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Chemistry. — *"Contribution to the knowledge of the action of absolute nitric acid on heterocyclic compounds."* By Prof. A. P. N. Franchimont.

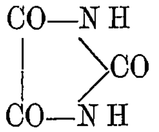
(Communicated in the meeting of January 26, 1907).

When searching about twenty years ago for the rules according to which nitric acid [1]) acts on hydrogen compounds, not only on those which contain the hydrogen in combination with carbon, but also on those which contain it in combination with nitrogen, I found that the hydrogen combined with nitrogen to the atomic group NH, does *not* act on nitric acid, when, in cyclic compounds, this group is placed between two groups of CO, but it *does* act if placed therein between the group CO and a saturated hydrocarbon residue [2]), and it may be added: *not* if placed therein between two saturated hydrocarbon residues, although I have not mentioned this previously.

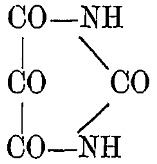
It is a peculiar fact that the hydrogen of the group NH does not act on nitric acid if this group is placed between two similar groups such as CO, or saturated hydrocarbon residues, but it does act if placed between two dissimilar ones; so that it might be thought that a tautomeric form is essential for the reaction.

There are, therefore, in reality three rules, which, when considered more closely, apply also to acyclic compounds and which, although the cycle also exerts an influence, appear to spring mainly from the nature of the substance in which the group NH is placed: viz. secondary amine, amide or imide. In acyclic amides it was found that not only the acyl group in particular, but also the alkyl group exerts an influence on the reaction; we may, therefore, expect something similar in the cyclic ones.

The first of the above rules was mainly deduced from the behaviour of penta- and hexa-atomic cyclic urea derivatives, but was confirmed also in the case of other compounds. For instance


parabanic acid

and


alloxan

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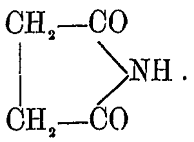
[1]) Namely the real (absolute) acid which may be obtained by distilling a mixture of nitric acid 1.42 with twice its weight of sulphuric acid at a gentle heat under reduced pressure (Recueil XVI. p. 386).

[2]) Which, however, need *not* be the group CH_2 as stated wrongly by Harries (Annalen 327. p. 358). The pages of the Recueil referred to by him contain exactly the proof of the contrary. I have also never spoken of "höchst concentrirter Salpetersäure" as he says, and of which he thinks he must "den Begriff festlegen", and for which he then recommends something which in many cases cannot give a good result.

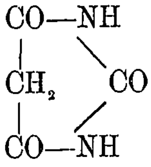
could be evaporated with nitric acid on a boiling waterbath without suffering any decomposition,

and also



succinimide

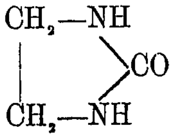
. The



malonureide

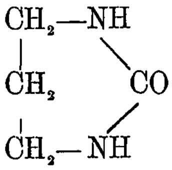
gives a nitroderivative, but with the nitro-group attached to the carbon; the two NH-groups do not act.

The second rule is also based mainly on the behaviour of penta- and hexa-atomic cyclic urea derivatives. For instance



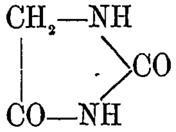
ethyleneureine

gave a dinitroderivative, which on boiling with water yielded carbon dioxide and ethylenedinitramine. To this I may now add:



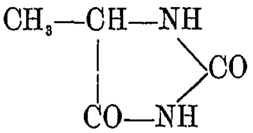
Trimethyleneureine

of which I have stated recently with Dr. FRIEDMANN that it gives directly a *dinitroderivative*, which on boiling with water yields carbon dioxide and trimethylenedinitramine.

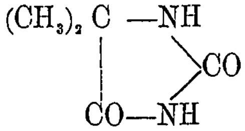


Hydantoin

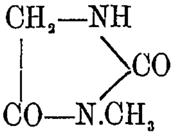
and its methyl derivatives



a lactylurea

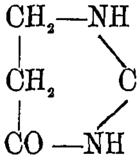


acetonylurea



1 *Nmethylhydantoin*

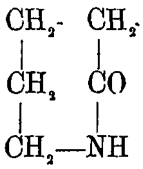
gave mononitroderivatives, which on boiling with water were decomposed with evolution of 1 mol. of carbon dioxide and formation of a nitramino-amide; for instance nitrohydantoïn yields nitramino-acetamide.

To this I may add the  recently investigated with Dr.

hydro-uracil
(*β lactylurea*)

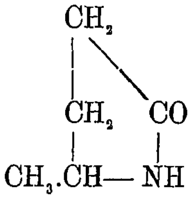
Friedmann, which yields, equally readily, a *mononitroderivative*[1]), which on boiling with water yields, in an analogous manner, carbon dioxide and *β nitraminopropionamide,* from which we have prepared *β nitraminopropionic acid,* also its barium and silver salt.

This decomposition proves the position of the nitrogroup, and at the same time these substances are all a confirmation of the first rule because the group NH, which is placed between the two CO-groups, has not taken part in the reaction.



α Piperidone

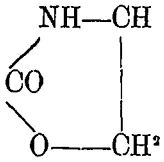
and



α methylpyrrolidone

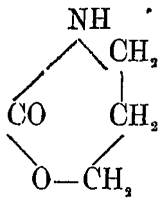
gave with nitric acid N_2O, presumably derived from a nitro-compound unstable towards nitric acid at the ordinary temperature; for it has been shown that some nitramides are decomposed by nitric acid at the ordinary temperature with evolution of nitrous oxide; whilst others may be evaporated with this acid on a boiling waterbath with impunity.

The rule was confirmed five years ago with cycles in which oxygen takes part, for instance



μ. céto tetrahydro-oxazole.

and



μ. céto pentoxazolidine

gave on evaporation with nitric acid, mononitroderivatives, which on boiling with water were decomposed with formation of carbon dioxide and a nitramino-alcohol.

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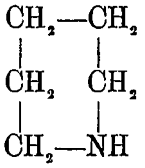
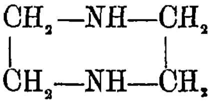
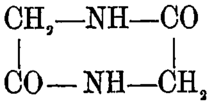
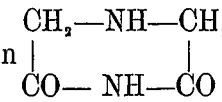
[1]) Tafel stated about this substance (Ber. d. D. ch. G. 33 p. 3385) that it is not affected even by prolonged boiling with concentrated nitric acid; evidently he has not used absolute nitric acid

The third rule is derived from the behaviour of  *piperidine* which yields with nitric acid a nitrate, but not directly a nitro-compound. This, however, may be prepared from a number of piperidides, to which we added recently the piperidides of *sulphuric* and *succinic acids*, or from the nitrate with acetic anhydride as found by **Bamberger.**

I have noticed recently that  *piperazine.* behaves in the same manner.

The above cited new investigations and those which follow originated in a research by Mr. A. **Donk.** He had prepared for practice  *glycocol anhydride* and we treated this with nitric acid. But even on evaporation on a boiling waterbath it gave no evolution of nitrous oxide, no nitroderivative, but a nitrate. I had expected this behaviour sooner from the unknown  *iminodiacetic imide* which is one of its isomeres, and in which one NH-group is placed between two CO-groups and the other between two saturated hydrocarbon residues, but not from glycocol anhydride in which each NH-group is placed between CO and a hydrocarbon residue, and about whose structure no doubt could be entertained. At most, we might suspect here a tautomer which does not react with nitric acid, or in all other cases in which nitric acid does act we might assume a tautomer and not here. [1])

Mr. **Donk**'s nitrate, a very loose compound, appeared to be a mononitrate, and on applying **Bamberger**'s method for amines (treatment

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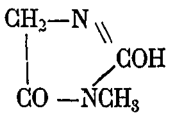
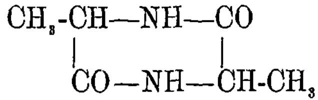
[1]) **Harries** l. c. suspects in 1 N methylhydantoin a tautomer  which, however, yields with nitric acid the same nitromethylhydantoin.

of the nitrate with acetic anhydride) he obtained a *mononitroderivative*, of which he proved the structure by acting on it with methyl-alcoholic potassium hydroxide, which yielded a properly crystallised acid, namely $NO_2\,NH\,CH_2\,CO\,NH\,CH_2\,CO_2\,H$.
nitraminoacetylaminoacetic acid

The reaction therefore took place as in all other cases where NO_2 and CO are both linked to a nitrogen atom; by absorbing the elements of water H and OH the group CO leaves the nitrogen whilst NO_2 remains attached to it.

After the departure of Mr. DONK, who did not wish to prosecute this matter, Dr. FRIEDMANN took it up and obtained the *dinitro-compound* from glycocol anhydride by treatment with excess of nitric acid and acetic anhydride. By the action of ammonia on dinitroglycocol anhydride nitroaminoacetamide was obtained, and by means of sodium hydroxide nitraminoacetic acid was formed in such a quantity that the formation of two molecules was no longer doubtful. The position of the two nitro-groups on the nitrogen atoms has, therefore been sufficiently proved.



$$\begin{array}{l} CH_3\text{-}CH\text{—}NH\text{—}CO \\ \quad | \qquad\qquad | \\ \quad CO\text{—}NH\text{—}CH\text{-}CH_3 \end{array}$$

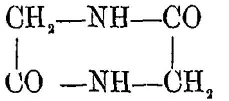
Alanine-anhydride

when evaporated with nitric acid also gave a nitrate only, which on treatment with acetic anhydride yielded a *dinitroalanine anhydride*.

These results, which formed a first deviation from the rule previously laid down, incited to further research For it was shown plainly that besides the placing of the group NH between CO and a saturated hydrocarbon residue, the other part of the molecule may also influence the reaction in such a manner that a direct nitration is prevented, even on warming, although nitro-compounds actually exist.

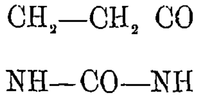
The question, therefore, arose as to the behaviour of those isomers of glycocol anhydride, which possess the same atom-groups, but arranged in another order.

There may be eleven cyclic compounds which consist of two groups of NH, two groups of CO and two groups of CH_2, of whom however three only are described in the literature, namely:



$$\begin{array}{l} CH_2\text{—}NH\text{—}CO \\ | \qquad\qquad | \\ CO\text{—}NH\text{—}CH_2 \end{array}$$

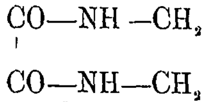
glycocol anhydride



$$\begin{array}{l} CH_2\text{—}CH_2\ CO \\ NH\text{—}CO\text{—}NH \end{array}$$

hydro-uracil

and



$$\begin{array}{l} CO\text{—}NH\text{—}CH_2 \\ \quad | \\ CO\text{—}NH\text{—}CH_2 \end{array}$$

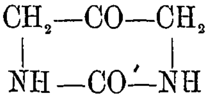
ethyleneoxamide

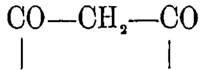
The last one, however, only in an impure condition, as described by HOFFMANN in 1872, and which we have not yet succeeded in obtaining in a pure state.

This substance had a special importance. It has the two groups

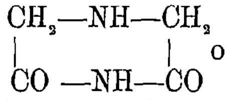
NH, also between CO and CH_2, and, according to the rule, it ought to yield readily a dinitro-derivative; either stable or unstable. Still it might be that it was not attacked at all by absolute nitric acid, for if we remember that diacetamide, although slowly, still evolves N_2O with nitric acid and, therefore, presumably forms an unstable nitro-compound under those circumstances, and if we compare this with the cyclic succinimide, which is not attacked at all even on warming and which is connected with it in such a manner that it contains two hydrogen atoms less, and thus causes the cyclic combination, one feels inclined to attribute to the cyclic combination the prevention of the action of the nitric acid. We might also compare ethyleneoxamide to dimethyloxamide which is readily nitrated, and is related to it in the same manner as diacetamide to succinimide, and if the cycle formation has the same effect here as it has in the other case, ethyleneoxamide should not be attacked.

Preliminary experiments with the impure substance showed that no stable dinitro-derivate appears to be formed; at most, one which is at once decomposed by nitric acid, or it is not attacked at all. A very slow evolution of N_2O and CO_2 takes place, but this may be due to the impurity.

Of the eleven possible isomers there are only two urea derivatives namely hydro-uracil, which, as stated, conforms to the rule and gives a mononitroderivative. The second is  $\begin{array}{l} CH_2—CO—CH_2 \\ | \qquad\qquad\quad | \\ NH—CO—NH \end{array}$ *acetoneureine* . Rugheimer thought in 1892 that he had obtained this substance by the action of chloro-formic ester on diaminoacetone, but it was merely a surmise; no analysis was made and the properties were not investigated; and from our investigations it is extremely doubtful whether he had this substance in hand, for although we made the experiments in various ways we could obtain nothing else but *acetondiurethane*, from which a *dinitro-derivative* was readily obtained. A number of other methods for preparing acetonureine from diaminoacetone were tried but always without good result. In the meanwhile we are continuing our experiments for, we attach great importance to this substance as a second urea derivative, seeing that the first one conforms to the rule.

A fifth isomer would be  $\begin{array}{l} CO—CH_2—CO \\ | \qquad\qquad\quad | \\ NH—CH_2—NH \end{array}$ *methylenemalonamide* which we have tried in vain to prepare from malonamide and formaldehyde. In this case it is the group CH_2 of the malonic acid which appears to react principally; but even with the amide of dimethylmalonic acid and formaldehyde we have not arrived at the desired result. Methylenemalonamide is of importance for this reason, that the CH_2-group of malonic acid might give a nitroderivative, whilst this may be equally expected from the two NH-groups.

A sixth isomer is the already quoted



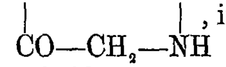
$$\begin{array}{ccccc} CH_2 & - & NH & - & CH_2 \\ | & & & & | \\ CO & - & NH & - & CO \end{array}$$

iminodiaceticimide

of which one might expect that it should yield with nitric acid only a nitrate, but not a nitro-derivative.

On heating the diamide of iminodiacetic acid in vacuo, Mr. **Jongkees** obtained a substance which sublimes and has the composition of the imide. This, however, does not behave as was expected, but when evaporated with nitric acid, seems to give a nitro-derivative, whose properties are, however, somewhat different from the usual ones of nitramines or nitramides.

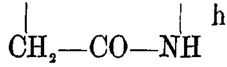
The last isomer of some significance for the problem under consideration, for the preparation of which no experiments have, as yet, been made, would be



$$\begin{array}{ccccc} CO & - & NH & - & CH_2 \\ | & & & & | \\ CO & - & CH_2 & - & NH \end{array}$$

, in which one NH-group between CO and CH_2 renders probable a nitro-compound, whereas the second, placed between two CH_2, could only yield a nitrate.

The other four are derivatives of hydrazine, and are of no importance for our problem, because the two NH-groups contained therein are in a state of combination. One of those



$$\begin{array}{ccccc} CH_2 & - & CO & - & NH \\ | & & & & | \\ CH_2 & - & CO & - & NH \end{array}$$

has been prepared by Dr. **Friedmann** and, when it was brought in contact with nitric acid a violent evolution of red vapours was noticed, evidently caused by oxidation.

The details of these researches which of course, are being continued will appear in the "Recueil des Travaux chimiques des Pays-Bas."

But it is evident that the second rule will have to be altered, namely in that sense that the direct nitration (if any) of the heterocyclic compounds, which contain NH placed between CO and C_nH_{2n} depends also on the manner in which the groups, between which the group NH is placed, are combined; therefore it is the same as has been noticed with acyclic compounds. In how far the cycle itself plays a rôle has not yet been satisfactorily made out but we may point, provisionally, to one peculiarity, namely, that the three compounds which do not seem to conform to the previously established rule contain the NH-groups in the *para* position in regard to each other.