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THESIS PRESENTED for the DEGREE of DOCTOR of SCIENCE

by

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(Carnegie Research Fellow.)

THESIS.

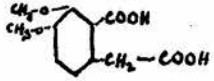

The action of aqueous potash on the products obtained by condensing hippuric acid with substituted benzaldehydes.

Chemistry Department,

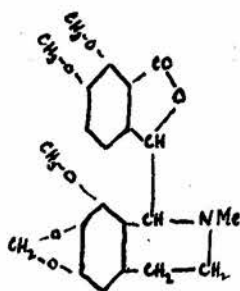
University of Edinburgh.

June 1912.

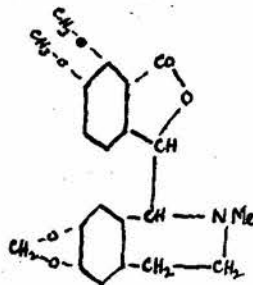


INTRODUCTION :- The following paper is the outcome of an attempt to prepare synthetically 2:carboxy 3: 4: dimethoxyphenylacetic acid . This acid would be of great importance in synthetic work on the alkaloids, because the methoxy-groups are in the relative positions in which they are believed to exist in a number of the alkaloids, and the carboxy- and acetic-groups, being in the ortho-position to each other, would probably give rise to the skeleton grouping  of a certain class of alkaloids; further, the acid is one which could readily be condensed with other substances.

The relation of the above acid to some of the alkaloids is seen, when one examines the generally accepted constitutional formula of two such well known alkaloids as narcotine and hydrastine.



Narcotine.

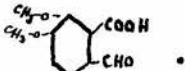


Hydrastine.

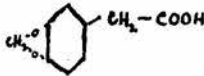
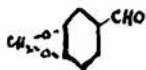
The difficulties to be faced in the synthetic preparation of such an acid as the above, are those of fixing /

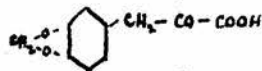
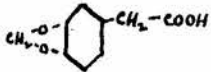
fixing on a substance, whose constitution is sufficiently established, as starting point; of subsequently making the parent substance take part in a series of reactions, which shall leave no doubt as to the constitution of the final product; and lastly, the difficulty of deciding on such reactions as will give sufficient yields of product in the intermediate stages to complete the series of reactions.

In the attempts to synthesise the above acid, a beginning was made with opianic acid, which has the generally accepted constitutional formula 2: carboxy

3: 4: dimethoxybenzaldehyde  .

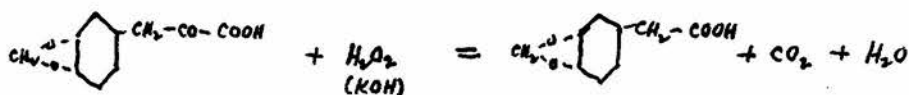
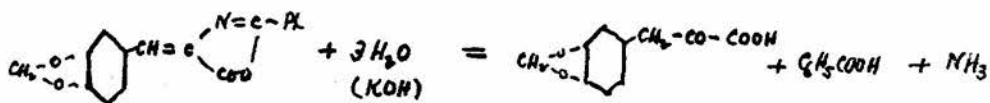
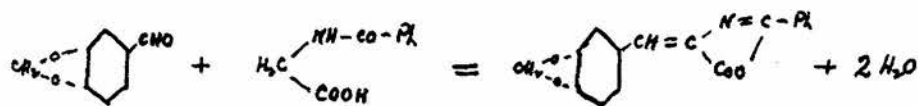
Having fixed on opianic acid as a suitable starting point in the investigation, some method had to be adopted for converting the aldehydic-group-CHO into the acetic-group $-\text{CH}_2 - \text{COOH}$. For such a transformation, the method which was thought would give the most satisfactory results was that of Kropp, Decker and Zoellner, (Ber. 1909, 42. 1184), who prepared the acid 3: 4:

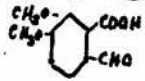
methylenedioxyphenylacetic acid  from 3: 4: methylenedioxybenzaldehyde (piperonal)  .

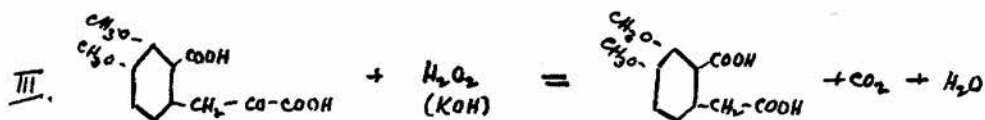
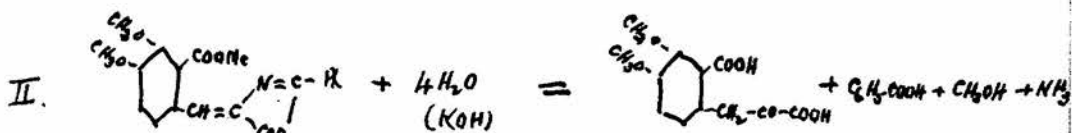
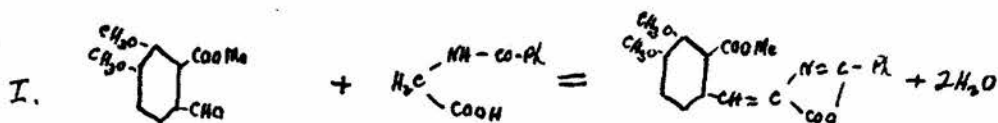
Their method depended on the fact, that the condensation product of piperonal with hippuric acid, when treated with alkali, gave a keto-acid,  which yielded the acetic acid derivative  on oxidation/

oxidation.

The series of reactions are represented thus:-

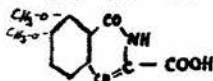


By applying the above method to methylpiperonic ester
M.P. 82°C  it was expected that the acid 2: carboxy 3:4: dimethoxyphenylacetic acid would be obtained thus:-



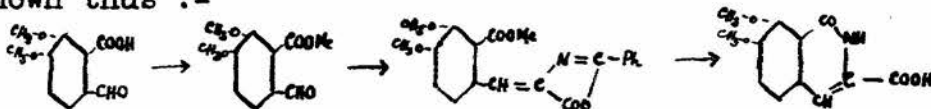
On attempting to carry out the above series of reactions/

reactions with methylopicnic ester, it was found that the reaction II. did not proceed in the manner indicated by the equation. Instead of obtaining the keto-acid above, a substance having the empirical formula $C_{12}H_{11}O_5N$ was obtained, which proved to be 2: 3: dimethoxy-isocarbostyrylcarboxylic acid



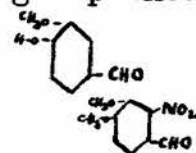
The

preparation of this substance from opianic acid is shown thus :-



This method for preparing 2: 3: dimethoxyisocarbostyrylcarboxylic acid was shown to be a general method for the preparation of isocarbostyryl derivatives, and is treated of fully in Part I. of this paper, which contains an investigation of the isocarbostyryls, and the allied substances, the isocoumarines.

Having found that the presence of the carboxy-group in opianic acid interfered with Kropp's method for preparing the acetic acid derivative, it was proposed to apply this method to the substance having a nitro-group in place of the carboxy-group, in the hope of afterwards being able to convert the nitro-group into a carboxy-group should the above method succeed. From vanillin

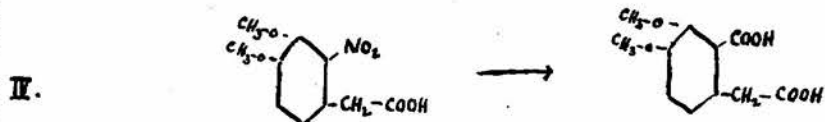
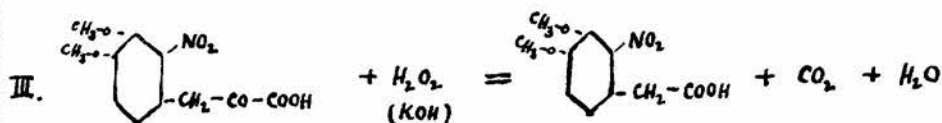
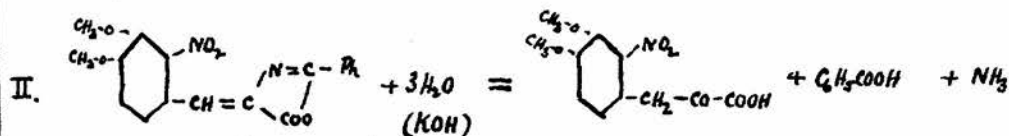
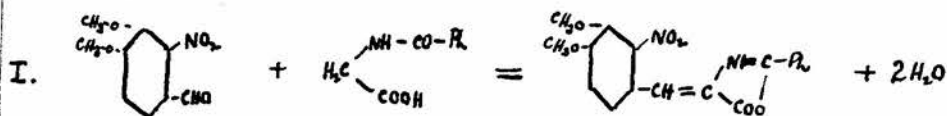


, 2: nitro 3: 4: dimethoxybenzaldehyde

was prepared according to the method of

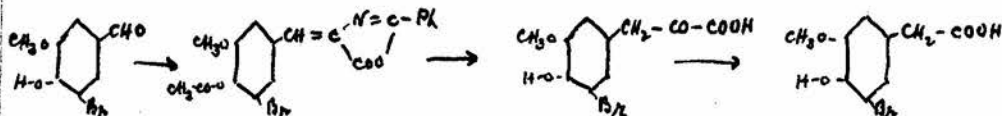
Pschorr /

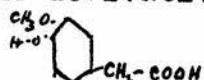
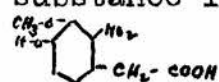
Pschorr and Sumuleanu (Ber. 32, 3405) and it was expected to yield the acid 2: carboxy 3: 4: dimethoxyphenylacetic acid thus :-

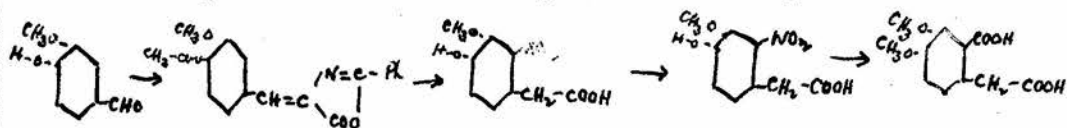


When the above series of reactions were tried however, it was found that reaction II yielded an oily substance which could not be made to crystallise. This oily substance was treated with hydrogen peroxide, and still an oily substance was obtained. This method, therefore, for preparing 2: carboxy 3: 4: dimethoxyphenylacetic acid had to be abandoned. This part of the investigation is described in Part II. of this paper, which deals with the condensation products of hippuric acid with aldehydes, containing a nitro-group in various positions in the benzene/

benzene nucleus. There is also to be found in Part II. a description of the application of Kropp's method to aldehydes containing bromine in the benzene nucleus. It was found that bromine, at least in the meta-position, did not interfere in any way with Kropp's method, and therefore, bromphenylacetic acids would be prepared from the corresponding aldehydes, for example, 3: methoxy 4: hydroxy 5: brombenzaldehyde yielded 3: methoxy 4: hydroxy 5: bromphenylacetic acid thus :-



Not having succeeded in preparing the acid 2:carboxy 3:4: dimethoxyphenylacetic acid by the above methods, it was next proposed to start from vanillin and obtain the derivative 3: methoxy 4: hydroxyphenylacetic acid  , and then nitrate this substance in such a way as to obtain the substance  . From this substance the acid 2: carboxy, 3:4: dimethoxy-phenylacetic acid could be prepared by the usual well known reactions. The preparation of the acid from vanillin by the above method, would be represented thus:-

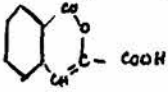
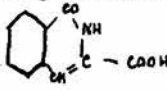
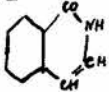


PART I.

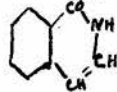
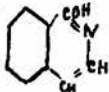
THE ISOCARBOSTYRILS:

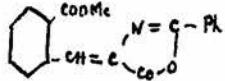
With special reference to a new
derivative, 2:3:dimethoxyisocarbostyryl.

The action of aqueous potash on the products obtained by
condensing hippuric acid with o-carboxybenzaldehydes. -
*
A new method for the preparation of isocarbostyryl
derivatives.

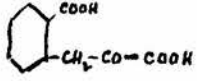
HISTORICAL. Isocarbostyryl was first prepared and described by Bamberger and Kitchelt (Ber. 25.1143) in their paper on the preparation of isoquinoline from naphthalene. Having prepared isocoumarinecarboxylic acid  they obtained from it isocarbostyryl-carboxylic acid  by treating the former substance with ammonia. Isocarbostyryl itself 

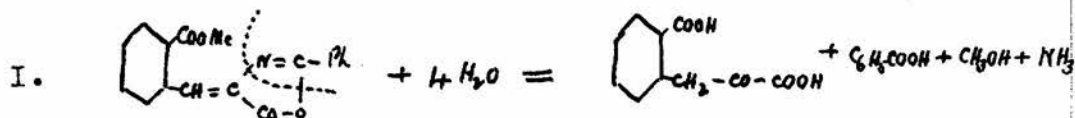
was obtained by heating the carboxylic acid or its silver salt. On reduction isocarbostyryl gives isoquinoline. Isocarbostyryl can be looked upon as having either the lactam or the lactim structure

 or  and others of both forms are known.

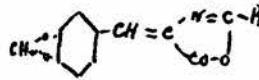
The method for the preparation of isocarbostyryls described in this paper was suggested, when the methyl ester of 2:carboxybenzylidenehippuric anhydride  had been prepared by condensing the methyl ester of o-phthalaldehydic acid with hippuric acid.

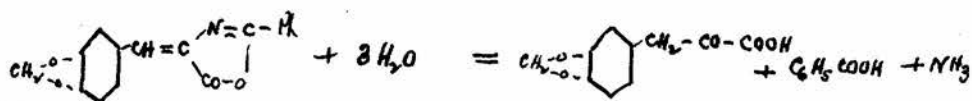
On treatment with aqueous potash there are two ways in which the substance might decompose.

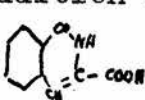
One might have the substance 2:carboxyphenylpyruvic acid  produced by the addition of H₂O after the molecule had split up in the manner indicated by the dotted line. At the same time benzoic acid, methyl alcohol and ammonia would be produced.

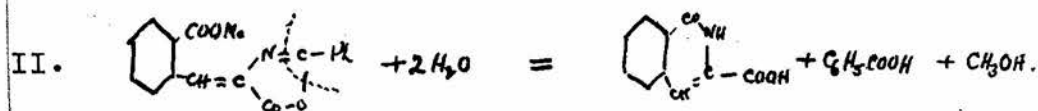


Kropp, Decker and Zoellner (Ber. 1909. 42. 1184)

for example showed that methylenedioxybenzylidene-hippuric anhydride  gave methylenedioxy-phenylpyruvic acid when treated with aqueous potash.



On the other hand, one might have the molecule splitting at the double bond between the C and N, and the addition of H₂O yielding, isocarbostyrylcarboxylic acid  benzoic acid and methyl alcohol.



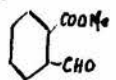
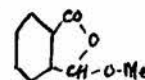
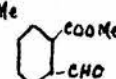
On treating the methyl ester of 2:carboxybenzylidene-hippuric anhydride with a 10% solution of aqueous potash it was found that the reaction proceeded in the manner indicated by equation II, and that a substance was obtained which had a melting point agreeing with the melting point of isocarbostyrylcarboxylic acid given by Bamberger and Kitchelt. On heating this acid, a substance was obtained which had the same melting point as that given for isocarbostyryl by those investigators. There is no doubt therefore, that this is a new method for preparing isocarbostyryl.

That/

That this new method for preparing isocarbostyrils is also a general one has been shown, since the new derivative 2:3:dimethoxyisocarbostyril has been prepared by the same series of reactions. Preliminary experiments have also shown that a substance which is no doubt γ -hydroxy β -methoxyisocarbostyril can be prepared by the same series of reactions.

This general method for preparing isocarbostyrils depends on the fact, that benzylidenehippuric anhydride derivatives which have a carboxy-group in the ortho-position in the benzene nucleus give on treatment with aqueous potash the corresponding isocarbostyril-carboxylic acid. As these benzylidenehippuric anhydrides are prepared by condensing benzaldehydes with hippuric acid, the method resolves itself into obtaining as starting substance for the preparation of isocarbostyrils, a benzene derivative having a carboxy-group in the ortho-position to an aldehyde-group. Having obtained an ortho-carboxybenzaldehyde, the corresponding isocarbostyril can be prepared by the following reactions. Prepare the methyl ester of the acid by heating the silver salt of the acid with methyl iodide.

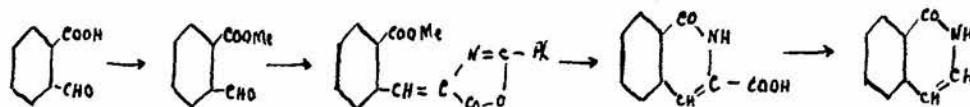
(o-carboxybenzaldehydes form two series of esters of

the type  and . It is necessary to have the ester of the type  to ensure having the CHO free to condense with the hippuric acid, the

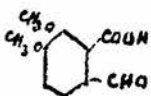
next/

next stage in the reaction.) Next, condense the methyl ester with hippuric acid in the presence of acetic anhydride, and decompose with aqueous potash the condensation product so formed, when the carboxylic acid of the isocarbostyryl will result. On heating the carboxylic acid or its silver salt the isocarbostyryl is obtained.

In the case of the preparation of isocarbostyryl from o-phthalaldehydic acid the reactions are represented thus:-

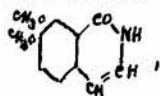


Similarly opianic acid



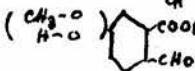
yields 2:3 dimethoxy-

isocarbostyryl

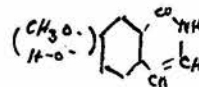


and preliminary experiments

show that



no doubt yields



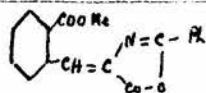
EXPERIMENTAL.

THE PREPARATION OF ISOCARBOSTYRIL.

O-phthalaldehydic acid having been prepared from naphthalene by the method of Gräbe and Trumpe (Ber. 31. 375), its methyl ester was obtained and condensed with hippuric acid, when the methyl ester of 2:carboxybenzylidene-hippuric anhydride separated. On treatment with aqueous potash this product gave isocarbostyrylcarboxylic acid, from which on heating isocarbostyryl was obtained.

METHYL ESTER of 2: CARBOXYBENZYLIDENEHIPPURIC

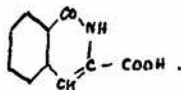
ANHYDRIDE.



1 mol. methyl ester of phthalaldehydic acid, 1 mol. hippuric acid, 1 mol. fused sodium acetate and 3 mols. acetic anhydride were intimately mixed in a geissler flask, and heated on the steam bath for half an hour. A yellow coloured solution was obtained from which on cooling a yellow crystalline substance separated. The anhydride crystallised from glacial acetic acid in groups of fine yellow needles. M.P. 171°.

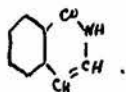
.1246 grams gave .3192 grams CO_2 and .0454 grams H_2O
 $\text{C} = 69.9 \quad \text{H} = 4.1 \quad \text{C}_{18}\text{H}_{13}\text{O}_4\text{N}$ requires $\text{C} = 70.3 \quad \text{H} = 4.2$

ISOCARBOSTYRILCARBOXYLIC ACID.



The above condensation product was heated with a 10% solution of potassium hydroxide until all the solid dissolved. The solution which was coloured red was cooled, and acidified, when the carboxy acid separated out as what appeared to be a flocculent precipitate but which was really crystalline. The acid was filtered off, dissolved in ammonia and reprecipitated with acid, and finally crystallised from acetone in which it is only sparingly soluble. The acid crystallised in colourless needles which melted at 320° with previous decomposition, and was therefore the same acid as that described by Bamberger and Kitchelt (Ber. 25:1143).

ISOCARBOSTYRIL.

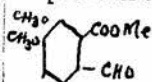


Isocarbostyryl was prepared by heating the silver salt of isocarbostyrylcarboxylic acid, and also by heating the carboxylic acid itself. The melting point of the substance was found to be 208° , which agreed with the melting point given by Bamberger and Kitchelt.

THE PREPARATION of 2:3:DIMETHOXYISOCARBOSTYRIL.

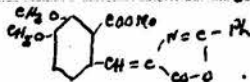
This new isocarbostyryl derivative was prepared from opianic acid by exactly the same series of reactions as isocarbostyryl was prepared from o-phthalaldehydic acid.

Opianic acid was converted into its methyl ester



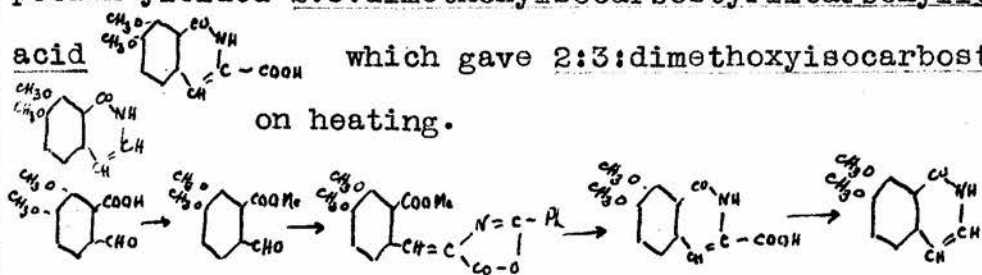
, and then condensed with hippuric acid,

when the methyl ester of 2:carboxy 3:4:dimethoxybenzyl-
idenehippuric anhydride separated



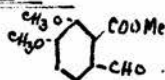
This condensation product on treatment with aqueous potash yielded 2:3:dimethoxyisocarbostyrylcarboxylic acid

which gave 2:3:dimethoxyisocarbostyryl acid on heating.



EXPERIMENTAL.

METHYL ESTER of OPIANIC ACID.

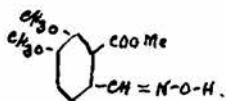


(Wegscheider, M. 3,358, 13, 254.)

21 grams of opianic acid were dissolved in 50 c.cms. of an aqueous solution containing 7 grams of potassium carbonate. To the solution were added 30 c.c.s., of a hot/

hot 50 per cent. solution of silver nitrate, when the silver salt of opianic acid separated out. The precipitate was filtered, washed with a little alcohol, and dried on a porous plate. The dried silver salt was heated for half-an-hour with 30 grams of methyl iodide and 100 c.c.s., of dry ether in a flask fitted with a reflux condenser. The silver iodide having been filtered off, and the ethereal solution evaporated, the methyl ester remained. M.P. 82° - 84° . The oxime and the semicarbazone of methyl opianate, not having been prepared before, are described here.

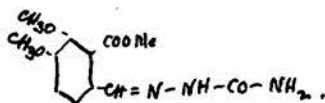
OXIME of METHYL OPIANATE.



5.6 grams of methyl opianate were dissolved in 100 c.c.s. of 80% alcohol, and 2.6 grams hydroxylamine hydrochloric were added. Anhydrous sodium carbonate in excess was then added and the mixture well shaken. After standing in the cold for twelve hours, the undissolved sodium carbonate was removed, and the greater part of the alcohol evaporated off. On the addition of water the oxime was precipitated. The oxime was crystallised by dissolving in a small quantity of ether and precipitating with ligroin. It crystallised in colourless needles which melted at 106° .

.1530 grams gave .3094 grams CO_2 and .0764 grams H_2O
 C = 55.2 H = 5.6 Theory requires C = 55.2 H = 5.4

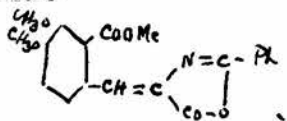
SEMICARBAZONE of METHYL OPIANATE.



7 Grams methyl opiate were dissolved in a small quantity of alcohol. 10 grams semicarbazide hydrochloride dissolved in 30 c.c.s., of water, and a few c.c.s. of a saturated solution of sodium acetate were added to the alcoholic solution, when a white crystalline precipitate appeared. The precipitate after being filtered off was washed with water and then crystallised from alcohol. It crystallised in colourless needles M.P. 187° - 188° .

.1793 grams gave .3370 grams CO_2 and .0838 grams H_2O
 C = 51.3 H = 5.2 Theory requires C = 51.2 H = 5.3.

METHYL ESTER of 2: CARBOXY 3:4:DIMETHOXYBENZILIDENE-HIPPURIC ANHYDRIDE.

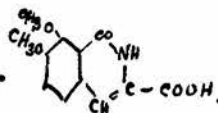


11 grams of opianic ester, 10 grams of hippuric acid, 4 grams of fused sodium acetate and 25 grams of acetic anhydride were well mixed in a geissler flask and warmed on the steam bath for three hours, when a red coloured solution was obtained. The contents of the/

the flask were poured into water, when an oil appeared which soon solidified. The solid was filtered off, washed with water, and spread on a porous plate to get rid of oil. This substance crystallised from glacial acetic acid in fine needle shaped crystals which were yellow in colour. M.P. 133° - 134° .

.1540 grams substance gave .3700 grams CO_2 and .0670 grams H_2O . C = 65.5 H = 4.8 $\text{C}_{20}\text{H}_{17}\text{O}_6\text{N}$ requires C = 65.4 H = 4.8.

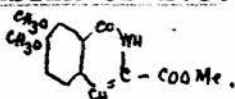
2:3: DIMETHOXYISOCARBOSTYRILCARBOXYLIC ACID.



3 grams of the condensation product were heated on the steam bath for half-an-hour with 50 c.c.s., of a 10% solution of potassium hydroxide. On acidifying the blood red coloured solution the acid separated out. The acid was filtered off and washed with hot water to get rid of the benzoic acid produced in the reaction. It is a colourless crystalline substance melting at 261° when recrystallised from glacial acetic acid.

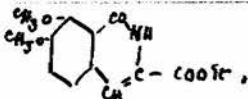
.1206 grams gave .2550 grams CO_2 and .0500 grams H_2O .
 .1898 grams gave 9.2 c.c.s. of N at 750 m.m.s. and 15°C .
 C = 57.7 H = 4.6 N = 5.6 $\text{C}_{12}\text{H}_{11}\text{O}_5\text{N}$ requires C = 57.8
 H = 4.4 N = 5.6 .1317 grams neutralised .0216 grams
 NaOH. An acid of formula $\text{C}_{11}\text{H}_{10}\text{O}_3\text{N COOH}$ requires .0212
 grams NaOH.

METHYL ESTER of 2:3: DIMETHOXYISOCARBOSTYRILCARBOXYLIC ACID.



The ester was prepared by heating on the steam bath a solution of the acid (5 grams) in 5% methyl alcoholic sulphuric acid (100 c.c.s.). On pouring the solution into water the ester separated. The ester crystallised from methyl alcohol in colourless needles melting at 195°.

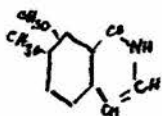
ETHYL ESTER of 2:3: DIMETHOXYISOCARBOSTYRILCARBOXYLIC ACID.



The ethyl was prepared as above, substituting ethyl alcohol for methyl alcohol. It crystallised from alcohol in colourless prisms melting at 179°.

.1760 grams gave .3875 grams CO₂ and .0852 grams H₂O
 C = 60.5 H = 5.4 C₁₄H₁₅O₅N requires C = 60.7 H = 5.4.

2:3: DIMETHOXYISOCARBOSTYRIL.



This substance was prepared by heating the carboxylic acid at a temperature a little below its melting point in a test tube immersed in an oil bath. Long colourless needle shaped crystals appeared as a sublimate/

sublimate on the side of the test tube. The crystals were washed with sodium carbonate solution and then crystallised from glacial acetic acid. M.P. 232°- 233°.

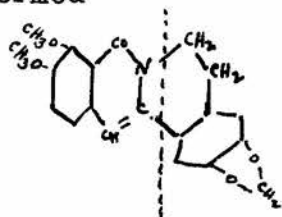
.1058 grams gave .2483 grams CO_2 and .0518 grams H_2O

C = 64.0 H = 5.4 $\text{C}_{11}\text{H}_{11}\text{O}_3\text{N}$ requires C = 64.4

H = 5.4.

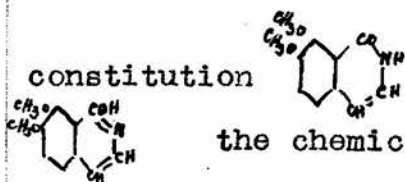
2:3:DIMETHOXYISOCARBOSTYRIL.

This dimethoxy derivative of isocarbostyryl is of considerable interest from the fact, that it, itself or derivatives of it are possible decomposition products of a class of alkaloids. A study of the constitutional formula for isooxyberberine proposed by Perkin and Robinson (Proc. Chem. Soc 1911, Vol.27.) shows that if the molecule splits up in the manner indicated by the dotted line, 2:3: dimethoxyisocarbostyryl or a derivative would be formed



Isooxyberberine.

With regard to the constitution of 2:3:dimethoxyisocarbostyryl whether it possesses the lactam constitution/

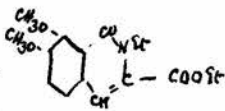
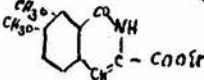


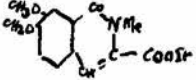
the chemical evidence seems to point to the latter formation. The chemical evidence rests on the fact that the substance shows the properties of an α -naphthol.

- (1). gives a blue green colouration with ferric chloride.
- (2). gives a red azo dye with diazosulphanilic acid.
- (3). gives a yellow sodium salt with sodium ethoxide in alcohol.
- (4). gives with chloroform and potassium hydroxide a solution coloured first blue, then green and finally brown.

The DECOMPOSITION of 2:3:dimethoxyisocarbostyryl by alkali was investigated, with the result that a gelatinous acid was obtained which could not be made to crystallise. This acid, however, formed a very sparingly soluble yellow sodium salt, and an analysis was made of it in the hope of throwing some light on the composition of the acid. The analysis showed that the acid had the empirical formula $C_{11}H_{15}O_5N$ which is the empirical formula for 2:3:dimethoxyisocarbostyryl + $2H_2O$. I have not been able to assign a constitutional formula to this acid as it is difficult to see how an acid having the above empirical formula could result from/

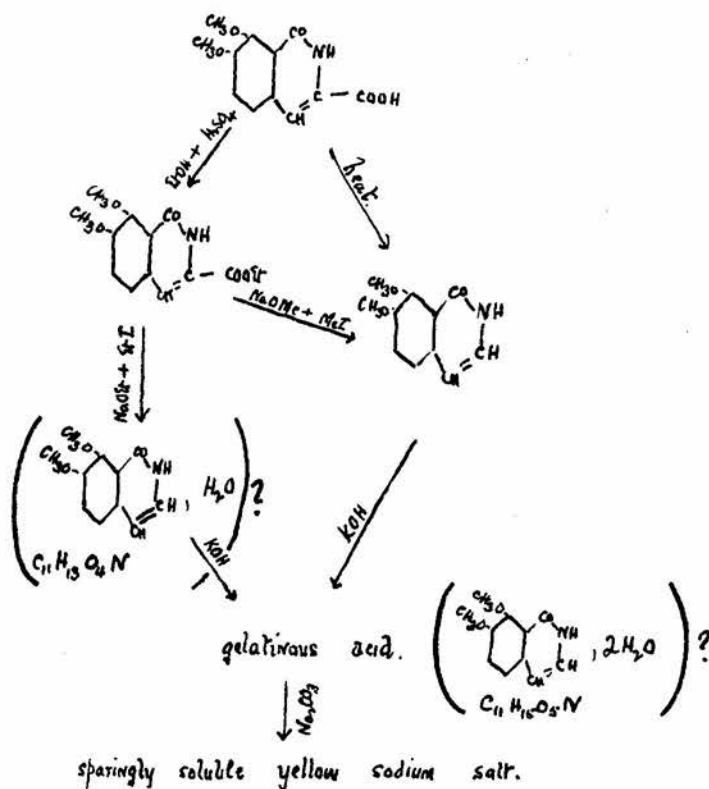
from the action of aqueous potash on 2:3:dimethoxyisocarbostyryl. This acid shall be referred to afterwards as the "gelatinous acid". It is proposed to try the action of aqueous potash on isocarbostyryl itself to find if by that means the constitution of this "gelatinous acid" can be solved.

The preparation of the ether , by treating the carboxy ester  in the usual manner with sodium ethoxide in alcohol and ethyl iodide, was attempted, when a crystalline substance melting at 211° was obtained. An analysis showed this was not the ether, but a substance having the empirical formula C₁₁H₁₃O₄N, which is the empirical formula for 2:3:dimethoxyisocarbostyryl + H₂O. This substance must have been produced by hydrolysis first taking place, followed by the loss of CO₂. On treating this substance with aqueous potash a gelatinous acid separated which had a sparingly soluble yellow sodium salt. This gelatinous acid was no doubt the same acid as the "gelatinous acid" described above.

When sodium methoxide in methyl alcohol was used along with methyl iodide, in an attempt to prepare the methyl ether  from the carboxy ester, a substance was obtained which was shown to be 2:3:dimethoxyisocarbostyryl.

The/

The following diagram represents the relationship between the substances mentioned above.



EXPERIMENTAL.

Colourless crystalline substance melting at 211° obtained when endeavouring to prepare the ethyl ether.

7 grams of the ethyl ester of 2:3:dimethoxyisocarbostyrylcarboxylic acid was treated with sodium ethoxide (.6grams sodium in 250 c.c.s. of ethyl alcohol) when a yellow insoluble sodium salt was obtained. 20 grams of ethyl iodide was then added and the solution boiled until/

until the sodium salt dissolved. On cooling the solution a colourless crystalline substance was obtained which melted at 211° . It was recrystallised from alcohol.

.1600 grams gave .3446 grams CO_2 and .0854 grams H_2O ,
 $\text{C} = 58.7$ $\text{H} = 5.9$.

.1676 grams gave .3616 " " " .0777 " "
 $\text{C} = 58.7$ $\text{H} = 5.1$.

.1830 grams gave at 755 m.m.s. and 25°C 10.0 c.c.s. N.
 $\text{N} = 6.0$.

The ether $\text{C}_{16}\text{H}_{19}\text{O}_5\text{N}$ requires $\text{C} = 63.0$, $\text{H} = 6.2$ $\text{N} = 4.6$

$\text{C}_{11}\text{H}_{13}\text{O}_4\text{N}$ $\text{C} = 59.2$, $\text{H} = 5.8$ $\text{N} = 6.3$

WHITE "GELATINOUS" ACID. ($\text{C}_{11}\text{H}_{15}\text{O}_5\text{N}$)

This acid was produced when the substance melting at 211° was heated with alkali and acidified, and also when 2:3:dimethoxyisocarbostyryl was similarly treated. This acid formed a very sparingly soluble yellow sodium salt, and an analysis was made of it in the hope of throwing some light on the composition of the acid. The sodium salt was combusted as if it were a pure organic compound. The sodium salt left behind after combustion was weighed/

weighed, and the percentage of sodium in the salt calculated from it. The percentage of sodium was also estimated directly from the sodium salt. Both determinations gave 8.6 as the percentage of sodium in the sodium salt. The weight of carbonic anhydride, corresponding to the sodium carbonate left after combustion, was calculated, and added to the weight of carbonic anhydride absorbed by the soda lime. From this was calculated the percentage of carbon in the sodium salt which was found to be 50.1 per cent. As the results of two determinations the percentage of hydrogen was found to be 4.3 per cent. and 5.2 per cent. The number of carbon atoms in the sodium salt was found to be eleven. This was determined by dividing the total weight of carbonic anhydride by the weight of carbonic anhydride corresponding to the weight of sodium carbonate left after combustion, and then halving the result, since the acid is no doubt monobasic. The following were the figures actually obtained.

.1803 grams sodium salt gave .3162 grams CO_2 and

.0694 grams H_2O .

.0360 grams sodium carbonate left in boat after combustion.

Therefore weight of CO_2 corresponding to .0360 grams sodium carbonate = .0150 grams CO_2 .

Total/

Total weight of $\text{CO}_2 = .3162 + .0150 = .3312$ grams.

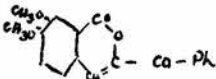
Number of carbon atoms in sodium salt = $\frac{1}{2} \frac{(.3162 + .0150)}{.0150} = \frac{1}{2}(22.08) = 11$.

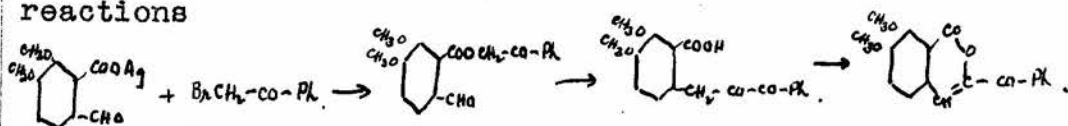
The above figures gave C = 50.1% H = 4.3% and Na = 8.6%

A second combustion gave C = 50.1% H = 5.2%

The empirical formula $\text{C}_{11}\text{H}_{14}\text{O}_5\text{N Na}$ requires C = 50.2% H = 5.3% and Na = 8.7% which agrees very closely with the above analyses.

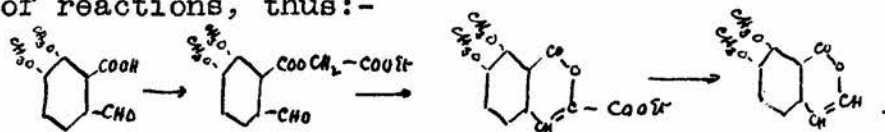
The close relationship existing in constitution between the isocarbostyrils and the isocoumarines, and the fact that the isocarbostyrils were formerly prepared from the corresponding isocoumarine derivative, led me to attempt the preparation of 2:3:dimethoxyisocoumarine, the isocoumarine corresponding to 2:3:dimethoxyisocarbostyril.

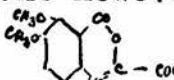
Having prepared the isocoumarine derivative, benzoyl 2:3: dimethoxyisocoumarine  by the following reactions



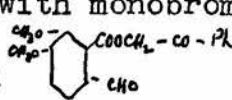
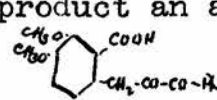
it was thought that 2:3:dimethoxyisocoumarine would result by substituting monobromacetic ester in place of/

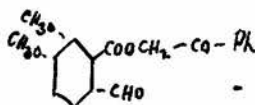
of monobromacetophenone and carrying out the same series of reactions, thus:-



On carrying out the experiment however, the reaction which was expected to yield ; yielded a substance which was not crystalline, and consequently the preparation of this substance by this method had to be abandoned.

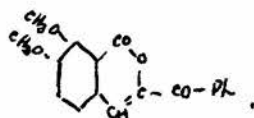
EXPERIMENTAL.

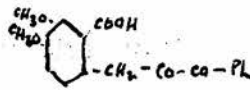
BENZOYL 2:3: DIMETHOXYISOCOUMARINE. For the preparation of this substance the silver salt of opianic acid was treated with monobromacetophenone when acetophenone-opianate  was obtained, a colourless crystalline solid melting at 112° . This substance when treated with "molecular" sodium yielded benzoyl 2:3: dimethoxyisocoumarine melting at 171° . There was also obtained as intermediate product an acid which had probably the constitution . This acid had no definite melting point as it passed into the isocoumarine on heating.

ACETOPHENONE OPIANATE.

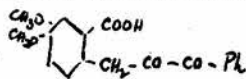
27 grams silver opiate, and 20 grams monobrom-acetophenone dissolved in 250 c.c.s. pure benzene, were heated together for four hours in a flask fitted with a reflux condenser. The silver bromide having been removed, most of the benzene was distilled off and alcohol added, when a white crystalline substance appeared. On being recrystallised from benzene by the careful addition of alcohol the substance had a melting point of 112°.

.1982 grams gave .4790 grams CO₂ and .0870 grams H₂O
 C = 65.9 H = 4.9 C₁₈H₁₆O₆ requires C = 65.8
 H = 4.9.

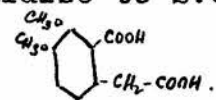
BENZOYL 2:3: DIMETHOXYISOCOUMARINE.

5 grams acetophenone opiate, 1 gram of "molecular" sodium and a small quantity of dry ether were heated in a flask fitted with a reflux condenser. After heating for a short time, yellow spangles separated and in from 1½ hours to 2 hours the action was completed. Alcohol was added to dissolve the excess of sodium when an intense red coloured sodium salt was formed - this sodium salt was probably the sodium salt of the acid  which is described in the next preparation/

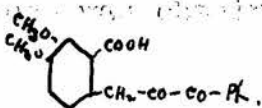
preparation. On acidifying the sodium salt with concentrated hydrochloric acid benzoyl 2:3: dimethoxyisocoumarine separated out. The precipitate was filtered off, washed free from organic acid by means of sodium carbonate solution and crystallised from alcohol. The substance crystallised in beautiful yellow plates. M.P. 171°.

On acidifying the sodium salt with concentrated hydrochloric acid, some of the acid  was obtained. It was found advisable, therefore, to warm the precipitate with alcoholic hydrochloric acid, when any acid present readily loses water giving the isocoumarine.

.1498 grams gave .3835 CO₂ and .0607 grams H₂O
 C = 69.8 H = 4.5 C H O requires C = 69.7, H = 4.5

The oxidation of benzoyl 2:3:dimethoxyisocoumarine with hydrogen peroxide was tried, with the result that o-hemipiric acid was obtained. It was thought that this substance might oxidise to 2:carboxy 3:4:dimethoxyphenylacetic acid .

PREPARATION OF



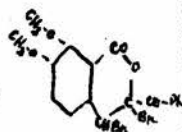
This substance was obtained as an intermediate product/

product in the preparation of benzoyl 2:3: dimethoxyisocoumarine. On acidifying the red coloured sodium salt with very dilute hydrochloric acid, an acid was precipitated having a yellow colour. After being washed with water and dried, it was crystallised from benzene. It is a yellow crystalline substance melting rather indefinitely in the neighbourhood of 130°. The sodium salt of this acid has a brilliant red colour and is sparingly soluble in water. The acid is readily converted into benzoyl 2:3: dimethoxyisocoumarine on heating with alcoholic hydrochloric acid.

.1584 grams gave .3800 grams CO₂ and .0720 grams H₂O.

C = 65.6 H = 5.0 C₁₈H₁₆O₆ requires C = 65.9 H = 5.0

DIBROMIDE of BENZOYL 2:3: DIMETHOXYISOCOUMARINE.

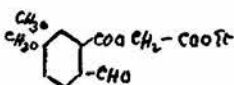


A small quantity of benzoyl 2:3: dimethoxyisocoumarine was dissolved in chloroform and the solution cooled in a freezing mixture. A solution of bromine in chloroform was slowly added until there was just excess of bromine when a bright red coloured substance separated. This substance was very unstable, losing bromine even on washing with ice cold chloroform. In an evacuated desiccator it lost all its bromine in quite/

quite a short time, leaving behind the pure isocoumarine. On treatment with a little alcohol the bromine was immediately removed leaving the isocoumarine. The dibromide had no definite melting point. The substance was quickly prepared for a determination of the bromine as silver bromide, but the result was unsatisfactory as was to be expected owing to the readiness with which it lost bromine.

.5328 grams gave .2485 grams silver bromide Br = 31.8
Theory requires Br = 34.

ETHYLACETATE OPIANATE.



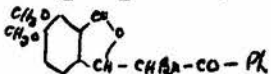
17 Grams silver opiate and 12 grams of monobrom-acetic ester dissolved in 200 c.c.s. of pure benzene were heated together in a flask until all the silver was converted into silver bromide. After removing the silver bromide, most of the benzene was distilled off and alcohol added when the ester separated out. The ester crystallised from a mixture of benzene and alcohol as a colourless substance melting at 85°.

.1520 grams gave CO₂ and .0740 grams H₂O

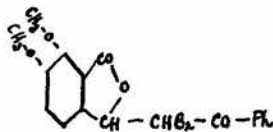
C = 56.9 H = 5.4 Theory requires C = 56.7 H = 5.4

ATTEMPT to PREPARE 2:3: DIMETHOXYISOCOUMARINECARBOXYLIC
ESTER from ETHYLACETATE OPIANATE.

6 grams ethylacetate opianate were dissolved in 200 c.c.s. of pure and dry ether, and approximately 1 gram of "molecular" sodium added. The reaction was completed after two hours heating on the water bath. After cooling the solution, a quantity of ethyl alcohol was added slowly in order to get rid of the excess of sodium. On acidifying the solution a red amorphous substance was precipitated. This was filtered off, and efforts were made to crystallise it from all the well known solvents but without success. On heating with alkali the red coloured substance dissolved and yielded a yellow coloured acid on acidification. All efforts to crystallise this acid also failed. Combustions of the red amorphous substance and of the acid obtained from it, were carried out, but the analyses of different samples of the same substance did not give concordant results.

An interesting derivative of monobromacetophenone and opianic acid was prepared, namely, meconine-bromacetophenone  This substance gave benzoyl 2:3: dimethoxyisocoumarine on treatment with caustic alkali.



MECONINEBROMACETOPHENONE.

5 grams opianic acid, 5 grams monobromacetophenone dissolved in 70c.c.s. alcohol, and 5 grams potassium carbonate dissolved in 20 c.c.s. of water, were mixed and allowed to stand in the cold for 24 hours. Crystals separated out which when recrystallised from alcohol melted at 148° with previous softening. When dissolved in alkali and acidified, this substance yielded benzoyl 2:3:dimethoxyisocoumarine.

.1337 grams gave .2705 grams CO_2 and .0434 grams H_2O

.1493 grams gave .0712 silver bromide.

C = 55.2. H = 3.6. Br. = 20.5 $\text{C}_{18}\text{H}_{15}\text{O}_5$ Br requires

C = 55.2, H = 3.8. Br = 20.4.

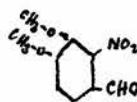
PART II.

The action of aqueous potash on the products obtained by condensing hippuric acid with nitrobenzaldehyde and brombenzaldehyde derivatives.

When endeavouring to prepare the acid 2: carboxy 3:4:dimethoxyphenylacetic acid, by applying to opianic acid Kropp's method for preparing acetic acid derivatives from carboxylic aldehydes, it was found that the presence of the carboxy-group, in the ortho-position to the aldehydic-group, prevented the formation of the acetic acid derivative, and gave rise instead to an isocarbostyryl derivative. (See introduction p. 4.).

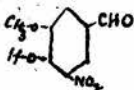
This being so, it was proposed to apply Kropp's method to the substance having a nitro-group in place of the carboxy-group of opianic acid, in the hope of afterwards being able to convert the nitro-group into a carboxy-group should the acetic acid derivative be obtained (See Introduction p.5.).


2:Nitro 3:4:dimethoxybenzaldehyde



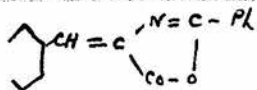
prepared from vanillin (Pschorr and Sumuleanu Ber. 32. 3405), was condensed with hippuric acid and treated according to the method of Kropp, when an oily substance was obtained which could not be made to crystallise.

In order to test whether, or not, it was the presence of the nitro-group in the ortho-position, which prevented the decomposition into a crystalline acetic acid derivative, a similar experiment was carried out with

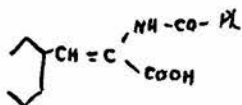
5: nitrovanillin  which has the nitro-group in the meta-position, and the result was the same. Neither did/

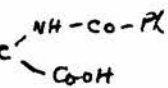
did 6: nitropiperonal  yield a crystalline acetic acid derivative when treated by Kropp's method. It may be concluded therefore, that Kropp's method for preparing acetic acid derivatives from aldehydes, does not yield a crystalline product when a nitro-group is attached to the benzene nucleus either in the ortho- or meta-position.

EXPERIMENTAL.



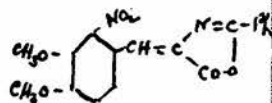
The condensation products of carbocyclic aldehydes with hippuric acid were all prepared in the same manner, as follows; 1 molecule of aldehyde, 1 mol. hippuric acid, 1 mol. fused sodium acetate, and 3 mols. of acetic anhydride were heated together in a geissler flask when a yellow solution was obtained. The condensation took place very readily, accompanied by a considerable evolution of heat, and the separation of yellow crystals from the solution. All the condensation products were yellow in colour and crystallised from acetic anhydride in groups of fine needles.



The acids of the type  were produced by the/

the hydrolysis of the anhydrides. They were prepared by dissolving the anhydride in aqueous potash and acidifying, or by dissolving the anhydride in glacial acetic acid containing a few c.c.s. of concentrated hydrochloric acid and heating for a short time, when the acid crystallised out from the solution. The acids crystallised from glacial acetic acid.

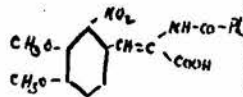
2:NITRO 3:4:DIMETHOXYBENZYLIDENEHIPPURIC
ANHYDRIDE.



This substance was prepared by condensing 2-nitro 3:4: dimethoxybenzaldehyde with hippuric acid in the presence of acetic anhydride. It crystallised from glacial acetic acid in yellow needle shaped crystals which melted at 145° with previous softening.

.1310 grams gave .2926 grams CO_2 and .0480 grams H_2O
C = 60.9 H = 4.1 Theory requires C = 61.0 H = 3.9.

2 NITRO 3:4: DIMETHOXYBENZYLIDENEHIPPURIC
ACID.



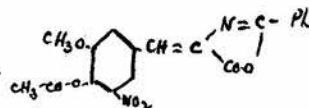
On hydrolysing the above anhydride, this acid was obtained. From glacial acetic acid it crystallised in yellow needles which melted at 227° - 228° .

.1350 grams gave .2880 grams CO_2 and .0525 grams H_2O
C = 58.2 H = 4.3 Theory requires C = 58.1 H = 4.3.

THE ACTION of CONCENTRATED AQUEOUS POTASH on 2: NITRO
3:4:DIMETHOXYBENZYLIDENEHIPPURIC ANHYDRIDE.

10 grams of the anhydride were dissolved in excess of a concentrated solution of aqueous potash and the solution heated until all the ammonia formed during the decomposition was evolved. On acidifying the solution an oily substance was precipitated. On standing for some time the substance solidified but it could not be made to crystallise from any of the well known solvents. This product was dissolved in alkali and treated with excess of a 30% solution of hydrogen peroxide in the hope that, if the substance was 2: nitro 3:4: dimethoxyphenylpyruvic acid, it would be oxidised to 2: nitro 3:4: dimethoxyphenylacetic acid, which one would expect to be a crystalline body. On acidifying the solution after treatment with hydrogen peroxide an oily substance was precipitated. All efforts to crystallise this product were unsuccessful.

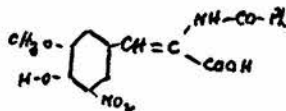
5:NITROACETVANILLINHIPPURIC ANHYDRIDE.



This anhydride was produced by condensing 5: nitrovanillin with hippuric acid in the presence of acetic anhydride. It crystallised from glacial acetic acid in yellow needles melting at 219° with previous softening.

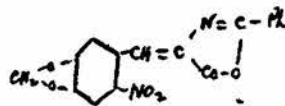
.1745 grams gave .3844 grams CO_2 and .0588 grams H_2O
 $\text{C} = 60.0$ $\text{H} = 3.7$ Theory requires $\text{C} = 60.0$ $\text{H} = 3.5$

5: NITROVANILLINHIPPURIC ACID.



Prepared from the above anhydride by hydrolysis.
 From glacial acetic acid it crystallised in yellow
 needles which melted at $200^\circ - 202^\circ$.

6: NITROPIPERONALHIPPURIC ANHYDRIDE.

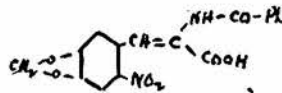


On condensing 6: nitropiperonal with hippuric acid
 in the presence of acetic anhydride this substance was
 produced.

It is a yellow crystalline substance melting at 198° .

.1906 grams gave .4180 grams CO_2 and .0517 grams H_2O
 $\text{C} = 59.8$ $\text{H} = 3.1$ Theory requires $\text{C} = 60.3$ $\text{H} = 2.9$.

6: NITROPIPERONALHIPPURIC ACID.



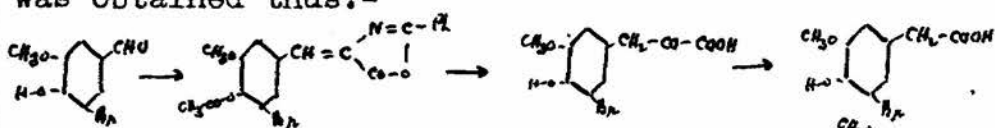
Prepared from the above anhydride by hydrolysis.
 It crystallised in yellow needles from glacial acetic
 acid. It melted at $213^\circ - 215^\circ$.

.2108 grams gave .4420 grams CO_2 and .0634 grams H_2O
 $\text{C} = 57.2$ $\text{H} = 3.3$ Theory requires $\text{C} = 57.3$ $\text{H} = 3.3$.

5: nitro acetvanillinhippuric anhydride and 6: nitro-piperonalhippuric anhydride were treated with a concentrated solution of aqueous potash in the same manner as 2:nitro 3:4:dimethoxybenzylidenehippuric anhydride, with the same result, namely, products were obtained which could not be made to crystallise.

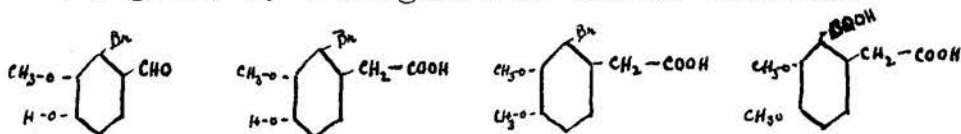
On finding that crystalline acetic acid derivatives could not be prepared, by Kropp's method, from aldehydes having a nitro-group attached to the same benzene nucleus, experiments were tried with bromine in place of the nitro-group.

Kropp's method was applied to 5: bromvanillin with the result that 5: bromhomovanillin acid was obtained thus:-

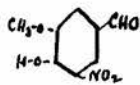


Unfortunately neither 2: bromvanillin nor 6: bromvanillin are known, so that the application of the above method to an isomer of 5: bromvanillin having bromine in the ortho-position could not be attempted. As it was considered likely that Kropp's method would apply to 2: bromvanillin, attempts were made to prepare it for this reason, that had it been prepared, and the acetic acid derivative prepared from/

from it, it is very probable the synthesis of 2: carboxy 3:4: dimethoxyphenylacetic acid could then have been effected, as the bromine could have been converted into a carboxy-group by a Grignard or Kekulé' reaction.

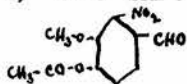


When vanillin is nitrated, the nitro-group occupies the 5:position



whilst on nitrating acetvanillin, the nitro-group is directed to the

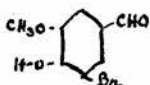
2:position



. It was thought therefore,

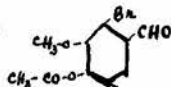
that since bromine occupies the 5: position on the

bromination of vanillin



the bromine would

be directed to the 2:position



on the

bromination of acetvanillin. Experiments showed however

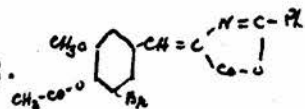
that on the bromination of either vanillin, or acet-

vanillin, the bromine occupies the 5:position.

Kropp's method when applied to ? brompiperonal gave ? bromhomopiperonylic acid. The position of the bromine atom in brompiperonal has not yet been defined.

From the above results it may therefore be concluded, that the preparation of acetic acid derivatives from aldehydes, according to the method of Kropp, is not interfered with, when a bromine occupies the meta-position to the aldehyde-group.

EXPERIMENTAL.

5: BROMACETVANILLINHIPPURIC ANHYDRIDE. 

This substance was prepared by condensing 5: bromvanillin with hippuric acid in the presence of acetic anhydride.

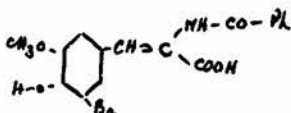
It crystallised in fine yellow needles from glacial acetic acid.

It melted at 191° with previous softening.

.3902 grams gave .1750 grams Ag Br

Br = 19.1

Theory requires Br = 19.2

5: BROMVANILLINHIPPURIC ACID. 

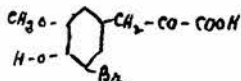
Prepared from the above anhydride by hydrolysis.

It crystallised in colourless needles from glacial acetic acid and melted at 225°-227°.

5: BROMHOMOVANILLIC ACID. 

The condensation product 5: bromacetvanillin-hippuric anhydride was dissolved in 30% aqueous potash and the solution heated until all the ammonia formed during the decomposition was evolved. It took from three to four hours to drive off all the ammonia. The solution/

solution after being cooled was acidified when the keto-acid



separated out along with benzoic acid. The precipitate was dissolved in aqueous potash and excess of 30% hydrogen peroxide was added. In a short time the solution began to get warm and it had immediately to be cooled under the tap. After standing in the cold for a few hours the solution was acidified when a white precipitate appeared. The precipitate after being filtered off, was dissolved in water and the benzoic acid got rid of by distilling in steam. The acid crystallised from water in colourless crystals melting at 164°.

ANALYSIS.

.1500 grams gave .2266 grams CO₂ and .0486 grams H₂O.
C = 41.2 H = 3.6 Theory requires C = 41.4 H = 3.4

?BROMPIPERONALHIPPURIC ANHYDRIDE.

Prepared from ?brompiperonal by condensing with hippuric in the presence of acetic anhydride. It crystallised from glacial acetic acid in yellow needles which melted at 219° with previous softening.

?BROMPIPERONALHIPPURIC ACID.

Prepared from the above anhydride by hydrolysis. It crystallised from glacial acetic acid in colourless needles which melted at 230°.

7BROMHOMOPIPERONYLIC ACID.

Prepared from 7brompiperonalhippuric anhydride in the same manner as 5: bromhomovanillic acid was prepared from 5: bromacetvanillinhippuric anhydride.

It crystallised from water in colourless crystals melting at 175° .

.1450 grams gave .2217 grams CO_2 and .0430 grams H_2O .

C = 41.7 H = 3.3

Theory requires C = 41.7

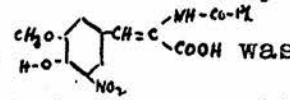
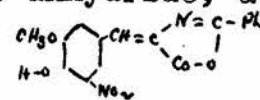
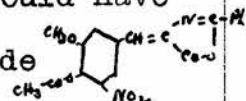
H = 2.7.

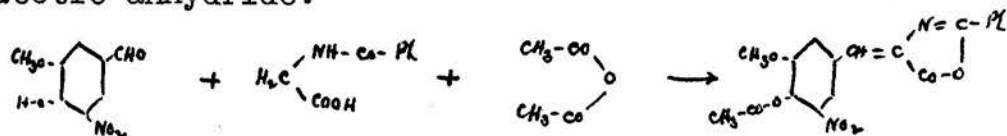
General remarks on the condensation products of substituted benzaldehydes with hippuric acid. These condensation products, a large number of which are described in this paper, are all beautiful yellow crystalline substances. The yellow colour is no doubt due to the ring formation $= \text{C} \begin{array}{l} \text{N} = \text{C} - \\ | \\ \text{CO} - \text{O} \end{array}$ as the corresponding acids $= \text{C} \begin{array}{l} \text{NH} - \text{CO} - \\ | \\ \text{COOH} \end{array}$, are colourless, provided there is no other group contributing towards the colouration of the acid.

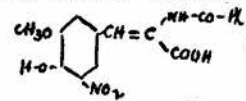
Acids of the type $= \text{C} \begin{array}{l} \text{NH} - \text{CO} - \\ | \\ \text{COOH} \end{array}$ corresponding to the anhydrides $= \text{C} \begin{array}{l} \text{N} = \text{C} - \\ | \\ \text{CO} - \text{O} \end{array}$, have been obtained of all the hippuric anhydrides prepared in connection with this work. These acids were produced by the hydrolysis of the anhydrides, and they gave the anhydrides on treatment with acetic anhydride.

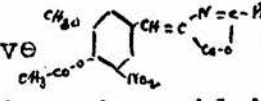
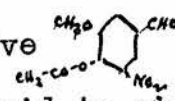
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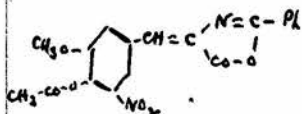
An interesting point was observed in connection with the preparation of some of the anhydrides from the corresponding acids on treatment with acetic anhydride.

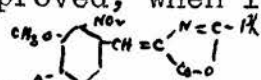
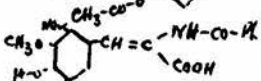
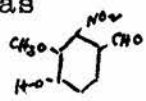
When 5: nitrovanillinhippuric acid  was treated with acetic anhydride, a substance was obtained which proved to be . Now, one would have expected the acetyl derivative of the anhydride  to have been formed, since it was the acetyl derivative of the anhydride which was obtained when 5: nitrovanillin was condensed with hippuric acid in the presence of acetic anhydride.



The explanation, why the acetyl derivative was obtained in the one case and not in the other, seems to be the following. In the case where the anhydride was prepared from the acid  the experiment showed that the hydroxy-group of such a condensation product could not be replaced by an acetyl-group on heating with acetic anhydride. You can explain, therefore,

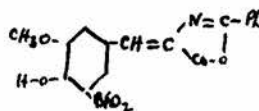
the formation of the acetyl derivative  when 5:nitrovanillin was condensed with hippuric acid in the presence of acetic anhydride, only on the assumption that the reaction took place in two stages. There must have been formed first the acetyl derivative  which afterwards condensed with hippuric acid to give



That the presence of the nitro-group next to the hydroxy-group prevented the acetylation of the condensation product, was proved, when it was shown that the acetyl derivative  was prepared either from  or from  and hippuric acid when treated with acetic anhydride. It was also shown that the presence of a bromine-group adjacent to the hydroxy-group prevented the acetylation of the condensation product.

EXPERIMENTAL.

5:NITROVANILLINHIPPURIC ANHYDRIDE.

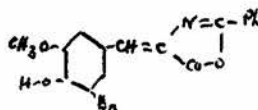


This substance was produced, and not 5:nitroacetvanillinhippuric anhydride, when 5: nitrovanillinhippuric acid was heated with acetic anhydride.

It crystallised in yellow needles from glacial acetic acid and melted at 247°-249°.

.1532 grams gave .3335 grams CO₂ and .0500 grams H₂O
 C = 59.4 H = 3.6 Theory requires C = 59.7 H = 3.6

5: BROMVANILLINHIPPURIC ANHYDRIDE.



Prepared from 5:bromvanillinhippuric acid by heating with acetic anhydride.

It crystallised from glacial acetic acid in yellow needles melting at 234 - 235°.

.3030 grams gave .1510 grams Ag Br
 Br = 21.2 Theory requires Br = 21.4.

S U M M A R Y.

- I. The anhydrides obtained by condensing hippuric acid with substituted benzaldehydes are all coloured yellow: the yellow colour being due to the ring formation = $c \begin{matrix} N=C- \\ | \\ O-O \end{matrix}$.
- II. The condensation products, which have a carboxy-group attached to the benzene nucleus in the ortho-position, yield isocarbostyryl derivatives when treated with aqueous potash.
- III. The condensation products, which have a bromine atom attached to the benzene nucleus in the meta-position, yield bromphenylacetic acids when treated according to the method of Kropp, Decker and Zoellner.
- IV. The condensation products, which have a nitro-group attached to the benzene nucleus in either the ortho- or meta-position, do not yield crystalline products when treated by Kropp's method.
- V. Acetyl condensation products are obtained when hydroxybenzaldehydes are condensed with hippuric acid in the presence of acetic anhydride. The reaction takes place in two stages; the acetbenzaldehyde is first/

first formed and then the condensation takes place.

- VI. Condensation products, having a hydroxy-group adjacent to a bromine- or nitro-group in the benzene nucleus, do not yield acetyl condensation products when heated with acetic anhydride.
- VII. When acetvanillin is brominated, the bromine occupies the 5: position.
-