SOME DERIVATIVES OF THE DIQUINOLINES

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of the requirements for the Degree of
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FOREWORD.

This research problem was conducted under the direction of Dr. R.F. Ruttan, and the writer wishes to take this opportunity of expressing his appreciation of the many valuable suggestions received from him.

The writer also desires to acknowledge the helpful assistance of Dr. W.H. Hatcher.

INTRODUCTION.

Quoting from a paper to The Royal Society of Canada in May 1892, entitled "The Synthesis of a New Diquinolin," by Dr. R.F.Ruttan, we have 'Our knowledge of that important class of natural nitrogenous organic substances called alkaloids has been largely increased through the study of artificial products of similar constitution. Their energetic action on the functions of the animal organism and their intricate composition make the vegetable alkaloids objects of the highest interest both to the physician and the chemist. Until comparatively recently the difficulties in the way of establishing formulae for these bodies appeared almost insuperable, owing to the complexity of their molecules and the apparent want of connection between their chemical behaviour and that of the well studied groups of organic substances. Many of the well known alkaloids have been prepared by synthetical processes from crude material and the molecular structure of others fully elucidated.

A very marked similarity has been traced between natural alkaloids and the artificial derivatives of quinolin in regard to composition and chemical behaviour. In both, for instance, the number of acid equivalents with which they can combine depends chiefly upon the number of pyridin or quinolin groups present in their molecule - thus diacid alkaloids are usually diquinolins. The practical outcome of the researches in this field has been the artificial preparation from coal tar products of many alkaloidal bodies of the highest therapeutic value. The same intensity of action on the human system is characteristic of both the artificial

and natural alkaloids.' Gerhardt in 1842 subjected strychnine, cinchonine and quinine to distillation with solid caustic potash and obtained an oil which he called quinoleine, afterwards changed to quinoline. It was then discovered that certain basic oils, found by Anderson in bone-oil and by Runge and Greville Williams in coal-tar, were identical with the compounds obtained by Gerhardt when distilling the alkaloids. In 1834 Runge separated the substance which he termed leucol from coal-tar, and in 1846 Anderson isolated pyridine and its homologues from bone-oil. Hofmann soon recognized in Runge's leucol and Gerhardt's quinoline identical substances. Subsequently other alkaloids - nicotine, conine, piperine, were converted into pyridine or one of its derivatives by heating with zinc dust. These discoveries, whilst they gave a fresh stimulus to the investigation of the alkaloids, opened up a new field for research in the study of pyridine and quinoline derivatives. The result has been that the process of graduated disintegration applied to the alkaloids on the one hand, and the construction of new products from pyridine and quinoline on the other, established points of contact between them which gradually disclosed the structure of many of the alkaloids and ultimately led to the synthesis of a few of them.

The quinolines proved so interesting and their alkaloidal derivatives so rich a field for chemical research that artificial quinolines with more than one pyridine group, such as the diquinolines, have received but little attention, indeed, of the few diquinolines that have been prepared artificially most

have been isolated by such reaction that their chemical relations are by no means clear. (Trans. Roy. Soc. Can. May 1892, Sec.III).

As the name indicates, the molecule of a diquinoline consists of two quinoline molecules mutually condensed in any one of a considerable number of possible methods of attachment.

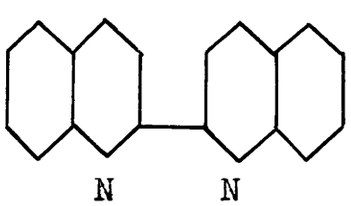
Quinoline possesses the formula C_9H_7N or, structurally.

Quinoline.

It will be seen, therefore, that two quinoline molecules may be mutually condensed in the following manners.

(1) By condensation through the pyridine nuclei of both quinoline molecules.

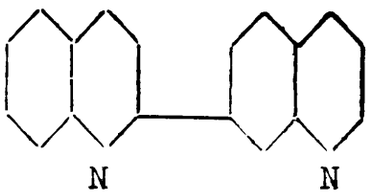
There are nine possible isomers of this type. An example



Pyridine -α- -α- Diquinoline.

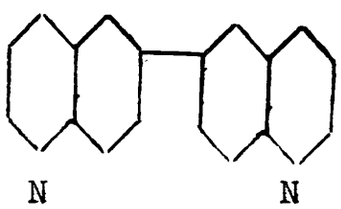
(2) By condensation through the benzene nucleus of one quinoline molecule and the pyridine nucleus of the other. Twelve isomeric possibilities obtain in this case.

An example:



Benzene -2- Pyridine -α- Diquinoline.

(3) By condensation through the benzene nuclei of both quinoline molecules. Ten isomers of this type are possible. An example:



Benzene - 3 - - 3 - Diquinoline.

It is with one of the types of diquinolines mentioned in the last section and one of its dimethoxy derivatives that this paper is concerned.

In 1880 Koenigs obtained quinoline by heating nitrobenzene with glycerol and sulphuric acid at 180°-190°, a reaction which was very soon replaced by the more effective process of Skraup. (Monatsh., 1880, 1, 316; 1881, 2, 141.) which appeared in the same year.

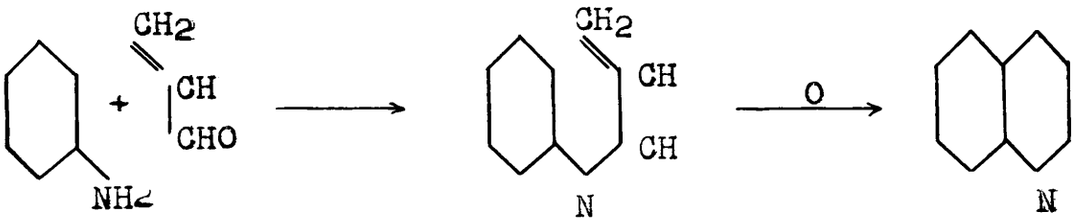
Skraup's reaction for the synthetical preparation of quinolines is a condensation process accompanied by the elimination of water and oxidation. It consists in heating an aromatic amino compound at a fairly high temperature with glycerol, sulphuric acid and nitrobenzene. The mechanism of Skraup's reaction

is usually explained by assuming that glycerol undergoes conversion into acrolein by the dehydrating action of the acid, and is followed by the formation of acrolein-aniline with the aniline or aniline derivative. Then the nitrobenzene oxidizes off the terminal hydrogen of the side chain together with the ortho-hydrogen of the ring. The reaction may be shown diagrammatically as follows:-

Glycerol loses two molecules of water giving acrolein,

Glycerol Acrolein

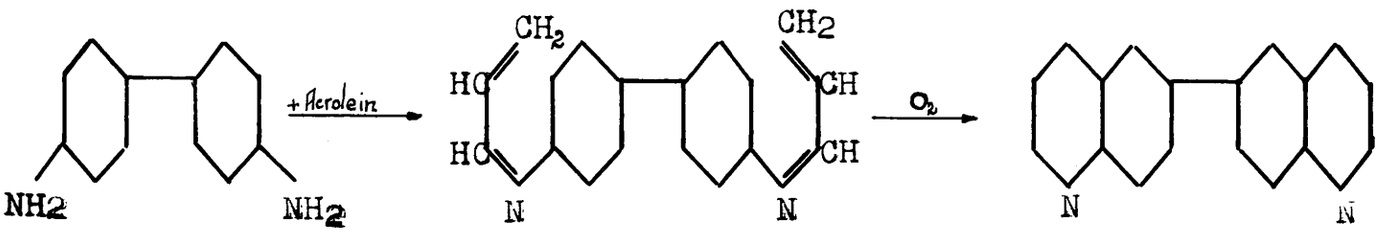
Then the following reactions take place,



Aniline - Acrolein Acrolein-aniline Quinoline

The method is of the greatest value, for, provided one ortho position to the amino group in the nucleus is free, any amino compound may be used, and the number of substituted quinolines which can be prepared in this way is very large. The substituent group in these cases is naturally restricted to the benzene nucleus.

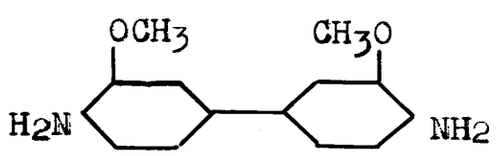
Thus it will be seen that if a compound such as Benzidine $NH_2 \cdot C_6H_4C_6H_4 \cdot NH_2$ be subjected to Skraup's reaction, a diquinoline, of the type mentioned in Section 3, that is to say, Benzene -3-3- Diquinoline, would be the end product obtained. The reaction by which Benzidine is converted into its corresponding diquinoline may be represented diagrammatically as follows:



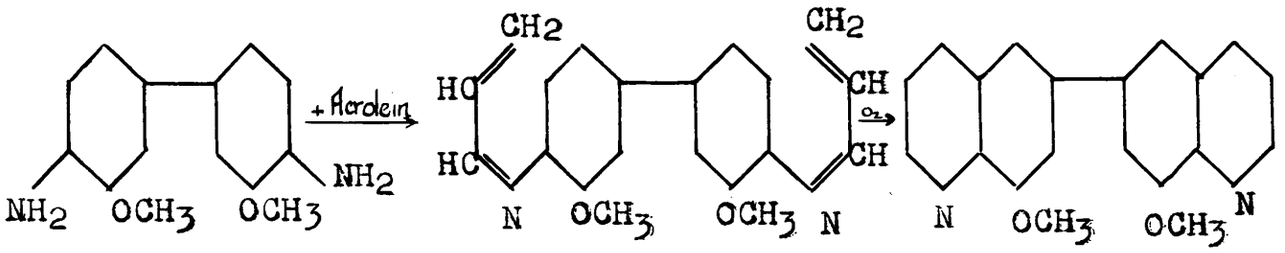
Benzidine Benzidine-diacrolein B.3.3. Diquinoline

(2)

Consequently, if a methoxy derivative of benzidine were employed, the result of the reaction would be a methoxy diquinoline. Subjecting 4-4'- diamino -3-3' - dimethoxy - diphenyl or ortho-dianisidin, as it is known, possessing the formula,



to Skraup's reaction there would be obtained Benzene - 1 - 1 - Dimethoxy - Benzene - 3 - 3 - Diquinoline having the formula $CH_3O.\ C_9H_5N.\ C_9H_5N.\ OCH_3$ Diagrammatically the reaction would be



Ortho-dianisidine

Ortho-dianisidine--diacrolein.

B-1-1-Dimethoxy-B-3-3-Diquinolin

The formula of Benzene - 1 - 1 - Dimethoxy B-3 - 3 - Diquinoline is $C_{20}H_{16}N_2O_2$. If this compound were hydrogenated and caused to assume ten atoms of hydrogen the resulting compound would be Quinonine $C_{20}H_{26}N_2O_2$, a well known alkaloid. Whereas, if it were caused to assume eight hydrogen atoms, the resulting compound would be an isomer of Quinine which possesses the formula $C_{20}H_{24}N_2O_2$ and is another very well known alkaloid, which was discovered in 1820 by Pelletier and Caventou.

Quinine occurs with cinchonine and several other allied alkaloids in all varieties of cinchona bark, some of which contain as much as 3 per cent. quinine. The alkaloids are contained in the bark combined with tannic and quinic acids.

Quinine crystallizes with three molecules of water, melts at 177° when anhydrous and is only sparingly soluble in water. It is a strong base and unites with two acid equivalents. In dilute solution the salts of quinine exhibit a splendid blue

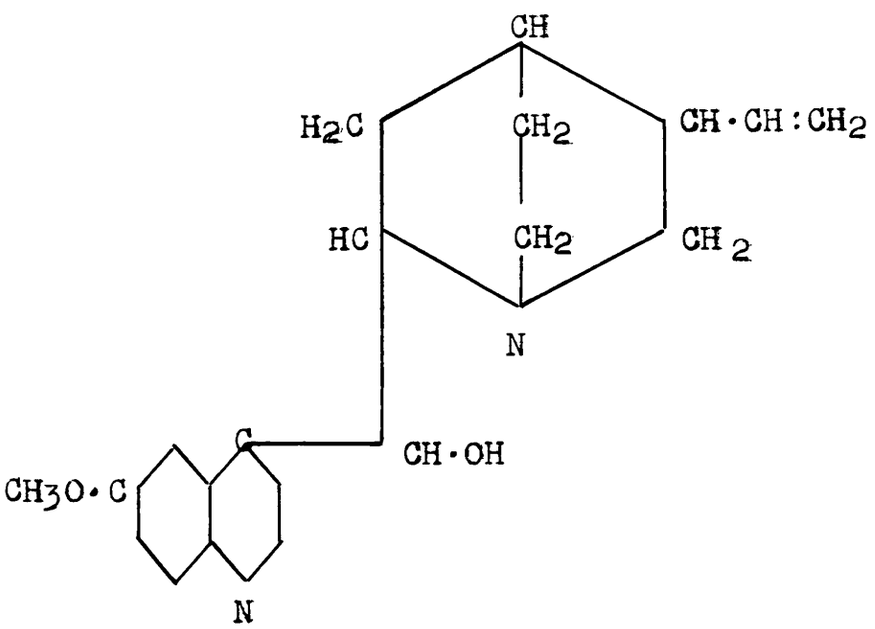
fluorescence, which serves as a test for the base.

It generally forms well-defined salts many of which are soluble in water, and much used in medicine as tonics and for lowering the body temperature in cases of fever.

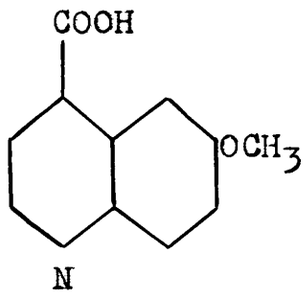
Consequently, there can be no doubt that the compound resulting from the addition of eight atoms of hydrogen to B- 1 - 1 - Dimethoxy B-3 - 3-Diquinoline; isomeric with quinine, would have very strong therapeutic properties.

Concerning the structure of quinine, this alkaloid is a bi-tertiary base, that is to say, both nitrogen atoms are present as tertiary groups. Of the two oxygen atoms of quinine one is present as methoxyl, and the other as hydroxyl.

Konigs assigns the following formula to quinine:-



On fusion with potassium hydroxide quinine yields quinoline, p-methyl quinoline or lepidine, p-methoxy-quinoline and β-ethylpyridine. The product obtained by oxidizing quinine has shown that the alkaloid is sharply divisible into two parts. With energetic oxidizing agents quinine yields quinic acid and another product of oxidation is α-β-γ- pyridine - tricarboxylic acid. Quinic acid has the formula



and is, therefore, a methoxy quinoline carboxylic acid. The molecule of quinine is, therefore, divided into two parts; the "quinoline half" and the "second half", Up to a certain point the explanations of Skraup regarding the constitution of quinine were satisfactory but the further investigation of its structure has presented unexpected difficulties and the constitution of the "second half" is not yet finally and definitely established. It will be evident, therefore, that by contrasting the chemical, physical and physiological properties of Octahydro - Benzene -1-1- Dimethoxy - Benzene -3 - 3 - Diquinoline with those of quinine and considering characteristic group reactions that it would be possible to throw additional light upon the structure of quinine, as the structural constitution of the octahydro compound would be

definitely known from its method of synthesis.

As the preparation of Benzene - 1 - 1 Dimethoxy - Benzene - 3 - 3 Diquinoline and its octahydro derivative and the investigation of their properties and reaction products was the end desired in this research, it was considered desirable to make an extensive study of Skraup's reaction applied to benzidine and thus prepare Benzene - 3 - 3 Diquinoline, laying particular stress upon the most suitable conditions of temperature, time, solvents, lengths of periods of extraction, decolorization methods and other purification processes necessary to obtain the maximum possible yield of the base from the reacting constituents. This preliminary work was necessitated by the lack of data as regards method of preparation, yields obtained and purification of the product. Undoubtedly, purification presents the greatest difficulties, as will be seen from the following extracts of the work done on the crude diquinoline product. The methods adopted in the purification of diquinoline by Roser (Berichte (1884) 17, 1817 and 2767) and Ostermayer and Henrichsen. (Ibid, 2444) were carefully compared and a satisfactory technique devised.

EXPERIMENTAL.

Preparation and Purification of B - 3 - 3 - Diquinoline.

Experiment No.1.

Reacting Constituents:	Weight in grams:	Molecular Proportions:
Benzidine sulphate	60	0.212
Glycerol	140	1.52
Conc. Sulphuric Acid	100	1.02
Nitrobenzene	24	0.195

The above constituents, in the proportions shown, were mixed well in a one-litre flask and heated under a reflux condenser on a sand bath. The reaction was carried out at a temperature of 165-170° and was of nine hours duration. A lively reaction took place shortly after heating had been started. As soon as bubbles commenced to form the source of heat was withdrawn. When the lively reaction had subsided the heating was continued. During the remainder of the period of heating a moderate amount of bubbling occurred. The melt was then allowed to cool somewhat, hot distilled water added and the mixture steam distilled to remove any unchanged nitrobenzene. However, the distillate was perfectly clear, indicating that there was no excess of the oxidizing agent present in the solution. The solution was then cooled, filtered and neutralized with caustic soda. On neutralizing, the solution became quite hot. It was allowed to cool, and filtered. The solid residue consisted of a circular mass of tar about five inches in diameter and half an inch thick. After washing the mass free

from sodium sulphate and other impurities, one litre of benzene was added to it and extraction carried out under a reflux for four hours. The solvent was then decanted and set aside, temporarily. The residue was extracted with 500 c.c. of fresh benzene for six hours, the solvent acquiring a brownish color. After decantation the solvent was found to contain a certain amount of oil.

Roser recommends purification by decolorization in sulphuric acid solution. Accordingly, a portion of the benzene extract was subjected to distillation, and when it was nearly all evaporated it had the appearance of a heavy dark red liquid, and when only a thin layer was left on the bottom of the flask the whole suddenly became solid. This was with difficulty dissolved in sulphuric acid and boiled with animal boneblack under a reflux for five hours. Apparently no decolorization had taken place as the intensity of the color was the same as before decolorization was attempted. It was then thought that if the solution were more dilute decolorization might possibly take place. Accordingly half a litre of distilled water was added and the process continued for two hours. At the end of this time the solution possessed a very slight straw yellow color and the flask was half filled with a white crystalline substance, the crystals possessing a needle-shaped

structure. Attempts were made to dissolve the white substance in order to separate it from the animal bone-black. It was found to be insoluble in hot or cold water, alcohol, and very difficultly soluble in concentrated sulphuric acid.

Referring to the above, it will be noted that it was stated that a considerable amount of concentrated sulphuric acid was necessary to dissolve the diquinoline raw product before subjecting it to decolorization with animal boneblack. As the latter process is carried out in boiling solution it was thought that at the high temperatures obtained the strong sulphuric acid might have some marked effect upon the diquinoline molecule, possibly rupturing it. It was decided, therefore, to essay a different method of accomplishing decolorization. To another portion of the benzene extract were added fifty grams of acid-treated animal boneblack. After boiling for one hour, twenty grams of light animal boneblack were added and the boiling continued for two hours longer.

The solution then possessed a straw yellow color and consisted of two layers, the upper being of a light brown color, and the lower portion consisting of a white oily liquid containing a brownish substance in suspension. These were separated and the upper layer subjected to distillation. After evaporation to dryness, a solid yellowish residue remained. This was recrystallized from aqueous alcohol, the most suitable proportions of these liquids consisting of two parts of alcohol to one of water. A yellow crystalline substance separated out accompanied by a very dark brown oil. The crystalline substance was separated and recrystallized, the result being a slightly yellowish crystalline mass melting at 173.5°. Admixed with the oil was a small amount of the yellow substance. A second crop of crystals were obtained and the oil, on being allowed to remain in contact with the crystals for some time, gradually changed over to a very impure form of the same substance.

The litre of solvent used in the extraction of the tar was allowed to stand for a day, and a considerable amount of brownish white crystals separated out. It was thought that if this substance were recrystallized from alcohol it would yield a purer product than that obtained by the decolorizing of the benzene extract and subsequent filtration, evaporation and recrystallization from aqueous alcohol. If this were found to be the case a considerable saving in time would be effected. Consequently, a small quantity was recrystallized

from alcohol,but the product was not as pure as the specimen melting at 173.5°; so this method was abandoned.

The result of these investigations pointed to the conclusion that the best method of purification of the reaction product would be to extract the tarry matter with benzene, decolorize with animal boneblack in this solution, filter and evaporate the benzene extract to dryness and recrystallize the residue from aqueous alcohol. This procedure,therefore, discarded the idea of decolorizing in an acid solution,as was recommended by a previous investigator. Therefore, more benzene was added to the solution from which crystals had separated out and the whole heated under a reflux. This treatment caused the crystals to go back into solution. On the addition of a small amount of alcohol an oil separated out and this on evaporation left a hard tarry residue. It was then decided to evaporate the benzene-alcohol solution and dissolve the residue in benzene and decolorize in a medium consisting of the latter solvent alone. On evaporation a brownish residue remained. This was dissolved in benzene alone and decolorization again attempted. A stirring apparatus projecting through the reflux and operated by means of a water-cooled hot air engine was installed and this overcame bumping,which was previously very pronounced. Ten grams of animal boneblack were added and solution boiled. After a period of two hours five grams of fresh animal bone-black were added and heating continued for another three hours.

The solvent was filtered and evaporated to dryness. This gave a greenish-colored substance, which, when dried, dissolved in alcohol, and filtered became brownish red. This solution was concentrated but as the substance was very soluble in alcohol, a crystallizing medium of aqueous alcohol was used. On the addition of this to the above solution, the latter turned black. The solution was evaporated until yellow striae appeared and it was then cooled quickly. The color of the solution changed to a yellow, and a dark heavy oil sank to the bottom of the crystallizing medium and froze there while yellow sparkling crystals remained in suspension in the liquid above. These were filtered off and dried, and upon repeated recrystallisation from alcohol yielded yellowish crystals melting at 171°C. The oil was melted, pressed between several layers of filter paper and recrystallized. This treatment yielded a further amount of dark yellow crystals.

EXPERIMENT NO.2.

The proportions of the reacting substances used in this experiment were identical with those employed in the preceding one. The temperature of the reaction was the same, but the heating covered a period of eight hours as compared with nine in Experiment No.1.

The melt was allowed to stand for some time, and consisted of a light brown mass covered by a very dark thick tarry liquid. To this were added 500 c.c. of distilled water and the solution steam-distilled, the first few drops

only of the distillate having an oily consistency, thus indicating that only a very small proportion of the nitrobenzene originally present in the mixture existed in an unchanged condition. Steam-distillation was carried on for a period of 1.5 hours. The crude base was thrown down with alkali, washed with water and then with alcohol. The use of the latter as a washing medium is not to be recommended as it was found that the tar was alcohol soluble, 450 c.c. of benzene were added and refluxed for 4.5 hours. The solvent was then decanted, 500 cc. fresh benzene added and the extraction continued for 3.5 hours. To the 950 c.c. of benzene extract 25 grams of animal boneblack were added and heat applied for three hours after which the benzene was filtered and 26 grams of fresh animal boneblack added, the refluxing being continued for another 5.5 hours, thus making a total decolorization period of 8.5 hours. The solution was filtered from animal boneblack evaporated to a volume of 100 c.c. and cooled quickly. A mass of brownish yellow crystals separated. These were filtered and dried.

Another 450 cc. of benzene was added to the tar after it had been subjected to extraction for 8 hours. The purpose of continuing the process beyond this point was to ascertain the proper length of time and exact amount of benzene required to extract most profitably all the diquinoline present. A small amount of highly coloured substance separated out upon evaporation of this, so that further extraction was deemed useless.

EXPERIMENT NO. 3.

It was decided at this point to try an oxidizing agent other than nitrobenzol. Accordingly .199 molecules of ortho-nitrophenol were mixed with 1.52 of glycerol, .177 benzidine sulphate and 1.02 mol. sulphuric acid. The use of nitrophenol was suggested by Ostermayer & Henrichsen, who claimed that the preparation was simplified to a certain extent and the yields correspondingly increased by the use of this substance as an oxidizing agent. The mixture was heated for 9 hours, at first in an oil bath and then on a sand bath. By lowering a thermometer through the reflux condenser it was found that the temperature inside the reaction flask did not rise above 120° although the outside temperature averaged 190°. It was noticed that as the reaction progressed, foaming occurred to a much greater extent that in the preceeding cases and, as the only difference in these methods was in the type of oxidizing agent employed, the latter was undoubtedly the cause of this phenomenon. Upon dilution and steam-distillation no excess of the oxidizing agent was noticeable. The solution was cooled and neutralized. A considerable quantity of a dark substance, possessing a lumpy consistency, was thrown down. This was unaccompanied by any tar and, therefore, this marks one superiority of ortho-nitrophenol over nitrobenzol as an oxidizing agent. This crude base was washed with water, dried, pulverized and extracted for a period of 4.5 hours with one litre of benzene. This

was decanted and a fresh supply of 300 c.c. added and boiled for five hours and apparently no further extraction of the substance took place,as the solvent at the end of this time possessed no appreciable color. The litre of solvent was subjected to the decolorization process for four hours. The color of the solution was only slightly less intense than before. On evaporation a dark brownish residue was left, as compared with the yellow crystals obtained using nitrobenzol as an oxidizing agent. This substance was recrystallized twice from alcohol but appeared no lighter in color. An attempt was made to decolorize by extraction with ether in Soxhlet apparatus. This method, however, proved unsuccessful for, on evaporating the ether, a mixture of fairly pure and impure crystals was obtained, the substance itself,and the impurity, being soluble to approximately the same extent in ether. The solid residue in the Soxhlet had lost but little of its color. The crystals were redissolved in aqueous alcohol and the boiling with animal boneblack continued. Recrystallization gave 13 grams of moderately pure Benzene -3-3- diquinoline melting at 179.5°.

EXPERIMENT NO.4.

It was decided in this experiment to heat the mixture for a longer period of time. The same molecular ratios were employed as in the preceding experiment but the time of heating was increased to 10 hours, at the usual temperature of 170°-190°. Then followed steam distillation, neutralization and washing. As in the previous case no ortho-nitrophenol

came over in the steam-distillate. 1250 c.c. of benzene were added and refluxed for 10 hours (with constant stirring). The solvent was filtered, evaporated to a volume of 200 c.c. and allowed to stand over night. Brownish scintillating crystals separated out and these were filtered off, washed and dried. The remaining portion of the solution was evaporated to dryness but the residue consisted of only a negligible amount of very impure crystals. The brown crystals were dissolved in aqueous alcohol and the solution decolorized, followed by filtration and a small amount of evaporation. White crystals of Benzene - 3 - 3 - Diquinoline separated out. These, on washing and drying, melted at 178°, the yield being 39.8% of the theoretical.

EXPERIMENT #5.

It was decided at this stage to essay another reaction with nitrobenzene as the oxidizing agent, the optimum experimental conditions for this type of reaction having been finally successfully worked out.

The mixture was heated for 10 hours. The amount of nitrobenzene used was 25 grams (0.203 molecules), the other constituents were present in the same proportions used in the preceding run. The average temperature was slightly higher than usual, namely, 185, and the time of heating 10 hours. Less foaming occurred than in either of the two preceding runs. Steam-distillation was carried on for 1.5 hours and, again, no excess of nitrobenzene was present.

On standing, a brownish substance separated out. This was filtered off and treated in the usual way. After drying, the tar was extracted for eleven hours with 1.5 litres of benzene. The solvent was decanted, the last portion contained considerable amounts of oil. This fraction was neglected. During the distillation of the benzene, more oil separated out and sank to the bottom. The distillation was discontinued when the volume of the solvent was 300 c.c. As before, on cooling, brownish crystals separated out. These were filtered. The filtrate on evaporation left as the residue, a black glassy tar. The treatment of the crystals was the same as that applied in the previous experiment. The ultimate product was a quantity of yellow crystals melting at 179°.

SUMMARY

In Table 1 are given the proportions of reagents employed, the time and temperature of heating, the volumes of extraction-solvent required, together with the time of extraction and of decolorization, and the percentage yields obtained, calculated on the basis of the benzidine used.

It will be observed that experiments Nos. 3,4 and 5 gave considerable yields of pure Benzene - 3 - 3 Diquinoline, the melting point of the compound obtained being in exact agreement with that given by former investigators.

It will also be observed that ortho-nitrophenol is to be recommended rather than nitrobenzene as the oxidizing agent in this reaction, as it leads to a purer product at parallel stages of the reaction and the yield obtained is higher. A greater amount of foaming takes place when using ortho-nitrophenol but it is not excessive or troublesome.

A satisfactory method of obtaining the base has been devised and is as follows:-

Make an intimate mixture of the reacting constituents under ordinary conditions. Heat slowly to a temperature of 180^{0}-190^{0}. Allow a fairly vigorous reaction to take place but remove the source of heat as soon as there is any indication of this reaction starting, otherwise it becomes very violent and the yields are correspondingly decreased. Heat the mixture for five hours after this reaction has taken place. Pour the melt into 1.5 litres of hot water and steam distill

until the distillate gives no trace of yellow color upon the addition of sodium hydroxide. This will occupy about three hours. On filtering it will be found that practically all the material has gone into solution. Neutralise the filtrate with alkali, wash, dry and extract the gray powder for ten hours under a reflux with 1.5 litres of benzene.

Decolorize with animal boneblack for seven hours in this medium . Filter and concentrate the filtrate and allow to stand. Filter and wash the crystals separating out. Recrystallize from aqueous alcohol (1;1) obtaining glistening crystals melting at 178°.

This method is a variation from that employed previously by other investigators (B. (1884) 17, 1817 and 2767; Ibid 2444.)

This process laid a firm foundation upon which it would be possible to build up a method for the preparation of Benzene - 1 - 1 - Dimethoxy - Benzene - 3 - 3 - Diquinoline, taking into consideration, of course, certain modifications of the various conditions which might prove necessary.

TABLE 1.

A - Benzidine Sulphate.
B - Glycerol.
C - Ortho-nitrophenol.
D - Nitrobenzene.
E - Concentrated sulphuric acid.

Experiment.	Reagent Proportions Mols.	Heating Process Time in Hours.	Heating Process Temp. °C.	Steam distillation Time in hours.	Extraction. Vol. alcohol.	Extraction. Vol. benzene	Extraction. Time in Hours	Decolorization Process Time Hrs.	REMARKS.
1)	A 0.212 B 1.52 D 0.195 E 1.02	9	165-170	2		1500	10	8	Moderate reaction. yield .663% Yellow crystals.
2)	A 0.212 B 1.52 C 0.195 E.1.02	8	165-170	1.5		1400	16	8.5	Yellow crystals
3)	A 0.177 B 1.3 C 0.201 E 1.02	9	190°	2		1300	9.5	4	Moderate reaction Yield 28.7% White scintillating crystals m.p. 178.5
(4)	A 0.177 B 1.3 C 0.201 E 1.02	10	170-190	2		1250	10	6	white scintillating crystals yield 39.8%.M.p.178.
(5)	A 0.177 B 1.3 C 0.203 E 1.02	10	185	1.5		1500	11	3	yield 26.5% yellowish crystals Mp. 179°

SKRAUP'S REACTION APPLIED TO ORTHO-DIANISIDINE.

The only mention of the preparation of Benzene - 1 - 1 - Dimethoxy - Benzene - 3 - 3 - Diquinoline that could be found was in the form of a Patent (Farbenfabriken, vorm. Fy. Bayer u. Co., Elberfeld; D.R.-P. Kl.22, Nr.38,790 vom. 21. Mai 1886; B (1887) 20, R.269) and the method outlined is very much lacking in detail. The quantities employed were large e.g., the amount of Dianisidine sulphate used was one kilogram and the amounts of the other reacting substances were proportionately large. No indication is given of the yield obtained, the melting point of the purified reaction product is given as "about 100°", and is described as having a "peculiar irritating odor". The available information concerning this compound and its preparation is thus, obviously, very vague.

The Dianisidine sulphate, employed in the following experiments, was prepared by dissolving dianisidine in alcohol and adding the theoretical amount of sulphuric acid. This treatment precipitated the sulphate which was washed and dried. When dry, dianisidine sulphate is exceedingly irritating to the eyes and mucous membrane, and it is necessary when working with it, to wear a gas mask and the use of glasses for the protection of the eyes is also recommended.

EXPERIMENT NO.6.

Reacting Constituents.	Weight in Grams.	Molecular Proportions.
Dianisidine Sulphate	60	0.175

Reacting Constituents.	Weight in Grams.	Molecular Proportions.
Glycerol	300	3.26
Ortho-nitrophenol	42	0.302
Conc. Sulphuric acid	350	3.57

The method of procedure adopted in these experiments differed somewhat from that followed in the preparation of the parent substance, Benzene - 3 - 3 - Diquinoline. In the latter case the mixing of all the reacting constituents was accomplished at room temperature, whereas, in this series, the course of action considered most suitable and the one recommended in the reference already referred to, was to dissolve the dianisidine sulphate and ortho-nitrophenol in the sulphuric acid, heat the mixture slowly to 100° and then add the glycerol gradually and in small portions.

Accordingly, the quantities of the reacting constituents indicated above were subjected to this treatment. The result was totally unexpected, however. On the addition of the first small portion of glycerol a violent reaction took place, whereas a gradual increase in temperature only was anticipated. When the violence of the reaction had subsided somewhat more glycerol was added and a large amount of frothing occurred. The melt was allowed to cool considerably before the last portions of the glycerol were added. Heat was then applied very cautiously. Suddenly, the violent frothing recommenced, on this occasion completely filling the reaction flask and overflowing from the reflux, in spite of the instant removal of the source of heat.

When the mixture had cooled somewhat the temperature was raised very slowly, at the rate of one degree in two minutes, and when the temperature reached 140° an abnormal amount of frothing occurred. Upon allowing the temperature to decrease slightly, the frothing diminished. In fact, 140° appeared to be a critical temperature as regards this phenomenon.

Consequently, the two litre reaction flask was replaced by one having a capacity of five litres. As long as the temperature was maintained at 140° the frothing was voluminous, almost completely filling the flask. When allowed to cool the mass set to a very hard black tar. This procedure of careful heating was continued for two days, the purpose of this extensive period of heating was to allow for the fact that the temperature could not be maintained at 140°, due to excessive amount of frothing, it being necessary to employ a temperature somewhat lower. The thick mass was stirred from time to time, as no mixing took place otherwise. To the melt were added two and one-half litres of distilled water, previously heated to a temperature of 90° C. Steam-distillation was then carried out for two and one-half hours; during the first period of this operation the tarry mass swelled up to huge proportions, almost filling the five litre distillation flask, then, towards the end, it subsided to one-half this volume. The mixture was then filtered with the aid of a suction pump. A large amount of black carbonized residue remained on the filter paper. This is altogether different to the parallel stage in the preparation of Benzene - 3 - 3 Diquinoline. It will be

noted that, in the case of the preparation of the latter compound, after the melt had been steam-distilled there was no solid residue, everything having gone into solution. The fact of so much material being insoluble after steam distillation in this preparation might possibly indicate a variety of side-reactions. The acid filtrate was then neutralized with caustic soda. As the condition of the solution approached the neutral point a grayish brown substance precipitated out, the solution still being acid to litmus. A small amount of caustic soda in excess of that required for exact neutralisation caused the substance to redissolve. The separation of the solid from the liquid was a matter of difficulty, due to the amorphous consistency of the former. It was present in such small quantities as to render further treatment useless. When dry it consisted of two well-defined portions, one a dark gray powder and the other, a black tar.

From the foregoing remarks it is evident that this reaction is a complex one and presents difficulties which were not encountered previously.

EXPERIMENT NO.7.

It was considered advisable to work with smaller quantities of the reacting constituents until the most suitable experimental conditions for the preparation of this compound were worked out. Consequently, on this occasion the amounts employed were one-half of those of the previous experiment. The same order of mixing and addition of the substances were

adhered to. After the glycerol had been added to the solution at 100° the temperature was slowly raised. In a short time bubbles commenced to form. The source of heat was removed immediately, but, in spite of this, a very violent reaction took place, the contents frothing up and filling the flask and condenser as in the preceding experiments. In addition to this a steady stream of acrolein vapour issued from the top of the reflux. To offset this loss, fifty grams of glycerol were added to the melt and the temperature raised to 140°. No further violent ebullition occurred but as the temperature approached 140°, the excessive frothing would recommence.

The mechanical stirrer, already referred to, and employed to prevent bumping of the decolorization solution in the previous experiments was used to advantage at this stage and the mass was heated at 130-140° for a period of eight hours, with constant stirring. The subsequent treatment was identical with that described in the preceding experiment and the result was the same, namely, a small quantity of a mixture of tar and dark gray powder.

EXPERIMENT NO. 8.

It was realized that if satisfactory yields of this substance were to be obtained radical changes were necessary in the method of procedure. Upon reconsidering the phenomena described in experiments No. 6 and No. 7 it was decided to prepare an intimate mixture of the reacting constituents at

room temperature and work slowly onwards from this point. This marked a distinct difference from the method adopted in the process referred to, in which the procedure was as indicated in the foregoing sections, that is to say, the glycerol was slowly added to a solution of the other constituents at a temperature of 100°.

The quantities used in this experiment were the same as in the preceding one. An exception, however, was that nitrobenzene was again resorted to as the oxidizing agent, and it was present in a larger proportion than formerly. In place of the 0.151 molecules of ortho-nitrophenol used in experiment No.7, 0.300 molecules of nitrobenzene were used in this case and, in addition, the order of addition of the substances was altered.

The dianisidine sulphate, glycerol and nitrobenzene were mixed thoroughly, forming a thick emulsion. The sulphuric acid was added, from time to time, in small quantities, with vigorous shaking until the heat produced by each addition of acid had become dissipated.

The flask was then placed under a reflux condenser and heated on a water bath for two and one-half hours, and stirred vigorously, at a rate of 250 revolutions per minute. By this means the reacting substances were exceedingly well mixed before any reaction might take place. The water-bath was replaced by a sand-bath and the temperature slowly raised. After one hour a vigorous reaction occurred. The melt was

then heated to 140° for five hours. In this case the foaming, though considerable, was not excessive and the mixture was of a liquid consistency rather than a thick magma, as in Experiments Nos. 6 & 7. One litre of hot water was added and the whole steam-distilled for one hour. A great deal of tarry matter was thrown around inside the flask during the steam distillation and this adhered to the walls of the vessel. The first few drops, only, of the distillate contained oil and the steam-distilled solution was brownish-black in color. On the addition of sodium hydroxide the color of the solution became somewhat lighter and near the neutral point a heavy precipitate settled out.

Each addition of alkali caused a local yellowish colour. When the solution was exactly neutral a small quantity of the gray powder separated out, accompanied by a fair quantity of tarry lumps which became very brittle on drying. The colour of the solution at its neutral point was yellow, on adding more alkali it became green and when this was acidified it turned brown. The solid was filtered, washed free from sodium sulphate, dried and powdered. It was then extracted in a Soxhlet apparatus with benzene for 27.5 hours. As the colour of the solvent at the end of this time was merely a light straw yellow it was decided to extract the solid in direct contact with the boiling solvent, the method which had proved most successful in the extraction of Benzene - 3 - 3 Diquinoline. The solid matter was, therefore, powdered and the slightly colored solvent, together with some fresh

benzene, was added and boiled under a reflux for four and one-half hours. The colour of the solvent was only slightly more intense than that obtained from the Soxhlet extraction. The treatment of this extract is described later.

The residue was extracted for another five hours with 400 c.c. of fresh solvent. No further extraction of the solid was deemed advisable, judging from the color of the benzene.

From a test it was evident that the substance is more soluble in alcohol than in benzene consequently, the residue from the benzene extraction was extracted with alcohol for five hours. Upon filtering the solution it was found to be black in color. The process mentioned previously indicates that the substance was isolated "by the purification of the sulphate or of the hydrochloride from alcohol." To the alcoholic extract was added dilute sulphuric acid,which threw down a light brown precipitate,the sulphate of the base. This was filtered off and dissolved in water, giving a black solution. It was attempted to decolorize this solution,but,after a period of one and one-half hours,none had taken place. Caustic alkali was added to the solution and this threw down a light brown substance,evidently the basic material. Accompanying this was a certain amount of tarry substance clinging to the beaker and distributed throughout the mixture. On filtering, the liquid was found to be light brown in color. The lumps of tar were removed

by mechanical means. The solid was dissolved in alcohol, filtered, and the sulphate thrown down with sulphuric acid. The acid salt possessed a light yellow color but its aqueous solution was black. Addition of alkali to this solution threw down a dark gray substance, again accompanied by tar, which was again separated by handpicking. It was dissolved in alcohol, animal boneblack added, and boiled for four and a half hours. Upon filtering, evaporating to half volume, and recrystallizing, yellowish crystals separated out. These became white on drying, and melted at 273.5° with a small amount of decomposition. Upon recrystallization from aqueous alcohol the crystals melted at 270°C.

When damp, the crystals were yellow but on drying they became fairly white. Exposure to air for sometime caused them to turn yellow, due, as was discovered later, to the formation of the hydrochloride from the hydrochloric acid fumes in the air.

Treatment of the Benzene Extract.

The solvent was evaporated to dryness, leaving a small quantity of solid matter, part of which consisted of yellow and brown crystals, while the remainder was of a pasty consistency due to the presence of an oil similar to that encountered in the preparation of Benzene - 3 - 3 - Diquinoline, using nitrobenzene as the oxidizing agent. The crystals were converted into the sulphate in alcoholic solution, this salt having a light yellow color while its aqueous solution was

light brown. On the addition of alkali a yellowish-white substance, which rapidly became green, was thrown down. After filtering and washing, the solid became dark gray in color.

Decolorization was carried on in alcoholic solution for three and one-half hours, fresh animal boneblack was then added and the process continued for another six hours. During this time the solution changed from a dark green to a light straw yellow. A white glossy substance was obtained by recrystallizing this substance from alcohol. It was found that the most suitable recrystallizing medium consisted of one part of alcohol to two of water. After several recrystallizations the solid melted at 270°, and when allowed to crystallize out slowly from alcohol, it separated in long white needles of this shape.

EXPERIMENT NO.9.

Ortho nitrophenol (0.252 molecules) was used in this case as the oxidizing agent, the other quantities remaining the same as in the last experiment.

The dianisidine sulphate and ortho-nitrophenol were ground up together in a mortar, and then dissolved in the sulphuric acid. The glycerol was added last, and slowly. On each addition the heat evolved was dissipated by means of a snow-bath. The addition of the glycerol caused the constituents to separate out of solution, thus forming a thick yellowish viscous mass. The method of gradual heating described in experiment No.8 was carried out, the mixture changing to a deep black color.

The heating consisted of two stages:-

2.5 hours at 100°

10 " at 140°

Steam-distillation was then carried on for four hours. The first few hundred cubic centimetres of distillate were yellow in color, due to the presence of ortho-nitrophenol, then it became colorless, but on the addition of alkali to the distillate it became yellow, indicating that some of the oxidizing agent was still in solution. This, therefore, served as a valuable test to ascertain when all the ortho-nitrophenol had been removed, and was carried out on all future steam-distillations, that is to say, alkali was added to the steam distillate until the latter did not become yellow upon the addition. As usual, a tar accompanied by a gray powder separated out on the addition of caustic soda. In order to ascertain whether the tar and powder were the same compound in different states of purity they were separated mechanically and treated apart.

Treatment of the Powder.

It was thoroughly extracted with 250 c.c. alcohol for six and one-half hours giving a solution, dark red to transmitted light and greenish to reflected light. The sulphate was then thrown down and dissolved in water, giving an orange yellow solution. Sodium hydroxide threw down from this a grayish white precipitate, which, when washed and dried, looked fairly impure. It was then extracted with benzene for 8 hours and when recrystallized melted at 270°.

Treatment of the Tar.

After washing thoroughly and extracting the tar with 300 c.c. of alcohol for five hours, the sulphate was then precipitated and dissolved in water. On neutralisation the substance came down as a dark powder accompanied by tar. It was extracted with benzene in the following way.

Volume	Time	Color
500 c.c.	4	light orange yellow
350 "	4.5	very light yellow

Evaporation of the total volume of benzene left a brown substance and throughout it could be noticed glistening crystals. These were dissolved in alcohol and subjected to decolorization in the same solution for ten and one-half hours. The crystals obtained from this solution, after recrystallisation, melted at 269°.

Evidently, therefore, the tar and the powder are one and the same substance in different states of purity and were, accordingly, treated together in the following experiments.

EXPERIMENT NO. 10.

The other proportions remaining the same, the quantity of ortho-nitrophenol was reduced to 0.237 molecules, a large excess having been noted with the 0.252 molecules employed in the preceding experiment.

The mixing was carried out in the usual way, the heating consisting of the following stages:

5 hrs at 100°

8.5 " " 140°

Contrary to expectation, no violent reaction occurred, only a moderate amount of bubbling taking place. Two and one-half litres of hot water were added and the melt steam-distilled for three hours. At the end of this time the addition of alkali to the distillate did not produce a yellow color. The tar, thrown down on neutralisation, was extracted in the following fractions.

Volume	Time	Color.
700 c.c.	3 hrs.	Orange.
500 "	8.5 "	Yellow
500 "	5.5 "	Light yellow
500 "	8 "	" "
2200 "	25 "	

The total volume was concentrated and allowed to stand twenty-four hours. Yellow crystals were deposited, these were filtered, dissolved and decolorized in aqueous-alcohol solution for five hours. The substance was then recrystallized and obtained as a yellowish amorphous powder.

Treatment of the Residue from the Benzene extraction.

This was extracted with 900 c.c. of alcohol for a period of eleven hours. Dry hydrochloric acid gas was passed through a portion of this solution, throwing down the yellow hydrochloride. This, when converted to the base yielded, a small amount of a white powder.

The rest of the solution was treated with sulphuric acid. The sulphate was converted to the base, extracted with 500 c.c. of benzene for four hours. The hydrochloride was precipitated, reconverted to the base and the process repeated, finally yielding a small quantity of yellow glistening crystals.

EXPERIMENT NO. 11.

Reacting Constituents.	Weight in grams.	Molecular Proportions.
Dianisidine Sulphate	50	0.146
Glycerol	250	2.71
Conc. Sulphuric acid	300	3.07
Ortho-nitrophenol	55	0.396

This experiment was carried out on a larger scale than those immediately preceding. The usual order and method of mixing were adhered to. A fairly vigorous bubbling ensued,

but no violent reaction occurred. The period of heating was fifteen hours, two hours at room temperature, eight at 100°C and five at 140°C. Steam-distillaion was then carried on for fourteen hours. After neutralization the resulting tar and powder were extracted with 1350 c.c. of alcohol for nineteen hours. The substance in solution was converted to the hydrochloride and back to the base. The latter came down from acid solution in two layers, a lower one of a tarry material and an upper one of a grayish white flocculent mass. This was dissolved in alcohol and subjected to the decolorization process for twelve and one-half hours. After filtering and concentrating, sparkling white crystals separated out. These became yellow on drying and then white again. Their melting point was 270-275. Upon recrystallization this changed to 271-273°. After another recrystallization the solid material became quite yellow and fluffy. Various solvents were resorted to in an attempt to eliminate the yellow color. Acetone appeared to extract a small amount of the impurity without materially affecting the substance, but the removal was not complete. It was then attempted to recrystallize the substance from benzene. However, it is not soluble in this solvent to the extent of one percent at ordinary temperatures and, consequently, practically no solution took place until a small quantity of alcohol was added. On cooling, a few crystals separated out on the sides of the beaker. These melted at 278°. After recrystallization, the yellow color persisted. A portion of the substance was converted to the hydrochloride and back to

the base. This treatment caused no diminution in the intensity of the color. The remaining portion of the solid was extracted with benzene for several hours and concentrated. Acetone was employed again, and a further small portion of the impurity was removed. On being converted to the sulphate and back to the base, there came down a white powder melting at 278°. This substance was perfectly white and the melting point quite sharp at 278°. It is therefore a pure substance and this is the true melting point.

EXPERIMENT NO. 12.

In this experiment the proportion of ortho-nitrophenol was increased to .446 molecules. The melt was stirred, for three hours in the cold, four at 100°, and then the temperature was slowly increased. In a short while a violent reaction occurred, acrolein vapour and ortho-nitrophenol being ejected from the reflux condenser. The temperature was maintained at 140° for eight hours. Steam-distillation was then carried on for nineteen and one-half hours. Each addition of sodium hydroxide produced a local yellowish color which disappeared on stirring and near the neutral point the substance was precipitated in large yellow flocks, turning green. On filtration, the quantity of powder and tar obtained was of such small proportions that it was considered futile to attempt to extract it.

ANALYSIS OF THE COMPOUND.

	Calculated for $C_{20}H_{16}N_2O_2$	Found.
C	75.95	76.30
H	5.07	5.43
N (Kjeldahl method)	8.87	2.76
N (Dumas ")		18.1
O	10.11	-----

MOLECULAR WEIGHT.

This was determined by two methods.

(1) The depression of the freezing point of para-toluidine.

Employing a solution, the concentration of which was 0.699%, a value of 247 was obtained, whereas, with a concentration of 0.422%, the value was 210.

(2) The equivalent weight of the base, found by weighing the platinum residue after ignition of the platinichloride. The value obtained in this case was 225.

SUMMARY.

In Table II are shown the proportions of the reacting constituents, the time and temperature of heating, the volumes of extraction-solvent required, the lengths of extraction periods, and decolorization periods and the yields obtained calculated on the basis of 100 grams of ortho-dianisidine. The proportions of the reacting constituents employed in these experiments were considerably smaller than

those used in the Patent previously mentioned, but definite yields, although they might be very small, should have been obtained. As will be seen, however, the method of preparation and purification applied successfully to the product obtained by subjecting benzidine to Skraup's reaction is not applicable in the case of ortho-dianisidine. The Patent states that Benzene - 1 - 1 - Dimethoxy - Benzene - 3 - 3 - Diquinoline, existing as silvery needles, is obtained by means of this reaction, and that this substance melts at "about" 100°C. and has a peculiar irritating odor.

The compound obtained in these experiments, however, has quite different characteristics. It melts at 278° C. and has no odor. When allowed to crystallize out slowly from aqueous alcohol it forms silvery needles but when recrystallized rapidly it separates as a white powder.

It was observed, during the process of purification, that when the hydrochloride of this substance was dissolved in water and sodium hydroxide added, to precipitate the base, if the solution was not dilute, the base, on separation, was accompanied by tar; by diluting the solution sufficiently, however, this undesirable condition was eliminated, the base separating out as a fine powder.

It is practically insoluble in water, slightly so in benzene and acetone, and easily in alcohol. The hydrochloride and sulphate are sparingly soluble in alcohol but very soluble in water.

From the extracts of the work done it will be seen

that when the reaction was violent, the yield was exceedingly low, practically negligible, and the best results were obtained when the reaction was conducted in such a way as to produce only a vigorous ebullition.

A noteworthy point is the close agreement existing between the percentages of carbon and hydrogen in the compound isolated and the proportions of these elements present in Benzene - 1 - 1 - Dimethoxy - Benzene - 3 - 3 - Diquinoline.

The process of identification of this compound, which, owing to lack of time, has not yet been completed, is being continued.

A.- Dianisidine Sulphate
B.- Glycerine
C.- Ortho-nitrophenol
D.- Nitrobenzene
E.- Concentrated Sulphuric acid.

TABLE NO. 2.

EXPT.	Proportions Mols.	Heating Time in hours	Process Temp. °C.	Steam Distillation. Time in hour.	Exatraction Vol. Alcohol	Exatraction Vol. Benzene	Exatraction Time in hours	Decolorization Time in Hours.	REMARKS.
(6)	A .175 B 3.26 C 0.302 E 3.57	3	135	2.5					Reaction very violent.
(7)	A 0.087 B 1.63 C 0.151 E 1.95	1 8	100 140	2.15					ditto
(8)	A 0.087 B 1.63 D 0.266 E 1.95	2.5 5	100 140	1		200 600 400	27.5 4.5 5	6	Vigorous reaction yield 1 gram m.p. 270
(9)	A 0.087 B 1.63 C 0.252 E 1.95	2.5 10	100 140	4	400 250 300	300	5 6.5 8 5	8	Vigorous reaction white powder yield 1.5 grams m.p. 269
(10)	A 0.087 B 1.63 C 0.237 E 1.95	5 8.5	100 140	3	850 2700 900		8.5 29 11	10.5	Vigorous reaction yellowish crystals 9 grams
(11)	B .146 B 2.72 C 0.396 E 3.06	2 8 5	20 100 140	14		1350	18	12.5	Vigorous reaction tield 8 grams white powder. m.p. 278
(12)	A .175 B 3.20 C 0.447 E 3.67	3 2 8	20 100 140	19.5					Reaction very violent.