acrylonitrile adduct of raw tung oil is also a satisfactory plasticizer. A detailed account of its properties will appear in a subsequent publication.

Summary

Acrylonitrile and fumaronitrile have been employed as dienophiles in the Diels-Alder reaction with butyl *alpha-* and *beta*-eleostearates, and infrared and ultraviolet spectra determined for the addition product as well as for the dienophiles.

The adducts have been tested as primary plasticizers for vinyl resins and compared with dioctyl phthalate. The fumaronitrile adducts were found superior to the acrylonitrile adducts with regard to compatibility; however the latter are satisfactory as secondary plasticizers. By incorporating the acrylonitrile adducts with DOP or TCP, it is possible to achieve either a reduction in volatility of DOP plasticized stocks or an improvement in the modulus and low-temperature performance of TCP plasticized stocks. This does not entail any sacrifice in the desirable plasticizing characteristics of DOP or TCP.

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Some Derivatives of Hydroxyhydroquinone as Antioxidants

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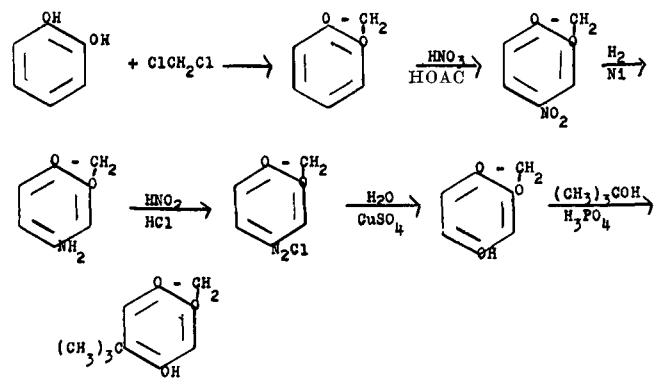
THE IMPROVEMENT of inhibiting potency of phenolic antioxidants by the introduction of certain substituents into the proper position of the aromatic nucleus has been observed for several compounds. For example, Rosenwald, Hoatson, and Chenicek (9) showed that addition of certain alkyl groups to the nucleus greatly enhanced potency; the addition of a tert-butyl group in the ortho position was especially favorable.

This enhancement also takes place with certain substituted hydroquinones. Thus the potency of 4-hydroxyanisole (8) is greatly increased by the introduction of a tert-butyl group in the nucleus; the increase is larger when the substituent is in a position ortho to the free hydroxy.

Gleim and Chenicek (6) showed that butylation of 5-hydroxycoumaran, *i.e.,* introducing a butyl group in the position ortho to the hydroxy, markedly increases inhibiting potency. Since 5-hydroxycoumaran, an analog of 3,4-methylene dioxyphenol (sesamol) was found to be an effective inhibitor (4), it was worthwhile to investigate the effect of introducing a tert-butyl group into 3,4-methylenedioxyphenol and related compounds of this type. If the increase in potency is comparable to that for 4-methoxyphenol, it should be possible to produce very effective antioxidants since the 3,4-methylenedioxyphenol is initially more potent than 4-methoxyphenol.

The investigation of compounds related to methylenedioxyphenol wherein a polymethylene chain or two alkyl groups were substituted for methylene should also be of interest.

Although methylene dioxyphenol and similarly constituted compounds may be regarded as derivatives of hydroxyhydroquinone, this trihydric phenol is an unsatisfactory starting material for synthesis. The following equations show the method used in the synthesis of all the compounds of this type.



None of these reactions is difficult to carry out although the introduction of the methylene group and hydrolysis of the diazonium chloride give yields in the order of 40–60%. Butylation, unlike the butylation of p-methoxyphenol wherein a mixture of isomers is produced (14), gives only one product. No proof of structure of the butylated compounds was made, but their low solubilities in aqueous caustic and the presence of a hindered hydroxy group as shown by the infrared spectrum leave little doubt but that the tert-butyl group is ortho to the hydroxy. Formation of diethers, in which, instead of methylene, dimethyl, diethyl, dimethylene, or trimethylene is used, gave materials that underwent the same series of reactions without difficulties.

The compounds of this series were tested as antioxidants in gasoline and lard. The results in gasoline shown in Table I can be examined most easily by consideration of the last column wherein the potency of the materials is compared on an equimolar basis. The standard is taken as 2-tert-butyl-4-methoxyphenol to which a ratio of 1.00 is assigned.

On the basis of molar ratio, introduction of the tert-butyl group into 4-methoxyphenol increases the

TABLE I

Hydroxyhydroquinone Derivatives as Gasoline Antioxidants
0.02% by weight in Pennsylvania[a] Thermal Gasoline

Compound	M.P.°C.	B.P.°C./mm.	Ind. Per., min. (11)	Ratio to Butylmethoxy phenol Molar Basis
4-methoxyphenol	—	—	390	0.25
2-tert-butyl-4-methoxyphenol	—	—	915	1.00
3,4-dimethoxyphenol (1)	78–79	134/1	695	0.64
2-tert-butyl-4,5-dimethoxyphenol	76	145–147/1	470	0.54
3,4-diethoxyphenol (13)	63–66	130–133/0.25	610	0.64
2-tert-butyl-4,5-diethoxyphenol	73–75	130–145/0.5	470	0.60
3,4-methylene dioxyphenol (3)	65	93–96/1	735	0.60
2-tert-butyl-4,5-methylene dioxyphenol	91–93	110–114/1	505	0.54
3,4-ethylene dioxyphenol (12)	—	115–125/1	400	0.31
2-tert-butyl-4,5-ethylene dioxyphenol	91–93	127–129/1	575	0.67
3,4-trimethylene dioxyphenol	94–95	122–125/0.25	285	0.21
2-tert-butyl-4,5-trimethylene dioxyphenol	133–135	—	415	0.49

[a] Induction period without inhibitor = 100 min.

potency by a factor 4. This ratio is not approached by the butylation of any of the other compounds, the greatest ratio being for 3,4-trimethylene dioxyphenol wherein butylation yielded a compound having a ratio of 2.3 compared with the unbutylated. But the potency of the unbutylated compound is so low that the butylated product is still an indifferent antioxidant.

The butylation of 3,4-methylene dioxyphenol affords a direct comparison with the results of butylating its analog (6). Butylation of 5-hydroxycoumaran gives a product having a molar inhibitor ratio of 2.3 in gasoline when compared to the unbutylated material. This is a marked contrast with the methylene dioxyphenol, which has a ratio of only 0.9 for analogous compounds.

Comparison can also be made of the effect of butylation of analogs containing six membered heterocyclic rings, namely, between 2,2-dimethyl-6-hydroxychroman and 3,4-ethylene dioxyphenol (6). Butylation of the chroman yields a product having a molar inhibitor ratio of 3.2 compared with the unbutylated; the corresponding ratio for 3,4-ethylene dioxyphenol is 2.2. These differences are not large enough to be of much significance, unlike the analogs having 5-membered rings. Size and nature of the ring fused to the substituted phenol has a profound influence on inhibitor potency.

It is desirable to test antioxidants in more than one substrate since frequently variations are quite large between the different substrates. The second substrate selected was lard; data showing A.O.M. times (7) in one lard are given in Table II. The molar ratios are calculated on the basis of methylene dioxyphenol as 1.00.

TABLE II

Hydroxyhydroquinone Derivatives as Lard Antioxidants
0.02% by weight in lard having blank A.O.M. time 4 hrs.

Compound	A.O.M. time, hrs.	A.O.M. Molar ratio
3,4-dimethoxyphenol	45	1.10
2-tert-butyl-4,5-dimethoxyphenol	43	1.42
3,4-diethoxyphenol	35	1.00
2-tert-butyl-4,5-diethoxyphenol	34	1.27
3,4-methylene dioxyphenol	46	1.00
2-tert-butyl-4,5-methylene dioxyphenol	46	1.41
3,4-ethylene dioxyphenol	17	0.41
2-tert-butyl-4,5-ethylene dioxyphenol	40	1.31
3,4-trimethylene dioxyphenol	<16	—
2-tert-butyl-4,5-trimethylene dioxyphenol	24	0.84

In general, these results are quite comparable with those obtained in gasoline. As before, the size of the ring has a profound influence on potency, and it appears worthwhile to compare data obtained on three other materials having fused 5- and 6-membered rings. Thus 4,7-dihydroxyindane (2) and 1,4-dihydroxy-5,8-methano-5,6,7,8-tetrahydronapthalene (5) have A.O.M. times of 59 and 61.5 hours, respectively, when tested in the same way as the compound of Table II. In contrast, 1,4-dihydroxy-5,6,7,8-tetrahydronapthalene (10), in which a fused six-membered ring is present, has an A.O.M. time of 8 hours.

The size of the ring profoundly affects potency since the effect of the 5-membered ring is predominant. The obvious idea that comes to mind in comparing compounds having fused 5- and 6-membered rings is that the Mills-Nixon Effect in some way influences potency. No evidence of the Mills-Nixon Effect has been offered when the 5-membered ring contains a heteroatom, but spacial relationships are very similar for the carbocyclic and heterocyclic rings. The Mills-Nixon Effect offers no explanation for the great difference between the methylene dioxyphenols and the 5-hydroxychroman, which differ only in that the latter have one less heterocyclic oxygen atom. It is also quite unexpected that the effect of the seven-membered heterocyclic ring is to decrease potency greatly. We believe that possibly these data offer a good support for the theory that there is a difference between the effects of fused 5-, 6-, and 7-membered rings, but unfortunately they offer no help in determining the cause of the effects or whether the Mills-Nixon Effect exists as originally pictured.

The varied effect of introducing the tert-butyl group indicates that opposing effects are, at least sometimes, present to influence inhibitor potency. Table I, in which the tert-butyl group increases potency in the case of the first pair of compounds, decreases it in the case of the next three pairs, and increases it for the last two pairs, clearly demonstrates this point. Apparently steric and electronic effects are important in determining final potency, but we cannot say when they will work to reenforce each other or will have opposing effects.

Experimental

The preparation of the majority of these compounds is described in the literature. A brief description of the method for the trimethylene dioxy compounds is given as an example.

Preparation of the Diether. A solution of 66 g. of catechol, 122 g. of trimethylene dibromide, and 68 g. of sodium methylate in 1.5 liter of methanol was heated to 120°C. in a bomb for 6 hrs. The methanol was evaporated, the diether extracted with ether and distilled at 18 mm., b.p. 110–114°C., m.p. 14–15°C. The yield is about 15% for this compound and much better for all the other ethers.

Nitration. To 17 g. of diether in 50 cc. of acetic acid is added 10 g. of nitric acid (D = 1.42) in 15 cc. of acetic acid. The reaction warms spontaneously. After cooling it was poured onto ice and filtered, m.p. 106–107°, yield about 95%.

Reduction. The nitro-trimethylene dioxybenzene absorbed hydrogen rapidly in methanol solution at room temperature and 60 p.s.i.g. in the presence of

nickel on kieselguhr. The product boiled at 105-110°C. at 1 mm. and melted at 74–75°C.

Preparation of the Phenol. Trimethylene dioxyaniline (24 g.) dissolved in dilute sulfuric acid (25 g. in 250 cc.) was diazotized at 0–5°C. with sodium nitrite in water (9.2 g. in 50 cc.). The diazotized solution was run into boiling copper sulfate solution, saturated at 30°C., (250 cc.) with vigorous stirring. The product after extraction with ether boiled at 122–125°C. at 0.25 mm. and melted at 94–95°C.

Butylation. To 5 g. of trimethylene dioxyphenol in 50 g. of 85% phosphoric acid, 2.5 cc. of acetic anhydride, and 2.5 cc. of acetic acid at 70–80° were added 5 g. of tert-butyl alcohol with vigorous stirring. The product crystallizes from the liquid catalyst. Water was added, the product was filtered and crystallized from ether-petroleum ether, m.p. 133–135°C.

All of the other preparations are essentially similar.

Preparation of the 4,7-dihydroxyindane (2) and 1,4-dihydroxy-5,6,7,8-tetrahydronapthalene (10) are both described in the literature. The quinone of 1,4-dihydroxy-5,8-methano-5,6,7,8-tetrahydronaphthalene (5) reduced in methanol with hydrogen in the presence of a platinum catalyst was sublimed at 145°C. at 1 mm. and crystallized from benzene, m.p. 154–155°.

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Relation of Amount and Quality of Protein in the Diet to Free Gossypol Tolerance by the Rat

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A NEGATIVE CORRELATION between free and bound gossypol contents of cottonseed meals and nutritive value of the cottonseed protein as estimated by several biological methods has been shown in reports from this laboratory (1) and (2). Furthermore current studies of gossypol toxicity in swine by Earle and Stevenson (3) have frequently given anomalous or irregular results with respect to the maximum level of free gossypol which will be tolerated when different sources of supplementary protein have been used. In these swine tests the level of free gossypol has been varied in different diets without varying the level of total protein. This was done by supplementing different low gossypol protein concentrates, which included several cottonseed meals and soybean meal, with a calculated small proportion of high gossypol cottonseed meal. The results have indicated that a level of free gossypol which is toxic when fed with some protein supplements may be well tolerated with others.

Parallel with the swine feeding tests, cottonseed meals used in the swine diets (both the basic meals and the blended mixtures) have been assayed by the rat repletion method. Such assays have indicated that those meals on which toxic symptoms are most easily produced in swine also give lower weight responses in rats receiving a borderline level of free gossypol. This is true without there being any significant difference in the content of free gossypol as determined by chemical methods. These results with swine and rats, when considered together, suggest the presence, or absence, in these meals of other factors than free gossypol which are related to the development of toxicity in swine and to the rate of weight gain during repletion in protein depleted rats.

The variation in availability of amino acids in different meals brought about by differences in processing conditions in manufacture has been studied by Lyman *et al.* (4), K. A. Kuiken (5), and Boatner *et al.* (6). That such differences in the protein component of the diets may be related to variations in gossypol tolerance of both swine and rats has been considered as a possibility. Information regarding possible effects on gossypol tolerance of some changes in the amino acid composition or balance, and also of increases in the amount of total protein as supplied by various protein supplements, has been sought in some rat-feeding tests.

Data are reported here from a number of such feeding trials in which the Cannon (7) protein-repletion, rat-assay technique has been used. By the use of various combinations of several cottonseed meals, casein, soybean meal, and crystalline amino acids, it has been possible to vary either a) the total nitrogen intake or the probable amino acid balance while maintaining a constant intake of free gossypol, or b) the free gossypol intake without greatly changing the other factors. In this manner an attempt has been made to measure the effect of gossypol tolerance of changes in total protein intake and of some variations in the amino acid composition of the nitrogen component of the diet.

Material and Methods

Protein Assays by Rat Repletion Method. Adult male rats weighing between 200 and 300 g. were depleted by feeding a low protein diet containing 0.1% Protomone (iodinated casein) for 3 weeks. The diet and experimental design used in the trials have been described previously (1). During the repletion