SUMMARY.

OF
THESIS

PRESENTED FOR THE
DEGREE OF MASTER OF SCIENCE

BY

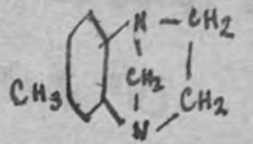
ELLA GLADYS KATHERINA COX.

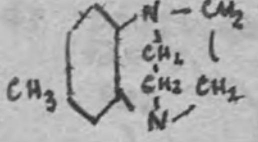
ROYAL HOLLOWAY COLLEGE.

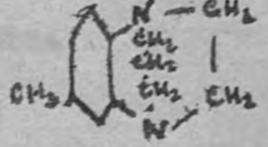
DECEMBER 1926.

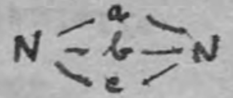
SUMMARY.

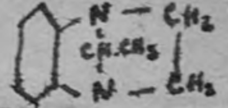
The following research was carried out primarily owing to the interest of the compounds.





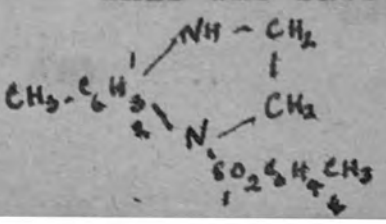


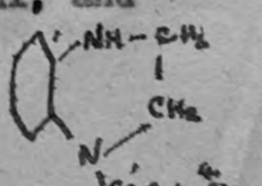
obtained in 1920 by Moore and Doubleday from the viewpoint of the stereochemistry of the nitrogen atom, and the lack of knowledge of the simple derivatives of the tetrahydroquinoxaline bases, and consisted mainly of attempts to obtain from tetrahydroquinoxaline bases of the above type,  where a, b, and c, are carbon chains.

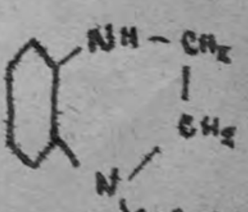
The direct condensation of tetrahydroquinoxaline with other substances was investigated. A compound of the desired type was obtained only with acetaldehyde, when  was obtained, examined and identified.

The failure to obtain a similar action with other reagents was attributed to the presence of two reactive imidic hydrogen atoms in the tetrahydroquinoxaline molecule, and attempts were made to replace one of these with a less reactive group.

This was successful, and

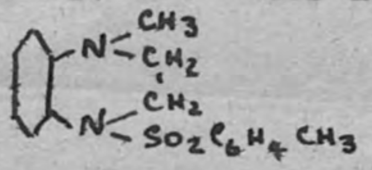




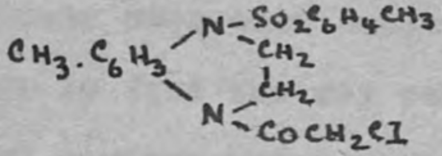


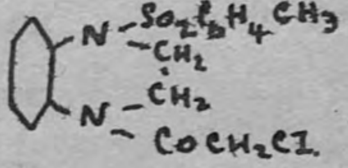
were obtained.

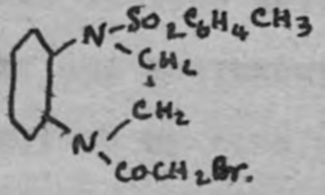
The next step was to substitute for the imidic hydrogen atom remaining in these compounds a carbon chain containing a reactive group, and after a trial experiment giving

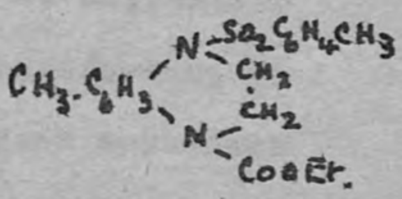


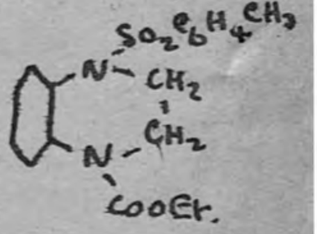
, five of such compounds





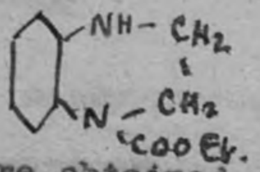


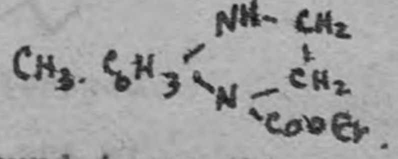




were obtained.

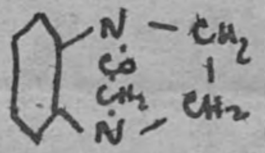
The next stage, more difficult, was the elimination of the inactive group first substituted, so that the desired condensation could occur. This was successful, and in all cases the toluolsulpho group was removed from the molecule; the two compounds

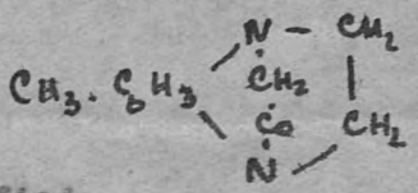




were obtained. It was found impossible to bring about the desired condensation with either of these compounds; all attempts to cause them to react resulted in the loss of carbon dioxide from the molecule.

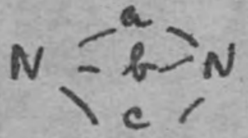
In the other cases, the subsequent condensation occurred so readily after the removal of the toluolsulpho group from the molecule that it was impossible to isolate the intermediate products. The two compounds





were obtained and identified.

Thus three new compounds of the type



where a,b, and c are carbon chains have been obtained, identified and examined, and a method of preparation of such compounds worked out. In addition, derivatives of tetrahydroquinoxaline and its methyl derivative in which another group has been substituted for one only of the two imidic hydrogen atoms have been obtained and examined.

A

T H E S I S

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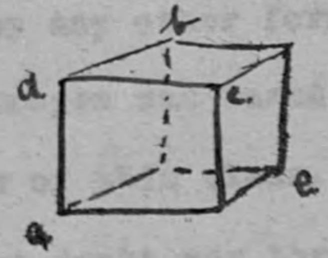
ELLA GLADYS KATHERINA COX.

N Monosubstituted derivatives of tetrahydroquinoxaline.

ROYAL HOLLOWAY COLLEGE
University of London.
December, 1926.

HISTORICAL AND INTRODUCTORY.

The first speculations as to the stereochemistry of nitrogen compounds were put forward by Van t Hoff in his Ansichten uber Organische Chemie. In this, he assumed that a tervalent nitrogen compound could be represented by a plane formula, the three atoms directly attached to the nitrogen atom and the nitrogen atom all lying in one plane. For pentavalent nitrogen compounds, he put forward the cubic formula, in which the nitrogen atom was represented at the centre of the cube, and the five atoms attached to it at five of the corners of the cube, as sketch



The reason for the first of these formulae was that no stereoisomers of nitrogen were known, and the plane formula was the only one which did not demand any isomerism. The cubic formula was ~~d~~ derived from the facts that pentavalent nitrogen compounds were usually prepared from tervalent compounds by the addition of two more radicles, one usually acidic and ionisable. The three radicles present in the tervalent compound were represented by a, b, and c, and were supposed now to havecbeen displaced from the same plane as the nitrogen atom by the differences between the two added radicles.

Thus a change of valency direction was assumed to occur in the passage from tervalent to pentavalent compounds.

Unlike the tetrahedron theory of the valency directions of the carbon atom, this theory of the stereochemistry of nitrogen was not put forward to explain an existing isomerism that could not be represented by any other formulae. The formula for tervalent nitrogen was based on the absence of any stereoisomers of this class.

The first doubt was thrown on this supposition only a very few years later, by the discovery in 1883 by Goldschmidt(1) and Meyer of an isomer of benzildioxime.

To explain this and the other similar isomeric oximes which were soon after discovered, Hantzsch(2) and Werner put forward in 1890 their celebrated theor that in a tervalent nitrogen compound the three atoms attached directly to the nitrogen atom did not necessarily lie in the same plane as the nitrogen atom. Their suggestion was that, in certain cases the nitrogen atom might be at the corner of a tetrahedron, and the three attached atoms at the three other corners, but they did not claim that this was the invariable arrangement.

This theory satisfactorily explained all the known cases of isomerism, for instance the existence of two benzilmonoximes and three benzildioximes, and rapidly gained ground in opposition to the theory of Auwers and Meyer (3), that this isomerism was based on the absence of free rotation between two singly linked carbon atoms (4). The isomerism of the oximes corresponded to the geometric isomerism of ~~the oxi~~ maleic and fumaric acids.

Much research was stimulated by the theory in the next few years, and many attempts were made to resolve substituted ammonias into optical isomers, for while isomerism, unassociated with optical activity was capable of explanation in terms of structural chemistry, as opposed to stereochemistry, isomerism associated with optical activity had been found only in the case of stereoisomers. The resolution of any of these compounds would be additional and conclusive proof of the Hantzsch Werner hypothesis, and would establish the stereochemistry of tervalent nitrogen Attempts to resolve a great variety of nitrogen, bases, thus benzylethylamine, p-tolyl hydrazine, and tetrahydroquinokine, with active acids, failed invariably.

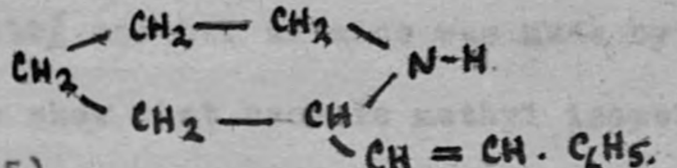
During the same years, beginning in 1891 with Lebel's resolution of methylethylpropylisobutyl ammonium chloride by the action of pencillium glaucum many successful attempts were made to resolve quinquevalent nitrogen bases containing one nitrogen atom attached to five different radicles, notably by Pope and (4) Peachey. Alternative structures to the Van t Hoff cubic formulae were put forward for these compounds. Willgerodt supposed that the atoms attached to pentavalent N were arranged at the corners of the figure obtained by placing two tetrahedra with one side of each superposed over a side of the other, and Bischoff suggested that they were at the corners of a four sided pyramid on a square base, in both cases the nitrogen atom being at the geometric centre of the figure.

Attempts were made to find the isomers

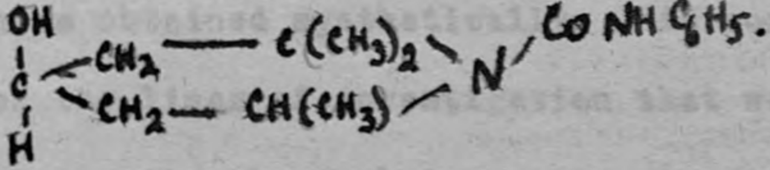
predicted by these theories by their exponents, until new light was shed on the subject by the resolution of methylethylaniline oxide, in which two of the valencies were attached to the one oxygen atom. This justified the supposition that four of the attached radicles were grouped round the nitroggn atom, giving a tetrahedron structure similar to that of a tetravalent carbon compound, and capable of giving stereoisomerides possessing optical activity, as in the case of the carbon compounds, and w ith the other valency direction less fixed, and with the attached group outside the other structure.

The failure to resolve ~~the~~ tervalent nitrogen was inconclusive evidence; racemic compounds might be formed, hydrolytic dissociation of the salt might occur in crystallisation, or most likely of all, the change of valency directions in the passage from ter-valent to pentavalent nitrogen during salt formation might affect the result. Many experiments were carried out which should avoid these possible causes of failure, but no positive results were obtained.

A few cases of isomerism were repotted in which the isomerism was apparently due to tervalent nitrogen. Ladenburg assumed that the change of stilbazoline to isostilbazoline on heating, accompanied by a change in optical activity, corresponded to a difference in configuration, the hydrogen atom attached to the ~~ni~~ nitrogen atom wandering from one side of the ring to the other during the transmutation.



Groschuff(5) discovered two forms of the phenyliso-cyanate derivative of a-vinyldiacetone alkamine



In all these cases, the possibility of structural isomerism was not excluded, while Jones(6) proved that the two isomerides of the compound of m-4-xylidine and acetaldehyde obtained by Miller and Plochl(7) in 1896 were structural isomerides, one possessing a ring and one an open chain formula.

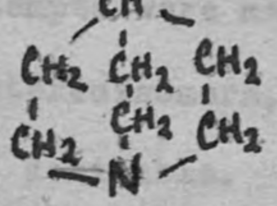
These results were difficult to reconcile with the Hantzsch Werner theory, but at the same time, this theory was confirmed by the isolation by Mills and Bain(8) of two optical isomerides of cyclohexanone 4-carboxylic acid by resolution with morphine or quinine, thus establishing a case of definite stereoisomerism which it was difficult to explain except by the Hantzsch Werner hypothesis.

This was followed by the resolution of the N-benzoyl and the semicarbazide derivatives of the same acid by Mills and Bain,(19) and later by the resolution of pyridylhydrazone of cyclohexanedithiocarbonate by Mills and Schnidler.(20)

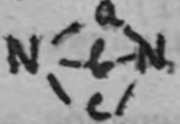
In 1919 another advance was made by Hess,(9) who was able to show that racemic methyl isopelletriene obtained from isopelletriene of pomegranate was stereoisomeric with the racemic compound of methyl conhydrinone obtained synthetically. This work was typical of the lines of investigation that were being pursued at the time by workers on the stereochemistry of nitrogen. Since all the previous known cases of stereoisomeric nitrogen compounds contained the nitrogen atom linked to a carbon atom by a double bond, which fixed the directions of two of the nitrogen valencies, attempts were being made to find cases of stereoisomerism among tervalent nitrogen compounds in which some of the valency directions were fixed by the nitrogen f forming part of a ring. Hess was successful in this.

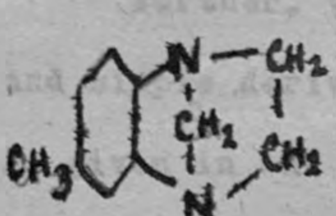
In the same year,

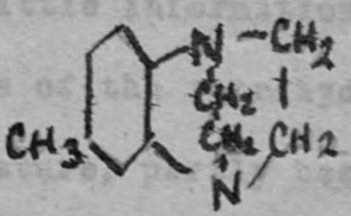
Meisenheimer (10) published the result of his work on quinuclidine

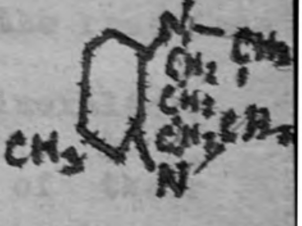


in which the directions of the three valencies ~~i~~ of the nitrogen atom were fixed, but was unable to resolve it. Finally, in 1923, Meisenheimer, after a great deal of time had been devoted to the subject, announced (11) that asymmetric saturated tervalent ~~at~~ nitrogen can give rise only in very special cases, if at all, to stereoisomerides.

In 1921, a new type of nitrogen compound, bases of the type  where a, b, and c, represent different carbon chain structures, were obtained by Moore and Doubleday (12), who discovered and investigated the compounds







In the light of the previous introduction, the interest of these compounds from the standpoint of the stereochemistry of tervalent nitrogen can be easily seen; all the valency directions of two tervalent nitrogen atoms are fixed, in a compound containing no other active groups.

Before attempts were made to resolve these compounds into stereoisomers, further investigation of the group was desirable.

In the first place, the properties of these substances were abnormal. Thus, although the bases were nearly colourless, and dissolved in benzene and nitrobenzene without changing the colour of the solvent yet in dilute mineral acids they dissolved to give red solutions. Their salts, and also their compounds with methyl iodide had a red or reddish brown colour both in the solid and in solution.

Then Meisenheimer (13) had been unable to obtain corresponding compounds when starting with tetrahydro quinoxaline, instead of with the methyl tetrahydroquinoxaline used by Moore and Doubleday.

Further, very little information on the reactions and simple derivatives of the tetrahydroquinoxalines is given in the literature, partly because of their great reactivity, which leads to the formation of complicated mixtures, and partly because of the considerable labour involved in the preparation of the tetrahydroquinoxalines themselves. This gave another reason for undertaking the work described below.

Experiments along the following lines were carried out.

(1) The condensation of o-aromatic diamines with mesoxalic and acetone dicarboxylic esters was investigated, to obtain oxytetrahydro-quinoxalines which could be used for the preparation of oxygen containing bases.

Condensation products were obtained, but of a type unsuitable for the purpose in view.

(2) Experimental details for the routine preparation of tetrahydroquinoxaline required for (3) (4) and (5) were worked out.

(3) Moore and Doubleday's work was repeated, using tetrahydroquinoxaline as the original compound. Meisenheimer's results were found to be correct: thus the behaviour of tetrahydroquinoxaline and of its methyl compound, under the conditions used, are quite different.

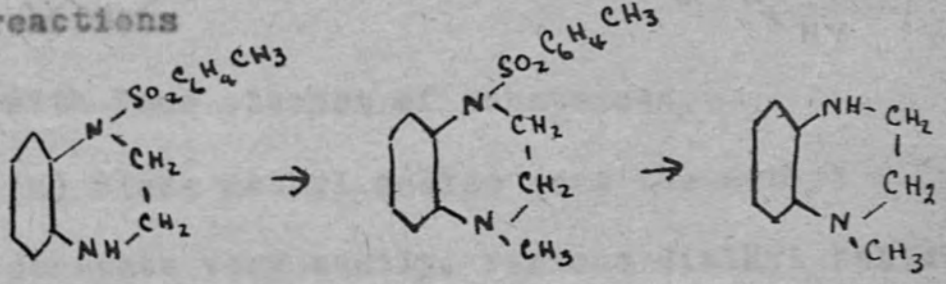
(3a) Grignard's reagent was used in an attempt to form halogen compounds for subsequent reaction with haloid compounds: this was not successful.

(4) The condensation of tetrahydroquinoxaline with substances containing reactive groups, other than those used under (2) was investigated. Reaction occurred only with acetaldehyde and chloroformic ester.

(5)THe results obtained under (3)and (4) indicated that the reactions gave rise to complicated and mixed products, and it was thought that this might be due to the presence of two very reactive -NH- groups in the original compounds. Meisenheimer had already attempted to obtain a monobenzoyl derivative of tetrahydroquinoxaline, in the hope of getting simpler reactions by using the monobenzoyl tetrahydroquinoxaline, containing only one -NH- group, but stated (13) that under all the conditions used, he was able only to isolate a dibenzoyl compound.

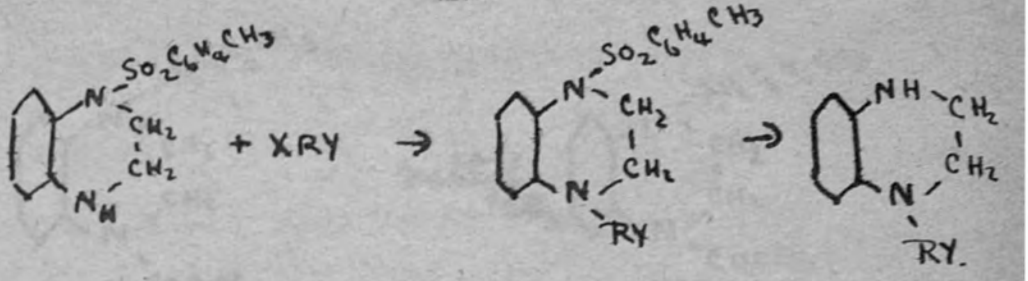
It has, however, been found possible to prepare both monobenzoyl and monotoluol-sulpho compounds from tetrahydroquinoxaline and from methyltetrahydroquinoxaline.

Using methyl iodide, it was found possible to replace the remaining imidic hydrogen in the monotoluolsulpho compounds with methyl, and then, by elimination of the toluolsulpho group, to obtain a monomethyl tetrahydroquinoxaline, according to the reactions

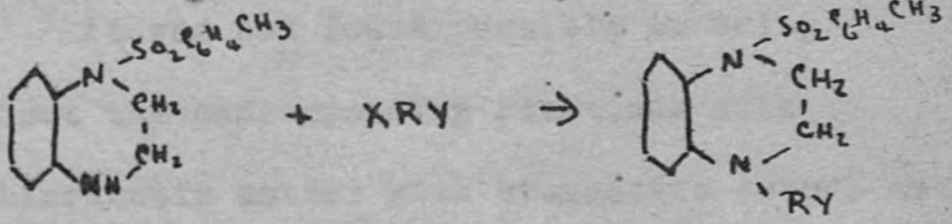


Attempts were then made to proceed along this line by substituting the imidic hydrogen in the monotoluolsulpho compounds by carbon chains containing a reactive group, so that after elimination of the toluolsulpho group, further condensation to give substances of the desired type could occur.

Where X-R-Y is a compound with a carbon chain R, and two reactive groups X and Y, it was hoped to bring about the following series of reactions



Attempts were made to bring about the first stage in this series, the reaction

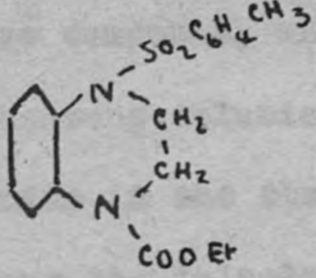


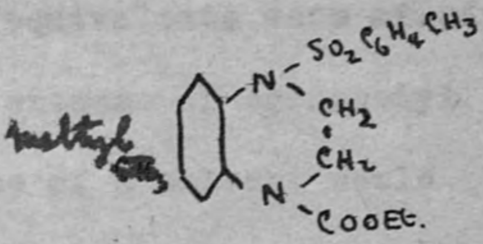
with four classes of substances.

(a) Since methyl iodide gave the methyl derivate very easily, various dialkyl halides were tried. These included methylene diiodide, ethylene dibromide, trimethylene dibromide, and trimethylene chlorobromide; none of these substances would react with the monotoluol-sulpho compound.

(b) Attempts with ethylene chlorhydrin were also unsuccessful.

(c) Since tetrahydroquinoxaline reacted readily with chloroformic ester, attempts were made to get this to react with the monotoluolsulpho derivative. These were successful, and both

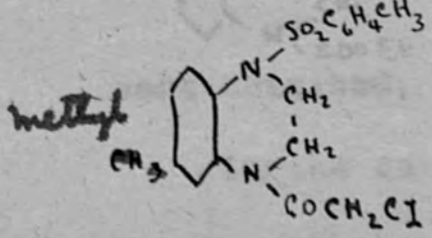


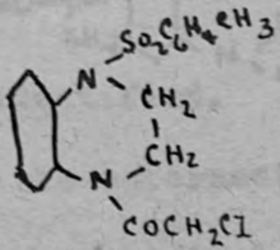


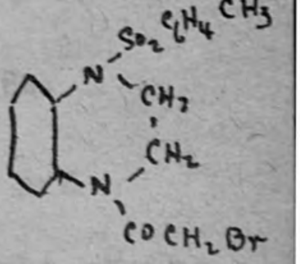
were obtained.

It was not found possible to bring about the corresponding reactions with chloracetic ester: with bromacetic ester, and more violent conditions, a little of an ester was obtained, but not sufficient for further investigation.

(d) Chloracetyl chloride and bromacetyl bromide both reacted in the desired way with the monotoluol sulpho derivative of tetrahydroquinoxaline, and the former with the monotoluolsulpho derivative of methyl tetrahydroquinoxaline. Thus the following compounds have been obtained

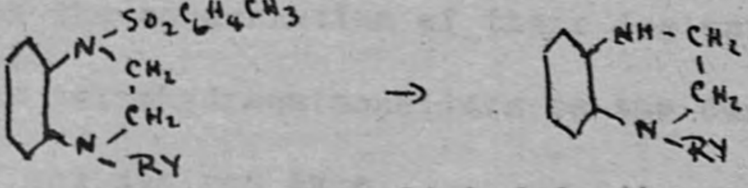




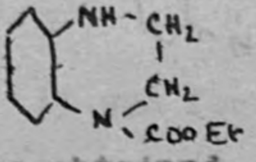


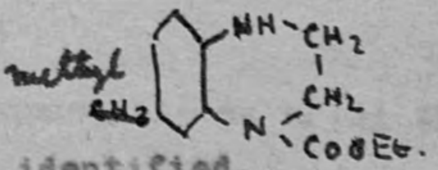
It was also discovered, that while bromacetyl bromide would react to give the above compound, when equivalents were mixed in benzene solution, excess of bromacetyl bromide in the absence of a solvent would remove the toluolsulpho group from the mono-toluolsulpho derivative of tetrahydroquinoxaline and yet not give the dibromacetyl derivative of tetrahydroquinoxaline, although this derivative could be obtained by the action of bromacetyl bromide on tetrahydroquinoxaline. This reaction was investigated.

The next stage was the removal of the t toluolsulpho group from the compounds obtained above, the desired reaction being of the type



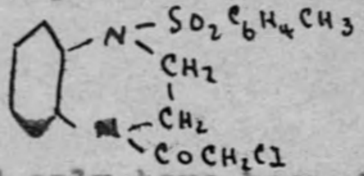
This was accomplished in the case of the esters, and the two compounds



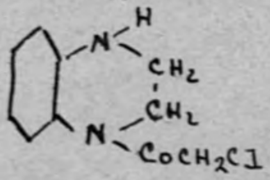


were obtained, and identified.

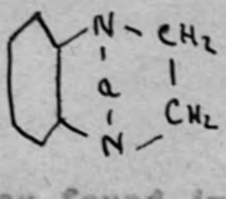
In the case of the chloracetyl and bromacetyl compounds, the toluolsulpho groups were eliminated, but a further condensation took place, so that it was not possible to isolate the monochloracetyl and bromacetyl tetrahydroquinoxalines. In the former case, however, the presence of the monochloracetyl tetrahydroquinoxaline among the reaction products was established by the fact that the reaction product contained no sulphur, yet gave with p-toluene sulphochloride some of the compound



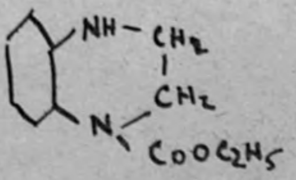
which could only have been derived from

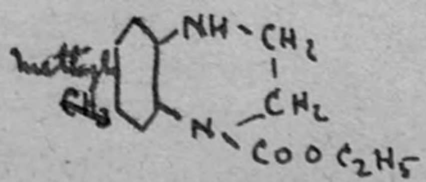


The third stage in the series of reactions was the condensation of these derivatives of the tetrahydroquinoxalines to the compounds of the desired type



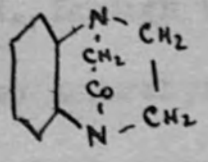
It was found impossible to bring this about in the case of the compounds

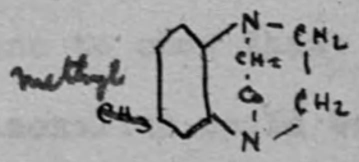




These compounds were very stable: they could be distilled unchanged, and did not lose alcohol with phosphorus pentachloride, sodium, or thionyl chloride; reaction only occurred with the disruption of the whole molecule. Attempts to hydrolyse the esters and obtain the corresponding acids were unsuccessful: the molecules always lost carbon dioxide and gave the tetrahydroquinoxalines again.

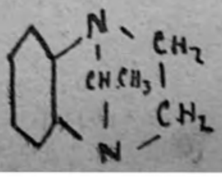
On the other hand, it has been stated above that it was impossible to isolate the monochloracetyl and monobromacetyl derivatives of the tetrahydroquinoxalines as further condensation took place so readily: this condensation was of the desired type, and the compounds





were obtained and analysed.

Another new compound of this type had been obtained by the direct action of acetaldehyde on an alcoholic solution of tetrahydroquinoxaline:this was shown to have the constitution



Thus three new compounds of the desired type were obtained and investigated.

(6)In view of the remarkable difference in behaviour between tetrahydroquinoxaline and its methyl derivative referred to above (page 9), it appeared desirable to investigate other derivative of the substance. To obtain such derivatives it is necessary to find methods for producing aromatic diamines of suitable constitution in quantity. Experiments on the preparation of 1.2.diamino4.ethoxy benzene and of 1.8.diamino naphthalene were carried out, but the line of work was given up in favour of those mentioned above before satisfactory results had been o obtained. Enough was done to show thatt 4. ethoxy tetrahydroquinoxaline could be obtained but only by a very laborious process.

EXPERIMENTAL.

(1) The condensation of 1.3.4.toluylene diamine with acetonedicarboxylic ester.

The base was ground up in a mortar with a little water and glacial acetic acid (2 mols. of the acid to 1. mol. of the base.) The product was heated with a large amount of water and filtered hot. Acetone dicarboxylic ester (1mol. of ester to 1 mol. of base) was added, and sufficient alcohol to make the whole homogeneous.

After standing several hours a white precipitate had appeared, which, after repeated recrystallisations from alcohol gave a pure product melting at 250 C.

Analyses.

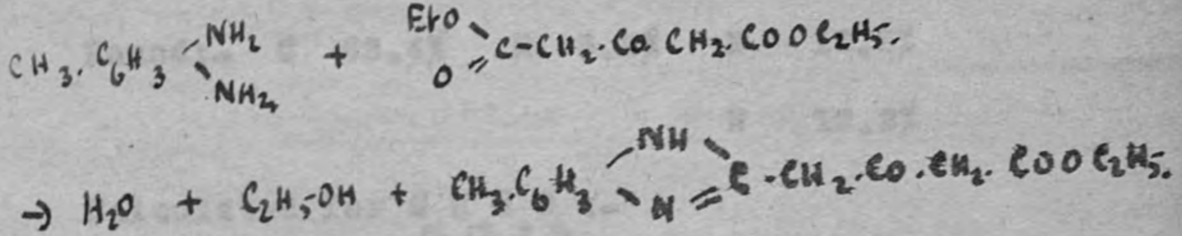
Found:- C 64.8% H 6.1% N10.8%

C64.7% H 6.0% N 10.8%

Calculated for $C_{14}H_{16}N_2O_3$:-

C 64.57% H 6.20% N 10.76%

This formula is that of a condensation product of one molecule of base with one molecule of ester by elimination of one molecule of water and one of ethyl alcohol. The most likely scheme of the reaction is



$$CH_3.C_6H_3\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix} + \begin{matrix}EtO\diagdown\\ O\mathbin{/\!\!/}\end{matrix}C-CH_2.Co\,CH_2.COOC_2H_5.$$

$$\rightarrow H_2O + C_2H_5OH + CH_3.C_6H_3\begin{matrix}\diagup NH\diagdown\\ \diagdown N=\end{matrix}C-CH_2.Co.CH_2.COOC_2H_5.$$

since that corresponds to the usual type of condensation between an aromatic o -diamine and an ester.(21).

(2) The condensation of 1.3.4.tolyulene diamine with mesoxalic ester.

The base was ground up with a little water and and glacial acetic acid (2 mols. of acid to 1 mol. of base), and the whole heated with a large amount of water, and filtered. Mesoxalic ester was added; after standing for some hours, the light yellow crystalline precipitate which had been formed was filtered off; after several recrystallisations from alcohol a pure product melting at 174 C was obtained. This crystallised in light yellow needles.

Analyses.

Found:- C 62.4% H 5.3% N 12.3%

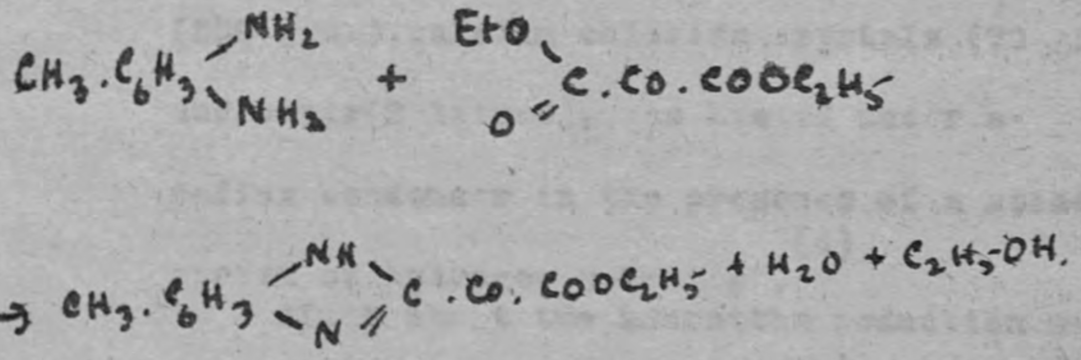
N 12.2%

Calculated for $C_{12}H_{12}N_2O_3$:-

C 62.07% H 5.17% N 12.97%

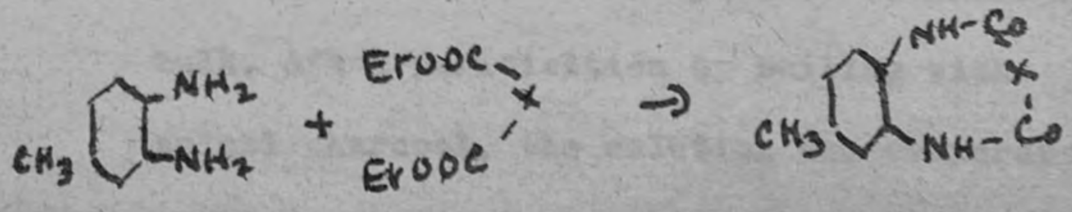
This formula is that of a condensation product of one molecule of base with one molecule of ester by elimination of one molecule of water and one of ethyl alcohol.

The most likely reaction is



and the production of this compound is again what (21) is likely to occur in this reaction.

Since in neither case did the reaction give derivatives with the two -NH- groups, according to the scheme



no further condensations of this kind were ~~at~~ attempted.

( ) Routine method for the preparation of tetrahydroquinoxaline.

The starting material used was o-nitraniline.

(a) The reduction of o-nitraniline to o-phenylene diamine.

A mixture of o-nitraniline (200 grs.) with ~~steel~~ cast iron. turnings (600 grs.), iron filings (200 grs.), calcium chloride crystals (70 grs.), and water (2 litres), was heated under a reflux condenser in the presence of a steady stream of hydrogen sulphide (4).

After about two hours the reduction was complete, as shown by the absence of colour in the condenser.

The reaction mixture was filtered, and the iron sludge washed. The combined filtrates were acidified with strong hydrochloric acid (140 c.cs.), and evaporated to smaller bulk. After purification by boiling with animal charcoal, the solution was evaporated until crystals were deposited, and then the hydrochloride of o-phenylene diamine was precipitated by the addition of excess of concentrated hydrochloric acid (280 c.cs.), and filtered off after cooling.

This hydrochloride was dissolved in the least amount of hot water, and the base precipitated by the addition of a slight excess of strong caustic soda solution. The o-phenylene diamine was filtered off after cooling, dried on a porous plate, and purified by distillation.

The average yield of base was 70% of a very pure compound.

(b) The formation of the symmetrical ditoluol sulpho compound of o-phenylene diamine.

The base was dissolved in ten times its weight of pyridine, and p-toluene sulphochloride (2m mols. to one mol. of base) was added gradually the temperature being kept below 25 C. After standing for an hour, the solution was heated on a water bath for two hours, cooled and poured into an excess of dilute hydrochloric acid with stirring. The derivative was precipitat as a light solid, which was filtered, washed with hot water, and dried in the steamoven.

Further purification was seldom necessary; this could be brought about either by crystallisation from glacial acetic acid, or by converting the substance into its sodium salt. The latter was done by dissolving the substance in a moderate amount of hot water containing about an equivalent amount of caustic soda in solution, filtering, and adding an excess of strong caustic soda solution. On cooling, the sodium salt crystallised out. This salt was then dissolved in water, and poured into an excess of dilute hydrochloric acid, when the pure derivative was precipitated.

The yield in this reaction was practically theoretical; the substances was in the form of nearly colourless crystals, melting at 202°C

(C) The conversion of the ditoluolsulpho derivative of o-phenylene diamine into the ditoluolsulpho derivative of tetrahydroquinoxali

This reaction was more difficult to bring about.

The derivative of the o-phenylene diamine was heated under a reflux condenser for ten hours with aproximately the equivalent amount of ethylene dibromide, and an amount of 2N potash solution exactly equivalentto the dibromide.

The solid product was dried in the steamoven, ground up, and heated repeatedly with dilute potash solution until nothing more went into solution, as shown by the absence of any precipitate when the potash was acidified.

The product was a light brown powder, melting at 168°C.

The usual yield was 70%.

The remainder of the yield was regained from the alkaline washings as the unchanged o-phenylene-diamine-derivative.

ditoluolsulphoderivative of o-phenylene diamine.

(B) The hydrolysis of the ditoluolsulpho derivative of tetrahydroquinoxaline.

This is the most difficult stage in the synthesis, since although the hydrolysis is readily brought about by means of strong sulphuric acid under strictly defined conditions the isolation of the product from the sulphuric acid solution in good yield is not easy.

The derivative (100 grs.), in a finely powdered state, was added slowly and with stirring to strong sulphuric acid (116 c.cs.)

The temperature was kept below 25 C.

After standing in a dessicator for 24 hours the hydrolysis was complete, as shown by the absence of a precipitate on adding a drop of the sulphuric acid solution to water.

The solution was then diluted by pouring into water(580 c.cs.) keeping the temperature below 25 C. The solution was filtered.

This solution was then made alkaline by pouring into an excess of strong ammonia, keeping the temperature below 25 C. Most of the tetrahydroquinoxaline was precipitated and could be filtered off. A little more could be obtained by extracting the filtrate with ether. The base was purified by recrystallisation from a mixture of 2 parts of alcohol to 1 parts of ether.

The tetrahydroquinoxaline obtained by this method was in the form of light brown crystals melting at96 97 C.

(3) The repetition of Moore' and Doubleday's work, using tetrahydroquinoxaline as the original compound.

Equivalents of the base and of methylene diiodide were dissolved in alcohol, sealed off in a hard glass tube, and heated to 80 C for several hours.

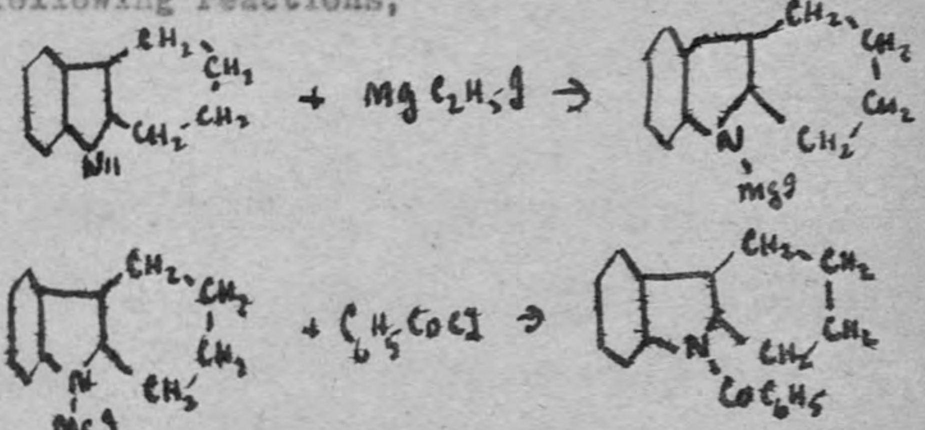
The contents of the tube were acidified, and extracted with ether. Aconsiderable amount of unchanged diiodide was obtained.

The acid solution was made alkaline with ammonia, and extracted with benzene; unchanged base was obtained, and a little of a dark solid, insoluble in benzene, was left.

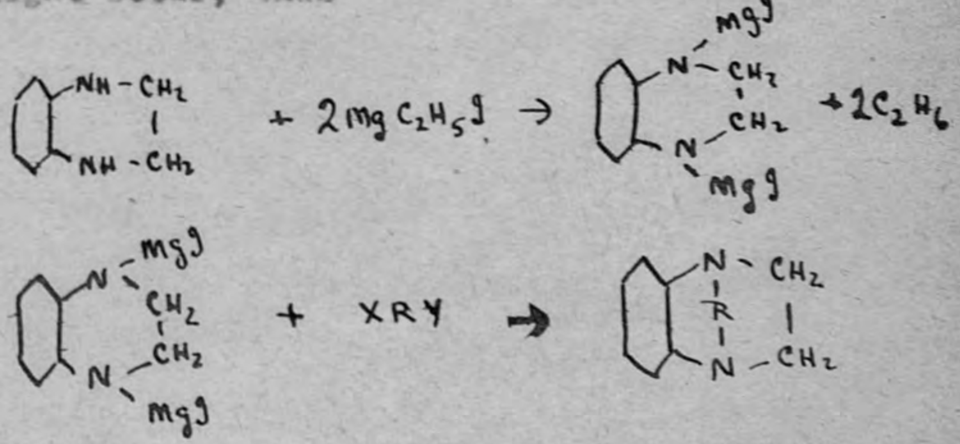
The experiment was repeated at higher temperatures, but, although a little more of the dark solid was obtained, it was very gelatinous, and could not be worked up.

Experiments on the same lines were tried, without a solvent and with benzene as a solvent. Also with ethylene dibromide, trimethylene dibromide and trimethylene chlorobromide in the place of the methylene diiodide: but in no case could a condensation product be isolated.

(3a) W.H.Perkin (5) found it possible to replace the imidic hydrogen of tetrahydrocarbazole to give the 9.benzoyl compound, by the following reactions,



There was thus a possibility that the corresponding reaction with tetrahydroquinoxaline might occur, thus



A solution of MgC_2H_5I was made, and an amount of the base(1 mol. of base to 2mols. of the Mg compound), dissolved in dry ether, was added slowly.

Effervescence occurred in the cold, and a solid separated; when no more ethane was evolved, even on warming, the solution was cooled, and methylene diiodide (1 mol. to 1 mol. of base) was added. Reaction occurred with the formation of tarry products from which nothing definite could be isolated except a small quantity of the original base.

In the hope of getting a simpler reaction by the use of methyl iodide, the experiment was repeated, using an amount of methyl iodide sufficient to give the dimethyl derivate of the base, in the place of the methylene diiodide, but again no definite product could be isolated.

(4) The condensation of tetrahydroquinoxaline with other substances.

Many experiments were made to effect condensation between tetrahydroquinoxaline and acetone, benzaldehyde, mesoxalic ester, acetone dicarboxylic ester, chloracetic ester and chloracetic acid, using acetic acid and piperidine as condens~~//~~ing agents, and carrying out the experiments in both aqueous and alcoholic solutions and in the absence of a solvent, but in no case was there any evidence of reaction.

When acetaldehyde was added to an alcoholic solution of tetrahydroquinoxaline, reaction occurred almost immediately with the formation of a light brown precipitate.

This substance was found to be very sparingly soluble even in hot alcohol or in ligroin; it dissolved quite readily in benzene, acetone and glacial acetic acid, giving in the last case a red solution, but in no case could a recrystallisation be effected.

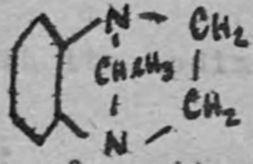
The substance was purified by repeated washings with hot alcohol, and then precipitation by ligroin from a solution in either benzene or chloroform.

In this way, a light brown microcrystalline substance was obtained; this had no definite melting point, but decomposed at about 200 C.

In appearance and properties it closely resembled the compounds obtained by Moore and Doubleday; thus the substance was basic, and dissolved in acids giving in each case a red solution, from which the base could be precipitated by alkalis.

Since no derivates of this base wer

with p- toluene sulphochloride, acetic anhydride or benzoyl chloride could be obtained, it was conclyded that the substance had the constitution expressed by the formula



The formation of a nitroso compound, giving Liebermann's reaction, can be explained, by analogy with Dr Whiteley's results in a similar case, (17) by the entry of the -NO- group into a para position in the benzene ring.

Analysis results.

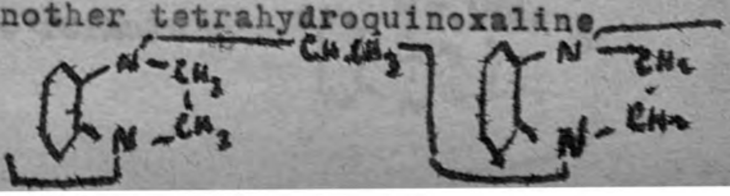
Found:- C 75.3% H 6.9% N 17.7%

C 75.6% H 6.9% N 17.8%

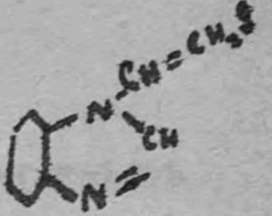
Calculated for $C_{10}H_{12}N_2$:-

C 75.01% H 6.81% N 17.58%

The constitution of this compound could not be regarded as settled until molecular weight determinations had been carried out, since the properties obtained could be given just as easily by a compound in which one nitrogen atom of a tetrahydroquinoxaline residue was linked to the nitrogen atom of another tetrahydroquinoxaline residue , thus

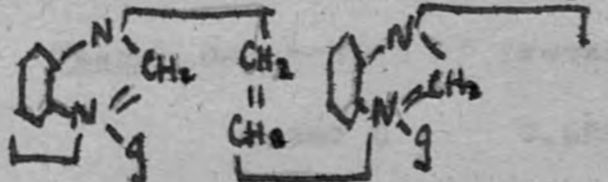


Meisenheimer found that the compound

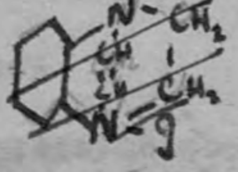


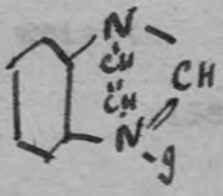
passed on heating on a water bath for some hours, from an almost clear, feebly yellow liquid to a solid, from which a white powder with the same composition as the base, but with its iodine all in the ionisable state, was obtained.

He concluded from its properties, although he did not give the results of molecular weight determinations, that the compound was



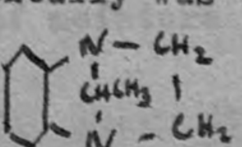
rather than



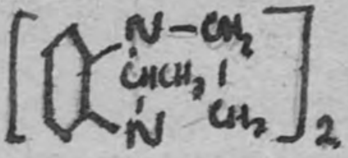


The results obtained for molecular weight by the depression of the freezing point of a solvent with the compound obtained from tetrahydroquinoxaline and acetaldehyde agreed closely with the results of Moore and Doubleday with the compounds described by them.

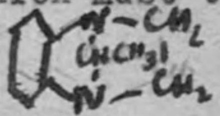
Thus, in phenol, a dissociating solvent, the molecular weight obtained experimentally was that corresponding to the formula



while in benzene solution, the molecular weight obtained experimentally corresponded to the double formula



These results show definitely that the substance can exist in solution in the form of the simple molecule, which must therefore have the formu la



Results.

Phenol. Depression of freezing point observed

0.450 C   0.523 C   0.638 C

Calculated molecular weights

169   175   158

Benzene Depression observed

0.671 C   0.725 C   0.890 C

Calculated molecular weight

339   345   326

Molecular weight of $C_{10}H_{12}N_2$ 159

Chloroformic ester, added to a solution of tetrahydroquinoxaline, caused an immediate precipitation of a light pink powder, not obviously crystalline, which decomposed in the presence of moisture to a brown oil, with an acid reaction.

A portion of this powder was analysed for

for chlorine by treating a weighed amount of it with sodium carbonate solution, and extracting the alkaline solution with ether before estimating the chlorine in the usual way as silver chloride.

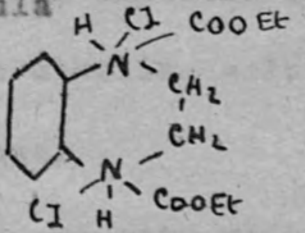
Analysis.

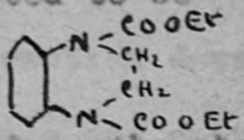
Found :- Cl 19.4%

Calculated for $C_{14}H_{20}N_2O_4Cl_2$:-

Cl 20.2 %

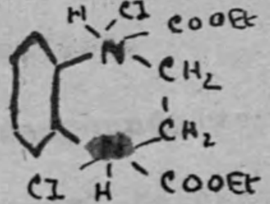
Owing to the difficulties of the analysis, this result, together with the properties of the substance, was taken as evidence in support of the formula



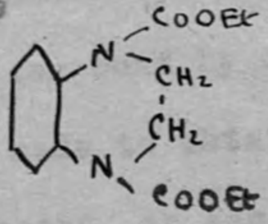
This compound would be expected to be unstable, and to give the ester  readily. The brown oil, obtained from the above substance, was too unstable for distillation, and could not be purified in any other way.

It decomposed very readily into tetrahydroquinoxaline,; thus a solution in dilute hydrochloric acid, cooled to 0 C, gave with sodium nitrite solution the nitroso compound of tetrahydroquinoxaline, while tetrahydroquinoxaline itself was obtained from all attempts to hydrolyse the ester.

Thus, so far as the evidence goes, it appears that an addition compound



is formed, which readily loses hydrochloric acid to give



which would be expected to break down, both in acid and in alkaline solution to give the original base.

The experiments with tetrahydroquinoxaline described above show that when reaction does occur at all between this substance and another containing two reactive groups complicated and tarry products are formed, and except in the case of the reaction with acetaldehyde, it was never found possible to isolate from the reaction mixture a product in which the two nitrogen atoms had been linked up by a third chain. It thus became necessary to obtain, if possible, compounds in which one of the imino hydrogens of tetrahydroquinoxaline was replaced by a group which could be removed after the second imino hydrogen had been replaced by a group suitable for subsequent bridge formation.

Such compounds were obtained as follows .

(1) Monobenzoyl tetrahydroquinoxaline.

Since Meisenheimer (2) had been unable to obtain this compound by direct action, an attempt was made to obtain it through the Grignard reagent, in the manner used by Perkin (5) to obtain the 9.benzoyl derivative of tetrahydrocarbazole.

Tetrahydroquinoxaline (1mol.) was added to a solution of magnesium ethyl iodide in dry ether (1mol.), and then benzoyl chloride (1mol.) was added.

A substance melting at 200 C after recrystallisation from alcohol was obtained. This was found to be the dibenzoyl derivative of the base.

Tetrahydroquinoxaline was dissolved in ether. $\frac{1}{2}$N caustic soda solution (1mol. of alkali to 1mol.of base) was added, and then benzoyl chloride (1mol. to 1mol. ofbase)dissolved in ether. The whole was vigorously shaken, and left to stand for some hours.

The ethereal solution was then separated off, dried with anhydrous sodium sulphate, and the ether distilled off.

The substance obtained did not give a test for tetrahydroquinoxaline, and after two recrystallisations from alcohol a product melting at 150 C was obtained.

This substance was in the form of light yellow crystals; it dissolved readily in ether, acetone, benzene and alcohol, and was not precipitated from its solution in benzene by ligroin. The substance dissolved in cold concentrated hydrochloric acid giving a purple solution; this solution gave an immediate prepipitate of a nitroso compound, when sodium nitrite solution was added to it at 0 C.

The nitroso compound of the substance melted at135 C ,and gave Liebermann's test.

The final proof that the compound obtained was the monobenzoyl compound of tetrahydroquinoxaline was given by the analyses.

Analyses.

Found:- C 75.9% H 6.1% N 11.9%

N 11.9%

Calculated for $C_{15}H_{14}N_2O$:-

C 75.58% H 5.93% N 11.77%

(2) Monotoluolsulpho tetrahydroquinoxaline.

Tetrahydroquinoxaline was dissolved in ten times its weight of pyridine, and p-toluene sulphochloride (1 mol.to 1 mol. of base) added slowly, the temperature being kept below 25 C. After being left to stand for some hours the solution was poured into excess of dilute hydrochloric acid, when red crystals were precipitated. These could be recrystallised from alcohol or from a mixture of benzene and ligroin.

The recrystallised product melted at 130 C, and the crystals were coloured red.

The yield was 90% of the theoretical yield for the monotoluolsulpho compound.

The substance was very sparingly soluble in water, fairly soluble in ether, and soluble in acetone, benzene, and alcohol.

The substance dissolved in strong hydrochloric acid; with sodium nitrite solution, the acid solutiongave a brown precipitate. This was a nitroso compound, melting at 110 C.

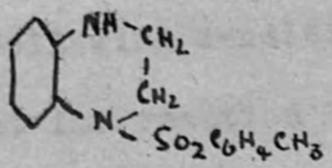
Analyses.

Found:- N 9.98% N 9.9%

Calculated for $C_{15}H_{16}N_2O_2S$:-

N 9.95%

Thus the substance is



In the same way, the monotoluol sulpho compound of the methyl tetrahydroquinoxaline was obtained, and found to be a similar red crystalline substance, melting at 131.5 C.

The solubilities of this substance were similar to those of the monotoluol sulpho derivative of tetrahydroquinoxaline.

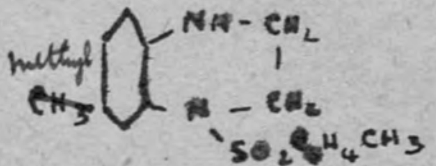
Analyses.

Found:- N 9.5% N 9.45%

Claculated for $C_{16}H_{18}N_2O_2S$:-

N 9.28%

Thus the substance is



A ttempts were then made to replacethe remaining imidic hydrogen in these compounds by another group.

(a) Experiments with methyl iodide.

The monotoluol sulpho compounds were found to be more reactive with methyl iodide than the benzoyl compound; thus all the subsequent work was done with the former compounds.

The following conditions were found to be the best for reaction between methyl iodide and the monotoluol sulpho derivative of tetrahydroquinoxaline.

The monotoluolsulpho compound was heated with an excess of methyl iodide under a reflux condenser for several hours, keeping the solution boiling.

A crystalline hydroiodide seperated out

out, and was filtered off. This dissolved in alcohol, and a light yellow crystalline solid was precipitated from this solution by the addition of caustic soda solution to the hot alcoholic solution. These crystals were filtered off after cooling, and recrystallised from alcohol.

The pure product consisted of light yellow crystals melting at 131 C. Although the melting point of the product was almost identical with that of the original compound, the substances were different, since the melting point of a mixture of the original substance and the product was 103 to110 C.

Also the product was much more soluble in hydrochloric acid than the original substance, and gave a light yellow platinichloride, while the platinichloride of the original compound was difficult to obtain.

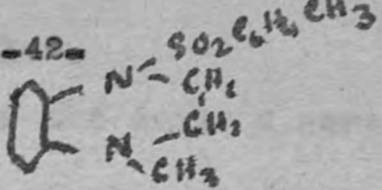
The product gave no nitroso compound.

Analysis.

Found:- N 9.3% N 9.3%

Calculated for $C_{16}H_{18}N_2O_2S$:-

N 9.28%

Thus the compound is 

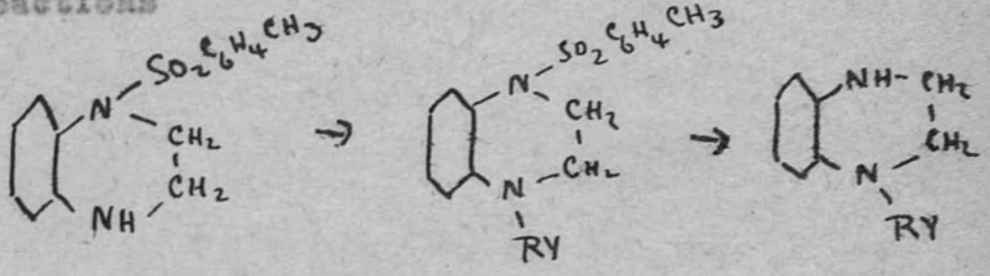
An attempt was then made to remove the monotoluolsulpho group from this compound, and obtain the monomethyltetrahydroquinoxaline.

The compound (2 grs.) was added to strong sulphuric acid (3 c.cs.). After standing for some hours, the solution was poured into water (15 c.cs.) filtered, made alkaline with strong ammonia, and extracted with ether. The ethereal solution was dried, and then the ether was evaporated off.

A small quantity of a yellow oil was obtained, which darkened in the air. This oil was soluble in acids, insoluble in water or alkalis, mixed readily with alcohol, ether, benzene and chloroform, and gave a nitroso compound. In addition it gave a blue colour with dilute ferric chloride solution. In all these circumstances it was identical with the ~~identical~~ monomethyltetrahydroquinoxaline described by G Ris (7).

With the same conditions, the monobenzoyl derivative of the tetrahydroquinoxaline did not all react with methyl iodide, and the product obtained was not easily crystallisable.

The possibility of the desired series of reactions



having been thus established, the following work upon the monotoluolsulpho compound of tetrahydroquinoxaline was carried out.

(b) With dialkyl halides.

(1) with methylene diiodide.

The monotoluol sulpho compound was dissolv in benzene, and a little methylene diiodide added. After standing for a few days, no reaction had occurred.

In a second experiment, the benzene solution of the monotoluol sulpho compound was heated to boiling with the iodide. Again no reaction occurred.

The monotoluol sulpho compound was heated with an excess of the diiodide to various temperatures, finally to the boiling point of the diiodide; then a tarry product was obtained, from which only the original compound could be isolated.

The same result was obtained when equivalent amounts of the two substances were heated together.

(2) with ethylene dibromide.

Similar results were obtained when the same series of experiments was carried out with ethylene dibromide and the monotoluol sulpho compound of tetrahydroquinoxaline.

(3) with trimethylene dibromide.

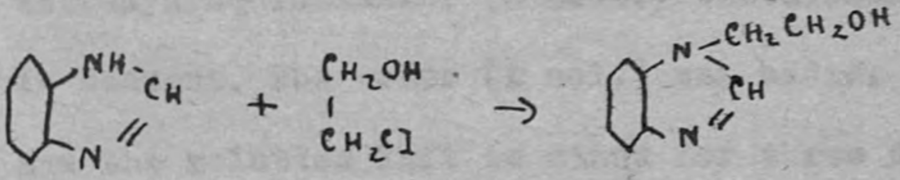
Similar results were obtained with trimethylene dibromide.

(4) with trimethylene chlorobromide.

The same series of experiments was carried out with the above compound, inthe hope that better results might be obtained in the case of a substance in which the two reactive groups were dissimilar, and might be supposed to have a different degree of reactivity towards the imino group.The results obtained were similar to those previousl however; no signs of any reaction were obtaineduunder the conditions used.

(c) with ethylene chlorhydrin.

Meisenheimer and Wieger(2) had been able to bring about a reaction between this substance and benzimidazol as follows:-



Experiments were tried, in the hope of bringing about a similar reaction between ethylene chlorhydrin and the monotoluol sulpho compound, using the conditions given by them.

The monotoluol sulpho compound (1mol.), in a finely powdered condition, was shaken for 48 hours with ethylene chlorhydrin (1 mol.) and N sodium hydrate solution (2mols.).

No reaction took place.

The toluolsulpho compound was heated for 24 hours with an excess of the chlorhydrin, but again no reaction occurred.

Equivalents of the two substances were heated together both in benzene solution and in toluene solution to boiling for a few days but again there were no signs of reaction.

(d) with halogen esters.

(1) with chloroformic ester.

The monotoluol sulpho compound of tetrahydroquinoxaline (2 mols.) was dissolved in benzene. The ester (1 mol.) was added, and the solution left to stand for three days.

Crystals had separated out, and on filtration were found to consist of about half of the monotoluol sulpho compound taken, in the form of a hydrochloride. The monotoluol sulpho compound could be regained from this, by dissolving the hydrochloride in alcohol and prtcipitating the monotoluol sulpho compound from this solution by caustic soda solution.

The original benzene solution was heated, and the benzene evaporated off, when a brown oil was obtained, which solidified after being left in a vacuum dessicatorfor a few days. Subsequently, the filtrate could be made to crystallise at once by scratching it up with a crystal from a previous experiment.

These crystals could be recrystallised from alcohol, when white crystals melting at

83 C. were obtained.

These crystals were very soluble in methyl alcohol, benzene, chloroform and ether, and moderately soluble in ligroin.

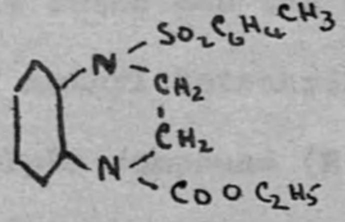
Analyses.

Found:- N 8.1% N 8.1%

Calculated for $C_{18}H_{20}N_{2}O_{2}S_{4}$:-

N 7.8%

Thus the substance corresponds to the formula



Since the reaction in the benzene solution was not complete for four days, the experiment was tried in dry ether solution; but as the monotoluol sulpho compound was so much less soluble in ether than in benzene the reaction was slower, and a very large bulk of ether was required. The same reaction occurred, however.

Experiments were also tried at higher temperatures. The monotoluol sulpho compound (1mol.) was heated in benzene solution for nine hours with the chloroformic ester (1 mol.) During this time, hydrochloric acid was evolved; the benzene was evaporated off, and the solid obtained and crystallised as before.

The reaction was complete; these were the best conditions when the substance was required quickly.

The same reaction occurred between chloroformic ester and the monotoluol sulpho compound of methyl tetrahydroquinoxaline.

The sulpho compound (2 mols.) was dissolved in benzene and the chloroformic ester (1 mol.) added. In this case the reaction was quicker, and was complete in 24 hours. The precipitate of the hydrochloride of the monotoluolsulpho compound (1 mol.) was filtered off, and the filtrate evaporated; the residue was a brown oil, which solidified in a week to light crystals. These crystals could be recrystallised from alcohol, and from ligroin, the pure product melting at 106 C.

This solid consisted of white crystals, readily soluble in many of the usual organic solvents; alcohol, ether, benzene, acetone & chloroform.

.Analysis.

Found :- N 7.52% N 7.5%

Calculated for $C_{19}H_{22}N_2O_4S$:-

N. 7.49%

As in the case of the tetrahydroquinoxaline derivative, the reaction could also be brought about by heating together the monotoluolsulpho derivative (1 mol.) and the chloroformicester (1 mol.) in benzene solution to boiling for nine hours.

(2) with chloracetic ester.

Experiments were next tried to obtain the corresponding compounds with chloracetic ester, but without success.

No reaction occurred in solution, or when the sulpho compound of tetrahydroquinoxaline was heated to 100°C with an excess of the ester without a solvent. When the sulpho compound was heated to 140 C with an equivalent amount of the ester, decomposition took place, and tarry products were obtained, from which nothing could be isolated.

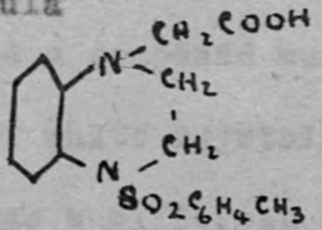
(3) with bromacetic ester.

In the hope that the reaction could be brought about with the more reactive brom acetic ester, experiments were tried with this.

It was found that a reaction took place between this ester and the monotoluol sulpho compound of tetrahydroquinoxaline of 80 C, the best conditions being either to heat the sulpho compound with an excess of ester for two days, in the presence of a stream of carbon dioxide, or else to heat the sulpho compound (2 mols.) with the ester (1 mol.) for two days.

By either of these methods a dark oily solid was obtained; it was found impossible to isolate the ester which it was believed was formed, and it was next attempted to hydrolyse this substance and get the acid. The solid was heated for 2 hours with 10% alcoholic (methyl) potash. Water was added, the alcohol boiled off, and the solution allowed to stand. The solid that came down was filtered off, and the solution acidified with acetic acid; a dark amorphous precipitate was obtained. It dissolved in, but could not be recrystallised from, ethyl and methyl alcohol; it could be precipitated from a benzene solution by ligroin. After this treatment, a very small amount of a solid was obtained, which melted from 140 to 150 C, and had acidic properties, and contained carbon, hydrogen, nitrogen, and sulphur, but no halogen.

This compound thus appears to correspond to the formula



as far as the evidence goes, but the yield was so poor that it appeared useless to spend further time on the identification of the product.

(e) with acid chlorides.

(1) with acetyl chloride.

The monotoluolsulpho compound of tetrahydroquinoxaline was ~~scratched~~ rubbed up with an excess of acetyl chloride at room temperature. No reaction occurred.

When, however, the acetyl chloride was added to the sulpho compound, and the whole boiled for four hours, the two substances reacted, and a compound was obtained which consisted of white crystals, melting at 133 C. That this was a different substance from the original was shown by the fact that a mixture of the product and the original compound melted at 102 C.

(2) with chloracetyl chloride.

The best conditions for the reaction between this substance and the monotoluol sulpho derivative of tetrahydroquinoxaline were found to be the following.

Excess of the acid chlofide was weighed into a small beaker, and the finely powdered sulpho compound added gradually with stirring, the temperature being kept below

25 C. The whole was left to stand for two days, and was then treated with an excess of water to decompose the excess of chloride; the red solid obtained was treated with a little dilute ammonia to remove the last traces of the chloride, and the solid was filtered. The solid was recrystallised from alcohol. The product was sufficiently pure for subsequent work, but a portion was further recrystallised from a large volume of ligroin for analysis.

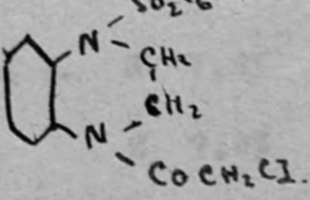
In this way colourless crystals were obtained, melting at 101 C.

Analyses.

Found :- N 8.0% Cl 10.1%
N 8.0% Cl 10.0%

Calculated for $C_{17}H_{17}N_2O_3SCl$:-
N 7.7% Cl 9.7%

Thus the substance is



In the same way, the monotoluol sulpho of methyl tetrahydroquinoxaline could be made to react with chloracetyl chloride by adding the finely powdered solid to an excess of the chloride, keeping the temperature below 25 C, and leaving the whole to stand. The product was isolated by decomposing the excess of chloride with water, and then washing the product with ammonia, and recrystallising the red solid obtained in this way from alcohol. The product was finally purified for analysis by crystallisation from alcohol

The final product melted 114 C, and as in the previous cases differed from the original compound by giving no nitroso compound.

The yield of this compound was not as good as the yield in the previous case, being only 30% of the theoretical yield.

<u>Analysis</u>.

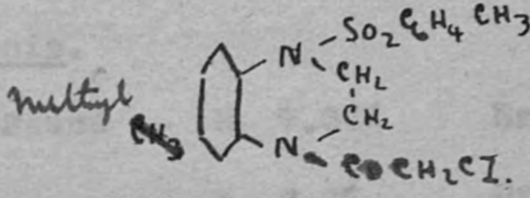
Found :- N 7.4% Cl 9.2%

N 7.6% Cl 9.1%

Calculated for $C_{18} H_{19} N_{2} O_{3} S Cl$:-

N 7.40% Cl 9.34%

Thus the substance is



(3) with bromacetyl bromide.

The desired reaction could be brought about between the above bromide and the monotoluolsulpho derivative of tetrahydroquinoxaline only under very mild conditions.

The sulpho compound (2 mols.) was dissolved in benzene and the bromide added, 1 mol. of bromide being added to 2 mols. of the solid.

On standing, the hydrobromide of the monotoluol sulpho compound (1 mol.) crystallised out, the reaction being complete in a few hours.

The hydrobromide was filtered off, and the benzene evaporated from the filtrate. A brown oil was left, which gave white crystals after being heated with alcohol. These crystals were recrystallised from alcohol, and the pure product melted at 104 C. For analysis, the substance was finally recrystallised from ligroin.

Analysis.

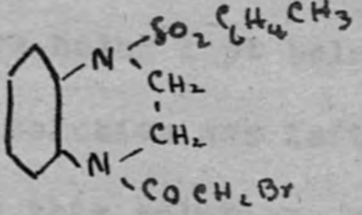
Found :- N 7.04% Br 20.5%

N 7.2% Br 19.80%

Calculated for $C_{17}H_{17}N_2O_3SBr$:-

N 6.85% Br 19.54%

The substance did not give a nitroso co compound, and thus corresponds with the formula



Under these conditions, a reaction did not occur between bromacetyl bromide and the monotoluolsulpho compound of the methyl tetrahydroquinoxaline.

In attempts to bring about the above reaction between bromacetyl bromide and the mono toluol sulpho derivative of tetrahydroquinoxaline, at first experiments were tried using more violent conditions than those described above.

At first the conditions which had been successful in the case of chloracetyl chloride were tried. The sulpho compound was added to an excess of bromacetyl bromide; the temperature rose, showing than a reaction had occurred.

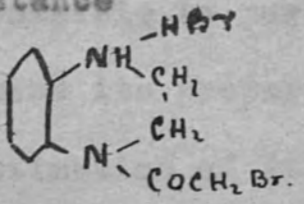
On decomposing the excess of bromide by the addition of water, a dark solid was obtained, from which it was found impossible to isolate any pure compound.

Next, the bromacetyl bromide was added drop by drop to the sulpho compound, which was cooled in a freezing mixture, the temperature being kept below 10 C. The resulting solution was left to stand for a day. From this solution, a light pink solid could be obtained by the action of dry ether. This was found to be a hydrobromide, which decomposed very readily in the presence of moisture; with water or caustic soda, only a soft red solid could be isolated, which could not be obtained in a pure solid form. The hydrobromide was analysed for bromine, although owing to the instability of the substance, the results were not liktly to be very accurate.

Analysis.

Found :- Br 45.2% Br 47.2%

These results corresponded most closely to the substance



Calculated for $C_{10}H_{11}N_2O\,Br$:- Br 47.15%

The substance did not contain any sulphur; thus the excess of bromacetyl bromide had replaced the toluolsulpho group by some other group, apparently by hydrogen from the above analysis.

It has been stated that no definite solid could be obtained from this substance by the action of water or caustic soda, but only a soft red substance, which could not be purified.

A yellow amorphous substance could be obtained from either the soft substance mentioned above, or from the hydrobromide, or from the original reaction product by the action of dilute ammonia.

This substance decomposed, rather than melted, from 220 C to 230 C, and contained carbon, hydrogen, nitrogen, halogen but no sulphur. It was found to be insoluble in all the ordinary organic solvents, so that it was impossible to purify it for analysis, or to examine its properties satisfactorily.

An estimation of its halogen content gave the following result

Found % :- Br 26.7%

This corresponded more closely to the calculated value for the monobromacetyl compound of tetrahydroquinoxaline than to the value required for any of the other probable formulae of the sunstance, but the value did not correspond closely enough for further work to be done upon this line, particularly as a compound of definite constitution could be obtained from bromacetyl bromide and the monotoluolsulpho compound of tetrahydroquinoxaline with the conditions given previously.

Since it was very interesting that the bromacetyl bromide should remove the toluolsulpho group from the derivative under the mild conditions of the experiment, the action of bromacetyl bromide on tetrahydroquinoxaline was investigated.

Excess of bromacetyl bromide was cooled

by water, and finely powdered tetrahydroquinoxaline was added gradually, keeping the whole cool.

After standing for several hours, the excess of bromide was decomposed by the addition of water, still keeping cool. A red solid was obtained, which could be recrystallised from alcohol. The pure solid obtained was in the form of white crystals, melting at 148 C.

Analyses.

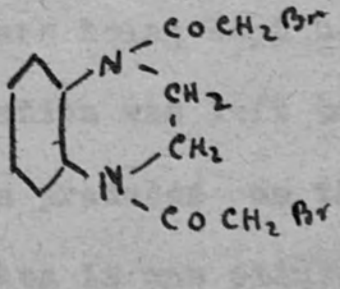
Found :- N 8.1% Br 42.5%

N 7.8% Br 42.5%

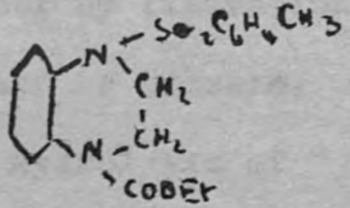
Calculated for $C_{12}H_{13}N_2O_2Br$:-

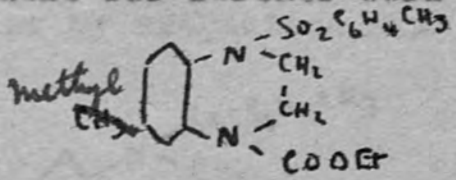
N 7.45% Br 42.40%

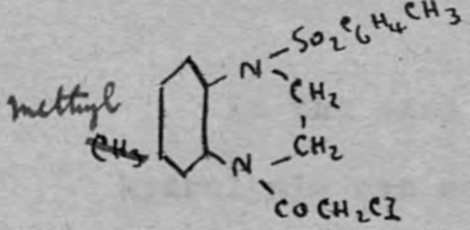
Thus the reaction had been quite normal, and the product obtained corresponded in composition and properties to the dibromacetyl derivative of tetrahydroquinoxaline

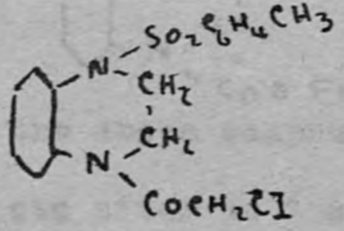


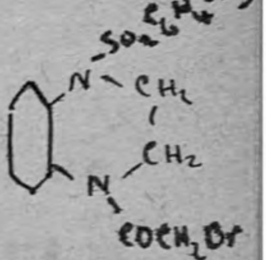
Thus the desired reaction had been brought about in five cases, and the following compounds were available for further work











The next stage was the removal of the monotoluolsulpho group from these substances, in the hope of getting monoderivatives of the tetrahydroquinoxalines containing an active group for subsequent condensation.

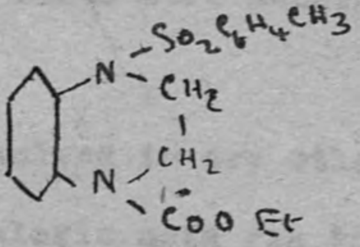
In each case, the method adopted was the same, and in each case the hydrolysis was brought about successfully.

The substance (20 grs.) was added gradually to strong sulphuric acid (24 grs.), the temperature being kept below 25 C .

The solution was left to stand until no milkiness was produced on the dilution of a drop ofit. Then it was diluted by pouring into a mixture of ice and water (100 C.cs.)

the solution filtered, and added to strong ammonia solution, and the product isolated either by filtration or by extraction with ether or benzene.

(a) Hydrolysis of



In the case of the above compound, the hydrolysis was complete after an hour and an half. After the solution had been made alkaline, a light brown oil separated, which was extracted with ether, dried with anhydrous sodium sulphate, after which the ether was evaporated off.

A light brown oil was obtained, which contained carbon, hydrogen and did not contain any sulphur. It dissolved readily in dilute hydrochloric acid, giving a red solution. This acid solution gave an oil with alkalis, and a nitroso compound with sodium nitrite solution, which was also an oil, but gave Liebermann's test.

The original oil was soluble in acetone, ether, alcohol, benzene and glacial acetic acid, but insoluble in ligroin.

A little of the ester was boiled in a tube, and found to boil without decomposition.

Two crystalline salts were obtained and analysed.

The oil was dissolved in dry ether, and a solution of hydrochloric ~~acid~~ acid gas in dry e ether added. A pink solid hydrochloride was prepicipated, washed with dry ether, kept in a vacuum dessicator, and analysed for halogen.

Analyses.

Found :- Cl 25.4% 24.5%

Calculated for $C_{11}H_{4}N_{2}O_{2}.2HCl$:-

Cl 24.24%

This points to the following formula for the hydrochloride, although the agreement is not very close. However, the hydrochloride was obtained by precipitation, and could not be purified as it decomposed in the presence of moisture.

Better results were obtained for the salt of the oil with p- toluene sulphonic acid.

This salt separated out during the

preparation of the ester, being obtained as a crystalline solid on the dilution of the strong sulphuric acid solution in which the hydrolysis had taken place. This salt could be recrystallised from water, and after this, was in the form of pink crystals, melting at 145 C. The ester could be obtained from the salt by alkalis.

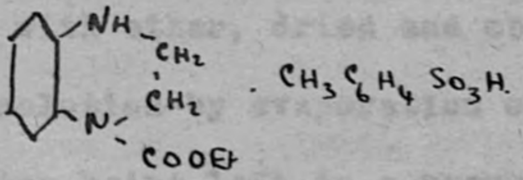
Analyses.

Found :- N 7.6% N 7.6%

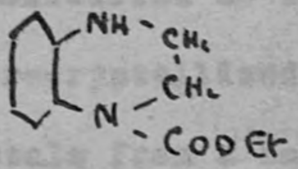
Calculated for $C_{11}H_{14}N_2O_2 . C_7H_8O_3S$:-

N 7.4%

This salt thus has the constitution

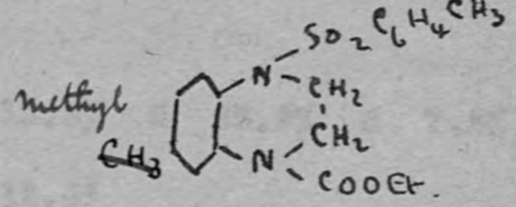


The constitution of the ester has thus been shown to be



The position of the ester group was verified by the fact that the ester would give with p- toluene sulphochloride in excess the compound from which it was obtained by hydrolysis, showing both that the only action of the sulphuric acid during the hydrolysis had been the removal of the toluolsulpho group, and that the ester group was attached to the nitrogen atom, since otherwise it would have been possible for the p-toluene sulphochloride to react with both nitrogen groups.

(b) Hydrolysis of



This hydrolysis was complete in about three hours.

When the diluted solution had been made alkaline, ano oil was obtained, which was extracted with ether, dried and obtained from the solution by evaporation of the ether. After being left in a vacuum dessicator, this oil solidified to a soft solid, which could be recrystallised and obtained as white crystals from a solution in methyl alcohol, by cooling the solution in ice and filtering quickly.

White crystals were obtained which melted at 75 C., but tended to go soft in the air.

These crystals were very soluble in alcohol, benzene and ether, and moderately soluble in ligroin. They dissolved readily in dilute acid, being reprecipitated by alkalis.

The acid solution gave an oil with sodium nitrite solution, which gave Liebermann's test for a nitroso compound.

Analysis.

Found :- N 12.2% C 65.9% H 7.6%

N 12.4%

Calculated for $C_{12}H_{16}N_2O_2$:-

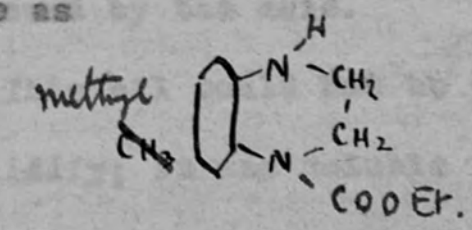
N 12.7% C 65.4% H 7.3%

The crystals gave a light yellow crystalline platinichloride, which was analysed.

Found for molecular weight od the base from this analysis :- 222

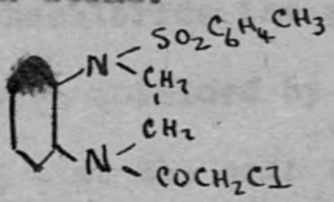
Calculated molecular weight of $C_{12}H_{16}N_2O_2$:- 222.6

This establishes the constitution of the substance as



ansd, as in the previous case, this constitution was verified by the fact that the compound from which the substance had been obtained could be obtained from it by the action of excess of p-toluene sulphochloride, again showing that the only action of the sulphuric acid had been the removal of the toluolsulpho group, and that the ester group was attached to one of the nitrogen atoms.

(c) Hydrolysis of



In this case, the hydrolysis was complete in about two hours.

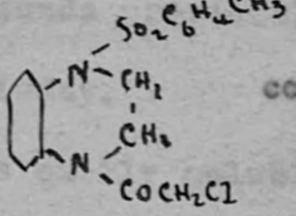
After making the diluted solution alkaline an oil separated out, which was extracted with ether, and dried.

From this solution, a brown oil was obt obtained. The aqueous alkaline solution gave a slight test for chloride, showing that a portion of the substance had been further decomposed by the acid.

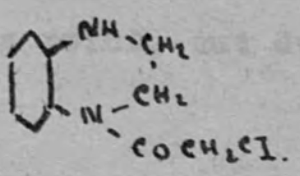
This oil could hot be purified, or made to solidify; it was soluble in glacial acetic acid, methyl alcohol, ethyl alcohol, acetone, benzene , chloroform and ether. Although the oil was easily soluble in acids, no salt capable of recrystallisation and analysis was obtained.

The existence of the desired monochloracetyl derivative of tetrahydroquinoxaline in the oil was established, however, by the fact that the oil did not contain any sulphur, but gave with p-toluene sulphochloride the solid from which the oil had been obtained by hydrolysis, thus showing that the main action of the sulphuric acid had only been the removal of the toluolsulpho group.

Thus, the substance



could only have been obtained from the substance



by the action of p-toluene sulphochloride.

On standing, even in a dessicator, the oil slowly changed into a brown crystalline solid. This solid was found to be an hydrochloride, and the base was isolated from it by precipitation from an alcoholic solution of the hydrochloride by the addition of alkali.

This base did not contain halogen, nor would it give a nitroso compound with nitrous acid. It could be recrystallised from alcohol, although it tended to come out of solution as a soft solid, and it was best purified by dissolving it in benzene, and precipitating the solid from this solution by ligroin.

The final product was a light brown powder, apparently amorphous, which closely resembled in appearance and properties the bridged ring nitrogen compounds previously obtained by Moore and Doubleday.

Thus the substance was easily soluble in acids, giving a red solution. The substance did not give a melting point, but decomposed at about 110 C.

That it was a compound of the desired type was finally confirmed by analysis.

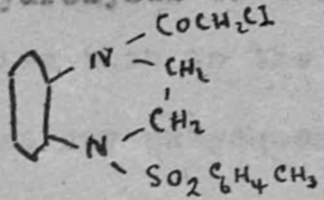
<u>Analysis</u>.

Found :- C 70.1% H 6.0% N 15.9%

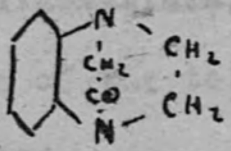
Calculated for $C_{10}H_{10}N_2O$:-

C 68.9% H 5.79% N 16.1%

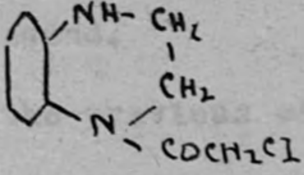
Thus, the hydrolysis of the compound



by the strong sulphuric acid appears to follow the usual course, giving the monochloracetyl derivative of the tetrahydroquinoxaline; this appears to be an oil, which decomposes on standing, giving the hydrochloride of the bridged ring compound

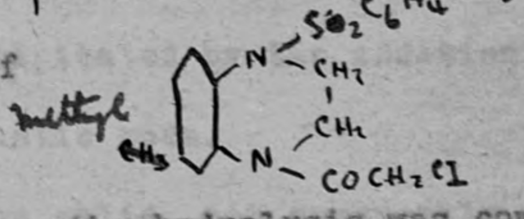


which is thus a more stable substance than the monoderivative



of the tetrahydroquinoxaline.

(d) Hydrolysis of



In this case, the hydrolysis was complete in about two hours.

After making the diluted solution alkaline an oil separated, which was extracted with ether. The aqueous alkaline solution contained more chloride than in the previous case, sho showing that any subsequent reaction had taken place to a larger extent in this case.

A brown oil was obtained from the ethereal solution, which very soon changed over into a crystalline hydrochloride, showing that the further condensation occurred more readily with the derivatives of the methyl tetrahydroquinoxalines, than with the derivatives of the tetrahydroquinoxaline as had been found.

Before it went solid, the oil was found to be readily soluble in acids, and to give a nitroso compound.

As in the previous case, the hydrochloride obtained from the oil was dissolved in alcohol, and the base precipitated by the addition of a solution of caustic soda.

A light brown solid, not apparently crystalline, was obtained, which could be purified by recrystalling it from alcohol, or by dissolving it in benzene, and then precipitating it by the addition of ligroin.

The purified product decomposed about 155 C, and very closely resembled the previous compound, obtained from the tetrahydroquinoxaline derivative.

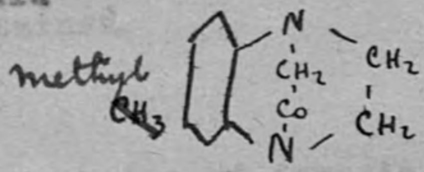
Analysis.

Found :- C 70.4% H 6.6% N 14.7%

Calculated for $C_{11}H_{12}N_2O$:-

C 70.18% H 6.43% N 14.89%

This substance thus corresponds to the formula



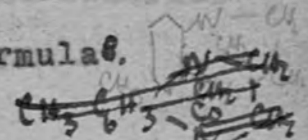
Further experiments were performed with this compound and the corresponding compound from the previous experiment, to investigate the stability of this type of compound.

The compounds were not decomposed by the action of phosphorus pentoxide or pentachloride, nor by thionyl chloride.

They would not give derivatives, such a would be expected from substances containing a ketonic group. This group thus is much less reactive in this class of compound; this would almost be expected, corresponding both with the formulae, and with the close resemblance existing between these compounds and the others of the same type previously known, the resemblance being both in physical properties and in chemical behaviour.

The final evidence of their structure was given by molecular weight determinations.

In phenolic solution, the depression of freezing point obtained corresponding with the formulae.



given was obtained.

Results.

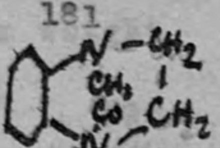
Phenol. Depression of freezing point observed

0.736 C   0.684 C   0.923 C

Calculated molecular weights

186   167   181

Molecular weight of



174

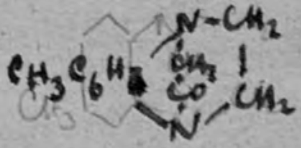
Phenol. Depression of freezing point.

0.885 C   0.913 C   0.763 C

Calculated molecular weight.

201   195   190

Molecular weight of



188

In benzene solution, as in the case of the compound obtained from tetrahydroquinoxaline and acetaldehyde, and in the case of the compounds previously obtained by Moore and Doubleday, the molecular weight obtained corresponded to a$_n$n associated molecule, being twice as great as the molecular weight in phenolic solution.

Results.

Benzene. Depression of freezing point observed

0.779 C	0.864 C	0.684 C

Calculated molecular weight.

370	385	369

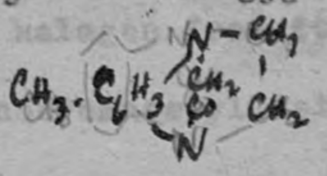
Molecular weight of  174

Benzene. Depression of freezing point observed

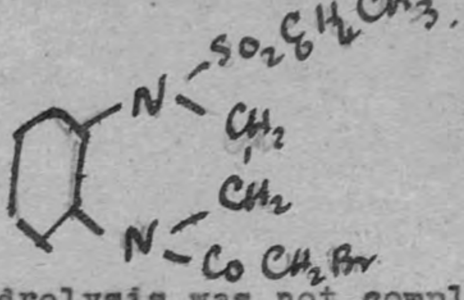
0.612 C	0.794 C	0 .625 C

Calculated molecular weight

388	379	396

Molecular weight of  188.

(e) Hydrolysis of



In this case, the hydrolysis was not complete for about four hours, and the product was more difficult to work up, as secondary reactions took place to a greater extent, and the reaction product was a mixture.

After the hydrolysis was complete, and the solution had been diluted and made alkaline, a light yellow crystalline solid was obtained, which was insoluble in ether.

This appeared to be the monobromacetyl compound of tetrahydroquinoxaline, but was insoluble in the non-hydroxylic solvents, while with methyl alcohol and alcohol, from which it could be recrystallised, the solvent also reacted with the substance, removing halogen from it. Thus the investigation of the monobromacetyl tetrahydroquinoxali was left, and the further product investigated.

This was found to be identical in all respects with the product obtained from the corresponding chloracetyl compound, thus showing that the reaction had been similar, involving in this case, the formation by hydrolysis of the monobromacetyl derivative of tetrahydroquinoxaline, and the subsequent condensation of this comparatively unstable compound to give the bridged ring compound.

Analysis.

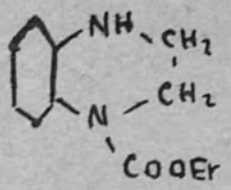
Found :- C 69.3% H 6.0% N 16.0%

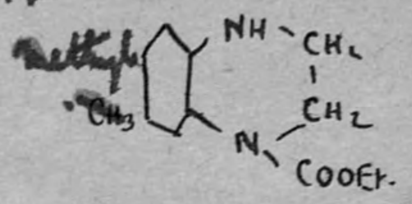
Calculated for $C_{10}H_{10}N_2O$:-

C 68.9% H 5.79% N 16.1%

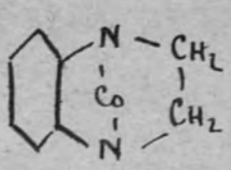
The last stage in the desired series of reactions, the condensation of the mono derivatives of the tetrahydroquinoxalines to give the bridged ring compounds, has thus been brought about (in the case of the chloracetyl and bromacetyl compounds.

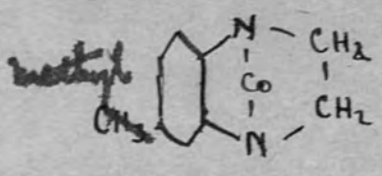
Many experiments were tried on the two other derivatives obtained, the esters





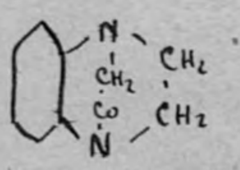
in the hope of bringing about a similar [illegible] condensation to the bridged ring compounds

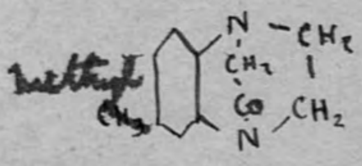




The esters were found, however, to be unexpectedly stable, and no evidence of the formation of these compounds would be obtained.

This must be regarded, therefore, as evidencethat the strain in these compounds would be much greater than in the compounds

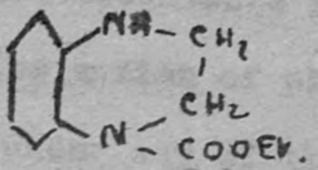




which were readily formed from the mono derivatives of the tetrahydroquinoxalines, being more stable than these derivatives, whereas in the case now considered the monoderivatives of the tetrahydroquinoxalines could be obtained, but not the bridged ring compounds.

In the case of the two esters, the following experiments were carried out, in attempts to bring about the condensation.

(1) with



(a) by the action of heat.

The ester boiled without apparent change or decomposition.

(b) with alkalis.

The ester did not change when heated with alcoholic sodium acetate solution for two days.

The ester did not change when heated with aqueous sodium carbonate solution for two days.

Heating the ester with with alcoholic potash solution for half an hour, decomposed it into tetrahydroquinoxaline.

Adding sodium to an ethereal solution of the ester did not decompose the ester, but sodium at 100 C decomposed it into tetrahydroquinoxaline.

(c) with acids.

Boiling a solution of the ester in dilute acid did not decompose the ester.

(d) with phosphorus pentachloride.

The ester was not decomposed or changed in any way by the action of phosphorus pentachloride under any of the following conditions.

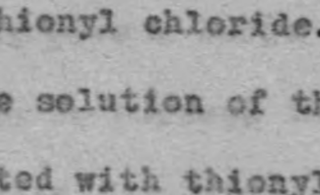
The two substances were scratched up together on a watchglass, heated together to 100 C, and heated together to 100 C, in solution in benzene acetyl chloride or phosphorus oxychloride.

(e) with thionyl chloride.

A benzene solution of the ester was charred when heated with thionyl chloride.

When thionyl chloride was addedto the ester which was kept cool, the two substances reacted, but as the product of the reaction contained sulphur, and was obviously not of the desired type, it was not investigated further.

(2) with methyl



The same experiments were tried with this compound, as with the former.

The results were similar, except that this compound charred when kept at 100 C for some hours.

(6) Work upon other aromatic diamines.

(a) upon 1.8.diamino naphthalene.

Commercial 1.8.dinitronaphthalene was purified by recrystallisation from acetone or glacial acetic acid.

The reduction of this compound, both by the method used in the case of o-nitraniline(4) previously, and by the method of Ullmann and Consonno(8) did not give a large enough yield for this branch to be pursued in reference to the work recorded.

(b) upon 1:2.diamino 4.ethoxy benzene.

This base was first prepared from phenacetin by the following method.

(1) Nitration of phenacetin.

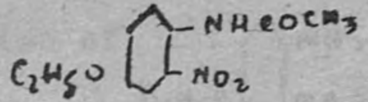
The phenacetin (225 grs.) was dissolved in glacial acetic acid (700 grs.); the temperatur of this solution was kept below 30 C, while a mixture of strong nitric acid (200 c.cs.) and water (200 c.cs.)was added. After standing overnight, the solution was poured into water, and the yellow solid filtered off and recrys

recrystallised from

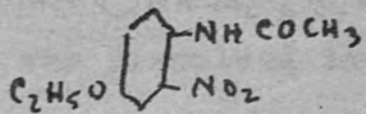
recrystallised from alcohol

This solid had the constitution

(22)



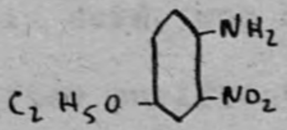
(2)Hydrolysis of



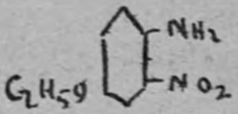
The above compound (224 grs.) was dissolved in a small amount of alcohol, heated under a reflux condenser, and the equivalent amount (1mol. to 1 mol. of the above) of potash, dissolved in a small amount of water was added, and the whole boiled for an hour.

The hot solution was poured into a dish and on cooling red needles separated.(180 gr.)

These were



(3) Reduction of



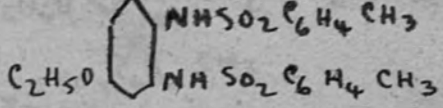
This compound was reduced by the method used in the case of o-nitraniline.

The compound was mixed with fine iron filings, coarse iron filings, calcium chloride crystals, and water, and heated in a stream of sulphuretted hydrogen.

The reduction was complete in four hours, but the yield was only 40% of theoretical.

The base obtained melted at 71 to 72 C.

(4) Preparation of



The base(3 grs.) was dissolved in pyridine (30 grs.) and p-toluene sulphochloride (7.52 grs.) were added, keeping the temperature below 25 C. After standing for an hour, the solution was heated to 100 C for an hour, cooled and poured into dilute hydrochloric acid.

A tar was obtained, which was dissolved in caustic soda, and poured into dilute acid, when a brown solid, which could be recrystallised from glacial acetic acid, was obtained.

This solid after purification melted at 117 to 118 C.

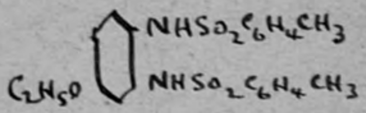
Analysis.

Found :- N 5.9% N 5.9%

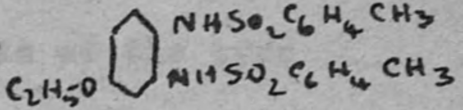
Calculated for $C_{22}H_{24}N_2O_5S_2$:-

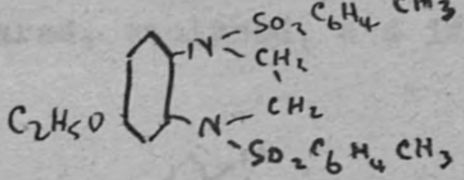
N 6.1%

Thus the desired compound



has been obtained.

(5) Conversion of 

into 

The compound (25 grs.) was heated under a reflux condenser with ethylene dibromide (15.14 grs.) caustic potash (13.56 grs.) and water (120 grs.), for twenty hours.

The solid obtained was filtered off, and extracted with potash until nothing more would dissolve.

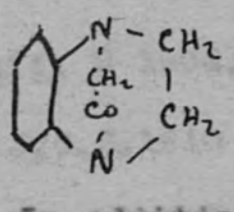
A product weighing 12 grs. was obtained.

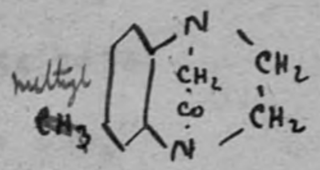
The possibility of getting an ethoxy derivative of tetrahydroquinoxaline by this method is thus definitely established, but the yields were so bad that no further work on this compound was attempted, as the work on the other lines described could be carried out more easily.

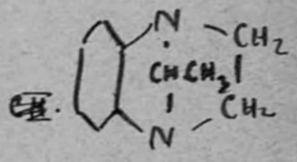
SUMMARY.

Three new compounds of the type

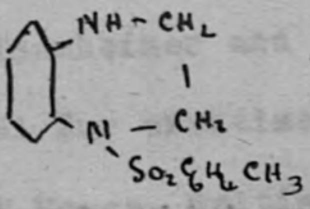
have been prepared, analysed, and investigated, namely

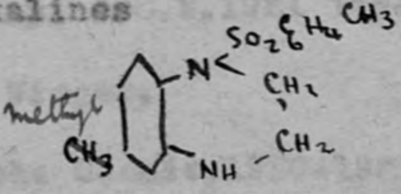


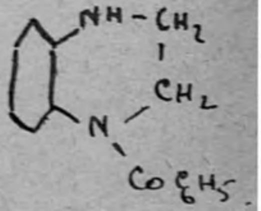




In addition, a new method for the preparation of these compounds from tetrahydroquinoxalines has been established, depending on the discovery of the possibility of obtaining the following derivatives of the tetrahydroquinoxalines







in which only one of the -NH- groups has been blocked.

The possibility of replacing the remaining imino hydrogen in these compounds by a group chain containing a reactive group, and then hydrolysing the toluolsulpho group, leaving another derivative of the tetrahydroquinoxalines, with one -NH- group has been established, and the properties of these compounds investigated.

(1) Goldschmidt B. 1883 15 1616

(2) Hantzsch and Werner. B. 1890 23 11.

(3) Meyer. B. 1890 23 567

(4) Pope and Peachey. J.C.S. 75 1127.

(5) Groschuff. B 1904. 34 2974

(6) Jones. J.C.S.1910 97 632.

(7) Miller and Plochl. B. 1896 29 1462.

(8) Mills and Bain. J.C.S. 1910 7 1866.

(9) Hess. B. 1919 52B 1622

(10) Meisenheimer.

(11) Meisenheimer and Schutze. B. 1923 56B 1353

(12) Moore and Doubleday. J.C.S.1921 1170

(13) Meisenheimer and Wieger.
Journal fur praktische Chemie.1920-1921.

(14) T.S.Moore. British Patent No. 155319.

(15) Perkin and Plant. J.C.S. 1921 1825.

(16) Whiteley and Usherwood. J.C.S.1923 1087.

(17) C.Ris. B.1888 21 578.

(18) Ullmann.and Consonno. B. 1902 35 2806.

(19) Mills & Bain T. 1914 · 105. 65.

(20) Mills & Schindler T. 1923 . 123 - 312.

(21) Beilstein IV . 614 onwards.