

mestic cottonseed oil can be converted into cocoa butter-like fat needed by the candy industry in the United States, not as a substitute for cocoa butter, but as a supplement to the natural fat. Increased domestic consumption of candy brought about by rising disposable income, gives additional emphasis to the need for this product.

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The Antioxidant Activity of 3,5-Di-tert-butyl-4-hydroxybenzyl Derivatives¹

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Abstract

Various electron donating groups such as alkoxy, alkylthio, and alkylamino groups were used to replace a hydrogen atom of the para-methyl group of 2,6-di-tert-butyl-4-methylphenol, BHT. The antioxidant activity of these 3,5-di-tert-butyl-4-hydroxybenzyl derivatives in stripped corn oil at 79.5° ± 1.0C was measured on the basis of the length of the induction period. A modified peroxide determination was devised and used in the present study. The overall average of the per cent accuracy, based on the standard error, was 2.5%.

The results indicated that the tertiary methyl and ethylamine derivatives had the strongest potency among all compounds tested. Both amine derivatives were able to prolong the induction period of the corn oil twice as much as BHT. The alkoxy derivatives were as effective as BHT. The alkylthio derivatives showed stronger activity than either BHT or the alkoxy derivatives. The secondary alkylamine derivatives, except the n-hexadecylamine derivative, demonstrated nearly the same degree of potency as BHT. However, the n-hexadecylamine derivative exhibited far stronger activity than either the three lower alkylamine derivatives or BHT. In all three homologous series, the methyl derivatives showed significantly lower activity than the ethyl or n-propyl derivatives. Differences between the ethyl and n-propyl derivatives were not significant. 3,5-Di-tert-butyl-4-hydroxybenzylpyridinium bromide acted as a prooxidant. An attempt has been made to explain the variation in activity of these derivatives in terms of the inductive effect exerted by the nucleophilic substituents and/or in terms of the structural features of the derivatives.

alkylphenols, a variation of the alkyl chain from a methyl to n-butyl group did not cause any significant modification in antioxidant activity (2). It has been reported that an electron donating group at the para-position of the alkylphenols would enhance antioxidant activity (3). On the other hand, an electron withdrawing group at the same position has been reported to retard or completely eliminate antioxidant activity (3,4). Furthermore, it has been observed that the removal of such an electron withdrawing group at the para-position of 3,5-di-tert-butyl-4-hydroxybenzaldehyde resulted in the recovery of antioxidant activity. 3,5-Di-tert-butyl-4-hydroxybenzaldehyde regained antioxidant activity when it was converted into 3,5-di-tert-butyl-4-hydroxybenzaldehyde isonicotinoylhydrazone (4).

In the present study a hydrogen atom on the para methyl group of 2,6-di-tert-butyl-4-methylphenol (BHT) was replaced with various electron donating groups such as the alkoxy, alkylthio, and alkylamino groups. We have assumed that replacement of a hydrogen atom of the para-methyl group of BHT with a strong electron donating group would enhance the functional activity of the compound. The antioxidant activity was measured and compared on the basis of the length of induction periods of substrates (stripped corn oil) containing the 3,5-di-tert-butyl-4-hydroxybenzyl derivatives. Efforts were made to correlate the variation in antioxidant potency with the inductive effect of the substituent groups and/or with structural features of the benzyl derivatives.

Experimental

The Synthesis of Test Compounds. 3,5-Di-tert-butyl-4-hydroxybenzyl bromide (III) was prepared directly from 2,6-di-tert-butyl-4-methylphenol (BHT) as described by Schmid and Karrer (5) and Dauben (6) (Fig. 1). The benzyl bromide was also obtained through rearrangement of 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone (II) (7,8). The synthesis of 3,5-di-tert-butyl-4-hydroxybenzylmethyl (V), ethyl (VI), and n-propyl (VII) ethers was achieved by alkylation of 3,5-di-tert-butyl-4-hydroxybenzyl alcohol (IV) with sodium alkoxide. The methyl derivative was also prepared by direct reaction of 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone (II) with sodium methoxide. 3,5-Di-tert-

IT HAS BEEN SHOWN (1) that tert-butyl groups in the ortho-positions and an alkyl group at the para-position resulted in the most effective antioxidant activity in the alkyl phenolic type of antioxidants of which 2,6-di-tert-butyl-4-methylphenol (BHT) is one of the best known to date. Among 2,6-di-tert-butyl-4-

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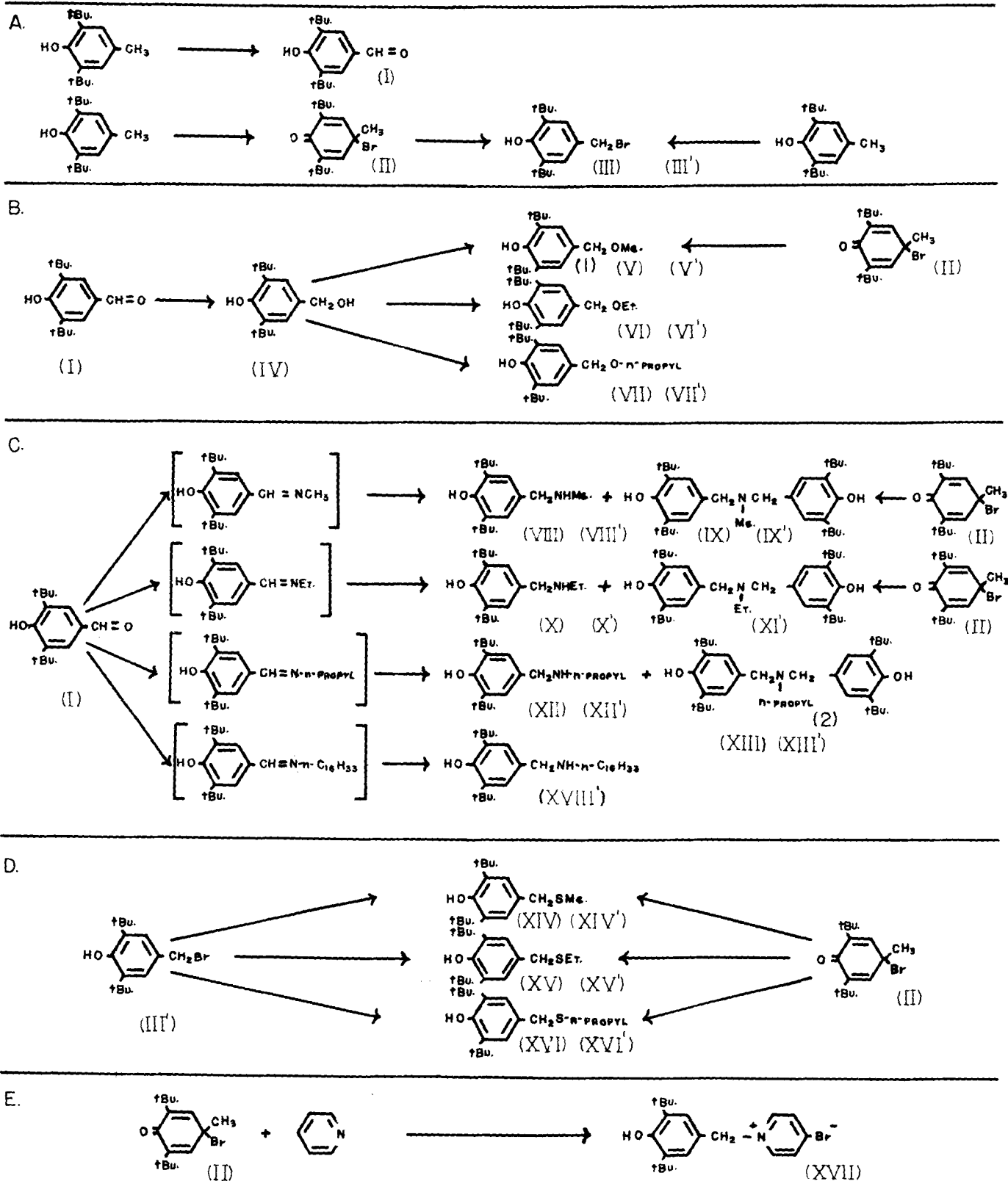


FIG. 1. Synthetic steps to 3,5-di-tert-butyl-4-hydroxybenzyl derivatives

(1) This compound is currently sold as antioxidant for rubber and plastic materials by the Ethyl Corporation.
 (2) The structure of this compound has not been confirmed.

butyl-4-hydroxybenzylmethyl (VIII), ethyl (X), and n-propylamines (XII) were prepared by reductive amination of 3,5-di-tert-butyl-4-hydroxybenzaldehyde (I) with the corresponding amines. Di-(3,5-di-tert-butyl-4-hydroxybenzyl)-methyl (IX) and ethylamine (XI) were synthesized either by reductive amination

of 3,5-di-tert-butyl-4-hydroxybenzaldehyde (I) with the corresponding amines or by direct amination of 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone (II) which was prepared according to the procedure reported by Coppinger and Campbell (9). 3,5-Di-tert-butyl-4-hydroxybenzaldehyde was prepared by

the method of Cohen (10). 3,5-Di-*tert*-butyl-4-hydroxybenzyl alcohol was obtained by reduction of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde with lithium aluminum hydride (9). 3,5-Di-*tert*-butyl-4-hydroxybenzylthiomethane (XIX), ethane (XX), and *n*-propane (XVI) were prepared by reacting the corresponding sodium mercaptides with 2,6-di-*tert*-butyl-4-methyl-4-bromo-2,5-cyclohexadienone (II).

Detailed Synthesis

A. *Preparation of 3,5-di-tert-butyl-4-hydroxybenzyl bromide*. This compound (III) was prepared from 22.0 g (0.10 M) 3,5-di-*tert*-butyl-4-methylphenol which was dissolved in 100 ml of carbon tetrachloride. *N*-Bromosuccinimide, 18.6 g (0.105 M), and 400 mg of benzoyl peroxide were added to the solution, the mixture was refluxed for 7 hr and filtered. The filtrate was concentrated and set aside for crystallization. The crystals weighed 17.2 g and melted at 53–54°C. The recrystallized product melted at 56–57°C [lit. 51–53°C (7), 54–55°C (8)]. Anal. calcd. for $C_{15}H_{23}OBr$: C, 60.20; H, 7.75; Br, 26.70. Found: C, 60.34; H, 7.46; Br, 26.80. A 5% carbon tetrachloride solution gave a sharp I.R. band around 3650 cm^{-1} (7), but no band at the region of 1626 cm^{-1} –1667 cm^{-1} (11), indicating the presence of a hindered hydroxyl group and the absence of a hindered carbonyl group. A 95% ethyl alcohol solution of the compound did not show any U.V. absorption band between 230 $m\mu$ and 240 $m\mu$ (9), indicating again the absence of a hindered carbonyl group.

B. *Preparation of ethers*. For the preparation of 3,5-di-*tert*-butyl-4-hydroxybenzylmethyl ether (V), 8 g of the cyclohexadienone (0.027 M) and 2.9 g of sodium methoxide (0.027 M) were dissolved in 200 ml of absolute methanol. The mixture was refluxed overnight, the methanol evaporated, the residue extracted with Skellysolve F, partially freed from solvent and set aside for crystallization. White crystals, which were purified by recrystallization, were obtained. Yield: about 2.0 g (30% of theoretical), M.P. 98°C [lit. 99.5°C (10), 101–102°C (8)]. Anal. calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 77.42; H, 10.47. This compound was also obtained by methylation of 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol with dimethyl sulfate in the presence of KOH. A mixed melting point of samples from each preparation gave no depression.

3,5-Di-*tert*-butyl-4-hydroxybenzylethyl ether (VI) was prepared as follows: Two g (0.0085 M) of benzyl alcohol (M.P. 137–139°C, lit. 137.7–138.1°C (9)) were allowed to react with 1.50 ml of diethyl sulfate (0.010 M) in the presence of 0.5 g of KOH in 200 ml of Skellysolve F. Total reaction time, including 1½ hr refluxing, was about 2 hr. The reaction mixture was concentrated in vacuo, the residue extracted with Skellysolve F, partially freed of solvent and set aside for crystallization. Yield: 0.8 g (36% of theoretical). The recrystallized product melted at 151–153°C. Anal. calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.32; H, 10.41.

The preparation of 3,5-di-*tert*-butyl-4-hydroxybenzyl-*n*-propyl ether (VII) was carried out as previously described for the ethyl ether. In another run, 2 g of the benzyl alcohol were dissolved in an excess of *n*-propyl iodide which contained 5 g of finely powdered potassium carbonate, the mixture was refluxed and freed of solvent, extracted with Skellysolve F and recrystallized. Both procedures gave crystals which melted at 147–149°C. Anal. calcd. for

$C_{18}H_{30}O_2$: C, 77.64; H, 10.86. Found: C, 77.89; H, 9.91. (Based on the product obtained by the first procedure.)

C. *Preparation of amine derivatives*. In the preparation of 3,5-di-*tert*-butyl-4-hydroxybenzylmethylamine (VIII) and di-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-methylamine (IX), 4.7 g (0.02 M) of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde were refluxed overnight with 2.7 g (0.04 M) of methylamine hydrochloride in the presence of 2.1 g of sodium methoxide in Skellysolve F. The product, presumably a Schiff's base, was dissolved in 200 ml of absolute methanol and was hydrogenated over 500 mg of platinum dioxide for 50 min at room temperature and an initial hydrogen pressure of 45 psi. The crystals which were obtained from the hydrogenated mixture weighed 1.4 g and melted at 175°C. The recrystallized product also melted at 175°C. The molecular formula based on di-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-methylamine was $C_{31}H_{46}O_2N$. Anal. calcd. for $C_{31}H_{46}O_2N$: C, 79.60; H, 10.56; N, 2.99. Found: C, 79.88; H, 10.38; N, 3.11. This tertiary amine was also obtained by direct amination of 2,6-di-*tert*-butyl-4-methyl-4-bromo-2,5-cyclohexadienone, a mixed melting point of the two tertiary amine derivatives gave no depression. A second crop of crystals, which weighed 0.6 g and melted at 93–94°C, was obtained from the hydrogenation mixture. The recrystallized product melted at 98–99°C. The molecular formula based on 3,5-di-*tert*-butyl-4-hydroxybenzylmethylamine was $C_{16}H_{27}ON$. Anal. calcd. for $C_{16}H_{27}ON$: C, 77.05; H, 10.91; N, 5.62. Found: C, 76.72; H, 10.16; N, 5.54. This secondary amine derivative was also obtained by direct amination of the cyclohexadienone. A mixed melting point of the two secondary amine derivatives gave no depression.

In the preparation of 3,5-di-*tert*-butyl-4-hydroxybenzylethylamine (X) and di-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-ethylamine (XI¹), 11 g of the aldehyde (0.044 M) and 9.6 cc of ethylamine (0.15 M) were dissolved in 300 ml of absolute methanol. The mixture was hydrogenated at room temperature over 500 mg of platinum dioxide as a catalyst and at an initial hydrogen pressure of 45 psi. The crystals which were obtained from the mixture melted at 78–79°C; a mixed melting point measurement with a compound obtained by direct amination of the cyclohexadienone gave no depression. The molecular formula based on 3,5-di-*tert*-butyl-4-hydroxybenzylethylamine was $C_{17}H_{29}ON$. Anal. calcd. for $C_{17}H_{29}ON$: C, 77.59; H, 11.10; N, 5.32. Found: C, 77.21; H, 10.73; N, 5.18. In another hydrogenation run, a compound which melted at 142–144°C was isolated. The recrystallized product melted at 144°C. A test for nitrogen was positive (13). The molecular formula based on di-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-ethylamine was $C_{32}H_{51}O_2N$ and the molecular weight, 481.8. The molecular weight determined by the Rast method was 479.0.

Hydrogenation of 3,5-di-*tert*-butyl-4-hydroxybenzyl-*n*-propylamine (XII) was conducted in a manner similar to that previously described for the ethylamine derivative. The first crystals which were obtained weighed 1.5 g and the recrystallized product melted at 143–144°C. This compound was presumably di-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*n*-propylamine (XIII), but no confirmative test was made. The second crop of crystals from the filtrate weighed 4.0 g and the recrystallized product melted at 49–50°C. The molecular formula based on 3,5-di-*tert*-butyl-4-hydroxybenzyl-*n*-propylamine (XVIII¹) was $C_{18}H_{31}ON$. Anal.

calcd.: C, 77.92; H, 11.26; N, 5.05. Found: C, 78.54; H, 11.11; N, 5.17.

D. *Preparation of thioether derivatives.* 3,5-Di-tert-butyl-4-hydroxybenzylthiomethane (XIV) was prepared as follows: Ten g (0.33 M) of 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone and 10.8 g of sodium thiomethylate (0.154 M) were refluxed in 150 ml of Skellysolve F overnight. The reaction mixture was then washed with water several times, dehydrated with sodium sulfate, concentrated in vacuo to 150 ml, set aside for crystallization and the crystals removed by filtration. These crystals were recrystallized from Skellysolve F, an approximate analysis indicated that they did not contain sulfur. They had a melting point of 188–189°C; furthermore a mixed melting point with 3,5-di-tert-butyl-4-hydroxybenzaldehyde gave no depression. As 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone had been shown to yield 3,5-di-tert-butyl-4-hydroxybenzyl alcohol (9) and the benzyl alcohol could be readily oxidized to 3,5-di-tert-butyl-4-hydroxybenzaldehyde, it was evident that these crystals were 3,5-di-tert-butyl-4-hydroxybenzaldehyde. A second crop of crystals (about 2.7 g) was obtained from the original filtrate. Several recrystallizations gave large needle-like crystals which melted at 53°C. Anal. calcd. for $C_{16}H_{26}OS$: C, 72.12; H, 9.84; S, 12.03. Found: C, 72.00; H, 9.56; S, 12.25. When 3,5-di-tert-butyl-4-hydroxybenzyl bromide was used instead of the cyclohexadienone, the results were the same.

3,5-Di-tert-butyl-4-hydroxybenzylthioethane (XV) was prepared from 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone and sodium thioethylate as previously described for the thiomethane derivative. The recrystallized product melted at 33–34°C. Anal. calcd. for $C_{17}H_{28}OS$: C, 72.80; H, 10.06; S, 11.43. Found: C, 72.41; H, 9.64; S, 11.69. A 5% carbon tetrachloride solution of the thioethane had a very sharp I.R. band at 3622 cm^{-1} (7), but no band around 1610–1660 cm^{-1} (11), indicating the presence of a hindered hydroxyl group and the absence of a hindered carbonyl group. There was no U.V. absorption band around 230 $m\mu$ –240 $m\mu$ (9) again indicating the absence of a hindered carbonyl group.

3,5-Di-tert-butyl-4-hydroxybenzylthio-n-propane (XVI) was prepared from 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone and sodium thio-n-propylate in a manner similar to that previously described for the thiomethane derivative. The recrystallized product melted at 39–40°C. Anal. calcd. for $C_{18}H_{30}OS$: C, 73.41; H, 10.27; S, 10.89. Found: C, 73.75; H, 10.41; S, 10.66.

E. *Preparation of pyridinium bromide.* 3,5-Di-tert-butyl-4-hydroxybenzylpyridinium bromide (XVII) was prepared as follows: Five g of 2,6-di-tert-butyl-4-methyl-4-bromo-2,5-cyclohexadienone (0.017M) were dissolved in 100 ml of n-propyl alcohol, 1.33 g of pyridine (0.017 M) were added and the mixture refluxed for 2 hr. The mixture was dried in vacuo and the residue was extracted with Skellysolve F. Two and four tenths g of white crystals were obtained from the extract. The recrystallized product decomposed at 226°C. Anal. calcd. for $C_{20}H_{28}ONBr$: C, 63.48; H, 7.45; N, 3.70; Br, 21.12. Found C, 63.03; H, 6.98; N, 3.76; Br, 21.36.

Test for Antioxidant Activity

The antioxidant activity of the derivatives was compared on the basis of the length of the induction period. Twenty g of stripped corn oil² were placed in a shallow beaker (4) and the test antioxidant was

added in 2 ml of absolute ethyl alcohol to provide a concentration of 1 μ mole per g of oil. The solvent was evaporated on a steam bath for 15 min. 2,6-Di-tert-butyl-4-methylphenol (BHT) was used as a standard, and a substrate without any antioxidant was used as the blank control. The substrates were incubated in an oven at $79.5^\circ \pm 1.0C$. Peroxide values were determined in duplicate at 0, 25, 50, and 75 hr intervals. A variation of the methods used by others (3,14,15, 16) was used to determine the peroxide values.

An accurately weighed fat sample of about 0.5 g was introduced into a 125 ml Erlenmeyer flask fitted with a ground glass stopper. The sample was dissolved in 10 ml of a mixture of acetic acid and chloroform (3:2 by volume). One ml of saturated potassium iodide solution was introduced, a stream of nitrogen passed into the flask and the mixture agitated by a rotary motion for 1 min. The reaction was carried out in a dimly lighted room. The flask was then stored for 15 min in a dark cabinet, 10 ml of distilled water added and the liberated iodine was titrated with 0.01 N standardized thiosulfate solution using 15 drops of 1% starch solution as an indicator. The peroxide value was expressed as the number of millimoles of peroxide per kg of oil.

Estimation of the Induction Period

The induction period was taken as the time required for a substrate to reach a peroxide value of 70. The induction period was estimated graphically. The stripped corn oil had an initial peroxide value of 2.5; a correction factor was therefore applied to all samples. The mean value of the induction periods and the standard error for the three replicate runs were calculated (Table I). In order to make comparison easier, the ratio of the length of the induction period of each substrate to that of the blank con-

² Refined corn oil of which natural antioxidants have been stripped by molecular distillation furnished through the courtesy of Stanley Ames, Distillation Products Industries, New York.

TABLE I
Comparative Stability of Various BHT Derivatives

Compound ^a	Mean induction per. plus std. error in hr	% Accuracy	Ratio plus standard error
Blank control.....	43.4 \pm 0.3	0.7	1.00
2,6-Di-tert-butyl-4-methylphenol, (BHT).....	73.2 \pm 1.4	1.9	1.70 \pm 0.04
3,5-Di-tert-butyl-4-hydroxybenzylmethyl ether.....	65.2 \pm 2.3	3.5	1.51 \pm 0.06
3,5-Di-tert-butyl-4-hydroxybenzylethyl ether.....	72.2 \pm 2.9	4.0	1.66 \pm 0.07
3,5-Di-tert-butyl-4-hydroxybenzyl-n-propyl ether.....	70.3 \pm 0.8	1.1	1.62 \pm 0.02
3,5-Di-tert-butyl-4-hydroxybenzylmethylamine.....	68.0 \pm 0.5	0.7	1.57 \pm 0.02
3,5-Di-tert-butyl-4-hydroxybenzylethylamine.....	73.5 \pm 3.1	4.2	1.69 \pm 0.07
3,5-Di-tert-butyl-4-hydroxybenzyl-n-propylamine.....	75.7 \pm 2.0	2.6	1.74 \pm 0.05
3,5-Di-tert-butyl-4-hydroxybenzyl-n-hexadecylamine.....	81.4 \pm 2.2	2.7	1.88 \pm 0.05
Di-(3,5-di-tert-butyl-4-hydroxybenzyl)-methylamine.....	96.5 \pm 1.3	1.3	2.22 \pm 0.03
Di-(3,5-di-tert-butyl-4-hydroxybenzyl)-ethylamine.....	96.5 \pm 3.3	3.4	2.22 \pm 0.08
3,5-Di-tert-butyl-4-hydroxybenzylthiomethane.....	76.7 \pm 2.1	2.7	1.77 \pm 0.05
3,5-Di-tert-butyl-4-hydroxybenzylthioethane.....	83.8 \pm 4.6	5.5	1.93 \pm 0.11
3,5-Di-tert-butyl-4-hydroxybenzylthio-n-propane.....	83.5 \pm 0.5	0.6	1.92 \pm 0.02
3,5-Di-tert-butyl-4-hydroxybenzylpyridinium bromide.....	38.5 \pm 0.5	1.3	0.89 \pm 0.02

^a Test compounds which were dissolved in 20.0 g of stripped corn oil at a level of 1 μ mole per g oil and incubated in shallow beakers in an oven at $79.5^\circ \pm 1.0C$.

trol was calculated. The over-all accuracy, based on the per cent accuracy of the average error, was 1.9%. The procedure used in the present study for measurement of antioxidant activity appears to have approximately the same degree of reproducibility as the one reported by Everson *et al.* (17). Comparison of the antioxidant activity of two different test compounds was made in terms of the length of the mean induction periods of the substrates that contained the test compounds. Significant differences at the 10% level were taken by means of the "t" test throughout the comparisons.

Results

The tertiary alkylamine derivatives, di-(3,5-di-tert-butyl-4-hydroxybenzyl)-methyl and -ethyl amines, revealed the strongest antioxidant activity among the various homologous series of compounds tested in the present study. The methyl and ethyl tertiary amine derivatives increased the induction period by approximately 120%. They were almost twice as effective as BHT in lengthening the induction period of the control.

The alkoxy derivatives 3,5-di-tert-butyl-4-hydroxybenzylethyl and n-propyl ether were as effective antioxidants as BHT. However, 3,5-di-tert-butyl-4-hydroxybenzylmethyl ether was a significantly weaker antioxidant than the ethyl or n-propyl derivative or BHT.

The secondary alkylamine derivative, 3,5-di-tert-butyl-4-hydroxybenzylmethylamine, prolonged the induction period of the control by 60%, although it was a significantly weaker antioxidant than BHT. The ethyl and n-propylamine derivatives showed approximately the same degree of potency as BHT. The n-hexadecylamine derivative demonstrated much stronger antioxidant activity than the lower homologs. It increased the induction period of the blank by approximately 90%. Its potency was comparable to the ethylthio and n-propylthio derivatives.

The alkylthio derivatives, 3,5-di-tert-butyl-4-hydroxybenzylthiomethane, -ethane, and -n-propane, were more effective antioxidants than the alkoxy derivatives. The methylthio derivative increased the induction period of the blank control by 77% and showed a similar degree of antioxidant activity to BHT. The difference in activity was not significant. The two higher homologs demonstrated a stronger antioxidant activity than either the methylthio derivative or BHT. Both the thio ethane and n-propane derivatives increased the induction period of the control by approximately 90%. There was no significant difference in antioxidant activity between them.

3,5-Di-tert-butyl-4-hydroxybenzylpyridinium bromide showed a prooxidant rather than an antioxidant activity. It decreased the induction period of the control by 10%.

Discussion

It has been established that an electron donating group attached to the ortho- or para-positions of a phenolic antioxidant will generally enhance the activity of the antioxidant (3). A substituent which is not directly attached to the phenolic nucleus may still exert a strong inductive effect on the nucleus via an interposed atom. For some acids and alcohols it has been estimated that the inductive effect of a group decreased by a factor of 2.8 for every additional atom that separated it from the acidic hydrogen atom (18). A quaternary nitrogen atom still exerted a dominant

orienting effect upon the nitration of the substituted benzene even when it was separated from the nucleus by two methylene groups (19).

Goldsworthy (20) has studied the relative strength of the inductive effect of various alkoxy groups upon the nitration of substituted benzenes. The relative strengths of the inductive effect of ethoxy, n-propoxy, and n-hexadecyloxy groups were 164, 180, and 214, respectively, when that of the methoxy group was taken as 100. These results were in agreement with the theory advanced by Robinson *et al.* (21). Although the inductive effect appears to have an important role in activating or deactivating a phenolic antioxidant, the nature of this effect does not seem to have been elucidated.

Lowry *et al.* (22) have reported that a correlation could be established between the effectiveness of some antioxidants and their critical potential.³ However the effectiveness of an antioxidant was not proportional to the magnitude of the potential. This is understandable because the potential applies only to a reversible process and may not be applicable to an irreversible one such as peroxide formation (23).

Cosgrove and Waters (23) have suggested that the ortho-substituted alkyl phenols function primarily as a chain terminating agent. It has generally been assumed that antioxidants terminate a chain propagating reaction such as peroxy radical formation by combining the free radicals (24). Furthermore, Walling *et al.* (25) have reported that the reactivity of para-substituted benzaldehydes toward a peroxy radical was increased by the introduction of electron donating substituents. They concluded that the reaction rate did not depend so much upon the resonance stabilization of the transition state as on the polarity of reacting molecules. The variation in antioxidant strength of the alkoxy derivatives used in the present study may have been due to the inductive effect of their electron donating groups.

The alkylthio derivatives, which contained nucleophilic groups, seemed to exert a strong inductive effect upon an alkylphenol and enhance the antioxidant activity of BHT. It has been reported that sulfides, which contained at least one aliphatic or one cycloaliphatic group attached to the sulfur atom, were effective antioxidants (26). The sulfides appeared to react very rapidly with hydroperoxides formed in a substrate such as lubricant oil and to form the corresponding sulfoxides and sulfones (27). The alkylthio derivatives may act bifunctionally as a sulfide and as a phenolic type antioxidant bringing about interaction between hydroperoxides and sulfides in a coautoxidation process (28). Reduction of the peroxide content in the substrate represented the result of such interaction.

Although the present study revealed that the alkylthio derivatives were stronger antioxidants than either the alkoxy derivatives or BHT, the same regularity with respect to variation of the antioxidant strength of the homologous derivatives was observed. The methylthio derivative showed weaker activity than the two higher homologs; however, no significant difference in antioxidant activity was noted between the ethylthio and n-propylthio derivatives. This could be explained by the inductive effect of the methyl and

³The concept of the critical oxidation potential was introduced by Fieser to make possible quantitative measurement of the oxidizability of reductants of oxidation-reduction systems in which the oxidants are unstable. It was defined as the potential at which the rate of oxidation of the reductant of an oxidation-reduction system became so small as to be barely detectable (21, cf. Fieser, L. F., *J. Am. Chem. Soc.*, 52, 5204, 1930).

ethyl or propyl groups. The inductive effect of a methyl group would be considerably smaller than that of the two higher homologs.

Kawai *et al.* (29) have studied the antioxidant activity of the ortho- and para-cresol derivatives for vitamin A in fish liver oil. They reported that antioxidant activity appeared to reach its maximum value when the alkyl side chain contained four to five carbon atoms. The n-hexadecylamine derivative showed a very strong functional activity which is difficult to explain by the inductive effect alone. Although the n-hexadecylamino group may have a larger magnitude of effect than the lower alkylamino groups, the difference could not be large enough to account for the increased activity. It is likely that the long aliphatic side chain would have some desirable effect upon the antioxidant function of the n-hexadecylamine. The side chain may orient the amine molecules in such a way as to facilitate the interaction of the molecules with free radicals. On the other hand, Rosenwald *et al.* (2) found that the functional activity of 2,6-di-tert-butyl-4-alkylphenols remained constant when the 4-alkyl side chain varied from a methyl to n-butyl group.

Bickoff (30) has reported that the interposition of a methyl group between the amino group and the benzene ring of p-aminophenol resulted in complete deactivation of the parent molecule. This suggested that both a hydroxyl and a para amino group are required for the functional activity of p-aminophenol. The secondary alkylamine derivatives may be regarded as products which would have resulted by the interposition of a methylene group between the alkyl-amino group and the benzene nucleus. The fact that these products were as active as BHT appears to indicate that in ortho-alkylated phenols the hindered hydroxyl group plays an essential role in functional activity. However, this does not imply that the nature of the para-substituent does not modify significantly the activity of the phenols. The hydrogen atom of the hindered hydroxyl group of the phenolic antioxidant is likely to be involved in the chain terminating step of autoxidation. On the other hand it has been reported that tetramethylphenylenediamine, which does not have a freely available hydrogen atom, acted as an efficient antioxidant (30).

Although there was no significant difference in activity between the methyl and ethylamine derivatives, the ethylamine derivative had been expected to have somewhat greater activity than the methylamine derivative because the electron donating ability of ethylamine groups would be slightly greater than that of methylamine groups. Brown *et al.* (32) have reported that the markedly weaker basicity of trimethylamine than that of methyl and dimethylamine could be explained by an extra strain of the nitrogen atom caused by bulky methyl groups. The ethylamine derivative may retain somewhat larger strain than the methylamine derivative because of a longer side chain. This would counteract the inductive effect of the ethylamino group which would otherwise be slightly stronger than that of the methylamino group. The strength of the inductive effect exerted by methyl and ethylamino groups apparently would be the same in this case.

Since the tertiary amine derivatives contain two units of the 3,5-di-tert-butyl-4-hydroxybenzyl residue, their effectiveness appears to be additive with respect to the number of the residue. However, such addi-

tivity does not seem to hold generally. For instance, 1,2-bis-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethane, which consists of two units of the 3,5-di-tert-butyl-4-hydroxyphenyl residue, has been reported to have only the same instead of twice the potency of BHT (3). Thus the nitrogen atom in the tertiary amine derivatives appears in some way to contribute to the strong activity of the derivatives. The nitrogen atom, being electron rich, may be able to alleviate the electron deficiency of the nucleus which may occur during autoxidation. Such implementation may be difficult when one or two 3,5-di-tert-butyl-4-hydroxybenzyl residues of 1,2-bis-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethane are involved in phenoxy radical formation during the autoxidation. However, that two 3,5-di-tert-butyl-4-hydroxybenzyl residues may reinforce the effectiveness of the tertiary amine derivatives as a whole can not be ruled out.

The strong electron withdrawing effect of the quaternary nitrogen group in 3,5-di-tert-butyl-4-hydroxybenzylpyridinium bromide seemed to deactivate the functional activity of the parent molecule, BHT. Since this bromide would be readily ionizable to the pyridinium cation and bromide anion, these ions may be involved in reactions which increase the rate of autoxidation. However, the substrate used in the present study would not be an effective medium for such dissociation. It is doubtful that such dissociation and hence the resultant ionic species alone would account for the prooxidant activity of the pyridinium bromide.

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