QUARTERLY REVIEWS

BENZILIC ACID AND RELATED REARRANGEMENTS

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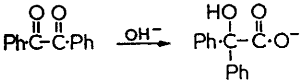
THE conversion of benzil into benzilic acid is organic chemistry's most venerable molecular rearrangement. It was discovered by von Liebig in 1838,[1] can now be recognised as the prototype of a general class of rearrangements, and has been the subject of numerous synthetic and mechanistic investigations, including applications of tracer techniques with isotopes of each of the three elements present in benzil. In the present Review an attempt has been made to rationalise a mechanism for the rearrangement in the context of all the pertinent experimental evidence, to rationalise similarly certain closely related reactions, and to correlate these and several other reactions into a general class of base-induced molecular rearrangements.

A. The Benzilic Acid Rearrangement

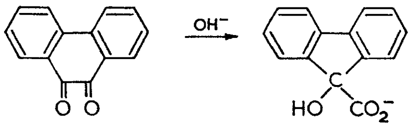
(a) Scope of the Reaction.—The benzilic acid rearrangement, the base-induced transformation of an α-diketone into the salt of an α-hydroxy-acid, can be effected in aromatic, in semiaromatic (*o*-quinones), in alicyclic, and in aliphatic, as well as in heterocyclic α-diketones. Examples of the rearrangement with these types of compounds are illustrated in the following equations.

Aromatic diketone:[1]



$$\mathrm{Ph{\cdot}\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}{\cdot}Ph} \xrightarrow{OH^-} \mathrm{Ph{\cdot}\underset{Ph}{\underset{|}{\overset{HO}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}{\cdot}O^-}$$

Semi-aromatic diketone:[2,3]



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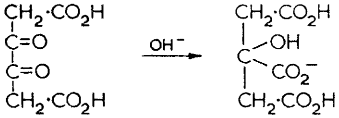
[1] J. von Liebig, *Annalen*, 1838, **25**, 27.

[2] A. von Baeyer and P. Friedländer, *Ber.*, 1877, **10**, 126; P. Friedländer, *Ber.*, 1877, **10**, 534.

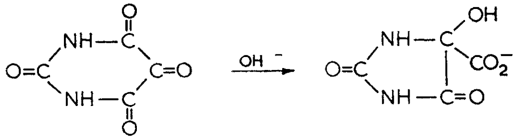
[3] R. Nietzki, *Ber.*, 1890, **23**, 3136.

Aliphatic diketone:[4,5]

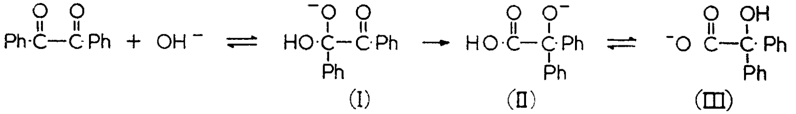


$$\mathrm{CH_2{\cdot}CO_2H{-}CO{-}CO{-}CH_2{\cdot}CO_2H} \xrightarrow{OH^-} \mathrm{(CH_2{\cdot}CO_2H)_2C(OH)CO_2^-}$$

Heterocyclic diketone:[6]



(b) Mechanism of the Reaction.—The currently accepted mechanism for the benzilic acid rearrangement was first proposed in its entirety by Ingold.[7] It consists of three distinct steps, the first of which is the reversible addition of a hydroxide ion to a carbonyl group of the α-diketone, giving rise to the negatively charged intermediate (I). This intermediate (I) undergoes a rate-determining intramolecular rearrangement, yielding a second intermediate (II), which is rapidly converted into the salt of the corresponding α-hydroxy-acid (III) by proton-transfers.



$$\mathrm{Ph{\cdot}CO{-}CO{\cdot}Ph} + OH^- \rightleftharpoons \underset{(I)}{\mathrm{HO{\cdot}C(O^-)(Ph){-}CO{\cdot}Ph}} \rightarrow \underset{(II)}{\mathrm{HO{\cdot}CO{-}C(O^-)(Ph){\cdot}Ph}} \rightleftharpoons \underset{(III)}{\mathrm{{}^-O{\cdot}CO{-}C(OH)(Ph){\cdot}Ph}} \quad \ldots\ldots (1)$$

That the initial step in the rearrangement is the addition of a hydroxide ion to one of the carbonyl groups of the α-diketone was apparently first suggested by Hoogerwerf and van Dorp.[8] Supporting this contention, Scheuing[9] has shown that, in pyridine solution, potassium hydroxide and benzil form an adduct containing only one molecule of base and that this adduct rearranges rapidly to potassium benzilate upon being heated. Schonberg and Keller[10] and Evans and Dehn[11] have similarly demonstrated that only one molecule of base is required to bring about the transformation of one molecule of benzil. The last authors have also shown that the presence of water is not a necessity for the rearrangement of benzil to benzilic acid. Roberts and Urey's finding[12] that benzil exchanges oxygen

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[4] H. von Pechmann, *Ber.*, 1884, **17**, 2534; R. Willstätter and A. Pfannenstiehl, *Annalen*, 1920, **422**, 5.

[5] O. Wallach, *Annalen*, 1916, **414**, 294; 1924, **437**, 148.

[6] H. Beltz, M. Heynand, and M. Bergius, *Annalen*,, 1916, **413**, 68.

[7] C. K. Ingold, *Ann. Reports*, 1928, **25**, 124.

[8] S. Hoogerwerf and W. A. van Dorp, *Rec. Trav. chim.*, 1890, **9**, 225.

[9] G. Scheuing, *Ber.*, 1923, **56**, 252.

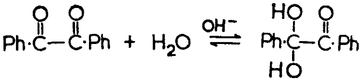
[10] A. Schonberg and K. T. Keller, *Ber.*, 1923, **56**, 1638.

[11] T. Evans and W. Dehn, *J. Amer. Chem. Soc.*, 1930, **52**, 252.

[12] I. Roberts and H. C. Urey, *J. Amer. Chem. Soc.*, 1938, **60**, 880.

in ^{18}O-enriched water in the presence of base much faster than it rearranges is the best evidence that (I) is an intermediate in the rearrangement and that its formation is rapid and reversible.

In recent years two groups of investigators,[13,14] in order to account for certain results in studies of relative migratory aptitudes in unsymmetrical benzils (see p. 226), have proposed that the initial step for the rearrangement is not the rapid and reversible addition of hydroxide ion. Clark, Hendley, and Neville[13] do not specify an alternative mechanism, but Ott and Smith[14] propose a concerted mechanism in which the hydroxide ion attacks benzil to form the benzilate anion directly in one step so that (I) is not an intermediate. Both groups account for the rapid ^{18}O-exchange between benzil and water by considering the base-catalysed hydration of benzil to be a reversible side-reaction (2). Neither group makes it clear why the ion (I) should not be an intermediate for both rearrangement (reactions 1) and hydration (reaction 2), and neither makes it clear why a concerted mechanism is indicated. Furthermore, as subsequently discussed



$$\mathrm{Ph{\cdot}\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}{\cdot}Ph + H_2O \overset{OH^-}{\rightleftharpoons} Ph{\cdot}\underset{HO}{\overset{HO}{C}}-\overset{O}{\overset{\|}{C}}{\cdot}Ph} \quad \ldots\ldots \ (2)$$

(see p. 224), with this concerted mechanism one would not expect the experimental results obtained in the reaction of benzil with deuteroxide ion in heavy water. In all, the evidence seems quite conclusive that the initial step in the mechanism of the benzilic acid rearrangement is the rapid and reversible addition of a hydroxide ion to a carbonyl group of the α-diketone.

There are essentially two reasonable modes for the transformation of intermediate (I) into a benzilate anion. The first of these, suggested by Ingold[7] and illustrated by reactions 1, is the rearrangement of intermediate (I) to a second anion (II) which is rapidly converted into the salt of the corresponding α-hydroxy-acid (III) by proton-transfers. The alternative mode initially proposed by Michael[15] and Robinson[16] and later restated by Clark, Hendley, and Neville,[13] by Doering, Taylor and, Schoenewaldt,[17] and by Hine,[18] is another concerted transformation, in which the rearrangement is accompanied rather than followed by migration of the oxygen-bound proton.

Both modes of transformation are consistent with findings by Westheimer:[19] the rearrangement is kinetically bimolecular, of first order in

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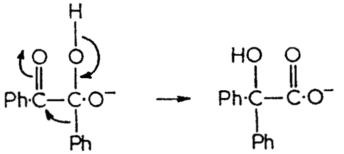
[13] M. T. Clark, E. G. Hendley, and O. K. Neville, *J. Amer. Chem. Soc.*, 1955, **77**, 3280.
[14] D. G. Ott and G. G. Smith, *J. Amer. Chem. Soc.*, 1955, **77**, 2325.
[15] A. Michael, *J. Amer. Chem. Soc.*, 1920, **42**, 787.
[16] R. Robinson, *Ann. Reports*, 1923, **20**, 118.
[17] W. von Doering, T. I. Taylor, and E. F. Schoenewaldt, *J. Amer. Chem. Soc.*, 1948, **70**, 455.
[18] J. Hine, "Physical Organic Chemistry", McGraw-Hill Book Co., Inc., New York, 1956, p. 315.
[19] F. H. Westheimer, *J. Amer. Chem. Soc.*, 1936, **58**, 2209; *J. Org. Chem.*, 1936, **1**, 1339.

benzil and in hydroxide ion; the reaction is not one of general base-catalysis (removal of a proton) since phenoxide or *o*-chlorophenoxide ions do not catalyse the reaction; the reaction does not involve a free radical since its rate is not affected by the addition of peroxides.



..... (3)

Up to 1956 it was generally acknowledged that the benzilic acid rearrangement could only be effected by hydroxide ion. This conviction was based on the failure of various workers to effect it with alkoxide ion. Treatment of benzil with potassium methoxide[9] alone gives an adduct, decomposition of which yields benzilic acid and benzil, but no methyl benzilate. Treatment of benzil with sodium ethoxide[20] alone also gives an adduct, which in water decomposes quantitatively into benzil, sodium hydroxide, and ethyl alcohol and in ethanol gives ethyl benzoate, benzaldehyde, sodium benzoate, and traces of benzilic acid and ethyl dibenzoin (2-benzoyltetrahydro-5-hydroxy-2,3-diphenylfuran, a condensation product of acetaldehyde, benzaldehyde, and benzoin[21]), but no ethyl benzilate. Treatment of benzil with potassium t-butoxide[22] in ether yields benzilic acid and no t-butyl benzilate.

The concerted mechanism (reaction 3) rationalises a specific hydroxide ion catalysis since the proton-transfer, which would accompany the rearrangement and would presumably lower the energy of the transition state, could only occur when hydroxide ion is the base. For this reason the concerted mechanism appeared preferable to Ingold's mechanism. However, it has recently been shown[23] that the reactions of benzil with sodium methoxide and with potassium t-butoxide do yield the corresponding benzilic esters and that the reaction with sodium ethoxide is complicated by oxidation–reduction by an equilibrium of the Meerwein–Pondorff–Verley–Oppenauer type. These observations indicate that the condition of specific hydroxide ion catalysis is invalid and need not be rationalised in the mechanism for rearrangement.

Hine and Haworth[24] have shown that the rearrangement of benzil to sodium benzilate occurs about 85% faster in 2 : 1 dioxan–D_2O at 50° than in 2 : 1 dioxan–H_2O at the same temperature. This interesting difference is ascribed to the greater basicity of deuteroxide ions in heavy water than of hydroxide ions in ordinary water. These results are in con-

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[20] A. Lachman, *J. Amer. Chem. Soc.*, 1923, **45**, 1509.
[21] J. B. Garner, *Amer. Chem. J.*, 1904, **32**, 600.
[22] G. Swan, *J.*, 1948, 1408.
[23] W. von E. Doering and R. S. Urban, *J. Amer. Chem. Soc.*, 1956, **78**, 5938.
[24] J. Hine and H. W. Haworth, *J. Amer. Chem. Soc.*, 1958, **80**, 2274.

trast to those expected from a normal isotope effect on a rate of hydrogen-migration and therefore suggest that the mechanism probably does not involve proton-transfer in its rate-determining step.

The mechanism of reactions (1) thus appears to be the most satisfactory of those proposed.

(c) **Interpretation of the Effects of Variables.**—If we let B represent benzil and C⁻ represent the ion (I) through which B rearranges to the product A⁻, then Ingold's mechanism can be represented as:

$$\mathrm{B} + \mathrm{OH}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C}^- \xrightarrow{k_2} \mathrm{A}^-$$

Since $k_1 \gg k_2 \ll k_{-1}$, and the ratio k_1/k_{-1} may be represented as an equilibrium constant K, the overall rate becomes $k_2K[\mathrm{B}][\mathrm{OH}^-]$. If k is an experimentally determined rate constant, $k = k_2K$, and steric, resonance, or inductive effects which influence either K or k_2 will be manifested in this apparent rate constant.

Since the magnitude of K will depend upon the ease with which the carbonyl group of the α-diketone is attacked by base, it could be expected that electron-releasing substituents at any positions, and bulky substituents at the 2-,2′-,6-, or 6′-position, on the benzil molecule would hinder this nucleophilic attack and thus decrease K to slow down the overall reaction. On the other hand, the actual rearrangement step entails the migration of a nucleophile towards an electrophilic centre, and electron-releasing substituents present on the migrating portion of the molecule should facilitate the overall reaction by increasing k_2. In addition, any group which would cause the migration terminus to be more electrophilic should also facilitate reaction by increasing k_2. Prediction of the effect of substituents on the overall reaction rate would seem difficult.

Fortunately, however, the transition state for this reaction is apparently not far along the reaction co-ordinate leading from ion (I) to rearrangement. Hammond and Roberts[25] and then other workers[26] have pointed out that the energy of this transition state must be similar to, and predictable from, that of structure (I). Hence, it can be expected that a substituted benzil, with electron-releasing groups in the *meta*- or *para*-position, will exhibit a diminished rate of rearrangement when compared with benzil itself. Similarly, a substituted benzil, with electron-attracting groups in the *meta*- or *para*-position, will show a greater rate of rearrangement than benzil itself.

It has been shown that rearrangement of methyl, amino-,[27] or methoxy-substituted[28] benzils is slower, while that of chloro-substituted benzils[29] is

[25] Quoted by G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

[26] J. F. Eastham, R. G. Nations, and C. J. Collins, *J. Org. Chem.*, 1958, **23**, 1764.

[27] M. L. Black, Ph.D. Dissertation, University of Tennessee, Knoxville, Tennessee, 1949.

[28] J. H. Blanksma and W. H. Zaayer, *Rec. Trav. chim.*, 1938, **67**, 883.

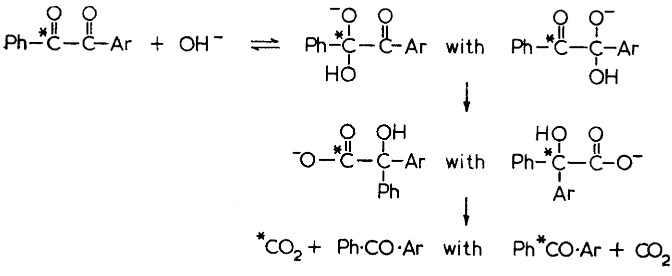
[29] E. Pfeil, G. Geissler, W. Jacqueman, and F. Lomker, *Ber.*, 1956, **89**, 1210.

faster, than that of benzil itself. While both 3,3′- and 4,4′-dichlorobenzil rearrange faster than benzil, the *meta*- shows a greater rate of rearrangement than the *para*-substituted compound. Similarly, 3,3′- and 4,4′-dimethylbenzil both rearrange more slowly than benzil, and in this case the *para*-substituted compound exhibits the slower rate of rearrangement. All of these experimental results are consistent with the generalisation that the more effective the electron-attraction by substituents in the benzil molecule, the greater will be its rate of rearrangement.

It could be expected that groups substituted in the *ortho*-positions of the benzil molecule would, by steric interaction, hinder the formation of the intermediate ion (I) and therefore decrease the rate of the overall reaction. The phenomenon manifests itself in the greater rate of rearrangement of 4,4′- than of 2,2′-dichlorobenzil, and of 4,4′- than of 2,2′-dimethylbenzil.

In the rearrangement of an unsymmetrical benzil the same product will be obtained whichever group migrates. For this reason the group which migrates cannot be ascertained from the products, as it can in certain pinacol rearrangements. However, this can be done by use of an unsymmetrical benzil labelled with ^{14}C. In an unsymmetrical benzil Ph·CO·CO·Ar, if the carbon atom adjacent to phenyl (Ph) is labelled and the rearrangement product is oxidised to a benzophenone, then the ratio of the radioactivity of the benzophenone to the radioactivity of the starting benzil will be the ratio of the migration of the aryl group Ar to the total amount of migration. These reactions are illustrated in Chart 1 and results from rearrangement of several substituted benzils are summarised in Table 1.

CHART 1.



Since the mechanism proposed by Ingold for the benzilic acid rearrangement involves the migration of an aryl group with its pair of electrons to an electrophilic carbon atom in the rate-determining step, aryl groups carrying electron-donor substituents might be expected to migrate to a greater extent than phenyl. The experimental results (Table 1), after elimination of the *ortho*-substituted benzils for steric reasons, indicate that precisely the reverse is occurring, *i.e.*, phenyl groups carrying electron-attracting substituents migrate to the greater extent. Similar results have been reported[14] for the migration of the substituted rings in the similar

TABLE 1.

Percentage migrations of Ar *groups in rearrangements of* Ph·CO·CO·Ar.

Ar	Migrn. (%) of Ar
p-Tolyl[13]	38·8
o-Tolyl[26]	2·7
p-Chlorophenyl[13]	67·2
o-Chlorophenyl[14]	31·2
m-Chlorophenyl[13]	81·2
p-Methoxyphenyl[30]	31·8
Benzyl[31]	100
H[17]	100
Benzoyl[30]	100

rearrangements of 2-, 3- and 7-chloro[9-^{14}C]phenanthraquinone. In addition, a plot of the logarithm of the migration ratios (corrected for an isotope effect) of the *meta*- and *para*-substituted benzils listed in Table 1 against the respective Hammett substituent constant, σ,[32] yields a straight line whose slope (reaction constant, ρ) is approximately 1·43.

If the data in Table 1 are not consistent with the proposed mechanism, the mechanism must be discarded and a different one proposed, as Clark, Hendley and Neville,[13] and Ott and Smith[14] have done. These authors contend that, in the rearrangement of an unsymmetrical benzil containing a group with a high intrinsic migratory aptitude (*e.g.*, 4-methoxybenzil), if the migration step is rate-determining, the rate of rearrangement of this substituted benzil should be greater than that for benzil itself. They then point out that anisil, 4,4′-diaminobenzil, and methyl-substituted benzils all rearrange more slowly than benzil. Another contention is that since the Hammett relationship correlates the migratory preferences in the rearrangement of substituted benzils and of chlorophenanthraquinones, hydroxide attack proably takes place directly in the rate-determining step. The oxygen-exchange between benzil and water must then be accounted for as discussed on p. 223.

It has already been pointed out that the overall rate of the benzilic acid rearrangement is a function of both the equilibrium constant for the formation of the intermediate ion (I) and the specific rate constant for the rearrangement step. Thus, a more rapid rearrangement does not necessitate a faster overall reaction. The Hammond postulate[25, 26] [that the controlling influence on the overall reaction rate and on the direction of rearrangement of unsymmetrical benzils will be that predicted from the relative stabilities of the intermediate ions (I)] justifies the Hammett correlation and makes unnecessary the proposal that attack by hydroxide ion occurs during the rate-determining step. In addition, the mechanism proposed by Smith and Ott and the transition state proposed by Clark,

[30] J. D. Roberts, D. R. Smith, and C. C. Lee, *J. Amer. Chem. Soc.*, 1951, **73**, 619.

[31] C. J. Collins and O. K. Neville, *J. Amer. Chem. Soc.*, 1951, **73**, 2471.

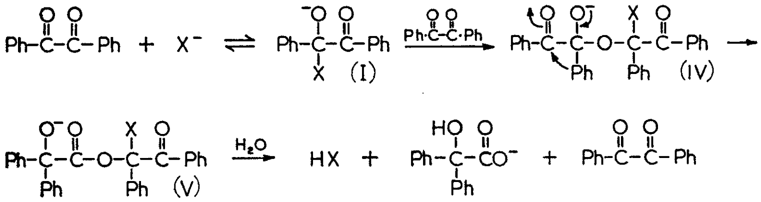
[32] L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co., Inc., New York, 1940, p. 188.

Hendley and Neville are not consistent with the evidence of Hine and Haworth[24] that there is no proton-transfer in the rate-determining step.

In short, little justification can be found for the objections to Ingold's mechanistic hypothesis, which does seem consistent with all experimental data, to date, on the benzilic acid rearrangement induced by an alkali-metal hydroxide. However, experimental data with certain other metal hydroxides reveal that a somewhat different course of rearrangement may sometimes be followed; with alkaline-earth hydroxides the reaction is accelerated and is not clearly of the second order, and with thallium hydroxide the reaction is of the third order.[29]

The accepted mechanism (reactions 1) cannot be utilised to explain the transformation of benzil to benzilic acid when the catalyst is not hydroxide ion. Some examples of this transformation utilising non-oxygen containing bases are the reactions of benzil with sodium amide[33] or acetylide[34] to yield benzilic acid, and of anisil with sodium amide[35] to yield anisilic acid. Applying the mechanism of the benzilic acid rearrangement to the amide-catalysed transformation, one would expect the product to be benzilamide. The mild hydrolytic working-up employed in these transformations will not bring about hydrolysis of the amide to the acid; nevertheless this is the product obtained. In the transformation of benzil into benzilic acid induced by amide ion in a non-hydroxylic solvent, the product's acquisition of an oxygen atom must be accounted for. Since in this system the only place from which oxygen can be obtained is another benzil molecule, the reaction sequence in Chart 2 is proposed. The base X⁻ (amide ion) attacks a benzil molecule to form an intermediate ion which, instead of rearranging as does (I) in the usual benzilic acid or ester rearrangements, attacks another benzil molecule. The second intermediate (IV), thus formed, rearranges to (V), which is subsequently hydrolysed upon addition of water. An indication that a mechanism such as this might be operative is the consistent recovery of starting material along with product in these transformations.

CHART 2.



[33] I. Kassivazi, *Bull. Chem. Soc. Japan*, 1926, **1**, 66.

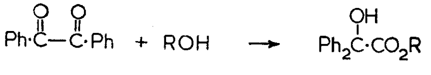
[34] J. C. Craig, M. Moyle, P. Rowe-Smith, and P. C. Wailes, *Austral. J. Chem.*, 1956, **9**, 391.

[35] S. Selman, Ph.D. Dissertation, University of Tennessee, Knoxville, Tennessee, 1959, p. 41.

The reaction of benzil with certain alkoxide ions in alcohols to produce benzilate esters is discussed in the next section. However, the reaction of benzil with methoxide[9] or t-butoxide ion[22] in ether yields, upon hydrolysis, benzilic acid. It is improbable that the acid arises from saponification of the ester under the hydrolytic conditions employed. It is more likely that acid arises by the route proposed in Chart 2 where, however, now X = MeO or Bu^tO.

B. The Benzilic Ester Rearrangement

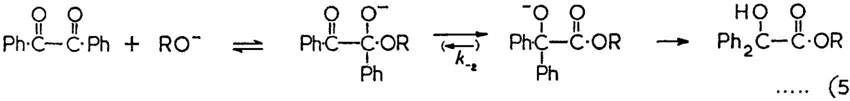
The benzilic ester rearrangement, discovered by Doering and Urban,[23] is the reaction of an aromatic α-diketone with alcohol in the presence of alkoxide ion to yield corresponding benzilic acid ester (reaction 4). The



$$\mathrm{Ph{\cdot}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{\cdot}Ph + ROH \longrightarrow Ph_2\overset{\overset{OH}{|}}{C}{\cdot}CO_2R} \quad \ldots\ldots (4)$$

choice of alkoxide ion is limited to those which are not readily oxidised, since oxidisable alkoxide ions such as ethoxide or isopropoxide readily reduce benzil to benzoin. The reaction also fails with phenoxides and substituted phenoxides,[19] presumably because these bases are too weak for the initial attack on the α-diketone.

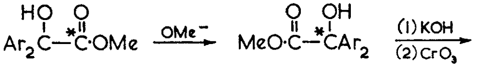
Doering and Urban[23] found the kinetics of the conversion of benzil into t-butyl benzilate to be of second order overall—of first order in benzil and of first order in butoxide. They also found that the reaction was appreciably slower in t-butyl alcohol than in benzene. The mechanism (5) proposed to fit these results, namely, rapid and reversible addition of alkoxide to



$$\mathrm{Ph{\cdot}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{\cdot}Ph + RO^- \rightleftharpoons Ph\overset{\overset{O}{\|}}{C}{-}\underset{\underset{Ph}{|}}{\overset{\overset{O^-}{|}}{C}}{\cdot}OR \underset{k_{-2}}{\overset{(\leftarrow)}{\rightleftharpoons}} Ph\underset{\underset{Ph}{|}}{\overset{\overset{^-O}{|}}{C}}{-}\overset{\overset{O}{\|}}{C}{\cdot}OR \longrightarrow Ph_2\overset{\overset{HO}{|}}{C}{-}\overset{\overset{O}{\|}}{C}{\cdot}OR} \quad \ldots\ldots (5)$$

benzil followed by a rate-determining migration, is entirely analogous to the mechanism of the benzilic acid rearrangement.

Selman[35] has investigated the reversibility of the migration step [k_{-2} in (5)] of the benzilic ester rearrangement. He synthesised methyl [*carboxy*-^{14}C]anisilate and subjected it to the reaction conditions of the rearrangement, reisolated the ester, degraded it to 4,4′-dimethoxybenzophenone, and assayed this ketone for radioactivity. If the rate-determining step were reversible, it can be seen (6) that activity would appear in the dimethoxy-



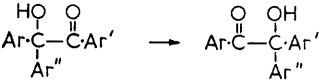
$$\mathrm{Ar_2\overset{\overset{HO}{|}}{C}{-}\overset{\overset{O}{\|}}{\overset{*}{C}}{\cdot}OMe \xrightarrow{OMe^-} MeO{\cdot}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{OH}{|}}{\overset{*}{C}}Ar_2 \xrightarrow[(2)\,CrO_3]{(1)\,KOH} Ar_2\overset{*}{C}O} \quad \ldots\ldots (6)$$

benzophenone. The results showed that the reverse rearrangement must be negligibly slow, if existent at all, at 97°. At a higher temperature (200°), the results were similar but not unequivocal owing to the possibility of certain competing reactions.

Apparently the resonance energy in the alkoxycarbonyl group causes the difference in energy between the ester and the transition state to be much greater than the energy difference between the benzil and the transition state. The difference in these activation energies is even greater in the benzilic acid rearrangement where the product contains the highly resonance-stabilised carboxylate anion. Therefore, because of the high activation energy for the reverse reaction, neither of these two rearrangements is reversible under the usual operating conditions. There are, however, a few transformations, effected under unusual conditions, which have been interpreted as reverse benzilic acid rearrangements.[36]

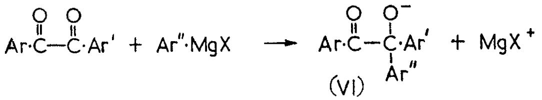
C. Tertiary Ketol Rearrangement

The tertiary ketol rearrangement (reaction 7) occurs upon treatment of



$$\mathrm{Ar{\cdot}\underset{Ar''}{\overset{HO}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ar'} \longrightarrow \mathrm{Ar{\cdot}\overset{O}{\overset{\|}{C}}{-}\underset{Ar''}{\overset{OH}{C}}{\cdot}Ar'} \quad \cdots\cdots (7)$$

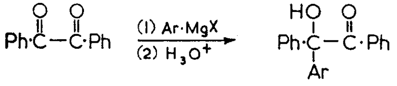
a tertiary alcohol containing an α-oxo-group with base. Presumably the rearranging species is the conjugate base of the alcohol. Since this type of base (VI) can also be produced when one equivalent of a Grignard reagent is added to benzil or a substituted benzil (reaction 8), rearrangement products can be obtained either by the addition of Grignard reagents to



$$\mathrm{Ar{\cdot}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ar'} + \mathrm{Ar''{\cdot}MgX} \longrightarrow \underset{\text{(VI)}}{\mathrm{Ar{\cdot}\overset{O}{\overset{\|}{C}}{-}\underset{Ar''}{\overset{O^-}{C}}{\cdot}Ar'}} + \mathrm{MgX^+} \quad \cdots\cdots (8)$$

benzils or by the treatment of such a keto-alcohol with base. Some confusion concerning these two possibilities has existed and a brief chronological review of the pertinent findings seems desirable.

In 1934, Roger and McGregor[37] added *o*-tolyl-, *m*-tolyl-, and *p*-tolylmagnesium bromide to benzil in an attempt to synthesise the corresponding α-tolylbenzoins (reaction 9). From α-*o*- and α-*m*-tolylbenzoin, these



$$\mathrm{Ph{\cdot}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ph} \xrightarrow[\text{(2) } H_3O^+]{\text{(1) Ar·MgX}} \mathrm{Ph{\cdot}\underset{Ar}{\overset{HO}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ph} \quad \cdots\cdots (9)$$

Ar = *o*-, *m*-, or *p*-tolyl

workers obtained solid compounds which they cleaved with alcoholic potassium hydroxide. The *meta*-isomer gave benzoic acid and 4-methyl-

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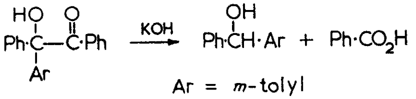
[36] O Wallach, *Annalen*, 1898, **300**, 200; 1902, **315**, 275; W. Huckel, "Theoretical Principles of Organic Chemistry", Vol. I, Elsevier Publ. Co., Amsterdam, 1955, p. 462.

[37] R. Roger and A. McGregor, *J.*, 1934, 442.

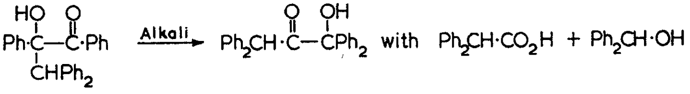
α-phenylbenzyl alcohol, the expected products (reaction 10). However, the *ortho*-isomer gave *o*-toluic acid and diphenylmethanol, the products of a rearrangement. Roger and McGregor suggested that the rearrangement could have occurred during the Grignard reaction or during the alkaline cleavage.



$$\mathrm{Ph{\cdot}}\underset{\mathrm{Ar}}{\overset{\mathrm{HO}}{\mathrm{C}}}\mathrm{-}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{\cdot}Ph} \xrightarrow{\mathrm{KOH}} \mathrm{Ph{\cdot}}\overset{\mathrm{OH}}{\mathrm{CH}}\mathrm{{\cdot}Ar + Ph{\cdot}CO_2H} \qquad \text{.....}\ (10)$$

$\mathrm{Ar} = m\text{-tolyl}$

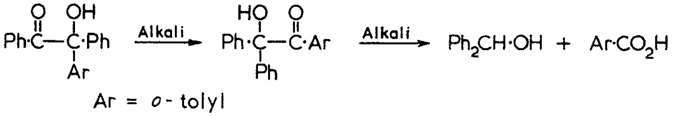
In 1951 Curtin and Leskowitz[38] demonstrated that the treatment of α-diphenylmethylbenzoin (VII) with alkali gave α-hydroxybisdiphenylmethyl ketone, diphenylacetic acid, and diphenylmethanol. Since the



$$\mathrm{Ph{\cdot}}\underset{\mathrm{CHPh_2}}{\overset{\mathrm{HO}}{\mathrm{C}}}\mathrm{-}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{\cdot}Ph} \xrightarrow{\mathrm{Alkali}} \mathrm{Ph_2CH{\cdot}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{-}\overset{\mathrm{OH}}{\mathrm{C}}\mathrm{Ph_2}\ \text{with}\ \mathrm{Ph_2CH{\cdot}CO_2H + Ph_2CH{\cdot}OH} \qquad \text{.....}\ (11)$$

(VII)

ketone yields diphenylmethanol and diphenylacetic acid when treated with base, it was reasoned that the rearrangement and cleavage of the benzoin (VII) was occurring consecutively in the same medium. Curtin and Leskowitz[38] also suggested that this same phenomenon (12) occurred when α-*o*-tolylbenzoin, supposedly obtained by Roger and McGregor[37] from the reaction of benzil with *o*-tolylmagnesium bromide, was treated with alkali.



$$\mathrm{Ph{\cdot}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{-}\underset{\mathrm{Ar}}{\overset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{\cdot}Ph} \xrightarrow{\mathrm{Alkali}} \mathrm{Ph{\cdot}}\underset{\mathrm{Ph}}{\overset{\mathrm{HO}}{\mathrm{C}}}\mathrm{-}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{\cdot}Ar} \xrightarrow{\mathrm{Alkali}} \mathrm{Ph_2CH{\cdot}OH + Ar{\cdot}CO_2H} \qquad \text{.....}(12)$$

$\mathrm{Ar} = o\text{-tolyl}$

In 1952 Sharp and Miller[39] investigated the alkaline cleavage of α-arylbenzoins and assumed that the compounds obtained from the addition of tolylmagnesium bromides to benzil were produced without rearrangement and were α-tolylbenzoins. The compounds, when treated with alkali, partially or totally rearranged before cleavage, according to the explanation of Sharp and Miller for the presence of diphenylmethanol and toluic acid as cleavage products.

In a thorough re-investigation of the alkaline cleavage of α-arylbenzoins,[40] Eastham, Huffaker, Raaen, and Collins showed that authentic α-*o*-tolylbenzoin upon treatment with alkali *is* converted into 2-methyl-α-phenylbenzoin which, in turn, is cleaved to diphenylmethanol and

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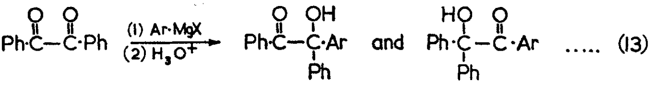
[38] D. Y. Curtin and S. Leskowitz, *J. Amer. Chem. Soc.*, 1951, **73**, 2633.

[39] D. B. Sharp and E. L. Miller, *J. Amer. Chem. Soc.*, 1952, **74**, 5643.

[40] J. F. Eastham, J. E. Huffaker, V. F. Raaen, and C. J. Collins, *J. Amer. Chem. Soc.*, 1956, **78**, 4323.

o-toluic acid. However, it also was found that the compound previously thought to be α-*o*-tolylbenzoin obtained from the reaction of benzil and *o*-tolylmagnesium bromide was in reality 2-methyl-α-phenylbenzoin. It was shown that the addition of the tolylmagnesium bromides to benzil can yield both the normal and the rearranged α-arylbenzoins (reaction 13).

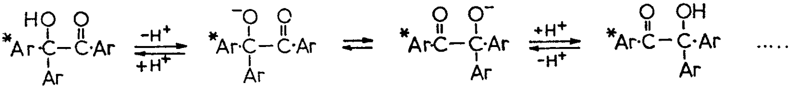


$$\mathrm{Ph{\cdot}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ph \xrightarrow[(2)\,H_3O^+]{(1)\,Ar{\cdot}MgX} Ph{\cdot}\overset{O}{\overset{\|}{C}}{-}\underset{Ph}{\overset{OH}{C}}{\cdot}Ar \quad and \quad Ph{\cdot}\underset{Ph}{\overset{HO}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ar} \quad \ldots\ldots \quad (13)$$

(VIII) (IX)

Numerous examples of rearrangement during addition of organometallic compounds to benzils are now known. Huffaker[41] found that addition of *o*-tolylmagnesium and of mesitylmagnesium bromide to anisil proceeds with rearrangement. Doering and Urban[23] added mesitylmagnesium bromide to benzil and obtained 2,4,6-trimethyl-α-phenylbenzoin, the rearrangement product. Selman[35] has shown that rearrangement also occurs upon addition of organolithium reagents to benzil: the reaction of *o*-tolyllithium and benzil yields α-methyl-2-phenylbenzoin. It appears that in general the rearrangement is likely to occur when the entering group (Ar in reaction 13) is bulky and relief of steric strains is attained by formation of product (IX) rather than of (VIII).

In addition to the tertiary ketol rearrangements observed when organometallic reagents are added to benzils, such rearrangements are known to occur when tertiary alcohols containing α-oxo-groups are subjected to alkaline conditions. Two rearrangements of this type have already been mentioned, the rearrangements of α-diphenylmethyl- and of α-*o*-tolylbenzoin. An interesting example of this type is the rearrangement of α-*p*-methoxyphenylanisoin labelled with ^{14}C in one of the methoxy-groups.[40] This reaction (14) is analogous to the racemisation of an optically



$$\mathrm{{}^{*}Ar{\cdot}\underset{Ar}{\overset{HO}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ar \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} {}^{*}Ar{\cdot}\underset{Ar}{\overset{{}^-O}{C}}{-}\overset{O}{\overset{\|}{C}}{\cdot}Ar \rightleftharpoons {}^{*}Ar{\cdot}\overset{O}{\overset{\|}{C}}{-}\underset{Ar}{\overset{O^-}{C}}{\cdot}Ar \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} {}^{*}Ar{\cdot}\overset{O}{\overset{\|}{C}}{-}\underset{Ar}{\overset{OH}{C}}{\cdot}Ar} \quad \ldots\ldots \quad (14)$$

active isomer in that there is no free energy difference between the reactants and the products.

Not all the factors which control the tertiary ketol rearrangement have been elucidated, and consequently some of the rearrangements appear fortuitous. In one case, that of α-methylbenzoin, three different groups of workers have treated the ketol with base, with widely varying results. Sharp and Miller[39] obtained diphenylmethanol in almost 50% yield upon treatment of α-methylbenzoin with alkali. Doering and Urban[23] performed the same reaction using potassium t-butoxide as the base and obtained only benzoic acid from the acid fraction and no diphenylmethanol from

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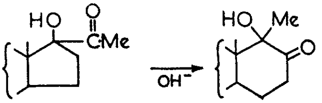
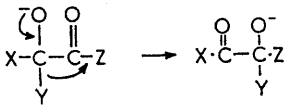
[41] J. E. Huffaker, M. S. Thesis, University of Tennessee, Knoxville, Tennessee, 1956.

the neutral fraction, indicating absence of rearrangement. Roger and McGregor[37] reported that traces of diphenylmethanol were obtained. The inability to reproduce quantitatively the extent of rearrangement in tertiary ketol rearrangements has also been noted[40] in the addition of Grignard reagents to benzils.

The tertiary ketol rearrangement is not restricted to benzoins; it has also been observed with acyloins. Rearrangement of the latter has been utilised almost exclusively in the steroid field and is illustrated below, where only the D-ring of a steroid is shown.[42]



The mechanism proposed[39,40,43] for the tertiary ketol rearrangement involves essentially the rate-determining step (reaction 15) of the benzilic acid and ester rearrangements. When structure (X) is formed by addition



..... (15)

(X)

of an organometallic reagent to a benzil or by removal of a proton from the ketol (X = Z = Y = Aryl or Alkyl), then reaction (15) represents the tertiary ketol rearrangement. If structure (X) is formed by reaction of benzil and hydroxide ion (Y = Z = Ar, X = OH), the equation represents the benzilic acid rearrangement. When Y = Z = Ar and X = OR, then it is the benzilic ester rearrangement.

D. Related Rearrangements

The key step in several additional rearrangements can be represented by reaction (15). Thus, the rearrangement of phenylglyoxal to mandelic acid has been shown by isotopic tracer techniques to proceed[17,44] by the intramolecular shift of a hydrogen atom. The key step of this rearrangement is then represented by reaction (15) when X = OH, Y = H, and Z = Ar.

Rearrangement of 4-methoxybenzilaldehyde yields 4-methoxybenzoin.[45] Since it is unlikely that the phenyl group could migrate in preference to the *p*-methoxyphenyl group, it is probable that this reaction occurs in two stages, as illustrated below (16). The first stage is another example of reaction (15), in this case with X = Y = Ar and Z = H. The second stage

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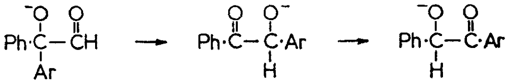
[42] C. W. Shoppee and E. Shoppee in Rodd's "Chemistry of Carbon Compounds", Vol. II-B, Elsevier Publ. Co., London, 1953, p. 926.

[43] R. B. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3486.

[44] O. K. Neville, *J. Amer. Chem. Soc.*, 1948, **70**, 3499.

[45] D. Y. Curtin and A. Bradley, *J. Amer. Chem. Soc.*, 1954, **76**, 5777.

is probably not intramolecular, but rather a series of base-catalysed, hydrogen exchange with solvent.



..... (16)

Rearrangements occur with several systems involving initially three or more adjacent carbonyl groups. In these cases it has been observed that one of the carbonyl groups migrates. For example, treatment of ethyl $\alpha\beta$-dioxobutyrate with base yields methyltartronic acid.[46] On the basis of isotopic tracer experiments, this is interpreted as proceeding through the intermediate (XI), which corresponds to structure (X) with X = OH, Y = CO_2Et, and Z = R (see p. 235).

TABLE 2. *α-Oxo-alcohol rearrangements.*

Reactant	Product[a]	Substituents in intermediate (X)[b]			Ref.
		X	Y	Z	
Benzil	Benzilic acid	OH	Ar	Ar	1
Benzil	Me benzilate	OMe	Ar	Ar	23
Cyclohexane-1,2-dione	1-Hydroxycyclopentanecarboxylic acid	OH	R	R	5
Benzyl phenyl diketone	α-Hydroxy-αβ-diphenylpropionic acid	OH	R	Ar	31
Glyoxal	Glycollic acid	OH	H	H	49
Phenylglyoxal	Mandelic acid	OH	H	Ar	17, 44
2-Phenylindoxyl	3-Phenyldioxindole	Ar·NH	Ar	Ar	28, 48
α-*o*-Tolylbenzoin	2-Methyl-2-phenylbenzoin	Ar	Ar	Ar	37, 39, 42
α-Methylbenzoin	α-Hydroxy-αα-diphenylacetone	R	Ar	Ar	37, 39
4-Methoxybenzilaldehyde	4-Methoxybenzoin	Ar	Ar	H	45
17α-Hydroxyprogesterone	17a-Hydroxy-D-homo-17-ketone	R	R	R	42
α-Fenchocarboxylic acid	Carbofenchonone	R	R	OH	36
Diphenyl triketone	α-Benzoylmandelic acid	OH	Ar·CO	Ar	30, 47
Et αβ-dioxobutyrate	Methyltartronic acid	OH	RO·CO	R	46
Alloxan	Alloxanic acid	OH	R·NH·CO	R·CO·NH	6
Rhodizonic acid	Croconic acid	OH	R·CO	R·CO	3

[a] In some cases the products have been recognised only as intermediates which undergo further reaction under conditions causing the rearrangement.

[b] R represents either an alkyl group or an alicyclic residue. Ar represents either an aryl group or an aromatic residue.

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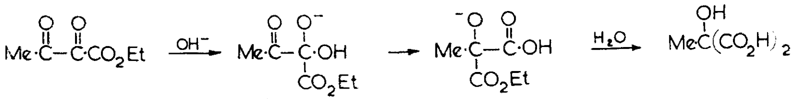
[46] W. Denis, *Amer Chem. J.*, 1907, **38**, 587; H. W. Davis, E. Grovenstein, and O. K. Neville, *J. Amer. Chem. Soc.*, 1953, **75**, 3304.

[47] de Neufoille and von Pechmann, *Ber.*, 1890, **23**, 3375.

[48] L. Kalb and J. Bayer, *Ber.*, 1912, **45**, 2150.

[49] H. Fredenhagen and K. F. Bonhoeffer, *Z. phys. Chem.*, 1938, *A*, **181**, 379.

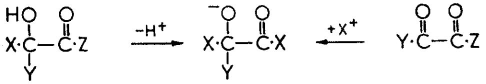
Table 2 contains examples of sixteen base-induced molecular rearrangements which can be correlated with reaction (15). The distinction between



$$\mathrm{Me{\cdot}\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}{\cdot}CO_2Et} \xrightarrow{OH^-} \mathrm{Me{\cdot}\overset{O}{\overset{\|}{C}}-\underset{CO_2Et}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}{\cdot}OH} \longrightarrow \mathrm{Me{\cdot}\underset{CO_2Et}{\underset{|}{\overset{^-O}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}{\cdot}OH} \xrightarrow{H_2O} \mathrm{Me{\cdot}\overset{OH}{\overset{|}{C}}(CO_2H)_2}$$

(XI)

the various rearranging systems is in the nature of the X, Y, and Z groups involved in their key intermediate (X), and in how that intermediate is attained. In some of the examples the intermediacy of structure (X) is only presumed, but in every case its formation is logical, is consistent with all of the available experimental data, and can be achieved (17) by the loss of a proton from an alcohol group or by attack of a base on a carbonyl group.



$$\mathrm{X{\cdot}\underset{Y}{\underset{|}{\overset{HO}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}{\cdot}Z} \xrightarrow{-H^+} \mathrm{X{\cdot}\underset{Y}{\underset{|}{\overset{^-O}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}{\cdot}X} \xleftarrow{+X^+} \mathrm{Y{\cdot}\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}{\cdot}Z}$$

..... (17)

Reactions (17) followed by (15) generalise a class of molecular rearrangements of broad scope for which a suitable generic name would be useful. Since numerous other specific examples are known for the sixteen different systems illustrated in Table 2, the scope of this class of base-induced reactions is comparable to some of the better known classes of acid-induced molecular rearrangements, for which generic names have been accepted ("Wagner–Meerwein," "pinacol," etc.) and for which there are extensive correlative studies and reviews. It is suggested that reactions involving reaction (15) be called "α-oxo-alcohol rearrangements".

Perhaps the most interesting feature of the rearrangement of structure (X) is the variety of groups, Y, which have been observed to migrate; these include hydrogen, alkyl, and aryl, together with carbonyl in four types of combination. The groups, X and Z, from which and toward which Y migrates may also be quite varied, as shown in Table 2. In certain cases adverse energy or steric requirements, or competing reactions, may hinder observation, but in general one should anticipate rearrangement with any ion of structure (X) or in any reaction which may give rise to that ion.