Synthetic Approaches to the Colchicine Molecule,

with additional paper

Synthesis of Polycyclic Hydrocarbons Related to Chrysene.

Thesis

submitted by

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Preface.

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I n d e x.

Synthetic approaches to the colchicine molecule.

Synthesis of polycyclic hydrocarbons related to chrysene.

SYNTHETIC APPROACHES TO THE COLCHICINE MOLECULE.

Introduction.

Colchicine is an alkaloid found in the seeds and corms of the autumn crocus (Colchicum autumnale). It was discovered first by Pelletier and Caventou[1] in 1819 but remained practically uninvestigated for many years until Zeisel[2] isolated it in a pure state and undertook researches into its structure. Colchicine is obtained commercially as a yellow varnish m.p. 143-147° and can be crystallised from chloroform as an additive compound with two molecules of chloroform. Colchicine has the formula $C_{22}H_{25}O_6N$.

Colchiceine, $C_{21}H_{23}O_6N$, has also been isolated from the autumn crocus by Oberlin[3] but Zeisel says it probably arises by hydrolysis of colchicine during the isolation of the alkaloid.

Clewer, Green and Tutin[4] have found that colchicine also occurs in Gloriosa superba. By crystallising from ethyl acetate they found that it had m.p. 155-157°. These workers isolated at the same time two other alkaloids, one, $C_{15}H_{17}O_4N$ or $C_{33}H_{38}O_9N_2$, leaflets m.p. 177-178°, the other, $C_{23}H_{27}O_6N$, needles m.p. 276° which may be a methyl colchicine.

Zeisel[2] obtained an insight into the structure of colchicine by a study of the effects of various conditions of saponification. By heating it with 0.5% HCl a methyl

group is hydrolysed off giving colchiceine, colourless leaflets m.p. 177°.

$$C_{21}H_{22}O_5N(OCH_3) + H_2O \longrightarrow C_{21}H_{22}O_5N(OH) + CH_3OH$$

Colchicine is an almost neutral compound, colchiceine behaves as a weak acid.

Saponification of colchiceine with stronger HCl (15%) causes the removal of an acetyl group with the formation of a compound, trimethylcolchicinic acid, which forms salts with both bases and acids. Thus an acetamido compound has been hydrolysed to an amine, which Zeisel has shown to be primary by exhaustive methylation.

$$C_{19}H_{18}O_4(OH)(NHCOCH_3) + H_2O \rightarrow C_{19}H_{18}O_4(OH)(NH_2) + CH_3COOH$$

Colchiceine Trimethylcolchicinic acid.

By boiling trimethylcolchicinic acid with concentrated HI three molecules of methyl iodide are given off. This shows that trimethylcolchicinic acid contains three methoxyl groups. The formula for colchicine can now be represented as follows:-

$$(CH_3O)_3C_{16}H_9O(OCH_3)(NHCOCH_3).$$

Zeisel found that colchicine with alcoholic ammonia loses a molecule of MeOH to give the compound $C_{21}H_{22}O_5N(NH_2)$ which gives colchiceine and ammonia on hydrolysis with caustic soda.

Having accounted for five of the six oxygen atoms in colchicine, four in methoxyl groups and one in an acetyl

group, Zeisel assigned the sixth oxygen atom to a carboxyl group and thus called colchicine the methyl ester of an acid, colchiceine being the free acid. According to Zeisel the formula for colchicine could be written thus:-

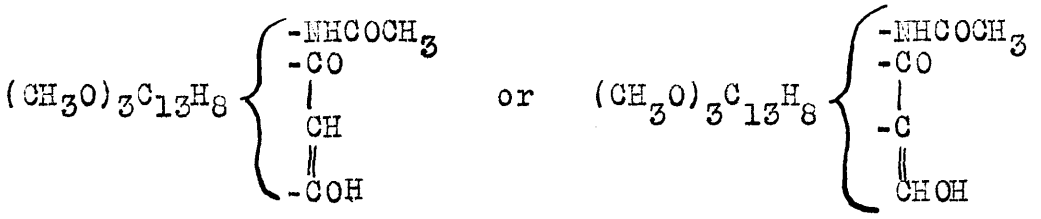
$$(CH_3O)_3C_{15}H_9 \left\{ \begin{array}{l} -COOCH_3 \\ -NHCOCH_3 \end{array} \right.$$

This formula would account for the ready saponification of colchicine with dilute HCl and for the formation of the above mentioned compound with ammonia which may be regarded as the amide of the acid colchiceine.

In a series of researches Windaus[5] has investigated the properties of colchicine and its degradation products and has assigned a complete formula to the alkaloid. Windaus points out that colchiceine is not an acid but may be an aldo- or a keto-enol. One reason is that it gives with ferric chloride solution a characteristic colour reaction, a reaction found with phenols and enols but not with acids.

Against the possibility of colchiceine being a phenol is the ease of saponification of its methyl ether, colchicine, a fact which is in accord with the latter being an enol methyl ether. An additional fact against the correctness of Zeisel's assumption of an acid group is the behaviour of trimethylcolchicinic acid, or as it is sometimes called desacetylcolchiceine, with acetylating agents.

Trimethylcolchicinic acid with benzenesulphonyl chloride and pyridine gives a dibenzenesulphonyl derivative which gives no ferric chloride colour reaction and which exists in two stereoisomeric forms. On careful hydrolysis both forms give the same N-benzenesulphonyltrimethylcolchicinic acid, which gives the ferric chloride reaction. The formation of cis-trans isomers is possible with a hydroxymethylene compound, as has been shown by Wislicenus and Bindemann[6] but not with an acid which should give on similar treatment a mixed acid anhydride. Accordingly colchiceine may be formulated as the enol form of a β-diketone or of a β-keto-aldehyde as follows:-



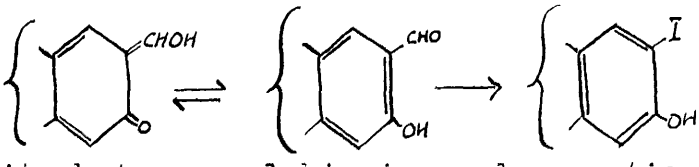
Windaus found that colchiceine when boiled with bromine in acetic acid is oxidised to an acid which he called tribromocolchiceinic acid which no longer contains an enol group. As it has the same number of carbon atoms as colchiceine together with one additional oxygen atom, it can have arisen only by oxidation of a -CHO group to a -COOH group.

$$C_{20}H_{22}O_5NCHO + 3Br_2 \longrightarrow C_{20}H_{22}O_5NBr_3COOH + 3HBr.$$

From this reaction colchiceine would appear to be a

β-keto-aldehyde and not a β-diketone. Another experiment carried out by Windaus[5] substantiates this view. When colchiceine is treated with a potassium iodide-iodine solution in alkali a compound N-acetyliodocolchinol is obtained in which the -CHO group is replaced by iodine. This reaction is in accordance with reports by Claisen[7] and Bruhl[8] that hydroxymethylene-ketone derivatives like hydroxymethylene camphor give α-halogeno ketones and by Windaus and Schiele[9] that aromatic hydroxy o- and p-aldehydes give o- and p-halogeno phenols.

N-acetyliodocolchinol does not behave as a ketone, it exhibits all the properties of a phenol and so it would appear that colchiceine, from which it arises, contains an aromatic hydroxy o- or p-aldehyde group, i.e., contains a phenolic-OH group. As has been pointed out, colchicine, the methyl ether of colchiceine, behaves as an enol methyl ether rather than a phenol methyl ether. This may be explained, together with the formation of N-acetyliodocolchinol as follows:-

$(CH_3O)_3C_9H_6(NHCOCH_3)$ 

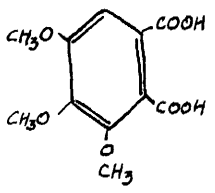
Another similarity between colchiceine and aromatic hydroxy aldehydes is that with concentrated acids in

aqueous or alcoholic solution colchiceine and trimethylcolchicinic acid (desacetylcolchiceine) give deeply coloured addition compounds which can be isolated in certain cases, e.g., a sparingly soluble dihydrochloride of trimethylcolchicinic acid can be obtained.

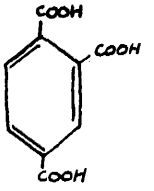
A fact which cannot be accounted for by this otherwise acceptable formula for colchicine and its derivatives is their failure to give reactions with any of the carbonyl reagents like hydroxylamine or semicarbazide.

Windaus has elucidated also the carbon skeleton of colchicine largely by a study of some products of oxidation of colchicine and of certain of its transformation products.

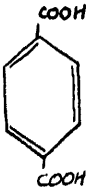
Colchicine and its derivatives with hot $KMnO_4$ all give 3:4:5-trimethoxy-1:2-phthalic acid, I. If all the methoxyl groups are demethylated before oxidation only succinic acid and oxalic acid are obtained. If besides the methoxyl groups the amino group is also split off from trimethylcolchicinic acid and the resulting compound oxidised, two other acids are obtained, trimellitic acid, II, and terephthalic acid, III,



I



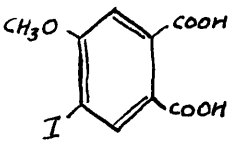
II



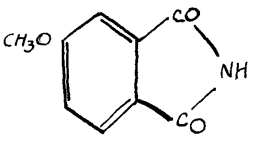
III

When N-acetyliodocolchinol is converted into its methyl ether and this compound oxidised with hot permanganate, the ring containing iodine is the most stable and is isolated as iodomethoxy-o-phthalic acid which can be reduced to 4-methoxyphthalic acid. Windaus assumed that the iodine was in position 5 and this assumption has been borne out by the synthesis of 5-iodo-4-methoxy-1:2-phthalic acid, IV, by Grewe[10].

When N-acetyliodocolchinol methyl ether is reduced N-acetylcolchinol methyl ether is obtained and the latter, when oxidised with chromic acid and sulphuric acid, gives as main oxidation product 4-methoxyphthalimide, V.



IV

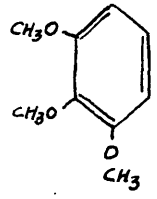


V

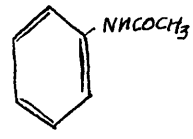
By these experiments Windaus proved the existence of three separate six membered rings in colchicine or its derivatives. One ring contains three vicinal methoxyl groups. A second ring in N-acetylcolchinol methyl ether contains one methoxyl group. This ring is the one which contains the hydroxymethylene-ketone grouping in colchiceine. The third ring present in colchicine is the one which gives

rise to trimellitic acid on oxidation and the one to which the N atom is attached. By obtaining the compound 4-methoxyphthalimide, V, it was shown that the amino group is attached to the α-carbon atom to the ring containing the one methoxyl group in N-acetylcolchinol methyl ether.

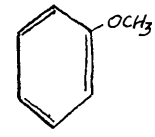
At this stage the structure of N-acetylcolchinol methyl ether, which is the simplest degradation product of colchicine so far considered, may be built up as follows:-



$(CH_3O)_3C_6H_3$



$C_6H_5NHCOCH_3$



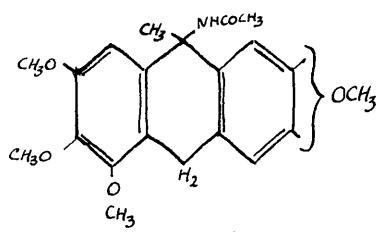
$C_6H_5OCH_3$

N-acetylcolchinol methyl ether has the formula $(CH_3O)_4C_{15}H_9(NHCOCH_3)$ while the three separate portions of the molecule represented above add up to $(CH_3O)_4C_{18}H_{13}(NHCOCH_3)$. The only arrangement of rings which will satisfy the given formula is a fused ring structure of the anthracene or phenanthrene type, $C_{14}H_{10}$. A structure of this type still leaves one C atom and four H atoms to be accounted for. These can be accommodated by regarding N-acetylcolchinol methyl ether as a methyldihydroanthracene or methyldihydrophenanthrene derivative. This methyl group

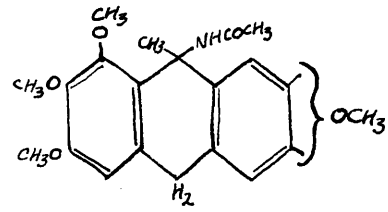
cannot be attached to either of the two rings containing methoxyl groups as on oxidation no methyl derivatives of methoxylated phthalic acids were obtained. On the other hand trimellitic acid was obtained and must have arisen from the third ring to which the methyl group is attached.

Zeisel[2] has shown that colchicine, $C_{22}H_{25}O_6N$, contains a reactive methylene group, $>CH_2$, as on oxidation with chromic acid it gives a ketone, $C_{22}H_{23}O_7N$, which is detectable with ketonic reagents.

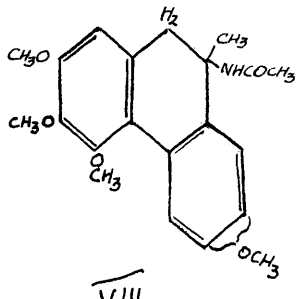
The following formulae all satisfy the facts enumerated so far for N-acetylcolchinol methyl ether.



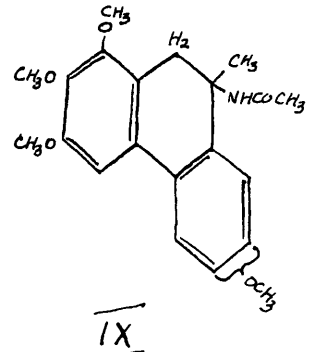
VI



VII

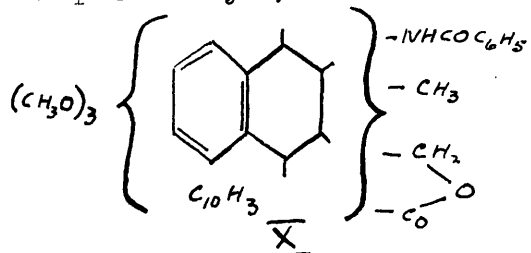


VIII

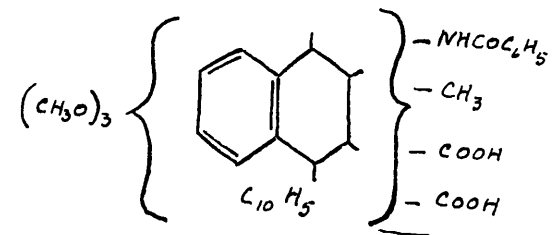


IX

Windaus, by a study of the products of oxidation of another colchicine derivative, decided which of the above structures was correct. He obtained by careful oxidation of N-benzoyltrimethylcolchicinic acid, $C_{26}H_{25}O_6N$, two compounds which he called N-benzoylcolchide, $C_{23}H_{23}O_6N$, and N-benzoylcolchinic anhydride, $C_{23}H_{21}O_7N$. These compounds give no colour with ferric chloride solution and so no longer have the characteristic hydroxymethylene grouping of colchiceine. Windaus has shown that N-benzoylcolchide is a lactone of a primary alcohol and on dry distillation it loses benzamide to give a compound $C_{16}H_{16}O_5$. Windaus concludes that this is a trimethoxymethylnaphthalene derivative and N-benzoylcolchide is accordingly a N-benzoyldihydromethylnaphthalene derivative which may be represented by formula X. N-benzoylcolchinic anhydride corresponds to this formula except that the $>CH_2$ of the lactone ring is replaced by $>CO$.



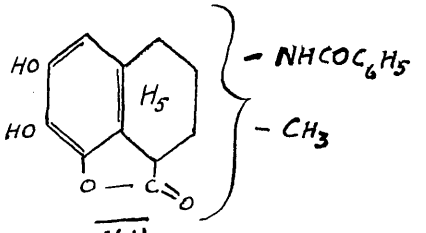
X



XI

When N-benzoylcolchinic anhydride is reduced with zinc dust and acetic acid, a tetrahydronaphthalene derivative, $C_{23}H_{25}O_8N$, is obtained which may be represented by formula XI. This compound, when treated with concentrated HI,

loses 3 molecules of methyl iodide, 1 molecule of water and 1 molecule of CO_2, giving an anhydride, $C_{19}H_{17}O_5N$, which can only arise by elimination of water between one of the phenolic OH groups and the remaining -COOH group. As has been shown by Sachs[11] this anhydride formation in naphthalenes can only occur if the OH group and the -COOH group are in the peri position. Thus the formula for the anhydride, $C_{19}H_{17}O_5N$, can be expressed by XII.



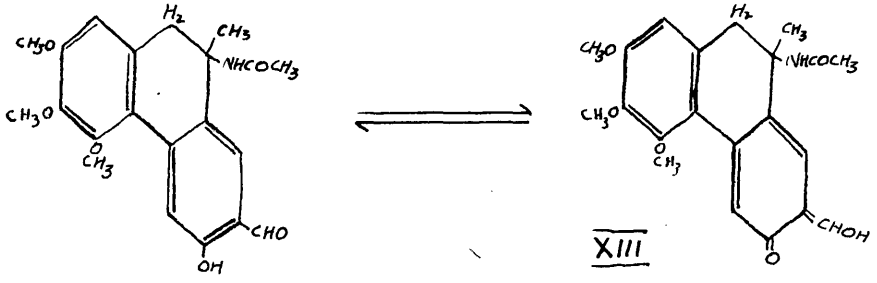
XII

By the formation of this compound two important points are settled: a) N-benzoylcolchicinic acid (and consequently colchicine and its transformation products) from which the anhydride was formed must be a phenanthrene and not an anthracene derivative as the -COOH group formed by oxidation of the third ring is in the α position in the naphthalene derivative. b) The position of the three vicinal methoxyl groups in the original compound is established, i.e., in positions 2:3:4 of the phenanthrene ring.

Since colchicine and its derivatives have the phenanthrene structure, the two formulae VI and VII, described

above for N-acetylcolchinol methyl ether, which contain an anthracene ring are ruled out. Formula IX can also be excluded as it has the methoxyl groups in positions 1:2:3- instead of the required positions 2:3:4-. Thus the formula for N-acetylcolchinol methyl ether is given by structure VIII. The position of the fourth methoxyl group is either at 6 or 7, no decision being obtainable from the product of oxidation, 4-methoxy-1:2-phthalic acid.

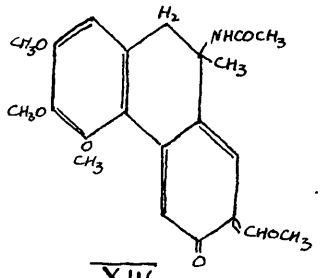
The formula for colchiceine, from which N-acetylcolchinol methyl ether is obtained by replacement of a -CHO group by iodine, followed by reduction and subsequent methylation by iodine, followed by reduction and subsequent methylation



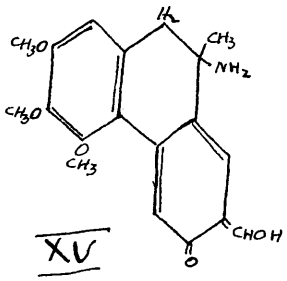
XIII

This is usually expressed in the form of the right hand formula, i.e., in the hydroxymethylene-ketone form as has been discussed earlier. The substituents in positions 6 and 7 may require to be interchanged as the position of the methoxyl group in N-acetylcolchinol methyl ether has not been fixed.

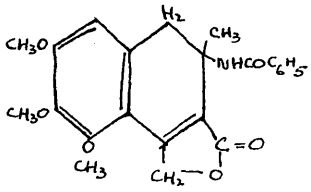
Colchicine is the methyl ether of colchiceine and Windaus has assigned it formula XIV with the usual reservation about the position of the substituents in the third ring.



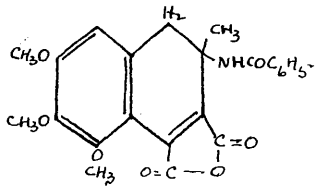
XIV



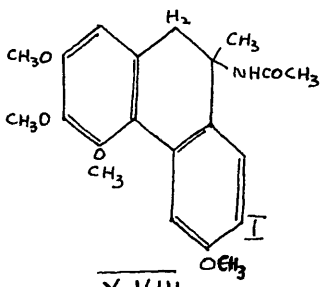
XV



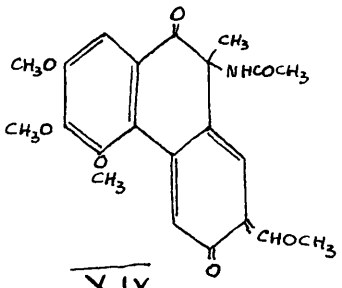
XVI



XVII



XVIII

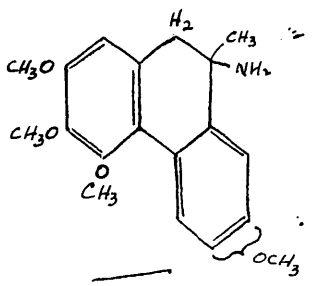


XIX

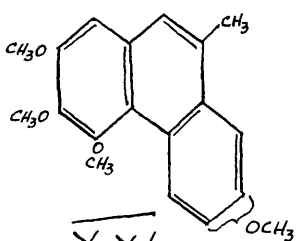
The structural formulae for five other compounds related to colchicine which have been mentioned earlier are given above. Trimethylcolchicinic acid or desacetylcolchiceine has formula XV. N-benzoylcolchide, obtained by oxidation of N-benzoyltrimethylcolchicinic acid, which was expressed earlier by structure X, is expressed more fully now by formula XVI. N-benzoylcolchinic anhydride is given structure XVII. Formula XVIII is given to N-acetyliodo-colchinol methyl ether, but the substituents in positions 6

and 7 may require to be interchanged. The oxycolchicine obtained by Zeisel[2] by oxidation of colchicine with chromic acid is assigned the structure XIX.

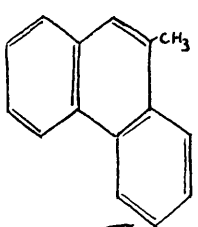
Windaus[12] in later work confirmed the phenanthrene ring system in colchicine by a method which did not involve oxidation as used in earlier researches. He hydrolysed N-acetylcolchinol methyl ether, VIII, to colchinol methyl ether, XX, and then exhaustively methylated this compound to a nitrogen free compound which he called 2:3:4:6- (or 7-) tetramethoxy-9-methylphenanthrene, XXI. This compound was demethylated with HI. Without isolating the product of demethylation Windaus carried out a zinc dust distillation when a hydrocarbon, $C_{15}H_{12}$, m.p. 89°, was obtained. This he called 9-methylphenanthrene, XXII. As 9-methylphenanthrene was unknown at that time Windaus[13] synthesised it and so confirmed the structure of the hydrocarbon obtained from colchinol methyl ether.



XX



XXI



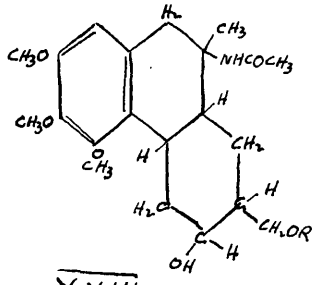
XXII

Windaus by his painstaking researches has assigned a formula to colchicine which satisfies practically all the known facts concerning the behaviour of the alkaloid and its related products. This formula established by Windaus is that still generally accepted; most of the small amount of work published since 1924 on the chemistry of colchicine with one or two exceptions confirms the Windaus structure.

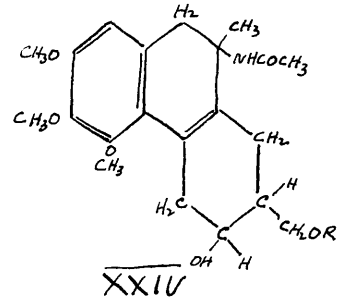
As has been mentioned earlier, the assumption made by Windaus that the iodomethoxyphthalic acid obtained from the oxidation of N-acetyliodocolchinol methyl ether, XVIII, is 4-methoxy-5-iodo-1:2-phthalic acid, has been borne out by the synthesis more recently of this compound by Grewe[10]. Bursian[14] by a study of the ultra-violet absorption spectra of colchicine and colchiceine in chloroform solution has confirmed the presence of a hydroxymethylene-ketone structure in ring 3 in both colchicine and colchiceine (which have very similar spectra). On the other hand, the ultra violet adsorption spectra of colchiceine in dilute ammonium hydroxide solution differs in certain respects from that of colchicine in the same solution and appears to indicate the presence of the aromatic hydroxy aldehyde structure in the former. This is in agreement with the formation in alkaline solution of N-acetyliodocolchinol from colchiceine.

Windaus[12] reduced colchicine and colchiceine with hydrogen in presence of Pt black catalyst and obtained what

he called octahydro derivatives of structure XXIII. Bursian[14] has investigated this reduction and has found that a hexahydro (of structure XXIV) and not an octahydro derivative is formed.



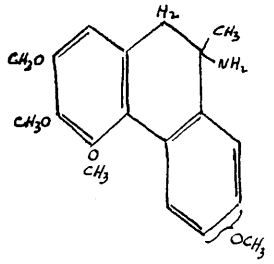
XXIII



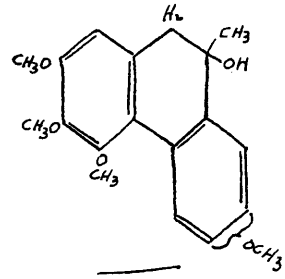
XXIV

However, there are a few cases in which the behaviour of colchicine and its derivatives is not in accordance with the structures assigned them by Windaus.

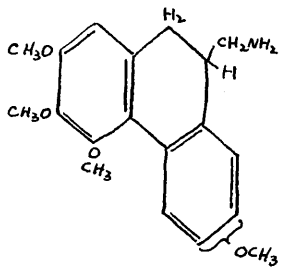
Bursian[14] has reported the fact that colchicine and colchiceine do not react with maleic anhydride as might be expected with a compound containing a 1:4-diene structure. Cohen, Cook and Roe[15] have pointed out other respects in which the formula postulated by Windaus does not satisfy.



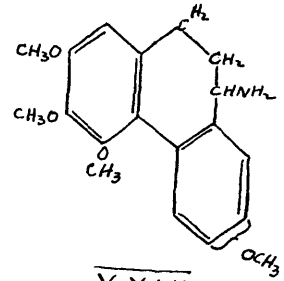
XX



XXV



XXVI



XXVII

Colchinol methyl ether, one of the degradation products of colchicine, should have structure XX which is a 9-amino-9:10-dihydrophenanthrene derivative, a type of compound which should readily lose ammonia. This type of behaviour has been demonstrated in the case of analagous phenanthrene derivatives synthesised by Windaus and his co-workers[13),16)]. Cohen, Cook and Roe, by the action of nitrous acid on colchinol methyl ether, have obtained a carbinol which, on the Windaus postulation, should have structure XXV. As a tertiary carbinol related to 9:10-dihydrophenanthrene this should readily lose water and pass into the fully aromatic state. This is not the case. These authors point out that colchinol methyl ether might have structure XXVI with corresponding structure for the carbinol. This type of compound would have unsubstituted H atoms at positions 9 and 10 and should be dehydrogenated readily, but Cohen, Cook and Roe found that N-acetylcolchinol methyl ether was recovered

unchanged after treatment with Pt black at 280°. However, the stability of polymethoxydihydrophenanthrenes to dehydrogenation has not been studied.

These authors suggested also the possibility of colchinol methyl ether containing a seven membered ring, structure XXVII. The 9-methylphenanthrene which Windaus[12] obtained from colchinol methyl ether might have arisen, they state, during the drastic reduction with zinc dust by a molecular rearrangement of the seven membered ring. They could not, however, distinguish with certainty the primary, secondary or tertiary nature of the carbinol obtained from colchinol methyl ether.

Cohen, Cook and Roe[15] also studied the ultra violet adsorption spectra of N-acetylcolchinol methyl ether and of this carbinol obtained from the amine. The curves of both are very similar to that given by 9:10-dihydrophenanthrene as regards wave length and intensity of adsorption.

Colchicine is a capillary poison and causes first excitement and then paralysis of the central nervous system. Colchiceine is less toxic than colchicine. Extract of the crude drug, "wine of colchicum", and colchicine (usually as the salicylate) are used in medicine for the treatment of gout and rheumatism. Colchicine acts in small doses either as a diuretic or a purgative; in man 2 mg. being required

for diuresis and 5 mg. for purgative effect. Elimination of the alkaloid from the kidneys is very slow and so small doses not poisonous in themselves may cause death by a cumulative effect within a few days.

During the last ten years colchicine has become of increasing biological importance because of its action on cells, both plant and animal. In 1908 Dixon and Malden[17] reported that colchicine had a stimulative effect on mitosis. This belief held until 1934 when Dustin[18], studying its effect on freely dividing animal cells, found that instead of increasing mitosis colchicine prevented it. Blakeslee[19] has reported that plants treated with colchicine contain cells with double the number of chromosomes. On treatment no visible effect appears in the cells until they reach the mitosis stage when chromosome division occurs, but chromosome separation and cell division are prevented; the chromosomes doubled in number metamorphose into the nuclear stage and form a nucleus double in chromosome number and in volume of the original. The earlier belief that colchicine causes increased mitosis was due to an accumulation of only partly divided cells in the treated portion of the tissue which gave the impression of an increased number of cells.

Lits[20], Dustin[18], Amoroso[21], and others have reported the inhibition of tumour growth in animal cells on treatment

with colchicine. Havas[22] has reported a similar effect on plant tumours. A difficulty in the use of colchicine for destroying tumours in animals is that the effective dose approaches the lethal dose.

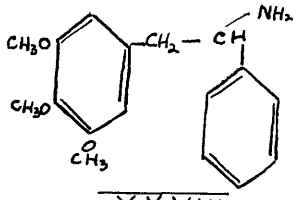
It has been known for a considerable time that the complete ring system of certain alkaloids is not required for the specific biological effect of the alkaloid, e.g., in the case of cocaine and nicotine. More recently it has been reported that a series of dicyclic compounds, mostly bis(phenylethyl)amine derivatives, have the specific action of papaverine and its tetrahydride[23].

On the same basis Lettré[24] adduces the similar physiological action of colchicine and certain dicyclic compounds to support the Windaus structure for the alkaloid. Brues and Cohen[25] have shown that several transformation products of colchicine have a similar effect on cell division although none is quite so effective as colchicine. Lettré[24] uses as test object for mitosis poisoning tissue culture of chicken heart fibroblasts or the ascites tumour of the mouse.

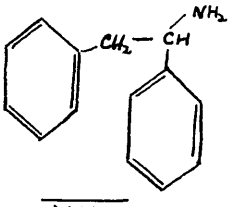
Lettré points out that α-phenylmescaline, XXVIII, which may be regarded as an open chain analogue of colchicine (Windaus structure) is an effective mitosis poison.

Mescaline itself is ineffective as is α-β-diphenylethylamine, XXIX, but α-phenyl-β-(p-methoxyphenyl)ethylamine,

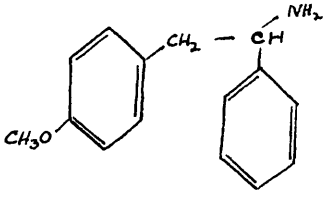
XXX, is an effective mitosis poison. p-Methoxybenzhydrylamine, XXXI, is without effect on cells.



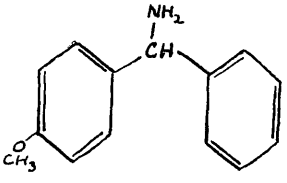
XXVIII



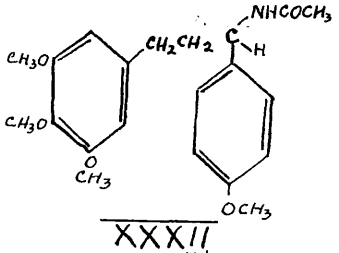
XXIX



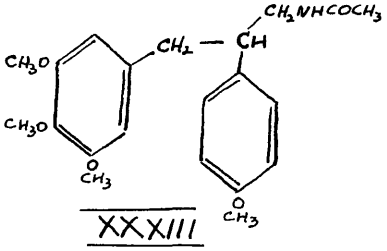
XXX



XXXI



XXXII



XXXIII

Compound, XXXII, which may be regarded as an open chain analogue of the colchinol methyl ether of structure, XXVII, suggested by Cohen, Cook and Roe[15], has no effect on mitosis. Compound XXXIII was prepared by Cook and Engel[26] and tested by Dr. Brues of Harvard who reported the characteristic effect on the liver of a rat, but Lettré

obtained no mitosis poisoning in his test object. This compound may be regarded as an open chain analogue of the alternative structure XXVI for colchinol methyl ether suggested by Cohen, Cook and Roe[15].

Lettré concludes that for mitosis poisoning a compound containing the linkage -C-C-N is required; a benzene ring containing at least one methoxyl group must be attached to the β-carbon atom to the nitrogen while a benzene ring or reduced benzene ring (cf. hexahydrocolchicine, XXIV, which is effective) must be attached to the α-carbon atom. Compounds XXXII and XXXIII which are dicyclic compounds corresponding to the tricyclic structures XXVII and XXVI suggested by Cohen, Cook and Roe for colchinol methyl ether, with corresponding structures for colchicine, do not have this type of linkage and are without effect on cell division. On the other hand, compounds XXVIII and XXX have this type of linkage and are effective mitosis poisons. This type of linkage is found also in the structure, XIV, given by Windaus[5),12)] to colchicine, which has strong mitosis poisoning action on cells.

From the similarity of physiological action between colchicine and other substituted α-β-diphenylethylamine structures Lettré concludes that colchicine has an analagous tricyclic structure and hereby finds evidence for the

correctness of the Windaus formula in preference to the alternative types of structure suggested by Cohen, Cook and Roe.

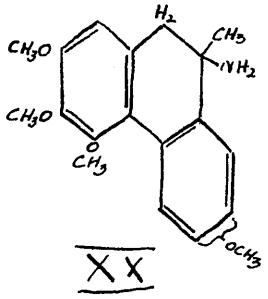
To summarise, the present position of the colchicine problem is that the formula for the alkaloid postulated in 1923 by Windaus has met with support and, to a lesser degree, criticism. It accommodates most of the facts known so far about the chemistry of colchicine but at the same time the following inconsistencies are noteworthy. Colchicine, colchiceine and trimethylcolchicinic acid, all of which should contain the carbonyl group, fail to react with carbonyl reagents. The apparent stability of colchinol methyl ether to loss of ammonia and of the carbinol obtained from it by the action of nitrous acid to dehydration is in contrast to the ready conversion of analagous dihydrophenanthrenes to the aromatic state. The appearance of succinic acid as a product of the oxidation of colchicine (after demethylation of the methoxyl groups) is inconsistent with the Windaus structure. Windaus[12] has found an explanation acceptable to him in that vanillin also gives succinic acid on oxidation[27]. This however may not be analagous as vanillin has the linkage -C=C-C=C- but no linkage of two or more carbon atoms containing unsubstituted H atoms in adjacent positions which might give rise to succinic acid is

to be found in the Windaus structure for colchicine. The oxidation of vanillin was carried out by hydrogen peroxide while that of colchicine was brought about by potassium permanganate.

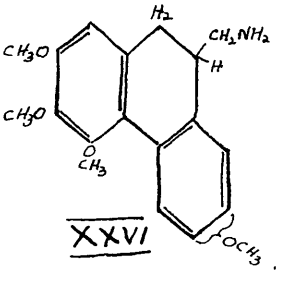
In conclusion a reference must be made to the field in which colchicine has become most important, namely, in botany. As has been reported earlier, treatment of plants with colchicine causes a doubling in the number of chromosomes in the cell and with this doubling there often results a general change in the plant itself. The mutation formed by this treatment shows many abnormalities, usually an increase in growth, often a change in colour and sometimes a hastening in the rate of growth. Extensive research is being carried out at present in all parts of the world on production of new species of plants by means of colchicine treatment, for the production of a species of wheat which has a few more ears, of a tree a few feet higher or of a cotton plant with fibres an inch or so longer could revolutionise a national economy.

The Syntheses.

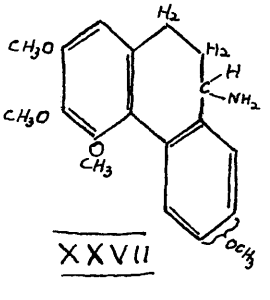
It has been reported in the introduction that Cohen, Cook and Roe[15] had pointed out various inconsistencies in the structure given to colchicine by Windaus[5),12)], and that they had suggested two alternative structures for colchinol methyl ether (which should have structure XX according to Windaus), a transformation product of colchicine. In one of the alternative forms, XXVI, given by Cohen, Cook and Roe the amino group is not attached directly to the ring but is in the side chain. The second formula suggested by these authors contains a seven membered ring and is represented by XXVII.



XX



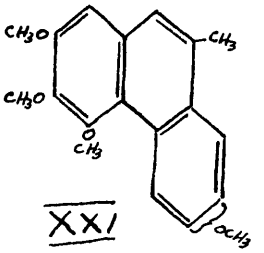
XXVI



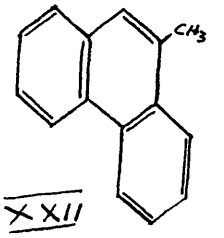
XXVII

One of the main points in the evidence of the presence of a phenanthrene ring structure in colchicine is that Windaus converted colchinol methyl ether by exhaustive

methylation into a tetramethoxy compound which he called 2:3:4:6 (or 7)-tetramethoxy-9-methylphenanthrene, XXI. This compound on demethylation followed by a zinc dust distillation gave 9-methylphenanthrene, XXII.

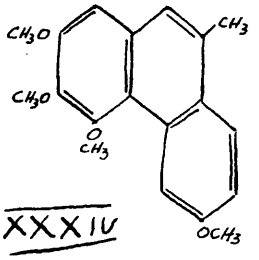


XXI

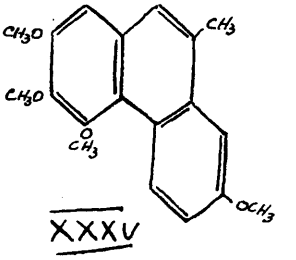


XXII

Cohen, Cook and Roe have pointed out that this 9-methylphenanthrene might have arisen by intramolecular rearrangement during the drastic reduction with zinc dust. If this were so, colchinol methyl ether might have a seven membered ring as in XXVII. This uncertainty could be removed by a synthesis of the tetramethoxy compound obtained by Windaus from colchinol methyl ether. According to Windaus this compound should be 2:3:4:6-tetramethoxy-9-methylphenanthrene, XXXIV, or 2:3:4:7-tetramethoxy-9-methylphenanthrene, XXXV. The syntheses of these two compounds have been the main object of this research.



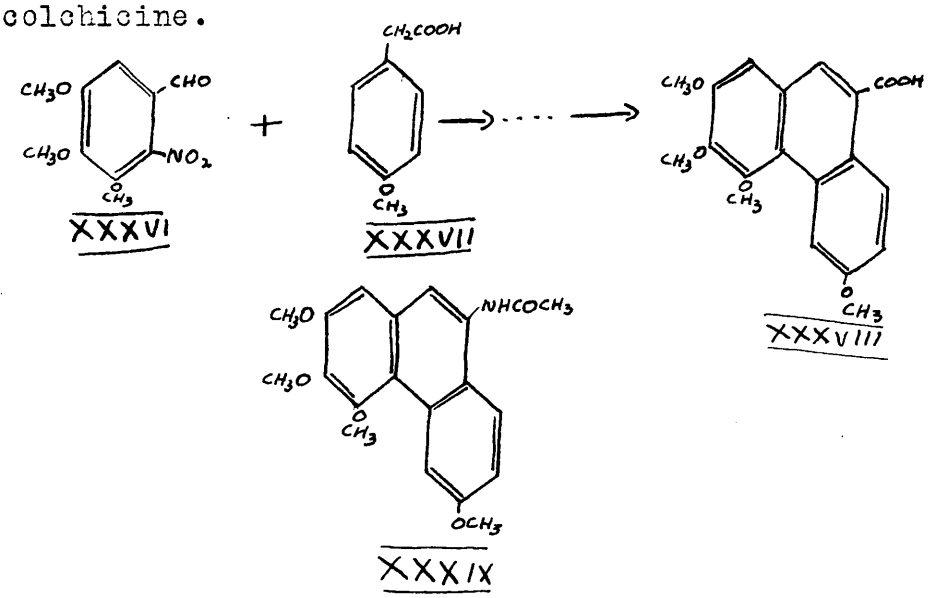
XXXIV



XXXV

Sharp[28] has synthesised 2:3:4:6-tetramethoxyphenanthrene 9-carboxylic acid, XXXVIII, by means of a

phenanthrene synthesis involving the Pschorr type of ring closure, starting from 2-nitro-3:4:5-trimethoxybenzaldehyde, XXXVI, and p-methoxyphenylacetic acid, XXXVII. He further converted the 9-carboxyl group of compound XXXVIII into a 9-acetamido group. This compound, XXXIX, exhibits several of the features characteristic of the Windaus structure for colchicine.



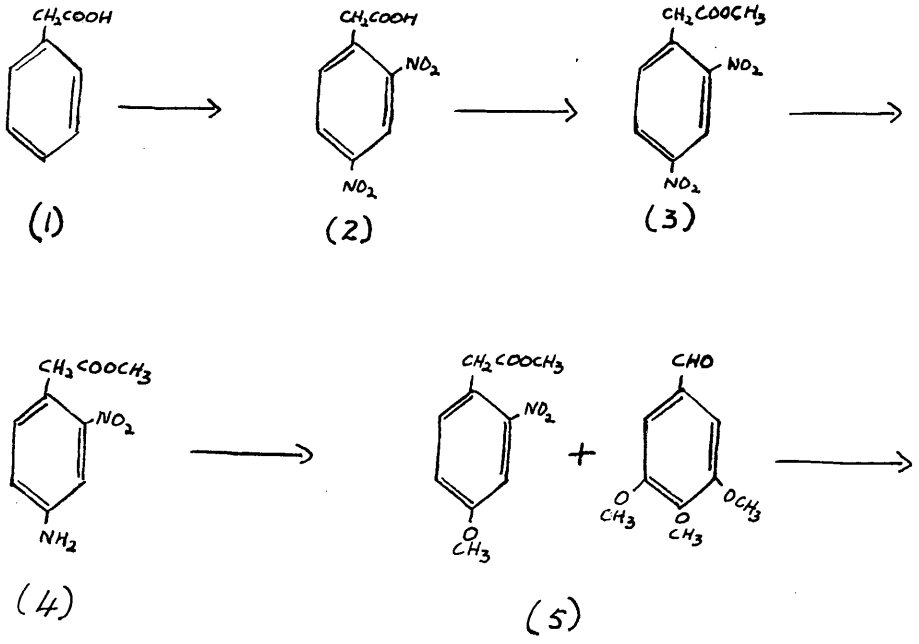
Compound XXXVIII can be regarded as a possible intermediate in the synthesis of one of the desired tetramethoxy-9-methylphenanthrenes, namely the 2:3:4:6-tetramethoxy isomer, XXXIV. The carboxyl group could be converted into an aldehyde group and this reduced by a Wolff-Kishner reduction to give the required 9-methyl derivative. The synthesis of 2:3:4:6-tetramethoxyphenanthrene 9-carboxylic acid, XXXVIII, is complicated by the very poor yield

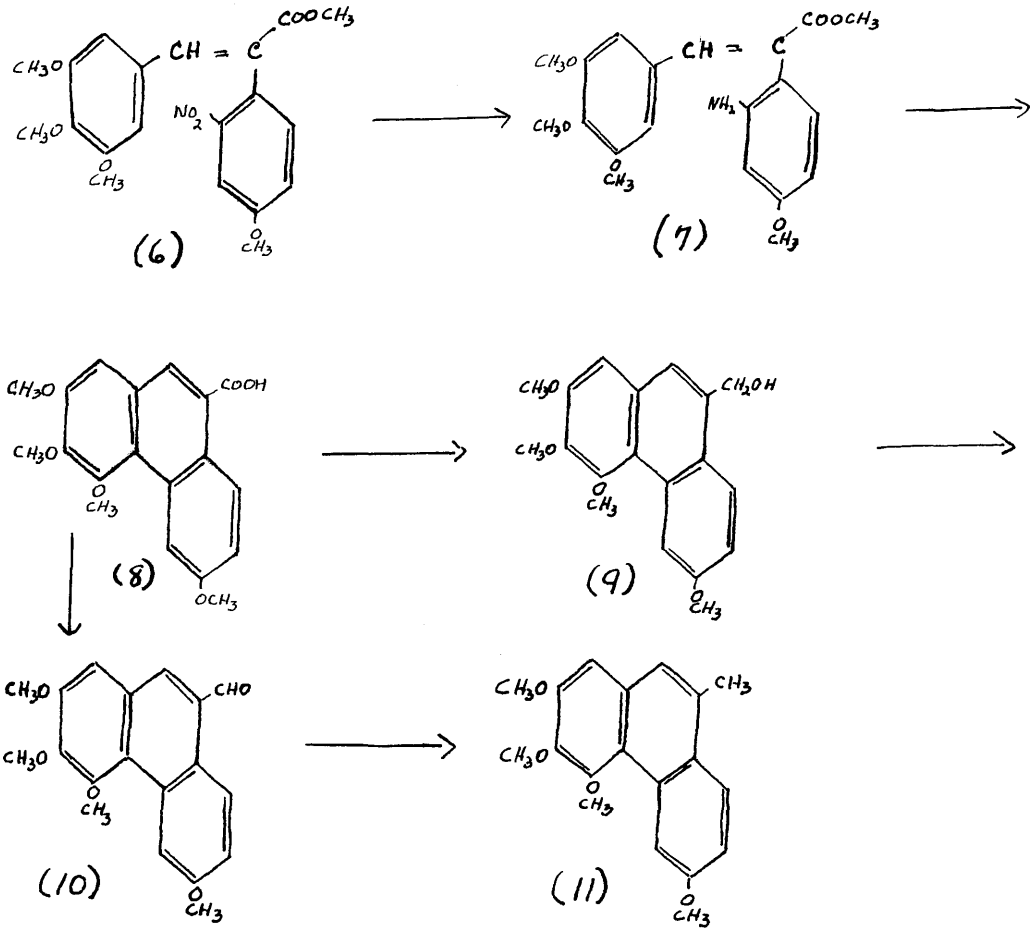
of 2-nitro-3:4:5-trimethoxybenzaldehyde, XXXVI, obtained by nitration of 3:4:5-trimethoxybenzaldehyde. Sharp[28] reports a yield of 20%. No better results were obtained by Cook and Engel[26] by nitration of the anil of trimethoxybenzaldehyde or by Lapsley[29] of its diacetate.

In view of the inaccessibility of this nitro aldehyde various alternative schemes for the synthesis of the required compounds were investigated. These are described below, the first of them having been already the subject of some exploratory work by Lapsley[29].

Synthesis of 2:3:4:6-tetramethoxy-9-methylphenanthrene.

Scheme A.





This scheme involves the preparation of compound (7) which on ring closure by the Pschorr method should give compound (8). This compound (8), already obtained by Sharp[28] by a different method, has to be converted into the 9-methyl derivative (11) in the manner outlined above.

2:4-Dinitrophenylacetic acid (2) was readily prepared by nitration of phenylacetic acid by the method of Borsche[31]. Gabriel and Meyer[32] claim to have reduced 2:4-dinitrophenylacetic acid to the corresponding 2-nitro-4-amino

compound by means of polysulphide but do not give many details. Lapsley[29] attempted to obtain 2-nitro-4-amino-phenylacetic acid by reduction with sodium sulphide. This resulted in decarboxylation of the acid with formation of 2:4-dinitrotoluene and 2-nitro-4-aminotoluene. Lapsley obtained 2:4-dinitrotoluene also on attempting to reduce 2:4-dinitrophenylacetic acid with hydrazine hydrate.

The methyl ester of 2:4-dinitrophenylacetic acid (3) was prepared and attempts were made to convert it into the corresponding 2-nitro-4-amino compound. An attempt, based on the method of Curtius[33], using 50% hydrazine hydrate, resulted in the formation of 2:4-dinitrophenylacetylhydrazide.

Experiments on the catalytic reduction of 2:4-dinitro-phenylacetic methyl ester were then carried out. A difficulty encountered was the sparing solubility of the ester in most solvents in the cold, about 1% in ether and 0.5% in alcohol. The ester dissolved in the solvent was shaken with Pd black catalyst until the theoretical amount of hydrogen required for the reduction of one nitro group was adsorbed. The working up of the reduced product presented some difficulty. It was found that on concentration of the solution after reduction, even in vacuo, considerable amounts of tar were obtained. Ether gave the most

satisfactory product, dioxan the least. Tarring also occurred at other stages during the isolation of the methyl ester of 2-nitro-4-aminophenylacetic acid. The best results were obtained when ether had been used as solvent during the reduction, but the yield of the 2-nitro-4-amino compound (4) was never greater than 15%. An attempt to convert the hydrochloride of this amine into the phenol by diazotisation without isolating the free base did not give a satisfactory result, a poor yield of a brown amorphous powder being obtained.

As no allowance had been made for the vapour pressure of the solvent in calculating the amount of hydrogen required for the reduction, it was thought that this might be a factor contributing to the poor yield. The reduction was repeated in ether solution allowing for the vapour pressure of the ether. From the solution after adsorption of the required amount of hydrogen there was isolated 2-nitro-4-amino, 2:4-diamino-, and unchanged 2:4-dinitrophenylacetic methyl ester. Thus it appears that the reduction of the 2-nitro-4-amino compound to the 2:4-diamino compound takes place before the 2:4-dinitrophenylacetic methyl ester has been completely converted to its mono-amino derivative.

A reduction of 2:4-dinitrophenylacetic methyl ester was

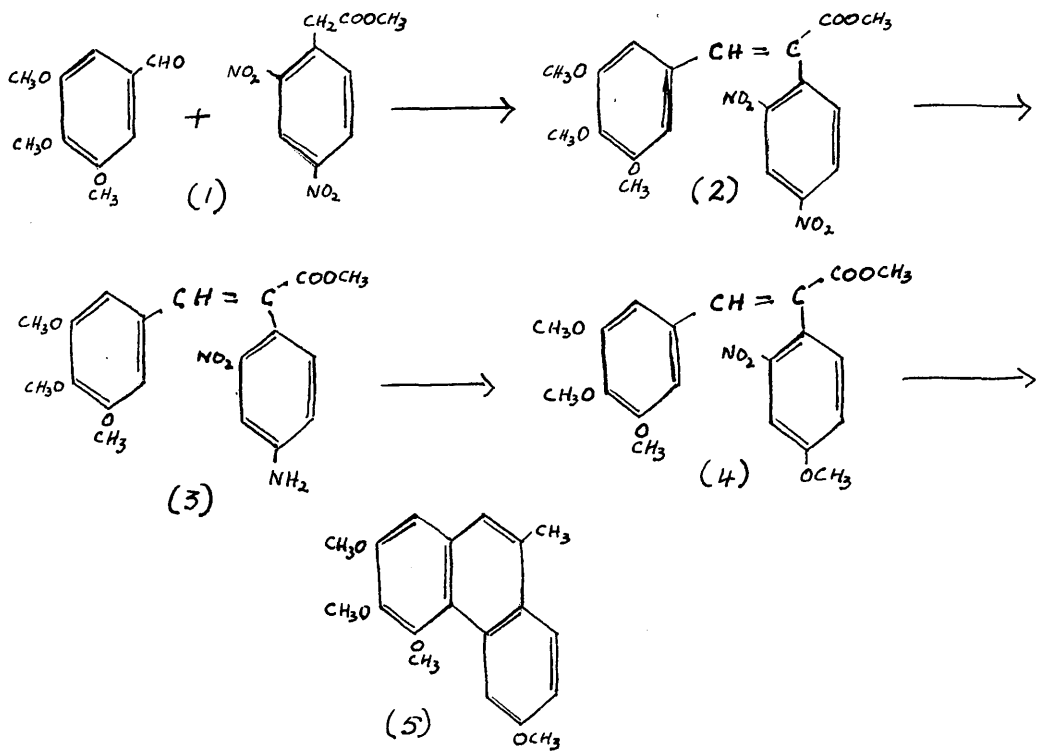
carried out using acetic anhydride as solvent. It was thought that the amine would be acetylated as it was formed, thus rendering its isolation less difficult. The product isolated, an amorphous white solid, could not be purified sufficiently for accurate analysis but appears to be 2:4-diacetaminophenylacetic methyl ester. It was identical with the product obtained by acetylating 2:4-diaminophenylacetic methyl ester. Again it would appear that the reduction of the 2-nitro-4-amino (or probably in this case 4-acetamino) compound to the diamino (or diacetamino) takes place in preference to the reduction of the 2:4-dinitro- to the 2-nitro-4-aminophenylacetic methyl ester.

Paradoxically the best yields (up to 15%) of 2-nitro-4-aminophenylacetic methyl ester occurred when the theoretical amount of hydrogen was not adsorbed, i.e., when carried out in ether solution without allowing for the vapour pressure of the solvent, when approximately only half the theoretical volume of hydrogen was adsorbed.

The following scheme, which was also proposed for the synthesis of 2:3:4:6-tetramethoxy-9-methylphenanthrene, is a modification of Scheme A. It was commenced before it was appreciated that a reduction of the 2:4-dinitro- to the 2-nitro-4-amino compound could not be carried out in satisfactory yield as shown above. This difficulty would apply

also in the case of compound (2) shown in Scheme B.

Scheme B.



In this synthesis the intermediate steps between (4) and (5) are identical with those between (6) and (11) in Scheme A.

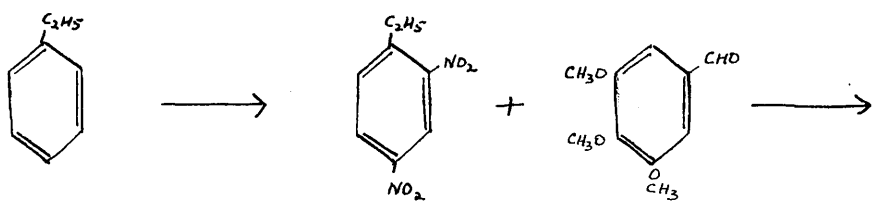
3:4:5-Trimethoxybenzaldehyde, which has been prepared with varying degrees of success by different workers (cf. Sharp[28]), was prepared by the method of Slotta and Heller[34] by reduction of trimethoxybenzoyl chloride with hydrogen in boiling xylene (sulphur free) using palladised barium

sulphate catalyst. All glass Quickfit apparatus was used and the yield of aldehyde found was 50%.

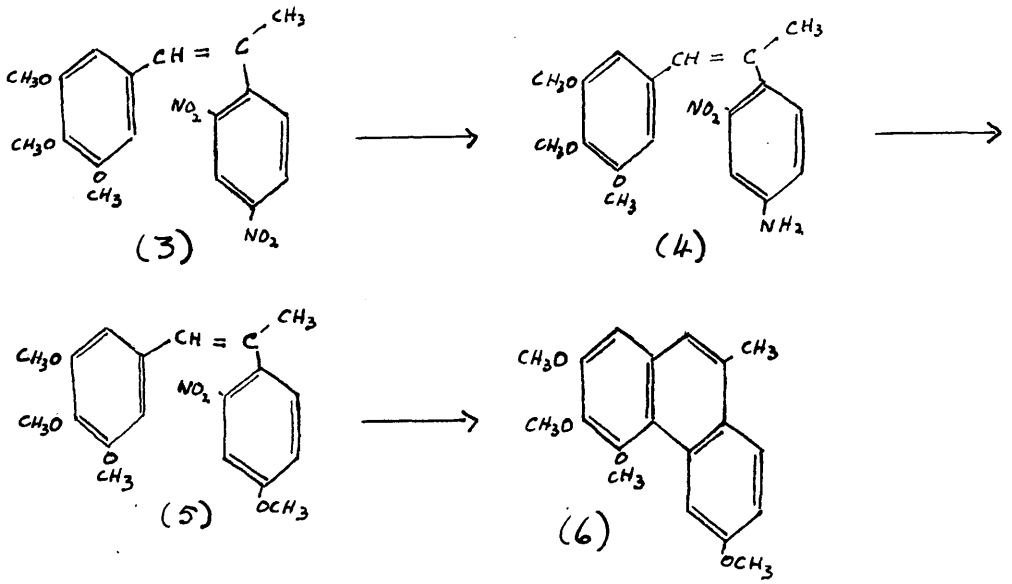
An attempt was made to condense this trimethoxybenzaldehyde with the sodium salt of 2:4-dinitrophenylacetic acid in acetic anhydride solution (Perkin condensation) but this resulted in the decarboxylation of the acid to 2:4-dinitrotoluene. Unsuccessful attempts were made to condense 3:4:5-trimethoxybenzaldehyde with 2:4-dinitrophenylacetic methyl ester to give the compound (2) using bases as condensing agents. Condensing agents used were pyridine, piperidine, piperidine in pyridine solution, and piperidine acetate.

Since the proposed route to 2:3:4:6-tetramethoxy-9-methylphenanthrene had not given the desired result, an alternative scheme, C, for the preparation of this compound was drawn up.

Scheme C.



(1) (2)



This scheme envisaged the condensation of 3:4:5-trimethoxybenzaldehyde and 2:4-dinitroethylbenzene, step (2) to (3), in a manner similar to the condensation of benzaldehyde and 2:4-dinitrotoluene using a base as condensing agent. The reduction of compound (3) to (4) could be carried out by means of polysulphide. Step (5) to (6) involves ring closure by the usual Pschorr method.

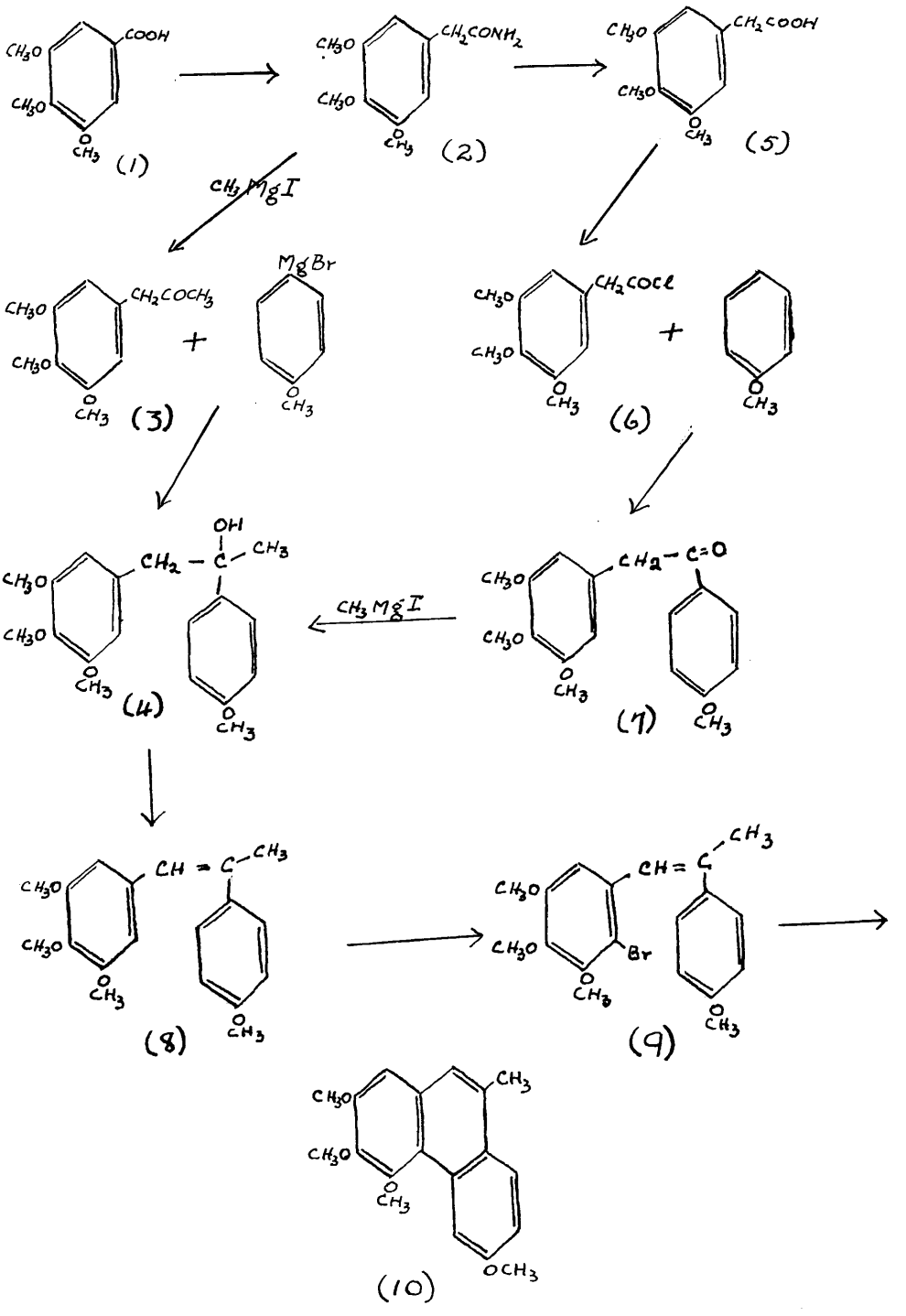
Ethylbenzene was readily prepared in good yield from benzene with ethyl bromide and $AlCl_3$ by a method similar to that used for the preparation of cumene[35]. Initial difficulty was found in preparing 2:4-dinitroethylbenzene by the method of Borsche[36]. As it was thought that sulphonation had preceded nitration thus rendering the latter more difficult, alterations were made in the conditions of nitration

whereby the required 2:4-dinitroethylbenzene was readily obtained. This is a yellow viscous oil (b.p. 168°/11 mm.) and was characterised by reduction with alcoholic ammonium sulphide to 2-nitro-4-aminoethylbenzene (m.p. 42-43°, acetyl derivative m.p. 111°). Borsche states that he had been unable to condense either benzaldehyde or p-nitrobenzaldehyde with 2:4-dinitroethylbenzene. As this proposed scheme did not necessitate the conversion of a COOH- group into a CH_3- group, as in Schemes A and B, it was thought advisable to attempt to carry out this condensation under different conditions. As benzaldehyde was more readily available than 3:4:5-trimethoxybenzaldehyde, it was used in place of the latter in the trial experiments undertaken. Various condensing agents were tried in order to effect this condensation, namely, pyridine, piperidine and piperidine acetate, alone and in pyridine and acetic anhydride solutions at temperatures ranging from 140° to 205° for periods from 2 to 12 hours. In all cases a dark tar was formed from which only benzaldehyde (by steam distillation) and 2:4-dinitroethylbenzene (as 2-nitro-4-aminoethylbenzene by reduction with alcoholic ammonium sulphide) could be isolated and identified. An attempt to condense 3:4:5-trimethoxybenzaldehyde with 2:4-dinitroethylbenzene was also unsuccessful.

The failure of 2:4-dinitroethylbenzene to condense with aldehydes may be due either to steric hindrance caused by the blocking of the $-CH_2-$ group by the o-nitro- group and the CH_3- substituent in the side chain or to the deactivating influence of the CH_3- group on the reactive methylene group. That steric hindrance has an important bearing on such reactions seems to be borne out by the fact that 3:4:5-trimethoxybenzaldehyde could not be condensed with the methyl ester of 2:4-dinitrophenylacetic acid in which the $-CH_2-$ group is activated by the two nitro groups in the ring and by the $-COOCH_3$ group. Borsche[37], however, has shown that o-nitrophenylacetic ethyl ester could be condensed with p-nitrobenzaldehyde but only with the greatest difficulty in contrast to the ease of condensation of aldehydes with p-nitrophenylacetic ethyl ester. It may be said, therefore, that the failure of 2:4-dinitroethylbenzene to condense with aldehydes is due mainly to steric hindrance, but that the deactivating effect of the CH_3- group in the side chain is also partly responsible.

As this synthesis of 2:3:4:6-tetramethoxy-9-methylphenanthrene had been unsuccessful, the following scheme was proposed for the synthesis of the compound:-

Scheme D.



The scheme outlined above involves the synthesis of 3:4:5-trimethoxybenzyl-p-anisyl-methylcarbinol (4) which, as shown, may be prepared in two ways. The first involves the conversion of 3:4:5-trimethoxybenzoic acid into the amide of its higher homologue, trimethoxyphenylacetic acid, by an Arndt-Eistert reaction. This amide has then to be converted into the ketone (3) by means of a Grignard reaction with methyl magnesium iodide. By means of a second Grignard reaction with p-anisyl magnesium bromide it was hoped to convert this ketone into the required carbinol (4). After dehydration to the compound (8) it was hoped to carry out a ring closure by means of lead tetra-acetate or, alternatively, form the bromo derivative (9) and ring close by means of a caustic potash fusion. It is expected that a bromine atom would enter position 2 of the ring containing the three methoxyl groups. This assumption is based on the fact, as will be shown later, that the bromine atom enters such a position in a similar type of compound.

3:4:5-Trimethoxybenzoic acid was readily converted into its acid chloride by means of thionyl chloride, which, in turn, was converted into ω-diazo-3:4:5-trimethoxyacetophenone. This compound prepared on separate occasions by almost identical methods was found to have two different

melting points. One, m.p. 96°, is in agreement with that reported by Baker, Morgans and Robinson[38]: the second had m.p. 101° which is similar to that of Slotta and Muller[39]. This diazo ketone was converted in good yield into 3:4:5-trimethoxyphenylacetamide by means of ammoniacal silver nitrate. An attempt to prepare 3:4:5-trimethoxybenzyl-methyl-ketone by means of a Grignard reaction between methyl magnesium iodide and trimethoxyphenylacetamide by a method based on that used by Jenkins[40] for the preparation of ketones from amides was unsuccessful. A gum was obtained which could not be crystallised nor identified as a ketone.

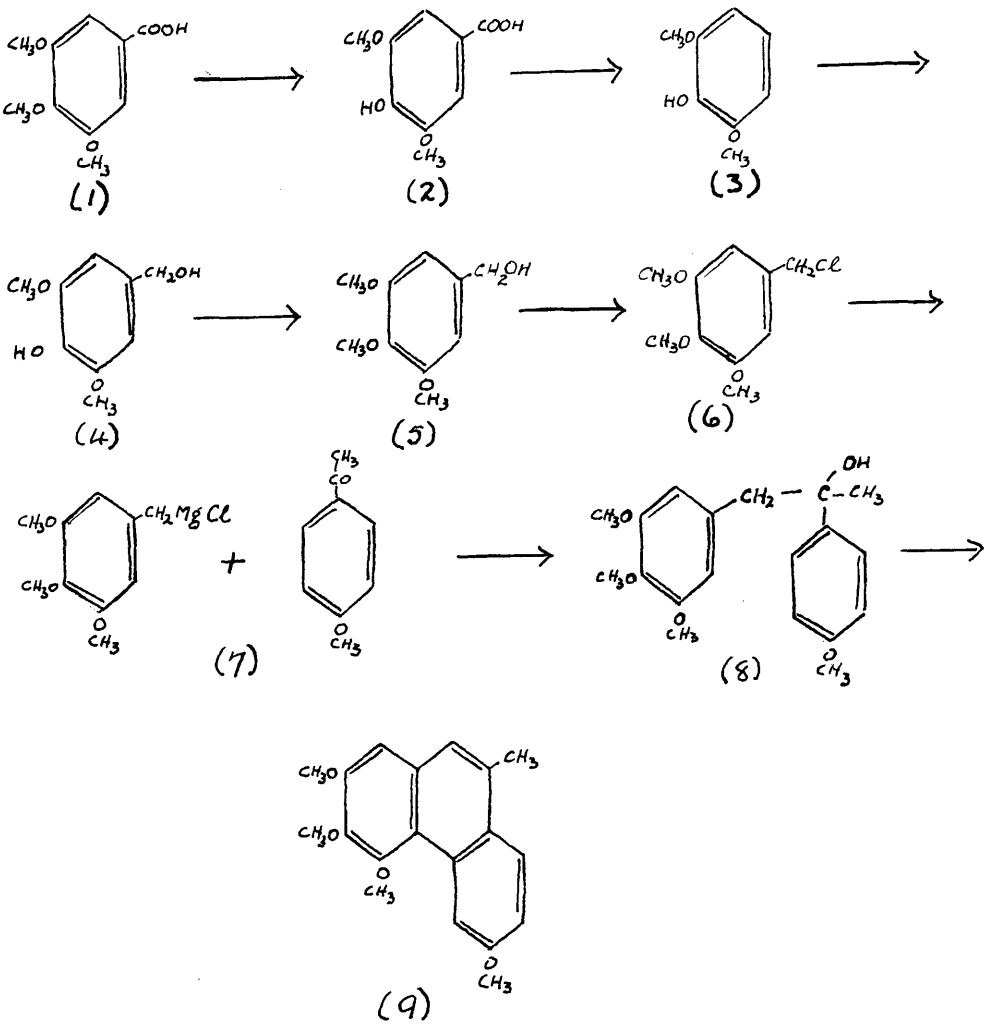
As this route to the carbinol (4) appeared to be unsuccessful, an attempt was made to prepare it in the alternative manner. This involves the hydrolysis of 3:4:5-trimethoxyphenylacetamide to the corresponding acid which, in turn, has to be converted into its acid chloride and condensed with anisole by a Friedel-Craft reaction to give 3:4:5-trimethoxybenzyl-p-anisyl-ketone (7). This ketone has then to undergo a Grignard reaction with methyl magnesium iodide to give the required carbinol (4).

3:4:5-Trimethoxyphenylacetamide was readily saponified to its acid by means of alkali. A difficulty was found in attempting to prepare the acid chloride. Treatment of the acid itself or in benzene solution led to decomposition of

the material even in the cold. Pictet and Finkelstein[41] have reported that on attempting to distil 3:4-dimethoxyphenylacetyl chloride, prepared from the acid with PCl_5 in chloroform, considerable decomposition occurred and so they used the crude acid chloride, after removal of $POCl_3$, in subsequent reactions. A similar technique has been used by us for the preparation of 3:4:5-trimethoxyphenylacetyl chloride. The crude acid chloride in CS_2 was treated with anisole and $AlCl_3$. From this reaction the only identifiable products obtained were unchanged anisole (by steam distillation) and trimethoxyphenylacetic acid. The failure to obtain 3:4:5-trimethoxybenzyl-p-anisylketone by this Friedel-Craft reaction may be due to the quality of the acid chloride used in the reaction. The presence of three methoxyl groups in trimethoxyphenylacetyl chloride appears to render the molecule somewhat unstable and it is possible that the acid chloride was not formed on treatment with PCl_5 or if formed it may have been decomposed while removing $POCl_3$.

This scheme was abandoned in favour of Scheme E, which still involves the preparation of 3:4:5-trimethoxybenzyl-p-anisyl-methylcarbinol, but by a method different to the two methods outlined in Scheme D.

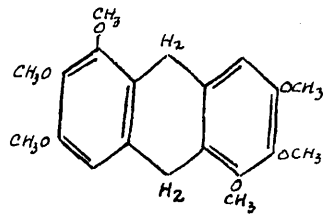
Scheme E.



This scheme involves the conversion of 3:4:5-trimethoxybenzoic acid (1) into 1:3-dimethylpyrogallol (3) by demethylation followed by decarboxylation. Step (3) to (4) involves the introduction of a $-CH_2OH$ by means of a Manasse[42] reaction. Trimethoxybenzyl chloride (6)

has to be converted into trimethoxybenzyl magnesium chloride and condensed with p-methoxyacetophenone to give the required carbinol (8). Intermediate steps between (8) and the final product 2:3:4:6-tetramethoxy-9-methyl-phenanthrene (9) are the same as the last steps in Scheme D.

3:4:5-Trimethoxybenzoic acid was demethylated with concentrated sulphuric acid to give syringic acid (2) which in turn was decarboxylated by distillation at 280-300° to 1:3-dimethylpyrogallol (3) as described by Hahn and Wassmuth[43]. By treatment with 40% formalin and caustic soda this dimethylpyrogallol was converted into syringic alcohol (4). This is the type of method used by Manasse for the introduction of a $-CH_2OH$ group into phenols. Syringic alcohol was methylated first by methyl p-toluene sulphonate, when a yellow oil was obtained which was characterised as the 3:5-dinitrobenzoate. This oil on standing some time became viscous and appeared to have polymerised and a compound which appears to be 1:2:3:5:6:7-hexamethoxy-9:10-dihydroanthracene, XL, formed by condensation of two molecules of the alcohol, was isolated from the resin. This polymerisation is probably due to traces of alkali in the oil which had not been purified by distillation.



XL

After this work had been accomplished it was found that the preparation of syringic alcohol and its methylation to 3:4:5-trimethoxybenzyl alcohol were the subject of German patents[44]. The method given in the German patent for the preparation of syringic alcohol is very similar to the method used by us. The method used by the German workers for the methylation of syringic alcohol, namely, methyl iodide and sodium ethoxide, was found to be better than that using methyl p-toluenesulphonate and alkali. Syringic alcohol was accordingly methylated by their method and then converted into the chloride with dimethylaniline and thionyl chloride as described by Dr. A. Cohen in a private communication to Professor J.W. Cook. In this communication Dr. Cohen states also that he had been unable to form a magnesium chloride from this 3:4:5-trimethoxybenzyl chloride. It has also been reported that 3:4-dimethoxybenzyl chloride does not form a Grignard compound[45]. It was thought that this difficulty might be overcome by the formation of trimethoxybenzyl lithium instead of the Grignard compound. A study of the literature showed that this would

not be feasible as the preparation of benzyl lithium itself presents considerable practical difficulties[46),47)], whilst the presence of methoxyl groups in a benzene ring causes the introduction of the lithium into the ring[48),49)]. It was decided therefore to attempt the preparation of trimethoxybenzyl magnesium chloride. The method used was similar to that used by Gilman and Zoellner[50)] for the preparation of p-methoxybenzyl magnesium bromide. These authors report that p-methoxybenzyl bromide forms a Grignard compound only with difficulty. 3:4:5-Trimethoxybenzyl chloride was treated with magnesium in ether and then in boiling benzene, but no apparent Grignard formation was noticed. However, the product obtained was treated with p-methoxyacetophenone prepared by the method of Strauss[51)]. From the reaction the p-methoxyacetophenone was recovered almost quantitatively by distillation; the remainder, a resin, could not be distilled or crystallised.

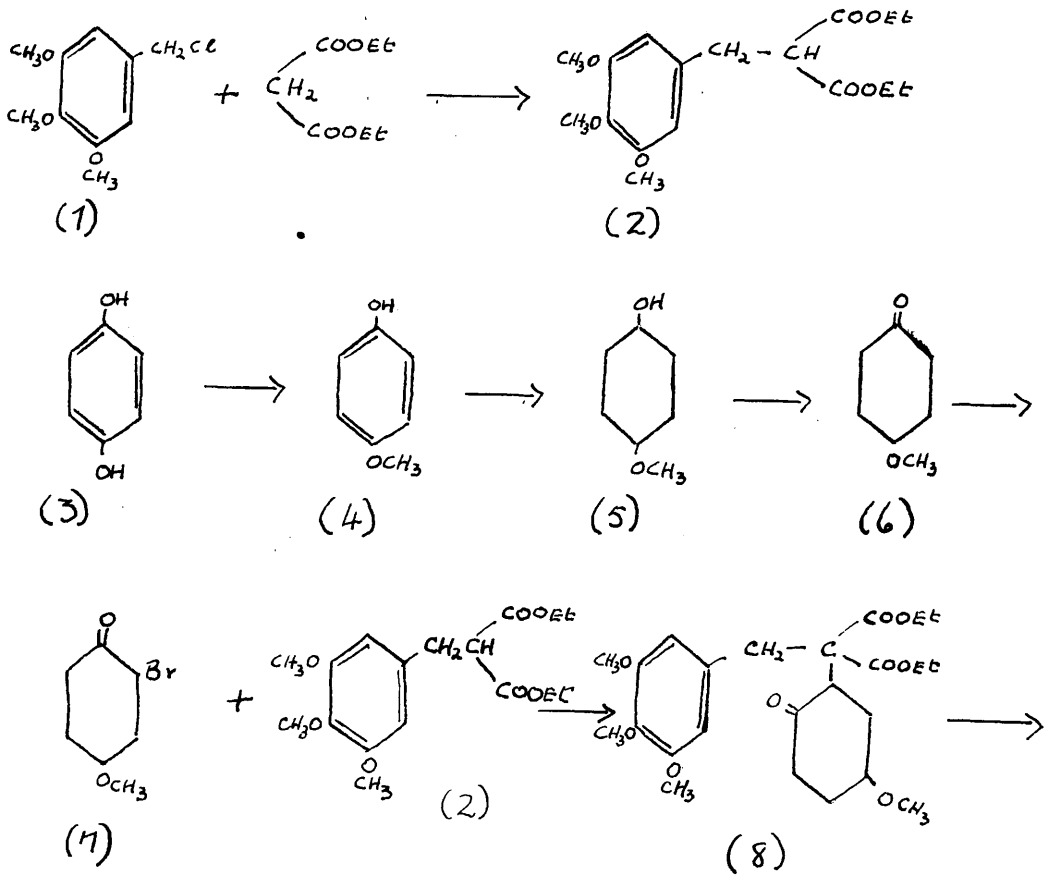
The failure of this attempt to prepare 3:4:5-trimethoxybenzyl-p-anisyl-methylcarbinol (8) by means of a Grignard reaction can be attributed to the fact that 3:4:5-trimethoxybenzyl chloride will not react with magnesium.

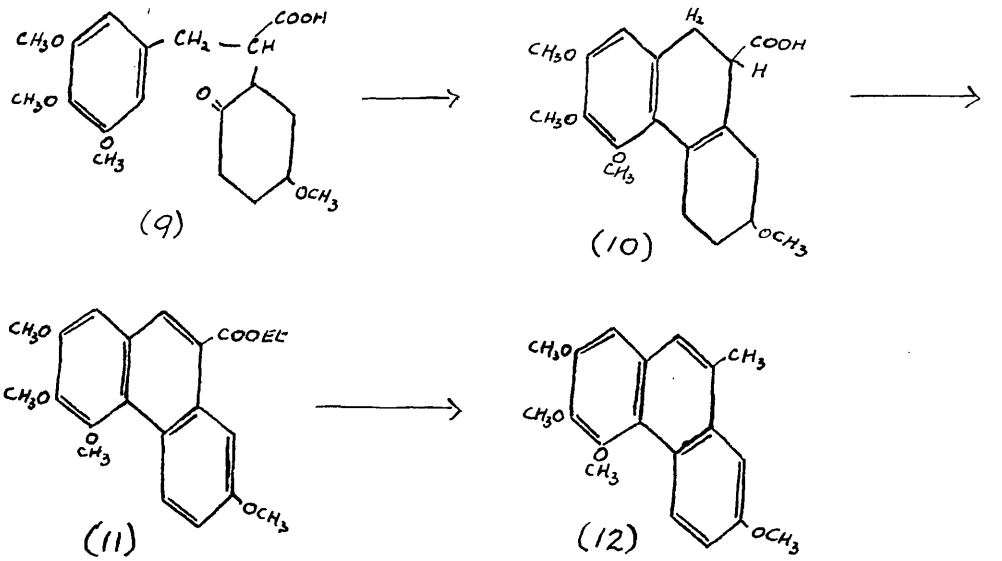
Although the failure to obtain 3:4:5-trimethoxybenzyl-p-anisyl-methylcarbinol has rendered the suggested synthesis

impossible, it has been decided to make use of the trimethoxybenzyl chloride in a synthesis of 2:3:4:7-tetramethoxy-9-methylphenanthrene, XXXV. This compound, as described earlier, is desired also for comparison with the tetramethoxy compound obtained by Windaus[12] from colchinol methyl ether, XX.

Synthesis of 2:3:4:7-tetramethoxy-9-methylphenanthrene.

Scheme F.





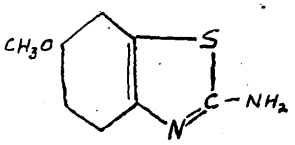
This synthesis is based on that used by Grewe[52] for the preparation of phenanthrene. 3:4:5-Trimethoxybenzyl chloride (1) is used in place of benzyl chloride and 2-bromo-4-methoxycyclohexanone (7) in place of 2-chlorocyclohexanone.

This scheme involves the condensation of trimethoxybenzyl chloride and diethyl malonate to give compound (2), which has then to be condensed with 2-bromo-4-methoxycyclohexanone (7) to give the compound (8). This compound after saponification and decarboxylation to the propionic acid derivative (9) has to be ring closed by means of syrupy phosphoric acid. It was hoped to dehydrogenate this tetramethoxyhexahydrophenanthrene carboxylic acid (10), after

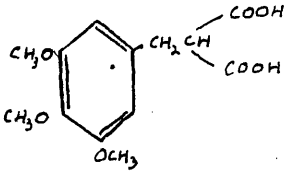
conversion to the ester, to the phenanthrene derivative (11). Conversion of this compound into 2:3:4:7-tetramethoxy-9-methylphenanthrene (12) could be brought about by the same series of reactions as outlined in Scheme A for the conversion of a -COOH group into CH_3-.

Freshly prepared 3:4:5-trimethoxybenzyl chloride, as described in previous scheme, was condensed with diethyl malonate in alcohol solution in presence of sodium ethoxide to give the diethyl ester of 3:4:5-trimethoxybenzylmalonic acid (2). Hydroquinone (3) was converted into its monomethyl ether by the method of Helfer[53] using methyl sulphate and caustic soda. This compound was then reduced to p-methoxycyclohexanol by the method, slightly modified, of Ruggli, Leupin and Bussinger[54]. Only a quarter of the Raney nickel prescribed by these workers was used in this experiment which was carried out at 120/130 atmospheres. The Raney nickel, prepared by a simplified method, was sufficiently active to carry out one complete hydrogenation. p-Methoxycyclohexanol was then oxidised to p-methoxycyclohexanone (6) by means of chromic acid in acetic acid. This method was found to be better than that described by Helfer[53] using dichromate and sulphuric acid. p-Methoxycyclohexanone was converted into 2-chloro-4-methoxycyclohexanone by a method similar to that used by Kotz and

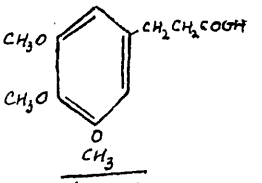
Grethe[55] for the preparation of 2-chlorocyclohexanone. It was obtained as a pale yellow oil, b.p. 105-119°/11 mm. by fractional distillation of the chlorinated product, but could not be characterised as a semicarbazone or other derivative given by a ketone due to the presence of the chlorine atom (Kotz and Grethe do not give any derivative of chlorocyclohexanone). On standing it gradually decomposed. 2-Bromo-4-methoxycyclohexanone was then prepared by direct bromination of p-methoxycyclohexanone with the requisite amount of bromine in chloroform solution. A colourless liquid, b.p. 127-135°/11 mm. was obtained by fractional distillation. This 2-bromo-4-methoxycyclohexanone was characterised as the thiazole derivative, 2-amino-6-methoxy-4:5:6:7-tetrahydrobenzthiazole, XLI. Traumann[56] has shown that α-halogenoketones on heating with thiourea give thiazoles. 2-Bromo-4-methoxycyclohexanone (7), having been thus characterised, was condensed with the sodio derivative of 3:4:5-trimethoxybenzylmalonic ester (2) in benzene to give the diethyl ester of 3:4:5-trimethoxybenzyl-2-keto-5-methoxycyclohexylmalonic acid (8). The product isolated was a yellow gum which could not be crystallised. This gum, without further purification, was hydrolysed with alcoholic alkali in order to convert it into the dicarboxylic acid derivative (9).



XLI



XLII



XLIII

From this hydrolysis there were obtained a sodium salt (A), and, on acidification of the alkaline solution, an insoluble tarry solid (B) and a soluble gum (C). The sodium salt on acidification gave a compound which appears to be 3:4:5-trimethoxybenzylmalonic acid, XLII, as it gave, after decarboxylation at 130° in vacuo, 3:4:5-trimethoxyphenylpropionic acid, XLIII, identified by means of a mixed melting point with synthetic trimethoxyphenylpropionic acid.

The tarry solid (B) was decarboxylated to a red gum which was then treated with syrupy phosphoric acid at 100° to bring about ring closure. This gave a dark gum which was partly soluble in benzene. The material soluble in benzene was obtained as a dark resin after chromatographing its solution in benzene-petroleum ether through a column of alumina. It could not be crystallised. The material insoluble in benzene was obtained, after purification by chromatography, as a white solid, m.p. 230°. This could not be identified from analysis figures.

The soluble gum (C) was decarboxylated in vacuo at 130° and the product obtained treated with syrupy phosphoric acid at 100°. From this attempted ring closure a black tar

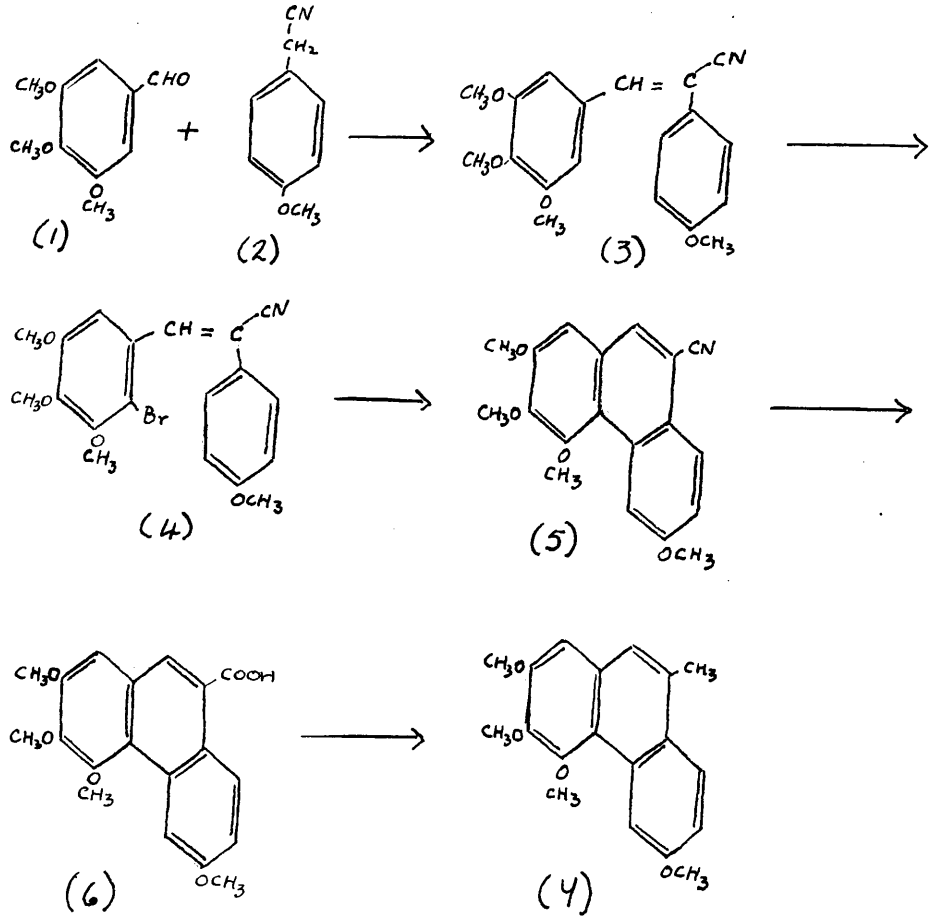
which was not further investigated, and a small amount of 3:4:5-trimethoxyphenylpropionic acid were obtained.

The appearance of 3:4:5-trimethoxyphenylpropionic acid at different stages in these last steps of the synthesis shows that the condensation of the diethyl ester of trimethoxybenzylmalonic acid (2) and 2-bromo-4-methoxycyclohexanone (7) had not been complete. Of the other products isolated in this synthesis, one was a resin which could not be crystallised, and the other was a solid m.p. 230° which was not identified.

This synthesis, which had proved rather disappointing, was not further investigated owing to a shortage of material. It was felt that this somewhat long and complex scheme for the synthesis of 2:3:4:7-tetramethoxy-9-methylphenanthrene did not offer sufficient prospect of success to warrant preparation of a fresh supply of material.

At this stage research on the colchicine problem was terminated and work on polycyclic hydrocarbons was undertaken. Most of the experiments on compounds related to colchicine described hereafter were carried out before the work on polycyclic hydrocarbons was begun.

Scheme G.



This synthesis involves the conversion of α-cyano-α-p-anisyl-β-(3:4:5-trimethoxyphenyl)ethylene, prepared by Cook and Engel[26], into its bromo- derivative (4). This has then to be ring closed by the method of Hewett[57] by means of a potash fusion. Intermediate steps between (6) and (7) are the same as those described in Scheme A for the conversion of 2:3:4:6-tetramethoxyphenanthrene-9-carboxylic acid into the 9-methyl derivative.

3:4:5-Trimethoxybenzaldehyde (1) and p-anisylacetonitrile (2) readily condense in the presence of alcoholic alkali to give compound (3). This compound was brominated in chloroform solution to a mono bromo derivative. That this compound has structure (4) was proved in the following way. This brominated product was hydrolysed with alcoholic potash to give a neutral product which was not isolated pure but is probably 3:4:5:4'-tetramethoxystilbene. This product, a gum, was oxidised with alkaline permanganate. From the products of oxidation there was isolated 2-bromo-3:4:5-trimethoxybenzoic acid, which proves that the bromine atom in compound (4) is attached to the same ring as the three methoxyl groups.

Attempts were made to ring close the bromo compound (4) to 2:3:4:6-tetramethoxy-9-cyanophenanthrene (5) with fused potash at 240°, with potash in boiling quinoline and with potassium acetate in naphthalene at 190°. These attempts were unsuccessful, most of the material being recovered unchanged in each case.

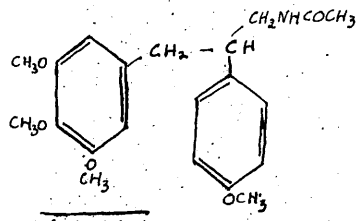
This scheme was not pursued further as 2:3:4:6-tetramethoxy-9-methylphenanthrene has now been synthesised in this department by Dr. J.D. Loudon by means of a Pschorr type synthesis from the hitherto rather inaccessible 2-nitro-3:4:5-trimethoxybenzaldehyde which he obtained by a novel method.

Additional experiments on compounds related to colchicine.

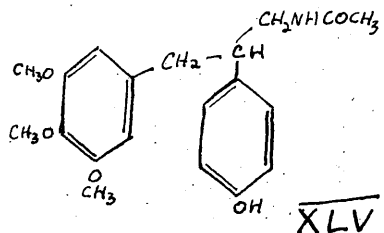
Attempted preparation of N-acetyl-β-4-hydroxyphenyl-γ-(3:4:5-trimethoxyphenyl)propylamine.

It has been known for a long time that the complete ring system of an alkaloid is not always essential for the specific action of the alkaloid. This has been known for many years in the case of cocaine and nicotine and more recently Buth, Kulz and Rosenmund[23] have shown that it is also the case with papaverine. In the introduction of this thesis some of the work of Lettré[24] has been described. He has shown that certain α-β-diphenylamines have the mitosis poisoning action of colchicine. He reported also that N-acetyl-β-p-anisyl-γ-(3:4:5-trimethoxyphenyl)propylamine, XXXIII, synthesised by Cook and Engel[26] was without effect on chicken heart fibroblasts. Dr. Brues of Harvard has tested the effect of this compound on the liver of a rat and has reported that 10 mg. gave a completely abnormal nuclear picture. The effects were at their best four days after administration of the dose. Dr. Brues says that this is probably due to the low solubility of the compound. It was decided to prepare N-acetyl-β-p-hydroxyphenyl-γ-(3:4:5-trimethoxyphenyl)propylamine, XLV, in the hope that it would have greater solubility than compound

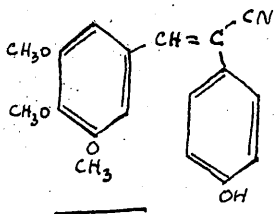
XXXIII, thus increasing the characteristic effect on mitosis in cells.



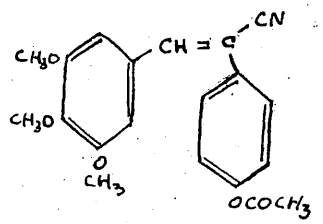
XXXIII



XLV



XLVI



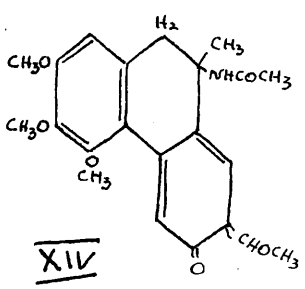
XLVII

∝-Cyano-∝-p-hydroxyphenyl-β-(3:4:5-trimethoxyphenyl)ethylene, XLVI, was prepared by the method of Cook and Lawrence[58] from 3:4:5-trimethoxybenzaldehyde and p-hydroxyphenylacetonitrile using NaOEt as condensing agent. When NaOH was used in place of NaOEt the same product, XLVI, was obtained and not the unidentified product obtained by Cook and Lawrence. Lapsley[29] has attempted to hydrogenate this unsaturated nitrile to the saturated propylamine using palladised charcoal as catalyst. He did not succeed in this attempt, adsorption of hydrogen ceasing before the requisite amount was adsorbed; nor could he identify the product of reduction.

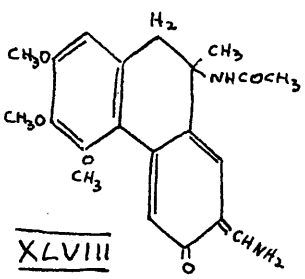
An attempt has been made to reduce the compound XLVI to (β-p-hydroxyphenyl-γ-(3:4:5-trimethoxyphenyl)propylamine by the method used by Freund and Remse[59] in the preparation of diphenylpropylamines from α-cyanostilbenes by a reduction with sodium and alcohol. This was not successful, the only material isolated besides unchanged unsaturated nitrile was a small amount of neutral material which appears to be the amide formed by hydrolysis of the nitrile. A hydrogenation of α-cyano-α-p-hydroxyphenyl-β-(3:4:5-trimethoxyphenyl)ethylene with Adams' catalyst in acetic anhydride solution was carried out. By this means it was hoped to acetylate the amine as it was formed to give compound XLV. After an initial adsorption of hydrogen equivalent to one third of the required amount, there was a very noticeable decrease in the rate of adsorption. After 48 hours the requisite amount of hydrogen appeared to have been adsorbed, but the fact that a high percentage of the starting material was recovered as its acetyl derivative, XLVII, indicated that the reaction had not taken the expected course. The remainder of the material isolated from the hydrogenation consisted of a small amount of gum which could not be crystallised.

Preparation of Colchiceineamide.

During his researches into the structure of the colchicine molecule Zeisel[60] obtained a compound $C_{21}H_{24}O_5N_2$ on treating colchicine, $C_{22}H_{25}O_6N$, with alcoholic ammonia. This compound on hydrolysis with alkali gave colchiceine. Zeisel considered this compound to be the amide of an acid, colchiceine being the acid and colchicine the methyl ester of the acid. The work of Windaus[5),12)] has shown that colchicine is not the methyl ester of an acid but appears to be the methyl ether of a hydroxymethylene-ketone and can be represented by structure XIV. This "amide" obtained by Zeisel can now be regarded as an aminomethylene ketone of structure XLVIII.



XIV



XLVIII

As the method of Zeisel[60] for the preparation of colchiceineamide by heating colchicine with 5% alcoholic ammonia did not prove entirely satisfactory, a modification was made in the method. Instead of using 5% alcoholic ammonia strong aqueous alcoholic ammonia was used. Zeisel

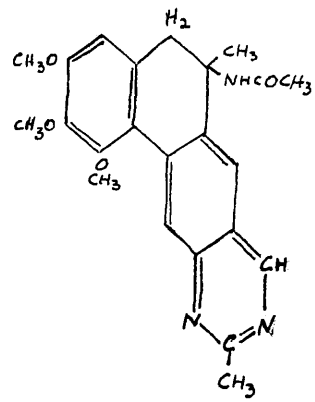
reported that on crystallising from alcohol he obtained the amide in two forms, one containing one molecule of alcohol of crystallisation. We have found that the amide can be obtained in two forms, one readily soluble in acetone, the other sparingly. They can be crystallised from acetone-benzene and acetone-alcohol respectively. Neither of the two forms melts sharply, both decompose about 250°, sintering earlier. They may be regarded as geometrical isomers. The existence of geometrical isomers of hydroxymethylene compounds has been shown already in the case of a colchicine derivative by the formation of two stereoisomeric dibenzenesulphonyltrimethylcolchicinic acids[5),12)].

In a short interim report on biological tests carried out on this colchiceineamide Dr. W.E. Gye of the Imperial Cancer Research Fund laboratories states that, like colchicine, it has the property of preventing cell division, consequently causing the destruction of the cells. Whereas colchicine attacks equally malignant and normal cells there is some indication that the amide has a greater effect on malignant cells. Colchicine causes haemorrhage in tumours, both local and metastases, of treated animals, the amide does not. Dr. Gye states that it does not appear feasible, however, to use colchiceineamide in the treatment of cancer on account of its general toxicity.

Attempted preparation of a pyrimidine derivative related to colchicine.

It was decided to make use of the reactive hydroxymethylene-ketone grouping $-\overset{O}{\overset{\|}{C}}-\overset{|}{C}=CHOR$, which Windaus has proved to exist, although not conclusively, in colchicine ($R=CH_3$) and colchiceine ($R=H$) in order to add a fourth ring on to the colchicine skeleton. It was thought that compounds of this type related to colchicine might be of biological importance.

An attempt was made to prepare the compound, 4:5-[6:7-(3:4:5-trimethoxy-9-methyl-9-acetamido-9:10-dihydrophenanthrene)]-2-methylpyrimidine, XLIX. This involves the addition of a methylpyrimidine on to the colchicine skeleton.



XLIX

As no method was known for the synthesis of pyrimidines from hydroxymethylene-ketones, it was decided to use a method similar to that used by Todd and his co-workers[61] and by Andersag and Westphal[62] in the preparation of

pyrimidines required in the vitamin B_1 synthesis. These workers condensed acetamidine with the compound containing the reactive group (in their case ethyl formylsuccinate) in the presence of sodium ethoxide.

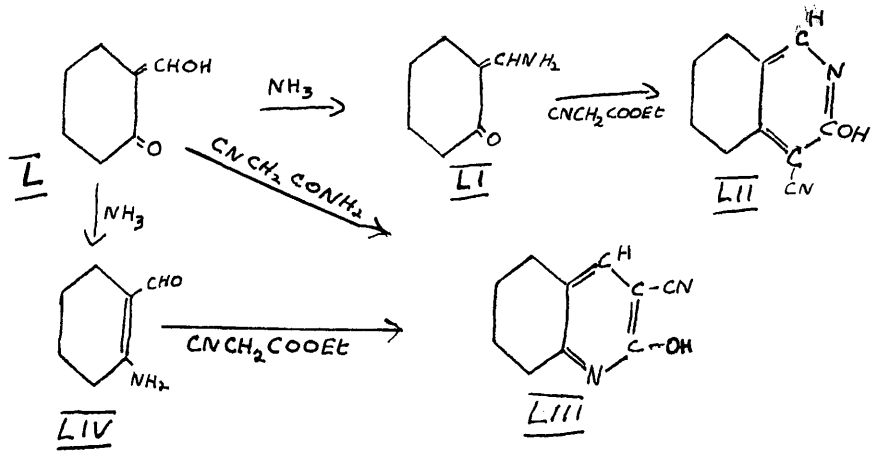
Colchicine was treated with acetamidine hydrochloride and sodium ethoxide in absolute alcohol. From the reaction there was isolated a dark green solid which could not be crystallised. It appears, however, to be crude unchanged colchicine as it gives colchiceine on hydrolysis with HCl.

An attempt to condense colchiceine with acetamidine was also unsuccessful, colchiceine being recovered unchanged. The apparent inability of acetamidine to condense with colchicine and colchiceine through the medium of the hydroxymethylene-ketone group, stated by Windaus to be present in these compounds, is in accord with the fact that they do not react with carbonyl reagents like semicarbazide, a reaction which would be expected of a compound containing the hydroxymethylene-ketone group.

Preparation of a pyridine derivative related to colchicine.

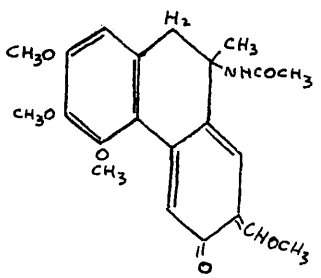
Another compound which was considered might be of biological interest was one in which a pyridine ring was added to the colchicine skeleton in a similar manner to the

formation of the pyrimidine above. A synthesis of this type involving a hydroxymethylene-ketone grouping has been used by Basu and Bannerjee[63] for the preparation of isoquinoline compounds and by Sen-Gupta[64] for the synthesis of quinoline derivatives. Basu[65] has also condensed ethyl cyclohexanone-2-carboxylate with cyanacetamide to give an isoquinoline derivative. Basu and Bannerjee condensed aminomethylene-cyclohexanone, LI, with cyanacetic ester and obtained a compound which they proved to be an isoquinoline, LII. Sen-Gupta condensed hydroxymethylene-cyclohexanone, L, with cyanacetamide and obtained a compound which he proved to be a quinoline derivative, LIII. He also claims to have obtained this same quinoline compound by condensing the amide of hydroxymethylene-cyclohexanone with cyanacetic ester. In this case the amide of hydroxymethylene-cyclohexanone would have to have structure LIV instead of LI. Sen-Gupta gives no particulars of his amide and so no comparison with the compound obtained by Basu and Bannerjee is possible.

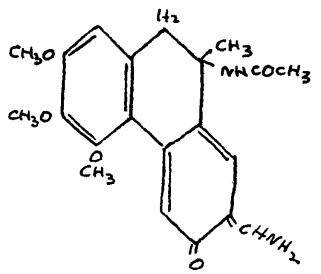


An explanation of this apparent difference in the structure of the aminomethylene-cyclohexanone may be that Basu and Bannerjee carried out the condensation with cyanacetic ester by means of sodium ethoxide in alcohol while Sen-Gupta used piperidine in alcohol as condensing agent. It is possible, however, that Sen-Gupta formed, not the amide of hydroxymethylene-cyclohexanone, but the ammonium salt which breaks up in solution to hydroxymethylene-cyclohexanone, L, and ammonia. The ammonia could then react with the cyanacetic ester to form cyanacetamide which then reacts with the hydroxymethylene cyclohexanone as before to form the quinoline derivative, LIII. It is noteworthy in this respect that colchiceine with ammonia forms the ammonium salt and not the amide.

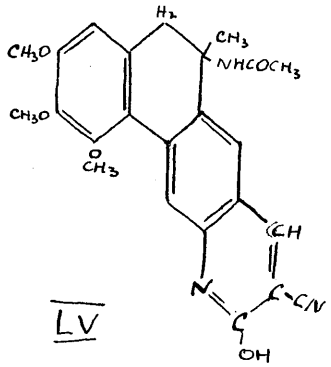
It was thought that colchicine, XIV, or colchiceine-amide, XLVIII, might be condensed with cyanacetic ester and cyanacetamide respectively to give a compound which may be either a quinoline, LV, or an isoquinoline derivative, LVI.



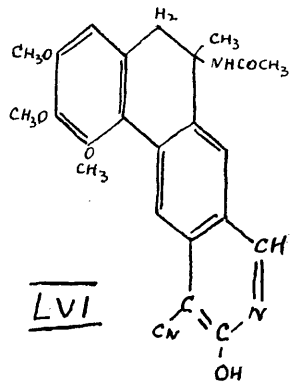
XIV



XLVIII



LV

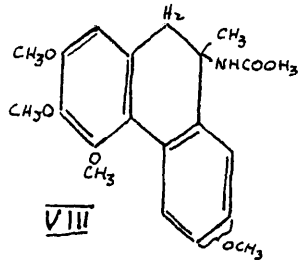


LVI

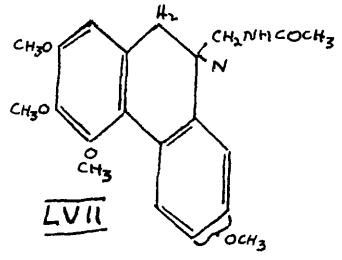
Unsuccessful attempts were made to condense colchiceine-amide with cyanacetic ester using NaOEt in alcohol and piperidine in alcohol as condensing agents, the amide being recovered in each case. Colchicine was condensed with cyanacetamide at room temperature using NaOEt in alcohol as condensing agent. The product isolated was an orange coloured amorphous solid, soluble in alkali and precipitated from alkaline solution with HCl. It could not be crystallised and was prepared for analysis by repeated dissolving in alcohol and precipitation from hot solution with benzene. The result of analysis was not very satisfactory as a residue was obtained on combustion, which may have been due to occluded salt. If allowance is made for the residue the analysis figures correspond to those required by the hydrochloride of compound LV or LVI. Further investigation of this compound has been restricted due to a shortage of colchicine.

Effect of a dehydrating agent on N-acetylcolchinol methyl ether.

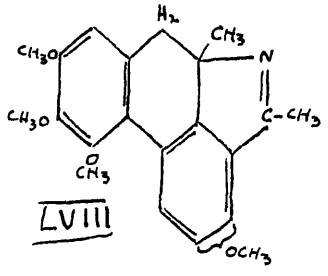
N-Acetylcolchinol methyl ether is a transformation product of colchicine and according to Windaus[5] should have structure VIII. As has been reported in the introduction, Cohen, Cook and Roe[15] have pointed out various inconsistencies in the Windaus structure and have suggested two possible alternative structures. One of their alternative structures for N-acetylcolchinol methyl ether would be LVII.



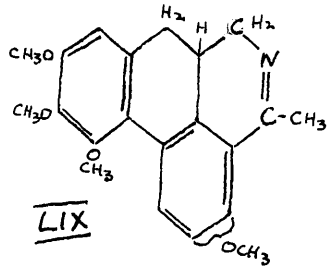
VIII



LVII



LVIII



LIX

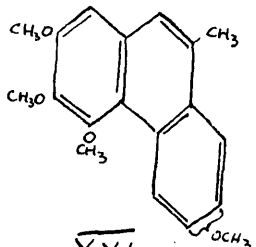
If N-acetylcolchinol methyl ether of structure VIII were ring closed by removal of a molecule of water, it should give a compound of structure LVIII. This would involve the formation of a five membered ring containing

nitrogen by a type of method not known for the synthesis of indoles. Actually this compound would be an isoindole, a type of compound which does not appear to exist. If N-acetylcolchinol methyl ether of structure LVII were ring closed by removal of a molecule of water to give compound LIX, this would involve the formation of a six membered ring containing nitrogen by a type of ring closure well known in the synthesis of isoquinoline derivatives.

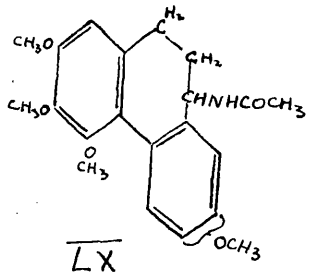
A report has recently appeared of the synthesis of trimethylene isoquinolines from the acyl derivatives of 1-aminomethyl-1:2:3:4-tetrahydronaphthalene by a similar method[66].

Should ring closure of N-acetylcolchinol methyl ether take place by removal of water, this would indicate to a large degree that N-acetylcolchinol methyl ether has structure LVII instead of the structure VIII, suggested by Windaus, with corresponding change in the structure of colchicine.

N-Acetylcolchinol methyl ether was heated with P_2O_5 in boiling xylene for 15 minutes. A compound was isolated from this reaction which crystallised from methyl alcohol in white plates m.p. 100°. This compound is a neutral substance and contains no nitrogen, and so ring closure of the type proposed above cannot have taken place.



XXI



LX

This compound m.p. 100° was analysed and figures corresponding to the formula $C_{19}H_{20}O_4$ were obtained. It was found also that this compound after melting at 100° solidifies on cooling and melts again at 109-111°. Windaus[12], by the exhaustive methylation of colchinol methyl ether, has obtained a compound $C_{19}H_{20}O_4$ which he calls 2:3:4:6-(or 7-)tetramethoxy-9-methylphenanthrene, XXI. This crystallises in plates from methyl alcohol and has m.p. 111°. Thus it appears that in the above dehydration experiment N-acetylcolchinol methyl ether has suffered loss of acetamide to give the same compound as Windaus obtained by exhaustive methylation.

It is of interest to note here that Bursian[14] obtained acetamide from colchicine when attempting to dehydrogenate the latter with selenium. Windaus[5),12] has also split off benzamide from N-benzoylcolchide, which he regards as a dihydronaphthalene derivative, to give a fully aromatic structure.

Loss of acetamide would appear to take place more readily from a compound of structure VIII which is a 9-amino-9:10-dihydrophenanthrene derivative than from one of structure LVII, as in the latter case molecular rearrangement of the H atoms would require to take place to give compound XXI. This, however, cannot be taken as confirmation of structure VIII for N-acetylcolchinol methyl ether and denial of the fact that it has structure LVII. As has been pointed out by Cohen, Cook and Roe[15], the structure might contain a seven membered ring as in LX, since the only proof that this tetramethoxy compound, m.p. 111° obtained by Windaus is a phenanthrene derivative is that it gives 9-methylphenanthrene on demethylation followed by a zinc dust distillation. It is possible that the phenanthrene structure could arise by molecular rearrangement of the seven membered ring during the zinc dust distillation.

Confirmation of the structure of this tetramethoxy compound obtained by Windaus by the synthesis of 2:3:4:6- and 2:3:4:7-tetramethoxy-9-methylphenanthrene has been the main object of this research, syntheses which have so far proved unsuccessful.

Since the completion of this work the compound 2:3:4:6-tetramethoxy-9-methylphenanthrene has been synthesised in

this department by Dr. J.D. Loudon by means of a Pschorr type of phenanthrene synthesis, as has been reported earlier. This compound, m.p. 108°, is not the same as the compound we obtained by the action of P_2O_5 on N-acetyl-colchinol methyl ether. If our compound is the same as that obtained by Windaus, as it appears to be, and the latter is a tetramethoxyphenanthrene derivative, then it must be 2:3:4:7-tetramethoxy-9-methylphenanthrene and not the 2:3:4:6- isomer.

Experimental.

(All melting points are uncorrected).

Methyl ester of 2:4-dinitrophenylacetic acid.

2:4-Dinitrophenylacetic acid (70 gms.) was suspended in methyl alcohol (525 cc.) and dry HCl gas passed in for about 1 hour. This was followed by refluxing on water bath for 3 hours. This solution on concentration gave an oil which solidified on standing and was taken up in benzene (350 cc.), washed with dilute sodium carbonate solution and then with water. The benzene solution was dried over $CaCl_2$ and then the solvent was distilled off leaving a pale yellow oil which crystallised on standing. Recrystallised from methyl alcohol (charcoal) in pale yellow needles, m.p. 83°. Yield 44 gms. 2:4-Dinitrophenylacetic acid can be recovered by acidification of the carbonate washings.

Catalytic reduction of the methyl ester of 2:4-dinitrophenylacetic acid to 2-nitro-4-aminophenylacetic methyl ester.

A). 2:4-Dinitrophenylacetic methyl ester (2.5 gms.) dissolved in dry ether (250 cc.) was shaken with palladium black (0.1 gm.) in an atmosphere of hydrogen under ordinary conditions of temperature and pressure until the requisite amount of hydrogen for the reduction of one nitro group was

absorbed (700 cc. at N.T.P.). The yellow coloured solution was then filtered off from catalyst and the solvent removed under slight vacuum. The residue, an oil, was taken up in dry benzene and dry HCl gas passed in. A flocculent precipitate of the hydrochloride of the base was formed which was filtered off and washed with dry benzene. Some tarring of the solid occurred during the filtration. The solid was then dissolved in cold water and neutralised carefully with ammonia. A dark yellow solid, somewhat sticky, was precipitated. This 2-nitro-4-aminophenylacetic methyl ester was recrystallised from aqueous methyl alcohol (charcoal) in fine yellow needles, m.p. 90° (literature, 93°). Best yield obtained was 0.3 gm.

B). 2:4-Dinitrophenylacetic methyl ester (1 gm.) dissolved in absolute alcohol (250 cc.) was reduced as above. On removal of the alcohol after reduction considerable tarring occurred. In this experiment it was also found that the amine hydrochloride was not completely soluble in water, a small amount of insoluble material was filtered off before neutralising the solution. The yield of 2-nitro-4-aminophenylacetic methyl ester was very small.

C). Reduction of 2:4-dinitrophenylacetic methyl ester (3 gm.) in dioxan (50 cc.) was carried out as above. In

this experiment also considerable tarring occurred during the removal of solvent, even in vacuo. A certain amount of insoluble hydrochloride was also found. Yield of 2-nitro-4-aminophenylacetic methyl ester, m.p. 89°, 0.15 gm.

D). 2:4-Dinitrophenylacetic methyl ester (2 gm.) dissolved in acetic anhydride (50 cc.) was reduced as above. After filtering off the catalyst the acetic anhydride solution was concentrated in vacuo to about 15 cc. On cooling a white amorphous solid was precipitated. This was filtered off and washed with hot benzene. It begins to darken about 175° and decomposes about 195°. It could not be crystallised. It was prepared for analysis by precipitation several times from acetic anhydride followed by washing with hot benzene.

Analysis. Found: C = 57.84%, H = 5.94%, N = 11.09%. 2:4-Diacetaminophenylacetic methyl ester, $C_{13}H_{16}O_4N_2$, requires C = 59.09%, H = 6.06%, N = 10.66%.

The acetic acid mother liquor, after removal of solid, on evaporation to dryness gave a red oil, neutral in character, which could not be crystallised.

E). 2:4-Dinitrophenylacetic methyl ester (2.5 gm.) in dry ether (250 cc.) was hydrogenated as above in A), except that allowance was made for the vapour pressure of

the solvent. The volume of hydrogen absorbed under these conditions was 1400 cc. On standing overnight after absorption of the hydrogen a white solid crystallised out. This was filtered off and recrystallised from ether in white needles, m.p. 100-101°. The original ether solution was concentrated in stages until no more solid m.p. 100° was obtained. This solid appears to be 2:4-diaminophenylacetic methyl ester, as on acetylation it gives the same compound as obtained in D) above. The ether solution was concentrated, giving an oil. This oil was dissolved in hot methyl alcohol and water added. A dark solid was deposited and on cooling a small amount of fine yellow needles, m.p. 86°, were obtained from the supernatent liquid. This gave no depression of melting point when mixed with 2-nitro-4-aminophenylacetic methyl ester (m.p. 89°). The dark solid deposited in this crystallisation was crystallised from methyl alcohol giving trace of orange solid, m.p. 76-79°. Mixed m.p. with 2:4-dinitrophenylacetic methyl ester (m.p. 83°) gave m.p. 77-79°.

Attempted preparation of 2-nitro-4-hydroxyphenylacetic methyl ester.

2:4-Dnitrophenylacetic methyl ester (2.5 gm.) was reduced as in previous experiment (method A). After removal of solvent the residue, an oil, was extracted with 3N HCl. To the hydrochloric acid solution, cooled to 0°, was added sodium nitrite (0.7 gm.) in a few cc. of water. The red coloured solution was then poured into boiling N H_2SO_4 and allowed to cool. On standing a red solid separated out. This was filtered off and the solution extracted with ether. The ether extract, together with the solid, was extracted with a dilute solution of NaOH. On acidification of the alkaline extract a red solid was precipitated. An attempt to recrystallise this from aqueous alcohol gave a red-brown amorphous powder, m.p. 180-185° (decomp.). Yield, 0.25 gm.

2:4-Dinitrophenylacetylhydrazide.

2:4-Dinitrophenylacetic methyl ester (2 gm.), 50% hydrazine hydrate (3.5 cc.) and methyl alcohol (20 cc.) were heated on the water bath for 1 hour. On cooling pale yellow needles crystallised out and a further crop was obtained by concentrating the mother liquor. Recrystallised from methyl alcohol they have m.p. 135.5-137°. On heating with dilute HCl this compound forms a hydrochloride, m.p.

$>180^{\circ}$, from which the original compound can be regenerated by treatment with carbonate solution.

Analysis. Found N = 23.44%. $C_8H_8O_5N_4$ requires N = 23.33%.

3:4:5-Trimethoxybenzoyl chloride.

3:4:5-Trimethoxybenzoic acid (50 gms.), dried at 120°, was heated under reflux with thionyl chloride (250 gms.) until SO_2 and HCl were no longer evolved, about 2 hours. Excess thionyl chloride was then distilled off, finally under reduced pressure. The 3:4:5-trimethoxybenzoyl chloride was distilled at $168\text{-}170^{\circ}/10$ mm. On cooling the liquid distillate crystallised to a white solid, m.p. 79.5-80.5°. Yield, 50 gms.

3:4:5-Trimethoxybenzaldehyde.

This preparation was carried out by a method slightly modified from that used by Slotta and Heller[34]. A steady stream of hydrogen purified by passing through $KMnO_4$ solution and dried by means of solid KOH and concentrated H_2SO_4, was passed into a boiling solution of 3:4:5-trimethoxybenzoyl chloride (40 gms.) in pure dry xylene (200 cc.), 4% palladised $BaSO_4$ (12.5 gms.) being present as catalyst. All glass Quickfit apparatus was used. After 30 hours the

reaction was stopped and the cold xylene solution was filtered off from insoluble material and catalyst. The xylene solution was then shaken with a saturated sodium bisulphite solution (250 cc.) until the bisulphite compound separated out. This was filtered off and the xylene separated from the bisulphite solution. The bisulphite compound, together with the aqueous mother liquor, was treated with excess concentrated HCl. On removal of SO_2 at the water pump the 3:4:5-trimethoxybenzaldehyde precipitated and was filtered off, washed with water and dried in a desiccator. Yield, 20 gms., m.p. 68-70°. Recrystallised from benzene/pet. ether in white plates, m.p. 71-73°. The insoluble material filtered off along with the catalyst was recrystallised from xylene in white needles, m.p. 160° and appears to be 3:4:5-trimethoxybenzoic anhydride as reported by Sharp[28].

Attempted condensation of 3:4:5-trimethoxybenzaldehyde and sodium salt of 2:4-dinitrophenylacetic acid.

Sodium 2:4-dinitrophenylacetate (1.45 gm.) and 3:4:5-trimethoxybenzaldehyde (1.16 gm.) were heated with acetic anhydride (20 cc.) on the water bath for 11 hours. The solution while hot was poured into water and left till the acetic anhydride had decomposed when a precipitate of fine

needles was obtained. This material has m.p. 70-71°. Mixed melting point with 3:4:5-trimethoxybenzaldehyde is 45-55°. Mixed melting point with 2:4-dinitrotoluene (m.p. 70°) is 70°.

Attempted condensation of 3:4:5-trimethoxybenzaldehyde and 2:4-dinitrophenylacetic methyl ester.

3:4:5-Trimethoxybenzaldehyde (1 gm.) and 2:4-dinitrophenylacetic methyl ester (1.25 gm.) were boiled with pure dry pyridine (10 cc.) for 2 hours. The dark red solution was then cooled and poured into water (75 cc.). A dark red oil separated out which solidified on standing. Recrystallisation from methyl alcohol containing a few drops of water gave substance m.p. 81-82°. Mixed m.p. with 2:4-dinitrophenylacetic methyl ester (m.p. 83°) is 81-82°. Substance is therefore unchanged ester.

Similar results were obtained using piperidine in pyridine, piperidine and piperidine acetate as condensing agents. The only product isolated from the dark condensation product in each case was 2:4-dinitrophenylacetic methyl ester.

Ethylbenzene.

Finely powdered aluminium chloride (12.5 gm.) was added to boiling benzene (thiophene free, 500 cc.) and boiling continued for a few minutes. Ethyl bromide(90 gm.) in

pure benzene (210 cc.) was then added to the boiling solution over a period of 3 hours, and refluxing continued one hour longer. The solution when cold was decomposed with ice and HCl. The aqueous layer was separated off and the benzene layer washed twice with water and dried over $CaCl_2$. Excess benzene was distilled off on the water bath. The remaining liquid was distilled from an oil bath using an efficient fractionating column. The fraction b.p. 131-135° was taken as pure ethylbenzene and was redistilled. Yield, 60 gms.

2:4-Dinitroethylbenzene.

As the preparation of 2:4-dinitroethylbenzene by the method of Borsche[36] had not proved satisfactory, the following method was used instead.

Ethylbenzene (10 gm.) was added drop by drop on to a mixture of nitric acid (sp.gr. 1.5, 9.5 cc.) and concentrated sulphuric acid (18.5 cc.), the temperature being kept below 70°. After addition of all the ethylbenzene the nitration mixture was heated on the water bath for 3 hours with occasional shaking. The mixture, now in two layers, was cooled and the upper layer separated off and the lower layer poured into water. The aqueous solution, together with the upper layer, was extracted with ether. The ether extract was washed with water until free from acid and dried over Na_2SO_4. On removal of ether a pale yellow oil was obtained. A

sample of this distilled at about 175°/12 mm. It was characterised by conversion into 2-nitro-4-aminoethylbenzene, m.p. 42-43°.

2-Nitro-4-aminoethylbenzene.

2:4-Dinitroethylbenzene (5 gm.) was dissolved in alcohol (16 cc.) and concentrated NH_3 (sp.gr. 0.88, 3 cc.) added. H_2S gas was then passed in till saturated and the solution was then refluxed for ½ hour. Saturation with H_2S followed by refluxing was repeated until the increase in weight was approximately 3 gm. The sulphur was then filtered off and the alcohol removed under reduced pressure. The residue was taken up in hot dilute HCl and filtered hot from sulphur. On cooling 2-nitro-4-aminoethylbenzene hydrochloride separated out. This was dissolved in water and neutralised with NH_4OH, when an orange-yellow solid separated out. More 2-nitro-4-aminoethylbenzene was obtained on neutralising the acid mother liquor. Recrystallised from ligroin in orange-yellow plates, m.p. 42-43°.

Acetyl derivative, recrystallised from ligroin, was found to have m.p. 110-111°. (Schultz[30] gives m.p. 100-101°). Analysis. Found C = 57.69% H = 5.55%. 2-Nitro-4-acetaminoethylbenzene, $C_{10}H_{12}O_3N_2$, requires C = 57.69% H = 5.77%.

Attempted condensation of benzaldehyde and 2:4-dinitroethylbenzene.

2:4-Dinitroethylbenzene (5.64 gm.) and freshly distilled benzaldehyde (3.45 gm.) dissolved in dry pyridine (10 cc.) with the addition of a few drops of piperidine were heated at 140-150° for 2 hours. The solution was cooled and poured into water, when a dark red oil separated out. The solution was made acid to congo red with dilute HCl and steam distilled to remove benzaldehyde. The residue in the flask, a red oil, was extracted with ether, dried over Na_2SO_4 and the ether distilled off. The residue was then reduced with alcoholic $(NH_4)_2S_x$ as in reduction of 2:4-dinitroethylbenzene above. 2-Nitro-4-aminoethylbenzene, m.p. 41-42°, was obtained in high yield.

Only benzaldehyde (by steam distillation) and 2-nitro-4-aminoethylbenzene (by reduction with $(NH_4)_2S_x$) were isolated from the product of the reaction between 2:4-dinitroethylbenzene and benzaldehyde using the following conditions:- a) Piperidine at 170° for 1 hour. b) Piperidine acetate at 160-170° for 2 hours, and at 170-180° for 12 hours. c) Piperidine in acetic anhydride solution at 150-160° (oil bath temperature) for 4½ hours. d) Piperidine acetate in pyridine solution at 140-150° (oil bath) for 5 hours.

Attempted condensation of 3:4:5-trimethoxybenzaldehyde and 2:4-dinitroethylbenzene.

3:4:5-Trimethoxybenzaldehyde (1 gm.) and 2:4-dinitroethylbenzene (1 gm.) were heated with a few drops of piperidine for 2 hours at 160-170°. From the product of reaction only 2-nitro-4-aminoethylbenzene (by reduction with $(NH_4)_2S_x$ as above) was isolated.

ω-Diazo-3:4:5-trimethoxyacetophenone.

3:4:5-Trimethoxybenzoyl chloride (5 gm.) dissolved in dry ether (60-70 cc.) was added portionwise to an ethereal solution of diazomethane (from 10 cc. N-nitrosomethylurethane). On standing overnight pale yellow crystals of ω-diazo-3:4:5-trimethoxyacetophenone crystallised out. Concentration of ether solution under reduced pressure gave further crop of crystals. Total yield 2.5 gms., m.p. 94-96°. A repeat experiment under the same conditions, with the exception that the diazomethane was prepared from nitrosomethylurea (10.5 gm.), gave 3.4 gms. of ω-diazoacetophenone, m.p. 101°.

Baker, Morgans and Robinson[38] gave m.p. of this compound as 98°, while Slotta and Muller[39] gave m.p. as 103°.

3:4:5-Trimethoxyphenylacetamide.

(cf. Method of Slotta and Muller[39].)

ω-Diazo-3:4:5-trimethoxyacetophenone (2 gm.) was added in small amounts to a mechanically stirred solution of NH_4OH (20%, 25 cc.) containing $AgNO_3$ solution (10%, 2.5 cc.) at a temperature of 50-60°. The temperature was raised gradually to 80° while effervescence occurred. When the effervescence appeared to be complete, the solution was diluted with water and refluxed for 1 hour and then filtered hot. On standing several hours yellow-white plates of 3:4:5-trimethoxyphenylacetamide crystallised out, m.p. 122-123°. A further crop was obtained by salting out the mother liquor. Yield, 1.75 gms.

3:4:5-Trimethoxyphenylacetic acid.

3:4:5-Trimethoxyphenylacetamide (2 gms.) was boiled under reflux with 10N NaOH solution (20 cc.) for 6 hours. The solution was then cooled and extracted with ether to remove any unchanged amide and acidified with HCl. On standing overnight in the ice box 3:4:5-trimethoxyphenylacetic acid crystallised out in white needles, m.p. 120° in almost quantitative yield.

3:4:5-Trimethoxyphenylacetyl chloride.

A). 3:4:5-Trimethoxyphenylacetic acid (0.25 gm.) was dissolved in benzene (10 cc.) and PCl_5 (0.20 gm.) added. The

solution was refluxed 1 hour, filtered from insoluble material and evaporated to dryness in vacuo. The residue was taken up in benzene and an equal volume of light petroleum added. Pale yellow crystals, m.p. 117°, separated out. This material gave no depression of melting point when mixed with the original acid.

B). 3:4:5-Trimethoxyphenylacetic acid (0.25 gm.) was treated with excess thionyl chloride. The solution became dark in colour almost immediately and was then heated for 1 hour on the water bath. On removal of the thionyl chloride in vacuo a black tar with considerable charring was obtained which was only sparingly soluble in most solvents.

C). 3:4:5-Trimethoxyphenylacetic acid (1.75 gm.) dissolved in dry chloroform (25 cc.) was treated with PCl_5 (1.5 gm.) in the cold, when an evolution of HCl was observed. When all the PCl_5 had dissolved the chloroform and the $POCl_3$ were removed in vacuo. The residue, a yellow solid, was used in the next experiment without further purification.

Attempted Friedel-Craft reaction between 3:4:5-trimethoxyphenylacetyl chloride and anisole.

3:4:5-Trimethoxyphenylacetyl chloride (as obtained in above experiment from 1.75 gms. of acid) was suspended in carbon disulphide (20 cc.), in which it is only sparingly

soluble, and anisole (1 gm.) added. The mixture was cooled in an ice bath and $AlCl_3$ (1.2 gm.) was added gradually with shaking. The reaction mixture was then left about 20 hours with occasional shaking. The purplish-red solution was then decomposed with ice and HCl. The solution was steam distilled, when CS_2, together with unchanged anisole, was obtained. The residue in the flask, a dark red solid, was separated from the aqueous solution and extracted with alkali in which it is mostly soluble. The small amount of insoluble material dissolved in alcohol did not give any indication of a ketone group when treated with 2:4-dinitrophenylhydrazine. Acidification of the alkaline extract gave a small amount of 3:4:5-trimethoxyphenylacetic acid. More trimethoxyphenylacetic acid was obtained by extracting with ether the aqueous mother liquor which had been steam distilled.

Attempted preparation of methyl-3:4:5-trimethoxybenzyl ketone.

To a cooled, well stirred solution of methyl magnesium iodide prepared from methyl iodide (13 gm.), magnesium filings (2.16 gm.) and dry ether (60 cc.), finely powdered 3:4:5-trimethoxyphenylacetamide (2 gm.) was added in small quantities. There was no apparent reaction except for a darkening of the colour of the solution and a separation of

a brown powder. After heating for a short time the ether was distilled off and dry benzene (50 cc.) was added and the mixture refluxed for 20 hours. A pasty solid remained which was decomposed with ice and HCl. The benzene layer was separated off and the aqueous layer extracted with benzene and then with ether. The combined ether and benzene solutions were washed with water, dilute sodium carbonate solution and water and then dried over Na_2SO_4. On removal of solvent a small amount of red oil remained which could not be crystallised, nor identified as a ketone with 2:4-dinitrophenylhydrazine in alcohol.

Syringic alcohol.

1:3-Dimethylpyrogallol was prepared from 3:4:5-trimethoxybenzoic acid by the method of Hahn and Wassmuth[43]. 1:3-Dimethylpyrogallol (7 gms., 1 mol.) was dissolved in a solution of NaOH (2.2 gms., slight excess 1 mol.) in water (150 cc.) and 40% formalin (10.5 cc., approx. 3 mols. formaldehyde) added. The solution was then left for 72 hours at room temperature. It was then acidified to litmus with acetic acid and extracted with ether (40 cc.) which removes preferentially unchanged dimethylpyrogallol, and then with chloroform (300 cc.). The chloroform solution, washed with a little water, was dried over Na_2SO_4 and then the solvent

was distilled off, when a red solid (6.3 gms.) was obtained. This was recrystallised from benzene in orange coloured needles, m.p. 129-130°. Yield 5 gms. Analysis specimen was obtained in white needles, m.p. 131-132°.

Analysis. Found: C = 58.60%, H = 6.60%, MeO = 33.62%.

$C_9H_{12}O_4$ requires C = 58.60%, H = 6.52%, MeO = 33.69%.

Unchanged dimethylpyrogallol recovered from the ether extract can be used to prepare a further amount of the alcohol.

3:4:5-Trimethoxybenzylalcohol.

A). Syringic alcohol (12 gms.) was stirred on the water bath for 1½ hours with a solution of KOH (10%, 45 cc.) and methyl-p-toluenesulphonate (15 gms.). KOH solution (10%, 50 cc.) was then added and stirring continued for a further hour and then more KOH solution (10%, 10 cc.) was added and stirring continued for ½ hour. A certain amount of oil separated out during the reaction and this was increased on dilution with water. The mixture was then extracted with ether. The ether extract, well washed with water and dried over Na_2SO_4, on evaporation gave a yellow oil (10.8 gms.) which could not be crystallised. It was characterised as 3:4:5-trimethoxybenzyl alcohol by means of its 3:5-dinitrobenzoate.

The 3:5-dinitrobenzoate, prepared from 3:5-dinitrobenzoyl chloride in pyridine in the cold, crystallised from methyl alcohol in yellow plates, m.p. 148.5-149.5°.

Analysis. Found: C = 52.04%, H = 4.38%.

$C_{17}H_{16}O_9N_2$ requires C = 52.09%, H = 4.10%.

On standing the yellow oil of 3:4:5-trimethoxybenzyl alcohol slowly resinified. From the resin there was isolated a small amount of material insoluble in ether which appears to be 1:2:3:5:6:7-hexamethoxy-9:10-dihydroanthracene formed by the condensation of two molecules of 3:4:5-trimethoxybenzyl alcohol. This was crystallised from alcohol in white prisms, m.p. 201°.

Analysis. Found: C = 67.07%, H = 6.68%, MeO = 52.00%.

$C_{20}H_{24}O_6$ requires C = 66.67%, H = 6.67%, MeO = 51.67%.

B). This is essentially the method described in the German patent D.R.P. 526172.

Syringic alcohol (1.5 gm.) was added to a solution of sodium (0.3 gm.) in absolute alcohol (25 cc.) and the solution warmed to complete conversion to the sodium derivative. Methyl iodide (3 cc.) was then added and the solution refluxed one hour. An additional amount of methyl iodide (2 cc.) was then added and boiling continued one hour longer. The alcohol was then distilled off and NaOH solution added, (colour change, orange to green indicates presence of unchanged phenol), and then extracted with ether. The ether extract was washed with water and dried over Na_2SO_4. The

ether was then distilled off and the residue distilled at 145-155°/0.5 mm., when 0.75 gm. of colourless oil was obtained. 3:5-Dinitrobenzoate has m.p. 148-149°.

By acidifying the aqueous mother liquor with acetic acid and extracting with chloroform unchanged syringic alcohol can be recovered.

3:4:5-Trimethoxybenzyl chloride.

3:4:5-Trimethoxybenzyl alcohol (1 gm.) dissolved in dimethylaniline (0.9 gm.) and cooled in a freezing mixture was treated with thionyl chloride (0.7 gm.). The mixture was kept 30 minutes at this temperature and then heated 15 minutes on the water bath. It was then cooled and ice and dilute HCl were added and the solution extracted with ether. Ether extract was washed with water, Na_2CO_3 solution and water and dried over Na_2SO_4. The ether was distilled at 140-150°/0.6 mm. Yield, 0.75 gm. of white crystalline solid, m.p. 59-61°.

Attempted preparation of 3:4:5-trimethoxybenzyl-4'-methoxyphenylmethyl carbinol.

Magnesium turnings (2.5 gm., 30 mols) were covered with dry ether (8 cc.) and a small amount of 3:4:5-trimethoxybenzyl chloride and a crystal of iodine added. The solution was refluxed 10 minutes without stirring and then the

remainder of the chloride (1.5 gm., 1 mol) in dry ether (12 cc.) was added gradually over a period of ½ hour with stirring and refluxing. As no apparent reaction had set in, a small amount of freshly prepared methyl magnesium iodide was added, when a slight reaction was noted. The mixture was refluxed for 1 hour and then dry benzene (10 cc.) was added and boiling continued a further hour. p-Methoxy-acetophenone (1.1 gm.) in dry ether (15 cc.) was then added gradually while boiling continued. After refluxing for 2 hours the mixture was cooled, decomposed with ice and NH_4Cl and extracted with ether. Ether extract was washed with water and NaOH and dried over Na_2SO_4. The ether was distilled off and the residue distilled. The fraction (1.1 gm.) b.p. 150-160/12 mm., m.p. 35-36° appears to be p-methoxyacetophenone. The residue could not be distilled at 0.5 mm., or crystallised.

Diethyl ester of 3:4:5-trimethoxybenzylmalonic acid.

Sodium (0.47 gm.) was dissolved in absolute alcohol (9 cc.) and diethylmalonate (3.26 gm.) added. The solution was slightly warmed to convert the diethylmalonate into the sodio derivative. It was then cooled and freshly prepared powdered 3:4:5-trimethoxybenzyl chloride (4.4 gms.) added. On gently shaking in the cold the chloride dissolved and

NaCl was precipitated. After standing ½ hour at room temperature the mixture was heated on the water bath for 15 minutes and then the alcohol was distilled off, finally under reduced pressure. The residue was treated with water and extracted with ether. The ether extract was washed with a little water and dried over Na_2SO_4. On removal of the ether a pale yellow oil was obtained which crystallised on standing and was recrystallised from '40-60' light petroleum with cooling in the ice box in white prisms, m.p. 67-71°.

Analysis. Found: C = 59.71%, H = 7.02%.

$C_{17}H_{24}O_7$ requires C = 60.00%, H = 7.06%.

Raney Nickel catalyst (modified preparation).

Nickel-aluminium alloy (50 gms.) was added over a period of 2 hours to a cooled solution of NaOH (50 gms.) in distilled water (900 cc.) with stirring, the temperature being maintained below 10°. Stirring was then continued for about 1 hour until the temperature rose to normal and then the temperature was raised to boiling on the water bath at such a rate that the evolution of hydrogen did not become too vigorous. When the evolution of hydrogen had ceased, about 3 hours, the solution was cooled and the catalyst allowed to settle. The liquor was then decanted off and

the catalyst washed several times by decantation with 5-6 litres of distilled water and then with about 500 cc. of absolute alcohol. The catalyst was then covered with about 200 cc. of absolute alcohol and used next day.

p-Methoxycyclohexanol.

This was prepared by a method slightly modified from that used by Ruggli, Leupin and Bussinger[54].

Hydroquinone monomethyl ether (150 gms.), Raney nickel catalyst (25 gms.) and absolute alcohol (500 cc.) were placed in an autoclave fitted with an electro-magnetic rod and disc stirrer. The autoclave was filled with hydrogen to a pressure of 105 atmospheres and heating commenced. After 1½ hours the temperature had risen to 90°C., and the pressure to 130 atmospheres. During a further hour's heating the temperature rose to 120°C., while the pressure fell to 90 atmospheres. The temperature was maintained at 120° while the pressure continued to fall for 1¼ hours longer until it was constant at 30 atmospheres, when reduction was complete. On cooling the catalyst was filtered off and the filtrate concentrated, finally in vacuo, on the water bath. The residue on testing was found to contain no unchanged hydroquinone monomethyl ether. It was then distilled at 129-131°/28 mm., yield, 139 gms. A small amount of lower boiling material was also obtained and is probably hexahydroanisole.

p-Methoxycyclohexanone.

As the method of Helfer[53] using dichromate and H_2SO_4 was found to give a yield of only 33%, the following method was used instead.

Chromic acid (5.7 gms. 10% excess) dissolved in acetic acid (80%, 24 cc.) was added over a period of ¾ hour to a well stirred, cooled solution of p-methoxycyclohexanol (10 gms.) in pure glacial acetic acid (100 cc.) at such a rate that the temperature did not rise above 10-12°. Stirring was continued for an hour or so until temperature returned to normal and the solution was left to stand overnight. The acetic acid was then distilled off in vacuo at as low a temperature as possible. The residue was then neutralised with 6N Na_2CO_3 solution and extracted with ether. The ether extract was washed with a little water and dried over Na_2SO_4. The ether was removed and the residue distilled under reduced pressure. Yield, 7 gms. of colourless oil, b.p. 81-83°/11 mm., and 0.5 gm., b.p. 83-85°/11 mm. This ketone forms a bisulphite compound and a semicarbazone, m.p. 179°.

2-Chloro-4-methoxycyclohexanone.

A slow stream of chlorine gas was led into a mechanically stirred mixture of p-methoxycyclohexanone (11.2 gm.), water (8 cc.) and $CaCO_3$ (5 gms.) at such a rate that the

temperature was maintained at 25-30°. After 3 hours all the $CaCO_3$ had dissolved and the stream of chlorine was stopped. Two liquid layers were formed and the red upper layer was separated off and the lower aqueous layer was extracted with ether. The upper layer, together with the ether extract, was washed with $NaHCO_3$ solution and with water and then dried over Na_2SO_4. The ether was distilled off and the residue fractionated. The fraction b.p. 105-119°/11 mm., 4.8 gms. of a pale yellow oil, was taken as 2-chloro-4-methoxycyclohexanone.

2-Bromo-4-methoxycyclohexanone.

Bromine (7.3 gm., 1 mol.) dissolved in dry chloroform (70 cc.) was added to a cooled, mechanically stirred solution of p-methoxycyclohexanone (5.9 gm., 1 mol.) in dry chloroform (60 cc.) at such a rate that the colour of the solution was kept faintly yellow. After 1 hour at this temperature the chloroform was removed in vacuo and the residue taken up in ether. The ether extract was washed with water, $NaHCO_3$ solution and water and dried. After removal of the ether the residue was fractionated. The fraction, b.p. 127-135°/12 mm., 3.85 gms. of colourless oil, was taken as 2-bromo-4-methoxycyclohexanone and characterised as the thiazole derivative below.

2-Amino-6-methoxy-4:5:6:7-tetrahydrobenzthiazole.

2-Bromo-4-methoxycyclohexanone, b.p. 127-135°/12 mm., (1.08 gm., 1 mol.) was mixed with thiourea (0.38 gm., 1 mol.), when an exothermic reaction set in and the syrup which was formed gradually solidified. The mixture was then heated a short time on the water bath to complete the reaction. Dilute NaOH was then added and the solid dissolved, followed by precipitation of an oil which solidified. This was filtered off, washed with a little ether and water and dried on a porous plate. Recrystallised from benzene/cyclohexane and finally from benzene in white prisms with a brownish tinge, m.p. 141.5-144°.

Analysis. Found: C = 52.37%, H = 6.52%.

$C_8H_{12}ON_2S$ requires C = 52.17%, H = 6.44%.

Diethyl ester of 3:4:5-trimethoxybenzyl-2-keto-5-methoxycyclohexylmalonic acid.

Diethyl ester of 3:4:5-trimethoxybenzylmalonic acid (4.2 gm.) and sodium (0.282 gm.) were heated together in dry benzene (30 cc.) until all the sodium had reacted. It was then cooled in ice and freshly prepared 2-bromo-4-methoxycyclohexanone (2.55 gm.) in dry benzene (15 cc.) was gradually added. After standing a short time at this temperature, the mixture was heated on the water bath for 4

hours, then cooled, diluted with benzene, shaken out with water and the solution then dried over Na_2SO_4. The benzene was then distilled off leaving a yellow oil (5.55 gms.) which did not solidify and could not be crystallised from light petroleum in which it is sparingly soluble, or from light petroleum/benzene. This oil was saponified in the next experiment.

Hydrolysis of diethyl ester of 3:4:5-trimethoxybenzyl-2-keto-5-methoxycyclohexylmalonic acid.

The above ester (5.4 gm.), as a gum, was heated for 5 hours on the water bath in a solution of alcohol (12 cc.) and water (12 cc.) containing sodium hydroxide (4.8 gm.). A white sodium salt A (1 gm.) was filtered off. The filtrate was diluted with water, excess alcohol distilled off and then extracted with ether to remove unchanged material. On acidification with HCl a solid was precipitated which formed a tarry solid, B, on filtration. This solid (1.8 gm. dry) was washed with water and dried in vacuo. The filtrate was evaporated to dryness in vacuo and the residue extracted with acetone. The acetone solution on evaporation to dryness gave a red gum, C (1.4 gm.), which could not be crystallised.

The sodium salt A was dissolved in water and acidified.

As no precipitate was obtained the solution was evaporated to dryness in vacuo and the residue extracted with dry acetone. The acetone solution on evaporation to dryness gave a yellow gum which was crystallised from benzene-alcohol in white prisms, m.p. 115-116°. This appears to be 3:4:5-trimethoxybenzylmalonic acid as it gives, on decarboxylation at 135° in vacuo, 3:4:5-trimethoxyphenylpropionic acid, m.p. 100° identified by a mixed melting point with an authentic specimen.

Analysis: Found: C = 55.17%, H = 5.40%. Trimethoxybenzylmalonic acid $C_{13}H_{16}O_7$ requires C = 54.94%, H = 5.64%.

Decarboxylation and attempted ring closure of products B and C obtained in above experiment.

The tarry solid B (1.8 gm.) was decarboxylated by heating in vacuo to a temperature of 135-140° in an oil bath. The product obtained, a red gum, was heated with excess syrupy phosphoric acid (88% w/w.) at 105° for a half hour. The solution was cooled and poured into water. A dark gum was deposited and this was removed, well washed with water and dried in vacuo. It was then extracted with hot benzene in which it is partly soluble. The gummy material which was soluble in benzene was chromatographed in a solution of benzene-petroleum ether through a column of alumina and eluted

with benzene. From the benzene solution a small amount of resin, m.p. 75-80°, was obtained but it could not be crystallised. The product of ring closure which was insoluble in benzene was dissolved in a solution of 2 parts benzene and 1 part alcohol and chromatographed through a column of alumina. On elution with alcohol a small amount of white solid was obtained which was crystallised from benzene-alcohol in white prisms, m.p. 230°.

Analysis: Found: C = 54.07%, H = 6.43%.

The gum C (1.4 gm.) was decarboxylated at 135° in vacuo and the product obtained heated with excess syrupy phosphoric acid at 105° for 30 minutes. The solution was then cooled and poured into water. A black tar which was formed was separated off. The solution was then partly neutralised (still acid to litmus) with 6N sodium carbonate and left a few days, when a small amount of solid crystallised out. This was identified by means of a mixed melting point as 3:4:5-trimethoxyphenylpropionic acid.

β-3:4:5-Trimethoxyphenylpropionic acid.

Diethyl ester of 3:4:5-trimethoxybenzylmalonic acid (0.2 gm.) was heated with alcohol (2 cc.) and water (2 cc.) containing sodium hydroxide (0.2 gm.) on the water bath for 5 hours. The solution was then extracted with ether

to remove unchanged material, acidified with dilute HCl and again extracted with ether. This ether extract was washed with water and dried over Na_2SO_4. On evaporation to dryness it gave an oil which after two crystallisations from benzene-petroleum ether formed colourless needles, m.p. 100-102°.

Analysis: Found: C = 60.21%, H = 6.38%.

$C_{12}H_{16}O_5$ requires C = 60.00%, H = 6.66%.

benzene from which a yellow crystalline solid, m.p. 170-175° (0.17 gm.) separated. The benzene solution taken to dryness gave a red gum (0.6 gm.) which was used in the following oxidation experiment. The compound, m.p. 170-175° was recrystallised from benzene (with a few drops of acetone) in white microcrystalline rhombs, m.p. 179-181°. This appears to be the amide of α-p-anisyl-β-(2-bromo-3:4:5-trimethoxyphenyl)acrylic acid.

Analysis. Found:C = 54.26%, H = 4.73%, MeO = 29.16%.

$C_{19}H_{20}O_5NBr$ requires C = 54.03%, H = 4.74%, MeO = 29.39%.

Oxidation of hydrolysis product of α-cyano-α-p-anisyl-β-(2-bromo-3:4:5-trimethoxyphenyl)ethylene.

The red gum (0.6 gm.) obtained above was heated to boiling with a solution of NaOH (1.2 gm.) in water (10 cc.) and a solution of $KMnO_4$ (1.2 gm.) in water (30 cc.) was added. After the addition of the permanganate the solution was refluxed for 1 hour and then cooled and filtered from MnO_2. The filtrate was acidified, when a pale yellow solid (0.35 gm.) was precipitated. On recrystallising twice from boiling water this formed white crystalline prisms, m.p. 151-152°. It gave a positive test for bromine. This appears to be 2-bromo-3:4:5-trimethoxybenzoic acid which has m.p. 151°.

Analysis. Found: C = 41.34%, H = 3.91%.

$C_{10}H_{11}O_5Br$ requires C = 41.23%, H = 3.78%.

By this isolation of 2-bromo-3:4:5-trimethoxybenzoic acid the fact that the bromine atom is in the same ring as the three methoxyl groups in the original compound has been proved.

Attempts to ring close α-cyano-α-p-anisyl-β-(2-bromo-3:4:5-trimethoxyphenyl)ethylene.

a). The above compound (0.4 gm.) was added to fused potash at 225° and stirred for 3-4 minutes while the temperature fell to 190°. On cooling, the melt was extracted with water and then with chloroform. The chloroform extract was washed with water and dried over Na_2SO_4. On removal of solvent a solid was obtained. This crystallised from alcohol in fine yellow needles (0.3 gm.), m.p. 140°, identified as unchanged material. The alcohol mother liquor, on evaporation to dryness, gave a small amount of red gum.

b). The above experiment was repeated with the exception that the temperature of fusion was maintained at 240° for 5 minutes. Unchanged material (0.25 gm.) and a little more gum were obtained.

An attempt to distil the gum obtained in these two

experiments was unsuccessful. A trace of the original material was obtained on distillation up to a temperature of 205° in a high vacuum.

c). The above bromo compound (0.2 gm.), caustic potash (1 gm.) and quinoline (1.5 cc.) were heated to boiling for five minutes. The mixture was then cooled and diluted with water. The oily solid which was deposited was extracted with hot water and then taken up in chloroform. The chloroform extract was washed with dilute HCl and with water and dried over Na_2SO_4. The chloroform was then distilled off and the residue obtained crystallised from alcohol, when unchanged material (0.16 gm.) was recovered as fine pale yellow needles, m.p. 141°.

d). The above bromo compound (0.3 gm.), naphthalene (2 gm.), potassium acetate (0.3 gm.) and a trace of cuprous iodide were heated at a temperature of about 190° for 4 hours. The melt was then steam distilled to remove naphthalene. The residue was dissolved in chloroform. The chloroform solution, after washing with water and drying over Na_2SO_4, was evaporated to dryness. The residue was crystallised from alcohol in yellow needles (0.25 gm.) identified as original compound.

α-Cyano-α-p-hydroxyphenyl-β-(3:4:5-trimethoxyphenyl) ethylene.

This is the method used by Cook and Lawrence (Unpublished work).

3:4:5-Trimethoxybenzaldehyde (4 gms.) and p-hydroxybenzyl cyanide (2.5 gms.) were dissolved in absolute alcohol (25 cc.) containing sodium (1 gm.) and left 48 hours at room temperature. This was then diluted to about 100 cc. with water and acidified with dilute HCl, when a pale yellow solid was precipitated. This was filtered off, washed with a little aqueous alcohol and then recrystallised from aqueous alcohol (charcoal) in fine pale yellow needles, m.p. 169.5-170.5°. Yield 3.2 gms. A further small amount of material could be obtained by diluting the acid mother liquor.

A similar experiment using NaOH (2 mols.) in place of NaOEt gave the same product and not the material, m.p. 148-150°, obtained by Cook and Lawrence.

Reduction of α-cyano-α-p-hydroxyphenyl-β-(3:4:5-trimethoxyphenyl)ethylene.

A). The above compound (1.5 gm.) dissolved in acetic anhydride (80 cc.) was shaken with Adams' catalyst (0.1 gm.) in an atmosphere of hydrogen. After 5½ hours 125 cc. of

hydrogen had been absorbed. In the next 24 hours 320 cc. were recorded as having been adsorbed but this may have been due to a leak in the apparatus. Theoretical absorption, 325 cc. at N.T.P. for 3 mols. of hydrogen. After filtering off catalyst the acetic anhydride was concentrated in vacuo. A white crystalline solid, m.p. 161-163° crystallised out on cooling. This was identical with α-cyano-α-p-acetoxyphenyl-β-(3:4:5-trimethoxyphenyl)ethylene prepared by acetylating the corresponding hydroxy compound with acetic anhydride and a trace of concentrated H_2SO_4. After concentrating the original acetic anhydride solution until no more of this material was obtained, the solution was taken to dryness, when a pale yellow syrup was obtained. This was taken up in absolute alcohol and on cooling in the refrigerator a small amount of white solid, m.p. 148-154° was obtained, but was not identified. The alcohol mother liquor was evaporated to dryness and the gum obtained hydrolysed with 10% alcoholic potash. After evaporating off excess alcohol the solution was acidified, when a brown gum was deposited. As this gum could not be the required amine, it was not further investigated. The acid mother liquor was then neutralised with K_2CO_3 solution. After standing several weeks a trace of crystalline material m.p. 76-78° was obtained.

B). α-Cyano-α-p-hydroxyphenyl-β-(3:4:5-trimethoxyphenyl) ethylene (1.5 gm.) and sodium (3.2 gm.) cut in small slices were mixed in a round bottomed flask fitted with a reflux condenser. Absolute alcohol (22.5 cc.) was added down the condenser and a violent reaction set in. Alcohol was added in small portions to keep the reaction going. When all the sodium had reacted, water (60 cc.) was added and excess alcohol distilled off. The solution was then cooled and acidified with dilute HCl, when a yellow solid, somewhat sticky, was precipitated. The solution, together with the solid, was extracted with ether in which the solid is not completely soluble. The ether solution after washing with water and drying over Na_2SO_4 was evaporated to dryness giving a yellow gum which was crystallised from aqueous alcohol in yellow crystals, m.p. 160-165°. A further recrystallisation gave m.p. 166-168°. This was identified as unchanged material. The small amount of material which was insoluble in ether was crystallised from benzene/acetone in pale yellow microscopic prisms, m.p. 211°. This is insoluble in carbonate solution and appears to be the amide of α-p-hydroxyphenyl-β-(3:4:5-trimethoxyphenyl)-acrylic acid.

Analysis. Found: C = 65.43%, H = 5.89%.

$C_{18}H_{19}O_5N$ requires C = 65.66%, H = 5.77%.

The original acidified mother liquor was neutralised with K_2SO_3 solution to liberate any basic product. No amine was obtained even after extraction with ether.

Colchiceineamide.

Colchicine (1.4 gm.) was dissolved in a solution of absolute alcohol (12 cc.) and concentrated ammonia (sp.gr. 0.88, 5 cc.). The solution became red and was heated on the water bath for 4 hours. The solvent was then removed in vacuo and the residue extracted with cold water to remove unchanged colchicine. The remaining solid was dried in vacuo and then dissolved in acetone. A certain amount of solid crystallised out on standing a short time and this was recrystallised from acetone containing a little alcohol in yellow diamond shaped rhombs decomposing at 252°.

Analysis. Found: C = 65.64%, H = 6.19%.

$C_{21}H_{24}O_5N_2$ requires C = 65.62%, H = 6.25%.

Benzene was added to the original acetone solution and the solution concentrated, when clumps of prisms crystallised out. This fraction crystallised from benzene/acetone in yellow prisms which sinter at 225° and decompose at 250°.

Analysis. Found: N = 7.15%.

$C_{21}H_{24}O_5N_2$ requires N = 7.28%.

The aqueous extract of the amide obtained above evaporated to dryness gives unchanged colchicine which can be re-treated.

Attempted condensation of colchicine and acetamidine.

Acetamidine hydrochloride (0.118 gm.) was added to a solution of sodium (0.03 gm.) in absolute alcohol (15 cc.). Colchicine (0.5 gm.) was added gradually with shaking. After standing 2 hours at room temperature the solution was refluxed for two hours on the water bath, when the colour of the solution became dark red in colour. After cooling in the refrigerator the sodium chloride was filtered off. As no solid crystallised out on concentrating the alcohol solution, nor after adding ethyl acetate, the solvent was removed in vacuo, when a green solid, varnish-like in texture, was obtained. This crude material, which smells of acetamidine, was soluble in water and alcohol and insoluble in benzene. It could not be crystallised. On boiling with 1% HCl for two hours colchiceine crystallised out, thus the dark green solid appears to have been crude colchicine.

In a similar experiment using colchiceine (0.4 gm.) in place of colchicine, no condensation took place, as colchiceine was recovered unchanged.

Attempted condensation of colchiceineamide and cyanacetic ester.

A). Colchiceineamide (0.2 gm.) dissolved in absolute alcohol (10 cc.) containing sodium (0.012 gm.) was treated with a solution of cyanacetic ester (0.06 gm.) in absolute alcohol (4.7 cc.). The solution was refluxed on the water bath for 5 hours and then left overnight. The alcohol was then distilled off and the residue extracted with cold water and filtered. The undissolved material was identified as unchanged colchiceineamide. The filtrate gave no precipitate on acidification, but on addition of strong alkali a yellow solid was precipitated which was also identified as colchiceineamide.

B). Colchiceineamide (0.1 gm.) and cyanacetic ester (0.03 gm.) in alcohol (1 cc.) were heated with a trace of piperidine for several hours. The alcohol was then evaporated off. The residue after crystallising from alcohol/benzene was identified as unchanged colchiceineamide.

Condensation of colchicine and cyanacetamide.

Colchicine (0.2 gm.) and cyanacetamide (0.045 gm.) were dissolved in absolute alcohol (9 cc.) containing sodium (0.012 gm.). The solution was allowed to stand for 4 days, when the colour had changed from yellow to orange to dark

red. The alcohol was then removed in vacuo and the residue taken up in water and acidified with dilute HCl. A yellow-orange solid was precipitated which was then filtered off and dried. The filtrate was extracted with chloroform, ether having effected no extraction. The chloroform solution after drying over Na_2SO_4 was evaporated to dryness and the residue was extracted with a little water to remove any unchanged colchicine, when a further small amount of the above yellow-orange solid was obtained. This condensation product is soluble in alcohol, chloroform and slightly in water, insoluble in ether, benzene and petroleum ether. It could not be crystallised. It was prepared for analysis by dissolving in alcohol and precipitating from hot solution with benzene. In this way it was obtained as a flocculent precipitate which dried to an orange-yellow amorphous powder. It commences to sinter about 175° and decomposes about 205°.

Analysis. Found: 3.260 mg. give 7.150 mg. CO_2 & 1.650 mg. H_2O Residue 0.0700 mg. C = 59.81%, H = 5.62%, N = 8.50%.

Allowing for residue:- C = 61.10%, H = 5.74%, N = 8.68%.

$C_{24}H_{24}O_5N_3Cl$ (hydrochloride of compound LV or LVI, p.62) requires C = 61.30%, H = 5.11%, N = 8.94%.

Action of dehydrating agent on N-acetylcolchinol methyl ether.

N-Acetylcolchinol methyl ether (0.4 gm.) in pure dry xylene (distilled over P_2O_5, 20 cc.) was treated with P_2O_5 (0.8 gm.) and the mixture refluxed for 15 minutes on the oil bath. When cold the xylene solution was decanted off and the residue washed with a little warm xylene. The residue, dissolved in water, was steam distilled to remove traces of xylene. On neutralising the aqueous solution with NaOH no material was precipitated, nor was any obtained by extraction with ether. The original xylene solution was decanted from a trace of resin and then evaporated to dryness in vacuo. A gum was obtained which was crystallised from a small amount of methyl alcohol in white plates, m.p. 99.5-100°. It was found that this compound after melting at 100° solidified on cooling and melted again at 109-110°. It was found to contain no nitrogen.

Analysis. Found: C = 73.08%, H = 6.13%.

Compound obtained by Windaus[12], m.p. 111°, $C_{19}H_{20}O_4$ requires C = 73.05%, H = 6.40%.

Bibliography.

1) Pelletier & Caventou, Ann.Chim.Phys., 1820, 14, 82.

2) Zeisel et alii, Montash., 1883, 4, 162,
1886, 7, 557,
1888, 9, 1, 865,
1913, 34, 1181, 1327, 1339.

3) Oberlin, Jahresber., 1856, 548.

4) Clewer, Green & Tutin, J., 1915, 835.

5) Windaus, Sitzungber. Heidelberg Akad. Wiss., 1910, 1 abhand.,
1911, 2 abhand.,
1914, 18 abhand.,
1919, 16 abhand.
Nach. Gesell. Wiss. Gottingen, 1923, 17.

6) Wislicenus & Bindemann, Ann., 1901, 316, 26.

7) Bishop, Claisen & Sinclair, Ann., 1894, 281, 345.

8) Bruhl, Ber., 1904, 37, 2156.

9) Windaus & Schiele, Ber., 1923, 56, 846.

10) Grewe, Ber., 1938, 71, 907.

11) Sachs, Ann., 1909, 365, 53.

12) Windaus, Ann., 1924, 439, 59.

13) Windaus, Jenzen & Schramme, Ber., 1924, 57, 1875.

14) Bursian, Ber., 1938, 71, 245.

15) Cohen, Cook & Roe, J., 1940, 194.

16) Windaus & Eickel, Ber., 1924, 57, 1871.

17) Dixon & Malden, J.Physiol., 1908, 37, 50.

18) Dustin, Bul.Acad.roy.Med.Belge, 1934, 14, 487.

19) Blackeslee, Compt.rend., 1937, 205, 476.

20) Lits, Compt.rend.Soc.Biol., 1934, 115, 1421.

21) Amoroso, Nature, 1935, 135, 266.

22) Havas, Nature, 1937, 140, 191.

23) Buth, Kulz & Rosenmund, Ber., 1939, 72, 19.

24) Lettré, Naturwiss., 1942, 30, 34.

25) Brues & Cohen, Biochem.J., 1936, 30, 1363.

26) Cook & Engel, J., 1940, 198.

27) Anderzen & Holmberg, Ber., 1923, 56, 2048.

28) Sharp, J., 1936, 1234.

29) Lapsley, Thesis, Glasgow University.

30) Schultz, Ber., 1909, 42, 2634.

31) Borsche, Ber., 1909, 42, 1313.

32) Gabriel & Meyer, Ber., 1881, 14, 824.

33) Curtius, J.pr.Chem., 1907, 76, 291.

34) Slotta & Heller, Ber., 1930, 63, 3042.

35) Haworth & Barker, J., 1939, 1302.

36) Borsche, Ann., 1912, 386, 365.

37) Borsche, Ber., 1909, 42, 3599.

38) Baker, Morgans & Robinson, J., 1933, 374.

39) Slotta & Muller, Z.physiol.Chem., 1936, 238, 14.

40) Jenkins, J.Amer.Chem.Soc., 1933, 55,703.

41) Pictet & Finkelstein, Ber., 1909, 42, 1985.

42) Manasse, Ber., 1894, 27, 2409.

43) Hahn & Wassmuth, Ber., 1934, 67, 701.

44) I.G.Farbenindustrie, D.R.P., 453277,
D.R.P., 526172.

45) Decker & Pschorr, Ber., 1904, 37, 3404.

46) Ziegler & Dersch, Ber., 1931, 64, 448.

47) Gilman, Pacivitz & Baine, J.Amer.Chem.Soc., 1940, 62, 1515.

48) Wittig, Pockels & Droge, Ber., 1938, 71, 1903.

49) Wittig & Pockels, Ber., 1939, 72, 89.

50) Gilman & Zoellner, Bul.Soc.Chim., 1931, 49, 7.

51) Strauss, Ann., 1910, 374, 139.

52) Grewe, Ber., 1939, 72, 426.

53) Helfer, Helv.Chim.Acta, 1924, 7, 952.

54) Ruggli, Leupin & Bussinger, Helv.Chim.Acta, 1941, 24, 339.

55) Kotz & Grethe, J.pr.Chem., 1909, 80, 487.

56) Traumann, Ann., 1888, 249, 35.

57) Hewett, J., 1938, 1286.

58) Cook & Lawrence, Unpublished work.

59) Freund & Remse, Ber., 1890, 23, 2859.

60) Zeisel, Montash., 1888, 9, 1.

61) Todd et alii, J., 1936, 1602.

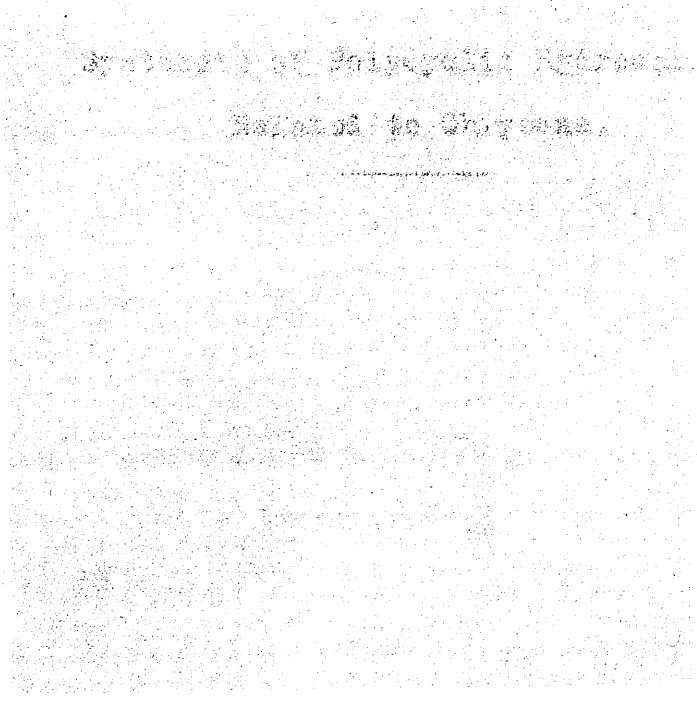
62) Andersag & Westphal, Ber., 1937, 70, 2046.

63) Basu & Bannerjee, Ann., 1935, 516, 243.

64) Sen-Gupta, J., 1915, 1354.

65) Basu, J.Ind.Chem.Soc., 1931, 8, 319.

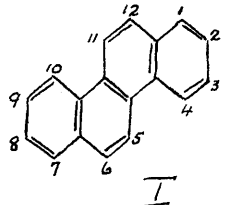
66) Spath & Kittel, Ber., 1940, 73, 478,
B.C.A., 1943, AII, 278.



Synthesis of Polycyclic Hydrocarbons Related to Chrysene.

Synthesis of 2:3-benzchrysene and its significance.

Chlorination, bromination and nitration of chrysene, I, leads to substitution in position 6*. In this respect chrysene behaves as a phenanthrene derivative, position 6 of chrysene being equivalent to position 9 of phenanthrene, II. In Friedel-Craft reactions, however, chrysene behaves differently from phenanthrene as it gives in carbon disulphide solution with oxalyl chloride, benzoyl chloride, or acetyl chloride, chrysene-6-carboxylic acid[1], 6-benzoylchrysene[2] or 6-acetylchrysene[2] respectively: substitution in phenanthrene occurs mainly in position 3, but also in position 2.



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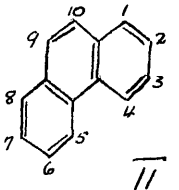

II

Beyer[3] carried out a Friedel-Craft reaction between chrysene and succinic anhydride in benzene and obtained β-(6-chrysenoyl)propionic acid, m.p. 197°. He repeated the experiment in nitrobenzene solution and obtained a β-chrysenoylpropionic acid, m.p. 221°. As β-(2-naphthoyl)propionic acid has a higher melting point than the corresponding 1-acid, Beyer, regarding chrysene as a naphthalene derivative,

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* The numbering of chrysene is that of the Patterson system as used in the American literature.

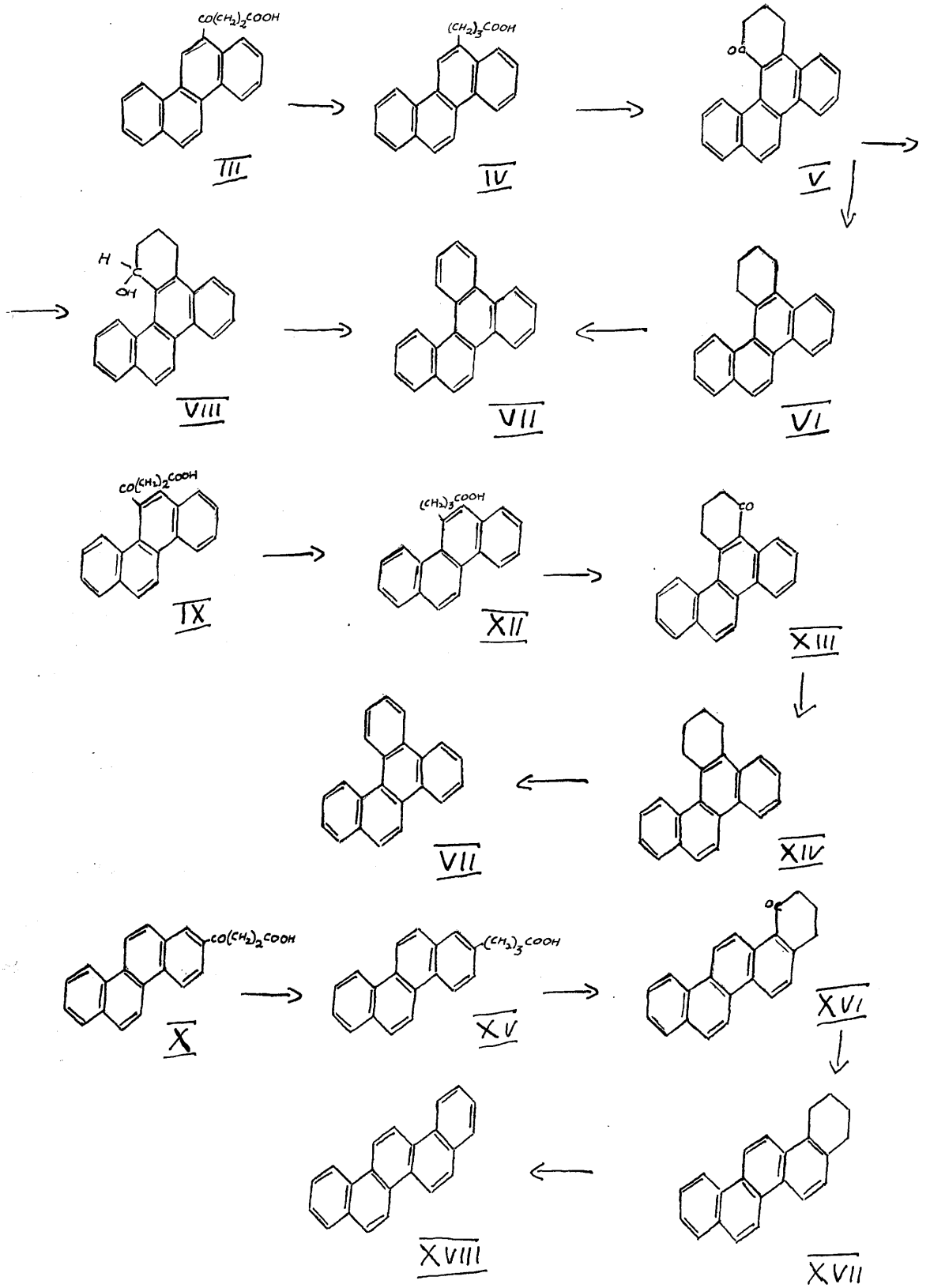
called the acid, m.p. 221°, (β-(5-chrysenoyl)propionic acid. This structure appeared to be supported by the failure of the acid to form a semicarbazone, phenylhydrazone or oxime, which Beyer attributed to steric hindrance at position 5.

The formation of a chrysenoylpropionic acid can lead to the fusion of another six membered ring on to the chrysene molecule with the formation of a pentacyclic structure, a benzchrysene. Syntheses of a similar type have been used extensively for the preparation of polycyclic hydrocarbons of the phenanthrene, benzanthracene and chrysene series.

With chrysene as starting material, no synthesis of any of the four possible benzchrysenes, all of which are known and have been synthesised, has been reported in the literature.

Beyer attempted to prepare 1:2:3:4-dibenzphenanthrene (5:6-benzchrysene), VII, from (β-(6-chrysenoyl)propionic acid, III, by the method outlined below, but he could not dehydrogenate the carbinol VIII, obtained instead of the hydrocarbon VI by the reduction of the ketone V, to the required compound VII.

A recent attempt of Bergmann and Eschinazi[4] to synthesise derivatives of 1:2:3:4-dibenzphenanthrene from chrysene as starting material, but by a different method, has also been unsuccessful.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III
(CH2)3COOH
IV
O
V
H
C
OH
VIII
VII
VI
CO(CH2)2COOH
IX
(CH2)3COOH
XII
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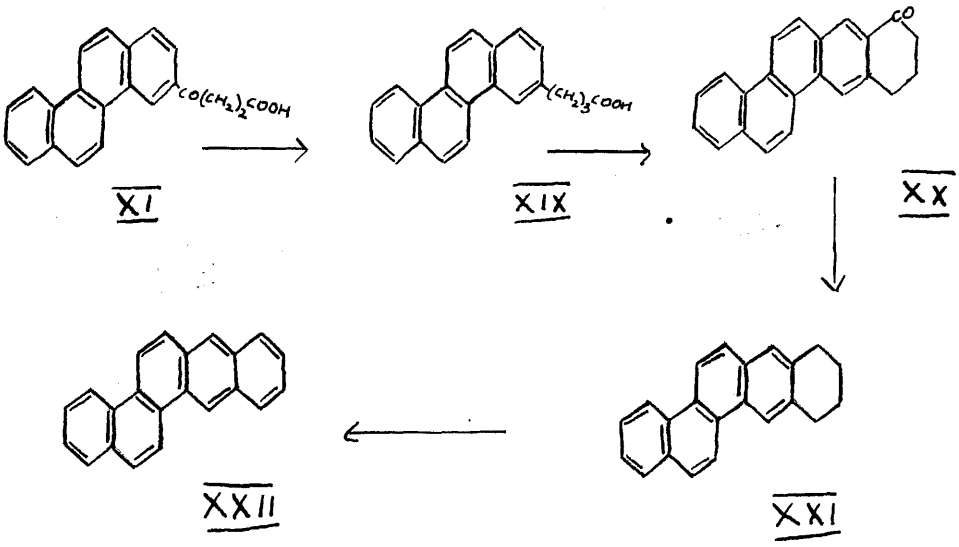
X
(CH2)3COOH
XV
O
XVI
XVIII
XVII



As it had not been proved that the β-chrysenoylpropionic acid, m.p. 221°, obtained by Beyer, was the 5- acid as suggested by him, it was thought that it might have an alternative structure, possibly β-(2-chrysenoyl)propionic acid, X, or the corresponding 3- acid, XI.

If the acid is β-(5-chrysenoyl)propionic acid, IX, 1:2:3:4-dibenzphenanthrene, VII, should be obtained from it by the synthesis outlined above. If, however, it is the 2-acid, X, it would be expected that 1:2-benzchrysene (picene), XVIII, would be obtained by the synthesis outlined, while 2:3-benzchrysene, XXII, would result from a synthesis from β-(3-chrysenoyl)propionic acid, XI. The reason for the expected cyclisation of γ-(2-chrysenyl)butyric acid, XV, and of γ-(3-chrysenyl)butyric acid, XIX, into compounds XVI and XX respectively will be discussed later.

Use has been made of the β-chrysenoylpropionic acid, m.p. 221°, to prepare a benzchrysene in the manner outlined above, the first synthesis of a benzchrysene from chrysene itself. From the structure of the benzchrysene so obtained an indication has been given as to the position of the substituent in the original chrysenoylpropionic acid.

By a Friedel-Craft reaction between chrysene and succinic anhydride in nitrobenzene solution the required β-chrysenoylpropionic acid, m.p. 218-221°, was obtained. It was found that the yield, which was of a low order, could be improved by raising the temperature of the reaction to 30° and by increasing the quantities used of succinic anhydride and aluminium chloride. Beyer carried out the reaction at 20° but he does not report the yield of pure acid obtained. From these Friedel-Craft reactions there was isolated also a smaller amount of β-(6-chrysenoyl)propionic acid, m.p. 192-194°, which Beyer makes no mention of having obtained in these reactions. When the Friedel-Craft condensation was carried out at 0° a mixture of β-chrysenoylpropionic acids was obtained from which the required acid could not be isolated. The higher temperature seems to favour the formation of the β-chrysenoylpropionic acid, m.p. 221°.

This β-chrysenoylpropionic acid was converted into

γ-chrysenylbutyric acid, m.p. 210.5-212.5°, by means of a Martin[5] modification of the Clemmensen reduction, which was employed in preference to the method of Beyer, who carried out the reduction in acetic acid. The γ-chrysenylbutyric acid was then converted into its acid chloride by means of phosphorus pentachloride in benzene and, without isolation or purification, was cyclised in the cold with stannic chloride in benzene to give a ketotetrahydrobenzchrysene which decomposes above 275°. This is the technique employed by Bachmann, Carmack and Safir[6] for the cyclisation of pyrenylbutyric acid.

The ketotetrahydrobenzchrysene so obtained was reduced to tetrahydrobenzchrysene, m.p. 217-218°, by the method of Kon and Soper[7] with hydrazine hydrate and sodium ethoxide in alcohol at 200°. A by-product in this reaction was a very high melting, extremely insoluble yellow compound which is probably an azine derivative.

The tetrahydrobenzchrysene was dehydrogenated with palladium black in an evacuated sealed tube at 300°. The pressure of the hydrogen liberated, however, did not allow the reaction to go to completion, but after a few crystallisations of the dehydrogenation product from xylene, 2:3-benzchrysene, m.p. 292-294°, was obtained, and was shown by means

of a mixed melting point, to be identical with 2:3-benzchrysene, m.p. 292-295°, obtained by Clar[8] by means of an arduous fractional crystallisation of the product obtained from an Elbs pyrolysis of a mixture of o-toluoylphenanthrenes. The 2:3-benzchrysene synthesised from chrysene was obtained as pale yellow plates: Clar's compound was deep yellow-green in colour.

It follows from the foregoing synthesis of 2:3-benzchrysene that the original β-chrysenoylpropionic acid, m.p. 221°, cannot be β-(5-chrysenoyl)propionic acid as suggested by Beyer, but must be the 2- acid or the 3- acid.

Chrysene, a benzphenanthrene, behaves in many respects like phenanthrene. γ-(2-Phenanthryl)butyric acid, when cyclised with stannic chloride in the cold, ring closes to position 1[9]; cyclisation of γ-(3-phenanthryl)butyric acid under the same conditions takes place in position 2[10]. Having used the same method of cyclisation of γ-chrysenylbutyric acid, we may assume that ring closure took place in a similar manner to that of the corresponding γ-phenanthrylbutyric acid. The product obtained was a 2:3-benzchrysene derivative which should have been formed from γ-(3-chrysenyl)butyric acid, as it would be expected, on the above analogy, that γ-(2-chrysenyl)butyric acid would ring close to a 1:2-benzchrysene (picene) derivative.

Thus it appears probable that the chrysenoylpropionic acid, m.p. 221°, obtained by Beyer is β-(3-chrysenoyl)-propionic acid. This is supported also by the fact that a Friedel-Craft reaction between phenanthrene and succinic anhydride in nitrobenzene solution gives β-(3-phenanthroyl)-propionic acid[11].

Funke and Muller[2], by a Friedel-Craft reaction in carbon disulphide, obtained two acetylchrysenes. The main product was 6-acetylchrysene, m.p. 114°, the other which was present in smaller amount had m.p. 254° and gave an ethylchrysene, m.p. 236°. Funke and Muller tentatively suggested that the second acetylchrysene was the 5- derivative. Newman[12], by a synthesis of 5-ethylchrysene, m.p. 92°, showed that this was not so. Bachmann and Struve[13] have also synthesised 1-ethylchrysene, m.p. 184°.

As the melting points of 1-methyl- (250°) and 2-methylchrysene (225°) are much higher than those of the other methylchrysenes, it would seem that the ethylchrysene, m.p. 236°, of Funke and Muller is 2-ethylchrysene. Accordingly it might appear that succinoylation of chrysene should also occur in this position so that the β-chrysenoylpropionic acid, m.p. 221°, would be the 2- acid. Against this can be set the fact that Funke and Muller used carbon disulphide as solvent in their reaction, while Beyer used nitrobenzene.

In addition the difference in melting point between β-(6-chrysenoyl)propionic acid (m.p. 197°) and the other chrysenoylpropionic acid (m.p. 221°) is not nearly so great as that between 1-methyl- (m.p. 250°) or 2-methyl- (m.p. 225°) and 6-methylchrysene (m.p. 161°) or between 1-ethyl- (m.p. 184°) and 6-ethylchrysene (m.p. 126°); indeed the melting points of γ-(6-chrysenyl)butyric acid (m.p. 208°) and the other γ-chrysenylbutyric acid (m.p. 214°) are very close together.

The evidence, although not conclusive, appears to indicate that, while the acetylchrysene, m.p. 254°, of Funke and Muller is probably 2-acetylchrysene, the β-chrysenoylpropionic acid, m.p. 221°, obtained by Beyer is β-(3-chrysenoyl)propionic acid.

Attempted synthesis of 1:2:3:4-dibenzphenanthrene.

It was decided to make use of the small amount of β-(6-chrysenoyl)propionic acid, obtained as a by-product in the preparation of β-(3-chrysenoyl)propionic acid, to attempt the synthesis of 1:2:3:4-dibenzphenanthrene outlined on page 115. Beyer[3] had been unable to complete this synthesis.

β-(6-Chrysenoyl)propionic acid, III, was reduced by a Martin modification of the Clemmensen reduction instead of

by Beyer's method in acetic acid. The resulting γ-(6-chrysenyl)butyric acid, IV, was cyclised by means of stannic chloride, as used for cyclisation of the isomeric chrysenylbutyric acid, instead of by aluminium chloride in nitrobenzene as used by Beyer. Using the Clemmensen reduction Beyer could not reduce the ketotetrahydrobenzchrysene, V, to the tetrahydrobenzchrysene, VI. He obtained the carbinol VIII. As it had been found that the isomeric ketotetrahydrobenzchrysene was reduced to a tetrahydrobenzchrysene with hydrazine hydrate and sodium ethoxide in alcohol at 200°, an attempt was made to reduce the ketotetrahydrobenzchrysene, V, to compound VI in the same way. The only crystalline product isolated was a small amount of the carbinol, VIII, obtained by Beyer. The rest of the material, without further purification, was dehydrogenated with palladium black at 300-330°. Considerable decomposition occurred and only a small amount of γ-(6-chrysenyl)-butyric acid, IV, was isolated. Beyer also obtained a trace of this acid as sole product of a selenium dehydrogenation of the carbinol, VIII.

The sterically hindered position of the keto group in 1'-keto-1':2':3':4'-tetrahydro-5:6-benzchrysene, V, appears to be the cause of the failure of hydrazine hydrate and

sodium ethoxide to reduce the ketone to $>CH_2$. It is probable that the hydrazone of the ketone was not formed as no azine derivative, similar to that found in the reduction of the isomeric ketotetrahydro-2:3-benzchrysene, was obtained as a by-product in this reduction.

Although it appears that 1'-hydroxy-1':2':3':4'-tetrahydro-5:6-benzchrysene is resistant to dehydrogenation, it is possible that if it were dehydrated to 3':4'-dihydro-5:6-benzchrysene, this compound would give 1:2:3:4-dibenzphenanthrene on dehydrogenation. Shortage of material and of time, however, has prevented further investigation of this synthesis along these lines.

Experimental.

β-(3-Chrysenoyl)propionic acid.

a). Chrysene (11.4 gm.) and succinic anhydride (5 gm.), both finely powdered, were suspended in nitrobenzene (100 cc.) and mechanically stirred while aluminium chloride (13.35 gm.) in nitrobenzene (75 cc.) was added at room temperature. Stirring was continued for 6 hours at 20° and then overnight at room temperature. The dark red solution was then poured on to crushed ice (150 gm.) and concentrated HCl (25 cc.). The nitrobenzene was removed in steam and the grey residue filtered off, washed with water and dried in vacuo. After washing with a little ether to remove tarry material it was extracted with hot sodium carbonate solution (4%, 200 cc. approx.) and filtered from unchanged chrysene (6.5 gm.). The filtrate was allowed to cool, filtered from a trace of precipitate and acidified with dilute HCl. The greyish coloured precipitate was filtered off and dried in vacuo. After washing with a little boiling ether it was extracted several times with boiling benzene (125 cc. portions). The benzene solution was allowed to stand overnight and the brownish product which was deposited was filtered off. After two crystallisations from glacial acetic acid, with the addition of norit, this

material gave pale yellow plates (0.9 gm.), m.p. 218-221° (corr.). Beyer[3] gives m.p. 221-223°.

Concentration of the benzene mother liquors gave a brown solid which, after recrystallisation from acetic acid, gave m.p. 165-175°. Concentration of the acetic acid mother liquors gave a solid, m.p. 185-190° which crystallised from glacial acetic acid in pale yellow needles, m.p. 192-194° (corr.). Mixed m.p. with the acid m.p. 218-221° was 170-175°. β-(6-Chrysenoyl)propionic acid has m.p. 197-198°.

b). By using 25% excess succinic anhydride and 12½% excess aluminium chloride and by carrying out the reaction at 30° instead of at 20° the yield of β-(3-Chrysenoyl)propionic acid, m.p. 218-221° was increased to 1.5 gm.

c). When the temperature was raised to 45° considerable tarring occurred and only 0.35 gm. of the required acid m.p. 217-220° was obtained.

d). When carried out at 0° a mixture of the two isomeric chrysenoylpropionic acids was obtained which could not be readily separated. An attempt to separate the two acids by fractional sublimation of their methyl esters was also unsuccessful.

γ-(3-Chrysenyl)butyric acid.

To amalgamated zinc (20 gm.) were added in order, water (16 cc.), concentrated HCl (36 cc.), toluene (80 cc.) and β-(3-chrysenoyl)propionic acid (2 gm.). This solution was boiled for 50 hours, concentrated HCl (12 cc.) being added every 6 hours. Care was taken to bring all of the keto acid into solution before the end of the reaction by boiling very vigorously On cooling a white solid crystallised out from the toluene and was filtered off. The zinc remaining in the flask was also extracted with boiling toluene from which a little more white solid was obtained. This γ-(3-chrysenyl)butyric acid was recrystallised from toluene in white plates (1.5 gm.), m.p. 210.5-212.5° (corr.). Beyer gives m.p. 213-214°. Mixed m.p. with β-(3-chrysenoyl)propionic acid, m.p. 218-220°, was 190-197°.

The solubility of the keto acid in the toluene can be increased by adding 15-20 cc. of glacial acetic acid.

1'-Keto-1':2':3':4'-tetrahydro-2:3-benzchrysene.

Finely powdered γ-(3-chrysenyl)butyric acid (1 gm.) was suspended in dry benzene (10 cc.) and phosphorus pentachloride (0.75 gm.) added gradually with shaking. After 1 hour all the acid had dissolved and to this solution was

added gradually with shaking, stannic chloride (0.5 cc.) in dry benzene (2 cc.). The solution became yellow in colour and a solid, which changed from yellow to red to dark red, was gradually precipitated. After standing for about 20 hours at room temperature with occasional shaking the tin complex was decomposed with ice and HCl. After stirring one hour the benzene was removed in steam and the cream coloured solid filtered off. This material was extracted with hot dilute sodium carbonate solution and the undissolved solid filtered off, washed with hot water and dried in vacuo. Yield 0.88 gm. Recrystallised from glacial acetic acid (200 cc. approx.) with the addition of norite this solid gave pale yellow plates (0.75 gm.) decomposing above 275°.

Analysis. Found: C = 89.11%, H = 5.43%.

$C_{22}H_{16}O$ requires C = 89.19%, H = 5.40%.

An attempt to ring close γ-(3-chrysenyl)butyric acid by means of 85% sulphuric acid at 100° was unsuccessful, probably due to the fact that the chrysenylbutyric acid was sulphonated during the prolonged heating required to effect solution of the acid.

1':2':3':4'-Tetrahydro-2:3-benzchrysene.

The above ketotetrahydrobenzchrysene (0.25 gm.) was heated for 18 hours at 200° in a sealed tube with absolute alcohol (11 cc.) containing sodium (0.5 gm.) and hydrazine hydrate (1 cc., 99%). The pale yellow solid was then filtered off and extracted four times with boiling absolute alcohol (40 cc. portions). From the alcohol extracts, filtered hot from the yellow solid, were obtained white plates with a faint yellow tinge, m.p. 215°. Recrystallised from absolute alcohol in white plates, m.p. 217-218° (corr.). 0.45 gm. of tetrahydrobenzchrysene was obtained from 0.8 gm. of ketotetrahydrobenzchrysene.

Analysis. Found: C = 93.54%, H = 6.26%.

$C_{22}H_{18}$ requires C = 93.62%, H = 6.38%.

The yellow material insoluble in alcohol was insoluble in most solvents and could not be crystallised. It melts above 300°.

2:3-Benzchrysene.

1':2':3':4'-Tetrahydro-2:3-benzchrysene (0.2 gm.) and palladium black (0.02 gm.) were heated in an evacuated sealed tube over a period of about 5 hours to a temperature of 300°, which was then maintained for a further 3 hours. On cooling the pale yellow solid was extracted with

absolute alcohol (40 cc. approx.), which extracts preferentially unchanged material. The remaining pale yellow solid was dissolved in hot xylene and filtered from catalyst. The yellow crystalline material obtained from the filtrate was crystallised several times from xylene till the pale yellow plates obtained had a constant melting point at 292-294°. This material gave no depression of melting point when mixed with an authentic specimen of 2:3-benzchrysene, m.p. 292-295°.

γ-(6-Chrysenyl)butyric acid.

β-(6-Chrysenoyl)propionic acid (1.5 gm.) in toluene (50 cc.) was reduced by a Martin modification of the Clemmensen method with amalgamated zinc (15 gm.), concentrated HCl (27 cc.) and water (12 cc.). A little acetic acid was added to assist solubility. Boiling was continued for 50 hours, concentrated HCl (10 cc.) being added every 6 hours. On cooling γ-(6-chrysenyl)butyric acid crystallised out from the toluene layer. Recrystallised from toluene in white plates, m.p. 207-208° (corr.). Beyer gives m.p. as 208-209°. Mixed m.p. with original keto acid, 180-187°. Yield 1 gm. A further quantity of this chrysenylbutyric acid can be obtained by concentrating the toluene mother liquor.

1'-Keto-1':2':3':4'-tetrahydro-5:6-benzchrysene.

γ-(6-Chrysenyl)butyric acid (0.95 gm.) was treated with phosphorus pentachloride (0.75 gm.) in dry benzene (10 cc.) in the cold. When all the acid had dissolved stannic chloride (0.4 cc.) in dry benzene (2 cc.) was added and the solution left to stand 20 hours at room temperature with occasional shaking. A purplish-red complex salt was deposited and this, together with the benzene solution, was decomposed in ice and HCl. After stirring one hour the benzene was distilled off and the insoluble material filtered off. This material was heated with sodium carbonate solution and filtered hot, when a pale yellow solid (0.85 gm.) was left undissolved. Recrystallised from glacial acetic acid in pale yellow prisms, m.p. 217° (corr.). Beyer gives m.p. of this keto-tetrahydrobenzchrysene as 220°.

Reduction of 1'-keto-1':2':3':4'-tetrahydro-5:6-benzchrysene.

The above ketotetrahydrobenzchrysene (0.25 gm.), sodium (0.5 gm.) in absolute alcohol (11 cc.) and hydrazine hydrate (99%, 1 cc.) were heated at 200° for 18 hours. On cooling the alcohol solution was filtered from a small amount of insoluble material. This solid was crystallised from absolute alcohol in pale yellow-white elongated prisms,

m.p. 177-178° (corr.). This appears to be 1'-hydroxy-1':2':3':4'-tetrahydro-5:6-benzchrysene as it has similar crystalline form and melting point (179-180°) to the carbinol obtained by Beyer[3] by means of a Clemmensen reduction of this ketone.

The original alcohol solution was evaporated to dryness, diluted with water and the insoluble material filtered off. This pale yellow solid was taken up in absolute alcohol and small amount of insoluble product filtered off. The material soluble in the alcohol could not be crystallised readily from ethyl or methyl alcohol. It melts at 155-160° and is probably a mixture of the carbinol with unchanged ketone. It was used without further purification in the following dehydrogenation experiment.

Attempted dehydrogenation of above reduction product.

The crude material (0.12 gm.) from the above reaction was heated with palladium black (0.015 gm.) in an atmosphere of carbon dioxide for 5 hours at 300-330°. Considerable charring occurred. The product was then extracted with boiling absolute alcohol. A small amount of white solid was obtained from the extract. This formed an orange coloured picrate, m.p. 157-160°, (picrate of

1:2:3:4-dibenzphenanthrene has m.p. 141°). The picrate when decomposed gave a white solid which crystallised from glacial acetic acid in plates, m.p. 206-208° (corr.), which gave no depression of m.p. when mixed with γ-(6-chrysenyl)butyric acid, m.p. 207°.

Bibliography.

1) Liebermann & Zsuffa, Ber., 1911, 44, 207.

2) Funke & Muller, J.pr.Chem., 1936, 144, 242.

3) Beyer, Ber., 1938, 71, 915.

4) Bergmann & Eschinazi, J.Amer.Chem.Soc., 1943, 65, 1413.

5) Martin, J.Amer.Chem.Soc., 1936, 58, 1438.

6) Bachmann, Carmack & Safir, J.Amer.Chem.Soc., 1941, 63, 1684.

7) Kon & Soper, J., 1940, 1335.

8) Clar, Ber., 1929, 62, 1578.

9) Bachmann & Struve, J.Org.Chem., 1939, 4, 460.

10) Bachmann, J.Org.Chem., 1938, 3, 439.

11) Haworth & Mavin, J., 1933, 1012.

12) Newman, J.Amer.Chem.Soc., 1940, 62, 871.

13) Bachmann & Struve, J.Org.Chem., 1940, 5, 416.