UNIVERSITY OF LONDON.

To be returned to the University with the Examiners' Report.

I

THESIS PRESENTED BY

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B.Sc.

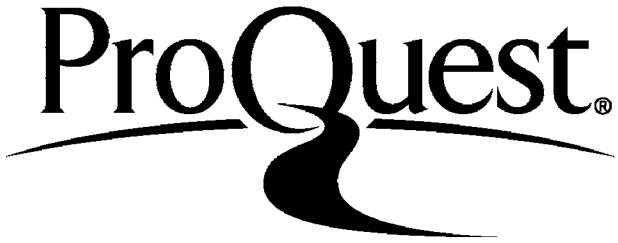
FOR THE DEGREE OF MASTER OF SCIENCE

IN THE

UNIVERSITY OF LONDON.

JULY, 1931.

The Cinchona Alkaloids and Substances Related to Them.



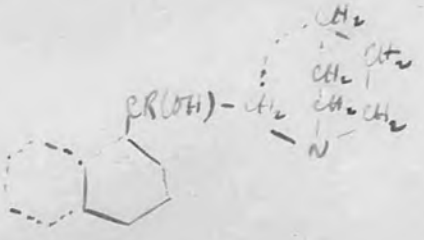
ABSTRACT.

A short survey is given of the known facts regarding the relation between the constitution and the antimalarial activity of the chief cinchona alkaloids, and it is concluded that further information on this matter can be obtained in two ways:

(1). By investigating the degradation products and some of the simpler derivatives of these alkaloids.

(2). By preparing some synthetic substances which contain certain characteristic features.

Under heading (2), a large number of compounds of the general formula:



have been synthesised. These all bear, as the formula indicates, marked pictorial resemblance to the essential cinchona structure. The antimalarial activity of the new substances has been determined, and the conclusion is drawn that a second basic centre must be present for a molecule of the above type to possess any marked antimalarial activity.

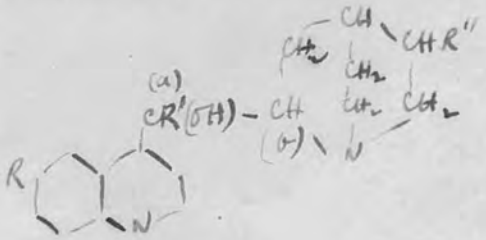
Under heading (2), a number of alkaloid methochlorides have been prepared by a new process, and considerable attention has been paid to the attempted decarboxylation of quitenine, since the decarboxylated product should exhibit definite antimalarial activity.

Experiments have also been performed on the preparation of quitenine amide, and of its benzoyl derivative.

THE INVESTIGATION OF SOME PIPERIDINOMETHYLCARBINOL HYDROCHLORIDES.

Despite extensive investigations on the part of numerous workers, there still remain two outstanding problems in cinchona alkaloid chemistry: (1) whether the specific physiological action is due to any group or groups, considering these from the chemical or the stereochemical point of view; and (2) whether it is possible to obtain a compound having similar or even more beneficial antimalarial action, by imitating what may be called the cinchonoid structure:

(I)



Owing to the fact that the earlier workers in the cinchona alkaloid series were concerned more with the constitution than with the pharmacological action of degradation products, it may be necessary to prepare many of these products again, in order to test them on a strictly comparative basis. At the present moment we are in possession of a limited number of observations as to the effect of modifying the essential cinchonoid molecule. These may be classified under the following headings:

(1) <u>The Quinoline System</u>.

It is known that complete removal of the methoxyl group in quinine is not accompanied by very serious effects on the pharmacological activity, whilst its replacement by some alkoxyl groups increases the latter.

Such changes may produce their effect by altering the basicity of the quinoline nitrogen atom. Moreover, it is known that cupreine, which only differs from quinine by a methyl group, (it has a hydroxyl instead of a methoxyl group in the quinoline nucleus) possesses little or no antimalarial activity.

(2) The Carbinol Grouping.

Little appears to be known regarding the effect of modifying this group, e.g. by converting it into -CR(OH), where R is a hydrocarbon radical. But modification of this kind might be of fundamental importance, since it would stabilise the group against oxidation. Compounds of the cinchoninone type should be considered under this heading, for the secondary carbinol group is no longer present, its place being taken by an unsaturated tertiary group of the enolic form of the ketone:

-CH(OH).CH: -CO.CH: -C(OH):C:

(3) The Vinyl Side-chain.

Since the present work was begun, Goodson, Henry and Macfie (Biochem. J.1930, 24, 874.) have published data showing that the antimalarial action of quinine is increased by reduction of the vinyl group, while similar reduction of quinidine, which differs from quinine only as regards the configuration of the carbon atoms (a) and (b),(I), (Rabe, Annalen, 1910, 373,89; Ber, 1922,55 (B),528. King and Palmer, J. 1922, 21, 2577.) does not increase its activity. It is very difficult to account for these facts, although it is reasonable to connect the disappearance of activity, when quinine is oxidised to quitenine, with the diminution of the basic character of the molescule, since the

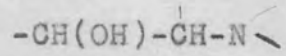
esters of quitenine are pharmacologically active.

(4) The Quinuclidine System.

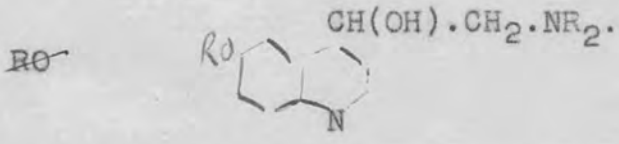
The effect of breaking one particular ring-linkage in this system is seen in the appearance of toxic properties in passing from the cinchonine to the cinchotoxine type, which effect is probably due to the exposure of the imino group. It should be observed that when a cinchona alkaloid is converted into its mono-acid salts, a new centre of dissymmetry appears, since salt formation first takes place on the tertiary nitrogen atom in the quinuclidine system:

This may be a significant factor in connexion with the pharmacological action.

Many attempts have been made to imitate the fundamental cinchonoid molecule, notably by Kaufmann and Rabe. The former author (Ber.1912, 45, 3090;1913, 46, 57, 2929; D.R-P. 268,931.) attributed the action of quinine to the group:

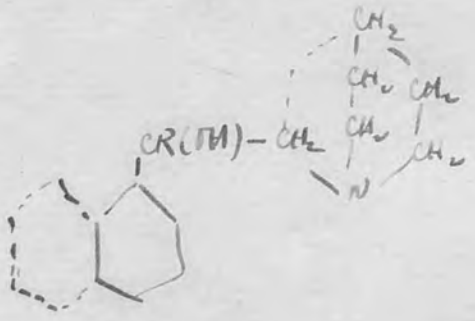


and showed that some compounds of the type:



resembled quinine on the basis of the physiological tests then available. The work of Rabe (Ber.1917, 50, 144, etc.) was similar to that of Kaufmann, but was developed on more complex synthetic lines. (Compare Ber. 1918, 51, 1360).

Within recent years, a large number of compounds have been investigated by different workers, in an attempt to obtain a satisfactory antimalarial drug. The majority of these compounds have been essentially structurally different from the cinchona alkaloids. In the present communication are described, amongst other experiments, the methods of preparation of a series of compounds of the general formula (II)(in which the dotted lines have no chemical significance), which bear what may be called pictorial resemblance to the cinchona alkaloids. (Compare the resemblance between the eucaines and cocaine.)



These compounds are for the most part readily prepared by treating I-phenacylpiperidine with a Grignard reagent, although in a few instances (e.g., when R is n-hexyl, n-heptyl or cyclohexyl) the synthesis has failed completely. For physiological tests, the carbinol hydrochlorides have been prepared, and the following are described in the experimental section: Phenyl-, phenylmethyl-, phenylethyl-, phenyl-n-propyl-, phenyl-n-butyl-, diphenyl-, phenylbenzyl-, phenyl-β-phenylethyl-, phenyl-γ-phenylpropyl-, phenyl-δ-phenylbutyl-, and phenyl-α-naphthyl-ω-piperidinomethylcarbinol hydrochlorides.

None of these compounds possesses any antimalarial activity, a fact which suggests that the essential missing factor is the basic

quinoline structure. The synthetic method, however, appears to be capable of general application, and is being used in the synthesis of the less readily accessible quinoline analogues of phenacylpiperidine.

A second synthetic method has been investigated, which is also apparently capable of extension to the synthesis of cinchonoid substances. For example, phenyl-β-phenylethyl ketone is readily converted into the bromo derivative, which reacts with piperidine:

$$Ph.CO.CH_2\text{-}CH_2\text{-}Ph \qquad Ph.CO.CHBr.CH_2\text{-}Ph$$

$$Ph.CO.CH_2\text{-}NC_5H_{10} \qquad Ph.CO.CH(NC_5H_{10})CH_2\text{-}Ph \quad III.$$

to give phenyl-α-piperidino-β-phenylethyl ketone (III). The latter may alternatively be obtained by the action of benzyl chloride on the sodium derivative of phenacylpiperidine. This method has been applied to the synthesis of piperidino-deoxybenzoin, $Ph.CO.CH.Ph.NC_5H_{10}$, a substance previously obtained by Rabe (Ber., 1912, 45, 2169), by treating sodiodeoxybenzoin with 1-chloropiperidine.

EXPERIMENTS ON THE BROMINATION OF 2:4 DIMETHYL-QUINOLINE.

In view of the fact that Hammick showed (J. 1923, 123, 2882) that quinaldine readily underwent tribromination in the side-chain, experiments were done on 2:4-dimethylquinoline, with a view to obtaining lepidine-2-carboxylic acid by a process similar to that used by Hammick for the preparation of quinaldinic acid, the object being the subsequent preparation of lepidine. In order to determine the scope of bromination, an attempt was first made to induce hexabromination, but the only product obtained was a tribromo compound. Monobromination also gave the same tribromo compound, but systematic experiments designed to produce the tribromo compound in satisfactory yields led to disappointing results. The tribromo compound, moreover, did not undergo the facile conversion into a carboxylic acid which was to be expected by analogy with Hammick's later work, (J. 1926, 1302), and since the main object of these experiments was to provide an easy synthesis of lepidine carboxylic acid, the work was abandoned. It must be pointed out that the constitution of the tribromo derivative may be different in type from Hammick's compound, and it is possible that it contains two bromine atoms in the 2-methyl group, and one in the 4-methyl group.

EXPERIMENTS ON QUITENINE.

It is known from the work of Henry, Goodson and Macfie that diminution of the acidity of quitenine by esterification partially restores antimalarial activity. Further evidence as to the relation between the basicity of the molecule and its antimalarial action has been sought in two directions. In the first place, attempts have been made to decarboxylate quitenine, but in spite of a large variety of experiments, no success has been achieved, although on one occasion a small quantity of a base was isolated which gave a solid picrate.

In the second place, attempts have been made to prepare quitenine amide and its benzoate. It was already known that thionyl chloride reacted in a rather complex way with quitenine, and it was surprising that John (J. Prakt. Chem. 1930, 128, 223) should have regarded the product he obtained by heating quitenine with a large excess of thionyl chloride, as the acid chloride of quitenine. The analysis that he gives to his compound has been found to agree much more satisfactorily with either of the following compounds:

1. (CHOH)(COCl) requires N. 7.7%
2. (CHCl)-(COCl) requires N. 7.4%
3. (CHOH)-(COCl)(HCl) requires N. 7.05%

John obtained N. 6.92%

It is obvious that in this reaction, a hydrochloride must be formed since no hydrochloric acid is given off. (Compare the preparation of benzoyl quitenine: Bucher, Monatsh. 1893, 14,598).

PREPARATION OF METHOHALIDES OF SOME CINCHONA ALKALOIDS.

These compounds were prepared for a twofold object: firstly, in order to produce methochlorides whose antimalarial activity could be tested and compared with those of the above mentioned synthetic hydrochlorides; and secondly, in order to obtain N-methyl cinchotoxine, it was necessary to prepare large amounts of cinchonine methobromide by a process more convenient than that given in the literature. It has been found that cinchonine and the other alkaloids combine very readily with methyl sulphate, from which, by the action of potassium bromide or ammonium chloride, the corresponding methohalides can be prepared. The conversion of an alkaloid into a methohalide now takes as many hours as it formerly took days.

EXPERIMENTAL.

Phenyl-α-Piperidino-β-phenylethyl ketone.

(1) Preparation of Phenyl-β-phenylethyl ketone. The methods described in the literature for the preparation of this substance are not satisfactory. We have found that when benzonitrile is added to two molecules of magnesium β-phenylethyl bromide, although obvious interaction occurs, only a small and variable yield of the expected ketone is obtained. The following method, however, was found convenient: β-Phenylethyl bromide was obtained in 91% yield by the interaction of 246 g. of β-phenylethyl alcohal and 115 c.c. of phosphorus tribromide. The bromide (337 g.) was refluxed for 3½ hours with a mixture of 135 g. of potassium cyanide, 135 g. of water, and 340 c.c. of alcohal. β-Phenylpropionitrile was obtained in 91% yield in the second stage, i.e. 81% calculated on the alcohol used. A Grignard reagent was prepared from 78 g. of bromobenzene, and was gradually treated with 26 g. of β-phenylpropionitrile. When the vigorous reaction had come to an end, the whole was heated for ½ hour on the water-bath, the mixture was decomposed in the usual manner, and the ketone was purified by distillation under reduced pressure 18 g. of pure phenyl-β-phenylethyl ketone, b.p. 196°/18mm., were obtained.

(2) Preparation of phenyl-α-bromo-β-phenylethyl ketone.

A solution of one mol. of the ketone in glacial acetic acid was treated with a glacial acetic acid solution of 1. mol. of bromide. Decolorisation occurred at about 50°. The solution

was poured into water, and the solid product was crystallised from alcohol, when the bromo compound (93%) was obtained as needles, m.p. 50-51°. (Found: Br, 27.4; $C_{15}H_{13}OBr$ requires Br, 27.7%).

(3) Action of piperidine on phenyl-α-bromo-β-phenylethyl ketone.

Equal weights of the bromo compound and piperidine were heated together in benzene solution for ½ hour at 100°. The cooled mixture was then well shaken with alkali, and the benzene layer was shaken with water and dried over sodium sulphate. Evaporation of the solvent gave phenyl-α-piperidino-β-phenylethyl ketone, which crystallised from alcohol in colorless leaflets, m.p. 77-78.5°. (Found: N, 5.3, $C_{20}H_{23}ON$ requires N, 4.8%).

(4) Preparation of phenacylpiperidine. Schmidt and van Ark, (Arch. Pharm. 1900, 238, 330.) obtained this compound in an impure condition, but did not characterise it. It can be obtained by either of the following methods:

(a). The method of Rabe, Schneider and Braasch (Ber. 1908, 41 874.) was modified as follows: A benzene solution of one part of phenacyl bromide was added to a solution of one part of piperidine in ether, and the mixture was allowed to stand for ½ hour after completion of the vigorous reaction. It was then treated with aqueous alkali, and the benzene layer was dried over sodium sulphate. After removal of the solvent, the residue was vacuum distilled, and gave an approximately 60% yield. (b.p. 168°/26 mm.).

(b). A considerable saving of piperidine was effected by using the following process: a solution of 80 g. of phenacyl bromide in 400 c.c. of benzene was added within 30 minutes to a well shaken mixture of 50 g. of piperidine, 70 g. of anhydrous potassium carbonate, and 400 c.c. of benzene in the cold. Water was added, and the benzene layer was separated and extracted three times with water, and then twice with 20% hydrochloric acid. The separated benzene layer was again extracted with a smaller quantity of acid and the united acid solutions were made ammoniacal, and extracted with ether. The ethereal layer was washed with a little water, was dried over sodium sulphate, and was evaporated. Distillation under reduced pressure of the residue gave 50 g. of almost pure colorless phenacylpiperidine of constant b.p.

(5) Preparation of Phenyl-α-piperidino-β-phenylethyl ketone.

Phenacylpiperidine (1 mol.) was added to one atom of powdered sodium, covered with 100 c.c. of toluene. The mixture was boiled until the sodium had disappeared, and then 1 mol. of benzyl chloride was added. The boiling was continued for ½ hour, the mixture was cooled, and extracted with water, the toluene was separated, dried and removed, and the residue was crystallised from methyl alcohol. The product had m.p. 80-81°, a mixture with the above product (m.p.77-78.5°) melting at 78-79°.

Preparation of m-Nitrophenacyl bromide.

The preparation of this substance by the method of Evans and

Brooks (J. Amer. Chem.Soc. 1908, 30, 406), was less satisfactory than the following modification of the process described by Hunnius (Ber. 1877. 10, 2008): phenacyl bromide was slowly added to ten parts of nitric acid (d.1.5), kept at -10° to -5°. The solution was poured onto ice, and the precipitate was collected, digested with ether to remove the o-nitro compound, and the residue was crystallised from alcohol; the yield of m-nitrophenacyl bromide, m.p. 80-81°, was 70%

Action of piperidine on m-Nitrophenacyl bromide.

Although the bromide condensed readily with piperidine under the conditions used for the preparation of phenacylpiperidine, (second method), the isolation of the product was not accomplished. Vacuum distillation caused explosive decomposition. Purification by crystallisation gave oily products, and although the picrate was obtained as a highly crystalline substance, m.p.175-176°, its subsequent decomposition by alkali gave amorphous products. In a second experiment, a benzene solution of m-nitrophenacyl bromide (1 mol.) was added to one of piperidine (2 mols.). After several hours, the precipitated hydrobromide was removed by filtration, and the filtrate evaporated. When the residue was stirred with dilute aceticaacid, an amorphous solid was obtained which could not be made to crystallise, and had an indefinite m.p.

Preparation of Piperidino-deoxybenzoin.

Chloro-deoxybenzoin was prepared by Schroeter, from benzoin and thyonyl chloride, (Ber. 1909, 42, 2348); the following modification of his method was used. A mixture of equal weights of

benzoin and thionyl chloride was warmed until a clear solution was obtained. After adding much warm water and stirring until cold, a solid product was obtained which crystallised from chloroform on adding light petroleum (b.p. 40-60°). The crystalline material was recrystallised from methyl alcohol, and them had m.p. 66-67°. Schroeter states that chlorodeoxybenzoin begins to soften at 66°, and melts at 68.5°, whereas Curtius and Lang (J.Prakt. Chem. 1891, II, 44, 548) gave mp. 65°.

The chloro compound was covered with its own weight of piperidine, and the mixture was slowly warmed to 100°, during 20 minutes. It was repeatedly extracted with water, and the gummy residue was crystallised from alcohol, when needles, mp. 85-86°, were obtained. (Rabe and Rieper, loc.cit., give m.p. 82°).

Phosphorus trichloride was found to be almost without action on benzoin, and phosphorus pentachloride gave a mixture which could not be purified.

Preparation of Phenyl-ω-piperidinomethyl carbinol.

Phenacyl piperidine was reduced as described by Rabe, (Annalen, 1909, 365, 377), but the product was worked up by the following, different method: the alkaline alcoholic reduction mixture was treated with water, and most of the alcohol was distilled off. The residue was extracted with ether, the extract was dried over sodium sulphate and evaporated, and the residue was distilled under reduced pressure. The base had the properties recorded by Rabe. The hydrochloride was prepared by passing dry hydrogen chloride through a light petroleum solution of the base, and had m.p. 192-194°.

(Found: Cl, 14.5, $C_{13}H_{20}ONCl$ requires Cl, 14.7%).

Preparation of Phenylmethyl-ω-piperidinomethyl carbinol hydrochloride.

An ethereal solution of phenacylpiperidine (1 mol.) was gradually added to a Grignard reagent prepared from 2 mols. of methyl iodide and 4 atoms of magnesium (with intermediate decantation from undissolved magnesium). After the addition was over, the mixture was gently boiled for ½ hour, and then decomposed with ammonium chloride solution. The ethereal solution was separated and extracted with dilute hydrochloric acid solution, and the acid layer, after being extracted with a little ether, was rendered ammoniacal, and extracted with light petroleum (b.p. 60-80°). This extract was dried over sodium sulphate and saturated with dry hydrogen chloride; when the carbinol hydrochloride was obtained as a white microcrystalline powder, which, after being heated at 100°, had m.p. 140-141°. (Found: N, 5.8; Cl, 14.0; $C_{14}H_{22}ONCl$ requires N, 5.5; Cl 13.9%).

Phenylethyl-ω-piperidinomethylcarbinol hydrochloride.

This substance was obtained by the same method as that used for the methyl analogue. The carbinol hydrochloride, precipitated by dry hydrogen chloride from a light petroluem solution of the base, was crystallised from a mixture of alcohol and ether, and dried at 100°; and was obtained as a microcrystalline powder, softening at 168°, and melting at 171-173°. (Found: N, 5.6; Cl, 13.5; $C_{15}H_{24}ONCl$ requires N, 5.2; Cl, 13,2%).

Phenyl-n-propyl-ω-piperidinomethylcarbinol Hydrochloride.

Interaction of phenacylpiperidine and magnesium propyl bromide (2 mols.) was very vigorous. The carbinol hydrochloride was obtained by the method described under the preceding compounds, and after being dried at 100°, was obtained as a microcrystalline powder, m.p.185-187°, (Found: Cl,13.0; $C_{16}H_{26}ONCl$ requires Cl, 12.5%).

Phenyl-n-butyl-ω-piperidinomethylcarbinol Hydrochloride.

When phenacylpiperidine was added to 2 mols. of ethereal magnesium butyl bromide, a solid formed on the surface, but later redissolved. The hydrochloride precipitated from light petroleum was crystallised from a mixture of alcohol and ether, and dried at 100°. It was a microcrystalline powder, m.p.166-169°, (Found: Cl,12.0; $C_{17}H_{28}ONCl$ requires Cl, 11.9%).

Action of Magnesium n-Hexyl Iodide on Phenacylpiperidine.

The preparation of this substance was performed in the same way as the other Grignard reactions, using 2 mols. of n-hexyl iodide, 1 mol. of phenacylpiperidine and 4 atoms of magnesium. On adding the phenacylpiperidine, a part of the precipitate formed redissolved. The hydrochloride of the base could only be obtained by passing dry hydrogen chloride into a petroleum ether (80-100°) solution of the base.

m.p. of the hydrochloride, 213-219°.

mixed m.p. of the hydrochloride with the hydrochloride of the heptyl compound, 215-220°.

Analysis of the hydrochloride.

Substance, 0.4300 g. AgCl, 0.2550 g.

whence Cl, 14.7%

$C_{19}H_{31}ON.HCl$ requires Cl, 10.9%

Phenacylpiperidine hydrochloride $C_{13}H_{18}ONCl$ requires Cl, 14.8%.

Action of Magnesium n-Heptyl Iodide on Phenacylpiperidine.

The details of this experiment are exactly the same as for the n-hexyl compound. The hydrochloride had m.p. 216-220°, and mixed m.p. with the hydrochloride of the n-hexyl compound was 215-220°.

Action of Magnesium Cyclohexyl Iodide on Phenacylpiperidine.

(1)
Preparation of cyclohexyl bromide.

100 G. of Boake Roberts cyclohexanol were heated under reflux over a gauze for 1½ hours with 700 c.cl of hydrobromic acid (d. 1.49). Separation of an oil occurred within 10 minutes. The product was cooled, the top layer of cyclohexyl bromide was separated, washed with water, and dried over ~~cal~~ calcium chloride.

Yield, 114 g. (70% yield).

B.p., 162-166°.

A.

The experiment was conducted as usual, using:

(1 mol.), 15 g. of phenacylpiperidine

(4 atoms), 8 g. of magnesium

(2 mils), 25 g. of cyclohexyl bromide.

The hydrochloride was prepared by the dry method, (H Cl gas in petroluem ether solution) and 14 g. of product were obtained, after drying at 100°. (58% of the theoretical yield).

Analysis.

Substance, 0.4304 g. - AgCl , 0.2386 g.

whence Cl , 13.7%

$C_{19} H_{24} ONCl$ requires Cl , 11.2%

B1

The experiment was repeated, using:

(1 mol.) 11 g. of phenacylpiperidine

(10 atoms) 13 g. of magnesium

(5 mols.) 45 g. of cyclohexyl bromide

After drying the hydrochloride at 100°, the yield was 9.5 g.

Analysis.

Substance, 0.4326 g. AgXl , 0.2214 g.

whence Cl , 12.7%.

C.

The experiment was again repeated, using:

(1 mol.) 10.5. g. of phenacylpiperidine

(20 atoms) 25 g. of magnesium

(10 mols.) 81.5 g. of cyclohexyl bromide

The precipitate which formed on adding phenacylpiperidine to the Grignard reagent redissolved. The whole product was precipitated with hydrochloric acid, and was crystallised from alcohol, in order to get not more than two g. of the product.

The m.p. was found to be 217-220°.

Analysis.

Substance, 0.4320 g. AgCl, 0.2496 g.

whence Cl , 14.3%

Diphenyl-ω-piperidinomethylcarbinol Hydrochloride.

After addition of the phenacylpiperidine to the magnesium phenyl bromide solution (2 mols.), the mixture was heated for some time, cooled, and decomposed with ammonium chloride solution. The ethereal layer was extracted with dilute hydrochloric acid, and the acid layer was once extracted with ether. The acid solution was boiled to remove ether, and kept; the carbinol hydrochloride then separated in long, colorless needles, which, after being dried at 100°, melted at 214-218°. (Found: N, 4.5; Cl, 11.9; $C_{19}H_{18}ONCl$ requires N, 4.5; Cl, 11.2%).

Phenylbenzyl-ω-piperidinomethylcarbinol Hydrochloride.

On addition of phenacylpiperidine to the magnesium benzyl chloride solution (2 mols.), a white precipitate was first formed, and later redissolved. The mixture was gently boiled for ½ hour, cooled, and then decomposed with ammonium chloride solution. The aqueous layer was extracted with ether, and the combined ethereal solutions were shaken with a mixture of equal volumes of concentrated hydrochloric acid and water, when the carbinol hydrochloride separated as a crystalline precipitate. The suspension was filtered, the solid was washed with ether, and was crystallised from alcohol. Spear-shaped needles were obtained, m.p. 238-244°. These were sparingly soluble in dilute hydrochloric acid of cold alcohol, were very soluble in warm alcohol. (Found: Cl, 10.7; $C_{20}H_{26}ONCl$ requires Cl, 10.7%)

Phenyl-β-phenylethyl-ω-piperidinomethylcarbinol Hydrochloride.

The mixture resulting from the interaction of phenacylpiperidine and 2 mols. of magnesium β-phenylethyl bromide was decomposed with ammonium chloride solution, and the ethereal layer was shaken with concentrated hydrochloric acid mixed with an equal volume of water. The carbinol hydrochloride which separated was washed with water and ether, and dried at 100°. The combined mother-liquors were separated from the ether layer, extracted with light petroleum, the extract was dried over sodium sulphate, and saturated with hydrogen chloride. The precipitated carbinol hydrochloride was crystallised from a little alcohol by addition of ether. The combined yields of the hydrochloride, m.p. 211-216°, was 65%. (Found: N, 4.0; Cl , 10.2; $C_{21}H_{28}ONCl$ requires N, 4.05; Cl , 10.3%).

Phenyl-γ-phenylpropyl-ω-piperidinomethylcarbinol Hydrochloride.

The product resulting from the interaction of phenacylpiperidine and 2 mols. of magnesium γ-phenylpropyl bromide was treated as usual, the hydrochloride separating when the ethereal solution was shaken with 20% hydrochloric acid. It was washed with ether and dried at 100°, and had m.p. 209-210°. (Found: Cl , 9.8; $C_{22}H_{30}ONCl$ requires Cl, 9.9%).

Phenyl-δ-phenylbutyl-ω-piperidinomethylcarbinol Hydrochloride.

The preparation from phenacylpiperidine and magnesium δ-phenylbutyl bromide (2 mols.) was carried out by the method used for the β-phenylethyl derivative. The hydrochloride crystallised from

alcohol, containing dilute hydrochloric acid, in colorless needles, which, after being dried at 100°, had m.p. 173-174°. The hydrochloride is very soluble in warm alcohol, and almost insoluble in cold dilute hydrochloric acid. (Found Cl , 9.5 ; $C_{23}H_{32}ONCl$ requires Cl , 9.5%).

Phenyl-α-naphthyl-ω-piperidinomethylcarbinol.

Phenacylpiperidine and magnesium α-naphthyl bromide reacted normally. The mixture was heated for 1 hour in warm water, cooled, and decomposed with ammonium chloride solution. The ethereal layer was shaken with its own bulk of 20% hydrochloric acid, and again with a smaller amount of dilute acid. The combined acid extracts were well shaken with ether, the ether was separated, and the acid solution was warmed until free from ether. Addition of dilute ammonium hydroxide produced a gum, which after much digestion with hot water became solid, and was then crystallised from alcohol. The crystalline product was recrystallised from light petroleum (b.p. 80-100°). From both solvents the carbinol separated in sparkling nodules, m.p. 114-115°. (Found: N, 4.2; $C_{23}H_{25}ONCl$ requires N, 4.2%).

EXPERIMENTS ON THE BROMINATION OF 2:4-DIMETHYL QUINOLINE.

Attempted Hexabromination of 2:4-Dimethyl Quinoline.

32 c.c. of bromine were added to a solution of 16 g. of 2:4 dimethyl quinoline and 100 g. of anhydrous sodium acetate in glacial acetic acid. The mixture was warmed until no further change occurred, and was then poured into water; the product was crystallised from light petroleum, (b.p. 80-100°). It melted with decomposition at 125°.

Analysis.

Substance, 0.1177; AgBr, 0.1722

whence Br , 61.7%.

Tribromination requires Br, 60.9%.

Dibromination requires Br, 50.8%.

Tetrabromination requires Br, 67.8%.

Attempted momobromination of 2:4-dimethyl quinoline.

This experiment was done similarly, and the product was identical with that above.

Analysis.

Substance, 0.1773; AgBr, 0.2515;

whence Br, 60.4%.

An attempt was made to hydrolyse the tribromo compound, using boiling alkali, or boiling dilute sulphuric acid or silver oxide. No success was achieved in any of these experiments.

ATTEMPTED DECARBOXYLATION OF QUITENINE.

(1). Using Copper Bronze.

One g. of quitenine was ground up with 30 g. of copper-bronze, and the mixture was heated in a metal bath at 200-210° for 1 hour. The powdery mass was then ground up with sodium carbonate solution, and extracted with ether. The ether extract was washed with water, and evaporated to dryness. There was no residue.

This experiment was repeated, using 1 g. of quitenine and 20 g. of copper-bronze, the mixture being heated to 290-300° for 40 minutes. During the first 10 minutes, steam came off from the mixture, and then for 30 minutes there was no change at all. The mixture was worked up as before. Again there was no residue from the ether extract.

(II). Using Soda-lime.

One g. of quitenine was ground up with 20 g. of soda-lime, and the mixture was heated for 1¼ hours at 210-240°, in a metal-bath. A small quantity of residue was obtained after the mixture had been refluxed with acetone, and the filtered acetone had been evaporated to dryness. The solid residue was insoluble in alkali or in water, showing that is was not unchanged quitenine.

The experiment was repeated using 3 g. of quitenine and 40 g. of soda-lime. The soda-lime and quitenine had previously been dried

separately. The mixture was heated in a metal-bath at 220-230°, for 1¾ hours. The same result as before was obtained.

(III). Using Barium Hydroxide.

20 g. of barium hydroxide and 2 g. of quitenine were ground together and heated in a metal-bath; at 240° decomposition began. The product became black, and pungent fumes mixed with steam were evolved. The heating was only continued for ½ hour at this temperature, and the mixture was extracted with ether, washed with alkali and then with water, and evaporated. Some residue was obtained, which gave a crystalline gold salt with gold chloride.

The experiment was repeated using 5 g. of quitenine and 70 g. of barium hydroxide. The mixture was heated in a metal-bath for ½ hour at 240°, ground up with water, shaken with chloroform, filtered, shaken again, separated, washed with water, separated from the water, and the chloroform was evaporated to dryness. A small yield of amorphous solid matter was obtained.

A modification ~~of~~ of the above experiment was made by first fusing 3 g. of quitenine with 40 g. of barium hydroxide, and then powdering the solid mass; which was heated at 200-240°, for ½ hour, ground with water, extracted with toluene, the toluene washed twice with water and once with distilled water, and then with dilute sulphuric acid. The acid layer was separated and basified with ammonia. A negligible precipitate was obtained.

(IV). Attempted decarboxylation of quitenine through the Lithium salt.

3.4 gl of quitenine were added to a solution of 1.5 g. of lithium hydroxide in 50 c.c. of boiling water. The mixture was evaporated to dryness, and when dry, heated in a metal-bath at 200°. On working up with ether, no residue was obtained.

(V). Attempted decarboxylation of quitenine by dry vacuum heating.

5 g. of dry quitenine were placed in a round-bottomed flask which was attached to a vacuum pump. The flask was heated in a metal-bath. No change in the quitenine was observed until the m.p. was reached (275° approximately). At this temperature the quitenine began to decompose rapidly. It became a black, tarry mass, and effervesced vigorously. (CO_2 coming off?). After the effervescence was over, the black tar was extracted with benzene, and the benzene was washed with alkali. The remaining tar which did not dissolve in benzene was extracted in a Soxhlet apparatus with acetone, the whole apparatus being wrapped in a thick layer of cotton wool to keep the temperature of extraction as high as possible. The acetone was evaporated off. The remaining tar was finally extracted with ether, the ether was extracted with potassium carbonate solution and washed with water. The three residues, obtained from the benzene, acetone and ether extractions, were dissolved in absolute alcohol, and a saturated solution of picric acid in alcohol was added. The picrate formed was a yellow solid, and

had m.p. of 225-226° with previous softening, and darkening.

0.1167 g. of the picrate were weighed out and dissolved in 20 c.c. of pure acetone. The solution was a deep red color and opaque to light, so it was diluted to ¼ of the original concentration, and put in a decimetre tube.

Zero of tube, 0. 17

Readings of rotation 0.40
0.40
0.41
0.40

Therefore the angle read=0.23 .

$$[\alpha]_{5791}^{20^\circ} = + 157.5$$

The base, both when the solutions were evaporated to dryness and after basification of the picrate, had a characteristic sweet, scent-like smell.

A modification of the above experiment was conducted in the following manner: 5 g. of quitenine at a time were heated by the reduced pressure method (as above), until all effervescence had stopped, and when 20 g. had been treated in this manner, the whole tarry matter was soxhleted with ether. The ether extracted nothing, so benzene was used. On examining the benzene solution polarimetrically, a rotation was obtained. (The benzene had been previously washed with alkali and then with water, to remove unchanged quitenine.) The base was then obtained free from benzene by evaporation on a water-bath, and was dissolved in 1:3 hydrochloric acid solution. A rotation of the hydrochloride was taken, and it was found to possess

some optical activity. The tarry matter was soxhleted again with benzene, the benzene solution was extracted with akkali, washed with water, and dried over sodium carbonate and blood charcoal, (to remove the color), Dry hydrogen chloride was passed into the filtered solution, in order to try and obtain the hydrochloride crystalline, but the only result was a just visible cloudiness.

ATTEMPTED PREPARATION OF QUITENINE AMIDE OR DERIVATIVES OF QUITENINE AMIDE.

(1). 8 g. of quitenine were treated with 30 g. of thionyl chloride. The quitenine was placed in a flask fitted with a condenser, and the thionyl chloride was gradually added. After the addition was complete, the mixture was warmed to about 60°, and the excess of thionyl chloride was removed under reduced pressure. Benzene was added repeatedly, and evaporated under reduced pressure, until all the thionyl chloride had been removed and the solid was a crystalline mass. The solid was removed from the flask, and ground up with solid ammonium carbonate. The whole was then added to water, the solution was extracted with chloroform, which was dried over sodium carbonate, and evaporated to dryness. No residue was obtained.

(11). 4 g. of quitenine were added to 20 g. of thionyl chloride, in which it all dissolved with the evolution of heat. The excess of thionyl chloride was removed as before. The acid chloride hydrochloride was ground up to a fine, dry powder and suspended in dry benzene; ammonia gas, dried over soda-lime was passed into the suspension for two hours. The benzene was then filtered from any unchanged solid material, and evaporated. The residue was powdered up, and analysed.

Analysis. Substance, 0.4290 g.

after combustion T = 20°
p = 759 mm.
volume of nitrogen 36.8 c.c.

N found 10.9%.

Quitenine amide $C_{19} H_{23} O_3 N_3$ requires N 12.4%

(III). Quitenine hydrochloride was prepared by evaporating 5 g. of quitenine with 5 c.c. of concentrated hydrochloric acid. An exactly equivalent amount of thionyl chloride was used to prepare the acid chloride. After working up as usual, dry ammonia gas was passed into a benzene suspension of the solid for 1 hour. Excess of ammonia was removed under reduced pressure, and dry hydrochloric acid gas was passed in. A negligible precipitate of the hydrochloride was obtained, and was not worked up.

The experiment was repeated, adding an excess ($\frac{1}{2}$ mol.) of thionyl chloride, and working up as before. The same negative result was obtained.

(IV). Quitenine amide hydrochloride.

The amide was prepared as in experiment II, but the benzene was not all evaporated off. Dry hydrochloric acid gas was passed into the solution, and a white amorphous precipitate was obtained. Ether was added, and the whole was filtered and left in a vacuum desiccator for 15 hours, over phosphorus pentoxide and paraffin wax.

Analysis. Substance, 0.2742 g.

After combustion.
temp. 18°.
press. 754 mm.
volume of nitrogen 20.8 c.c.

Found N, 8.7%

Calc. N, 10.1%.

Attempted preparation of benzoyl quitenine amide.

A.

4 g. of quitenine were heated with 10 g. of benzoyl chloride on a boiling water-bath for one hour. The solid obtained was washed free from benzoyl chloride with ether, was dissolved in a littel absolute alcohol, and was precipitated with ether. The yield was 4 g.

This experiment was repeated using 9 g. of quitenine and 25 g. of benzoyl chloride, and the yield was 13 g.

B.

Preparation of the acid chloride of benzoyl quitenine.

Benzoyl quitenine hydrochloride was refluxed for ½ hour at 100°, with 20g. of thionyl chloride, in which it almost immediately dissolved on warming. The excess of thionyl chloride was removed as usual, and the precipitate was washed with dried benzene, ground up, left in vacuo for 20 hours over phosphorus pentoxide, potassium hydroxide, sulphuric acid and paraffin wax.

yield = 4 g.

Analysis.

Substance, 0.4317 g. AgCl , 0.3899 g.

whence Cl, 22.4%

Quitenine chloride hydrochloride requires Cl 17.9%.

2 HCl requires Cl 24.6%

Benzoyl quitenine chloride hydrochloride requires Cl 14.2%

2 HCl requires Cl 19.8%

C.

Repeated attempt of the preparation of benzoyl quitenine amide.

2 g. of the acid chloride hydrochloride were ground up with 0.880 ammonia. Heat was liberated during the reaction. The product was extracted with benzene which was washed with water, and the benzene was distilled off. The solution was evaporated to dryness, the residue was washed with petroleum ether (b.p. 60-80°) and left in a vacuum desiccator over phosphorus pentoxide, caustic potash, sulphuric acid and paraffin wax.

Yield of solid matter 0.5 g.

Analysis. 3.262 mg. gave 3.615 mg. of carbon dioxide, 1.840 mg. of water. Ash 0.026 mg.

7.526 mg. gave 0.490 c.c. of nitrogen at 750 mm and 24.

Ignoring the ash:

C 63.6%
H 6.3%
N 7.3%

Benzoyl quitenine amide ($C_{26} H_{28} O_4 N_3$) requires:

C 70.0%
H 6.3%
N 9.4%

PREPARATION OF CINCHONINE METHOBROMIDE.

The method described in the literature was first used, and gave the following result;

A suspension of 60 g. of cinchonine in 1000 c.c. of absolute methyl alcohol was saturated with methyl bromide, and kept in the cold for two days. The clear solution was distilled until the volume was 150 c.c. On cooling the solution, crystals separated, but 150 c.c. of water were added to precipitate the product. The heated solution was filtered to remove the scum and allowed to crystallise. Filtration followed by drying at 100° gave 73 g. of cinchonine methobromide (90% yield).

The difficulty of obtaining methyl bromide, and the time required for the above operations made it necessary to effect improvements. The following method was found satisfactory: A suspension of 59 g. of cinchonine in 60 c.c. of absolute methyl alcohol was treated with a solution of 19 c.c. of methyl sulphate in 100 c.c. of methyl alcohol. On warming gently, the cinchonine dissolved; the solution was evaporated under reduced pressure, 500 c.c. of water were added; the solution was filtered from unchanged cinchonine (3 g.); the filtrate was heated to about 60°, and treated with a solution of 48 g. of potassium bromide in 500 c.c. of water. On cooling, 67 g. of colorless, highly crystalline cinchonine methobromide were obtained. (87% yield, or 92%, allowing for the recovered cinchonine).

PREPARATION OF THE METHOCHLORIDES OF SOME CINCHONA ALKALOIDS.

Methochlorides of cinchonine, cinchonidine, quinine and quinidine were prepared by a suitable modification of the process used for cinchonine methobromide; i.e., by substituting ammonium chloride for potassium bromide, and where necessary, using considerably less methyl alcohol, (e.g., for cinchonidine). It is interesting that cinchonine and its methohalides are very much less soluble in hydroxylic solvents than cinchonidine and its methohalides.

Quinidine Methochloride.

This substance, which owing to its considerable solubility in the alcohols and water, was only obtained with difficulty, is not described in the literature. Analysis of this compound was therfore carried out:

(1). Substance, 0.3523 g.
AgCl 0.2158 g.

Whence Cl, 9.7%.

(2). Substance, 0.4865 g.
AgCl 0.1985 g.

Whence Cl, 10.1%.

(3). Substance, 0.7296 g.
AgCl 0.2884 g.

Whence Cl, 9.8%.

The methochloride was found to be a hydrate:

0.6946 g. of the salt lost:

0.0300 g. of water in 1 hour at 110°.

a further 0.001 g. after an additional ½ hour at 110°.

After 15 hours in vacuo over phosphorus pentoxide a further loss of 0.003 g. was obtained.

The loss was not increased by further drying at 110°.

Total loss 0.0330.g. of water.

For a monohydrate, the loss should be 0.0319 g.

Therefore the salt forms a monohydrate.

Reprinted from the Journal of the Chemical Society, 1931.

CLIV.—*The Reactions of Substituted Ammonium Aryloxides and of Related Compounds. Part I. The Preparation and Thermal Decomposition of Some Tetrasubstituted Ammonium Aryloxides.*

By Rosalind Venetia Henley and Eustace Ebenezer Turner.

Compounds of the class described in this communication may be written as of the general type $R_4\overset{+}{N}\}\overset{-}{O}Ar$, and are related to the metallic phenoxides in structure, but differ from these in that the phenoxide radical can only be electrovalently attached to the tetrasubstituted ammonium radical, on the assumption that nitrogen is only capable of quadricovalency, whereas many of the metallic

phenoxides may exhibit the physical properties of covalent compounds (*viz.*, the solubility of sodium β-naphthoxide and of sodium *p*-chlorophenoxide in anhydrous ether) (Tijmstra and Eggink, *Ber.*, 1906, **39**, 14; Hantzsch and Mai, *Ber.*, 1895, **28**, 978).

In view of the fact that many of the reactions of phenols in alkaline solution are regarded as being caused by the ionisation of the metallic phenoxide, we thought that such typical processes as the Kolbe–Schmitt carboxylation and the Reimer–Tiemann reaction could with advantage be studied in the ammonium series. In the present communication we describe the preparation of some tetrasubstituted ammonium aryloxides, and their behaviour towards heat, since we required a knowledge of their thermal stability before undertaking an examination of their reactions.

A number of tetrasubstituted ammonium picrates are known, but these are clearly unsuitable for this work. The preparation of *phenyltrimethylammonium* o-*nitrophenoxide* was first attempted, so as to gauge the experimental difficulties likely to be encountered when less acidic phenols were used. We realised that, according to commonly accepted theory, *o*- and *p*-nitrophenoxides are salts of the coloured quinonoid forms, and not therefore true phenoxides. This theory, however, is less satisfactory than is sometimes assumed, for it does not entirely accord with the experimental observations of the action of alkyl halides on silver nitrophenoxides, and does not explain the bright red colour of sodium *m*-nitrophenoxide, nor the existence of orange-red forms of 2 : 4 : 6-tribromophenol and similar compounds (Torrey and Hunter, *Ber.*, 1907, **40**, 4333; Hantzsch and Scholtze, *ibid.*, p. 4881).

Although phenyltrimethylammonium *o*-nitrophenoxide is extremely hygroscopic, it was isolated as a scarlet, highly crystalline substance: the corresponding p-*nitrophenoxide*, also very hygroscopic, was yellow. So far the *m*-nitrophenoxide has remained as a deep red oil in spite of all attempts to make it crystallise.

The isolation of *phenyltrimethylammonium phenoxide* proved difficult, but the substance was eventually obtained in quantity. It exhibited true salt-like insolubility in anhydrous ether, but was very soluble in water and in alcohol, and was sufficiently soluble in nitrobenzene to crystallise from this solvent. *Phenyltrimethylammonium α-naphthoxide* was even more difficult to isolate in the pure state, but was finally crystallised from nitrobenzene and also from acetone.

Phenyltrimethylammonium thiophenoxide and *phenyltrimethylarsonium thiophenoxide* have been prepared. Their isolation is much less difficult than that of the above phenoxides.

We propose to study all the relevant reactions of the new series of

phenoxides in the solid state, in weakly ionising solvents such as nitrobenzene, and in hydroxylic solvents. Preliminary work has already shown that the ammonium phenoxides are very much more reactive than those of the alkali metals. In the present communication, however, we confine our attention to two sets of observations : (1) on the thermal decomposition of the aryloxides and (2) on their interaction with alkyl iodides.

Initial experiments on the thermal decomposition of the phenoxides showed that these compounds undergo particularly smooth and quantitative scission :

$$R_1R_2R_3R_4\overset{+}{N}\}\bar{O}Ar = R_1R_2R_3N + R_4OAr.$$

In fact, in a study of its thermal decomposition a tetrasubstituted ammonium aryloxide may for all practical purposes be regarded as a mixture of its decomposition products, which has to be purified by vacuum distillation. In all the cases examined, thermal decomposition proceeds quantitatively in a few minutes. For example, if phenyltrimethylammonium phenoxide is " distilled " under reduced pressure by means of a heating bath kept at about 120°, dimethylaniline and anisole pass over as rapidly as the apparatus allows, and are obtained in quantitative yield.

A convenient method is thus made available for a study of the mode of decomposition of tetrasubstituted ammonium aryloxides of a number of different types. The course of any such thermal decomposition may be controlled either by the groups R_1, R_2, R_3, and R_4 contained in the ammonium ion, or by the aryl group of the aryloxide ion, but consideration of the probable mechanism of the decomposition suggests that, although the aryloxy-group may affect the *speed* of decomposition, it is unlikely to have any effect on the *sense* of that decomposition. The simplest expression for the decomposition appears to be as below :

$$\left[\begin{array}{c} R_2 \\ R_1{:}\overset{\cdot\cdot}{N}{:}R_3 \\ \cdot\cdot \\ R_4 \end{array}\right]^{+} \bar{O}Ar \longrightarrow R_1{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}{:}R_3 + \overset{+}{R_4} + \bar{O}Ar \longrightarrow R_1R_2R_3N + R_4OAr.$$

That is, since the ammonium ion is forced to eject one of its R components, it expels that one which is least firmly attached. This ejected fragment R_4 will have a brief existence as a positive ion, and neutrality will be attained by its combination with the aryloxide ion. It is known that during the thermal decomposition of lead tetramethyl, methyl ions do persist during a short time (Paneth and Hofeditz, *Ber.*, 1929, **62**, 1335). Although it is possible that the aryloxide ion may have preference for one or other of the groups R,

it seems clear that the main controlling mechanism is the initial decomposition of the ammonium complex.

The thermal decomposition of phenyltrimethylammonium phenoxide, *o*-, *m*-, and *p*-nitrophenoxide, 2 : 4-*dinitrophenoxide*, α-naphthoxide, and *m*-4-xylyloxide leads in every instance to dimethylaniline and the methyl ether of the phenol. In no case was a detectable quantity of the diphenyl ether type formed. The thermal decomposition of *phenylbenzyldimethylammonium* o-*nitro*- and 2 : 4-*dinitrophenoxide* and the xylyloxide all give dimethylaniline, the benzyl radical in each case undergoing most ready ejection from the ammonium ion, and appearing as the corresponding benzyl aryl ether. To a limited extent, these results suggest that even profound modification of the aryloxide does not have any effect on the course of the decomposition.

Thermal decomposition of *phenyldimethylethylammonium* 2 : 4-*dinitrophenoxide*, on the other hand, is not unidirectional, dimethylaniline, methylethylaniline, 2 : 4-dinitroanisole and 2 : 4-dinitrophenetole all being formed.

Phenyltrimethylammonium thiophenoxide undergoes quantitative thermal decomposition into dimethylaniline and thioanisole. When phenyltrimethylarsonium thiophenoxide is heated, slight sublimation takes place, but again quantitative decomposition occurs, giving phenyldimethylarsine and thioanisole.

We have also examined the effect of boiling aqueous solutions of some tetrasubstituted ammonium aryloxides. It was not surprising to find that phenyltrimethylammonium phenoxide was rapidly and completely converted, when boiled in 10% aqueous solution, into dimethylaniline, phenol and methyl alcohol, and that no anisole could be detected, but it was not anticipated that prolonged boiling, followed by evaporation to dryness of the corresponding *p*-nitrophenoxide, would be unaccompanied by appreciable hydrolysis or decomposition, which was our experimental observation. Experiments are in progress on the effect of limited amounts of water and other solvents on the decomposition of the phenoxides.

After the above work was completed, we found that Hanhart and Ingold (J., 1927, 997), in their study of a different problem, had decomposed trimethyl-*n*-propylammonium phenoxide and *m*-nitrophenoxide, without attempting to isolate them. We have been in communication with Professor Ingold, who expressed his willingness for us to proceed with our work.

Tetrasubstituted ammonium aryloxides react with methyl (ethyl) iodide to give the quaternary ammonium iodide and a phenolic ether:

$$\overset{+}{\mathrm{NR_4}}\}\overset{-}{\mathrm{O}}\mathrm{Ar} + \mathrm{MeI} = \overset{+}{\mathrm{NR_4}}\}\overset{-}{\mathrm{I}} + \mathrm{MeOAr}$$

and here the speed of the reaction is affected largely by the nature of the groups substituted in the aryloxide ion.

Of the phenyltrimethylammonium phenoxides at our disposal, the *m*-4-xylyloxide and the α-naphthoxide reacted vigorously with cold methyl iodide, and the phenoxide almost as readily. The *o*-nitrophenoxide reacted completely with methyl iodide after five minutes' boiling in alcoholic solution, whereas the 2 : 4-dinitrophenoxide was unaffected by this treatment, although, after being boiled in methyl-alcoholic solution with methyl iodide for three hours, it was entirely converted into the quaternary iodide and dinitroanisole. These results indicate quite definitely that substitution in the aryloxide ion nucleus of electron-attracting groups decreases the rate of reaction with methyl iodide, but groups having electron-donating properties increase it.

Phenyltrimethylarsonium thiophenoxide reacts instantaneously with cold methyl iodide to give phenyltrimethylarsonium iodide and thioanisole. Phenyltrimethylammonium thiophenoxide reacts readily with cold methyl iodide to give the analogous products.

We hope shortly to report on the action of halogens, chloroform, and other compounds on the new phenoxides.

Experimental.

Phenyltrimethylammonium o-*Nitrophenoxide.*—A concentrated warm aqueous solution of phenyltrimethylammonium iodide (1 mol.) was treated with freshly precipitated silver oxide until the black oxide was clearly visible on shaking, and the solution gave no test for iodide. The liquid was filtered and, after being treated with 1 mol. of *o*-nitrophenol, was evaporated under reduced pressure in a bath kept at 50—60°, alcohol being added from time to time to accelerate evaporation. When no further diminution in volume occurred, the syrupy red product was dissolved in a little absolute alcohol, and anhydrous ether was added until crystallisation set in, whereupon excess of ether was added, and the precipitate was rapidly collected and washed with ether. After being dried in a vacuum over sulphuric acid, the o-*nitrophenoxide* was obtained as scarlet plates, m. p. 117—117·5° (Found : N, 10·0. $C_{15}H_{18}O_3N_2$ requires N, 10·2%). The nitrophenoxide is excessively hygroscopic, but can be kept for an indefinite period in a dry atmosphere. It may also be prepared by the interaction of phenyltrimethylammonium iodide and silver *o*-nitrophenoxide in boiling alcoholic solution.

The nitrophenoxide was warmed for 5 minutes with a methyl-alcoholic solution of methyl iodide. Ether was then added, and the crystalline precipitate was identified as phenyltrimethylammonium iodide, m. p. 225°.

Thermal Decomposition of Phenyltrimethylammonium o-*Nitrophenoxide.*—The phenoxide (7·5 g.) was heated at 180° in a large boiling tube fitted with a calcium chloride tube. After a few minutes, dimethylaniline began to form, and after an hour the decomposition was complete. The product was dissolved in benzene and the solution extracted with 20% hydrochloric acid. From the benzene solution were obtained 3·5 g. of *o*-nitroanisole, and from the acid layer, by treatment with ammonium hydroxide, followed by extraction with benzene, the dimethylaniline was isolated. It was converted into the methiodide, of which 5 g. were obtained, m. p. 229—230°.

Phenyltrimethylammonium p-*Nitrophenoxide.*—The preparation of this compound was carried out similarly to that of the *o*-isomeride. The phenoxide was obtained crystalline by adding anhydrous ether to the concentrated alcoholic solution, and formed yellow prismatic needles, m. p. 118—119°, with considerable previous softening. It is very hygroscopic, but may be crystallised (yellow needles) from nitrobenzene if it has previously been well dried (Found: N, 10·0. Calc.: N, 10·2%). Decomposition at 170° by the process used for the *o*-isomeride gave almost theoretical yields of dimethylaniline and *p*-nitroanisole.

The *p*-nitrophenoxide reacts rapidly with potassium iodide in alcoholic solution to give phenyltrimethylammonium iodide. A solution of 2 g. of the *p*-phenoxide in 40 c.c. of water was boiled under reflux for 4 hours. No odour of dimethylaniline was produced, and the solution was then evaporated to dryness on the water-bath. The residue became solid, after being dried in a vacuum over phosphoric oxide, and then melted at 115—120°. It produced no depression of the m. p. of the original material.

Methyl iodide slowly converts phenyltrimethylammonium *p*-nitrophenoxide in boiling alcoholic solution into the quaternary iodide and *p*-nitroanisole.

Phenyltrimethylammonium m-*Nitrophenoxide.*—This substance was obtained as a deep red oil, which, even after prolonged extraction with anhydrous ether and vacuum desiccation over phosphoric oxide, refused to crystallise. By this process, however, all impurities are effectively removed.

Thermal decomposition of the phenoxide by the process used above gave almost theoretical yields of dimethylaniline and *m*-nitroanisole (m. p. 36° when crude).

Phenyltrimethylammonium 2:4-*Dinitrophenoxide.*—This substance crystallised from the concentrated alcoholic solution obtained at the evaporation stage of its preparation by the usual process. It crystallised from absolute alcohol in yellow prisms, softening at 90°

and melting at 121—123° (Found : N, 13·2. $C_{15}H_{17}O_5N_3$ requires N, 13·2%).

The phenoxide was heated for ¼ hour at 135—140°. On cooling, it was found to be unchanged. At temperatures up to 165°, the same result was obtained, even after 1 hour's heating. At 170—175°, decomposition took place in 1 hour, and at 180° or higher temperatures, profound decomposition set in suddenly with charring.

The successful decomposition at 170—175° gave a mixture which was treated with 20% hydrochloric acid. The 2 : 4-dinitroanisole obtained was identified by comparison with an authentic specimen and by conversion into 2 : 4-dinitrophenylpiperidine. The dimethylaniline produced was identified by its b. p. and by conversion into the methiodide.

A methyl-alcoholic solution of the 2 : 4-dinitrophenoxide and methyl iodide was kept at 50—60° for an hour : the phenoxide was recovered unchanged. After 3 hours' boiling, however, theoretical yields were obtained of phenyltrimethylammonium iodide, m. p. 225°, and of 2 : 4-dinitroanisole, which was identified by conversion into 2 : 4-dinitrophenylpiperidine.

Phenyltrimethylammonium Phenoxide.—An aqueous solution of 1 mol. of phenyltrimethylammonium hydroxide was concentrated under reduced pressure at about 50°, with occasional addition of absolute alcohol. An alcoholic solution of phenol (1 mol.) was then added, and the evaporation continued. When no more alcohol came off, the syrup was dissolved in alcohol and excess of anhydrous ether was added. The *phenoxide*, which separated in pearly plates, was dried in a vacuum over sulphuric acid and phosphoric oxide, and then melted at 58—59°. After being crystallised from nitrobenzene, with subsequent washing with light petroleum (b. p. 60—80°), it melted at 75—76° (Found : N, 6·0. $C_{15}H_{19}ON$ requires N, 6·1%). The substance also crystallised from acetone–light petroleum in white plates.

A solution of 2 g. of the phenoxide in 20 c.c. of water was boiled for 2 hours under reflux. The mixture was then freed by routine methods from basic and acidic substances. An ethereal solution obtained, which must have contained any anisole, was evaporated, and left no appreciable residue, although the odour of anisole was detected. The amount of anisole produced was less than 0·1 g. Dimethylaniline, phenol and methyl alcohol were found in the expected extracts.

The phenoxide reacted with cold methyl iodide, and when heated for a few minutes with alcoholic methyl iodide, was quantitatively converted into phenyltrimethylammonium iodide.

The decomposition of the phenoxide was carried out as follows :

17·5 g. were placed in a Claisen distilling flask, which was evacuated, and gradually heated at 120° during 10 minutes. Distillation was then complete, and no appreciable residue was left after the flask had been warmed with a flame. The distillate (17 g.) was dissolved in ether, and extracted with 20% hydrochloric acid. The acid solution was extracted with ether, and the ethereal solution with dilute hydrochloric acid. From the ethereal extracts were obtained, after distillation, 8 g. of pure anisole; and from the acid solutions, after treatment with ammonium hydroxide, extraction and distillation, 8 g. of pure dimethylaniline. The calculated ratio of anisole to base is 107 : 121.

Phenyltrimethylammonium m-4-*Xylyloxide*.—Evaporation of the solution obtained in the usual manner gave a colourless syrup, which was washed with absolute ether and kept in a vacuum over concentrated sulphuric acid and phosphoric oxide. It decomposed, in a bath kept at 110°, without leaving a weighable residue. From 21 g. of syrupy xylyloxide, 20 g. of distillate were obtained, and this yielded 10 g. of pure *m*-xylyl methyl ether, b. p. 180—190°, and 9 g. of pure dimethylaniline. The calculated ratio of ether to base is 136 : 121.

The xylyloxide reacted vigorously with cold methyl iodide to give phenyltrimethylammonium iodide and xylyl methyl ether.

Phenyltrimethylammonium α-Naphthoxide.—This substance, which was obtained in the usual manner, crystallised when its concentrated alcoholic solution was cooled and left in a vacuum over concentrated sulphuric acid and phosphoric oxide. It was recrystallised from nitrobenzene or from acetone, from which it separated in white needles and plates, m. p. 107—108° (Found: N, 4·8. $C_{19}H_{21}ON$ requires N, 5·0%). When the alcoholic solution was allowed to concentrate slowly over concentrated sulphuric acid, large square flat plates were obtained.

The naphthoxide reacted with cold methyl iodide, and on addition of alcohol and warming, the reaction became quantitative. Phenyltrimethylammonium iodide and α-naphthyl methyl ether were identified as the sole products. Decomposition of the naphthoxide (14 g.) occurred at 140—150°, and gave 13 g. of total distillate. This, after the usual separation process, yielded 5 g. of dimethylaniline and 6 g. of α-naphthyl methyl ether, whereas the calculated ratio of base to ether is 121 : 158.

Phenyldimethylethylammonium 2 : 4-*Dinitrophenoxide*.—This substance was prepared as usual, and crystallised from alcohol–ether in small mustard-coloured needles, m. p. 55—57° (Found: N, 12·6. $C_{16}H_{19}O_5N_3$ requires N, 12·6%).

This phenoxide is not particularly hygroscopic. It did not react

with methyl iodide in boiling alcoholic solution after 5 minutes. Decomposition of 5 g. of the phenoxide occurred at 170°, and was complete in one hour. From the products were obtained 2·5 g. of acid-insoluble material, m. p. 39—50°, and 2 g. of a mixture of bases, b. p. 190—200°. The acid-insoluble material was heated with twice its weight of piperidine, excess of 20% hydrochloric acid was added, and the precipitated solid was collected (3 g.). It melted at 91—94° and was almost pure 2 : 4-dinitrophenylpiperidine. The filtrate contained both methyl and ethyl alcohol. The mixture of bases was submitted to micro-distillation; the lower-boiling fraction was converted into the chloroplatinate (Found : Pt, 29·6. Calc. for the chloroplatinate of dimethylaniline : Pt, 29·9%). The higher-boiling fraction was converted into the methiodide, which melted at 133—136°, and at 132—134° when mixed with phenyldimethylethylammonium iodide (m. p. 132—133°), but at below 115° when mixed with phenyltrimethylammonium iodide. Dimethyl- and methylethyl-aniline were therefore both formed in the above decomposition, together with dinitroanisole and dinitrophenetole.

Phenylbenzyldimethylammonium o-*Nitrophenoxide.*—This substance crystallised in vermilion needles when dry ether was added to the concentrated alcoholic solution, and had m. p. 91—92° (Found : N, 8·05. $C_{12}H_{22}O_3N_2$ requires N, 8·0%).

Decomposition of 12 g. of the phenoxide occurred at 155—165°, and gave a mixture of products, b. p. 92—220°/28 mm., consisting of 4 g. of dimethylaniline and 7·5 g. of benzyl *o*-nitrophenyl ether. The calculated ratio of base to ether is 121 : 229.

Phenylbenzyldimethylammonium 2 : 4-*dinitrophenoxide* crystallised from alcohol–ether in fern-like aggregates of mustard-coloured needles, m. p. 138—138·5° (Found : N, 10·5. $C_{21}H_{21}O_5N_3$ requires N, 10·6%). It is not hygroscopic.

Phenylbenzyldimethylammonium *m*-4-xylyloxide was not obtained crystalline, but was freed from impurities by extraction with absolute alcohol and anhydrous ether. After being left in a vacuum over concentrated sulphuric acid and phosphoric oxide, it was decomposed. Decomposition was not marked below 145—150°, and was effected at 175—185°. The portion of the product which was soluble in acid was pure dimethylaniline. No benzylmethylaniline was present. The acid-insoluble product was benzyl xylyl ether.

Phenyltrimethylammonium Thiophenoxide.—When the aqueous-alcoholic solution of the quaternary hydroxide and thiophenol was concentrated, the *thiophenoxide* crystallised. It was recrystallised by addition of ether to an alcoholic solution, and formed white plates, m. p. 83—83·5° (Found : N, 5·7. $C_{14}H_{19}NS$ requires N, 5·7%). It is not hygroscopic. Ethyl iodide reacted vigorously

with it in the cold, phenyltrimethylammonium iodide, m. p. 227—228°, being formed.

Decomposition of the thiophenoxide (20 g.) took place at 125°. Within 5 minutes, 18 g. of liquid distilled at 80—85°/14 mm. This, after separation, gave 8·5 g. of thioanisole and 8 g. of dimethylaniline, whereas these two should have been formed in the proportion of 124 : 121.

Phenyltrimethylarsonium Thiophenoxide.—We first attempted to prepare this substance by heating silver thiophenoxide with an alcoholic solution of phenyltrimethylarsonium iodide, but after several hours' boiling, the latter was recovered almost unchanged. By evaporation of the quaternary hydroxide with thiophenol, the *thiophenoxide* was readily obtained; it crystallised from alcohol on addition of ether in white leaflets, m. p. 144—145°, and was soluble in water or alcohol, but insoluble in ether (Found: S, 10·5. $C_{15}H_{19}SAs$ requires S, 10·5%).

Although the phenyldimethylarsine required for the preparation of phenyltrimethylarsonium iodide is very readily obtained from dimethyliodoarsine (Burrows and Turner, J., 1920, **117**, 1378), we desired to prepare it from phenyldichloroarsine. Winmill (J., 1912, **101**, 723) treated this substance with magnesium methyl iodide in a mixture of ether and light petroleum (b. p. 30—40°) and obtained a 75% yield. We find that higher-boiling petroleum (b. p. 60—80°) can be used, and that if 4 molecular proportions of Grignard reagent are taken, the yield of pure phenyldimethylarsine is over 90%, even in small preparations. Starting with 22 g. of phenyldichloroarsine, it is thus possible to obtain 27—28 g. of the quaternary arsonium iodide.

The thiophenoxide (15 g.) began to decompose at 160°, and, apart from a little sublimation, was completely converted in 10 minutes into a mixture, b. p. 71—72°/11 mm., of phenyldimethylarsine and thioanisole (14·5 g.). 5 G. of this were dissolved in absolute alcohol, methyl iodide was added, and the mixture was left for 3 hours. Absolute ether was added, and the precipitated phenyltrimethylarsonium iodide was dried at 100° (6 g., corresponding to 2·8 g. of phenyldimethylarsine).

Our thanks are due to the Royal Society for a grant in aid of this investigation, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us.

BEDFORD COLLEGE,
UNIVERSITY OF LONDON. [*Received, February 19th,* 1931.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED, BUNGAY, SUFFOLK.

Reprinted from the Journal of the Chemical Society, 1930.

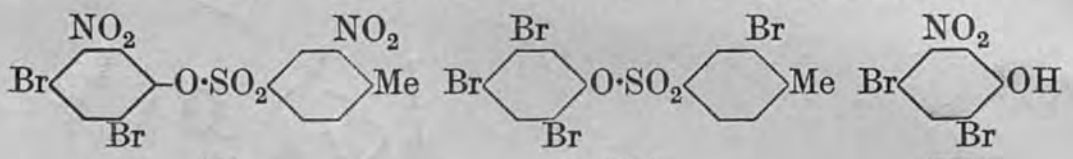
Subsidiary 2

CXIV.—*The Scission of Diaryl Ethers and Related Compounds by Means of Piperidine. Part III. The Nitration of* 2 : 4-*Dibromo-*2′ : 4′-*dinitrodiphenyl Ether and of* 2 : 4-*Dibromophenyl* p-*Toluenesulphonate and Benzoate. The Chlorination and Bromination of* m-*Nitrophenol.*

By Rosalind Venetia Henley and Eustace Ebenezer Turner.

In continuation of previous work (Part II, J., 1929, 512), the nitration of 2 : 4-*dibromophenyl* p-*toluenesulphonate* has been investigated. The sole product of dinitration was 2 : 4-*dibromo-*

5-nitrophenyl o-*nitro*-p-*toluenesulphonate* (I), the constitution of which was established by its conversion successively into 2 : 4-*di-*



(I.) (II.) (III.)

bromo-5-aminophenyl o-*amino*-p-*toluenesulphonate* and 2 : 4 : 5-*tribromophenyl* o-*bromo*-p-*toluenesulphonate* (II). The latter substance was converted by piperidine at 100° into 2 : 4 : 5-tribromophenol, identical with the product obtained by the replacement of the amino-group by hydroxyl in 2 : 4 : 5-tribromoaniline.

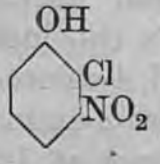
When 2 : 4-dibromo-5-nitrophenyl *o*-nitro-*p*-toluenesulphonate was heated with piperidine, there were formed 1-*o*-nitro-*p*-toluenesulphonylpiperidine and 2 : 4-*dibromo-5-nitrophenol* (III), the constitution of which is determined by that of the above tribromophenol. After crystallisation from light petroleum, with subsequent normal drying, the dibromonitrophenol melted at 77—78°, and an identical product was obtained by nitrating 2 : 4-dibromophenyl benzoate, followed by hydrolysis. It seemed probable that the compound obtained by Garzino (*Atti R. Accad. Sci. Torino*, 1889, **25**, 250) by nitrating 2 : 4-dibromophenyl propionate should also be 2 : 4-dibromo-5-nitrophenol, but he gave the m. p. as 90—91°. Crystallisation of our compound from dilute acetone gave a *monohydrate*, m. p. 92—94°, which is probably the product obtained by Garzino.

Another dibromonitrophenol, m. p. 91°, was described by Lindner (*Ber.*, 1885, **18**, 612) as resulting from the dibromination of *m*-nitrophenol, and in Beilstein's "Handbuch" (4th Edn., Vol. VI, 246, 248) it is suggested that this compound is possibly identical with Garzino's dibromonitrophenol. In view of the fact (Part II) that *m*-nitrophenol is dichlorinated in the 2- and 4-positions, it at first seemed unlikely that the dibromination would proceed so differently, and we have accordingly investigated the bromination of *m*-nitrophenol afresh.

Attempts to prepare the dibromo-compound according to Lindner's directions did not yield any chemically pure substance. When, however, bromine, diluted with carbon dioxide, was passed through *m*-nitrophenol at 120—140°, until the latter acquired the correct increase in weight, and the product was worked up exactly in accordance with Lindner's instructions, material was obtained which behaved as regards crystallisation as an individual, melted at 82—98°, and appeared to be a mixture of 4-bromo- and 2 : 4 : 6-tribromo-3-nitrophenol.

When an attempt was made to dibrominate *m*-nitrophenol in glacial acetic acid in presence of anhydrous sodium acetate, the tribromo-compound, m. p. 89—90°, was alone isolated. This substance, m. p. 85°, was obtained by Lindner (*loc. cit.*) by brominating *m*-nitrophenol, and by Daccomo (*Ber.*, 1885, **18**, 1167) by nitrating 2 : 4 : 6-tribromophenyl benzoate. Its constitution has now been definitely proved by converting it in stages into 2 : 3 : 4 : 6-tetrabromophenol. Monobromination of 4-bromo-3-nitrophenol also failed to give a dibromo-3-nitrophenol.

In preparing the monobromo-derivatives of *m*-nitrophenol, we again encountered conflicting results. Pfaff (*Ber.*, 1883, **17**, 612) treated *m*-nitrophenol with bromine in the cold, and described his monobromo-compound as bright yellow needles melting at 110°. Lindner (*loc. cit.*) and Schlieper (*Ber.*, 1892, **25**, 552), using similar methods, obtained what they took to be Pfaff's substance, but they gave the m. p. as 147—148°. Schlieper (*Ber.*, 1893, **26**, 2469) regarded this substance as 2-bromo-3-nitrophenol, since he had obtained the following evidence that the analogous chloro-compound was 2-chloro-3-nitrophenol (IV) : the chloro-compound was methylated, and the ether reduced and then deaminated. The product obtained was thought by Schlieper to be *o*-chloroanisole for two reasons : (1) it had the correct b. p., and (2) nitration gave a chloronitroanisole, m. p. 93—94°, which he took to be (V), because a substance having this constitution and this m. p. had been described by Fischli (*Ber.*, 1878, **11**, 1463). It seemed possible, however, that Schlieper's chloronitrophenol was the 4-compound, in which



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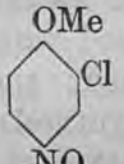

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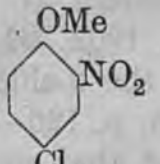


(VI.)

case his chloronitroanisole would be (VI), which melts at 97·5° (Reverdin, *Ber.*, 1893, **26**, 1689).

We have found that the monobromination of *m*-nitrophenol at 120—140° (the lowest temperature at which bromination is practicable) gives a mixture of products, at least 50% of which is 4-bromo-3-nitrophenol, m. p. 146·5—147·5°, the constitution of which has been established by its synthesis from *ON*-diacetyl-3-nitro-*p*-aminophenol. Schlieper's supposed 2-bromo-compound is therefore 4-bromo-3-nitrophenol, which substance has indeed already been prepared (Heller and Kammann, *Ber.*, 1909, **42**, 2179) from 3-nitro-*p*-aminophenol.

Monobromination of *m*-nitrophenol in glacial acetic acid in

presence of sodium acetate gave indefinite results, but in absence of sodium acetate the product was a monobromo-compound, m. p. 118·5—121°. This we at first thought to be 2-bromo-3-nitrophenol, and in order to prove its constitution, we converted it into the p-*toluenesulphonyl* derivative, reduced the latter, and replaced the amino-group by bromine. During the last stage, the *p*-toluenesulphonyl group was removed by hydrolysis and a dibromophenol, m. p. 73—74°, was formed. At the same time we performed an analogous synthesis, starting from 3-bromo-2-nitrophenol. The dibromophenol obtained in the second synthesis melted at 68—69°, was different from the first, and was clearly the hitherto unknown 2 : 3-*dibromophenol*. It therefore seemed certain that the isomeric compound was 2 : 5-*dibromophenol*. Raiford and Bren (*J. Amer. Chem. Soc.*, 1929, **51**, 2539) recently attempted the preparation of this substance from 2 : 5-dibromoaniline. It has now been obtained in excellent yield by applying the method of Noelting and Kopp (*Ber.*, 1905, **38**, 3506) to this base, and was found to be identical with the product from the bromo-3-nitrophenol, which is therefore the 6-derivative (2-bromo-5-nitrophenol) already described by Heller and Kammann (*loc. cit.*), who obtained it from 5-nitro-2-aminophenol.

Although it has already been shown (Part II) that *m*-nitrophenol is readily converted into 2 : 4-dichloro-3-nitrophenol, the above results made it desirable to investigate the monochlorination. Schlieper (*Ber.*, 1893, **26**, 2466), by direct chlorination of *m*-nitrophenol, obtained a compound, m. p. 120°, which, as is shown above, may be either the 2- or the 4-chloro-compound. Meldola and Eyre (J., 1902, **81**, 996) agreed with Schlieper's conclusion that this was the 2-chloro-compound; they obtained 4-chloro-3-nitrophenol, m. p. 126—127°, by synthesis from 3-nitro-*p*-aminophenol.

We find that monochlorination of *m*-nitrophenol at 120—140° gives approximately equal amounts of 4-chloro-3-nitrophenol (A), m. p. 127—128°, and 2-chloro-3-nitrophenol (B), m. p. 120°. A was identical with a specimen prepared from *ON*-diacetyl-3-nitro-*p*-aminophenol, and the constitution of B follows from two facts: (1) dichlorination of *m*-nitrophenol under similar conditions gives the 2 : 4-dichloro-compound in good yield, and (2) reduction of B, followed by replacement of the amino-group by chlorine, gives 2 : 3-dichlorophenol. Although the first of these appears to be sufficient proof, it was desired to prove beyond doubt that B was not 6-chloro-3-nitrophenol (m. p. 118—119°; prepared synthetically by Meldola, Woolcott, and Wray, J., 1896, **69**, 1322).

It is therefore possible that, in this case, Schlieper actually had a 2-chloro-compound, but it is difficult to believe this, since the

4-chloro-compound, which was presumably present, is so readily isolated.

We have not investigated the iodination of *m*-nitrophenol, as the statements in the literature seem to be accurate. Schlieper (1893, *loc. cit.*) described the monoiodo-compound as the 2-iodo-derivative, m. p. 134°, and Datta and Prosad (*J. Amer. Chem. Soc.*, 1917, **39**, 441) state that iodination in the 2-position proceeds quantitatively. There seems little doubt that this substance is different from the 4- and the 6-iodo-derivative, m. p. 156° and 146—147° respectively (Hähle, *J. pr. Chem.*, 1891, **43**, 72; Meldola and Eyre, P., 1901, 238).

In endeavouring to prepare 4-bromo-3-nitrophenol by a different method, we nitrated N-p-*bromophenylphthalimide* in presence of excess of concentrated sulphuric acid, expecting to obtain a considerable proportion of the *m*-nitro-derivative (compare Brady, Quick, and Welling, J., 1925, **127**, 2264). The main product, however, was the *o*-nitro-derivative. This result is interesting, since nitration of *p*-bromoaniline in presence of excess of sulphuric acid gives almost entirely the *m*-nitro-compound (Noelting and Collin, *Ber.*, 1884, **17**, 261) (see Experimental).

The nitration of 2 : 4-dibromo-2′ : 4′-dinitrodiphenyl ether proceeds similarly to that of the analogous dichloro-compound and gives 2 : 4-*dibromo*-5 : 2′ : 4′-*trinitrodiphenyl ether*. This ether readily undergoes scission by piperidine into 2 : 4-dibromo-5-nitrophenol and *N*-2′ : 4′-dinitrophenylpiperidine.

Experimental.

2 : 4-*Dibromophenyl* p-*toluenesulphonate*, readily obtained by the usual type of process, crystallised from glacial acetic acid in colourless plates, m. p. 120° (Found : Br, 39·8. $C_{13}H_{10}O_3Br_2S$ requires Br, 39·4%).

Dinitration of 2 : 4-*Dibromophenyl* p-*Toluenesulphonate*.—The compound was added to 10 parts of nitric acid (*d* 1·5), the resulting solution being left for an hour and then poured into a large bulk of water. Filtration, followed by crystallisation from glacial acetic acid, gave 2 : 4-*dibromo*-5-*nitrophenyl* o-*nitro*-p-*toluenesulphonate* in pale greenish-yellow leaflets, m. p. 122—123° (Found : Br, 32·6. $C_{13}H_8O_7N_2Br_2S$ requires Br, 32·3%).

2 : 4-*Dibromo*-5-*nitrophenol*.—The last-mentioned compound was heated for 1 hour at 100° with 2 parts of piperidine. No piperidine hydrobromide separated. Excess of dilute alkali was added, and the solution shaken with benzene; this extracted the 1-*o*-nitro-*p*-toluenesulphonylpiperidine, but, contrary to expectation, it also extracted the piperidine salt of the phenol. It was therefore shaken

with dilute hydrochloric acid and then with alkali. Acidification of the alkaline solution precipitated 2 : 4-*dibromo*-5-*nitrophenol*. This crystallised from light petroleum (b. p. 80—100°) in long yellow needles, m. p. (after being dried over-night in a vacuum over concentrated sulphuric acid) 77—78° (Found: Br, 53·5. $C_6H_3O_3NBr_2$ requires Br, 53·9%), and from very dilute acetone as the *hydrate*, $C_6H_3O_3NBr_2,H_2O$, in long yellow needles, m. p. 92—94° (with previous softening), the m. p. depending on the rate of heating (0·5236 g. lost 0·0309 g. in 14 days in a vacuum over phosphoric oxide. Loss of $1H_2O$ requires 0·0299 g. The specially dry material so obtained melted at 84—86°).

2 : 4-*Dibromo*-5-*aminophenyl* o-*Amino*-p-*toluenesulphonate*.—The corresponding dinitro-compound was added with shaking to a hot solution of stannous chloride (1·5 times the calculated quantity) in a mixture of glacial acetic acid and concentrated hydrochloric acid. After the mixture had been heated at 100° for a few minutes, vigorous reduction set in, and was allowed to become complete during an hour at 100°. The resulting solution was poured into excess of 20% potassium hydroxide solution, and the suspension was cooled and filtered (asbestos). The washed and dried precipitate crystallised from dilute acetone in colourless leaflets, m. p. 174—175° (Found: Br, 37·5. $C_{13}H_{12}O_3N_2Br_2S$ requires Br, 36·7%).

2 : 4 : 5-*Tribromophenyl* o-*Bromo*-p-*toluenesulphonate*.—The diamino-compound was diazotised at 20—25°, in a mixture of equal parts of concentrated hydrochloric acid and water, with a solution of sodium nitrite. The diazo-perbromide was precipitated by means of a solution of bromine in aqueous potassium bromide, collected, washed, and decomposed in glacial acetic acid, the temperature of the latter being slowly raised until the b. p. was reached. Water was added, and the precipitate crystallised from alcohol, colourless leaflets, m. p. 107—108°, being obtained (Found: Br, 56·9. $C_{13}H_8O_3Br_4S$ requires Br, 56·7%).

2 : 4 : 5-*Tribromophenol*.—(*a*) A solution of the preceding compound in excess of piperidine was boiled under reflux for an hour; the solution was then strongly acidified and submitted to steam distillation. The tribromophenol passed over rapidly, and crystallised from light petroleum (b. p. 40—60°) in long colourless needles, m. p. 85—86° (Found: Br, 73·0. $C_6H_3OBr_3$ requires Br, 72·5%).

(*b*) 2 : 4 : 5-Tribromoaniline, prepared for the purpose from *p*-dibromobenzene, was converted into the corresponding phenol by adapting the method of Noelting and Kopp (*loc. cit.*). The product was identical with that from process (*a*).

Kohn and Pfeifer (*Monatsh.*, 1927, **48**, 211) obtained what was

evidently mainly 2 : 4 : 5-tribromophenol, m. p. 79°, by heating pentabromophenol with zinc dust and glacial acetic acid. We failed to trace this work for some time, since in the original paper and in the British abstracts the substance was incorrectly called 3 : 4 : 6-tribromophenol.

Nitration of 2 : 4-Dibromo-2′ : 4′-dinitrodiphenyl Ether.—The ether, described by Le Fèvre, Saunders, and Turner (J., 1927, 1168), is more conveniently obtained as follows : 21 g. of 2 : 4-dibromophenol were added to 4·6 g. of potassium hydroxide previously fused with 0·5 c.c. of water. To the still hot mixture were added 17·5 g. of 1-chloro-2 : 4-dinitrobenzene. After a few minutes' shaking, potassium chloride began to separate, and after an hour's heating at 100°, interaction was complete. Excess of dilute alkali was added, and the mixture cooled and shaken. The solid mealy product was collected, washed with water, and crystallised from glacial acetic acid (23 g., m. p. 133°).

The ether was added rapidly to 10 parts of nitric acid (*d* 1·5). After 0·5 hour, the solution was poured into water. The precipitated solid was collected, washed, and crystallised from glacial acetic acid, 2 : 4-*dibromo*-5 : 2′ : 4′-*trinitrodiphenyl ether* being obtained in very pale yellow needles, m. p. 142° (Found : Br, 35·1. $C_{12}H_5O_7N_3Br_2$ requires Br, 34·9%).

Scission of 2 : 4-Dibromo-5 : 2′ : 4′-trinitrodiphenyl Ether.—(a) *With piperidine.* The trinitro-compound was heated with twice its weight of piperidine at 100° for an hour. The solution was treated with alkali and extracted several times with benzene. The benzene layer was extracted first with hydrochloric acid and then with alkali. Acidification of the alkaline solution gave 2 : 4-dibromo-5-nitrophenol, identical with the above product, and the benzene layer yielded 2 : 4-dinitrophenylpiperidine.

(b) *With aniline.* The trinitro-compound was heated for an hour at 100° with excess of aniline. On addition of much dilute hydrochloric acid, 2 : 4-dinitrodiphenylamine separated in almost quantitative yield.

Nitration of 2 : 4-Dibromophenyl Benzoate.—The benzoate was added slowly to 10 parts of nitric acid (*d* 1·5), kept below 30°. After a further 15 minutes, the solution was poured into excess of cold water. The gummy precipitate was separated, and heated with water until it became hard. It crystallised from alcohol in colourless needles, m. p. 155—156° (Found : Br, 36·2. $C_{13}H_6O_6N_2Br_2$ requires Br, 35·9%). The nitro-compound was heated for an hour at 100° with excess of piperidine. The excess of piperidine was removed by extraction with benzene in presence of alkali. The 2 : 4-dibromo-5-nitrophenol obtained, after crystallisation from

light petroleum, had m. p. 77—78°, and did not depress the m. p. of the dibromo-compound described above.

The *m*-nitrophenol used in these experiments was prepared as described in Adams's "Organic Syntheses," Vol. VIII, p. 80, but it was found advisable to remove all traces of sulphuric acid from the crude product by dissolving it in alkali and reprecipitating it with hydrochloric acid before distilling it under reduced pressure; otherwise, towards the end of the distillation, explosive decomposition set in. From 212 g. of *m*-nitroaniline, 135—140 g. of pure *m*-nitrophenol were consistently obtained.

m-*Nitrophenyl* p-*toluenesulphonate*, obtained in the usual way, separated from alcohol in prisms, m. p. 112—113° (Found: S, 10·7. $C_{13}H_{11}O_5NS$ requires S, 10·9%).

Experiments on the Dibromination of m-*Nitrophenol.*—(A) *Dry.* (1) The method described by Lindner (*loc. cit.*) led to mixtures, the examination of which proved unprofitable.

(2) A current of carbon dioxide laden with bromine vapour was passed through *m*-nitrophenol in a bath at 120—140° until the desired increase in weight had occurred. The product was worked up by Lindner's method. Precipitation of the barium-salt fraction gave a solid, m. p. 82—98°. A mixture of this with 2 : 4 : 6-tribromo-3-nitrophenol melted below 75°, and one with 4-bromo-3-nitrophenol melted at 76—135°. On the assumptions that the product, m. p. 82—98°, is approximately 50% of 4-bromo- and 50% of tribromo-3-nitrophenol, and that the mixed melting-point curve is of the simplest type, these results are explicable, as is also the bromine content of the bromination product (51·3%; a 1 : 1 mixture of mono- and tri-bromo-compounds requires Br, 53·9%).

(3) On one occasion, by Schlieper's method of monobromination, a product was obtained corresponding very closely to that just described. It had m. p. 85—95°, and Br, 51·2%.

(B) *Wet.* (1) A solution of *m*-nitrophenol (1 mol.) and bromine (2 mols.) in 90% acetic acid was left in the cold for an hour. Since bromination did not begin, the solution was heated at 100° for 0·5 hour and then boiled for 0·5 hour. The product was worked up by Lindner's method and gave no substance corresponding to his dibromo-derivative.

(2) A solution of *m*-nitrophenol (1 mol.) and anhydrous sodium acetate (2 mols.) in glacial acetic acid was treated with a solution of bromine (2 mols.) in glacial acetic acid. A number of experiments were carried out, with variation of concentrations, temperature, and time of mixing. In every case the main product was 2 : 4 : 6-tribromo-3-nitrophenol, m. p. 89—90° (Found: Br, 63·4. Calc.: Br, 63·8%).

2 : 4 : 6-*Tribromo*-3-*nitrophenyl* p-*Toluenesulphonate*.—The tribromo-compound was readily converted into the p-*toluenesulphonyl* derivative, which crystallised from alcohol in colourless needles, m. p. 146—147° (Found : Br, 45·2; S, 6·0. $C_{13}H_8O_5NBr_3S$ requires Br, 45·3; S, 6·0%).

2 : 4 : 6-*Tribromo*-3-*aminophenyl* p-*Toluenesulphonate*.—Reduction of the preceding compound was effected by West's method (J., 1925, **127**, 494). The *amino*-compound separated from alcohol or dilute acetic acid in colourless prisms, m. p. 146—147° (mixture with the nitro-compound, m. p. 120—125°) (Found : Br, 47·9. $C_{13}H_{10}O_3NBr_3S$ requires Br, 48·0%).

2 : 3 : 4 : 6-*Tetrabromophenol*.—A solution of the preceding amino-compound in concentrated sulphuric acid was diazotised at 15° with a solution of sodium nitrite in concentrated sulphuric acid (made at − 10°). When the resulting solution was poured on ice, a yellow crystalline precipitate of the diazo-compound separated. Addition of water produced a clear solution, to which was added a solution of bromine in potassium bromide until no further precipitate was obtained. The diazo-perbromide was collected, washed with water, and decomposed in hot glacial acetic acid. On cooling, a crystalline product separated, which was washed with water and then heated with excess of piperidine at 100° for 4 hours. Addition of water precipitated 2 : 3 : 4 : 6-tetrabromophenol, which soon became solid and crystallised from dilute alcohol in colourless needles, m. p. 113—114°. An identical specimen was obtained by using the Sandmeyer instead of the perbromide process (Found : Br, 76·8. Calc. : Br, 78·0%).

N-p-*Bromophenylphthalimide*.—A mixture of *p*-bromoaniline (1 mol.) with finely ground phthalic anhydride (1 mol.) was heated at 250—300° for 2 hours. The molten mass was poured into cold alcohol and the solid product was ground and extracted with a large volume of boiling alcohol. The residual solid and the long silky needles that separated from the extract both melted at 204° (Found : Br, 26·8. $C_{14}H_8O_2NBr$ requires Br, 26·5%). Yield, 88%.

Nitration of N-p-*Bromophenylphthalimide*.—The imide (1 mol.) was dissolved in 10 parts of warm concentrated sulphuric acid. To the solution, cooled in running water, 1 mol. of nitric acid (*d* 1·5), dissolved in 5 vols. of concentrated sulphuric acid, was added slowly, with stirring. After an hour, the solution was poured on ice, and the resulting gummy precipitate collected. It was heated for an hour at 130° with 90% sulphuric acid, and the resulting solution was much diluted and then basified. The product was mainly 4-bromo-2-nitroaniline, and did not contain more than 20% of 4-bromo-3-nitroaniline (fractional crystallisation of the mixed sulphates).

Nitration of *p*-bromoaniline in excess of sulphuric acid as described by Noelting and Collin (*loc. cit.*) gave 4-bromo-3-nitroaniline in good yield, but an attempt to effect replacement of the amino-group by hydroxyl by the diazo-method proved unsuccessful.

Mononitration of ON-*Diacetyl*-p-*aminophenol.*—Hähle (*loc. cit.*) recommends nitration at 0° with fuming nitric acid. We have found that the best results are obtained when 50 g. of the diacetyl compound are added gradually to 75 c.c. of nitric acid (*d* 1·5) kept at about 5°. (Only partial nitration occurs at temperatures just below 0°, and the diacetyl compound may be recovered unchanged from its solution in a mixture of equal volumes of acids of *d* 1·5 and *d* 1·42, kept at 0° to − 5°.) The solution is poured on ice, and the precipitate obtained is crystallised from alcohol.

4-*Bromo*-3-*nitrophenol.*—*ON*-Diacetyl-3-nitro-4-aminophenol was slowly added to 10 times its weight of boiling hydrobromic acid (*d* 1·49). Boiling was continued for ¼ hour and the suspension of 3-nitro-4-aminophenol hydrobromide was then diluted and diazotised: diazotisation was slow. The excess of nitrous acid was removed by addition of urea and the solution obtained was poured into a suspension of copper powder in 25% hydrobromic acid. The copper slowly dissolved and needles separated. These crystallised from water in brown needles, m. p. 146·5—147·5°, and from dilute hydrochloric acid in yellow needles having the same m. p.

4-Chloro-3-nitrophenol was obtained in a precisely similar manner from diacetyl-3-nitro-4-aminophenol. The diazotisation proceeded more easily than with the bromo-compound. The product crystallised from dilute hydrochloric acid in yellow needles, m. p. 127—128°.

3-Bromo-2-nitrophenol was prepared by Hodgson and Moore's method (J., 1926, 157). In the intermediate sulphonation we obtained good results with 20% oleum, but with acid of the composition (27% oleum) used by Hodgson and Moore, our sulphonation mixture set almost solid and would not dissolve even in a large quantity of concentrated sulphuric acid.

3-*Bromo*-2-*nitrophenyl* p-*toluenesulphonate*, readily obtained in the usual way, crystallised from alcohol, in which it was very sparingly soluble, in colourless rectangular plates, m. p. 136·5—137·5° (Found: Br, 21·4. $C_{13}H_{10}O_5NBrS$ requires Br, 21·5%).

3-*Bromo*-2-*aminophenyl* p-*Toluenesulphonate.*—The preceding nitro-compound was reduced with a mixture of 2 parts of crystalline stannous chloride, 2 parts of concentrated hydrochloric acid, and 7 parts of glacial acetic acid at 100°. Much alkali was added and the suspension produced was extracted with ether. Evaporation of the dried ethereal extract, followed by crystallisation from alcohol,

gave colourless needles of the *amino*-compound, m. p. 120—121° (Found : Br, 23·6. $C_{13}H_{12}O_3NBrS$ requires Br, 23·4%).

2 : 3-*Dibromophenol.*—The amino-compound was diazotised in concentrated sulphuric acid at 15—20°, with a solution of sodium nitrite in concentrated sulphuric acid prepared at — 10°. The reaction mixture was poured on ice. A small portion was found to couple normally with alkaline β-naphthol, and the main portion was added to cuprous bromide–hydrobromic acid. The resulting solution was heated on a boiling water-bath under reflux for ¾ hour and then distilled in steam. The white solid that passed over was dried over concentrated sulphuric acid (desiccator) and crystallised from light petroleum (b. p. 40—60°). The 2 : 3-*dibromophenol* obtained formed stout prisms, m. p. 68—69° (Found : Br, 63·6. $C_6H_4OBr_2$ requires Br, 63·6%). It is much less soluble in light petroleum than 2 : 3-dichlorophenol and is very much less volatile.

Monobromination of Wet m-*Nitrophenol.*—(a) When a dilute solution of bromine (1 mol.) was added to a cold dilute solution of *m*-nitrophenol (1 mol.) and anhydrous sodium acetate (1 mol.) in glacial acetic acid, a mixture of substances was formed, the examination of which led to no positive results.

(b) A solution of 20 g. of *m*-nitrophenol and 8·8 c.c. of bromine in 30 c.c. of glacial acetic acid was gently boiled under reflux for 2 hours; it then became almost colourless. The solvent was evaporated on a boiling water-bath and the residue, which became crystalline on cooling, was dissolved in dilute aqueous alkali. Addition of acid precipitated an almost colourless solid which, after being crystallised from dilute hydrochloric acid, melted at 117—120°, and after a further crystallisation from light petroleum (b. p. 80—100°), at 118·5—121° (Found : Br, 36·4. $C_6H_4O_3NBr$ requires Br, 36·7%). The following experiments show that this substance is 2-*bromo*-5-*nitrophenol.*

2-*Bromo*-5-*nitrophenyl* p-*toluenesulphonate* was formed in good yield by the usual process; it crystallised from alcohol in colourless plates, m. p. 131·5—132·5° (Found : Br, 21·6. $C_{13}H_{10}O_5NBrS$ requires Br, 21·5%).

2-*Bromo*-5-*aminophenyl* p-*toluenesulphonate*, obtained by the reduction of the nitro-compound with stannous chloride, hydrochloric acid, and acetic acid, crystallised from alcohol in colourless bunches of prisms, m. p. 135—136° (Found : Br, 23·3. $C_{13}H_{12}O_3NBrS$ requires Br, 23·4%).

2 : 5-*Dibromophenol.* (*a*) The last-named amino-compound was diazotised in concentrated sulphuric acid exactly as described under the preparation of 2 : 3-dibromophenol. The steam-distilled 2 : 5-*dibromophenol* was dried over concentrated sulphuric acid

(desiccator) and then crystallised from light petroleum (b. p. 40—60°); it formed prismatic needles, m. p. 73—74° (Found: Br, 63·4. $C_6H_4OBr_2$ requires Br, 63·6%). It was readily converted into 2 : 5-*dibromophenyl* p-*toluenesulphonate*, which separated from alcohol in colourless prisms, m. p. 109—110° (Found: Br, 39·7. $C_{13}H_{10}O_3Br_2S$ requires Br, 39·4%).

(*b*) 2 : 5-Dibromoaniline (44 g.), obtained in good yield by reducing 2 : 5-dibromonitrobenzene by West's method, was dissolved in 150 c.c. of warm concentrated sulphuric acid. The solution was cooled to room temperature and treated with a solution of 13 g. of sodium nitrite in 150 c.c. of concentrated sulphuric acid (prepared at − 10°). After an hour, 150 c.c. of water were added and the resulting solution, after addition of purified sand, was heated under reflux over a small flame for 2 hours. (A small portion of the diluted diazo-solution coupled readily with alkaline β-naphthol.) The whole was then distilled in steam, 37 g. of 2 : 5-dibromophenol, containing a trace of 2 : 5-dibromoaniline, passing over. The phenol was freed from the base by solution in alkali and filtration and then recovered by acidification; it had m. p. 73—74°, b. p. 256—257° (corr.)/755 mm. The *p*-toluenesulphonyl derivative melted at 109—110°.

Mixtures of the phenols or of their *p*-toluenesulphonyl derivatives obtained by methods (*a*) and (*b*) had the same m. p. as those of the single substances.

Monobromination of Dry m-*Nitrophenol.*—(1) A current of dry carbon dioxide was passed through bromine and then through 10·5 g. of *m*-nitrophenol heated at 120—140°. When the calculated increase of weight had occurred, the product was freed from the excess of bromine by a rapid current of carbon dioxide and at once dissolved in excess of dilute sodium hydroxide solution. After addition of dilute hydrochloric acid, yellow needles of 4-bromo-3-nitrophenol separated for some time, and later, an oil made its appearance. At this stage the liquid was filtered and the solid was crystallised from dilute hydrochloric acid, 7 g. of the 4-bromo-compound, m. p. 146·5—147·5°, being obtained.

(2) *m*-Nitrophenol (28 g.) was brominated, the weight being allowed to increase to 43 g. When the product was worked up as before, 22 g. of pure 4-bromo-3-nitrophenol were obtained.

The products from both experiments did not depress the m. p. of 4-bromo-3-nitrophenol prepared from diacetyl-*p*-aminophenol.

Attempted Monobromination of 4-*Bromo*-3-*nitrophenol.*—When the monobromo-compound (1 mol.), dissolved together with 1 mol. of anhydrous sodium acetate in glacial acetic acid, was treated with 1 mol. of bromine dissolved in the same solvent, a mixture was obtained containing unchanged 4-bromo-3-nitrophenol.

Attempted Monobromination of 2-*Bromo*-5-*nitrophenol*.—This appeared to proceed readily. The acetic acid was evaporated, and the hard solid obtained (on cooling) crystallised from light petroleum (b. p. 80—100°). The product had the appearance of an individual substance, but melted at 68—108°.

Monochlorination of m-*Nitrophenol*.—Chlorine was passed into *m*-nitrophenol (42 g.) at 120—140° until the weight increased by 9·5 g. A rapid current of carbon dioxide was passed through the molten product until the excess of chlorine had disappeared and the whole was then dissolved in dilute alkali solution. Dilute hydrochloric acid was added until no further evident precipitation occurred and the yellow needles produced were washed and dried (14 g.). After crystallisation from dilute hydrochloric acid, 12 g. of pure 4-chloro-3-nitrophenol, m. p. 127—128°, were obtained. The mother-liquor from the first filtration was strongly acidified, and filtered after some time: the yellow precipitate obtained, having been washed and dried, weighed 16 g. and after crystallisation from dilute hydrochloric acid gave 10 g. of 2-chloro-3-nitrophenol, m. p. 120° (Found: Cl, 19·6. Calc.: Cl, 20·0%). The mother-liquor from the second precipitation was evaporated to a small bulk under reduced pressure and then extracted with ether. Evaporation of the extract gave 12·5 g. of an oily mixture of chloro-compounds. The total yield of crude chloro-compounds was 85% of the theoretical yield.

The 4-chloro-3-nitrophenol obtained produced no depression of the m. p. of the material prepared from *ON*-diacetyl-*m*-nitro-*p*-aminophenol.

The 2-chloro-3-nitrophenol was reduced with iron, hydrochloric acid, and alcohol, and the filtered solution evaporated to dryness. Diazotisation, followed by addition of copper powder and hydrochloric acid, gave 2 : 3-dichlorophenol, m. p. 56—57°: this depressed the m. p. of 2 : 5-dichlorophenol (m. p. 57°). 2 : 3-Dichlorophenol is extraordinarily volatile, and vacuum desiccation over sulphuric acid and phosphoric oxide was accompanied by considerable loss. This property and the intense odour of the compound appear to differentiate this dichlorophenol from its isomerides (compare Holleman, *Rec. trav. chim.*, 1917, **37**, 96), and the volatility accounts for the poor analytical figure obtained (Found in air-dried specimen: Cl, 41·7. Calc.: Cl, 43·6%).

Some of the preliminary work on the dibromodinitrodiphenyl ether was carried out by Miss G. I. Sharp, B.Sc.

BEDFORD COLLEGE,
UNIVERSITY OF LONDON. [*Received, January 30th*, 1930.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

(9)

ABSTRACT OF WORK PRESENTED

Thesis submitted for M.Sc. Degree (Internal) by V.S. Basnet

A critical review of the existing methods available for the synthesis of coumarins and chromones has been made, with special references to the contributions of Pechmann and collaborators, Simonis, Ruhemann and others, Jacobson and Ghosh, Kostanecki and collaborators, Robinson and Baker and co-workers, and to the papers of Clayton, Dey and others.

The following work was then studied experimentally. Phloretin acetylated at (I) I00°C. (2) I80°C. was separately de-acetylated and subsequently methylated. Identical products were obtained in both the cases at the three stages of reactions. Arguments based on analogous cases lead to the recognition of these phloretyl derivatives as chromones; but for fuller comparisons the following work was undertaken.

(I). Synthesis of trimethoxy-phloretyl-coumarin from ethyl-para-methoxy-phenyl-propioacetate (planned to be synthesised from para-methoxy-cinnamic acid through several stages) . Ethyl-para-methoxy-phenyl-propionate was successfully prepared, but later stages of synthesis did not materialise.

(II). Synthesis of 5:7:4'-trimethoxy-2-methyl-chromone from Ethyl-para-methoxy-α-benzyl-acetoacetate (prepared from para-methoxy-benzyl-chloride and sodio-acetoacetic ester) and phloroglucinol-dimethyl-ether using P_2O_5 (cf. Simonis). This synthesis however ended in giving the isomeric coumarin instead of the expected chromone. To ascertain this fact

more fully further investigation was undertaken. Ethyl-benzyl-acetoacetate was prepared and condensed (a) with phloroglucinol using H_2SO_4 and the resulting coumarin methylated, and (b) with phloroglucinol-dimethyl-ether using P_2O_5, the resulting product being identical with the methylated coumarin in (a). Independent attempt at the synthesis of 5:7-dimethoxy-3-benzyl-2-methyl-chromone by acetylating at 180° the ortho-hydroxy-ketone prepared by the Hoesh method from pheny-propio-nitrile and phloroglucinol-dimethyl-ether brought to light the true chromone contrasting with the above isomeric coumarins. This settles that coumarins and not chromones are obtained from the esters in question by the Simonis reaction.

(III). Lastly, the possibility of synthesising trimethoxy-phloretyl-coumarin from malonic ester derivatives was investigated. The required di-ethyl-para-methoxy- -phenyl-propio-malonate decomposed in preparation, though the di-ethyl- -phenyl-propio-malonate was successfully synthesised.

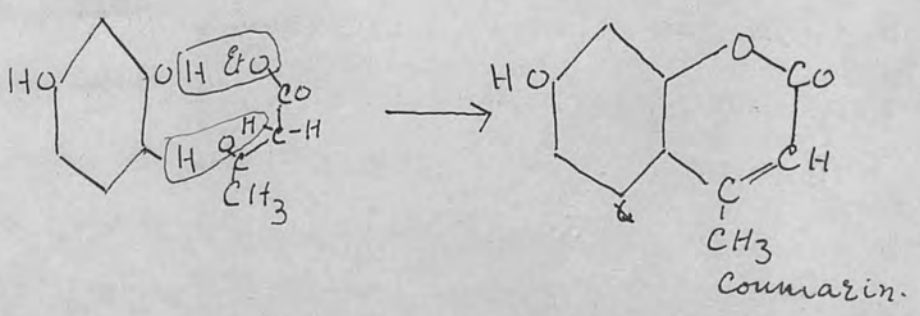
Part I

METHODS AVAILABLE FOR THE SYNTHESIS OF COUMARINS AND CHROMONES

The coumarins are the derivatives of the simple substance coumarin, the lactone of o-coumaric acid (o-hydroxy-cinnamic acid). The first artificial synthesis of coumarin was due to Sir W.H.Perkin, from Salicylaldehyde, acetic anhydride and sodium acetate, and acidifying the sodium ortho-coumarate so formed. In his paper (J.C.S. I868, 2I, 53) the author describes the preparation of coumarin by heating aceto-ortho-coumaric acid (which is obtained from sodium-salicylaldehyde and acetic anhydride) and proves the product of this reaction to be identical with the coumarin which occurs in Tonka beans etc. He then goes on to show the possibility of preparing the homologues of this simple coumarin and explains how, by using Butyric-, or Valeric anhydrides in the place of acetic anhydride, butero- and valero-ortho-coumaric acids ~~acids~~ were obtained by him and how the corresponding coumarins were prepared from these.

This is so far as our earliest information on the coumarins is concerned. But in I883, there came to be known another method for the synthesis of coumarins — a method capable of almost infinite application — the one due to V.Pechmann and Duisberg. In Ber. I883. P.2II9, these authors published their paper describing a synthesis of coumarins by the interaction of phenols with β-ketonic esters, in the presence of dehydrating agents. The first

dehydrating agent used for this purpose by these authors was concentrated sulphuric acid. The method as described by them, merely consists in mixing equivalent quantities of the required β-Ketonic ester and the phenol, and adding concentrated sulphuric acid, drop by drop, preferably with constantly stirring the mixture which may be cooled in ice. The reaction was explained as taking place thus;-



In some cases the mixture has been warmed from IO to I5 minutes on a water bath, though in most cases the reaction takes place in the cold when left for a day or two. The mixture is then poured on to crushed ice and the coumarin is purified by crystallisation.

This method has been very widely used in coumarin synthesis. Ever since its introduction in I883, successive workers the earlier of whom were Pechmann himself and various collaborators, have freely employed it; and though on one occasion the work of Jacobson and Ghosh (J.C.S. I9I5, T. pp. 425, 959, I05I; J.C.S. I9I6 T, p. I06) had introduced some erroneous ideas about the working of this method when applied to certain heavily substituted β-Ketonic esters, the work and criticism by Robinson and

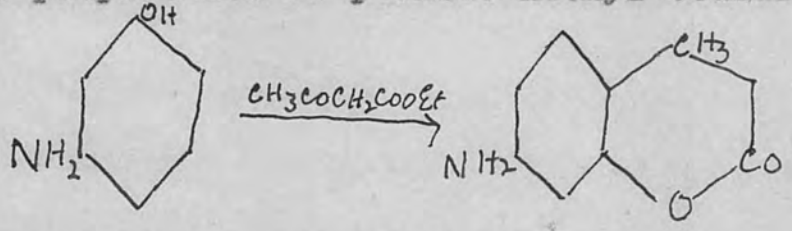
Baker and other collaborators which conclusively refutes Jacobson and Ghosh's ideas, has established the sulphuric acid method on an indisputable footing. (Cf. this account further whilst dealing with the work on chromones.)

To illustrate the wide applicability of this method a few examples may be quoted. Pechmann and Duisberg prepared methyl-coumarin from phenol and acetoacetic ester, β-methylambilliferon from resorcinol and acetoacetic ester, phenyl umbelliferon from resorcinol and benzoylacetic ester (Ber. I885, p. 2II9), whilst para-cresol, pyrogallol , phloroglucinol etc. have also been condensed with these esters, using conc. H_2SO_4. Pechmann and Crafft used the method to get 4-methylasculetin, and Kostanecki and Weber employed it in the preparation of their m-dihydroxy-phenyl-coumarin. In (J.C.S. I908, T, 20I8) Clayton describes the preparation of some coumarins by this method and so does Dey (J.C.S. I908 T, I606) . Finally Jacobson and Ghosh have given this very method a fairly wide application and have introduced in the field of chemistry a number of coumarins (as shown by Baker and Robinson and collaborators, cf. loc. cit. later.)

There are however two serious drawbacks to this method. Firstly, being a strongly dehydrating agent conc. sulphuric acid very often tends to char the reacting substances and introduces decomposition products mixed with the coumarins. Secondly, the strong acid, being a sulphonating agent, sulphonates many of the phenols, some of them even in the cold. Thus a good portion of the

reacting substances are led away from the field of reaction, and this impoverishes the yield. In most papers describing the synthesis of coumarins by the use of conc. H_2SO_4, no mention of the yield is made. Just one or two cases available might be quoted for illustration. Thus, Peckmann and Kafft record a yield of only 3% in their synthesis of 4-methyl- coumarin (Ber. I90I, 34, p. 425). In (Ber. I90I, p. 42I) the same authors describe a yield of only 8% for certain other coumarins they prepared. Working with such poor yields would be very inconvenient when synthesisimg coumarins from more complex ketonic esters. The difficulty was however considerably minimised when Simonis and Goldenzweig (Ber. I908, p. 830; J.C.S. I9I6, A i, 57) showed that the yield could be improved by using 73% H_2SO_4 in place of the concentrated acid. Thus rapid decomposition ~~and~~ as well as sulphonation can be remedied against and a more reasonable yield of coumarin obtained. Simonis and Goldenzweig actually got a yield of 2I% in their preparation of methyl-coumarin, as against 3 to 8% whem conc. H_2SO_4 was used. Other workers have also used 73% H_2SO_4, and always to an advantage. Bargellini and Martegiani got improved yield of methyl esculetin.(Gazz. Ital. Chem. 4 (2) 6I5, I9II). Although in most cases of coumarin synthesis workers have chiefly given preference to sulphuric acid whether concentrated or 73%, attempts at coumarin-condensations with the uses of other dehydrating agents have certainly been tried.

Quite as early as I899 (Ber. I899, III, 3696) Pechmann and Otto Schwarz have used $ZnCl_2$ in alcoholic solution for dehydrating a mixture of p-amido-phenol and acetoacetic ester in the preparation of p-amido-methyl-coumarin.



Here the method consists in mixing equal quantities of phenol and the ester and refluxing it with the addition of anhydrous $ZnCl_2$ in absolute alcohol. This preparation seems to have given a yield of 20 to 25%. No loss by sulphonation is possible here, and in this the method scores an advantage over the H_2SO_4 method. It has been used by Pechmann and Krafft (Ber. I90I, I. 424) in the preparation of coumarin-carboxylic ester (yield 3gms. for 5 gms. of phenol used), and also by later workers from time to time.

Another early method for coumarins is that due to E.Siebort (Ber. I905, I. 478) involving the use of HCl gas in warm glacial acetic acid solution. The original author prepares α-o-pthalyl-aldehyde saure methyl umbelliferon by this method. The ester and the phenol are mixed in molecular proportions and are dissolved in slightly warm glacial acetic acid. The solution is then saturated with dry HCl gas . This method has been used by later workers also (Robinson and Baker, J.C.S. I925 T. 2350).

An interesting method for coumarin synthesis is due to

Pechmann and Krafft (Ber. I90I, 34, p. 423). Here the authors first of all acetylate the phenol and then condense it with the β-ketonic ester using H_2SO_4 for dehydration. The method has been used for the preparation of β-methylasculetin. The acetylation of the phenol prtects it against the sulphonating action of concentrated sulphuric acid and this helps to give a better yield of coumarin.

In addition to, these several methods of coumarin synthesis with the use of phenols and β-Ketonic esters , there are others where phenols have been condensed with maic and malonic esters to get coumarin-carboxylic acids, which may be further hydrolysed to a simpler coumarin. Clayton states (J.C.S. I908, T. p. 20I8) that phenols can be condensed with malic esters to give coumarin derivatives. He describes the preparation of 6-8-dimethyl-coumarin using I:3:4-Xylenol and malic acid with conc. H_2SO_4. He heats these substances for a few minutes and pours them on to crushed ice. A yield of 30% is recorded. In J.C.S. I9I5 T, I606, Dey describes the preparation of several coumarins where he mentions the use of ethyl malonate and resorcinol in the synthesis of ethyl-hydroxy-coumarin-4-acetate, after the method described by Michael for condensing resorcinol with sodiomelonate (J.per.Chem. I888, II, 37,469). A number of coumarin derivatives have been prepared by the condensation of phenols with acetone dicarboxylic acid. The latter has been condensed with naphthol to give I:2-naphthapyrone-4-acetic acid, and also with quinol, xylenol etc., all to give coumarin

~~in~~ derivatives (Dey, J.C.S. I9I8, T, I606).

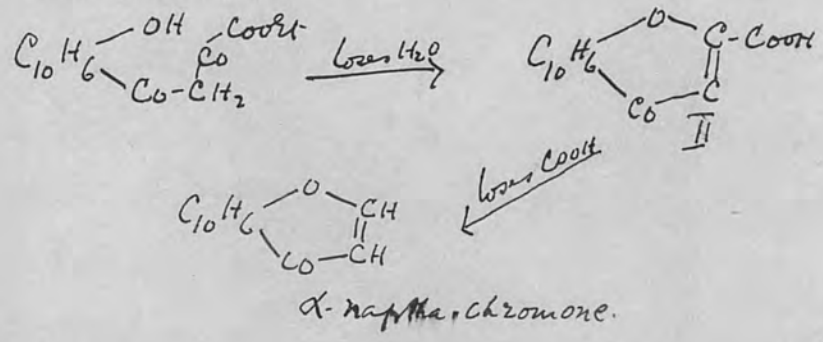
Coumarins have been prepared from nitriles also. Thus Mayer (J. per. Chem.I903, 67, 342) benzo-aceto-di-nitrile ~~N.H.CPh.CH$_2$~~ $NH \cdot CPh \cdot CH_2 \cdot CN$ with resorcinol and obtained what has been proved to be 7-hydroxy-4-phenyl coumarin by Sonn (~~Gazz. I9II, 4I, i, 747)~~ Ber. I9I8, 5I=/82I). Again Bargellini and Forti-Forli (Gazz. I9II, 4I, i, 747) condensed p-methoxy-benzoyl-aceto-nitrile with resorcinol in the presence of conc. H_2SO_4 to get 7-hydroxy-4-p-methoxy-phenyl coumarin.

Thus various methods have evolved for the synthesis of coumarins. But most of the existing coumarins have been prepared from β-ketonic esters by the methods of Pechmann and others.

Closely allied to and strictly analogous with the coumarins are the chromones. The name chromone was first introduced by Kostanecki and Bloch (Ber. I900, 33, 47I to 476) to designate pheno- -pyrone or benzo- -pyrone, as against benzo- -pyrone for the coumarin, and it is to Kostanecki and his collaborators that much of our early information on chromones is due.

Kostanecki and his collaborators have contributed a number of papers describing several of the complex chromones they have prepared. In all, the methods employed for these, there is but one central principle. The workers first obtain a complex benzo-ketone with a hydroxy or an ethoxy group in the ortho-position to the ketone grouping, and then by a process of boiling with HI or HCl (conc.) a molecule of H_2O or Et(OH) is removed,

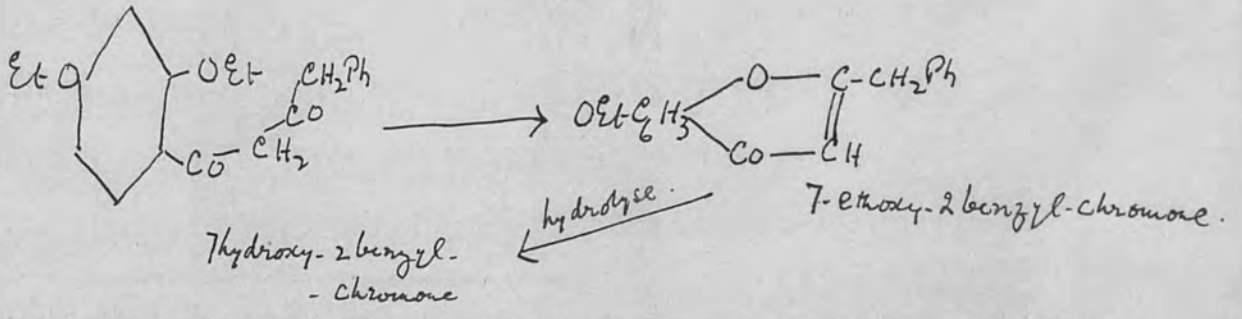
thus effecting a ring-closure. And in most cases, this first ring-closure produces a complex chromone with an easily hydrolisable hydroxy-group, which on being removed, leaves a simple chromone. A few examples may be quoted in illustration. Thus Kostanecki and Froemsdorff (Ber. 1902, 35, 59 to 961) (also J.C.S. 1902, A. 303) prepare ethyl-hydroxy-2-naphthyl pyruvate (I) . This on boiling with conc. HCl loses water and gives a chromone II



In an identical manner, Kostanecki and ~~Roytzes~~ RUIJTER De Wildt prepared 5-hydroxy-7-methoxy chromone from ethyl-2-hydroxy-4:6-di-methoxy-benzoyl-pyruvate, by boiling the latter with conc. HCl and decomposing the 5:7-di-methoxy-chromone di-carboxylic acid so obtained (Ber. 1902, 35, 861 — 865). And so with the suitable complex pyruvic acid ester derivatives Kostanecki and others have prepared more chromones. [Ber. 1902, 35, 2547 & 1903, 36, 190 David and Kostanecki.]

Another slightly different ptocess used by Kostanecki and his collaborators is that of using aceto-phenone derivatives instead of the pyruvic acid derivatives. Here also the process simply consists of effecting a ring-closure in the aceto-phenone derivative by boiling it with the concentrated HCl. This gives a chromone which in its turn may be utilised to yield a simpler chromone by degradation.

Thus Kostanecki and Hannach (Ber. I902, 35, 866 to 868) boiled w-phenacetyl-2:4-di-ethoxy-aceto-phenone with conc. HI and obtained the following reaction:-



Other examples of the same process are afforded by the preparation of 3:3':4':5'-tetra-hydroxy-flavone from 2:4-di-ethoxy-3':4':5'-tri-methoxy-benzoyl-acetophenone (Kostanecki & Plattner, Ber. I902, 35, 2544). Cf. also Kostanecki & Tambor (Ber. I900, 33, 330) and Kostanecki & Rozyeki (Ber. I90I, 34, I07) .

This principle introduced by Kostanecki of ring-closing suitable ketonic derivatives for the preparation of chromones is really very ingenious; and the value of the work can now be better appreciated when one considers how closely allied in principle are those methods of Kostanecki to those ~~of~~ revealed by the work of Robinson and Baker for the synthesis of chromones ~~sa~~ as will be seen later in this account (Robinson & Baker, loc. cit. later) .

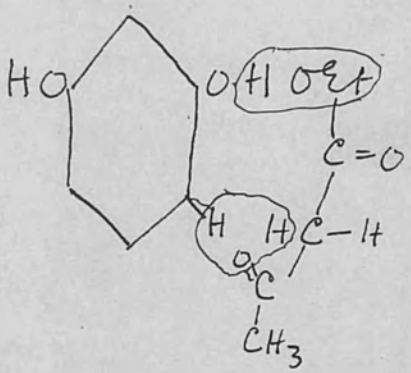
A fair amount of work has been added to the study of chromones by Ruhemann and his co-workers and from substances of quite a different nature. They start with the esters of the acetylene series and condense them with phenols in the presence of conc.

sulphuric acid as a dehydrant. They describe the preparation of quite a number of chromones by this method. A few examples may be quoted by way of illustration:- e.g., the authors prepared ethyl-phenyl-fumarate by condensing Na-phenolate with ethyl-acetylene-di-corboxylates. This was then dehydrated with conc. H_2SO_4 to give a benzo-pyrone-mono-carboxylate which on distillation in vacuo loses CO_2 to give (Cf. J.C.S. 1900 7, Pay 984, 1119, 1174) Flavone, the parent substance of flavones and the yellow plant dyes such as chrysine, quercetin and fisetin. The authors have thus prepared several chromones. For example, they have used creosoxy fumaric acids to get benzo-pyrones (J.C.S. I90I? T. 470, Ruhemann and Bansor) In J.C.S. I90I, T. 9I8, Ruhemann and has extended his study using thymol and carvacrol and there he describes some more chromones such as 5-propyl-8-methyl-I:4-benzo-pyrone etc.

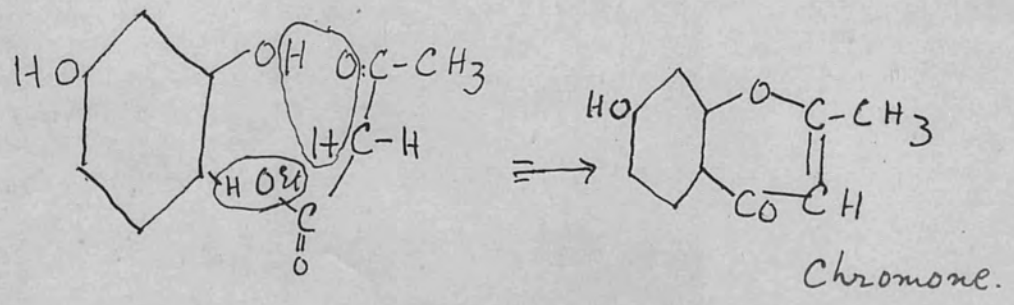
Now comes the work of Simonis and his collaborators. This is worth considering in some detail as it marks an important point in the study of benzo-pyrones (Ber. I9I3, p. 20I4, Pet^{s}chek & Simonis)

Hitherto since the work of Pechmann and his workers it was recognised that β-ketonic esters condense with phenols in the presence of dehydrating agents to give coumarins. As for such dehydrating agents , several have been used, conc. H_2SO_4, 73% H_2SO_4, $ZnCl_2$, HCl gas etc. (see this account earlier) In this formation of coumarins the

reaction was supposed to be proceeding in the following manner :-



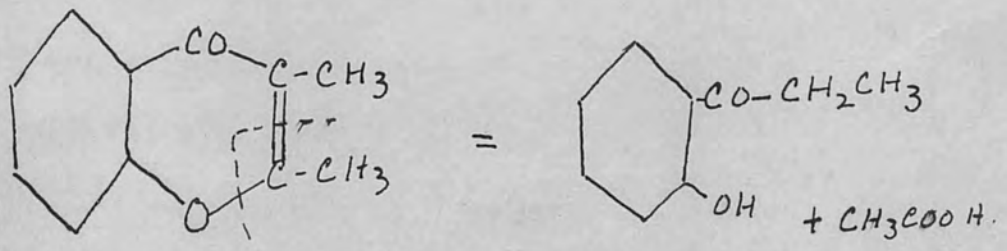
But, Simonis while he recognised the above change to take place when the dehydrating agents enumerated above were used, explained that when P_2O_5 was used instead, the reaction took an entirely different course resulting in the formation of chromones in the place of coumarins.



Chromone.

None of the previous workers however have used P_2O_5 in this manner. The process has been described by Petschek and

Simonis (Ber. I9I3, Pro. I4) for the preparation of dimethyl chromone from phenol and methyl-acetoacetic ~~acid~~ ester. It consists merely in mixing equal quantities of the ester and the phenol with excess of P_2O_5 and warming on a water bath with constant stirring. The resulting viscid mass is poured on to ice and the resulting solid purified. In the same paper, after preparing the dimethyl-chromone, the authors have tried to bring forward a proof to substantiate the fact that the substance of thier reaction is a chromone and not a coumarin. They have hydrolised the chromone with sodium alcoholate and have split the chromone as shown below, giving ortho-oxypropiophenone:-



They regard this fission ~~along the line indicated~~ giving o~~-~~hydroxy-propiophenone as a sufficient proof for the substance to be a chromone.

In a later paper (Ber. I9I4, 47, 2229) Simonis utilises his reaction to attempt the preparation of certain other

chromones. By condensing methyl-methyl-acetoacetate with resorcinol, the author gets 7-hydroxy-2:3-dimethyl-chromone which has already been prepared by Kostanecki and Lloyd (J.C.S. A. 735. ; Ber. I90I, 34, 2942 — 2950) by acetylating propionylresorcinol-mono-ethyl-ether with acetic anhydride and sodium acetate, and hydrolysing the product.

In his critcism of the methods known for the synthesis of chromones, Baker (J.C.S. I925, T. 2349) agrees that Simonis and his collaborators have prepared chromones by the P_2O_5 method and expresses his belief that the reaction is of a general application. A mark of caution is necessary here, because though in some cases Simonis claims to have prepared chromones which compare favourably with known chromones made by Kostanecki and others (Kostanecki and Lloyd, loc. cit.), still, without further consideration investigation the reaction cannot be taken to be of a general application. For, after all, the proof which Simonis gives for calling his substances chromones is based on the same principle as that brought forward by Jacobson and Ghosh (see later loc. cit.), namely of hydrolising the substances and studying then nature of fission produced. This kind of proof, as will be seen later, has been amply criticised by Baker himself and has been disposed of as any safe factor in distinguishing the chromones and coumarins. In this light then, it seems yet too early to accept the

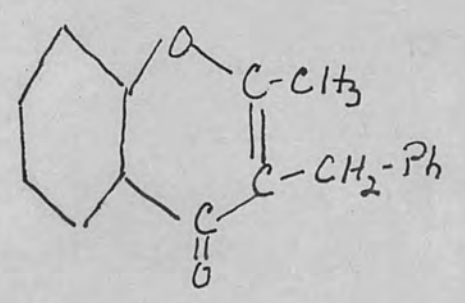
Simonis reaction as being of a general application.

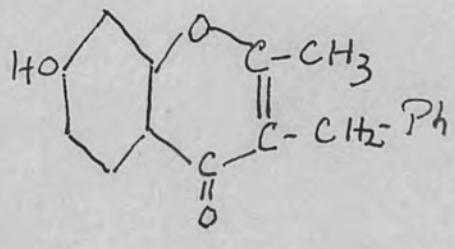
One simple reaction may be tried to test the Simonis reaction. As will be seen later, Baker and Robinson have fully investigated the method of Pechmann and others of condensing β-ketonic esters with ~~with~~ phenols using H_2SO_4 and have established that this reaction only gives coumarins. If then a particular ester is condensed with the same phenol using H_2SO_4 and then using P_2O_5, and if the two reactions give ~~two different~~, ~~but isomeric~~ IDENTICAL products, the Simonis reaction may be relied upon with greater certainty. Pending such scrutinising study, the reaction explained by Simonis cannot be directly accepted as being of a general application.

The work of Jacobson and Ghosh may now be reviewed (Jacobson & Ghosh, J.C.S. I9I5, T. pp. 425, 959, I05I; and Ghosh, ibid. T. I06). They have synthesised what they called chromones by a method identically the same as that described by Pechmann and collaborators (loc. cit.) for synthesising coumarins, namely, the one by condensing β-ketonic ester with phenols in conc. H_2SO_4.

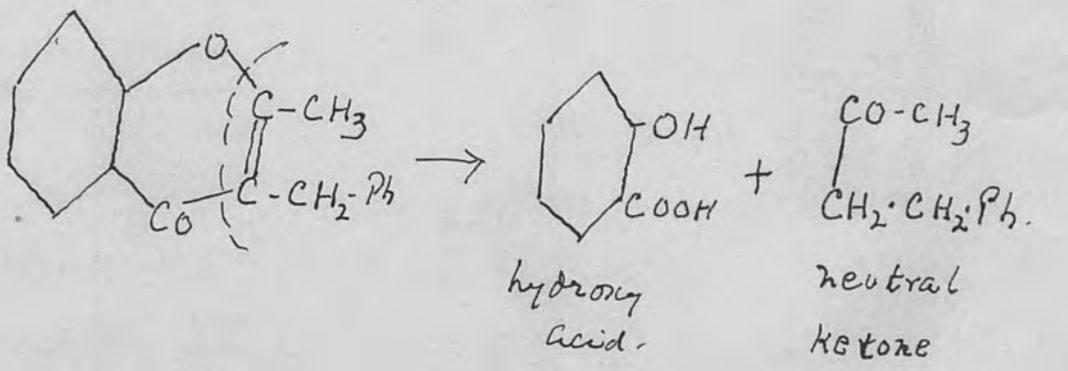
In analogy with Bulow and Wagner's work (Ber. I900, 34, II98) and other work privately communicated by Collie and White, Jacobson and Ghosh expected to get chromones by interacting ethyl-acetoacetate (with both its H-atoms substituted) with phenols in H_2SO_4. This expectation failed as the reaction did not work. But they still entertained the hope of getting chromones

even from mono-substituted ethyl-acetoacetate, in which the reacticity ofm the methylene hydrogen atom was diminished to a minimum by appropriate substitution. So one of them carried out the condensation of ethyl-ethyl-acetoacetate with resorcinol and got a product that was a mixture, and yet which analysed satisfactorily though melting indefinitely. They interpreted this result as being due to the fact of the reaction having a produced a mixture of a chromone and a coumarin. From this they calculated that as unsubstituted and methyl-substituted ethyl-acetoacetae gave a coumarin and the ethyl-substituted ester gave a mixture of a coumarin and a chromone, a more heavily substituted ester would give solely a chromone. They therefore started with the benzyl-substituted ethyl-acetoacetate and condensing it with resorcinol, phloroglucinol etc. and believed to have obtained what they thought were chromones:-





They then set off to prove the constitution of these so called chromones by decomposing them with alkali and ascertaining the nature of the decomposition product. Thus:-

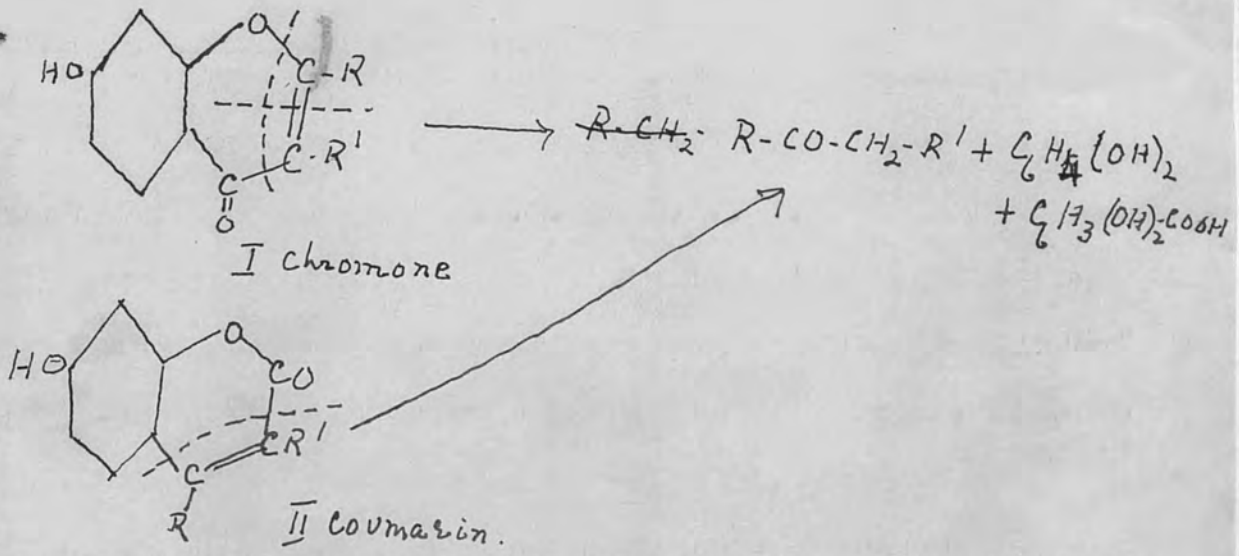


They regarded this manner of splitting as sufficient proof for calling the products of their reactions chromones and claimed to have introduced a new method for the synthesis of chromones, " in addition to the indirect and difficult processes of Kostanecki, Tambor, Nagai, Ruhemann, Simonis and others."

On the whole, Jacobson and Ghosh believe that in coumarin and chromone condensations, it is not the dehydrating agent that directs the course of the reaction so much, but that it is the nature of the substituents which determines the course of the reaction by diminishing the reacticity of the hydrogen atom in ethyl-acetoacetic ester. This then, is the main idea which leads the workers to believe that in the cases of so many benzo-pyrones they have synthesised frim heavily substituted acetoacetic esters they have always got chromones and not coumarins; and then they tried to substantiate this belief by the above proof. They then proceed to describe the condensation of benzyl-acetoacetic ester, benzoyl and phenyl propionate, ethyl-phenyl-acetoacetate, etc. with various members of the phenolic series and claim to have obtained chromones in all cases.

The arguments and conclusions of Jacobson and Ghosh have however received a very careful criticism at the hands of Robinson and Baker. In (J.C.S. I925, T. p.2349) Baker has amply criticised Jacobson and Ghosh by attacking the very arguments by which they endeavour to prove the constitution of their substances as being chromones and not coumarins. As seen before Jacobson and Ghosh treat their substances with 33% or 50% aqueous caustic potash and examined the products of hydrolysis. They get as a result of hydrolysis (I) an o-hydroxy acid (2) a neutral ketone. They then contend themselves with the argument that this kind of fission is characteristic of a chromone, and therefore their substances are chromones, as against coumarins which would hydrolyse only to give (I) a hydroxy ketone and (2) a phenyl-propionic acid. Baker fully attacks this argument after a careful study of these processes of hydrolysis in the case of the chromones and the coumarins respectively. He takes the so called 7-hydroxy-3-benzyl-2-methyl-benzo-γ-pyrone (in reality the isomeric coumarin) prepared by Jacobson and Ghosh and hydrolising it gets benzyl acetone and β-resorcilic acid. He then takes the actual 7-hydroxy-3-benzyl-2-methyl-chromone prepared by Crabtree and Robinson (J.C.S. I9I8, II3, p. 859) and hydrolising it gets exactly the same neutral ~~tha same~~ ketone as above, namely benzyl-acetone, and benzyl-resacetophenone. This formation of the same neutral ketone by hydrolising a coumarin on the one hand and the isomeric chromone on the other is explained by Baker

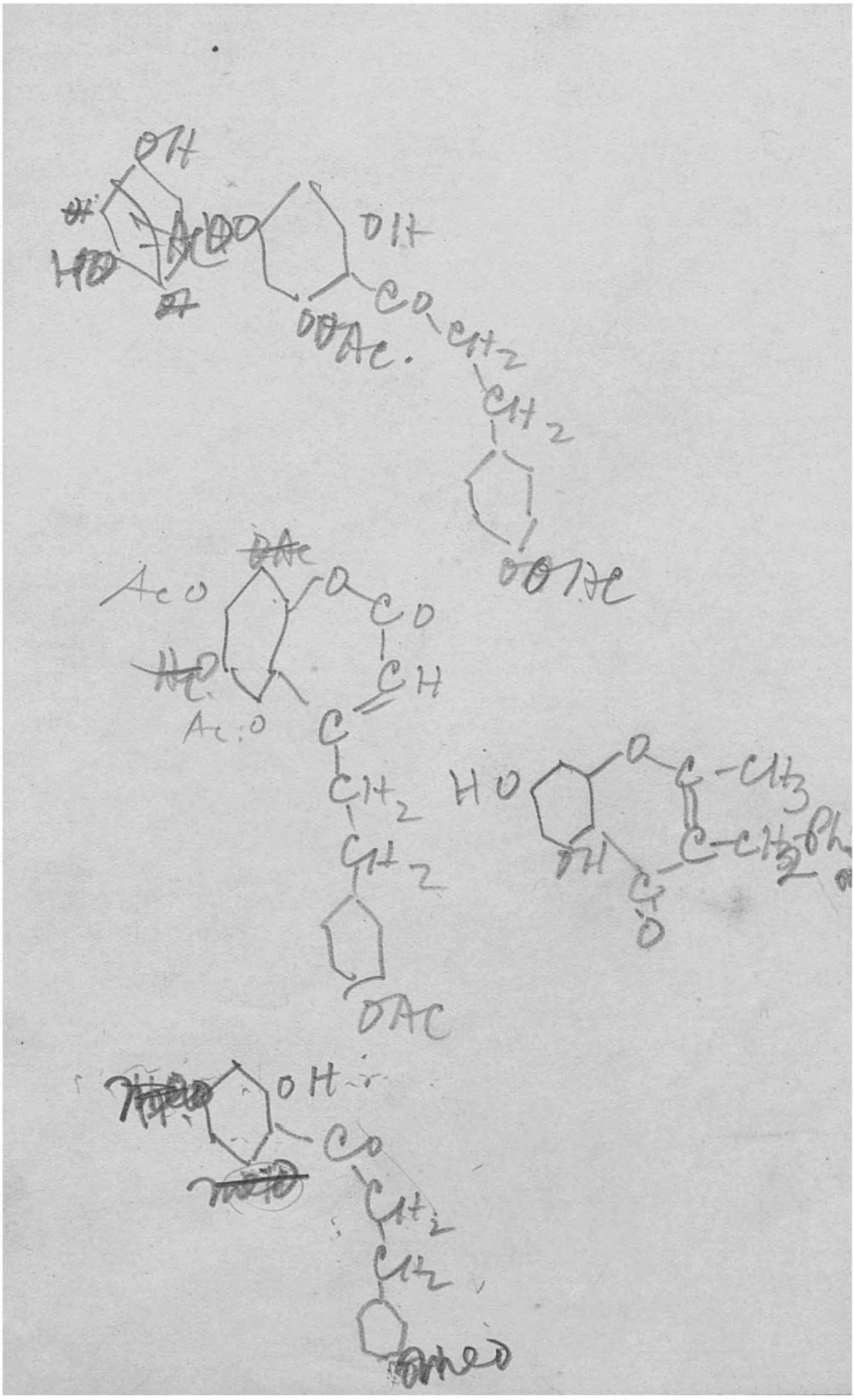
thus:-



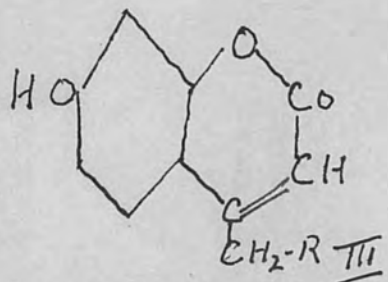
It is evident from this then, that if both the chromones and the coumarins on hydrolysis are capable of giving the same neutral ketone which they were not supposed to give according to Jacobson and Ghosh, the whole argument weakens down and the study of the effects of hydrolysis ceases to be any safe criterion for distinguishing chromones from coumarins.

In the hydrolysis of II, resorcinol is also formed. This formation was explained by Jacobson and Ghosh by assuming the decomposition of resorcilic acid. But Baker (loc. cit.) explains that when an actual coumarin (chromone as Jacobson and Ghosh called it) was hydrolised resorcinol was principally formed and very little resorcilic acid so that them latter is the bye-product nad not the former, contrary to Jacobson and Ghosh's explanation.

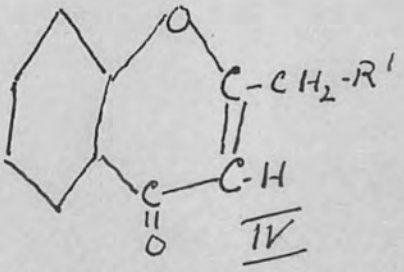
All this shows the extreme necessity of caution needed in deciding the constitution of chromones and coumarins by merely studying the effects of hydrolysis on them; the matter



being further complicated in cases where R= R = methyl in the above formulae, for in such a case, not only will I and II above but also the isomeric coumarin III and the chromone IV give the same ketone, as Baker has experimentally proved.



III

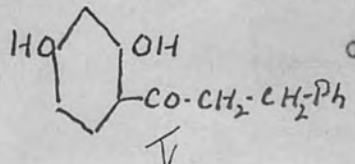


IV

In addition to all this criticism and the new light thrown on the effects of hydrolysis of chromones and coumarins Baker, Robinson and other collaborators have actually prepared most of the true chromones and contrasted them with the so called chromones, in fact the isomeric coumarins, of Jacobson and Ghosh. All, this then conclusively disproved Yacobson and Ghosh's view that chromones can ever be obtained by condensing phenols and ketonic esters with H_2SO_4, and places the ideas of Pechmann and co-workers on firmer grounds.

The method which Robinson and Baker have adopted for synthesising chromones is the following:-

They acetylate with acetic anhydride and sodium acetate ketones of the type V and effect a ring-closure to give a chromone.



V

Among the chromones they have prepared by this method are:-

7-hydroxy-3-benzyl-2-methyl-benzo-γ-pyrone (Crabtree & Robinson, J.C.S. I9I8, II3, p. 867)

7:8-di-hydroxy-3-benzyl-2-methyl-benzo-γ-pyrone (J.C.S. I925,, T. p. 2355)

- hydroxy-3-phenyl-2-methyl-benzo-γ-purone (Baker & Robinson,) and several others, including a number of naturally occuring iso-flavones and flavones such as prunitol etc. (J.C.S. I926, T . p. 27I4)

Finally in J.C.S. I929, T. p. I468, Robinson, Baker and Pollard give a new general method for synthesising derivatives of 7-hydroxy-isoflavone from 7-methoxy-isoflavone-2-carboxylic acid which is synthesised by a complex process.

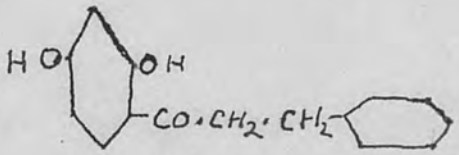
Of all the chromones synthesised by Robinson and Baker the one that most attracted attention was 5:7-di-hydroxy-3-benzyl-methyl-chromone from benzyl-phloracetophenone by acetylation at I80° C. and subsequent hydrolysis. For, this benzyl-phloracetophenone is very similarly constituted as the substance known aa phloretin (cf. later) on the acetylation of which a paper was long published by Ciamician and Silber (Ber. I874, 27 , I627).

The rest of this account will then deal in detail with reference to practical work carried out on the ring-closure of this phloretin; and with allied synthetical experiments.

Part II. Section (1) - Theoretical.

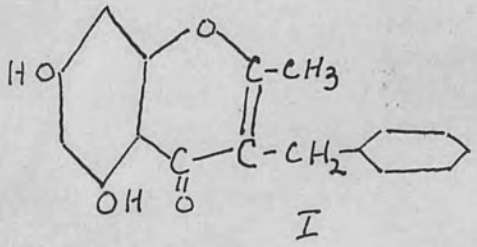
Studies in hydroxy—carbonyl compounds.

As has already been seen, Robinson, Baker and others have prepared a number of chromones from ketones of the type

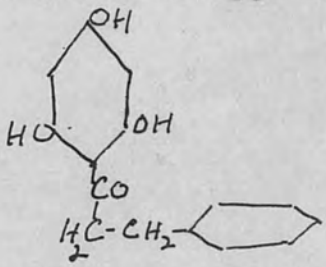


by acetylating them with acetic anhydride and sodium acetate at 180°C. Most striking of these is the chromone 5:7-dihydroxy-3 benzyl-2 methyl-benzo-pyrone I from benzylphloracetophenone. With analogy to this, it might have been expected that p-hydroxy-benzylphloracetophenone or phloretin, on acetylation and subsequent hydrolysis, in a similar manner would give 5:7:4' trihydroxy 3 benzyl-2-methyl benzo-pyrone II (see formulae below). But Ciamician and Silber, who have actually carried out such an acetylation of phloretin, cáll the resulting benzo-pyrone, a coumarin (Ber. 1874, 27, 1627), and so does Wessley (Monatsch. 1929, 53 & 54, p. 554) even in the light of Robinson and Baker's work. Of the innumerable chromones, flavones, and isoflavones due to Baker, Robinson and others, practically all have been prepared by this acetylation of the type of ketone shown above, and it seems impossible to contend that Phloretin alone would form such a singular exception to all these ketones which it resembles, particularly the phloracetophenone - and it seems fairly safe to assume that what Ciamician and Silber have called Triacetylphloretyl coumarin is only the isomeric chromone 5:7:4'Tri~~methoxy~~acetyl-3 benzyl-2 methyl

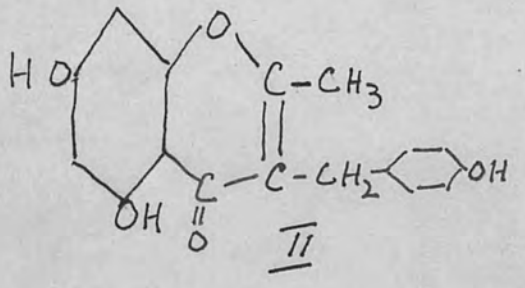
chromone. Still, it seemed of interest to repeat the work of Ciamician and Silber of preparing what they call Tri-hydroxy-Phloretyl-coumarin, methylate this, and examine how far this product of methylation would compare with (1) a regularly synthesised Tri-methoxy-phloretyl-coumarin, ~~or 5:7:4'Trimethoxy-3 benzyl-4 methyl-coumarin, and~~ (2) a synthesised chromone isomeric with this coumarin, i.e. 5:7:4'Trimethoxy-3 benzyl-2 methyl 1:4 benzo-pyrone.



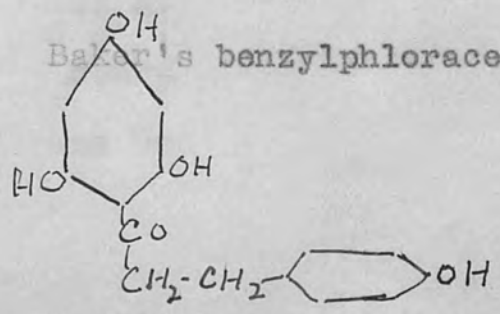
I



Baker's benzylphloracetophenone.



II



Phloretin.

Work was then started on Phloretin and the following scheme was pursued:- Phloridzin —— Phloretin ____Triacetyl-substance _____ Tri-hydroxy-product _____ Tri-methoxyphloretyl-benzopyrone.

Accordingly, Phloridzin, the glucoside present in the bark of the apple, cherry, pear, etc., was hydrolysed by the method shown by Stas in Ann. Chim. Phys. 1836, 61, p. 367 (cf. Rennie, J.C.S. 1886, 49, 864) and pure phloretin was obtained.

In acetylating Phloretin, there was one point of interest. In J.C.S. 1930, Jan. p. 21, Johnson and Robertson found that by acetylating 6-hydroxy-2:4:4'-Trimethoxy-β-phenyl-propiophenone at 100°C with acetic anhydride and sodium acetate have just an ordinary acetyl derivative without any ring-closure. It therefore seemed a matter of curiosity to try an acetylation (in the same way at 100°) of Phloretin, which after all has the same constitution as the above ketone, differing from it only in having hydroxyls in 2 : 4 positions instead of methoxy groups, and see if tetra-acetyl-phloretin could be the result. Accordingly then, Phloretin was mixed with excess of acetic anhydride and sodium acetate and was heated for 6 hours on a steam bath. The reaction mixture was cooled and poured into cold water to decompose the unchanged Ae_2O during 24 hours. The fairly clear looking product was then filtered, washed and recrystallised. After several crystallisations, a pure substance was obtained, melting exactly as the Tri-acetyl body prepared by Ciamician and Silber. This gave the first clue to the idea that Phloretin underwent the same process of acetylation at 100°, as at 180°. The substitution of the 2 : 4 hydroxyls by methylation evidently alters the reactivity of the substance to acetylation.

This acetyl body was then hydrolysed by a method which was more convenient than Ciamician and Silber's of hydrolysing in conc. HI. It consisted in deacetylating the pure, dry,

acetyl compound with methyl-alcoholic caustic soda (8% soln.). This product, though melting very indefinitely, analysed correctly enough to be called Tri-hydroxy-Phloretyl-benzo-pyrone.

At this stage, another acetylation of Phloretin was carried out - that by a process identically the same as Ciamician's (Ber. 1894, 27, 1627) the object being to ascertain whether this gave the same substances as those obtained above on the steam-bath. The acetylation certainly gave the tri-acetyl body though in a very crude form, and it required several crystallisations to get it in a state of analytical purity. It melted finally at 170°. This was then deacetylated as described above with alcoholic caustic soda, as the process of hydrolysis described by Ciamician (Ber. 1894, 27, 1632) by boiling with concentrated hydriodic acid proved to be far less convenient.

The deacetylated product was crystallised out of dilute methyl alcohol, when it gave a body melting at 213°C - that is, exactly as Ciamician's so-called Tri-acetyl-Phloretyl-coumarin. (This, however, when reacetylated, again gave the above Triacetyl substance melting at 170°, and not at 173° as Ciamician states.) The sharp melting of this tri-hydroxy body at 213° was in strange contrast to that of the steam-bath method melting indefinitely at 204 to 209°C. The case presented some incomprehensible difficulty. The parent-triacetyl-bodies melted quite the same, and the difficulty was only with the de-acetylated body.

One solution to the problem was possible. If the de-acetylated bodies were separately methylated to completion and

the properties and analyses of the methylated products compared, a similarity would prove that acetylation of Phloretin, when carried out with excess of acetic anhydride and sodium acetate, whether on a steam-bath at 100°C or on a gauze or preferably on an oil-bath at 180°C, produces the same kinds of results; whilst dissimilarity in the properties of these methylated products would prove to the contrary. With this end in view, a methylation of the product obtained by acetylation at 100°C was first started, in acetone solution with methyl iodide, using potassium carbonate. Refluxing for 22 hours gave a completely methylated product (as tested by $FeCl_3$) which crystallised out in light, long needles, melting at 166°C. (method shown by Robinson, J.C.S. 1928, p. 1457).

The deacetylated product of the oil-bath method (m.p. 213°) was also similarly methylated, the complete methylation here also producing a substance identical with the above, m.p. 166°, mixed m.p.166°C.

This result then proves the fact of the acetylation of Phloretin as proceeding in an identical manner, whether carried out at 180° on oil-bath, or at 100°C. Only the case of the two deacetylated substances melting differently baffles any attempt at a satisfactory explanation, though it may be perhaps contended that acetylation at 100° may retain some impurity which becomes pronounced in the deacetylated substance, and which gets removed during methylation. The

fact that the methylation of the steam-bath substances takes 22 hours as against 14 hours of the other one, and also the large amount of impure gum that separates in the purification of the former, lends some support to this explanation also.

The methylated product also bears absolute similarity to the 5:7:4'-Trimethoxy-3 benzyl-2 methyl-1:4 benzopyrone obtained by Johnson and Robertson (J.C.S. 1930, Jan. p. 21), by first methylating Phloridzin, then hydrolysing it and ring-closing the 6 hydroxy-2:4:4'-Trimethoxy β phenyl-propiophenone so obtained by acetylation at 180°C. (Cf. Wessley, Monatsch. 1929, 53 & 54, pp. 554-561). So far, then, is it clear that a certain definite benzo-pyrone is obtained from Phloridzin thus:-

(1) by hydrolysing it at the very start and acetylating whether at 100° or at 180°C, the Phloretin so obtained; and deacetylation and subsequent methylation of this acetyl-benzo-pyrone leads to the formation of the corresponding Trimethoxy-benzo-pyrone.

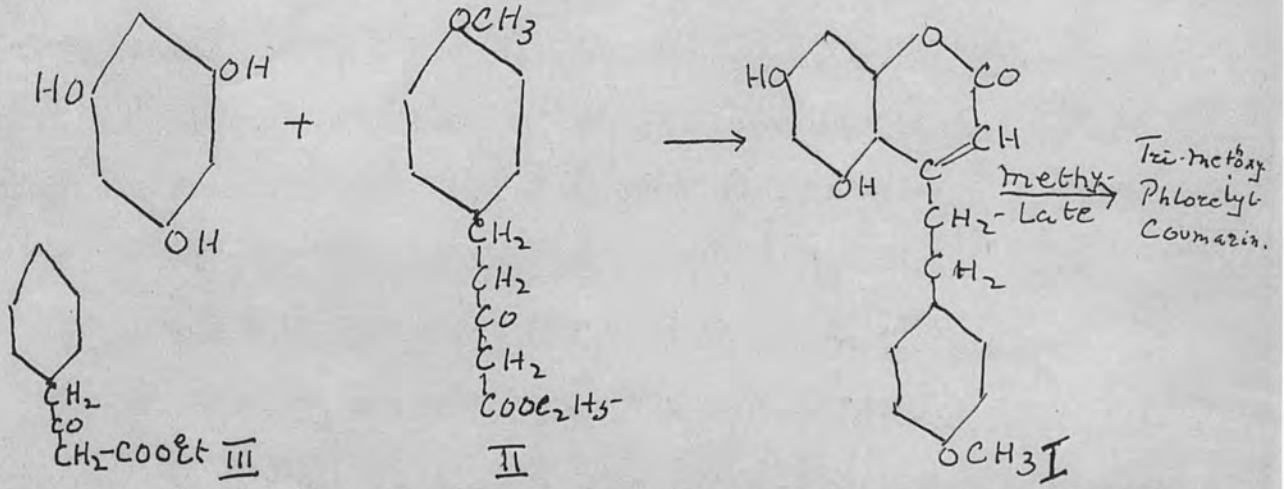
(2) by first methylating the Phloridzin and then hydrolysing it, and ultimately acetylating the complex ketone so obtained, the above trimethoxy-benzo-pyrone being directly the result in this case.

Now the benzo-pyrone in question has to be given its proper constitution as being either a coumarin as Ciamician and Silber, and Wessley, call it, or a chromone as it clearly seems to be in the light of Robinson and Baker's work. (Cf.

loc. cit.). To do this, as chalked out in the beginning, the synthesis of a known trimethoxy-phloretyl-coumarin was undertaken.

As has been seen in the first part of this account, a very important method of coumarin synthesis has been introduced by von Pechmann and his collaborators, - (Ber. 1883, p. 2119), namely that of condensing β-ketonic esters with phenols in the presence of dehydrating agents. Working downwards with the coumarin I. below, it is evident that the ester required for its synthesis is ethyl p-methoxy-phenyl-propio-acetate (II), which on condensing with phloroglucinol after the manner prescribed by Pechmann and others, might be expected to give the required result.

Thus:-



Hence the synthesis of this ester II. was to be considered.

Now in (J.C.S. 1923, T. p. 1755) Atwood, Thorpe and Stevenson described the preparation of ethyl-phenylacetoacetate III. by condensing ethylphenylacetate with ethylacetate by refluxing a mixture in the presence of sodium wire in dry etherial solution. The ester II. above is but the higher

homologue of this ester III., only with a p-methoxy grouping in it. So, if in an identical manner, ethyl acetate could be condensed with ethyl-p-methoxy-phenyl-propionate, ester II. might be the result. Hence, for all this the preparation of ethyl-p-methoxy-βphenylpropionate was undertaken, according to the following scheme.

p-methoxy cinnamic acid ——— p-methoxyphenylpropionic acid → its ester.

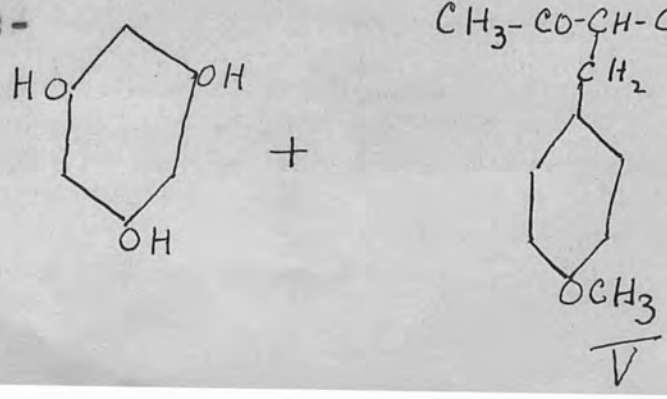
The paramethoxy cinnamic acid was prepared by the well known method of mixing anisaldehyde, malonic acid, pyridine and piperidine and heating the mixture for 8 hours on a steam-bath, refluxing the product for 2 hours, pouring into water, acidifying with HCl, filtering and crystallising the precipitate out of dilute alcohol. (Cf. Perkin J.C.S. 1877, 31, 408; Einhorn, Annalen 1883, 243, p. 363; Knoevenagel Ber. 1898, 31 2606.).

This p-methoxy cinnamic acid was reduced with sodium-amalgam, and the p-methoxy-phenyl-propionic acid so formed was esterified with excess of ethylalcohol (absolute) and concentrated sulphuric acid. Now came the final stage for the synthesis of the ethyl-p-methoxy-βphenylpropio-acetate (ester II.) and this was attempted with the above obtained p-methoxy-β phenyl-propionate and ethyl acetate by the method of Atwood, Thorpe and Stevenson (loc. cit.) Unfortunately here, the condensation gave an ester which analysed badly, and

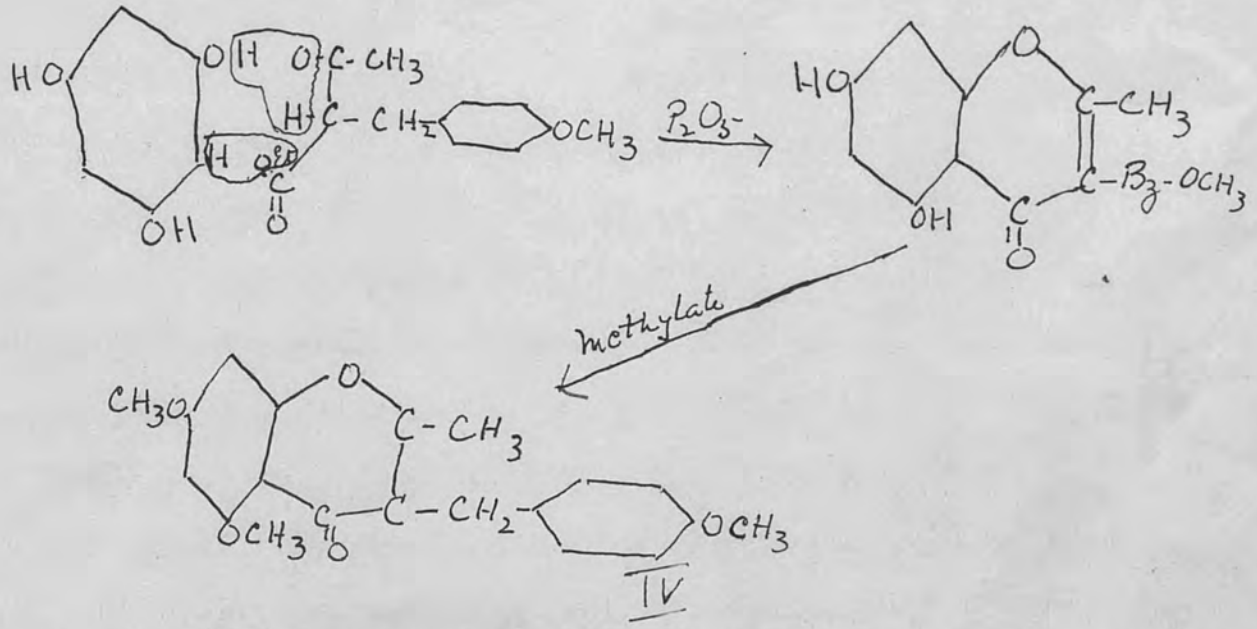
this held up the attempt at synthesising the Tri-methoxyphloretyl-coumarin.

At this stage it seemed advisable to transfer the attention on the possibility of synthesising the chromone corresponding to the trimethoxyphloretyl coumarin, i.e., 5:7:4'trimethoxy-3 benzyl-2 methyl-1:4 benzo-pyrone IV. As has been seen already the paper in Ber. 1913, p. 2014 by Simonis deals with a method of chromone synthesis based on the condensation of β ketonic esters with phenols with the use of phosphorus pentoxide. So a synthesis of the above chromone IV. could be possibly achieved, if a suitable β ketonic ester, which would possibly condense with a phenol giving the required result, could be had. In considering the possibility of coumarin synthesis above for tri-methoxyphloretyl-coumarin, it was seen that ethyl-p-methoxy-β phenylpropio-acetate if condensed with phloroglucinol in H_2SO_4, would give the required coumarin. So to get the corresponding chromone by the method of Simonis, it would be evident, as shown by the following formulae, that the ester needed is only an isomer of this above p-methoxy ester, that is, ethyl-p-methoxy-α benzyl-acetoacetate V. which with phloroglucinol would give the chromone IV. on subsequent methylation of the hydroxy-groups.

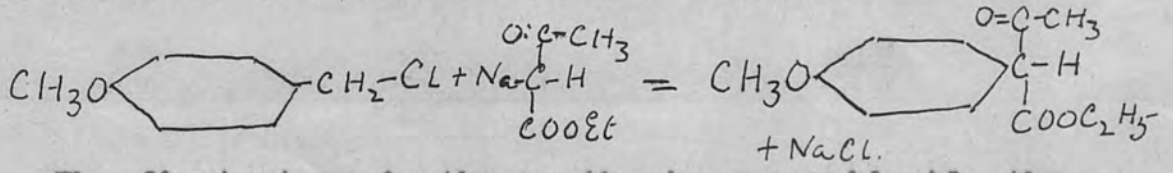
Thus:-



V



Now to synthesise this ester, ethyl-p-methoxy-α benzylaceto-acetate was a comparatively simple task, as the ester most similar to it, namely ethyl-α benzyl-acetoacetate has already been known (Cf. Conrad and Bischoff, Annalen 204, p. 180). So it could certainly be more hopefully expected that just as Conrad and Bischoff had successfully condensed benzyl-chloride with sodio-acetoacetic ester in benzene solution, the p-methoxy-benzylchloride could also be condensed with sodioacetoacetic ester to give p-methoxy-α benzyl-acetoacetic ester. Thus:-



The first stage in the synthesis was evidently the preparation of p-methoxy-benzyl-chloride or anisylchloride. For this, p- meo-benzyl alcohol which was prepared from anisaldehyde by the Cannizarro method (Monatsch.1913, 34, 1963-2014) by refluxing with alcoholic caustic potash was chlorinated with PCl_5 in the manner described by Cannizarro (Annalen 98, p. 191).

The anisyl-chloride so obtained was condensed with the sodio-acto-acetic ester prepared by reacting acetoacetic ester with sodium (powdered under Xylene) in dry benzene solution. The reaction went on quite readily at the boiling temperature of benzene, and the required ethyl-p-methoxy-α benzyl-aceto-acetate was prepared. It was characterised by preparing its phenyl-hydrazone in acetic acid solution.

The ester was then utilised for the expected chromone condensation. It was found to be exceedingly reactive with P_2O_5, and when a sample of it was mixed with phloroglucinol and P_2O_5, a rapid charring occurred even on gentle warming, and no product was isolated. The reaction when tried in cold did not proceed at all, even on keeping for several days. The case was that the ester, being very reactive, always reacted with P_2O_5 leaving the solid phloroglucinol alone as soon as the mixture was warmed, though in cold it did not react at all. However, it seemed probable that if the ester could first enter into an absolutely intimate mixture with phloroglucinol, its reactivity could possibly be slightly diminished so as to avoid rapid charring, and if a reaction took place it would affect the mixture as a whole, and not the ester alone. Now the possibility of such an intimate mixture was not easily possible between the ester and the solid phloroglucinol. A new idea occurred at this moment. The use of phloroglucinol-di-methyl ether has been long known in the synthesis of benzo-phenones by the Hoesh method; but the use of this ether in chromone synthesis has not been tried before. If now this

ether was used instead of phloroglucinol in this synthesis of the chromone, two advantages could be gained at one stroke. Firstly, the ether being a liquid, would certainly mix perfectly with the above ester, and this would probably help towards the successful working of the above Simonis reaction. Secondly, the use of the dimethyl ether would directly give the required tri-methoxy chromone with the above ester, without formation of the intervening di-hydroxy chromone as seen in the formulae above.

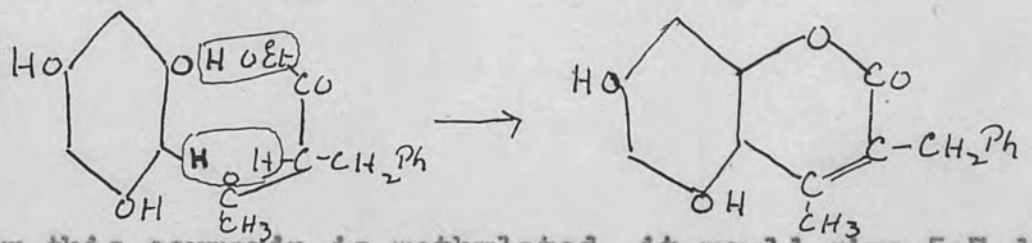
No time was then lost in giving a practical trial to this idea. The ester and the dimethyl ether were mixed and P_2O_5 added in slight excess. The mixture was left standing for 48 hours, was then warmed on a water-bath with s ome more P_2O_5, and the reaction went on with perfect success. On treating the reaction product with dilute caustic soda, a solid was obtained which crystallised out of alcohol and analysed quite satisfactorily. But the crystalline product of this reaction was not at all what it was expected to be. It was not at all the 5:7:4'trimethoxy-3 benzyl-2 methyl 1:4 benzopyrone which it was hoped would result by this mode of synthesis. It was quite a different product, melting sharply at 137°C.

This result could be due to either of the two causes - (1) that the benzo-pyrone from phloretin is not a chromone. But this seemed very unlikely, in the light of so much work and literature on the ring-closure by acetylation of such types of ketones as phloretin happens to be.

(2) that the Simonis reaction does not give a chromone as it is supposed to give - at least not in cases of all β ketonic esters, if it does give chromones in any cases at all. For after all the chief factor on which Simonis bases his argument for calling the product of his reaction a chromone is the one of hydrolysing his chromones and examining the nature of the split taking place. This factor has been thoroughly criticised by Baker (J.C.S. T.1925, p. 2349) with full reference to the work of Jacobson and Ghosh, in which the author clearly shows how the nature of the decomposition produced in a benzo-pyrone by hydrolysis does not cast any reliable light on the constitution of the benzo-pyrone as to its being either a coumarin or a chromone. This criticism also applies to the work of Simonis, and in the light of his argument alone, it cannot be readily agreed that his reaction of β ketonic esters with phenols in the presence of P_2O_5 will always give chromones. It therefore seemed to be of utmost necessity to investigate this point fully, at least in the case of the esters of the type of α-benzylacetoacetic ester.

A reference to the work of Jacobson and Ghosh shows that these authors had already condensed α-benzylacetoacetic ester with phloroglucinol using conc. H_2SO_4 and got a substance m.p. 216° C. which they called a chromone. (J.C.S. 1915, T, p.424.) But Baker has criticised this work and has actually prepared the real chromone corresponding to this and proved that this so-called chromone of Jacobson and Ghosh is only the isomeric

coumarin. This then settles the point that α-benzylaceto-acetic ester when condensed with phloroglucinol with conc. H_2SO_4 gives only a coumarin. Thus :-



If now this coumarin is methylated, it would give 5:7 dimethoxy-3 benzyl-4 methyl 1:2 benzo-pyrone. Well, now, the corresponding chromone isomeric with this would be 5:7 dimethoxy-3 benzyl-2 methyl-1:4 benzo-pyrone, and if Simonis were right, this chromone ought to be obtained by condensing α-benzyl-acetoacetic ester with phloroglucinol dimethyl ether, using P_2O_5, and in that case this product would be different from the above methylated coumarin of Jacobson and Ghosh. If, on the contrary, this product of Simonis' reaction happened to be identical with the methylated coumarin, it is a clear fact that the Simonis reaction, at least when applied to α-benzyl acetoacetic ester, gives definitely a coumarin and not a chromone. Work to ascertain these facts was undertaken.

Ethyl α-benzylacetoacetate was prepared by condensing benzyl chloride with sodio-acetoacetic ester in benzene solution after the manner of Conrad and Bischoff (Annalen 284, p. 180) and the ester was prepared. It was also characterised by preparing its phenyl-hydrazone. Then two experiments were tried with it.

I. The ester was condensed with phloroglucinol with 80%

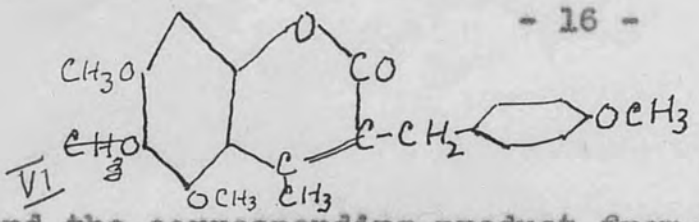
H_2SO_4 by mixing the three together and keeping them in cold for 24 hours. The coumarin was purified and crystallised.

This was then methylated in acetone solution using methyliodide and anhydrous K_2CO_3 by refluxing for 6 hours. Filtration and removal of acetone left the methylated coumarin which crystallised out of dilute alcohol. It melted sharply at 173°C.

II. The same ester was condensed with phloroglucinol dimethyl ether using P_2O_5 and warming the mixture. The product was treated with dilute NaOH, washed and crystallised, m.p. 173°C. Mixed m.p. with the above 173°C., and both products showed the same marked bluish fluorescence in conc. H_2SO_4 in ordinary light.

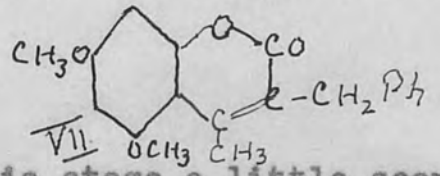
This absolute identity of the two substances definitely proves that α-benzylacetoacetic ester gives a coumarin and none other when condensed with phloroglucinol, after the method of Simonis. So it remains an indisputable fact that the chromone synthesis is impossible with esters like ethyl-α-benzylacetoacetate after the method of Simonis.

This fact then explains why the expected 5:7:4'trimethoxy-3 benzyl-2 methyl 1:4 benzopyrone was not obtained when ethyl-p-methoxy-α benzylacetoacetate was condensed with phloroglucinol-dimethyl ether in the presence of P_2O_5; the real product obtained by this reaction being merely the isomeric coumarin 5:7:4'trimethoxy-3 benzyl-4 methyl-1:2 benzopyrone,



VI

and the corresponding product from the ethyl-α benzylacetoacetate being the coumarin 5:7 dimethoxy-3 benzyl-4 methyl-coumarin -



VII

At this stage a little scope for some new work seemed open. In J.C.S. 1930, Jan. 21, Johnson and Robertson have described a Hoesh reaction with phloroglucinol dimethyl ether and p-methoxy-phenyl-propio-nitrile. They separated the isomeric benzophenones so obtained and acetylated the o-hydroxy-ketone so prepared on an oil bath at 180°. They obtained a product exactly identical with the benzo-pyrone obtained from phloretin (m.p.166°). This, as has been pointed out, differs from the coumarin VI. above. Now it seemed of interest to try a similar synthesis to (Johnson and Robertson's loc. cit.), using ordinary phenyl-propio-nitrile instead of the p-methoxy derivative, and try and synthesise the benzo-pyrone isomeric with the coumarin VII above. In analogy with 5:7:4' Trimethoxy-3-benzyl-2-methyl chromone (above) this would be 5:7 dimethoxy-3 benzyl-2-methyl-chromone.

The phenyl-propio-nitrile was prepared by dehydrating the amide of the phenylpropionic acid. The phenylpropionic acid was prepared by reducing cinnamic acid with sodium amalgam. It was then purified by crystallisation, dried and was converted into its acid chloride by treating with PCl_5 in dry chloroform

solution. This solution was then added to 50% Fortis ammonia solution, the chloroform layer separated, the chloroform removed, and the amide of the phenylpropionic acid was crystallised out of water and dried. This dry amide was then dehydrated to give the nitrile.

This nitrile was then condensed with phloroglucinol di-methyl ether after the method of Hoesh, following up the procedure of Klarmann (J.A.C.S. 1926, 48, 2358). An etherial solution of the nitrile and the di-methyl ether was saturated with dry HCl at 0°C. in the presence of anhydrous zinc chloride. After 30 hours excess of ether was added and the solid was completely precipitated, filtered, and boiled with water for 15 to 20 minutes. The aqueous layer was decanted, and the heavy oil was dissolved in alcohol, and allowed to cool. 2 hydroxy-4:6 dimethoxy-β phenyl-propiophenone crystallised out.

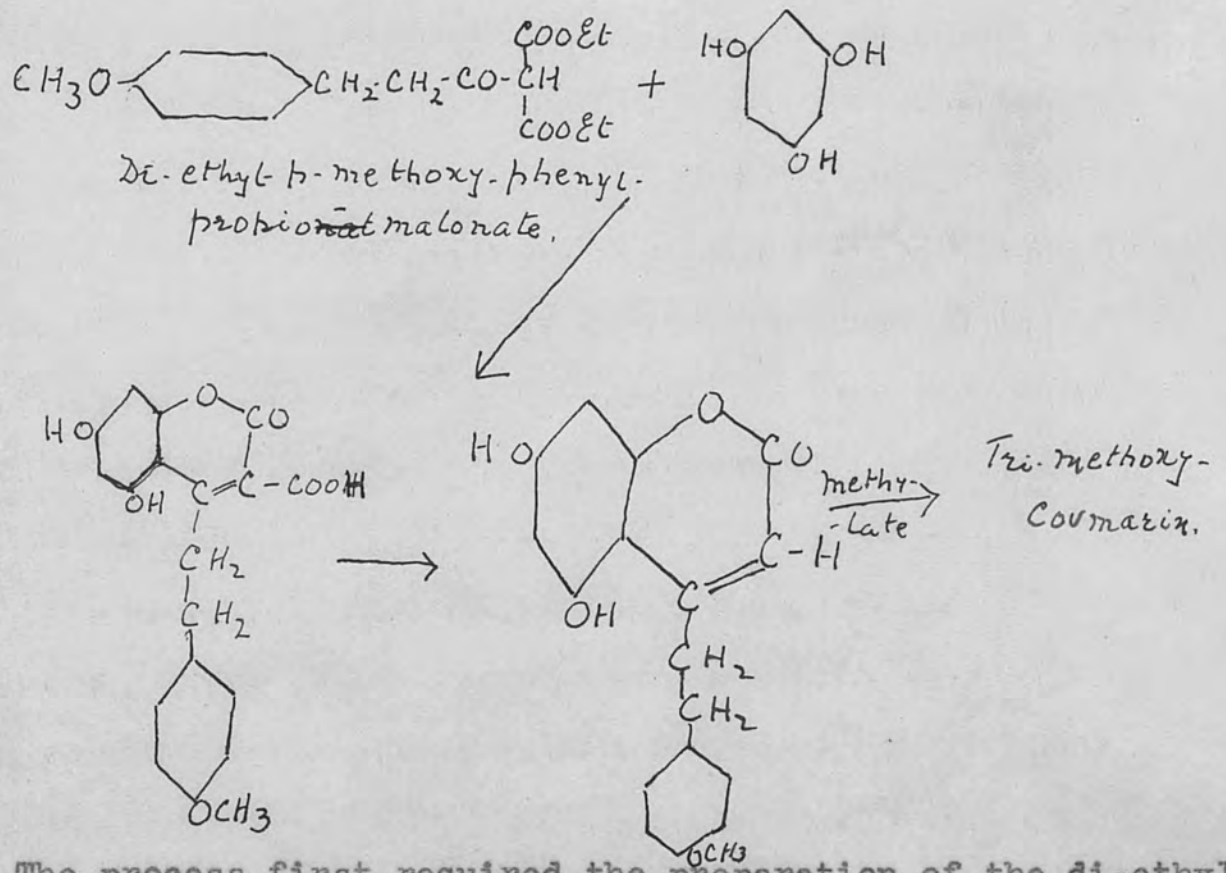
This propio-phenone was then subjected to ring-closure by acetylation on an oil-bath at 180°C., with acetic anhydride and sodium acetate. The resulting product, 5:7 dimethoxy-3 benzyl 2 methylchromone, m.p. 168°C., was markedly different from the isomeric coumarin prepared from α benzyl-acetoacetic ester, m.p. 173°. The chromone was also far less fluorescent than the coumarin, dissolving to a colourless solution in conc. H_2SO_4, which hardly showed any fluorescence in ordinary daylight. The 4-hydroxy-2:6 dimethoxy-β phenylpropiophenone which was produced along with its ortho-hydroxy isomer in the above Hoesh synthesis was also isolated by boiling with water its ketimine which was

deposited out of the alcoholic filtrate from the first crystallisation of the above 2-hydroxy-4:6 dimethoxy-β phenyl-propiophenone.

So, whereas, on the one hand, the 5:7-dimethoxy-3 benzyl-4 methyl-coumarin obtained by methylating the coumarin which Ghosh had originally prepared from ethyl-α-benzyl-acetoacetate, and this was proved to be identical with the product of condensation of the same ester with phloroglucinol di-methyl ether after the method of Simonis, the isomeric chromone viz. 5:7-dimethoxy-3 benzyl-2 methyl-chromone was also prepared on the other hand, and the whole contrast between these coumarins and the isomeric chromone was completely established. This then indisputably shows what the Simonis product with the said ester and phloroglucinol should have been if it did give a chromone, and also what it actually is, now that it has been proved to be a coumarin.

The unexpected result from the Simonis reaction rendered the synthesis of the 5:7:4'trimethoxy-3 benzyl-2 methyl-1:4 benzopyrone from the ethyl-p-methoxy α benzyl-acetoacetate impossible, only the isomeric coumarin being obtained in the course. The failure of the Atwood, Thorpe and Stevenson method of condensing ethyl-p-methoxy-phenyl-propionate with acetic ester to give ethyl-p-methyl-phenyl-propio-acetate cut off the possibility of synthesising the tri-methoxy-phloretyl coumarin by the originally intended method. Now it seemed of interest to have another go at synthesising this coumarin by a slightly

different method - that of condensing a suitable malonic ester derivative with phloroglucinol, to give a coumarin-carboxylate, which, by partial hydrolysis to remove the carboxyl-group, might be made to yield the required coumarin. The process would work thus:-



The process first required the preparation of the di-ethyl-p-meo-phenyl-propiomalonate. But a consideration of the difficulty involved in the preparation of the p-methoxy-ester directly, which meant the tedious preparation of p-methoxy-phenylpropionic acid and its acid chloride, pointed to the advisability of trying the synthesis of such an ester by first preparing the much simpler di-ethyl-phenyl-propiomalonate as a pilot reaction.

The task was accordingly undertaken. The phenylpropionyl-chloride was prepared from its acid by chlorination in dry benzene solution, the benzene and the $POCl_3$ were removed in vacuo, and the acid-chloride was distilled under diminished pressure. This acid chloride was then condensed with sodio-malonic ester, prepared from sodium powdered under Xylene and malonic ester in ether solution. The reaction went on as expected, and on ether extraction and distillation, the ester distilled quite pure in vacuum. The di-ethyl-phenyl-propio-malonic ester was thus synthesised and correctly analysed.

An attempt was made to synthesise the di-ethyl-p-methoxy-β phenyl-propio-malonate. As above, p-methoxy-β phenyl-propionyl chloride was condensed with sodio-malonic ester. An oil distilled at 195°C. under 25 m.m. But it analysed differently, due to some decomposition having taken place. The yield was exceedingly poor too, and it seemed that the long hoped synthesis of tri-methoxy-phloretyl-coumarin could not be achieved by this means. The last method for reaching this aim seems to be in attempting some more rigorous method of condensing the acetic ester with ethyl-p-methoxy-β phenyl-propionate, if that is possible.

SECTION II. EXPERIMENTAL.

(1) Acetylation of Phloretin at 100°.

Phloretin (10 g.) was mixed with acetic anhydride (65 gms) and anhydrous sodium acetate (65 gms.) on a steam-bath, using an air condensor for 8 hours. The product was poured into water, the excess of Ac_2O was allowed to decompose overnight, the solid was filtered, washed with water and dilute alcohol, and crystallised out of 96% ~~of~~ Ethyl alcohol. After the first crystallisation it melted at 168° and further crystallisation from alcohol or glacial acetic acid raised it to 170°. It crystallises in long, colourless, transparent needles.

Found C = 65·2, H = 49. $C_{23}H_{20}O_8$ requires C = 65·09, H = 4·76

(2) De-acetylation of the above product.

The pure acetyl-compound (5 gms.) was slightly warmed with an 8% solution of NaOH in 96% alcohol (30 ccs.) to a clear solution. It was left in cold for two hours, after which the alcohol was evaporated off on a water-bath and excess of water added to the solution. The de-acetylated product was precipitated thus. It was filtered, and it crystallised in brownish-pink needles out of dilute methylalcohol or dilute acetic acid. M.p. very indefinite, softening between 204 - 208, and disappearing gradually until at 230° giving a black liquid. It analysed fairly satisfactorily.

Found C = 68·1, H = 5·0. $C_{17}H_{14}O_5$ requires C = 68·45, H = 4·69.

(3) Methylation of the above de-acetylated product.

The pure substance (2·5 g.) dissolved in acetone (50 ccs.) was mixed with anhydrous potassium carbonate (10 gms.) and was refluxed on a steam-bath, with methyliodide (3 ccs.) added through the bulb-condensor. After 8 hours, a further portion of methyl iodide (2 ccs.) was added and the heating continued until a test-portion ceased to give a coloration with $FeCl_3$ in alcohol solution. This reaction in all needed 23 hours of refluxing. After this time the hot reaction mixture was filtered off from the K_2CO_3, the acetone was removed in vacuum, and the syrupy residue was crystallised out of 96% methylalcohol. Several crystallisations and filtrations were needed to purify the crystalline product from the much adhering gummy impurity. It at last was deposited in light, feathery needles. M.p. 166°C. mixed m.p. with 5:7:4'trimethoxy-3 benzyl-2 methyl-1:4 benzo-pyrone of Johnson and Robertson (loc. cit.) 166°C.

Found C = 70·4, H = 6·1. $C_{20}H_{20}O_5$ requires C = 70·6, H = 5·9 It is insoluble in ether, and dissolved slowly in 96% ethyl and methyl alcohols on gentle boiling. It dissolves in conc. H_2SO_4 giving a bluish fluorescence visible only under the arc.

Acetylation of Phloretin at 180°.

Here the process was carried on exactly as in the previous case of acetylation at 100°, and using the same quantities, but using an oil-bath at 180° instead of a steam-bath. Heating was continued for 6 hours, excess of Ac_2O was decomposed by standing in cold water. Filtration and crystallisation out

of 96% alcohol several times, gave a glistening, transparent needle-shaped product m.p. 170°C.

Found C = 65·0, H = 4·9. $C_{23}H_{20}O_8$ requires C = 65·09
H = 4·76.

Hydrolysis of the above product.

The pure acetylated product was de-acetylated exactly as on the previous occasion with 8% NaOH in 96% methyl alcohol, using exactly the same quantities. The product was precipitated with water and crystallised out on dilute acetic acid. After one crystallisation it was deposited in dirty-pinkish, crystalline needles (not yellow as Ciamician says) m.p. 213° sharp.

Found C = 68·3, H = 4·8. $C_{17}H_{14}O_5$ requires C = 68·45,
H = 4·69.

Methylation of this de-acetylated product.

This also was carried out in an identical manner with that for the de-acetylated product of the steam-bath method. The product of methylation here crystallised and purified much more easily. M.p. 166°C. mixed with the above methylated product, and also with the 5:7:4'trimethoxy-3 benzyl-2 methyl-1:4 benzopyrone, m.p. 166°C.

(Cf. Johnson and Robertson, loc.cit

Preparation of Ethyl-p-methoxy-β phenyl-propioacetate.

(a) Para methoxy cinnamic acid was prepared by heating a mixture of anisaldehyde (30 gms.), malonic acid (40 gms.), pyridine (150 ccs.), piperidine (·5 ccs.) on a water bath for 8 hours using an air condensor and then refluxing on a gauze for 2 hours. The product was poured into excess of water and acidified with HCl. The precipitate was filtered, washed, and crystallised out of dilute alcohol in colourless needles. m.p. 170°C. Yield = 40 gms.

(b) The above acid (40 gms.) was dissolved in 500 ccs. water containing NaOH (8 gms.) and was reduced with 2½% sodium amalgam (1700 gms.) until a test portion (washed and purified) ceased to decolourise $KMnO_4$ solution. It was then filtered and precipitated with SO_2 gas, after adding to the solution a few ccs. of strong $KMnO_4$ solution. The product was purified by re-dissolution in NaOH solution and re-precipitation with SO_2. m.p. 104°C.

(c) The pure p-methoxy-phenyl-propionic acid prepared in (b) was esterified thus:- The pure acid (50 gms.) was dissolved in 300 ccs. absolute ethyl alcohol containing 30 ccs. conc. sulphuric acid, and the solution refluxed for 6 hours on a steam-bath. The product was poured on to crushed ice mixed with sodium carbonate, just enough to render the solution alkaline on being stirred with it. The mixture was then extracted with ether, dried over powdered $CaCl_2$, the ether removed, and the ester distilled in a vacuum. It came over as a colourless

oil at 162-163°C. under 25 m.m. pressure. Some 200 gms. of it were prepared. It has a pleasant fruity odour.

Found C = 69·0, H = 7·5, $C_{12}H_{16}O_3$ requires C = 69·2, H = 7·7.

(d) This ethyl-β phenyl-propionate (65 g.) was then mixed with ethyl-acetate (92 gms) and the mixture was added on to sodium-wire (23 gms) in 600 ccs. of dry ether. The mixture was refluxed for 6 hours and was then poured on to crushed ice with stirring. It was acidified with cold, dilute H_2CO_4 and extracted with ether. On removing the ether, the product was distilled at 136°C. under 14 m.m. pressure. It analysed unsatisfactorily.

Preparation of Ethyl-p-methoxy-α benzyl-acetoacetate.

(a) Preparation of anisic alcohol was done by the method of Cannizarro, by refluxing anisaldehyde with alcoholic potash for 10 hours. The anisic acid was removed and the anisylalcohol was converted into the anisyl-chloride as described below. (Annalen 98, p. 189).

(b) This anisalcohol was then chlorinated with PCl_5 as suggested by Koeniggs and Bernhart (Ber. 41, p. 499). The alcohol was refluxed with slight excess of PCl_5 in dry benzene solution. The benzene and the excess PCl_5 etc. were removed in vacuo and the anisylchloride was distilled. It distilled at 122° under 16 m.m. pressure. It is a colourless, pungent

liquid which decomposes on exposure to air.

(c) For the actual preparation of Ethyl-p-methoxy-α benzyl-acetoacetate, sodium (9 gms) was powdered under Xylene, the Xylene was removed, and the sodium was covered with dry benzene (500 ccs.). It was then refluxed for an hour with freshly distilled ethyl-acetoacetate (50 gms.) and the sodio-acetoacetic ester so formed was kept over-night. The above anisylchloride (60 gms.) was then added to it slowly through the condensor. No reaction was apparent in the cold, but at the boiling temperature of benzene there was a brisk ebulition, and the solid was all dissolved rapidly and was soon replaced by a fine suspension of NaCl in the benzene solution. The reaction mixture was allowed to reflux for 6 hours, when it was cooled, the sodium chloride formed was dissolved in a few ccs. of water, and the mixture was acidified with glacial acetic acid, and the benzene-layer separated. The aqueous layer was extracted 3 times with a large volume of benzene, and the total extract was dried over powdered $CaCl_2$. The benzene was distilled, and the residue subjected to distillation in vacuum. Unchanged acetoacetic ester came over up to about 120° under 30 m.m. Then the temperature rose steadily and some liquid which afterwards proved itself (by its change in colour on exposure) to be unchanged anisylchloride distilled up to about 155° under 30 m.m. Finally at about 210°C. under 30 m.m. the ester started distilling. It was purified by redistillation at 203°C under 22 m.m. Yield was only about

30% of theory, much of the ester condensing with itself to form a dark, thick residue.

Found C = 67·6, H = 7·3. $C_{14}H_{18}O_4$ requires C = 67·2, H = 7·2. The ester has a characteristic, slightly pungent odour. It gives a red colouration with $FeCl_3$ in alcoholic solution. It is very reactive, and chars on warming with P_2O_5.

The phenylhydrazone of Ethyl-p-methyl-α benzylacetoacetate.

The ester (1 cc.) was mixed phenylhydrazone (1 cc.) and glacial acetic acid(1½ cc) and the whole mixture, diluted with water (10 ccs.) was warmed on a water-bath for 20 minutes. The reaction mixture was poured into cold water and was allowed to stand for a long time, when a solid was deposited. This was washed, and crystallised out of dilute alcohol in long, colourless needles. M.p. 163°C.

Found N = 8·6. $C_{20}H_{24}O_3N_2$ requires N = 8·23.

The Simonis reaction with ethyl-p-methoxy-α benzyl-aceto-acetate, resulting in the preparation of 5:7:4'Trimethoxy-3 benzyl-4 methyl coumarin:- The ester (2·5 g.), Phloroglucinol dimethyl ether (1·6 gms.), P_2O_5 (3 gms.) were mixed and the mixture was kept in cold for 48 hours. It was then warmed for 3 to 5 minutes with a fresh addition of P_2O_5(2 g.), and when cool was treated with 2% solution of NaOH. The residue was filtered and crystallised out of methyl alcohol. Yield ·4 gms. in needle-shaped crystals. M.p. =

Found C = 70·6, H = 6·3. $C_{20}H_{20}O_5$ requires C = 70·6, H = 5·9

Its solution in conc. H_2SO_4 showed properties similar to the 5:7-dimethoxy-3 benzyl-4 methyl coumarin described below.

Ethyl-α benzyl-acetoacetic ester.

This was prepared in exactly the same manner as was the above ethyl-p-methoxy-α benzyl-acetoacetate, by refluxing benzylchloride (50 gms.) with sodio-acetic ester in dry benzene solution. Yield 28 gms. Its phenylhydrazone was prepared as in the previous case. Colourless needles, m.p. 136°C.

Found N = 9·03, requires N = 9·3.

I. Preparation of 5:7 dimethoxy-3 benzyl-4 methyl-coumarin.

The ethyl-α-benzyl-acetoacetate (3 gms.) was mixed with phloroglucinol (5 g.) and was stirred with a slow addition of 80% H_2SO_4 (3 to 4 ccs.). The mixture was kept for 24 hours, was poured into water, the solid filtered and dissolved in dilute NaOH and precipitated with CO_2. The precipitate was again washed and crystallised out of dilute acetic acid. M.p. 216°C. (Cf. Ghosh.)

This product (2 g.) was then dissolved in 20 ccs. dry acetone and was refluxed with methyliodide (10 gms., in small doses) in the presence of anhydrous K_2CO_3. After 6 hours the acetone solution was filtered from the K_2CO_3, and removal of acetone in vacuo left the slightly crude 5:7-dimethoxy-3 benzyl-4 methyl-coumarin. It was crystallised out of dilute alcohol in colourless needles, m.p. 173°C.

It dissolved in conc. H_2SO_4 forming a solution showing a marked bluish-green fluorescence in ordinary light. Found C = 73·3, H = 5·6. $C_{19}H_{18}O_4$ requires C = 73·5, H = 5·8

II. The α benzyl-acetoacetic ester (5 g.) was mixed with P_2O_5 (4 g.) and phloroglucinol-dimethyl ether (3.g.) and the mixture was warmed for 15 minutes on a water-bath with occasional stirring. The reaction mixture was then poured into water, and treated with a 2% NaOH solution. The solid residue was filtered and crystallised out of dilute alcohol. M.p. 173°, mixed m.p. with the above 5:7 dimethoxy-3 benzyl-4 methyl-chromone = 173°. Both these substances fluoresce similarly in conc. H_2SO_4 solution.

Synthesis of 5:7-dimethoxy-3 benzyl-2 methyl chromone.

(a) Phenyl propionic acid was prepared by the usual reduction of cinnamic acid (100 g.) in NaOH solution with sodium amalgam. The product was filtered, and precipitated with SO_2. M.p. 47°C.

(b) The acid chloride of the phenylpropionic acid was prepared by dissolving the acid in chloroform and chlorinating with PCl_5. The product was poured into 50% Fortis ammonia solution, the chloroform layer was separated, chloroform moved and the phenylpropionamide was crystallised out of boiling water. M.p. 104°C.

(c) The amide was then converted into its nitrile by distilling the dry amide with P_2O_5 in vacuo. About 50 gms.

of the acid amide gave 29 gms. of the nitrile.

(d) The nitrile was then subjected to Hoesh synthesis after the manner of Klarmann. The nitrile (12 g.), dimethyl ether of phloroglucinol was dissolved in dry ether (70 ccs.) and was saturated with HCl at 0°C. in the presence of anhydrous $ZnCl_2$ (3 g.). After 30 hours, the precipitation was completed by the addition of ether (150 ccs.), and the filtered product was boiled with water (75 ccs.) for 15 to 20 minutes. The aqueous layer was decanted, and the heavy oil was dissolved in the least amount of boiling absolute alcohol. On cooling, 2 hydroxy-4:6 dimethoxy-β phenyl-propiophenone (5 to 6 gms.) in thin hexagonal plates was deposited, which after further crystallisation melted at 105°C.

Found C = 71·1, H = 6·4. $C_{17}H_{18}O_4$ requires C = 71·1, H = 6·4. The substance gives a violet coloration with $FeCl_3$.

(e) This propiophenone (4 g.) was then heated for 16 hours with acetic anhydride (30 ccs.) and sodium acetate (7 gms.) on an oil-bath at 180°C. On pouring into water and decomposing the Ac_2O, the 5:7 dimethoxy-3 benzyl-2 methyl-chromone crystallises out of methyl alcohol in tufts of long hair-like needles; m.p. 168°C., and markedly differs from the 5:7 dimethoxy-3 benzyl-4 methyl-coumarin in the nature of its fluorescence which is hardly visible in ordinary day-light.

Found C = 73·3, H = 5·9. $C_{19}H_{18}O_4$ requires C = 73·54, H = 5·8.

(f) 4 hydroxy 2:6 dimethoxy-β phenyl-propiophenone.

The alcoholic filtrate from the first crystallisation of the

2 hydroxy ketone on standing, deposited crystals (3 to 3·5 gms.) of the ketimine of the 4-hydroxy isomer, which when purified crystallised from ethyl-alcohol in pale yellow rods m.p. 206-208°C. (decomp.) Boiling with water (30 ccs.) for 15 minutes gave an oil soluble in 50% alcohol from which the 4-hydroxy-2:6 dimethoxy-β phenyl-propiophenone crystallised in very long, thin, rectangular plates m.p. 72°C. On drying over P_2O_5 in vacuo, the solid lost in crystalline form to a large extent, and then melted at 104-105°. This isomer only gives a pale-yellow colour with $FeCl_3$.

The mother-liquor of the alcoholic crystallisation on evaporation left an oil which partly crystallised and contained more of the 4-hydroxy isomer produced by the partial hydrolysis of the ketimine during the original 15 to 20 minutes boiling.

Found C = 70·8, H = 6·8. $C_{17}H_{18}O_4$ requires C = 71·32, H = 6·29

Preparation of Di-ethyl-β phenyl-propio-malonic ester.

(a) Phenyl-propionyl chloride was prepared from phenyl-propio-acetic ester, which was prepared by reducing cinnamic acid with sodium amalgam. The phenyl-propionic acid (60 gms.) was mixed with thionylchloride (84 ccs.) and was warmed under reflux for ½ hour. The reaction mixture was dissolved in dry benzene and the benzene and excess of thionyl chloride were removed in vacuo. The residual acid chloride was distilled in vacuum at 121°C. under 16 m.m.

(b) The diethyl-β phenyl-malonic ester was then prepared by condensing the above acid chloride with sodio-malonic ester thus:- Sodium (7·5 gms.) was powdered under Xylene and covered with dry ether in the usual way. Malonic ester (50 gms.) was added drop by drop through the condensor, and the thick, bulky sodio-malonic ester so formed was refluxed for ½ hour in ether, and allowed to stand over-night. Phenyl-propionyl-chloride was then added to the above sodio-ester, in cold, but on warming the expected reaction was started. After 8 hours heating, the reaction product was cooled, the NaCl formed was dissolved in a few ccs. of water, the mixture was acidified and extracted with ether. The extract was shaken with some Na_2CO_3 solution, washed, and dried over $CaCl_2$, then subjected vacuum distillation after removal of the ether on an electric water-bath. The malonic ester distilled up to 130°C under 22 m.m., and finally the diethyl-β-phenyl malonic ester came over at 156°C. under 22 m.m.

Found C = 66·0, H = 7·2. $C_{16}H_{20}O_5$ requires C = 65·7 or 8
H = 6·8

It is a slightly yellowish oil, with a fairly pungent smell. It gives a deep red coloration with $FeCl_3$ in alcoholic solution.

(F)

THESIS PRESENTED BY

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B.Sc.

FOR THE DEGREE OF MASTER OF SCIENCE

IN THE

UNIVERSITY OF LONDON.

JULY, 1931.

The Cinchona Alkaloids and Substances Related to Them.

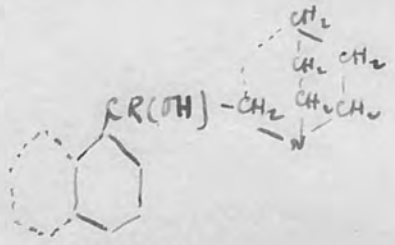
ABSTRACT.

A short survey is given of the known facts regarding the relation between the constitution and the antimalarial activity of the chief cinchona alkaloids, and it is concluded that further information on this matter can be obtained in two ways:

(1). By investigating the degradation products and some of the simpler derivatives of these alkaloids.

(2). By preparing some synthetic substances which contain certain characteristic features.

Under heading (2), a large number of compounds of the general formula:



have been synthesised. These all bear, as the formula indicates, marked pictorial resemblance to the essential cinchona structure. The antimalarial activity of the new substances has been determined, and the conclusion is drawn that a second basic centre must be present for a molecule of the above type to possess any marked antimalarial activity.

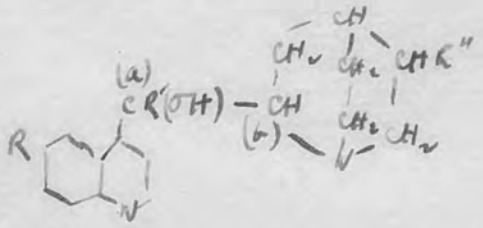
Under heading (2), a number of alkaloid methochlorides have been prepared by a new process, and considerable attention has been paid to the attempted decarboxylation of quitenine, since the decarboxylated product should exhibit definite antimalarial activity.

Experiments have also been performed on the preparation of quitenine amide, and of its benzoyl derivative.

THE INVESTIGATION OF SOME PIPERIDINOMETHYLCARBINOL HYDROCHLORIDES.

Despite extensive investigations on the part of numerous workers, there still remain two outstanding problems in cinchona alkaloid chemistry: (1) whether the specific physiological action is due to any group or groups, considering these from the chemical or the stereochemical point of view; and (2) whether it is possible to obtain a compound having similar or even more beneficial antimalarial action, by imitating what may be called the cinchonoid structure:

(I)



Owing to the fact that the earlier workers in the cinchona alkaloid series were concerned more with the constitution than with the pharmacological action of degradation products, it may be necessary to prepare many of these products again, in order to test them on a strictly comparative basis. At the present moment we are in possession of a limited number of observations as to the effect of modifying the essential cinchonoid molecule. These may be classified under the following headings:

(1) <u>The Quinoline System</u>.

It is known that complete removal of the methoxyl group in quinine is not accompanied by very serious effects on the pharmacological activity, whilst its replacement by some alkoxyl groups increases the latter.

Such changes may produce their effect by altering the basicity of the quinoline nitrogen atom. Moreover, it is known that cupreine, which only differs from quinine by a methyl group, (it has a hydroxyl instead of a methoxyl group in the quinoline nucleus) possesses little or no antimalarial activity.

(2) The Carbinol Grouping.

Little appears to be known regarding the effect of modifying this group, e.g. by converting it into -CR(OH), where R is a hydrocarbon radical. But modification of this kind might be of fundamental importance, since it would stabilise the group against oxidation. Compounds of the cinchoninone type should be considered under this heading, for the secondary carbinol group is no longer present, its place being taken by an unsaturated tertiary group of the enolic form of the ketone:

-CH(OH).CH: -CO.CH: -C(OH):C:

(3) The Vinyl Side-chain.

Since the present work was begun, Goodson, Henry and Macfie (Biochem. J.1930, 24, 874.) have published data showing that the antimalarial action of quinine is increased by reduction of the vinyl group, while similar reduction of quinidine, which differs from quinine only as regards the configuration of the carbon atoms (a) and (b),(I), (Rabe, Annalen, 1910, 373,89; Ber, 1922,55 (B),528. King and Palmer, J. 1922, 21, 2577.) does not increase its activity. It is very difficult to account for these facts, although it is reasonable to connect the disappearance of activity, when quinine is oxidised to quitenine, with the diminution of the basic character of the molescule, since the

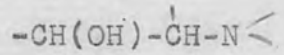
esters of quitenine are pharmacologically active.

(4) The Quinuclidine System.

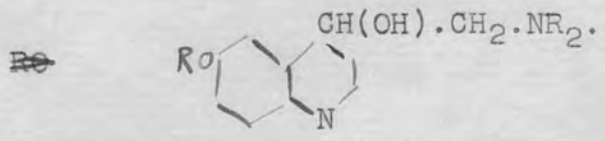
The effect of breaking one particular ring-linkage in this system is seen in the appearance of toxic properties in passing from the cinchonine to the cinchotoxine type, which effect is probably due to the exposure of the imino group. It should be observed that when a cinchona alkaloid is converted into its mono-acid salts, a new centre of dissymmetry appears, since salt formation first takes place on the tertiary nitrogen atom in the quinuclidine system:

This may be a significant factor in connexion with the pharmacological action.

Many attempts have been made to imitate the fundamental cinchonoid molecule, notably by Kaufmann and Rabe. The former author (Ber.1912, 45, 3090;1913, 46, 57, 2929; D.R-P. 268,931.) attributed the action of quinine to the group:

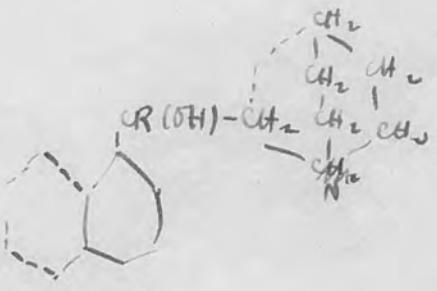


and showed that some compounds of the type:



resembled quinine on the basis of the physiological tests then available. The work of Rabe (Ber.1917, 50, 144, etc.) was similar to that of Kaufmann, but was developed on more complex synthetic lines. (Compare Ber. 1918, 51, 1360).

Within recent years, a large number of compounds have been investigated by different workers, in an attempt to obtain a satisfactory antimalarial drug. The majority of these compounds have been essentially structurally different from the cinchona alkaloids. In the present communication are described, amongst other experiments, the methods of preparation of a series of compounds of the general formula (II)(in which the dotted lines have no chemical significance), which bear what may be called pictorial resemblance to the cinchona alkaloids. (Compare the resemblance between the eucaines and cocaine.)



These compounds are for the most part readily prepared by treating I-phenacylpiperidine with a Grignard reagent, although in a few instances (e.g., when R is n-hexyl, n-heptyl or cyclohexyl) the synthesis has failed completely. For physiological tests, the carbinol hydrochlorides have been prepared, and the following are described in the experimental section: Phenyl-, phenylmethyl-, phenylethyl-, phenyl-n-propyl-, phenyl-n-butyl-, diphenyl-, phenylbenzyl-, phenyl-β-phenylethyl-, phenyl-γ-phenylpropyl-, phenyl-δ-phenylbutyl-, and phenyl-α-naphthyl-ω-piperidinomethylcarbinol hydrochlorides.

None of these compounds possesses any antimalarial activity, a fact which suggests that the essential missing factor is the basic

quinoline structure. The synthetic method, however, appears to be capable of general application, and is being used in the synthesis of the less readily accessible quinoline analogues of phenacylpiperidine.

A second synthetic method has been investigated, which is also apparently capable of extension to the synthesis of cinchonoid substances. For example, phenyl-β-phenylethyl ketone is readily converted into the bromo derivative, which reacts with piperidine:

$$Ph.CO.CH_2\text{-}CH_2\text{-}Ph \qquad Ph.CO.CHBr.CH_2\text{-}Ph$$

$$Ph.CO.CH_2\text{-}NC_5H_{10} \qquad Ph.CO.CH(NC_5H_{10})CH_2\text{-}Ph \quad \text{III.}$$

to give phenyl-α-piperidino-β-phenylethyl ketone (III). The latter may alternatively be obtained by the action of benzyl chloride on the sodium derivative of phenacylpiperidine. This method has been applied to the synthesis of piperidino-deoxybenzoin, $Ph.CO.CH.Ph.NC_5H_{10}$, a substance previously obtained by Rabe (Ber., 1912, 45, 2169), by treating sodiodeoxybenzoin with 1-chloropiperidine.

EXPERIMENTS ON THE BROMINATION OF 2:4 DIMETHYL-QUINOLINE.

In view of the fact that Hammick showed (J. 1923, 123, 2882) that quinaldine readily underwent tribromination in the side-chain, experiments were done on 2:4-dimethylquinoline, with a view to obtaining lepidine-2-carboxylic acid by a process similar to that used by Hammick for the preparation of quinaldinic acid, the object being the subsequent preparation of lepidine. In order to determine the scope of bromination, an attempt was first made to induce hexabromination, but the only product obtained was a tribromo compound. Monobromination also gave the same tribromo compound, but systematic experiments designed to produce the tribromo compound in satisfactory yields led to disappointing results. The tribromo compound, moreover, did not undergo the facile conversion into a carboxylic acid which was to be expected by analogy with Hammick's later work, (J. 1926, 1302), and since the main object of these experiments was to provide an easy synthesis of lepidine carboxylic acid, the work was abandoned. It must be pointed out that the constitution of the tribromo derivative may be different in type from Hammick's compound, and it is possible that it contains two bromine atoms in the 2-methyl group, and one in the 4-methyl group.

EXPERIMENTS ON QUITENINE.

It is known from the work of Henry, Goodson and Macfie that diminution of the acidity of quitenine by esterification partially restores antimalarial activity. Rurther evidence as to the relation between the basicity of the molecule and its antimalarial action has been sought in two directions. In the first place, attempts have been made to decarboxylate quitenine, but in spite of a large variety of experiments, no success has been achieved, although on one occasion a small quantity of a base was isolated which gave a solid picrate.

In the second place, attempts have been made to prepare quitenine amide and its benzoate. It was already known that thionyl chloride reacted in a rather complex way with quitenine, and it was surprising that John (J. Prakt. Chem. 1930, 128, 223) should have regarded the product he obtained by heating quitenine with a large excess of thionyl chloride, as the acid chloride of quitenine. The analysis that he gives to his compound has been found to agree much more satisfactorily with either of the following compounds:

1. (CHOH)(COCl) requires N. 7.7%
2. (CHCl)-(COCl) requires N. 7.4%
3. (CHOH)-(COCl)(HCl) requires N. 7.05%

John obtained N. 6.92%

It is obvious that in this reaction, a hydrochloride must be formed since no hydrochloric acid is given off. (Compare the preparation of benzoyl quitenine: Bucher, Monatsh. 1893, 14,598).

PREPARATION OF METHOHALIDES OF SOME CINCHONA ALKALOIDS.

These compounds were prepared for a twofold object: firstly, in order to produce methochlorides whose antimalarial activity could be tested and compared with those of the above mentioned synthetic hydrochlorides; and secondly, in order to obtain N-methyl cinchotoxine, it was necessary to prepare large amounts of cinchonine methobromide by a process more convenient than that given in the literature. It has been found that cinchonine and the other alkaloids combine very readily with methyl sulphate, from which, by the action of potassium bromide or ammonium chloride, the corresponding methohalides can be prepared. The conversion of an alkaloid into a methohalide now takes as many hours as it formerly took days.

EXPERIMENTAL.

Phenyl-α-Piperidino-β-phenylethyl ketone.

(1) Preparation of Phenyl-β-phenylethyl ketone. The methods described in the literature for the preparation of this substance are not satisfactory. We have found that when benzonitrile is added to two molecules of magnesium β-phenylethyl bromide, although obvious interaction occurs, only a small and variable yield of the expected ketone is obtained. The following method, however, was found convenient: β-Phenylethyl bromide was obtained in 91% yield by the interaction of 346 g. of β-phenylethyl alcohal and 115 c.c. of phosphorus tribromide. The bromide (337 g.) was refluxed for 3½ hours with a mixture of 135 g. of potassium cyanide, 135 g. of water, and 340 c.c. of alcohal. β-Phenylpropionitrile was obtained in 91% yield in the second stage, i.e. 81% calculated on the alcohol used. A Grignard reagent was prepared from 78 g. of bromobenzene, and was gradually treated with 26 g. of β-phenylpropionitrile. When the vigorous reaction had come to an end, the whole was heated for ½ hour on the water-bath, the mixture was decomposed in the usual manner, and the ketone was purified by distillation under reduced pressure 18 g. of pure phenyl-β-phenylethyl ketone, b.p. 196°/18mm., were obtained.

(2) Preparation of phenyl-α-bromo-β-phenylethyl ketone.

A solution of one mol. of the ketone in glacial acetic acid was treated with a glacial acetic acid solution of 1. mol. of bromide. Decolorisation occurred at a bout 50°. The solution

was poured into water, and the solid product was crystallised from alcohol, when the bromo compound (93%) was obtained as needles, m.p. 50-51°. (Found: Br, 27.4; $C_{15}H_{13}OBr$ requires Br, 27.7%).

(3) Action of piperidine on phenyl-α-bromo-β-phenylethyl ketone.

Equal weights of the bromo compound and piperidine were heated together in benzene solution for ½ hour at 100°. The cooled mixture was then well shaken with alkali, and the benzene layer was shaken with water and dried over sodium sulphate. Evaporation of the solvent gave phenyl-α-piperidino-β-phenylethyl ketone, which crystallised from alcohol in colorless leaflets, m.p. 77-78.5°. (Found: N, 5.3, $C_{20}H_{23}ON$ requires N, 4.8%).

(4) Preparation of phenacylpiperidine. Schmidt and van Ark, (Arch. Pharm. 1900, 238, 330.) obtained this compound in an impure condition, but did not characterise it. It can be obtained by either of the following methods:

(a). The method of Rabe, Schneider and Braasch (Ber. 1908, 41 874.) was modified as follows: A benzene solution of one part of phenacyl bromide was added to a solution of one part of piperidine in ether, and the mixture was allowed to stand for ½ hour after completion of the vigorous reaction. It was then treated with aqueous alkali, and the benzene layer was dried over sodium sulphate. After removal of the solvent, the residue was vacuum distilled, and gave an approximately 60% yield. (b.p. 168°/26 mm.).

(b). A considerable saving of piperidine was effected by using the following process: a solution of 80 g. of phenacyl bromide in 400 c.c. of benzene was added within 30 minutes to a well shaken mixture of 50 g. of piperidine, 70 g. of anhydrous potassium carbonate, and 400 c.c. of benzene in the cold. Water was added, and the benzene layer was separated and extracted three times with water, and then twice with 20% hydrochloric acid. The separated benzene layer was again extracted with a smaller quantity or acid and the united acid solutions were made ammoniacal, and extracted with ether. The ethereal layer was washed with a little water, was dried over sodium sulphate, and was evaporated. Distillation under reduced pressure of the residue gave 50 g. of almost pure colorless phenacylpiperidine of constant b.p.

(5) Preparation of Phenyl-α-piperidino-β-phenylethyl ketone.

Phenacylpiperidine (1 mol.) was added to one atom of powdered sodium, covered with 100 c.c. of toluene. The mixture was boiled until the sodium had disappeared, and then 1 mol. of benzyl chloride was added. The boiling was continued for ½ hour, the mixture was cooled, and extracted with water, the toluene was separated, dried and removed, and the residue was crystallised from methyl alcohol. The product had m.p. 80-81°, a mixture with the above product (m.p.77-78.5°) melting at 78-79°.

Preparation of m-Nitrophenacyl bromide.

The preparation of this substance by the method of Evans and

Brooks (J. Amer. Chem.Soc. 1908, 30, 406), was less satisfactory than the following modification of the process described by Hunnius (Ber. 1877. 10, 2008): phenacyl bromide was slowly added to ten parts of nitric acid (d.1.5), kept at -10° to -5°. The solution was poured onto ice, and the precipitate was collected, digested with ether to remove the o-nitro compound, and the residue was crystallised from alcohol; the yield of m-nitrophenacyl bromide, m.p. 80-81°, was 70%

Action of piperidine on m-Nitrophenacyl bromide.

Although the bromide condensed readily with piperidine under the conditions used for the preparation of phenacylpiperidine, (second method), the isolation of the product was not accomplished. Vacuum distillation caused explosive decomposition. Purification by crystallisation gave oily products, and although the picrate was obtained as a highly crystalline substance, m.p.175-176°, its subsequent decomposition by alkali gave amorphous products. In a second experiment, a benzene solution of m-nitrophenacyl bromide (1 mol.) was added to one of piperidine (2 mols.). After several hours, the precipitated hydrobromide was removed by filtration, and the filtrate evaporated. When the residue was stirred with dilute acetic acid, an amorphous solid was obtained which could not be made to crystallise, and had an indefinite m.p.

Preparation of Piperidino-deoxybenzoin.

Chloro-deoxybenzoin was prepared by Schroeter, from benzoin and thyonyl chloride, (Ber. 1909, 42, 2348); the following modification of his method was used. A mixture of equal weights of

benzoin and thionyl chloride was warmed until a clear solution was obtained. After adding much warm water and stirring until cold, a solid product was obtained which crystallised from chloroform on adding light petroleum (b.p. 40-60°). The crystalline material was recrystallised from methyl alcohol, and them had m.p. 66-67°. Schroeter states that chlorodeoxybenzoin begins to soften at 66°, and melts at 68.5°, whereas Curtius and Lang (J.Prakt. Chem. 1891, II, 44, 548) gave mp. 65°.

The chloro compound was covered with its own weight of piperidine, and the mixture was slowly warmed to 100°, during 20 minutes. It was repeatedly extracted with water, and the gummy residue was crystallised from alcohol, when needles, mp. 85-86°, were obtained. (Rabe and Rieper, loc.cit., give m.p. 82°).

Phosphorus trichloride was found to be almost without action on benzoin, and phosphorus pentachloridegave a mixture which could not be purified.

Preparation of Phenyl-ω-piperidinomethyl carbinol.

Phenacyl piperidine was reduced as described by Rabe, (Annalen, 1909, 365, 377), but the product was worked up by the following, different method: the alkaline alcoholic reduction mixture was treated with water, and most of the alcohol was distilled off. The residue was extracted with ether, the extract was dried over sodium sulphate and evaporated, and the residue was distilled under reduced pressure. The base had the properties recorded by Rabe. The hydrochloride was prepared by passing dry hydrogen chloride through a light petroleum solution of the base, and had m.p. 192-194°.

(Found: Cl, 14.5, $C_{13}H_{20}ONCl$ requires Cl, 14.7%).

Preparation of Phenylmethyl-ω-piperidinomethyl carbinol hydrochloride.

An ethereal solution of phenacylpiperidine (1 mol.) was gradually added to a Grignard reagent prepared from 2 mols. of methyl iodide and 4 atoms of magnesium (with intermediate decantation from undissolved magnesium). After the addition was over, the mixture was gently boiled for ½ hour, and then decomposed with ammonium chloride solution. The ethereal solution was separated and extracted with dilute hydrochloric acid solution, and the acid layer, after being extracted with a little ether, was rendered ammoniacal, and extracted with light petroleum (b.p. 60-80°). This extract was dried over sodium sulphate and saturated with dry hydrogen chloride; when the carbinol hydrochloride was obtained as a white microcrystalline powder, which, after being heated at 100°, had m.p. 140-141°. (Found: N, 5.8; Cl, 14.0; $C_{14}H_{22}ONCl$ requires N, 5.5; Cl 13.9%).

Phenylethyl-ω-piperidinomethylcarbinol hydrochloride.

This substance was obtained by the same method as that used for the methyl analogue. The carbinol hydrochloride, precipitated by dry hydrogen chloride from a light petroluem solution of the base, was crystallised from a mixture of alcohol and ether, and dried at 100°; and was obtained as a microcrystalline powder, softening at 168°, and melting at 171-173°. (Found: N, 5.6; Cl, 13.5; $C_{15}H_{24}ONCl$ requires N, 5.2; Cl, 13,2%).

Phenyl-n-propyl-ω-piperidinomethylcarbinol Hydrochloride.

Interaction of phenacylpiperidine and magnesium propyl bromide (2 mols.) was very vigorous. The carbinol hydrochloride was obtained by the method described under the preceding compounds, and after being dried at 100°, was obtained as a microcrystalline powder, m.p.185-187°, (Found: Cl,13.0; $C_{16}H_{26}ONCl$ requires Cl, 12.5%).

Phenyl-n-butyl-ω-piperidinomethylcarbinol Hydrochloride.

When phenacylpiperidine was added to 2 mols. of ethereal magnesium butyl bromide, a solid formed on the surface, but later redissolved. The hydrochloride precipitated from light petroleum was crystallised from a mixture of alcohol and ether, and dried at 100°. It was a microcrystalline powder, m.p.166-169°, (Found: Cl,12.0; $C_{17}H_{28}ONCl$ requires Cl, 11.9%).

Action of Magnesium n-Hexyl Iodide on Phenacylpiperidine.

The preparation of this substance was performed in the same way as the other Grignard reactions, using 2 mols. of n-hexyl iodide, 1 mol. of phenacylpiperidine and 4 atoms of magnesium. On adding the phenacylpiperidine, a part of the precipitate formed redissolved. The hydrochloride of the base could only be obtained by passing dry hydrogen chloride into a petroleum ether (80-100°) solution of the base.

m.p. of the hydrochloride, 213-219°.

mixed m.p. of the hydrochloride with the hydrochloride of the heptyl compound, 215-220°.

Analysis of the hydrochloride.

Substance, 0.4300 g. AgCl, 0.2550 g.

whence Cl, 14.7%

$C_{19}H_{31}ON.HCl$ requires Cl, 10.9%

Phenacylpiperidine hydrochloride $C_{13}H_{18}ONCl$ requires Cl, 14.8%.

Action of Magnesium n-Heptyl Iodide on Phenacylpiperidine.

The details of this experiment are exactly the same as for the n-hexyl compound. The hydrochloride had m.p. 216-220°, and mixed m.p. with the hydrochloride of the n-hexyl compound was 215-220°.

Action of Magnesium Cyclohexyl Iodide on Phenacylpiperidine.

(1)
Preparation of cyclohexyl bromide.

100 G. of Boake Roberts cyclohexanol were heated under reflux over a guaze for 1½ hours with 700 c.c. of hydrobromic acid (d. 1.49). Separation of an oil occurred within 10 minutes. The product was cooled, the top layer of cyclohexyl bromide was separated, washed with water, and dried over anh. calcium chloride.

Yield, 114 g. (70% yield).

B.p., 162-166°.

A.

The experiment was conducted as usual, using:

(1 mol.), 15 g. of phenacylpiperidine

(4 atoms), 8 g. of magnesium

(2 mils), 25 g. of cyclohexyl bromide.

The hydrochloride was prepared by the dry method, (H Cl gas in petroluem ether solution) and 14 g. of product were obtained, after drying at 100°. (58% of the theoretical yield).

Analysis.

Substance, 0.4304 g. - AgCl , 0.2386 g.

whence Cl , 13.7%

$C_{19} H_{24} ONCl$ requires Cl , 11.2%

B1

The experiment was repeated, using:

(1 mol.) 11 g. of phenacylpiperidine

(10 atoms) 13 g. of magnesium

(5 mols.) 45 g. of cyclohexyl bromide

After drying the hydrochloride at 100°, the yield was 9.5 g.

Analysis.

Substance, 0.4326 g. AgXl , 0.2214 g.

whence Cl , 12.7%.

C.

The experiment was again repeated, using:

(1 mol.) 10.5. g. of phenacylpiperidine

(20 atoms) 25 g. of magnesium

(10 mols.) 81.5 g. of cyclohexyl bromide

The precipitate which formed on adding phenacylpiperidine to the Grignard reagent redissolved. The whole product was precipitated with hydrochloric acid, and was crystallised from alcohol, in order to get not more than two g. of the product.

The m.p. was found to be 217-220°.

Analysis.

Substance, 0.4320 g. AgCl, 0.2496 g.

whence Cl , 14.3%

Diphenyl-ω-piperidinomethylcarbinol Hydrochloride.

After addition of the phenacylpiperidine to the magnesium phenyl bromide solution (2 mols.), the mixture was heated for some time, cooled, and decomposed with ammonium chloride solution. The ethereal layer was extracted with dilute hydrochloric acid, and the acid layer was once extracted with ether. The acid solution was boiled to remove ether, and kept; the carbinol hydrochloride then separated in long, colorless needles, which, after being dried at 100°, melted at 214-218°. (Found: N, 4.5; Cl, 11.9; $C_{19}H_{18}ONCl$ requires N, 4.5; Cl , 11.2%).

Phenylbenzyl-ω-piperidinomethylcarbinol Hydrochloride.

On addition of phenacylpiperidine to the magnesium benzyl chloride solution (2 mols.), a white precipitate was first formed, and later redissolved. The mixture was gently boiled for ¼ hour, cooled, and then decomposed with ammonium chloride solution. The aqueous layer was extracted with ether, and the combined ethereal solutions were shaken with a mixture of equal volumes of concentrated hydrochloric acid and water, when the carbinol hydrochloride separated as a crystalline precipitate. The suspension was filtered, the solid was washed with ether, and was crystallised from alcohol. Spear-shaped needles were obtained, m.p. 238-244°. These were sparingly soluble in dilute hydrochloric acid of cold alcohol, were very soluble in warm alcohol. (Found: Cl, 10.7; $C_{20}H_{26}ONCl$ requires Cl , 10.7%)

Phenyl-β-phenylethyl-ω-piperidinomethylcarbinol Hydrochloride.

The mixture resulting from the interaction of phenacylpiperidine and 2 mols. of magnesium β-phenylethyl bromide was decomposed with ammonium chloride solution, and the ethereal layer was shaken with concentrated hydrochloric acid mixed with an equal volume of water. The carbinol hydrochloride which separated was washed with water and ether, and dried at 100°. The combined mother-liquors were separated from the ether layer, extracted with light petroleum, the extract was dried over sodium sulphate, and saturated with hydrogen chloride. The precipitated carbinol hydrochloride was crystallised from a little alcohol by addition of ether. The combined yields of the hydrochloride, m.p. 211-216°, was 65%. (Found: N, 4.0; Cl , 10.2; $C_{21}H_{28}ONCl$ requires N, 4.05; Cl , 10.3%).

Phenyl-γ-phenylpropyl-ω-piperidinomethylcarbinol Hydrochloride.

The product resulting from the interaction of phenacylpiperidine and 2 mols. of magnesium γ-phenylpropyl bromide was treated as usual, the hydrochloride separating when the ethereal solution was shaken with 20% hydrochloric acid. It was washed with ether and dried at 100°, and had m.p. 209-210°. (Found: Cl , 9.8; $C_{22}H_{30}ONCl$ requires Cl, 9.9%).

Phenyl-δ-phenylbutyl-ω-piperidinomethylcarbinol Hydrochloride.

The preparation from phenacylpiperidine and magnesium δ-phenylbutyl bromide (2 mols.) was carried out by the method used for the β-phenylethyl derivative. The hydrochloride crystallised from

alcohol, containing dilute hydrochloric acid, in colorless needles, which, after being dried at 100°, had m.p. 173-174°. The hydrochloride is very soluble in warm alcohol, and almost insoluble in cold dilute hydrochloric acid. (Found Cl , 9.5 ; $C_{23}H_{32}ONCl$ requires Cl , 9.5%).

Phenyl-α-naphthyl-ω-piperidinomethylcarbinol.

Phenacylpiperidine and magnesium α-naphthyl bromide reacted normally. The mixture was heated for 1 hour in warm water, cooled, and decomposed with ammonium chloride solution. The ethereal layer was shaken with its own bulk of 20% hydrochloric acid, and again with a smaller amount of dilute acid. The combined acid extracts were well shaken with ether, the ether was separated, and the acid solution was warmed until free from ether. Addition of dilute ammonium hydroxide produced a gum, which after much digestion with hot water became solid, and was then crystallised from alcohol. The crystalline product was recrystallised from light petroleum (b.p. 80-100°). From both solvents the carbinol separated in sparkling nodules, m.p. 114-115°. (Found: N, 4.2; $C_{23}H_{25}ONCl$ requires N, 4.2%).

EXPERIMENTS ON THE BROMINATION OF 2:4-DIMETHYL QUINOLINE.

Attempted Hexabromination of 2:4-Dimethyl Quinoline.

32 c.c. of bromine were added to a solution of 16 g. of 2:4 dimethyl quinoline and 100 g. of anhydrous sodium acetate in glacial acetic acid. The mixture was warmed until no further change occurred, and was then poured into water; the product was crystallised from light petroleum, (b.p. 80-100°). It melted with decomposition at 125°.

Analysis.

Substance, 0.1177; AgBr, 0.1722

whence Br , 61.7%.

Tribromination requires Br, 60.9%.

Dibromination requires Br, 50.8%.

Tetrabromination requires Br, 67.8%.

Attempted momobromination of 2:4-dimethyl quinoline.

This experiment was done similarly, and the product was identical with that above.

Analysis.

Substance, 0.1773; AgBr, 0.2515;

whence Br, 60.4%.

An attempt was made to hydrolyse the tribromo compound, using boiling alkali, or boiling dilute sulphuric acid or silver oxide. No success was achieved in any or these experiments.

ATTEMPTED DECARBOXYLATION OF QUITENINE.

(1). Using Copper Bronze.

One g. of quitenine was ground up with 30 g. of copper-bronze, and the mixture was heated in a metal bath at 200-210° for 1 hour. The powdery mass was then ground up with sodium carbonate solution, and extracted with ether. The ether extract was washed with water, and evaporated to dryness. There was no residue.

This experiment was repeated, using 1 g. of quitenine and 20 g. of copper-bronze, the mixture being heated to 290-300° for 40 minutes. During the first 10 minutes, steam came off from the mixture, and then for 30 minutes there was no change at all. The mixture was worked up as before. Again there was no residue from the ether extract.

(II). Using Soda-lime.

One g. of quitenine was ground up with 20 g. of soda-lime, and the mixture was heated for 1¼ hours at 210-240°, in a metal-bath. A small quantity of residue was obtained after the mixture had been refluxed with acetone, and the filtered acetone had been evaporated to dryness. The solid residue was insoluble in alkali or in water, showing that is was not unchanged quitenine.

The experiment was repeated using 3 g. of quitenine and 40 g. of soda-lime. The soda-lime and quitenine had previously been dried

separately. The mixture was heated in a metal-bath at 220-230°, for 1¾ hours. The same result as before was obtained.

(III). Using Barium Hydroxide.

20 g. of barium hydroxide and 2 g. of quitenine were ground together and heated in a metal-bath; at 240° decomposition began. The product became black, and pungent fumes mixed with steam were evolved. The heating was only continued for ½ hour at this temperature, and the mixture was extracted with ether, washed with alkali and then with water, and evaporated. Some residue was obtained, which gave a crystalline gold salt with gold chloride.

The experiment was repeated using 5 g. of quitenine and 70 g. of barium hydroxide. The mixture was heated in a metal-bath for ½ hour at 240°, ground up with water, shaken with chloroform, filtered, shaken again, separated, washed with water, separated from the water, and the chloroform was evaporated to dryness. A small yield of amorphous solid matter was obtained.

A modification of the above experiment was made by first fusing 3 g. of quitenine with 40 g. of barium hydroxide, and then powdering the solid mass; which was heated at 200-240°, for ½ hour, ground with water, extracted with toluene, the toluene washed twice with water and once with distilled water, and then with dilute sulphuric acid. The acid layer was separated and basified with ammonia. A negligible precipitate was obtained.

(IV). Attempted decarboxylation of quitenine through the Lithium salt.

3.4 gl of quitenine were added to a solution of 1.5 g. of lithium hydroxide in 50 c.c. of boiling water. The mixture was evaporated to dryness, and when dry, heated in a metal-bath at 200°. On working up with ether, no residue was obtained.

(V). Attempted decarboxylation of quitenine by dry vacuum heating.

5 g. of dry quitenine were placed in a round-bottomed flask which was attached to a vacuum pump. The flask was heated in a metal-bath. No change in the quitenine was observed until the m.p. was reached (275° approximately). At this temperature the quitenine began to decompose rapidly. It became a black, tarry mass, and effervesced vigorously. (CO_2 coming off?). After the effervescence was over, the black tar was extracted with benzene, and the benzene was washed with alkali. The remaining tar which did not dissolve in benzene was extracted in a Soxhlet apparatus with acetone, the whole apparatus being wrapped in a thick layer of cotton wool to keep the temperature of extraction as high as possible. The acetone was evaporated off. The remaining tar was finally extracted with ether, the ether was extracted with potassium carbonate solution and washed with water. The three residues, obtained from the benzene, acetone and ether extractions, were dissolved in absolute alcohol, and a saturated solution of picric acid in alcohol was added. The picrate formed was a yellow solid, and

had m.p. of 225-226° with previous softening, and darkening.

0.1167 g. of the picrate were weighed out and dissolved in 20 c.c. of pure acetone. The solution was a deep red color and opaque to light, so it was diluted to ¼ of the original concentration, and put in a decimetre tube.

Zero of tube, 0. 17

Readings of rotation 0.40
0.40
0.41
0.40

Therefore the angle read-0.23 .

$$[\alpha]_{5791}^{20^\circ} = +157.5$$

The base, both when the solutions were evaporated to dryness and after basification of the picrate, had a characteristic sweet, scent-like smell.

A modification of the above experiment was conducted in the following manner: 5 g. of quitenine at a time were heated by the reduced pressure method (as above), until all effervescence had stopped, and when 20 g. had been treated in this manner, the whole tarry matter was soxhleted with ether. The ether extracted nothing, so benzene was used. On examining the benzene solution polarimetrically, a rotation was obtained. (The benzene had been previously washed with alkali and then with water, to remove unchanged quitenine.) The base was then obtained free from benzene by evaporation on a water-bath, and was dissolved in 1:3 hydrochloric acid solution. A rotation of the hydrochloride was taken, and it was found to possess

some optical activity. The tarry matter was soxhleted again with benzene, the benzene solution was extracted with akkali, washed with water, and dried over sodium carbonate and blood charchal, (to remove the color), Dry hydrogen chloride was passed into the filtered solution, in order to try and obtain the hydrochloride crystalline, but the only result was a just visible cloudiness.

ATTEMPTED PREPARATION OF QUITENINE AMIDE OR
DERIVATIVES OF QUITENINE AMIDE.

(1). 8 g. of quitenine were treated with 30 g. of thionyl chloride. The quitenine was placed in a flask fitted with a condenser, and the thionyl chloride was gradually added. After the addition was complete, the mixture was warmed to about 60°, and the excess of thionyl chloride was removed under reduced pressure. Benzene was added repeatedly, and evaporated under reduced pressure, until all the thionyl chloride had been removed and the solid was a crystalline mass. The solid was removed from the flask, and ground up with solid ammonium carbonate. The whole was then added to water, the solution was extracted with chloroform, which was dried over sodium carbonate, and evaporated to dryness. No residue was obtained.

(11). 4 g. of quitenine were added to 20 g. of thionyl chloride, in which it all dissolved with the evolution of heat. The excess of thionyl chloride was removed as before. The acid chloride hydrochloride was ground up to a fine, dry powder and suspended in dry benzene; ammonia gas, dried over soda-lime was passed into the suspension for two hours. The benzene was then filtered from any unchanged solid material, and evaporated. The residue was powdered up, and analysed.

Analysis. Substance, 0.4290 g.

after combustion T = 20°
p = 759 mm.
volume of nitrogen 36.8 c.c.

N found 10.9%.

Quitenine amide $C_{19} H_{23} O_3 N_3$ requires N 12.4%

(III). Quitenine hydrochloride was prepared by evaporating 5 g. of quitenine with 5 c.c. of concentrated hydrochloric acid. An exactly equivalent amount of thionyl chloride was used to prepare the acid chloride. After working up as usual, dry ammonia gas was passed into a benzene suspension of the solid for 1 hour. Excess of ammonia was removed under reduced pressure, and dry hydrochloric acid gas was passed in. A negligible precipitate of the hydrochloride was obtained, and was not worked up.

The experiment was repeated, adding an excess ($\frac{1}{2}$ mol.) of thionyl chloride, and working up as before. The same negative result was obtained.

(IV). Quitenine amide hydrochloride.

The amide was prepared as in experiment II, but the benzene was not all evaporated off. Dry hydrochloric acid gas was passed into the solution, and a white amorphous precipitate was obtained. Ether was added, and the whole was filtered and left in a vacuum desiccator for 15 hours, over phosphorus pentoxide and paraffin wax.

Analysis. Substance, 0.2742 g.

After combustion.
temp. 18°.
press. 754 mm.
volume of nitrogen 20.8 c.c.

Found N, 8.7%

Calc. N, 10.1%.

Attempted preparation of benzoyl quitenine amide.

A.

4 g. of quitenine were heated with 10 g. of benzoyl chloride on a boiling water-bath for one hour. The solid obtained was washed free from benzoyl chloride with ether, was dissolved in a littel absolute alcohol, and was precipitated with ether. The yield was 4 g.

This experiment was repeated using 9 g. of quitenine and 25 g. of benzoyl chloride, and the yield was 13 g.

B.

Preparation of the acid chloride of benzoyl quitenine.

Benzoyl quitenine hydrochloride was refluxed for ½ hour at 100°, with 20g. of thionyl chloride, in which it almost immediately dissolved on warming. The excess of thionyl chloride was removed as usual, and the precipitate was washed with dried benzene, ground up, left in vacuo for 20 hours over phosphorus pentoxide, potassium hydroxide, sulphuric acid and paraffin wax.

yield = 4 g.

Analysis.

Substance, 0.4317 g. AgCl , 0.3899 g.

whence Cl, 22.4%

Quitenine chloride hydrochloride requires Cl 17.9%.

2 HCl requires Cl 24.6%

Benzoyl quitenine chloride hydrochloride requires Cl 14.2%

2 HCl requires Cl 19.8%

C.

Repeated attempt of the preparation of benzoyl quitenine amide.

2 g. of the acid chloride hydrochloride were ground up with 0.880 ammonia. Heat was liberated during the reaction. The product was extracted with benzene which was washed with water, and the benzene was distilled off. The solution was evaporated to dryness, the residue was washed with petroleum ether (b.p. 60-80°) and left in a vacuum desiccator over phosphorus pentoxide, caustic potash, sulphuric acid and paraffin wax.

Yield of solid matter 0.5 g.

Analysis. 3.262 mg. gave 3.615 mg. of carbon dioxide, 1.840 mg. of water. Ash 0.026 mg.

7.526 mg. gave 0.490 c.c. of nitrogen at 750 mm and 24.

Ignoring the ash:

C 63.6%
H 6.3%
N 7.3%

Benzoyl quitenine amide ($C_{26}H_{28}O_4N_3$) requires:

C 70.0%
H 6.3%
N 9.4%

PREPARATION OF CINCHONINE METHOBROMIDE.

The method described in the literature was first used, and gave the following result:

A suspension of 60 g. of cinchonine in 1000 c.c. of absolute methyl alcohol was saturated with methyl bromide, and kept in the cold for two days. The clear solution was distilled until the volume was 150 c.c. On cooling the solution, crystals separated, but 150 c.c. of water were added to precipitate the product. The heated solution was filtered to remove the scum and allowed to crystallise. Filtration followed by drying at 100° gave 73 g. of cinchonine methobromide (90% yield).

The difficulty of obtaining methyl bromide, and the time required for the above operations made it necessary to effect improvements. The following method was found satisfactory: A suspension of 59 g. of cinchonine in 60 c.c. of absolute methyl alcohol was treated with a solution of 19 c.c. of methyl sulphate in 100 c.c. of methyl alcohol. On warming gently, the cinchonine dissolved; the solution was evaporated under reduced pressure, 500 c.c. of water were added; the solution was filtered from unchanged cinchonine (3 g.); the filtrate was heated to about 60°, and treated with a solution of 48 g. of potassium bromide in 500 c.c. of water. On cooling, 67 g. of colorless, highly crystalline cinchonine methobromide were obtained. (87% yield, or 92%, allowing for the recovered cinchonine).

PREPARATION OF THE METHOCHLORIDES OF SOME CINCHONA ALKALOIDS.

Methochlorides of cinchonine, cinchonidine, quinine and quinidine were prepared by a suitable modification of the process used for cinchonine methobromide; i.e., by substituting ammonium chloride for potassium bromide, and where necessary, using considerably less methyl alcohol, (e.g., for cinchonidine). It is interesting that cinchonine and its methohalides are very much less soluble in hydroxylic solvents than cinchonidine and its methohalides.

Quinidine Methochloride.

This substance, which owing to its considerable solubility in the alcohols and water, was only obtained with difficulty, is not described in the literature. Analysis of this compound was therfore carried out:

(1). Substance, 0.3523 g.
AgCl 0.2158 g.

Whence Cl, 9.7%.

(2). Substance, 0.4865 g.
AgCl 0.1985 g.

Whence Cl, 10.1%.

(3). Substance, 0.7296 g.
AgCl 0.2884 g.

Whence Cl, 9.8%.

The methochloride was found to be a hydrate:

0.6946 g. of the salt lost:

0.0300 g. of water in 1 hour at 110°.

a further 0.001 g. after an additional ½ hour at 110°.

After 15 hours in vacuo over phosphorus pentoxide a further loss of 0.003 g. was obtained.

The loss was not increased by further drying at 110°.

Total loss 0.0330.g. of water.

For a monohydrate, the loss should be 0.0319 g.

Therefore the salt forms a monohydrate.

Reprinted from the Journal of the Chemical Society, 1931.

CLIV.—*The Reactions of Substituted Ammonium Aryloxides and of Related Compounds. Part I. The Preparation and Thermal Decomposition of Some Tetrasubstituted Ammonium Aryloxides.*

By Rosalind Venetia Henley and Eustace Ebenezer Turner.

Compounds of the class described in this communication may be written as of the general type $R_4\overset{+}{N}\}\overset{-}{O}Ar$, and are related to the metallic phenoxides in structure, but differ from these in that the phenoxide radical can only be electrovalently attached to the tetrasubstituted ammonium radical, on the assumption that nitrogen is only capable of quadricovalency, whereas many of the metallic

phenoxides may exhibit the physical properties of covalent compounds (*viz.*, the solubility of sodium β-naphthoxide and of sodium *p*-chlorophenoxide in anhydrous ether) (Tijmstra and Eggink, *Ber.*, 1906, **39**, 14; Hantzsch and Mai, *Ber.*, 1895, **28**, 978).

In view of the fact that many of the reactions of phenols in alkaline solution are regarded as being caused by the ionisation of the metallic phenoxide, we thought that such typical processes as the Kolbe–Schmitt carboxylation and the Reimer–Tiemann reaction could with advantage be studied in the ammonium series. In the present communication we describe the preparation of some tetrasubstituted ammonium aryloxides, and their behaviour towards heat, since we required a knowledge of their thermal stability before undertaking an examination of their reactions.

A number of tetrasubstituted ammonium picrates are known, but these are clearly unsuitable for this work. The preparation of *phenyltrimethylammonium* o-*nitrophenoxide* was first attempted, so as to gauge the experimental difficulties likely to be encountered when less acidic phenols were used. We realised that, according to commonly accepted theory, *o*- and *p*-nitrophenoxides are salts of the coloured quinonoid forms, and not therefore true phenoxides. This theory, however, is less satisfactory than is sometimes assumed, for it does not entirely accord with the experimental observations of the action of alkyl halides on silver nitrophenoxides, and does not explain the bright red colour of sodium *m*-nitrophenoxide, nor the existence of orange-red forms of 2 : 4 : 6-tribromophenol and similar compounds (Torrey and Hunter, *Ber.*, 1907, **40**, 4333; Hantzsch and Scholtze, *ibid.*, p. 4881).

Although phenyltrimethylammonium *o*-nitrophenoxide is extremely hygroscopic, it was isolated as a scarlet, highly crystalline substance: the corresponding p-*nitrophenoxide*, also very hygroscopic, was yellow. So far the *m*-nitrophenoxide has remained as a deep red oil in spite of all attempts to make it crystallise.

The isolation of *phenyltrimethylammonium phenoxide* proved difficult, but the substance was eventually obtained in quantity. It exhibited true salt-like insolubility in anhydrous ether, but was very soluble in water and in alcohol, and was sufficiently soluble in nitrobenzene to crystallise from this solvent. *Phenyltrimethylammonium α-naphthoxide* was even more difficult to isolate in the pure state, but was finally crystallised from nitrobenzene and also from acetone.

Phenyltrimethylammonium thiophenoxide and *phenyltrimethylarsonium thiophenoxide* have been prepared. Their isolation is much less difficult than that of the above phenoxides.

We propose to study all the relevant reactions of the new series of

phenoxides in the solid state, in weakly ionising solvents such as nitrobenzene, and in hydroxylic solvents. Preliminary work has already shown that the ammonium phenoxides are very much more reactive than those of the alkali metals. In the present communication, however, we confine our attention to two sets of observations : (1) on the thermal decomposition of the aryloxides and (2) on their interaction with alkyl iodides.

Initial experiments on the thermal decomposition of the phenoxides showed that these compounds undergo particularly smooth and quantitative scission :

$$R_1R_2R_3R_4\overset{+}{N}\}\bar{O}Ar = R_1R_2R_3N + R_4OAr.$$

In fact, in a study of its thermal decomposition a tetrasubstituted ammonium aryloxide may for all practical purposes be regarded as a mixture of its decomposition products, which has to be purified by vacuum distillation. In all the cases examined, thermal decomposition proceeds quantitatively in a few minutes. For example, if phenyltrimethylammonium phenoxide is " distilled " under reduced pressure by means of a heating bath kept at about 120°, dimethylaniline and anisole pass over as rapidly as the apparatus allows, and are obtained in quantitative yield.

A convenient method is thus made available for a study of the mode of decomposition of tetrasubstituted ammonium aryloxides of a number of different types. The course of any such thermal decomposition may be controlled either by the groups R_1, R_2, R_3, and R_4 contained in the ammonium ion, or by the aryl group of the aryloxide ion, but consideration of the probable mechanism of the decomposition suggests that, although the aryloxy-group may affect the *speed* of decomposition, it is unlikely to have any effect on the *sense* of that decomposition. The simplest expression for the decomposition appears to be as below :

$$\left[\begin{array}{c} R_2 \\ R_1{:}\dot{N}{:}R_3 \\ R_4 \end{array}\right]^{+} \bar{O}Ar \longrightarrow R_1{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}{:}R_3 + \overset{+}{R}_4 + \bar{O}Ar \longrightarrow R_1R_2R_3N + R_4OAr.$$

That is, since the ammonium ion is forced to eject one of its R components, it expels that one which is least firmly attached. This ejected fragment R_4 will have a brief existence as a positive ion, and neutrality will be attained by its combination with the aryloxide ion. It is known that during the thermal decomposition of lead tetramethyl, methyl ions do persist during a short time (Paneth and Hofeditz, *Ber.*, 1929, 62, 1335). Although it is possible that the aryloxide ion may have preference for one or other of the groups R,

it seems clear that the main controlling mechanism is the initial decomposition of the ammonium complex.

The thermal decomposition of phenyltrimethylammonium phenoxide, *o*-, *m*-, and *p*-nitrophenoxide, 2 : 4-*dinitrophenoxide*, α-naphthoxide, and *m*-4-xylyloxide leads in every instance to dimethylaniline and the methyl ether of the phenol. In no case was a detectable quantity of the diphenyl ether type formed. The thermal decomposition of *phenylbenzyldimethylammonium* o-*nitro*- and 2 : 4-*dinitrophenoxide* and the xylyloxide all give dimethylaniline, the benzyl radical in each case undergoing most ready ejection from the ammonium ion, and appearing as the corresponding benzyl aryl ether. To a limited extent, these results suggest that even profound modification of the aryloxide does not have any effect on the course of the decomposition.

Thermal decomposition of *phenyldimethylethylammonium* 2 : 4-*dinitrophenoxide*, on the other hand, is not unidirectional, dimethylaniline, methylethylaniline, 2 : 4-dinitroanisole and 2 : 4-dinitrophenetole all being formed.

Phenyltrimethylammonium thiophenoxide undergoes quantitative thermal decomposition into dimethylaniline and thioanisole. When phenyltrimethylarsonium thiophenoxide is heated, slight sublimation takes place, but again quantitative decomposition occurs, giving phenyldimethylarsine and thioanisole.

We have also examined the effect of boiling aqueous solutions of some tetrasubstituted ammonium aryloxides. It was not surprising to find that phenyltrimethylammonium phenoxide was rapidly and completely converted, when boiled in 10% aqueous solution, into dimethylaniline, phenol and methyl alcohol, and that no anisole could be detected, but it was not anticipated that prolonged boiling, followed by evaporation to dryness of the corresponding *p*-nitrophenoxide, would be unaccompanied by appreciable hydrolysis or decomposition, which was our experimental observation. Experiments are in progress on the effect of limited amounts of water and other solvents on the decomposition of the phenoxides.

After the above work was completed, we found that Hanhart and Ingold (J., 1927, 997), in their study of a different problem, had decomposed trimethyl-*n*-propylammonium phenoxide and *m*-nitrophenoxide, without attempting to isolate them. We have been in communication with Professor Ingold, who expressed his willingness for us to proceed with our work.

Tetrasubstituted ammonium aryloxides react with methyl (ethyl) iodide to give the quaternary ammonium iodide and a phenolic ether:

$$NR_4^+\}\bar{O}Ar + MeI = NR_4^+\}\bar{I} + MeOAr$$

and here the speed of the reaction is affected largely by the nature of the groups substituted in the aryloxide ion.

Of the phenyltrimethylammonium phenoxides at our disposal, the *m*-4-xylyloxide and the α-naphthoxide reacted vigorously with cold methyl iodide, and the phenoxide almost as readily. The *o*-nitrophenoxide reacted completely with methyl iodide after five minutes' boiling in alcoholic solution, whereas the 2 : 4-dinitrophenoxide was unaffected by this treatment, although, after being boiled in methyl-alcoholic solution with methyl iodide for three hours, it was entirely converted into the quaternary iodide and dinitroanisole. These results indicate quite definitely that substitution in the aryloxide ion nucleus of electron-attracting groups decreases the rate of reaction with methyl iodide, but groups having electron-donating properties increase it.

Phenyltrimethylarsonium thiophenoxide reacts instantaneously with cold methyl iodide to give phenyltrimethylarsonium iodide and thioanisole. Phenyltrimethylammonium thiophenoxide reacts readily with cold methyl iodide to give the analogous products.

We hope shortly to report on the action of halogens, chloroform, and other compounds on the new phenoxides.

Experimental.

Phenyltrimethylammonium o-*Nitrophenoxide.*—A concentrated warm aqueous solution of phenyltrimethylammonium iodide (1 mol.) was treated with freshly precipitated silver oxide until the black oxide was clearly visible on shaking, and the solution gave no test for iodide. The liquid was filtered and, after being treated with 1 mol. of *o*-nitrophenol, was evaporated under reduced pressure in a bath kept at 50—60°, alcohol being added from time to time to accelerate evaporation. When no further diminution in volume occurred, the syrupy red product was dissolved in a little absolute alcohol, and anhydrous ether was added until crystallisation set in, whereupon excess of ether was added, and the precipitate was rapidly collected and washed with ether. After being dried in a vacuum over sulphuric acid, the o-*nitrophenoxide* was obtained as scarlet plates, m. p. 117—117·5° (Found : N, 10·0. $C_{15}H_{18}O_3N_2$ requires N, 10·2%). The nitrophenoxide is excessively hygroscopic, but can be kept for an indefinite period in a dry atmosphere. It may also be prepared by the interaction of phenyltrimethylammonium iodide and silver *o*-nitrophenoxide in boiling alcoholic solution.

The nitrophenoxide was warmed for 5 minutes with a methyl-alcoholic solution of methyl iodide. Ether was then added, and the crystalline precipitate was identified as phenyltrimethylammonium iodide, m. p. 225°.

Thermal Decomposition of Phenyltrimethylammonium o-*Nitrophenoxide.*—The phenoxide (7·5 g.) was heated at 180° in a large boiling tube fitted with a calcium chloride tube. After a few minutes, dimethylaniline began to form, and after an hour the decomposition was complete. The product was dissolved in benzene and the solution extracted with 20% hydrochloric acid. From the benzene solution were obtained 3·5 g. of *o*-nitroanisole, and from the acid layer, by treatment with ammonium hydroxide, followed by extraction with benzene, the dimethylaniline was isolated. It was converted into the methiodide, of which 5 g. were obtained, m. p. 229—230°.

Phenyltrimethylammonium p-*Nitrophenoxide.*—The preparation of this compound was carried out similarly to that of the *o*-isomeride. The phenoxide was obtained crystalline by adding anhydrous ether to the concentrated alcoholic solution, and formed yellow prismatic needles, m. p. 118—119°, with considerable previous softening. It is very hygroscopic, but may be crystallised (yellow needles) from nitrobenzene if it has previously been well dried (Found: N, 10·0. Calc.: N, 10·2%). Decomposition at 170° by the process used for the *o*-isomeride gave almost theoretical yields of dimethylaniline and *p*-nitroanisole.

The *p*-nitrophenoxide reacts rapidly with potassium iodide in alcoholic solution to give phenyltrimethylammonium iodide. A solution of 2 g. of the *p*-phenoxide in 40 c.c. of water was boiled under reflux for 4 hours. No odour of dimethylaniline was produced, and the solution was then evaporated to dryness on the water-bath. The residue became solid, after being dried in a vacuum over phosphoric oxide, and then melted at 115—120°. It produced no depression of the m. p. of the original material.

Methyl iodide slowly converts phenyltrimethylammonium *p*-nitrophenoxide in boiling alcoholic solution into the quaternary iodide and *p*-nitroanisole.

Phenyltrimethylammonium m-*Nitrophenoxide.*—This substance was obtained as a deep red oil, which, even after prolonged extraction with anhydrous ether and vacuum desiccation over phosphoric oxide, refused to crystallise. By this process, however, all impurities are effectively removed.

Thermal decomposition of the phenoxide by the process used above gave almost theoretical yields of dimethylaniline and *m*-nitroanisole (m. p. 36° when crude).

Phenyltrimethylammonium 2 : 4-*Dinitrophenoxide.*—This substance crystallised from the concentrated alcoholic solution obtained at the evaporation stage of its preparation by the usual process. It crystallised from absolute alcohol in yellow prisms, softening at 90°

and melting at 121—123° (Found : N, 13·2. $C_{15}H_{17}O_5N_3$ requires N, 13·2%).

The phenoxide was heated for ¼ hour at 135—140°. On cooling, it was found to be unchanged. At temperatures up to 165°, the same result was obtained, even after 1 hour's heating. At 170—175°, decomposition took place in 1 hour, and at 180° or higher temperatures, profound decomposition set in suddenly with charring.

The successful decomposition at 170—175° gave a mixture which was treated with 20% hydrochloric acid. The 2 : 4-dinitroanisole obtained was identified by comparison with an authentic specimen and by conversion into 2 : 4-dinitrophenylpiperidine. The dimethylaniline produced was identified by its b. p. and by conversion into the methiodide.

A methyl-alcoholic solution of the 2 : 4-dinitrophenoxide and methyl iodide was kept at 50—60° for an hour : the phenoxide was recovered unchanged. After 3 hours' boiling, however, theoretical yields were obtained of phenyltrimethylammonium iodide, m. p. 225°, and of 2 : 4-dinitroanisole, which was identified by conversion into 2 : 4-dinitrophenylpiperidine.

Phenyltrimethylammonium Phenoxide.—An aqueous solution of 1 mol. of phenyltrimethylammonium hydroxide was concentrated under reduced pressure at about 50°, with occasional addition of absolute alcohol. An alcoholic solution of phenol (1 mol.) was then added, and the evaporation continued. When no more alcohol came off, the syrup was dissolved in alcohol and excess of anhydrous ether was added. The *phenoxide*, which separated in pearly plates, was dried in a vacuum over sulphuric acid and phosphoric oxide, and then melted at 58—59°. After being crystallised from nitrobenzene, with subsequent washing with light petroleum (b. p. 60—80°), it melted at 75—76° (Found : N, 6·0. $C_{15}H_{19}ON$ requires N, 6·1%). The substance also crystallised from acetone–light petroleum in white plates.

A solution of 2 g. of the phenoxide in 20 c.c. of water was boiled for 2 hours under reflux. The mixture was then freed by routine methods from basic and acidic substances. An ethereal solution obtained, which must have contained any anisole, was evaporated, and left no appreciable residue, although the odour of anisole was detected. The amount of anisole produced was less than 0·1 g. Dimethylaniline, phenol and methyl alcohol were found in the expected extracts.

The phenoxide reacted with cold methyl iodide, and when heated for a few minutes with alcoholic methyl iodide, was quantitatively converted into phenyltrimethylammonium iodide.

The decomposition of the phenoxide was carried out as follows :

17·5 g. were placed in a Claisen distilling flask, which was evacuated, and gradually heated at 120° during 10 minutes. Distillation was then complete, and no appreciable residue was left after the flask had been warmed with a flame. The distillate (17 g.) was dissolved in ether, and extracted with 20% hydrochloric acid. The acid solution was extracted with ether, and the ethereal solution with dilute hydrochloric acid. From the ethereal extracts were obtained, after distillation, 8 g. of pure anisole; and from the acid solutions, after treatment with ammonium hydroxide, extraction and distillation, 8 g. of pure dimethylaniline. The calculated ratio of anisole to base is 107 : 121.

Phenyltrimethylammonium m-4-*Xylyloxide.*—Evaporation of the solution obtained in the usual manner gave a colourless syrup, which was washed with absolute ether and kept in a vacuum over concentrated sulphuric acid and phosphoric oxide. It decomposed, in a bath kept at 110°, without leaving a weighable residue. From 21 g. of syrupy xylyloxide, 20 g. of distillate were obtained, and this yielded 10 g. of pure *m*-xylyl methyl ether, b. p. 180—190°, and 9 g. of pure dimethylaniline. The calculated ratio of ether to base is 136 : 121.

The xylyloxide reacted vigorously with cold methyl iodide to give phenyltrimethylammonium iodide and xylyl methyl ether.

Phenyltrimethylammonium α-Naphthoxide.—This substance, which was obtained in the usual manner, crystallised when its concentrated alcoholic solution was cooled and left in a vacuum over concentrated sulphuric acid and phosphoric oxide. It was recrystallised from nitrobenzene or from acetone, from which it separated in white needles and plates, m. p. 107—108° (Found: N, 4·8. $C_{19}H_{21}ON$ requires N, 5·0%). When the alcoholic solution was allowed to concentrate slowly over concentrated sulphuric acid, large square flat plates were obtained.

The naphthoxide reacted with cold methyl iodide, and on addition of alcohol and warming, the reaction became quantitative. Phenyltrimethylammonium iodide and α-naphthyl methyl ether were identified as the sole products. Decomposition of the naphthoxide (14 g.) occurred at 140—150°, and gave 13 g. of total distillate. This, after the usual separation process, yielded 5 g. of dimethylaniline and 6 g. of α-naphthyl methyl ether, whereas the calculated ratio of base to ether is 121 : 158.

Phenyldimethylethylammonium 2 : 4-*Dinitrophenoxide.*—This substance was prepared as usual, and crystallised from alcohol–ether in small mustard-coloured needles, m. p. 55—57° (Found: N, 12·6. $C_{16}H_{19}O_5N_3$ requires N, 12·6%).

This phenoxide is not particularly hygroscopic. It did not react

with methyl iodide in boiling alcoholic solution after 5 minutes. Decomposition of 5 g. of the phenoxide occurred at 170°, and was complete in one hour. From the products were obtained 2·5 g. of acid-insoluble material, m. p. 39—50°, and 2 g. of a mixture of bases, b. p. 190—200°. The acid-insoluble material was heated with twice its weight of piperidine, excess of 20% hydrochloric acid was added, and the precipitated solid was collected (3 g.). It melted at 91—94° and was almost pure 2 : 4-dinitrophenylpiperidine. The filtrate contained both methyl and ethyl alcohol. The mixture of bases was submitted to micro-distillation; the lower-boiling fraction was converted into the chloroplatinate (Found : Pt, 29·6. Calc. for the chloroplatinate of dimethylaniline : Pt, 29·9%). The higher-boiling fraction was converted into the methiodide, which melted at 133—136°, and at 132—134° when mixed with phenyldimethylethylammonium iodide (m. p. 132—133°), but at below 115° when mixed with phenyltrimethylammonium iodide. Dimethyl- and methylethyl-aniline were therefore both formed in the above decomposition, together with dinitroanisole and dinitrophenetole.

Phenylbenzyldimethylammonium o-*Nitrophenoxide.*—This substance crystallised in vermilion needles when dry ether was added to the concentrated alcoholic solution, and had m. p. 91—92° (Found : N, 8·05. $C_{12}H_{22}O_3N_2$ requires N, 8·0%).

Decomposition of 12 g. of the phenoxide occurred at 155—165°, and gave a mixture of products, b. p. 92—220°/28 mm., consisting of 4 g. of dimethylaniline and 7·5 g. of benzyl *o*-nitrophenyl ether. The calculated ratio of base to ether is 121 : 229.

Phenylbenzyldimethylammonium 2 : 4-*dinitrophenoxide* crystallised from alcohol–ether in fern-like aggregates of mustard-coloured needles, m. p. 138—138·5° (Found : N, 10·5. $C_{21}H_{21}O_5N_3$ requires N, 10·6%). It is not hygroscopic.

Phenylbenzyldimethylammonium *m*-4-xylyloxide was not obtained crystalline, but was freed from impurities by extraction with absolute alcohol and anhydrous ether. After being left in a vacuum over concentrated sulphuric acid and phosphoric oxide, it was decomposed. Decomposition was not marked below 145—150°, and was effected at 175—185°. The portion of the product which was soluble in acid was pure dimethylaniline. No benzylmethylaniline was present. The acid-insoluble product was benzyl xylyl ether.

Phenyltrimethylammonium Thiophenoxide.—When the aqueous-alcoholic solution of the quaternary hydroxide and thiophenol was concentrated, the *thiophenoxide* crystallised. It was recrystallised by addition of ether to an alcoholic solution, and formed white plates, m. p. 83—83·5° (Found : N, 5·7. $C_{14}H_{19}NS$ requires N, 5·7%). It is not hygroscopic. Ethyl iodide reacted vigorously

with it in the cold, phenyltrimethylammonium iodide, m. p. 227—228°, being formed.

Decomposition of the thiophenoxide (20 g.) took place at 125°. Within 5 minutes, 18 g. of liquid distilled at 80—85°/14 mm. This, after separation, gave 8·5 g. of thioanisole and 8 g. of dimethylaniline, whereas these two should have been formed in the proportion of 124 : 121.

Phenyltrimethylarsonium Thiophenoxide.—We first attempted to prepare this substance by heating silver thiophenoxide with an alcoholic solution of phenyltrimethylarsonium iodide, but after several hours' boiling, the latter was recovered almost unchanged. By evaporation of the quaternary hydroxide with thiophenol, the *thiophenoxide* was readily obtained; it crystallised from alcohol on addition of ether in white leaflets, m. p. 144—145°, and was soluble in water or alcohol, but insoluble in ether (Found: S, 10·5. $C_{15}H_{19}SAs$ requires S, 10·5%).

Although the phenyldimethylarsine required for the preparation of phenyltrimethylarsonium iodide is very readily obtained from dimethyliodoarsine (Burrows and Turner, J., 1920, **117**, 1378), we desired to prepare it from phenyldichloroarsine. Winmill (J., 1912, **101**, 723) treated this substance with magnesium methyl iodide in a mixture of ether and light petroleum (b. p. 30—40°) and obtained a 75% yield. We find that higher-boiling petroleum (b. p. 60—80°) can be used, and that if 4 molecular proportions of Grignard reagent are taken, the yield of pure phenyldimethylarsine is over 90%, even in small preparations. Starting with 22 g. of phenyldichloroarsine, it is thus possible to obtain 27—28 g. of the quaternary arsonium iodide.

The thiophenoxide (15 g.) began to decompose at 160°, and, apart from a little sublimation, was completely converted in 10 minutes into a mixture, b. p. 71—72°/11 mm., of phenyldimethylarsine and thioanisole (14·5 g.). 5 G. of this were dissolved in absolute alcohol, methyl iodide was added, and the mixture was left for 3 hours. Absolute ether was added, and the precipitated phenyltrimethylarsonium iodide was dried at 100° (6 g., corresponding to 2·8 g. of phenyldimethylarsine).

Our thanks are due to the Royal Society for a grant in aid of this investigation, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us.

BEDFORD COLLEGE,
UNIVERSITY OF LONDON. [*Received, February 19th*, 1931.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED, BUNGAY, SUFFOLK.

Reprinted from the Journal of the Chemical Society, 1930.

CXIV.—*The Scission of Diaryl Ethers and Related Compounds by Means of Piperidine. Part III. The Nitration of* 2 : 4-*Dibromo*-2′ : 4′-*dinitrodiphenyl Ether and of* 2 : 4-*Dibromophenyl* p-*Toluenesulphonate and Benzoate. The Chlorination and Bromination of* m-*Nitrophenol.*

By Rosalind Venetia Henley and Eustace Ebenezer Turner.

In continuation of previous work (Part II, J., 1929, 512), the nitration of 2 : 4-*dibromophenyl* p-*toluenesulphonate* has been investigated. The sole product of dinitration was 2 : 4-*dibromo*-

presence of sodium acetate gave indefinite results, but in absence of sodium acetate the product was a monobromo-compound, m. p. 118·5—121°. This we at first thought to be 2-bromo-3-nitrophenol, and in order to prove its constitution, we converted it into the p-*toluenesulphonyl* derivative, reduced the latter, and replaced the amino-group by bromine. During the last stage, the *p*-toluenesulphonyl group was removed by hydrolysis and a dibromophenol, m. p. 73—74°, was formed. At the same time we performed an analogous synthesis, starting from 3-bromo-2-nitrophenol. The dibromophenol obtained in the second synthesis melted at 68—69°, was different from the first, and was clearly the hitherto unknown 2 : 3-*dibromophenol*. It therefore seemed certain that the isomeric compound was 2 : 5-*dibromophenol*. Raiford and Bren (*J. Amer. Chem. Soc.*, 1929, **51**, 2539) recently attempted the preparation of this substance from 2 : 5-dibromoaniline. It has now been obtained in excellent yield by applying the method of Noelting and Kopp (*Ber.*, 1905, **38**, 3506) to this base, and was found to be identical with the product from the bromo-3-nitrophenol, which is therefore the 6-derivative (2-bromo-5-nitrophenol) already described by Heller and Kammann (*loc. cit.*), who obtained it from 5-nitro-2-aminophenol.

Although it has already been shown (Part II) that *m*-nitrophenol is readily converted into 2 : 4-dichloro-3-nitrophenol, the above results made it desirable to investigate the monochlorination. Schlieper (*Ber.*, 1893, **26**, 2466), by direct chlorination of *m*-nitrophenol, obtained a compound, m. p. 120°, which, as is shown above, may be either the 2- or the 4-chloro-compound. Meldola and Eyre (J., 1902, **81**, 996) agreed with Schlieper's conclusion that this was the 2-chloro-compound; they obtained 4-chloro-3-nitrophenol, m. p. 126—127°, by synthesis from 3-nitro-*p*-aminophenol.

We find that monochlorination of *m*-nitrophenol at 120—140° gives approximately equal amounts of 4-chloro-3-nitrophenol (A), m. p. 127—128°, and 2-chloro-3-nitrophenol (B), m. p. 120°. A was identical with a specimen prepared from *ON*-diacetyl-3-nitro-*p*-aminophenol, and the constitution of B follows from two facts: (1) dichlorination of *m*-nitrophenol under similar conditions gives the 2 : 4-dichloro-compound in good yield, and (2) reduction of B, followed by replacement of the amino-group by chlorine, gives 2 : 3-dichlorophenol. Although the first of these appears to be sufficient proof, it was desired to prove beyond doubt that B was not 6-chloro-3-nitrophenol (m. p. 118—119°; prepared synthetically by Meldola, Woolcott, and Wray, J., 1896, **69**, 1322).

It is therefore possible that, in this case, Schlieper actually had a 2-chloro-compound, but it is difficult to believe this, since the

4-chloro-compound, which was presumably present, is so readily isolated.

We have not investigated the iodination of *m*-nitrophenol, as the statements in the literature seem to be accurate. Schlieper (1893, *loc. cit.*) described the monoiodo-compound as the 2-iodo-derivative, m. p. 134°, and Datta and Prosad (*J. Amer. Chem. Soc.*, 1917, **39**, 441) state that iodination in the 2-position proceeds quantitatively. There seems little doubt that this substance is different from the 4- and the 6-iodo-derivative, m. p. 156° and 146—147° respectively (Hähle, *J. pr. Chem.*, 1891, **43**, 72; Meldola and Eyre, P., 1901, 238).

In endeavouring to prepare 4-bromo-3-nitrophenol by a different method, we nitrated N-p-*bromophenylphthalimide* in presence of excess of concentrated sulphuric acid, expecting to obtain a considerable proportion of the *m*-nitro-derivative (compare Brady, Quick, and Welling, J., 1925, **127**, 2264). The main product, however, was the *o*-nitro-derivative. This result is interesting, since nitration of *p*-bromoaniline in presence of excess of sulphuric acid gives almost entirely the *m*-nitro-compound (Noelting and Collin, *Ber.*, 1884, **17**, 261) (see Experimental).

The nitration of 2 : 4-dibromo-2′ : 4′-dinitrodiphenyl ether proceeds similarly to that of the analogous dichloro-compound and gives 2 : 4-*dibromo*-5 : 2′ : 4′-*trinitrodiphenyl ether*. This ether readily undergoes scission by piperidine into 2 : 4-dibromo-5-nitrophenol and *N*-2′ : 4′-dinitrophenylpiperidine.

Experimental.

2 : 4-*Dibromophenyl* p-*toluenesulphonate*, readily obtained by the usual type of process, crystallised from glacial acetic acid in colourless plates, m. p. 120° (Found : Br, 39·8. $C_{13}H_{10}O_3Br_2S$ requires Br, 39·4%).

Dinitration of 2 : 4-*Dibromophenyl* p-*Toluenesulphonate*.—The compound was added to 10 parts of nitric acid (*d* 1·5), the resulting solution being left for an hour and then poured into a large bulk of water. Filtration, followed by crystallisation from glacial acetic acid, gave 2 : 4-*dibromo*-5-*nitrophenyl* o-*nitro*-p-*toluenesulphonate* in pale greenish-yellow leaflets, m. p. 122—123° (Found : Br, 32·6. $C_{13}H_8O_7N_2Br_2S$ requires Br, 32·3%).

2 : 4-*Dibromo*-5-*nitrophenol*.—The last-mentioned compound was heated for 1 hour at 100° with 2 parts of piperidine. No piperidine hydrobromide separated. Excess of dilute alkali was added, and the solution shaken with benzene; this extracted the 1-*o*-nitro-*p*-toluenesulphonylpiperidine, but, contrary to expectation, it also extracted the piperidine salt of the phenol. It was therefore shaken

with dilute hydrochloric acid and then with alkali. Acidification of the alkaline solution precipitated 2 : 4-*dibromo*-5-*nitrophenol*. This crystallised from light petroleum (b. p. 80—100°) in long yellow needles, m. p. (after being dried over-night in a vacuum over concentrated sulphuric acid) 77—78° (Found : Br, 53·5. $C_6H_3O_3NBr_2$ requires Br, 53·9%), and from very dilute acetone as the *hydrate*, $C_6H_3O_3NBr_2,H_2O$, in long yellow needles, m. p. 92—94° (with previous softening), the m. p. depending on the rate of heating (0·5236 g. lost 0·0309 g. in 14 days in a vacuum over phosphoric oxide. Loss of $1H_2O$ requires 0·0299 g. The specially dry material so obtained melted at 84—86°).

2 : 4-*Dibromo*-5-*aminophenyl* o-*Amino*-p-*toluenesulphonate*.—The corresponding dinitro-compound was added with shaking to a hot solution of stannous chloride (1·5 times the calculated quantity) in a mixture of glacial acetic acid and concentrated hydrochloric acid. After the mixture had been heated at 100° for a few minutes, vigorous reduction set in, and was allowed to become complete during an hour at 100°. The resulting solution was poured into excess of 20% potassium hydroxide solution, and the suspension was cooled and filtered (asbestos). The washed and dried precipitate crystallised from dilute acetone in colourless leaflets, m. p. 174—175° (Found : Br, 37·5. $C_{13}H_{12}O_3N_2Br_2S$ requires Br, 36·7%).

2 : 4 : 5-*Tribromophenyl* o-*Bromo*-p-*toluenesulphonate*.—The diamino-compound was diazotised at 20—25°, in a mixture of equal parts of concentrated hydrochloric acid and water, with a solution of sodium nitrite. The diazo-perbromide was precipitated by means of a solution of bromine in aqueous potassium bromide, collected, washed, and decomposed in glacial acetic acid, the temperature of the latter being slowly raised until the b. p. was reached. Water was added, and the precipitate crystallised from alcohol, colourless leaflets, m. p. 107—108°, being obtained (Found : Br, 56·9. $C_{13}H_8O_3Br_4S$ requires Br, 56·7%).

2 : 4 : 5-*Tribromophenol*.—(*a*) A solution of the preceding compound in excess of piperidine was boiled under reflux for an hour; the solution was then strongly acidified and submitted to steam distillation. The tribromophenol passed over rapidly, and crystallised from light petroleum (b. p. 40—60°) in long colourless needles, m. p. 85—86° (Found : Br, 73·0. $C_6H_3OBr_3$ requires Br, 72·5%).

(*b*) 2 : 4 : 5-Tribromoaniline, prepared for the purpose from *p*-dibromobenzene, was converted into the corresponding phenol by adapting the method of Noelting and Kopp (*loc. cit.*). The product was identical with that from process (*a*).

Kohn and Pfeifer (*Monatsh.*, 1927, **48**, 211) obtained what was

evidently mainly 2 : 4 : 5-tribromophenol, m. p. 79°, by heating pentabromophenol with zinc dust and glacial acetic acid. We failed to trace this work for some time, since in the original paper and in the British abstracts the substance was incorrectly called 3 : 4 : 6-tribromophenol.

Nitration of 2 : 4-Dibromo-2′ : 4′-dinitrodiphenyl Ether.—The ether, described by Le Fèvre, Saunders, and Turner (J., 1927, 1168), is more conveniently obtained as follows: 21 g. of 2 : 4-dibromophenol were added to 4·6 g. of potassium hydroxide previously fused with 0·5 c.c. of water. To the still hot mixture were added 17·5 g. of 1-chloro-2 : 4-dinitrobenzene. After a few minutes' shaking, potassium chloride began to separate, and after an hour's heating at 100°, interaction was complete. Excess of dilute alkali was added, and the mixture cooled and shaken. The solid mealy product was collected, washed with water, and crystallised from glacial acetic acid (23 g., m. p. 133°).

The ether was added rapidly to 10 parts of nitric acid (*d* 1·5). After 0·5 hour, the solution was poured into water. The precipitated solid was collected, washed, and crystallised from glacial acetic acid, 2 : 4-*dibromo*-5 : 2′ : 4′-*trinitrodiphenyl ether* being obtained in very pale yellow needles, m. p. 142° (Found: Br, 35·1. $C_{12}H_5O_7N_3Br_2$ requires Br, 34·9%).

Scission of 2 : 4-Dibromo-5 : 2′ : 4′-trinitrodiphenyl Ether.—(a) *With piperidine.* The trinitro-compound was heated with twice its weight of piperidine at 100° for an hour. The solution was treated with alkali and extracted several times with benzene. The benzene layer was extracted first with hydrochloric acid and then with alkali. Acidification of the alkaline solution gave 2 : 4-dibromo-5-nitrophenol, identical with the above product, and the benzene layer yielded 2 : 4-dinitrophenylpiperidine.

(b) *With aniline.* The trinitro-compound was heated for an hour at 100° with excess of aniline. On addition of much dilute hydrochloric acid, 2 : 4-dinitrodiphenylamine separated in almost quantitative yield.

Nitration of 2 : 4-Dibromophenyl Benzoate.—The benzoate was added slowly to 10 parts of nitric acid (*d* 1·5), kept below 30°. After a further 15 minutes, the solution was poured into excess of cold water. The gummy precipitate was separated, and heated with water until it became hard. It crystallised from alcohol in colourless needles, m. p. 155—156° (Found: Br, 36·2. $C_{13}H_6O_6N_2Br_2$ requires Br, 35·9%). The nitro-compound was heated for an hour at 100° with excess of piperidine. The excess of piperidine was removed by extraction with benzene in presence of alkali. The 2 : 4-dibromo-5-nitrophenol obtained, after crystallisation from

light petroleum, had m. p. 77—78°, and did not depress the m. p. of the dibromo-compound described above.

The *m*-nitrophenol used in these experiments was prepared as described in Adams's "Organic Syntheses," Vol. VIII, p. 80, but it was found advisable to remove all traces of sulphuric acid from the crude product by dissolving it in alkali and reprecipitating it with hydrochloric acid before distilling it under reduced pressure; otherwise, towards the end of the distillation, explosive decomposition set in. From 212 g. of *m*-nitroaniline, 135—140 g. of pure *m*-nitrophenol were consistently obtained.

m-*Nitrophenyl* p-*toluenesulphonate*, obtained in the usual way, separated from alcohol in prisms, m. p. 112—113° (Found: S, 10·7. $C_{13}H_{11}O_5NS$ requires S, 10·9%).

Experiments on the Dibromination of m-*Nitrophenol.*—(A) *Dry.* (1) The method described by Lindner (*loc. cit.*) led to mixtures, the examination of which proved unprofitable.

(2) A current of carbon dioxide laden with bromine vapour was passed through *m*-nitrophenol in a bath at 120—140° until the desired increase in weight had occurred. The product was worked up by Lindner's method. Precipitation of the barium-salt fraction gave a solid, m. p. 82—98°. A mixture of this with 2 : 4 : 6-tribromo-3-nitrophenol melted below 75°, and one with 4-bromo-3-nitrophenol melted at 76—135°. On the assumptions that the product, m. p. 82—98°, is approximately 50% of 4-bromo- and 50% of tribromo-3-nitrophenol, and that the mixed melting-point curve is of the simplest type, these results are explicable, as is also the bromine content of the bromination product (51·3%; a 1 : 1 mixture of mono- and tri-bromo-compounds requires Br, 53·9%).

(3) On one occasion, by Schlieper's method of monobromination, a product was obtained corresponding very closely to that just described. It had m. p. 85—95°, and Br, 51·2%.

(B) *Wet.* (1) A solution of *m*-nitrophenol (1 mol.) and bromine (2 mols.) in 90% acetic acid was left in the cold for an hour. Since bromination did not begin, the solution was heated at 100° for 0·5 hour and then boiled for 0·5 hour. The product was worked up by Lindner's method and gave no substance corresponding to his dibromo-derivative.

(2) A solution of *m*-nitrophenol (1 mol.) and anhydrous sodium acetate (2 mols.) in glacial acetic acid was treated with a solution of bromine (2 mols.) in glacial acetic acid. A number of experiments were carried out, with variation of concentrations, temperature, and time of mixing. In every case the main product was 2 : 4 : 6-tribromo-3-nitrophenol, m. p. 89—90° (Found: Br, 63·4. Calc.: Br, 63·8%).

2 : 4 : 6-*Tribromo*-3-*nitrophenyl* p-*Toluenesulphonate*.—The tribromo-compound was readily converted into the p-*toluenesulphonyl* derivative, which crystallised from alcohol in colourless needles, m. p. 146—147° (Found : Br, 45·2; S, 6·0. $C_{13}H_8O_5NBr_3S$ requires Br, 45·3; S, 6·0%).

2 : 4 : 6-*Tribromo*-3-*aminophenyl* p-*Toluenesulphonate*.—Reduction of the preceding compound was effected by West's method (J., 1925, **127**, 494). The *amino*-compound separated from alcohol or dilute acetic acid in colourless prisms, m. p. 146—147° (mixture with the nitro-compound, m. p. 120—125°) (Found : Br, 47·9. $C_{13}H_{10}O_3NBr_3S$ requires Br, 48·0%).

2 : 3 : 4 : 6-*Tetrabromophenol*.—A solution of the preceding amino-compound in concentrated sulphuric acid was diazotised at 15° with a solution of sodium nitrite in concentrated sulphuric acid (made at — 10°). When the resulting solution was poured on ice, a yellow crystalline precipitate of the diazo-compound separated. Addition of water produced a clear solution, to which was added a solution of bromine in potassium bromide until no further precipitate was obtained. The diazo-perbromide was collected, washed with water, and decomposed in hot glacial acetic acid. On cooling, a crystalline product separated, which was washed with water and then heated with excess of piperidine at 100° for 4 hours. Addition of water precipitated 2 : 3 : 4 : 6-tetrabromophenol, which soon became solid and crystallised from dilute alcohol in colourless needles, m. p. 113—114°. An identical specimen was obtained by using the Sandmeyer instead of the perbromide process (Found : Br, 76·8. Calc. : Br, 78·0%).

N-p-*Bromophenylphthalimide*.—A mixture of *p*-bromoaniline (1 mol.) with finely ground phthalic anhydride (1 mol.) was heated at 250—300° for 2 hours. The molten mass was poured into cold alcohol and the solid product was ground and extracted with a large volume of boiling alcohol. The residual solid and the long silky needles that separated from the extract both melted at 204° (Found : Br, 26·8. $C_{14}H_8O_2NBr$ requires Br, 26·5%). Yield, 88%.

Nitration of N-p-*Bromophenylphthalimide*.—The imide (1 mol.) was dissolved in 10 parts of warm concentrated sulphuric acid. To the solution, cooled in running water, 1 mol. of nitric acid (*d* 1·5), dissolved in 5 vols. of concentrated sulphuric acid, was added slowly, with stirring. After an hour, the solution was poured on ice, and the resulting gummy precipitate collected. It was heated for an hour at 130° with 90% sulphuric acid, and the resulting solution was much diluted and then basified. The product was mainly 4-bromo-2-nitroaniline, and did not contain more than 20% of 4-bromo-3-nitroaniline (fractional crystallisation of the mixed sulphates).

Nitration of *p*-bromoaniline in excess of sulphuric acid as described by Noelting and Collin (*loc. cit.*) gave 4-bromo-3-nitroaniline in good yield, but an attempt to effect replacement of the amino-group by hydroxyl by the diazo-method proved unsuccessful.

Mononitration of ON-*Diacetyl*-p-*aminophenol.*—Hähle (*loc. cit.*) recommends nitration at 0° with fuming nitric acid. We have found that the best results are obtained when 50 g. of the diacetyl compound are added gradually to 75 c.c. of nitric acid (*d* 1·5) kept at about 5°. (Only partial nitration occurs at temperatures just below 0°, and the diacetyl compound may be recovered unchanged from its solution in a mixture of equal volumes of acids of *d* 1·5 and *d* 1·42, kept at 0° to — 5°.) The solution is poured on ice, and the precipitate obtained is crystallised from alcohol.

4-*Bromo*-3-*nitrophenol.*—*ON*-Diacetyl-3-nitro-4-aminophenol was slowly added to 10 times its weight of boiling hydrobromic acid (*d* 1·49). Boiling was continued for ¼ hour and the suspension of 3-nitro-4-aminophenol hydrobromide was then diluted and diazotised: diazotisation was slow. The excess of nitrous acid was removed by addition of urea and the solution obtained was poured into a suspension of copper powder in 25% hydrobromic acid. The copper slowly dissolved and needles separated. These crystallised from water in brown needles, m. p. 146·5—147·5°, and from dilute hydrochloric acid in yellow needles having the same m. p.

4-Chloro-3-nitrophenol was obtained in a precisely similar manner from diacetyl-3-nitro-4-aminophenol. The diazotisation proceeded more easily than with the bromo-compound. The product crystallised from dilute hydrochloric acid in yellow needles, m. p. 127—128°.

3-Bromo-2-nitrophenol was prepared by Hodgson and Moore's method (J., 1926, 157). In the intermediate sulphonation we obtained good results with 20% oleum, but with acid of the composition (27% oleum) used by Hodgson and Moore, our sulphonation mixture set almost solid and would not dissolve even in a large quantity of concentrated sulphuric acid.

3-*Bromo*-2-*nitrophenyl* p-*toluenesulphonate*, readily obtained in the usual way, crystallised from alcohol, in which it was very sparingly soluble, in colourless rectangular plates, m. p. 136·5—137·5° (Found: Br, 21·4. $C_{13}H_{10}O_5NBrS$ requires Br, 21·5%).

3-*Bromo*-2-*aminophenyl* p-*Toluenesulphonate.*—The preceding nitro-compound was reduced with a mixture of 2 parts of crystalline stannous chloride, 2 parts of concentrated hydrochloric acid, and 7 parts of glacial acetic acid at 100°. Much alkali was added and the suspension produced was extracted with ether. Evaporation of the dried ethereal extract, followed by crystallisation from alcohol,

gave colourless needles of the *amino*-compound, m. p. 120—121° (Found : Br, 23·6. $C_{13}H_{12}O_3NBrS$ requires Br, 23·4%).

2 : 3-*Dibromophenol.*—The amino-compound was diazotised in concentrated sulphuric acid at 15—20°, with a solution of sodium nitrite in concentrated sulphuric acid prepared at — 10°. The reaction mixture was poured on ice. A small portion was found to couple normally with alkaline β-naphthol, and the main portion was added to cuprous bromide–hydrobromic acid. The resulting solution was heated on a boiling water-bath under reflux for ¾ hour and then distilled in steam. The white solid that passed over was dried over concentrated sulphuric acid (desiccator) and crystallised from light petroleum (b. p. 40—60°). The 2 : 3-*dibromophenol* obtained formed stout prisms, m. p. 68—69° (Found : Br, 63·6. $C_6H_4OBr_2$ requires Br, 63·6%). It is much less soluble in light petroleum than 2 : 3-dichlorophenol and is very much less volatile.

Monobromination of Wet m-*Nitrophenol.*—(a) When a dilute solution of bromine (1 mol.) was added to a cold dilute solution of *m*-nitrophenol (1 mol.) and anhydrous sodium acetate (1 mol.) in glacial acetic acid, a mixture of substances was formed, the examination of which led to no positive results.

(b) A solution of 20 g. of *m*-nitrophenol and 8·8 c.c. of bromine in 30 c.c. of glacial acetic acid was gently boiled under reflux for 2 hours; it then became almost colourless. The solvent was evaporated on a boiling water-bath and the residue, which became crystalline on cooling, was dissolved in dilute aqueous alkali. Addition of acid precipitated an almost colourless solid which, after being crystallised from dilute hydrochloric acid, melted at 117—120°, and after a further crystallisation from light petroleum (b. p. 80—100°), at 118·5—121° (Found : Br, 36·4. $C_6H_4O_3NBr$ requires Br, 36·7%). The following experiments show that this substance is 2-*bromo*-5-*nitrophenol.*

2-*Bromo*-5-*nitrophenyl* p-*toluenesulphonate* was formed in good yield by the usual process; it crystallised from alcohol in colourless plates, m. p. 131·5—132·5° (Found : Br, 21·6. $C_{13}H_{10}O_5NBrS$ requires Br, 21·5%).

2-*Bromo*-5-*aminophenyl* p-*toluenesulphonate*, obtained by the reduction of the nitro-compound with stannous chloride, hydrochloric acid, and acetic acid, crystallised from alcohol in colourless bunches of prisms, m. p. 135—136° (Found : Br, 23·3. $C_{13}H_{12}O_3NBrS$ requires Br, 23·4%).

2 : 5-*Dibromophenol.* (*a*) The last-named amino-compound was diazotised in concentrated sulphuric acid exactly as described under the preparation of 2 : 3-dibromophenol. The steam-distilled 2 : 5-*dibromophenol* was dried over concentrated sulphuric acid

(desiccator) and then crystallised from light petroleum (b. p. 40—60°); it formed prismatic needles, m. p. 73—74° (Found: Br, 63·4. $C_6H_4OBr_2$ requires Br, 63·6%). It was readily converted into 2 : 5-*dibromophenyl* p-*toluenesulphonate*, which separated from alcohol in colourless prisms, m. p. 109—110° (Found: Br, 39·7. $C_{13}H_{10}O_3Br_2S$ requires Br, 39·4%).

(*b*) 2 : 5-Dibromoaniline (44 g.), obtained in good yield by reducing 2 : 5-dibromonitrobenzene by West's method, was dissolved in 150 c.c. of warm concentrated sulphuric acid. The solution was cooled to room temperature and treated with a solution of 13 g. of sodium nitrite in 150 c.c. of concentrated sulphuric acid (prepared at — 10°). After an hour, 150 c.c. of water were added and the resulting solution, after addition of purified sand, was heated under reflux over a small flame for 2 hours. (A small portion of the diluted diazo-solution coupled readily with alkaline β-naphthol.) The whole was then distilled in steam, 37 g. of 2 : 5-dibromophenol, containing a trace of 2 : 5-dibromoaniline, passing over. The phenol was freed from the base by solution in alkali and filtration and then recovered by acidification; it had m. p. 73—74°, b. p. 256—257° (corr.)/755 mm. The *p*-toluenesulphonyl derivative melted at 109—110°.

Mixtures of the phenols or of their *p*-toluenesulphonyl derivatives obtained by methods (*a*) and (*b*) had the same m. p. as those of the single substances.

Monobromination of Dry m-*Nitrophenol.*—(1) A current of dry carbon dioxide was passed through bromine and then through 10·5 g. of *m*-nitrophenol heated at 120—140°. When the calculated increase of weight had occurred, the product was freed from the excess of bromine by a rapid current of carbon dioxide and at once dissolved in excess of dilute sodium hydroxide solution. After addition of dilute hydrochloric acid, yellow needles of 4-bromo-3-nitrophenol separated for some time, and later, an oil made its appearance. At this stage the liquid was filtered and the solid was crystallised from dilute hydrochloric acid, 7 g. of the 4-bromo-compound, m. p. 146·5—147·5°, being obtained.

(2) *m*-Nitrophenol (28 g.) was brominated, the weight being allowed to increase to 43 g. When the product was worked up as before, 22 g. of pure 4-bromo-3-nitrophenol were obtained.

The products from both experiments did not depress the m. p. of 4-bromo-3-nitrophenol prepared from diacetyl-*p*-aminophenol.

Attempted Monobromination of 4-*Bromo*-3-*nitrophenol.*—When the monobromo-compound (1 mol.), dissolved together with 1 mol. of anhydrous sodium acetate in glacial acetic acid, was treated with 1 mol. of bromine dissolved in the same solvent, a mixture was obtained containing unchanged 4-bromo-3-nitrophenol.

Attempted Monobromination of 2-Bromo-5-nitrophenol.—This appeared to proceed readily. The acetic acid was evaporated, and the hard solid obtained (on cooling) crystallised from light petroleum (b. p. 80—100°). The product had the appearance of an individual substance, but melted at 68—108°.

Monochlorination of m-*Nitrophenol.*—Chlorine was passed into *m*-nitrophenol (42 g.) at 120—140° until the weight increased by 9·5 g. A rapid current of carbon dioxide was passed through the molten product until the excess of chlorine had disappeared and the whole was then dissolved in dilute alkali solution. Dilute hydrochloric acid was added until no further evident precipitation occurred and the yellow needles produced were washed and dried (14 g.). After crystallisation from dilute hydrochloric acid, 12 g. of pure 4-chloro-3-nitrophenol, m. p. 127—128°, were obtained. The mother-liquor from the first filtration was strongly acidified, and filtered after some time: the yellow precipitate obtained, having been washed and dried, weighed 16 g. and after crystallisation from dilute hydrochloric acid gave 10 g. of 2-chloro-3-nitrophenol, m. p. 120° (Found: Cl, 19·6. Calc.: Cl, 20·0%). The mother-liquor from the second precipitation was evaporated to a small bulk under reduced pressure and then extracted with ether. Evaporation of the extract gave 12·5 g. of an oily mixture of chloro-compounds. The total yield of crude chloro-compounds was 85% of the theoretical yield.

The 4-chloro-3-nitrophenol obtained produced no depression of the m. p. of the material prepared from *ON*-diacetyl-*m*-nitro-*p*-aminophenol.

The 2-chloro-3-nitrophenol was reduced with iron, hydrochloric acid, and alcohol, and the filtered solution evaporated to dryness. Diazotisation, followed by addition of copper powder and hydrochloric acid, gave 2 : 3-dichlorophenol, m. p. 56—57°: this depressed the m. p. of 2 : 5-dichlorophenol (m. p. 57°). 2 : 3-Dichlorophenol is extraordinarily volatile, and vacuum desiccation over sulphuric acid and phosphoric oxide was accompanied by considerable loss. This property and the intense odour of the compound appear to differentiate this dichlorophenol from its isomerides (compare Holleman, *Rec. trav. chim.*, 1917, **37**, 96), and the volatility accounts for the poor analytical figure obtained (Found in air-dried specimen: Cl, 41·7. Calc.: Cl, 43·6%).

Some of the preliminary work on the dibromodinitrodiphenyl ether was carried out by Miss G. I. Sharp, B.Sc.

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PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.