SOME INTERMEDIATES FOR THE SYNTHESIS OF β-(3-METHOXY-4-HYDROXY-PHENYL)-β - HYDROXY-ETHYLAMINE.

Part II

A Thesis submitted by

RICHARD WILLOUGHBY ALEC ATTREE

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Head of the Dept. of Chemistry.

ABSTRACT

The synthesis of β-(3-methoxy-4-hydroxy phenyl-)-β-hydroxy ethylamine was attempted, as the initial step in the investigation of its pharmacological properties. Attempted reduction of 3-methoxy-4-hydroxy-ω-nitrostyrene gave no isolated products. Bromination of the side chain of the nitrostyrene, followed by treatment with potassium acetate and potassium hydroxide in methanol gave an amorphous material and not the expected β-(3-methoxy-4-hydroxy phenyl-)-β,β-dimethoxy-nitroethane.

Vanillin was then converted into benzoyl vanillyl chloride which on treatment with diazomethane, gave the substituted ω-diazoacetophenone which in turn was converted through the ω-chloro derivative to the ω-iodoacetophenone. This was condensed with hexamethylene tetramine. Further work on the problem is under way.

ACKNOWLEDGEMENTS.

I would like to thank Dr. R. H. Clark, under whom the work described in this thesis was carried out, for guidance and criticism throughout. I would also like to thank Dr. R. F. Patterson of the Powell River Co. Ltd., for certain suggestions, and also for supplying a complete survey of the literature of Vanillin; Mr. J. K. Hamilton, my associate in this research, for assistance and discussion; also to Mr. R. F. Robertson and Mr. R. Stewart for suggestions. All these mentioned have been very helpful in criticising the work undertaken, and much benefit has been derived from the many discussions and consultations in which they have taken an active part.

PREFACE.

The description of the research found in this thesis represents only a portion of the entire research carried out in these laboratories on this subject.

The thesis "Some intermediates in the Synthesis of β-(3-methoxy-4-hydroxy-phenyl)-β-hydroxy-ethylamine, Part I" by Mr. J. K. Hamilton, my associate in this research, should also be consulted if a complete picture of the problem is desired.

Some Intermediates for the Synthesis of β-(3-methoxy-4-hydroxy-phenyl)-β - hydroxy Ethylamine.

Part II.

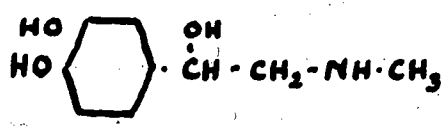
Introduction.

Since adrenaline was first synthesised in 1906, numerous compounds have been synthesised to test their pharmacological properties. Using the mass of data obtained by the various workers in this field, it is possible to corelate the structure of a compound with its sympathomimetic action, and thus predict more or less accurately the most promising lines of research. From a study of the relationship between structure and activity, certain facts appear, which may be summarised in the statement that the more important sympathomimetic agents posses a phenethylamine skeleten, with one or more hydroxyl groups attached to the benzene ring, and usually a hydroxyl group attached to the beta carbon atom in the side chain. It is found that methylation of the phenolic hydroxyl groups lowers both the potency and the toxicity of the drug.

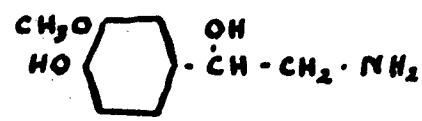
Adrenaline (I) still remains the most important of the existing sympathomimetics, but it is not without toxic effects. It seems reasonable, in view of the known facts as outlined above, to suppose that β-(3-methoxy-4-hydroxy-phenyl)-β - hydroxy ethylamine (II) would possess pharma-

cological properties similar to adrenaline, but would perhaps be less toxic. It was therefore decided to undertake the synthesis of this compound.

Because of certain obligations, as holder of the Powell River Company Limited Scholarship, it was necessary for the author to use vanillin as the starting material in such a synthesis. This would not appear to present great difficulties, as many methods are described in the literature for the conversion of aromatic aldehydes into phenethanolamines. The principal of these will be described below.



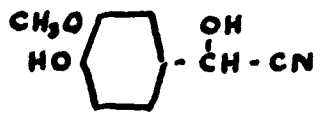
I



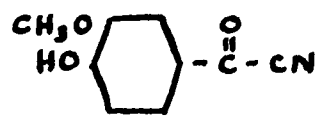
II

The most direct method would appear to be the reduction of the cyanohydrin of the aldehyde (III). This method has been used to produce both phenethylamines (1) and phenethanolamines (2). Another worker, Mr. J. K. Hamilton, is at present investigating this method.

A second method which suggests itself is the reduction of vanillyl cyanide (IV). The cyanide could be prepared from the aldehyde by oxidising the latter to the acid, converting to the chloride, thence to the desired cyanide by the usual method. Mr. Hamilton is also investigating this method.



III



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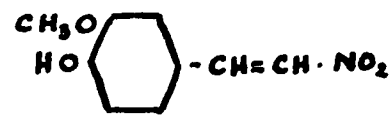


V

A third possible method is via the nitrostyrene (V). This intermediate may be prepared in excellent yield by condensing the aldehyde with nitromethane in the presence of a suitable catalyst. Several methods are available for the conversion of this nitrostyrene to the corresponding phenethanolamine.

Apparently some nitrostyrenes add water to the double bond in the side chain in the presence of suitable hydrating agents, notably acetic acid. The resulting compound may be reduced to the phenethanolamine. (3).

A slightly more complicated method is that of Reichert and Koch (4) following the earlier work of Thiele and Haekel (5). These workers brominated the double bond of the nitrostyrene, then split off hydrogen bromide to yield the ω-bromo-ω-nitrostyrene (VI) which was then treated with alcoholic potassium hydroxide to give an acetal (VII). This intermediate could be hydrolysed to the ω-nitro-acetophenone which could be reduced to the desired phenethanolamine. The synthesis is represented diagramatically below. A slight modification of this synthesis was used by Neber, Burgard and Thier (7).

R = substituted phenyl group.

$$R\cdot CH=CH\cdot NO_2 \xrightarrow{Br_2} R\cdot CHBr\cdot CHBr\cdot NO_2$$

$$\xrightarrow{KOAc} R\cdot CH=CBr\cdot NO_2 \xrightarrow[CH_3OH]{KOH} R\cdot \underset{\underset{OCH_3}{|}}{\overset{\overset{OCH_3}{|}}{C}}-CH_2\cdot NO_2 \xrightarrow{H^+}$$

VI VII

$$R\cdot \overset{O}{\overset{\|}{C}}\cdot CH_2\cdot NO_2 \xrightarrow{[H]} R\cdot CHOH\cdot CH_2\cdot NH_2$$

Two methods have been described for conversion of ω-nitro-styrenes into N-methyl phenethanolamines (8, 9).

The corresponding acetophenone or its derivatives can be used as intermediates in a number of different syntheses of phenethanolamines. The synthesis of the ω-nitroacetophenone and its subsequent reduction has already been mentioned above.

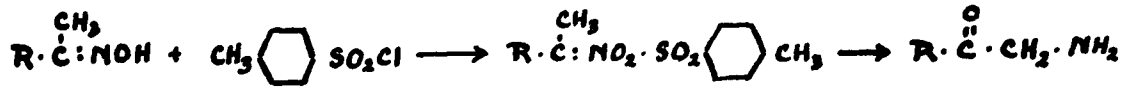
The acetophenone itself, which may be readily obtained from the aldehyde by a modification of Grignard's reaction (10) may be converted to the isonitrosoacetophenone (Viii) by means of isamyl nitrite and sodium ethylate (11), or by the action of sodium nitroprusside. (12). This compound may then be reduced to the phenethanolamine with sodium and ethanol (13).

$$R\cdot \overset{O}{\overset{\|}{C}}\cdot CH=NOH$$

VIII

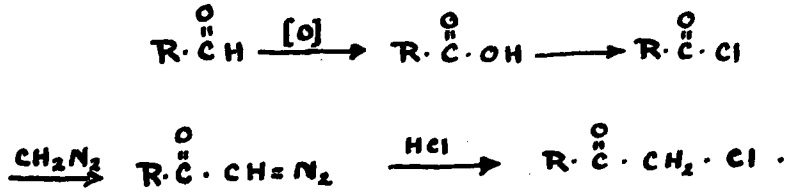
Neber, Burgard and Thier found that p-toluene sulfonyl

chloride reacted with acetopiperone oxime in pyridine to give a compound which could be rearragned to give aminoacetopiperone, which could then be reduced(7).



ω-haloacetophenones may be converted to the corresponding amines by one of three methods: the Gabriel synthesis using potassium phthalimide: by reaction with aqueous ammonia (14), or by condensing with hexamethylene tetramine to give a product which may be hydrolysed to the amine.

The desired haloacetophenone may be obtained in the case of the chloro or bromo compound, by direct halogenation of the acetophenone prepared from the aldehyde as outlined above (15), or from the aldehyde, by means of the following series of reactions.#



Once the chloroacetophenone has been obtained, it may be converted into the bromo or iodo derivative by treatment with sodium, potassium or ammonium bromide or iodide in absolute acetone. (16). The iodoacetophenone can be converted into the nitro derivative by treatment with silver nitrate

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see below for references.

(17), and this may be reduced as described above, but this method does not seem to offer any improvement over those described.

Of the methods outlined in the introduction, four have been chosen for investigation in this synthesis. These are the methods involving the cyanohydrin, the cyanide, the nitrostyrene, and the chloroacetophenone. Of these the first two are being investigated by Mr. Hamilton, and a report of the results will be found elsewhere(18).

A critical discussion of the methods used in the research reported in this thesis with a statement of results obtained, and a comparison of the conditions and methods employed in this laboratory with those reported in the literature will be found in the next chapter.

II.

DISCUSSION OF THE METHODS USED.

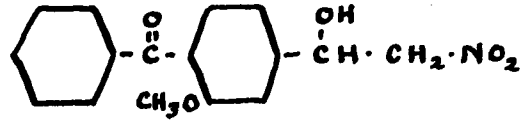
Methods involving the nitrostyrene.

Synthesis of 3-methoxy-4-hydroxy-ω-nitrostyrene offered little difficulty. It was effected by condensation of vanillin with nitromethane. Various catalysts and solvents have been used for this and similar condensations, e.g., sodium hydroxide (19), ammonium acetate in glacial acetic acid (20), potassium hydroxide in alcohol (7, 21) sodium

methylate (23), and methylamine (21, 24). Of these, methylamine appears to give the highest yields (97-100%). It may best be added to the reaction mixture in the form of methylamine hydrochloride. An equivalent amount of sodium carbonate is then added, which liberates the methylamine. It is recommended that the nitromethane be purified by repeated distillation before use, otherwise resinous polymers appear.

Since some workers (25) we of the opinion that para-hydroxy groups interfered with this type of condensation, acetyl vanillin was first used. However, this product gave only the unacetylated ω -nitrostyrene, and only in low yield. Further investigation disclosed than vanillin itself readily undergoes this condensation, and hence the intermediate acetylation was dispensed with.

Rosenmund (26) states that when benzoyl vanillin is condensed with nitromethane, and the reaction mixture acidified with acetic, boric or oxalic acid, the corresponding nitroethanol (IX) is formed.

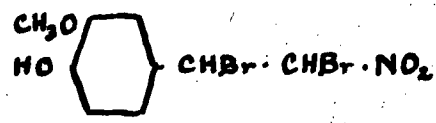


(IX)

A similar reaction was tried using acetyl vanillin, but, as mentioned above, only the nitrostyrene formed.

It was then decided to follow the method of Reichert and Koch (4). As stated no difficulty was encountered in synthesising the nitrostyrene, using commercial vanillin, triply distilled nitromethane, methylamine hydrochloride and sodium carbonate in absolute ethanol. The yields are almost quantitative, and the product could usually be used without further purification. If further purification was desired the product was recrystallised from 98% ethanol.

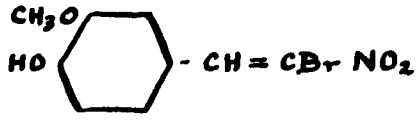
Great difficulty was encountered in the attempted preparation of the dibromo derivative of the nitrostyrene.



The nitrostyrene was found to be only slightly soluble in inert solvents suitable for bromination, such as chloroform or carbon tetrachloride. The method finally used was to dissolve a small portion of the nitro-styrene to be brominated, in chloroform, which is a better solvent than carbon tetrachloride and a solution of bromine in chloroform was added dropwise until a slight excess was present. More of the nitrostyrene was added and the process repeated until the desired quantity of nitrostyrene had been brominated. After the reaction mixture had stood for a short time, the chloroform and any unreacted bromine was removed under reduced pressure, leaving a crystalline and a liquid residue. The yellow crystalline product could be recrystallised from

chloroform to give a pure white compound, unstable in the air and decomposing from 125 - 150° with the evolution of brown fumes. It was assumed for a time that this was the desired dibromo derivative.

The next step in the synthesis was the elimination of hydrogen bromide with potassium acetate in alcohol to give (VI)



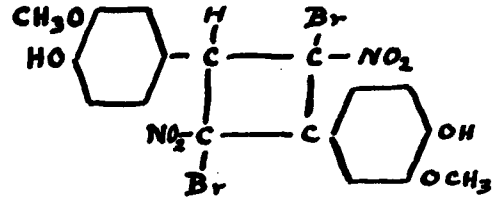
VI

When this procedure was carried out, using the method of Reichert and Koch, a light brown, amorphous precipitate was formed, soluble in dioxane, alcohol and benzene, slightly soluble in water, and insoluble in petroleum ether. It did not melt below 300°, and showed none of the expected properties of the desired compound.

Since all analogous derivatives described in the literature melt in the neighbourhood of 100°, it was assumed that the product formed by this reaction was not the expected ω -bromo-ω -nitrostyrene (VI). No satisfactory explanation of this fact has been found. It is possible that the dibromo derivative was not formed in the initial halogenation, but rather brominated in the ring (see 29). Another possible explanation is that the ω -bromo-ω -nitrostyrene formed initially but polymerised under the influence of the elevated temperature at which reaction was carried out, or

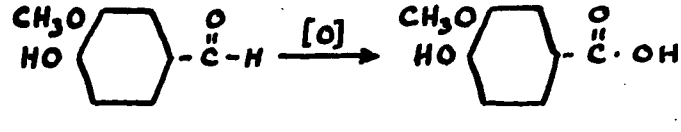
of the basic solution.

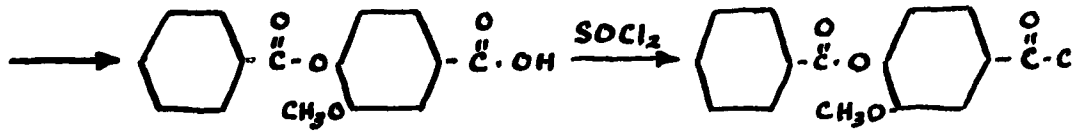
Cyclisation is also a possible explanation.

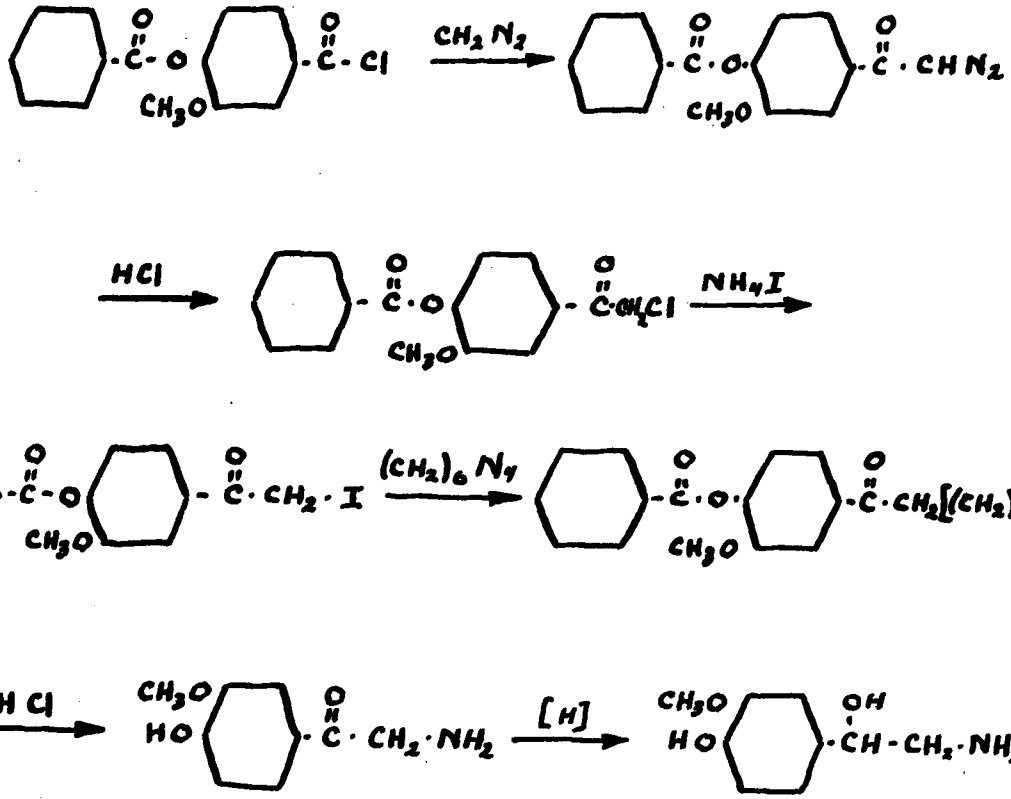


Because of these unsatisfactory results, it was decided to abandon this method of synthesis, and concentrate on the reduction of the nitrostyrene under conditions which would favour addition of water to the double bond. Zinc and acetic acid, with or without the addition of formaldehyde (see 27); and aluminum with acetic acid were tried as reducing agents under a wide variety of conditions. No products of interest were isolated from the reaction mixture, so this method, too, was abandoned.

The next method which came under consideration was that mentioned briefly in the outline under the reactions involving acetophenones. The complete synthesis which was finally arrived at is diagrammed below.







There are several points worthy of notice in connection with this synthesis. Since vanillin possesses a para hydroxyl group, it will not undergo the Canizzaro reaction which is perhaps the most convenient method for obtaining the acid from an aromatic aldehyde.#

#. A number of explanations have been proposed for this apparent anomaly. The one most generally accepted today is as follows: Although vanillin and other aromatic aldehydes with a hydroxyl group either ortho or para to the aldehyde group do not enolise in the usual sense of the word, the

Further, any attempt to use oxidising agents on vanillin either has no effect, forms dehydrovanillin (30a) or else results in the complete destruction of the aromatic nucleus. Low yields of vanillin acid have been obtained by the oxidation of vanillin with peracetic acid (30b), nitrobenzene(6) or ozone (31), but it was not until Pearl proposed the use of silver oxide that the oxidation of vanillin became a

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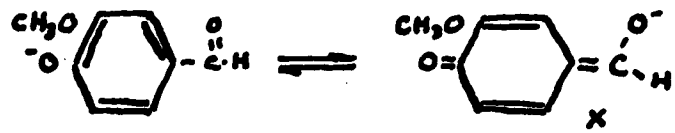
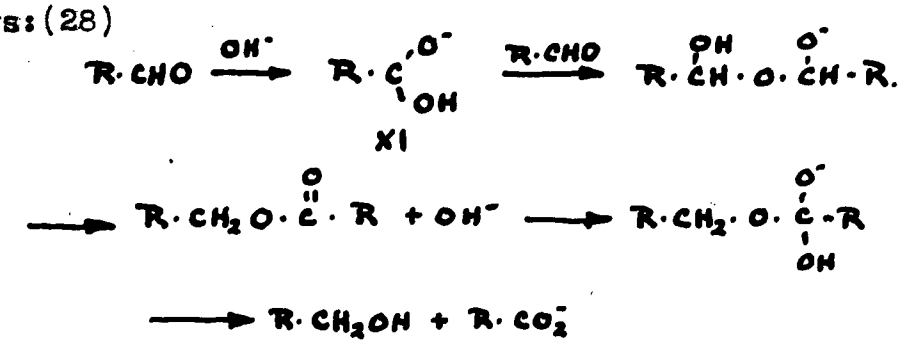
Contd.) anion formed in basic solution is capable of undergoing a mesomeric shift to give structures such as (X)



The mechanism of the Canizzaro reaction is not definitely known, but it seems probable that it takes place as follows:(28)



From this it will be seen that if the aldehyde were present as the mesomer (X) the Canizzaro reaction would be unable to take place, since the postulated intermediate(XI) would not be able to form.

practical method of synthesising vanillic acid. By this method (32a), vanillin is treated with sodium hydroxide and either silver oxide, or silver nitrate. When the reaction mixture is warmed, a modified Canizzaro reaction takes place probably catalysed by traces of metallic silver (32b). The vanillyl alcohol formed is immediately oxidised by the silver oxide to vanillic acid. Hydrogen is evolved, and fluffy silver metal is deposited. The silver is removed by filtration, and the solution is treated with sulfur dioxide. If a mineral acid is used, it is found that considerable 5-nitrovanillic acid is formed.

Vanillic acid may be obtained in two crystalline forms by this method. If the basic solution obtained as above is saturated with sulfur dioxide while it is still hot, the precipitate of vanillic acid which forms is dense, and slightly yellow. The crystals are compact and the whole has a granular appearance. If, however, the alkaline solution is allowed to cool before saturation with the acid, the vanillic acid is precipitated in a flocculent, pure white form, in which the crystals are exceedingly long and felted together. These forms have not been noted previously. Either form may be used for the following procedures without further purification.

Pearl states that the silver metal may be recovered most conveniently by oxidising it to the oxide with potassium permanganate. However, as the second method listed by

Pearl uses silver nitrate rather than silver oxide, the method is of no use. It was found that the silver metal resulting from the oxidation of the vanillin was readily soluble in nitric acid. The impurities, presumably principally 5-nitro vanillic acid, could be removed by filtration and by treating the solution with decolourising charcoal. Usually three treatments with charcoal were sufficient to give a substantially colourless solution of silver nitrate. The water was removed by evaporation in a current of air, and the silver nitrate crystals resulting were used for subsequent syntheses. However, it was found desirable to filter the solution of the silver nitrate before addition to the vanillin solution, to remove traces of silver chloride and 5-nitro vanillic acid. No decrease in yields or purity of product were noted using this recovered silver nitrate.

Because of the great reactivity of the phenolic hydroxyl group, it was decided to protect it either by acetylation or by benzoylation. It was decided to attempt the preparation of the acetyl derivative, but after numerous attempts, including a Schotten-Baumann reaction, and refluxing vanillic acid with acetic anhydride, or acetyl chloride, either with or without pyridine or ether as solvents, only minute yields of the O-acetyl vanillic acid were obtained. That some reaction had taken place was confirmed by examining, under the microscope, portions of the reaction product after

recrystallising. A change of crystal form was noted.

The synthesis of bonzoyl vanillic acid was next attempted. No product would be isolated from a refluxed mixture of ether, benzoyl, chloride, and vanillic acid, although some reaction had taken place, as evidenced by the heat of reaction which was sufficient to boil the ether.# Vanillic acid was recovered unchanged.

However, benzoyl vanillic acid could readily be prepared by the Schotten-Baumann reaction, in about 65-70% yield, which is higher than that reported in the literature(4). It was found, by this worker, that much higher yields could be obtained if a large excess of benzoyl chloride were employed, than if the usual quantities were used. The benzoyl chloride hydrolyses on standing in contact with the solution forming benzoic acid as well as the benzoyl vanillic acid, Since benzoic acid is a stronger acid than benzoyl vanillic acid, the latter is liberated from the salt, and precipitates out of solution. It may be filtered off, and freed from any benzoic acid which may have been precipitated at the same time by boiling with water and filtering while hot. If it is not deemed advisable to add such a large excess of benzoyl chloride, the benzoyl vanillic acid may be precipitated from the reaction mixture with hydrochloric acid.

This may have been due to reaction between the thionyl chloride and the ether.

It is recommended that in this case the acid be added slowly with much stirring, as the benzoyl vanillic acid exhibits a tendency to form an oil, which sinks to the bottom and then suddenly crystallises to form a hard mass, which is very difficult to free from occluded benzoic acid.

The next step in the synthesis is conversion of the benzoyl vanillic acid to the chloride. The two reagents usually used for this type of reaction are phosphorous pentachloride and thionyl chloride . Use of the former has been reported in the literature(33), but these results could not be duplicated in this laboratory (see 18). Fortunately thionyl chloride gave the desired product in nearly quanitative yield. It is desirable to purify the thionyl chloride before use by distilling from linseed oil and quinoline(34). However it was found that the commercial product could be used without detrimental effects if it were not too highly coloured. After refluxing the benzoyl vanillic acid with twice its weight of thionyl chloride until a clear solution resulted, ligroin was added, and the whole refluxed once more until clear. If the resulting solution were too highly coloured, it was refluxed for a few moments with Darco decolourising charcoal, and filtered through scintered glass. Upon cooling in a freezing mixture of dry ice and alcohol, the benzoyl vanillyl chloride precipitated out in small crystals. Small quantities of a

brown oil, of unknown composition, formed the principal impurity, but this could be easily removed by washing the precipitate on the filter with cold ligroin. The product was used without further purification.

The diazo compound, $(C_6H_5COO)(CH_3O)C_6H_3.CO.CHN_2$, which has not been reported previously, was obtained in excellent yield by treating a solution of benzoyl vanillyl chloride in benzene-ether with diazomethane. The latter was prepared by a method suggested by Dr. R. F. Patterson(35), from N-nitrosomethyl urea, which in turn was prepared from methylamine hydrochloride, sodium nitrite, and potassium cyanate (36). If it is desired to isolate the diazo acetophenone, the solution of benzoyl vanillyl chloride must be added dropwise to a cooled solution of excess diazomethane in ether. In this manner formation of the ω-chlor-acetophenone as a side product is reduced to a minimum, since the excess diazo methane, rather than the diazo acetophenone, reacts with the hydrogen chloride produced. The diazo-acetophenone may be obtained by evaporating the solvent in a current of dry air, and may be recrystallised from ligroin. A solution of this material evolves nitrogen on boiling with water, or upon the addition of acid. It takes the form of short, lemon yellow crystals.

The diazo-acetophenone was not usually isolated, but instead dry hydrogen chloride was bubbled through the etherial solution obtained as above. In this case, it is

not necessary to add the benzoyl vanillyl chorlide solution to the diazo methane solution slowly, as the "by-product" resulting from too rapid addition is actually the product desired. The chloracetophenone may be obtained by evaporating the solvent in a current of dry air, and may be recrystallised from aqueous alcohol. (50%). It is a greyish, micro-crystalline material. It has not been reported in the literature.

There are several methods for converting chloroaceteophenones to the amine. The two classical methods, the Gabriel synthesis and treatment with an aqueous solution of ammonia, have both been used.(vide supra). A more modern method, which seems to be suprior to the others, is based on certain observations of Mannich and Hahn(37). These workers discovered that when hal-acetophenone is treated with a chloroform solution of hexamethylene tetramine, a complex addition product of undetermined structure precipitated out of solution. This material proved to be soluble in water, and the halogen present was completely ionised by this aqueous solution, This complex addition compound could be hydrolysed to the corresponding amino acetophenone by allowing it to react with alcoholic hydrochloric acid for several days. Recently Baltzly and Buck (15), have proposed that this hydrolysis be carried out by refluxing the addition product with alcoholic hydrochloric acid, thus increasing the rate of reaction. Inasmuch as

the amino acetophenones are as a general rule, unstable in alkaline solution, and since this method is carried out only in acid or neutral solutions, higher yields of purer products are obtained than with the classical methods.

It has been found (37) that relatively low yields of the addition product are formed if the halogen in the acetophenone is chlorine. Higher yields are reported if it is bromine, while if it is iodine, the yield is almost quantitative. For this reason it would appear advantageous to convert the acloroacetophenone obtained as outlined above into either bromo or the iodo compound.

This may be accomplished by allowing an acetone solution of the chloroacetephenone to react with an absolute acetone solution of sodium, ammonium or potassium bromide or iodid (16). After a few days, the sodium, ammonium, or potassium chloride which is insoluble in absolute acetone, may be filtered off, and the bromo- or iodo-acetophenone may be obtained by evaporation of the solvent. The yields are reported to be almost quantitative.

In this investigation, ammonium iodide was used, because it is far more soluble in acetone than the sodium or potassium salt. A disadvantage, however, is that the ammonium chloride reacts slwoly with the acetone, thus introducing impurities in the final product.

Hexamethylene tetramine was prepared by the usual method of evaporating a mixture of 30% formaldehyde and concentrated ammonium hydroxide. The product so obtained

is practically 100% pure.

The condensation of the iodo acetophenone and the hexamethylene tetramine takes place in chloroform. It is complete in about 48 hours at room temperature. The product may be filtered off, since the addition compound is insoluble in chloroform.

Hydrolysis to the aminoacetophenone should take place as described by Batlzly and Buck (15). The material is refluxed for up to eight hours with alcohol and concentrated hydrochloric acid, and the amine recovered by evaporation of the solvent.

Once the amino acetophenone is obtained, it may be reduced to the desired phenethanolamine. Catalytic hydrogenation is probably the best method, although a number of reducing agents have been used for similar reductions. Zinc and acetic acid, or sodium and acetic acid are those reported most frequently.

EXPERIMENTAL

Part I. Method of Reichert and Koch.

Synthesis of Acetyl Vanillin.

51 g. of acetic anhydride was added dropwise with rapid stirring to a solution of 67 g. of commercial vanillin in 1.N. potassium hydroxide. Depending on conditions, either a thick oil which crystallised almost at once, or fine white crystals were obtained. The product was filtered off from the mother liquors, washed twice with cold water, and recrystallised twice from 50% alcohol. Yield: 65.7 g. or 76% of the theoretical. Melting point 78°.

Attempted synthesis of (3-methoxy-4-acetoxy-phenyl)--hydroxy ethylamine: 6 g. of the acetyl vanillin prepared as above were dissolved in 400 Ml. of absolute ethanol. The solution was cooled to 40° and 2.8 g. of triply distilled nitromethane was added. Sodium ethoxide solution, prepared by adding 1.07 g. of sodium metal to an excess of absolute ethanol, was added dropwise. When reaction had ceased, usually after 24 hours, the solution was diluted with an equal volume of water, and made slightly acid with 3 N. acetic acid, neutralising the excess with sodium bicarbonate solution. Upon standing, a yellow precipitate separated out. This product, when recrystallised twice from 50% ethanol, melted indistinctly in the neighbourhood of 156°. It gave all the reactions of 3-methoxy-4-hydroxy-

ω-nitrostyrene (M.P. 168°)

Synthesis of 3-methoxy-4-hydroxy-ω-nitro styrene

60 g. of commercial vanillin and 30 ml. of triply distilled nitromethane were dissolved in 150 ml. of absolute alcohol, and 2 g. of methylamine hydrochloride and 2 g. of sodium carbonate added. The reaction mixture was allowed to stand at room temperature overnight, after which the product was filtered from the mother liquor, using suction and washed with 0.75N. HCl. After recrystallising twice from 95% alcohol, the product melted sharply at 170-172°. (this value is slightly higher than those previously reported in the literature.) Yield 80-90%.

Attempted synthesis of 2(3'-methoxy-4'-methoxy-phenyl-)-1, 2-dibromo nitroethane. 10 g. of 3-methoxy-4-hydroxy-ω-nitro-styrene, prepared as above, were shaken with 100 ml. of chloroform, and the solvent decanted. 11 g. of bromine in 25 ml. of chloroform was added dropwise to the solution of nitrostyrene in chloroform, adding the remaining nitrostyrene from time to time. At the end of ½ hr., the chloroform and a slight excess of bromine which remained were removed by distillation under vacuum, giving a yellow crystalline mass. This product was recrystallised twice from chloroform, to give pure white crystals, with no melting point, but which decomposed with the evolution of a brown gas at temperatures above 125°. The product turned yellow when exposed to the air for several hours. The product is

very soluble in ether, soluble in petroleum ether-ether, but insoluble in petroleum ether.

Attempted synthesis of 3-methoxy-4-hydroxy-ω-bromo-ω -nitrostyrene, 5 g. of 2-(3'methoxy-4'hydroxy-phenyl)-1, 2, -dibromo-nitroethane were dissolved in 20 ml. of absolute alcohol and heated to boiling. 2 g. of potassium acetate dissolved in absolute alcohol were added to the boiling mixture. The resulting solution was filtered while hot, and the filtrate, after cooling, was diluted with 70 ml. of water. A fine light brown precipitate settled out, which was filtered off. The material appears to be microcrystalline. It is soluble in 50-50 dioxane-petroleum ether, in benzene, in alcohol, but only slightly soluble in water. With alkaline solutions it gives a rose colour. Yield: 3 grams. The compound did not melt below 300°.

In view of the high melting points and chemical reactions of these two compounds, this method of synthesis was abandoned.

Attempted Reduction of 3-methoxy-4-hydroxy ω -nitrostyrene.

The following table summarises the quantities of reagents used, the naute of the solvent, and the conditions employed. The only products isolated and characterised were zinc acetate, aluminum hydroxide, and benzoic acid. In each case a number of fractions of other products were obtained, none of which could be purified or characterised

further, and in general gave the appearance of high molecular weight polymers and byproducts. No material containing an amino group could be isolated, although in several cases the reaction mixture gave a positive test with nitrous acid.

Table showing the

methods of reduction of 3-methoxy-4-hydroxy -ω-nitrostyrene

Wt. of nitro-styrene	Reducing Agent	Solvent	Conditions	Remarks.
2 g.	2 g.Al	100ml 6N.HAC	Heated under reflux ½ hr.	Product sol. in NH_4OH, NaOH, glacial HAc., insol. concHCl
2 g.	excess Zn dust	80 ml. 3N.HCl.	Reflux for ½ hour.	no product isolated.
2 g.	ditto	ditto plus 5ml. 30% formaldehyde	ditto	ditto
2 g.	ditto	40 ml. 6N. acetic acid	ditto	ditto
2 g.	ditto	ditto plus 5 ml. 30% formaldehyde	ditto	ditto
4 g.	ditto	150 ml.alcohol 20 ml. glacial acetic acid & 20 ml. 30% formaldehyde.	Reflux until colourless	Zn. precipitated as far as possible with H_2S. Three fractions isolated each containing zinc. Mother liquor when treated with acetic anhydride gave small quantity red brown oil.
ditto	ditto	ditto	ditto	Evaporated to dryness under vacuum after pptn of Zn. Residue benzoylated using KOH and benzoyl Chloride. Product consisted of a viscous brown oil containing benzoic acid.

Synthesis of Vanillic Acid:(32)

30.4 g. of vanillin were dissolved in 400 ml. of water to which 48 g. of sodium hydroxide had been added. The mixture was heated to 55°, and a solution of 34 g. of silver nitrate in 150 ml. of water was added. Silver oxide immediately precipitated out. The mixture was heated with mechanical stirring until the temperature of the reaction mixture rose rapidly, indicating that the reaction was proceeding. The source of heat was removed, until the maximum temperature was reached, usually about 10-15° higher than the initial temperature. After this point had been reached, the mixture was heated for a further period of five minutes to assist in the coagulation of the silver, which in some cases showed a tendency to pass through the filter. The solution was filtered while hot, and the precipitate of finely divided silver was thoroughly washed with water, the washings being added to the filtrate. The filtrate was usually pale yellow at this point, but was occasionally deep brown. It was found that the more dilute the alkali, the higher the temperature necessary for the reaction, and the deeper the colour of the solution. In general, the lighter coloured solutions gave better yields of purer products, but this was not always the case.

The filtrate from the above treatment was neutralised with sulfur dioxide, prepared from sodium bisulfite and concentrated sulfuric acid. The vanillic acid which precipitated out was separated by filtration, wash and dried.

Yield: 22.4 or 66% of the theoretical. Melting point 211-212°.

Conversion of Silver to Silver Nitrate:

The silver obtained from the synthesis of Vanillic acid was stirred to a pasty mass with a small quantity of water, and concentrated nitric acid was added, with vigourous stirring, until no further reaction took place. Any lumps of silver must be broken up by hand. The mixture was then filtered to remove the precipitate of 5-nitrovanillic acid (?) which formed, and the deep yellow solution was boiled with decolourising charcoal until pale straw colour. The silver nitrate was obtained by evaporating the solution to dryness.

Synthesis of Benzoyl Vanillic Acid: Method 1.

25 g. of vanillic acid were dissolved in 400 ml. of water containing 24 g. of sodium hydroxide, and the solution treated with 32 g. of benzoyl chloride. The reaction mixture was kept in an ice bath, and stirred mechanically for 30 minutes. At the end of this time, the solution was acidified with three portions of hydrochloric acid. The first fraction, which was gray, consisted principally of benzoyl vanillic acid and benzoic acid, and the third, which was pure white, consisted of benzoic acid. The first two fractions were extracted five times with 200 ml. of boiling water, leaving a residue of substantially pure benzoyl vanillic acid. Yield 25.4 g. of 61% of the

theoretical. Melting point, 160-163°.

Method 2. 25 g. of vanillic acid were dissolved in 400 ml. of water containing 24 g. of sodium hydroxide, and the solution treated with 50 ml. of benzoyl chloride. The reaction mixture was cooled in an ice bath and mechanically stirred for ¾ hour. At the endof this time the precipitate of benzoyl vanillic acid was filtered off, and extracted three times with boiling water. Acidification of the filtrate with hydrochloric acid yielded only benzoic acid. Yield of Benzoyl vanillic acid, 28.5 g. or 70% of the theoretical.

Synthesis of benzoyl vanilloyl chloride: 15 g. of benzoyl vanillic acid prepared as above were refluxed with 30 g. of purified thionyl chloride until the acid had gone into solution, and for 15 minutes more. 30 ml. of ligroin were then added, and the mixture refluxed until clear. If necessary, decolourising charcoal was added and after refluxing for a short time, was filtered off from the hot solution through scintered glass. The solution was then cooled in a mixture of solid carbon dioxide and ethanol and the benzoyl vanilloyl chloride fultered from the cold solution, and washed with a little cold ligroin. Yield 15.2 g. or 95% of the theoretical. Melting point 95-97.5°.

Synthesis of N-nitroso methyl urea. (36).

20 g. methylamine hydrochloride and 30 g. of potassium cyanate were dissolved in 120 ml. water, and the solution

heated to 80° for fifteen minutes, then boiled for a short time. The solution was then filtered, cooled to 0°, and a cold solution of 20 g. sodium nitrite in 40 ml. water was added, followed by the dropwise addition with strong cooling of 100 ml. 25% sulfuric acid. After standing a short time, the cream coloured product which separated out was removed by filtration, washed with cold water and stored in an ice box over calcium chloride. The addition of a little acetic acid to the product helps to prevent decomposition. (35).

Synthesis of ω-diazo acetovanillone: Diazo methane was prepared from the N-nitrosomethyl urea by treatment with potassium hydroxide, and was purified by codistillation from the reacting mixture with ether(35). Details of the method used are to be published elsewhere and hence may not be given here.

10.g. of benzoyl vanilloyl chloride in sufficient ether-benzene to effect solution was added dropwise to the ethereal solution of diazo methane prepared from 12 g. of N-nitro methyl urea, with vigorous shaking. A brisk evolution of nitrogen was observed. The reaction mixture was allowed to stand at room temperature overnight, and the solvents evaporated in a current of dry air. Yield: 8.7 g. of crude material, or 85% of the theoretical. Melting point 114-118°.

Synthesis of ω-chloroacetovanillone: The residue of crude ω-diazo acetovanillone obtained as above was dissolved in 200 cc. of ether and dry hydrogen chloride was bubbled through the solution for 1 hr. At the end of that time, the ether was evaporated in a current of dry air, leaving the ω-chloroacetovanillone. This appeared as pale cream coloured granules, melting point 121-123°. Yield: 8.6 g. or practically the theoretical.

Synthesis of ω-iodo acetovanillone: 0.60 g. of ω-chloro-acetovanillone was dissolved in 25 ml. absolute acetone, and 15 ml. of a solution of 2 g. of ammonium iodide in 100 ml. absolute acetone were added, and the mixture filtered immediately through scintered glass. Reaction appeared to be complete after 16 hours. The precipitate of ammonium chloride was filtered off, and the acetone removed by evaporation. The material remaining was not purified, nor were melting points taken. The whole material was reserved for the following procedure.

Condensation of ω-iodoacetovanillone: with hexamethylene tetramine: The material obtained above was dissolved in 10 cc. of chloroform, and 0.2 g. of hexamethylene tetramine in 25 ml. chloroform added. After standing 48 hours a brown precipitate was obtained. Melting point 192-7°. The yield was high.

Condensation of ω-chloro aceto vanillone with hexamethylene tetramine: An experiment similar to the condens-

ation of the ω-iodo derivative was conducted. At the end of three weeks, only a very small portion of a white condensation product had formed.

Work on remaining synthesis is progressing.

Summary of Results Obtained.

It has not been found possible to synthesise the compound β-(3-methoxy-4-hydroxy-phenyl-)-β-hydroxy-ethylamine. However, a number of new compounds have been synthesised as intermediates in unsuccesful attempts at this synthesis. These are listed below with any physical data which is known.

Compound.	Colour	Melting Point	Solubility
(3-methoxy-4-benzoyloxy)-ω-diazoacteophenone	lemon yellow	114-118°	sol. hot 80% alcohol
(3-methoxy-4-benzoyloxy)-ω-chloroacetophenone	pale yellow white	121-128°	v.s.s. in 50-50 ligroin ether inso. ligroin.
(3-methoxy-4-benzoyloxy)-ω-iodoacetophenone	orange	--	Sol. chloroform acetone
(3-methoxy-4-benzoyloxy)-ω-iodoacetophenone addition product with hexamethylene tetramine.	brown	192-7°	Sol. water, ins. chloroform
1-(3'methoxy-4'hydroxy-phenyl-)-1,2-dibromo-2-nitroethane.(#)	white	no m.p. below 300°	

(#) There is doubt as to whether this was the compound actually obtained.

REFERENCES.

1. Rupe and Engel, Helv. Chim. Acta. 18, 1190-1203 (1935).

2. (a) Kindler, Peschke and Brandt, Ber. 68B, 2241-5, (1935).
   (b) D.R.O. 157, 300; 193, 634; and 195, 814.

3. Friedländer, Ann., 229, 217, 225

4. Reichert and Koch, Ber. 68B, 445, (1935).

5. Thiele and Haekel, Ann. 325, 1 (1902).

6. Ciamician and Silber, Ber. 38, 3821 (1905).

7. Neber, Burgard and Thier, Ann. 526, 277-94 (1036).

8. Mannich, Chem. Z. 1909, I, 923.

9. Fosdick et al., J. A. C.S. 68, 840 (1946)

10. Finnemore, J. Chem. Soc. 93, 1517.

11. Claissen and Manasse, Ber. 20, 2194 (1887)

12. Cambi, R. A. L. (5) 22 I, 380.

13. Kolshorn, Ber. 37, 2482 (1904)

14. Gabriel, Ber. 41, 1144 (1908)
    Goedeckemeyer, Ber. 21, 1280 (1888)

15. Baltzly and Buck, J.A.C.S. 62, 164, (1940).

16. Collet, Compt. Rendu. 128, 312.
    Paal and Stern, Ber. 32, 532 (1899)

17. Lucas, Ber. 32, 601 (1899)

18. Hamilton, J.K. Thesis, "Some intermediates for the Synthesis of β-(3-methoxy-4-hydroxy-phenyl-)-β-hydroxy ethylamine. Part I" University of British Columbia, May 1947.

19. Worall, Organic Syntheses, 9, 66 (1929).
    Hahn and Rumpf, Ber. 71B, 2141, (1938)

20. Raiford and Fox, Proc. Iowa Acad. Sci. 40, 111, (1933)
    J. Org. Chem, 9, 170-4, (1944)

21. (a) Koboyoshi and Shozo, Sci.Papers.Inst. Phys. Chem. Research (Tokyo), 6, 149-65(1927).

22. Lange and Hambourger, J.A.C.S. 53, 3865-71, (1931).

23. Rosenmund, Ber. 46, 1034 (1913)

24. Tomita and Watahabe, J.Pharm.Soc. Japan,58, 783 (1938)

25. Rosenmund Ber. 46, 1036, (1913)

26. Rosenmund, D.R.P. 247, 817.

27. Kanao, J. Pharm. Soc. Japan, 49, 238(1929)

28. Adams, Organic Reactions, Vol. II, p. 96

29. Raiford and Fox, J. Org. Chem. 9, 170 (1944)

30. (a) Tiemann, Ber. 18, 3493 (1885).
Elbs and Lerch, J. Prakt. Chem 93, 1-9, (1916)

(b) Dorland and Hibbert, Can. J. Research. 18B, 30 (1940)

32. (a) Pearl, J.A.C.S. 67, 1628(1945), 68, 429,1100 (1946)

33. Heap and Robinson, J. Chem. Soc., 1926, 2336-44

34. Gilman and Blatt, Organic Syntheses, Co. Vol.II p. 570

35. Dr. R. F. Patterson, Private communication.

36. Gatterman-Wielands, Laboratory Methods of Organic Chemistry. MacMillan, p. 271.

37. Mannich and Hahn, Ber. 44, 1542 (1911)

38. Pisovschi, Ber. 43, 2137 (1910).