil B on keeping in contact with hexane for several weeks partly crystallized. The hexane layer was decanted off and the oil redissolved in hexane and left for further crystallization. The process was repeated several times till a colourless crystalline material free from oil was obtained. It was filtered, washed with hexane and recrystallized from hexane to give the pure erythro compound (0.2 g), m.p. 86°. (Found: C, 79.7; H, 7.3. $C_{25}H_{28}O_3$ requires: C, 79.7; H, 7.4%).

Hexane washings from oil B were concentrated and seeded with the crystalline solid, m.p. 86°, to obtain more of this product, but the oil could not be crystallized further.

The oil A also could not be crystallized by giving a similar treatment. The oil A and washings from B were mixed together and distilled at 190-195°/4.83 x 10^{-4} mm.

(Found: C, 80.0; H, 7.4. $C_{25}H_{28}O_3$ requires: C, 79.7; H, 7.4%).

Phenolic alcohol (erythro)

Dibenzyl ether of phenolic alcohol (erythro) (0.17 g), m.p. 86°, 10% palladized carbon (0.07 g) and methanol (15 ml) were agitated in an atmosphere of hydrogen at room temp till 2 moles of hydrogen were absorbed (4 hr). The carbon was filtered off and washed with warm methanol (20 ml); the filtrate and washings were taken to dryness under vacuum, when an almost colourless oil was obtained. Crystallization from ethyl acetate gave colourless prisms (0.05 g), m.p. 169°. (Found: C, 67.3; H, 8.0. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.1%). Mixed m.p. with phenolic alcohol (B), prepared from citrinin was depressed to 155°. The IR spectra of the two products are shown in Fig. 9.

Phenolic alcohol (mixture of threo and erythro)

Dibenzyl ether of phenolic alcohol, the mixture of the oil (A) and washings from (B) (0.6 g), 10% palladized carbon (0.2 g) and methanol (30 ml) were agitated in an atmosphere of hydrogen at room temp (4 hr). The carbon was filtered off and washed with warm methanol (50 ml); the filtrate and washings were taken to dryness under vacuum. Crystallization from a mixture of ethyl acetate-hexane gave

colourless prisms (0.25 g), m.p. 155-160°. (Found: C, 67.5; H, 7.8. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.1%).

Preparation of citrinin[10]

The stock culture of Aspergillus candidus was plated out on Czapek-Dox agar. For the preparation of an aqueous spore suspension as an inoculum. Yellow colony slopes were inoculated and incubated at 37° for 7 days. Sterile distilled water (6 ml) was added to the agar slopes and gently shaken for the effective removal of spores from the surface. Erlenmeyer's flasks of 1 litre capacity each containing 300 ml of Czapek-Dox fluid medium were inoculated with 2 ml of spore suspension and incubated at 37° for 10-12 days till the colour of the metabolism solution became deep wine-red. It was finally filtered and citrinin precipitated by adding approximately 5 ml N HCl for 100 ml of the filtrate. After standing overnight at 0°, the precipitate was collected, washed with cold distilled water and dried in a drying-oven at 100° overnight. It was crystallized from ethanol in lemon-yellow needles, m.p. 171°.

4-Methyl-5-(1-methyl-2-hydroxy)-propylresorcinol Phenolic alcohols (A) and (B)

Citrinin was hydrolysed according to the method of COYNE et al.[13] by refluxing with 10% aqueous caustic soda

in an atm of nitrogen. The phenolic alcohol (A) crystallized from chloroform as colourless needles, m.p. 128-129° (lit. m.p. 127-128°).[13] Phenolic alcohol (B) was obtained by the hydrolysis of citrinin with 2N H_2SO_4 according to the method of COYNE *et al*.[13] Crystallization from ethyl acetate gave colourless prisms, m.p. 169-170° (lit. m.p. 169-170°).[13]

STUDIES ON PHENOLIC ALCOHOL (A)

Benzylation of phenolic alcohol (A)

A mixture of phenolic alcohol (A) (3 g)(obtained by alkaline hydrolysis of citrinin), acetone (120 ml), anhydrous potassium carbonate (15 g) and benzyl bromide (10 ml) was refluxed on a steam-bath for 8 hr. The reaction mixture was filtered hot and the potassium carbonate washed with acetone several times. The filtrate and the washings were concentrated and the excess benzyl bromide was removed by steam distillation. The residue was ether extracted. The ether extract was washed with a solution of sodium hydroxide (2%) and with water, and dried over sodium sulphate. Evaporation of the solvent gave a colourless oil which on distillation under reduced pressure gave a colourless oil (5.1 g), b.p. 190-200° (air-bath temp)/1 x 10^{-4} mm $[\alpha]_D^{25}$ - 30° in chloroform. (Found: C, 79.6; H, 7.6. Calc. for $C_{25}H_{28}O_3$: C, 79.7; H, 7.4%).

Oxidation of dibenzyloxy ether of phenolic alcohol (A)

To a mixture of the above dibenzyl ether of phenolic alcohol (A) (4 g), dimethylformamide (60 ml) and chromic anhydride (4 g) was added conc sulphuric acid (1.2 ml) under cooling. The reaction mixture was vigorously stirred for 15 hr, poured into water and extracted with ether thoroughly (5 x 50 ml). The ether extract was washed with water and dried over sodium sulphate, and the red coloured oil obtained was distilled at 170-180°/1 x 10^{-4} mm (3.5 g). IR spectrum of the oil showed a carbonyl frequency at 1700 cm^{-1} and also a hydroxyl peak at 3350 cm^{-1} (the latter peak showed the presence of the unconverted alcohol in small traces). The oil was taken up in benzene and chromatographed on alumina (grade I) using hexane as eluant. The oil thus obtained after distillation of hexane showed no hydroxyl peak in its IR spectrum and the carbonyl band was observed at 1708 cm^{-1}, $[\alpha]_D^{25}$ - 2° in chloroform. (Found: C, 80.0; H, 7.2. Calc. for $C_{25}H_{26}O_3$: C, 80.2; H, 7.0%). The dinitrophenylhydrazone crystallized from benzene-hexane in brownish-yellow plates, m.p. 153°. Mixed m.p. with the 2,4-dinitrophenylhydrazone of (XXV) obtained from the synthetic route was undepressed.

Racemization of the methyl α-(3,5-dibenzyloxy-2-tolyl) ethyl ketone

The above ketone (2 g) in methanol (20 ml) and methanolic potassium hydroxide (5%; 50 ml)(solution became turbid), was refluxed on a steam-bath for 4 hr. The methanol was distilled off and the oil so obtained was treated with water (30 ml). The mixture was extracted with ether (3 x 50 ml) and the ether extract washed with water and dried over sodium sulphate. Removal of the solvent gave a pale-yellow oil, which was distilled at 177-180° (air-bath temp)/10^{-4} mm to a colourless viscous oil (1.5 g). (Found: C, 80.2; H, 7.2. $C_{25}H_{26}O_3$ requires: C, 80.0; H, 7.0%).

Reduction of the ketone to dibenzyl ether of phenolic alcohol

The above ketone (1.5 g) in ether (50 ml) was added to a refluxing solution of lithium aluminium hydride (2 g) in ether (200 ml). The mixture was refluxed for 4 hr. The excess lithium aluminium hydride was decomposed with wet ether and cold dil sulphuric acid (20%; 80 ml). The ether layer separated and the aqueous layer extracted with ether (3 x 100 ml). The combined ether extracts were washed with water and dried over sodium sulphate. Distillation of ether gave a pale yellow oil. The oil was taken up in a small volume of benzene (5 ml) and adsorbed

over an alumina column (25 x 2.5 cm) and eluted with hexane (12 l.) and then with benzene 1.5 l.). The hexane eluate on distillation gave an oil A (0.29 g). The benzene eluate on distillation gave an oil B (1.1 g).

The oil B on keeping in contact with hexane for several days partly crystallized. The hexane layer was decanted off and the oil redissolved in hexane and left for further crystallization. The process was repeated several times till a colourless crystalline solid free from oil was obtained.

The solid crystalline material was recrystallized from hexane in colourless needles (0.75 g), m.p. 66°. (Found: C, 79.6; H, 7.4. Calc. for $C_{25}H_{28}O_3$: C, 79.7; H, 7.4%). The mixed m.p. with dibenzyl ether of the phenolic alcohol (B), m.p. 66°, was undepressed. The oil could not be crystallized further by seeding with the solid crystalline material and was mixed with washings from oil B and distilled under reduced pressure, b.p. 190-195° (air-bath temp)/10^{-4} mm. (Found: C, 79.7; H, 7.7. $C_{25}H_{28}O_3$ requires: C, 79.7; H, 7.4%).

Isolation of phenolic alcohol (mixture of threo and erythro)

The oily product obtained in the preceding experiment (0.3 g), 10% palladized carbon (0.1 g), and methanol (50 ml) were agitated in an atm of hydrogen at room temp till 2 moles

of hydrogen were absorbed (4 hr). The carbon was filtered off and washed with warm methanol (20 ml). The filtrate and washings were taken to dryness under vacuum, when an almost colourless oil was obtained. Crystallization from ethyl acetate-hexane gave colourless prisms (0.11 g), m.p. 155-160°. (Found: C, 67.5; H, 8.2. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.1%). The mixed m.p. with the compound obtained in the synthetic route at the same step was undepressed.

STUDIES ON PHENOLIC ALCOHOL B

Benzylation of phenolic alcohol (B)

A mixture of phenolic alcohol (B) (0.8 g) (obtained by sulphuric acid hydrolysis of citrinin) in acetone (50 ml), anhydrous potassium carbonate (5 g) and benzyl bromide (3.5 ml) was refluxed on a steam-bath for 8 hr. The reaction mixture was filtered hot and the potassium carbonate washed with acetone several times. The filtrate and washings were concentrated and the excess benzyl bromide was removed by steam distillation. The residue was ether extracted. The ether layer was washed with dil caustic soda, then with water and dried. Evaporation of the solvent gave a pale-yellow oil, which on distillation under reduced pressure gave a colourless oil, b.p. 195-205° (air-bath temp)/1 x 10^{-3} mm (1.4 g). The oil obtained crystallized on keeping in contact with hexane in a refrigerator.

Oxidation of the dibenzyl ether of phenolic alcohol (B)

To a mixture of dibenzyl ether of phenolic alcohol (B) (1.0 g), dimethylformamide (12 ml) and chromic anhydride (1.2 g) was added cone sulphuric acid (10 drops) under cooling. The reaction mixture was vigorously stirred for 15 hr and then poured into cold water, extracted exhaustively with ether (5 x 30 ml). The ether extract was washed with water and dried over sodium sulphate. The solvent was removed and the residue distilled at 170-180°/10^{-4} mm (0.8 g) to yield an oily product. The IR spectrum of the oil indicated the presence of some of the unreacted alcohol (hydroxyl frequency at 3350 cm^{-1}) in the reaction product. The oil was taken up in a small volume of benzene and chromatographed over alumina (grade I), using hexane as eluant. The hexane eluate was distilled to remove the solvent, and the oily residue was again distilled, 10^{-4} mm. The distillate, a colourless oil boiling at 175-180°, amounted to 0.7 g. The IR spectrum of this product did not indicate the presence of any starting material (absence of OH peak in IR). (Found: C, 80.4; H, 7.2. Calc. for $C_{25}H_{26}O_3$: C, 80.2; H, 7.0%).

The 2,4-dinitrophenylhydrazone of the ketone was crystallized from a mixture of benzene-hexane in brownish-yellow plates, m.p. 152°. Mixed m.p. with the 2,4-dinitrophenylhydrazone of XXV obtained in the synthetic route was

undepressed.

Dibenzyl ether of phenolic alcohol

A solution of the above ketone (0.6 g) in ether (25 ml) was added to a refluxing solution of lithium aluminium hydride (0.3 g) in ether (50 ml) over a period of 15 min. The mixture was refluxed for 4 hr and then decomposed by moist ether and cold 20% sulphuric acid (8 ml). The ether solution was washed with aqueous sodium bicarbonate and dried over anhydrous sodium sulphate. The ether solution on removal of the solvent gave a light-yellow coloured oily product. This was chromatographed over alumina (grade II), using in succession hexane, benzene-hexane and benzene as eluants. The hexane eluate on distillation gave a pale-yellow oil A (0.1 g). The benzene-hexane mixture did not yield any product. The benzene eluate on evaporation gave an oil B (0.43 g).

The oil B on keeping in contact with hexane for several days partly crystallized. The hexane layer was decanted off and the oil redissolved in hexane and left for further crystallization at 0°. The process was repeated several times till a colourless crystalline solid free from oil was obtained. The first major crystalline fraction (0.35 g), m.p. 66°, was recrystallized from hexane. (Found: C, 80.0; H, 7.2. $C_{25}H_{28}O_3$ requires: C, 79.7; H, 7.4%).

The mixed m.p. with dibenzyl ether of phenolic alcohol (B), m.p. 66°, was undepressed. The remaining oil from A and washings of B (0.18 g) was distilled at 180-185°/[air-bath temp]/1 x 10^{-4} mm. (Found: C, 79.7; H, 7.4. Calc. for $C_{25}H_{28}O_3$: C, 79.7; H, 7.4%).

Phenolic alcohol (threo)

The crystalline solid, m.p. 66°, obtained from the oil B in the previous experiment (0.25 g) was dissolved in methanol (25 ml) and hydrogenated, using 10% palladized carbon (0.1 g) as catalyst. After the hydrogenation (4 hr), the product was filtered, and the filtrate concentrated under vacuum to remove the solvent. The residue, a brown solid, on crystallization from a mixture of ethyl acetate and hexane gave the phenolic alcohol as colourless prisms (0.11 g), m.p. 169°. (Found: C, 67.3; H, 8.0. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.1%). The mixed m.p. of this product, m.p. 169°, with phenolic alcohol (B), m.p. 169°, was undepressed, but the mixed m.p. with the hydrogenolysis product of the pure erythro isomer obtained in the synthetic route, m.p. 169°, was depressed by 15°. Their IR spectra are shown in Fig. 9.

Phenolic alcohol (mixture of threo and erythro)

The oily fraction of the dibenzyl ether from A and B above (0.14 g) was dissolved in methanol (15 ml) and

hydrogenated, using 10% palladized carbon (0.05 g) as catalyst. After the hydrogenation the product was filtered and the filtrate concentrated under vacuum to remove the solvent. The residue, a brown solid, on crystallization from a mixture of ethyl acetate and hexane gave the phenolic alcohol as colourless prisms (0.05 g), m.p. 155-160°. (Found: C, 67.6; H, 8.0. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.1%). The m.p. of this compound when mixed with the hydrogenolysis product of the oil from the synthetic dibenzyl ether, m.p. 155-160°, was not depressed.

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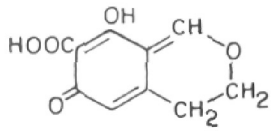
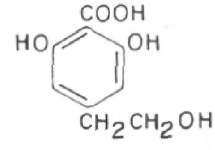
PART II. SYNTHESIS OF SOME ANALOGUES OF CITRININ

The simplest analogue of citrinin is norcitrinin (I), and its synthesis was attempted by RAMANATHAN[1] by three methods. (1) 4-Carboxy-3,5-dihydroxy-β-phenylethyl alcohol (II) was synthesized and subjected to the ethyl orthoformate reaction. The product was amorphous powder, which did not melt below 300° and could not be obtained in crystalline form; the iodine-brown ferric colour and other properties indicated however that cyclization to the citrinin type had probably taken place. (2) The aldehyde III prepared from the acid II also failed to cyclize by the action of sulphuric acid as described by ROBERTSON et al.[2] (3) 6,8-Dihydroxyisochroman (IV) was synthesized, and it could not be carboxylated by the usual method to dihydronorcitrinin derivative (V).



I



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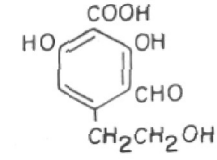

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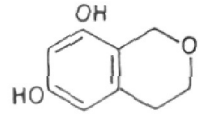

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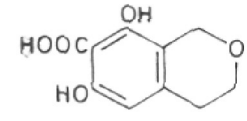
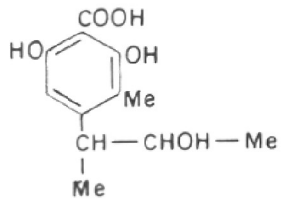


V

By the use of ethyl orthoacetate and orthopropionate on the acid VI RAMANATHAN[1] prepared 1-alkyl derivatives

(VII; R = Me or Et) of citrinin.



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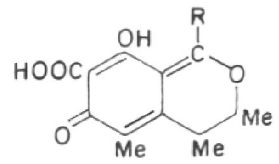


(R=Me; Et; Ph)

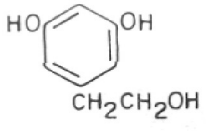
VII

WARREN et al.[3] obtained 1-alkyl derivatives of citrinin by the condensation of the acid VI with acetals or aldehydes and oxidation of the resultant dihydrocitrinin derivatives (VII; R = Me or Et or Ph). They observed that these derivatives of citrinin possessed considerably lower antibiotic activity than citrinin. WARREN et al.[4], in more recent work, prepared a homologous series of 1-n-alkyl derivatives of dihydrocitrinin ranging from n-propyl to n-nonyl by the condensation of normal aliphatic aldehydes with the acid VI, but they failed to convert these dihydrocitrinins to the corresponding citrinins. However, they observed that the 1-alkyl homologues VII of citrinin could be prepared very easily by the method described by GORE et al.[5] of reacting the acid VI with the appropriate ortho-esters. They found that the replacement of hydrogen by CH_3 in the 1-position results in a marked decrease in antibacterial activity and progressive lengthening of the chain causes

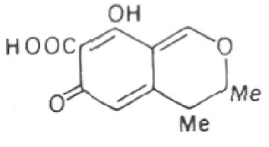
an increase in activity which exceeds that of citrinin in the C_6 and higher derivatives.

Present work

The object of the present work was twofold. One was to study the effect of substitution in β-(3,5-dihydroxy)-phenylethyl alcohol (VIII on its reactivity towards ethyl orthoformate under the simple conditions at room temp and in the absence of a solvent or acid or base catalyst, which was used for the synthesis of citrinin. Secondly, the object was to study the effect of removing one or more of the three C-methyl groups in citrinin on the antibacterial activity of the molecule. Following the line of synthesis of citrinin, the synthesis of analogues of citrinin of the structure IX, X and XI was undertaken.



VIII



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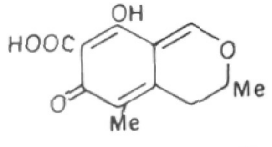

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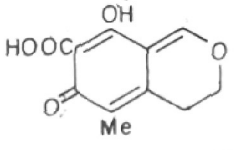
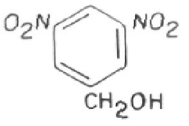


XI

It was also desired to have a simpler method to obtain 3,5-dihydroxyphenylacetic acid. 3,5-Dinitrobenzoic

acid on reduction with diborane in monoglyme gave the alcohol XII in 80 per cent yield. The alcohol XII was converted to 3,5-dinitrobenzyl chloride (XIII) with phosphorus trichloride. Attempts to convert the chloride (XIII) to 3,5-dinitrobenzyl cyanide (XIV) were unsuccessful. 3,5-Dinitrobenzyl bromide (XV) also failed to give the nitrile (XIV). Under different conditions, only red gummy products were formed, which could not be purified or characterized.



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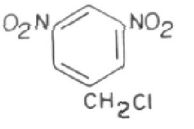

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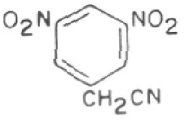

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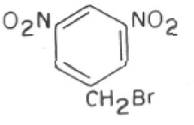
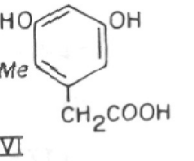


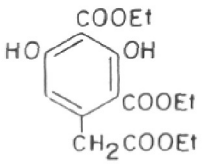
XV



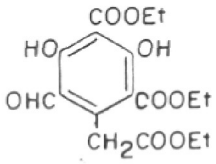
XVI

Attempts were made to simplify the procedure, described in Part I, for the preparation of the acid XVI. The action of dimethylformamide and phosphorus oxychloride on the readily available tri-ester (XVII) did not yield the aldehyde (XVIII). An alternate procedure appeared to be the introduction of the dimethylamino group in XVII, which could then give XX by hydrogenolysis with Raney nickel.

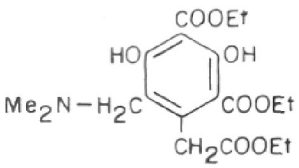
The action of dimethylamine and formaldehyde on XVII yielded XIX in 10 per cent yield.



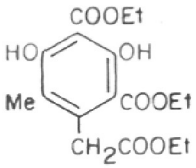
XVII



XVIII



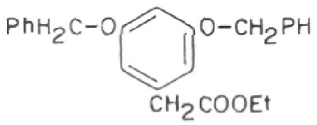
XIX



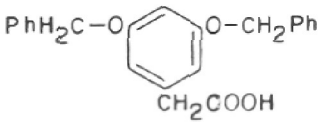
XX

Ethyl 3,5-dihydroxyphenylacetate was benzylated with benzyl bromide and fused potassium carbonate in acetone to give 3,5-dibenzyloxyphenylacetate (XXI) as a viscous oil which was purified by distillation under reduced pressure. The ester XXI was hydrolysed with ethanolic potassium hydroxide to give the acid XXII. The acid XXII on treatment with methyllithium in ether led to the ketone XXIII in 85 per cent yield. The ketone was characterized as its 2,4-dinitrophenylhydrazone. C-Methylation of the ketone was effected with sodium hydroxide and methyl iodide to give methyl α-(3,5-dibenzyloxyphenyl)-ethyl ketone (XXIV as a colourless oil, which was purified by distillation under reduced pressure. The ketone XXIV

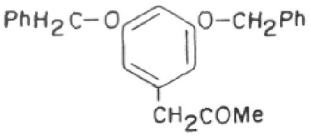
was also characterized by the 2,4-dinitrophenylhydrazone derivative.



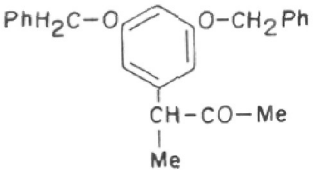
XXI



XXII



XXIII

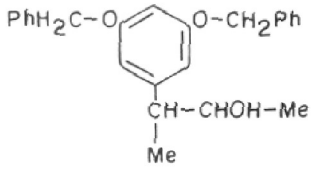


XXIV

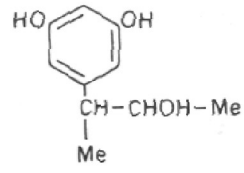
Reduction of the ketone XXIV with lithium aluminium hydride in ether afforded the corresponding alcohol, methyl ∝-(3,5-dibenzyloxyphenyl)ethylcarbinol (XXV) as a viscous oil which could not be crystallized. Hydrogenolysis of the alcohol XXV led to methyl ∝-(3,5-dihydroxyphenyl)ethylcarbinol (XXVI) as a colourless glass. Attempts to crystallize the phenolic alcohol XXVI by vacuum distillation or sublimation were unsuccessful, and it was characterized as a crystalline bisbenzeneazo derivative. Carboxylation of the phenolic alcohol (XXVI) in glycerine, with potassium hydrogen carbonate and carbon dioxide gave 2,6-dihydroxy-5-(∝-methyl- β-hydroxy-n-propyl)benzoic acid (XXVII) as a crystalline solid. An aqueous solution of the acid gave

an intense blue colouration with ferric chloride characteristic of γ-carboxylic acids.

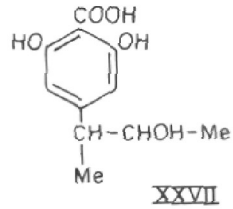
The action of ethyl orthoformate on γ-acid (XXVII) gave a deep-red gummy product which resembled citrinin in its iodine-brown ferric colouration and other properties.



XXV



XXVI

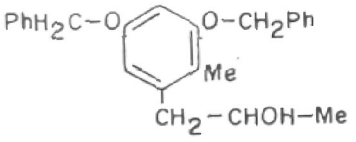


XXVII

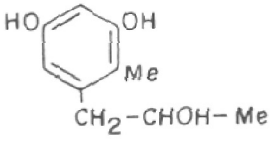
The preparation of another analogue X, in which the 5-position in the isochroman nucleus was substituted by a methyl group as in citrinin, was then undertaken. In this instance 3,5-dibenzyloxy-2-methylphenylacetone (Part I; XXIV) on reduction with lithium aluminium hydride in ether gave the corresponding alcohol (XXVIII) as a viscous oil. Hydrogenolysis of XXVIII led to the phenolic alcohol (XXIX) as a colourless glass. Attempts to crystallize this phenol, using various solvents or purification by sublimation, were not successful, and was characterized as a crystalline bisbenzeneazo derivative.

Carboxylation of the phenol XXIX in glycerine led to the acid XXX with the characteristic intense blue ferric colouration.

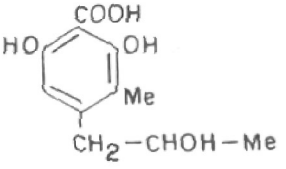
The acid XXX, on treatment with ethyl orthoformate at room temp, cyclized to give X as lemon-yellow needles. It gave the characteristic iodine-brown ferric colour. Blocking of 4-position in the resorcinol nucleus thus results in ready cyclization of compounds such as XXX and VI to readily crystallizable compounds of the citrinin type; when both the 4- and 6-positions are free, polymerization appears to take place.



XXVIII



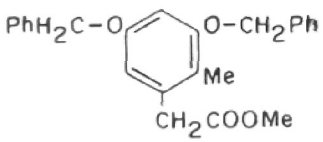
XXIX



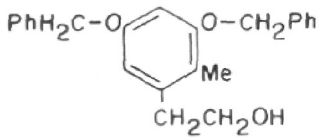
XXX

The synthesis of a third analogue of citrinin (XI) was then attempted. 3,5-Dibenzyloxy-2-methylphenylacetic acid (Part I; XXIII) was esterified with diazomethane; reduction of the methyl ester XXXI with lithium aluminium hydride in ether afforded the alcohol XXXII as a colourless crystalline solid. Hydrogenolysis of XXXII led to the

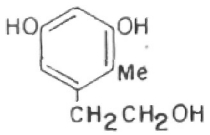
phenol XXXIII as a viscous oil, which was carboxylated to XXXIV, which crystallized in white needles. Treatment of the acid XXXIV with ethyl orthoformate yielded lemon-yellow needles, but on attempting to separate the product by the addition of ice, the quinonoid compound turned into a red gummy product with characteristic citrinin-like properties.



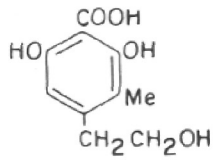
XXXI



XXXII



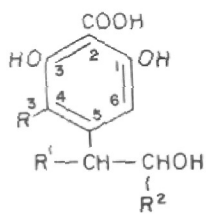
XXXIII



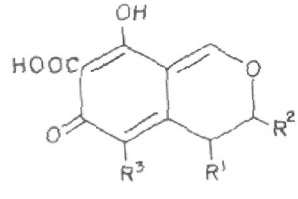
XXXIV

From the results obtained by RAMANATHAN and in the present work the following conclusions can be drawn concerning the action of ethyl orthoformate on a molecule of the type XXXV. If R^2 is absent, cyclization to the citrinin type XXXVI as shown by the colour reactions characteristic of citrinin, is accompanied by polymerization by the further action of ethyl orthoformate and the intervention of methine groups. If R^1 and R^2 are hydrogen and R^3 is a methyl group, and there is no evidence to

show that R^3 may not be other alkyl groups, halogen, etc., the β-phenylethanol (XXXIV) appears to react in the same manner as the carboxylic acid (VI) from phenolic alcohol (A) (*See Part I*); *a few minutes after* dissolution in ethyl orthoformate, yellow needles separate, but on attempting to separate the product by the addition of ice, the quinonoid compound turns to a red gummy product, which needs to be investigated more fully. If both R^3 and R^2 are methyl groups, as in XXX, the citrinin analogue separates in nearly quantitative yield as a lemon-yellow crystalline substance. The methyl group in the side-chain of XXX appears to have a conformational effect on the facile cyclization, and further the methyl group in the 3-position of the isochroman nucleus appears to impart stability to the citrinin type. RAMANATHAN observed that the amide of VI undergoes cyclization as readily as the carboxylic acid VI; but the ester gave an amorphous product which he was not able to purify or characterize. The effect of substitution in the 2-position in XXXV can only be explained after much more extensive experimental work.



XXXV



XXXVI

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

3,5-Dinitrobenzoic acid

Benzoic acid was nitrated with sulphuric acid-nitric acid mixture by the method given in Org. Synth.[6]

3,5-Dinitrobenzyl alcohol (XII)

3,5-Dinitrobenzoic acid (6.3 g) was taken in monoglyme (50 ml) and diborane gas passed slowly for 2 hr under nitrogen atm. The reaction mixture was allowed to stand overnight at room temp (26°) and then taken to dryness under reduced pressure and treated with ethanol (25 ml), when a yellow precipitate appeared, which was filtered and crystallized from dil ethanol in fine yellow needles (5.2 g), m.p. 89°. (Found: C, 42.7; H, 3.1; N, 14.4. $C_7H_6N_2O_5$ requires: C, 42.4; H, 3.0; N, 14.5%).

3,5-Dinitrobenzyl chloride (XIII)

Phosphorus trichloride (1.5 ml) was added to the alcohol (XII; 2.0 g) at 0° over a period of 10 min, and the reaction mixture left at room temp (26°) overnight. The solid obtained in the reaction mixture was added to ice-cold water, filtered and washed with plenty of water. Crystallization from hexane gave pale-yellow needles (2.1 g), m.p. 73°. (Found: C, 38.6; H, 2.0; N, 13.0; Cl, 16.0. $C_7H_5N_2O_4Cl$ requires: C, 38.9; H, 2.3; N, 13.0; Cl, 16.2%).

3,5-Dinitrobenzyl bromide (XV)

Phosphorus tribromide (1.7 ml) was added to the alcohol (XII) at 0° over a period of 10 min, and the reaction mixture left at room temp (26°) overnight. The solid obtained in the reaction mixture was added to ice-cold water, filtered, washed with plenty of water, dried and crystallized from methanol, m.p. 93°. (Found: C, 32.3; H, 1.8; N, 10.5; Br, 30.1. $C_7H_5N_2O_4Br$ requires: C, 32.5; H, 1.9; N, 10.7; Br, 30.6%).

Ethyl 3,5-dihydroxy-2,4-dicarbethoxy-5-N-dimethylamino-methyl phenyl acetate (XIX)

The ester (XVII; 2.0 g) was dissolved in a minimum amount of aqueous dimethylamine solution (30%; 5 ml) and cooled to 0°, to which was added an aqueous solution of formaldehyde (37%; 0.5 ml) over a period of 5 min under constant stirring. The reaction mixture was left at 0° for 1 hr and then stirred at room temp (28°) for 3 hr. No separation of solid was observed. The reaction mixture was then left at 10° for 3 days, when a solid separated out. It was filtered, dried and crystallized from ethanol in colourless needles (0.22 g), m.p. 210°(dec). (Found: C, 57.4; H, 6.6; N, 3.5. $C_{19}H_{27}O_8N$ requires: C, 57.4; H, 6.8; N, 3.5%).

Ethyl 3,5-dibenzyloxyphenylacetate (XXI)

A mixture of ethyl 3,5-dihydroxyphenylacetate (10 g), fused potassium carbonate (30 g), acetone (300 ml), and benzyl bromide (22 g) was refluxed on a steam-bath for 12 hr. The reaction mixture was filtered and the residue washed with acetone. The filtrate and washings were concentrated and the excess benzyl bromide removed by steam distillation. The oil was ether extracted and the ether extract washed with 2% solution of sodium hydroxide and water, and dried over sodium sulphate. Distillation of ether gave a brown coloured oil (15 g). A colourless viscous oil was obtained at 190-200° (air-bath temp)/10^{-3} mm. (Found: C, 76.8; H, 6.3. $C_{24}H_{24}O_4$ requires: C, 76.6; H, 6.4%).

3,5-Dibenzyloxyphenylacetic acid (XXII)

The above ester (XXI; 3.5 g) was refluxed with ethanolic potassium hydroxide (3%; 200 ml) for 4 hr. The reaction mixture was concentrated under vacuum to 25 ml, and water (50 ml) added and extracted with ether to remove unconverted ester. The aqueous phase was acidified with dil HCl, cooled and extracted with ether. The ether extract was washed with water and dried over sodium sulphate. Distillation of ether gave a yellow coloured oil (2.3 g), which on addition of pet ether solidified. Crystallization

from a mixture of chloroform-pet ether (60-80°) (norit) gave fine colourless needles, m.p. 106° (lit.106°).[1] (Found: C, 76.2; H, 6.1. Calc. for $C_{22}H_{20}O_4$: C, 75.8; H, 5.8%).

3,5-Dibenzyloxyphenylacetone (XXIII)

A solution of the acid (XXII; 5 g) in dry ether (100 ml) was added to a solution of methyllithium (prepared from 2.2 g of lithium and 22 g of methyl iodide in dry ether, 250 ml, at 0°) slowly over a period of 45 min. The reaction mixture was refluxed for 4 hr, cooled, filtered through glass wool, and decomposed carefully with wet ether and water. The ethereal layer was separated and the aqueous phase extracted with ether twice (2 x 100 ml). The ether extract was washed with aqueous sodium carbonate to recover unconverted acid, and dried over sodium sulphate. Evaporation of the ether gave yellow coloured oil (4.3 g), b.p. 198-205°/0.1 mm. (Found: C, 79.3; H, 6.4. $C_{23}H_{22}O_3$ requires: C, 79.7; H, 6.4%).

The 2,4-dinitrophenylhydrazone derivative was crystallized from a mixture of dimethylformamide-alcohol in dark-orange needles, m.p. 149°. (Found: N, 10.3. $C_{29}H_{26}N_4O_6$ requires: N, 10.6%).

Methyl α-(3,5-dibenzyloxyphenyl)ethyl ketone (XXIV)

An intimate mixture of powdered sodium hydroxide

(6 g) and the ketone (XXIII; 3.6 g) was warmed on a water-bath at 70° for ½ hr, and after cooling to room temp (28°), methyl iodide (9.4 g) was added. The reaction mixture was left at room temp for 3 hr, and then gently refluxed for 3 hr and, finally, heated at 100° for 2 hr. After decomposition with water, the product was isolated by ether. The ether extract was washed with water and dried over sodium sulphate. Distillation of ether gave a brown oil which was distilled at 170-180°(air-bath temp)/ 1 x 10^{-3} mm to give a pale yellow oil (2.9 g). (Found: C, 79.7; H, 7.0. $C_{24}H_{24}O_3$ requires: C, 79.9; H, 6.7%). The 2,4-dinitrophenylhydrazone derivative was crystallized from a mixture of dimethylformamide-ethanol in deep-yellow plates, m.p. 129°. (Found: C, 66.8; H, 5.0; N, 10.2. $C_{30}H_{28}O_6N$ requires: C, 66.6; H, 5.0; N, 10.3%).

Methyl ∝-(3,5-dibenzyloxyphenyl)ethylcarbinol (XXV)

A solution of the ketone (XXIV; 2.5 g) in dry ether (40 ml) was added over a period of 30 min to a refluxing solution of lithium aluminium hydride (2.0 g) in dry ether (150 ml), and the mixture refluxed for 4 hr. The mixture was decomposed by moist ether and cold 20% sulphuric acid (40 ml). The ether layer was separated and the aqueous phase extracted with ether (3 x 100 ml). The ether extract was washed with water, aqueous sodium bicarbonate and dried over sodium sulphate. Distillation

of ether gave a pale-yellow oil which was distilled at 180° (air-bath temp)/4.81 x 10^{-4} mm to give a colourless oil (2.1 g). (Found: C, 79.5; H, 7.5. $C_{24}H_{26}O_3$ requires: C, 79.5; H, 7.2%).

Methyl α-(3,5-dihydroxyphenyl)ethylcarbinol (XXVI)

The alcohol (XXV; 2.0 g), 10% palladized carbon (0.5 g) and methanol (40 ml) were agitated in an atm of hydrogen at room temp till 2 moles of hydrogen were absorbed (6 hr). The carbon was filtered off and washed with warm methanol (4 x 20 ml). The filtrate and washings were taken to dryness under vacuum when a light-brown coloured oil was obtained. The oil was taken up in ether and extracted with aqueous sodium carbonate, to remove the unreacted compound. Carbon dioxide was passed into aqueous carbonate extract till saturated. It was extracted with ether and the ether extract was washed with water and dried over sodium sulphate. Distillation of ether gave a clear viscous oil (0.85 g), which could not be induced to crystallization even after keeping in contact with hexane at 0° for a number of days. Sublimation of the oil at 166°/0.1 mm gave the sublimed product as an oil only. It was distilled at 190-200°/7.7 x 10^{-3} mm. (Found: C, 66.4; H, 7.9. $C_{10}H_{14}O_3$ requires: C, 65.9; H, 7.7%).

The bisphenylazo derivative of the phenol (XXVI) was prepared, which crystallized from ethanol in red needles,

m.p. 202°. (Found: N, 14.1. $C_{22}H_{22}O_3N_4$ requires: N, 14.3%).

2,6-Dihydroxy-5(α-methyl-β-hydroxy-n-propyl)benzoic acid (XXVII)

An intimate mixture of phenol (XXVI; 800 mg), anhydrous potassium carbonate (5 g) and glycerol (15 ml) was heated in a current of dry carbon dioxide for 8 hr at 140° ± 5° for 7 hr. After cooling, the mixture was treated with water (20 ml), saturated with ammonium sulphate and exhaustively extracted with ether to remove the unconverted phenol. The aqueous liquor was acidified with dil HCl and extracted with ether (5 x 50 ml). The ether extract was washed with a saturated solution of sodium chloride and dried over sodium sulphate. Distillation of ether gave a solid which crystallized from a mixture of ether and pet ether (40-60°) in colourless plates (350 mg), m.p. 156° (dec). (Found: C, 58.7; H, 6.5. $C_{11}H_{14}O_5$ requires: C, 58.4; H, 6.2%).

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

Attempted cyclization of 2,6-dihydroxy-5(α-methyl-β-hydroxy-n-propyl)benzoic acid (XXVII) to (IX)

The acid (XXVII; 0.2 g) was weighed in a dry test tube and ethyl orthoformate (freshly distilled) (0.5 ml) was added to it at room temp (26°). The acid went into solution immediately, and the reaction mixture first turned

yellow and, finally, dark-red. Crushed ice was added to it after ½ hr, when red oil globules separated out. It was ether extracted and dried over sodium sulphate. Distillation of ether gave a red oil which could not be induced to crystallization. It showed a greenish fluorescence and its alcoholic solution exhibited a typical iodine-brown ferric colour characteristic of citrinin.

1-(3,5-Dibenzyloxy-2-methyl)phenylpropan-2-ol (XXVIII)

A solution of 3,5-dibenzyloxy-2-methylphenylacetone (2.2 g) in dry ether (40 ml) was added during the course of 25-30 min to a vigorously refluxing solution of lithium aluminium hydride (1 g; excess) in dry ether (100 ml). The mixture was refluxed for 4 hr, after which the excess hydride was carefully decomposed with water and ice-cold sulphuric acid (20%; 20 ml). The ether layer was separated and aqueous phase extracted with ether (2 x 50 ml). The ether extract was washed with aqueous sodium bicarbonate, water and dried over sodium sulphate. Distillation of ether gave a pale-brown coloured oil (2.0 g) which on distillation under reduced pressure, b.p. 185-190° (air-bath temp)/ 37 x 10^{-3} mm, gave a nearly colourless oil. (Found: C, 79.2; H, 7.6. $C_{24}H_{26}O_3$ requires: C, 79.5; H, 7.2%).

1-(3,5-Dihydroxy-2-methyl)phenylpropan-2-ol (XXIX)

The above alcohol (XXVIII; 1.7 g) was dissolved in 95% methanol (25 ml); palladized carbon (10%; 0.5 g) was added, and the mixture agitated in an atm of hydrogen at room temp

(26-27°) till 2 moles of hydrogen were absorbed (6 hr). The carbon was filtered off, washed with warm methanol, and the filtrate and washings were taken to dryness, when a nearly colourless glass (0.8 g) separated, which could not be induced to solidify. The oil was again taken up in ether and extracted with aqueous sodium carbonate solution to remove the unreacted phenol. Carbon dioxide was passed into the carbonate extract till saturation. It was extracted with ether and the ether extract washed with water and dried over sodium sulphate. Distillation of ether gave a clear viscous oil which could not be crystallized. It sublimed as an oil at 140°/0.1 mm and was distilled at 180-185° (air-bath temp)/0.1 mm. (Found: C, 66.1; H, 7.8. $C_{10}H_{14}O_3$ requires: C, 65.9; H, 7.7%).

The bisphenylazo derivative was prepared by coupling with diazotized aniline. Crystallization from ethanol gave red needles, m.p. 200°. (Found: N, 13.8. $C_{22}H_{22}O_3N_4$ requires: N, 14.3%).

1-(4-Carboxy-3,5-dihydroxy-2-methylphenyl)propan-2-ol(XXX)

An intimate mixture of the above phenol (XXIX; 0.25 g), anhydrous potassium hydrogen carbonate (2.2 g) and glycerol (6 ml) was heated in a current of dry carbon dioxide at 150° ± 2° for 8 hr. After cooling, the mixture was treated with water (10 ml), saturated with ammonium sulphate and

exhaustively extracted with ether to remove the unconverted phenol. The aqueous liquor was acidified with dil HCl and extracted with ether (4 x 50 ml). The ether extract was washed with a saturated solution of sodium chloride and dried over sodium sulphate. Distillation of ether gave an oil which immediately solidified on addition of hexane. Crystallization from ether-pet ether (40-60°) gave colourless needles (0.07 g), m.p. 172° (dec). (Found: C, 58.5; H, 6.3. $C_{11}H_{14}O_5$ requires: C, 58.4; H, 6.2%). An alcoholic solution of the substance gives an intense blue ferric colouration.

Cyclization of 1-(4-carboxy-3,5-dihydroxy-2-methylphenyl)-propan-2-ol (XXX) to (X)

To the acid (XLIV; 40 mg) in a dry test tube was added ethyl orthoformate (0.3 ml) at room temp (28°). The reaction mixture immediately turned yellow and a bright yellow crystalline solid separated. Crushed ice was added after 10 min, and the yellow crystalline product collected, washed and dried. Crystallization from cyclohexane gave lemon-yellow needles (30 mg), m.p. 181° (dec). (Found: C, 61.2; H, 5.2. $C_{12}H_{12}O_5$ requires: C, 61.0; H, 5.1%).

The product exhibited a typical iodine-brown colouration in ethanol with ferric chloride.

Methyl 3,5-dibenzyloxy-2-methylphenylacetate (XXXI)

To 3,5-dibenzyloxy-2-methylphenylacetic acid (2 g) in methanol (25 ml) was added diazomethane in ether till a yellow colour was persistent. The reaction mixture was left at 10° overnight and the excess diazomethane destroyed by addition of a few drops of acetic acid. Distillation of the reaction mixture gave an oil which crystallized from hexane (60-80°) in colourless long needles (1.8 g), m.p. 66°. (Found: C, 77.0; H, 6.5. $C_{24}H_{24}O_4$ requires: C, 76.6; H, 6.4%).

β-3,5-Dibenzyloxy-2-methylphenylethyl alcohol (XXXII)

The above ester (XXXI; 1.6 g) in anhydrous ether (25 ml) was added to a refluxing solution of lithium aluminium hydride (1.0 g; excess) in anhydrous ether (80 ml). The mixture was refluxed for 4 hr and worked up as usual. Crystallization from hexane (60-80°) gave white needles (1.3 g), m.p. 82°. (Found: C, 79.7; H, 6.7. $C_{23}H_{24}O_3$ requires: C, 79.9; H, 6.7%).

β-3,5-Dihydroxy-2-methylphenylethyl alcohol (XXXIII)

The above alcohol (XXXII; 1.0 g) was dissolved in methanol (25 ml) and to it was added palladized carbon (10%; 0.4 g) and the mixture agitated in an atm of hydrogen (26-28°) till 2 moles of hydrogen were absorbed (4 hr).

After working up the reaction mixture as usual, the yellow coloured viscous oil (0.4 g) was distilled at 170-180°/(air-bath temp)/7.7 x 10^{-3} mm to yield a colourless viscous glass. (Found: C, 64.7; H, 7.3. $C_9H_{12}O_3$ requires: C, 64.2; H, 7.1%). The bisphenylazo derivative was prepared by coupling with diazotized aniline. Crystallization from ethanol gave bright red needles, m.p. 212°. (Found: N, 14.4. $C_{21}H_{20}O_3N_4$ requires: N, 14.8%).

β-(4-Carboxy-3,5-dihydroxy-2-methylphenyl)ethyl alcohol (XXXIV)

An intimate mixture of the above phenol (0.3 g), anhydrous potassium hydrogen carbonate (2.5 g) and glycerol (10 ml) was heated under the atmosphere of carbon dioxide at 150° ± 5 for 8 hr. The reaction mixture was worked up as usual. Crystallization from a mixture of benzene-hexane gave colourless needles (0.1 g), m.p. 166° (dec). (Found: C, 56.5; H, 5.9. $C_{10}H_{12}O_5$ requires: C, 56.6; H, 5.7%). An alcoholic solution of the acid gave intense blue ferric colouration with ferric chloride.

Attempted cyclization of β-(4-carboxy-3,5-dihydroxy-2-methylphenyl)ethyl alcohol (XXXIV) to (XI)

To the acid (0.06 g) was added ethyl orthoformate (10 drops) at room temp (28°). The reaction mixture immediately turned yellow and bright yellow needles separated out. After addition of crushed ice, the reaction mixture first

turned light-red and then deep-red. It was ether extracted and the ether extract dried over sodium sulphate. Distillation of ether gave a deep-red gummy product. It showed a greenish fluorescence and its alcoholic solution exhibited a typical iodine-brown ferric colour.

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PART III

SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED BIPHENYLS

Introduction

Biphenyls and polyphenyls are of interest because of their thermal stability, conductivity, optical isomerism, and scintillation activity. A recent interest in biaryls is their use as coolants for reactors. It has been shown that deuterodiphenyl is more stable than diphenyl by a factor of about 2, for pyrolysis and radiolysis.[1]

The preparation of a biphenyl derivative of given structure is often difficult, although many methods of preparation are available. Unsymmetrical substitution in the biphenyl nucleus further complicates the synthesis. The present survey deals mainly with the synthesis of unsymmetrically substituted biphenyls; several excellent reviews on methods of synthesis of polyphenyl derivatives have appeared elsewhere.[2-7]

The available methods for the preparation of unsymmetrical biphenyls may be classified as follows:-

(A) Synthesis without alteration of the aromatic carbon skeleton

(1) By direct substitution

(2) Grignard synthesis

(3) Elimination of functional groups

(B) Synthesis with the formation of the biphenyl linkage

(1) Pyrolysis

(2) From aromatic amines

(a) The Gomberg-Bachmann-Hey reaction

(b) By the action of diazonium salts on phenols

(c) Arylation of phenylhydrazine by oxidation

(3) Arylation with aromatic acid peroxides

(4) From aryl halides

(a) Ullmann reaction

(b) Grignard synthesis

(c) From organo-metallic compounds

(d) The Wurtz-Fittig reaction

(e) Catalytic reduction of aryl halides

(5) Elimination of sulphur and selenium

(6) Cyclohexylation of aromatic compounds and dehydrogenation

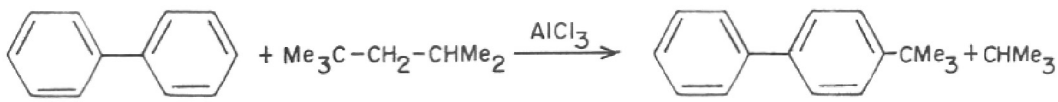
(A) Synthesis without alteration of the aromatic carbon skeleton

(1) By direct substitution

The hydrogen atom of biphenyl can be replaced by various reagents to form substituted biphenyls. The inductive effect of one phenyl group results in o- and p-orientation of an entering electrophilic group in the attached benzene ring. Thus direct nitration or halogenation may be employed to prepare unsymmetrical biphenyls.[8] For large-scale preparation of 2- and 4-nitrobiphenyl, the most

satisfactory method is direct nitration. The separation of isomers formed in many cases is a difficult problem.[9] The orientation of the second group entering the biphenyl nucleus is decided by the substituent already present, and this property is often used for synthesis. Thus the direct influence of an amino group may be utilized to form the desired substitution followed by deamination. Several unsymmetrical nitrobiphenyls have been prepared by deamination[8] of aminonitrobiphenyls.

The Friedel-Crafts reaction has been largely used to get various alkyl and acyl derivatives of biphenyl. Olefins and alkyl halides react with biphenyl in presence of aluminium chloride to give mixtures of mono-, di- and tri-alkyl derivatives.[10,11] An overall yield of 80 per cent of a mixture of mono- and di-hexylbiphenyls is obtained by condensation with n-hexylbromide in hexane solution.[12] 2,2,4-Trimethylpentane (I) in presence of aluminium chloride reacts with biphenyl to give a mixture of mono-t-butylbiphenyls from which the p-isomer (II) can be frozen out in 27 per cent yield.[13]



I II

(2) Grignard synthesis from halogenated biphenyls

Several alkyl and alkenyl biphenyl derivatives have been made by reaction of biphenyl magnesium halides with aliphatic ketones.[14-17] Unsaturated side-chains in the o-position have been introduced by this method.[17] Allyl bromide reacts in a similar way to give o-allylbiphenyl in 60 per cent yield. Ethylene oxide likewise reacts to give alcohols.[18]

(3) Elimination of functional groups

Functional groups, such as carboxyl, amino and hydroxyl, may be removed by known methods to provide unsymmetrically substituted biphenyl derivatives.

o-Terphenyl is formed by dry distillation of the silver salt of o-terphenyl-2-carboxylic acid.[19] The removal of hydroxyl and methoxyl group is achieved by distillation over zinc dust.[20,21] Reduction of diethyl p-biphenylphosphate with alkali metal in liquid ammonia gave biphenyl in about 80 per cent yield.[22] The deamination of various biphenyl derivatives is often employed to obtain the desired compound;[23] benzidine and its derivatives, readily available as dye intermediates, are obvious starting materials for the preparation of both symmetrical and unsymmetrical biphenyl

derivatives. Isolated examples are also available where dehalogenation[24] and elimination of selenium[25] have been used for the preparation of biphenyl derivatives.

(B) Synthesis with the formation of the biphenyl linkage

(1) Pyrolysis

No unsymmetrically substituted biphenyl has been obtained by pyrolysis, although this route represents one of the earliest methods of synthesis of biphenyl itself. The reaction conditions are very drastic and the yields of pure components are often poor. Extensive research has made it possible to utilize this method for the production of biphenyl from benzene.[26]

(2) From aromatic amines

(a) The Gomberg-Bachmann-Hey reaction. In the Gomberg-Bachmann-Hey reaction biaryls are formed by the treatment of an aryl diazonium salt solution with sodium hydroxide or sodium acetate in the presence of a liquid aromatic compound which is to be arylated.[7,27,28] Better yields are usually obtained by replacing sodium hydroxide with sodium acetate. Using p-nitrophenyldiazonium chloride stabilized by means of naphthalene-1,5-disulphonic acid, a 70 per cent yield of 4-nitrobiphenyl can be obtained. The Gomberg-Bachmann-Hey reaction very probably

proceeds by a free radical mechanism. CADOGAN[29] has very recently shown that the low yields often obtained in this reaction, largely because of the heterogeneity of the reaction and the instability of the diazonium solution, can be avoided by using pentyl nitrite for diazotization. He has claimed that his procedure affords "the simplest one-step route to biaryls yet recorded."

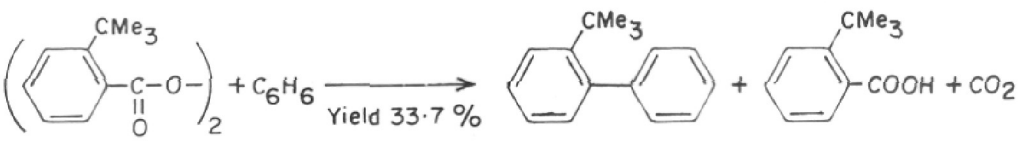
Pyrolysis of diazoaminobenzene in aromatic solvents at 150-160° generates phenyl and anilino radicals; the former attacks the solvent, giving relatively high yields of biphenyl derivatives.[30] N-Nitroso-N-aryl acetates, which are tautomeric with diazonium acetates, can be used as arylating agents.[31,32]

(b) By the action of diazonium salts on phenols. Aryl diazonium salts, such as chlorides or sulphates, react with phenols to give hydroxybiphenyls if no alkali is added.[33,34,35] Diazotized aniline in a large excess of phenol gives a good yield of a mixture of 2- and 4-hydroxybiphenyl in addition to diphenyl ether. BORSCHE[36] obtained an 8 per cent yield of 2-hydroxy-5-nitrosobiphenyl from diazotized aniline and p-nitrosophenol.

(c) Arylation of phenylhydrazine by oxidation.[37] Arylation is effected by the oxidation of phenylhydrazine in an aromatic solvent, using metallic oxides, preferably silver oxide. Phenylation by this method almost always gives mixtures which are very difficult to separate.

(3) Arylation with aromatic acid peroxides

Benzoyl peroxide and boiling benzene give mainly biphenyl and benzoic acid.[38] Peroxides of monosubstituted acids yield monosubstituted biphenyls. Arylation with benzoyl peroxide involves the following sequence of reactions:[39] (i) breakdown into radicals; (ii) combination of the radical with the hydrocarbon molecule; and (iii) removal of a hydrogen atom by another radical. For example, t-butylbiphenyl can be prepared by using substituted peroxides, but not t-butylbenzene.[40] A mixture of isomers is always formed when substituted hydrocarbons are used.



III IV

In a very recent note HEY, PERKINS and WILLIAMS[41] have shown that arylation of benzene and fluorobenzene with benzoyl and other aroyl peroxides is substantially modified by the presence of small quantities of aromatic nitro-

compounds. There is a large increase in the yields of the bimuclear products and of benzoic acids, and a corresponding decrease in the yields of the high-boiling residues, which are often obtained in these reactions. Thus the 4-chlorobiphenyl can be prepared from p-chlorobenzoyl peroxide and benzene in 90 per cent yield.

(4) From aryl halides

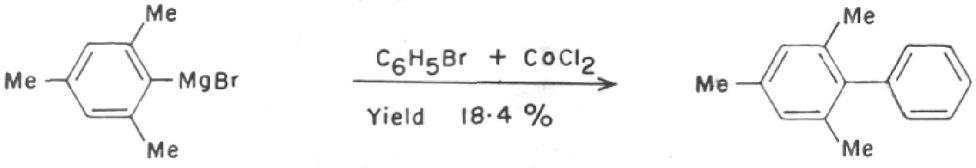
(a) Ullmann reaction. The Ullmann[42] reaction, in which a halogenated aromatic compound or a mixture of two halogenated aromatic compounds is heated with copper, can be used for the synthesis of both symmetrical and unsymmetrical biaryls as well as polyaryls. Thus biphenyl can be obtained in 82 per cent yield from iodobenzene. Dimethylformamide[43] and dimethyl sulphoxide[44] are useful solvents. However, 2,2'-dinitrobiphenyl is obtained in nearly quantitative yield by heating o-iodonitrobenzene at 190° with four equivalents of freshly precipitated copper.[45] In a series of papers FORREST[46] has recently discussed the Ullmann biaryl synthesis, and he has reported the optimum conditions for the formation of unsymmetrical biaryls. He has also produced evidence to show that the free radical mechanism for the Ullmann reaction suggested by RAPSON and SHUTTLEWORTH[47,48] is irreconcilable with several experimental observations. The preparation of unsymmetrical biaryls by this method is complicated by the formation of a mixture of products. Thus three bitolyls are obtained from a mixture of o- and m-iodotoluenes[49] and the separation of these three hydrocarbons is extremely difficult.

(b) Grignard synthesis. By heating phenyl magnesium bromide with iodobenzene or bromobenzene in ether or toluene or without a solvent (140-180°), biphenyl is obtained in low yield (10-13 per cent).[48a] Preparative methods for obtaining biphenyl became possible from organo-magnesium compounds with the use of certain metal halides, such as CuCl, AgBr, $MoCl_5$, $CoCl_2$ and $CrCl_3$. The oxidation reaction occurs in two stages.[50,51]

$$Ar-MgX + MX \longrightarrow Ar-M + MgX_2$$

$$2Ar-M \xrightarrow{O_2} Ar-Ar + 2M\ (M_2O)$$

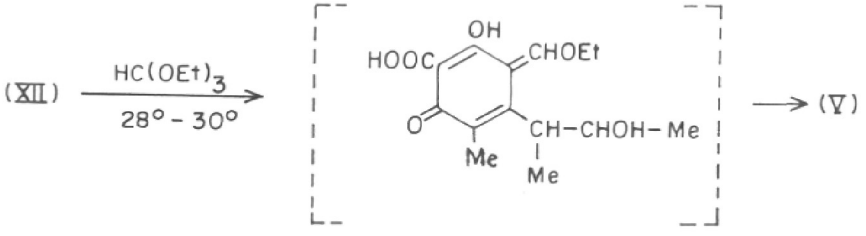
Reaction of p-tolylmagnesium bromide and bromobenzene with $CoCl_2$ gives 95 per cent 4,4'-dimethylbiphenyl.[52] Phenyl mesitylene has been prepared in 18.4 per cent yield from mesityl magnesium bromide and fourfold excess of bromobenzene.[53]



V VI

(c) From organo-metallic compounds. Certain organo-metallic compounds, when oxidized, give rise to biphenyls. Phenyllithium, when oxidized by butyl bromide in presence of $CoCl_2$ gives a 67 per cent yield of biphenyl.[54]

ethoxymethylene derivative XIIIa.



The biosynthesis of citrinin has been examined by BIRCH et al.[26] by feeding experiments with ^{14}C-labelled acetic and formic acids. They suggest that citrinin can arise from five acetic acid units and three formic acid units, but a better defined route will need further investigation.

The NMR spectrum of citrinin has been discussed by TERHARARA and collaborators.[27]

Present work

It is to be noted that the syntheses of citrinin reported above have been accomplished, starting from the phenolic alcohol (VIII),[19,24,25] which was obtained by the hydrolysis of citrinin itself. Although the structure of the phenolic alcohol (VIII) has been conclusively proved,[16] and its dimethyl ether synthesized, the recorded syntheses of citrinin can only be regarded as "partial" or "formal." The present work was undertaken to achieve a total synthesis of citrinin and also to develop procedures

Phenyl aluminium diiodide, when heated with bromobenzene in benzene, yields 98 per cent biphenyl.[55]

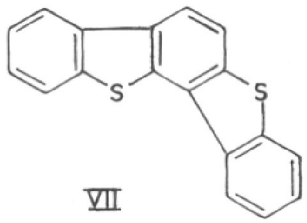
(d) The Wurtz-Fittig reaction.[56] Although it is one of the oldest methods known for the preparation of biphenyl, it has been used to a very limited extent. The preparation involves the treatment of an aryl halide with metallic sodium and isolation of the product by fractional distillation.

(e) Catalytic reduction of aryl halides. Reduction of an aryl halide with hydrazine and a palladium catalyst in presence of alkali gives some diaryl, but the yields, generally, are low. Bromobenzene treated with 4-6 per cent alkali in methanol with palladium on calcium carbonate catalyst gives 35 per cent of biphenyl.[57] This method has been used for the syntheses of higher polyphenyls.[58]

(5) Preparation by elimination of sulphur and selenium

When aromatic thioethers, disulphides, thioesters, and thiols are treated at 220° with degassed Raney nickel or nickel prepared after SABATIER, biphenyls are formed.[59] Diphenyl disulphide thus gives a 65-80 per cent yield of biphenyl. Reduced iron catalysts react with diphenyl sulphide at 350°, giving chiefly biphenyl.[60] Organic compounds containing selenium behave in a similar way; thus diphenyl diselenide at 180° gives 72 per cent of

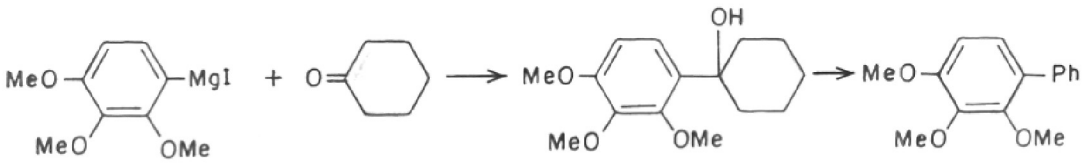
biphenyl.[61] An interesting method for obtaining m-terphenyl is by the elimination of sulphur from VII by means of Raney nickel.[62]



VII

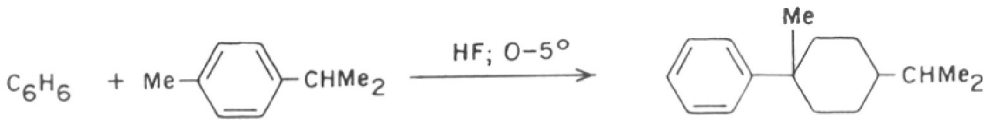
(6) Cyclohexylation of aromatic compounds and dehydrogenation

A variation of the synthesis of biaryls by the formation of the biaryl linkage is to cyclohexylate an aromatic compound, using Grignard reaction conditions for example,[64] and then dehydrogenate the cyclohexylbenzene

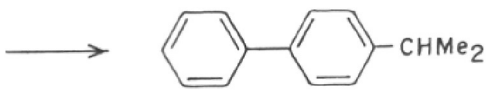


VIII IX X XI

derivative by conventional methods.[63,64] Thus p-isopropyl-biphenyl can be prepared as follows:[65]



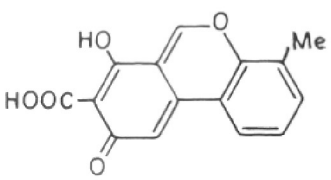
XII XIII



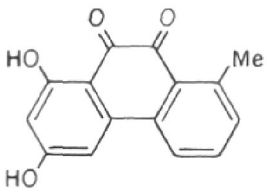
XIV

Present work

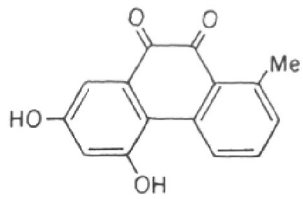
The synthesis of certain substituted biphenyls has been included in the present work because of the possibility of using them for the synthesis of pigments of the type of denticulatol and some analogues of citrinin such as XV discussed in Part II. Denticulatol was isolated by CHI et al. from the root of Rumex chinensis Campd. (Polygonaceae), the species now being called Rumex maritimus L. On the basis of inadequate experimental evidence CHI et al.[66] concluded that denticulatol had the structure XVI or XVII. After this work was completed, it was found from the chapter on "Quinones: Structure and Distribution" by R. H. THOMPSON in Comparative Biochemistry[67] that, according to unpublished work of A. J. BIRCH, structures XVI and XVII have been disproved by synthesis. The method of biaryl synthesis now investigated has also a wider interest in this laboratory in connection with the chemistry of chalkones prepared as intermediates for flavones, flavanones and flavonols.



XV



XVI

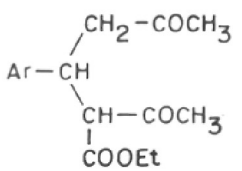


XVII

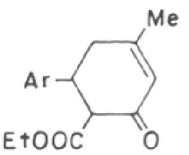
The Michael condensation, especially with the extensions to compounds activated by groups other than carbonyl and alkoxycarbonyl (COOR), is probably the most widely applicable synthetic reaction in organic chemistry. In their excellent survey of nearly 400 pages BERGMANN, GINSBURG and PAPPO[68] have given a comprehensive account of the Michael reaction, including the mechanisms, scope and limitations, synthetic applications and experimental procedures. A few of the applications of the Michael condensation to the synthesis of aromatic ring systems are outlined below as a background to the present work.

Michael adducts of unsaturated aldehydes or ketones with ethyl acetoacetate readily undergo a subsequent condensation with loss of a molecule of water between a methyl or methylene group and a carbonyl group. Thus the adduct XVIII may undergo cyclization to form XIX or XX. Condensing o-methoxybenzalacetone with ethyl acetoacetate in presence of aqueous sodium hydroxide FORSTER and HEILBRON[69] obtained a product which they considered to be the methoxy analogue of XIX or XX, but did not decide between the isomeric structures. HORNING and FIELD[70] anticipated the possibility of the formation of the two cyclohexenones XIX and XX when they prepared the Michael

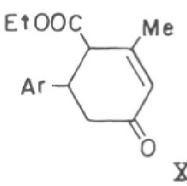
adduct from anisalacetone and ethyl acetoacetate, using piperidine as catalyst, and submitted it in a separate step to cyclization by means of acetic acid, acetic anhydride and phosphoric acid; but they only isolated (in 22 per cent yield) the 4-ethoxycarbonyl derivative XX. They proved the structure of XX by hydrogenation and synthesis of the cyclohexanone thus obtained by an independent method. It appears very probable that the isomer XIX was also obtained, perhaps as the major product, but was not crystallizable and was not specially looked for. Condensing p-dimethylaminobenzalacetone with ethyl acetoacetate in presence of aqueous sodium hydroxide HEILBRON et al.[71] obtained only the aldol XXI corresponding to XIX.



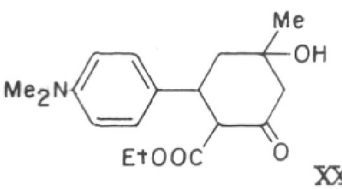
XVIII



XIX



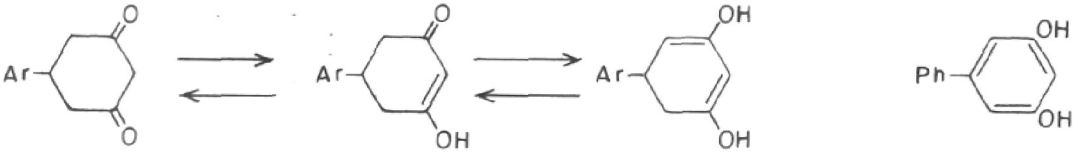
XX



XXI

The references to the use of the Michael adducts from chalkones for the synthesis of m-terphenyls are cited later.

When ethyl acetoacetate is replaced by diethyl malonate in the Michael condensation with benzalacetone, the product is a 5-phenyldihydroresorcinol. Thus a series of 5-phenyldihydroresorcinols (XXII) have been prepared by the condensation of benzalacetones with diethyl malonate in presence of ethanolic sodium ethoxide.[72] SUTER and SMITH[73] have prepared 5-phenylresorcinol (XXIII) from the Michael adduct XXII of benzalacetone and diethyl malonate, which was ethylated, aromatized by heating with sulphur at 300°, and finally de-ethylated by means of hydriodic acid.

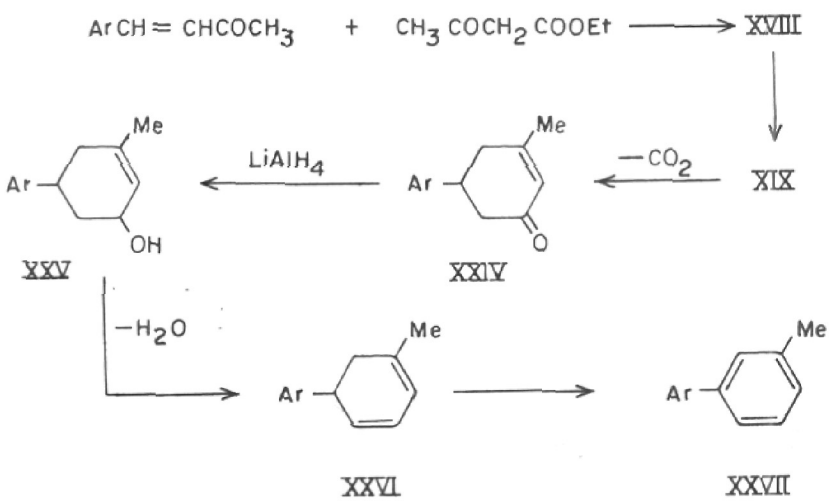


XXII XXIII

The present synthesis of unsymmetrically substituted biphenyls was achieved in an overall yield of 25-30 per cent by the series of reactions shown in Chart 1. The first step is the Michael addition of an arylideneacetone with ethyl acetoacetate. The adduct XVIII immediately cyclizes to XIX, which is then submitted to hydrolysis and decarboxylation to give an aryl cyclohexenone derivative (XXIV). The reduction of the ketone XXIV to the alcohol

XXV is followed by dehydration to give the aryl cyclohexadiene (XXVI), which on aromatization yields the biphenyl XXVII.

CHART—1

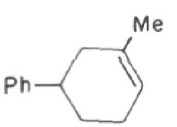


Following the experimental conditions of CONNOR and ANDREWS,[74] piperidine was used as the base catalyst. When benzylideneacetone and ethyl acetoacetate were refluxed on a steam-bath in absolute ethanol containing a little piperidine, and the product submitted to fractional distillation under reduced pressure, the product, obtained in 65-70 per cent yield, was not the

Michael adduct (XVIII; Ar = Ph). It was observed that cyclization to (XIX; Ar = Ph) occurred during the reaction. The structure XIX should be preferred because of the ease with which the acid obtained from the ester can be decarboxylated; the red colour obtained on treatment with ferric chloride also goes more in favour of structure XIX. The IR absorption spectrum of (XIX; Ar = Ph) showed the carbonyl frequency of the ethyl ester group at 1723 cm^{-1} and the carbonyl frequency of the α,β-unsaturated ketone appeared at 1655 cm^{-1}. That a small part of the compound existed in the enol form was shown by the IR absorption at 3400 cm^{-1} as a very weak band, and this was confirmed by the red ferric chloride colour in ethanolic solution. The ester (XIX; Ar = Ph) was characterized by its 2,4-dinitrophenylhydrazone derivative. This reaction was attempted without success by KNOEVNAGEL and SPEYER.[75]

The acid formed by hydrolysis of the ester (XIX; Ar = Ph), with ethanolic potassium hydroxide and subsequent acidification, decarboxylated readily to the ketone (XXIV; Ar = Ph); the oily product, on fractional distillation under reduced pressure, crystallized from hexane in colourless needles, m.p. 30°. The ketone (XXIV; Ar = Ph) was characterized by its IR spectrum;

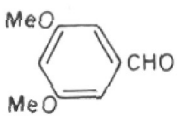
the ester carbonyl absorption of (XIX; Ar = Ph) at 1723 cm^{-1} had disappeared, and the $\alpha\beta$-unsaturated ketone carbonyl band had shifted slightly to 1647 cm^{-1}. The ketone XXIV was also characterized by its 2,4-dinitrophenylhydrazone derivative. An attempt to reduce the ketone to XXIV$_a$ by Clemmensen reduction was unsuccessful. The product obtained was a viscous oil, which distilled at 240°/10^{-3} mm and had apparently polymerized. Reduction of the ketone XXIV with sodium borohydride in methanol gave an almost quantitative yield of the corresponding alcohol (XXV; Ar = Ph). The IR spectrum showed the absence of carbonyl frequency, and the band at 3300 cm^{-1} characteristic of a secondary alcohol was observed. Dehydration of the alcohol with pyridine and phosphorus oxychloride yielded 1-methyl-3-phenylcyclohex-4,6-diene (XXVI; Ar = Ph) as a colourless oil. Its IR spectrum was marked by the absence of OH absorption. Dehydrogenation with 10 per cent palladium on carbon at 250° for 6 hr did not give the required 3-methylbiphenyl (XXVII; Ar = Ph), but the starting material was recovered. However, when dehydrogenation was carried out with chloranil in boiling benzene, the desired biphenyl (XXVII; Ar = Ph) was obtained in quantitative yield.



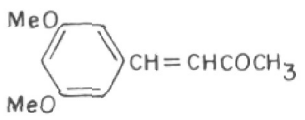
XXIV *a*

Substitution in one nucleus of a diaryl can be modified by starting with a suitably substituted aromatic aldehyde, and the limitations of this method of synthesis of unsymmetrically substituted diaryls are decided by the difficulties in the synthesis of the aldehyde.

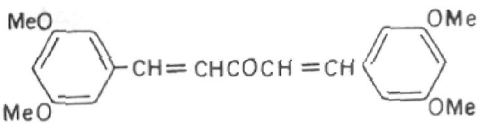
3,5-Dimethoxybenzaldehyde (XXVIII),[76] prepared by the Rosenmund reduction of 3,5-dimethoxybenzoyl chloride, was condensed with acetone to give XXIX as a low-melting solid, which was fractionated under reduced pressure. The first fraction obtained was 3,5-dimethoxybenzylideneacetone (XXIX), which crystallized from hexane in colourless needles, m.p. 72°. Its IR spectrum showed the $\alpha\beta$-unsaturated carbonyl peak at 1666 cm^{-1}. It was also characterized as its 2,4-dinitrophenylhydrazone derivative. The residue, which was a viscous oil, crystallized after keeping in contact with hexane for several days. This substance, m.p. 133°, was identified as the bisbenzylideneacetone derivative (XXX). The compound (XXX) was also characterized as its 2,4-dinitrophenylhydrazone derivative.



XXVIII

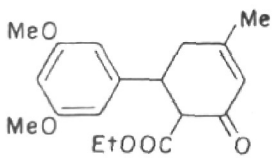


XXIX

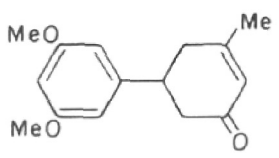


XXX

The Michael addition of XXIX with ethyl acetoacetate yielded the β-keto-ester (XXXI) in 70 per cent yield. The IR absorption spectrum of XXXI showed the carbonyl frequency of the carbethoxy group at 1729 cm^{-1} and the carbonyl frequency of the α,β-unsaturated ketone at 1656 cm^{-1}. The ketone XXXI was also characterized as its 2,4-dinitrophenylhydrazone derivative. The ester XXXI on hydrolysis with ethanolic potassium hydroxide and subsequent acidification decarboxylated to give the ketone XXXII. As observed with the ketone XXIV, the spectrum showed a shift of the α,β-unsaturated carbonyl to 1647 cm^{-1}. The ketone XXXII was also characterized as its 2,4-dinitrophenylhydrazone derivative.



XXXI

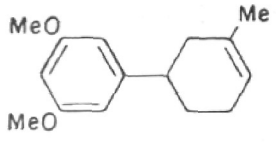


XXXII

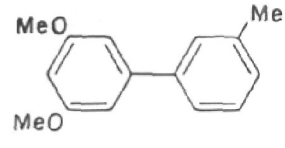
In one of the experiments the cyclization, hydrolysis and decarboxylation of the ketone XXIX to give XXXII were tried in one step. It was observed that the yield of the ketone XXXII obtained by this modification was about 85 per cent and that there was no need to isolate the keto-ester XXXI.

Clemmensen reduction of the ketone XXXII gave 1-methyl-3(3,5-dimethoxyphenyl)cyclohex-6-ene (XXXIII) as an oil,

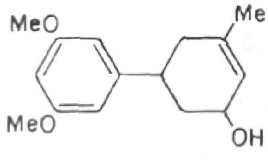
and the IR spectrum showed that it still contained traces of unreduced ketone. It was therefore treated with Girard Reagent P to remove the residual ketone XXXII; the product showed the absence of carbonyl frequency in the IR spectrum and analysed correctly for XXXIII. Dehydrogenation of XXXIII to 3,5-dimethoxy-3'-methylbiphenyl (XXXIV) with palladium on carbon in p-cymene or with 10 per cent palladium on carbon at 250° was unsuccessful. Attempts were therefore made to reduce the ketone XXXII with sodium borohydride to the corresponding alcohol XXXV. It was found that the oil obtained after reduction polymerized during distillation to a colourless glass, not melting below 350°, and insoluble in the common organic solvents. However, it was observed that the ketone XXXII on reduction with lithium aluminium hydride gave the alcohol XXXV as colourless needles, m.p. 92°. The IR spectrum showed the characteristic OH peak of a secondary alcohol at 3325 cm^{-1}.



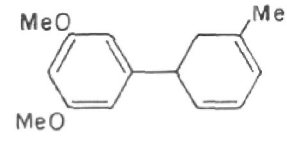
XXXIII



XXXIV



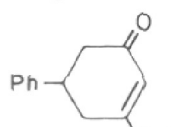
XXXV



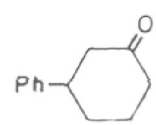
XXXVI

The alcohol XXXV on dehydration with pyridine and phosphorus oxychloride yielded the cyclohexadiene XXXVI as a colourless oil. Its IR spectrum showed the absence of hydroxyl. Dehydrogenation of XXXVI with chloranil in boiling benzene gave an almost quantitative yield of 3,5-dimethoxy-3'-methylbiphenyl (XXXIV).

The next attempt was then directed towards the synthesis of m-terphenyl. FRANCE, HEILBRON and HEY[77] have synthesized m-terphenyl by two methods and they have also reviewed all the earlier work on the synthesis of m-terphenyl. Their first synthesis consisted of the Michael condensation of benzalacetone with malonic ester to the phenyldihydroresorcinol (XXXVII), which was then converted



XXXVII

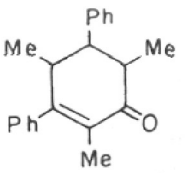


XXXVIII

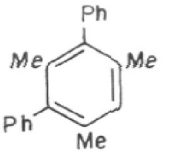
to 3-phenylcyclohexanone (XXXVIII) by successive treatment with phosphorus trichloride and reduction with sodium in moist ether. The Grignard reaction between XXXVIII and phenyl magnesium bromide gave a tertiary alcohol, which was dehydrated with formic acid and dehydrogenated with sulphur in boiling quinoline to m-terphenyl in an overall yield of 15 per cent. In their second synthesis 3-nitrobiphenyl was prepared by the interaction of nitroso-m-nitroacetanilide with benzene, reduced to amine, acetylated,

nitrosoated and again treated with benzene in an overall yield of 10 per cent based on m-nitroacetanilide. FRANCE, HEILBRON and HEY[78] have also synthesized m-terphenyl in 23 per cent yield from the N-acetyl-N-nitroso derivative of m-phenylenediamine. m-Terphenyl is formed (29 per cent yield) by the action of phenyllithium on m-dichlorobenzene.[79] The reaction of aryl halides with phenyllithium takes place with piperidine as catalyst. Thus 4-chlorobiphenyl gives 56 per cent m- and 44 per cent p-terphenyl.[80]

LANGER and WEISELY[81] condensed α-benzalpropiophenone with diethyl ketone in presence of sodium methoxide and obtained a 60-70 per cent yield of XXXIX; the ketone was reduced to the secondary alcohol by sodium in moist ether and then dehydrogenated by palladium on carbon at 300-320° to 1,3,5-trimethyl-2,4-diphenylbenzene (XL).



XXXIX

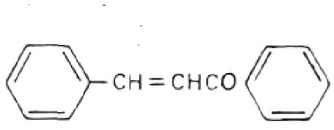


XL

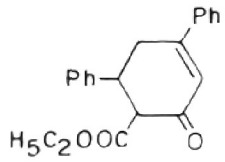
AMES and DAVEY[82] have developed a route to p-terphenyls by the Michael addition of diethyl malonate to benzyl styryl ketone.

The new synthesis described in the present work consisted of the same sequence of reactions as that followed for

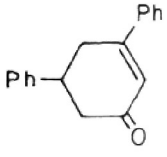
the synthesis of 3-methylbiphenyl (XXVII) and 3,5-dimethoxy-3'-methylbiphenyl (XXXIV). Michael addition of the chalkone XLI with ethyl acetoacetate afforded the keto-ester XLII,[74] which on hydrolysis with ethanolic potassium hydroxide, yielded the ketone XLIII. On reduction of XLIII with lithium aluminium hydride, the corresponding alcohol XLIV was obtained in quantitative yield. Dehydration of the alcohol with phosphorus oxychloride and pyridine gave in about 60 per cent yield the diene XLV, which was aromatized to m-terphenyl (XLVI) with 10 per cent palladium on carbon at 290-310° in nearly quantitative yield.



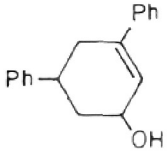
XLI



XLII



XLIII



XLIV

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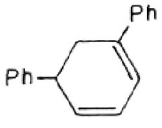
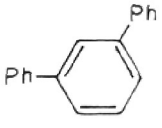


XLV



XLVI

EXPERIMENTAL

Benzylideneacetone

Benzylideneacetone was prepared according to the method given in Org. Synth.[83]

Ethyl-3-methyl-5-phenyl-6-carbethoxy-2-cyclohexen-1-one (XIX; Ar = Ph)

A mixture of benzylideneacetone (14.6 g), ethyl acetoacetate (13 g), absolute ethanol (150 ml), and piperidine (2 g) was refluxed on a steam-bath for 72 hr under anhydrous conditions. The ethanol was removed under reduced pressure on a steam-bath and the pale-yellow oil on distillation under reduced pressure gave first a minor fraction (3 g), b.p. 120-140°/1.0 mm, and a second fraction (12 g), b.p. 160-165°/1.0 mm. The second fraction was redistilled at 160-165°/1.0 mm. (Found: C, 74.8; H, 7.0. $C_{16}H_{18}O_3$ requires: C, 74.4; H, 7.0%).

The 2,4-dinitrophenylhydrazone derivative of the second fraction was prepared and crystallized from methanol in orange needles, m.p. 172°. (Found: C, 60.4; H, 5.1; N, 12.8. $C_{22}H_{22}N_4O_6$ requires: C, 60.3; H, 5.1; N, 12.8%).

3-Methyl-5-phenyl-2-cyclohexen-1-one (XXIV; Ar = Ph)

A mixture of the ester (XIX; 11.1 g) and potassium hydroxide (6.6 g) in ethanol (150 ml) was refluxed on a

steam-bath for 5 hr. The solvent was removed under reduced pressure, and water (100 ml) was added to the residue and acidified with conc hydrochloric acid. The solution was extracted with ether (3 x 120 ml). The ether extract was washed with aqueous sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a pale-yellow oil, which was purified by distillation under reduced pressure. A colourless oil was obtained (7.1 g) at 155° (air-bath temp)/0.5 mm, which crystallized on keeping in contact with hexane at 10°, m.p. 30°. (Found: C, 84.2; H, 7.7. $C_{13}H_{14}O$ requires: C, 83.8; H, 7.6%).

The 2,4-dinitrophenylhydrazone derivative was prepared, which was crystallized from a mixture of ethyl acetate-hexane in red prisms, m.p. 170°. (Found: C, 62.0; H, 4.8; N, 14.9. $C_{19}H_{18}N_4O_4$ requires: C, 62.3; H, 4.9; N, 15.3%).

1-Methyl-3-phenylcyclohex-6-ene (XXIVa)

The ketone (XXIV; 1 g) was dissolved in 50% ethanol (30 ml) added to a mixture of amalgamated zinc (6 g), and conc hydrochloric acid (2 ml). The reaction mixture was refluxed on a steam-bath for 16 hr. On cooling and treatment with water (80 ml) it was extracted with ether.

The ether extract, after washing with aqueous sodium bicarbonate and water, was dried over anhydrous sodium sulphate. Removal of the ether yielded a pale-yellow viscous oil (0.7 g), which was distilled at 240-250°/0.1 mm to give a nearly colourless viscous oil. (Found: C, 86.8; H, 9.0. $C_{13}H_{16}$ requires: C, 90.6; H, 9.3%).

3-Methyl-5-phenyl-2-cyclohexen-1-ol (XXV; Ar = Ph)

The ketone (XXIV; 5 g) in methanol (30 ml) was added to sodium borohydride (2 g) in methanol (40 ml) at 0° over a period of 30 min under vigorous stirring. The reaction mixture was gently refluxed for 3 hr, cooled, and the excess of sodium borohydride was decomposed by dil hydrochloric acid. The methanol was removed by distillation and the reaction mixture was cooled and extracted with ether. The ether extract was washed with aqueous sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. After evaporating off the excess ether, the residue was distilled at 95-100°/2 mm to give a colourless liquid (4.2 g). (Found: C, 83.3; H, 8.8. $C_{13}H_{16}O$ requires: C, 82.9; H, 8.6%).

1-Methyl-3-phenylcyclohex-4,6-diene (XXVI; Ar = Ph)

To a solution of the alcohol (XXV; 3.8 g) in pyridine (12 g) was added phosphorus oxychloride (2.5 ml)

at 0° and the reaction mixture was left overnight at room temp (28°). It was then heated on a steam-bath for 2 hr, cooled, and poured over crushed ice (35 g). On extraction with benzene and washing the benzene extract with dil hydrochloric acid followed by dil sodium hydroxide solution (2%) and water, it was dried over calcium chloride. The excess of benzene was removed and the residual brown coloured oil was distilled at 120-125° (oil-bath temp)/2 mm to yield a colourless oil (2.9 g). (Found: C, 91.5; H, 8.0. $C_{13}H_{14}$ requires: C, 91.7; H, 8.3%).

3-Methylbiphenyl (XXVII; Ar = Ph)

To the compound (XXVI; 2.5 g) in anhydrous benzene (30 ml) was added chloranil (4 g), and the mixture was refluxed on a steam-bath for 72 hr. On cooling a solid separated out, which was filtered off and the benzene solution concentrated to 10 ml and percolated through a column of alumina (30 x 2.5 cm) and eluted with hexane (250 ml). The colourless eluate was distilled to remove the hexane, and the pale-yellow oil obtained was distilled at 88-90°/0.7 mm to give a colourless oil (2.2 g). (Found: C, 92.7; H, 7.4. Calc. for $C_{13}H_{12}$: C, 92.8; H, 7.2%).

3,5-Dimethoxybenzaldehyde

3,5-Dimethoxybenzaldehyde was prepared by the Rosenmund reduction of 3,5-dimethoxybenzoyl chloride.[76]

3,5-Dimethoxybenzylideneacetone (XXIX)

A 10% solution of aqueous sodium hydroxide (3.5 ml) was added gradually over a period of 10 min to a vigorously stirred mixture of 3,5-dimethoxybenzaldehyde (13 g), acetone (30 ml) and water (15 ml) maintained between 25-30°. On further stirring at room temp (28°) for 3 hr, a light-yellow solid separated. The reaction mixture was acidified with dil hydrochloric acid and filtered. The residue was washed with water, dried and combined with the benzene extract (4 x 50 ml) of the filtrate.

After removal of benzene on a steam-bath, the oily product was fractionated with the following fractions:

Fraction I (1.9 g), b.p. 125°/1 mm. This was not examined further.

Fraction II (12.6 g), b.p. 164°/1 mm. This product solidified on cooling and was crystallized from hexane in colourless needles, m.p. 72°. (Found: C, 69.6; H, 6.6. $C_{12}H_{14}O_3$ requires: C, 69.9; H, 6.8%).

The 2,4-dinitrophenylhydrazone derivative crystallized from dimethylformamide in orange needles, m.p. 220°.

(Found: C, 55.8; H, 4.7; N, 14.3. $C_{18}H_{18}N_4O_6$ requires: C, 55.9; H, 4.7; N, 14.5%).

Fraction III (XXX). The residual oil (3.4 g) did not distil below 220°/1 mm. This oil on keeping in contact with hexane for several days solidified. It was filtered and crystallized from benzene in pale greenish-yellow plates (3 g), m.p. 133°. (Found: C, 71.6; H, 6.4. $C_{21}H_{22}O_5$ requires: C, 71.2; H, 6.2%).

The 2,4-dinitrophenylhydrazone derivative crystallized from dimethylformamide in bright red needles, m.p. 213°. (Found: N, 10.8. $C_{27}H_{26}N_4O_8$ requires: N, 10.5%).

Ethyl-3-methyl-5(3,5-dimethoxyphenyl)-6-carbethoxy-2-cyclohexen-1-one (XXXI)

A mixture of 3,5-dimethoxybenzylideneacetone (XXIX; 10.2 g), ethyl acetoacetate (8 ml), piperidine (0.5 ml) and absolute ethanol (75 ml) was refluxed for 72 hr. The light red viscous oil which was obtained on removal of the solvent was distilled under reduced pressure and the following fractions were obtained:

Fraction I (0.5 g), up to 130°/10^{-2} mm, discarded.

Fraction II (2.5 g), 147-150°/10^{-2} mm, discarded.

Fraction III (11.9 g), 170-175°/10^{-2} mm. This was redistilled at 170-175°/10^{-2} mm to give a colourless oil.

(Found: C, 68.0; H, 7.1. $C_{18}H_{22}O_5$ requires: C, 67.9; H, 7.0%).

The 2,4-dinitrophenylhydrazone derivative was prepared and crystallized from ethyl acetate in dark-orange needles, m.p. 219°. (Found: N, 11.5. $C_{24}H_{26}O_8N_4$ requires: N, 11.2%).

3-Methyl-5(3,5-dimethoxyphenyl)-2-cyclohexen-1-one (XXXII)

The mixture of ester (XXXI; 1.3 g) and ethanolic potassium hydroxide (1.2 g) in ethanol (12 ml) was refluxed on a steam-bath for 5 hr. The excess of ethanol was distilled off at the water-pump pressure and the oil obtained was mixed with water (10 ml) and acidified with conc hydrochloric acid (acid to Congo Red). On addition of ice the oil solidified. It was filtered off, washed free of acid with water and crystallized from a mixture of benzene-hexane in long colourless needles (0.8 g), m.p. 92°. (Found: C, 73.3; H, 7.0; OMe, 26.0. $C_{15}H_{18}O_3$ requires: C, 73.2; H, 7.3; OMe, 25.2%).

The 2,4-dinitrophenylhydrazone derivative was prepared and crystallized from a mixture of dimethylformamide-ethanol in bright red irregular plates, m.p. 210°. (Found: C, 59.1; H, 5.2; N, 13.4. $C_{21}H_{22}N_4O_6$ requires: C, 59.1; H, 5.2; N, 13.2%).

One-step cyclization and hydrolysis of XXXII

A mixture of 3,5-dimethoxybenzylideneacetone (XXIX; 5.1 g), ethyl acetoacetate (4.2 ml), piperidine (0.25 ml) in absolute ethanol was refluxed on a steam-bath for 72 hr. To the same flask was added ethanolic potassium hydroxide (3.0 g) in 50% ethanol (50 ml) and it was further refluxed for 5 hr. While the reaction mixture was still hot, hydrochloric acid was added to it gradually (excess frothing due to decarboxylation taking place) till acid to Congo Red. The reaction mixture was poured over crushed ice (250 g), when a yellow coloured solid separated out, filtered off, washed free of acid with water and crystallized from a mixture of benzene-hexane in long colourless needles (4.5 g), m.p. 92°. Mixed m.p. with the compound obtained in the previous experiment was undepressed.

1-Methyl-3(3,5-dimethoxyphenyl)cyclohex-6-ene (XXXIII)

The ketone (XXXII; 1 g) dissolved in ethanol (10 ml) was added to amalgamated zinc (prepared from 10 g of zinc wool), and the mixture refluxed on a steam-bath for 24 hr. After addition of hydrochloric acid (1:1; 5 ml), the reaction mixture was refluxed further for a period of 24 hr. On cooling and treating with water (40 ml), it

was extracted with ether. The ether extract was washed with aqueous sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. Distillation of ether gave a yellow oil. The IR spectrum of the compound so obtained showed the presence of a carbonyl at 1647 cm^{-1}. The oil was therefore taken up in a mixture of ethanol (45 ml), Girard Reagent P (200mg) and acetic acid (5 ml). The reaction mixture was refluxed on a steam-bath for 2 hr. The excess ethanol distilled off and the residue treated with water (50 ml) and extracted with ether (3 x 100 ml). The ether extract was washed with water, aqueous sodium hydroxide solution (2%), water and dried over anhydrous sodium sulphate. After evaporation of ether, the residue was distilled to a colourless oil (0.6 g) at 150-160° (air-bath temp)/0.1 mm. (Found: C, 77.3; H, 8.6. $C_{15}H_{20}O_2$ requires: C, 77.6; H, 8.6%). The IR spectrum showed absence of carbonyl band.

3-Methyl-5(3,5-dimethoxyphenyl)-2-cyclohexen-1-ol (XXXV)

A solution of the ketone (XXXII; 2.5 g) in dry ether (150 ml) was added to a refluxing solution of lithium aluminium hydride (1.8 g) in dry ether (150 ml) over a period of 30 min. The mixture was refluxed for 6 hr under stirring, cooled, decomposed by wet ether and cold dil sulphuric acid (25 ml; 20%). The ether extract was

separated and the aqueous phase extracted with ether (3 x 100 ml). The ether extract was washed with water, aqueous sodium bicarbonate solution, water and dried over anhydrous sodium sulphate. Distillation of ether gave an almost colourless oil, which solidified on addition of a few drops of hexane. Crystallization from hexane gave colourless needles (2.2 g), m.p. 92°. IR spectrum showed the presence of a hydroxyl peak at 3325 cm^{-1} and absence of a carbonyl band. (Found: C, 72.5; H, 8.2. $C_{15}H_{20}O_3$ requires: C, 72.5; H, 8.1%).

1-Methyl-3(3,5-dimethoxyphenyl)cyclohex-4,6-diene (XXXVI)

To the solution of alcohol (XXXV; 1.8 g) in pyridine (6 ml) was added phosphorus oxychloride (1.5 ml) at 0° over a period of 10 min. The reaction mixture was maintained at room temp (30°) for 3 hr and then heated on a steam-bath for 2 hr. The mixture after cooling was poured over crushed ice and extracted with benzene. The benzene extract was washed with water, aqueous sodium bicarbonate solution, water and dried over sodium sulphate. After evaporation of the benzene, the residue was distilled at 122-125°/0.1 mm to a colourless oil (1.1 g). (Found: C, 78.0; H, 7.8. $C_{15}H_{18}O_2$ requires: C, 78.2; H, 7.9%). The IR spectrum showed the absence of a hydroxyl group.

3,5-Dimethoxy-3'-methylbiphenyl (XXXIV)

To the compound (XXXVI; 0.8 g) in anhydrous benzene (15 ml) was added chloranil (1.8 g), and the mixture was refluxed on a steam-bath for 72 hr. On cooling, a solid separated out which was filtered off, and the benzene solution concentrated to 4 ml, percolated through a column of alumina (20 x 2.5 cm) and eluted with hexane. The colourless eluate (120 ml) was distilled to remove hexane, and the pale-yellow oil obtained was distilled at 115-116° (air-bath temp)/0.1 mm to give a colourless oil (0.6 g). (Found: C, 79.1; H, 7.2. $C_{15}H_{16}O_2$ requires: C, 78.9; H, 7.0%).

Ethyl 3,5-diphenyl-6-carbethoxy-2-cyclohexen-1-one (XLII)

Ethyl 3,5-diphenyl-6-carbethoxy-2-cyclohexen-1-one was prepared according to the method described by CONNOR and ANDREWS[74] and crystallized from ethanol in colourless needles, m.p. 116° (lit. 113°).[74] The 2,4-dinitrophenylhydrazone derivative was prepared and crystallized from a mixture of dimethylformamide-ethanol in dark-red needles, m.p. 202°. (Found: N, 10.4. $C_{29}H_{28}N_4O_8$ requires: N, 10.0%).

3,5-Diphenyl-2-cyclohexen-1-one (XLIII)

A mixture of (XLII; 25 g) and potassium hydroxide (12 g) in 95% ethanol (125 ml) was refluxed on a steam-bath

for 5 hr. The reaction mixture, after cooling, was acidified with conc hydrochloric acid and poured over crushed ice (300 g), when a brown coloured oil first obtained solidified on scratching. It was filtered off, washed free of acid with water and crystallized from ethanol in pale-yellow needles (16.5 g), m.p. 81°. (Found: C, 87.1; H, 6.4. $C_{18}H_{16}O$ requires: C, 87.1; H, 6.5%).

The 2,4-dinitrophenylhydrazone derivative was crystallized from a mixture of dimethylformamide-ethanol in red fibrous needles, m.p. 221°. (Found: N, 12.8. $C_{24}H_{20}N_4O_4$ requires: N, 13.1%).

3,5-Diphenyl-2-cyclohexen-1-ol (XLIV)

A solution of the ketone (XLIII; 6.5 g) in dry ether (200 ml) was added to the refluxing solution of lithium aluminium hydride (2.5 g) in dry ether (200 ml) over a period of 40 min. The reaction mixture was refluxed for 6 hr, cooled, and decomposed by moist ether, and cold sulphuric acid (35 ml; 20%). The ether extract was separated and the aqueous phase extracted with ether (4 x 100 ml). The ether extract was washed with water, aqueous sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. Distillation of ether gave a pale-yellow oil distilled at 140°/0.01 mm to a colourless

viscous oil (5.8 g). (Found: C, 86.7; H, 7.0; Active H, 1.0. $C_{18}H_{18}O$ requires: C, 86.4; H, 7.2; Active H, 1.0%).

1,3-Diphenylcyclohex-4,6-diene (XLV)

To a solution of alcohol (XLIV; 5 g) in pyridine (20 g) was added phosphorus oxychloride (8 ml) at 0° over a period of 10 min. The reaction mixture was left at room temp overnight and then heated on a steam-bath for 2 hr. The mixture after cooling was poured over crushed ice and extracted with benzene (3 x 120 ml). The benzene extract was washed with aqueous sodium bicarbonate solution and water, and dried over sodium sulphate. After evaporation of the benzene, the brown coloured residue distilled at 120°/10^{-3} mm to a colourless oil (3.8 g). (Found: C, 92.7; H, 7.1. $C_{18}H_{16}$ requires: C, 93.1; H, 6.9%).

m-Terphenyl (XLVI)

The mixture of (XLV; 3 g) and palladium on carbon (10%) (0.8 g) was heated at 290-310° for 12 hr. After cooling, the reaction mixture was treated with benzene (30 ml) and filtered. The residue was washed with hot benzene (60 ml). The filtrate and washings were taken to dryness, when a colourless crystalline solid was obtained. It was recrystallized from ethanol in colourless needles, m.p. 89° (lit. 89°)[77]. (Found: C, 93.9; H, 6.1. Calc. for $C_{18}H_{14}$: C, 93.9; H, 6.1%).

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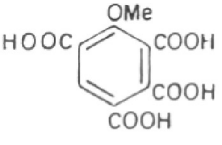
PART IV

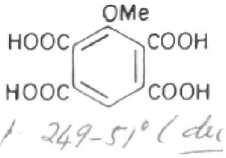
SYNTHESIS OF ANISOLE-2,3,4,5-TETRACARBOXYLIC ACID

Present work

In the course of a programme of work on the chemistry of naturally occurring quinones PATWARDHAN[14] isolated an anisoletetracarboxylic acid (A) by oxidation of an ether-ester obtained from laccaic acid, the major constituent of lac dye. There are three possible structures, I, II, and III for this acid.

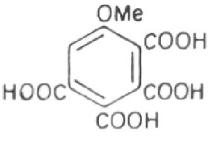


I



m.p. 249-51° (dec.)

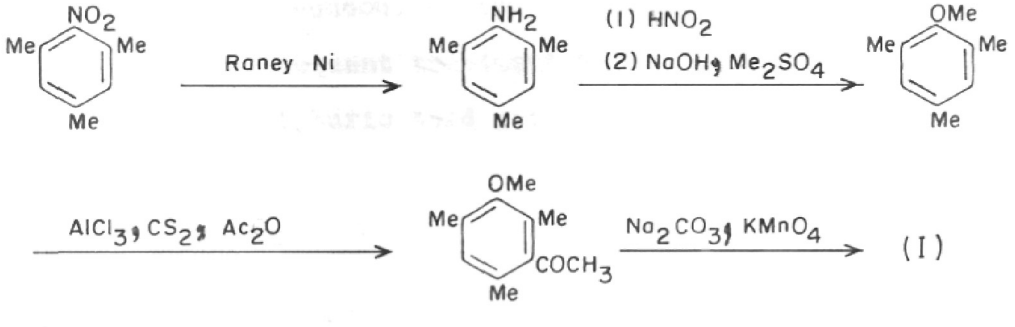
II



III

The acid I melting at 176-181° (dec), resetting at about 220° and remelting at 256° (dec), was isolated by RAISTRICK et al.[1] and GROVE[2] by alkaline potassium permanganate oxidation of dihydrogladiolic acid and gladiolic acid, the metabolic products of Penicillium gladioli Machacek. This was also synthesized by GROVE[2] from nitromesitylene by the series of reactions shown in Chart 1.

Chart 1



A second synthesis of the acid I was carried out by CHARLESWORTH et al.[3] from mesitylene by a modified method shown in Chart 2. The properties of the acid I were different from those of the acid A. The acid A had a higher m.p. (230°) and gave a solid tetramethyl ester (m.p. 104°), whereas the tetramethyl ester of the acid I was a liquid, b.p. 180-182°/10^{-2} mm.

The acid II, m.p. 250-251°, was first isolated by NIKUNI[4] by the alkaline permanganate oxidation of α-sorigenin methyl ether. As one of the reference compounds in connection with the identification of the acids obtained by the oxidation of purpurogenone, a metabolic product of Penicillium purpurogenum Stoll, the acid II was synthesized by ROBERTS[5] from m-5-xylenol (IV) by the series of reactions in Chart 3. The tetramethyl ester was not described. Hydroxymethylation of IV can yield the (V) as well as the 2,6-isomer; although the orientation of V was proved by FINN, LEWIS and MEGSON.[6] An unambiguous route to II, shown in Chart 4, was therefore first attempted in the present work.

Monochlorination of IV p- to the hydroxyl was effected by sulphuryl chloride in carbon tetrachloride at room temp. Methylation with aqueous sodium hydroxide and dimethyl sulphate and subsequent treatment with chloromethyl methyl ether in conc sulphuric acid gave the bischloromethyl

Chart 2

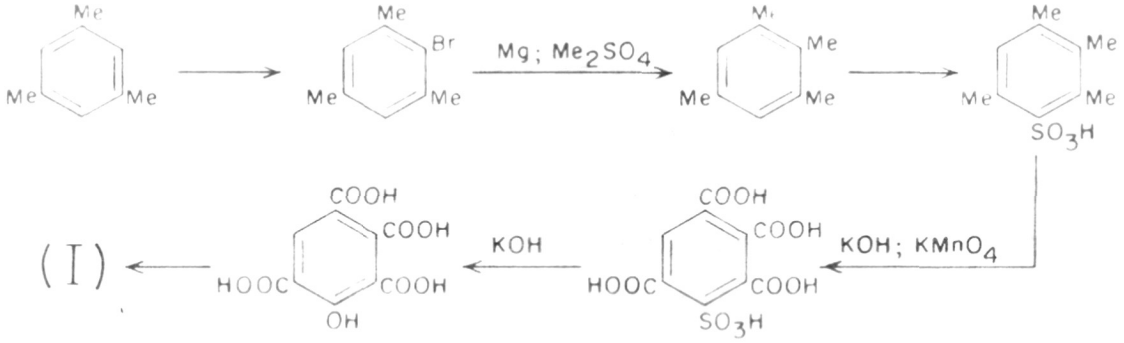


Chart 3

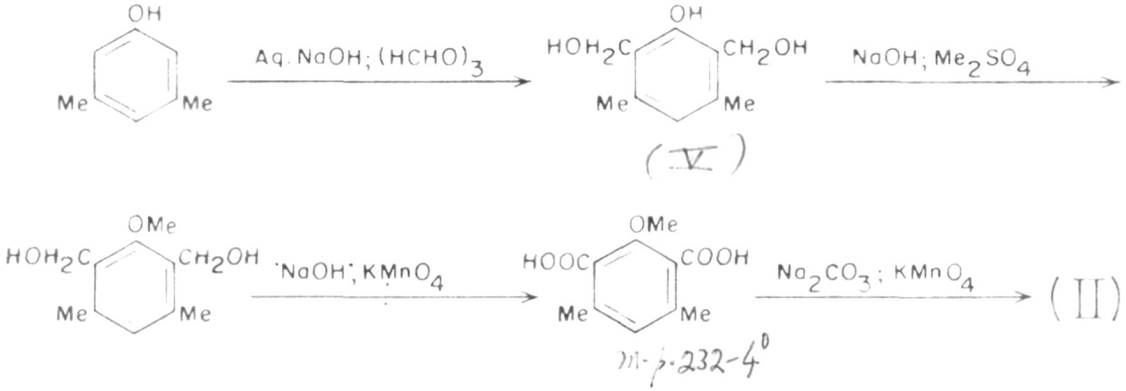
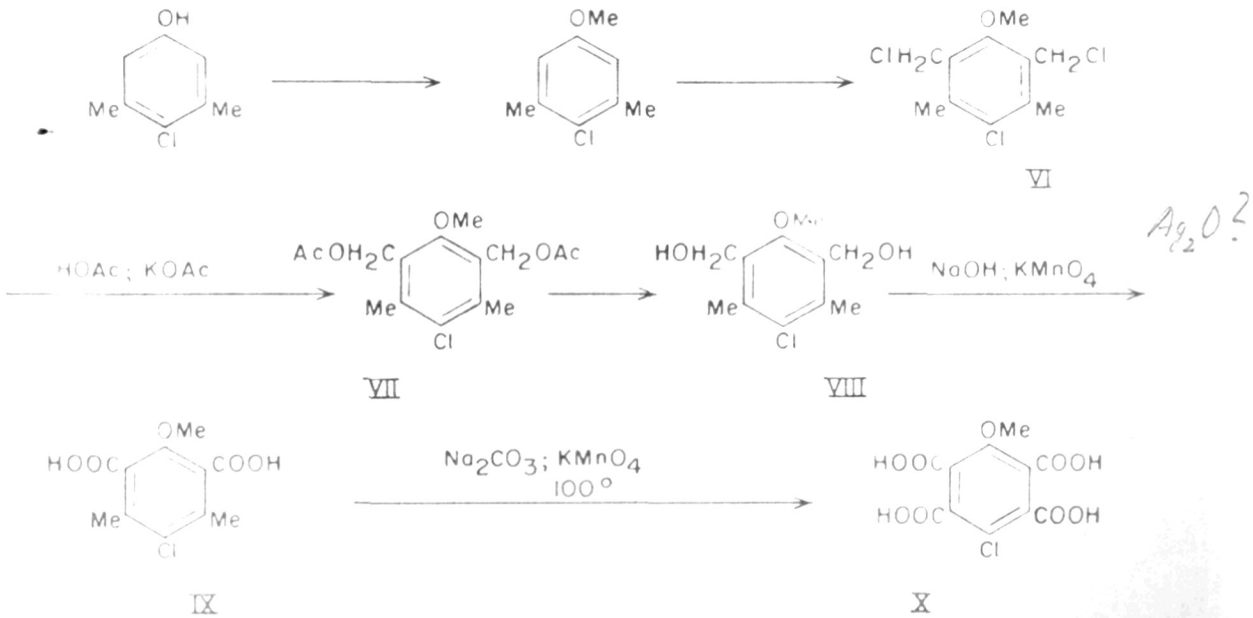


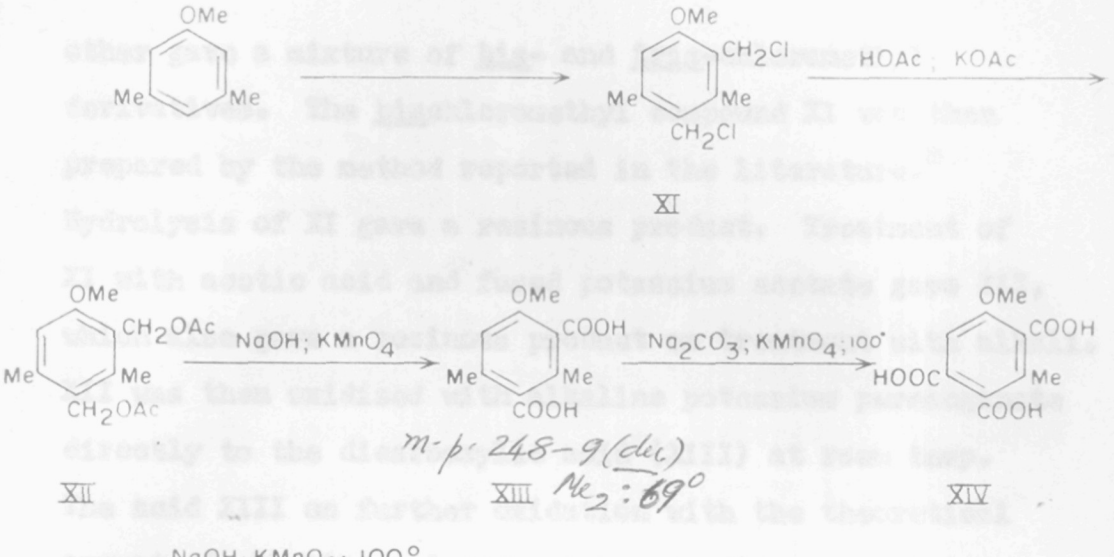
Chart 4



derivative (VI). Treatment of VI with acetic acid and potassium acetate gave VII, which on treatment with methanolic sodium hydroxide gave only a resinous compound. Attempted oxidation of VII with alkaline potassium permanganate at room temp left the compound unaffected. However, on treatment with aqueous sodium hydroxide in acetone solution VI hydrolysed to give VIII. On treatment with alkaline potassium permanganate at room temp VIII gave the dicarboxylic acid (IX). Further oxidation with alkaline potassium permanganate at 100° yielded the tetracarboxylic acid (X), which failed to undergo dehalogenation with Raney nickel in aqueous sodium hydroxide at room temp. The acid II was therefore synthesized by the procedure of ROBERTS,[5] and treatment with diazomethane in methanol yielded the tetramethyl ester, m.p. 103-104°.

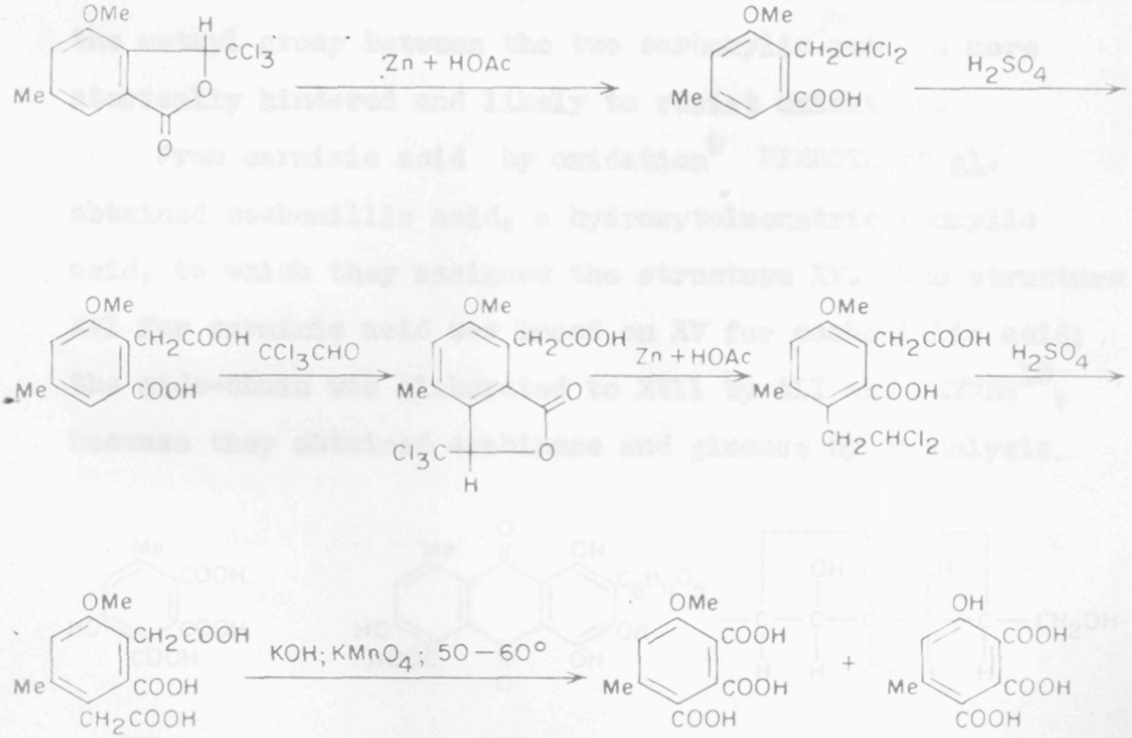
Since the acid II and its ester were found to be different from (A) and its ester, a synthesis of the unknown III was undertaken by the method outlined in Chart 5. Phenol-2,3,4,6-tetracarboxylic acid, m.p. 212-214°, has been reported by DIMROTH et al.[7] as a degradation product of laccaic acid, but extensive work in this laboratory has shown that DIMROTH was not dealing with a pure homogeneous pigment and that both the molecular formula and the structure assigned by him to his "laccaic acid" are erroneous. Chloromethylation of 3,5-dimethylanisole by treatment with chloromethyl methyl

Chart 5



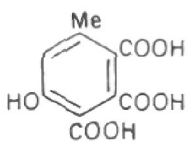
XI XII XIII XIV

Chart 6.

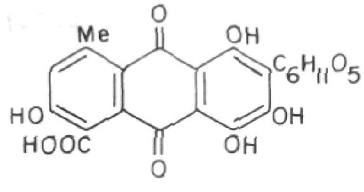


ether gave a mixture of bis- and tris-chloromethyl derivatives. The bischloromethyl compound XI was then prepared by the method reported in the literature.[8] Hydrolysis of XI gave a resinous product. Treatment of XI with acetic acid and fused potassium acetate gave XII, which also gave a resinous product on treatment with alkali. XII was then oxidized with alkaline potassium permanganate directly to the dicarboxylic acid (XIII) at room temp. The acid XIII on further oxidation with the theoretical amount of alkaline potassium permanganate gave a tricarboxylic acid instead of the expected tetracarboxylic acid (III). This acid obviously has the constitution XIV since the methyl group between the two carboxylic groups is more sterically hindered and likely to resist oxidation.

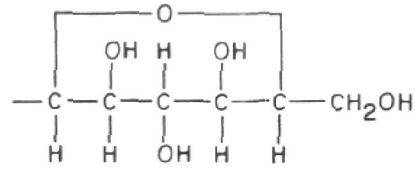
From carminic acid by oxidation[9] DIMROTH et al. obtained cochenillic acid, a hydroxytoluenetricarboxylic acid, to which they assigned the structure XV. The structure XVI for carminic acid was based on XV for cochenillic acid; the side-chain was elaborated to XVII by ALI and HEYNES[10], because they obtained arabinose and glucose by ozonolysis.



XV



XVI



XVII

MELDRUM and VAIDYANATHAN[11] synthesized both XV and its methyl ether by the series of reactions shown in Chart 6 and stated that the synthetic compound of the structure XV was identical with cochenillic acid in m.p. and mixed m.p.; but the mixed m.p. of the two methyl ethers was not recorded, though the authors state that the two resembled each other. Recently OVEREEM[12] has claimed that the methyl ether of cochenillic acid has the structure XIV. He has stated that he has synthesized both XIV and the methyl ether of XV by unambiguous methods; but these have not been indicated. An authentic sample of the methyl ether of cochenillic acid is now being prepared from carminic acid for direct comparison with XIV synthesized in the present work. The trimethyl ester of XIV has the m.p. 110-111°, and LANDAU[13] has quoted m.p. 111-113° for the methyl ether-ester of cochenillic acid.

The acid XIV on further treatment with alkaline potassium permanganate gave the desired acid III, the tetramethyl ester of which, obtained by treatment with diazomethane, was found to be identical with the tetramethyl ester of anisoletetracarboxylic acid from the oxidation of laccaic acid.

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

3,5-Dimethyl-4-chlorophenol and 3,5-dimethyl-4-chloroanisole

3,5-Dimethyl-4-chlorophenol was prepared by the action of sulphuryl chloride on m-xylenol according to the method described in literature, m.p. 119° (lit. m.p. 119°).[15] 3,5-Dimethyl-4-chloroanisole was prepared by the action of dimethyl sulphate in alkali on 3,5-dimethyl-4-chlorophenol by the same method.

3,5-Dimethyl-4-chloro-2,6-bischloromethyl anisole (VI)

3,5-Dimethyl-4-chloroanisole (50 g) was added to a mixture of conc sulphuric acid (30 g) and chloromethyl methyl ether (110 g) dropwise, maintaining the reaction temperature at 0° in the course of one hour under vigorous stirring. During the addition some solid separated out. Stirring was continued for an hr more after the addition was complete. The reaction mixture was diluted with ice-cold water (150 g) and the solid so obtained was filtered, washed free of acid with water and crystallized from hexane in colourless needles, m.p. 116°. (Found: C, 49.4; H, 5.1; Cl, 40.3. $C_{11}H_{13}O_3Cl$ requires: C, 49.6; H, 4.9; Cl, 39.9%).

3,5-Dimethyl-4-chloro-2,6-bisacetoxymethyl anisole (VII)

A mixture of (VI; 5 g), glacial acetic acid (80 ml) and fused potassium acetate (10 g) was refluxed for 5 hr.

The reaction mixture was cooled and poured into cold water (300 ml), when a white solid precipitated out. This was filtered, washed with water and dried. Crystallization from dil acetic acid gave white needles (4.8 g), m.p. 118°. (Found: C, 5.7; H, 6.0; Cl, 10.4. $C_{15}H_{19}O_5Cl$ requires: C, 57.3; H, 6.0; Cl, 10.1%).

3,5-Dimethyl-4-chloro-2,6-bishydroxymethyl anisole (VIII)

A mixture of (VII; 5 g), acetone (100 ml) and aqueous sodium hydroxide (2%; 200 ml) was refluxed on a steam-bath for 14 hr. The acetone was distilled off, and after cooling, the reaction mixture was acidified with conc hydrochloric acid, when a solid precipitate was obtained, which was filtered and crystallized from dil acetone in colourless needles (2.5 g), m.p. 181-182°. (Found: C, 57.7; H, 6.8; Cl, 15.6. $C_{11}H_{15}O_3Cl$ requires: C, 57.4; H, 6.5; Cl, 15.7%).

3,5-Dimethyl-4-chloro-2,6-dicarboxyanisole (IX)

The above compound (VIII; 5.7 g), well powdered, was suspended in aqueous solution of sodium hydroxide (2N; 24 ml) and to it was added potassium permanganate (8 g in 120 ml of water) and the mixture shaken at room temp (28°) for 15 min and then heated on a steam-bath for 45 min. The excess permanganate was destroyed by the addition of a few drops of ethanol, and manganese dioxide was destroyed by passing in sulphur dioxide gas, cooled and filtered (residue was

insoluble in sodium bicarbonate solution). The filtrate was acidified with conc hydrochloric acid and left overnight in a refrigerator. Colourless crystals which separated out were filtered and recrystallized from acidulated water (4.5 g), m.p. 192°. (Found: C, 51.0; H, 4.5; Cl, 13.5; N.E. 133. $C_{11}H_{11}O_5Cl$ requires: C, 51.2; H, 4.2; Cl, 13.5; N.E. 129%).

Anisole-4-chloro-2,3,5,6-tetracarboxylic acid (X)

The acid (IX; 1.2 g) was dissolved in aqueous sodium bicarbonate solution (2N; 18 ml) and to it was added potassium permanganate solution (4.33 g in 60 ml of water) and the mixture heated on a steam-bath for 4 hr. The excess permanganate was destroyed with few drops of ethanol. The reaction mixture was filtered and the residue washed with hot water (20 ml). The filtrate and washings were concentrated under reduced pressure to 10 ml, acidified with conc hydrochloric acid and left in the refrigerator for 48 hr, when a solid separated out. Crystallization from a mixture of water-conc hydrochloric acid gave colourless rhombic crystals (0.6 g), m.p. softens at 247° and melts at 256-257°. (Found: C, 41.7; H, 2.5; Cl; 11.0; N.E. 80. $C_{11}H_7O_9Cl$ requires: C, 41.4; H, 2.2; Cl, 11.5; N.E. 80%).

The methyl ester was prepared by treatment with diazomethane and it crystallized from a mixture of benzene-

hexane in colourless needles, m.p. 99°.

Anisole-2,3,5,6-tetracarboxylic acid (II)

Anisole-2,3,5,6-tetracarboxylic acid was prepared according to the method of ROBERTS.[5] The tetramethyl ester of the acid II was prepared and crystallized from a mixture of benzene-hexane, m.p. 103-104°. (Found: C, 52.6; H, 4.8. $C_{15}H_{16}O_9$ requires: C, 52.9; H, 4.7%). The mixed m.p. with the acid obtained by degradation of laccaic acid, m.p. 105°, was depressed to 90°).

Chloromethylation of 3,5-dimethylanisole

(a) 3,5-Dimethylanisole (20 g) was added dropwise to a vigorously-stirred mixture of chloromethyl methyl ether (20 g) and conc sulphuric acid (100 g) at 0° in the course of 1 hr. The colour of the reaction mixture was initially yellow and it turned light-red and then dark-brown. During the addition, separation of some solid was observed. After the completion of addition, HCl gas was passed into the reaction mixture for ½ hr, still maintaining the temperature at 0°. Then the reaction mixture was poured over crushed ice, when a gritty brown solid separated. The product was filtered, washed free of acid and dried (28 g). Crystallization from benzene-hexane mixture gave yellow needles (20 g), m.p. 120°. (Found: C, 50.3; H, 5.8; Cl, 34.6. Calc. for $C_{11}H_{14}OCl_2$: C, 56.4; H, 6.0; Cl, 30.0%).

(b) 3,5-Dimethyl-2,4-bischloromethylanisole (XI)[8]

Dry hydrogen chloride gas was passed through a mixture of 3,5-dimethylanisole (25 g), conc HCl (18 g), paraformaldehyde (12 g) and carbon tetrachloride (90 g) at room temp (26°) under vigorous stirring for 5 hr and then at 60-70° for 2 hr. The semi-solid reaction product obtained was poured over crushed ice, when a light gritty brown solid separated. It was filtered, washed free of acid, dried and crystallized from benzene in colourless needles (25 g), m.p. 136° (lit. 135-137°).[8] (Found: C, 56.5; H, 6.3; Cl, 30.2. Calc. for $C_{11}H_{14}OCl_2$: C, 56.4; H, 6.0; Cl, 30.0%).

2,4-Bisacetoxymethyl-3,5-dimethylanisole (XII)

2,4-Bischloromethyl-3,5-dimethylanisole (XI; 5 g), acetic acid (80 ml) and fused potassium acetate (10 g) were refluxed gently for 5 hr. The reaction mixture was cooled and poured into cold water (300 ml), when a white solid precipitated out. This was filtered, washed with water, and dried. Crystallization from dil acetic acid gave colourless needles (5 g), m.p. 87°. (Found: C, 64.7; H, 7.4. $C_{15}H_{20}O_5$ requires: C, 64.3; H, 7.2%).

6-Methoxy-2,4-dimethyl-isophthalic acid (V):—
~~Anisole-3,5-dimethyl-2,4-dicarboxylic acid (XIV)~~

The above diacetate (XII; 4 g) was suspended in 2N sodium hydroxide solution (50 ml) and to it was added potassium permanganate (6.6 g in 100 ml of water). The reaction

mixture was left at room temp for 3 hr and then heated on a steam-bath for 10 min. The excess permanganate was destroyed with ~~drops of~~ ethanol, and manganese dioxide was destroyed by passing in sulphur dioxide ~~gas~~ till the solution was clear. The reaction mixture was cooled and filtered. ~~(The residue was insoluble in bicarbonate solution).~~ The filtrate was acidified with conc hydrochloric acid and left overnight in a refrigerator. The precipitate ~~which separated out was filtered and~~ crystallized from water in colourless ~~crystals~~ needles (2.4 g), m.p. 248-249° (dec). (Found: C, 58.9; H, 5.5; N.E. 112. $C_{11}H_{12}O_5$ requires: C, 58.9; H, 5.4; N.E. 112%).

The methyl ester, ~~was~~ obtained by treatment with diazomethane, ~~and it~~ crystallized from hexane in colourless needles, m.p. 69°. (Found: C, 61.7; H, 6.7. $C_{13}H_{16}O_5$ requires: C, 61.8; H, 6.3%).

5-Methoxytoluene-2,3,6-~~Diols-3-methyl-3,4,5-~~tricarboxylic acid (~~XIV~~ I)

To the acid (~~XIII~~ V; 170 mg) in sodium carbonate (2N; 1.5 ml) was added a warm solution of potassium permanganate (480 mg) in water (10 ml), and the mixture heated on a steam-bath for 3 hr. Excess permanganate was destroyed by the addition of a few drops of ethanol. The solution was filtered and the residue washed with hot water (3 x 5 ml). The filtrate was concentrated under

reduce pressure
vacuum to 2.5 ml, and acidified with conc hydrochloric acid, and left in a refrigerator overnight, when colourless crystals separated out. Recrystallization from acidulated water gave colourless needles (80 mg) which softened at 183°, resolidified and remelted at 213°. (Found: C, 52.4; H, 4.3; N.E. 85. $C_{11}H_{10}O_7$ requires: C, 52.0; H, 4.0; N.E. 85%). (A)

The methyl ester, was prepared by treatment with diazomethane and it crystallized from a mixture of benzene-hexane in colourless needles, m.p. 110-111° (lit. 110°), (Found: C, 56.6; H, 5.5; OMe, 41.7. $C_{14}H_{16}O_7$ requires: C, 56.8; H, 5.4; OMe, 41.8%).

Anisole-2,3,4,5-tetracarboxylic acid (III)

The acid (XIV; 1.5 g) was dissolved in aqueous solution of sodium hydroxide (1.5 g in water, 10 ml) and to it was added a warm solution of potassium permanganate (2.8 g; excess) in water (30 ml), and the mixture heated on a steam-bath for 6 hr. Excess permanganate was destroyed by addition of a few drops of ethanol and filtered. The residue was washed with hot water (4 x 5 ml) and the filtrate acidified with conc HCl. The acidified solution was concentrated under vacuum to 15 ml, saturated with sodium chloride and thoroughly extracted with ethyl acetate (5 x 60 ml). The ethyl acetate extract was dried over sodium sulphate and filtered. Distillation of the

(A) Acc. to Overeem & van der Kerk, the ester sublimes at 200° & softens, finally melting at 228-230°; in an oil-bath preheated at 190° the m.p. was about 200°. PTO

solvent gave a crystalline solid; recrystallization from acidulated water gave colourless prisms (0.6 g), m.p. 216-217° (dec). (Found: C, 46.9; H, 3.2; N.E. 73.8. $C_{11}H_8O_9$ requires: C, 46.5; H, 3.0; N.E. 71.0%).

The methyl ester, ~~was~~ prepared by treatment with diazomethane, ~~on the above acid and~~ crystallized from ~~a mixture~~ of benzene-hexane in colourless needles, m.p. 105°. (Found: C, 52.9; H, 4.9. $C_{15}H_{16}O_9$ requires: C, 52.9; H, 4.7%). Mixed m.p. with the acid obtained by the degradation of laccaic acid, m.p. 105°, was undepressed.

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SUMMARY

Part I. A total synthesis of citrinin

The present work was undertaken to achieve a total synthesis of citrinin, because the synthesis recorded by ROBERTSON can only be regarded as a partial or formal synthesis, and also to develop procedures for the synthesis of analogues of citrinin which may be less toxic and have more powerful antibacterial properties than citrinin.

A total synthesis of citrinin has now been effected (Chart 3), starting from ethyl 3,5-dihydroxyphenylacetate (XIX), which in turn was prepared from citric acid. The method now devised is entirely different, except at the stage of carboxylation of the phenolic alcohol (XXVII), from either of the two methods of ROBERTSON. The Gattermann-Adams reaction on XIX gave ethyl 2-aldehydo-3,5-dihydroxyphenylacetate (XX). Clemmensen reduction of XX yielded ethyl 3,5-dihydroxy-*o*-tolylacetate (XXI), which was benzylated by means of benzyl chloride and potassium carbonate in acetone, and hydrolysed with alkali to 3,5-dibenzyloxy-*o*-tolylacetic acid (XXIII). The acid (XXIII) on treatment with methyllithium yielded 3,5-dibenzyloxy-*o*-tolylacetone (XXIV). *C*-Methylation of the ketone (XXIV) was effected with sodium hydroxide

and methyl iodide to give methyl α-(3,5-dibenzyloxy-o-tolyl)ethyl ketone (XXV). Reduction of the ketone XXV with lithium aluminium hydride yielded methyl α-(3,5-dibenzyloxy-o-tolyl)ethylcarbinol (XXVI). Hydrogenolysis of XXVI in presence of palladium on carbon gave α-(3,5-dihydroxy-o-tolyl)ethylcarbinol (XXVII). Carboxylation of XXVII in glycerine, potassium hydrogen carbonate and carbon dioxide at 150-155° gave 2,6-dihydroxy-4-methyl-5-(α-methyl-β-hydroxy-n-propyl)benzoic acid (XII), which on cyclization with ethyl orthoformate gave citrinin. The synthetic citrinin (optically inactive) was identical with natural l-citrinin in its m.p., mixed m.p., UV absorption spectrum (Fig. 7) and IR spectrum in carbon tetrachloride (Fig. 6). The IR spectra of citrinin and dihydrocitrinin are discussed.

Citrinin (V), phenolic alcohol (XXVII), dibenzyl ether (XXVI) and dimethyl ether (XI), all of which have two asymmetric carbon atoms, can exist in four optically active forms (two diastereoisomers and their enantiomers) and two racemic forms. Phenolic alcohol (B) is a single racemate and no information is available regarding the identity of the other racemic form of the phenolic alcohol (XXVII) or its dimethyl ether (XI). In the present

synthetic studies it was observed that the dibenzyl ether (XXVI) of the phenolic alcohol (XXVII) was a mixture of both racemates. Chromatography followed by fractional crystallization led to the pure erythro form and a mixture of threo and erythro racemates, which could not be separated further.

Part II. Synthesis of some analogues of citrinin

The object of the present work was twofold. One was to study the effect of substitution in β-(3,5-dihydroxy)-phenylethyl alcohol (VIII) on its reactivity towards ethyl orthoformate under the simple conditions used in the synthesis of citrinin. The other object was to study the effect of removing one or more of the three C-methyl groups in citrinin on the antibacterial activity of the molecule.

Following the line of synthesis of citrinin, the synthesis of analogues of citrinin of the structures IX, X and XI was undertaken. The required β-phenylethanol derivatives (XXVI, XXIX, and XXXIII) and the corresponding γ-resorcylic acids (XXVII, XXX, and XXXIV) were synthesized. Ethyl orthoformate at room temp cyclized XXX readily to X; but the action of ethyl orthoformate on XXVII and XXXIV led to products which had the qualitative properties of the citrinin type, but which were uncrystallizable. In the

light of these results and the earlier work of N. RAMANATHAN, the action of ethyl orthoformate on a molecule of the type of XXXV are discussed.

Part III. Synthesis of unsymmetrically substituted biphenyls

The available methods for the synthesis of biphenyls have been reviewed with particular emphasis on unsymmetrically substituted biphenyls.

The synthesis of certain biphenyls has been included in the present work because of the possibility of using them for the synthesis of pigments of the type of denticulatol (XVI; XVII) and some analogues of citrinin, such as XV.

In the present method 3-methylbiphenyl (XXVII), 3,5-dimethoxy-3'-methylbiphenyl (XXXIV) and m-terphenyl (XLVI) have been prepared in an overall yield of 25-30 per cent through a series of reactions outlined in Chart 1.

Michael addition of benzylideneacetone and ethyl acetoacetate by refluxing in ethanol and piperidine gave a 65-70 per cent yield of 3-methyl-5-phenyl-6-carbethoxy-2-cyclohexen-1-one (XIX); results have been reported negative in literature. Alkaline hydrolysis and acidification of (XIX) effected decarboxylation to give 3-methyl-5-phenyl-2-cyclohexen-1-one (XXIV), which by the action of sodium borohydride was reduced to XXV. Dehydration of XXV with

pyridine and phosphorus oxychloride gave 1-methyl-3-phenylcyclohex-4,6-diene (XXVI) which was dehydrogenated with chloranil in benzene to 3-methylbiphenyl.

For the unknown 3,5-dimethoxy-3'-methylbiphenyl the starting point was 3,5-dimethoxybenzaldehyde. The same sequence of reactions on chalkone (XLI) led to m-terphenyl (XLVI).

Part IV. Synthesis of anisole-2,3,4,5-tetracarboxylic acid

In the course of a programme of work on the chemistry of naturally occurring quinones, an anisole tetracarboxylic acid (A) was isolated by oxidation of an ether-ester of laccaic acid, the major constituent of lac dye. The acid (A) on treatment with diazomethane gave a tetramethyl ester (B). There are three possible structures (I, II and III) for this acid.

The acid (I) and its tetramethyl ester are known and its properties were different from (A). The acid (II) is also known, but its tetramethyl ester has not been described. The acid (II) was synthesized by the procedure of ROBERTS and its tetramethyl ester was prepared; they were found to be different from (A) and (B). In order to remove the slight ambiguity in the route followed by ROBERTS, a method which would leave no doubt regarding the orientation of the carboxyl

groups was also attempted. Monochlorination of 3,5-dimethylphenol with sulphuryl chloride, methylation, and subsequent treatment with chloromethyl methyl ether in conc sulphuric acid gave the bischloromethyl derivative (VI). Treatment of VI with acetic acid and potassium acetate gave VII. Treatment with aqueous sodium hydroxide in acetone solution gave the bishydroxymethyl compound (VIII), which on treatment with alkaline potassium permanganate at room temp gave the dicarboxylic acid (IX). Further oxidation of IX with alkaline potassium permanganate at 100° afforded the tetracarboxylic acid (X); it failed to undergo dehalogenation with Raney nickel in aqueous sodium hydroxide at room temp, and more vigorous conditions are under study.

3,5-Dimethylanisole on chloromethylation afforded the bischloromethyl compound (XI), which on hydrolysis could not be converted to the bishydroxymethyl derivative. However, treatment of XI with acetic acid and fused potassium acetate gave XII, which was oxidized with alkaline permanganate at room temp to the dicarboxylic acid (XIII). The acid (XIII) on controlled oxidation with alkaline permanganate yielded a tricarboxylic acid (XIV). The structure XVI for carminic acid was based on

XV for cochenillic acid. Recently OVEREEM has claimed that the methyl ether of cochenillic acid has the structure XIV; he synthesized both XIV and the methyl ether of XV, but he has not indicated his synthetic routes. An authentic sample of the methyl ether of cochenillic acid is now being prepared from carminic acid for direct comparison with XIV.

The acid (XIV) on oxidation with excess of alkaline permanganate gave the desired acid III; treatment with diazomethane gave the tetramethyl ester, which proved to be identical with the tetramethyl ester of the anisoletetracarboxylic acid produced by the oxidation of laccaic acid.

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