

The research herein described was carried
out under the supervision of Professor I.M. Heilbron ,
D.S.O., D.Sc. etc. to whose guidance and never
failing interest the successful prosecution of the
work is largely due.

A T H E S I S.

In fulfilment of the requirements of the
Degree of Doctor in Philosophy of the
UNIVERSITY OF LIVERPOOL

THE REACTIVITY OF CONJUGATED UNSATURATED KETONES.

By

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At the University of Liverpool , 1921-1923.

C O N T E N T S

| | Page |
|---|------|
| 1. Nomenclature | 1 |
| 2. General Introduction | 2 |
| 3. Part I - Addition of cyan-acetic ester to 4'-dimethylamino-2-hydroxydistyryl ketone | 4 |
| 4. Part II - Condensation of acetoacetic ester with 4'-dimethylamino-2-hydroxydistyryl ketone and its methyl ether. | 16 |
| 5. Part III - Condensation of acetoacetic ester with certain substituted distyryl and styryl methyl ketones. | 60 |
| 6. Appendix <u>I</u> Experimental | 74 |
| 7. Appendix <u>II</u> Attempted preparation of certain aminoaldehydes and the corresponding distyryl ketones. | 88 |
| 8. Bibliography. | 98 |

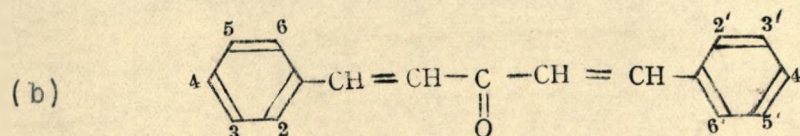
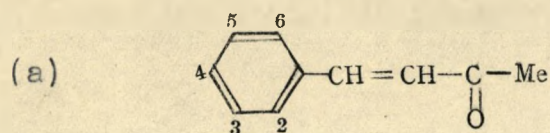
NOMENCLATURE.

In the following thesis, KETONES are designated as derivatives of

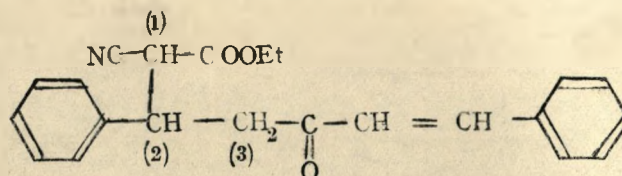
(a) Styryl methyl ketone (benzylidene acetone)

(b) Distyryl ketone (dibenzylidene acetone)

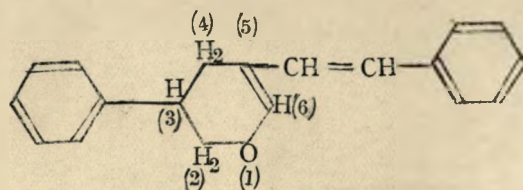
the positions being indicated as follows:-



Cyan-acetic ester additive products of distyryl ketones are indicated as shown, the central carbon atom of the cyan-acetic ester residue being numbered one, whilst the positions in the benzene rings are designated by the usual prefixes ortho, meta, para:-



Cyclohexenones derived from styryl methyl and distyryl ketones are named on the system of Borsche (Ann. 1910, 375, 145-180).



GENERAL INTRODUCTION.

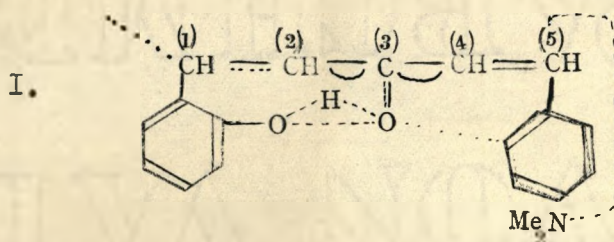
The research herein described is conveniently divided into several distinct parts, each having a bearing on the general theme of the reactivity of unsaturated ketones. In its wider aspects this subject has been examined by a number of investigators from the point of view of halochromy, reactivity of the carbonyl group and additivity, whilst Borsche (Ann.1910, 375, 145.) put forward some very suggestive hypotheses to account for the reactivity in general. In the particular case of 4'-dimethylamino-2-hydroxydistyryl ketone, (Heilbron and Buck J.S.C. (T). 1921., 1500,), the pronounced effect of the substituent groups causes very extraordinary reactivity. In order to account for this, these authors postulate the free affinity to be situated at a particular carbon atom. The fundamental importance of their conclusions was so great that the present author undertook an investigation of the additive compounds of this ketone with ethyl cyanacetate and ethyl acetoacetate as a means of verifying their theoretical considerations. Whereas the additive product obtained with cyan-acetic ester, Part I completely proved their contentions the acetoacetic ester compound, Part II, introduced certain anomalies. In the latter instance the inference is drawn that the addition of ethyl acetoacetate to 4'-dimethylamino-2-hydroxydistyryl ketone follows a different course to that of

ethyl cyan-acetate, and it is contended that the reason for this marked difference lies in the fact that ethyl acetoacetate has a profound effect on the configuration of unsaturated ketones. On general grounds this is by no means unlikely when one takes into consideration the possibility of geometric isomers of the ketone, and the peculiar activity of the ester. Although, as yet, these contentions have not been definitely proved, sufficient results have been obtained indicating that they are in the main, correct. 2-hydroxystyryl methyl ketone, for example being definitely changed by acetoacetic ester. With the object of obtaining a clearer understanding of the course of acetoacetic ester addition to ketones containing orthohydroxyl, orthomethoxyl and paradimethylamino groups, the series of condensation products prepared from these substances were studied - Part III. Two types of compounds are possible (a cyclohexenone or a pyrane derivative) in the case of orthohydroxy conjugated unsaturated ketones, and it is proposed to investigate this question further.

REACTIVITY OF CONJUGATED UNSATURATED KETONES.

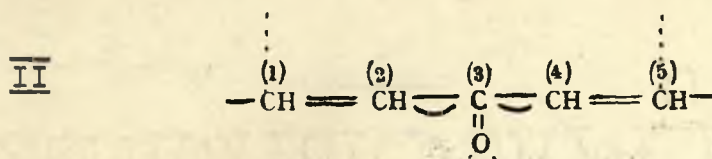
Part I. Addition of Cyan-acetic ester to 4'-dimethylamino-2-hydroxydistyryl ketone.

It was observed by Heilbron and Buck (J.C.S. (T), 1921, 1500) that 4'-dimethylamino-2-hydroxydistyryl ketone exhibited an extraordinary reactivity in the sense that it formed additive compounds with very great ease. In order to account for this striking reactivity these authors made the strong assumption that the free affinity of this ketone is concentrated at C (1), (Formula I).



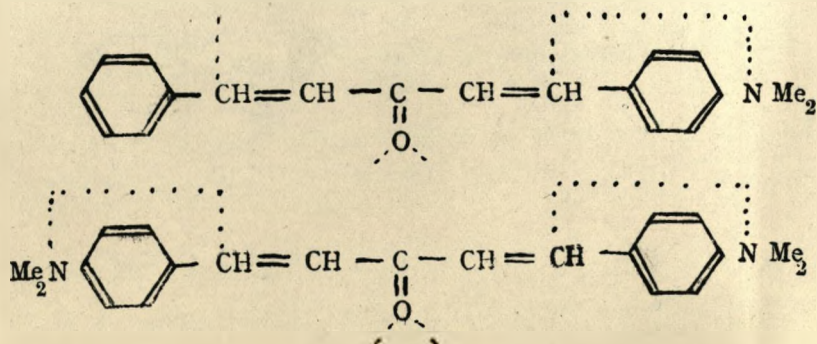
The fundamental importance of their theoretical considerations was so great that a definite experimental proof of the position of this free affinity was desirable. An investigation was undertaken with this object in view, and this section deals with an account of the method by which the aim was attained. Before entering into a detailed description of the investigation, a short review of the evidence brought forward by Heilbron and Buck, in support of their contentions, is given.

In the first place Borsche (Annalen 1910, 375, 145) was led to conclusions which account for the varied degree of activity of certain distyryl ketones by the action on these substances of compounds possessing a reactive methylene group. He observed that, whereas distyryl ketone reacts readily with acetoacetic ester, diethylmalonate and acetyl acetone, 4-dimethylaminodistyryl ketone reacts with difficulty, whilst 4-4'-tetramethyldiamino-distyryl ketone is quite unreactive under the same conditions. Basing his views on the Thiele conception of residual affinity he concludes that the reactivity of the distyryl ketone is due to the large amount of the unsaturated affinity on both the oxygen atom and on the two terminal carbon atoms



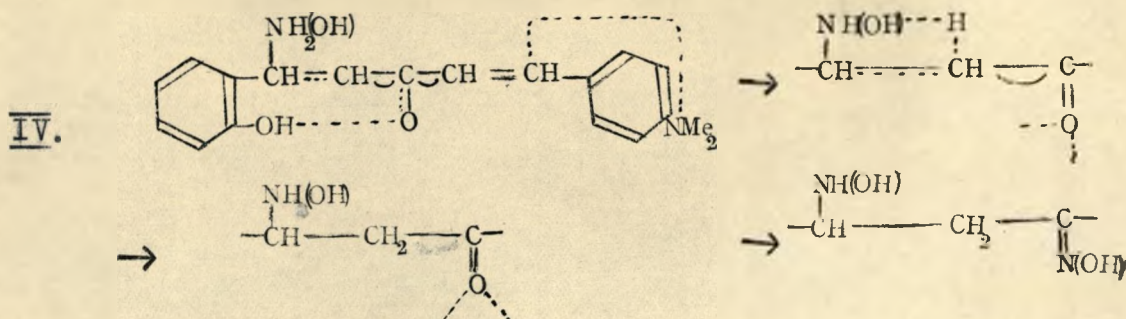
The reduced reactivity of 4-dimethylaminodistyryl ketone is accounted for by assuming neutralisation of the excess affinity at C (5), (II) by the residual valency of the para-dimethylamino grouping; whilst the reactivity of the symmetrical ketone is explained by a similar valency saturation process.

III



In the case of 4'-dimethylamino-2-hydroxydistyryl one portion of the system may therefore be considered to be in equilibrium and consequently the enhanced activity of the ketone must be primarily due to the presence of a hydroxyl group in the ortho position. That the increased reactivity is directly due to the hydroxyl group is shown by the much diminished reactivity of its methyl ether. By utilising Pfeiffer's theory of halochromy (Ann. 1910, 376, 285; 1911, 383, 92), which states that the more the residual affinity of the carbonyl oxygen is neutralised the more pronounced becomes the unsaturation on the carbon atom of this group, in conjunction with Borsche's (loc. cit.) conclusion, a complete ring system involving the hydroxyl group and the carbonyl oxygen atom is postulated (Formula I.). As a consequence of such valency distribution there results a large amount of free affinity at C (1) . Moreover, strong evidence is adduced in favour of their ideas from the behaviour of hydroxylamine, semicarbazide and phenylhydrazine with 4'-dimethylamino-2-hydroxydistyryl ketone. It was found that no simple oxime, semicarbazone or phenylhydrazone could be prepared but definite additive compounds of these derivatives were isolated; firstly, a labile hydroxylamine additive product, secondly a definite oximino derivative and finally an oximino-oxime were prepared. In order to account for the existence of these three products it was assumed that the reaction took place in three

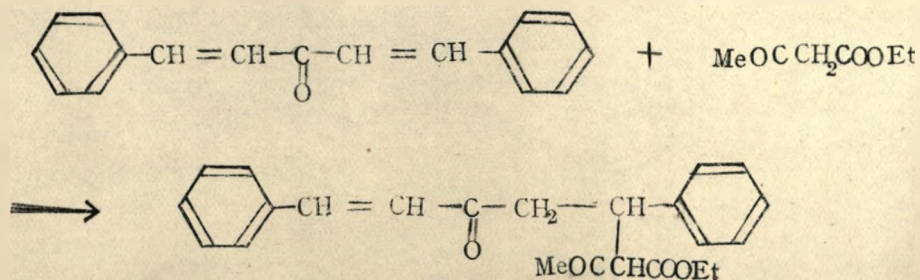
successive stages as indicated (Formula (IV)).



It is thus evident that before the carbonyl group can function as such, it is essential for the free affinity of the ketone to be saturated and finally for the labile ring system to be broken.

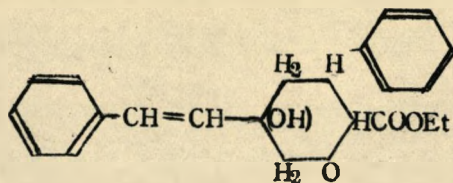
Nevertheless in spite of these observations made by Heilbron and Buck it was necessary to bring forward more positive proof. To this end a stable additive product was sought whose constitution could be elucidated.

Knoevenagel and his collaborators (Ber. 1902, 35, 395) have previously shown that acetoacetic ester first adds on to ketones containing the system $c:c \cdot co \cdot c : c$ under the influence of secondary amines in the following manner:-

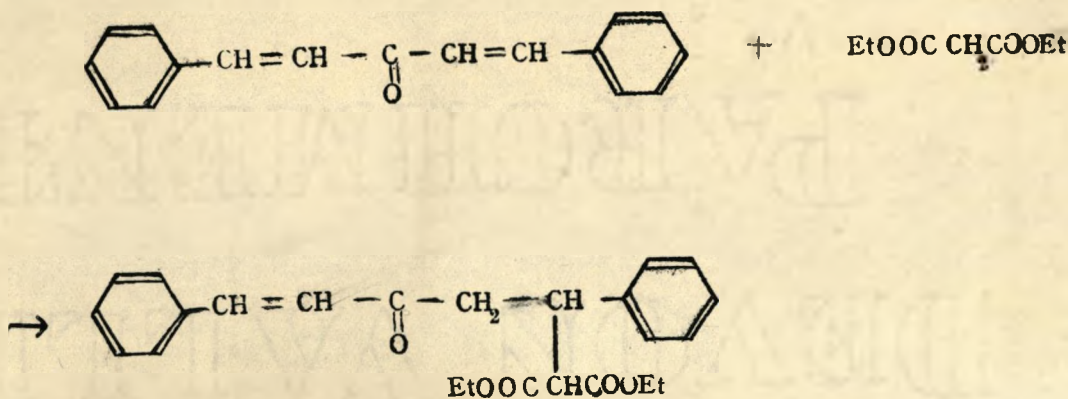


This latter compound may also exist in the form of a

cyclohexanone



It has also been demonstrated that distyryl ketones will react with diethylmalonate under the influence of piperidine to give 2-phenyl-3-cinnamoyl propane-1,1-dicarboxyl diethylester (Borsche Annalen, 1910, 375, 145).

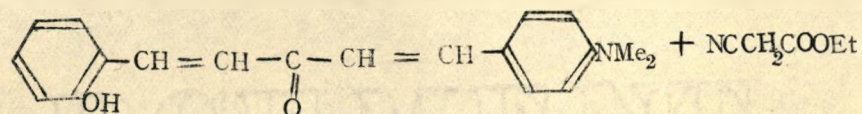


Similar types of additive products were sought between these substances containing a reactive methylene group and 4'-dimethylamino-2-hydroxydistyryl ketone since it was considered that addition would take place at either C(1.) or C(5.), (Formula I), depending on which carbon atom possessed the greater amount of free affinity. By this means a stable additive product would

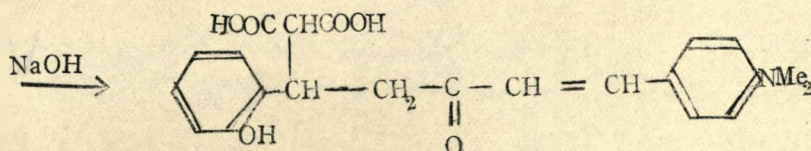
be obtained whose constitution it was hoped to elucidate. In consequence of the unusual reactivity of 4'-dimethylamino-2-hydroxydistyryl ketone it was expected that addition would take place with very great ease even in the absence of secondary amines. However, such was not the case, indeed the solvent free ketone was obtained on crystallisation from cyan-acetic or acetoacetic ester. Repeated attempts were made under various conditions in the presence of amines, but in all cases the free unchanged starting product was isolated. The author succeeded in condensing both cyanacetic ester and acetoacetic ester with the ketone under the influence of fairly strong alkali; but whilst the constitution of the cyan-acetic ester additive product was definitely established that of the acetoacetic ester product introduced certain anomalies which latter will be fully dealt with in Part II.

By the action of cyan-acetic ester on 4'-dimethyl-amino-2-hydroxydistyryl ketone in alcoholic solution under the influence of 50 per cent. caustic soda solution

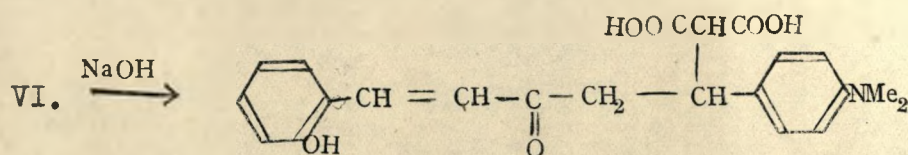
a compound was obtained which after recrystallisation from nitrobenzene melted sharply at 220° C. and possessed the empirical formula $C_{22}H_{23}O_6N$. The substance was completely soluble in sodium carbonate solution and in sodium hydroxide solution whilst a green solution was obtained with dilute acids. Commencing on a priori reasoning it will be observed that the addition of one molecule of cyan-acetic ester to 4'-dimethylamino-2-hydroxydistyryl ketone could give rise to two distinct products as represented below.



V.



2-orthohydroxyphenyl-3-paradimethylaminocinnamoyl-1-1-dicarboxy propane.



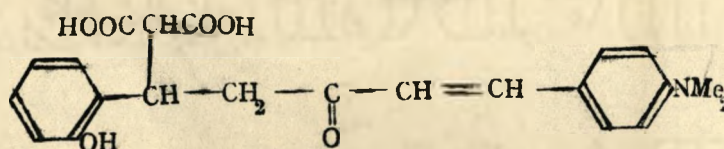
2-paradimethylaminophenyl-3-orthoxycinnamoyl-1-1-dicarboxy propane.

By splitting the molecule at the styryl double bond and identifying the fission products it would definitely be decided which formula was the correct representation of fact. Should formula V be in accordance with fact then paradimethylaminobenzaldehyde or acid should be present amongst the fission products; whereas if formula VI represented the truth then salicylic aldehyde or salicylic acid should be found in the decomposition mixture. Many attempts were made to effect this splitting and finally by means of a powerful alkaline hydrolysis paradimethylaminobenzaldehyde was isolated and identified by means of its phenylhydrazone. The residue was carefully examined but no definite chemical compound could be obtained. It is clearly evident therefore, that the compound M.P. 220° C. is represented by formula V since under the conditions of decomposition it is impossible to obtain paradimethylaminobenzaldehyde from such a substance depicted by formula VI. From this deduction it necessarily follows that addition has taken place at C(1), (Formula I.) at which point, therefore, the excess valency of 4'-dimethylamino-2-hydroxydistyryl ketone must be situated, and consequently the theoretical considerations of Heilbron and Buck are completely substantiated by experiment.

EXPERIMENTAL.

In the first place crystallisation of 4'-dimethylamino-2-hydroxydistyryl ketone from cyan-acetic ester gave the free ketone whilst in the presence of piperidine and diethylamine no addition resulted. By using 10 per cent and 20 per cent sodium hydroxide solution evidences of addition were observed, but the products obtained resisted all attempts to crystallise them. Under the influence of 50 per cent sodium hydroxide a definite additive compound was isolated.

2-ortho-hydroxyphenyl-3-paradimethylaminocinnamoyl-1-1-dicarboxyl-propane. $C_{22} H_{23} O_6 N.$



The following rather vigorous method gave the most satisfactory yield of the above compound. 8.2 grams of 4'-dimethylamino-2-hydroxydistyryl ketone (chloroform additive compound) were dissolved in 25 c.c. alcohol and 8 c.c. cyan-acetic ester. To the clear hot solution 8 c.c. 50 per cent sodium hydroxide were added when the reaction mixture turned deep red. Ammonia was evolved and a small amount of inorganic substance was deposited but after 16 hours the reaction was complete, and the solution

possessed a dull orange colour. The condensation mixture was filtered from tarry matter and inorganic material and the liquors diluted to two litres with water. When the clear orange red solution was neutralised with dilute acetic acid a light brown precipitate was deposited. The latter was filtered off and dried, but for a considerable period the product resisted all attempts to crystallise it owing probably to its heterogeneous nature. Finally by heating the mixture with sodium carbonate solution filtering and reprecipitating with dilute acetic acid a brown substance was obtained, which was eventually crystallised from benzene, in which it is only very slightly soluble. On heating the product with strong sodium hydroxide solution, ammonia was evolved. Examination of the crystals under the microscope indicated that two distinct types were present. By two recrystallisations from nitrobenzene a compound M.P. 220° C. empirical formula $C_{22}H_{23}O_6N$, was isolated in the form of orange glittering needles. A clear orange coloured solution was obtained with sodium carbonate solution, whilst heating with sodium hydroxide caused no evolution of ammonia. Acids dissolved the compound with formation of a green solution.

For analysis the specimen was recrystallised three times from nitrobenzene and refluxed for half an hour with benzene before drying in the exsiccator,

0.2084 gave 0.5069 CO_2 and 0.1084 H_2O $C = 66.3$; $H = 5.8$.

$C_{22}H_{23}O_6N$ requires $C = 66.5$, $H = 5.8$.

For the purpose of elucidating the structure of the compound M.P. 220° C. many oxidation experiments were carried out in order to split the product at the styryl double bond. No definite substances could be isolated by this process, but a strong alkaline hydrolysis proved efficacious.

Decomposition of 2-orthoxyphenyl-3-paradimethylamino-cinnamoyl-1-1-dicarboxyl-propane.

Eight grams of the ^{crude}cyanoacetic ester product after one recrystallisation from nitrobenzene were dissolved in 20 c.c. of 10 per cent caustic soda solution. The resulting red solution was slowly run on to 50 c.c. of boiling 70 per cent caustic potash solution contained in a distillation flask. A few minutes after the addition steam accompanied by ammonia passed over into the receiver. Pale greenish coloured crystals commenced to separate from the distillate as the reaction proceeded, and after half an hour water alone collected. The crystalline substance amounting to 0.7 grams was filtered off and the liquor extracted with ether. The solid melted at 66°C . and its admixture with an authentic specimen of paradimethylaminobenzaldehyde melted at 68°C . The phenylhydrazone prepared in alcohol, after recrystallisation melted at 148°C . whilst a mixed melting point with a prepared specimen of the phenylhydrazone of paradimethylamino

benzaldehyde (M.P. $148^{\circ}\text{C}.$) showed no depression.

The ether extract of the distillate gave traces of the amino aldehyde. The residue left in the flask was lixiviated with water and extracted with ether when alkaline, neutral, and acid, but in no case could a definite chemical compound be isolated.

FAIR CHAMBERN

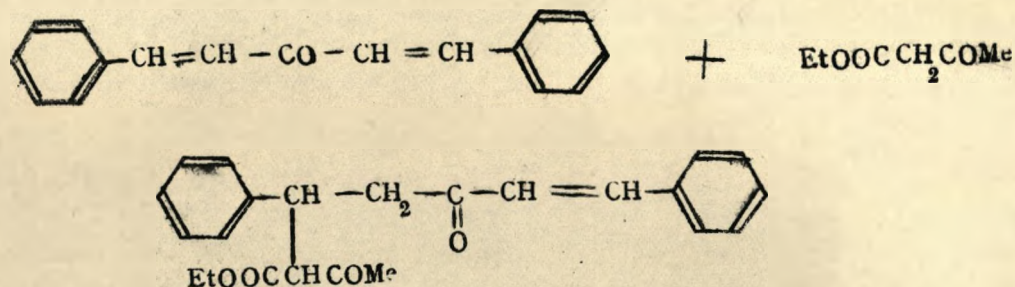
DEWON VALLEY

REACTIVITY OF CONJUGATED UNSATURATED KETONES.

Part II. Condensation of Acetoacetic ester with
4'-dimethylamino-2-hydroxydistyryl ketone and
its Methyl Ether.

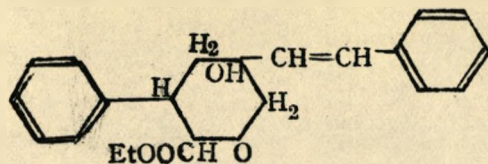
In the previous section a brief reference was made to the condensation of acetoacetic ester with 4'-dimethylamino-2-hydroxydistyryl ketone, and it was during the course of subsequent work on the elucidation of the structure of this condensation product as well as its methyl ether that the anomalies mentioned in Part II, arose.

Earlier workers, Knoevenagel and his collaborators (*loc.cit.*) have demonstrated that addition of acetoacetic ester to ketones containing a doubly conjugated system follows the course indicated by the formulæ.

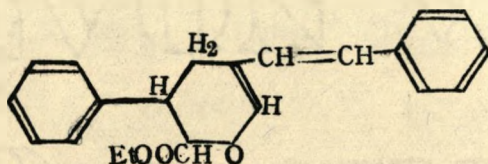


Rabe and Elsze (*Annalen* 323, 83.) conclusively demonstrated that such additive products can exist in a ring form due to the migration of one hydrogen atom of the end methyl group of the acetoacetic ester residue on to the

carbonyl oxygen atom of the unsaturated ketone.



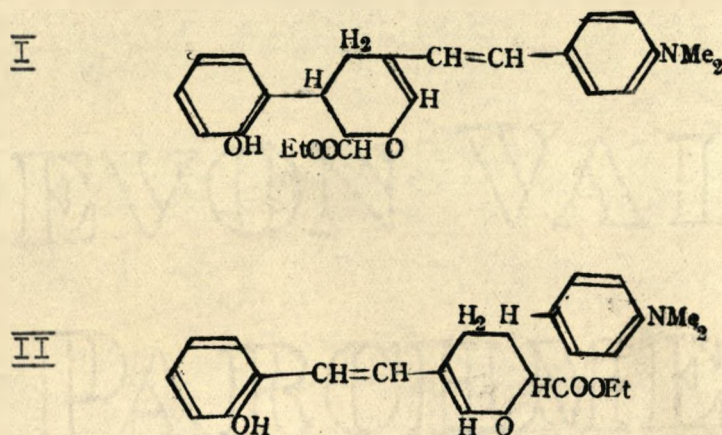
The later work of Borsche (Annalen, 1910, 375, 145.) confirmed these facts. In addition by prolonged treatment with piperidine or moderate treatment with other "water splittings" agents he prepared the corresponding cyclohexenone.



In the same significant paper Borsche proves the formation of the cyclohexenone derivative by direct condensation of acetoacetic ester with distyryl ketone under the influence of 10 per cent sodium hydroxide solution or sodium ethylate.

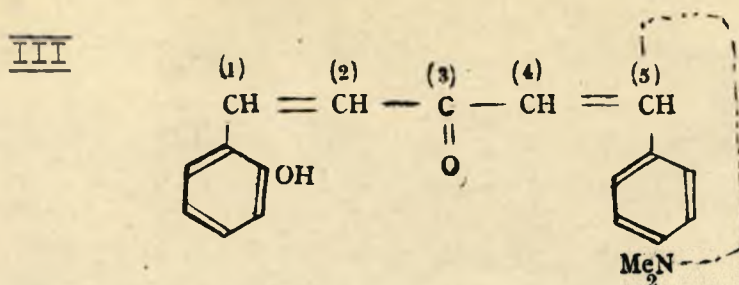
The present author endeavoured to prepare a similar series of compounds from acetoacetic ester and 4'-dimethylamino-2-hydroxydistyryl ketone using the same conditions. In spite of the reactive nature of the ketone more drastic treatment was necessary. In the presence of 20 per cent potassium hydroxide solution a definite condensation product was isolated which melted at 199°C. and possessed the empirical formula $C_{25}H_{27}O_4N$. This latter indicates that one molecule of water had been lost between one molecule of each of the starting materials. It is a

noteworthy fact that the compound M.P.199°C. still retains a certain amount of the additive power of 4'-dimethylamino-2-hydroxydistyryl ketone in the sense that it crystallises with one molecule of the solvents alcohol and benzene. It is evident that either one or other of the two possible formulae I and II represents the constitution of the cyclohexenone derivative M.P.199°C.

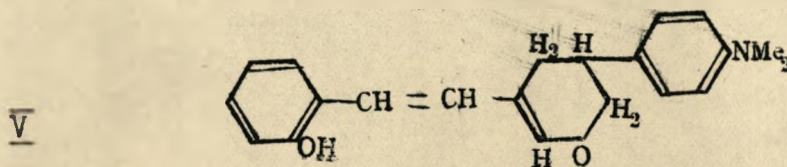
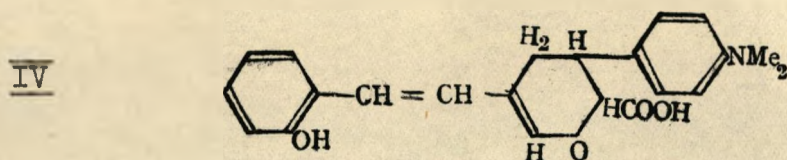


By utilising Heilbron's and Buck's (loc.cit.) theoretical conclusions together with their experimental verification in Part I, it would appear that if acetoacetic ester behaves in an analogous manner to cyan-acetic ester towards 4'-dimethylamino-2-hydroxydistyryl ketone, formula I represents the constitution of the compound $C_{25}H_{27}O_4N$. Consequently by fission at the styryl double bond para-dimethylaminobenzaldehyde or acid should result as one of the decomposition products. No such substances were isolated, and in view of subsequent work it would appear that addition takes place at C(5) (Formula III) and not C(4) in the case of

acetoacetic ester.



That is in acetoacetic ester solution 4'dimethyl-amino-2-hydroxydistyryl ketone exists in a different structural form from that present in cyan-acetic ester solution and this results in the activation of C (5) and not C (1). The general trend of the following work indicates that such is the case, and therefore formula II represents the substance M.P.199°C. By saponification, this cyclohexenone derivative was converted to an acid M.P. 225°C (IV), whilst further treatment with sulphuric acid split off carbon dioxide giving a compound M.P. 233°C, (V), These two compounds were tentatively formulated as follows:-



Before entering into a theoretical discussion in order to account for the anomalous behaviour of 4'-dimethyl-amino-2-hydroxydistyryl ketone in acetoacetic ester solution, a general description will be given of the experimental facts which suggested that there was a marked difference in structural form of the ketone in acetoacetic ester, and cyan-acetic ester solution.

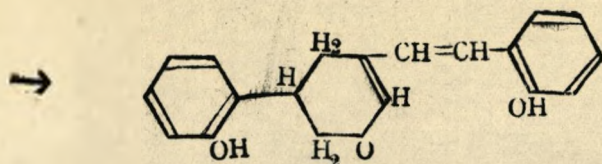
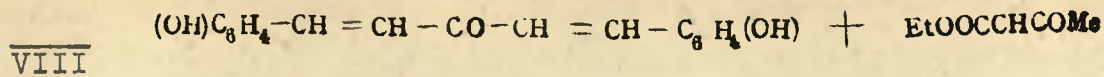
In the first place by condensation of acetoacetic ester with the methyl ether of 4'-dimethylamino-2-hydroxydistyryl ketone using similar conditions to those attaining in the case of the hydroxy ketone, a substance M.P. 114°C . possessing an empirical formula $\text{C}_{26}\text{H}_{29}\text{O}_4\text{N}$ was obtained, and was evidently formed from one molecule of each starting material by loss of a molecule of water. When the condensation was repeated at higher temperature, two compounds were isolated and partially separated by fractional crystallisation from carbon bisulphide. One component was identical with the above methyl ether M.P. 114°C ., whilst the second melted at 162°C . The subsequent work indicated that two methyl ethers corresponding to I and II had evidently been generated. In order to ascertain which methyl ether corresponded to the hydroxy cyclohexenone M.P. 199°C . the latter was methylated. By carrying out the methylation in acetone solution and using methyl sulphate a crystalline compound M.P. 164°C . empirical formula $\text{C}_{26}\text{H}_{29}\text{O}_4\text{N}$ was isolated and found to be identical with

latter compound with concentrated sulphuric acid gave none of the red colouration characteristic of cyclohexenones. The foregoing experimental work shows clearly that the two methyl ethers corresponding to formulæ I and II have been prepared, so that experiments were undertaken to prepare the hydroxy isomer of the compound M.P. 199°C. In the first place 4'-dimethylamino-2-hydroxy-distyryl ketone (designated the "parent ketone") was acetylated (Heilbron and Buck, J.C.S.(T), 1921, 1500) by means of acetic anhydride. It was considered that the acetyl derivative would condense with acetoacetic ester giving a compound which would possess a constitution similar in all respects to that of the methyl ether M.P. 114°C. Subsequent de-acetylation of the condensation product would then yield a compound isomeric with the cyclohexenone M.P. 199°C. since the latter when methylated gives a methyl ether M.P. 164°C. Such experiments that were carried out indicate that the acetyl group of the parent ketone is very labile and consequently the conditions required for condensation results in the loss of the acetyl group, and then condensation of the original hydroxy ketone with acetoacetic ester to produce the compound M.P. 199°C.

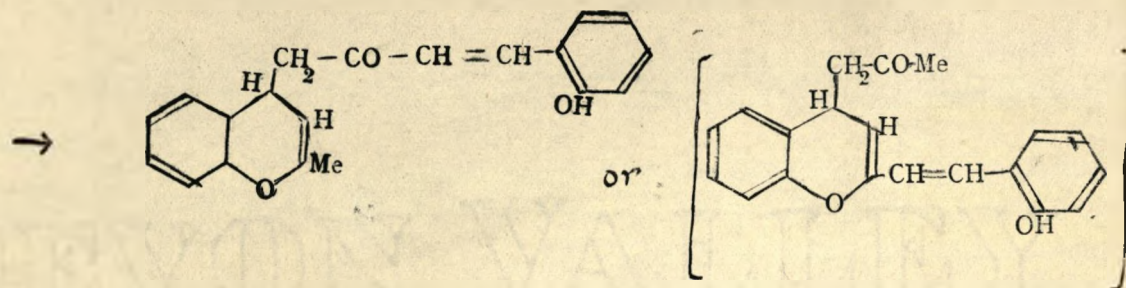
With a view to obtaining a clearer understanding of the effects of paradimethylamino and orthohydroxyl groups on the ability of doubly conjugated ketones to condense with acetoacetic ester, experiments were undertaken to condense 4-4'-tetramethyldiaminodistyryl ketone (Sachs and Lewin Ber.1902, 35, 3576) and 2-2'-dihydroxydistyryl ketone (Decker and Felsler, Ber. 1908, 41, 2997) with acetoacetic ester. When mild catalytic agents such as secondary amines and dilute alkalies were used unchanged ketones

were isolated in both cases, which fact confirms the work of Borsche (loc. cit.) who failed to detect any addition of acetoacetic ester to 4-4'-tetramethyldiaminodistyryl ketone under such conditions. Under the influence of hot 50 per cent sodium hydroxide solution acetoacetic ester condenses with the symmetrical diamino ketone. The compound produced M.P. 174.5°C. possessed an empirical formula $C_{27} H_{32} O_3 N_2$ and consisted of one molecule of ester combined with one molecule of ketone by the loss of a molecule of water. The isolation of this cyclohexenone derivative indicates that the presence of the two paradimethylamino groups does not inhibit condensation altogether but addition seems to be largely a matter of conditions. It is evident, therefore, that acetoacetic ester can attach itself to C (5) III, in the case of 4'-dimethylamino-2-hydroxy-distyryl ketone. The dihydroxy ketone condenses with acetoacetic ester in the presence of 50 per cent sodium hydroxide solution to give a product M.P. 240°C. empirical formula $C_{20} H_{18} O_3$. In the formation of this latter substance a molecule of water and a carboethoxy group had been lost between one molecule of each of the genitors. Two alternative explanations are possible to account for this loss; either a cyclohexenone derivative is produced or condensation has taken place with the formation of a peculiarly substituted pyrane derivative. Whether the end methyl group of the acetoacetic residue condenses with the carbonyl oxygen atom of the ketone to form a cyclohexenone VIII; or whether condensation occurs between the orthohydroxyl group and the carbonyl oxygen of the ester to produce a pyrane derivative IX; the fact remains that during the process a carboethoxyl group has been split off. The whole question

is considered in greater detail in Part III



IX



It is to be inferred, therefore, that if acetoacetic ester had attached itself to C (1) III in the case of the parent ketone, condensation would have resulted in the formation of a product (whether a cyclohexenone or a pyrane) in which a carboethoxyl group had been lost.

Although it was definitely shown that cyan-acetic ester (Part 1) attaches itself to C (1) III, it appears as a result of the foregoing conclusions that acetoacetic ester is indeed attached to C (5), and consequently formula II is assigned to the compound M.P. 199°C . In the medium of cyan-acetic ester the excess affinity of 4'-dimethylamino-2-hydroxydistyryl ketone is concentrated at C (1) whilst it appears that in acetoacetic ester solution the free affinity is situated at C (5). The question therefore arises

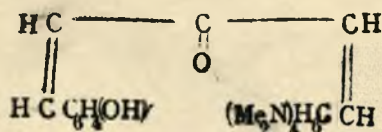
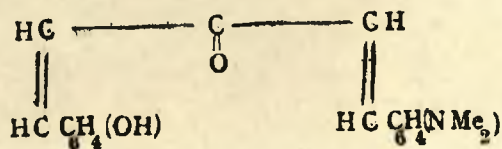
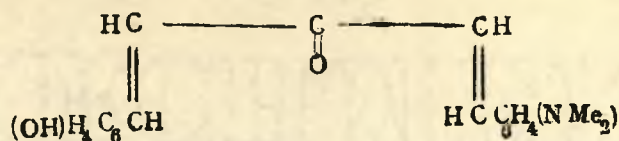
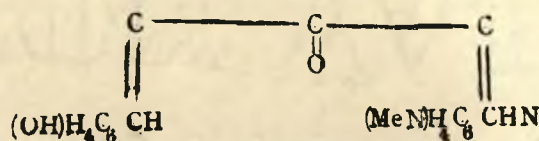
as to whether 4'-dimethylamino-2-hydroxydistyryl ketone exists in the presence of these two esters in the same structural form.

That 4'-dimethylamino-2-hydroxydistyryl ketone may exist in different forms was observed by Heilbron and Buck (J.C. S.(T), 1921, 1500) and the following is an extract from the original paper.

"The free ketone which is most readily obtained by heating the alcohol additive product at 100°C is a dull crimson crystalline powder. Other coloured varieties have been isolated, but the differences in colour are not especially strongly marked and all possess a red streak. That however, the forms are not altogether identical is shown by the fact that, whilst the brilliant scarlet variety obtained from ethyl aceto-acetate readily combines in alcohol solution with p-dimethylamino-benzaldehyde the red black modification obtained from ethyl acetate - heptane is unreactive. It must, therefore, be concluded that the free ketone exists in different phases and that these retain their special configuration, at least temporarily even in solution".

The present author considers these coloured varieties and differences of reactivity of certain specimens of the ketone may be explained by a consideration of the

space formulæ of 4'-dimethylamino-2-hydroxydistyryl ketone.

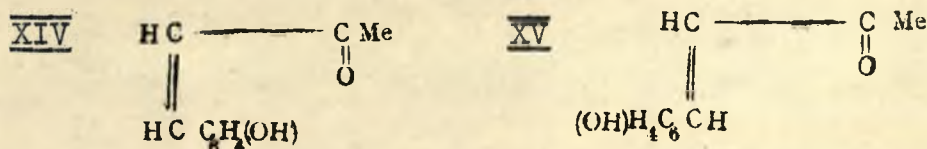
XXIXIIXIII

Although no isomer exhibiting a different melting point has been isolated the writer considers that the explanation indicated above would account for the differences in colour as well as reactivity of the parent ketone. It will be observed that in formulæ X and XI, complex ring formation between the orthohydroxyl group

and the carbonyl oxygen atom could readily take place; whilst in XII and XIII there is no likelihood of such ring formation. It would therefore appear that the considerations of Heilbron and Buck (loc. cit) do not cover the whole of the possibilities. Should the ketone possess a structure indicated by XII or XIII then addition could take place at either C.(1) of C.(5) (Formula III), since the orthohydroxyl group can then have no undue influence on the valency distributions throughout the system. These points are rendered much clearer by a consideration of the model structure.

That acetoacetic ester itself has some profound effect on hydroxy unsaturated ketones is borne out by the following experimental facts. If the ordinary yellow varieties of (a) 2-hydroxystyryl methyl ketone (Harries, Ber. 1891, 24, 3180), (b) 3-methoxy -4-hydroxystyryl methyl ketone (Centr, 1908, (2), 1102), (c) 3-4-methylenedioxy styryl methyl ketone (Haber, Ber. 1891, 24, 618), be recrystallised from pure acetoacetic ester the respective white modifications are obtained in each case. The same white modification of (a) was isolated by Heilbron and Buck (J.C.S. (T), 1922, 1095) by a totally different method; whilst the white form of (c) is mentioned by Haber (loc. cit.). The yellow hydroxystyryl ketones

and their corresponding white forms exhibit marked differences in properties towards alkalies and acids. It will be observed that in this series also there is the possibility of the existence of geometric isomers as indicated below, where the 2-hydroxystyryl methyl ketone is taken as an example.



The whole question of cis - and trans - isomerism in the styryl methyl series is being studied by another investigator in the same laboratories and so far it is generally thought that the white modification corresponds to the trans formula XV.

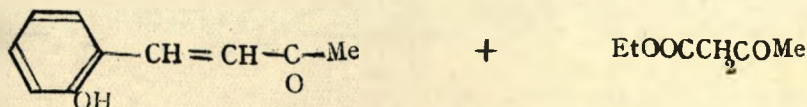
It is abundantly clear from the foregoing theoretical considerations together with the experimental facts that it is not only possible for 4'-dimethylamine-2-hydroxystyryl ketone to exist in various forms, but also the acetoacetic ester appears to possess the peculiar power of effecting some change in the configuration of unsaturated ketones. On the other hand when the yellow modifications of the styryl

methyl ketones are crystallised from cyan-acetic ester the ketones still retain their yellow appearance. As a consequence of these observations it is not possible to assume that the parent ketone is present in acetoacetic ester solution in the same structural form as in cyanacetic ester solution. Moreover molecular weight determinations and spectrographic evidence indicate that the variety of 4'-dimethylamino-2-hydroxydistyryl from acetoacetic ester is highly polymerised. By taking these deductions in conjunction with the experimental facts in respect to the condensation of acetoacetic ester with the methyl ether of the parent ketone, 4-4', tetramethyl-diminodistyryl ketone and 2-2' dihydroxydistyryl ketone, the conclusion is drawn that the ester is linked to C (5) III, and therefore formula II represents the cyclohexenone derivative M.P. 199°C.

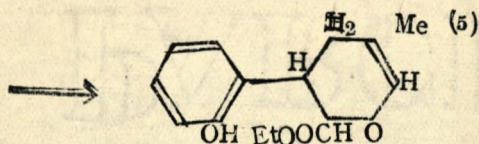
In order to verify this inference endeavours were made to prove definitely the constitution of the compound M.P. 199°C or of the methyl ethers M.P.'s 114, 164°C, by means of a degradation process. Notwithstanding the use of several oxidising agents under various conditions no definite chemical compounds could be isolated. It would appear that, the dimethylamino and hydroxyl groups together with the cyclohexenone ring introduce serious complications, and the directing influence of these groupings would probably account for the fact that only unidentifiable oils were obtained. As a result of

the failure of this method it was considered possible to synthesise one or both the compounds represented by I and II or alternatively one of the two methyl ethers. With this object in view three schemes suggest themselves.

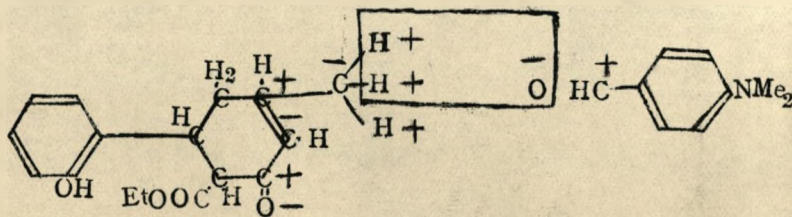
(a) By the condensation of acetoacetic ester with 2 - hydroxystyryl methyl ketone a compound represented by XVI was sought.



XVI

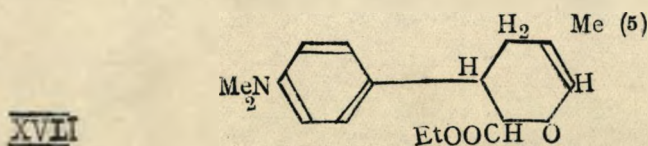


On general theoretical grounds the (5) methyl group should be reactive towards aldehydes owing to the influence of the carbonyl group and the proximity of the double linking.



When paradimethylaminobenzaldehyde is used the resulting compound would have the constitution represented by formula I. By condensing acetoacetic ester with styryl methyl ketone the unsubstituted cyclohexenone derivative corresponding to XVI was prepared (Vorländer Ber. 1894. 27, 2053); 1899 32,335,432) The identical substance depicted by XVI could not be produced but a body was isolated from the condensation of acetoacetic ester with 2-hydroxystyryl methyl ketone, consisting of one molecule of each starting substance combined by loss of water and a carboethoxyl group. As in the case of 2-2'-dihydroxydistyryl ketone two possible compounds may be formed - namely - a cyclohexenone and a pyrane derivative. In view of this fact the alternative syntheses were prosecuted.

(b) In order to attack the problem from the point of view indicated by formula II a substance possessing the constitution below was sought.

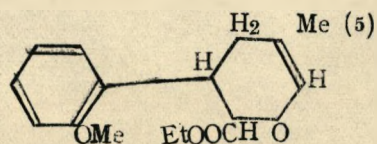


On similar grounds to those stated in (a) the (5) - methyl group should react with salicyl-aldehyde, under suitable conditions, to produce a compound represented by II

Under the influence of alkali acetoacetic ester adds on to 4'-dimethylaminostyryl methyl ketone to give a product melting point 149°C , empirical formula $\text{C}_{18}\text{H}_{25}\text{O}_4\text{N}$. This substance under further treatment with alkali loses a molecule of water and gives the cyclohexenone derivative XVII. Repeated experiments were carried out on the subsequent condensation of this compound with salicylaldehyde and orthomethoxybenzaldehyde but without success.

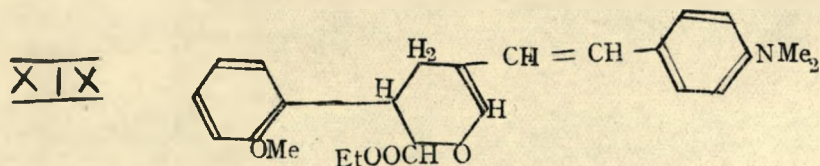
(c) Better prospects of success in attaining the desired object were held out by the synthesis of the methyl ether of the hydroxy cyclohexenone indicated by formula I. The 2-Methoxystyryl methyl ketone (Heilbron and Buck, loc. cit.) was readily condensed with acetoacetic ester. The product which was isolated possessed a M.P. 139°C and the empirical formula $\text{C}_{17}\text{H}_{20}\text{O}_4$ and was represented by the only possible constitution shown by formula XVIII

XVIII



On the aforementioned reasoning the (5)-methyl group should condense with paradimethylaminobenzaldehyde

to give a substance whose constitution would be depicted by XIX. It would be observed that such a compound is identical with one or other of the methyl ethers M.P.'s 114 and 164°C.



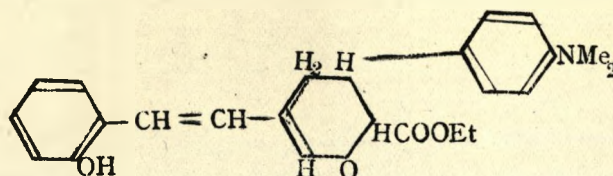
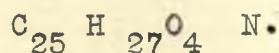
A number of condensing agents were used in attempts to effect this latter reaction but without success; yet certain signs are given that sodamide might bring about the desired result.

Although the inferential evidence brought forward strongly indicates that the compound M.P. 199°C. possesses the constitution shown by II, the successful prosecution of the synthesis (C) would definitely verify this conclusion and at the same time support the theoretical deductions described herein.

EXPERIMENTAL

It has been generally observed during the experimental work that the difficulties of isolation of the products obtained by condensing the hydroxy ketones with acetoacetic ester have been much greater than those in the case of the non-hydroxy compounds.

3-orthohydroxystyryl-5-paradimethylaminophenyl
-1-keto-6-carboxyethylester Δ 2-(3)-cyclohexenone



When either piperidine or diethylamine were used to catalyse the addition of acetoacetic ester to 4'-dimethylamino-2-hydroxydistyryl ketone the free unchanged ketone was isolated in all cases.

4.1 grams of 4'-dimethylamino-2-hydroxydistyryl ketone (crystallised from chloroform) were dissolved in 4 c. c. acetoacetic ester and 5 c.c. alcohol, and on the addition of 3 c.c. ten per. cent. potassium hydroxide solution a deep red solution resulted.

After heating for one hour on the water bath a small precipitate amounting to 0.5 grams (A) was filtered off. The hot filtrate, diluted with 50 c.c. eighty per. cent. alcohol ~~which~~ on standing deposited yellow prisms M.P. 190° C. After two recrystallisations the product amounting to 1.6 grams, melted at 199° C.

A more satisfactory yield of this substance was obtained when the condensation was carried out in the cold in the following manner.

4.1 grams of the ketone (crystallised from chloroform) were dissolved in 20 c.c. absolute alcohol and 8 c.c. of acetoacetic ester, and to the cold solution 3 c.c. of twenty per. cent. potassium hydroxide were added. After two hours at the room temperature the condensation mixture was inoculated with a crystal of the compound M.P. 199° C. At the end of twenty four hours an orange yellow mass collected. The crystalline product, M.P. 196° C, weighing 2 grams, was filtered off and recrystallised from absolute alcohol from which solvent it is deposited in orange yellow prisms. The substance crystallises in thick yellow prisms from benzene, but in all other neutral solvents it is sparingly soluble. The ketone crystallises with one molecule of solvent from which it can be freed by heating in the steam oven. When dissolved in concentrated sulphuric acid a deep red solution

characteristic of cyclohexenones of this type, is given; whilst hydrochloric acid produces a green solution. Numerous attempts were made to prepare a semi-carbazide, hydroxylamine or phenylhydrazine derivative, but although evidences were given that such had been formed no crystalline specimen could be isolated. For analysis each specimen of the cyclohexenone was crystallised four times from the particular solvent.

ALCOHOL.

0.2107 gave 0.5564 CO₂ and 0.1408 H₂O. C = 72.0, H = 7.4
 0.621 " 16.4 c.c. N₂ at 19°C, and 740 m.m. N = 3.1.
 C₂₅H₂₇O₄N & C₂H₆O requires C = 71.9, H = 7.3, N = 3.1.

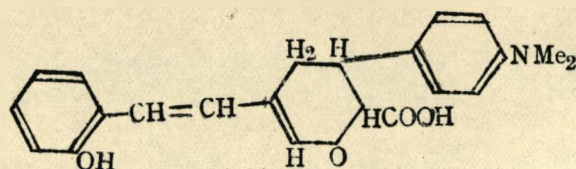
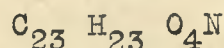
This specimen was weighed and heated for two days in the steam oven and then analysed.

1.2058 lost 0.1247. Loss = 10.3%
 Calculated loss C₂₅H₂₇O₄N & C₂H₆O = 10.2%
 0.2184 gave 0.5926 CO₂ and 0.1310 H₂O C = 73.9, H = 6.7
 0.6005 " 16.5 c.c. N₂ at 19° C and 736.5 m.m. N = 3.1
 C₂₅H₂₇O₄N requires C = 74.1, H = 6.7, N = 3.4.

BENZENE.

0.1975 gave 0.5559 CO₂ and 0.1230 H₂O, C = 76.8, H = 6.9.
 0.6010 " 16 c.c. N₂ at 19°C and 737 m.m. N = 2.9.
 C₂₅H₂₇O₄N & C₆H₆ requires. C = 77.0, H = 6.9, N = 2.9

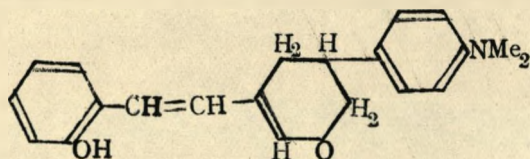
3-orthohydroxystyryl-5-paradimethylaminophenyl
-1-keto-6-Carboxy. $\Delta^2(3)$.cyclohexenone.



For the saponification of the ester M.P. $199^{\circ}C$.
 6 grams of the latter were heated with 25 c.c. of
 twentyfive per. cent. sodium hydroxide solution for
 three hours on the water bath. The red pasty mass
 was dissolved in water, neutralised, and the yellow
 product crystallised, when dried, from alcohol.
 The substance consisted of glistening yellow plates
 M.P. $225^{\circ}C$, The same substance was isolated from
 an oxidation attempt, in which manganic sulphate and
 dilute sulphuric acid were used. The residue (A) in
 the previous preparation when recrystallised melted
 at $223^{\circ}C$ and showed no depression when mixed with the
 above.

0.1242 gave 0.3340 CO_2 and 0.0673 H_2O . C = 73.3, H = 6.0.
 $C_{23} H_{23} O_4 N$ requires C = 73.3, H = 6.1.

3-ortho-hydroxystyryl-5-para-dimethylaminophenyl
-1-keto- Δ^2 .(3)cyclohexenone. $C_{23}H_{23}O_2N$

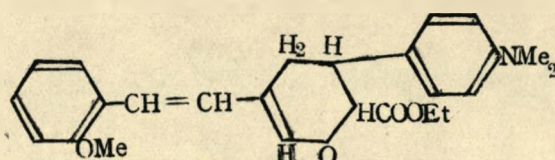
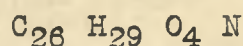


This cyclohexenone was prepared by the action of hot 40 per. cent. sodium hydroxide solution on the compound M.P. $199^{\circ}C$ but only in minute quantities. The most satisfactory method was the following. 5 grams of the compound M.P. $225^{\circ}C$. were dissolved in glacial acetic acid and then heated for one hour with 50 c.c. of twenty per. cent. sulphuric acid during which period traces of carbon dioxide were evolved. After cooling the greenish liquid was poured into ice water and neutralised with dilute caustic soda solution. The orange yellow solid was crystallised from pyridine - water but only a very small yield of the substance M.P. $231^{\circ}C$. was isolated. From methyl alcohol the substance was deposited in the form of yellow felted needles M.P. $232^{\circ}C$.

0.1783 gave 0.5161 CO_2 and 0.1102 H_2O . $C = 78.9$, $H = 6.9$

$C_{22}H_{23}O_2N$ requires $C = 79.3$, $H = 6.9$.

3-orthomethoxystyryl-5-paradimethylaminophenyl
-1-keto-6-carboxyethyl ester Δ (2.3)cyclohexenone



Direct methylation of the corresponding hydroxy body by the usual methods of methyl iodide and methyl sulphate gave only uncrystallisable products. However by carrying out the methylation in acetone solution, after the manner of Heilbron and Buck (*loc.cit*), an excellent yield of a crystalline ether was obtained.

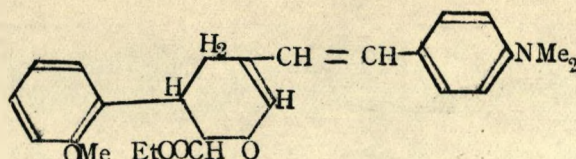
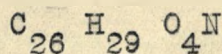
4.6 grams of the hydroxy cyclohexenone M.P. $199^{\circ}C$ were dissolved in 50 c.c. acetone and 5 c.c. twenty per cent. potassium hydroxide. To the hot solution 1.3 c.c. of methyl sulphate were gradually added over a period of half an hour and the heating continued until the red solution turned orange. Excess caustic potash was added and the heating prolonged for ten minutes. The solution, when filtered and slowly diluted with water, deposited pale yellow needles. The product, weighing 2.3. grams, was filtered off and purified by recrystallisation from high boiling ligroin, from which solvent it is deposited in beautiful lemon yellow prisms M.P. $164^{\circ}C$. The ether gave no red coloured solution with alcoholic alkali

but dissolved in concentrated sulphuric acid with the formation of a red solution.

0.2262 gave 0.6136 CO_2 and 0.1385 H_2O C = 74.4, H = 7.0

$\text{C}_{26}\text{H}_{29}\text{O}_4\text{N}$ requires C = 74.5, H = 6.9

3-methoxyphenyl-5-paradimethylaminostyryl
-1-keto-2-carboxyethyl ester Δ5(6)cyclohexenone.



A solution of three grams 4'-dimethylamino-2-methoxydistyryl ketone in 3 c.c. acetoacetic ester and 10 c.c. alcohol was treated with 3 c.c. twenty per cent potassium hydroxide solution. The reaction mixture was heated for three hours on the water bath during which period the colour changed from red to orange. On gradual dilution with water a semi-solid mass was deposited. Great difficulty was experienced before a crystalline compound could be isolated, but finally by long boiling of an alcoholic solution and the use of much blood charcoal a crystalline substance was obtained. Examination of the crystals under the microscope showed two distinct types of crystals. Careful fractionation from carbon bisulphide separate the mixture into two portions ; the main component melted at 112 °C whilst the smaller portion melted at 160°C. The latter when mixed the methyl ether prepared by the previous method melted at 162°C. The portion M. P. 112 °C when recrystallised from ether melted at

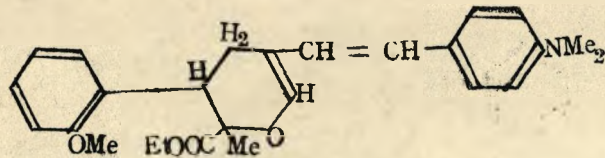
114°C, but a more satisfactory yield of this product was obtained by using the following conditions.

Six grams of 4'-dimethylamino-2-methoxydistyryl ketone were dissolved in 25 c.c. absolute alcohol together with 8 c.c. of acetoacetic ether. To the cold solution 6 c.c. of twenty per. cent. potassium hydroxide were added and the resulting red solution allowed to stand. At the end of two hours the condensation mixture was inoculated with a crystal of the compound M.P. 114°C and the reaction allowed to proceed during two days. At the end of this period 5 grams of orange needles were deposited melting at 104°C. The substance was purified by recrystallisation from ether until the melting point remained constant at 114°C. The compound was soluble in the ordinary organic solvents whilst in alcoholic alkalies an orange red solution was formed. On exposure to the air the crystals assumed an orange red appearance with simultaneous absorption of water.

0.2275 gave 0.6162 CO₂ and 0.1486 H₂O. C = 74.2, H = 7.2.

C₂₆ H₂₉ O₄N requires C = 74.5, H = 6.9.

3-orthomethoxyphenyl-5-para-dimethylamino--styryl-1-
keta-2-methyl-2-carboxyethyl ester. $\Delta^5(6)$ cyclohexenone



Endeavours were made to prepare a benzyl derivative in order to obtain a substance possessing a greater carbon content, but efforts to this end failed.

A solution of 4.2 grams of the methyl ether M.P. 114°C , in 10 c.c.'s absolute methol alcohol containing 0.23 grams sodium was heated for five minutes on the water bath. To the contents of the flask under the reflux 2.3. grams methyl iodide were slowly added during a period of one hour. The reaction mixture was heated for two hours and then filtered whilst still hot. A yellow crystalline product was deposited in small yield. The substance was purified by recrystallisation from ether from which solvent it crystallises in pale yellow needles M.P. 148°C .

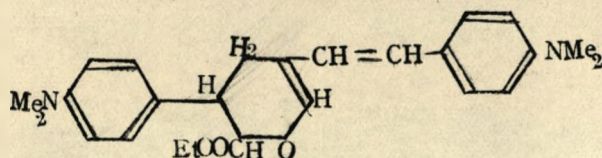
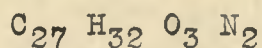
0.1749 gave 0.4753 and 0.1240 H_2O $\text{C} = 74.2, \quad \text{H} = 7.4$

$\text{C}_{27} \text{H}_{31} \text{O}_4 \text{N}$ requires $\text{C} = 74.8, \quad \text{H} = 7.2.$

Condensation of 4'-dimethylamino-2-acetoxydistyryl
ketone with acetoacetic ester.

All attempts to carry out this condensation failed. When either piperidine or diethylamine was used unchanged acetyl compound was isolated. In the presence of cold aqueous alkali or dry sodium ethylate the hydroxy cyclohexenone M.P. 199°C was obtained.

3-paradimethylaminophenyl-5-paradimethylaminostyryl
-1-keto-2-carboxyethylester- Δ 5(6)cyclohexenone.



A solution of 3.2 grams 4-4'- tetramethyldiamino-distyryl ketone (Sachs and Lewin Ber. 1902,35 2576) in 5 c.c's of acetoacetic ester and 10 c.c's alcohol was treated, whilst hot, with 1 c.c. of 50 per. cent. sodium hydroxide solution and the mixture heated for half an hour on the water bath. The red liquid was filtered from the sodium carbonate which was deposited, and when cool a mass of orange yellow needles M.P. 170°C crystallised out. The substance was purified by repeated crystallisation from absolute alcohol and finally melted at 174.5 C. An orange coloured solution was obtained with acetic acid and sulphuric acid. A phenylthylrazone M.P. 239°C, was prepared in acetic acid from which solvent it crystallised by adding a few drops of ether.

| | | | | | | | | |
|---|----------|--------------------------|-----|-------------------------|-----|--------|-----|-----------------|
| 0.2427 | gave | 0.6659 CO ₂ | and | 0.1638 H ₂ O | C = | 74.84, | H = | 7.5 |
| 0.2000 | " | 0.5497 CO ₂ | " | 0.1371 H ₂ O | C = | 74.96 | H = | 7.6 |
| 0.4638 | " | 26.8 c.c. N ₂ | at | 20°C and 753 m.m. | N = | 6.65 | | |
| C ₂₇ H ₃₂ O ₃ N ₂ | requires | | | | C = | 75.00 | H = | 7.41, N = 6.46. |

Condensation of 2-2'dihydroxydistyryl ketone with
acetoacetic ester $C_{20}H_{18}O_3$, VIII & IX

13.5 grams of 2-2' dihydroxydistyryl ketone (Decker and Felser, Ber. 1908, 41, 2997) were dissolved in 50 c.c's acetoacetic ester. Whilst the solution was still hot 12 c.c's of 50 per. cent sodium hydroxide (3 moles) were added with constant shaking. It is sometimes necessary at this stage to add a little water to keep the sodium salt of the distyryl ketone in solution. After one hour a sodium salt commenced to crystallise from the reaction mixture in the form of red glistening plates. These latter were filtered off, suspended in ice water and the free hydroxy body liberated by neutralisation with dilute acetic acid. The resulting pale yellow substance was crystallised from methyl alcohol, from which solvent it is obtained in pale yellow flat prisms M.P. $236^{\circ}C$. It may be mentioned that the sodium salt does not always crystallise out, but in that case great difficulty is experienced in isolating a crystalline substance from the diluted liquors after acidification. The product was repeatedly crystallised from methyl alcohol until the melting point was constant at 239 to $240^{\circ}C$. Unlike its parent ketone concentrated hydrochloric acid does not produce a red solution due to pyrylium salt formation, but concentrated sulphuric acid gives a red solution. It is not definitely known whether this substance is a cyclohexenone or a pyrane derivative

but a research is in progress with the object of proving the constitution of this compound. Much difficulty was accounted in preparing a pure specimen for analysis on account of its power to hold tenaciously to a molecule of methyl alcohol.

The analytical specimen was dried for 4 days in the exsiccator and then heated in the steam oven for one day.

- (1) 0.2170 gave 0.5945 CO_2 and 0.1281 H_2O $\text{C} = 74.7, \text{H} = 6.56$
 $\text{C}_{20}\text{H}_{18}\text{O}_3$ X CH_4O requires $\text{C} = 74.3, \text{H} = 6.5$
- (2) 0.2298 gave 0.6578 CO_2 and 0.1238 H_2O $\text{C} = 78.1 \text{ H} = 6.0$
 $\text{C}_{20}\text{H}_{18}\text{O}_3$ requires $\text{C} = 78.4 \text{ H} = 5.9.$

White modifications of certain styryl methyl ketones

(a) 2-hydroxystyryl methyl ketone

The normal yellow variety M.P. 139°C. was dissolved in acetoacetic ester and allowed to crystallise over two days. The product obtained was recrystallised from hot benzene from which solvent it crystallises in pure white prisms M.P. 139°C. No depression of the melting point was observed when mixed with the pure yellow form and also with an authentic white specimen, prepared by Heilbron and Buck's method (J.C.S.(T), 1922, 1095). The white modification gives a yellow solution with alkali, and faint pink colouration with hydrochloric acid, whereas the yellow modification gives intense red solutions in both cases.

(b) 4-hydroxy-3-methoxystyryl methyl ketone

The first specimen of white 4-hydroxy-3-methoxy-styryl ketone was obtained during an attempt to condense the yellow form with acetoacetic ester (Part 111) latterly it was prepared by recrystallisation from acetoacetic ester. The white modification melted at 129°C and showed no depression when mixed with a pure yellow specimen M.P. 129°C. The two forms gave the same striking colour differences with alkali as observed in the case of the two

specimens of 2-hydroxystyryl methyl ketone.

(c) 3-4-methylene dioxystyryl methyl ketone.

This substance, the piperonylidene acetone of Haber (Ber. 1891. 24 618) was obtained in the white form by crystallisation from acetoacetic ester.

Oxidation of -3-orthohydroxystyryl-5-paradimethylaminophenyl-1-keto-2-carboxyethylester Δ 2(3)cyclohexenone. M.P.199°C.

The following oxidising agents were used under various conditions but in all cases unchanged ester a derivative of the latter or unidentifiable oils were obtained. A detailed description of each process is not given, the products obtained only being mentioned.

- (1) 2 per. cent. potassium permanganate added to an alcoholic solution of the compound M.P.199°C, -- oils.
- (2) Alkaline permanganate-oils
- (3) Hydrogen peroxide - unchanged.
- (4) Alkaline hydrogen peroxide - oils.
- (5) Yellow mercuric oxide - unchanged.
- (6) Caro's acid - unchanged.
- (7) Chromic acid in glacial acetic acid - oils
- (8) Manganic sulphate in sulphuric acid -
- acid M.P. 225°C.

(9). Sodium perborate in sulphuric acid - unchanged

(10) Sodium hypobromite - oils.

Condensation of 2-hydroxystyryl methyl ketone with
acetoacetic ester $C_{13}H_{14}O_2$

A solution of 16 grams 2-hydroxystyryl methyl ketone in 14 c.c. acetoacetic ester and 40 c.c.'s absolute alcohol were heated for one hour with 8 c.c.'s of 50 per cent. sodium hydroxide solution. On cooling a mass of white crystals contaminated with sodium carbonate was deposited. The inorganic matter was removed with water and the residue crystallised first from alcohol then from benzene, from which solvents it is deposited in the form of pure white glistening needles M.P. $134.5^{\circ}C$. The filtrate from the condensation liquor on gradual dilution gave the same product. The total yield amounted to 10 grams. By the use of two molecules of cold sodium ethylate over a period of two days instead of hot 50 per cent alkali, a product, identical with the compound M.P. 134.5, was isolated but the yield was not especially improved. The substance was only slightly soluble in hot dilute alkali which seems to suggest that the compound is a pyrane derivative, and not a cyclohexenone. This aspect of the question is dealt with in Part III.

0.2268 gave 0.6414 CO_2 and 0.1420 H_2O $C = 77.1, H = 6.9.$

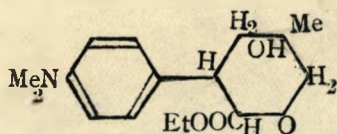
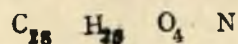
$C_{13}H_{14}O_2$ requires $C = 77.2, H = 6.9$

A phenylhydrazone of the above compound was readily formed in good yield by adding 2.2 grams of phenylhydrazine to 4 grams of the substance in 10 c.c's absolute alcohol. At the end of twelve hours a mass of white needles were deposited, which after recrystallisation from alcohol melted sharply at 200 °C.

0.3031 gave 26.0 c.c. N_2 at 21°C and 748 m.m. $N = 9.7$

$C_{19}H_{20}ON_2$ requires $N = 9.7$.

3-para-dime--thylaminophenyl-5-methyl-5-hydroxy
-1-keto-2-carboxyethylester $\Delta^5(6)$ cyclohexanone.



To a clear hot solution of 4 grams 4-dimethylaminostyryl methyl ketone (Sachs and Lewin, Ber. 1902 35, 2576) in 6 c.c.'s acetoacetic ester and 5 c.c.'s alcohol, 1c.c. of 50 per cent, sodium hydroxide was gradually added with constant shaking. A clear red solution was formed which gradually deposited a small quantity of yellow needles After 12 hours the crystalline body was filtered off dried and purified by recrystallisation from high boiling ligroin. The substance when pure consists of white needles M.P. 149 °C. The liquors were worked up but only oils and unchanged ketone was isolated. Whether the substance M.P. 149°C possesses the formula given above, or whether acetoacetic ester has just added on at the double bond has not, as yet, been definitely decided.

0.2078 gave 0.5132 CO₂ and 0.1514 H₂O C = 67.7 H = 8.1

0.6316 " 24.4 c.c. N₂ at 22.5 °C and 753 m.m. N = 4.4.

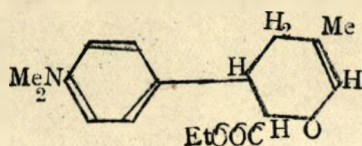
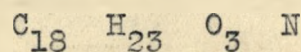
C₁₈ H₂₅ O₄ N requires C = 67.8. H = 7.9 N = 4.3

The phenylhydrazone derivative was prepared in alcohol by adding 2 grams phenylhydrazine to 4 grams of the above compound in 10 c.c.'s absolute alcohol. After standing 10 days a discoloured crystalline mass was formed, which after recrystallisation from absolute alcohol melted sharply at 179°C .

0.2771 gave 25.2 c.c. N_2 at 19°C and 748 m.m. $\text{N} = 10.3$

$\text{C}_{24}\text{H}_{31}\text{O}_3\text{N}_3$ requires $\text{N} = 10.3$

3.-paradimethylaminophenyl-5-methyl-1-keto-2- -carboxyethylester
 Δ 5(6)cyclohexenone

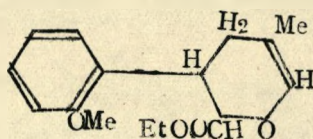
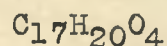


4 grams of the compound obtained in the previous preparation were dissolved in 10 c.c's alcohol and heated for an hour with 40 c.c's 10 per cent. sodium hydroxide solution on the water bath. An oily mass, weighing 2 grams, separated and on standing solidified to a dark brown solid. The substance was dissolved in methyl alcohol and refluxed for half an hour in the present of blood charcoal. The filtered solution on gradual dilution with water deposited white glistening plates M.P. $66^{\circ}C$

0.5468 gave 22.8c.c. N_2 at $18^{\circ}C$ and 746 m.m. $N = 4.8$

$C_{18}H_{23}O_3N$ requires $N = 4.65$.

A phenylhydrazone prepared in alcohol melted at $117^{\circ}C$.

3-orthomethoxyphenyl-5-methyl-1-keto-2-carboxylethylester Δ 5(6)-cyclohexenone

Nine grams of 2-methoxystyryl methyl ketone were dissolved in 50 c.c.'s absolute alcohol together with 10 c.c.'s acetoacetic ester. Whilst the solution was still hot 20 c.c.'s of 10 per cent sodium hydroxide solution (1 mole) were added in one lot. The yellow solution turned bright red and at the end of one hour yellow needles commenced to crystallise out. After 12 hours the reaction was complete. The solid was well washed with water in order to get rid of sodium acetate and carbonate and the residue, after drying, crystallised from high boiling ligroin. Yield 10 grams. After three recrystallisations from this solvent the substance was obtained in the form of pale yellow needles M.P. 139° C. The compound was very soluble in most organic solvents whilst concentrated sulphuric acid gave a brilliant red solution.

When sodium ethylate instead of 10 per cent. alkali was used in the above condensation the identical substance M.P. 139°C. was isolated but with no improvement

in the yield.

0.2136 gave 0.5562 CO_2 and 0.1309 H_2O . C = 71.0, H = 6.8.

$\text{C}_{17}\text{H}_{20}\text{O}_4$ requires C = 70.9, H = 6.9.

SYNTHESES.

The following experiments were carried out in attempts to prepare 3-orthohydroxystyryl-5-paradimethylaminophenyl-1-keto-6-carboxyethyl ester- $\Delta 2(3)$ cyclohexenone (formula 11.) by condensation of salicyl aldehyde with 3-paradimethylaminophenyl-5-methyl-1-keto-2-carboxyethyl ester $\Delta 5(6)$ -cyclohexenone (formula XVII). M.P. 66°C .

A solution of 4 grams of the cyclohexenone M.P. 66°C and 2 grams salicylaldehyde in 10 c.c. absolute alcohol were treated under various conditions with different quantities of :-

- (1) Piperidine
- (2) Ten, twenty, and fifty per cent sodium hydroxide solution.
- (3) Sodium ethylate
- (4) Dry hydrogen chloride.

Owing to the negative results obtained further methods involving the use of calcium carbide, sodamide, and phosphorous pentoxide are being investigated.

A similar series of experiments were undertaken to synthesise 3-orthomethoxyphenyl-5-paradimethylaminostyryl-1-keto-2-carboxyethyl ester $\Delta 5(6)$ cyclohexenone by the condensation of paradimethylaminobenzaldehyde with

3-orthomethoxy-phenyl-5-methyl-1-keto-2-carboxyethyl-ester

Δ 5(6)cyclohexenone (formula XVIII) M.P. 139°

At the time of writing either unchanged products or uncrystallisable tars only have been isolated, but the use of sodamide and calcium carbide hold out prospects of success.

REACTIVITY OF CONJUGATED UNSATURATED KETONES.

Part. III. Condensation of Acetoacetic ester with certain substituted Distyryl and Styryl methyl ketones.

With a view to ascertaining the relative effects of orthohydroxyl, orthomethoxyl and paradimethylamino groups on the course of acetoacetic ester condensations, it was sought to condense the ester with distyryl as well as styryl methyl ketones containing these groups. It was considered that such an investigation would greatly assist in obtaining a more definite understanding of the manner in which acetoacetic ester condenses with 4'-dimethylaminoamino-2-hydroxydistyryl ketone, and its methyl ether. In general the ester reacts with such ketones under the influence of sodium hydroxide solution or sodium ethylate to form cyclohexenone derivatives, but the added complication of the formation of a pyrane derivative is introduced in the case of the orthohydroxy ketones.

Few cyclohexenones obtained by this method are known, examples being those obtained from distyryl 4-methoxydistyryl and paradimethylamino distyryl ketones (Borsche Ann. 1910 375, 145), while the cyclohexenone derived from styryl methyl ketone (Vorländer. 1894, 27, 2053) is probably the only representative of this class. These compounds marked with an asterisk are included in the complete list on page 63.

The following (a) distyryl (b) styryl methyl ketones were selected for this work as being sufficiently representative.

- (a). 4-4'-tetramethyldiaminodistyryl ketone.
 2-2'-dihydroxydistyryl ketone.
 2-2'-dimethoxydistyryl ketone.
 2-hydroxy-2'-methoxydistyryl ketone.
- (b). 4-dimethylaminostyryl methyl ketone.
 2-hydroxystyryl methyl ketone.
 2-methoxystyryl methyl ketone.

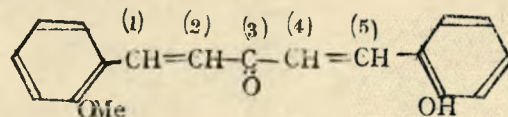
All these ketones were known with the exception of 2-2'-dimethoxydistyryl ketone which was readily prepared by direct methylation of the corresponding dihydroxy body. No general method of condensing these substances with acetoacetic ester could be found, owing to the varying solubilities in alcohol of the parent ketones, as well as to the presence, in some cases, of a hydroxyl group. For example whereas the symmetrical 2-2'-dimethoxydistyryl ketone in warm alcoholic solution, reacted with the ester under the influence of one molecule of 10 per cent sodium hydroxide solution, the sparingly soluble symmetrical 4-4'-tetramethyl diaminodistyryl ketone required heating with stronger alkali whilst the 2-2'-dihydroxy ketone only condensed in the

XII respectively; a molecule of water being eliminated in each case.

The presence of a hydroxyl group in the ortho-position introduces certain complications. In the first place 2-2'-dihydroxydistyryl ketone under the influence of 50 per cent. sodium hydroxide solution reacts with acetoacetic ester to give a substance M.P. 240°C. empirical formula $C_{20}H_{18}O_3$, corresponding to one molecule of each reactant less a molecule of water and a carbethoxyl group. This compound can be represented by two formulae - namely, a cyclohexenone XIII, or a pyrane XIV. Under similar conditions or by the use of sodium ethylate, 2-hydroxystyryl methyl ketone when condensed with acetoacetic ester can also give rise to either a cyclohexenone XV or a pyrane, XVI, both having the composition $C_{13}H_{14}O_2$. The fact that the actual compound obtained is only very slightly soluble in aqueous alkali would suggest that it is a pyrane derivative.

As would be expected from previous results 2-hydroxy-2'-methoxydistyryl ketone when condensed with acetoacetic ester gives rise to two products. One substance M.P. 159°C. $C_{24}H_{24}O_5$ was formed by loss of a molecule of water between a molecule of each starting substance. By analogy with the condensation products obtained from 2-2'-dimethoxydistyryl ketone, XI and 2-methoxystyryl methyl ketone XII, the substance M.P. 159°C. was formulated with the acetoacetic

ester attached to the carbon atom C (1) of the distyryl system.



This compound however was only isolated in very small yield, but it is hoped to ascertain whether the constitution represented by XVII is correct or otherwise. If this formula were correct methylation of the phenolic hydroxyl group would give a compound identical with that obtained from 2-2'-dimethoxydistyryl ketone XI.

The second compound which was also isolated in small quantities from the condensation mixture corresponded to the formula $C_{21}H_{20}O_3$; one molecule of ketone combining with one molecule of ester by the elimination of one molecule of water and a carbethoxyl group. There are two possibilities, a cyclohexenone XVIII and a pyrane XIX, as in the case 2-2'-dihydroxydistyryl ketone. This compound $C_{21}H_{20}O_3$, M.P. $164^{\circ}C$. was slightly soluble in alcoholic alkali which suggests the presence of a phenolic hydroxyl group and consequently the formula of a cyclohexenone XVIII would appear to represent its constitution.

General survey of the series

In the first place it was shown by Borsche (loc.cit)

that acetoacetic ester condenses with distyryl, 4-methoxydistyryl- and 4-dimethylaminodistyryl ketones to give cyclohexenone derivatives; the difficulty of condensation increasing in the order named. The research described in Part II demonstrates that whereas 4'-dimethylamino-2-hydroxydistyryl ketone forms a single cyclohexenone, its methyl ether gives rise to two isomeric cyclohexenones under the same conditions.

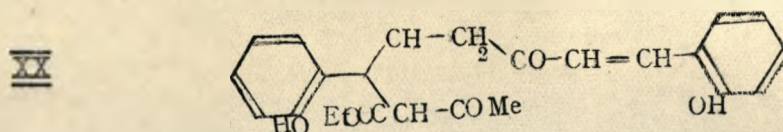
It will be observed from the foregoing discussion that distyryl as well as styryl methyl ketones containing dimethylamino groups in the para positions react with difficulty with acetoacetic ester to form cyclohexenones. The ketones possessing orthomethoxyl groups condense with acetoacetic ester under less drastic treatment, but they also give rise to cyclohexenones.

On the other hand unsaturated ketones of this type possessing hydroxyl groups in the ortho-positions introduce a serious complication, owing to the added possibility of the formation of a pyrane derivative.

A theoretical discussion of this latter problem is given in the following pages, and a scheme is put forward whereby it is hoped to prove whether the actual substances obtained are cyclohexenones or pyranes.

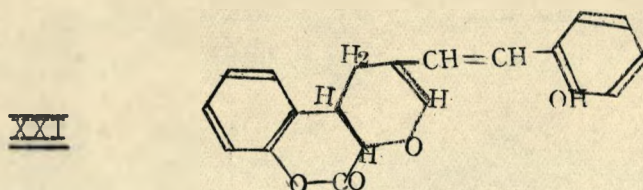
Theoretical discussion

It is a noteworthy fact that when unsaturated ketones containing an orthhydroxyl group are condensed with acetoacetic ester the resulting compounds are formed by loss of a molecule of water as well as a carboethoxyl group. With a view to obtaining a clearer understanding of the function of the hydroxyl group in this double loss, the condensation system was built up by models. 2-2'-dihydroxydistyryl ketone was taken as an example. It appears from a consideration of the model that a cyclohexenone or a pyrane derivative is produced according to the manner in which the acetoacetic ester is initially attached to the ketone, if indeed the actual process of condensation takes this course. When the ester is attached in the manner indicated by formula XX, the conditions are ideal for the production of a cyclohexenone derivative.



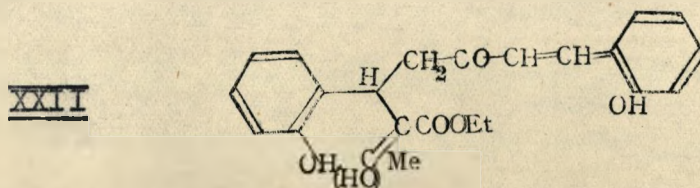
The model clearly shows that the orthhydroxyl and carboethoxyl groups lie in juxtaposition whilst the same applies to the carbonyl oxygen atom of the ketone and the terminal methyl group of the acetoacetic ester chain. The proximity of these groups would tend to the elimination of a molecule of water and also possibly to the loss of alcohol, with the formation

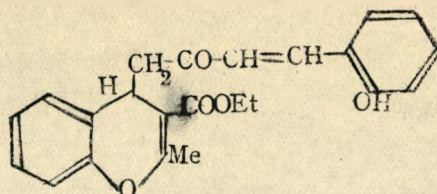
in the first place of a cyclohexenone and then a labile ring,
formula XXI



In the presence of strong alkali however, the labile ring would be easily broken and carbon dioxide lost, a cyclohexenone $C_{20}H_{18}O_3$ XIII (page, 63) being produced.

On the other hand if the acetoacetic ester first attaches itself to the ketone as depicted in XXII the conditions are eminently suitable for the production of a pyrane derivative, by the loss of water between the orthohydroxyl group, and the enolic hydroxyl group of the ester. The carbethoxyl group of the pyrane XXIII would then be hydrolysed in the presence of strong alkali giving the substance $C_{18}H_{20}O_3$, represented by formula XIV in the annexed table.



XXIII

Proposed continuation of the investigation

In order definitely to decide whether the carbethoxyl group were lost before condensation took place or during the reaction, control condensations between 2-2'-dihydroxy-distyryl ketone and acetone were attempted. Under all conditions, unchanged substances or decomposition products of the ketone were isolated. The negative results obtained in these condensations indicate that acetoacetic ester first reacts as such, the carbethoxyl group then becoming very labile, and easily split off in the presence of alkali.

As a result of the possible formation of two substances from the condensation of acetoacetic ester with orthohydroxy distyryl and styryl methyl ketones it became necessary to prove conclusively the constitutions of the actual compounds obtained.

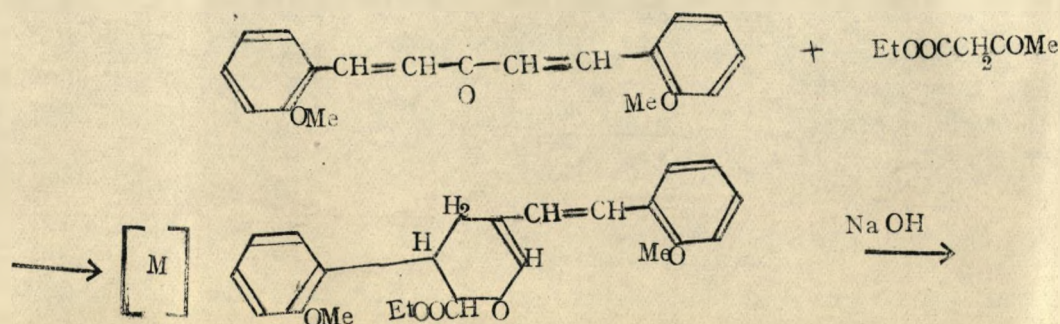
In the first place in order to ascertain the precise effect of an orthohydroxyl group in these reactions, the condensation of ketones containing a hydroxyl group in the meta or para position was undertaken. The symmetrical 5-3'-dihydroxydistyryl ketone was prepared,

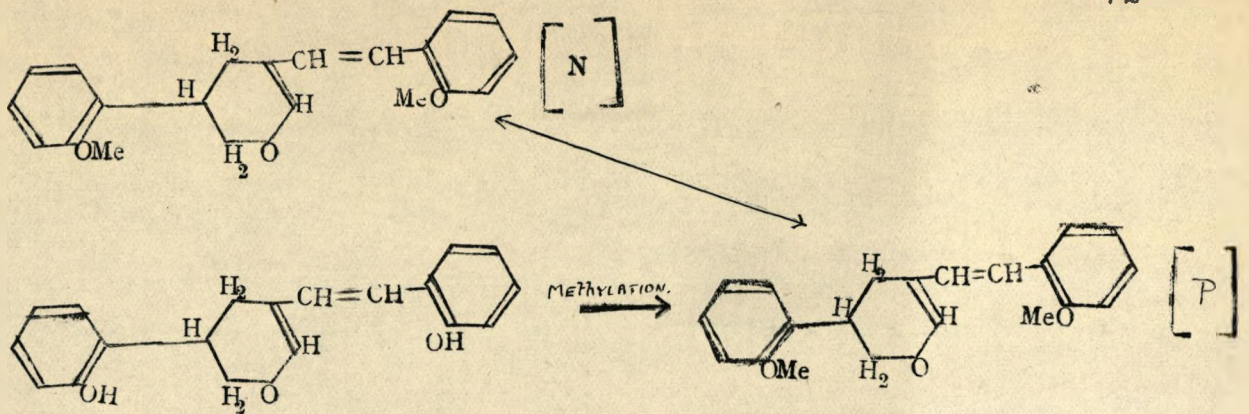
but subsequent attempts to condense this compound with acetoacetic ester resulted in the formation of amorphous products. Endeavours were also made to condense 3-methoxy-4-hydroxystyryl methyl ketone (Centr. 1908, (2) 1102), with the ester but even under the most drastic conditions the original ketone was recovered unchanged.

It will be observed that the substances obtained from ortho-methoxy ketones when condensed with acetoacetic ester can only possess the structures of cyclohexenones. If, therefore, the compounds obtained from the corresponding hydroxy bodies be methylated and the resulting compounds are found to be identical with the methoxy cyclohexenone derivatives then the hydroxy substances must be cyclohexenones and not pyranes.

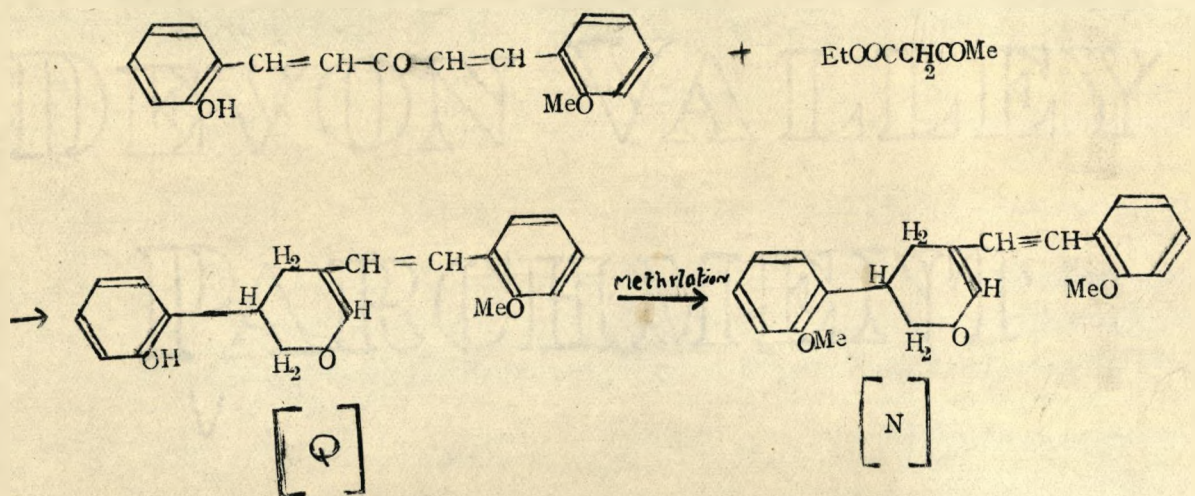
The accompanying diagrams (A), (B), (C), will render the process much clearer.

(A). It will be noted that the cyclohexenone (M) obtained from 2-2'-dimethoxydistyryl ketone possesses a carbethoxyl group but if this latter be split off the resulting compound (N), should be identical with the compound $C_{20}H_{18}O_3$ (P) if a cyclohexenone, when methylated.

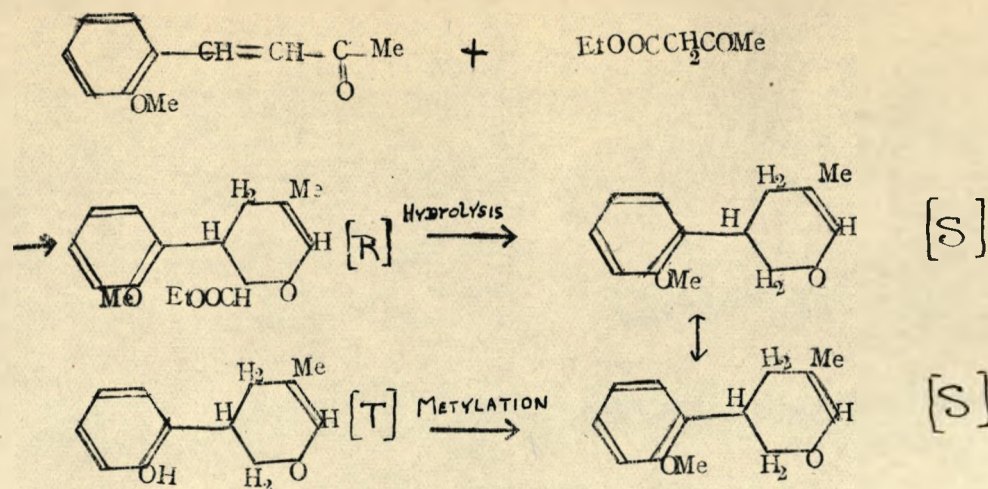




(B). Similarly, methylation of the substance $C_{21}H_{20}O_3$ (Q) obtained from 2-hydroxy-2-methoxydistyryl ketone should give the same substance (N) above.



(C). In the same manner loss of a carbethoxyl group from the cyclohexenone (R) should produce a compound (S) identical with the substance $C_{13}H_{14}O_2$ (T), if a cyclohexenone, obtained from the corresponding 2-hydroxystyryl methyl ketone when methylated.



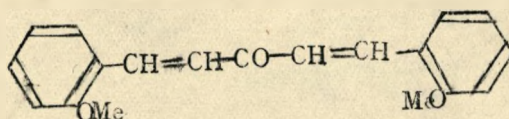
Great difficulty has been experienced in the attempt to carry out these schemes, and so far only products which resist all attempts to purify have been isolated.

Research to this end is still in progress and it is considered that the successful prosecution of the work on these lines will adequately demonstrate the course of acetoacetic ester condensations, in the case of conjugated unsaturated ketones containing a hydroxyl group in the ortho-position.

EXPERIMENTAL.

The undermentioned unsaturated ketones were condensed with acetoacetic ester as described in Part II, and consequently a description of the preparation of their condensation products is not included in this section.

- (1) 4-4'-tetramethyldiaminodistyryl ketone. (page 45.)
- (2) 2-2'-dihydroxydistyryl ketone. (page 46.)
- (3) 2-hydroxystyryl methyl ketone. (page 51.)
- (4) 4-dimethylaminostyryl methyl ketone. (page 53.)
- (5) 2-methoxystyryl methyl ketone. (page 56.)

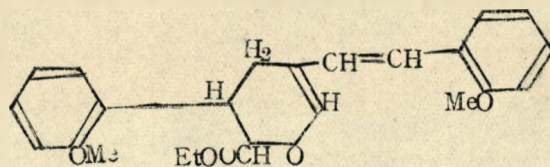
2-2'-dimethoxydistyryl ketone.

26.6 grams of 2-2'-dihydroxydistyryl ketone were dissolved in 150 c.c. 10 per cent. alkali. The hot solution was rapidly treated with 26 c.c. methyl sulphate and the solution kept at the temperature of the water bath for half an hour. The original deep red solution became orange in colour and finally yellow. An extra 10 c.c. of 10 per cent. sodium hydroxide were added and the heating continued for thirty minutes. When cool the reaction mixture was diluted to one litre with water. The yellow flocculent precipitate deposited, was crystallised from alcohol in which it is only moderately soluble. The compound consisted of beautiful yellow plates insoluble in alkali and melting sharply at 127°C . A mixed melting point determination was made with the monomethyl ether M.P. 128°C . when a depression of 20°C . was noted.

0.2077 gave 0.5903 CO_2 and 0.1166 H_2O . C = 77.5, H = 6.2

$\text{C}_{19}\text{H}_{18}\text{O}_3$ requires C = 77.55, H = 6.1.

3-orthomethoxyphenyl-5-orthomethoxystyryl-1-keto-2-carboxyethyl ester Δ 5 (6) cyclohexenone.



6 grams of 2-2'-dimethoxydistyryl ketone dissolved in a mixture of 4 C.C. acetoacetic ester and 70 c.c. alcohol was treated, whilst still hot, with 8 c.c. of 10 per cent. sodium hydroxide solution. The solution assumed a reddish appearance with simultaneous separation of a crystalline product. After two hours the crystalline mass was filtered off, dried, and recrystallised from high-boiling ligroin from which solvent it is deposited in beautiful pale yellow needles M.P. 159°C yield 7 grams. The product was practically insoluble in alcohol, very soluble in benzene and moderately soluble in hot ligroin. When the compound was dissolved in concentrated sulphuric acid a deep red solution was formed; whilst in alcoholic alkalies the substance was totally insoluble.

0.2526 gave 0.6831 CO₂ and 0.1474 H₂O. C = 73.8, H = 6.5

C₂₅H₂₆O₅ requires C = 73.9, H = 6.4.

Condensation of 2-hydroxy-2'-methoxydistyryl ketone with acetoacetic ester.

Seven grams of 2-hydroxy-2'-methoxydistyryl ketone (Heilbron and Buck, J.C.S. (T), 1922, 1095) were dissolved in 20 c.c. alcohol and 5 c.c. acetoacetic ester. To the hot solution 4 c.c. of hot 50 per cent. sodium hydroxide solution were added in one lot. After thirty minutes the deep red solution commenced to deposit a pale red solid intermingled with sodium carbonate. At the end of twelve hours the solid was filtered off, washed with a little water, and suspended in one litre of the latter.

(a). Solid.

To the turbid water suspension of the solid, dilute acetic acid was added, and the orange coloured precipitate filtered off. The substance was crystallised with difficulty from absolute alcohol from which solvent it is deposited in pale yellow needles M.P. 164 C. A red solution was produced with concentrated sulphuric acid whilst alcoholic alkali gave a yellow solution with the product. For analysis the substance was twice recrystallised from absolute alcohol, and tentatively formulated as

styryl

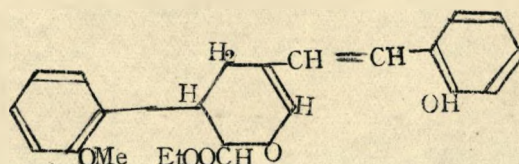
3-orthohydroxyphenyl-5-orthomethoxy/1 Keto Δ 2 (3)
cyclohexenone. Formula XVIII

0.2315 gave 0.6583 CO₂ and 0.1416 H₂O. C = 77.6, H = 6.3

C₂₁H₂₀O₃ requires C = 78.7, H = 6.3

Isolation of-3-orthomethoxyphenyl-5-orthhydroxystyryl

1 keto-2-carboxyethylester Δ 5 (6) cyclohexenone.



(b). Filtrate.

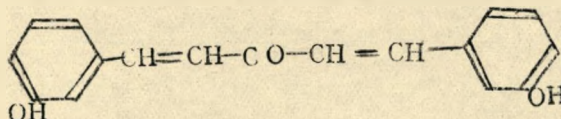
The filtrate from the reaction mixture was diluted to two litres with water, and the turbid suspension acidified with dilute acetic acid. The pale yellow substance which separated was filtered off and thoroughly dried. For a long period this substance resisted all attempts to crystallise, but finally by refluxing with one litre of carbon bisulphide a workable product was obtained. From the carbon bisulphide solution oily matter first separated but from the supernatant liquid when decanted off yellow cubes were deposited. This solid amounting to 1.5 grams was twice recrystallised from carbon bisulphide with the addition of blood charcoal and finally beautiful pale yellow flat prisms M.P. 159 C. were isolated. The compound was very soluble in most organic solvents with the exception of petroleum ether and carbon bisulphide. Sulphuric acid gave a red colouration and alkalies a yellow colouration with this compound.

0.2361 gave 0.6342 CO₂ and 0.1357 H₂O C = 73.4, H = 6.4

C₂₄H₂₄O₅ requires C = 73.9, H = 6.4.

Control condensations of acetone with 2-2'-dihydroxydistyryl
Ketone.

A number of solutions of 2.7 grams of the ketone dissolved in acetone were made, and separately treated with various quantities of ten, twenty and fifty per cent. sodium hydroxide solutions, under various conditions, but unchanged Ketone or its decomposition products only, were isolated.

3-3'-dihydroxydistyryl ketone.

12.3 grams (2 mols) of meta-hydroxybenzaldehyde were dissolved in 40 c.c. absolute alcohol and 3 c.c. acetone. The cold solution was treated with 12.5 c.c. (3 mols) 50 per cent. sodium hydroxide solution. Heat was developed and the solution became red in colour. After one hour the reaction mixture was cooled and poured into one litre of ice water. On neutralisation with dilute acetic acid a yellow gummy mass was deposited. This was filtered off and when dry, recrystallised from absolute alcohol. Three recrystallisations from this solvent gave yellow cubes, M.P. 200°C. A mixed melting point determination of this compound with a specimen of meta-hydroxybenzoic acid (M.P. 200 C.) showed a large depression.

0.2268 gave 0.6358 CO₂ and 0.1119 H₂O. C = 76.5, H = 5.4.
 C₁₇O₁₄O₃ requires C = 76.7, H = 5.3.

The condensation products with acetoacetic ester were amorphous, and could not be obtained crystalline. They were therefore not further investigated.

Condensation of 3-methoxy-4-hydroxystyryl methyl ketone
with acetoacetic ester.

Several preparations starting with 4 grams of 3-methoxy-4-hydroxystyryl methyl ketone dissolved in 2.6 c.c's acetoacetic ester were treated with different quantities of alcohol and then with various quantities of (a) piperidine (b) 10 per cent. alkali (c) sodium ethylate. In all cases the ketone was recovered. It appears that 3-methoxy-4-hydroxystyryl methyl ketone, unlike other ketones of this class, is unusually stable towards alkalies. The peculiar stability of this ketone, in alkaline media, is in conformity with the observations made by other investigators on 4-hydroxystyryl methyl ketone etc., which indicate that a parahydroxyl group in a benzene ring diminishes or inhibits the reactivity of the terminal methyl group.

The following experiments were undertaken in pursuance of schemes (A) and (C)

Hydrolysis :- The following hydrolyses were attempted

- (a) 3-orthomethoxyphenyl-5-orthomethoxystyryl-1-keto
2-carbethoxy- Δ^5 (6) cyclohexanone. XI
- (b) 3-orthomethoxyphenyl-5-methyl-1-keto 2-carbethoxy
 Δ^5 (6) cyclohexanone. XII

Attempts were made to obtain first the corresponding acids by saponification with alkali and heating with 20 per cent sulphuric acid in order to split off carbon dioxide. In all cases the substances produced so far have resisted all attempts to purify them.

Methylation :- Attempts were made to methylate the compounds obtained by condensing acetoacetic ester with

- (a) 2-2' dihydroxydistyryl ketone XIII $\begin{matrix} \text{C} & \text{H} & \text{O} \\ 20 & 18 & 3 \end{matrix}$
- (b) 2-hydroxystyryl methyl ketone (XV) - $\begin{matrix} \text{C} & \text{H} & \text{O} \\ 13 & 14 & 2 \end{matrix}$

The methylation of these substances was carried out by the usual method using methyl sulphate. The oily products obtained have not as yet been purified.

APPENDIX I.(EXPERIMENTAL).4-dimethylamino-2-hydroxydistyryl ketone and its methyl ether.

These compounds were prepared after the manner of Heilbron and Buck (J.C.S. (T); 1921, 1500) and it was found that the conditions which these authors used were productive of the most satisfactory yields.

2-hydroxydistyryl methyl ketone This product which was required in quantity for the preparation of the above distyryl ketone was prepared according to Heilbron and Buck's modification of the method given by Harries (Ber. 1891, 24, 3180). The product was obtained pure by repeated crystallisation from benzene using blood charcoal instead of the laborious steam distillation described in the original preparation.

paradimethylaminobenzaldehyde. This substance was also required in quantity for the production of the substituted distyryl ketone mentioned above. The technique described below is the modification introduced by Heilbron and Buck in the method described by Ingvaldsen and Baumen (J. Biol. chem. 1920. 41. 145). The process results in a very satisfactory yield. Three hundred grams of (technical) dimethylamine are dissolved in 1500 c.c. of dilute (1 : 1) hydrochloric

acid. A heavy beaker containing the mixture is cooled in a freezing mixture and a saturated solution of 180 grams sodium nitrate is run into the vessel. The temperature is kept below 3°C and the contents of the vessel are mechanically stirred during three hours. The yellow precipitate is filtered off, drained at the pump and divided into two equal portions. Two 3000 c.c. flasks are taken and into each is placed 180 grams dimethylamine, 125 c.c. formalin, 300 c.c. of concentrated hydrochloric acid and one portion of the nitroso-dimethylamine. The flasks are shaken to break up the lumps, and are then heated on the water bath. A violent reaction sets in and the contents of the flask are allowed to cool. After dilution sodium hydroxide solution is added until the red colour disappears. The yellow precipitate is filtered off, drained, and dissolved in one litre of glacial acetic acid to which 500 c.c.'s formalin have been added. The whole is mechanically stirred till thirty minutes after complete solution. On gradual dilution of the reaction mixture the dimethylaminobenzaldehyde separates out in reddish nodules. One crystallisation from dilute hot acetic acid suffices to obtain the compound in the necessary state of purity for use. Yield 200 grams.

4-hydroxy-3-methoxystyryl methyl ketone.

(Vanillylidene acetone, Centr., 1908, (2), 1102).

The details given in this paper were not very complete but the following method is expeditious and results in a satisfactory yield of the styryl methyl derivative.

Twenty-five grams of vanillin were dissolved in 100 c.c. acetone, and 80 c.c. of 10 per cent. sodium hydroxide solution were added. The reaction mixture was warmed on the water bath for 30 minutes and then allowed to stand for twelve hours. The clear red solution was diluted to one litre with water, and then gradually neutralised with dilute acetic acid. By vigorous scratching a yellow crystallised product is thrown down M.P. 126 C. Yield 24 grams. Re-crystallisation of this substance from aqueous alcohol gave the 4-hydroxy-3-methoxy styryl methyl ketone M.P. 129C.

3-4-methylenedioxy styryl methyl ketone.

(Piperonylidene acetone. Haber, Ber., 24, 618).

The method described by this author gave a satisfactory yield of the ketone.

4-dimethylamino styryl methyl ketone.

(Sachs and Lewin, Ber., 1920,25, 2576).

No definite conditions of condensing paradimethylamino benzaldehyde with acetone were described in this reference. By using the following conditions a good yield of the required ketone was obtained.

Twenty-five grams of p-dimethylamino-benzaldehyde were dissolved in 50 c.c. absolute alcohol and 60 c.c. acetone and then treated in the cold with 10 c.c. 10 per cent sodium hydroxide solution. After 12 hours an excellent yield of the ketone separated. One recrystallisation of the latter from absolute alcohol was sufficient to give the pure 4-dimethylamino styryl methyl ketone M.P. 134^o, 5 C.

The corresponding 4-4'-tetramethyldiamino distyryl ketone was satisfactorily prepared by the method described by the same authors.

2-2'-dihydroxydistyryl ketone.

This, the dicumar ketone of Decker, and Felser, was prepared by the instructions described by these investigators in Ber., 1908, 41, 2997.

2-methoxystyryl methyl ketone.

A quantitative yield of this substance was obtained by the direct methylation of 2-hydroxystyryl methyl ketone (Heilbron and Buck, J.C.S., (T). 1921, 1500).

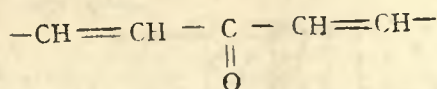
2-hydroxy-2'-methoxydistyryl ketone.

The method of preparation of this ketone described by Heilbron and Buck (J.C.S. (T). 1922, 1095). gave a satisfactory yield of the above substance and left nothing to be desired.

APPENDIX. II

Attempted preparation of certain doubly-conjugated
unsaturated ketones of the type of
4'-dimethylamino-2-hydroxydistyryl ketone.

As a preliminary research the preparation of ketones of this type was undertaken with a view to examining the effect of certain substituent groups on the valency distributions in ketones containing the system -



Another investigator (Mr. Witworth) in the same laboratory prepared a series of ketones in which extra substituents had been introduced into the phenolic nucleus of ketone 4'-dimethylamino-2-hydroxydistyryl. The present author attempted the production of ketones in which the basic paradimethylamino- nucleus had been modified.

Two schemes are possible whereby such compounds can be obtained. By means of Claisen's reaction aminoaldehydes should condense with 2-hydroxystyryl methyl ketone to give the same product as salicyl-aldehyde when condensed with the corresponding styryl methyl derivatives of the

aminoaldehydes. For this purpose aminoaldehydes were required in quantity. A study of the literature relevant to these substances revealed the fact that it would be totally impracticable to use free aminoaldehydes in the presence of alkali, owing to the ease with which polymerisation occurs. The desired ketones in such cases were sought through the aminostyryl compounds. The only methylated aminoaldehyde readily obtainable, apart from the p-dimethylaminobenzaldehyde, was the meta-nitro derivative of the latter. In consequence of the above limitations the investigation was seriously handicapped in the initial stages.

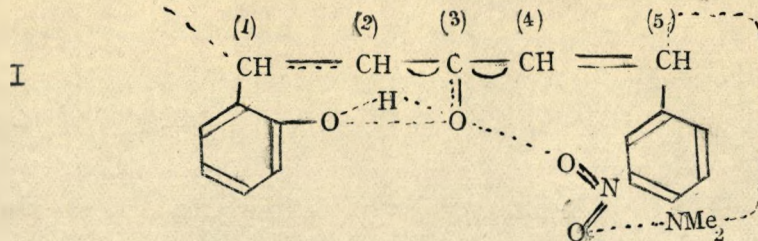
The 3'-amino- and 4'-amino 2-hydroxydistyryl ketones were sought by the condensation of salicylaldehyde with 3-aminostyryl methyl ketone (Ber., 1890, 23, 1885). and 4-aminostyryl methyl ketone (Centr., 1906, (11), 1324.).

Neither of the distyryl ketones could be isolated. The aminostyryl methyl ketones appeared to be easily decomposed in alkaline media. That such is the case is shown by the formation, in each instance, of 2-hydroxystyryl methyl ketone, which could only have been formed by hydrolysis of the aminostyryl ketones into their genitors and subsequent reaction between salicylaldehyde and acetone.

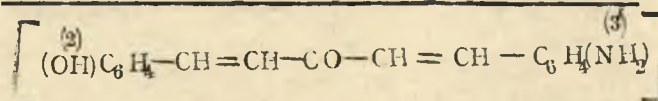
This fact, the reversibility of the Claisen reaction, has been noted by other investigators.

The only distyryl ketone obtained presented many difficulties at the outset owing to the insoluble nature of the starting aldehyde. By the condensation of 5-nitro-4-dimethylamino benzaldehyde with 2-hydroxystyryl methyl ketone in pyridine - alcohol solution in the presence of 10 per cent. alkali a compound M.P. 174 C. was isolated (Formula I) This substance gave no solvate or solid additive products, and the ketone M.P. 174 C. was recovered unchanged under all circumstances. A chloroformic ester derivative of this substance was prepared and behaved in all respects like the corresponding hydroxy ketone. The existence of a semicarbazide-semicarbazone indicated that although the introduction of the nitro group has diminished the reactivity of the parent ketone the system still retains a certain amount of free affinity.

The reasons put forward by Heilbron and Buck (loc. cit.) to account for the reactivity of 4'-dimethylamino-2-hydroxydistyryl ketone have been discussed in Part I of this thesis. The presence of the nitro group in the 5'-position (Formula I) would tend to diminish the stabilising effect of the para-grouping, and at the same time absorb some of the free affinity at the carbonyl oxygen atom, with the net result that the excess affinity at C (1) would not be so greatly enhanced.



The nitro group in the 5'-position reduces, therefore, the additive power of the parent ketone very considerably; whereas, 4'-dimethylamino-2-hydroxydistyryl ketone forms additive products with very great ease the corresponding 5-nitro derivative forms no solvate additive products.

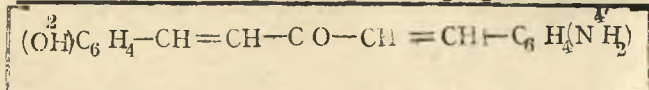
EXPERIMENTAL. (APPENDIX. II)3'-amino-2-hydroxydistyryl ketone.

The author failed to obtain this ketone in spite of many attempts under various conditions, and the following description is typical of one of these.

The 3-aminostyryl methyl ketone required for this condensation was prepared in a very unsatisfactory yield by the reduction of 3-nitrostyryl methyl ketone (Baeyer, Ber., 1882, 15, 2055; 16 1636), using freshly prepared ferrous hydroxide (Miller, Ber., 1890, 23, 1885).

3.6 grams of 3-aminostyryl methyl ketone were dissolved in 30 c.c. absolute alcohol and 2.5 c.c. salicylaldehyde. The cold solution was treated with 12 c.c. of 10 per cent. sodium hydroxide and the reaction mixture allowed to stand for two days. A semi-solid mass giving tests of a primary amine was filtered off and appeared to be the resinous free *m*-aminobenzaldehyde. By acidifying the diluted liquors a brown solid was deposited which on recrystallisation from benzene melted at 137 C. Its admixture with a specimen of 2-hydroxystyryl methyl ketone showed no depression.

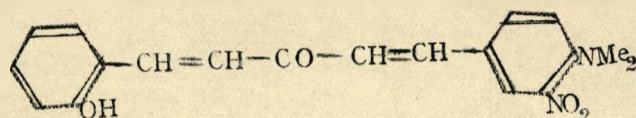
4'-amino-2-hydroxydistyryl ketone.



A series of condensations similar to the one described under the last preparation was carried out in order to obtain this substance but either unchanged 4-aminostyryl methyl ketone, tarry matter or 2-hydroxystyryl methyl ketone were isolated.

The *p*-aminobenzaldehyde required for the 4-aminostyryl methyl ketone (Centr., 1906, (2) 1324,) was produced in good yield but in the form of a hard resin by a modification of the preparation described by Friedländer and Henriques (Ber., 1912, 45, 2083). The base was isolated in the form of its hydrochloride from the residue left after steam distillation by extraction with ether, and the salt of the base precipitated from the ether extract by means of dry hydrogen chloride. An equivalent weight of this hydrochloride was used in the condensations and a corresponding amount of alkali was added to liberate the free base.

5'-nitro-4'-dimethylamino-2-hydroxydistyryl ketone.



19.4 grams of 5-nitro-4-dimethylaminobenzaldehyde (prepared in good yield according to the instructions given in D.R.P. 92010), and 16 grams of 2-hydroxystyryl methyl ketone were dissolved in 200 c.c. of pyridine -alcohol. On the addition of 60 c.c. 10 per cent. sodium hydroxy solution a dark red solution resulted. After standing for 36 hours the mixture deposited a red solid (A). The condensation liquors were poured into iced-water containing 100 c.c. of glacial acetic acid, when an orange red curdy precipitate was formed (B). On crystallisation of (B) from absolute alcohol chocolate coloured prisms M.P. 174 C. were obtained. Residue (A) contained sodium, but recrystallisation from acetic acid- alcohol gave a product identical with (B). The ketone was moderately soluble in glacial acetic acid pyridine, absolute alcohol and ethyl acetate, but was practically insoluble in all other organic solvents. When warmed with concentrated hydrochloric acid a red solution is first formed which on further heating turns green.

Dilution of the latter solution causes similar colour phenomena to those observed by Heilbron and Buck (loc. cit) in the case of 4'-dimethylamino-2-hydroxydistyryl ketone, and are undoubtedly due to phenopyryllium salt formation. For analysis the substance was twice recrystallised from the particular solvent in each case.

Absolute alcohol

0.2219 gave 0.5461 CO₂ and 0.1081 H₂O. C = 67.1, H = 5.4

0.453 " 31.2 cc N₂ at 18°C and 745 m.m N = 8.1

Pyridine - Water

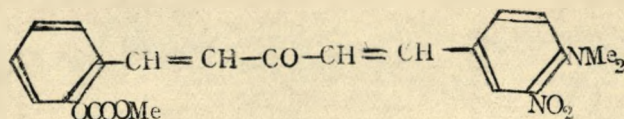
0.402 gave 29.0 cc N₂ at 23°C and 746 m.m N = 8.2

Ethyl acetate.

0.450 gave 31.0 cc N₂ at 14.5°C and 74 m.m. N = 8.1

C₁₉H₁₈O₄N₂ requires C = 67.4, H = 5.3, N = 8.3

Chloroformic ester derivative of 5'-nitro-4'-dimethylamino
-2-hydroxydistyryl ketone.

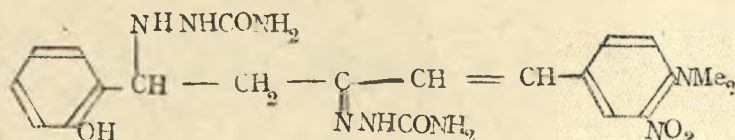


5.4 grams of the ketone M.P. 174 C. were dissolved in 30 c.c. absolute alcohol containing 0.23 grams sodium. The cold solution was slowly treated with 1.1 grams of methyl chloroformate. At the point when the solution changed from dark red to orange yellow an orange solid was precipitated. After half an hour the product was filtered off and recrystallised from absolute alcohol, from which solvent it is deposited in glittering orange red needles M.P. 128 C. With alcoholic alkali a red colour was developed after standing for a few minutes. The substance behaved in all other respects like the hydroxy ketone.

0.406 gave 26.4 c.c N₂ at 17.5 c. and 738 m.m. N - 7.3

C₂₁H₂₀O₆ N₂ requires N - 7.1%

Semicarbazide derivative of 5'-nitro-4'-dimethylamino-2-hydroxydistyryl ketone semicarbazone.



4 grams of the ketone dissolved in the least quantity of pyridine were mixed with 4 grams of semicarbazide hydrochloride in 8 c.c. water. Alcohol was added until the solution became homogeneous. The reaction mixture was gradually diluted over five days when a pale yellow mass was deposited. The semicarbazide - semicarbazone was recrystallised with difficulty from pyridine - ether and was finally obtained in pale yellow needles M.P. 218 C.

0.187 gave 39.0 c.c. N_2 at 18 C. and 745 m.m. N - 24.2 %

$C_{21}H_{26}O_5N_8$ requires N - 24.4 %

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