Fatty Oxazolines and Imidazolines

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ABSTRACT

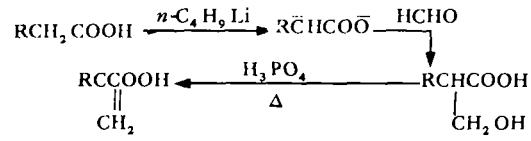
Fatty acids are converted, almost quantitatively, into oxazolines by reaction with 2-methyl-2-aminopropanol. These oxazolines are of high purity. They can be reacted further with paraformaldehyde to yield a mixture of mono- and *bis*-methylol derivatives in the α-position. Heating causes dehydration to form α-methylene oxazolines, which on hydrolysis provide good overall yields of α-alkylacrylic acids. Substituted anilides of the acrylic acids possess substantial antibacterial properties against Gram-positive microorganisms. The reaction of two moles of fatty acid with one of diethylenetriamine yields a primary amine with the structure of $RCON(CH_2CH_2NH_2)$-CH_2CH_2NHCOR, instead of a secondary amine as reported in the literature. Imidazoline is also formed. Removal of water by vacuum results in almost quantitative ring closure. The unquaternized imidazolines are highly unstable to hydrolysis and will revert to the above diamido amine at room temperature. Open-chain compounds are more water repellent than the imidazolines. Repellency of the saturated fatty acid derivatives increases with increasing molecular weight. Unsaturation decreases repellency, particularly for the *cis* derivative, whereas the *trans* derivative (from elaidic acid) possesses better repellent properties. Branching of the alkyl chains is also detrimental to water repellency. Application of repellents to soil dramatically reduces water absorption and seed germination.

INTRODUCTION

The purpose of this paper is to review research of our laboratory on fatty oxazolines and imidazolines. These heterocyclic derivatives are important since they are readily prepared from triglycerides, fatty acids, or methyl esters of fatty acids. The tertiary amine functionality thus obtained is useful in achieving chemical properties, so that imidazolines or oxazolines can be utilized as intermediates for subsequent synthetic steps to form other compounds.

The initial objective of our oxazoline investigations was to prepare α-hydroxy or α-methylene-substituted acids. Such derivatives of fatty acids have been prepared very elegantly by abstracting the α-proton of the fatty acid with *n*-butyllithium at −70 C in the presence of diisopropylamine in a solvent mixture of tetrahydrofuran and hexamethylphosphoramide. The resulting dianion may then be reacted with gaseous formaldehyde to yield an α-methylol derivative, which is dehydrated to form the α-methylene compound according to the following Scheme 1 (1). Reaction of the dicarbanion with oxygen would yield the α-hydroxy acid (1). However, the use of costly metalating agent, expensive and hazardous solvents, and extremely low temperatures makes such an approach unsuitable for large scale synthesis.

The synthesis of α-substituted fatty acids via the intermediate carbanion could be made simpler and at lower costs by using the fatty acid dimethylamide rather than the acid as starting material. This process cuts the *n*-butyllithium requirement in half, and the use of a more conventional solvent system reduces the refrigeration substantially (2). Attempted substitution of *n*-butyllithium by the less expensive phenylmagnesium bromide is not recommended since it results in greatly reduced yields (2). To arrive at a more practical synthetic approach, particularly for the preparation of α-methylene substituted fatty acids (α-alkylacrylic acids), an entirely different and novel synthesis was developed.



SCHEME 1

DISCUSSION

Oxazoline and α-Alkylacrylic Acid Synthesis

The oxazolines obtained from the reaction between fatty acids and 2-methyl-2-amino-1-propanol (AMP) prove to be ideal intermediates for the synthesis of α-alkylacrylic acids (3). The imidazoline is treated with paraformaldehyde followed by dehydration, and the desired α-alkylacrylic acid is obtained by acid hydrolysis. The overall reaction scheme is shown in Scheme 2.

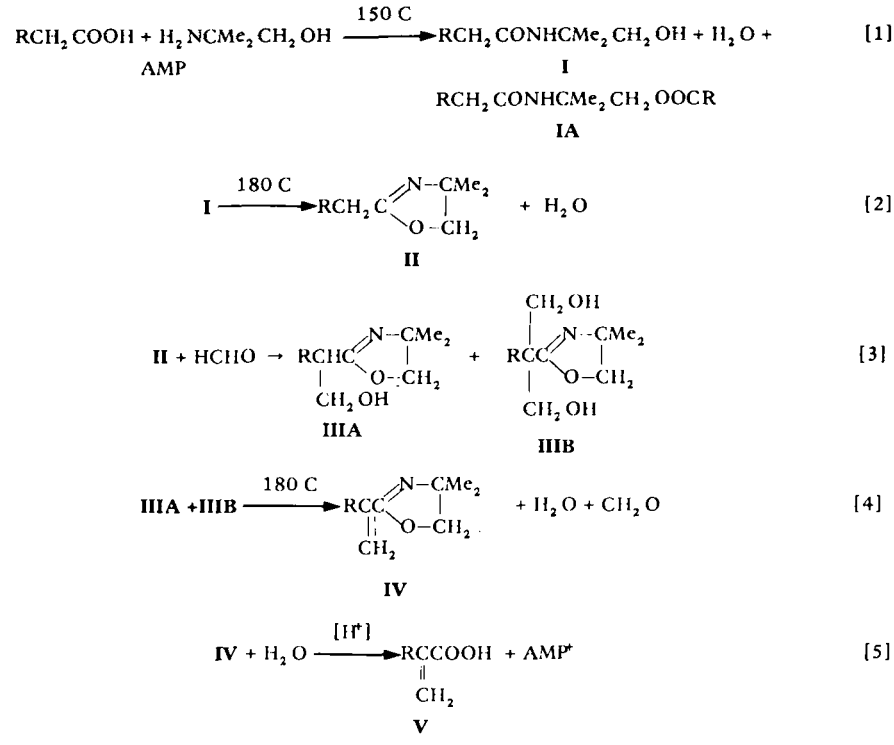
The synthetic route involves essentially three major processing steps carried out in the same vessel, and the product needs to be removed from the reaction vessel only for purification.

Either an acid or its methyl ester can be used as a starting material. The reaction to form oxazoline **II** proceeds via the intermediate amide **I**, which is not isolated. When the reaction is done below 150 C, **I** is the major reaction product. Cyclization occurs at or above 180 C even at atmospheric pressure. Formation of amide **I** is always accompanied by some ester amide **IA** formation which is suppressed by use of excess AMP. Thus, while stoichiometric ratio of reactants gives 35% of **IA**, use of 100% excess AMP reduces **IA** to less than 10%. Addition of an alkaline catalyst in the presence of AMP eliminates practically all of **IA**.

When a fatty acid is treated with two equivalents of AMP in such a manner that the vapor is passed through a 1-ft Vigreaux column so that the vapor temperature on top of the column never exceeds 105 C, water will distill out while AMP refluxes back in, and the reaction mass temperature gradually rises to 180-190 C. After 8-9 hr, the free fatty acid content is below 2%. Addition of a small amount of alcoholic KOH and refluxing for 3 hr eliminates free fatty acid (FFA) and ester content. After removal of the excess AMP, an almost quantitative yield of oxazoline **II** is obtained. The crude oxazoline is generally light in color and can be used without further purification.

Addition of paraformaldehyde is readily accomplished, and subsequent dehydration is brought about by raising the reaction temperature. These two steps may have to be repeated to assure fairly complete conversion to the α-methylene oxazoline derivative **IV**. Experimental details are described elsewhere (3). Since the desired α-alkylacrylic acid is usually purified by crystallization or distillation, oxazoline **IV** need not be purified. The crude α-alkylacrylic acid is formed by acid hydrolysis with dilute hydrochloric acid containing some acetic acid.

The α-alkylacrylic acids cannot be readily separated from the starting alkanoic acid by distillation. However, separation can be achieved by taking advantage of the hindered nature of the α-alkylacrylic acids which react very



SCHEME 2

TABLE I

Physical Constants and Yields of α-Substituted Acrylic Acids (CH_2=CRCOOH)

R	mp (C)	bp (C) [mm]	Overall yield (%)
C_6H_5	not isolated pure		70 (crude)
$C_6H_5CH_2$	66-68	170-174 [20]	80
C_4H_9		107 [25]	75
C_5H_{11}		129 [15]	65
C_6H_{13}		108 [20]	75
C_7H_{15}		152-155 [14]	65
C_8H_{17}		176 [20]	75
$C_{10}H_{21}$	33-34	134-135 [0.25]	80
$C_{12}H_{25}$	43-44		80
$C_{16}H_{31}$ (from oleic acid)		196-197 [0.4]	80
$C_{16}H_{33}$	50-60		80

sluggishly with methanol in the presence of BF_3 catalyst, whereas the starting alkanoic acid reacts rapidly. The methyl ester of the latter can be readily removed from the former by fractional distillation.

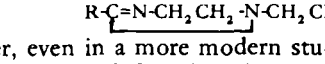
The above synthetic approach is not restricted to derivatives of fatty acids, as Table I shows. Phenylacetic acid and hydrocinnamic acids are also suitable starting materials, although it is not possible to isolate the pure α-phenylacrylic acid.

Biologically Active α-Alkylacrylanilides

The α-alkylacrylic acids are readily reacted with oxalyl chloride to form acid chlorides, which can be converted into substituted anilides possessing interesting biological properties (4). Table II shows a comparison of the antibacterial properties between the substituted anilides of fatty acids and the analogous anilides of α-alkylacrylic acids. These compounds are active against Gram-positive organisms only, and the screening tests were run with *S. aureus*. MIC refers to minimum inhibitory concentration, i.e., the lowest concentration of active agent at which growth is inhibited. As Table II shows, the presence of the double bond does not enhance or reduce antibacterial properties appreciably. This finding is in conflict with a statement in the patent literature, according to which antibacterial activity is enhanced by the presence of a double bond in the acyl group (5). The chemistry of oxazolines, including fatty oxazolines, has been reviewed by Frump (6).

Fatty Imidazoline Synthesis

Fatty imidazolines have been prepared and utilized industrially for a long time, but the chemistry of the reaction product of a fatty acid with diethylenetriamine (DETA) has not been documented well or accurately in the literature. An early misconception (7) was that one mole of DETA reacted with one mole of fatty acid to yield the imidazoline



However, even in a more modern study involving structure identification by infrared (IR) spectrophotometry (8) the author failed to assign an amido group, even though the

TABLE II

Substituted Anilides of Fatty Acids and Analogous α-Alkyl Acrylic Acids

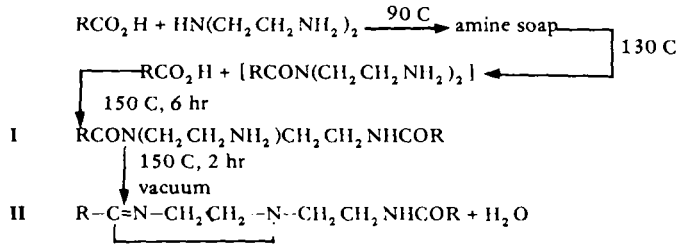
$RCH_2CONHAr$				$RC(CH_2)CONHAr$	
R	Ar	mp (C)	*S. aureus* MIC (ppm)	mp (C)	*S. aureus* MIC (ppm)
C_4H_9	$3,4\text{-}Cl_2C_6H_3$	74-75	10	50-51	1000
C_4H_9	$3,5\text{-}Cl_2C_6H_3$	66-67	10	oil	10
C_4H_9	$2\text{-}OH\text{-}5\text{-}ClC_6H_3$	97-98	10	114-115	100
C_5H_{11}	$3,4\text{-}Cl_2C_6H_3$	58-59	10	42-43	10
C_5H_{11}	$3,5\text{-}Cl_2C_6H_3$	72-73	1	oil	1
C_5H_{11}	$2\text{-}OH\text{-}5\text{-}ClC_6H_3$	95-96	10	108-109	100
C_5H_{11}	$2\text{-}OH\text{-}5\text{-}NO_2C_6H_3$	171-172	10	169-171	10
C_5H_{11}	$3\text{-}NO_2\text{-}4\text{-}ClC_6H_3$	38-39	10	43-44	10
C_6H_{13}	$3,4\text{-}Cl_2C_6H_3$	39-40	1	53-54	1
C_6H_{13}	$3,5\text{-}Cl_2C_6H_3$	55-56	1	37-39	1
C_6H_{13}	$2\text{-}OH\text{-}5\text{-}ClC_6H_3$	94-95	10	92-93	1
C_6H_{13}	$2\text{-}OH\text{-}5\text{-}NO_2C_6H_3$	127-128	1	173-174	1
C_6H_{13}	$3\text{-}NO_2\text{-}4\text{-}ClC_6H_3$	51-52	1	42-43	1
C_7H_{15}	$3,4\text{-}Cl_2C_6H_3$	69-70	1	43-45	1
C_7H_{15}	$3,5\text{-}Cl_2C_6H_3$	69-70	1	52-54	10
C_7H_{15}	$2\text{-}OH\text{-}5\text{-}ClC_6H_3$	93-94	1	101-102	1
C_7H_{15}	$2\text{-}OH\text{-}5NO_2C_6H_3$	140-141	10	160-161	5
C_7H_{15}	$3\text{-}NO_2\text{-}4\text{-}ClC_6H_3$	44-45	1	49-50	1
C_8H_{17}	$3,4\text{-}Cl_2C_6H_3$	64-65	10	46-47	1
C_8H_{17}	$3,5\text{-}Cl_2C_6H_3$	65-66	10	oil	10

presence of an IR peak at 1620^{-1} cm clearly indicated its presence.

The reaction between DETA and fatty acid was studied in our laboratory (9), and it was established that the reaction proceeds as in Scheme 3.

The course of the above reactions can be followed readily by conventional wet methodology by determining free fatty acid, primary, secondary and tertiary amine content of the reaction mixture at suitable time intervals. The results of such a reaction at 150 C are shown in Figure 1. The figure shows that the fatty acid content decreases by two-thirds of the original amount after a 2-hr reaction time and during the same time interval practically all of the secondary amine disappears. This indicates that DETA and fatty acid do not react in a 1:1 molar ratio. Thus, the secondary amino group of DETA is substantially more reactive than the primary. After 6 hr, the FFA content of the product is insignificant, and the material is predominantly a primary amine of the structure **I** indicated in Scheme 3. On application of vacuum, the product turns into a tertiary amine, the imidazoline **II** of Scheme 3.

The reaction of DETA with a triglyceride such as tallow can be followed in the same manner, the ester content being determined by IR. As Figure 2 shows, tallow reacts quite rapidly with DETA, and imidazoline formation is in evidence even after a 2-hr reaction time and attained 28% after 6 hr heating. The imidazoline is readily hydrolyzed to the diamide of structure **I**, which possesses a primary amino



SCHEME 3

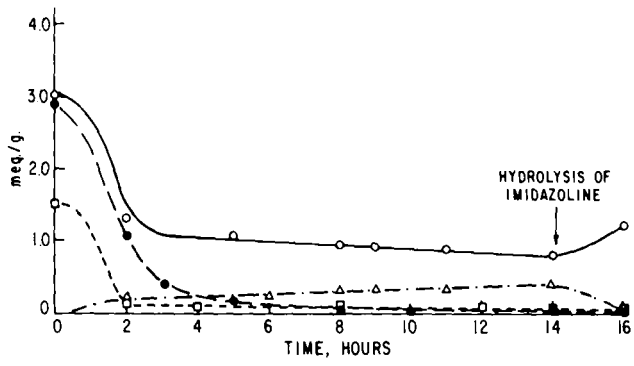


FIG. 1. Reaction rate study, 2 mol tallow fatty acid per mol diethylenetriamine. (•) Fatty acid; (○) primary amine; (□) secondary amine; (△) tertiary amine (imidazoline).

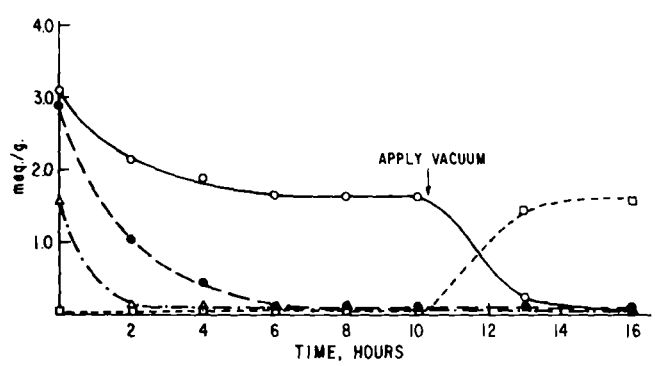


FIG. 2. Reaction rate study, tallow and diethylenetriamine. (•) Ester; (○) primary amine; (□) secondary amine; (△) tertiary amine (imidazoline).

TABLE III

Physical Properties of Diethylenetriamine Reaction Products

R	R-C=N-CH_2CH_2N-CH_2CH_2NHCOR			RCON($CH_2CH_2NH_2$)CH_2CH_2NHCOR		
	mp (C)	Contact angle (°)	Percolation test	mp (C)	Contact angle (°)	Percolation test
C_8H_{17}	45-46	62	i	91-92	94	i
C_9H_{19}	48-49	59	i	101-102	104	i
$Ch_{11}H_{23}$	67-68	95	1 hr	110-111	99	1 hr
$C_{13}H_{27}$	70-71	89	1.5 hr	112-113	99	7 days
$C_{15}H_{31}$	78-79	97	7 days	116-117	96	>7 days
$C_{17}H_{35}$	84-85	103	>7 days	118-119	98	>7 days
Δ^9-$C_{17}H_{33}$ *cis*	liquid	0	5 min	52-53	50	5 min
Δ^9-$C_{17}H_{33}$ *trans*	46-47	55	5 min	91-92	62	1 day
$C_{19}H_{39}$	88-89	104	>7 days	110-111	104	>7 days
$C_{21}H_{43}$	92-93	103	>7 days	98-99	109	>7 days
Tallow fatty acid	40-50	54	i	45-55	63	i
Tallow fatty acid (elaidinized)	45-55	97	i	55-65	97	i
Hydrogenated tallow fatty acid	65-75	78	>7 days	90-95	94	>7 days

[a]T-22 Fatty acids, C_{18} *cis* = 36%; C_{18} *trans* = 7%.

[b]T-11 Fatty acids, C_{18} *cis* = 6%; C_{18} *trans* = 24%.

i = Instantaneous.

group. One of the problems with the synthesis, where triglyceride is the starting material, is the formation of glycerol which is difficult to remove quantitatively. Traces of glycerol interfere with the surface-active properties of the product.

Use of methyl ester as the starting material is feasible but the reaction rate is much slower than that of the fatty acid, so that the use of methyl ester offers no advantage. This phenomenon has also been observed in the reaction of methyl esters with alkanolamines and other amines. It is difficult to explain why the triglyceride is more reactive. Heating under vacuum will readily convert the amides **I** into the imidazolines **II**. The latter are hydrolytically very unstable and in the presence of water revert back to **I** by standing overnight at room temperature. The conversion of **I** to **II** thus is a reversible reaction.

Diamides **I** and imidazolines **II** were prepared from various fatty acids as well as from tallow, and their physical properties are shown in Table III.

Physical Properties of Fatty Acid–DETA Reaction Products

Contact angle measurements refer to sessile drop measurements on a thin molten film of test compound cast on a glass plate. The percolation test period refers to the time required for water to percolate through a column of sand treated with test compound. Details may be found elsewhere (9). The data show that the diamides give higher contact angles than the corresponding imidazolines except in the case of the stearic acid derivative. Unsaturation in the fatty acid chain causes a drastic reduction in contact angle and the angle for the *cis* derivative is much lower than that for the *trans* compound.

The contact angle measurements for the derivatives of lauric acid and its saturated higher homologs are so close together that no clear distinction can be made between them with respect to hydrophobicity, but the percolation test discriminates between the C_{11}, C_{13} and C_{15} derivatives.

Water passes quickly through sand treated with the C_9, C_{11} and C_{13} derivatives and also the imidazoline of oleic acid. Whereas water penetrates the oleic diamide-coated sand within 5 min, a period of one day is required for penetration of the elaidic diamide-coated sand, showing the effect of *cis-trans* isomerism.

Although the elaidic diamide derivative is more linear in configuration, its unsaturation still results in surface properties inferior to those of the analogous stearic acid derivatives. Sand coated with derivatives of the C_{16} and higher molecular weight saturated fatty acids prevents water percolation for more than a week, demonstrating the influence of saturation and molecular weight on hydrophobicity. A sharp delineation between hydrophilic and hydrophobic properties is observed between the lauric and myristic diamide derivatives, i.e., 1 hr vs 7 days. These data make it possible to interpret the results obtained from the tallow derivatives.

The tallow fatty acid-DETA reaction product, high in oleic acid content, gives instantaneous wetting of sand. A more hydrophobic product is obtained by the partial hydrogenation and concurrent elaidinization of tallow fatty

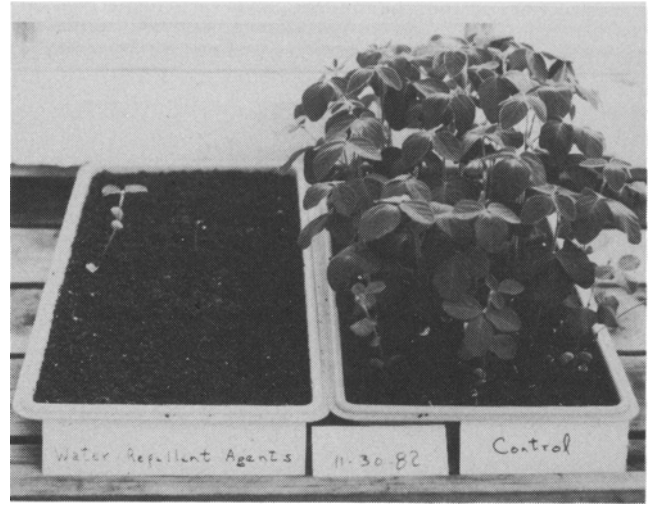


FIG. 3. Soy seed germination after 4 weeks treated soil flat left, control at right.

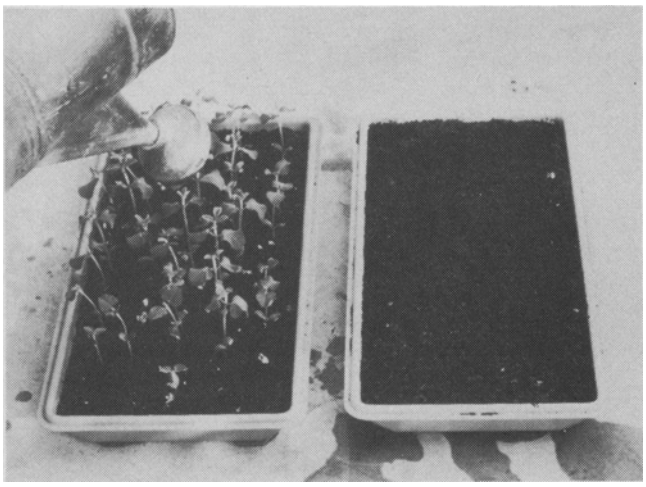


FIG. 4. Water repellency of soil. Control flat left, treated flat right.

acids. Although a high contact angle (97 C) is obtained for the partially hydrogenated tallow fatty acid-DETA reaction product, the percolation test still indicates inadequate hydrophobic properties. The completely hydrogenated tallow fatty acid-DETA reaction product, has a high contact angle and water fails to penetrate a bed of sand coated with this material even after a week.

A practical application of soil water repellents is shown in Figure 3. Soy seeds had been planted in treated soil and in an untreated control. After 4 weeks, only one seed in the treated soil germinated, as shown in the photograph. Figure 4 shows the two test flats after watering. Whereas the control flat held the water, the test flat permits the water to run around the soil and out through perforations in the bottom of the flat.

It has thus been shown that oxazolines and imidazolines derived from fats are useful intermediates for the synthesis of antibacterial agents and agricultural chemicals, respectively. It is hoped that the research reported here will further expand the utilization of fats and oils.

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Reaction of Oxygen and Unsaturated Fatty Acids

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ABSTRACT

Oxygen reacts readily with unsaturated fatty acids so that every time these compounds are handled there is a danger they will become contaminated with oxidation products. The products formed first are allylic hydroperoxides which are labile molecules that change rapidly to other compounds, some of which are highly flavorous. Sometimes these changes are desirable and may be promoted; frequently they are not and have to be inhibited. Instrumental procedures recently introduced – especially separation by high performance liquid chromatography and identification by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy – have led to a renewed interest in this subject. For the nonenzymic processes of autoxidation and photooxygenation we now have a better understanding of the routes leading to the first-formed allylic hydroperoxides and an improved appreciation of the structure of further oxidation products including dihydroperoxides and hydroperoxides which also contain one or more cyclic peroxide units. Direct chemical routes to several of these compounds have also been developed. Oxidation of linoleic acid by plant-derived lipoxygenases gives diene hydroperoxides similar to those produced by autoxidation, except that the former are optically active and the latter racemic. Enzymic oxidation of arachidonic acid and certain related C_{20} acids in animal systems produces a wide variety of prostaglandins, thromboxanes and leukotrienes, all of which show interesting physiological properties. These compounds have been described as "tomorrow's drugs".

INTRODUCTION

The interaction of oxygen with unsaturated acids is an important reaction occurring under a wide range of conditions. Nonenzymic oxidation, occurring by autoxidation or photooxygenation, furnishes allylic hydroperoxides as primary reaction products. These can be oxidized further to products which are now being identified. Recent advances have relied particularly on high performance liquid chromatography (HPLC) as an improved separation technique and on ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry for complete structure identification. Still further reaction leads to a wide range of compounds, including some of lower molecular weight associated with the development of flavor. This is sometimes desirable but frequently not so. Autoxidation and photooxygenation will be discussed and compared.

Enzymic oxidation, particularly in animal systems, is attracting considerable attention and the 1982 Nobel Prize for medicine was awarded to workers in this field. Such reactions are both regiospecific and stereospecific so that, compared with nonenzymic oxidation, the products of enzymic oxidation are often simpler in the number of components present although they may be more complex in structure. They are produced in enantiomeric form rather than as racemates. Many of the enzymic oxidation products have profound physiological properties with the curious observation that compounds which are structurally similar sometimes show antagonistic behavior. The possible involvement of lipid oxidation products in the cause of cancer, heart disease, asthma, arthritis, bronchial complaints and aging processes and also in their treatment, is a sufficient pointer to their importance.

AUTOXIDATION AND PHOTOOXYGENATION

Before oxygen and unsaturated fatty acids react nonenzymically, one of them must be activated. Either the