It is evident from the above that the 9:10- and 15:16- double bonds of the linolenic acid undergo a shift during the hydrogenation of this acid at the 12:13-double bond, to the 8:9 and 10:11; and 14:15 positions respectively. That these shifts of both the double bonds is simultaneous is indicated by the presence of 8,14- and 10,14-isolinoleic acids.

Glutaric acid would result from the oxidation of 9,14- or 10,15-isolinoleic acids, whose presence would demonstrate the shift in part of either the 9:10- or 15:16-double bonds in linolenic acid. Glutaric acid would be oxidized to succinic acid and thus not be identified among the oxidation products. For this reason the absence of 9,14- and 10:15-isolinoleic acids is not entirely confirmed and hence these isomers may exist in a small proportion.

Configurational Isomerism. The infrared absorption spectra of two concentrates (fraction A-15, Figure 2; fraction B-12-1, Figure 3) (see paper No. 1 of this series [1]) of methyl isolinoleate revealed large absorption peaks at 10.3μ (968 cm^{-1}). Lemon (6) obtained an absorption peak at the same wave length for a relatively pure sample of methyl isolinoleate, isolated by chromatographic procedures from hydrogenated linseed oil.

The peak at 968 cm^{-1} has been found by various investigators for other unsaturated acids, e.g., elaidic (7) and vaccenic acid (8). It indicates a *trans*-configuration for the double bond in the unsaturated acid.

The present work confirms the work of Lemon in that at least one of the double bonds of isolinoleic acid has a *trans*-configuration. As a large number of isolinoleic acids are possible, three of which have been definitely shown to be present, it is possible that the double bonds in these octadecadienoic acids may have a *cis-cis-*, *cis-trans-*, *trans-cis-*, or a *trans-trans-*configuration.

The Twitchell lead salt-alcohol method (9) of separation gave a "solid" fraction having an iodine value (I.V., 94.4) greater than that for a monoenoic acid (theory I.V., 89.9). This seems to indicate the presence of a "solid isolinoleic" acid (17.2%) in the solid acids. It is quite likely that this acid if present has its double bonds in a *trans-trans*-configuration. The presence of a solid isolinoleic acid (12,15- isolinoleic acid) has been reported by Bauer and Ermann (7).

According to van der Veen (5), 9,15- and 10,14-isolinoleic acids are produced during the hydrogenation of methyl linolenate using palladium black as the catalyst. The present work confirms this viewpoint. The formation and presence of another isomer, 8,14-isolinoleic acid, is also indicated.

The view of various workers (1, 2, 5), that an isolinoleic acid is formed on the preferential hydrogenation of the 12:13- or middle double bond of linolenic acid is confirmed. Further it has been proved definitely that both the double bonds (9:10- and 15:16-) in the linolenic acid molecule undergo a shift by at least one carbon atom, during the partial hydrogenation of this acid. This shift in part or whole produces a *trans*-configuration in at least one of the double bonds of the isolinoleic acid isomers.

However it does not follow that other isomeric isolinoleic acids, besides the ones mentioned above (8,14-, 9,15-, 10,14-, and 10,15-octadecadienoic acids) are not formed during the hydrogenation. The isolinoleic acids which form quite a large proportion of the solid fractions crystallized at temperatures above 70° C. may have structures (positional and configurational isomers) different from the ones already proposed.

Summary

The methyl isolinoleate fraction obtained by the low temperature crystallization procedure was found to be a mixture of at least three isomers, the 8,14-, 9,15-, and 10,14- isolinoleic acids. The infrared absorption spectrum of this fraction indicated a *trans*-configuration for at least one of the double bonds of isolinoleic acid.

The Twitchell lead salt-alcohol method was found unsuitable for the determination of saturated acids, due to the presence of a "solid isolinoleic" acid in the "solid" acids separated by this method.

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Alkyl Hydroxyanisoles as Antioxidants

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IT has been demonstrated that the antioxidant known as butylhydroxyanisole possesses very desirable properties and is desirable in the stabilization of oils and waxes. Among these desirable properties are: a high solubility in oils, a carry-through of its antioxidant properties into baked goods, nontoxicity as witnessed by approval for use in foods (1, 2), no color, odor, or taste imparted to the substrate to which the antioxidant is added, low cost, and effectiveness in low concentrations of 0.005% to 0.02%. It has been reported that butylhydroxyanisole and the mixtures containing it more nearly meet the requirements of an ideal antioxidant than any other antioxidant studied (3).

Butylhydroxyanisole (4) is a trisubstituted benzene compound containing as substituents a butyl group, a hydroxy group, and a methoxy group. However antioxidant activity is not assured by mere presence of these three substituents for it is essential that these groups be properly arranged or oriented in the ring. Consequently it is of interest to point out the salient features so essential to obtain effec-

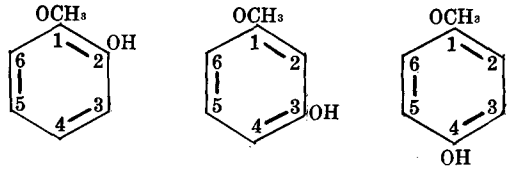
tive stabilization with butylhydroxyanisole. The relationship between structure and inhibitor effectiveness was investigated by the synthesis of a number of hydroxyanisoles and evaluation of these compounds in lard. This paper is a report of such an examination.

A primary consideration in evaluating any food antioxidant is its effectiveness in inhibiting oxidation or rancidity. Therefore the compounds herein reported are considered primarily as to antioxidant potency. Other properties such as toxicity, carry-through, and solubility are factors which can be considered after satisfactory potency has been found to exist. The evaluation of potencies was done by use of the Active Oxygen Method (5, 6) in a single lard with an initial three-hour stability. The potencies as presented are the average of two or more determinations. Since the comparative potencies often depend on the concentration, it was considered wise to determine potencies at two concentrations, namely 0.005% and 0.02%. While the effectiveness of a material can be indicated by giving the length of the induction period at a stated concentration, it is believed often advantageous to express a comparative potency, called inhibitor ratio, relative to some standard by use of the equation

$$\text{Inhibitor Ratio} = \frac{L_x - L_c}{L_s - L_c}$$

where L_x is the length of the induction period with the unknown, L_c the induction period of the uninhibited lard, and L_s the induction period with the standard at the same concentration of the unknown. In this work the standard selected is pure 3-t-butyl-4-hydroxyanisole, which was assigned an inhibitor ratio of 1.0.

In examining the effect of structure on potency, these are some of the factors to be considered: the number and position of alkyl substituents, the size and configuration of the substituents, and the position of the hydroxy group relative to the methoxy group. An attempt will be made to define some of the effects by the study of the potency values as presented in the following tables. The following system of numbering is used in the nomenclature of the hydroxyanisoles:



Consideration will first be given to those compounds with the hydroxyl group in the 4-position relative to the methoxy group. The first member of the series, 4-hydroxyanisole, possesses an inhibitor ratio in the range of 0.25-0.36. Insertion of a methyl group in the 2-position gives a compound with an 0.17 inhibitor ratio at 0.005% concentration and 0.48 inhibitor ratio at 0.02% concentration. Substitution of a methyl group in the 3-position gives a compound with an inhibitor ratio of about 0.55. Inhibitor ratios of about 0.55 are obtained by the insertion of two methyl groups in either the 3,5- or 2,5-positions. However substitution of methyl groups in the 2,6-positions is detrimental for a drop in inhibitor ratio to less than 0.1 results. Substitution of an n-propyl group, allyl group, isopropyl group, or two isopropyl groups in 4-hydroxyanisole produces compounds with inhibitor ratios of about 0.4.

A comparison of the four isomers of the butyl derivatives, substituted in the 3-position, is of particular interest for it reveals that the structure of the butyl substituent is of importance in realizing maximum potency. The normal and isobutyl derivatives possess inhibitor ratios of about 0.5, the secondary butyl isomer an inhibitor ratio of 0.6, while the tertiary configuration is unique in its effect of enhancing potency. In fact, of all the alkyl substituents placed in the 3-position, the t-butyl grouping is the most effective in raising potency.

In order to realize maximum potency it is essential that the t-butyl group be in the 3-position, for 2-t-butyl-4-hydroxyanisole is relatively ineffective as shown by its inhibitor ratio of 0.36 at 0.02% and 0.17 at 0.005%. It appears that the placement of a t-butyl substituent adjacent to the methoxy group is detrimental as indicated further by the inferior potency of 2,5-di-t-butyl-4-hydroxyanisole with an inhibitor ratio of 0.5.

Included in the evaluation are the three butyl isomers with a double bond in the alkyl group. As observed, the potencies of 3-crotyl-, 3-β-methallyl-, and 3-α-methallyl-4-hydroxyanisole are all in the vicinity of 0.5 at 0.02% concentration. The presence of an olefin linkage neither increases nor decreases to any great extent the potency in comparison to the corresponding saturated compounds.

The remaining three 4-hydroxyanisoles are disubstituted compounds, possessing one methyl and one t-butyl group. Substitution of a methyl group in 3-t-butyl-4-hydroxyanisole to form 3-t-butyl-5-methyl-4-hydroxyanisole (inhibitor ratio 1.1) slightly raises the inhibitor potency at 0.02% concentration. Substitution of a methyl group to form 5-t-butyl-2-methyl-4-hydroxyanisole lowers the inhibitor ratio to 0.8. The position isomer of the latter compound 2-t-butyl-5-methyl-4-hydroxyanisole possesses a low inhibitor ratio of about 0.4. These observations stress the importance of the orientation of substituents in relation to potency.

TABLE I

Potencies of 4-Hydroxyanisoles and Derivatives

Compound	Induction Period, Hours		Inhibitor Ratio	
	0.005%	0.02%	0.005%	0.02%
None	3	3	....	....
4-Hydroxyanisole	7.5	13.5	.25	.36
2-Methyl-4-hydroxyanisole	6	17	.17	.48
3-Methyl-4-hydroxyanisole	12.5	19	.53	.55
3,5-Dimethyl-4-hydroxyanisole	12	15	.50	.41
2,5-Dimethyl-4-hydroxyanisole	13	17	.56	.48
2,6-Dimethyl-4-hydroxyanisole	<4	<5	<.1	<.1
3-n-Propyl-4-hydroxyanisole	12.5	15.5	.53	.43
3-Allyl-4-hydroxyanisole	10	15.5	.39	.43
3-Isopropyl-4-hydroxyanisole	10	16	.39	.45
Di-isopropyl-4-hydroxyanisole	11	15	.44	.41
3-n-Butyl-4-hydroxyanisole	12	17.5	.50	.50
3-iso-Butyl-4-hydroxyanisole	11.5	16	.47	.45
3-sec-Butyl-4-hydroxyanisole	14	20.5	.61	.60
3-t-Butyl-4-hydroxyanisole	21	32	1.0	1.0
2-t-Butyl-4-hydroxyanisole	6	13.5	.17	.36
2,5-Di-t-butyl-4-hydroxyanisole	12	17	.50	.48
3-Crotyl-4-hydroxyanisole	9	15.5	.33	.43
3-β-Methallyl-4-hydroxyanisole	10.5	16	.42	.45
3-α-Methallyl-4-hydroxyanisole	11	18	.44	.52
3-t-Butyl-5-methyl-4-hydroxyanisole	21	35	1.0	1.10
5-t-Butyl-2-methyl-4-hydroxyanisole	18	24	.83	.72
2-t-Butyl-5-methyl-4-hydroxyanisole	10	13.5	.39	.36
Hydroquinone	40	93.5	2.05	3.1
mono-t-Butylhydroquinone	24	80	1.2	2.65
2,5-Di-t-butylhydroquinone	6	14	.17	.38
t-Butyl-1,4-dimethoxybenzene	....	3	....	0

Since the compounds in Table I can be considered as derivatives of hydroquinone, it is of interest to compare potencies of hydroquinone and its derivatives. Hydroquinone is an effective antioxidant with an inhibitor ratio of 2 to 3. However its apparent toxicity (7, 8) and lack of solubility limit its use as an antioxidant. Mono-t-butylhydroquinone likewise is an effective antioxidant but apparent toxicity, lack of solubility, and the high concentrations which are required to realize its high potency likewise limit its use as an antioxidant. Di-t-butylhydroquinone is ineffective. The presence of a free hydroxy group is necessary for inhibitor action as made evident by further methylation of 3-t-butyl-4-hydroxyanisole to t-butyl-4-dimethoxybenzene which possesses no potency.

The replacement of the methyl group in the methoxy function by an ethyl group does not alter the relationship between structure and antioxidant potency. The effectiveness of four such compounds, called 4-hydroxyphenetoles, is listed in Table II.

TABLE II

Potencies of 4-Hydroxyphenetoles

Compound	Induction Period, Hours		Inhibitor Ratio	
	0.005%	0.02%	0.005%	0.02%
4-Hydroxyphenetole	7.5	12	.25	.31
3-t-Butyl-4-hydroxyphenetole	18.5	29	.86	.90
2-t-Butyl-4-hydroxyphenetole	7.5	14	.25	.38
2,5-Di-t-butyl-4-hydroxyphenetole	12.5	19	.53	.55

TABLE III

Potencies of 3-Hydroxyanisoles and Derivatives

Compound	Induction Period, Hours		Inhibitor Ratio	
	0.005%	0.02%	0.005%	0.02%
3-Hydroxyanisole	<4	3	<.1	<.1
4-t-Butyl-3-hydroxyanisole	<4	7	<.1	.1
4,6-Di-t-butyl-3-hydroxyanisole	<5	7	<.1	.1
Resorcinol	3	<4	<.1	<.1

The inhibitor ratios for 2-hydroxyphenetole, the two mono-t-butyl isomers, and the di-t-butyl compound are similar to the corresponding four hydroxyanisoles.

Consideration has been given so far only to compounds in which the hydroxyl group is in the 4-position relative to the methoxy group. In order to determine the feasibility of using compounds with the hydroxyl group in the 3- and 2-positions, a number of such compounds was synthesized and evaluated. The potencies of these materials, listed in Tables 3 and 4, in general are disappointing.

TABLE IV

Potencies of 2-Hydroxyanisole and Derivatives

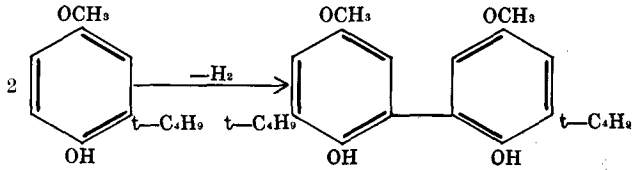
Compound	Induction Period, Hours		Inhibitor Ratio	
	0.005%	0.02%	0.005%	0.02%
2-Hydroxyanisole (guaiacol)	<4	<4	<.1	<.1
3-t-Butyl-2-hydroxyanisole	<5	<5	<.1	<.1
4-t-Butyl-2-hydroxyanisole	<5	<5	<.1	<.1
5-t-Butyl-2-hydroxyanisole	<5	<5	<.1	<.1
5-Methyl-2-hydroxyanisole (creosol)	....	<4	....	<.1
3-t-Butyl-5-methyl-2-hydroxyanisole	<5	7	<.1	.1
4-t-Butyl-5-methyl-2-hydroxyanisole	<4	7	<.1	.1
Catechol	25	55	1.2	1.8
t-Butylcatechol	37	65.5	1.9	2.15

The potencies of the 3-hydroxyanisoles are all low including that of resorcinol. The observation is in agreement with the opinion that the substitution of a hydroxyl group in the number 3 position does not favor high potency.

2-Hydroxyanisole (guaiacol) and derivatives have been suggested on numerous occasions as antioxidants. As observed in Table IV, their potencies are actually low. 2-Hydroxyanisole itself possesses an inhibitor ratio of less than 0.1. Insertion of a t-butyl group in the 3-, 4-, or 5-positions to form a t-butyl-2-hydroxyanisole is without effect in raising potency. Likewise two butyl derivatives of 5-methyl-2-hydroxyanisole (creosol) are ineffective as antioxidants. This lack of activity for 2-hydroxyanisole is in contrast to the potencies of catechol and t-butyl catechol. The dihydric phenols, including catechol, are skin irritants and can cause systemic poisoning, so use of these compounds may be considered hazardous and has not been approved (9).

It is evident that the structure of the hydroxyanisole is of importance in deciding the antioxidant effectiveness of that compound. A similar situation is believed to exist as to carry-through. This contention is based on the carry-through properties of 2- and 3-t-butyl-4-hydroxyanisole. The stability of soda crackers containing lard inhibited with 0.01% of each of these isomers gave the following Schaal Oven (10) (145°F.) results: no antioxidant 3 days, 2-t-butyl-4-hydroxyanisole 10 days, 3-t-butyl-4-hydroxyanisole 26 days.

In the functioning of a compound as an antioxidant the question is often raised as to the fate of the antioxidant molecule. It is generally conceived that the antioxidant is oxidized in the stabilization process. In an attempt to characterize any oxidation step which may be involved, 3-t-butyl-4-hydroxyanisole was subjected to mild oxidation by such reagents as potassium ferricyanide or oxygen in the presence of caustic. It was found that a colorless compound was formed, possessing a high melting point (225° C.), low solubility, and a carbon and hydrogen content for the dimer minus one mole of hydrogen. This oxidation product is believed to be a diphenyl derivative formed as follows:



This oxidation product is not devoid of antioxidant properties for it possesses an inhibitor ratio of 0.33 at 0.005% concentration and 0.50 at 0.02% concentration. It has not been established that this material actually is formed during the inhibiting process; it is likely that other products may be involved.

This paper is an attempt to describe and correlate structural effects as to antioxidant activity for a selected group of compounds. It is hoped that such information will be of value in the selection, development, and application of antioxidants.

Summary

The antioxidant potency of a substituted hydroxyanisole greatly depends on the orientation of the substituents which make up the molecule. This fact is demonstrated by the synthesis and evaluation of

a number of alkyl substituted hydroxyanisoles as to antioxidant effectiveness in the stabilization of lard. In the case of the derivatives of 4-hydroxyanisole, maximum potency is realized by placement of a t-butyl group in the number 3 position relative to the methoxy group. The substitution of other groups such as one or two methyl groups, a butyl group of normal, iso, or secondary configuration, or a t-butyl group in the number 2 position leads to an antioxidant of lower potency. The potencies of the three t-butylhydroxyphenetoles are comparable to those of the corresponding t-butylhydroxyanisoles. The effectiveness of butylated 2- and 3-hydroxyanisoles are all low; it is essential that the hydroxy group be in the 4-position relative to the methoxy group.

The stability of baked goods (soda crackers) is greater with lard inhibited with 3-t-butyl-4-hydroxyanisole than with 2-t-butyl-4-hydroxyanisole.

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Reactions of Fatty Materials With Oxygen. VIII.[1] Cis-Trans Isomerization During Autoxidation of Methyl Oleate[2,2a]

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THE initial stages of autoxidation of olefins are immensely important in investigating the mechanisms of this reaction. Ultra-violet spectrophotometric examination of certain non-conjugated polyolefins (5, 15) during the early stages of oxidation has given much useful information on the type and amount of oxygen-induced conjugation. With monoolefins, unfortunately, ultra-violet spectrophotometric examination of the oxidation mixture during the early stages is of little value because the starting materials and the oxidation products do not show any absorption bands within the operating range of conventional laboratory spectrophotometers. The ease with which oxygen causes changes in double bond systems however suggested that an examination of autoxidation mixtures should be made with the object of determining whether an oxygen-induced cis-trans isomerization occurs, particularly during the initial stages of oxidation.

Positive evidence for the occurrence or non-occurrence of oxygen-induced cis-trans isomerization is of considerable theoretical importance for many reasons, several of which are given. a) Although both isomeric 9,10-dihydroxystearic acids (m.p. 95° and 130°) can be isolated (about 5-15% yields) from methyl oleate or oleic acid autoxidation mixtures, the high-melting isomer predominates (32), whether the autoxidation mixture contains metal-salt catalysts or is irradiated with ultra-violet. High-melting 9,10-dihydroxystearic acid can be obtained by cis hydroxylation (31) of oleic acid or methyl oleate (direct addition of two hydroxyl groups formed possibly from hydroperoxides by radical decomposition) or from elaidic acid or methyl elaidate (formed by isomerization of oleic acid or methyl oleate) by epoxidation (cis addition) followed by hydrolysis (inversion occurs). b) The 9,10-epoxystearic acid isolable (about 5-15% yields) from methyl oleate or oleic acid autoxidations is the low-melting (trans) isomer (10, 11). This isomer can presumably only be obtained by epoxidation (cis addition) of methyl elaidate or elaidic acid (formed by isomerization of oleic acid or methyl oleate). c) In the autoxidation of other cis-monoolefins the α-glycol obtained mainly is the isomer comparable in configuration to that obtained from the autoxidation of methyl oleate or oleic acid (see a) above). It is obvious that several reactions are probably going on simultaneously in the same autoxidation system.

The development of infrared spectrophotometric techniques within the past few years has provided a method for the detection and quantitative determination of trans monoolefins in the presence of large amounts of cis isomer (1, 2, 16, 17, 19, 20, 27, 29, 35). This method is based on the fact that trans monoolefins show an intense absorption band in the infrared region at a wavelength of about 10.3-10.4 microns whereas cis monoolefins do not. So far as we know, there is no other method available for the detection of small quantities of trans monoolefins in mixtures.

Methyl oleate irradiated with ultra-violet light has been autoxidized at 35°. Samples were withdrawn at intervals and infrared absorption spectra were determined on the liquids from 2 to 15 microns. In the present investigation we were mainly interested in interpretation of the spectra in the region between

[1] The previous paper in this series is reference 30.
[2] Presented at the Fall Meeting of the American Oil Chemists' Society in San Francisco, Calif., Sept. 26-28, 1950.
[2a] Report of a study in which certain phases were carried on under the Research and Marketing Act of 1946.
[3] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.