Some Reactions of Unsaturated Fatty Acids and Their Derivatives in Molten Alkalies

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The labeling pattern of saturated fatty acids formed by treatment of unsaturated fatty acids with molten potassium deuteroxide indicates that reactions of the Varrentrapp type proceed by an initial sequence of discrete, reversible, prototropic rearrangements. The principal reactions during the alkali fusion of aleuritic acid have been identified. Alkali fusion of epoxy derivatives of unsaturated fatty acids has been shown to involve initial opening of the epoxide ring in at least three ways: hydrolysis, reduction or rearrangement, and β-elimination. Reactions of the latter type predominated in the alkali fusion of ω-alkoxy fatty acids.

Among the most interesting reactions of fatty acids and their derivatives are the intriguing transformations which take place under appropriate conditions in alkalies. Studies on these processes not only serve to suggest new ways of utilizing the abundant supplies of some naturally occurring fatty acids, such as oleic and linoleic acid, but also provide a reliable framework of information which permits a rational interpretation of the behavior of organic compounds in general under strongly alkaline conditions. This article reports some recent progress in these pilot studies on fatty acids and their oxygenated derivatives.

Alkali Fusions in Deuterated Media

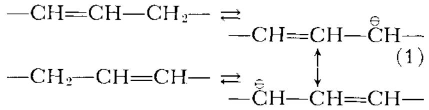
Of the reactions of fatty acids in molten alkalies, perhaps the best known is that of ethylenic acids (*1*). This gives saturated acids with two carbon atoms fewer than the starting material, acetic acid and hydrogen, in yields which frequently exceed 90%. Thus oleic acid (I), as first reported by Varrentrapp (*9*) in 1840, gives palmitic acid (II), and undec-10-enoic acid (III) gives nonanoic acid (IV).

$$\underset{\text{I}}{CH_3.(CH_2)_7.CH{=}CH.(CH_2)_7.CO_2H} \rightarrow \underset{\text{II}}{CH_3.(CH_2)_{14}.CO_2H}$$

$$\underset{\text{III}}{CH_2{=}CH.(CH_2)_8.CO_2H} \rightarrow \underset{\text{IV}}{CH_3.(CH_2)_7.CO_2H}$$

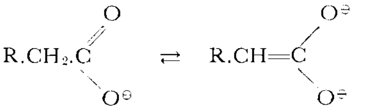
As this reaction (usually referred to as the Varrentrapp reaction), and minor variations of it, are frequently encountered during drastic alkaline degradations, it seems desirable to investigate fully the nature of the transformations involved.

The most reasonable interpretation is that the double bond migrates up and down the fatty acid chain by a sequence of prototropic rearrangements (Equation 1) and that the $\alpha\beta$-enoate, as and when formed, undergoes a fission of the retro-aldol or retro-Claisen type (*2*). Despite the evidence in support of this mechanism, there has not hitherto been any conclusive proof that a stepwise migration of the double bond constitutes an essential part of the main reaction, and that the small amounts of positional isomers of the starting materials which have been detected under some conditions are not the result of side reactions. To investigate this and related points, a number of alkali fusions were carried out in potassium deuteroxide (about 95% and 5% KOH, referred to elsewhere in this paper as KOD).



$$\begin{array}{l} -CH{=}CH{-}CH_2{-} \rightleftarrows -CH{=}CH{-}\overset{\ominus}{C}H{-} \\ \qquad\qquad\qquad\qquad\qquad\qquad \updownarrow \qquad\qquad (1) \\ -CH_2{-}CH{=}CH{-} \rightleftarrows -\overset{\ominus}{C}H{-}CH{=}CH{-} \end{array}$$

As a necessary preliminary to the main studies, both nonanoic and palmitic acid—i.e., the saturated acids produced by alkali fusion of undec-10-enoic and oleic acids—were fused with KOD (using 20*x* moles of alkali, where *x* is the number of hydrogen atoms available for exchange on the fatty acid chain). The methyl esters of the products were isolated by preparative gas-liquid chromatography and examined by nuclear magnetic resonance spectroscopy (on a Varian A60 instrument, using neat liquids or solutions in carbon tetrachloride, and tetramethylsilane as an internal standard) and mass spectrometry (on A.E.I. MS9 mass spectrometers). In the KOD fusion products, both α-hydrogen atoms had been replaced by deuterium in 50 to 60% of the molecules, and one of the α-hydrogens by deuterium in another 20 to 30% of the molecules. This is consistent with the formation, Equation 2, from carboxylates of an enolate of the type which has been postulated previously to explain, for example, the cyclization of 6-keto-acids (*5*). Moreover, the results showed that about 15 to 20% of the α-deuterated molecules were also deuterated at another (and occasionally two other) positions. This additional deuteration appeared to have occurred randomly along the chain, with perhaps some preference for the C-5 and neighboring positions. Although insufficient to influence the general conclusions drawn below for the alkali fusion of unsaturated fatty acids, it is now clear that even saturated alkyl chains are capable of attack by alkali. It is possible that a number of the side reactions encountered during alkali fusions may originate in this way.



(2)

The absence of any preferential deuteration at the β-position of a fatty acid chain was confirmed by KOD fusion of 4-phenylbutyric acid, $PhCH_2.CH_2.CH_2.CO_2H$ (V). Since the three methylene groups give rise to different nuclear magnetic resonance bands, it was possible to follow the fate of the three groups separately. Under conditions which led to extensive deuteration of the α- and benzylic methylenes, the β-position was not attacked. The results also provided a clear demonstration of the susceptibility of the aromatic ring to attack by alkali hydroxide. It was of interest that deuteration of the aromatic ring in both V and benzoic acid seemed to occur to a comparable extent at all positions, but a discussion of these substitutions is beyond the scope of this paper.

Attention was next turned to the KOD fusion of unsaturated acids. Undec-10-enoic acid (III) was selected for initial study as all positions of the carbon chain should be affected if the postulated mechanism of the Varrentrapp reaction is correct. The methyl ester of the nonanoic acid produced was isolated and examined by the techniques described above. Of all available hydrogen atoms, an average of about 70% had been replaced by deuterium. Heaviest labeling had occurred in the α-position, and a roughly uniform, but lower, degree of labeling at all other positions along the fatty acid chain.

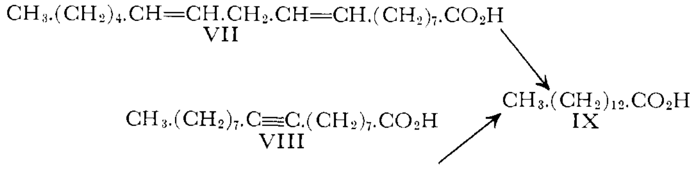
Molecular ions were observed in the mass spectrum over the whole range *m/e* 178–190. Although the most abundant of these was found at *m/e* 186, corresponding to molecules containing 14 deuterium atoms, it was particularly interesting to note the presence of a small proportion of ions at *m/e* 189, corresponding to the derivative of perdeutero-nonanoic acid in which all 17 hydrogens along the chain of nonanoic acid have been replaced by deuterium.

The observed labeling of the chain finally disproves the suggestion made by Chuit and coworkers (*4*) that alkali fusion of undec-10-enoic acid involves fission of the double bond in positions remote from the carboxylate group. It also makes improbable the occurrence of rearrangements whereby the double bonds in some molecules can migrate from these remote positions directly into the αβ-position. The results are, however, completely in accord with the postulated sequence of prototropic rearrangements (*2*). Moreover, contrary to the claim of Farmer (*7*), such rearrangements must be reversible, since the average deuteration exceeds 50% and some fully deuterated molecules are produced. Bearing in mind that the media used were not fully deuterated, and that this probably introduced an adverse isotope effect, the observed 70% average deuteration indicates that the Varrentrapp reaction occurs very largely, if not entirely, by means of the postulated sequence of (intermolecular) prototropic rearrangements.

Oleic acid (I) was next fused with KOD. The over-all deuteration (about 30%) in the resulting palmitic acid was considerably lower than in the product from undec-10-enoic acid. Although molecules were detected in which up to 29 of the 31 hydrogen atoms along the carbon chain had been replaced by deuterium, the most abundant species contained 7 to 10 deuterium atoms per molecule. Labeling of the alkyl chain was most pronounced in that region which originally separated the double bond and the carboxyl group in the starting material. However, the rest of the chain, as far as the terminal ethyl group, was more highly labeled than could be accounted for by random labeling of the resulting palmitic acid. This suggested that in some molecules the double bond, which initially had an equal chance of migrating either way, moved as many as seven positions away from the carboxyl group before finally ending up in the αβ-position and undergoing fission.

The palmitic acid produced by KOD fusion of octadec-2-enoic acid, $CH_3.(CH_2)_{14}.CH{=}CH.CO_2H$ (VI), was somewhat more highly deuterated than palmitic acid recovered from molten KOD. This supports the view reached earlier (*2*) that even with αβ-unsaturated acids some reversible migration of the double bond beyond the γδ-position occurs before fission of the αβ-enoate is complete.

Both linoleic acid (VII) and its acetylenic isomer, stearolic acid (VIII), undergo the Varrentrapp reaction to give mainly myristic acid (IX), 2 moles of acetic acid, and hydrogen (*1*).



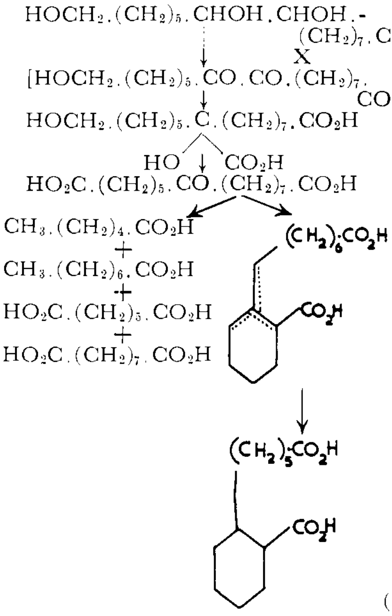
Myristic acid from KOD fusion of these unsaturated acids is heavily labeled, the number of deuterium atoms per molecule ranging from 3 to 26 and from 2 to 23, respectively. As with the oleic acid product, labeling is concentrated in the acid half of the molecule, but extends well down the carbon chain.

These deuteration studies leave very little doubt that reactions of the Varrentrapp type proceed by an initial sequence of discrete, reversible, prototropic rearrangements.

It may be of interest to comment briefly on some of the properties of the highly labeled products. Substitution of hydrogen by deuterium is accompanied by a reduction in the intensity of the C—H stretching frequencies in the infrared light absorption spectrum, and the appearance of new bands at lower frequencies attributable to C—D stretchings. There is, of course, a reduction in the intensity of the appropriate nuclear magnetic resonance bands, and the latter are also noticeably broadened. The *p*-anisidides of the highly deuterated mixtures crystallize less readily, and melt about 2° lower than their unlabeled analogs. In gas-liquid chromatograms (polyethylene glycol adipate) the bands due to heavily deuterated esters are noticeably broader, and have slightly shorter retention times than those of the parent esters.

Alkali Fusion of Oxygenated Fatty Acids

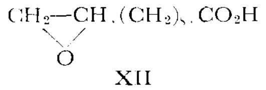
Previous studies with simple derivatives of fatty acids have clarified the reactions of hydroxylic and ketonic functions in molten alkali (*5*, *6*). Although the behavior of aleuritic acid (X) on alkali fusion appeared anomalous (*6*), a recent re-investigation of the problem has shown that this acid also conforms to the general principles established with simpler oxygenated acids. The apparent anomalies were mainly due to complications from the simultaneous occurrence of so many standard reactions. The transformations involved with aleuritic acid, the most important of which are summarized in Equation 3, will therefore serve as a convenient reminder that primary alcohols are smoothly dehydrogenated in molten alkali to acids and secondary alcohols to ketones (*5*). α-Glycols dehydrogenate, presumably to α-hydroxyketones and α-diketones, and the latter immediately undergo a benzylic acid type of rearrangement to give α-hydroxy acids in high yield (*6*). Under more drastic conditions these α-hydroxy acids lose one carbon atom to give ketones. These can react in a variety of ways, the most important being hydrolysis. However, with 6- and 7-keto acids, cyclization can occur to 5- and 6-membered rings, respectively (*3*, *5*). In these two series, the carbanion produced by removal of a proton from the α-position in the carboxylate is sterically well situated for an intramolecular attack on the keto group. The resulting unsaturated products can subsequently undergo reactions of the Varrentrapp type. Thus the main product finally produced from aleuritic acid is cyclohexanedicarboxylic acid (XI).



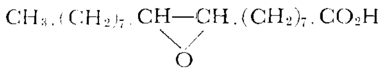
(3)

XI

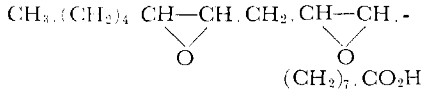
To complete the survey of simple oxygen functions, it seemed desirable to extend these studies to ethers, in particular to the epoxides which are so readily derived from unsaturated fatty acids.



XII



XIII



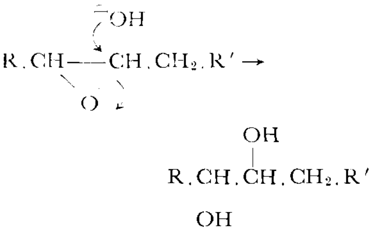
XIV

Alkali fusion of the epoxide (XII) of undec-10-enoic acid gave the C_{10}-dicarboxylic acid (about 60%), about 10% of the C_{11}-dicarboxylic acid in which the whole carbon chain is preserved, and a number of minor by-products.

A surprisingly complex mixture was obtained from the alkali fusion of the *cis-* and *trans-* epoxides (XIII) derived from the oleic acid. Although the main products were, as expected by analogy with the alkali fusion of the corresponding dihydroxy acids (*6*), octanoic, nonanoic, and azelaic acids (about 20% each), many by-products were detected and identified. A similar situation was encountered with the di-epoxide (XIV) derived from linoleic acid, though here some of the side reactions assumed even greater relative importance.

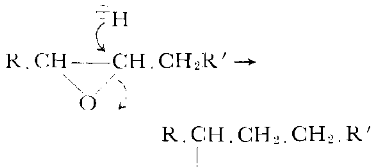
Consideration of the products obtained from the various epoxides leads to the conclusion that, in molten alkali, initial opening of the epoxide ring occurs in at least three ways:

Hydrolysis to the α-glycol, Equation 4:

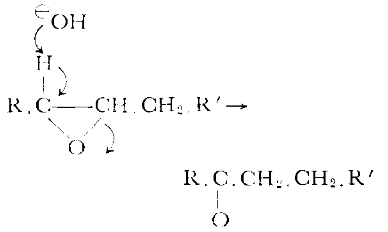


(4)

Formation of a secondary alcohol or ketone, either by reductive ring opening with a hydride ion from another reacting species, Equation 5, or by an alkali-induced rearrangement, Equation 6:

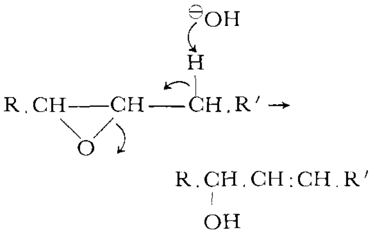


(5)



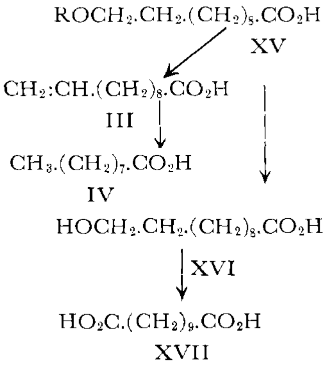
(6)

A β-elimination of a type that has previously been encountered only in more activated systems, Equation 7:



(7)

The β-elimination is more pronounced with the *trans*-epoxide, and the other reactions with the *cis*-epoxide. This is in keeping with some previous reports that *cis*-epoxides are more susceptible to nucleophilic attack—e.g., by lithium aluminum hydride—than the *trans*-isomers (*8*). Reactions such as Equations 5 and 6 assume greater importance with the diepoxide of linoleic acid, where there are possibilities of intramolecular attack on the epoxide groups. However, with all the epoxides studied, hydrolysis is clearly the most important initial reaction, and one that assumes overwhelming importance with the terminal epoxide.



To determine the behavior of simple alkyl ethers in molten alkali, studies were carried out with a series of 11-alkoxyundecanoic acids (XV; R = Me, Et, Pr, $CHMe_2$, C_4H_9, $CH_2.CHMe_2$, C_5H_{11}, C_6H_{13}, C_7H_{15}, C_8H_{17}).

In all cases, β-elimination was the predominant reaction. Depending on whether this occurred from the carboxyalkyl or the alkyl group, undec-10-enoic acid (III) or 11-hydroxy-undecanoic acid (XVI) was first formed. These initial products were identified in some reactions under carefully controlled conditions, but in molten alkali they were rapidly transformed into nonanoic acid (IV), by a Varrentrapp reaction, and into the C_{11}-dicarboxylic acid (XVII), by dehydrogenation, respectively. The methyl ether gave nonanoic acid in 65% yield and only traces of the dicarboxylic acid, whereas the ethyl and isopropyl ethers gave the dicarboxylic acid in 80% yield and only traces of nonanoic acid. The proportions of these two final products afforded a rough guide as to the relative importance of the two β-eliminations with each compound. Examination of the results showed that in most cases the elimination reactions of ethers in molten alkali follow the course expected from normal stereo-electronic considerations.

Conclusion

With the completion of this series of studies on fatty acids and their oxygenated derivatives, it is possible (*10*) to give a much more comprehensive and consistent account of the behavior of aliphatic and alicyclic compounds under strongly alkaline conditions than previously. Contrary to the impression often gained from the extensive literature on alkali fusions and related processes, all of these results affirm that the reactions which occur under these drastic conditions are still capable of simple explanation in terms of modern mechanistic concepts, and the very high yields sometimes encountered encourage the belief that these processes will ultimately afford useful new outlets for some of the abundant agricultural chemicals.

Acknowledgment

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