OXIDATIVE-HYDROLYTIC SPLITTING OF CARBON–CARBON BONDS OF ORGANIC MOLECULES

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Oxidative processes accompanied by splitting of the bonds between carbon atoms are one of the commonest types of chemical and biochemical transformation of organic molecules. In considering such changes the final result and the intermediate stages of the reactions are usually treated as being due to the action of only one factor on the molecule, *viz.*, the oxidant. It is often neglected that in all cases where the reactions take place in aqueous solution, especially in the presence of alkalis or acids, another factor may exert a considerable influence, namely, the hydrolysing action of the medium. The effect of this factor should be most pronounced at intermediate stages of oxidative processes, since the carbon–carbon bonds of partly oxidised molecules are especially subject to hydrolytic splitting. Hence, if oxidation is carried out under conditions where such action is not excluded, the occurrence of hydrolytic molecular changes should be taken into account along with changes due to oxidation.

This important problem, which was neglected for a long time, attracted our attention more than 10 years ago. In 1944 together with a number of collaborators (Y. B. Shvetsov, D. P. Vitkovsky, A. S. Khokhlov, and others) we began a systematic study of various reactions induced by the simultaneous or alternate action of oxidants and hydrolysing agents on organic molecules.

A comparison of the results of these studies with data published in the literature led to the conclusion that, when the oxidative cleavage of carbon–carbon bonds is brought about in the presence of hydrolysing agents, this reaction should be regarded as an oxidative-hydrolytic and not a purely oxidative reaction. Indeed, if the initial compounds are subjected to the action of oxidants under conditions excluding, or unfavourable to, hydrolysis of carbon–carbon bonds, the result is most frequently merely the introduction of various oxygen-containing substituents into the molecules without any splitting of carbon–carbon bonds or any changes in the carbon skeleton.* But the accumulation of such oxygen-containing substituents gradually gives rise to structural alterations determining the possibility of hydrolysis of carbon–carbon bonds at certain levels of oxidation. Thus, in many cases the oxidising agents are incapable of splitting carbon–carbon bonds by themselves, but predetermine the subsequent cleavage by hydrolysing agents ; that is why changes of this type should be regarded as oxidative-hydrolytic. At present this type of reaction of organic compounds may be

* Exceptions may be oxidative reactions taking place by a radical mechanism through stages of peroxide formation, as well as reactions resulting in the formation of oxidation products thermally unstable under the given temperature conditions.

considered as one of the important kinds of oxidative processes, inasmuch as the latter are very often brought about under conditions which promote the hydrolytic splitting of carbon–carbon bonds.

An extensive study of oxidative-hydrolytic changes has made it possible gradually to elucidate not only the nature of this phenomenon, but some of the laws it obeys as well. The solution of this problem was facilitated by the fact that one of the authors, in collaboration with I. A. Red'kin, investigated, as early as 1938—1941, the causes and mechanism of purely hydrolytic splitting of carbon–carbon bonds in organic compounds. On the basis of these studies we were able to determine the causes of the influence exerted by preliminary oxidation of the molecules on their subsequent hydrolytic cleavage; we also elucidated the relation between the degree of oxidation of the molecules and the ease of hydrolysis of their carbon–carbon bonds. This helped to explain the chief directions along which oxidative-hydrolytic changes evolve most frequently, as well as to understand the subsequent fate of the substances initially formed. All this permitted a new approach to an understanding of the nature and mechanism of many oxidation reactions, both those described previously in the literature and those newly studied.

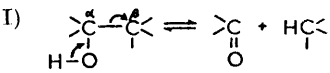
Since the oxidative-hydrolytic splitting of carbon–carbon bonds is a result of the simultaneous or alternate action of oxidants and hydrolysing agents on the molecules, reactions of this kind can often be studied only by investigating the action of each of these two factors separately. The following procedures were found expedient for the study both of individual particular problems and of the phenomenon as a whole: (1) stepwise oxidation of the initial substances in the absence of hydrolysing agents; (2) investigation of the hydrolytic splitting of carbon–carbon bonds in the absence of oxidants (in particular of atmospheric oxygen) at each level of oxidation of the original substances; (3) oxidative-hydrolytic splitting of molecules under very mild conditions in order to induce as little change as possible in the primary fission products, which are frequently very susceptible to further alteration. These methods of investigation have made it possible to elucidate many of the questions mentioned above, and the following paragraphs of this article are devoted to a discussion of those problems.

Hydrolytic Splitting of Carbon–Carbon Bonds

The possibility of hydrolytic splitting of certain carbon–carbon bonds has repeatedly been mentioned in the literature and is commonly known (for a survey of the most important papers in this field, see refs. 1—4). However, little was known about the causes and the mechanism of the reaction, or of the scope of its occurrence. A special study of these

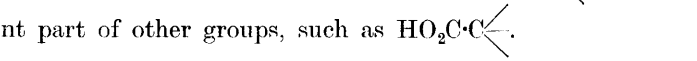
[1] R. C. Fuson and B. A. Bull, *Chem. Rev.*, 1934, **15**, 275.
[2] F. Kröhnke and W. Heffe, *Ber.*, 1937, **70**, 864.
[3] M. M. Shemyakin and I. A. Red'kin, *Zhur. obshchei Khim.*, 1941, **11**, 1142.
[4] M. M. Shemyakin and L. A. Shchukina, *ibid.*, 1948, **18**, 1925.

problems [3, 5–9] showed that in general such a reaction is possible with all molecules in which an atomic group of the common type (I) is contained or may arise. Given certain structural prerequisites and the necessary external conditions, such an atomic group can undergo splitting according to the following general scheme :



(I) (1)

The range of compounds capable of such changes is very wide. It includes not only many types of substituted alcohols, but also various kinds of substituted unsaturated compounds, carbonyl compounds, and other types, since the grouping (I) is formed readily as a result of hydration of polarised double bonds ; it also arises by addition of water, ammonia, or alcohols to the carbonyl group in compounds of the type —CO·C<, and may be a constituent part of other groups, such as $HO_2C{\cdot}C<$.



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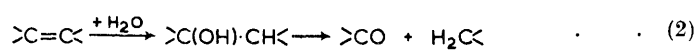
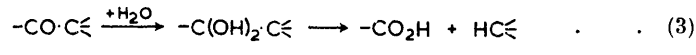
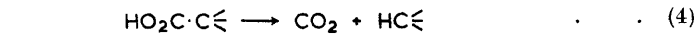


(3)



(4)

The nature of all these changes became much easier to understand when we applied E. H. Usherwood's idea [10] concerning the analogy between reversible splitting-addition reactions and the corresponding tautomeric changes. A comparison,[3] based on this analogy, of the processes of hydrolysis of carbon–carbon bonds with related tautomeric processes of the keto–enol type (scheme 5) gave grounds from which the first of them could be approached from the standpoint of the ionotropy theory developed by C. K. Ingold.



(5)

This approach proved to be quite justified and very fruitful. Indeed, all the principal theses of the ionotropy theory [11] were found to hold good for the hydrolytic splitting of carbon–carbon bonds. This is borne out by experimental evidence previously published in the literature (see reviews [1–4]), by numerous data obtained in the course of our investigations

[5] I. A. Red'kin and M. M. Shemyakin, *Zhur. obshchei Khim.*, 1941, **11**, 1157.
[6] M. M. Shemyakin and I. A. Red'kin, *ibid.*, p. 1163.
[7] M. M. Shemyakin and N. I. Oranskii, *ibid.*, p. 1169.
[8] I. A. Red'kin and M. M. Shemyakin, *ibid.*, p. 1175.
[9] M. M. Shemyakin and N. I. Oranskii, *ibid.*, 1943, **13**, 175.
[10] E. H. Usherwood, *Chem. and Ind.*, 1923, 1246 ; *J.*, 1923, **123**, 1717.
[11] J. W. Baker, " Tautomerism ", Routledge, London, 1934 ; C. K. Ingold, " Structure and Mechanism in Organic Chemistry ", Bell, London, 1953.

of various hydrolytic [5–9] and oxidative-hydrolytic (see below) reactions, as well as in more recent studies by other authors.[12–15]

Hydrolytic splitting of carbon–carbon bonds in compounds of type (I) can actually be brought about in all cases where the hydrogen of the hydroxyl group exhibits marked tendency to dissociate owing to the influence of the substituents present in the molecule, as well as under the action of the medium, catalysts, and temperature, and where, owing to the same causes, the carbon–carbon bond to be split simultaneously becomes sufficiently polarised in the direction shown in scheme 1. At the present time we can predict to a considerable extent, not only the general possibility of hydrolytic splitting of carbon–carbon bonds, but also the necessary conditions for this process. This becomes possible because the influence of the nature, number, and positions of the substituents in the molecules on these processes, as well as the effect of the external conditions, can be foretold on the basis of a number of earlier derived relations,[3] although the latter are of a qualitative kind.

Thus, it was established that the presence of electron-donating substituents (such as Me, O^-, etc.) on the α-carbon atom, and of electron-acceptor substituents (such as CO_2H, CHO, CCl_3, NO_2, R_3N^+, etc.) on the β-carbon atom of group (I) always promotes hydrolysis. The stronger the electron-donor or electron-acceptor properties of the substituents the more marked is this effect. If, however, the electronic character of the substituents on the α- and the β-carbon atom in group (I) is similar (*i.e.*, both substituents are electron-donors or both are electron-acceptors), their influence on the hydrolysis of the carbon–carbon bonds is neutralised, and the more this is so, the closer is the magnitude of the polarising effect of the substituents. When the α- and the β-carbon atom carry identical substituents, the influence of the latter is completely cancelled and cleavage of the carbon–carbon bond in group (I) becomes very difficult or completely impossible, just as when there are no substituents at all or when they are remote from the α- and the β-carbon atom.

With regard to the hydration preceding the hydrolysis of unsaturated or carbonyl compounds (schemes 2 and 3) it should be noted that this reaction usually proceeds much more readily than the splitting of the hydrated molecules. That is why the latter can, in many cases, be isolated or detected indirectly.[3, 4, 8, 15–18] It is also important that, in the case of the addition of water to the double bonds $>C{=}C<$ or $>C{=}O$, the lower the electron density at the carbon atom to which the hydroxyl is to be attached, the more readily will the reaction take place. This circumstance may sometimes determine the bond at which the molecule will split; such,

[12] A. S. Sultanov, *Zhur. obshchei Khim.*, 1946, **16**, 1835.
[13] I. J. Postovskii and A. M. Eidlin, *ibid.*, p. 2053.
[14] V. V. Feofilaktov and N. K. Semenova, *ibid.*, 1953, **23**, 450.
[15] R. G. Pearson and E. A. Mayerle, *J. Amer. Chem. Soc.*, 1951, **73**, 926; R. G. Pearson and A. C. Sandy, *ibid.*, p. 931.
[16] Yu. B. Shvetsov and M. M. Shemyakin, *Zhur. obshchei Khim.*, 1949, **19**, 480.
[17] Yu. B. Shvetsov, I. A. Red'kin, and M. M. Shemyakin, *ibid.*, 1951, **21**, 339.
[18] L. A. Shchukina, *ibid.*, 1952, **22**, 668.

for instance, is the case with some polycarbonyl compounds ; see p. 271, and refs. 4, 16, 17, 19—21.

As regards the external conditions, the greatest influence on the hydrolytic splitting of carbon–carbon bonds is exerted by the pH of the solution and the temperature. The reaction is catalysed by both acids and bases but the latter have a much greater effect. The less the course of the hydrolytic process is facilitated by structural factors, the higher must be the temperature and the acidity or basicity of the solution. In more favourable cases, however, simple heating with water is sufficient. Evidently, the influence of the catalysts is of the same nature in this case as in prototropic changes, where the reaction may proceed according to a uni- or a bi-molecular mechanism.[11]

Thus, the tendency of carbon–carbon bonds to be split hydrolytically is inherent in all compounds the molecules of which contain or can easily acquire the prototropic group (I), but such changes can actually take place only if the molecules possess the structural features discussed above, and under a definite set of external conditions.*

It will be appropriate to give several examples in illustration of this.

It follows from the above considerations that in compounds (II) and (III) hydrolytic splitting according to scheme 2 is practically impossible because the carbon–carbon bonds to be split in these compounds and their hydration products are polarised very little or not at all. On the other hand, in monocarboxylic acids (IV) hydrolysis is possible, although it proceeds with great difficulty owing to the comparatively low electron-acceptor capacity of the carboxyl group (the reaction requires prolonged boiling of

$$\underset{(II)}{>C=\underset{|}{C}\cdot CH_2\cdot CH(CO_2H)_2} \qquad \underset{(III)}{HO_2C\cdot\underset{|}{C}=\underset{|}{C}\cdot CO_2H} \qquad \underset{(IV)}{>C=\underset{|}{C}\cdot CO_2H} \qquad \underset{(V)}{>C=C(CO_2H)_2}$$

[19] Yu. B. Shvetsov, L. A. Shchukina, and M. M. Shemyakin, *Zhur. obshchei Khim.*, 1949, **19**, 498.

[20] A. S. Khokhlov, L. A. Shchukina, and M. M. Shemyakin, *ibid.*, 1951, **21**, 106.

[21] M. M. Shemyakin, L. A. Shchukina, Y. B. Shvetsov, D. P. Vitkovskii, and A. S. Khokhlov, *ibid.*, p. 1667.

[22] G. A. Holmberg, *Acta Acad. Aboensis, Math. Phys.*, 1949, **16**, 6 ; 1950, **17**, 1 ; 1952, **18**, 9.

[23] A. N. Nesmeyanov, E. G. Perevalova, N. A. Volkenau, and I. F. Shalavina, *Izvest. Akad. Nauk S.S.S.R., Otdel khim. Nauk*, 1951, 692 ; A. N. Nesmeyanov, N. A. Volkenau, and E. G. Perevalova, *ibid.*, p. 699.

* It should be noted that Holmberg [22] recently described the hydrolytic splitting of carbon–carbon bonds in several triarylmethylmalonates and 5-triarylmethylbarbituric acids, the molecules of which do not contain and cannot acquire the prototropic group (I) :

$$Ar_3C\cdot CH(CO\text{-})_2 + H_3O^+ \longrightarrow Ar_3C\cdot OH + CH_2(CO\text{-})_2$$

This observation, however, does not contradict the above considerations, because Nesmeyanov and his co-workers [23] showed that in such compounds this carbon–carbon bond is specifically weak. It is capable of being split and of combining with reagents not only under the action of aqueous solutions of acids, but also under the influence of various other substances.

concentrated alkaline solutions). Hydrolysis occurs readily (upon heating with water) only in dicarboxylic acids (V), where the two carboxyl groups exert a sufficiently strong polarising influence on the bond to be split.[3, 6]

Similar results were obtained in other cases, *e.g.*, in the hydrolytic splitting of symmetrically and asymmetrically substituted nitrostilbenes.[9]

The next example shows to what extent the electron-acceptor capacity of certain substituents affects the hydrolytic splitting of carbon–carbon bonds. In full conformance with the polarising strength of the substituents, hydrolytic splitting according to scheme 2 occurs very readily in nitro-compounds (VI) (usually upon heating with water), less readily in ketones (VII) (sometimes upon heating with water, more often with dilute acid or alkali), and with great difficulty in monocarboxylic acids (IV) (see above).[3, 7]

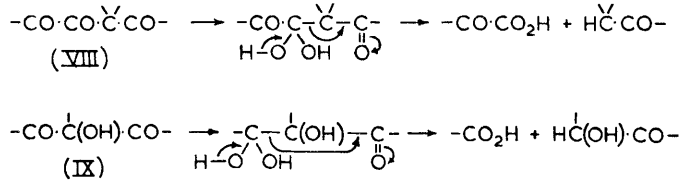
$$\underset{(\text{VI})}{>C=\underset{|}{C}-NO_2} \qquad \underset{(\text{VII})}{>C=\underset{|}{C}\cdot COR} \qquad \underset{(\text{IV})}{>C=\underset{|}{C}\cdot CO_2H}$$

A similar picture is observed in the hydrolytic splitting of analogously substituted carbonyl compounds of the type —CO·CX< (cf. scheme 3) and in the decarboxylation, according to scheme 4, of the α-substituted acids $HO_2C\cdot CX<$ (X = NO_2, CN, CO, CO_2H, R_3N^+).[1–4, 21]

Another example illustrating the extent of influence of the nature and number of substituents is the pronounced difference between the conditions for hydrolytic cleavage of substituted alcohols (or unsaturated compounds), according to scheme 2, and the conditions for the hydrolysis of similarly substituted carbonyl compounds, according to scheme 3. Compounds of the latter type (*e.g.*, β-keto-acids) are always split incomparably more readily than the former (αβ-unsaturated or β-hydroxy-acids) owing to the fact that the hydrated forms of carbonyl compounds contain two easily ionisable hydroxyl groups with high electron-donating capacity.[3, 15]

Finally, several cases should be considered, which are directly connected with the problem of oxidative-hydrolytic changes in organic compounds. It is well known that the oxidation of the latter is very often accompanied by the formation of hydroxyl and carbonyl groups in the molecules, resulting in α- and β-ketol as well as in α- and β-diketone structures. Hence, it is important to know the tendency of the carbon–carbon bonds in such structures to hydrolyse, in order to foresee the direction in which the molecules are apt to split if they contain both these groups. Although it has long been established that all the structures mentioned are capable of being split under the action of hydrolysing agents, the comparative readiness of their splitting has not yet been investigated. It might be expected that β-ketols and β-diketones (or, more exactly, the hydration products of β-diketones) should undergo hydrolytic splitting much more readily than α-ketols and α-diketones, owing to the hyperconjugation of σ- and π-bonds in the former. This conjecture was confirmed by an experimental investigation, carried out with compounds containing jointly the types of structures to be compared. It was shown in a number of

examples [16–19, 24–29] in triketones (VIII), containing both an α- and a β-diketone group, and in hydroxy-diketones (IX), containing an α-ketol and a β-diketone group, that only the β-diketone group undergoes hydrolytic splitting.



The above conception gives a uniform standpoint for interpretation of the hydrolysis (as well as alcoholysis and ammonolysis) of carbon–carbon bonds in a wide range of organic compounds of various types, and makes it possible to predict approximately the conditions and trends not only of hydrolytic but also of oxidative-hydrolytic transformations of molecules. The latter problem will be dealt with in the following section of this Review.

Oxidative-hydrolytic Splitting of Carbon–Carbon Bonds

As mentioned at the beginning of this Review, the action of oxidants on organic compounds under conditions unfavourable for hydrolysis of carbon–carbon bonds is often limited to the introduction of various oxygen-containing groups into the molecule. Thus, the oxidation of a number of olefins and several quinones under the specified conditions with chromic acid, per-acids, hydrogen peroxide, oxygen, and other oxidants goes no further than the formation of the oxides,[30–32] while the oxidation of poly-hydroxy-quinones by lead tetra-acetate, nitric acid, etc., results only in the formation of cyclic polycarbonyl compounds.[4] But if these oxidative reactions are performed in the presence of hydrolysing reagents, or when the previously oxidised molecules are acted upon by hydrolysing reagents (as, for instance, in the case of cyclic polycarbonyl compounds [4, 19–21]), the carbon–carbon bonds are easily split in a number of cases.

[24] L. A. Shchukina, A. P. Kondratieva, and M. M. Shemyakin, *Zhur. obshchei Khim.*, 1948, **18**, 2121.

[25] L. A. Shchukina and M. M. Shemyakin, *ibid.*, 1949, **19**, 193.

[26] D. P. Vitkovskii and M. M. Shemyakin, *ibid.*, 1951, **21**, 540.

[27] *Idem*, *ibid.*, p. 547.

[28] L. A. Shchukina, A. S. Khokhlov, and M. M. Shemyakin, *ibid.*, p. 908.

[29] M. M. Shemyakin and L. A. Shchukina, Collection of papers, "Problems of Chemical Kinetics, Catalysis, and Reactivity", U.S.S.R. Academy of Sciences, Moscow, 1955, p. 757.

[30] A. Byers and W. J. Hickinbottom, *Nature*, 1947, **160**, 402; *J.*, 1948, 285, 1328, 1331, 1334; W. J. Hickinbottom and D. G. Wood, *Nature*, 1951, **168**, 33; *J.*, 1951, 1600; 1953, 1906; D. P. Archer and W. J. Hickinbottom, *J.*, 1954, 4197; W. J. Hickinbottom, D. R. Hogg, D. Peters, and D. G. Wood, *J.*, 1954, 4400; W. J. Hickinbottom, D. Peters, and D. G. Wood, *J.*, 1955, 1360.

[31] E. J. Gasson, A. F. Millidge, G. R. Primavesi, W. Webster, and D. P. Young, *J.*, 1954, 2161; E. J. Gasson, A. R. Graham, A. F. Millidge, J. K. M. Robson, W. Webster, A. M. Wild, and D. P. Young, *J.*, 1954, 2170; A. R. Graham, A. F. Millidge, and D. P. Young, *J.*, 1954, 2180; G. E. Hawkins, *J.*, 1955, 3288.

[32] L. A. Shchukina, E. I. Vinogradova, and M. M. Shemyakin, *Zhur. obshchei Khim.*, 1951, **21**, 1661.

A special investigation of this question has been carried out, mainly with carbocyclic compounds (see below). The results showed that the action of oxidants on organic molecules very often facilitates hydrolysis of the carbon–carbon bonds at definite levels of oxidation of the molecules and that, on the other hand, partially oxidised molecules sometimes acquire an increased tendency to further oxidation after hydrolytic splitting. Thus, in many cases the splitting of carbon–carbon bonds becomes possible only as a result of the simultaneous or alternate action of oxidants and hydrolysing agents.

For the understanding of the nature of such oxidative-hydrolytic changes in organic compounds it is important first to ascertain : (1) why preliminary oxidation of the molecules may influence the subsequent hydrolysis of the carbon–carbon bonds, and (2) what relation exists between the degree of oxidation of the molecules and the capacity of their carbon–carbon bonds to undergo hydrolytic splitting.

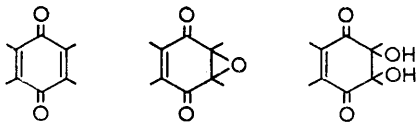
The answer to both these questions follows logically from the conception expounded in the previous section of this Review. Indeed the oxygen-containing substituents (>O, —OH, >CO, etc.), formed in the molecules when they are oxidised, can not only take part in the formation of prototropic groups of type (I), prerequisite for the hydrolysis (see p. 263), but can also influence the polarisation of the carbon–carbon bonds in these groups, and hence their tendency to hydrolytic splitting. Thus, it becomes clear why the action of oxidants on organic compounds influences the hydrolysis of their carbon–carbon bonds very greatly during definite stages of oxidation of these compounds. An explanation is also obtained for the relation between the level of oxidation of the molecules and the capacity of their carbon–carbon bonds for hydrolytic splitting. This relation may be formulated as follows : the more strongly the oxygen-containing substituents, formed in the molecules under the action of the oxidants, polarise the carbon–carbon bonds subject to hydrolytic splitting, the more readily will the latter process take place [provided, of course, that the carbon–carbon bonds undergo polarisation in the direction indicated in scheme 1 for compounds of type (I)].

Indeed, the results of investigations [4, 16–21, 24–29, 32–46] of the conditions

[33] L. A. Shchukina, A. P. Kondratieva, and M. M. Shemyakin, *Zhur. obshchei Khim.*, 1948, **18**, 1945.
[34] *Idem*, *ibid.*, 1949, **19**, 183.
[35] *Idem*, *ibid.*, p. 468.
[36] Ye. I. Vinogradova, Yu. B. Shvetsov, and M. M. Shemyakin, *ibid.*, p. 507.
[37] L. A. Shchukina, Yu. B. Shvetsov, and M. M. Shemyakin, *ibid.*, 1951, **21**, 346.
[38] L. A. Shchukina, A. S. Khokhlov, and M. M. Shemyakin, *ibid.*, p. 917.
[39] D. P. Vitkovskii and M. M. Shemyakin, *ibid.*, p. 1033.
[40] M. M. Shemyakin, D. A. Bochvar, and L. A. Shchukina, *ibid.*, 1952, **22**, 439.
[41] O. M. Shemyakina, B. M. Bogoslovskii, and M. M. Shemyakin, *ibid.*, p. 675.
[42] D. P. Vitkovskii and M. M. Shemyakin, *ibid.*, p. 679.
[43] L. A. Shchukina and E. P. Syomkin, *ibid.*, 1956, in the press.
[44] L. A. Shchukina, *ibid.*
[45] L. A. Shchukina and M. M. Shemyakin, *ibid.*
[46] O. M. Shemyakina, B. M. Bogoslovskii, and M. M. Shemyakin, *ibid.*

and nature of hydrolytic splitting of carbocyclic compounds at various stages of oxidation show that this process is in direct relation with the polarisation of the carbon–carbon bonds subject to splitting. This polarisation, in its turn, depends on the nature, number, and positions of the substituents, either contained in the original molecules or formed in them under the action of the oxidants.

Thus, oxidation of aromatic hydrocarbons and their derivatives to *p*-quinones fails to give rise to the peculiar structural features in the molecules required to promote to a sufficient degree the splitting of the ring systems in the presence of hydrolysing agents. The reason for this lies in the fact that the carbonyl groups of *p*-quinones (X) are unable to polarise the bonds between the carbon atoms of the ring. That is why, *e.g.*, 1 : 4-naphthaquinone cannot be split hydrolytically as such, but only after preliminary oxidation.[33] 2-Methyl- and 2-ethyl-1 : 4-naphthaquinone behave in a similar manner [33] owing to the fact that alkyl radicals are but weak polarisers.* Even further oxidation of these *p*-quinones to the oxides (XI) and hydration of the latter to glycols (XII) do not yet result in compounds with a tendency to hydrolysis in the presence of hydrolysing agents, because the introduction of an oxide-oxygen atom or two hydroxyl groups at positions 2 and 3 of the quinone molecules cannot promote polarisation of the bond between these carbon atoms. This is why the oxides and the corresponding glycols, just as the initial quinones, do not undergo hydrolytic splitting unless their molecules are preliminarily altered.[25, 32, 34, 38, 45]



(X) (XI) (XII)

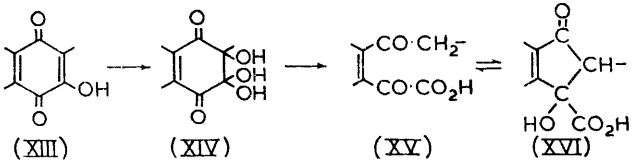
An entirely different result [18, 24, 28, 43, 47, 48] is observed, however, in the case of hydroxy-quinones (XIII) which may be formed through dehydration of glycols (XII). These hydroxy-quinones can easily be hydrated at the double bond which is polarised under the influence of the hydroxyl group, giving rise to the hydration products (XIV). In the latter the ordinary bond between $C_{(2)}$ and $C_{(3)}$ is also very highly polarised, owing to the presence of two easily ionisable hydroxyl groups in position 3. Accordingly, hydroxy-quinones (XIII) undergo hydrolytic splitting quite readily when boiled in aqueous solution at pH 7, yielding compounds of type (XV $\rightleftarrows$ XVI).

Depending on the number and position of hydroxyl groups formed in

[47] L. F. Fieser, *J. Amer. Chem. Soc.*, 1929, **51**, 940, 1896.

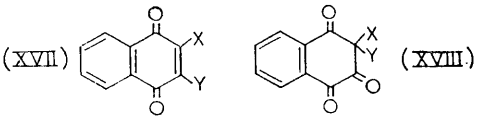
[48] L. F. Fieser and A. Bander, *ibid.*, 1951, **73**, 681.

* Failure of alkyl and aralkyl radicals to influence perceptibly the hydrolytic splitting of carbon–carbon bonds, and a weak influence in this respect of the aryl radical, were observed in a number of cases, for instance, in 2-substituted 1 : 4-naphthaquinone 2 : 3-oxides, in the glycols corresponding to these oxides, and in 2-substituted 3-hydroxy-1 : 4-naphthaquinones ; [24, 25, 28, 34, 38, 43] cf. also the conditions of hydrolysis of the corresponding $\alpha\beta$-unsaturated nitro-compounds and monocarboxylic acids.[3, 6]



the molecule in the course of its oxidation, the influences of the hydroxyl groups on the ease of fission of carbon–carbon bonds in the ring may be widely different. In this connection it will be of interest to compare the properties of glycols of type (XII) with those of isomeric compounds of type (XIV), which differ in structure only as regards the position of the hydroxyl groups. It is owing to this difference that compounds of type (XII), as mentioned above, are incapable of hydrolytic splitting under conditions in which compounds of type (XIV) are split quite readily, because only in the latter do the hydroxyl groups polarise the bond between $C_{(2)}$ and $C_{(3)}$. Another instance is the difference in stability to hydrolysis of the ring systems in 2-hydroxy- (XVII ; X = H, Y = OH) and 2 : 3-dihydroxy-1 : 4-naphthaquinone (*iso*naphthazarin) (XVII ; X = Y = OH). The latter quinone is incomparably more resistant to hydrolytic splitting than the former, since the 2- and 3-hydroxyl groups in the *iso*naphthazarin molecule are incapable of polarising the bond between $C_{(2)}$ and $C_{(3)}$.[20, 28]

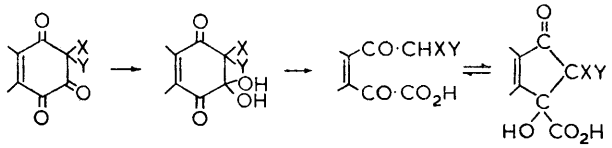
The bond between $C_{(2)}$ and $C_{(3)}$ in monohydroxy-quinones (XIII) can be depolarised, not only by introducing a hydroxyl group in position 2, but also by introducing certain other substituents of a similar electronic nature. Indeed, 2-amino-3-hydroxy-1 : 4-naphthaquinone (XVII ; X = NH_2, Y = OH) is no less stable to hydrolysing agents than *iso*naphthazarin (XVII ; X = Y = OH) ; both these quinones remain almost unchanged when boiled for many hours with 1% sodium hydroxide solution in the absence of atmospheric oxygen.[20, 39] Another compound, which is fairly stable, though to a lesser degree, is 1-[3(1)-hydroxy-1 : 4(3 : 4)-naphthaquinon-2-yl]pyridinium betaine (XVII ; X = $C_5H_5N^+$, Y = O^-) ; in this compound the bond between $C_{(2)}$ and $C_{(3)}$ is also quite highly depolarised [26] (the pathways of the hydrolytic changes of this betaine are considered on p. 276).



Relations similar to those just described are observed whenever an additional carbonyl group appears in the *p*-quinone ring owing to oxidation or any other cause. The appearance of such a group usually renders the molecules very unstable towards hydrolysing agents. Thus, it was shown [16, 19, 27, 35, 37, 44] (see also ref. 49) that a great variety of triketones

[49] T. Zincke and E. Winzheimer, *Annalen*, 1896, **290**, 321 ; T. Zincke and B. Francke, *ibid.*, 1896, **293**, 120 ; *Ber.*, 1896, **29**, 965 ; T. Zincke and C. Gerland, *Ber.*, 1887, **20**, 3216 ; 1888, **21**, 2379.

of the tetralin series of general type (XVIII) not only are readily hydrated at the double bond of the 3-carbonyl group but also undergo subsequent hydrolytic splitting between positions 2 and 3 of the ring.



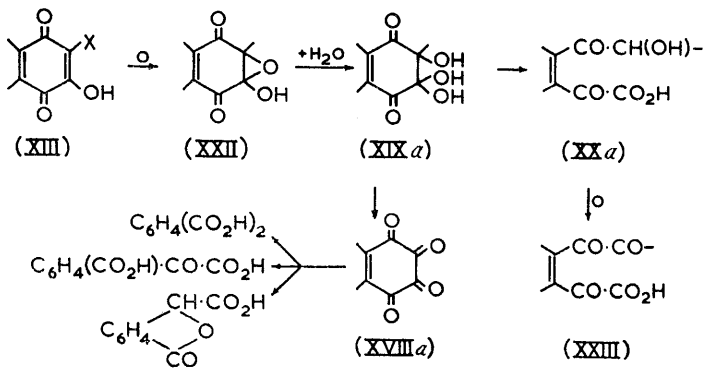
(XVIII) (XIX) (XX) (XXI)

It is interesting to note in this respect that it is always the 3-carbonyl group and not that in position 1 or 4 that is hydrated in triketones of the tetralin series (XVIII). This is important, because in this way the place is determined where the subsequent hydrolytic splitting of the ring will occur. The cause of this regularity lies in the fact that the electron density of carbon atoms in carbonyl groups situated next to the aromatic nucleus is lowered less than in a 3-carbonyl group. It must also be stressed that, although the hydrolytic splitting of these triketones occurs very readily, the conditions under which this process can be effected also depend to a considerable extent on the nature of the substituents at position 2. For example, owing to the presence of both a pyridinium residue and a chlorine atom in the hydrated triketone chloride (XIX ; X = $C_5H_5N^+$, Y = Cl), the 2 : 3-bond is so highly polarised that it is split in aqueous solution even without heating.[27] In the hydrated triketone series (XIX ; X = Me or Ph, Y = OH, OAc, or Cl) the same bond is less strongly polarised, and hence this bond can undergo hydrolytic splitting only when aqueous solutions of these compounds are heated.[16, 17, 19, 25, 45] The 2 : 3-bond should be still less strongly polarised in the hydrated triketones (XIX ; X = H, Me, CH_2Ph, Ph, etc., Y = H) which are formed by hydration of the corresponding hydroxynaphthaquinones (XIII). Accordingly, the hydrated forms of the latter will readily undergo splitting only when boiled in aqueous solution at pH 7 (see p. 269 and refs. 18, 24, 28, 43). Only the hydrated triketone (XIX ; X = Ph, Y = H) can be hydrolysed by boiling water ;[43] this is due to the electron-acceptor properties of the phenyl residue.

The occurrence of a still greater number of carbonyl groups in molecules of carbocyclic compounds should result in compounds with an especially high tendency for hydrolytic cleavage. It might be expected, for instance, that the ring in tetralin tetraketone (XVIII ; XY = O) will be split very readily, because in this case hydration of the carbonyl group in position 2 or 3 causes strong polarisation of the 2 : 3-bond owing to the presence of two carbonyl groups in positions 3 : 4 or 1 : 2. Indeed,[20] this tetraketone was found to be split very rapidly in hot aqueous solution ; in solution at pH 7 this process is almost instantaneous even at room temperature. Polycarbonyl compounds belonging to other types of carbocyclic, as well as of fatty-aromatic, compounds, *viz.*, *o*-pyruvoylphenylglyoxylic acid,[35]

triquinonyl,[50] ninhydrin,[20] and anthra-1 : 4-9 : 10-diquinone,[51] behave in a similar manner. They are exceedingly unstable in the presence of hydrolysing agents, although in the absence of the latter all these compounds are quite stable to oxidants, to heating, and to other modes of treatment.

From the above-mentioned results the pathways of oxidative-hydrolytic changes in aromatic compounds, leading to the splitting of carbon–carbon bonds in the ring, become evident. Oxidation of aromatic compounds to *p*-quinones (X), oxides (XI), and glycols (XII) is not sufficient to induce splitting of the ring systems (see p. 269). Only upon dehydration of glycols (XII) to monohydroxy-quinones (XIII) can there arise the structural features in the molecules which favour hydrolytic splitting of the bonds according to the scheme: (XIII)→(XIV)→(XV ⇌ XVI). If, however, for some reason, excessively drastic conditions are needed to bring about hydrolytic cleavage of the hydroxy-quinones (XIII), or if these hydroxy-quinones are not formed at all, it becomes necessary to subject the molecule to additional oxidation in order to convert it into more oxidised and more readily hydrolysable compounds: to monohydroxy-quinone oxides (XXII), hydroxy-triketones or their hydrates (XVIII and XIX; X = OH), tetraketones (XVIII; XY = O), etc. Thus [35, 37, 44] the oxidative-hydrolytic transformation of hydroxy-quinones (XIII; X = Me, Ph, *o*-tolyl, β-$C_{10}H_7$) into the corresponding triketo-acids (XXIII) takes place under the action of cold alkaline potassium permanganate according to the scheme: (XIII)→(XXII)→(XIX*a*)→(XX*a*)→(XXIII). The oxidative-hydrolytic cleavage of hydroxy-quinones (XIII; X = OH, NH_2, Cl, etc.) proceeds in a similar way;[39, 42] in boiling alkaline aqueous solution in the presence of atmospheric oxygen these compounds are transformed into phthalide-3-carboxylic, phthalonic, and phthalic acid through the intermediate stages: (XXII)→(XIX*a*)→(XVIII*a*).

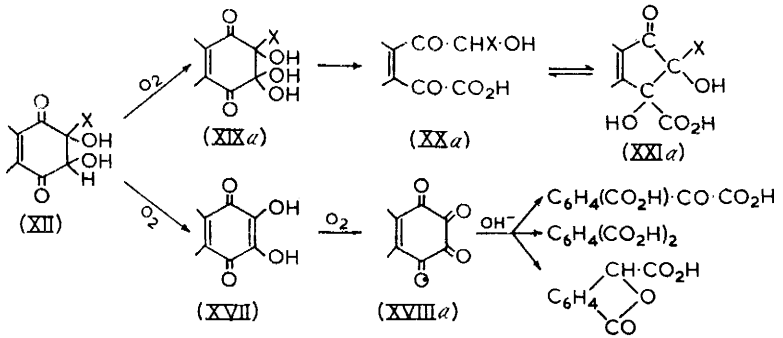


It is important also that, not only the above-mentioned hydroxy-quinones (XIII), but likewise their precursor glycols (XII) often have a very marked

[50] R. Nietzki and T. Benckisser, *Ber.*, 1885, **18**, 499, 1833; 1886, **19**, 293; T. Zincke, *Ber.*, 1887, **20**, 1265; A. Hantzsch, *Ber.*, 1888, **21**, 2421.

[51] O. Dimroth and E. Schultze, *Annalen*, 1916, **411**, 345.

tendency to further oxidation, owing to their special structural features, and can readily be oxidised even with such weak oxidants as atmospheric oxygen.[25, 34, 38, 45] However, in certain cases transition to the next degree of oxidation may not result in the formation of a compound readily split under the action of hydrolysing agents. Indeed, while the oxidation of 2-substituted glycols (XII; X = Me or Ph) results in hydrated hydroxy-triketones (XIX*a*) which are split readily upon mere heating with water into compounds of type (XX*a* ⇌ XXI*a*),[25, 34, 45] oxidation of the unsubstituted glycol (XII; X = H) leads to the formation of *iso*naphthazarin (XVII) which, owing to its structural peculiarities, shows but little tendency (see p. 270) for hydrolytic splitting.[20, 38] In this compound hydrolysis can be brought about only by oxidising the molecule still further, *viz.*, by transforming the *iso*naphthazarin (XVII) into tetraketone (XVIII*a*), the ring system of which is very unstable in the presence of hydrolysing agents (see p. 271 and ref. 20).



Thus, in many cases the greater the degree of oxidation of the molecules, the more readily will the hydrolytic splitting of the carbon–carbon bonds occur. But sometimes the introduced oxygen-containing substituents do not influence the hydrolysis of the bonds at all, and in certain cases they even hinder this process; in such cases further oxidation of the molecules usually results at certain stages in the formation of compounds in which carbon–carbon bonds will undergo hydrolytic splitting very readily.

Secondary and Side Reactions

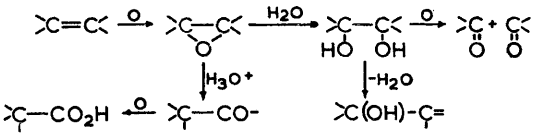
The oxidative-hydrolytic transformation of organic compounds is often associated with secondary and side reactions since the substances formed during intermediate stages of these changes [*e.g.*, types (XI, XII, XIII, XV ⇌ XVI, XVIII, XX ⇌ XXI, XXII)] have in a number of cases a great tendency to undergo various changes.

A considerable number of secondary and side reactions is usually connected with the further action of oxidants and hydrolysing agents upon the primary compounds produced. The pathways of these changes are trivial, and need not be considered in detail. They include, for instance,[17, 20, 24, 35, 37, 39, 42–45] the common oxidation processes:

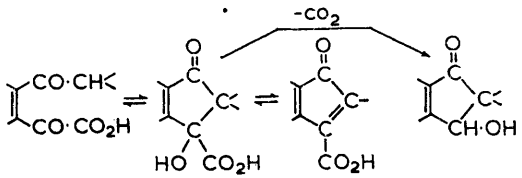
$$—CO\cdot CH_2— \longrightarrow —CO\cdot CH(OH)— \longrightarrow —CO\cdot CO— \text{ or } —CO\cdot CO_2H \longrightarrow —CO_2H$$

as well as the hydrolytic cleavage of β-dicarbonyl, β-hydroxycarbonyl, and other compounds.

In the course of oxidative-hydrolytic changes of alkenes, *cyclo*alkenes, and some of their derivatives, side reactions sometimes arise owing to the fact that the oxides primarily formed are capable of partial isomerisation to carbonyl compounds under the influence of acids. In turn, the glycols formed from these oxides have a tendency for dehydration. These side reactions lead, along with the formation of normal products of oxidative-hydrolytic cleavage of unsaturated compounds at their double bonds, to the appearance of so-called anomalous oxidation products—unsaturated alcohols, carboxylic acids, and other substances retaining the initial number of carbon atoms.[30, 31]

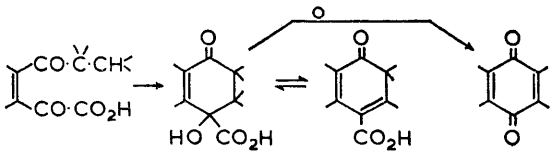


In the course of oxidative-hydrolytic changes of six-membered carbocyclic compounds the most characteristic secondary reactions are those which result in the formation of new five- and six-membered ring compounds from acyclic intermediates. The reason for this is that many of the intermediate substances tend to tautomerism of the type (XV $\rightleftharpoons$ XVI), and, the tautomeric form (XVI) being readily subject to dehydration, to decarboxylation and a number of other changes.*



(XV) (XVI)

On the other hand, if there are structures of type (XXIV) in the intermediate substances, six-membered cyclic compounds of type (XXV) may be formed, which also are readily subject to various changes (dehydration, oxidative decarboxylation, etc.).[4, 19, 34–37, 44]



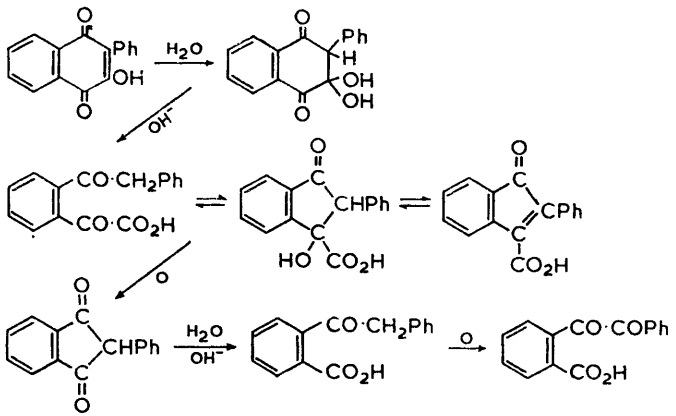
(XXIV) (XXV)

It is typical that in the course of oxidative-hydrolytic changes of organic compounds various secondary and side reactions often proceed simultane-

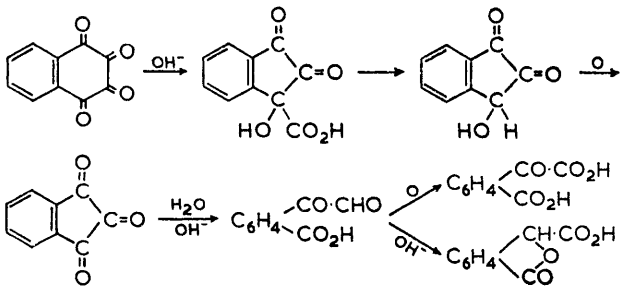
* See ref. 4 ; cf. also more recent investigations (refs. 16, 20, 24, 27, 28, 36, 38, 39, 42, 43, 48).

ously in different directions or alternate with one another. By way of illustration a number of reactions are considered below, most of which were investigated by isolation or synthesis of the intermediates, followed by a study of the conditions and directions of their subsequent changes.

Thus, it has been established [43] that boiling 2-hydroxy-3-phenyl-1 : 4-naphthaquinone in the presence of atmospheric oxygen in aqueous solution at pH about 9 results in the annexed series of hydrolytic and oxidative reactions : *



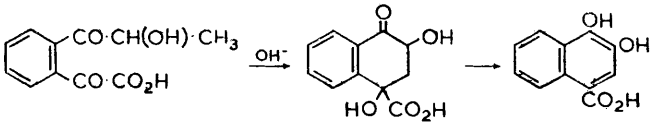
Transformations of the tetraketone (XVIII), which is formed as an intermediate in the oxidative-hydrolytic cleavage of certain 2-substituted 3-hydroxynaphthaquinones of type (XIII) (see p. 272), likewise proceed in several stages. In this case [20, 39] the annexed sequence of reactions occurs under the influence of atmospheric oxygen and a boiling solution of sodium hydroxide.



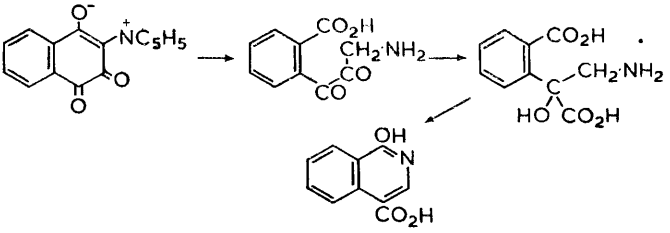
An example of a secondary reaction's resulting in the formation of six-membered carbocyclic compounds is the cyclisation of *o*-lactylphenylglyoxylic acid, one of the hydroxydiketo-acids of type (XX*a*) which arise in the course of oxidative-hydrolytic changes of hydroxy-quinones or quinone

* With 3-hydroxynaphthaquinones carrying H, Me, or CH_2Ph in position 2 the hydrolytic cleavage of the ring system, when effected under similar conditions, is not associated with oxidative changes.[24, 28, 43]

oxides (see pp. 277, 280). When heated in aqueous alkali in the absence of atmospheric oxygen, *o*-lactoylphenylglyoxylic acid is rapidly transformed into 3 : 4-dihydroxynaphthoic acid :[34]



Finally, an instance of secondary reactions resulting in the formation of heterocyclic six-membered rings is the transformation of 1-[1(3)-hydroxy-3 : 4(1 : 4)-naphthaquinon-2-yl]pyridinium betaine into 1-hydroxy*iso*quinoline-4-carboxylic acid,[26] brought about by hot aqueous alkali in the absence of atmospheric oxygen. This change evidently proceeds through the annexed intermediate stages.

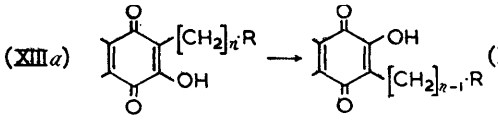


The secondary and side reactions considered above might seem quite different at first sight. However, in many cases their course is so uniform that on the basis of relations previously established the main directions of the processes under investigation and the structure of both the intermediates and the final compounds can often be predicted.

Examples of Oxidative-hydrolytic Transformations of Organic Compounds

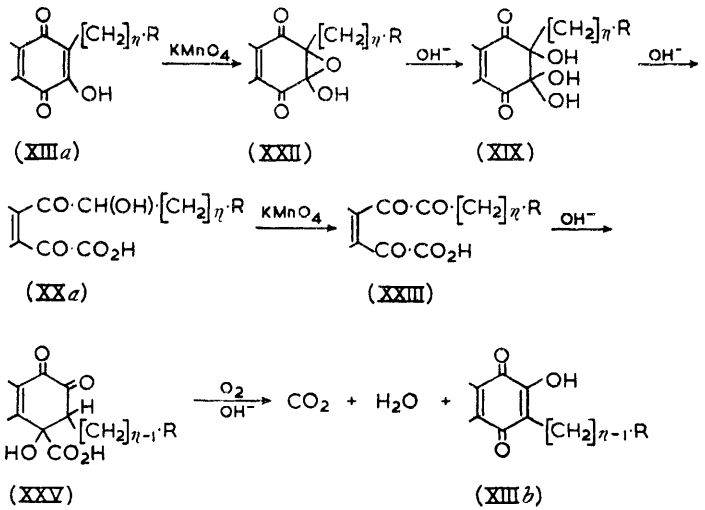
Beside the examples given in the previous sections several further cases of oxidative-hydrolytic transformations of organic compounds should be considered, which characterise the complexity and peculiar features of reactions of this kind.

Of particular interest from this standpoint is the mechanism of Hooker's reaction, which has been specially studied many times. Hooker's reaction,[52] first described in 1936, is the transformation of hydroxy-quinones (XIII*a*) into hydroxy-quinones (XIII*b*) under the action of an alkaline



[52] S. Hooker, *J. Amer. Chem. Soc.*, 1936, **58**, 1168, 1174, 1190 ; S. Hooker and A. Steyermarck, *ibid.*, pp. 1179, 1198.

solution of potassium permanganate.* It involves not only the shortening of the side chain by one methylene group, but also a shift of the substituents in the quinone ring ; the latter was proved by Fieser and his collaborators [53] as early as 1936. Both Hooker and Fieser were right in considering that processes of this kind must be associated with opening and subsequent recyclisation of the quinone ring, but they interpreted the mechanism of the intermediate stages of reaction differently ; [54, 55] the hypothetical schemes they proposed in 1936 and 1944 were not verified experimentally. The results of our investigations [4, 35, 56] of the mechanism of Hooker's reaction were published in 1946—1949. Our concept of oxidative-hydrolytic transformations of organic compounds enabled us to explore the chief stages of this reaction experimentally and to elucidate the nature of the process as a whole. It has been established that Hooker's reaction proceeds according to the scheme given below. The reaction is a result of the simultaneous action both of oxidants (potassium permanganate and atmospheric oxygen) and of the aqueous alkali on the original molecule and on intermediates ; the alkali brings about not only hydrolysis, but also condensation. In a re-investigation of the mechanism of Hooker's reaction Fieser and Fieser suggested in 1948 a scheme for this reaction [57] which in its first part is in essential agreement with our scheme but differs from it substantially in its

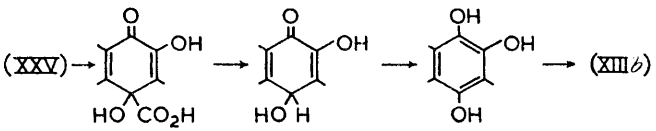


second part, beginning with the stage of decarboxylation of the hydroxy-acid (XXV) formed as an intermediate. However, experimental data

[53] L. F. Fieser, J. Hartwell, and A. Seligman, *J. Amer. Chem. Soc.*, 1936, **58**, 1223.
[54] S. Hooker, *ibid.*, p. 1174.
[55] L. F. Fieser and M. Fieser, " Organic Chemistry ", Heath, Boston, 1944, p. 755.
[56] L. A. Shchukina, Thesis, Moscow, 1946.
[57] L. F. Fieser and M. Fieser, *J. Amer. Chem. Soc.*, 1948, **70**, 3215.
* Beside permanganate the oxidants may be hydrogen peroxide–copper sulphate, and in some cases, apparently, atmospheric oxygen.[48, 52]

available to-day [4, 35, 37, 44, 45, 52, 53, 55–57] and illustrated in the formulæ on page 277 are all in favour of our scheme.

The validity of the first stages (XIII*a* → XXII → XIX → XX*a*) is confirmed by the fact that the glycol (XIX ; $n = 1$, R = H), synthesised for this purpose in a different way, was converted under the usual conditions of Hooker's reaction, first, into the hydroxydiketo-acid (XX*a*), and then into the final hydroxy-quinone (XIII*b*).[19, 35] Also, in two cases it was possible to stop the reaction at the intermediate hydroxydiketo-acids (XX*a* ; $n = 1$, R = CH:CMe_2 and Ph), and to isolate them.[44, 57] The next stage (XX*a* → XXIII) was verified by the same methods. It has been shown [35, 45] that hydroxydiketo-acids (XX*a* ; $n = 1$, R = H ; $n = 0$, R = Ph) can be oxidised by potassium permanganate to the triketo-acids (XXIII) under the conditions of Hooker's reaction. Further, we succeeded in isolating, under certain conditions, a number of triketo-acids (XXIII ; $n = 1$, R = H ; $n = 0$, R = Ph, *o*-tolyl, and β-$C_{10}H_7$) directly from the reaction solution.[35, 44] Finally, with the individual triketo-acids (XXIII) on hand, it was possible to study the last stages of Hooker's reaction (XXIII → XXV → XIII*b*). Here it was shown in the instance of the triketo-acid (XXIII ; $n = 1$, R = H) [34, 35] that the final hydroxy-quinones (XIII*b*) can be obtained only in the presence of oxidants (permanganate, atmospheric oxygen) since the intermediate hydroxy-acids of type (XXV) can undergo only oxidative decarboxylation. This does not agree with the mechanism suggested by Fieser and Fieser [57] for the final stages of Hooker's reaction, which implies the possibility of decarboxylation of hydroxy-acids (XXV) in the absence of oxidants :

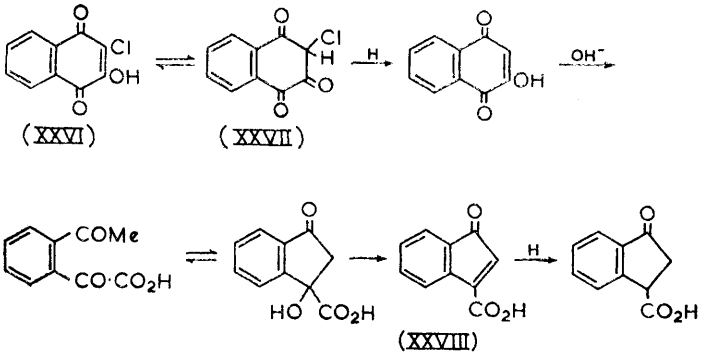


It will be useful to discuss briefly the oxidative-hydrolytic reactions in which the initial or intermediate compounds themselves act as oxidants. Transformations of this kind were noted when certain quinones,[28, 33] quinone oxides,[25, 32, 34, 38, 40] nitro-compounds,[9, 46, 58] etc., were subjected to the action of hydrolysing agents. All these substances were found capable of manifesting their oxidising properties in the course of the reactions. In all these cases the processes of oxidation–reduction and hydrolysis take an especially complicated course, usually resulting in a considerable variety of final compounds.

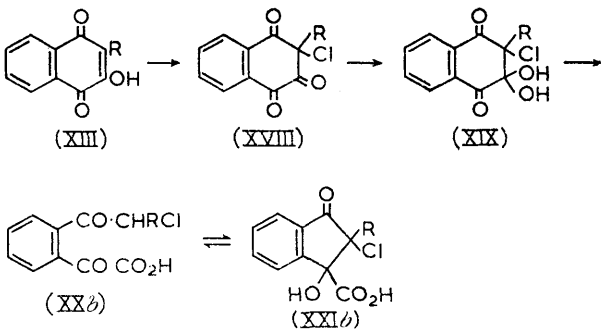
By way of example we may mention the behaviour of 2-chloro-3-hydroxy-1 : 4-naphthaquinone (XXVI) when boiled in aqueous alkali in the presence or absence of atmospheric oxygen.[39, 42] In both cases this quinone undergoes a long sequence of oxidative-hydrolytic changes resulting finally in the formation of phthalide-3-carboxylic, phthalonic, and phthalic

[58] F. M. Rowe and S. Ueno, *J. Soc. Dyers and Colourists*, 1931, **47**, 35 ; F. M. Rowe and F. H. Jowett, *ibid.*, p. 163 ; F. M. Rowe and C. H. Giles, *ibid.*, 1935, **51**, 278.

acid (see p. 272); in the absence of atmospheric oxygen these changes are possible because they are associated with a parallel series of reductive-hydrolytic reactions (see annexed scheme). A detailed study of these reactions showed that two compounds acted as oxidants in this system, namely the initial quinone (XXVI), or rather, the tautomeric triketone (XXVII), the chlorine atom of which possesses oxidising properties, and intermediate oxoindenecarboxylic acid (XXVIII), which is capable of effecting dehydrogenation.

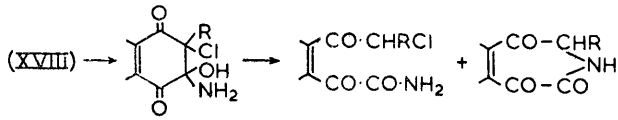


It is interesting that the oxidative-hydrolytic cleavage of carbon–carbon bonds forms the basis for a number of methods of synthesising polyfunctional compounds produced by splitting of the corresponding cyclic compounds. As an example we may cite the production of halogeno-acids of type (XX*b* ⇌ XXI*b*) from 2-substituted 3-hydroxynaphthaquinones (XIII). This reaction has been studied by Fieser and Fieser [57] and simultaneously by us.[4, 16, 27] According to Fieser and Fieser, it can be brought about by the action of sodium hypochlorite on the hydroxy-quinones (XIII) in the presence of sodium carbonate, which results in the direct formation of halogeno-acids (XX*b* ⇌ XXI*b*). This procedure is interesting for preparative purposes, but it throws no light on the mechanism of the reaction. We performed this reaction stepwise, by first acting upon the hydroxy-quinones (XIII) with chlorine, then exposing the intermediate triketones (XVIII) to the action of water, and finally treating the hydrated triketones



(XIX) with aqueous sodium hydroxide or carbonate. In this way we were able to ascertain that in this case, just as in Hooker's reaction, the ring is split only after the necessary prototropic structure has been formed in the molecule and substituents have been introduced which are capable of polarising to a sufficient extent the bond to be split.

It is worthy of note that the intermediate triketones (XVIII) are readily subject, not only to hydrolysis, but also to ammonolysis, being converted in the latter case into amides of chlorodiketo-acids or the corresponding lactams : [17]



Among other synthetical methods based on reactions of oxidative-hydrolytic or purely hydrolytic cleavage of carbon–carbon bonds, mention should be made of two methods for the synthesis of hydroxy-acids of type (XX*a* ⇌ XXI*a*) which were published almost simultaneously. According to one of these methods [4, 34, 45] acids of this kind can be obtained by boiling naphthaquinone oxides (XI) with water in the presence of atmospheric oxygen ; this reaction proceeds [25] through the intermediate stages (XI), (XII), (XIX), (XX*a*), and (XXI ; X = OH). The other method [48, 57] consists in treating 2-substituted 3-hydroxynaphthaquinones (XIII) with hydrogen peroxide in the presence of sodium carbonate, and is superior to the former as a preparative procedure.[45] Its mechanism is identical [37] with the first three stages of Hooker's reaction (see p. 277).

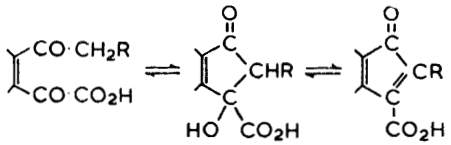
Hooker's reaction was also utilised recently [35, 44] for the preparation of triketo-acids (XXIII) from 2-substituted 3-hydroxynaphthaquinones (XIII) according to the scheme : (XIII*a*) → (XXII) → (XIX) → (XX*a*) → (XXIII). This method is especially suitable when the substituents in position 2 of the hydroxy-quinone do not contain a methylene group (*e.g.*, XIII*a* ; $n = 0$, R = Ar), because the reaction cannot then go beyond formation of the desired triketo-acids. In other cases [*e.g.*, with (XIII*a*, $n = 1$, 2, etc.)] special precautions must be taken and even then it is sometimes [*e.g.*, with (XIII*a* ; $n = 1$, R = Ph)] impossible to stop the process at the desired intermediate stage.

Mention should also be made of a convenient method for the synthesis of keto-acids of type (XV ⇌ XVI) by hydrolytic cleavage of 2-alkyl(or aralkyl or aryl)-3-hydroxy-quinones (XIII) of the benzene, naphthalene, and phenanthrene series,[18, 24, 28, 43, 47, 48] according to the scheme : (XIII) → (XIV) → (XV ⇌ XVI).

Various points of view concerning the conditions and mechanism of this reaction have been set forth. On the one hand, we suggested,[4, 24] as early as 1948, our usual scheme of hydrolytic splitting of carbon–carbon bonds. According to this, the hydroxy-quinones should undergo hydration more easily than fission ; in contrast to the fission, hydration does not require an alkaline medium. On the other hand, Fieser and Bander, in 1951, came to

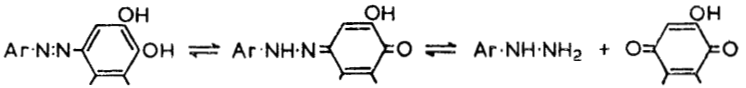
the conclusion [48] that only the hydroxy-quinone anion can be hydrated, an alkaline medium being required for this purpose, whereas the subsequent hydrolytic splitting (or rearrangement of the benzilic acid type) can be brought about without the influence of alkali. However, a further investigation of this reaction for the case of 2-hydroxy-5-methyl-*p*-benzoquinone [18] confirmed the validity of our viewpoint. With this quinone we were able to separate the process into two steps and to isolate the hydrated hydroxyquinone (XIV), the formation of which is much easier than its cleavage: hydration can be brought about in neutral solution, while the hydrolytic splitting is possible only in alkali.

In a number of cases it is advisable to carry out the hydrolytic splitting of the hydroxyquinones (XIII) by boiling them in aqueous buffer solutions at pH values between 7·5 and 9·5. Under such conditions an equilibrium is usually set up between the resultant keto-acids (XV ⇌ XVI) and their dehydration products, *i.e.*, compounds of type (XXIX); the position of this equilibrium depends very markedly on the structure of the compounds produced.[24, 28, 43]



(XV) (XVI) (XXIX)

It is noteworthy that the azo-compounds (whose tautomeric forms are hydroxynaphthaquinone arylhydrazones) are subject in some cases to hydrolytic cleavage under the same conditions as the hydroxynaphthaquinones themselves. The azo-compounds are first split into arylhydrazine and hydroxynaphthaquinone, which then undergo the subsequent changes.[41, 46]



To conclude, we shall mention a few additional problems in the solution of which the application of our conceptions concerning hydrolytic and oxidative-hydrolytic changes of organic compounds has played a part. These conceptions proved useful in developing the theory of amino-acid metabolism catalysed by pyridoxal enzymes, published by Braunshtein and one of us [59] in 1952—1953 (similar ideas were developed in 1954 by Snell and his collaborators [60]). The conceptions were utilised recently in elucidating pathways of biogenesis of branched-chain carbohydrates and the mechanisms of some of their transformations,[61] and also in explaining the hydrolytic

[59] A. Ye. Braunshtein and M. M. Shemyakin, *Doklady Akad. Nauk S.S.S.R.*, 1952, **85**, 1115; *Biokhimiya*, 1953, **18**, 393.

[60] D. E. Metzler, M. Ikawa, and E. E. Snell, *J. Amer. Chem. Soc.*, 1954, **76**, 648.

[61] M. M. Shemyakin, A. S. Khokhlov, and M. N. Kolosov, *Doklady Akad. Nauk S.S.S.R.*, 1952, **85**, 1301.

splitting of certain antibiotics (actidione, citrinin [62]); they were also applied to the study of hydrolytic transformations of compounds such as aurins,[13] azo-substituted keto-acids,[14] and others.[12] It can be expected that our conception concerning the essential mechanism of oxidative-hydrolytic processes will prove helpful in clarifying the nature of certain other types of hydrolytic and oxidative transformations. This applies, in particular, to some reactions of splitting of different di- and tri-hydroxyanthraquinones [63] and of purpurogallin [64]—reactions which have already been described but have not been studied sufficiently.

[62] M. M. Shemyakin and A. S. Khokhlov, " The Chemistry of Antibiotic Substances ", Moscow, 1953, pp. 48, 192.

[63] E. Bamberger and A. Praetorius, *Monatsh.*, 1901, **22,** 587; R. Scholl, P. Dahll, and E. Hansgirg, *Ber.*, 1923, **56,** 2548; R. Scholl and A. Zinke, *Ber.*, 1918, **51,** 1419; 1919, **52,** 1142; O. Dimroth and E. Schultze, *Annalen*, 1916, **411,** 339; R. Scholl and P. Dahll, *Ber.*, 1924, **57,** 80; K. Fries and E. Auffenberg, *Ber.*, 1920, **53,** 23.

[64] H. Wichelhaus, *Ber.*, 1872, **5,** 846; R. D. Haworth, B. P. Moore, and P. L. Pauson, *J.*, 1948, 1045; D. R. Haworth and J. D. Hobson, *J.*, 1951, 561; W. D. Crow and R. D. Haworth, *J.*, 1951, 1325; P. L. Pauson, *Chem. Rev.*, 1955, **55,** 110.