Huygens Institute - Royal Netherlands Academy of Arts and Sciences (KNAW)

Chemistry. — *"The replacement of substituents in benzene deriva-tives."* By Prof. Holleman.

(Communicated in the meeting of December 30, 1914).

In close connexion with the problem of the introduction of sub-stituents in aromatic compounds exists another : that of the replace-ment of substituents already present, for after all the introduction is really also a substitution, namely of hydrogen. It, therefore, appeared to me desirable to also take in hand the study of the replacement, in addition to my researches on the introduction of substituents.

Some generalities on this subject are to be found in every text-book on organic chemistry. We know that the substituent in mono-substituted benzene derivatives is very difficult of substitution ; that in the disubstituted derivatives it is the combination of halogen and the nitro-group in which halogen is replaceable if the groups are o or p in regard to each other; that in compounds C_6H_3ABC replace-ment also occurs if the substituents consist of halogen, nitro, car-boxyl, cyanogen or the sulpho-group (with this understanding, how-ever, that except in a very few cases, there is no such thing as $A = B = C$) ; finally that also in the higher substituted benzene deri-vatives instances of replacement occur. As interacting substances have been employed almost exclusively alcoholates, ammonia and amines. In order to obtain a better insight in this problem the com-pounds C_6H_5X could be passed over ; on the other hand the literature on the compounds C_6H_4AB and C_6H_3ABC had to be studied more closely.

Statistically, this yielded the following results : If we consider the compounds C_6H_4AB and C_6H_3ABC, in which also A, B, and C may be equal, and if for these substituents we take the following 14 : F, Cl, Br, J, NO_2, SO_3H, Alkyl (Aryl), CO_2H, NH_2 (amine), OH (O Alk), CN, NO, CHO, COR, we can derive from $C_6H_4AB \dfrac{n(n+1)}{1.2} = \dfrac{14 \times 15}{2} = 105$ repeated combinations all of which can form three isomerides ; hence a total of 315 cases (included $A = B$).

Of $C_6H_5A_3$ are possible 14 combinations ; 3 isomerides of each $= 42$ cases.

Of $C_6H_3A_2B$ are possible $n(n-1) = 14 \times 13 = 182$ combinations ; each can occur in 6 isomerides, thus representing 1092 cases.

Of C_6H_3ABC are possible $\dfrac{n(n-1)(n-2)}{1.2.3} = \dfrac{14 \times 13 \times 12}{6} = 364$ com-binations ; 10 isomerides of each $= 3640$ cases.

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For all compounds C_6H_3ABC with repetitions this gives a total of 42 + 1092 + 3640 = 4774 cases. [1])

If now we inquire how many of these theoretically possible isomerides have been tested as to the replacement of their substituents we get the following information:

Of the 315 possible isomerides C_6H_4 AB (incl. A = B) 130 have been tested as to substitution and the results are distributed over 214 papers.

For the 4774 possible isomerides C_6H_3ABC (incl. A_2B and A_3) these figures are: of 232 compounds the substitution has been described in 360 papers.

This shows that only a very small portion of the possible compounds C_6H_4AB and C_6H_3ABC has been tested as to the replacement of their substituents; it only amounts to fully 7 %.

Hence, it is hardly to be expected that from this general conclusions might be drawn even if all published cases of substitution were suitable for the object in view. But this is by no means the case. After a careful study of the above named 214 + 360 = 574 articles we even arrive at the disappointing result that this vast material is almost valueless for a closer study of the substitution. For in such a study we not only want to know in what particular combinations substitution can occur, but also how this takes place under the same conditions. For only then will it be possible to compare mutually the substitution in the different groups and thus obtain a better insight by investigating this problem. And exactly in this regard, the material at disposal almost entirely forsakes us.
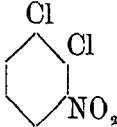
The reason is obvious. The experiments on substitution carried out up to the present have always been executed with quite a different purpose and were not intended for a systematic study of this problem. Hence, the work was conducted hardly ever under comparable conditions. The only results obtained up to the present is that we know that in a comparatively limited number of cases substitution is possible. From this we may predict with great probability that there is a possibility of substitution in a number of other cases. If, for instance we know that in chloronitrobenzenes with one or several chlorine atoms or nitro-groups the chlorine is mobile, it is to be considered as very probable that this will also be the case with the other halogen-nitrobenzenes of the same structure.

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[1]) Our fellow member HK. DE VRIES was kind enough to furnish me with the formulae used here.

The first thing to do here must be an orientating investigation to see which combinations of substituents give rise to the mobility of one or more of the same when they are examined under exactly the same conditions. It is, of course, impossible to include all the 5089 compounds C_6H_4AB and C_6H_3ABC, of which 4727 have never as yet been tested in any way as to substitution, and of which a good many are sure to be still unknown, in such an orientating investigation. A choice had to be made. It appeared to me desirable to start with a gauging of the intricateness of this problem by (1) measuring in a complete set of isomerides the velocity of the transformation; (2) to do this for two different substances acting thereon; (3) to execute this at different temperatures. From this would then be shown in the first place the influence of the position of the substituents. In the second place it would show whether there exists a definite ratio between the constants when working with different reagents and in the third place whether that ratio also remains permanent at various temperatures. If this really were so this would cause a considerable simplification of the problem. We then would only have to work at a well chosen temperature and with a ditto reagent to generally obtain comparable velocity constants.

The subjoined investigation of Dr. DE MOOIJ briefly described here has taught, however, that the said ratio does not exist either for temperature or for difference in reagent. This shows that the substitution problem possesses such a degree of complicateness that an accurate insight therein is still a matter of the distant future.

As objects for the research of Dr. DE MOOIJ were chosen the six isomeric nitrodichlorobenzenes. All these are comparatively readily prepared in quite a pure condition; only for the isomeride

an easier process of preparation had to be discovered and was successfully worked out.

He brought these six isomerides in contact with absolute-methyl-alcoholic solutions of sodium methoxide and of diethylamine, isolated all the products of transformation and determined the velocity constants at three different temperatures. The symmetric isomeride gave with methoxide a complicated reaction product consisting presumably of azoxycompounds; diethylamine did not act on it on heating for seven days at 110°, so that with this isomeride no velocity measurements could be carried out.

The three chloronitrobenzenes, likewise the three dichlorobenzenes were also treated in the same manner when it appeared, however, that the last named did not react with diethylamine even at 180°, but they reacted with NaOCH₃. The disubstituted products were tested to ascertain whether from the velocity constants of their transformations, those of the compounds $C_6H_2Cl_2NO_2$ could be deduced. Also this did not appear to be so.

From the results obtained by Dr. DE MOOY the following will be communicated. In all the cases investigated only chlorine was replaced, not the nitro-group.

1. *Chloronitrobenzenes*. Of these was measured the reaction velocity with sodium methoxide and with diethylamine both in absolute methylalcoholic solution. Whereas with the first named compound the velocity constant for the p-compound was found greater than that of the o-compound, this was just the reverse with diethylamine. The reaction with diethylamine proceeds here as well as in all other cases much more slowly than with methoxide. (see table III).

2. *Dichlorobenzenes*. These were heated with sodium methoxide at 175—176° when one Cl-atom was replaced by OH, as the solution was not quite anhydrous. For the constants (time in hours) was found, when 1 mol. of dichlorobenzene was made to react with 5 mols. of methoxide:

TABLE I.

$C_6H_4Cl_2$	K	Ratio
ortho	0.0382	3.35
meta	0.0506	4.44
para	0.0114	1

from which is shown the very remarkable result that the *m*-compound is the one most rapidly converted, a fact that was quite unexpected.

3. *Nitrodichlorobenzenes*. The most successful measurements obtained here are those with sodium methoxide as the values of K at different reaction periods were found to be pretty constant. In the measurements with diethylamine this was only the case with the isomerides 1,2,4 and 1,2,5 (NO₂ on 1); with the others the value K diminished as time proceeded. Particularly interesting was the behaviour of the

isomerides 1,2,4 and 1,2,6. In the first compound, at the interaction of $NaOCH_3$, both chlorine atoms appeared to be already mobile at 85°, but contrary to what takes place with monochloronitrobenzenes, the chlorine atom on 2 is being replaced first. The consequence was that at this temperature the constant became greater as time proceeded. At 25° and 50°, however, the reaction with the p-Cl-atom in regard to that of the o-Cl-atom was so retarded that very concordant values were now found for K. With diethylamine, only the o-Cl-atom was mobile.

In the isomeride 1,2,6 the two Cl-atoms were situated in o-positions in regard to the nitro-group. Nevertheless only one Cl-atom could be made to react with $NaOCH_3$ at 85°; and the same likewise with diethylamine at 150°.

The subjoined table II gives a survey of the measured velocity

TABLE II.

Isomeride	25°	50°	85°	110°
1, 2, 3	—	—	1.74	14.3
1, 2, 4	0.030	0.628	19.41	—
1, 2, 5	0.0063	0.121	3.93	33 0
1, 2, 6	—	—	0.135	1.34
1, 3, 4	0.033	0.601	17.42	—
1, 2	—	—	0.369	3.09
1, 4	—	—	1.39	11.45

constants with Na-methoxide. The figures in heavy type indicate the Cl-atom that is being replaced. NO_2 on 1. Time in hours. On 1 mol. of nitrodichlorobenzene one mol. of methoxide was employed. Both were in about gas-concentration. From this we notice that the position of the groups in regard to each other exerts a very great influence on the velocity of the reaction. If we put the reaction velocity of 1,2,4 at 85° = 100, that of 1,2,6 will then be only 0.7. also in the case of the other vicinal isomeride the reaction constant is very small, namely only 8.9 for 1, 2, 4 = 100.

If we compare the reaction constant of o-chloronitrobenzene with that of the nitrodichlorobenzenes in which also one of the Cl-atoms is situated in the o-position in regard to NO_2, the introduction of a second chlorine atom then appears to considerably increase that constant, except in the case where the second Cl-atom occupied the

position 6. Likewise the reaction constant of 1,3,4 is considerably greater than that of 1,4.

The reaction constants with diethylamine were determined with the proportion of 1 mol. of nitro-dichlorobenzene to 2 and to 10 mols. of diethylamine, which did not yield quite the same values for those constants. In table III the values found are united. The time has again been recorded in hours. $NO_2 = 1$.

TABLE III.

Isomeride	85°		110°	
	1 : 2	1 : 10	1 : 2	1 : 10
1, 2, 3	0.0023	0.0016	0.0094	0.0073
1, 2, 4	0.025	0.027	0.12	0.095
1, 2, 5	0.0068	0.0067	0.032	0.023
1, 2, 6	—	0 00024	—	0.0011
1, 3, 4	0.0052	0.0044	0.020	0.017
1, 2	—	0.0014	—	0.0053
1, 4	—	0.00065	—	0.0024

The impression made by this table is in the main the same as that of table II. Also here the reaction constants of the two vicinal isomerides are considerably smaller than those of the other nitro-dichlorobenzenes and that for the isomeride 1,2,6 is also the smallest. The isomeride 1,2,4 has also here the greatest reaction constant but now this is not followed up by that of 1, 3, 4 as in the case of the methoxide reaction; presumably this is connected with the fact that the reaction constant for 1,4 with diethylamine is smaller than that of 1,2, whereas with methoxide this is just the reverse. That, however, also in the other cases which run parallel, there can be no question of a constant relation between the reaction constants with methoxide and with diethylamine may be seen at once from table IV. p. 1033.

Not only are the figures in a same column very divergent, but the corresponding figures of the two columns differ very much; those at 110° are all about twice greater than those at 85°, which indicates that the reaction velocity for methoxide increases much more rapidly with the temperature than that for diethylamine.

Table V gives the figures as to the influence of the temperature on the reaction constant. Whereas the ratios for methoxide on the

TABLE IV.

Isomeride	$K_{NaOCH_3} : K_{amine}$	
	$T = 85°$	$T = 110°$
1, 2, 3	892	1744
1, 2, 4	747	—
1, 2, 5	582	1200
1, 2, 6	563	1218
1, 3, 4	3629	—
1, 2	264	583
1, 4	2138	4771

one side and for diethylamine on the other side agree fairly well, this is by no means the case for the two reagents mutually.

TABLE V. Na-methoxide.

Isomeride	$K_{25} : K_{50} : K_{85} : K_{110}$	$K_{85} : K_{110}$	Diethylamine (1 : 10) $K_{85} : K_{110}$
1, 2, 3	—	1 : 8.2	1 : 4.4
1, 2, 4	1 : 20.9 : 647	—	1 : 3.5
1, 2, 5	1 : 19.2 : 624 : 5238	1 : 8.4	1 : 3.4
1, 2, 6	—	1 : 10	1 : 4.6
1, 3, 4	1 : 18.2 : 528	—	1 : 3.9
1, 2	—	1 : 8.4	1 : 3.8
1, 4	—	1 : 8.2	1 3.7

Summarising we arrive at the following conclusions:

1. The number of cases of replacement of substituents in the compounds C_6H_4AB and C_6H_3ABC quoted in the literature is small in comparison with the number of possible cases.

2. The data of the literature are of little value for a systematic research as to the substitution problem as they have rarely been obtained under comparable conditions.

3. From the study of the replacement of chlorine in the three dichlorobenzenes, the three chloronitrobenzenes and the six nitro-dichlorobenzenes by OCH_3 and $N(C_2H_5)_2$ it is shown:

a. that the replacement of the halogen is largely dependent on the position of the substituents:

b. that it is dependent on the reacting agent.

c. that the influence of the temperature on the extent of the velocity constants is different for the two reactions, although fairly equal for the different isomerides in each reaction.

A more detailed communication of the above will appear in the Recueil.

*Amsterdam,* Dec.1914.   *Org. Chem. Lab.   University.*

Chemistry. — *"On the interaction of ammonia and methylamine on 2.3.4-trinitrodimethylaniline."* By Prof. VAN ROMBURGH and Miss D. W. WENSINK.

3.4.6.- as well as 2.3.4.-trinitrodimethylaniline, contains a mobile nitro-group (in the position 3) ·which is readily substituted in the interaction of ammonia and amines [1]). The mobility of that group in the second mentioned product is, however, considerably greater, as was to be expected. If, for instance we pour strong alcoholic ammonia on the 2.3.4.-trinitrodimethylaniline melting at 154°, the nitro-group gets substituted by the amino-group already at the ordinary temperature, whereas the other product melting at 196° does not exhibit any reaction whatever in these circumstances and requires heating to enable the reaction to take place.

If, however, we heat the compound melting at 154°, or the 2.4.-dinitro-3-aminodimethylaniline generated thereof by ammonia, in a sealed tube at 125° with alcoholic ammonia, the dimethylaminogroup appears to become substituted in a remarkable manner by amino, with formation of 2.4.-dinitro-1.3.-phenylenediamine. [2])

In a perfectly analogous manner reacts methylamine in which, case 2.4.-dinitrodimethylphenylenediamine is formed;

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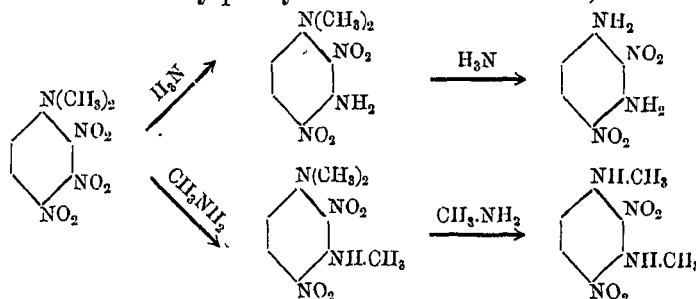
[1]) VAN ROMBURGH, Verslagen Kon. Akademie Amsterdam Febr. 1895.

[2]) In the said paper it is stated that indeed derivatives of m-phenylenediamine are formed.