N Monosubstituted derivatives of piperazine

RHC.

A Thesis presented by Vera M. Thorn for the M.Sc. degree
in the University of London.
under the supervision of Prof. T.S. Moore,
Royal Holloway College.

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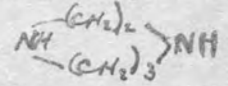
Abstract of Thesis.

The preparation of optically active bases of the type  $N\overset{a}{\underset{c}{-b-}}N$ will prove conclusively the trihedral distribution of the valencies of trivalent nitrogen. All the aromatic derivatives of this type which have been prepared hitherto, have proved to be unsatisfactory for further work. As a preliminary to attempts to prepare bridged compounds from the aliphatic base  $NH\begin{matrix}(CH_2)_2\\(CH_2)_3\end{matrix}NH$ it was decided to determine the experimental conditions for such preparations with piperazine.

A method for the successful preparation of monocarbethoxy piperazine has been worked out. This has made possible the preparation of other monoN.substituted derivatives of piperazine, and monotolyl sulphenyl, monoethyl, and monoethanol piperazines have been obtained.

Addition compounds of the monosubstituted bases with carbondioxide and carbon bisulphide have been prepared, but the formulation of these compounds, with any certainty is impossible since the ~~proper~~ properties are such as not to allow of molecular weight determinations. A quantitative investigation of the metallic derivatives of these pompounds will probably be of great assistance in elucidating the structure of these anomalous substances.

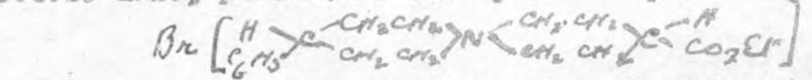
Some metallic salts of piperazine diacetic and mono acetic acids have been investigated with a view to comparing their internal complex nature with that of analogous salts of other amino acids. The copper, nickel and cobaltous salts of the diacetic acid show no evidence of internal complex formation. From piperazine monoacetic acid two isomeric copper salts have been obtained which exibit properties characteristic of internal complex salts. Possible formulae for the salts have been discussed tentatively, but no final conclusions can yet be drawn.

DERIVATIVES OF PIPERAZINE.

PART 1. PREPARATION OF MONO N SUBSTITUTED DERIVATIVES.

INTRODUCTION.

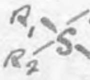
In compounds of pentavalent nitrogen e.g. NR_4X, the four nonionised groups are arranged tetrahedrally. This was proved conclusively by the resolution by Mills & Warren (J.C.S. 1925, p.2307) of the Spiran compound



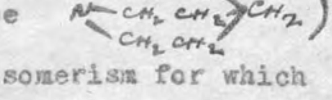
$$Br\left[{}^{H}_{C_6H_5}\!>C<{}^{CH_2CH_2}_{CH_2CH_2}\!>N<{}^{CH_2.CH_2}_{CH_2\ CH_2}\!>C<{}^{H}_{CO_2Et}\right]$$

through the bromo camphor sulphonate, and according to the electronic theory of valency one would expect such an arrangement since the neutral carbon atom and the positive nitrogen atom have the same number of electrons.

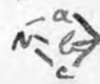
The distribution of the groups in compounds of trivalent nitrogen of the type N.abc. is, however, still a matter of doubt. All attempts to resolve such compounds have so far not been successful.

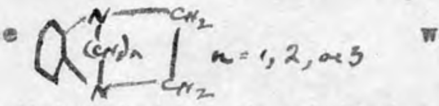
Compounds of sulphur, tin and selenium of the type  $^{R_1}_{R_2}\!>S<^{R_3}_{X}$ are resolvable, which means that the groups occupying three points of a tetrahedron can retain their positions even when the fourth point is unoccupied, and it is difficult to explain why the trivalent nitrogen atom with the same electronic arrangement should have been found incapable of giving active forms.

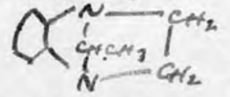
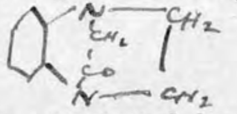
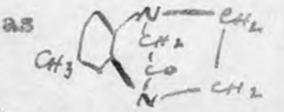
Further experimental work is necessary to settle the question.

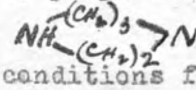
Meisenheimer, recently reviewing the suoject (Ber. 1924 p.1744) comes to the conclusion that saturated trivalent nitrogen can either never, or only in exceptional cases (as e.g. in the quinuclidines of the type  $N\!\begin{smallmatrix}-CH_2\ CH_2-\\-CH_2\ CH_2-\\-CH_2\ CH_2-\end{smallmatrix}\!CH_2$), produce stereoisomers, and no doubt cases of isomerism for which it has been held responsible must be explained in some other way. Meisenheimer and his co-workers assume that although the three valencies of the amine N.abc. are probably not at an angle of 120° to each other and hence form two mirror image tetrahedrons, yet

yet they continuously vibrate through a middle position in which they are at 120° to each other in the same plane. This, in compounds of amines, becomes a plane of symmetry, so racemisation goes on always and resolution is only possible when the isomeric forms are stabilised by the occupation of the fourth coordination position of the nitrogen atom by a positively charged hydrogen atom, alkyl residue (quaternary ammonium compound), by an oxygen ~~a~~ atom (amine oxide), or by a complex metallic residue (complex amines).

In 1914 T.S.Moore (Proc.30 p.182) had also suggested that the failure of attempts to obtain compounds of the type  in optically active forms was due to rapid racemisation, and he made the suggestion that compounds of the type  and  in which a,b and c are three different divalent groups or chains of which one at least is unsymmetrical with regard to the two nitrogen atoms, should exist in two enantiomorphic forms, since in such compounds racemisation will be slow or non-existant. Compounds of the type  were found to be resolvable and compounds of the type  have since been prepared.

In 1921 derivatives of methyl tetrahydro quinoxaline of the type 

were prepared by Moore & Doubleday. Meisenheimer found that similar derivatives of tetrahydro quinoxaline itself could not be prepared owing to the great reactivity of tetrahydro quinoxaline, but recently the compounds  and  as well as  have been prepared by Prof.Moore & Miss Cox.

All these aromatic derivatives in which the introduction of the bridge between the two nitrogen atoms has been effected, have proved to be unsatisfactory for further work on account of their instability, the difficulty in their purification and their anomolous colour reactions and molecular weights (Moore & Doubleday). As a preliminary to attempts to to prepare bridged compounds from the aliphatic base  $NH\begin{matrix}(CH_2)_3\\(CH_2)_2\end{matrix}NH$ it was decided to determine the experimental conditions for such preparations with piperazine.

Experience with the aromatic compounds mentioned above has shown that it is better , wherever it is possible, to carry out such preparations in the following stages,-

(1) To introduce into the base one easily removable group e.g.
$HN=(R)=NH \rightarrow HN=(R)=NX$

(2) TO intrduce next another group, itself containing a reactive atom or group. e.g. $HN=(R)=NX \rightarrow Br.Y=N(R)=N.X$

(3) TO remove X e.g. $Br-Y-N=(R)=N.H$

(4) To remove HBr from the compound thus obtained.

The initial difficulty in the work with piperazine is in the preparation of mono N. substituted derivatives of which no single example is given in the literature.

For success in stage I of the series of reactions outlined above, the following considerations are important:-

(1) The group X must be capable of easy removal, and for practical purposes this limits the group X to one of the three - benzoyl, toluene sulphonyl and carbethoxy groups.

(2) Since it is certain that some disubstituted derivative will be formed, it is desirable that the mono and di-derivative should be easily separated. Such separations would be easy in the case of the benzoyl and toluene sulphonyl groups, since the di-derivatives in these cases are insoluble in water and dilute acid, while the mono derivatives might be expected to disolve in water (since the extreme solubility of piperazine is undoubtedly due to the -NH group, of which one would remain in the mono derivative) and in any case would be soluble in dilute acid. Nothing could be foreseen with regard to the carbethoxy derivative.

(3) The conditions should be chosen so that no unchanged piperazine remains, since the separation of the mono substituted derivative from piperazine would be expected to be difficult.

(4) Conditions must be chosen which will protect the

mono substituted derivative as far as possible from further attack. Success in this, the most important condition of all, was achieved by taking advantage of the mode of hydrolysis of piperazine salts in aqueous solution. Since piperazine is a di-acid base, its salts will hydrolyse in two stages:-

$$\begin{array}{lll} \mathrm{HCl.HN(CH_2)_4.NH.HCl + H_2O} & \rightleftarrows & \mathrm{\overset{HCl}{HN}(CH_2)_4.NH.H_2O + HCl} \\ & & \downarrow\uparrow \\ & & \mathrm{HCl.NH(CH_2)_4.NH + H_2O} \end{array}$$

and

$$\begin{array}{lll} \mathrm{HCl.NH(CH_2)_4NH + H_2O} & \rightleftarrows & \mathrm{H_2O.NH(CH_2)_4.NH. + HCl} \\ & & \uparrow\downarrow \\ & & \mathrm{NH(CH_2)_4NH} \end{array}$$

but the second stage proceeds to a much smaller extent than the first.

From the equilibrium relations corresponding to these equations it follows that the concentration of both free piperazine and of piperazine monohydrochloride will diminish with addition of hydrochloric acid, but that the concentration of the free piperazine will diminish more rapidly than that of the mono-hydrochloride. It is thus clear that on addition to an acid solution of piperazine of e.g. chlorformic ester the two reactions :-

$$\mathrm{HCl.NH(CH_2)_4.NH + Cl.COOEt = HCl + HCl.NH(CH_2)_4.N.COOEt}$$

and

$$\mathrm{NH.(CH_2)_4NH + 2Cl.COOEt = 2HCl + EtOOC.N.(CH_2)_4.COOEt}$$

will take place. The rate of both reactions will be diminished by an increase in concentration of acid, but such increase will increase the proportion of the mono carbethoxy derivative in the reaction product.

Since the hydrochloride of the mono carbethoxy derivative will be to some extent hydrolysed, and thus open to attack by the chlorformic ester, it is clear that for this reason also an excess of acid is desirable.

From the above it follows that condition (4) is best fulfilled by maintaining the reaction mixtuee as strongly acid as is consistent with a practicable reaction velocity.

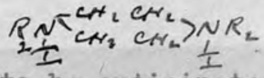
The work described below shows, in fact, that although chlorformic ester under the apprppriate conditions can be made to give a high yield of mono carbethoxy piperazne, only traces of mono benzoyl piperazine and mono toluol sulphonyl piperazine are obtained when benzoyl chloride and p.toluene sulphonyl chloride are used in the same way.

The separation of the mono carbethoxy from the di-carbethoxy piperazine proved to be a simple matter, since the whole of the latter and very little of the former is removed from aqueous alkaline solution by ether extraction. It is only when the aqueous solution is saturated with potassium carbonate that the mono carbethoxy piperazine can be extracted by ether or chloroform. The preparation of mono carbethoxy piperazine has opened the way to the preparation of mono N derivatives of piperazine some of which are described in the following pages. Apart from the possible use of such derivatives in further work (such as the formation of bridged compounds already referred to) there is a considerable interest in comparing the properties of these substances with the very remarkable properties of piperazine.

Mono alkyl derivatives of piperazine.

The most general method for preparing alkyl derivatives of amine compounds consists in treating with alkyl halide preferably the iodide since this reacts more readily than bromide or chloride, or with methylsulphate.

Previous work on the alkylation of piperazine itself has yielded no methods for the successful preparation of the dialkyl tertiary bases $RN\left\langle\begin{matrix}CH_2\,CH_2\\CH_2\,CH_2\end{matrix}\right\rangle RN$ in a pure condition owing to their extreme readiness to form the quaternary piperazonium halides



$$\underset{I}{R_2N}\left\langle\begin{matrix}CH_2\,CH_2\\CH_2\,CH_2\end{matrix}\right\rangle\underset{I}{NR_2}$$

It was therefore to be anticipated that a similar difficulty might arise with piperazine mono carboxylic ester and this was found to be the case.

Methyl iodide, either alone , or diluted with methyl alcohol reacts very raedily with the monocarbethoxy piperazine. Heat is developed and the solution becomes dark red in colour. Using one molecule of methyl iodide to one of mono carbethoxypiperazine, a reaction product containing the hydriodide of unchauged original substance and of mono carbethoxypiperazine $EtOOC.N(CH_2)_4N.CH_3$ and the quaternary iodide $EtOOC.N(CH_2)_4N.(CH_3)_2I$ resulted. From this the quaternary iodide could be obtained in a pure state, but not the moncmethyl derivative. (p.7)

When attempts were made to introduce the ethyl group instead of the methyl it was found that the reaction with ethyl iodide was less vigorous, and there was a slight darkening of colour on standing, but, as before, the product contained some unchanged ester (results of combustion analyses showed the proportion of the latter to be about 20%). Other methods of preparation were then tried. To prevent the formation of quaternary iodide anhydrous sodium carbonate was introduced to neutralise the hydriodioc acid as liberated and the reaction was tried sudstituting ethyl bromide and ethyl p. tolylsulphonate for iodide. Finally successful results were obtained by heating together the mono carbethoxy piperazine, ethyl p. tolylsulphonate and anhydrous sodium carbonate with absolute alcohol as solvent. It was found that the ethyl carbethoxy piperazine boils under reduced pressure at a temperature very near to that at which the mono carbethoxy piperazine itself distills, and like the latter, is a colourless syrupy liquid extremely soluble in water. This similarity in properities explains the want of success experienced in the attempts to isolate the pure ethyl

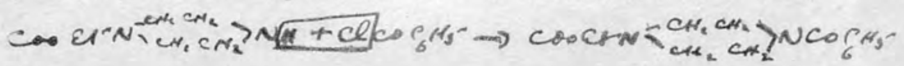
ethyl derivative from the mixture containing the original ester.

The carbethoxy group was found to be easily removed by heating for a short time with 2N aqueous soda but the actual isolation of the mono ethyl piperazine was rendered impracticable owing to the extreme solubility of this base. Examination of small quantities, obtained as residues from chloroform extractions, showed it to be a strongly alkaline base, with a pungent smell, easily volatile in steam—in fact resembling piperazine in many respects.

The mono ethyl piperazine was most easily conveniently isolated as its hydrochloride by hydrolysing the ester with strong hydrochloric acid. It forms double salts with platinic chloride and auric chloride analagous to those formed by piperazine hydrochloride.

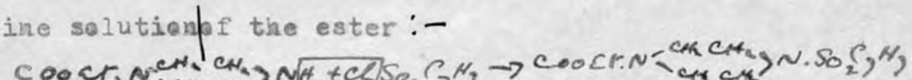
Mono benzoyl and mono toluene sulphonyl piperazine.

Monocarbethoxy piperazine readily forms a benzoyl derivative by the action of benzoyl chloride in alkaline solution :—



$$\mathrm{COOEt{\cdot}N}\begin{smallmatrix}\mathrm{CH_2\,CH_2}\\ \mathrm{CH_2\,CH_2}\end{smallmatrix}\mathrm{N}\boxed{\mathrm{H+Cl}}\mathrm{COC_6H_5} \rightarrow \mathrm{COOEtN}\begin{smallmatrix}\mathrm{CH_2\,CH_2}\\ \mathrm{CH_2\,CH_2}\end{smallmatrix}\mathrm{NCOC_6H_5}$$

and also a p.tolylsulphonyl derivative by shaking up an ethereal solution of p. tolyl sulphonyl chloride with an alkaline solution of the ester :—



$$\mathrm{COOEt.N}\begin{smallmatrix}\mathrm{CH_2\,CH_2}\\ \mathrm{CH_2\,CH_2}\end{smallmatrix}\mathrm{N}\boxed{\mathrm{H+Cl}}\mathrm{SO_2C_7H_7} \rightarrow \mathrm{COOEt.N}\begin{smallmatrix}\mathrm{CH_2\,CH_2}\\ \mathrm{CH_2\,CH_2}\end{smallmatrix}\mathrm{N.SO_2C_7H_7}.$$

The latter derivative on hydrolysis with alcoholic potash behaved quite normally and a reasonable yield of mono tolyl sulphonyl piperazine was obtained. On the other hand no conditions were found for the hydrolysis of the carbethoxy group of the benzoyl derivative which did not at the same time produce considerable hydrolysis of the benzoyl group. In fact of all the conditions tried, hydrolysis by cold dilute aqueous alkali alone gave mono benzoyl piperazine, and then only in very small yield.

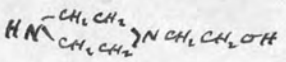
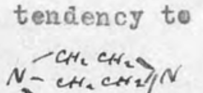
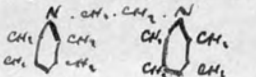
In view of the remarkable instability of mono benzoyl piperazine towards hydrolysing agents it was of interest to compare the behaviour of di benzoyl piperazine and the p.tolyl sulphonyl piperazines under the same conditions. The reagent chosen was 15% alcholic potash since this had the most drastic effect upon the monobenzoyl piperazine ester and removed the benzoyl group completely in the cold.

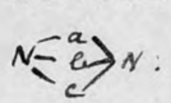
It was found that dibenzoyl piperazine remained unattacked in the cold although it had nearly all dissolved. But after heating on the steam bath for 3-4 hours benzoic acid was isolated on acidification and the amonnt was sufficient to justify the conclusion that the removal of the benzoyl group had proceeded to a considerable degree. Further, after removal of all the alchhol the alkaline residue was completely soluble in water, smelt strongly of piperazine and gave the characteristic dibenzoyl piperazine with benzoyl chloride, and in view of the extreme instability of mono benzoyl piperazine, it may be concluded that dibenzoyl piperazine is decomposed by hot alcoholic potash into piperazine and benzoic acid.

Mono p.tolyl sulphonyl piperazine on the other hand was found to be much more resistant to the attack of alcoholic potash and even after long heating could be recovered prattically completely unchanged and the evidence for any piperazine in the solution was very slight. The stability in this case is not to be attributed to insolubility since mono p.tolyl sulphonyl piperazine though insoluble in water is easily soluble in alcohol. The ditolyl sulphonyl piperazine is also a highly resistant compound and the tolyl sulphonyl group can only be removed by the action of hot chlorsulphonic acid. The comparison indicates that dibenzoyl piperazine is definately much more stable to alcoholic potash than monobenzoyl piperazine.

Reaction between monocarbethoxy piperazine and a compound of the type .XRY inwhich both X and Y are reactive groups.

The reactant chosen was ethylene chlorhydrin. The piperazine N.1.4. diethanol has been described in the literature (J.C.S.1908p-1802) and it was to be expected thatthe monoester

would react under similar conditions with the production of its mono ethanol derivative which on hydrolysis should yield piperazine monoethanol 
$HN\langle{}^{CH_2CH_2}_{CH_2CH_2}\rangle N\,CH_2CH_2OH$
This substance has been prepared and some of its reactions investigated and it is suggested that, whereas the hydroxybody itself shows no tendency to lose a molecule of water with the formation of  yet it is highly probable that the chloro compound obtained by substitution of halogen for the hydroxyl will give in acid solution the hydrochloride of triethylene diamine. This is tha base which Hofmann(J 1858 p.343) obtained in small quantities by tha action of ammonia on ethylene bromide; but his attempts to produce it by other synthetical means failed. As Harries has suggested,(Annalen 1896 p.97) the free base will most probably readily polymerise to hexaethylene tetramine 

The successful preparation of triethylene diamine will be of great interest and importance since it will have established a general method of obtaining the tricylic bases of the type  :

Additional compounds of mono N substituted piperazine derivatives.

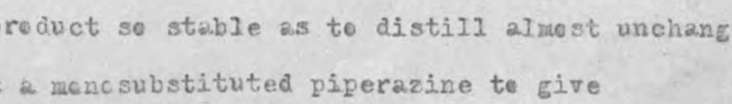
Having prepared some mono nitrogen substituted derivatives of piperazine it was of interest to compare their reactions with those of piperazine and in particular to investigate the addition reactions of the former. It is well known that piperazine, as well as forming the usual double salts characteristic of bases, e.g.:-

$C_4H_{10}N_2 \cdot 2HCl \cdot PtCl_4$
$C_4H_{10}N_2 \cdot 2HCl \cdot 2AuCl_3$ and $C_4H_{10}N_2 \cdot 2C_6H_2(NO_2)_3OH$

also forms insoluble addition compounds with aldehydes carbon dioxide, carbon bisulphide, carbonyl chloride etc. The preparation of these compounds has been described by Hertz (Ber. 1897.p.1584) but very little is known regarding the structure of the compounds formed and no recent investigation on the subject appears to have been made. It was thought that by investigating the reactions of some of these substances with compounds in which one of the imine groups has already been blocked it would throw some light upon the subject, for it is reasonable to suppose that the two imine groups in piperazine by reason of their positions relative to each other in the ring may confer unusual re-activity upon each other. The reactions investigated were those of carbon dioxide and carbon bisulphide on the monoester and mono p.tolyl sulphonyl piperazine and, except that no compound could be isolated with carbon dioxide and the mono carbethoxy piperazine it was found that, whereas with piperazine addition took place between the substituents in the proportions of one molecule of base to one molecule of carbon dioxide or carbon bisulphide, with the mono substituted derivatives the addenda were in the proportion of two molecules of base to one molecule of carbon dioxide or carbon bisulphide.

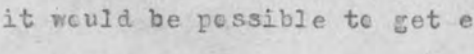
These results indicate that the added molecule is, in the case of piperazine attached to both the NH groups. The formulation of the addition compounds of piperazine and of its mono substituted derivatives with any certainty is impossible since the properties of these compounds are such as not to allow of molecular weight determinations.

On the analogy of the action of secondary amines on carbon bisulphide e.g.



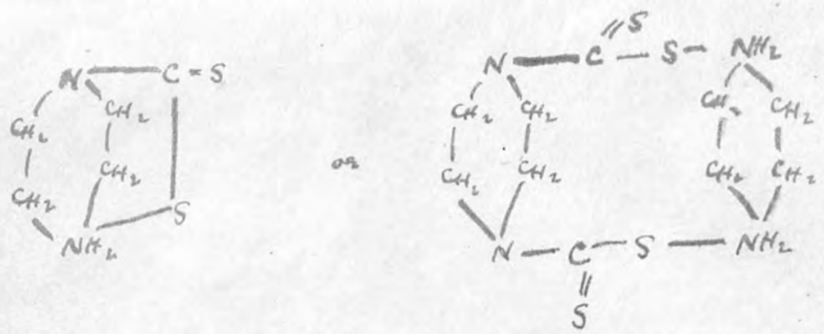
$$2(C_2H_5)_2NH + CS_2 = (C_2H_5)_2N-C\overset{=S}{-}S.NH_2(C_2H_5)_2$$

which gives a product so stable as to distill almost unchanged one might expect a monosubstituted piperazine to give



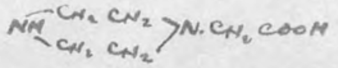
$$RN.(CH_2)_4N-C\overset{=S}{-}SNH_2(CH_2)_4NR$$

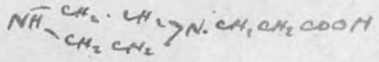
With piperazine it would be possible to get either

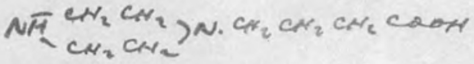


The fact that mercuric chloride and mercuric oxide do not remove sulphuretted hydrogen from the compound of piperazine with carbon bisulphide is in agreement with this formulation. The carbon dioxide compounds would be formulated similarly. Alcoholic solutions of picric acid produce with the monoester and mono p.tolylsulphonyl piperazine the characteristic picrates in which the latter are behaving as normal monoacid bases.

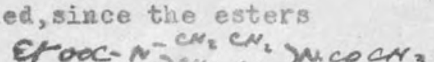
It is of interest to note that methods similar to those described above for the preparation of mono N. substituted piperazines have been found successful by Prof. Moore& Dr. Boyle in the preparation of the three acids

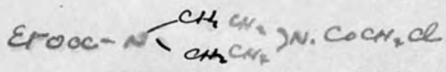

$$NH<\begin{matrix}CH_2\ CH_2\\ CH_2\ CH_2\end{matrix}>N.CH_2COOH$$


$$NH<\begin{matrix}CH_2.\ CH_2\\ CH_2\ CH_2\end{matrix}>N.CH_2CH_2COOH$$


$$NH<\begin{matrix}CH_2\ CH_2\\ CH_2\ CH_2\end{matrix}>N.CH_2CH_2CH_2COOH$$

But attempts to prepare monoacetyl and monochloracetyl piperazines have so far failed, since the esters


$$EtOOC-N<\begin{matrix}CH_2\ CH_2\\ CH_2\ CH_2\end{matrix}>N.COCH_3$$


$$EtOOC-N<\begin{matrix}CH_2\ CH_2\\ CH_2\ CH_2\end{matrix}>N.COCH_2Cl$$

which are easily prepared from monocarbethoxy piperazine, go over completely into piperazine under all conditions of hydrolysis tried.

EXPERIMENTAL.

Preparation of piperazine mono ethyl carboxylate.

In the first trial method the following quantities of reactants were used:-

0.05 molecules of piperazine.

2x0.05 molecules of dilute hydrochloric acid.

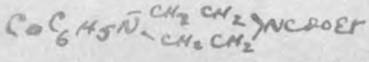
0.05 molecules of ethyl chlorformate in ether.

0.05 molecules of dilute caustic soda.

The piperazine was dissolved in the acid and some ether added. A little of the ethereal solution of chlorformic ester was shaken up with the piperazine hydrochloride until the smell of it had nearly disappeared. A few c.c. of N/10 caustic soda were then added from a burette and the mixture well shaken up. The alternate additions of ester and soda were repeated until all had been used. The excess chlorformic ester was shaken out with ether. The main solution was cooled and made alkaline and extracted with ether several times. The ethereal extract was ~~dri~~ dried over anhydrous sodium sulphate, and after distillation of the ether a small quantity of syrupy liquid was left which partly solidified when left in a vacuum desiccator over sulphuric acid. The solid consisted of dicarbethoxy piperazine, and the liquid was investigated and proved to be the monocarbethoxy piperazine.

Investigation of the liquid derivative.

(1) To a few drops of the liquid were added a few c.c. of benzoyl chloride and excess caustic soda. The mixture was well shaken until no smell of benzoyl chloride remained. A semi solid was formed which solidified on the sides of the tube when scratched with a glass rod, and it was found to have a low melting point. Thus it differed from dibenzoyl piperazine which is a crystalline solid m.pt. 191 C. and it was considered to be



$$CoC_6H_5N\left\langle\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}\right\rangle NCOOEt$$

Subsequently this conclusion was proved to be correct by combustion analysis of a later preparation.

(2) Dry hydrochloricacid gas was passed into a little of the

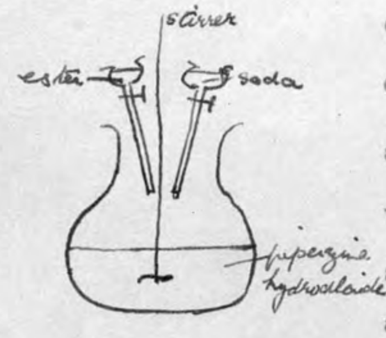
liquid dissolved in dry ether. A white deliquescent solid was formed which completely solidified when left in a vacuum desiccator. A chlorine estimation gave the following results:-

Weight of ester hydrochloride	0.2100grms.
Weight of silver chloride	0.1832grms.
% chlorine	21.59

Theoretical for $COOCrN(CH_2)_4NH \cdot HCl$ is 21.32%

Evidently then the mono derivative had been obtained although the yield was very small, and it was necessary to modify the procedure until satisfactory results were obtained.

After a series of trials, successful results were obtained by adopting the following method:-



The piperazine and chlorformic ester were used in the proportion of one molecule of piperazine to 1.3 molecules of chlorformic ester. The piperazine was dissolved in a little water and a few drops of the indicator bromophenol blue added, and hydrochloric acid just sufficient to turn the indicator greenish yellow. The solution was stirred by a mechanical arrangement and a few c.c. of ester dropped into it. After a few minutes, when no drops of the ester were present in the liquid, dilute soda was dropped in until the indicator just began to change colour from yellow to blue. For the success of the experiment it is most important that no soda should be added while unchanged ester remains in the solution, and also the amount of soda must not be enough to make the liquid alkaline. The alternate additions of ester and soda were repeated until all the ester had reacted. The solution was cooled in ice and treated with excess cooled soda and twice extracted with ether in order to remove the diester formed. The remaining solution was still kept cold, saturated with potassium carbonate and extracted several times with ether.

The ethereal solutions were dried over anhydrous sodium sulphate for several days, and then the ether distilled off. The di ester solidified in a desiccator and the mono ester was finally distilled under reduced pressure:-

Boiling points 131°C at 22 m.m.of mercury.

126°C at 14 m.m.of mercury.

Yield from 19.4 grms. of piperazine hydrate

Weight of diester	1.5 grms.
Weight of crude monoester	12.5 grms.

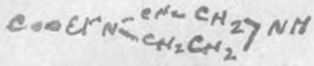
Hence proportion of piperazine converted into monoderivative is

$$\frac{12.5}{15.8} = 79\%$$

Combustion analysis of monoester.

Weight of ester combusted	0.2440grms.
Weight of CO_2 absorbed	0.4766grms.
Weight of H_2O absorbed	0.1973grms.

% carbon	53.26.
% hydrogen	9.19.

Theoretical for  $COOEt\cdot N{<}^{CH_2CH_2}_{CH_2CH_2}{>}NH$ is C 53.16%

H 8.8%

Methylation of monocarbethoxy piperazine.

Mono ester 20grms.
Methyl iodide 17.8grms.
} i.e. in proportion of one molecule each.

60c.c. of methyl alcohol were added to the monoester and then the methyl iodide was added in small quantities at a time. Much heat was developed during the addition (the flask was therefore cooled in water) and the cplour of the solution changed to dark red. The solution was heated on a water bath under a reflux condenser for 2or 3 hours and then a small quantity was tested for unchanged monoester in the following way. All the alcohol was evaporated and the residue was shaken up with soda and a few drops of benzoyl chloride. Apparently no benzoyl compound was formed but the solution was hydrolised by boiling for 10 minutes and the benzoyl reaction tried again on the cooled solution. As small quantity of dibenzoyl piperazine was obtained and it was therefore concluded that a very small quantity of monoester remained unchanged.

The methyl alcohol was distilled from the main bulk of the solution and an ice cooled very strong solution of caustic potash added to the residue. The free base was extracted with ether and the ethereal solution dried. The aqueous extract was neutralised with hydraodic acid and taken to dryness on the water bath.

The organic iodide was extracted with absolute alcohol but was found still to be mixed with a little potassium iodide from which it was finally freed by dissolving in chloroform From the chloroform solution was obtained a dark coloured deliquescent strongly alkaline iodide. It was recrystallised from a mixture of alcohol and ether. An iodide estimation gave the following results:-

Weight of salt	0.1381 grms.
Weight of silver iodide	0.1018 grms.
% iodide	39.82

Theoretical for $COOEtN\begin{array}{l}<CH_2CH_2\\<CH_2CH_2\end{array}>N\begin{array}{l}-Me\\-Me\\\ \ I\end{array}$ is 39.87% I_2

From the account of quaternary iodide obtained it was clear that the methyl derivative of the monoester in the second ethereal extract would contain an appreciable amount of unchanged ester.

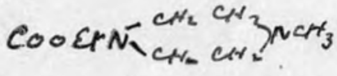
The ether was distilled from dried ethereal extract and then attempts were made to purify the product. The unchanged monoester was converted into the nitroso derivative by the addition of sodium nitrate to an acid solution and the nitroso ester was extracted with ether. The aqueous solution was cooled in ice, neutralised and saturated with potassium carbonate and ether extracted. The dried extract after removal of the ether gave a syrupy liquid with a pungent amino smell. It was distilled at reduced pressure.

Yield. 6 grms. boiling between 150^0 & 160^0 C. at 15m.m.of mercury

Combustion analysis of methyl derivative of monoester.

Weight of ester	0.2380 grms.
Weight of CO_2	0.4642 grms.
Weight of H_2O	0.1643 grms.

%Carbon	53.21 .
%Hydrogen	7.67.

Theoretical for  $COOEtN\begin{matrix}CH_2\,CH_2\\CH_2\,CH_2\end{matrix}NCH_3$ is 55.82% C

9.3% H_2

The product then still contains a considerable proportion of the original substance.

Reaction between ethyl iodide and monoester.

0.1 molecules of monoester 15.8 grms.
0.1 molecules of ethyl iodide 15.6 grms.

The monoester was dissolved in 50 c.c.absolute alcohol and the ethyl iodide added in small quantities at a time, very little heat was evolved. The mixture was then heated under a reflux condenser for one hour, at the end of which time it was cooled and a few c.c.solution tested for presence of unchanged ester by benzoylation. The test gave negative results. The alcohol was removed by distillation and the residue on cooling crystalised. It was dissolved in a very little water, cooled in ice and the equivalent of strong potash added. The free base was extracted several times with ether, the extract dried and distilled. On distillation under reduced pressure a colourless syrup with a pungent smell was obtained.

Yield 12 grms Boiling point 150^0 C. under 45 m.m.Mercury.

Combustion Analyses.

(1) Ester	0.3063 grms.			
CO_2	0.6241 grms.		% carbon	56.78
H_2O	0.2572 grms.		% hydrogen	9.33

(2) Ester 0.3662 grms.)
CO_2 0.7630 grms.) %carbon 56.82
H_2O 0.3093 grms.) %hydrogen 9.38

Theoretical for $COOEtN\left<{}^{CH_2\cdot CH_2}_{CH_2\cdot CH_2}\right>NC_2H_5$ is 58.06% Carbon
9.68% Hydrogen.

It is evident that some monoester remains unchanged in the reaction with ethyl iodide, and probably some quaternary compound is produced here, though not to such an extent as it is when methyl iodide reacts with the monoester.

Several other attempts were made to obtain the ethyl derivative :-

(a) Ester + EtBr + aqueous Na_2CO_3 in equivalent quantities were shaken together until all the EtBr had disappeared. Benzoylation showed little or no reaction had taken place.

(b) Ester + ethyl p. tolyl sulphonate + alcohol in the presence of solid sodium carbonate were heated on a water bath for some time. The alcohol was then distilled off, the residue cooled on ice, treated with strong potash solution and ether extracted. Evaporation of ether left a liquid which on hydrolysis and benzoylation gave a semi-solid benzoyl derivative. This solidified on leaving in the cold. It was quite unlike dibenzoyl piperazine and most probably contained tha benzoyl derivative of ethyl piperazine. It would therefore appear that ethyl p.tolyl sulphonate is a suitable ethylating agent.

Preparation of ethyl monocarbethoxy piperazine.

12grms. of piperazine mono ester.

20grms. of p.ethyl tolyl sulphonate.

5.3grms. of Sodium carbonate (anhydrous).

50 c.c. absolute alcohol.

The mono ester and the tolyl sulphonate were dissolved in the alcohol and the finely powered sodium carbonate added. The mixture was heated under a reflux condenser on a steam bath for 3 to 4 hours. There was an evolution of CO_2 carbon dioxide. It was finally heated to 120°C in an oil bath until there was no further action and all the alcohol had distilled over. The product was colled in ice, 100c.c. of water and 100c. of N. soda were added. Unchanged ethyl p.tolyl sulphonate was extracted with ether(1). The aqueous residue was cooled in ice and saturated with anhydrous potassium carbonate and extracted several times with ether(2). Both extracts were dried over anhydrous sodium sulphate for some days. On distillation of the ether, extract(1) left a dark coloured syrup which on keeping in a desiccator deposited some solid(ethylp.tolylsulphonate) It was distilled under reduced pressure and the main product consited of a colourless syrupy liquid b.pt.120-121C. at 16m.m.Hg. Extract(2) distilled completely at 121C under 16m.m.Hg.

Total crude yield of ethyl derivative was 9grms, representing 60%conversion of monoester.

Combustion ~~anl~~ analysis of ethyl ester.

Ester	0.3434grms.	
CO_2	0.7214grms.	%carbon 57.3
H_2O	0.2996.grms.	%hydrogen 9·69.

Theoretical for $C_2H_5.C_4H_8N_2.COOEt$ is 58.06%carbon.
9·68%hydrogen.

Hydrolysis of ethyl piperazine ethyl carboxylate.

(1) With normal aqueous caustic soda.

A few grams of ester were heated with soda on a water bath for one hour. ~~The solution was saturated with soda on a water bath for one hour.~~ The solution was saturated with potassium carbonate, extracted with chloroform and the extracte ~~d~~ dried. The solution, after distilling off the chloroform gave a small residue of colourless oil boiling at approximately 68°C under 55m.m. Hg

Since it was too small to do anything with as liquid it was benzoylated and the solution extracted with :(a) ether,(b) chloroform. The latter solution contained a trace of a hygroscopic solid. The solution gave on evaporation a small quantty of a strongly alkaline oil whose hydrochloride gave a platinic chloride double salt. It seemed obvious from this experiment that no piperazine resulted on hydrolysis of the ester, but probably the solution contained ethyl piperazine, the extraction of which was incomplete and difficult owing to its great solubility in water. It was therefore considered preferable to use strong hydrochloric acid as the hydrolytic agent.

(2) The ester was heated under a reflux with excess hydrochloric acid (consitting of equal volumes of concentrated acid and water).The heating was continued for two days and then the solution was evaporated nearly to dryness to remove all excess acid.It was diluted with water ,decolourked with animal charcoal and taken to dryness. The residue was recrystalled from alcohol. A cstalline, nearly colourless hygroscopic hydrochloride was obtained. A chlorine estimation gave the following results:-

Hydrochloride 0.2178grms.

Silver chloride 0.3356grms.

% chlorine 37.84

Theoretical for $C_2H_5\cdot C_4H_9N_2\cdot 2HCl$ is 37.97% chlorine.

Double salt of ethyl piperazine hydrochloride and platinic chlorid

The hydrochloride was dissolved in a little concentrated hydrochloric acid ,heated and treated with excess platinic chloride solution. It was allowed to stand for a day when deep yellow crystalls separated . These were collected and dried. A platinum estimation gave the following results:-

Weght of salt 0.1193grms.

Weight of platinum(left after igniting salt) 0.0443grms.

%platinum 37.1

Theoretical for $C_2H_5-C_4H_9N_2\cdot 2HCl\cdot PtCl_4$ is 37.12 % platinum.

Double salt of ethyl piperazine hydrochloride with auric chloride.

This was prepared in a manner analogous to the above. Golden yellow crystals were obtained, and were analysed for their gold content.

Weight of salt	0.1433grms.
Weight of gold	0.0705grms.

% of gold 49.02.

Theoretical for $C_2H_5 \cdot C_4H_9N_2 \cdot 2HCl \cdot 2AuCl_3$ is 49.6% gold.

Preparation of mono benzoyl piperazine.

0.05grm. molecule piperazine hydrochloride.

0.06grm. molecule benzoyl chloride.

N. soda solution.

Bromophenol blue was used as indicator as in the preparation of carbethoxy piperazine and small quantities of benzoyl chloride and soda were added alternately. A solid separated during the process. This was collected and found to be dibenzoyl piperazine The solution was made alkaline and ether extracted(1). To the aqueous residue solid potassium carbonate was added in excess and the solution again extracted several times with ether(2).

After drying the extracts for a day or two over anhydrous sodium sulphate the ether was removed. Extract (1) gave a trace of residue . From extract(2) was obtained a small qpantity of syrupy liqpid which solidified after being in a vacuum desiccator for some days. It was found to be very soluble in alcohol and chloroform, insoluble in ligroin. It was recrystallised by dissolving in benzene and precipitating with ligroin. It was concluded that the substance so obtained was mono benzoyl piperazine but the quantity was too small to make any analysis possible. As this method gave mainly the dibenzoyl piperazine, attempts were made to obtain the mono derivative in the following way.

Benzoylation of mono carbethoxy piperazine.

Mono carbethoxy piperazine was dissolved in excess normal soda. Benzoyl chloride slightly more than equivalent to the ester was added slowly, keeping the ester solution cold. The mixture was then shaken in a mechanical shaker for about ¾ hour. The solid formed was collected and recrystallised from ligroin M.Pt. 180° C.

Combustion of benzoyl derivative.

Weight of benzoyl ester	0.1052 grms.
Weight of CO_2	0.2446 grms.
Weight of H_2O	0.0649 grms.

% carbon 63.51. % hydrogen 6.85.

Theoretical for $C_6H_5.Co.N_2C_4H_8COOEt$ 64.12% C. 6.87% H_2.

(A more accurate combustion on the same compuond has been carried out by Dr. Boyle.)

Hydrolysis of benzoyl ester.

(1) The derivative was heated under a reflux with excess N/10 soda for about two hours. The solution was saturated with K_2CO_3 and extracted with chloroform. After drying and removing the solvent a small quantity of a dark coloured syrup was obtained. There was not sufficient to redistill. It was therefore converted into a hydrochloride by passing dry hydrochloric acid gas into the ethereal solution. The solid precipitated was collected and recrystallised from alcohol and ether.

A chlorine analysis gave the following results:-

Hydrochloride	0.1415 grms.
Silver chloride	0.0907 grms.

% chlorine 15.86.

Theoretical for $C_6H_5-Co.N_2C_4H_9.HCl$ is 15.67% chlorine.

It was evident that some mono benzoyl piperazine had been obtained by the aqueous alkaline hydrolysis of the corresponding ester.

Other methods of hydrolysis were tried. The benzoyl ester was dissolved in alcoholic potash solution(15%) and left to stand in the cold for a day or two. It was found that a solid precipitated very soon; it consisted of potassium benzoate, as a result of the decomposition of the benzoyl ester. The amount of benzoate was sufficient to justify the conclusion that the removal of the benzoyl group from the ester was practically complete.

Strong hydrochloric acid. (The carbethoxy group is stable to dilute acid solution.)

A small quantity of benzoyl derivative was heated with hydrochloric acid for about 10 minutes. On cooling the solution, benzoic acid was precipitated in considerable quantity.

Dilute aqueous soda.

The ester was allowed to stand for a week with dilute caustic soda solution, without warming at all. At the end of this time practically all solid had gone into solution. Part of the solution was acidified and gave a precipitate of benzoic acid. Another part was benzoylated and gave a precipitate of di-benzoyl piperazine. The rest of the solution was saturated with K_2CO_3 and extracted with chloroform. On drying and removing the solvent a very small quantity of a dark coloured, alkaline syrupy liquid was obtained.

Preparation of mono tolyl sulphonyl piperazine.

10 grms. mono carbethoxy piperazine.
12.06 grms. p.tolyl sulphonal chloride.
1½ equivalents of soda.

The ester was dossolved in the soda and the p.tolyl sulphonal chloride was dissolved in ether. The ethereal solution was added in small quantities at a time to the solution containing the ester which was stirred mechanically. A white solid separated and was collected. Yield 15.3 grms. It was recrystallised from ligroin m.pt. 115° C.

A combustion analysis of the derivative gave the following results:-

Weight of substance	0.1640 grams.
Weight of H_2O	0.0956 grms.
Weight of CO_2	0.3259 grms.
% carbon	54.20
% hydrogen	6.48.

Theoretical for $C_7H_7.SO_2.C_4H_8N_2.COOEt$ is 53.84% Carbon.
6.40% Hydrogen.

Hydrolysis of ester derivative.

The ester was heated on a water bath under a reflux condenser, with 20% alcoholic potash for two or three hours. Water was added and the alcohol distilled off. An oil separated from the water and on cooling, solidified. The solid was collected and recrystallised with ligroin m.pt. 112° C. A mixed melting point determination was also made with this substance and the unhydrolysed ester owing to the proximity of the melting points. The mixed melting points proved them to be two different substances.

Combustion analysis of mono p.tolyl sulphonyl piperazine.

Weight of substance	0.2263 grms.
Weight of CO_2	0.4616 grms.
Weight of H_2O	0.1372 grms.
% carbon	55.63
% hydrogen	6.67.

Theoretical for $C_7H_7SO_2.C_4H_9N_2$. is 55.00% carbon.
6.67% hydrogen.

Hydrochloride of mono p.tolyl sulphonyl piperazine.

This was prepared by passing dry hydrochloric acid gas into an ethereal solution of the base. A white solid was obtained. A chlorine estimation gave the following results:-

Weight of hydrochloride 0.1817 grms.
Weight of silver chloride 0.0958 grms.
% chlorine 13.02.

Theoretical for $C_7H_7So_2.C_4H_9N_2 \cdot HCl$ is 12.86% chlorine.

Action of alcoholic potash upon (a) dibenzol piperazine (b) mono tolyl sulphonyl piperazine.

(a) About 1 grm. of dibenzoyl piperazine was allowed to stand with 15% alcoholic potash, in the cold, for several days. A portion of the aqueous solution (from which all the alcohol had been removed) was tested for benzoic acid by addition of hydrochloric acid, and for piperazine by benzoylation. In neither case was a precipitate obtained. The rest of the solution was then heated on a steam bath for three to four hours. Water was added and the alcohol distilled. The residue smelt strongly of piperazine. To part was added hydrochloric acid when a copious precipitate of benzoic acid was obtained. Another portion was dissolved in soda solution and benzoylated when dibenzoyl piperazine was obtained.

(b) Mono p.tolyl sulphonal piperazine and cold alcoholic potash were left together several days and the solution tested for piperazine as before and with a similar result. It was then heated on a steam bath for several hours, diluted with water and the alcohol removed. Mono p.tolyl sulphonyl piperazine was recovered in a practically quantitative yield. The aqueous solution was benzoylated when a trace of dibenzoyl was obtained.

Preparation of ethanol derivative of mono carbethoxy piperazine.

Trial methods.

(1) Ethylene chlorhydrin the monoester and sodium carbonate in equivalents quantities were shaken up for some time in water.

Benzoylation of the liquid showed that the monoester remained unchanged.

(2) The operation was repeated using alcohol as the solvent and the mixture was heated on a water bath. The liquid was filtered from the solid and the alcohol evaporated. The solid was tested for the presence of chloride and carbonate and was found to contain a little of the latter but was mainly chloride. The liquid remaining after removal of the alcohol was distilled under reduced pressure. It boiled (probably with decomposition) at 180-195°C under 40m.m.Hg. This was converted into its hydrochloride and a chlorine estimation gave the following result:-

Weight of hydrochloride	0.2121grms
Weight ofs silver chloride	0.1231grms.

%chlorine 14.24

Theoreticzal for $COOEt.C_4H_8N_2 \cdot CH_2CH_2OH.HCl$ is 13.83% chlorine. Evidently a reaction has taken place. Finally the following method was adopted:-

30grms	ester
20grms	ethylene chlorhydrin
13.5grms	anhydrous sodium carbonate.

The mixture was heated under a reflux condenser on an oil bath at 110°C for six hours at the end of which time the evolution of CO_2 had ceased. Finally the temperature was raised to 140°C for a short while. There was no further reaction and the product was therefore cooled in ice and treated with 50c.c. of 10% caustic potash. Itwas extracted several times with ether. The ethereal extract was dried over anhydrous sodium sulphate and after removal of the ether the remaining liquid was distilled under reduced pressure, a colourless syrup was obtained b.pt. 184°-184°C at 17m.m.HG.

Yield. 30grms ,corsesponding to 75% conversion of the original ester.

Combustion analysis of Ethanol ester.

Weight of ester	0.2536 grms.
Weight of CO_2	0.4954 grms.
Weight of hydrogen	0.2164 grms.
% carbon	53.28.
% hydrogen	9.49.

Theoretical for $COOEt\cdot C_4H_8N_2\cdot C_2H_4OH$ is 53.46% Carbon.

8.92% Hydrogen.

Hydrolysis of ethanol ester.

The ester was heated with strong hydrochloric acid under a reflux for two or three days. The solution was then concentrated, decolourised with animal charcoal, filtered and evaporated to a very small bulk. A white crystalline solid was obtained which was very soluble in water, giving a strongly acid reaction. It was recrystallised from boiling alcohol, in which it was not very easily solouble.

Analysis of ethanol piperazine hydrochloride.

(1) Water-crystallised salt.

Weight of salt	0.2175 grms.
Weight of silver chloride	0.2716 grms.
% chlorine	32.2.

Theoretical for $2HCl.C_2H_4OH.C_4H_8N_2.H_2O$ is 32.1% Chlorine.

(2) Salt recrystallised from alcohol and dessicator dried.

Weight of salt	0.1204 grms.
Weight of silver chloride	0.1669 grms.
% chlorine	34.30

Theoretical for $2HCl.C_2H_4OH-C_4H_8N_2$ is 34.97 Chlorine.

Preparation of double salts of mono ethonal piperazine hydrochloride with (a) platinic chloride and (b) auric chloride.

(a) The hydrochloride was dissolved in a little concentrated hydrochloric acid and heated. Excess platinic chloride was added and the solution allowed to concentrate in a vacuum dessicatorl A yellow crystalline salt was deposited after a day or two.

Platinum estimation.

Weight of double salt	0.0674 grms.
Weight of platinum	0.0246 grms.
% platinum	36.48.

Theoretical for $C_2H_4OH.C_4H_{10}N_2.PtCl_6$ is 36.15% platinum.

(b) A double salt of the ethanol hydrochloride with auric chloride was prepared in an analogous manner. It consisted of very beautiful golden crystals.

Gold estimation.

Weight of salt	0.1167 grms.
Weight of gold.	0.0567 grms.
% gold	48.7

Theoretical for $2AuCl_4 \cdot C_2H_4OH.C_4H_{10}N_2$ is 48.62% Gold.

Preparation of addition compound of CO_2 with (a) piperazine mono ester and (b) mono p.tolyl sulphonal piperazine.

(a) A current of dry CO_2 was passed into an alcoholic solution of mono carbethoxy piperazine. No precipitate was obtained and after evaporation of the alcohol the unchanged ester alone remained.

(b) An alcoholic solution of mono p.tolyl sulphonyl piperazine was saturated with CO_2. A white precipitate with a microscopic crystalline structure was obtained. It was insoluble in cold water but decomposed on heating, with the evolution of CO_2.

Sulphur estimation. (Carius' method)

Weight of compound	0.1503 grms.
Weight of $BaSO_4$	0.1325 grms.

% Sulphur	12.13.

Theoretical for $CO_2 . 2C_7H_7SO_2 . C_4H_9N_2$ is 12.21% sulphur.

Preparation of addition compound of CS_2 with (a) mono carbethoxy piperazine and (b) mono p.tolyl sulphonyl piperazine.

(a) The mono carbethoxy piperazine was dissolved in alcohol and CS2 added slowly in excess. A cream coloured crystalline compound was precipitated. It was insoluble in cold water but decomposed on heating, with the evolution of CS_2.

Sulphur estimation.

Weight of compound	0.2071 grms.
Weight of $BaSO_4$	0.3534 grms.
% sulphur	16.75.

Theoretical for $CS_2 . 2.COOEt.C_4H_9N_2$ is 16.32% sulphur.

(b) CS_2 was added to an alcoholic solution of mono p.tolyl sulphonyl piperazine. A cream coloured insoluble compound was obtained which was not decomposed by boiling water.

Sulphur Estimation.

Weight of compound	0.0966 grms.
Weight of $BaSO_4$	0.1653 grms.
% Sulphur	23.19

Theoretical for $CS_2 . 2C_7H_7SO_2C_4H_9N_2$ is 23.02% sulphur.

Preparation of picrates of (a) mono carbethoxy piperazine and (b) mono tolyl sulphonal piperazine.

(a) An alcoholic solution of picric acid was added to the mono carbethoxy piperazine also dissolved in alcohol. On stirring and standing, a mustard yellow crystalline compound was obtained. It was difficulty soluble in cold water but more readily so in hot water. m.pt. 197^0 C.

A nitrogen estimation gave the following result.

Weight of picrate	0.1884 grme.
Volume of nitrogen	29.9 c.c. (at 10^0 C and 742 m.m.mercury)
% nitrogen	18.48

Theoretical for $C_6H_2(NO_2)_3.OH.C_4H_9N_2.COOEt$ is 18.62% nitrogen

(b) On mixing alcoholic solutions of picric acid and mono tolyl sulphonyl piperazine a greenish-yellow crystalline compound was immediately precipitated. This was only very slightly soluble in cold water but dissolved more readily in hot. On heating it darkened in colour at about 215-220° C and melted with decomposition at 225° C.

Nitrogeh Estimation.

Weight of picrate 0.1161 grms.

Volume of nitrogen 15.2 c.c. at 16.5 C and 752m.m.mercur

% nitrogen 14.79

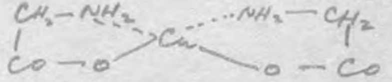
Theoretical for $C_6H_2(NO_2)_3OH.C_4H_9N_2.C_7H_7$ is 14.81% nitrogen.

PART 11. METALLIC SALTS OF PIPERAZINE DIACETIC AND MONOACETIC ACIDS.

INTRODUCTION AND GENERAL.

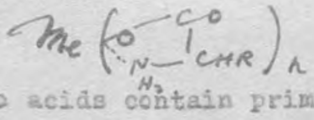
Internal complex metallic salts are a particularly interesting class of compounds, the existence and abnormal properties of which received no satisfactory explanation until the enunciation of Werner's theory of co-ordination. According to this theory an atom, even when according to the classical doctrine of Valency has its combining possibilities exhausted (as represented by the principal Valencies) may still possess a particular kind of affinity which enables it to form molecular complexes (by virtue of the auxiliary valencies) provided the amount of residual affinity is sufficient to bring about a stable combination between the single molecules.- Just as principal valencies exhibit a maximum - and for a particular element this number is determined by its position in the Periodic Table, so also do the auxiliaries. The maximum value of the latter is determined by the number of groups attached in the inner nonionisable zone, and for many elements this is 6 and for some only 4. This number represents the co-ordination number of the central atom. E.G. In Potassium chloroplatinate K_2PtCl_6, platinum has a co-ordination number 6, the six chlorine atoms being directly attached to it and occupying the inner zone. They are not ionised in solution, but the two potassium atoms are represented as being in an outer zone and are ionised.

The internal complex metallic salts are a particular type of co-ordination compounds in which the metallic atom is linked up by both principal and auxiliary Valencies within one molecule, the latter link being derived from an unsaturated group in the acid radical, e.g. in the amino acids there are present the unsaturated groups $-NH_2$, NHR, or NR_2. These acids are particularly suitable for the study of inner complex salts. Copper glycine is a typical example and is given the structure



The copper atom here has a co-ordination number 4, is linked to the amino groups by auxiliary valencies and to the oxygen atoms of the carboxyl groups by its two principal valencies.

The investigations of Bruni (1904) Ley (from 1909) and Tschugajeff (1911) show that the tendency to form inner complex salts of amino acids is strongly pronounced in α acids, in the β acids less so, and in the γ and δ acids there is none. These facts are in agreement with the general idea of stereochemistry, that inner complex salts are perticularly stabile when 5 membered rings can be formed, and such rings are present in the salts of α amino acids of the general form



Whether the amino acids contain primary, secondary, or tertiary amino groups plays no intrinsic part in the inner complex salt formation. All internal complex salts show an anomalous behaviour with reference to electrolytic dissociation, and analytical reactions. The metal is prevented from appearing as an ion in solution and therefore in aqueous solution the salt has a normal molecular weight and a very low conductivity. An abnormal colour is also characteristic of these salts, thus the copper salts are deep violet blue in solid state and give very deep blue solutions, and chrâmium and cobalt give red and violet salts. The metal in the complex salt may be Fe, Co, Ni, Cr, Pt, Cu or Zn, and the acid, glycine, alanine, diethylaminoacetic, piperidoacetic, phenlglycocol etc. but the stability of the salt varies with the metal and with the acids. Expressing the reaction between a metal acetate and the amino acid as an equilibrium reaction:-

$$Me\,X_2 + 2NH_2R.COOH \rightleftarrows Me(CO_2RNH_2)_2 + 2HX$$

then obviously the less the dissociation of $Me(CO_2RNH_2)_2$ the further is the equilibrium in the direction ⟶

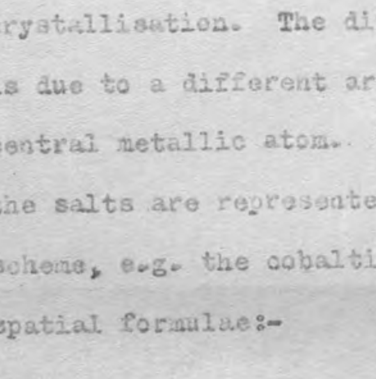
Also, if Δ_1 represents the conductivity of metal acetate

Δ_2 represents the conductivity of solution after addition of amino acid,

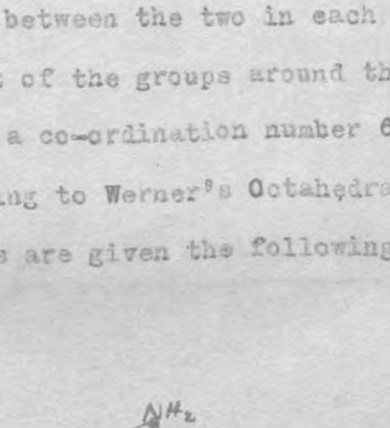
Then $\Delta_1 - \Delta_2$ gives an idea of the extent of formation of the complex salt. If the complex salt formation is large the conductivity approaches that for acetic acid, if small, then the conductivity is mainly due to metallic acetate. Ley's experiments showed that for various salts with glycine the extent of complex salt formation decreased in the order

$$Cu^{''},\ Ni^{''},\ Zn.\ Co^{''},\ Cd.\ Mn.\ Ba.$$

and measurements with Nickel acetate and various acids gave values of $\Delta_1 - \Delta_2$ decreasing in the order glycine, α amino propionic, β amino propionic, piperido acetic acids.
The salts of chromium and trivalent cobalt were found to exist in two isomeric forms, both showing the characteristics of internal complex salts but differing from each other in colour and crystallic form and the number of molecules of water of crystallisation. The difference between the two in each case is due to a different arrangement of the groups around the central metallic atom. This has a co-ordination number 6 and the salts are represented according to Werner's Octahedral scheme, e.g. the cobalti glycines are given the following spatial formulae:-



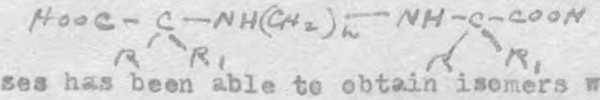
trans



cis

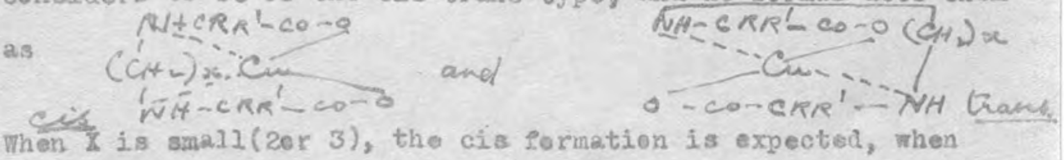
Two different spatial arrangements of the groups about the central cobalt atom are possible. Hence two salts exist which exhibit cis-trans isomerism.

Recently, Schlesinger(B.1925.p.1877.), has investigated internal complex copper salts of dibasic amino acids, of the general type



$HOOC-C(R)(R_1)-NH(CH_2)_n-NH-C(R)(R_1)-COOH$

and in some cases has been able to obtain isomers which he considers to be of the cis-trans type, and he formul ates them as

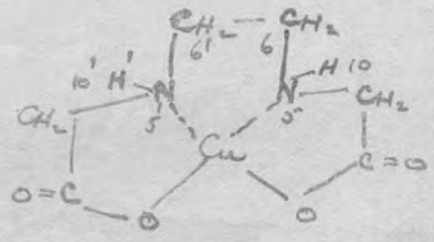


cis and trans

When X is small(2or 3), the cis formation is expected, when large(10) trans is favoured, and when intermediary both can be obtained and their mutual transformation studied.

In assigning these formulae to the salts Schlesinger makes the assumption that the 4 co-ordination bonds of copper have a plane arrangement, whereas Mills & Gotts by their resolution of copper salts of benzoyl pyruvic acid into optically active isomers have definitely proved the 4 groups to occupy the vertices of a tetrahedron at the centre of which is the copper atom. (J.C.S.1926 p.3[illegible]

Reihlen (Zeit. AnorgChemie 1926 vol.151 p.71), explains Schlesingers results. Considering the simplest salt of this type ,viz. copper ethylene bis imine acetate, the formula assigned contains 3 five-membered rings without double bonds. At first sight this arrangement appears to be plane, but if one examines both the nitrogen atoms, one sees that in this case the four links are directed



towards the corners of a tetrhedron of which the nitrogen atom is at the centre of gravity. These salts are examples of spiran asymmetry and are analogous to the cobalt chloride complexes of sarcosine investigated by Meisenheimer.

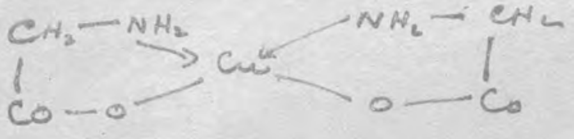
We are now in a position to give an electronic interpretation to coordination. In his book "The Electronic Theory of Valency", Sidgwick classfied the 3 kinds of linkages between the atoms in a molecule:-

1) Polar or ionised linkages due to the transference of electrons from one atom to another.

2) Nonpolar, nonionisable covalent linkages due to the sharing of electrons, two to each link between the atoms. These can arise in two ways:-

(a) One electron contributed by each atom --normal covalen

(b) Both electrons contributed by the same atom. This type of linkage is a coordinate covalency and is present in all the coordination compounds referred to above. The links which join the units of a coordination complex to the central atom are covalent. The maximum coordination number is the maximum covalenc number, and a covalency of 6 implies a valency group of 12 shared electrons, that of 4 a valency group of 8. e.g. in copper glycine the nitrogen atoms act as donors and provide the central copper atom with two pairs of electrons thereby completing the stable valency group of eight. In all co-ordination compounds there exist two different kinds of atoms, one a donor and the other an acceptor. The covalent links are represented by arrows as in the following:-



The term "chelate" has also been applied by Morgan to these co-ordinatàon compoundxs in which the co-ordination takes place between two atoms already forming part of the same molecule.

The electronic theory , therefore makes it possible to reconcile the theory of coordination of Werner with structural chemistry, and this interpretation breaks down the supposed distinction between organic and inorganic chemistry, which the opposition of the coordination and structural theories had hitherto suggested.

Theoretical Discussion.

Of the acids previously studied from the point of view of internally complex formation piperidine acetic most nearly resembles the piperazine acetic acids , in constitution. It may therefore be interesting to note here some general remarks upon piperadine acetic acids and its salts, before the piperazine acid and their salys are considered.

Bischoff in 1898(Ber.31.p.2841) prepared ethyl piperaidine acetate by the addition of ethyl chloracetate to piperidine. Hydrolysis of this ester with baryta gave piperidine acetic acid. It is soluble in organic solvents and crystallises from water with one molecule of water of crystallisation, which it loses when heated to 125°C. Further it has a neutral reaction. In these respects it differs from piperazine diacetic acid which has an acid reaction, and contains two molecules of water of crystallisation which it easily loses in a dry atmospphere. Piperazine monoacetic acid ,on the other hand, is extremely soluble in water, but from strong solutions can be precipitated with alcohol, and has a strongly alkaline reaction. These properties are to be attributed to the free imino group in the molecule. It crystallises with one molecule of water. Ley(Ber.1909.p.354), working with piperidine acetic acid obtained a copper salt which showed some characteristics of internally complex salts, but which in dilute aqueous solution was considerably hydrolysed, and gave a precipitate of copper hydroxide with caustic soda. A complex nickel salt of this acid could not be produced on account of the even greater hydrolysis . The preparation of internally complex platinum and chromium salts are also recorded(Ber.1912.p.372), but the corresponding cobaltic salts do not appear to have been investigated. The two general methods employed by Ley for preparing the copper salts were(1) solution of copper hydroxide in amino acid,

(2) addition of copper sulphate to an equivalent mixture of the amino acid and baryta. Both of these methods are satisfactory if the salts are soluble in water, though the latter is preferable when there is a tendency for the salt to be hydrolytically dissociated as e.g. copper piperidine acetate. When, however, the copper salts os piperazine diacetid acid were prepared these methods were not so convenient, on account of the insolubility of the salts, and precipitation methods were employed, viz: addition of copper salt solutions (sulphate or acetate) to solution of the acid itself or its sodium salt. On mixing the solutions a very deep purplish blue colour resulted which might be taken to indicate complex salt formation, and then pfactically immediately a rather gelatinous salt was precipitated. Four different copper salts were obtained of which only one was moderately soluble in water, the other three being insoluble in water, alcohol and phenol and acetic acid. The soluble salt (1) an azure blue crystalline compound , gave the normal reagtions of a copper salt, i.e tnere was no evidence for co-ofdination within the molecule. The other three consisted of-

(11) a green anhydrous salt,

(111) a light blue hydrated salt,

(1V) a deep blue hydtate dsalt.

All three showed a minute crystalline structure when viemed under the microscope. They dissolved on boiling with very dilute acids and the solutions then gave normal copper reactions. The acids brought about the decomposition of the salts, and on account of the insolubility of the latter in all solvents tried ,investigations regarding the internally complex nature could not be carried out. As a result of analysis of these salts the following formulae have been assigned to them:-

(1) $Cu \cdot C_8H_{12}N_2O_4 \cdot 2H_2O$

(11) $Cu\ C_8H_{12}N_2O_4\ 4CuO$

(111) $Cu.\ C_8H_{12}N_2O_4 \cdot Cu(OH)_2$ [$6H_2O$ and $1H_2O$]

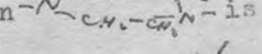
(IV) $Cu.\ C_8H_{12}N_2O_4.\ Cu\ C_4H_6O_4.$ [$5H_2O$ and $1H_2O$]

The difference between the pairs of hydrates of the salts 111& 1V is only one of hydration and they are not chemical isomers. The lower hydrate is obtained by heating the higher above 100°C, and addition of water reverses the change immediately.
A nickel and cobaltous salt of piperazine diacetic acid analogous to the simple copper salt $Cu.C_8H_{12}N_2O_4.2H_2O$ were obtained as insoluble substances, with a microscopic crystalline structure, by the addition of a nickel or cobalt salt to the sodium salt of the amine acid. Owing to their insolubility, investigations with regard to their molecular weights and conductivities could not be carried out, but as they were perfectly normal in colour it was concluded that internally complex formation had not taken place. Ley's method for preparing cobaltic salts of amine acids, which consisted of heating the acid with freshly precipitated cobaltic hydroxide for several hours, was attempted with piperazine diacetic acid, but without success and various other methods that were tried wre equally unsuccessful.

In view of Schlesinger's work on the copper salt of

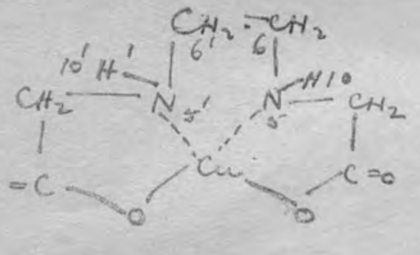
$$HOOC-C(CH_3)_2-NH.CH_2.CH_2.NH.C(CH_3)_2.COOH$$

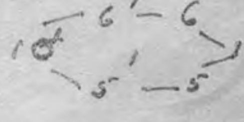
(which bears considerable resemblance to the piperazine diacetic acid,) it appears very remarkable that no salt has been isolated here which shows signs of complexity. This is perhaps explained by Reihlens view of the constitution of Schlesingers salts (see p.4) Adopting Reihlens point of view and applying it to the salts of piperazine diacetic acid, it is seen that the two hydrogen atoms 10-10' in the formula are replaced in the piperazine derivative by the chain $-CH_2-CH_2-$. The resulting plane configuration



$$-N\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}N-$$

is according to Reihlen,





which is not in one plane. Hence in the piperazine diacetic salts the nitrogen atoms cannot be coordinated with the metal atom

Since these nitrogen atoms are then free to coordinate with other suitable substances, there is a reason for the very ready production of basic salts. But since on account of their insolubilty the molecular weights cannot be determined, no definite suggestions as to their formulae can be made.

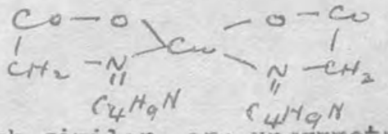
The results obtained with piperazine monoacetic acid were however very interesting. This acid has a strongly alkaline reaction, but stable salts have been prepared from it of which only the copper salts have as yet been investigated in detail. Two isomeric copper salts have been obtained, one deep blue and the other dark green. Both dissolve very easily in water, imparting their own particular colour to the solution and there is evidence for a very small proportion of free copper ions in both cases. On addition of a few drops of hydrochloric acid to the blue salt a yellow solution was obtained from which alcohol precipitated a very light green crystalline precipitate. Addition of alkali restores the original blue solution. With dilute sulphuric acid the same type of colour was produced, but with more brown in it. Addition of alcohol caused the precipitation of a very light green gum. The green salt when similary treated gave reddish brown solutions from which alcohol precipitated, in one case, a light yellow crystalline solid, and on the other case, a gum. Addition of alkali restored the original green solution.

The blue salt can be converted into the green either by heating it above 100°C, or by warming with alcohol, but no conditions have been found under which the green salt reverts to the blue one.

The results appear to make it certain that we have here a case of true isomerism. The molecular weight determinations, though carried out with quantities of substances too small to allow of accuracy, at any rate shut out the possibility of polymerism. Hydration isomerism would appear to be excluded by the persistenc of the two forms in solution and by their wholly different reactio with acid.

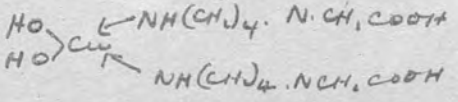
From analysis it would appear that the blue salt is $Cu.C_{12}H_{22}O_4N_2.8H_2O$ which readily loses $5H_2O$ to give a lighter blue salt. The green salt is also $Cu.C_{12}H_{22}O_4N_2.3H_2O$ and can be obtained anhydrous.

The simplest formula $Cu(O_2C.CH_2.N(CH_2)_4NH)_2$ is excluded for both salts on account of the non-occurence of some reactions of the copper ion. The formula represents a spiro compound



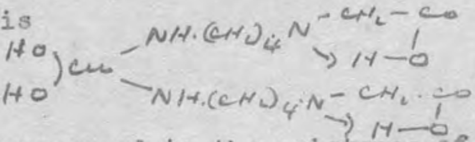
formed from two rings, which though similar, are unsymmetrical. Such a salt could exist in two enantiomorphic forms, but these would only be obtained by resolution, so the formula offers no explanaton of the isomerism found, though it could represent one of the two salts.

The other formula which can be written on the basis of 4-covalent copper is:-(assuming $2H_2O$ in the inner complex),

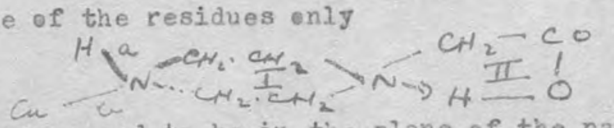


II

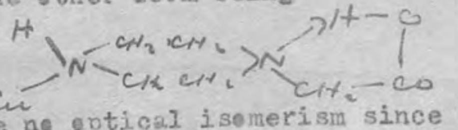
or the betaine form of this



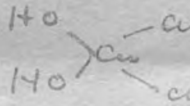
This betaine formula would correspond to the existence of isomers Considering one of the residues only

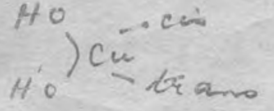


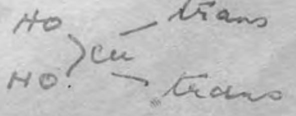
if a and b are supposed to be in the plane of the paper, the ring (11) will be in the same plane and the ring (1) in a vertical plane. Thus this part of the molecule is capable of cis-trans isomerism, the other form being



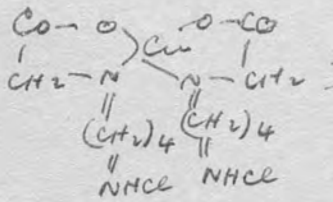
There will be no optical isomerism since the horizontal plane is a plane of symmetry. Since the copper is joined to two such systems the possible isomers are :—

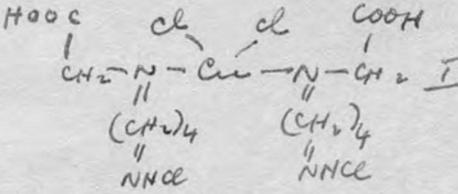




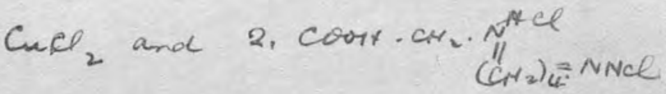


It is, however, very doubtful whether such isomerism could exist, at any rate in aqueous solution, since the glycine ring is readily broken and reformed so that the transformation from cis to trans would be rapid. There remains the question, whether the formulae (1) and (11) can be taken to represent the isomeric salts. The action of hydrochloric acid might be expected to result in the following stages


I a

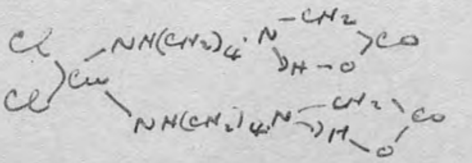

I b

and with excess acid

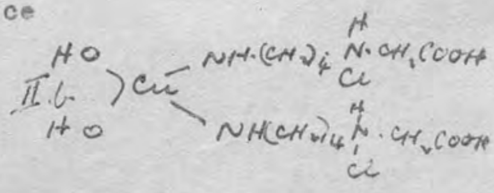

$CuCl_2$ and $2.\ COOH.CH_2.\overset{HCl}{N}{=}(CH_2)_4{=}NNCl$

On ~~the~~ $\overrightarrow{II}$ the first action might produce

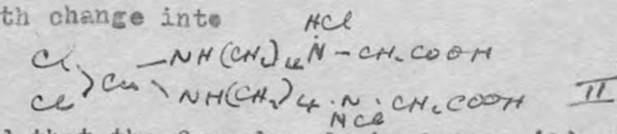
II a



or

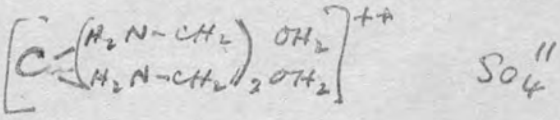

II b

and these could both change into


$$\begin{array}{l} Cl \quad -NH(CH_2)_4\overset{HCl}{N}-CH_2.COOH \\ Cl \rangle Cu \diagdown NH(CH_2)_4.\underset{NCl}{N}.CH_2.COOH \end{array}$$
II C.

It is to be noticed that the formulae derived from (1) are different from those derived from (11) in that the copper coordination is with a different nitrogen atom in the two cases. According to this scheme, acids acting on substances I and II, would produce substances of the same type but different in constitution. This corresponds with the facts so far as they are known, but until it is seen whether the properties of the acid derivatives are consistent with these formulae, no decision is possible. Against this view, there are the following facts. The green salt loses water to give an anhydrous salt and therefore cannot have the formula II which must be assigned to the blue salt.

Although compounds in which copper possesses the coordination number 6 are usually unstable [(c.f. Werner 1899, Z.a.Ch 21.p.201 and Pfeiffer 1906.Z.a Ch. 48.p.104)]. W.Wahl (Soc.Scient.Comment. Physico Mathematicae. lV.14), has shown that in certain cases the copper ion can form stable compounds with the coordination number 6, and has effected a partial resolution of



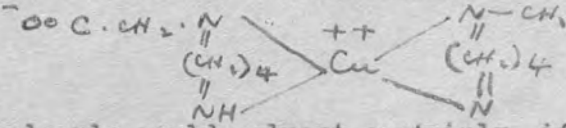
$$\left[C\begin{matrix}(H_2N-CH_2)\\(H_2N-CH_2)\end{matrix}_2\begin{matrix}OH_2\\OH_2\end{matrix}\right]^{++}\quad SO_4''$$

It is therefore worth considering the possibilty of one or both of the copper salts under discussion having a constitution analogous to Wahls compound. Since ethylene diamine and trimethylene diamine both readily coordinate with metallic atoms at both ends, there appears to be no reason why piperazine should not do the same, although no cases appear to have been recorded in the literature.

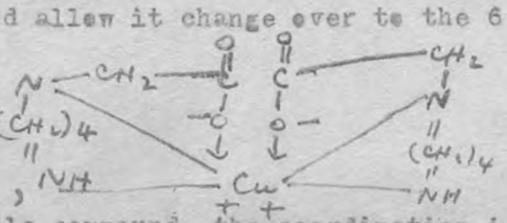
Assuming that the simple uncoordinated salt is first formed and is ionised, there would be present in the solution

$$Cu''\ \text{and}\ \begin{matrix}'OOC.CH_2.N(CH_2)_4.NH\\'OOC CH_2.N.(CH_2)_4\ NH\end{matrix}$$

If the copper ion were to form a 4 covalent ion in which each piperazine residue coordinated at both ends we should get

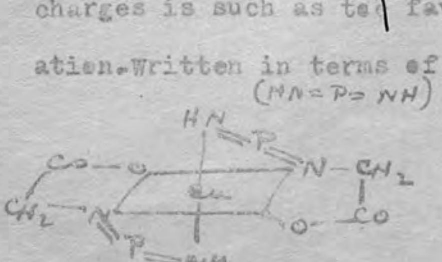


Such a molecule would, almost certainly, if the stereochemical conditions would allow it change over to the 6 coordinated compound

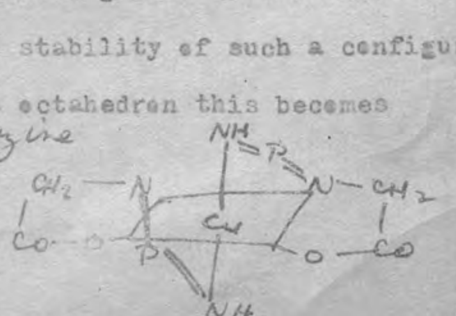


Here, as in Wahls compound, the coordination is with 4 nitrogen atoms and 2 oxygen atoms, and the arrangement of the electric charges is such as to favour the stability of such a configuration. Written in terms of Werner's octahedron this becomes

(HN=P=NH) = piperazine

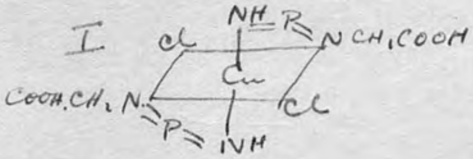


and



Whether these configurations are ~~stereo~~ stereochemically possible it is impossible to say. The leng th of the chains $(NH=P=NH)$ is comparable with those of compounds already prepared, but nothing is known with certainty of the angles of strain which the quadrivalent nitrogen atom will tolerate. It is necessary to see what interpretation of the action of acids on the salts can be given by these formulae. The possibilities are :—

I



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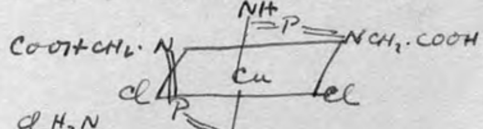

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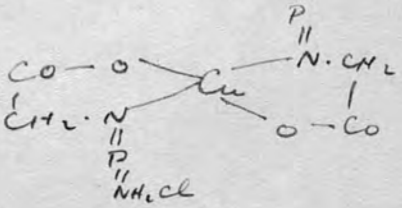
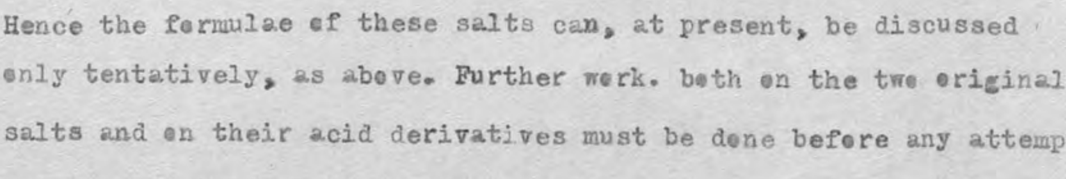
II

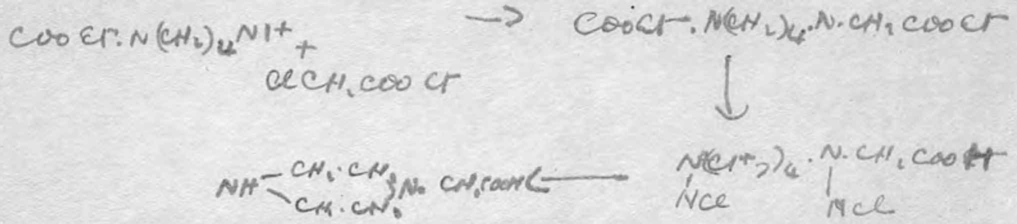


The facts do not correspond with(11), since both salts would, on this hypothesis give the same compound, and in fact they do not. Hence the formulae of these salts can, at present, be discussed only tentatively, as above. Further work. both on the two original salts and on their acid derivatives must be done before any attemp can be made to draw final conclusions.

The piperazine diacetic acids used in the first series of investigations was prepared by a method worked out by Dr. Boyle, and analogous to that for the preparation of piperidine acetic acid, viz:-, the piperazine diacetic ethyl ester was prepared by the interaction of piperazine with chloracetic ester(in the molecular proportions of 1 to 2). This was hydrolysed and at the s same time converted into piperazine diacetic hydrochloride, and finally the hydrochloric acid was removed with silver carbonate:-



The monoacid was first prepared in a similar way using the reactants in the proportion 1 to 1, but some diacid was obtained at the same time, and a complete separation was very difficult. Therefor after the successful preparation of piperazine monocarboxylate, an improved method of preparation was adopted, which consisted in first preparing the acetic ester derivative of the carbethoxy compound and then hydrolysis gave the dihydrochloride of mono~~acet~~ acetic acid from which the hydrochloric acid was removed as before



EXPERIMENTAL.

Preparation of Piperazine diacetic acid.

An anhydrous alcoholic solution of piperazine was first obtained by dissolving piperazine hexahydrate in alcohol and drying over anhydrous sodium sulphate. The amount of piperazine in the solution was estimated by removing 1 c.c. from a known volume of solution, diluting it with water and titrating it against standard hydrochloric acid, using bromo phenol blue as indicator. The calculated amount of bromoacetic ester was then added to the piperazine solution and the mixture well shaken and allowed to stand for some hours. (In the first preparation chloracetic ester was used but as bromoacetic ester is more reactive it was found preferable to use this in subsequent preparations.)

The solution was heated under a reflux for five hours on a water bath at the end of which time it was cooled, unchanged piperazine will here separate out as its hydrobromide and therefore indicates whether the reaction has proceeded to completion. About half the volume of alcohol was distilled off and dry HCl.gas passed into the solution. The gas must not be introduced beyond the stage at which a very fine precipitate of piperazine diacetic ester hydrochloride starts to be precipitated. The object of introducing HCl. is to completely precipitate piperazine hydrochloride if any is present, but this is not usually the case. The solution was diluted with water and heated on a water bath to remove all the alcohol. It was then heated under a reflux for 3 hours to bring about the hydrolysis. On cooling the solution the difficultly soluble hydrobromide of piperazine diacetic acid crystallised out. Further fractions were obtained on concentrating the solution. The various batches were recrystallised and analysed before proceeding to the next stage. Yield from 17.31 grms piperazine, 40.4 grms hydrobromide represents 65 per cent conversion of piperazine into diderivative. The monoacid obtained at the same time remains in solution owing to its much greater solubility. The removal of the Halogen acid was carried out in the following way :- Silver carbonate was prepared by the addition of sodium carbonate solution to the equivalent solution of silver nitrate. The precipitate was filtered at the pump and well washed. The diacid halide was dissolved in plenty of hot water and the silver carbonate added gradually while the solution was kept stirred. A few drops of filtrate were tested from time to time for the absence of the halide. When only slight excess of the silver carbonate had been added the solution was filtered, and washed with hot water. Sulphuretted hydrogen was immediately passed into the solution in order to precipitate any silver dissolved as silver salt of the diacid. The solution was again filtered and concentrated. The diacid crystallised on cooling.

Yield. from 26 grms. hydrochloride - 19.5 grms. acid.

The acid was recrystallised from hot water and analysed for water of crystallisation as well as carbon and hydrogen content.

Estimation of number of Molecules of Water of Crystallisation = n

Weight of diacid 0.3045 grms. Heated to 150 degrees C.

Weight of diacid	0.2583 grms.
Loss of water	0.0462 grms.
% Loss of water	15.17
($n = 2$ gives	15.12% water)

Combustion analysis of dehydrated acid.

Weight of acid	0.1518 grms.
" CO_2	0.2644 grms.
" H_2O	0.0938 grms.

% carbon	47.51
% hydrogen	6.87

Theoretical for $C_8H_{14}N_2O_4$ is 47.52% carbon
6.93% hydrogen.

Investigation of Sodium Salt of Piperazine diacetic acid.

Preparation of Salt.

A hot solution of the acid was treated with an equivalent of caustic soda. Methylated spirits just sufficient to give a precipitate was then added and the solution allowed to cool, when feathery needles separated out. Part of the salt was air dried and another portion dried in a desiccator.

Analysis of desiccator dried salt.

Sodium analysis.

Weight of salt	0.1105 grms.
" sodium sulphate	0.0589 grms.
% sodium	17.27

Water of crystallisation.

Weight salt	0.2556gms.
Loss of water at 150C.	0.0175"
%loss of water	6.84 "
Theoretical for $Na_2C_6H_{12}O_4N_2 \cdot H_2O$	17.43% sodium. 6.82 water.

Analysis of air-dried salt.

Water of crystallisation.

Weight salt	0.2773gms.
Loss of water at 150C.	0.1169"
% loss of water	42.16

Theoretical for 10 H_2O is 42.26 water.

Sodium analysis in anhydrous salt.

Weight salt	0.1029gms.
Weight sodium sulphate	0.0589"
% sodium	18.55

Theoretical for $Na_2C_8H_{12}N_2O_4$ is 18.7% sodium

Preparation of Copper Salts of diacid.

Excess copper sulphate solution was added to a solution of the sodium salt of the diacid.

A bright blue gelatinous precipitate (1a) was obtained at once. On boiling with sodium carbonate the precipitate became green and then brown, but on addition of a little sulphuric acid the blue precipitate was produced again. On heating with excess acid the salt dissolved. The blue salt was collected and dried, and to the filtrate was added just enough dilute sodium carbonate to make the solution alkaline and a drop of dilute sulphuric acid rendered it acid again. A green precipitete (1 b) was obtained which was quite insoluble in hot and cold water, but dissolved on boiling with dilute acid.

Solutions of copper sulphate and the diacid were mixed in equivalent quantities. A deep blue solution was obtained, and on warming a precipitate appeared. The solution was allowed to stand until cold and then the salt was collected. In washing with hot water part went into solution and was afterwards obtained as light blue crystals II by concentration of the solution. The insoluble part proved to be identical with (1.a) above.

Equivalent solutions of copper acetate and the diacid were mixed together, and a deep blue solution was obtained at first but almost immediately a deep blue salt III was precipitated. It was quite unlike any of those described above. All the salts were observed under the microscope and found to be homogeneous crystalline compounds.

Analysis of copper salts.

The copper content of the salts were determined by dissolving the salts in water containing dilute sulphuric acid and then precipitating copper thio cyanate in the usual way. The amount of water of crystallisation was found by determining the loss in weight of the salt when heated to a suitable temperature.

Copper estimation in salt 1.a.(Air dried).

Weight of salt	0.1380 grms.
" CuCNS	0.0701 "

% copper 26.44.

Water of Crystallisation in Air Dried Salts. .

Weight of salt	0.1256 grms.
Loss of water at 150^{0}C	0.0249 "

% loss of water 19.83.

Copper in lower hydrate.

Weight of salt	0.1007 grms.
" CuCNS	0.0641 "

% copper . 33.15.

Value of copper content for fully hydrated salt as calculated from above is 26.57%.

A salt $Cu\,C_8H_{12}N_2O_4\,Cu(OH)_2 \cdot 6H_2O$ contains 27.01% copper.

A salt $Cu\,C_8H_{12}N_2O_4\,Cu(OH)_2 \cdot H_2O$ contains 33.50% copper.

Loss of $5H_2O$ from hexahydrate corresponds to 19.4%.

Analysis of green copper salt 1 b.

Weight of salt.	0.2589 grms.
" CuCNS	0.2666 grms.

% copper 53.7.

Water estimation.

Weight of salt	0.1436 grms.
Loss of water ae 150^{0}C	0.0031 grms.

% less of water 2.2

% copper calculated for dehydrated salt 54.11.

Copper estimation in anhydrous salt.

Weight of salt	0.0773 grms.
" CuCNS	0.0809 grms.

% copper 54.48

Theoretical for a salt $Cu.C_8H_{12}N_2O_4\,4CuO$ is 54.40% copper.

Analysis of blue copper salt II.

Copper in hydrated salt

Weight of salt	0.1211 grme.
" CuCNS	0.0536 Grms.

% copper 21.02.

Water of crystallisation.

Weight of hydrated salt	0.1656 grms.
Loss of water at 150 degrees C	0.0200 grms.

% loss of water 12.08

Calculated for anhydrous salt % copper 23.91.

Theoretical for $Cu\,C_8H_{12}N_2O_4$ 23.95 % copper.
Theoretical for $Cu\,C_8H_{12}N_2O_4 \cdot 2H_2O$ 21.12 % "
Loss of water corresponds to 11.71%.

Analysis of blue copper salt III.

Weight of salt	0.2367 grms.
" CuCNS	0.0183 grms.

% copper 23.82

Water of crystallisation.

Weight of salt	0.1517 grms.
Loss of water at 150 degrees C.	0.0204 grms.

% loss of water 13.5

Calculated on this, % copper in dehydrated salt is 23.84.

Copper in dehydrated salt.

Weight of salt	0.0808 grms.
" CuCNS	0.0427 grms.

% copper 27.51.

For a salt $Cu \cdot C_8H_{12}N_2O_4 \cdot Cu\,C_4H_6O_4 \cdot 3H_2O$ % copper is 23.6.
" $Cu \cdot C_8H_{12}N_2O_4 \cdot Cu \cdot C_4H_6O_4 \cdot H_2O$ % copper is 27.45
Loss of water corresponds to 13.48.

Formula was confirmed by a combustion.

Analysis of lower hydrate

Weight of salt	0.1932 grms.
" CO_2	0.2250 grms.
" H_2O	0.1012 grms.

% carbon	31.85	Theoretical	31.20% C.
% hydrogen	5.63		4.35% H_2.

Preparation of Cobaltous salt.

A solution of the sodium salt of the diacid was added to slight excess of cobalt nitrate solution. A very pale pink precipitate was obtained at once. The salt became pale mauve by the loss of water above 100 degrees C. No other cobalt salt could be obtained by treating the filtrate with

Sodium carbonate as in the case of copper.

Analysis of salt. Cobalt estimation.

Weight of salt 0.1400 grms.
" cobalt 0.0257 grms.

% cobalt 18.32.

Water of crystallisation.

Weight of salt 0.2150 grms.
Loss of water at 150° C. 0.0189 grms.

% loss of water 8.79

Calculated from this result % cobalt in lower hydrate is 20.09.

A salt $Co \cdot C_8H_{12}N_2O_4 \cdot 2H_2O$ has 20.00% cobalt.

Combustion analysis.

Weight of salt 0.1673 grms.
" CO_2 0.2002 grms.
" H_2O 0.0926 grms.

% carbon 32.63
% hydrogen 6.15

Theoretical for $Co \cdot C_8H_{12}N_2O_4 \cdot 2H_2O$ is 32.54% C.
5.30% H_2.

Nitrogen estimation.

Weight of salt 0.1245 grms.
Volume of Nitrogen 10.4 c.c. at 17 degrees C. & 741 mm Hg
% Nitrogen 9.39 (Theoretical is 9.4%).

Preparation of Nickel Salt.

A solution of Nickel acetate was heated with an equivalent solution of the sodium salt of the diacid. A pale green precipitate was at once obtained. The same salt was obtained using nickel sulphate instead of nickel acetate, and also with the diacid itself.

Analysis of salt.

Weight of salt 0.1624 grms.
" Nickel dimethyl glyoxime 0.1433 grms.

% Nickel 17.94.

Water of crystallisation.

Weight of salt 0.1371 grms.
Loss of water at 150°C. 0.0161 grms.
% loss of water 11.74.

Theoretical for $Ni.C_8H_{12}N_2O_4.4H_2O$ is 17.75% Nickel

" " $Ni.C_8H_{12}.N_2O_4.2H_2O$ is 19.92% nickel.

% loss of water corresponding to $2H_2O$ is 11.90.

Combustion Analysis.

Weight of salt	0.1545 gms.
weight of carbon dioxide	0.1857 gms.
weight of water	0.0870 gms.
% carbon	32.8
% hydrogen	6.24

Nitrogen estimation.

Weight of salt	0.1166 gms.
Volume of nitrogen	9.8 c.c. @ 17C and 741m.m. Hg. % nitrogen 9.44

Theorectical for $Ni.C_8H_{12}N_2O_4.2H_2O$ is 32.58% carbon
5.43% hydrogen
9.50% nitrogen.

Preparation of Piperazine monoacetic acid.

Equivalent weights of piperazine mono carboxylate, chloracetic ester and anhydrous sodium carbonate were shaken together under a reflux condenser. When the evolution of heat had ceased the mixture was heated on a steam bath for 3 to 4 hours, until the evolution of carbon dioxide had ceased. It was then cooled in ice, soda added and the solution extracted several times with ether. The extract was dried and the ether distilled. The liquid residue was distilled under reduced pressure- b.pt. 185°C at 20m.m. Hg.

Hydrolysis of the compound $COOEt.C_4H_8N_2.CH_2.COOEt$.

The ester was heated with strong hydrochloric acid for 2 or 3 days and then evaporated to small bulk, on a water bath. On addition of alcohol the mono acid hydrochloride was thrown out. The removal of the halogen acid was carried out in a manner exactly similar to that used in preparing the diacid. The acid, being extremely soluble in water, was precipitated from a strong solution by the addtion of alcohol. m.pt. 275°C.

Preparation of copper salts.

Cupric hydroxide was prepared by mixing cold equivalent solutions of copper sulphate and canstic soda. The blue gelatinous precipitate obtained was well washed until free from alkali. Excess of the hydrate was added to a solution of the monoacid. A very deep blue solution was obtained, which on concentrating to a very small bulk and leaving in a desiccator for 2 or 3 days, gradually crystallised. The very deep blue crystals were drained from the uncrystallisable syrup and dried. On leaving some of the finally powdered salt over sulphuric acid, in a desiccator for a week, it became partially dehydrated, and lighter blue in colour. On heating to 110° C. the salt lost its crystalline structure and became a green gum. This gum dissolved very readily in water imparting a deep green colour to the solution. and the colour remained unchanged after several weeks. The Blue Salt was not soluble in alcohol but on warming the two together for a short time the green salt was obtained. When dried it was found to have a crystalline structure. It lost water at 110° C. without any appreciable change in colour, but at higher temperatures it started to decompose. This was also true for the blue salt. The same blue salt was obtained by dissolving copper carbonate in the mono acid, and also by adding copper sulphate to an equivalent mixture of monoacid and baryta. It was not found in any way possible to convert the green salt into the blue.

Analysis of Copper salts.

Blue salt. Estimation of copper in air dried salt.

Weight of salt		0.0246 grms.
" Cu_2S		0.0411 grms.
% copper	12.73	

Theoretical for $Cu.C_{12}H_{22}N_4O_6.8H_2O$ is 12.77% copper.

Loss of water in desiccator.

Weight of salt 0.1923 grms.
Loss of water after a week 0.0354 grms.
% loss of water 18.42

Theoretical for loss of 5 H_2O from above hydrate is 18.26%.

Green salt. Copper in dehydrated salt.

Weight of salt. 0.2142 grms.
" Cu_2S 0.0490 grms.
% copper 18.11

Theoretical for $Cu.C_{12}H_{22}N_4O_4$ is 18.17%.

Water of crystallisation in air dried salt.

Weight of salt. 0.2466 grms.
Loss of water at 120° C. 0.0324 grms.
% loss of water 13.14
Calculated for hydrated salt % copper is 15.75.
Theoretical for $Cu.C_{12}H_{22}N_4O_4.3H_2O$ is 15.77% copper.

Molecular weight of Blue salt in aqueous solutions.

Weight of salt. Hydrated	Anhydrous.	Weight of water.	Depression of freezing point.	Molecular weight.	mean.
0.3105	0.2195	24.91	0.07	228	247
0.4634	0.3215	17.94	0.12	266	
Molecular weight of Green salt in aqueous solutions.					
0.3398	0.2901	32.46	0.07	235	242
0.7042	0.6120	32.46	0.14	250	

Theoretical for $Cu\,C_{12}H_{22}.N_4O_4$ is 321.

Reactions of the copper salts.

Reagent.	Blue salt.	Green salt.
H_2S	Precipitate of CuS	Precipitate of CuS
NaOH	Blue precipitate of $CuOH_2$	No ppt., solution became yellow
Ammonia	No ppt. and no colour change	No ppt. and no colour change
KI	No iodine set free	No iodine set free
Reduced with SO_2 & added Am CNS	No ppt. of CuCNS	No ppt of CuCNS
Few drops dil. HCl.	Yellow sol. alcohol ppt. light green crystals alkali restores blue sol^n	Reddish-brown sol. light yellow ppt. with alcohol. alkali restores green colo
Dil. H_2SO_4	Similar colour sol. alcohol gives light green gum	Similar colour, light yellow gum with alcohol.