XLVII.--*A Possible Basis of Generalisation of Intramolecular Changes in Organic Compounds.*

By ARTHUR LAPWORTH, D.Sc.

THE question of the manner in which substitution, isomeric change, &c., are interrelated has for a long time engaged the attention of many chemists. Up to the present, however, no consistent generalisation has been made.

Perhaps the only attempt to solve any considerable portion of the

* 0.2691 gave 0.5131 CO₂ and 0.1223 H₂O.

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attach itself to the γ -atom, the suitable rearrangement of the linkings taking place between the three fixed atoms R_α , R_β , and R_γ .

In desmotropic substances, both forms corresponding to A_1 and A_2 are known. Tautomerism, as is now generally recognised, may be taken as the expression of the instability of one form, as each form may usually be obtained in one or more of its more stable derivatives.

The following examples of the above type of change will serve to make clear its applicability.

The following is a most interesting example noticed by Claisen (*Ber.*, 1896, 29, 2931).

It will be seen that in the special form A, R_α and R_γ may be O, N, or C, and R_β may be N or C; obviously, oxygen is excluded from occupying the position R_β , as in (A_1) and (A_2) this must be at least a triad element. As will be shown later, other groups may functionate in place of C, N, or O.

If now, labile groups M_1 and M_2 are attached to R_α and R_γ , as in (B_1), we should expect by a logical extension of A to observe on occasion a change such as

that is, in a grouping such as (B_1), labile groups attached to R_α and R_γ might change places without any final alteration of the original disposition of the single and ethylenic linkings.

A "mechanical" explanation of the forms A and B is not hard to find, as will be seen by a consideration of the following diagram, where carbon atoms in the form of tetrahedra are shown, for convenience, in projection as triangles, as in A and B we are only concerned with triad or diad atoms or radicles R_α , R_β , and R_γ . The

single linkings are, as usual, supposed to exist at the corners, and the ethylenic, or double linking, is represented in the conventional manner, as union of the edges of two tetrahedra.

FIG. 1.

As will be clearly seen by means of the diagram, the formation of an ethylenic union between the atoms α and β brings one of the labile groups, which are represented by the small black and white circles, into close proximity with the point of attraction of the atom γ , and, as the latter is released, its union with the labile group is a most natural result.

It is not necessary, of course, to imagine that the group M ever actually becomes free, but rather that it is always under the influence of the attraction of R_α or R_γ , and possibly, at some instant, of both simultaneously; thus the lability of the molecule may be imagined to depend on a species of "dissociation." By the latter word, the author wishes to express more especially the idea that the combination of two portions of a molecule is of so little intimacy that, under the influence of disturbing attractions, the union between the dissociated portions may be readily overcome.

Now, should the grouping A_1 or B_1 be merely the commencement of a chain of alternately singly and doubly linked atoms as in C_1 and D_1 , it would be most naturally expected that successive changes, exactly similar to A and B respectively, would go on under favourable conditions, as represented by forms C and D, R'_α , R''_α , &c., functioning in turn as R_γ does in the forms A and B.

that is, a labile group might move along a chain of alternately singly

and doubly bound atoms, *the ethylenic and single linkings changing places in the path of the labile group.*

Again, by B, we have

that is, in a chain composed of alternately singly and doubly linked atoms, labile groups attached in γ -positions (once, twice, or even more removed) with regard to one another, might change places without any final alteration of the original disposition of linkings in the chain.

For examples of changes corresponding with types C and D, reference may be made to benzenoid derivatives. If benzene and its derivatives be represented by Kekulé's formula, it is at once seen that the alternate single and double linkings are here existent, thus

and, as it is probable that all benzenoid derivatives act, on occasion, as if they had Kekulé's formula, no exception can be taken to this mode of representing them.

A few examples of isomeric change, probably referable to forms C and D, may conveniently be taken here. Thus, on making nitroso-phenol, the product obtained is quinone-oxime, and the following scheme represents their tautomerism most perfectly. (In this, and in all the following examples, the labile group is in *italics* for the sake of clearness.)

In like manner, orthohydroxyazobenzene is tautomeric with ortho-phenylquinone hydrazone.

As examples of type D, the changes observed in many sulphonic acids of the benzenoid series may be quoted; namely, those which undergo isomeric change in absence of any considerable quantity of free sulphuric acid (in which case hydrolysis and re-sulphonation and

like changes are doubtless impossible or highly improbable). In these cases the sulphonic groups wander into γ -positions (possibly once or twice removed) with regard to their original ones.

1st. The change of phenylsulphamic acid, successively, to ortho- and para-anilinesulphonic acids (here $S = SO_3H$).

As the barium salt of phenylsulphamic acid, when heated, changes into that of paranilinesulphonic acid, the occurrence of hydrolysis and resulphonation is in this case entirely excluded.

An even more striking instance of this type of isomeric change is seen in the changes of β -naphtholsulphonic acids. These (by analogy with phenol), probably from β -naphthyl sulphate as initial compound, go through three changes, which, as the author has shown (Proceedings, 1895, 49) by the investigation of the corresponding compounds of β -ethoxynaphthalene, may be regarded as successive.

In the following scheme, as in many of the succeeding cases, the nuclei are represented by means of the ordinary skeleton formula, the double linkings being left out.

The change of methylaniline into toluidine is doubtless of a similar kind.

It is probable, however, as in many similar cases, that the molecule does not revert to the benzenoid condition until the labile group is in the para-position. In this event, an intermediate compound would

adjust itself, the methyl group being the first to move.

To this type also, may be referred the formation of parachlor-

acetanilide from phenylchloracetamide (Benda, *Ber.*, 1886, 19, 2273), &c., and the more complicated cases of ortho- and para-amidoazobenzenes from diazoamidobenzenes, as well as that of benzidines from hydrazobenzenes.

The latter may be represented for simplicity thus

The changes being in each case labelled according to their form. The last pictured compound would furnish benzidine in the same manner as methylaniline yields toluidine.

The two changes thus represented, however, must probably be regarded as simultaneous and not successive, and it is not suggested that paramidodiphenylamine is actually an intermediate compound, although the latter would probably yield benzidine under suitable treatment.

Before proceeding with the discussion of isomeric change in the benzene series, it will be advantageous if, at this stage, some further consequences of change A be pointed out.

If, in a compound containing the group E₁, the union between R₂ and R₃ be a readily severable one, a change similar to that of A₁ to A₂ will produce that of E₁ to E₂, that is to say, separation of the molecule into 2 parts between R_β and R_γ will result.

This formula may for convenience be termed the "scission formula."

Of this type of change, examples are, of course, without number, and its "mechanical" explanation is readily understood by a glance at Fig. 2, where it is seen that the changes are exactly comparable with those of A and B as represented in Fig. 1.

The following examples may be quoted.

(Schutzenberger. *Leçons professées en 1868 and 1869 devant la Société Chimique de Paris*).

Amongst unsaturated acids, many interesting cases are known. (Compare Fittig, *Ber.*, 1894, 27, 2658). Thus, as an example of ring scission on the basis of type E.

We are now in a position to derive conclusions of considerable value from the use of the foregoing considerations, more especially if we combine with Kekulé's hypothesis that addition as a rule precedes substitution, the idea (first brought forward for a special case by Armstrong) that isomeric change is, in many cases, an intermediate phenomenon in the formation of the final products.

The following cases of hydrolysis may serve to make clear the manner in which the theoretical methods of investigation brought forward in the present paper may be employed. The type of change is in each case labelled with the appropriate letter for convenience in reference.

1. Hydrolysis of acetic anhydride by alkalis.

Probably, however, the labile group is the metallic ion introduced. In any case, the final product is, of course, two molecules of acetate.

The enormous difference in stability between acidyl and alkyl oxides receives in this manner an excellent explanation, as in the latter, additive compounds of the above type are not formed, and the hydrolysis must be preceded by the dissociation of the saturated alkyl oxide.

2. The hydrolysis of ethylic acetoacetates, &c., by alkali in several different ways may be represented in an exactly similar manner.

3. The interesting change of unsaturated lactones into ketonic acids may be written in this manner.

The changes observed in the formation of pinacolins from pinacones, of benzoic acid from benzil, &c., are readily explained on assumptions which the author has not been the first to make, and are doubtless closely related to those exhibited by orthodiketohexamethylene compounds (Zincke, *Ber.*, 1888, 21, 2381, &c.) and by carbohydrates in presence of alkali (Lobry de Bruyn, *Rec. Trav. Chem.*, 1893, 14, 203—216, &c.). In all these cases, it will be noticed that the change occurs at a point where it is possible that a ring compound of the type $\text{---R}_\alpha \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \end{array} \text{R}_\beta$ may be produced.

The simple change of α -glycols may be taken first. It is well known that, *under conditions which cause the production of oxides from γ - and δ -glycols, the α -glycols yield either unsaturated alcohols (in the normal manner), aldehydes, or pinacolins, according to their constitution.* Hence the production of aldehydes or pinacolins from α -glycols may be preceded by the formation of the corresponding unstable "ethylene oxides," when the course of change becomes abundantly clear.

With this assumption, the change of pinacones into pinacolins is seen to be in complete accordance with the author's views. Thus

In like manner, as has been pointed out apparently for the first time by Armstrong and Groves (Miller's *Elements of Chemistry*, iii, 787), the production of benzoic acid from benzil is possibly preceded

by that or an oxide of the formula $\begin{array}{c} \text{Ph} \cdot \text{C} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{O} \end{array} \\ | \\ \text{Ph} \cdot \text{C} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{O} \end{array} \end{array}$. The subsequent change may, for clearness' sake, be written as follows.

that is, affording benzoic acid, $\text{Ph}_2\text{C(OH)} \cdot \text{COOH}$.

A similar change in an orthodiketohexamethylene derivative would afford an α -hydroxypentamethylenecarboxylic acid, one portion of the chain functioning as M in form E. The simplest possible case of this change may be here shown.

Then, as above, for clearness, the final change may be represented as follows.

Substitution in Benzenoid Compounds. The Meta Law.

Perhaps the only attempt made to discuss the question of substitution in benzenoid derivatives from a broad standpoint was that of Armstrong's in the paper already referred to at the commencement of the present contribution (Trans., *loc. cit.*). In order to account for the fact that, whereas ortho- and para-derivatives are almost the only products when certain mono-derivatives of benzene are acted on by substituting agents, and that mono-derivatives, notably those containing acid radicles, yield chiefly meta-derivatives, the following suggestion was made. Armstrong supposed that the difference in behaviour between the two classes of mono-derivatives is attributable to the different manner in which they form additive compounds, and that where meta-derivatives are produced, initial combination of the side group with the reacting agent took place and was followed by an isomeric change resulting in substitution in the meta-position with

regard to the first group. The view was also advanced that para-derivatives were for the most part attributable to isomeric change.

Armstrong's explanation of the production of meta-derivatives has recently been revived by Collie (*Trans.*, 1897, **71**, 1018); but Collie's explanation of this point fails, in the author's opinion, to account for the fact that many benzene derivatives substituted in the side group, such as phenylsulphamic acid, phenylnitramine, &c., yield, not meta-derivatives by isomeric change, but only ortho- and para-derivatives. Some explanation, therefore, other than Collie's in its original form, must be introduced in order to make the whole consistent.

The following view, a modification of Armstrong's, appears to put the matter in a perfectly consistent manner. The difference in behaviour between the two classes of benzenoid mono-substitution derivatives may, in part, be explained on Armstrong's hypothesis with the help of the principles advanced in the present paper.

Armstrong's view as regards the production of ortho- and para-derivatives is in complete accordance with these principles. It is, in fact, only the formation of large quantities of meta-compounds which at present requires further discussion, and isomeric changes, such as that of phenylsulphamic acid into anilineorthosulphonic acid and parasulphonic acid successively, have already been brought into line with other isomeric changes.

The rule of Crum Brown and Gibson (*Trans.*, 1892, **61**, 367) is an empirical one and does not attempt to offer any explanation; hence it is unnecessary to discuss this particular point fully. It may be said, however, that the rule does not apply to all cases, and where it does apply, it can be demonstrated that the constitution of the mono-derivative may be expressed by the formula $\text{Ph} \cdot \text{R}_1 \cdot \text{R}_2$, so that it is in a sense unsaturated in the side group (compare Collie, *loc. cit.*).

It will be most convenient to discuss this question with reference to a special case, and the sulphonation of nitrobenzene will therefore be chosen as a fairly suitable one.

There can be little doubt that, in nitrobenzene, the nitrogen is pentad, and the only likely form in which the nitro-group can be written is $-\text{N} \begin{smallmatrix} \text{O} \\ \diagup \\ \text{O} \end{smallmatrix}$.

The group is therefore of an unsaturated type, and nitrobenzene might therefore be expected to form an additive compound with sulphuric acid, and which would have the constitution

In this additive product some initial alteration of structure must occur before the sulphonic group can become attached to any carbon atom of the benzene nucleus without causing simultaneous separation of the nitro-group, and, although the change may, in accordance with the foregoing principles, be supposed to occur in at least three different ways, any simple change, not involving the production of new ring compounds, or the occurrence of polymerisation must result in the production of a metanitrobenzenesulphonic acid.

Thus, one of the following initial changes may occur.

(1) Migration of the OH group.

(2) „ of the $\text{O}\cdot\text{SO}_3\text{H}$ group as a whole.

(3) „ of a hydrogen atom of the ring, in the meta-*position with regard to the side group.

Of these, (3) is the most simple to represent, and as it is probably the correct one, it will therefore be chosen to explain the possible series of change.

It is possible that, simultaneously with the formation of products of addition to the side group, addition to the benzene nucleus occurs, when, as usual, ortho- and para-derivatives will, for the most part, be produced. Further, it is probable that every possible additive compound is formed in slight amount, and, as in all such cases, it is only the great preponderance of one or two substitution derivatives which requires explanation.

The result of the immediately preceding discussion may be formulated as follows. Where a substitution product is formed by isomeric change of a product of addition or substitution on the side chain, in which the substituting radicle is separated from the benzenoid nucleus by two intermediate atoms, a meta-substitution derivative must be produced, or replacement of the side group by the new substituting radicle will occur (that is, with the reservations already alluded to).

The production from aniline derivatives, under some conditions, of ortho- and para-sulphonic acids only, and, under others, of meta-acids only, is doubtless accounted for by the fact that it is possible to form,

* Migration of any other H atom into the side group is manifestly impossible, unless scission occurs. Moreover, it seems probable that, in many cases, migration of the meta-H-atom into the side group takes place as the initial step. Just as, for example, it is probable that migration of a hydrogen atom into the nitro-group of nitromethane occurs before the latter is brominated, that is, the substance reacts in its tautomeric form.

as initial product, either a phenylsulphamic acid or an aniline hydrogen sulphate.

Thus $\text{N}\cdot\text{SO}_3\text{H}$ would afford an *ortho*- or *para*- and $\text{NH}_3\cdot\text{OSO}_3\text{H}$

probably a *meta*-acid only, and similar considerations hold for all amido-benzenoid derivatives.

The following interesting case of interaction in the benzene series is readily explained on the assumption that the nitro-group is unsaturated. Parabromonitrobenzene, when acted on by potassium cyanide, yields metacyanobromobenzene. It may be assumed that the group -NO:O reacts with HCN in the same manner as does the group -C:O . The compound formed would then change as follows.

Influence of Residual Affinity on Tautomerism and Intramolecular Change.

The foregoing discussion has been based entirely upon the assumption that change of valency in the atoms in question is excluded. Where change of valency does occur, it must be supposed that a second type of change goes on, which, in its most general form, may be represented thus.

where R_β represents an atom having a residual affinity of two units.

This type is exhibited in the tautomerism of hydrogen cyanide, of sulphurous acid, and of nitrous acid, and changes such as that of phenylic cyanide into the isocyanide are, of course, of the same kind.

From this type, X, we may of course derive others corresponding with B and E. Thus we might have

that is, exchange of M_1 and M_2 taking place, as was the case in form B.

To type Z doubtless pertain such changes as the formation of α -methylpyridine hydriodide from pyridine methiodide.

Whilst it is not impossible that the above type is, in some cases at least, dependent on A, any speculations on this point would be ill-advised, especially as our knowledge of the stereochemistry of nitrogen, &c., is practically nil. It may be pointed out, however, that polymerisation may be an intermediate factor in the change, as many

substances which undergo the above transformation exhibit a great tendency to polymerise or form double molecules, as, for instance, hydrogen cyanide, sulphites, and oximes.

A detailed series of examples of changes dependent on type X seems unnecessary, as its mode of application would be exactly similar to those employed in the more general $\alpha\gamma$ -change. It may be of interest, however, to note that changes such as that of benzophenone-oxime into benzanilide and of amides into amines (Hofmann's reaction) are probably of this kind, although some of them may be represented by means of type E without difficulty.

Thus the change of benzophenoneoxime chloride may be written

Conclusion.

The author has chosen, as far as possible, examples of isomeric change in which it is not sufficient to assume successive addition and subtraction of the element of the solvent or other substance within the sphere of action. The employment of such an assumption would, of course, be of great value in many cases, and possibly this process is a partial factor in some of the examples which have been given in this paper.

The question of the "residual affinity," exerted by many elements, has been but briefly touched on, and, no doubt, in extending the principles which the author is here endeavouring to introduce, this point must receive far more attention than has been devoted to it in the present paper.

It would, perhaps, be not unwise to draw attention to a factor of some importance with regard to the isomeric changes represented by the most general type A. It has already been assumed that a species of dissociation is accountable for the change which occurs, and a glance at Figs. 1 and 2 will make it clear that it is only necessary to imagine dissociation between the labile group and the atom to which it is attached, at the instant when the change actually takes place in the molecule, and it is possibly due to the attractive influence of the γ -atom at the period of the disturbance, where the labile group is brought under its direct influence. Thus the dissociation between Ra and M is probably only a temporary one, and it is not necessary to assume that any extensive dissociation exists, except at the instant of change. Further, a consideration of the diagrams, and the methods by which the types dependent on A_1 were derived from the latter, makes it clear that only one change at a time must be supposed to occur. Were the dissociation extensive and permanent,

two changes might go on simultaneously and the generalisation would be inapplicable; hence changes in electrolytically dissociated substances, or where violent action and extensive charring occurs (involving, say, complete dissociation of two or more portions of a molecule simultaneously), may result in interchange of groups not in γ -positions, as in B. Such changes, therefore, should be as far as possible excluded in the consideration of the applicability of the foregoing generalisation.

It appears likely that the use of the generalisation here advanced will be of value in connecting a large number of apparently independent types of change, and that its employment may serve as a means of elucidating the course of many changes hitherto regarded as extraordinary or obscure. Further, it may appropriately be pointed out that some supposed instances of isomeric change, incompatible with this generalisation, have recently been disproved by Victor Meyer and his collaborateurs.

In conclusion, I beg to thank Dr. Collie and Dr. Kipping for much kindly criticism and advice during the elaboration of this paper.