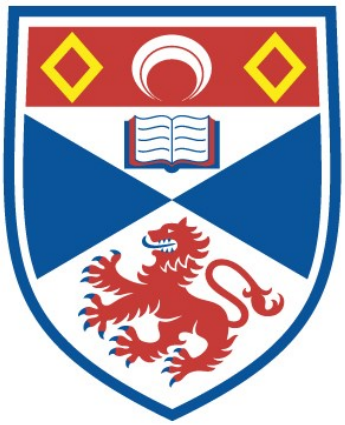
RESEARCHES INTO THE SYNTHESIS OF SOME DEGRADATION PRODUCTS OF EMETINE

George Reid Ure

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1954

RESEARCHES INTO THE SYNTHESIS OF SOME DEGRADATION PRODUCTS OF EMETINE

being a Thesis

presented by

GEORGE REID URE, B.Sc.

to the

UNIVERSITY OF ST. ANDREWS

in application for the

Degree of

DOCTOR OF PHILOSOPHY

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DECLARATION

I hereby declare that the following Thesis is a record of experiments carried out by me, that the Thesis is my own composition and that it has not been presented previously for a Higher Degree.

The investigation was carried out in the Chemical Research Laboratory of the University of St. Andrews under the direction of H. T. Openshaw, M.A., D.Phil.

Date: 30th June, 1954.

George R. Ure.

CERTIFICATE

I hereby certify that Mr. George R. Ure, B.Sc., has spent nine terms at Research work under my direction, that he has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and that he is qualified to submit the accompanying Thesis in application for the Degree of Ph.D.

Date: 30-6-54.

H. T. Openshaw,
Director of Research.

UNIVERSITY CAREER AND RESEARCH EXPERIENCE

I entered the University of St. Andrews originally in October, 1941, completing the course for the pass degree of B.Sc. (War-time) in June, 1943. After a period of three years in a Research Establishment of the Ministry of Supply, I returned to St. Andrews in October, 1946 and obtained first-class Honours in Chemistry (Post-Graduate) in June, 1948.

Immediately thereafter, I was awarded a University of St. Andrews Post-Graduate Scholarship and a D.S.I.R. grant (Honorary). I was admitted as a Research Student of the University of St. Andrews in October, 1948. The University Post-Graduate Scholarship was renewed for a second and third year and I remained in St. Andrews until June, 1951.

CONTENTS

INTRODUCTION

The root bark of several species of the ipecacuanha plant, notably Cephaelis ipecacuanha and Psychotria acuminata, contains at least five alkaloids, of which the principal one is emetine. The minor alkaloids are all closely related to emetine, and the elucidation of their structures follows directly from the structure of emetine.

The chief interest in emetine lies in its peculiar therapeutic powers as a treatment for amoebic dysentery. The drug has other medicinal properties as an emetic and diaphoretic, but these have largely been superseded, and in any case do not compare with its importance as a specific against Entamoeba histolytica, the organism responsible for the occurrence of amoebic dysentery. Its local irritant effects, however, render it unsuitable in some cases, and although various simple derivatives have been used in its place, none of them appear to be a significant improvement on emetine itself. The main hope of producing a more suitable therapeutic agent lies in a more radical alteration of the molecule, and before this can be attempted, the structure and properties of emetine must be known beyond all doubt. Natural and synthetic substitutes for emetine, produced without this knowledge, have so far proved ineffective. The structure of emetine, however, is now known with virtual certainty, apart from a complete

synthesis of the molecule itself, and progress in this field should be more rapid.

The investigations recorded herein are part of a continuation of the series (1, 2, 3, 4) which has finally shown the structure of emetine clearly, and with it the structures of the minor alkaloids and the rubremetine salts (2). The present work is mainly concerned with synthetic investigations of the more immediate degradation products from emetine, with the aim of further confirming the molecular structure. A parallel aim has been the provision of suitable intermediates for analogous syntheses.

HISTORICAL BACKGROUND

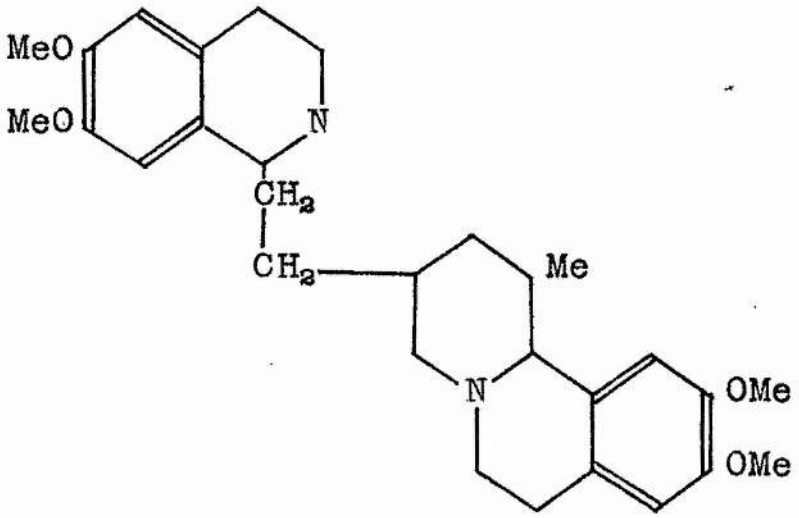
The root bark of the ipecacuanha plant has held the attention of men of science for more than two hundred years. The original interest was purely medical, and arose from its peculiar therapeutic powers as a specific agent for the treatment of amoebic dysentery. These powers were described first by Helvetius (5) as long ago as 1688, and apart from purification of the active constituents, have not been surpassed to this day. Its activity is due to the alkaloid emetine which occurs to the extent of about 1.7% of the dried root, together with a smaller amount of four other closely associated alkaloids, viz., psychotrine, cephaeline, emetamine and O-methylpsychotrine. The relationship between emetine and the associated minor alkaloids has been worked out in detail by Pyman *et alii* (6, 7, 8, 9). Psychotrine and O-methylpsychotrine contain one double bond in the molecule, and on reduction lead respectively to cephaeline and emetine. Emetine and O-methylpsychotrine are the O-methyl ethers of the singly phenolic cephaeline and psychotrine respectively. Emetamine differs from emetine in having two double bonds, there being no other differences. Apart therefore from questions of spatial configuration which lead to the formation of two new bases, *iso*emetine and *iso*cephaeline, in reduction processes which create a new asymmetric centre, the chemistry of the remainder of the ipecacuanha alkaloids is

the same as that of the principal alkaloid, emetine.

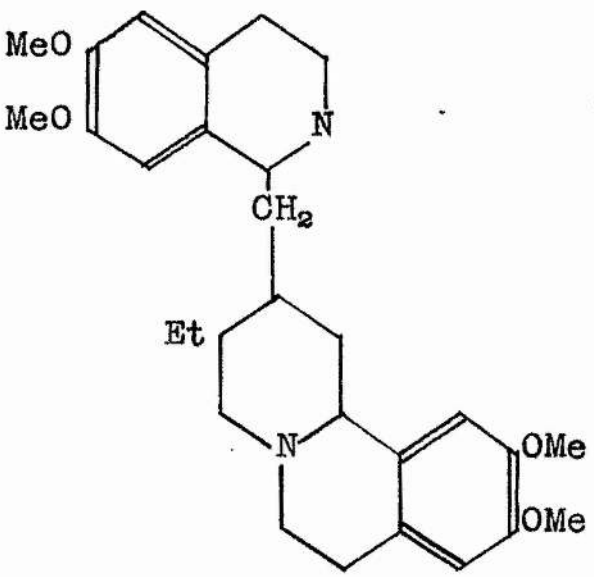
Although ipecacuanha root extracts were first investigated chemically by Pelletier and others (10, 11) in 1817, sixty years were to pass before a specimen of emetine (12) was obtained sufficiently free from associated bases and other impurities to enable the molecular formula to be ascertained as $C_{29}H_{40}O_4N_2$. Carr and Pyman (6) were responsible for much of the correlation of fragments of emetine chemistry, the main features of which are as follows.

Emetine is a diacid base, containing one secondary and one tertiary nitrogen atom. The four oxygen atoms are concerned in four methoxyl groups. The fundamental cyclic structure consists of tetrahydro<u>iso</u>quinoline rings of which two separate ones have been shown to be present by at least two independent methods (13, 4). The methoxyl groups are attached to the 6:7 positions of each of the <u>iso</u>quinoline nuclei. The formulation requires the presence of one other ring in emetine, and as no N-methyl groups are present, one of its points of attachment must be the tertiary nitrogen atom. The <u>iso</u>quinoline heterocycles are attached to the rest of the molecule by carbon chains in the 1-position, as is the case with practically all <u>iso</u>quinoline alkaloids. These and associated observations led Brindley and Pyman (9) to publish a complete structure (p. 5) for emetine in 1927. This formula, backed by theories of

Structure of Emetine



Brindley and Pyman, 1927 (9)



Battersby and Openshaw, 1949 (4)

biogenesis (14) was not seriously challenged until the last few years, through investigations carried out by Späth and Pailer (15) and Battersby and Openshaw (1, 4). Karrer and his collaborators (16) made some suggestions, but they were led into error by their determination of the number of C-methyl groups in the molecule [cf. (1)].

Derivation of the 'Pyridine Base' from Emetine.

The Hofmann degradation of emetine has received a considerable amount of attention. The first investigator was Hesse (17), who obtained N-methylemetinemethine by thermal decomposition of N-methylemetine dimethohydroxide. The methine was further characterised by Pyman (7, 8), and it is easily hydrogenated over platinum in ethanol to N-methylemetinetetrahydromethine (1), characterised as the crystalline perchlorate. An N-methylemetinetetrahydromethine is also obtained directly by the reduction of N-methylemetine dimethochloride (Emde's degradation), but the product has never been characterised and may not be identical with that from the hydrogenation of the methine. The formation of diquaternary salts of emetine leads to the formation of a new asymmetric centre at the tertiary nitrogen atom, N(b); but as both of the stereoisomers give rise to the same methine this is of no consequence here.

While a second stage of the Hofmann degradation has been carried out on N-methylemetinemethine (18), no crystalline derivatives have been obtained, although the reaction appears to take a normal course. With the tetrahydromethine, the second stage may take a normal course, i.e. formation of the quaternary dimethiodide, followed by distillation of the corresponding dimethohydroxide. The process may, however, take place in stages and the first

stage is of particular interest for our purpose. Battersby and Openshaw (1) found that if N-methylemetinetetrahydromethine is refluxed with methyl iodide in methanol, the product is not the expected quaternary dimethiodide, but a mixture. Tetramethylammonium iodide is one component, showing clearly that at least some of the material has undergone a Hofmann type of degradation without being basified or distilled in vacuo. The nitrogen elimination must therefore occur with great facility.

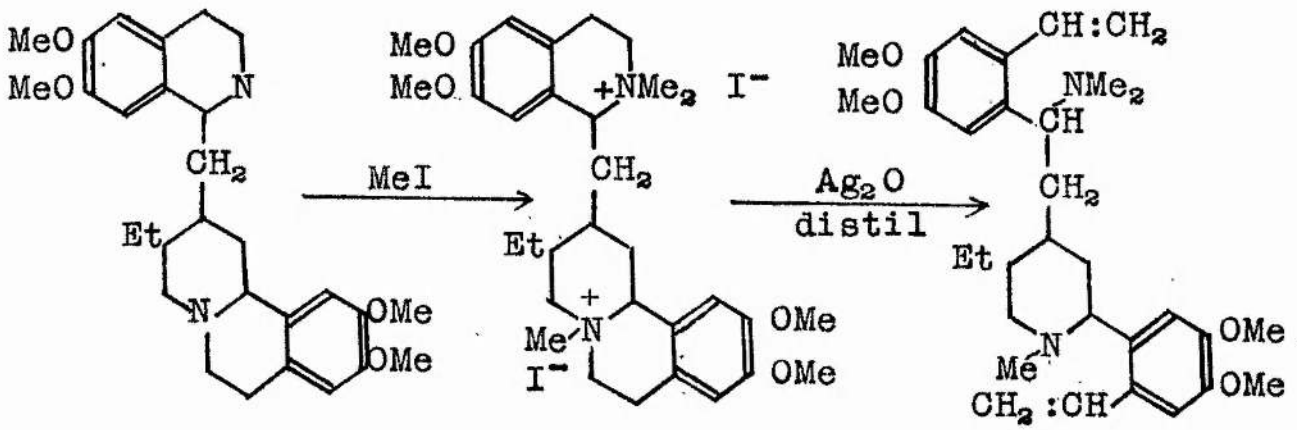
The expected dimethiodide is formed in cold ethereal solution, but gives rise to the same des-N(a)-emetinetetrahydromethine methiodide on heating in water or diethyl ketone to 100°. The methiodide is peculiarly resistant to reduction, either catalytically or by sodium amalgam. The corresponding methochloride, however, is hydrogenated over platinum in aqueous solution to the methochloride of des-N(a)-emetinehexahydromethine, characterised as the crystalline methiodide and platinichloride. It may be more convenient to obtain the des-N(a)-tetrahydromethine as a free base by distillation of the methochloride, followed by purification through the perchlorate. Hydrogenation then leads to the hexahydromethine also as a free base (4).

The hexahydromethine is dehydrogenated with silver acetate at as low a temperature as 180°, which is unlikely to cause any rearrangement. More effective dehydrogenation

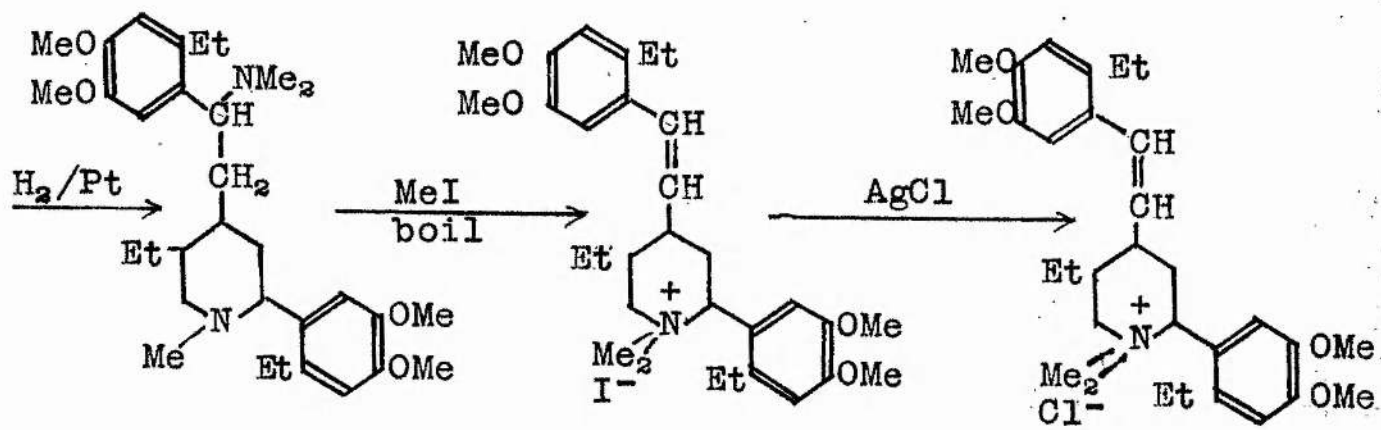
is obtained using palladium-charcoal at 250-270°, when the corresponding pyridine base is obtained in 30% yield. The product is freed from unchanged methine, which is a stronger piperidine base, by extraction of an ethereal solution with M/50 citric acid.

Further degradation by oxidation to 5-ethylpyridine-2:4-dicarboxylic acid and other considerations indicate a structure (* p.10) for the 'pyridine base', which might therefore be designated 4-[β-(3:4-dimethoxy-6-ethylphenyl)-ethyl]-2-(3:4-dimethoxy-6-ethylphenyl)-5-ethylpyridine. The schematic derivation of the 'pyridine base' from emetine, using the newly established and unambiguous structure for the alkaloid (p.5) is set out on p.10. It was thought that the 'pyridine base' should be capable of synthesis as further conclusive proof of its structure, and the following investigations were carried out with this end in view.

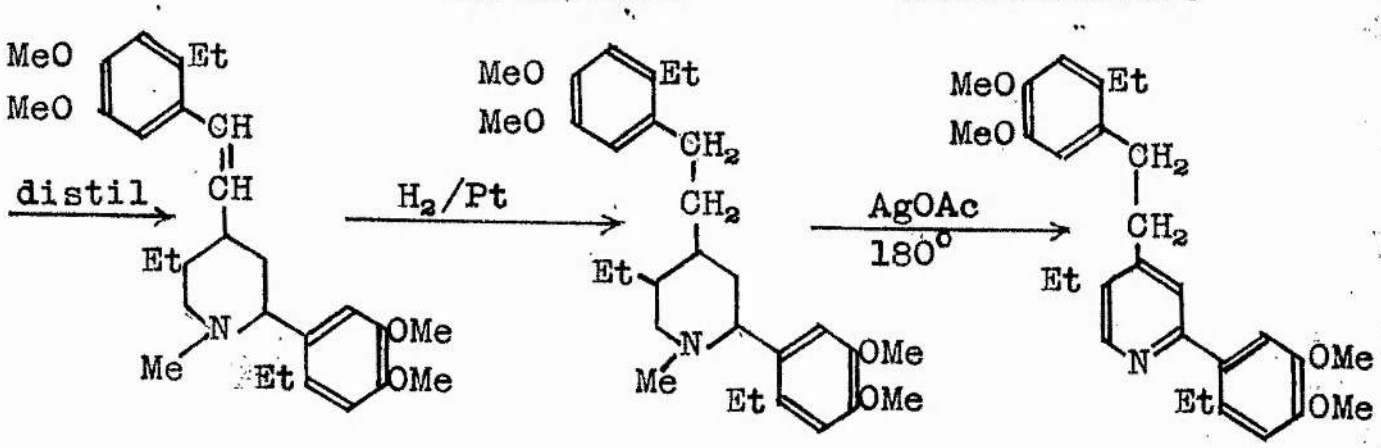
Derivation of 'Pyridine Base' from Emetine



Emetine — N-methylemetine dimethiodide — N-methylemetine-methine



N-methylemetine-tetrahydromethine — des-N(a)-emetine-tetrahydromethine methiodide — des-N(a)-emetine-tetrahydromethine methochloride



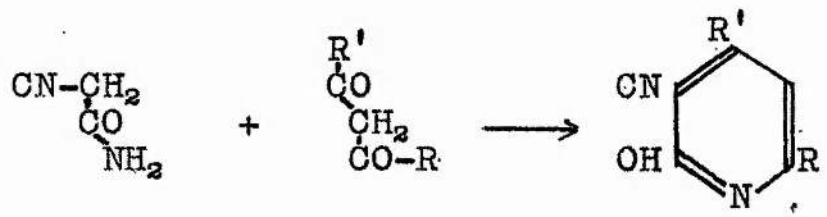
des-N(a)-emetine-tetrahydromethine — des-N(a)-emetine-hexahydromethine — 'Pyridine Base'

Synthesis of Pyridines

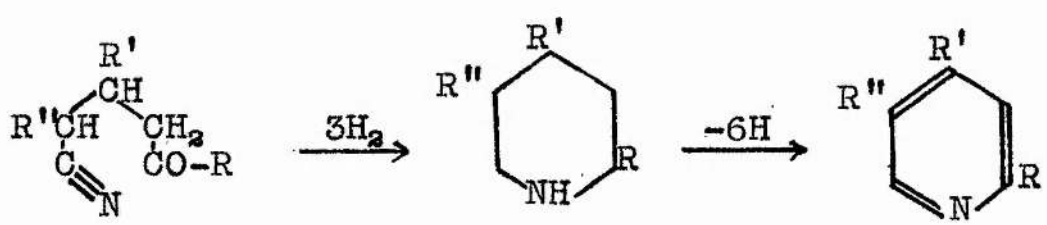
Methods of synthesising pyridines and their derivatives are very numerous (19), and no attempt can be made to mention or even classify them all exhaustively. Perhaps it is sufficient to say that a synthesis of a pyridine suitable for application to the 'Pyridine base' from emetine (p.10) or its precursor, 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine must fulfil certain requirements, viz. (1) that the orientation of the product must be reasonably certain and unambiguous, (2) harsh conditions likely to cause extensive rearrangement must be avoided and (3) conditions likely to cause destruction of methoxyl groups must be employed with caution.

The methods which have been employed in the present work belong essentially to three types:

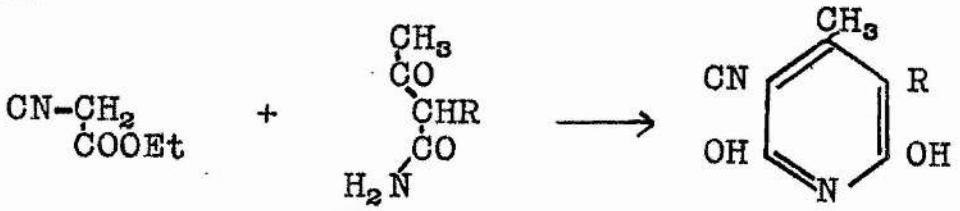
(1) Condensation of a β-diketone with cyanacetamide:



(2) Dehydrogenation of the appropriate piperidine base, made by the reductive cyclisation of a δ-ketonitrile:

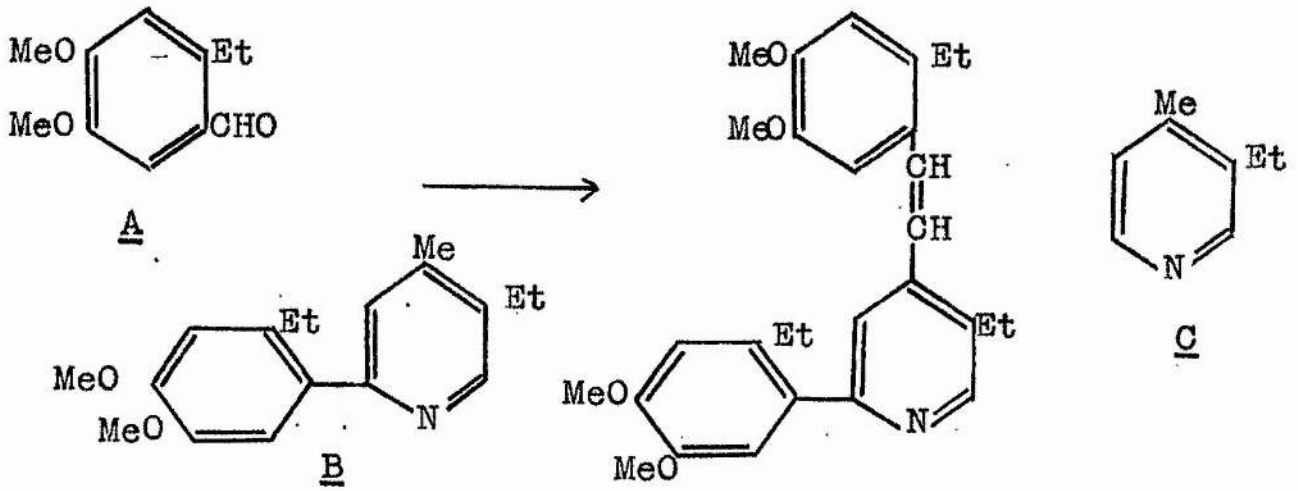


(3) Condensation of an acetoacetamide with cyanoacetic ester:



Proposed route for Synthesis of 'Pyridine Base' from Emetine.

The simplest method envisaged for the introduction of the substituted β-phenylethyl group at the 4-position of the pyridine ring involves the condensation of the appropriate aldehyde (6-ethylveratraldehyde, A) with a suitably substituted 4-methylpyridine (B). The reactivity towards aldehydes of a methyl group attached to the 4-position in pyridine is well established; moreover, the successful achievement of such condensations with β-collidine (C) [see, for instance, the synthesis of dihydroquinine (117)] shows that it is not prevented by the steric hindrance of a 3-ethyl group.



The aldehyde, A, has been prepared by Koepfli and Perkin (20) by applying Gattermann's aldehyde synthesis (21) to 4-ethylveratrole, which is now easily obtainable from commercial 4-ethylguaiacol. Attention was therefore directed to the synthesis of the second component, B. Various routes have been explored and these are outlined separately below.

Synthetic approach to 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine (B).

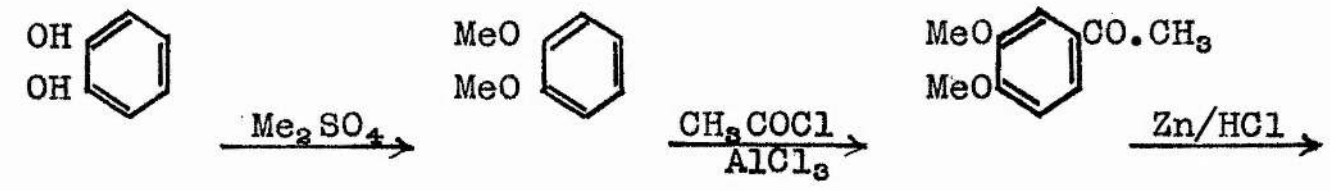
The most straightforward synthesis of (B) that could be devised involves ten stages, starting from either catechol or guaiacol. Fortunately, when this series was partly completed, 4-ethylguaiacol became available. The source of this material was not known*, but careful comparison of its methyl ether with synthetic 4-ethyl-veratrole showed it to be of high purity. Two stages are thus eliminated at the beginning of the synthesis. A schematic sequence, which will be referred to as Route I, is shown on p.14.

Methylation of catechol

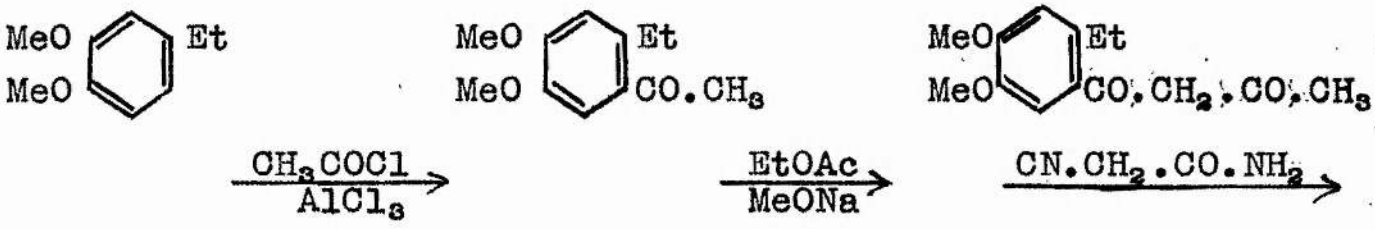
According to Perkin and Weizman (22) veratrole can be obtained in high yield (95%) by a 'flash' methylation. The catechol is dissolved in twice its weight of methanol and a 10% excess of dimethyl sulphate is added. After cooling in ice and salt, a substantial excess of sodium hydroxide

* 4-Ethylguaiacol was purchased from L. Light and Co.

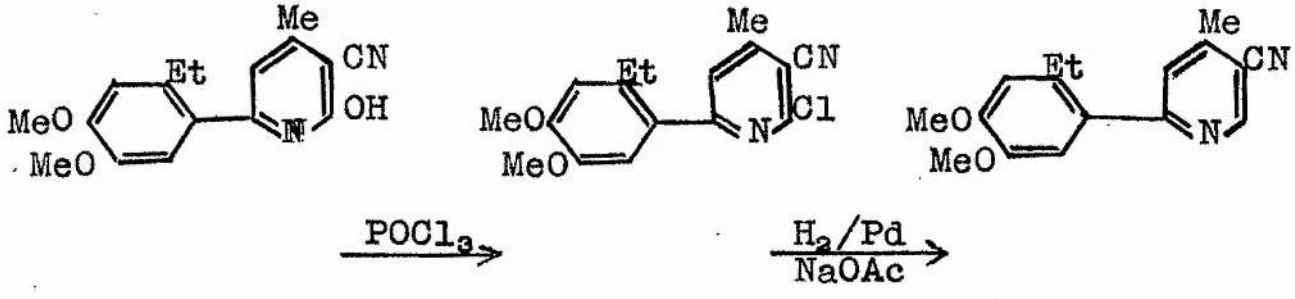
Attempted Synthesis of 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine Route I



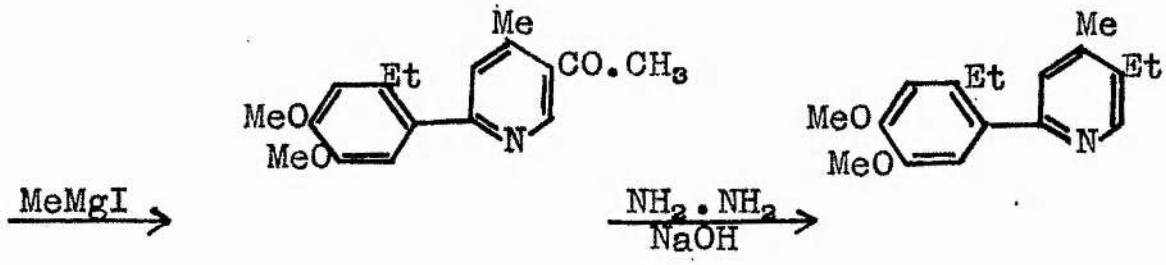
Catechol — Veratrole — Acetoveratrone



4-Ethylveratrole — 6-Ethylaceto-veratrone — 6-Ethylveratroyl-acetone



3-Cyano-6-(3:4-dimethoxy-6-ethyl-phenyl)-4-methyl-pyrid-2-one — 2-Chloro-3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine — 3-Cyano-6-(3:4-dimethoxy-6-ethyl-phenyl)-4-methyl-pyridine



5-Acetyl-2-(3:4-dimethoxy-6-ethylphenyl)-4-methyl-pyridine — 2-(3:4-Dimethoxy-6-ethyl-phenyl)-5-ethyl-4-methyl-pyridine

as a 40% solution is added all at once. The ensuing violent reaction is moderated by methanol evaporation. The reaction is finished in three minutes. Large supplies of veratrole were necessary for these syntheses, and the method was used several times. In spite of careful purification of the reagents, especially the dimethyl sulphate, low yields (30-35%) were the invariable result, even with a substantial excess of the methylating reagent. That the catechol employed was not at fault is shown by the excellent yields obtained by other methods, using the same reagents in the same proportions. The methods used latterly were essentially those of Barger and Silberschmidt (23) or Kostanecki and Tambor (24), both of which have been refined in Organic Syntheses (25, 26). The latter method, recommended for the preparation of veratraldehyde from vanillin, gave virtually theoretical yields of good quality veratrole, crystallising in the receiver.

Acetoveratrone and 4-ethylveratrole

In a Friedel-Crafts ketone synthesis, the reactivity of veratrole is so much greater than that of benzene, that the latter may be used as a solvent. Far from decreasing the yield, a greatly enhanced yield may often be obtained, as shown by Battersby and Openshaw (1) in the case of 6-ethylacetoveratrone. Yields were usually in the region of 60-70%, even allowing for recovered veratrole and extensive demethylation. The yield was found to depend on

efficient stirring more than on any other factor, and yields over 80% could be obtained regularly by careful attention to this point.

Ordinary Clemmensen reduction was very satisfactory for the reduction of acetoveratrone, provided a two-phase solvent system was used (110). The solvent layer (toluene) not only kept both product and starting material in solution, leaving just sufficient in the aqueous layer to react, but successfully prevented extensive demethylation during the long boiling with hydrochloric acid. In some cases no demethylated material could be detected. Good yields (75%) of 4-ethylveratrole were obtained on fractionation. Some unchanged acetoveratrone was recovered, making the true yield even higher.

When 4-ethylguaiacol became available commercially, it was used as a source of 4-ethylveratrole. The method of methylation found most successful for veratrole (26) was used with excellent results (97-98.5% yield). No difference could be detected in the products from the two sources.

6-Ethylacetoveratrone

6-Ethylacetoveratrone was made by the improved method of Battersby and Openshaw (1), on a much larger scale than before. Again it was found that fast, efficient stirring was the most important condition, and yields up to 94% on unrecovered ethylveratrole could be obtained.

6-Ethylveratroylacetone

6-Ethylveratroylacetone was made by a Claisen condensation of 6-ethylacetoveratrone with ethyl acetate. Trial experiments, as carried out by Claisen himself (27), gave yields slightly below those reported, probably due to the use of commercial, dry sodium methoxide. However, the yields with the methoxylated acetophenone were better, and most of the unused 6-ethylacetoveratrone could be recovered.

Condensation of β-diketones with Cyanacetamide

The condensation of cyanacetamide with β-diketones has been studied by Issoglio (28), Umaprasanna Basu (29) and Bardhan (30) of which accounts the last is most general and exhaustive. In many cases, notably with aliphatic diketones, the reaction is swift and exothermic, although it is noteworthy that the product is usually collected in portions over about 24 hours unless external heating is employed. Diethylamine appears to be a universal catalyst for the condensation. With aromatic diketones, heating is always necessary. With symmetrical β-diketones only one product is possible, and the orientation is fixed, as for example when acetyl acetone is reacted with cyanacetamide to form 3-cyano-4:6-dimethylpyrid-2-one. If the diketone is asymmetric, there are immediately two isomers possible, depending on which carbonyl group condenses with the amide nitrogen. With benzoylacetone, for instance, both 6-phenyl-

4-methyl- and 4-phenyl-6-methyl-3-cyanopyrid-2-ones are formed. The isomers are not usually formed in equal quantities, the main disproportionating influence being the relative sizes of the eventual 4- and 6- substituents. In the case of benzoylacetone, Bardhan (30) reports a 75-25% mixture of 6-phenyl-4-methyl- and 4-phenyl-6-methyl-pyridones, but in repeating this work at least 90% of the total condensate was found to be a single substance, corresponding to his 6-phenyl-4-methyl- isomer, the one that should be favoured by steric factors. In the case of (3:4-dimethoxy-6-ethylbenzoyl)acetone, where one substituent is even more bulky than a phenyl group, only one product could be isolated, and this was assumed to be the required 6-(3:4-dimethoxy-6-ethylphenyl)-3-cyano-4-methylpyrid-2-one. The presence of a little of the isomer may have been indicated by slight sintering, persisting after several successive recrystallisations, 10° below the melting point.

Maximum yield in these condensations could only be obtained after two or three days refluxing in alcohol. The same yield could be obtained in a few hours by using higher boiling solvents, of which ethylene glycol monoethyl ether was found to be most suitable, but the product from ethyl alcohol was slightly cleaner.

Substitution of Cl for .OH in α-pyridones

The substitution of chlorine for a hydroxyl group in hydroxypyridines (pyridones) should be more facile than the

corresponding substitution of a phenolic group in the benzene series on account of the lesser ionising tendency of the pyridone. With α-pyridones, however, the stability of the amide structure and the necessity for a tautomeric change appears to slow down the reaction. Several reagents have been used for the purpose, the most closely analogous case being in the synthesis of Vitamin B_6 (31). Harris and Folkers employed a slight excess of phosphorus pentachloride, refluxing in chlorobenzene as a diluent, but only low yields were obtained. With our heavily substituted pyridone only intractable tarry material, insoluble in ether, was obtained, possibly due to demethylation to phenolic bodies. Similar results were obtained by using a little phosphorus pentachloride in a slight excess of phosphorus oxychloride. The method employed by Baddiley and Topham (32) for the preparation of chloropyrimidines, involving the use of at least a molecular proportion of dimethylaniline gave a small yield of the desired 2-chloropyridine, but the product was difficult to purify. The method from Organic Syntheses (33) for the preparation of 2-chlorolepidine using phosphorus oxychloride alone was most satisfactory, but even so only one third of the pyridone was converted in one cycle, more than half the starting material being recovered intact. By increasing the proportion of phosphorus oxychloride to about three moles and extending the time of reflux the conversion could be raised to nearly 70% in one operation.

Selective reduction of chlorine in presence of nitrile

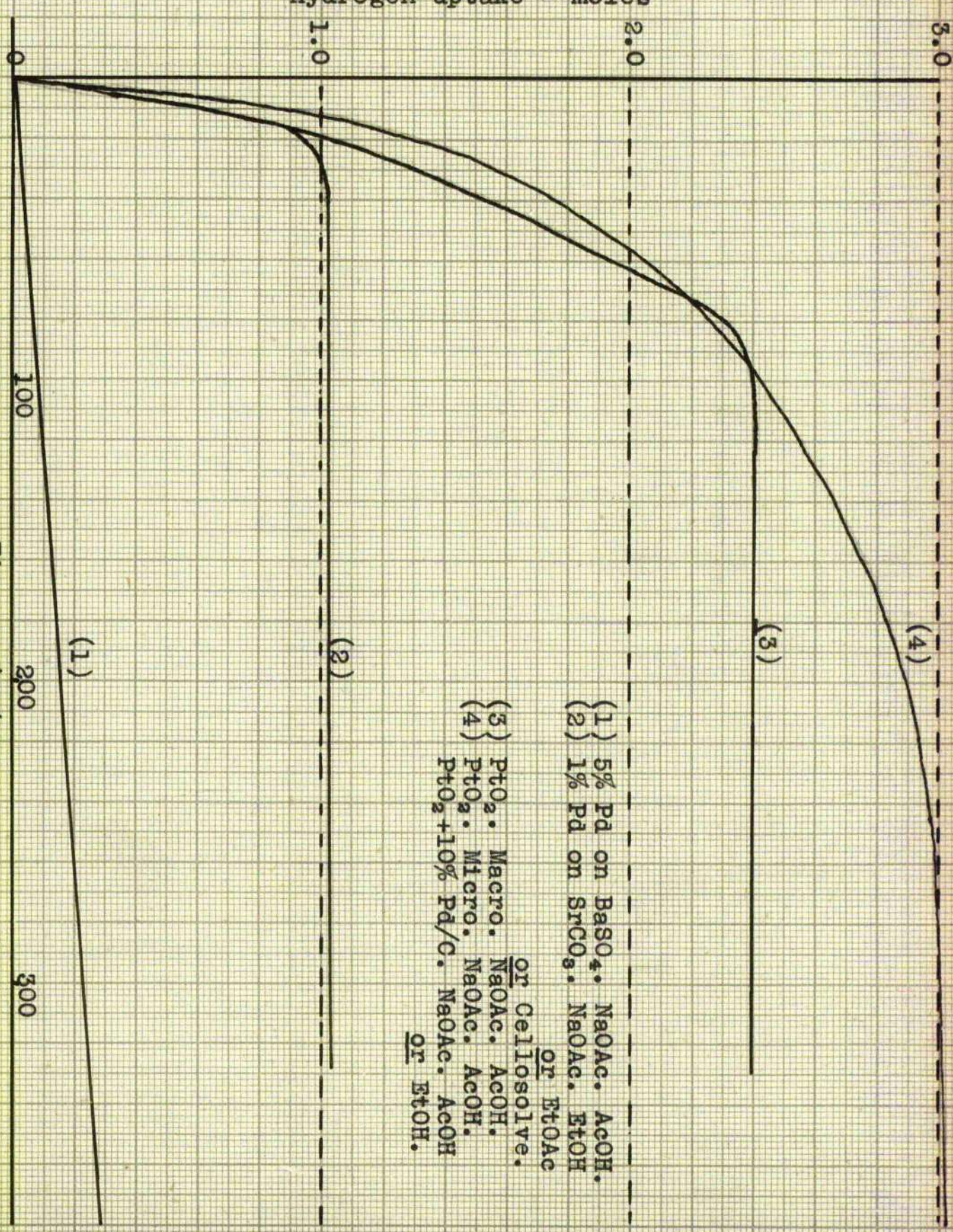
In the molecule of 2-chloro-3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine there are at least three distinct sites of attack for catalytic hydrogenation, viz., (1) the chlorine atom, (2) the nitrile group and (3) the aromatic rings of benzene and pyridine. The last is the most difficult, and is not likely to occur at atmospheric pressure and low temperatures. No evidence of ring hydrogenation was found under the conditions employed and (3) will not be considered further.

Aromatic chloro-compounds are easily hydrogenated in the presence of sodium acetate to the parent compound, and in view of the activated* state of chlorine in the 2-position of a pyridine ring, it might be expected that the chlorine atom would be the first point of attack. In certain solvents with some catalysts at least, this has proved not to be the case. In glacial acetic acid containing sodium acetate, palladium on barium sulphate caused negligible hydrogenation, while palladium on charcoal or Adam's platinum oxide catalyst led to a smooth hydrogenation of both the chlorine and the nitrile group. There was no discontinuity in the hydrogen uptake curve, and the reaction

*'Activation' of the chlorine atom refers to its behaviour in anionoid displacement reactions. Reduction by hydrogenation involves a different mechanism, and 'activation' in this sense may be irrelevant.

Fig. 1

Hydrogenation of 2-Chloro-3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine



cannot therefore take place stepwise, or in other words the chlorine hydrogenation is the initial slow stage and the nitrile is reduced comparatively fast once the chlorine is removed, but not before (see Fig. 1, p.21). That this is indeed the case was shown by stopping such a hydrogenation when one mole of hydrogen had been taken up, whereupon no sign of the 3-cyanopyridine could be found, but two-thirds of the 2-chloro-3-cyanopyridine was recovered intact and the remainder was fully reduced to the 3-aminomethylpyridine.

In alcoholic solution, again with sodium acetate, both palladised charcoal and Adam's catalyst showed the same behaviour as in glacial acetic acid. There was some evidence that platinum as contrasted with palladium favoured the reduction of the nitrile first (see Experimental Section, p.68), but no pure 2-chloro-3-aminomethylpyridine was isolated from a hydrogenation stopped after two moles of hydrogen had been absorbed, although its presence was demonstrated.

These catalysts were thought to be too active, and although palladium on barium sulphate had been unsuccessful, palladium on strontium carbonate was used in dry ethanol containing sodium acetate. This catalyst cannot, of course, be used in acetic acid, and might have been attacked by the small amount of acetic acid produced in the reaction, but no evidence of carbon dioxide evolution was observed. In this case hydrogen uptake ceased abruptly when one mole

of the gas had been absorbed and the desired 3-cyanopyridine was isolated in nearly theoretical yield, and characterised as the picrate. In this system there was apparently no danger of reducing the nitrile group, as the temperature could be raised or the hydrogenation could be continued for some hours without exceeding an uptake of one mole of hydrogen. Other solvents of a relatively non-polar character were also found to be suitable, e.g. 'Cellosolve' and ethyl acetate. These, especially the latter, were extremely useful, as the solubility of the 2-chloro-3-cyanopyridine was 10%, 5% and 2% in ethyl acetate, 'Cellosolve' and ethanol respectively.

A number of other chemical methods of reducing chloropyridines to the parent pyridine have been used. Of these, treatment with phosphorus and hydrogen iodide is probably the most drastic (34), and obviously unsuitable for a substituted pyridine containing methoxyl groups. A further general method is the formation of the corresponding hydrazinopyridine by reaction with hydrazine, followed by treatment with a copper salt (36, 38, 39, 40, 41) or hydrogen peroxide (42). This method has been used successfully in the case of 2-chloropyridine itself (35), 2-chlorolepidine (36) and α:α'-dichloroisonicotinic acid (37). The yields of pyridylhydrazines recorded in the literature are never very high, but in the case of 2-chloro-3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine, the crude

yield was only 4%, which was subjected to Thielepape's (36) procedure for decomposition with copper sulphate without result. None of these methods have the elegance of catalytic hydrogenation and were not investigated further.

Transformation of Nitriles to Methyl Ketones

The most efficient transformation of a nitrile group to a ketone appears to be the treatment of the nitrile with a lithium alkyl or aryl. Müller and Hertel (43) report a quantitative yield of 4:4'-dibenzoyl-3:3'-dimethyldiphenyl from 4-4'-dicyano-3:3'-dimethyldiphenyl and phenyl lithium. The method can obviously be effective, as here, in the presence of hindering o-substituents. Besides the fact that lithium aryls are much more effective in this respect than alkyls, it is known that lithium compounds in reaction with pyridines invariably substitute the nucleus in the α-position if one of them is free, and would therefore be unsuitable for the transformation of 3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine.

Less reactive metal derivatives are more likely to be of service, and of these zinc dimethyl has been used (44) on the acid to yield up to 75% of methyl ketone. Ethyl zinc iodide and methyl zinc iodide (45) have also been employed in the same way, but not in highly hindered cases.

If the nitrile is hydrolysed and transformed to the acid chloride, cadmium dimethyl is rather easier to handle, and can be made to react with acid chlorides to give high

yields of methyl ketones. This reagent was tried (see Experimental Section, p.113), totally unsuccessfully, on the acid chloride of isonicotinic acid, and also on the acid chloride of 4:6-dimethylpyridine-3-carboxylic acid. In neither case was sufficient methyl ketone obtained to be detectable by any of the routine tests used for the purpose, viz. (1) Brady's 2:4-dinitrophenylhydrazine reagent, (2) Feigl's test for methyl ketones with o-nitrobenzaldehyde (46), (3) the iodoform reaction as refined by Fuson and Tullock (47, 48) and (4) formation of the thiosemicarbazone and corresponding silver salt (49). In any case the acid chlorides of amino acids are not easy to prepare, especially free from the base hydrochloride (50, 51, 52).

The nitrile might be hydrolysed and the calcium salt of the resulting acid heated with calcium acetate, a classical preparation of methyl ketones, but in view of the harsh pyrolytic conditions necessary and contamination with by-products, the method was not investigated.

Three further methods of transforming a nitrile to a methyl ketone or ethyl group were investigated, (a) reaction with methyl magnesium iodide, (b) hydrolysis and esterification, followed by a Claisen condensation with ethyl acetate and ketonic hydrolysis and (c) reduction to an aminomethyl group, followed by deamination, bromine substitution and reaction with a metal methyl or dimethyl. The various routes are set out schematically on p.29 and the last three

are discussed individually below.

The Grignard Reaction with Nitriles

Although aromatic nitriles of the benzene series give good yields of methyl ketones on treatment with methyl magnesium iodide, yields are always much lower in the pyridine series. Frank and Weatherbee (53) obtained 40% of 3-pyridyl n-propyl ketone from nicotinonitrile after total reaction times of 15 hours, the yield falling with longer periods. The same authors state that the yield in the simplest case with a methyl Grignard reagent is only 27% of 3-acetylpyridine. Craig (54) obtained 47% of a substance, possibly ketonic, by reacting nicotinonitrile with 3-ethoxypropyl magnesium bromide, but he could obtain no crystalline derivatives. As Frank and Weatherbee (loc. cit.) subsequently reduced their pyridyl ketones to alkyl pyridines by a Kischner-Wolff method with good results, their procedure was attempted with 3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine with a view to its subsequent reduction to the corresponding 3-ethylpyridine. No ketone was obtained, and on prolonging the Grignard reaction time to 24 hours reflux under dry nitrogen gas, ketone was just detectable in the product, and none could be isolated even after extensive fractionation of the picrates. An attempt to carry out the same reaction with 2-chloro-3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine was equally unsuccessful.

The Grignard Reaction with Carboxylic Esters

While the reaction of Grignard reagents with carboxylic esters is usually regarded as a preparation of tertiary alcohols, various side-reactions take place and anomalous products are often obtained. Fuson et alii (55), for instance, reacted phenyl magnesium iodide with butyl mesitylenate and obtained 61% mesitylenic acid, 54% butyl iodide, 20% butyl mesitylenate and a little diphenyl as products. No ketone or carbinol was formed. With p-tolyl-mesitylenic ester and p-tolyl magnesium bromide some ketone was formed, but not of the expected constitution (55). Phenyl magnesium bromide and sodium butyrate yield ketone, but the salts of higher acids do not, the main product being diphenyl. Ethyl magnesium bromide and sodium butyrate yield ethyl propyl ketone, but always in low yield (25% or less). Tertiary butyl magnesium bromide and benzoic acid yield benzophenone and diphenylcarbinol. The formation of ketone occurs mostly in hindered cases (115). It was thought possible, however, that alkyl magnesium halides might react with esters to yield ketones if the Grignard reagent was reduced to one molar proportion instead of the two moles necessary for complete conversion to the tertiary carbinol, and precautions were taken to ensure that the reagent was never present in excess.

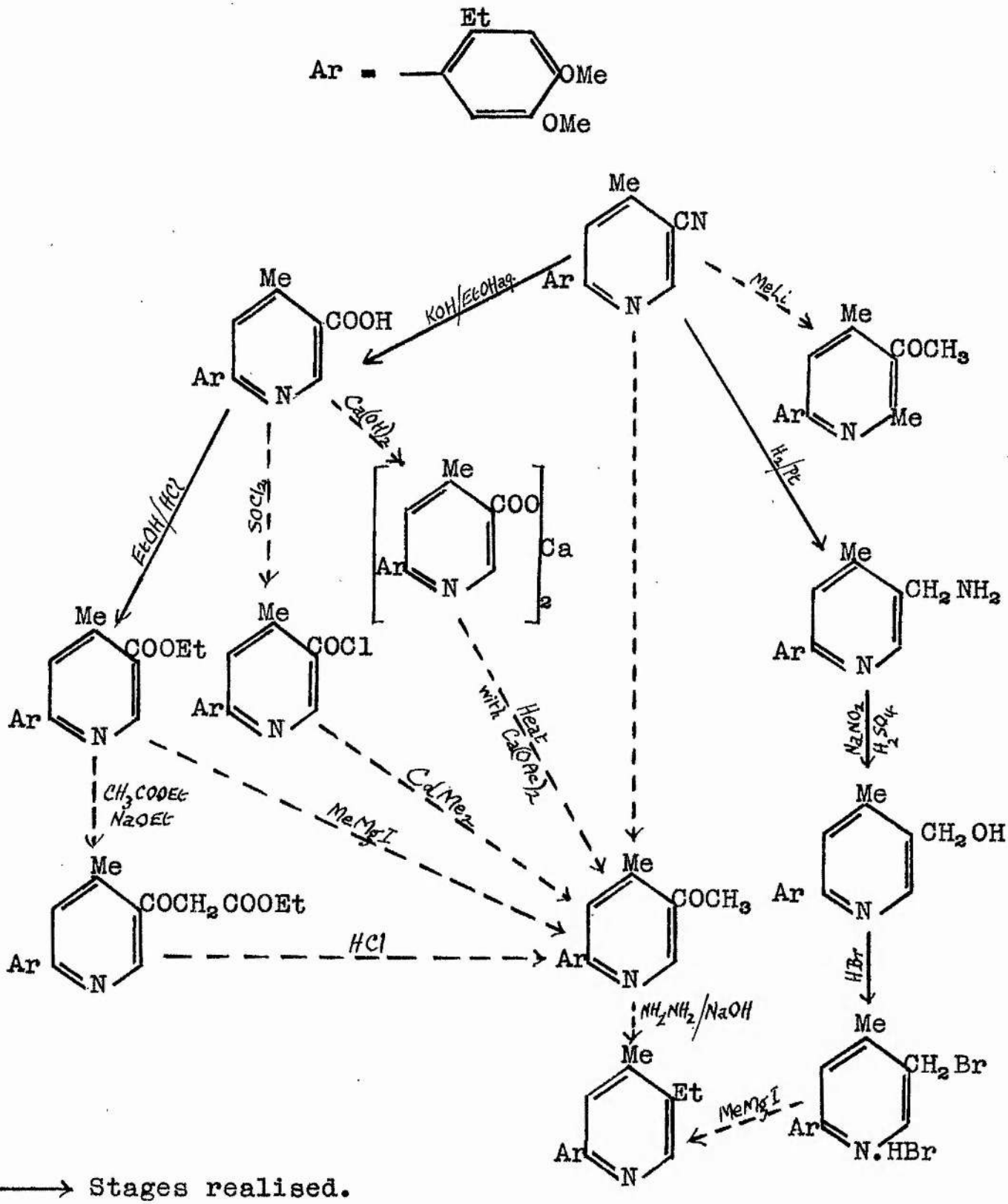
Methyl magnesium iodide was reacted under these conditions (see Experimental Section, p. 81) with ethyl benzoate.

The product contained 55% of unchanged ethyl benzoate, and traces of ketone were just detectable. It was concluded that the second mole of Grignard reagent reacts more easily or faster than the first, and that the intermediate ketone is never present in appreciable yield. As a test with an ester containing an ortho hindering group, o-chlorobenzoic ester was reacted with one mole of methyl magnesium iodide under the same conditions as before. The resulting mixed product was the same as in the simple case, i.e. 55% of unchanged ester and a detectable trace of ketone. This leads to the same conclusion as before, and it is not possible to prepare ketones from carboxylic esters by a Grignard method, even in hindered cases.

Nitrile to Methyl Ketone, via Hydrolysis, Esterification and Claisen Condensation

The direct substitution of a carbethoxy group for a cyano group is possible in many cases, but there is no recorded case of its achievement with a hindering ortho substituent. There are several methods of hydrolysing nitriles to carboxylic acids in high yield, but not all of them are applicable to the hydrolysis of 3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine. The most effective reagents, with little danger of intermediate amide formation, are the halogen acids, but demethylation is bound to be extensive, especially with hydrobromic acid, and the product cannot be remethylated in the normal fashion

Transformation of Nitrile to Methyl Ketone or Ethyl group with hindering ortho substituent



——→ Stages realised.

-----→ Stages realised only with model compounds, proposed routes and failures.

as the pyridine system would be methylated under the same conditions. Sulphuric acid does not demethylate to the same extent and it has been used by Chardonnens and Schlapbach (56) for the hydrolysis of ortho hindered compounds such as 3-cyano-4-methylbenzophenone with good results. The method did succeed with the 3-cyano-4-methylpyridine, but yields were low, probably due to the difficulty of isolating a soluble amino acid from a large volume of sulphuric acid.

Long and Burger (57), on the other hand, used alkali for the same purpose, specifically to avoid demethylation of their 7-methoxy-α-naphthoic acid. Either sodium or potassium hydroxide was used, and it was claimed that n-propanol and ethylene glycol were suitable solvents, whereas ethanol and isopropanol were not as they tended to allow the reaction to stop at the amide stage. We have found in the case of the hindered 3-cyanopyridine that in n-propanol the hydrolysis stops at the formation of amide, which is very stable, and that the difficulty can best be surmounted by using ethanol, which is gradually replaced by water as the reaction proceeds. Even after 48 hours reflux some of the amide had not been completely hydrolysed.

After hydrolysis, the acid was relatively easily esterified by the normal Fischer-Speier method, and crystalline ester was obtained after purification through the picrate (see Experimental Section, p.74).

Rabe and Jantzen (58) have studied the Claisen condensation of a few pyridine carboxylic esters with ethyl acetate and their cleavage to methyl ketones. Nicotinic ester itself gave practically quantitative yields, while homonicotinic ester [ethyl 4-methylpyridine-3-carboxylate], in spite of prolonged heating and varying proportions of the reactants, did not yield more than 30% of 3-acetyl-4-methylpyridine. This effect was said to be due entirely to the hindering o-methyl substituent. Pinner (59) recorded the preparation of 2-, 3- and 4-acetylpyridine by a Claisen method, but did not deal with hindered cases, while a further method using sodium metal was developed by Fuson, Parham and Reed (60). Dornow and Machens (61) have prepared 3-acetyl-2:4-lutidine from 2:4-dimethylnicotinic ester by a Claisen method and obtained a yield of only 8%, which was, however, the best yield from any method investigated. We have repeated this preparation using 4:6-dimethylnicotinic ester in place of the 2:4-isomer, as a model substance for ethyl 6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine-3-carboxylate, the crude yield being only 7%, despite long reflux in toluene to raise the reaction temperature.

Nitrile to Ethyl group via Reduction, Deamination, Bromination and Reaction with Methyl Magnesium Iodide.

3-Cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine was easily hydrogenated to the corresponding 3-amino-

methyl compound. The best method was found to be that of Harris and Folkers (31) using both palladium and platinum catalysts, but other methods were also suitable (see also 'Selective Reduction of Chlorine in Presence of Nitrile', p.20).

The direct replacement of an amino group by a halogen is common in the aliphatic series, by the use of nitrous acid in the concentrated halogen acid, but only one example is recorded in the pyridine series. Overhoff, Boeke and Gorter (62) prepared the unstable 2-pyridylchloromethane from 2-pyridylaminomethane by the action of sodium nitrite in concentrated hydrochloric acid. Using this method, the 3-aminomethyl-4-methylpyridine was not deaminated at all, and the starting material was recovered quantitatively. Various other methods have been used for similar deaminations, among the more promising being those of Graf, Perathoner and Tatzel (63) using silver nitrite and very dilute hydrochloric acid, or sodium nitrite and sulphuric acid. Unfortunately their most relevant example, 2-aminomethyl-6-methylpyridine, did not yield a measurable quantity of the desired product. Harris and Folkers (31) used a similar method of deamination in the synthesis of pyridoxine, the yield being just over 20%, and using their method, slightly modified, 3-aminomethyl-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine was successfully deaminated in about 40% yield.

Harris and Folkers (loc. cit.) were able to transform their methylolpyridine to the bromomethyl compound by boiling it for 10 minutes with 48% hydrobromic acid. More drastic treatment would certainly cause extensive demethylation. In the case of 3-hydroxymethyl-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine, 30 minutes heating with 48% hydrobromic acid caused no substitution, but three days reaction in the cold produced a compound analysing correctly for 3-bromomethyl-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine hydrobromide.

Bromomethyl compounds do react with methyl magnesium iodide in the benzene series to yield the corresponding ethyl compounds, but the reaction is far from complete, and side reactions interfere greatly. The reaction was tested with benzyl bromide and excess of methyl Grignard reagent, and yielded about 45% of ethylbenzene, together with a little unchanged benzyl bromide, methanol (from excess Grignard reagent) and dibenzyl equivalent to about 37% yield. In order to obtain bromomethylpyridines as model compounds, several attempts were made to brominate both β- and γ-picoline in the side chain by the method of Buu-Hoi (64) using N-bromsuccinimide [see also Chemical Reviews (65)], but only traces of the desired compounds were obtained. The reaction products decomposed violently even on gentle warming. In a further experiment the mixture was allowed

to stand at room temperature, and the consumption of N-bromsuccinimide was followed by treating aliquot portions with iodide and titrating with standard thiosulphate solution. Although 75% of the bromsuccinimide was consumed, only unchanged starting material could be isolated. The older method of Dehnel (66) for the direct bromination of β-picoline by heating it with bromine and hydrobromic acid in a bomb furnace was found more satisfactory. The free base is unstable and highly irritant, and it was therefore purified as the picrate and recovered as the hydrobromide by suspending in hydrobromic acid and extracting the picric acid with nitrobenzene. The hydrobromide was the only crystalline salt obtained, apart from the picrate, and this was reacted with a substantial excess of methyl magnesium iodide. A little crystalline picrate, probably that of 1:2-di-3'-pyridylethane, the analogue of dibenzyl in the pyridine series, was obtained from the mixed products, but there was no sign of any ethylpyridine [cf. (116)].

Further Synthetic Approach to 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine. Route II.

After repeated failure to introduce the 3(5)-ethyl group into the pyridine ring in compound B (p.12), further efforts were directed to synthesising it by a route where the 3-ethyl group was in position before the pyridine ring was formed. Such a scheme is set out on p.36, and is discussed in more detail below.

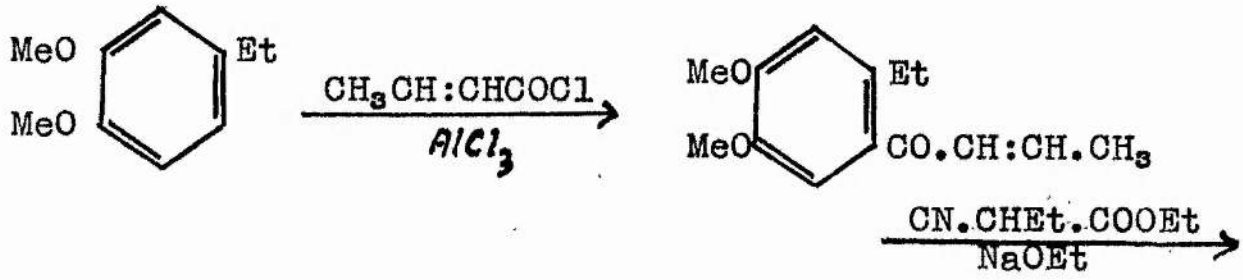
5-Crotonyl-4-ethylveratrole

Two methods at least are available for the formation of this type of unsaturated ketone. The earlier is that of Staudinger and Kon (67) which involves the condensation of acetophenone with, for instance, acetaldehyde to yield benzoylisopropyl alcohol in reasonable yield. Dehydration with zinc chloride leads to the unsaturated ketone. The more recent and somewhat more direct method of Auwers (68), depending on a Friedel-Crafts reaction with crotonyl chloride is more attractive.

Crotonyl chloride was first prepared by Henry (69), and later by Kohler (70) from dry sodium crotonate and phosphorus oxychloride, but both these methods were superseded by that of Staudinger *et alii* (71), using thionyl chloride in petroleum ether as a diluent, and we have used the last method only.

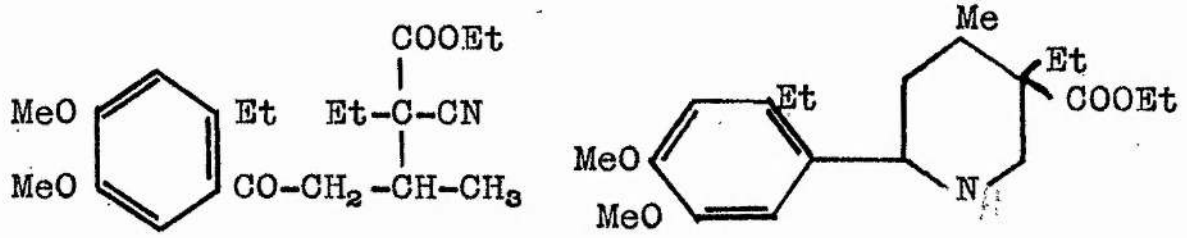
Kohler (70) has prepared crotonylbenzene [propenyl

Attempted Synthesis of 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine Route II



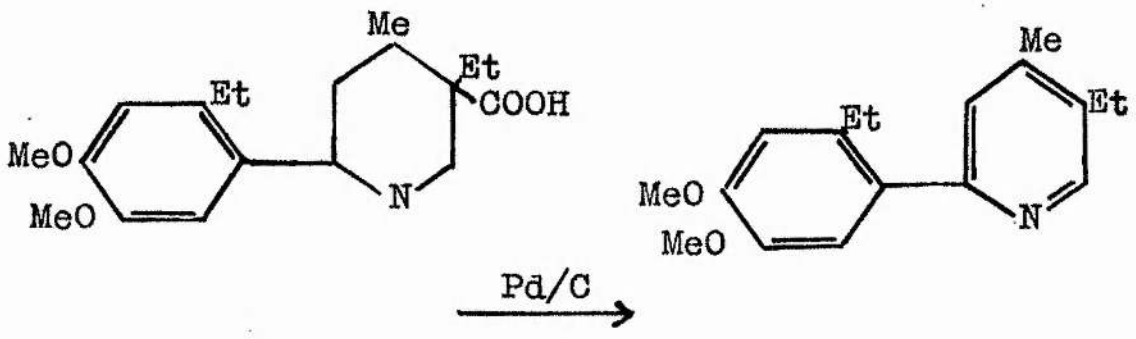
4-Ethylveratrole

5-Crotonyl-4-ethylveratrole



4-Carbethoxy-4-cyano-1-(3:4-dimethoxy-6-ethylphenyl)-3-methylhexan-1-one

6-(3:4-Dimethoxy-6-ethylphenyl)-3-carbethoxy-3-ethyl-4-methylpiperidine



6-(3:4-Dimethoxy-6-ethylphenyl)-3-carboxy-3-ethyl-4-methylpiperidine

2-(3:4-Dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine

phenyl ketone] and Auwers (68) has prepared p-crotonyl-anisole by Friedel-Crafts methods, and both employed carbon disulphide as the medium. 5-Crotonyl-4-ethylveratrole was prepared by this method, but the yield was low (28%), although a large part of the 4-ethylveratrole was recovered unchanged. With a substance as reactive as 4-ethylveratrole, benzene is a sufficiently inert diluent, and the preparation was modified by analogy with 5-aceto-4-ethylveratrole [p. 59, (72)(1)]. The maintainance of fast, efficient stirring was again found to be of paramount importance, leading to yields of nearly 70%.

Michael Reaction with 5-Crotonyl-4-ethylveratrole

α-Cyanobutyric ester has been prepared by Henry (73), Hessler (74), and Nishikawa (75). Hessler's first method, using cyanacetic ester and ethyl iodide is the most convenient, but the physical properties of the product are very similar to those of the starting material, and we obtained so much higher a yield than Hessler reports that we suspected contamination with unchanged cyanacetic ester, and we therefore also prepared the ester by Nishikawa's method which starts from α-bromobutyric ester and is unambiguous. Diethylcyanacetic ester cannot take part in the Michael reaction, having no α-hydrogen, so that slight contamination with this substance is not important.

The addition of cyanacetic esters to unsaturated

ketones has been studied by Späth (76) and very recently by Henecka (77). Under the conditions used by the latter, the reaction between ethylcyanacetic ester and 5-crotonyl-4-ethylveratrole was not exothermic, and no condensation took place in 24 hours. Refluxing for a period had the desired effect, but increasing the time of reflux from two to five hours decreased instead of increasing the yield of 4-carbethoxy-4-cyano-1-(3:4-dimethoxy-6-ethylphenyl)3-methylhexan-1-one.

Henecka (loc. cit.) hydrogenated a number of similar condensation products to form piperidine derivatives, presumably by spontaneous cyclodehydration of the intermediate amino-ketone and further reduction. His most relevant example, the condensate of benzalacetone and n-butylcyanacetic ester, produced only 17% of piperidine base, together with a much larger quantity of neutral material of unknown constitution. His other examples all gave higher yields. The condensate of 5-crotonyl-4-ethylveratrole and ethylcyanacetic ester was hydrogenated with a Raney nickel catalyst at 100° and 60 atmospheres pressure, and in this case the basic fraction amounted to 59% yield calculated on the starting material, of which a small fraction was a high-boiling, ether-insoluble base of unknown constitution. The piperidine base is likely to be a mixture of stereoisomers, of which eight are possible, and it was not surprising that it did not crystallise. The

derived picrate was well crystallised and apparently homogeneous, but neither the base nor the picrate analysed correctly, the discrepancy being consistently high nitrogen, which is difficult to explain unless hydrogenation under these conditions causes a major rearrangement.

Dehydrogenation of the Piperidine Base

The 3-carbethoxy-3-ethylpiperidine would not dehydrogenate with a large proportion of palladium-charcoal, even at 330°. The base was therefore hydrolysed first, a process which was remarkably difficult, requiring many hours heating with alkali in a high-boiling solvent. The resulting crude amino-acid readily evolved hydrogen in the presence of palladium-charcoal at 270-300°, but there were signs of extensive decomposition as well. Basic material, recovered in very low yield, was separated into strong and weak bases by the method of Battersby and Openshaw (4) using M/50 citric acid. The small quantity of weakly basic material was distilled, but no crystalline derivatives could be obtained and the substance was obviously a complex mixture.

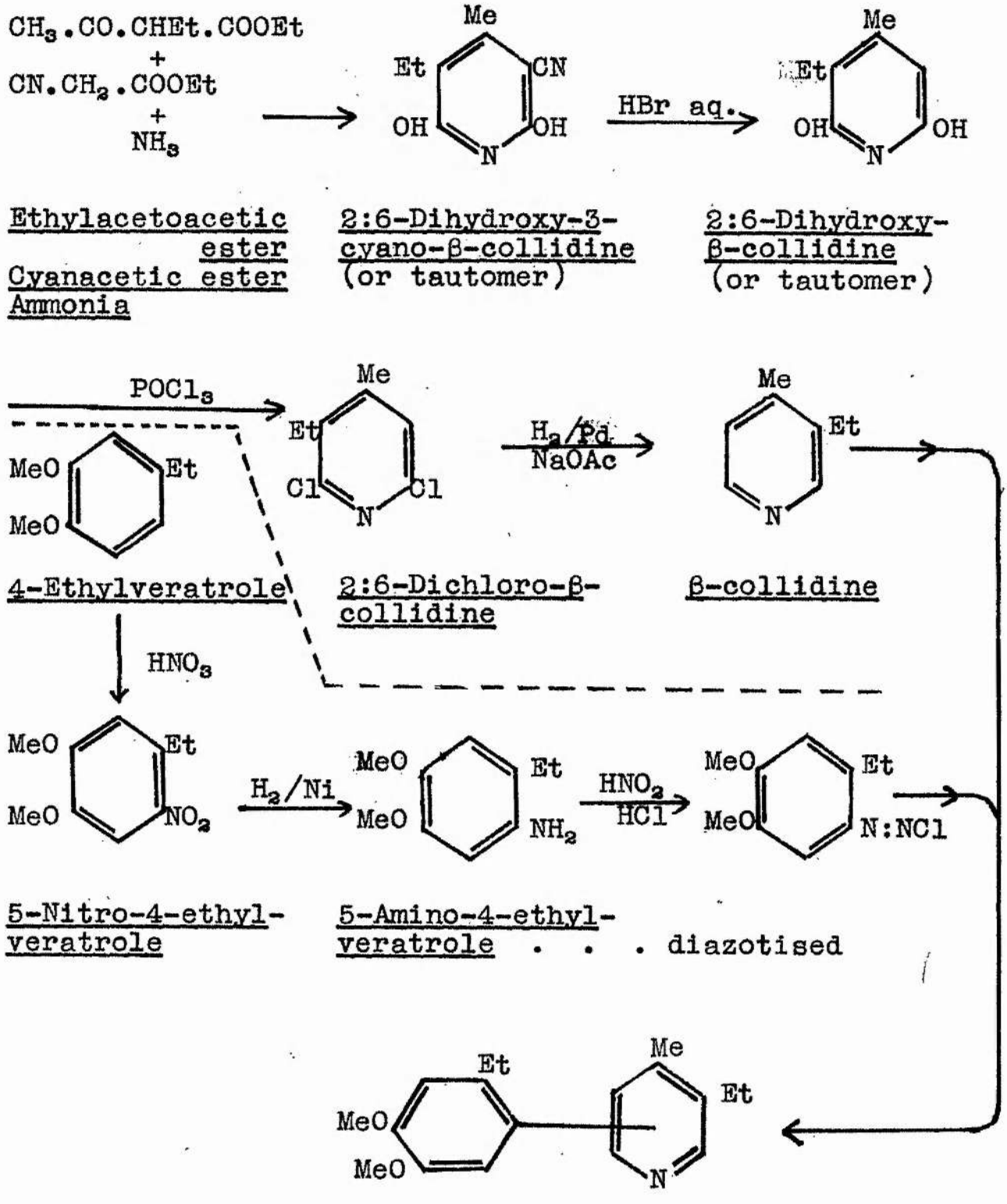
Further Synthetic Approach to 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine. Route III.

After experiencing the difficulties of introducing a 3-ethyl group into a hindered position in a pyridine ring (Route I) and the failure to dehydrogenate satisfactorily the corresponding piperidine structure (Route II), attention was turned to a third method in which both the ethyl group and the pyridine ring are present at an early stage. The desired base may be regarded as a β-collidine derivative, and the latter was taken as the starting point.

β-Collidine was not readily available at the time this work was undertaken. One method of obtaining it would involve the handling of very large quantities of reagents, viz., the preparation of aldehyde collidine and the careful fractionation of the total product to separate the β-collidine, which constitutes considerably less than 1% of it. A product free from isomers may be obtained by the lengthy method of Ruzicka and Fornasir (34), and this was followed with some modifications (see Experimental Section, p.94), the more notable being the preparation of dichloro-β-collidine in a sealed tube and subsequent hydrogenation to β-collidine in high yield.

Haworth, Heilbron and Hey (78) in part of a series of publications on 'Homolytic Aromatic Substitution' discuss the homolytic substitution of pyridine by free radicals obtained from the decomposition of diazonium compounds.

Attempted Synthesis of 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine Route III



This type of reaction was first studied in the benzene series by Gomberg *et alii* (79). By this means the former workers were able to prepare a mixture of o-anisylpyridines by decomposing diazotised o-anisidine in an excess of hot pyridine. They state that the α-product predominates. 2(3:4-Dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine is an α-substitution product of β-collidine, and furthermore the α-position substituted is the less hindered of the two. It was therefore considered feasible to decompose diazotised 5-amino-4-ethylveratrole in β-collidine and isolate as the main product the desired base.

4-Ethylveratrole was nitrated (80, 81) and reduced catalytically to 5-amino-4-ethylveratrole in good yield. Diazotisation proceeded normally, except that the hydrochloride of the amine was sparingly soluble in hydrochloric acid. As a model experiment, the diazonium solution was run into a ten-fold excess of pyridine at 80°. The residue, after removal of the unreacted pyridine, yielded a mixture of bases from which two of the three possible isomeric (3:4-dimethoxy-6-ethylphenyl)-pyridines were isolated in the pure state as the picrates, the yields being of the same order (3 : 2). The third isomer was not isolated, but it was probably present to a fair extent in the uncrystallisable residues. The tendency to substitute preferentially in the α-position of the pyridine ring is therefore not very pronounced. Nevertheless, the amine was shown to be

suitable for this type of reaction from a steric point of view.

Preliminary attempts to carry out analogous substitution of β-collidine failed completely, until it was realised that the substituting free radicals arise from the instability of diazotate structures, and in particular from the syn-diazotate, which is only found immediately after the basification of a diazonium salt. The large excess of base, as with pyridine, is necessary not only to create a basic environment, but also to take up the excess acid in the diazonium solution. As yields were very low, a large quantity of β-collidine was necessary, which was not available at the time. The amine was therefore diazotised in the absolute minimum of acid, and sufficient dry sodium carbonate was violently stirred with the β-collidine to neutralise the acid. Under these conditions only a few milligrams of substituted β-collidine were obtained, which melted over such a wide range as to indicate a mixture of isomers.

These homolytic substitution reactions do not follow the normal rules of heterolytic substitution. The laws of orientation are not the same, and steric hindrance in the usual sense is not encountered. It is therefore probable from general considerations [see also (78)] that the aryl radical would not enter the pyridine nucleus predominantly in the desired α-position, although the α-position is usually favoured in pyridine itself. The most likely point of

attack would appear to be the one free β-position. At any rate the product would probably be a mixture of all three isomers (α, α' and β) which would be difficult to separate and even more difficult to orientate.

Grignard Reaction with Pyridines

While Grignard reagents do not normally react with the pyridine nucleus, they do form insoluble addition compounds with it, and at high temperatures and pressures these addition compounds may be transformed into substituted pyridines. Bergström and McAllister (82), for instance, prepared 2-phenyl- and 2-ethylpyridine from pyridine and phenyl or ethyl magnesium bromide in 45 and 44% yield respectively. Similarly they prepared 2-ethylquinoline and 1-ethylisoquinoline from the respective bases and ethyl Grignard reagents. Only α-substituted products were found in the reaction mixture, and hence it should be possible to prepare 2-(3:4-dimethoxy-6-ethylphenyl)-5-ethyl-4-methyl-pyridine by this method from 3:4-dimethoxy-6-ethylphenyl magnesium bromide and β-collidine, the only possible unwanted product being the 6-aryl-5-ethyl-4-methylpyridine, which is more hindered and less likely to be formed.

Bergström (83) has reviewed such reactions extensively and Bergström et alii (84) discuss the difficulties of the reaction with aryl magnesium halides.

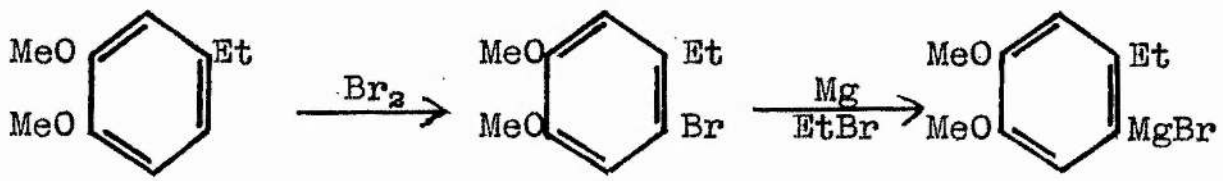
Veratroles react very easily with bromine (113, 114),

the main difficulty with veratrole itself being to stop the substitution at a monobromo derivative. This difficulty was overcome by Gaspari (104) by passing bromine vapour largely diluted by air into veratrole in acetic acid. The same method gave excellent results with 4-ethylveratrole, where there is not the same danger of oversubstitution.

The magnesium compounds of methoxyphenyl halides are difficult to prepare. Grignard himself (85) mentions the difficulty with 3:4-dimethoxyphenyl bromide, and the low (25%) maximum yield of veratric acid obtainable from it. We have confirmed this in carrying out the preparation of 6-ethylveratric acid from 5-bromo-4-ethylveratrole, for purposes of orientation (p.88). Grignard (loc. cit.) advocates the 'entrainment' method in difficult, hindered cases, e.g. pentamethylbromobenzene. A molar proportion of ethyl bromide is mixed with the hindered halide, when the reaction with a slight excess of magnesium is facilitated. 'Entrainment' with ethyl bromide was found to increase the reaction of magnesium with 5-bromo-4-ethylveratrole. It was naturally impossible to separate or destroy the content of ethyl magnesium bromide, and after reaction with β-collidine in a sealed tube, it was not easy to separate all the possible products, eight in all, allowing α-substitution only. In practice, over 70% of the β-collidine was recovered unaltered. The small yield of other bases in the reaction mixture formed a crystalline picrate, but the analysis did

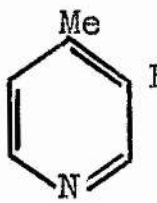
not correspond to any of the expected products, and represented a more highly substituted pyridine.

Grignard Reagent and β-Collidine



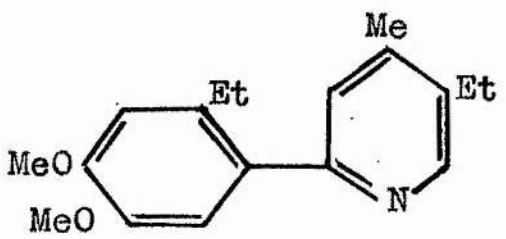
4-Ethylveratrole

5-Bromo-4-ethyl-veratrole



β-Collidine

Autoclave
160°



2-(3:4-Dimethoxy-6-ethylphenyl)-5-ethyl-4-methylpyridine (?)

Oxidation of the 'Pyridine Base'

Battersby and Openshaw (4) oxidised the 'Pyridine Base' (p.10) to 5-ethylpyridine-2:4-dicarboxylic acid, sufficiently characterised by decarboxylation to 3-ethylpyridine and by further vigorous oxidation to pyridine-2:4:5-tricarboxylic acid [berberonic acid].

An attempt was made to obtain berberonic acid for comparison by a new method. 'Alleged acetone anil'(86) [2:3:4- or 3:4:4-trimethyl-1:2-dihydroquinoline] was dehydrogenated, using sodium anilide in preference to amide (86) to 2:4-dimethylquinoline. The quinoline was oxidised exhaustively with alkaline permanganate, but no pure acidic or amphoteric substance could be isolated. Theoretically the oxidation should have produced pyridine-2:3:4:6-tetracarboxylic acid, which has previously been prepared by Mumm and Henecke (87) by a similar oxidation of α:α'-dimethylcinchomeronic acid. The acid is known to decarboxylate smoothly at 120° to berberonic acid.

Berberonic acid could no doubt have been obtained easily from one of the many 2:4:5-substituted pyridines prepared in the attempted synthesis of the 'Pyridine Base', e.g. 5-carboxy- or 5-hydroxymethyl-2-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine or 5-aceto-2:4-dimethylpyridine, but the acid was more easily prepared by an established method (88) from berberine.

A Synthesis of Homoveratrylamine

In synthetic studies of the isoquinoline alkaloids, to which emetine and its derivatives belong, the ring structure itself is often formed by a Bischler-Napieralski method. The method is convenient on account of the certainty of the orientation of the rings, and on account of the ease with which the 1-substituent in the isoquinoline ring may be varied. The synthesis requires two components, viz., a carboxylic acid R.COOH, where R is the ultimate 1-substituent and a β-phenylethylamine for the ring skeleton. In the emetine series the latter is often homoveratrylamine [3:4-dimethoxy-β-phenylethylamine], and a simple method of preparing it in good yield was required.

In the past homoveratrylamine has been prepared by a number of methods, notably from vanillin by methylation to veratraldehyde, condensation with nitromethane to the *w*-nitrostyrene and reduction to homoveratrylamine. The last step is difficult and is usually electrolytic. The yield is low (ca. 50%) and the conditions, particularly current density, are critical. Commercially the reduction is said to be carried out with zinc or iron dust, but the method is apparently not satisfactory on a laboratory scale. The following method also employs vanillin as the starting material, but there are no difficult stages and the overall yield is much improved.

Vanillin was converted to veratraldehyde by a standard

method (26) and condensed with malonic acid. A mixture of pyridine and piperidine was used as a catalyst, and the mixture decarboxylated spontaneously to 3:4-dimethoxycinnamic acid. A Knoevenagel reaction of this type was used by Rajagopalan (89) for the synthesis of β-2-furylacrylic acid.

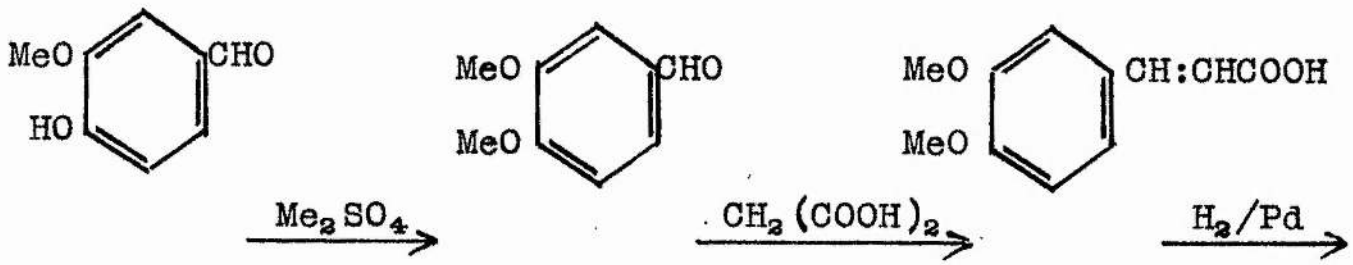
The dimethoxycinnamic acid was conveniently and inexpensively hydrogenated in sodium carbonate solution with a colloidal palladium catalyst (90). Extensive purification at each stage was not necessary.

Many methods are available for the formation of acid amides, but few possess the general application and simplicity combined with consistently high yields of the 'Acidolysis of Urea' described by Cherbuliez and Landolt (91). The method appears to work with any acid or its ammonium salt, whether aliphatic, aromatic, heterocyclic, heavily substituted or even inorganic, and may yield N-substituted amides through the use of substituted ureas. The method worked well with either dihydrocinnamic acid or 3:4-dimethoxycinnamic acid to furnish the amide in high yield (ca. 80%).

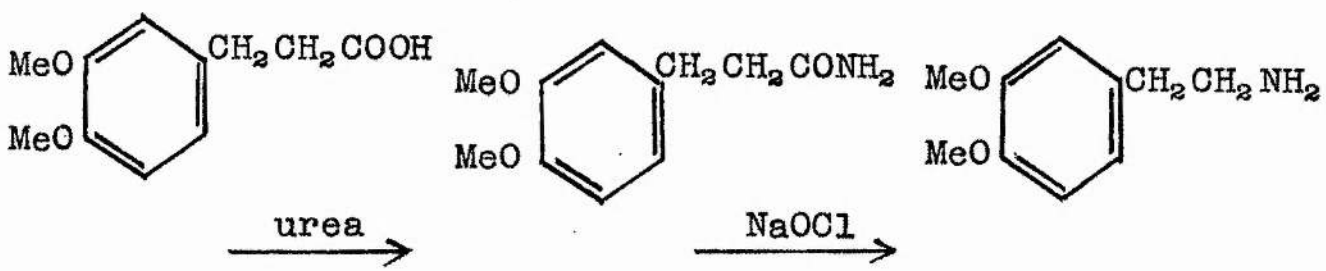
The amide was degraded by Hofmann's hypochlorite method (92, 93) to yield homoveratrylamine of high purity, the overall yield from vanillin being estimated as 44%, although this figure was not achieved in practice, no attempt being made to determine the optimum conditions for the last stage. The series of reactions involved in this synthesis of

homoveratrylamine is shown schematically below.

A Synthesis of Homoveratrylamine

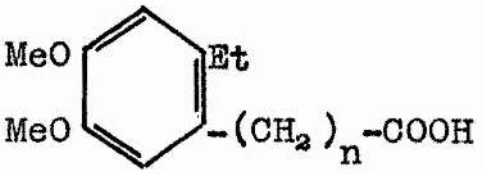


Vanillin — Veratraldehyde — 3:4-Dimethoxy-cinnamic acid



3:4-Dimethoxydihydrocinnamic acid — β-3:4-Dimethoxyphenylpropionamide — Homoveratrylamine

Homologous Series of 6-Ethylveratric Acids

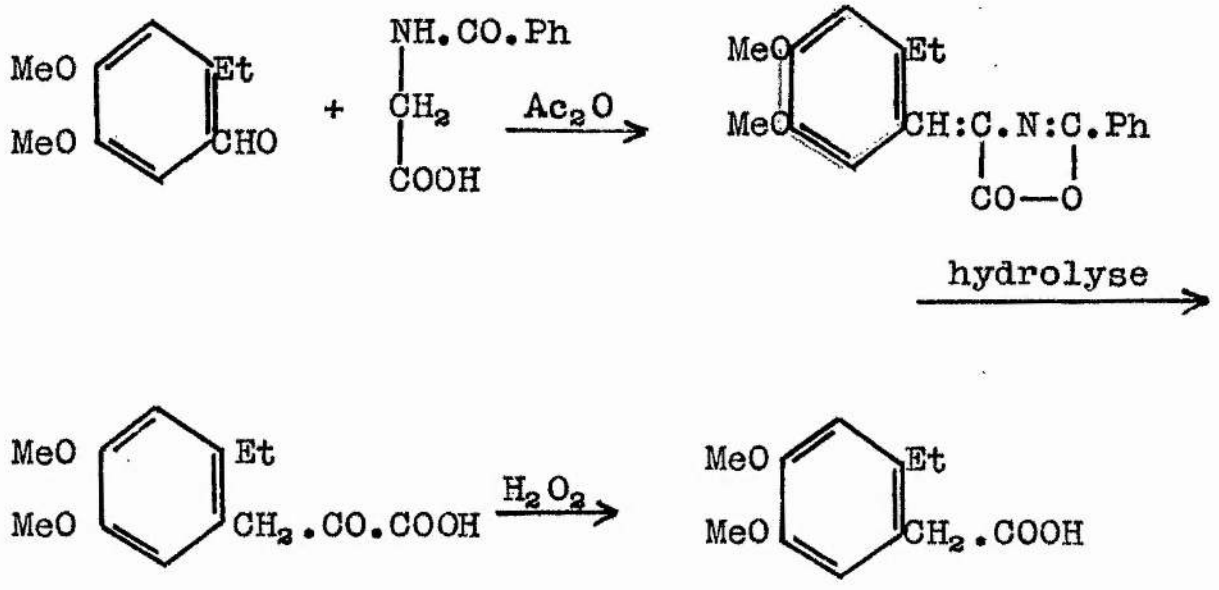


While the Pyman (9) type of structure for emetine (p.5) was still under consideration, the nature of the final, nitrogen-free, singly unsaturated substance obtained by the repeated Hofmann degradation of N-methylemetine was not known. Ozonolysis of the neutral substance provided a ketone, also of unknown constitution at that time. It was thought advisable to attempt the synthesis of the various possible structures, and to this end several of the homologous series of 6-ethylveratric acids were necessary as starting materials. As the structure of emetine became clear (4)(p.5) the work was not continued, but it is convenient to review the series briefly at this point.

6-Ethylveratric acid itself (n = 0) was prepared by Shinoda and Sato (72) by the oxidation of 6-ethylacetoveratrone with hypochlorite, a method since improved by Battersby and Openshaw (1). We have prepared the same acid from 5-bromo-4-ethylveratrole by a Grignard method (p.88). Koepfli and Perkin (20) oxidised 3:4-dimethoxy-6-ethylbenzaldehyde, obtained by a Gattermann aldehyde synthesis from 4-ethylveratrole, to the same compound.

3:4-Dimethoxy-6-ethylphenylacetic acid (n = 1) is also known, and has been prepared from 6-ethylveratraldehyde

by Koepfli and Perkin (loc. cit.) through the azlactone of the hippuric acid derivative which was hydrolysed to 3:4-dimethoxy-6-ethylphenylpyruvic acid and oxidised by hydrogen peroxide to the corresponding phenylacetic acid.



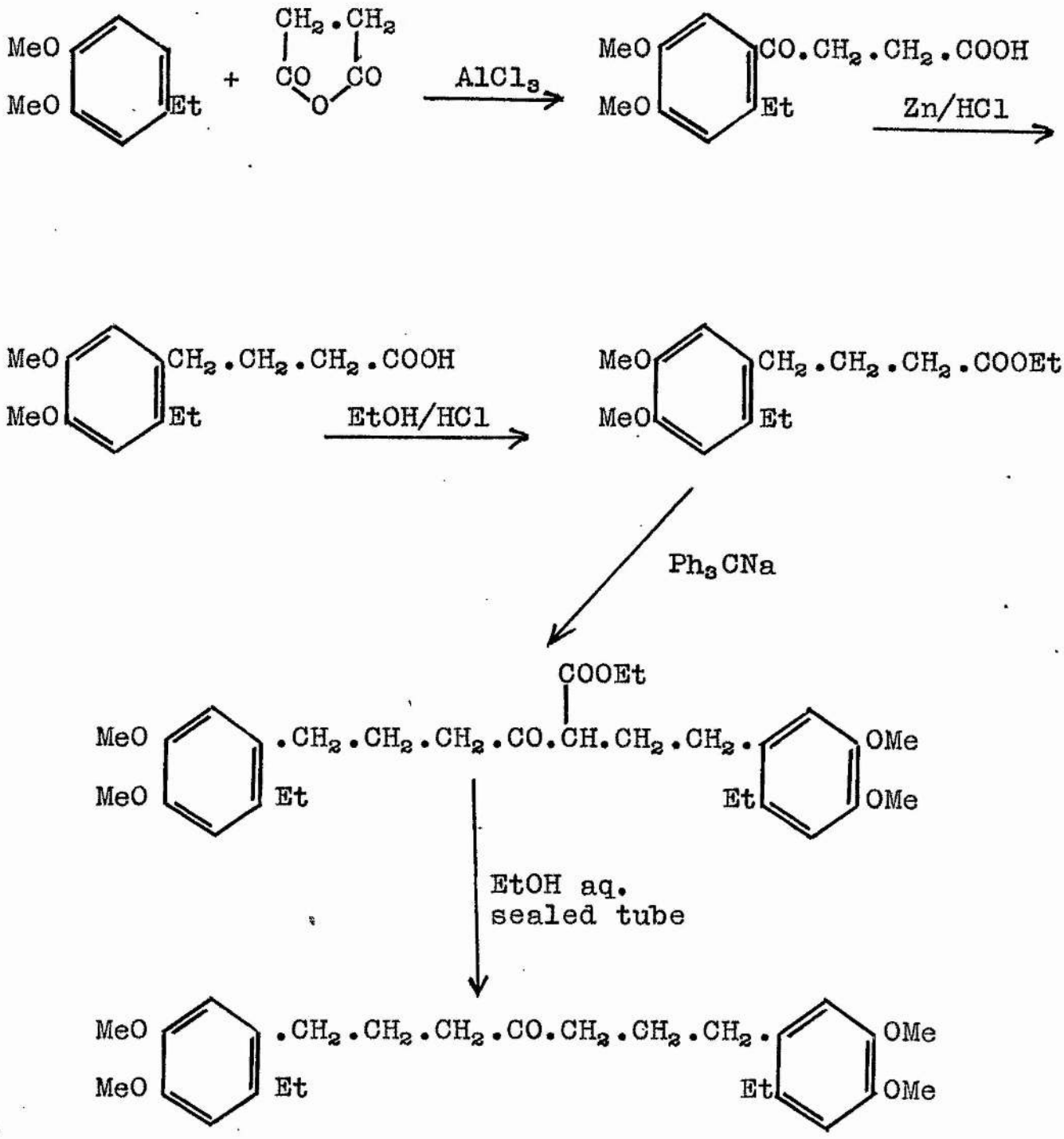
A somewhat simpler synthesis of the same compound was suggested by the Willgerodt (95) reaction, whereby 6-ethylacetoveratrone might be directly converted to the required acid. Such a conversion of acetophenone to phenylacetic acid has been achieved (94) using ammonium sulphide as the reagent. We have attempted this method with 6-ethylacetoveratrone under various conditions, including the modification of Kindler (96) using morpholine and sulphur, but no crystalline products could be obtained. It was concluded that either the methoxyl groups were too sensitive for such treatment or the 6-ethyl group caused a certain amount of

steric hindrance.

β-3:4-Dimethoxy-6-ethylphenylpropionic acid (n = 2) is more difficult, and has not been synthesised so far. Again a Willgerodt reaction starting from 6-ethylpropioveratrone would be convenient, but it is not likely to succeed when the acetoveratrone case fails. Again the unsubstituted case has been realised (97). There is a possibility that the 3:4-dimethoxy-6-ethylphenylpyruvic acid obtained (20) in the preparation of the lower homologue might be reduced, chemically or catalytically, to the required acid. Probably the most promising method would be to start from 6-ethyl-veratraldehyde (20) and convert it by a Knoevenagel reaction with malonic acid to 3:4-dimethoxy-6-ethylcinnamic acid, which could be hydrogenated to the saturated acid. This last series has been used (p.50) in the slightly simpler case without the 6-ethyl substituent for the synthesis of homoveratrylamine.

γ-3:4-Dimethoxy-6-ethylphenylbutyric acid (n = 3) was obtained by a Clemmensen reduction (110) of β-3:4-dimethoxy-6-ethylbenzoylpropionic acid, made by a Friedel-Crafts method from 4-ethylveratrole and succinic anhydride. The substituted phenylbutyric acid was esterified and the ester condensed with itself (111) under the influence of triphenylmethyl sodium (112, 98) in ether to yield α:γ-bis-(6-ethylhomoveratryl)acetoacetic ester. The β-ketoester was cleaved by the method of Meerwein (99, 100) to form

the symmetrical ketone, bis-γ-(3:4-dimethoxy-6-ethylphenyl)-n-propyl ketone, but no crystalline derivatives of the carbonyl compound could be obtained.



GENERAL NOTES

for Experimental Section.

(1) All melting points are corrected.

(2) Micro analytical results are by Drs. Weiler and Strauss, Oxford.

Preparation of Catalysts

(1) Palladised charcoal was made by a literature method (101) from highly purified 'Norit' charcoal to give 10% or 5% palladium as required. The reduced catalyst was stored over calcium chloride in a desiccator.

(2) Palladised strontium carbonate. Strontium carbonate (50g.) was suspended in water at 70°. Palladium chloride (1.0g.) was dissolved in a few drops of concentrated hydrochloric acid, a little water was added, and the solution was heated to 70° and poured into the strontium carbonate suspension with vigorous stirring. The temperature was maintained at 70° and stirring was continued for 20 minutes, after which time the catalyst was allowed to settle. The powder was washed several times with distilled water by decantation, filtered off and dried in a vacuum desiccator over concentrated sulphuric acid. The powder contains approx. 1% Pd.

(3) Colloidal palladium was made by the method of Hughesdon, Smith and Read (90).

(4) Adam's platinum oxide catalyst was obtained in a highly active state by the method of Organic Syntheses (102), using a calibrated thermocouple.

EXPERIMENTAL

Veratrole. (A) Pyrocatechol was methylated by the method of Perkin and Weizman (22). In several experiments, the yield of veratrole, m.p. 15°, b.p. 205°, varied between 33 and 35% of theoretical, and could not be increased. Perkin and Weizman claim 95% yield.

(B) Catechol was most satisfactorily methylated by the method used for the methylation of vanillin by Kostanecki and Tambor (26). 100g. of catechol produced 119g. (95%) of pure, redistilled veratrole, m.p. 15°, b.p. 205°/760mm.

Acetoveratrone. The method employed was essentially that used by Norcross and Openshaw (3) for the preparation of isobutyroveratrone. To a mixture of veratrole (35g.) and powdered, anhydrous aluminium chloride (40g.) in pure, anhydrous benzene (150ccs.), was added during the course of one and a half hours a solution of acetyl chloride (29g.) in dry benzene (70ccs.). The reactants were agitated mechanically throughout the addition and for a further hour, during which time the mixture was heated with refluxing of the solvent. The deep red mass was decomposed by pouring on to a mixture of ice (300g.) and concentrated hydrochloric acid (70ccs.). After the aqueous and benzene layers had been stirred and shaken together, the benzene layer was removed and the aqueous layer was extracted with more benzene (2 x 60ccs.). The combined benzene extracts

were washed with sodium hydroxide solution (8%; 2 x 50ccs.) and then with water (50ccs.) before drying over calcium chloride. The sodium hydroxide washings were filtered, and any phenolic substances present, due to demethylation in the Friedel-Crafts reaction, were remethylated by warming and shaking the alkaline solution twice with dimethyl sulphate (10ccs., 5ccs.) which had previously been washed with water. The alkaline liquor was then extracted with benzene (2 x 50ccs.), these extracts being added to the benzene solution drying over calcium chloride. The residual oil, after removal of the benzene, was fractionally distilled through a short column (Vigreux). The fraction boiling at 169-172°/20mm. (25.6g.)(56%) was collected as acetoveratrone. Veratrole (1.0g.), b.p. 100-101°/20mm., was recovered.

In subsequent preparations on a larger scale, much faster, more efficient stirring was used. The conditions were otherwise the same, and the yield was thereby raised to 81% (100g. scale), with no appreciable veratrole fraction.

4-Ethylveratrole. (A) Zinc filings (50g.) were washed quickly with dilute hydrochloric acid, and then with water. The zinc was amalgamated by shaking with mercuric chloride (3.5g.), concentrated hydrochloric acid (3.5ccs.) and water (50ccs.) for five minutes. After pouring off the liquor and washing with water, the amalgam was covered with water (35ccs.) and concentrated hydrochloric acid (50ccs.).

Acetoveratrone (25.6g.) in toluene (110)(50ccs.) was added and the mixture was refluxed for thirty hours, portions of hydrochloric acid (5ccs. each) being added every two hours. After cooling, the toluene layer was separated and the aqueous layer was extracted with toluene. The combined toluene solutions were dried over anhydrous sodium sulphate, and the toluene was distilled off as far as possible using a short column. The residue was distilled under reduced pressure, the first fraction (to 105°) being discarded as residual toluene and traces of veratrole formed in the reduction. The main fraction was 4-ethylveratrole, a slightly yellow oil, b.p. 126-129°/23mm., 121°/17mm. or 114°/13mm. The yield was 17.2g. (73%) which was increased to 75% in subsequent, larger scale experiments. A third fraction (to 160°) represented a small quantity of unreduced acetoveratrone. Any phenolic material was worked up separately in one preparation, but no additional yield was obtained on remethylation with dimethyl sulphate and alkali, showing that no appreciable demethylation occurred during the reduction.

(B) 4-Ethylguaiacol was methylated by the method of Kostanecki and Tambor (24) as set out in Organic Syntheses (26) for the preparation of veratraldehyde from vanillin. 4-Ethylveratrole (97-98.5%) was obtained as a slightly yellow oil, b.p. 124-126°/21mm., n_D^{18} 1.5213 [product from method (A) above had n_D^{18} 1.5219].

6-Ethylacetoveratrone. 4-Ethylveratrole was treated with freshly distilled acetyl chloride and aluminium chloride in anhydrous benzene following the instructions of Battersby and Openshaw (1). Yields varied from 80-86%, depending on the scale of the preparation and the efficiency of stirring, the higher value representing 94%, calculated on the unrecovered 4-ethylveratrole. The product had m.p. 63° (Battersby and Openshaw give 62-63°), b.p. 138-141°/3mm.

Benzoylacetone. Acetophenone (10g.) was condensed with ethyl acetate (18g., freshly distilled) by the method of Claisen (27), except that commercial sodium methoxide powder was used, to yield benzoylacetone (5.8g., 43%), m.p. 59-61°.

6-Ethylveratroylacetone. In a similar fashion, sodium methoxide (35g.) was dissolved in ethyl acetate (150ccs.), well cooled in ice-water, and allowed to stand for 15 minutes. 6-Ethylacetoveratrone (110g.) was added, and the flask was closed with a stopper carrying a calcium chloride tube and allowed to stand for two hours. Precipitation of the sodium salt of the condensate had begun when dry ether (200ccs.) was added and the mixture was stood at room temperature for 16 hours. After filtering and washing with dry ether until the washings were colourless, the residue was thoroughly dried in a cool oven and then dissolved in cold water. On acidification with acetic acid, 6-ethylveratroylacetone was precipitated as a pale orange powder

(63g., 48%), m.p. 62-63°. After two recrystallisations from ethyl alcohol, the product formed pale orange, rhombic plates, m.p. 64-65.5° (Found: C 67.4, H 7.12; $C_{14}H_{18}O_4$ requires: C 67.2, H 7.20).

In other preparations, the product was extracted from the acetic acid mixture with ether, dried over anhydrous sodium sulphate and the ether evaporated. Ethyl alcohol was added to the residual melt, when the diketone crystallised in 55% yield. In addition, some 6-ethylacetoveratrone was recovered from the ethereal washings of the sodium salt of the condensate.

6(4)-Phenyl-4(6)-methyl-3-cyanopyrid-2-one. Following Bardhan (30), benzoylacetone (2.6g.) and cyanacetamide (1.4g.) were dissolved by warming in ethyl alcohol (25ccs.). After cooling, diethylamine (0.8ccs.) was added and the mixture was heated on the steam-bath for 40 minutes. The crude pyridone (2.2g., 64%), m.p.>250° was collected and recrystallised from glacial acetic acid. The recrystallised material represented 90% of the total yield, and had m.p. 310-311° (decomp.). Bardhan gives m.p. 310° (decomp.) for the 6-phenyl isomer and estimates a 75-25% mixture, with the 6-phenyl isomer predominating.

6-(3:4-Dimethoxy-6-ethylphenyl)-3-cyano-4-methylpyrid-2-one. Similarly, 6-ethylveratroylacetone (5g.), m.p. 64° and cyanacetamide (1.7g.), m.p. 117-118° were dissolved in

warm ethanol (25ccs.) and diethylamine (1cc.) was added. After refluxing for four hours and cooling, the crystalline material was collected and washed with a little cold ethanol. The crude material (2.7g., 46%), m.p. 258-268°, was recrystallised from glacial acetic acid with very slight loss to yield the 6-substituted pyridone, m.p. 271-273° (slight sintering at 264-265°), not further raised by further recrystallisation, as hard, pale yellow prisms (Found: C 68.4, H 6.06, N 9.05; $C_{17}H_{18}O_3N_2$ requires: C 68.45, H 6.04, N 9.4).

Greater yields were obtained by treating larger quantities as follows: 6-Ethylveratroylacetone (60g.) and cyanacetamide (21g.) were dissolved in ethanol (500ccs.), diethylamine (10ccs.) was added and the mixture was refluxed until precipitation had almost ceased (about 8 hours). After cooling, the solid was filtered off, the ethanol was evaporated to half volume, further diethylamine (5ccs.) was added and the refluxing was continued as before. Filtration, evaporation and refluxing were repeated again, yielding successively 28, 24 and 23% of theory, a total of 54g. (75%).

The condensation was also carried out in 'cellosolve' [ethylene glycol monoethyl ether] in an attempt to reduce the reaction time (which may be 3 days in ethanol). The reaction was finished in a few hours and the yield was the same. The product from ethanol was slightly cleaner.

2-Chloro-3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine. (A) The pyridone (5g.) was added to freshly distilled chlorobenzene (35ccs.) containing phosphorus pentachloride (4.4g., 25% excess), and refluxed for a short period (3l). Only intractable tarry material was obtained, which was insoluble in ether.

(B) The pyridone (5g.) was refluxed for a short period with phosphorus oxychloride (4ccs.) containing some phosphorus pentachloride (0.5g.). Again only tarry decomposition products were obtained.

(C) Following the method employed by Baddiley and Topham (32) for the preparation of chloropyrimidines, the method was modified to include dimethylaniline as a catalyst. A very small yield of the desired product was obtained (vide infra), which was not easily purified from dimethylaniline and its derivatives.

(D) Following the method in Organic Syntheses (33) for the preparation of 2-chlorolepidine, the pyridone (5g.) was added to phosphorus oxychloride (4ccs.) in a flask fitted with an air condenser and calcium chloride tube. After 10 minutes on the water bath about half the solid had dissolved, and the mixture was heated to reflux for a further 15 minutes. The clear solution was poured hot into ice and water (100ccs.) with stirring, and the resulting mixture was extracted with ether (3 x 50ccs.). On drying over sodium sulphate and evaporating the ether, there remained a residue

(2.4g., 46%), largely diminished (to 31%) by recrystallisation from ethanol. More than half of the pyridone (2.6g., 52%) was recovered unchanged from the ice-water mixture.

(E) The optimum method derived from the above and other trials was found to be as follows: Three molar proportions of phosphorus oxychloride were used, and the time of reflux was increased to one and a half hours. The mixture was poured on to ice containing sufficient ammonia to neutralise the excess phosphorus oxychloride. The total precipitated material was collected and exhaustively extracted with large volumes of warm ether. A conversion of 68% was achieved, and pyridone was recovered for recycling amounting to 25% of the starting material. The ethereal solution was dried and evaporated and the residue was recrystallised from ethanol to yield 2-chloro-3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine, m.p. 109°. A further recrystallisation from the same solvent yielded bright yellow, diamond-shaped plates, m.p. 110° (Found: C 64.6, H 5.31, N 9.05; $C_{17}H_{17}O_2N_2Cl$ requires: C 64.5, H 5.37, N 8.85).

<u>3-Cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine</u>.

(A) The 2-chloro compound (27.9mg.) was dissolved in glacial acetic acid (5ccs.) containing sodium acetate (40mg.) and palladised barium sulphate (50mg., 5% Pd) and hydrogenated at atmospheric pressure. After 10 hours the hydrogen uptake was only 0.8ccs. (0.38 mole) and the experiment was aban-

donned.

(B) Using Adam's platinum catalyst in place of palladised barium sulphate, there was a smooth uptake of hydrogen to three moles, without discontinuity (see Fig. 1, p.21). The result was the same when the experiment was repeated using ethanol as the solvent in place of glacial acetic acid.

(C) The hydrogenation was repeated on the micro scale, using palladised charcoal (10% Pd) as catalyst in acetic acid and also in ethanol with similar results (see Fig. 1, p.21). On a larger scale, the 2-chloro compound (1.0g.) was dissolved in glacial acetic acid (30ccs.) and sodium acetate (1.0g.) and palladised charcoal (0.5g., 10% Pd) were added. After 9 hours hydrogenating, 110ccs. of hydrogen had been absorbed (1.1 moles, allowing 25ccs. for the known adsorption of the catalyst alone) and the reaction was stopped. The catalyst was filtered off ('Filtercel') in the usual manner, and the acetic acid was evaporated in a slight vacuum. The 2-chloro compound (57%), m.p. 110°, mixed m.p. with starting material 110°, was recovered by recrystallisation from ethanol, showing that the hydrogenation did not proceed stepwise under these conditions. From the ethanol mother liquors, added warm to ethanolic picric acid, a picrate was obtained, m.p. 218-220° (decomp.) which was not the picrate of the cyanopyridine base [see (D)

below] or of the 2-chloro compound (which does not form a picrate under the usual conditions). It proved to be the dipicrate of 3-aminomethyl-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine, more fully characterised below.

(D) The 2-chloro compound (16.3mg.) was dissolved in ethanol (5ccs., magnesium dried) containing sodium acetate (90mg.), which did not all dissolve, and palladised strontium carbonate (100mg., 1% Pd), and hydrogenated at atmospheric pressure. The uptake of hydrogen ceased when exactly one mole of the gas had been absorbed (see Fig. 1, p.21). On a larger scale, the chloro compound (2.45g.) was dissolved in dry ethanol (120ccs.), which solution was saturated, and sodium acetate (5g.) and palladised strontium carbonate (2g.) were added. On hydrogenation the uptake of gas ceased when 1.1 moles had been absorbed (228ccs. at 18°/743mm.; catalyst alone 30ccs.). The solution was heated, the catalyst was filtered off ('Filtercel') in the usual way and the alcohol was evaporated. The residue was triturated with water and the oil was extracted with ether (3 x 30ccs.). After drying over anhydrous sodium sulphate, the ether was evaporated to leave a residue which crystallised on scratching (1.3g.), m.p. 87-91°. Recrystallisation from petroleum ether (b.p. 80-100°) containing a little benzene gave 3-cyano-6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine (1.1g., 50%), m.p. 93-94°, further recrystal-

lised from a large volume of petroleum ether (b.p. 80-100°) to furnish colourless rhombs, m.p. 95.5-96.5° (Found: C 71.4, 71.6; H 6.22, 6.26; N 9.58, 10.15; $C_{17}H_{18}O_2N_2$ requires C 72.3, H 6.38, N 9.92).

Nitriles are known to give slightly low figures for carbon in combustion analyses. The picrate was prepared in warm ethanol in the usual manner, m.p. 180-182°. After a further recrystallisation from ethanol there were obtained yellow, hair-like needles, m.p. 181-182° (Found: C 54.3, H 4.32, N 13.5; $C_{17}H_{18}O_2N_2, C_6H_3O_7N_3$ requires: C 54.0, H 4.14, N 13.7).

The yield from this reaction was increased to nearly theoretical by combining several reduction liquors, evaporating the ethanol and crystallising directly from petroleum ether (b.p. 80-100°). To overcome the low solubility of the 2-chloropyridine in ethanol (ca. 2%) the hydrogenation was carried out in 'Cellosolve' (solubility ca. 5%) or ethyl acetate (solubility ca. 10%). The process was equally efficient in either solvent. By carrying out the hydrogenation at 40°, the time necessary for the whole absorption (1 mole) at atmospheric pressure was reduced to two hours.

(E) Following the method of Fargher and Furness (35), the 2-chloro compound (3g.) was treated with 50%, 90% and 100% hydrazine hydrate in separate experiments. In each case most of the starting material was recovered unchanged. In the most favorable case (100%) the 2-chloropyridine-

(1.9g.) was recovered and in addition a small yield (0.12g.) of a substance, m.p. 182°, which might be the hydrazide. It was not further characterised. The whole of this substance was subjected to the procedure of Thielepape (36) for the production of lepidine from lepidylhydrazine. In this case neither the blood-red colour described, nor any evolution of nitrogen gas could be detected. No pure products were obtained from the reaction mixture.

6-(3:4-Dimethoxy-6-ethylphenyl)-3-aminomethyl-4-methylpyridine. (A) 2-Chloro-6-(3:4-dimethoxy-6-ethylphenyl)-3-cyano-4-methylpyridine (5g.) was dissolved in glacial acetic acid (100ccs.) containing sodium acetate (5g.) and palladised charcoal (3g., 5% Pd), and hydrogenated at room temperature and atmospheric pressure. After 16 hours 1.2 moles of hydrogen had been adsorbed. On heating to 60°, the uptake was greatly accelerated and a total of 3 moles had been adsorbed in a further 3 hours. The catalyst was filtered off ('Filtercel') in the usual way and the acetic acid was evaporated as far as possible in a vacuum. The residue was thoroughly extracted several times with dry ethanol, the insoluble sodium chloride being filtered off. The ethanol was evaporated somewhat and a warm ethanolic solution of picric acid (7.2g., 2 moles) was added. The dipicrate of the aminomethylpyridine (4.5g.), m.p. 218-220° (decomp.), crystallised on repeated heating and cooling.

Recrystallisation from acetone raised the m.p. to 220-221° (decomp.) varying slightly with the rate of heating. Further recrystallisation from aqueous ethanol (50%), gave fine, yellow needles, m.p. 219-221° (decomp.) when plunged in a bath at 200° and heated at 2°/minute. Drying at 100° in vacuo for 3 hours caused no change (Found: C 47.1, H 3.58, N 14.9; $C_{17}H_{22}O_2N_2, 2C_6H_3O_7N_3$ requires: C 46.8, H 3.79, N 15.05).

(B) More efficient hydrogenation than (A) above was achieved by the method of Harris and Folkers (31). The chlorocyanopyridine (5.5g.) was dissolved in glacial acetic acid (120ccs.), and sodium acetate (5g.), palladised charcoal (1g., 5% Pd) and platinum oxide (0.25g.) were added. The mixture was heated to 60° and hydrogenated at atmospheric pressure. The uptake of hydrogen ceased abruptly in one hour when 3.0 moles (1280ccs.) had been absorbed. The catalyst was filtered off in the usual way and the acetic acid was evaporated as far as possible. A little water was added to the residue and the solution was exactly neutralised with sodium hydroxide. The diacid base was then extracted with ether (2 x 50ccs.) and chloroform (2 x 50ccs.), and the extracts were dried and evaporated to yield a thick, colourless oil (95%), which was not purified further, but was used directly for the next stage (deamination).

(C) 2-Chloro-6-(3:4-dimethoxy-6-ethylphenyl)-3-cyano-4-

methylpyridine (5g.) was dissolved in glacial acetic acid (100ccs.) and sodium acetate (5g.) and Adam's platinum oxide catalyst (0.15g.) were added. The solution was heated to 60°, and although 2.4 moles of hydrogen had been absorbed in 70 minutes, the uptake ceased abruptly and could not be persuaded to proceed further. The product was isolated as in (A) above, but the picrate only solidified after evaporation and storage at 0° for several days. Recrystallisation from aqueous ethanol yielded yellow agglomerates, m.p. 230-232° (4.7g.), which after further crystallisation from methanol had m.p. 238° (decomp.). The picrate was shown to contain halogen (Lassaigne) (Found: N 8.35, Cl 7.38; $C_{17}H_{21}O_2N_2Cl, C_6H_3O_7N_3$ requires: N 12.74, Cl 6.45; $C_{34}H_{38}O_4N_8Cl_2, C_6H_3O_7N_3$ requires: N 9.85, Cl 8.31). The analysis corresponds to neither the picrate or dipicrate of the 2-chloro-3-aminomethylpyridine nor the picrate of the derived secondary amine. The base was recovered from the picrate in the usual way using lithium hydroxide and exhaustively hydrogenated as in (B) above.

<u>6-(3:4-Dimethoxy-6-ethylphenyl)-3-hydroxymethyl-4-methylpyridine</u>. (A) The aminomethylpyridine (5g.) was dissolved in concentrated hydrochloric acid (35ccs.), cooled in ice and salt, and treated dropwise with a slight excess of sodium nitrite in a minimum quantity of water. There was no sign of reaction, even when the mixture was allowed to

warm up to room temperature. The solution was evaporated somewhat and stored in a refrigerator, but no crystals of hydrochloride separated. The solution was neutralised, saturated with potassium carbonate, and extracted with ether. The extract was dried over potassium carbonate, and the ether was evaporated. The m.p. of the picrate obtained from the residual gum was undepressed on admixture with the picrate of the starting material, m.p. 220-221° (decomp.). Recovery of the starting material was substantially quantitative. (62).

(B) Slightly modifying the method of Harris and Folkers (31) used in the synthesis of pyridoxin, the aminomethylpyridine (9g.) was dissolved in dilute sulphuric acid (2N, 50ccs.), a few drops of concentrated sulphuric acid being added to complete the solution. The solution was heated on the water bath to 70°, and sodium nitrite (5g.) in a little water was added dropwise with continuous mechanical stirring over the course of one hour. The stirring and heating were continued for a further hour, and the solution was cooled and made alkaline with sodium hydroxide solution. The product was extracted with chloroform (3 times), dried over anhydrous sodium sulphate, and the chloroform evaporated. The residue was dissolved in ethanol (20ccs.) and a warm ethanolic solution of picric acid (7.5g.) was added. There was an immediate, voluminous precipitate of picrate (13g.), m.p. 148-150°. After four recrystallisations from

ethanol the m.p. was raised with great loss to 156-157°. A small portion further recrystallised from ethanol yielded light fluffy, yellow needles, m.p. 157° (Found: C 54.2, H 4.79, N 12.4; $C_{17}H_{21}O_3N,C_6H_3O_7N_3$ requires: C 53.5, H 4.69, N 10.9).

The base was recovered from the picrate in the usual manner using lithium hydroxide to yield the hydroxymethylpyridine (4.4g., 96% on picrate) as a thick colourless oil which partly crystallised, m.p. ~196°. The base could not be distilled without decomposition. On reforming the picrate of the partially purified base in ethereal solution, and recrystallising it from ethanol the m.p. was raised to 159-160°, with slight sintering from 151°, unaltered by further recrystallisations from various solvents (Found: C 53.7, H 4.25, N 11.3; $C_{17}H_{21}O_3N,C_6H_3O_7N_3$ requires: C 53.5, H 4.68, N 10.9).

6-(3:4-Dimethoxy-6-ethylphenyl)-3-bromomethyl-4-methylpyridine hydrobromide. (A) The hydroxymethylpyridine (3g.) was dissolved in hydrobromic acid (15ccs., 40%) and heated on the water bath for 30 minutes. After cooling, ethanol (20ccs.) and ether (300ccs.) were added, when soft needles (2.5g.) were slowly deposited, m.p. 196°, only slightly depressed on admixture with the starting material. The substance was reheated with further lots of hydrobromic acid and distilled in a vacuum to yield a substance (1.4g.),

m.p. 109-110°, which was used directly for the next stage (see Grignard reactions).

(B) The hydroxymethylpyridine (0.5g.) was dissolved in hydrobromic acid (3ccs., 48%) and heated on the water bath for 30 minutes. On cooling and scratching no crystals were deposited. The liquor was evaporated over potassium hydroxide in a vacuum desiccator for three days to form a syrup which was dissolved in methanol and a large volume of ether was added. An oil was deposited, which eventually solidified to a pale yellow powder (0.1g.), m.p. 210-211° (sintering at 205°). Further recrystallisation from methanol yielded pale yellow clusters of rhombs, which after drying at 100°/1mm. for 2 hours had m.p. 216-217° (decomp.), darkening slightly from 207° (Found: C 47.9, H 5.29, N 3.26, Br 36.0; $C_{17}H_{20}O_2NBr,HBr$ requires C 47.4, H 4.91, N 3.25, Br 37.0).

6-(3:4-Dimethoxy-6-ethylphenyl)-4-methylpyridine-3-carboxylic acid. (A) The 3-cyano-6-aryl-4-methylpyridine (1.0g.) was added to concentrated sulphuric acid (10ccs.) and water (8ccs.) and the mixture was boiled under reflux for 2 hours. [cf. (56)]. On cooling, there was no precipitate of insoluble acid (the product is amphoteric) and the liquid was boiled with an excess of barium carbonate (50g.), water being added to make a workable mixture. On filtering and evaporating the filtrate to dryness, no crystalline material of any sort could be isolated. The amorphous residue was

reserved crude for esterification (*vide infra*).

(B) Following the method of Long and Burger (57), the cyanopyridine (0.24g.) was dissolved in n-propanol (20ccs.) containing potassium hydroxide (2g.). The mixture was refluxed for 4 hours and the product was isolated by the literature method (57). On recrystallisation from petroleum ether (b.p. 80-100°) white needles were obtained, apparently homogeneous, m.p. 143.5-144.5°. (Found: C 67.6, H 7.58, N 7.76; $C_{17}H_{19}O_4N$ (acid) requires: C 67.8, H 6.31, N 4.65; $C_{17}H_{20}O_3N_2$ (amide) requires: C 68.0, H 6.67, N 9.33). In spite of drying a sample at 100° *in vacuo* for two hours, the closest correspondence is to the amide with propanol of crystallisation ($C_{17}H_{20}O_3N_2, C_3H_8O$ requires: C 66.7, H 7.78, N 7.78). Hydrolysis of the nitrile was obviously incomplete.

(C) Potassium hydroxide (2g.) was dissolved in ethanol (20ccs.) and the cyanopyridine (1.0g.) was added. The mixture was refluxed, and a little water was added from time to time to incipient precipitation, the equivalent volume of alcohol being evaporated. After 48 hours refluxing, the vapour was substantially free from ammonia, whereupon a little activated charcoal was added, and the mixture was boiled for a minute and filtered hot. On cooling, a substance (0.086g.) was deposited, m.p. 155-159°, which was collected and recrystallised from ethanol to yield a white, microcrystalline powder, m.p. 157-158° (Found:

C 65.5, H 6.95, N 8.29, Ash 8.45). This does not correspond to either the potassium salt of the pyridine carboxylic acid, nor the acid amide. It was nevertheless homogeneous, and differed from the corresponding product from the propanol hydrolysis [(B) above].

The filtrate from the above substance was evaporated to dryness *in vacuo* and dissolved in dry ethanol. Hydrogen chloride gas was added until the reaction was slightly acid. The precipitated potassium chloride was filtered off, and the ethanol solution was evaporated to dryness. Repetition of the solution in dry ethanol, filtering and evaporating yielded the pyridinecarboxylic acid (0.88g.) free from inorganic material. The product was used directly for esterification (*vide infra*).

Ethyl 6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine-3-carboxylate. The crude pyridinecarboxylic acid (0.88g.) was dissolved in magnesium-dried ethanol (10ccs.), a little dry hydrogen chloride gas was added and the mixture was refluxed for 4 hours. The solvent and hydrogen chloride were removed in a vacuum as far as possible to leave a residue (1.14g.) of crude ester. Water and sodium acetate were added and the ester was extracted three times with ether. The ethereal solution was washed with water, dilute sodium hydroxide (twice) and water again. After drying over anhydrous potassium carbonate, the ether was evaporated

to yield a residue (0.45g.) which was distilled in a high vacuum, bath temperature 100-105°/10^{-5}mm. The distillate was taken up in a little ethanol and ethanolic picric acid (0.25g.) was added. On warming, cooling and scratching a picrate was precipitated (0.64g.), m.p. 170-172°, which was recrystallised from ethanol to yield yellow needles, m.p. 171-172° (Found: C 53.5, H 4.52, N 10.3; $C_{19}H_{23}O_4N,C_6H_3O_7N_3$ requires: C 53.8, H 4.66, N 10.0).

The picrate (0.40g.) was suspended in sodium hydroxide solution (50ccs., 10%), shaken well and extracted with ether (3 x 50ccs.). In order to minimise hydrolysis of the ester by concentrated alkali, the ethereal solution was washed a total of eight times with sodium hydroxide (10%) when the washings were colourless. After a wash with water, the solution was dried over anhydrous sodium sulphate with the addition of a little anhydrous potassium carbonate. After filtering, the ether was evaporated. The residue (0.29g.) crystallised on scratching, m.p. 69°. The ester was very soluble in ethanol and ether, and was therefore recrystallised from petroleum ether (b.p. 60-80°) twice, being filtered each time through a thick pad of 'Filtercel' and alumina (to remove traces of acid). Ethyl 6-(3:4-dimethoxy-6-ethylphenyl)-4-methylpyridine-3-carboxylate was obtained as nearly colourless, hard rhombs, m.p. 74.5-75.5° (Found C 69.3, H 6.87, N 4.23; $C_{19}H_{23}O_4N$

requires: C 69.4, H 7.04, N 4.26). The yield was slightly higher on a larger scale.

The low yield of ester was probably due to demethylation during esterification. The phenolic fraction (extracted in alkali) cannot be remethylated in the normal way, as the pyridine ring would also be affected.

3-Acetyl-4:6-dimethylpyridine. 4:6-Dimethylnicotinic ester, b.p. 138°/20mm., made from acetylacetone and cyanacetamide, followed by hydrolysis and esterification, was used as the starting material. The ester (4.6g.) and ethyl acetate (3.5ccs.) were dissolved in toluene (sulphur free) containing sodium ethoxide (2.8g., from 1g. sodium) and refluxed for 5 hours. The product was poured on to ice (250g.) and ether was added. The layers were separated and the ether-toluene layer was extracted twice with ice-cold sodium hydroxide (2 x 20ccs., 8%), which was added to the aqueous layer. To the total aqueous mixture (300ccs.) was added concentrated hydrochloric acid (300ccs.) and the mixture was refluxed for 4 hours. After cooling, it was extracted with ether (3 x 150ccs.), saturated with sodium chloride and extracted twice more with ether and three times with chloroform. The ether and chloroform layers were dried separately over anhydrous sodium sulphate and the solvents were evaporated. From the ether solution was obtained tarry material (0.31g.) which partially crystallised. A further small quantity (0.06g.) of the same material was

obtained from the chloroform solution, making a total yield of 7% crude ketone. Over 90% (4.3g.) of the starting material was recovered unchanged from the ether washings of the original condensate, satisfactorily accounting for the low yield. The crude tarry material from the reaction (small portion) was warmed for a few minutes with a saturated solution of o-nitrobenzaldehyde in sodium hydroxide (0.2N). On cooling and extracting with chloroform a powerful indigo colour developed (Feigl's test for methyl ketones). The crude substance also gave a powerful iodoform reaction using the refined method of Fuson and Tullock (47).

Grignard Reactions with Nitriles.

Acetophenone. As a check on a standard procedure for the preparation of methyl ketones from nitriles, a Grignard reagent was prepared from methyl iodide (8.5g.) and magnesium (1.5g., 3% excess) in dry ether (30ccs.). To this was added with continuous stirring benzonitrile (5.15g.) in dry ether (20ccs.). After one hour a solution of ammonium chloride (12g.) in concentrated hydrochloric acid (12ccs.) and water (50ccs.) was added cold and the mixture was stirred for one hour. The aqueous layer was separated and refluxed for one hour, most of the acid was neutralised with sodium hydroxide and the mixture was extracted with ether (4 x 50ccs.). The ether solution was washed with water and dried over anhydrous sodium sulphate, after which

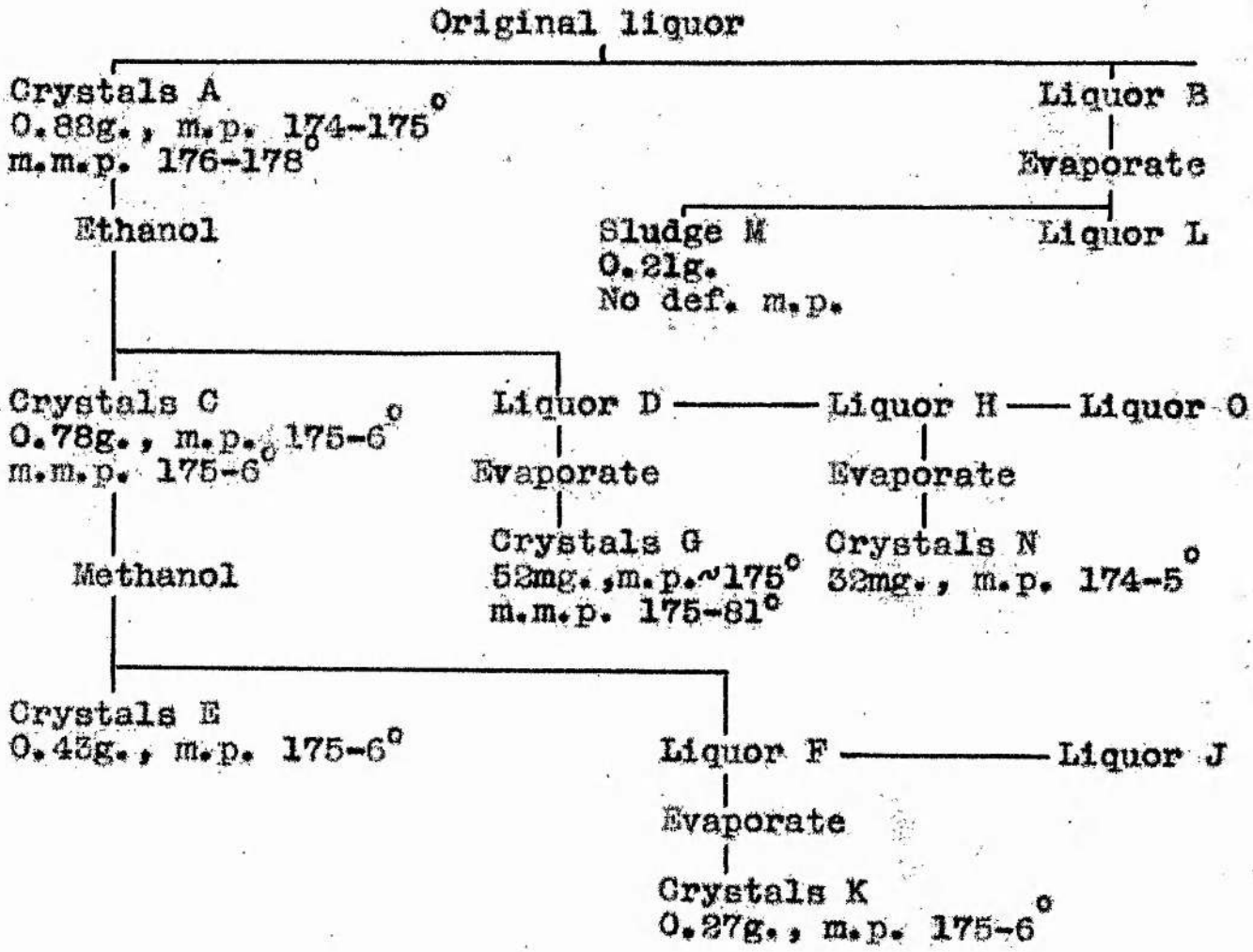
the ether was evaporated and the residue was distilled to yield acetophenone (3.62g., 60%), b.p. 196-198°. The product was characterised as the semicarbazone, which crystallised as cubes, m.p. 200°, or needles, m.p. 199° (lit. m.p. 199-200°).

Attempted preparation of 6-(3:4-dimethoxy-6-ethylphenyl)-3-acetyl-4-methylpyridine. (A) 6-(3:4-Dimethoxy-6-ethylphenyl)-3-cyano-4-methylpyridine (0.8g.) was dissolved in dry benzene (10ccs.) and added dropwise with stirring to a Grignard reagent made from methyl iodide (1.8g.) and magnesium (0.33g.) in dry ether (25ccs.). The Grignard reagent was in excess (4 moles). A heavy orange-yellow precipitate appeared. The mixture was stirred and refluxed for two hours. A solution of ammonium chloride (5g.) and concentrated hydrochloric acid (5ccs.) in water (20ccs.) was added and stirred until no solid material was present. The aqueous layer was separated and refluxed for one hour, cooled and made alkaline with sodium hydroxide. The alkaline solution was extracted with ether (4 x 30ccs.), which was separated, dried over anhydrous sodium sulphate and evaporated. The residue would not crystallise from ether, ethanol, benzene or petroleum ether, and it was therefore dissolved in warm ethanol and added to an ethanolic solution of picric acid (0.7g.). A picrate (0.88g.) was precipitated, m.p. 174-175°, which on admixture with the picrate of the starting material, m.p. 182°, melted at 176-178°. No reaction

had taken place.

(B) To a Grignard reagent made from methyl iodide (12.1g.) and magnesium (2.35g.) in dry ether (100ccs.) was added over the course of 30 minutes a solution of the nitrile (6g.) in dry benzene (50ccs.). A voluminous yellow precipitate developed and the mixture was left stirring under reflux for 24 hours, a stream of dry nitrogen gas being passed through the flask the whole time to prevent deterioration of the Grignard reagent. At the end of this period the precipitate had not noticeably diminished. The complex was decomposed by the addition of sulphuric acid (50ccs., 10%) and water (150ccs.). The ether layer was separated and the aqueous layer was extracted three times with ether, the extract being added to the ether layer. The aqueous layer was boiled for a short time, rendered just alkaline with sodium bicarbonate solution and extracted three more times with ether. The ethereal solutions were dried separately over anhydrous sodium sulphate and evaporated. The residue from the acid extract crystallised when triturated with petroleum ether and proved to be unchanged nitrile. The residue from the alkaline extract would not crystallise, and on treatment with ethanolic picric acid yielded a picrate, m.p. 174-175°, almost identical with that from (A) above. The residual oil from the alkaline extract gave a positive test for methyl ketone by Fiegl's method and the refined iodoform test (47). There was also

a cloudiness when a solution of the oil was added to methanolic 2:4-dinitrophenylhydrazine, but there was insufficient to isolate. No thiosemicarbazide or its silver salt could be isolated from as much as 100mg. of extract. The remainder of the crude extract (0.70g.) was added to warm ethanolic picric acid and fractionated as below:



Fractions A, C, E, K and N were orange prisms, which were combined. The base was recovered using lithium hydroxide to yield the nitrile (0.125g.), m.p. 92-96°, undepressed on admixture with the starting material, m.p. 96°. Fraction G was yellow needles and the base was recovered separately.

The same material resulted, and fraction G must be a different crystal habit of the picrate. The mother liquors of the recovered bases were combined with the base recovered from the other picrate fractions and liquors, but no pure material was isolated, nor other crystalline picrate obtained.

Attempted Grignard reaction with 2-chloro-6-(3:4-dimethoxy-6-ethylphenyl)-3-cyano-4-methylpyridine. The chloropyridine (3.2g.) was dissolved in dry ether (50ccs.) and added to a Grignard reagent made from methyl iodide (1.7g.) and magnesium (0.33g.). After several hours the reaction products were worked up as in the preceding cases. The main product crystallised, m.p. 107°, raised to 110° by one recrystallisation from ethanol, and undepressed on admixture with the starting material, m.p. 110°.

Grignard Reactions with Carboxylic Esters.

Reaction with ethyl benzoate. A Grignard reagent was made in the usual manner from methyl iodide (5.2g.) and magnesium (1g.) in dry ether (50ccs.) and transferred by pressure of dry nitrogen to a dropping funnel. Ethyl benzoate (5g., 1 equiv.) was dissolved in dry ether (50ccs.) and placed in a reaction vessel protected from moisture and equipped with good mechanical stirring. The Grignard solution was added dropwise over the course of one hour. The complex was broken up by the addition of sulphuric acid (100ccs., N)

and the aqueous layer was extracted with ether (2 x 60ccs.). The combined ethereal solutions were washed with sodium carbonate solution and water, dried and evaporated to yield a total of 4.81g. of residue. Some of the residue (0.28g.) was dissolved in a little methanol and added to a solution of 2:4-dinitrophenylhydrazine (10ccs., 5%), whereupon only a faint turbidity was observed. Quantitative saponification indicated 54.7% ethyl benzoate, assuming this to be the only saponifiable substance present. The remainder was assumed to be largely dimethylphenylcarbinol, as carbonyl compounds were present only in traces.

Reaction with o-chlorobenzoic ester. o-Chlorobenzoic acid was esterified in nearly theoretical yield with dry ethanol containing 3% dry hydrogen chloride. The ester was twice distilled, b.p. 122-125°/15mm., 128°/18mm., or 243°/760mm. A Grignard reagent was prepared from methyl iodide (5.3g.) and magnesium (0.95g.) in dry ether (50ccs.) as before and transferred to a dropping funnel by pressure of dry nitrogen. The o-chlorobenzoic ester (6g.) was dissolved in dry ether (50ccs.) and the Grignard reagent was added with continuous stirring over the course of one hour. The resulting mixture was decomposed with sulphuric acid (100ccs., N) and the mixed product (5.81g.) was isolated as before. Again the product gave a slight turbidity with a solution of 2:4-dinitrophenylhydrazine, insufficient to isolate or identify.

Quantitative saponification indicated 54.6% ester calculated as ethyl o-chlorobenzoate. The bulk of the remainder was probably dimethyl-o-chlorophenylcarbinol.

β-(3:4-dimethoxy-6-ethylbenzoyl)propionic acid. The method used was analogous to that employed by Battersby and Openshaw (1) in the preparation of 6-ethylacetoveratrone (p.59). 4-Ethylveratrole (5g.) and pure, anhydrous benzene (20ccs.) were stirred at room temperature with powdered, anhydrous aluminium chloride (3.5g.). Freshly recrystallised succinic anhydride (3.9g., m.p. 119.5°) in dry benzene (10ccs.) was added gradually over the course of one hour. After heating for a further hour under reflux, the complex was decomposed in the usual way with ice and hydrochloric acid and the product was extracted twice with benzene. The total product, containing some phenolic material, was re-extracted into an excess of sodium hydroxide solution and remethylated by warming and shaking with dimethyl sulphate (2 x 2ccs.). After acidifying, the product was again extracted into benzene, which was dried over anhydrous sodium sulphate and evaporated. The residue (3.1g., 39%) was recrystallised from water to yield β-(3:4-dimethoxy-6-ethylbenzoyl)propionic acid* (2.9g.), m.p. 126.5°, unchanged by further recrystallisation.

γ-(3:4-Dimethoxy-6-ethylphenyl)butyric acid. Mossy zinc

* see footnote, p.84.

(12g.) was amalgamated (103) by shaking for five minutes with mercuric chloride (1g.), concentrated hydrochloric acid (0.5ccs.) and water (15ccs.). The aqueous liquor was decanted and the zinc was washed twice with a little water. To the amalgamated zinc was added water (7ccs.), concentrated hydrochloric acid (17ccs.), sulphur-free toluene (10ccs.) and β-(3:4-dimethoxy-6-ethylbenzoyl)propionic acid (2.8g.) in that order. The mixture was refluxed briskly for 40 hours, during which time concentrated hydrochloric acid (3ccs.) was added every 6 hours. After cooling to room temperature, the aqueous layer was separated, diluted with water (25ccs.) and extracted with ether (3 x 15ccs.). The ether and toluene solutions were combined and extracted with a solution of sodium bicarbonate (3 x 20ccs.). No phenolic material was detectable, and no remethylation was carried out. The bicarbonate solution was warmed and filtered, and, on acidification with concentrated hydrochloric acid and cooling to 0°, an opaque, white powder was collected (2.18g., 82%), m.p. 72°. Recrystallisation from petroleum ether (b.p. 40-60°) containing a few drops of benzene yielded γ-(3:4-dimethoxy-6-ethylphenyl)butyric acid as*

* No elementary analyses were carried out on these substances as it was assumed that the preparations would be repeated on a larger scale. Further work in this direction became unnecessary (see p.51 et foll.) and no specimens were available without repetition.

opaque white agglomerates of small crystals, m.p. 72-72.5°.

Ethyl γ-(3:4-dimethoxy-6-ethylphenyl)butyrate. γ-(3:4-Dimethoxy-6-ethylphenyl)butyric acid (2.06g.) was dissolved in magnesium-dried ethanol (40ccs.) and dry hydrogen chloride gas (1.3g.) was added. After refluxing for 6 hours, the alcohol was evaporated as far as possible on the water bath. Water (10ccs.) was added, followed by sufficient sodium carbonate solution (5%) to render the solution alkaline. The ester was extracted with ether (3 x 15ccs.), the ethereal solution was dried over anhydrous potassium carbonate (to remove any unchanged acid) and the ether was evaporated. The residue was distilled *in vacuo* to yield the ester as a slightly greenish oil (1.25g., 54%), b.p. 155-158°/0.5mm. A little more impure yield was obtained by reworking the residues. The relatively low yield was undoubtedly due to demethylation, and the conditions were not optimum.

Triphenylmethylsodium. Following the method given in Organic Reactions (98, 112), a supply of triphenylmethylsodium in ethereal solution was prepared. An aliquot portion analysed to 0.114 molar.

α:γ-Bis-(6-ethylhomoveratryl)-acetoacetic ester. An ethereal solution of triphenylmethylsodium (45ccs., 0.114 molar) was transferred to a dry flask by pressure of dry nitrogen. The flask had been previously graduated for the purpose. An equivalent quantity of ethyl γ-(3:4-dimethoxy-6-ethyl-

phenyl)-butyrate (1.4g.) was added immediately, the flask was well stoppered, shaken to effect complete mixing and stood at room temperature for three days. The solution was acidified by the addition of glacial acetic acid (0.4ccs.) and extracted with water (10ccs.). After washing with sodium carbonate solution (2 x 5ccs., 10%) the ethereal solution was dried over anhydrous sodium sulphate. The ether was evaporated, the residue was cooled and ethanol (5ccs., 95%) was added, followed by a seed of triphenylmethane. The triphenylmethane which was deposited was filtered off and washed with a little ethanol. The filtrate was again evaporated and the residue was distilled *in vacuo*. The fraction boiling at 190-215°/10mm. was collected as the β-ketoester (1.05g., 82%). The product gave a strong purple colour with ferric chloride solution. The recovered triphenylmethane was recrystallised from ethanol to yield pale yellow prisms, m.p. 94°.

Di-3-(3:4-dimethoxy-6-ethylphenyl)-n-propyl ketone (alleged). Essentially following the method of Meerwein (99), the β-ketoester (1.0g.) and water (2ccs.) were placed in a double weight 'Pyrex' test tube and sufficient ethanol was added to form a clear solution. The tube was sealed and heated in a Carius furnace at 200-210° for four hours. After cooling, the tube was opened, the contents were diluted with water (20ccs.) and extracted with ether

(3 x 20ccs.). After drying over anhydrous sodium sulphate and evaporating the ether, the residue was distilled in a short path distillation apparatus to yield a very viscous, yellow oil (0.624g., 72%), b.p. 150° (bath)/0.1mm. The gum could not be induced to crystallise from any of the usual solvents. No crystalline 2:4-dinitrophenylhydrazone, semicarbazone, thiosemicarbazone or the corresponding silver salt could be obtained.

5-Bromo-4-ethylveratrole. The following is a modification of a method used by Gaspari (104) for the preparation of monobromoveratrole. In a typical preparation, 4-ethylveratrole (11g.) was dissolved in glacial acetic acid (60ccs.) contained in a gas-washing bottle (150ccs.), cooled to 10°. Bromine (11g.) was contained in a smaller gas-washing bottle (25ccs.) kept at room temperature (18°). A slow current of air, regulated by four inches of water in a bubbler, was drawn through the bromine bottle and then through the acetic acid solution by a filter-pump. The air was arranged to pass over the surface of the liquid bromine and not through it. Under these conditions the complete reaction of the bromine took one and a half hours. The acetic acid was distilled away as far as possible and the residue was fractionated *in vacuo* through a short column. A small fraction (up to 135°/13mm.) of unchanged 4-ethylveratrole was discarded. The main fraction, b.p. 144-145°/13mm. (12.3g., 76%) was practically pure 5-bromo-

4-ethylveratrole (Found: C 49.9, H 5.32, Br 29.8; $C_{10}H_{13}O_2Br$ requires: C 49.0, H 5.30, Br 32.5). The oil was redistilled and characterised as follows.

6-Ethylveratric acid from 5-bromo-4-ethylveratrole. Bromoveratroles do not form Grignard reagents readily (p.45). However, 5-bromo-4-ethylveratrole (1.6g.) was refluxed with magnesium (0.17g.) in anhydrous ether (10ccs.) for four hours, a few drops of methyl iodide being added as an activator. The solution of magnesium had not proceeded very far, but the whole mixture was poured on to solid, powdered carbon dioxide (2g.) with vigorous stirring. The complex was broken up by the addition of ammonium chloride solution (10ccs.). The solution was made alkaline and the ether layer was separated and set aside for the recovery of the bromoveratrole. The aqueous layer was further washed with ether, filtered and acidified with concentrated hydrochloric acid to yield 6-ethylveratric acid (0.25g.), m.p. 142-143°, as a white powder. On slow recrystallisation from water containing a few drops of dilute hydrochloric acid the m.p. was raised to 144-145°. 6-Ethylveratric acid made from 6-ethylacetoveratrone by hypochlorite oxidation (1) had m.p. 143°, undepressed on intimate mixing with the material prepared above.

5-Nitro-4-ethylveratrole. Essentially following King and L'Ecuyer (80), 4-ethylveratrole (34.1g.) was dissolved in

glacial acetic acid (35ccs.), and added dropwise with stirring to concentrated nitric acid (21ccs.) maintained at 0° by an ice-bath. After an hour the mixture was heated onthe water bath to 60° for 30 minutes. On one occasion the temperature was allowed to rise somewhat higher, whereupon the reaction became uncontrollable. The mixture from the 60° nitration was poured into cold water (400ccs.) and allowed to stand overnight. The solid product was filtered off and the aqueous liquor was extracted with ether (3 x 100ccs.). The solid material was dissolved in the ether which was dried over anhydrous sodium sulphate and a few pellets of potassium hydroxide to remove residual acid, and evaporated. The residue was distilled through a short column to yield 5-nitro-4-ethylveratrole (24.5g., 62% on unrecovered 4-ethylveratrole), b.p. 170-180°/15mm. and 4-ethylveratrole (3g.) unchanged. In further experiments the yield was increased to 70% by (1) extending the heating to 60° of the nitrating mixture to one and one half hours and eliminating the ether extraction, the solid mass being dried in a vacuum desiccator and (2) distilling at a lower pressure, b.p. 141-143°/1mm., which prevented some decomposition which occurred at water-pump vacua. The product solidified in the receiver, m.p. 54-55° (King and L'Ecuyer give m.p. 54-54.5°).

5-Amino-4-ethylveratrole. (A) 5-Nitro-4-ethylveratrole

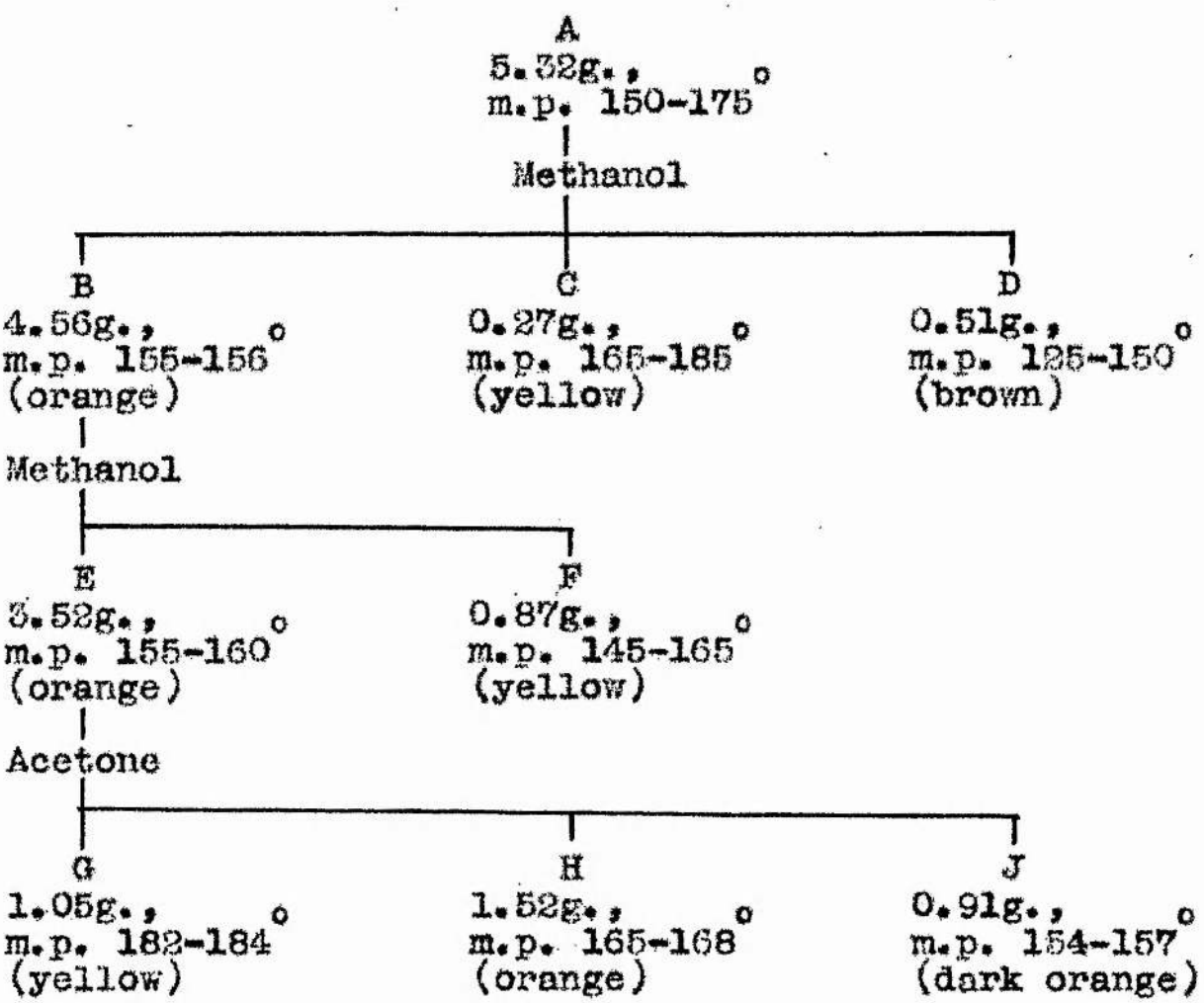
(20g.) was dissolved in dry ethanol (150ccs.) and palladium supported on strontium carbonate (10g., 1% Pd) was added. Hydrogenation was carried out at atmospheric pressure. The uptake of hydrogen was greatly accelerated by slight warming to 40-50°, when the theoretical volume (6.9 litres) was absorbed in three hours. The catalyst was filtered off ('Filtercel') and the ethanol was evaporated. The residue was distilled in vacuo to yield 5-amino-4-ethylveratrole (12g., 68%), b.p. 133-134°/1mm., crystallising in the receiver, m.p. 63° (King and L'Ecuyer give m.p. 63°). The acetyl derivative, formed in the usual way, had m.p. 146° (King and L'Ecuyer give m.p. 147°).

(B) 5-Nitro-4-ethylveratrole (89.4g.) was dissolved in dry ethanol (500ccs.) and a few grams of Raney nickel catalyst were added. Hydrogenation was carried out at 30 atmospheres pressure and 100° for two hours. The catalyst was filtered off ('Filtercel'), the ethanol was evaporated and the residue was distilled in vacuo, b.p. 133-134°/1mm., to yield 5-amino-4-ethylveratrole (71g., 93%).

(3:4-Dimethoxy-6-ethylphenyl)pyridines. 5-Amino-4-ethylveratrole (10g.) was dissolved in hydrochloric acid (100ccs., 20%) and diazotised at 0-5° with a solution of sodium nitrite (4g.) in water (10ccs.). Pyridine (120ccs., freshly distilled from solid potassium hydroxide) was stirred mechanically on a water bath maintained at 70-80° and the diazonium solution was added dropwise over the course of one

hour. The bulk of the diazonium solution was preserved as long as possible at 0°. After stirring for a further hour on the water bath, water (200ccs.) was added, the mixture was rendered distinctly alkaline with ammonia solution and the excess of pyridine was distilled in steam (about two litres of distillate were sufficient). The remaining aqueous liquor was cooled and extracted with benzene (3 x 100ccs.). Basic material in the benzene was extracted into hydrochloric acid (2 x 50ccs., 4N), which was then neutralised with ammonia, and the bases were re-extracted with ether (3 x 100ccs.). The ethereal solution was dried over anhydrous sodium sulphate and subsequently over pellets of potassium hydroxide, and the ether was evaporated. The residual oil was distilled in vacuo to yield a pale yellow, viscous oil (3.0g.), b.p. 135-138°/0.04mm. The last two drops were collected separately and dissolved in warm ethanol, and warm ethanolic picric acid (0.1g.) was added. A picrate was precipitated immediately, m.p. 182-183.5°. The whole distillate was dissolved in warm ethanol and an ethanolic solution of picric acid (2.5g.) was added. The yield of orange, crystalline picrate (5.15g.) corresponds to 100% calculated on the picric acid, and a further portion of picric acid (1g.) was added to the mother liquors. A further small crop (0.18g.) of picrate, m.p. 140-160° was obtained which was added to the main crop, m.p. 150-175°,

Assuming the product to be a mixture of isomers, the picrates were fractionally crystallised as shown below:



Fraction G was undepressed on admixture with the picrate from the last two drops of distillate, m.p. 183-185°. After a further recrystallisation fraction G had m.p. 186-187° (Found: C 53.4, H 3.51, N 11.8; $C_{15}H_{17}O_2N,C_6H_3O_7N_3$ requires: C 53.4, H 4.27, N 11.9). Fraction H after further recrystallisation formed orange rhombs, m.p. 167-168° (Found: C 53.3, H 4.46, N 11.6; $C_{15}H_{17}O_2N,C_6H_3O_7N_3$ requires: C 53.4, H 4.27, N 11.9). Fractions F, J, C and D, along with other residues and mother liquors were com-

bined and recrystallised from acetone. A small additional amount of slightly impure H fraction, m.p. 165-168° was obtained, but a third isomer could not be induced to crystallise.

Attempted preparation of 6-(3:4-dimethoxy-6-ethylphenyl)-3-ethyl-4-methylpyridine from β-collidine. (A) 3:4-Dimethoxy-6-ethylaniline (11.2g.) was dissolved in concentrated hydrochloric acid (30ccs.) and water (20ccs.) and diazotised at 0° with a solution of sodium nitrite (4.5g.) in a little water. The hydrochloride of the base separated temporarily from the concentrated solution, but the diazonium salt was freely soluble. The bulk of the solution was kept at 0°, and transferred dropwise over the course of one hour to β-collidine (23g.) stirred continuously at 80°. After heating and stirring for a further hour, the solution was cooled and basified with ammonia solution. The unreacted β-collidine (19g.) was distilled in steam and recovered by extraction with ether. The remainder was a black tar, probably largely 3:4-dimethoxy-6-ethylphenol and its demethylation products, from which no useful product of any description could be recovered.

(B) 5-Amino-4-ethylveratrole (10g.) was dissolved in the minimum quantity of concentrated hydrochloric acid (18ccs., 2.5 molar proportions) and diazotised with a solution of sodium nitrite (4.2g.) in a little water. The

resulting diazonium solution was added as before to β-collidine (18g.) violently stirred at 80° with anhydrous sodium carbonate (7.5g., 2 molar proportions). The product was worked up as before and the β-collidine (14g.) was recovered. Basic material not volatile in steam was extracted into ether, which was dried and evaporated. A very impure high-boiling fraction (bath temp. 210°/10^{-2} mm.) was obtained in very poor yield. There was considerable decomposition during distillation, even at 10^{-2} mm. A crystalline picrate was obtained from the distillate, but the yield was only 3 milligrams, insufficient for analysis and melting uncertainly over a range of at least 40° up to ca. 240° (decomp.).

β-Collidine. The method used was essentially that of Ruzicka and Fornasir (34), but several of the steps were modified and, in some cases, improved. These are given in outline below.

5-Cyano-2:6-dihydroxy-3-ethyl-4-methylpyridine. Ethylacetoacetic ester (200g.)(made from acetoacetic ester and ethyl iodide) and ammonia solution (800ccs., 0.880 sp. gr.) were mixed in a Winchester bottle which was firmly stoppered and shaken mechanically for 6 days. An oil had separated which crystallised on scratching and was removed by filtration. The dry crystals (109g.) are 1-ethyl-2-aminocrotonic ester and are lost to the synthesis. Cyanoacetic ester

(65g.) sufficient to combine with the remainder in the filtrate was added and quickly dissolved. The solution darkened slightly and a precipitate began to appear after about 24 hours. After 14 days the solution was practically solid with precipitate, which was filtered off to yield the ammonium salt of 5-cyano-2:6-dihydroxy-3-ethyl-4-methyl-pyridine (73g.). A further small quantity (2.5g., making 74% total) was obtained by concentrating the mother liquors to small bulk. The crude substance, dried at 105° had m.p. 315° (Ruzicka and Fornasir claim up to 85%, m.p. 315°). In several subsequent runs the yield could not be raised above 74%.

2:6-Dihydroxy-β-collidine. The dried ammonium salt from the previous condensation (75g.) was refluxed in a 2-litre round-bottom flask with concentrated hydrobromic acid (600ccs., redistilled to constant boiling, 126°) for 10 hours, after which time nearly all the solid was in solution. The bulk of the hydrobromic acid was distilled away at atmospheric pressure and the remainder in vacuo on the water bath. The hydrobromide of dihydroxy-β-collidine was dissolved in dry ethanol (2 x 200ccs.) in which ammonium bromide is insoluble. The ethanol was evaporated nearly to dryness, a little water was added (filtering was unnecessary) and the 2:6-dihydroxy-β-collidine was allowed to crystallise on cooling. A yield of 45g. (64%) was obtained from the

first crop, and in some experiments no further crop was obtained on concentrating the mother liquors. Although the free base is alleged to crystallise from hydrobromic acid of most concentrations, it was necessary to adjust the solution with alkali to the iso-electric region of the substance, whereby the yield was increased by a further 20%. The crude material had m.p. 173-174° (Ruzicka and Fornasir claim a theoretical yield, m.p. 175°).

2:6-Dichloro-β-collidine. (A) 2:6-Dihydroxy-β-collidine (10g.) was refluxed with phosphorus oxychloride (20g.). The maximum temperature observed was 170°. After 6 hours a little hydrogen chloride was still being evolved, but the reaction was stopped and the solution was poured on to ice (100g.). On extracting with ether, no substance corresponding to dichloro-β-collidine was obtained. There was no sign of 'insoluble black crystals', and the light-coloured, insoluble fraction was found to be slightly impure dihydroxy-β-collidine, the bulk of which was recovered.

(B) Introducing the modification of Todd, Topham et alii (105, 32), as used in the preparation of chloropyrimidines, 2:6-dihydroxy-β-collidine (10g.) was dissolved in phosphorus oxychloride (40ccs.) and dimethylaniline (10g.) was added. The mixture was refluxed for three hours, by which time only traces of hydrogen chloride were being evolved. Most of the phosphorus oxychloride was distilled away in vacuo and the residue was poured on to ice (100g.)

as before. On basifying, no substance was extracted by petroleum ether (b.p. 60-80°), nor by ether. The insoluble material was a strange blue powder, insoluble in all common reagents, and it was not investigated further. About 50% of unchanged starting material was recovered from the residue.

(C) Following the method of Levelt and Wibaut (106) which gave low yields (34%) of dichloroisonicotinic acid from the corresponding dihydroxy compound, 2:6-dihydroxy-β-collidine (10g.) and phosphorus oxychloride (25ccs.) were sealed in a Carius tube, heated to a temperature of 200-210° for two hours in a Carius furnace and allowed to cool overnight. The tube was opened carefully (there was some pressure of hydrogen chloride; calculated maximum 15 atmospheres at 210°) and the contents were stirred into crushed ice (100g.). The ice-water was extracted with a generous quantity of ether (3 x 200ccs.), leaving practically no insoluble residue. The ethereal extract was dried over anhydrous sodium sulphate, the ether was evaporated and the residue was distilled *in vacuo* to yield dichloro-β-collidine (10.6g., 85%), b.p. 145-146°/18mm. (Ruzicka and Fornasir give 140°/18mm.). All the material was reacted similarly in 10g. portions, as it was not considered safe to seal larger quantities in one tube.

β-Collidine. No attempt was made to reduce the dichloro-β-

collidine with phosphorus and hydrogen iodide, for which reaction Ruzicka and Fornasir (34) give the yield as 35%.

Dichloro-β-collidine (10.4g.) was dissolved in dry ethanol (120ccs.) and sodium acetate (10g., A.R.) and palladised strontium carbonate (5g., 1% Pd) were added. The mixture was hydrogenated at atmospheric pressure and after three hours the theoretical volume of hydrogen (2700ccs.) had been absorbed. The catalyst, together with remaining sodium acetate and chloride, was filtered off ('Filtercel') and the ethanol was evaporated largely. Water (100ccs.) was added and the product was extracted thoroughly with ether (5 x 100ccs.). The ethereal extract was dried over solid potassium hydroxide and the ether was evaporated, to leave an apparently quantitative residue of β-collidine. The base must retain ether very tenaciously, however, as the residue distilled to yield pure β-collidine (5.65g., 84%), b.p. 76°/12mm.

Crotonyl chloride. The following method is essentially that of Staudinger et alii (71), an improvement on Henry's method (69). Crotonic acid (100g.), carefully dried, was added to petroleum ether (b.p. 40-60°, redistilled over that range). Thionyl chloride (180ccs., freshly redistilled) was added and the mixture was refluxed for 5 hours, protected against the ingress of moisture by drying tubes. At

the end of this time the mixture was fractionated through an 8" point column, the fraction boiling over the range 118-134° being collected separately (84.7g.). Refractionation of that fraction yielded practically pure crotonyl chloride (82.5g., 66%) as a colourless, pungent-smelling, fuming liquid, b.p. 121-124°/760mm.

5-Crotonyl-4-ethylveratrole [3:4-dimethoxy-6-ethylphenyl propenyl ketone]. (A) By analogy with the preparation of p-crotonylanisole by Auwers (68), 4-ethylveratrole (20g.) was dissolved in carbon disulphide (60ccs.) and powdered, anhydrous aluminium chloride (18g.) was added. The mixture was stirred mechanically and crotonyl chloride (10.5g.) was added in small portions over the course of 30 minutes. Stirring was continued for a further four hours with refluxing on the water bath, the carbon disulphide was distilled away and the dark red residual mass was broken down into ice (300g.) and concentrated hydrochloric acid (50ccs.). The products were extracted into benzene (3 x 100ccs.) and the combined extracts were washed with dilute sodium hydroxide solution (2 x 20ccs., 8%). The phenolic material in the alkaline solution was remethylated by warming and shaking with dimethyl sulphate (2 x 5ccs.), a little alkali being added to keep the solution alkaline. The alkaline solution was extracted with benzene (2 x 30ccs.) which was added to the main benzene extract and the total was dried over anhydrous sodium sulphate. The benzene was evaporated

and the residue was fractionated through a short point column in vacuo to yield unchanged 4-ethylveratrole (11.6g.) and 5-crotonyl-4-ethylveratrole (8.0g., 28% or 67% on unrecovered 4-ethylveratrole), b.p. 138-140°/1mm.

(B) Modifying the method as in the case of 5-aceto-4-ethylveratrole (72, 1), 4-ethylveratrole (20g.) was dissolved in dry benzene (60ccs.) and anhydrous aluminium chloride (18g.) was added. The flask was fitted with a fast, efficient stirring mechanism, and a solution of crotonyl chloride (10.5g.) in dry benzene (20ccs.) was added dropwise over the course of one hour. Stirring was continued for a further four hours while the mixture was refluxed on the water bath. The mixture was cooled and decomposed by pouring on to a mixture of ice (300g.) and concentrated hydrochloric acid (50ccs.). The benzene layer was separated and the acid layer was extracted twice more with benzene. The phenols were extracted from the benzene solution and remethylated as before. After drying and evaporating the benzene the residue was fractionated as before to yield unchanged 4-ethylveratrole (4.3g.) and 5-crotonyl-4-ethylveratrole (14.7g., 52% or 67% on unrecovered 4-ethylveratrole as before), b.p. 152-155°/3mm.

α-Cyanobutyric ester. (A) As recommended by Hessler (74), cyanoacetic ester (100g.) was dissolved in magnesium-dried ethanol (500ccs.) and treated with an ethanolic solution of sodium metal (20.3g.). Ethyl iodide (176g.) was added,

whereupon the temperature rose to 45°. After standing for 30 minutes the reaction of the mixture was neutral to litmus. The excess ethanol and ethyl iodide were distilled away and water (300ccs.) was added in which the precipitated sodium iodide dissolved. The product was extracted with ether (3 x 200ccs.), which was dried over anhydrous sodium sulphate and evaporated. The residue was distilled to yield α-cyanobutyric ester (111.4g., 89%; Hessler only claims 74%), b.p. 100-102°/17mm. There was no appreciable fraction representing diethylcyanoacetic ester. The product has the same boiling point and refractive index as the starting material (nearly), but its purity may be demonstrated by density or saponification equivalent:

α-Cyanobutyric ester:-	Cyanoacetic ester:-
B.p. 208°/760mm.	B.p. 207°/760mm.
n_D^{20} 1.4190	$n_D^{20.5}$ 1.4179
$d_4^{22.3}$ 0.985	d_4^{20} 1.063
Sap. eq. 141.	Sap. eq. 113.

(B) The same substance was made in 70% yield by the method of Nishikawa (75) from α-bromobutyric ester and potassium cyanide. The product was identical in all respects with that obtained by method (A) above.

4-Carbethoxy-4-cyano-1-(3:4-dimethoxy-6-ethylphenyl)-3-methylhexan-1-one. (A) Following the method of Henecka (77) for Michael condensations, 5-crotonyl-4-ethylveratrole

(5g.) and α-cyanobutyric ester (3.1g.) in ether (3ccs.) were treated with a solution of sodium ethoxide in ethanol (0.2ccs., 2 gram-atoms Na per litre). There was no noticeable rise in temperature and after standing overnight more ether (20ccs.) was added. The ether solution was washed with acetic acid (5ccs., 10%), sodium bicarbonate solution and water, dried over anhydrous sodium sulphate and evaporated. The residue on fractionating yielded only unchanged cyanobutyric ester and 5-crotonyl-4-ethylveratrole virtually quantitatively.

(B) 5-Crotonyl-4-ethylveratrole (4.2g.) and α-cyanobutyric ester (2.6g.) in ether (3ccs.) were treated with a little sodium ethoxide solution (5 drops), refluxed for two hours and allowed to stand overnight. The products were isolated as in (A) above, and fractionated as follows: (1) to 120°/1mm., which was recovered cyanobutyric ester; (2) to 160°/0.6mm., which was recovered unsaturated ketone; (3) to 200°/0.6mm., which was small in bulk and was discarded; (4) 216-220°/0.3mm. Fraction (4) was redistilled to yield 4-carbethoxy-4-cyano-1-(3:4-dimethoxy-6-ethylphenyl)-3-methylhexan-1-one (2.93g., 44%) as a thick oil, b.p. 192°/0.03mm. (Found: C 66.8, H 7.61, N 3.98; $C_{21}H_{29}O_5N$ requires: C 67.2, H 7.74, N 3.74).

In other preparations longer reflux periods (up to 6 hours) were used for the condensation, but the yield was not improved.

6-(3:4-Dimethoxy-6-ethylphenyl)-3-carbethoxy-3-ethyl-4-methylpiperidine (alleged). 4-Carbethoxy-4-cyano-1-(3:4-dimethoxy-6-ethylphenyl)-3-methylhexan-1-one (9.3g.) was dissolved in dry ethanol (300ccs.), a small quantity (ca. 2g.) of Raney nickel catalyst was added and the mixture was hydrogenated at 100° and 50 atmospheres pressure for 90 minutes. After cooling, the catalyst was filtered off ('Filtercel') and the ethanol was evaporated under a slight vacuum. The residue was triturated with water (100ccs.) and concentrated hydrochloric acid (30ccs.) and the insoluble neutral material was extracted with ether (2 x 100ccs.). The acid solution was basified with concentrated sodium hydroxide solution (40%) and the liberated base was extracted with ether (3 x 100ccs.), which was dried over potassium hydroxide pellets and evaporated. The residue was distilled to yield the piperidine base (5.3g., 59%) as a pale, viscous oil, b.p. 194-197°/0.2mm. or 169-171°/5 x 10^{-3}mm. The base was redistilled in a short path distillation apparatus, b.p. 180° (bath)/10^{-3}mm. (Found: C 70.5, H 9.85, N 4.60; $C_{21}H_{33}O_4N$ requires: C 69.4, H 9.15, N 3.85).

The picrate of the base was formed in warm ethanol, and although it was probably a mixture of stereoisomers, it crystallised well, m.p. 173-174°, raised to 174-175.5° by two recrystallisations from ethanol (Found: C 54.4, H 5.80, N 10.3; $C_{21}H_{33}O_4N,C_6H_3O_7N$ requires: C 54.7, H 6.12, N 9.5).

In addition to the piperidine a small quantity of high

boiling ether-insoluble base was obtained which was not investigated further.

Attempted dehydrogenation of alleged 6-(3:4-dimethoxy-6-ethylphenyl)-3-carbethoxy-3-ethyl-4-methylpiperidine. The piperidine base (0.5g.) was intimately mixed with palladised charcoal (1g., 10% Pd). A slow stream of carbon dioxide was passed through the flask and the issuing gases were collected over potassium hydroxide solution (50%). The mixture was heated to 270° for 30 minutes, raised to 300° for a further period and eventually to 330°. There were some signs of decomposition, but less than 1cc. of hydrogen was evolved.

Saponification of alleged piperidine base. The base was extremely resistant to hydrolysis. Quantitative saponifications gave the following results:-

	% saponified
Potassium hydroxide in methanol, 45 min. reflux . . .	9%
Potassium hydroxide in diethylene glycol, 45 min. at 130° . . .	23%
Potassium hydroxide in diethylene glycol, 4 hours at 150° . . .	64%

The piperidine base was refluxed for 6 hours with a weighed excess of barium hydroxide solution. The calculated quantity of sulphuric acid was added to precipitate the barium and, after boiling to coagulate the precipitate, the barium sulphate was filtered off and washed with a little

boiling water. The filtrate and washings were evaporated to dryness to give (presumably) 6-(3:4-dimethoxy-6-ethylphenyl)-3-carboxy-3-ethyl-4-methylpiperidine in low yield. The acid was not purified further, but was used directly for dehydrogenation.

Dehydrogenation of alleged 6-(3:4-dimethoxy-6-ethylphenyl)-3-carboxy-3-ethyl-4-methylpiperidine. The crude amino-acid (0.118g.) was intimately mixed with palladised charcoal (0.5g., 10% Pd) and dehydrogenated as before in a stream of carbon dioxide. No reaction was apparent at 250°, but on gradually raising the temperature from 270° to 300°, a gas (31ccs., required for 3 moles, 26ccs.) shown to be hydrogen was evolved. Some more vigorous decomposition was also evident. The total contents of the reaction vessel were extracted with several small lots of boiling ethanol, which was evaporated to dryness to yield a total of 0.083g. of residue. The strong and weak bases and neutral material were separated by the method of Battersby and Openshaw (4) using M/50 citric acid. The weakly basic fraction (0.032g.) was distilled in a short path sublimation apparatus, b.p. ca. 150°(bath)/10^{-5} mm. The distillate was dissolved in a few drops of methanol and methanolic picric acid (0.024g.) was added. The resulting gummy picrate would not crystallise in any common solvent, and was obviously far from homogeneous.

3:4-Dimethoxycinnamic acid. The method is based on that employed by Rajagopalan (89) for the synthesis of furylacrylic acid. A large number of variations were investigated and the following was the optimum found, especially for the 100g. scale.

Veratraldehyde (86g.), made by methylating vanillin (26), and malonic acid (54g.) were mixed in a 1-litre methylating flask and melted on the water bath. Some small pieces of porous plate (a very necessary addition) were added and a mixture of pyridine (25ccs.) and piperidine (15ccs.) was run in slowly. There was immediate foaming with the evolution of carbon dioxide. Heating was continued for about two hours when the evolution of gas had practically ceased. If the heating is intermittent for any reason, the mass solidifies and cannot be remelted on the water bath. The melt was cooled with vigorous stirring to prevent the formation of a solid block and dissolved in sufficient dilute (8%) sodium hydroxide. After filtering from any insoluble material and sludge (normally negligible) the product was precipitated by the slow addition of concentrated hydrochloric acid in slight excess (Congo red). The voluminous white acid precipitate was filtered off on a suction filter, washed with a little water containing a trace of hydrochloric acid and pressed as dry as possible. After drying in the steam oven there remained 3:4-dimethoxycinnamic acid (98g., 91%), m.p. 177°. Recrystallisation

from water raised the m.p. to 180° with slight loss, but the acid was sufficiently pure for the following stage if redissolved in dilute (8%) sodium hydroxide, filtered and reprecipitated with hydrochloric acid.

β-(3:4-Dimethoxyphenyl)propionic acid. The substituted cinnamic acid could probably be hydrogenated under a variety of conditions, but the following was found to be the most convenient. 3:4-Dimethoxycinnamic acid (24g.) was dissolved in the minimum volume of sodium carbonate solution (A.R.) and colloidal palladium catalyst (25ccs.)(see p.55) was added. Adam's platinum catalyst was not very effective in aqueous solution. The mixture was hydrogenated in a Parr hydrogenator at room temperature and 40 lb. per sq. in. initial pressure until the theoretical volume of hydrogen had been absorbed (ca. 3 hours). The catalyst was filtered off as well as possible ('Filtercel') and the solution was gradually acidified by the addition of concentrated hydrochloric acid. The dihydro acid was slightly soluble in water, but practically insoluble in a slight excess of hydrochloric acid. The β-(3:4-dimethoxyphenyl)propionic acid was filtered off, washed with a very small volume of acidified water and dried in a vacuum desiccator over concentrated sulphuric acid or, alternatively, in a cool (60°) oven. The crude yield was 21.8g. (90%), m.p. 97°. The acid could be recrystallised from water, but the m.p. was not altered and the crude material was sufficiently

pure for the following stage.

Dihydrocinnamemide. As a model for the dimethoxy acid, dihydrocinnamic acid (2.28g.) and urea (0.92g.) were intimately mixed in a small round-bottom flask fitted with an air condenser. An oil bath was heated to 150° and the flask was plunged into it. The temperature was gradually raised to 200-210° over the course of four hours. After cooling, the crystalline mass was broken up and recrystallised from water to yield dihydrocinnamamide (1.58g., 70%), m.p. 102° [King (107) gives 101.5°; other values vary from 97°].

β-(3:4-Dimethoxyphenyl)propionamide. Using the general method of Cherbuliez and Landolt (91) for the 'acidolysis of urea', the following is a typical preparation near the optimum conditions. β-(3:4-Dimethoxyphenyl)propionic acid (74g.) was intimately mixed with urea (21g.) in a 1-litre round-bottom flask fitted with a wide air condenser. A large oil bath was preheated to 160°, and the flask was plunged into the oil. This technique effectively cuts down loss of urea and contamination of the product with cyanuric acid. The temperature was gradually raised to 220° over the course of four hours, by which time ammoniacal vapours had almost ceased to be emitted. Ammonium carbonate forms a heavy sublimate in the condenser, and this was either shaken down into the flask or carefully volatilised with a Bunsen flame. After cooling thoroughly and breaking up,

the ammonium carbonate was washed out of the product with a little cold water and the remainder was recrystallised from a large volume of hot water to yield the amide (57g., 78%), m.p. 119° [Sugasawa and Shigehara (108) give m.p. 118-120°], increased slightly by a very impure second crop. This product was sufficiently pure for the next stage, but a further recrystallisation from either water or benzene raised the m.p. to 121°. A purer product, completely free from cyanuric acid, could be obtained by extracting the solidified melt from the acidolysis with boiling benzene, but very large volumes were required and the process was very wasteful.

Homoveratrylamine. The exact conditions for the Hofmann degradation were taken from Child and Pyman (92) and Buck and Perkin (93). A solution of sodium hypochlorite was prepared by passing the chlorine produced by dropping concentrated hydrochloric acid on to potassium permanganate (17.5g.) into a cold solution of sodium hydroxide (670ccs., 10%). β-(3:4-Dimethoxyphenyl)propionamide (58g.) was dissolved in the hypochlorite solution with slight warming, and gradually heated on the water bath to 70-75°, which temperature was maintained for one hour. A layer of very dark coloured oil had formed. Solid potassium hydroxide (175g.) was added and the solution was heated to 80-85° for 10 minutes and allowed to cool slowly for several hours.

The oil was extracted with benzene (3 x 150ccs.), which was dried over solid potassium hydroxide pellets and evaporated. The residue was distilled to yield homoveratrylamine (22g., 44%) as a nearly colourless oil, b.p. 188°/15mm. This was probably not the optimum yield, as it was subsequently discovered that care is necessary in the preparation of the hypochlorite solution to prevent local heating and the resultant disproportionation. Most yields quoted by the authors are in the region of 70%. The yield could probably be improved by the exclusion of carbon dioxide from the reaction as the amine readily forms a white incrustation of carbamate in air and must be kept in well-stoppered bottles.

2:4-Dimethylquinoline. (A) Following Craig (86), 'alleged acetone anil' [2:2:4- or 2:4:4-trimethyl-1:2-dihydroquinoline](17.3g., redistilled b.p. 126°/10mm.) was heated in an oil bath with coarsely powdered sodamide (1.95g.) to 160°. The temperature was gradually raised to 200-210° over the course of one hour, by which time no ammoniacal vapours were detectable. After cooling, ethanol (100ccs.) and concentrated hydrochloric acid (5ccs.) were added. The insoluble sodium chloride was filtered off and a hot solution of picric acid (23g.) in ethanol was added. The precipitated picrate (1.5g.) was collected after cooling, m.p. 192° [Craig (86) gives 191-193°]. The low yield may have

been due to faulty sodamide (commercial).

(B) The alternative method of Craig (86) was more satisfactory. Sodium (0.25g.) was dissolved in aniline (3.0g.) with the aid of a little bronze powder as a catalyst. 2:4:4-Trimethyl-1:2-dihydroquinoline (17.3g.) was added and the mixture was refluxed for 5 hours. The products were distilled straight from the bronze dust, and the low-boiling fraction (aniline) was discarded. The main fraction, b.p. 140-155°/16mm. was dissolved in hot ethanol and added to a hot solution of picric acid (25g.) in ethanol. The total yield of crystalline picrate was 34.3g. or 89%, m.p. 191° [Craig (86) claims 86%, m.p. 191-193°]. The picrate was shaken mechanically for several hours with sodium hydroxide solution (200ccs., 8%) and ether (300ccs.) in a Winchester bottle. The ether layer was separated from the insoluble sodium picrate sludge, and the ether extraction was repeated twice more, a little sodium hydroxide solution being added each time. The combined ether extracts were shaken with concentrated sodium hydroxide (2 x 30ccs., 30%) to remove picric acid, washed with water and dried over anhydrous sodium sulphate with a few pellets of solid potassium hydroxide. After evaporating the ether, the residue was distilled to yield 2:4-dimethylquinoline as a colourless oil, b.p. 143°/15mm., in substantially quantitative yield.

Attempted oxidation of 2:4-dimethylquinoline. 2:4-Dimethyl-

quinoline (6.7g.) was mixed with a litre of water in a 3-litre 'Pyrex' flask with an air condenser and heated on the water bath. A solution of potassium permanganate (33.7g. in 1 litre of water) was added over the course of 20 hours heating. A further quantity of permanganate (33.7g.) was added solid in small lots. After a further 3 days heating the solution was colourless, and the manganese dioxide was filtered off and washed twice by boiling with water (500ccs.). The combined filtrates were concentrated to about 100ccs. and neutralised with hydrochloric acid exactly. A small quantity of silicic acid was removed by filtration ('Filter-cel'). The filtrate was heated and added to a hot solution of copper acetate (25g.) in water (200ccs.). Only a small quantity of slimy, green insoluble salt was obtained on standing on the water bath for several hours. The copper salt was decomposed with hydrogen sulphide [Mumm and Henecke (87)] but no tetracarboxylic acid could be obtained from the filtrate.

Attempted Willgerodt reaction with 6-ethylacetoveratrone.

6-Ethylacetoveratrone (2.0g.) was mixed with sulphur (0.5g.) and morpholine (1.3g.) and cautiously heated in a flask with a ground-in air condenser in a fume cupboard. After some time frothing ceased and the mixture was heated to reflux for 12 hours. The hot mixture was poured into warm ethanol (20ccs.), but no crystalline morpholide was obtained on long standing (6 months) or evaporation.

Quantities of dark tar indicated extensive decomposition.

Isonicotinyl chloride. Following the method of Meyer and Graf (52), isonicotinic acid (2.0g.) was refluxed with thionyl chloride (20ccs.) for 3 days, moisture being excluded. The excess thionyl chloride was distilled on a water bath at atmospheric pressure and the residue was distilled *in vacuo* to yield isonicotinyl chloride as a pungent, fuming, colourless liquid (0.71g.), b.p. 83-84°/15mm.

Attempted reaction of isonicotinyl chloride with cadmium dimethyl. A Grignard reagent was prepared from magnesium (0.4g.) and methyl iodide (2.2g.) in dry ether (50ccs.). Cadmium chloride (1.29g.), finely powder and dried at 120°, was added portionwise with continuous stirring, followed by dry benzene in small portions. The ether was gradually distilled until it was completely replaced by benzene. Isonicotinyl chloride (0.71g.) in a little dry benzene was added with continuous, vigorous stirring. After a few minutes further heating, the solution was cooled and poured on to ice (100g.). Insoluble matter was filtered off, the benzene was separated and the aqueous layer was extracted with ether. On drying and evaporating the benzene and ether extracts there was virtually no residue of 4-acetyl-pyridine. It may possibly form a complex with cadmium salts, and an orange powder, m.p. 209°, was obtained from the insoluble residues, but it was not investigated further.

Attempted preparation of 5-acetyl-4:6-lutidine through cadmium dimethyl. Ethyl 4:6-dimethylnicotinate (4.0g.) was hydrolysed by refluxing for 4 hours in a solution of potassium hydroxide (5.0g.) in methanol (25ccs.). The solution was neutralised with hydrochloric acid and evaporated to dryness. The residue was triturated with dry ethanol several times and filtered from the insoluble potassium chloride. The ethanolic solution was evaporated to dryness and the residue was treated with thionyl chloride (40ccs.) and refluxed for two days. The excess thionyl chloride was distilled away to leave a residue of crude acid chloride which was carefully protected from moisture. A Grignard reagent was made from magnesium (2.0g.) and methyl iodide (11g.) in dry ether, to which mixture anhydrous cadmium chloride (6.1g.) was added portionwise with continuous stirring. The ether solvent was gradually replaced by dry benzene and the crude acid chloride in a little dry benzene was added with stirring. The proportion of cadmium added (3 moles) should be sufficient excess, even if the acid chloride was in the form of the hydrochloride, as was probable. The products were worked up as in the preceding experiment, but no methyl ketone could be detected either by the refined iodoform reaction (47) or Fiegl's o-nitrobenzaldehyde reagent (46).

Bromination of γ-picoline. γ-Picoline (10g.) was dissolved in carbon tetrachloride (10ccs.) and N-bromsuccinimide

(10g.) was added cautiously. After 30 minutes at room temperature there was no sign of reaction and the suspension was refluxed on the water bath. After a further 30 minutes there was a sudden violent reaction and a mass of black, tarry polymer was formed. The mass was extracted as far as possible with more carbon tetrachloride, and the combined extracts were shaken with hydrobromic acid (2 x 30ccs., 10%). The hydrobromic acid was evaporated, dry ethanol was added and the evaporation was repeated several times. The final ethanol extract was treated with ether dropwise, when cream coloured crystals (2.12g.), m.p. 85-90° were deposited. After thorough drying in a vacuum desiccator over concentrated sulphuric acid the m.p. rose to 120-122°, with residual crystals melting at 140°. Neimann, Lewis and Hays (109) give 4-bromomethylpyridine hydrobromide, m.p. 145-150°. Continued recrystallisation showed that the crystals consisted largely of ammonium bromide containing a little of the desired product.

Bromination of β-picoline. (A) β-Picoline was carefully redistilled, b.p. 143-144°/770mm., from potassium hydroxide pellets. Using the same quantities as in the previous experiment, the mixture was heated carefully. After a time the reaction became more and more vigorous and was eventually uncontrollable even by drastic cooling. Again the principal product was only ammonium bromide.

The preparation was repeated using more carbon tetrachloride (40ccs.) and shaking continuously at room temperature. The course of the reaction was followed by removing an aliquot portion (1cc.) at intervals, acidifying with a few drops of hydrochloric acid in water, adding a crystal of potassium iodide and titrating with thorough shaking with standard sodium thiosulphate solution (N/10). After 24 hours 75% of the N-bromsuccinimide had become unavailable. The carbon tetrachloride solution was filtered and extracted with hydrobromic acid (2 x 20ccs., 10%) which was made just alkaline with sodium hydroxide solution and extracted with ether (3 x 30ccs.). The ether was dried and evaporated and the residual, mobile oil transformed to the picrate (13.5g.), m.p. 140-146°. One recrystallisation from aqueous ethanol raised the m.p. to 146-148°, undepressed on admixture with authentic β-picoline picrate, m.p. 149-150°.

(B) Modifying the method of Dehnel (66), β-picoline (12g.), concentrated hydrobromic acid (15ccs., 48%) and bromine (42g.) were sealed in a Carius tube and heated in a bomb furnace for 10 hours at 150-160°. There was considerable pressure of hydrogen bromide when the tube was opened. The contents were poured into water (300ccs.) with stirring and sulphur dioxide gas was passed in until the liquid was a light amber colour. The clear liquor was decanted from

the oily precipitate (1.- 2g.), rendered alkaline by the addition of sodium carbonate solution (500ccs., 10%) and extracted with ether (200, 100, 100ccs.). The total ether extract was washed with a little dilute acetic acid and with sodium carbonate solution and dried over anhydrous sodium sulphate. After filtering, picric acid (20g.) in ethanol was added slowly with good stirring to form a voluminous precipitate of picrate (26g.), m.p. 105-108°. Recrystallisation from ethanol did not raise the m.p. Recrystallisation (3 times) from large volumes of benzene raised the m.p. to 112-114° [Dehnel (66) gives m.p. 114°], substantial quantities of insoluble oil being discarded each time and reducing the yield to 11g. The picrate was suspended in hydrobromic acid (150ccs., 10%) and the picric acid was extracted with redistilled nitrobenzene (5 x 50ccs.), followed by ether (50ccs.). The hydrobromic acid was evaporated *in vacuo*, the residue was taken up in ethanol and ether was added dropwise. The precipitated hydrobromide was only partly crystalline, and further recrystallisation from ethanol produced β-bromomethylpyridine hydrobromide (1.2g.), m.p. 143-144° (softening at 138°), sufficiently pure for the next stage.

Ethylbenzene from benzyl bromide. A Grignard reagent was prepared from magnesium (8.6g.), methyl iodide (49.5g.) and dry ether (200ccs.). Benzyl bromide (18g.) was dissolved

in dry ether (50ccs.) and added slowly to the Grignard reagent with continuous stirring. The mixture was refluxed and stirred for 6 hours, when a solution of ammonium chloride was added (200ccs., 2N) followed by a little ammonia (unnecessary here, but required for analogy with the pyridine series). The ether layer was separated and the aqueous layer was extracted twice more with ether (150ccs. total). The combined ether extracts were dried over anhydrous sodium sulphate and the ether was evaporated. The residue was distilled through an 8" point column to yield (1) methanol (3.0g.) from excess Grignard reagent, (2) a fraction, b.p. 110-140° (5.15g.) which was mostly ethylbenzene (n_D^{20} 1.5102; ethylbenzene n_D^{20} 1.4960; benzyl bromide n_D^{20} 1.5760) but contained a little benzyl bromide and (3) the residue in the flask which was dissolved in ethanol, treated with charcoal and filtered. On standing, soft crystals of dibenzyl (3.5g.), m.p. 53°, were deposited, undepressed on admixture with authentic dibenzyl, m.p. 53°, made by the reduction of benzoin.

Reaction of methylmagnesium iodide and 3-bromomethylpyridine hydrobromide. A Grignard reagent made from magnesium (0.42g.) and methyl iodide (2.25g.) in dry ether (50ccs.) was transferred to a dry dropping funnel by pressure of dry nitrogen. 3-Bromomethylpyridine hydrobromide (1.0g.) was finely powdered and suspended in dry ether (100ccs.) vigorously

stirred at room temperature and protected from moisture. The Grignard solution was added dropwise over 30 minutes and after a slight induction period the ether refluxed briskly as hydrogen bromide decomposed the reagent. After the addition was complete the mixture was refluxed for a further 4 hours, cooled and decomposed with a solution of ammonium chloride (50ccs., 0.5N) and basified with ammonia solution. The bases were extracted with ether (3 x 50ccs.), washed with water, dried over anhydrous sodium sulphate and the ether was evaporated. The residue was taken up in warm ethanol and added to hot ethanolic picric acid (2.0g.). There was an immediate oily precipitate of picrate which refused to crystallise from any of the common solvents. The bases were recovered from the picrate by the usual method using lithium hydroxide, and distilled at a bath temperature of 300°, the pressure being gradually lowered to 20mm. Only two drops of distillate were obtained, the large residue in the flask being a refractory tar. A picrate was formed in the usual way from the distillate, m.p. 244° (decomp.) which was probably the dipicrate of 1:2-di-3'-pyridylethane. No picrate corresponding to that of 3-ethylpyridine, m.p. 127° could be obtained.

Action of Grignard reagents on 8-collidine. 5-Bromo-4-ethylveratrole (p.87)(6.0g.) and ethyl bromide (2.7g.)

were dissolved in dry ether (40ccs.) and added to magnesium (1.47g., 25% excess) stirring on a water bath. After 3 hours the mixture was transferred to a dry Carius tube by decantation, β-collidine (5.1g.) was added, and the tube was cooled in liquid air and sealed. After allowing time for the tube to regain room temperature, it was heated to 150-160° in a Carius furnace for two hours (calculated maximum pressure 21 atmospheres). After cooling, the tube was opened and the contents were poured into a solution of ammonium chloride (50ccs., 2N) and neutralised with ammonia. The ether layer was separated and the aqueous layer was extracted twice more with ether. The total ether extracts were dried over potassium hydroxide pellets and evaporated. The residue was distilled at 18mm. to yield β-collidine (3.6g.), b.p. 86-87°/18mm., compared with an authentic specimen through the picrate, m.p. and mixed m.p. 149-150°. The residue in the distillation flask was not easily distilled, and was dissolved in methanol and filtered. On cooling, waxy crystals of no definite m.p. were deposited in low yield. From these a picrate was made in the usual way, which after several recrystallisations from ethanol and acetone had m.p. 215-216° (Found: C 59.8, H 4.84, N 9.6). The analysis does not correspond to that required for either the picrate of 2:5-diethyl-4-methylpyridine ($C_{10}H_{15}N,C_6H_3O_7N_3$ requires C 50.8, H 4.80, N 14.8) or the picrate of

6-(3:4-dimethoxy-6-ethylphenyl)-3-ethyl-4-methylpyridine ($C_{18}H_{23}O_2N$,$C_6H_3O_7N_3$ requires C 56.0, H 5.09, N 10.9).

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