TABLE I

| Compound | Yield, % | M. p., °C. | Formula | Analyses, % Calcd. | Found |
|---|---|---|---|---|---|
| 4-Methoxyisophthalyl chloride | 83 | 78 | $C_9H_6O_3Cl_2$ | Cl, 30.47 | 30.18 |
| -(isophthalate)- | | | | | |
| Dimethyl-4-methoxy-(-) | 98 | 94 | $C_{11}H_{12}O_5$ | C, 58.93 | 59.01 |
| Diethyl-4-methoxy-(-) | 74 | 57 | $C_{13}H_{16}O_5$ | C, 61.90 | 61.80 |
| Diethylaminoethyl-4-methoxy-(-) | 70 | 209–210 | $C_{21}H_{38}O_5N_2Cl_2$ | N, 6.00 | 5.94 |
| Di-*n*-propylaminoethyl-4-methoxy-(-) borate | 69[a] | [b] | $C_{25}H_{50}O_{24}N_2B_{10}$[c] | N, 3.20 | 3.58 |
| Di-*n*-propylaminoethyl-4-methoxy-(-) | 61 | [d] | $C_{25}H_{42}O_5N_2$ | N, 6.22 | 6.12 |
| Di-*n*-butylaminoethyl-4-methoxy-(-) | 60 | 120–122 | $C_{29}H_{54}O_5N_2Cl_2$ | N, 4.84 | 4.79 |
| Diethylaminopropyl-4-methoxy-(-) hydrochloride | 75 | 193–195 | $C_{23}H_{42}O_5N_2Cl_2$ | N, 5.66 | 5.75 |
| Di-*n*-propylaminopropyl-4-methoxy-(-) hydrochloride | 69 | 150–152 | $C_{27}H_{50}O_5N_2Cl_2$ | N, 5.08 | 5.05 |
| Di-*n*-butylaminopropyl-4-methoxy-(-) | 69 | [d] | $C_{31}H_{56}O_5N_2$ | N, 4.84 | 4.79 |

[a] Yield based on free base. [b] Decomposes. [c] By analogy with formula for procaine borate given in May, "Chemistry of Synthetic Drugs," Longmans, Green & Co., New York, 1939, p. 123. [d] Darkens without boiling at 210° < 0.1 mm.

prepare the hydrobromide and the borate were unsuccessful, sticky products being obtained in each case.

The constants and yields of the compounds prepared are given in Table I.

## Summary

1. Some normal and alkamine esters of 4-methoxyisophthalic acid have been prepared.

2. Preliminary pharmacological data indicate an anesthetic efficiency approximately equal to that of procaine.

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[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, STATE UNIVERSITY OF IOWA]

# Antioxidants and the Autoxidation of Fats. XIII. The Antioxygenic Action of Ascorbic Acid in Association with Tocopherols, Hydroquinones and Related Compounds

BY CALVIN GOLUMBIC AND H. A. MATTILL

The capacity of ascorbic acid to act as an inhibitor of fat oxidation has been suggested or implied in a number of recent papers.[1] Notwithstanding the slight solubility in lipids, both *d*- and *l*-ascorbic acid alike have an appreciable antioxygenic action in various fat substrates (Table I). To lengthen the induction period of lard a fairly high concentration must be used, but in cottonseed oil or its esters much smaller quantities suffice. These substrates contain inhibitols, principally tocopherols, and ascorbic acid reinforces their stabilizing action. When tocopherol is removed from vegetable oils, as can be done by various means, the recovered oils are no longer stabilized by ascorbic acid.

According to Isler[2] the extent of oxidation of α-tocopherol adsorbed on an inert carrier in the presence of ascorbic acid was only 6% of that which occurred during the same period in the absence of ascorbic acid. The oxidation of α-tocopherol when dissolved in an animal fat substrate is also retarded by ascorbic acid; this appears from the figures given in Table II. With like amounts of tocopherol initially present, in-

TABLE I

THE ANTIOXYGENIC PROPERTIES OF ASCORBIC ACID

| Substrate | Inhibitors added | Induction period[a] at 75° With inhibitor, hr. | Induction period[a] at 75° Control, hr. |
|---|---|---|---|
| Lard | 0.40% Ascorbic acid | 39 | 19 |
| | .20% Ascorbic acid | 31 | 19 |
| | .10% Ascorbic acid | 24 | 21 |
| | .04% β-Tocopherol | 169 | 21 |
| | .04% β-Tocopherol + 0.10% Ascorbic acid | 268 | 21 |
| Hydrogenated cottonseed oil | .01% Ascorbic acid | 73, 80[b] | 40, 45[b] |
| Crude ethyl esters of hydrogenated cottonseed oil | .02% Ascorbic acid | 210<br>223 | 4<br>5 |

[a] Oxygen absorption method. [b] The induction period is given in days (oven test, 63°).

(1) Kieferle and Seuss, *Milchw. Forsch.*, **20**, 23 (1939); Trout and Gjissing, *J. Dairy Sci.*, **22**, 271 (1939); Gray and Stone, *Food Indust.*, **2**, 629 (1939).

(2) Isler, *Helv. Chim. Acta*, **21**, 1756 (1938).

TABLE II

THE OXIDATION OF α-TOCOPHEROL IN THE ETHYL ESTERS OF LARD FATTY ACIDS, IN THE PRESENCE AND ABSENCE OF ASCORBIC ACID

| Time, hours | Amount of α-Tocopherol in 1 g. of Ester[a] (No ascorbic acid) γ | (0.05% ascorbic acid) γ | (0.10% ascorbic acid) γ |
|---|---|---|---|
| 0 | 1000 | 1000 | 1000 |
| 3 | | 540 | 482 |
| 5 | 66 | | |
| 10 | trace | | |
| 20 | 0 | 313 | 336 |
| 44 | | 120 | 164 |
| 66 | | 0 | 35 |
| 70 | | | 0 |
| Length of induction period,[b] hours | 11 | 59 | 68 |

[a] Determined by the method of Emmerie and Engel.[3]
[b] Determined by the oxygen absorption method, at 75°.

creasing amounts of ascorbic acid prolonged the induction period and at its termination, in each case, the tocopherol was completely oxidized. Determination of ascorbic acid by the method of Bukatsch[4] showed that it too was being oxidized but at a much slower rate.

This reinforcing action of ascorbic acid is not confined to tocopherol but extends to hydroxy chromans and related compounds which are also fat stabilizers[5] and to hydroquinones and quinones. When, with the successive introduction of alkyl groups, hydroquinones and quinones progressively lose their capacity as inhibitors, added traces of ascorbic acid no longer have a stabilizing effect.

Although the mechanism of the reaction between ascorbic acid and tocopherols and hydroquinones is not yet understood, certain suggestive observations may be made. The oxidation potentials of the antioxygenic hydroquinones[6] and of tocopherol[7] (0.656–0.597 v.) are appreciably higher than that of ascorbic acid[8] (0.390 v.). Fat peroxides oxidize tocopherols and hydroquinones, hence their oxidation potentials are higher than those of the phenolic inhibitors. Despite the large difference in potential which must exist between the fat peroxides and ascorbic acid, the latter is not appreciably oxidized during the induction period and does not delay the accumulation of fat peroxides unless hydroquinones or tocopherols are also present.[9] This type of sluggish two-step oxidation between systems at widely different potential levels and requiring an intermediary agent is not unknown even in inorganic chemistry[10] and has been particularly exemplified by certain biological oxidations.[11] A study of these relations in fat systems involves many complications which are being further investigated.

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## Summary

Ascorbic acid is an effective antioxidant for certain vegetable oils, their hydrogenated products and esters. It enhances the antioxygenic activity of tocopherols, hydroxy chromans, hydroquinones and related compounds.

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(3) Emmerie and Engel, *Rec. trav. chim.*, **57**, 1351 (1938).
(4) Bukatsch, *Z. physiol. Chem.*, **262**, 20 (1939).
(5) Golumbic, THIS JOURNAL, **63**, 1142 (1941).
(6) Conant and Fieser, *ibid.*, **46**, 1858 (1924).
(7) Golumbic and Mattill, *J. Biol. Chem.*, **134**, 535 (1940).
(8) Ball, *ibid.*, **118**, 219 (1937).
(9) Golumbic, unpublished work.
(10) Shaffer, *J. Phys. Chem.*, **40**, 1021 (1936).
(11) Barron, *Physiol. Rev.*, **19**, 184 (1939).