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Isolation and Identification of 3,3′,5,5′-Tetrabis(*tert*-butyl)stilbenequinone from Polyethylene Closures Containing Titanium Dioxide and Butylated Hydroxytoluene

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Abstract □ A yellow compound was isolated from commercially available, discolored, polyethylene ophthalmic closures containing titanium dioxide and butylated hydroxytoluene (I). This compound was present at 7.46 ppm (w/w). It was identified by UV, IR, and mass spectra as 3,3′,5,5′-tetrabis(*tert*-butyl)stilbenequinone (II), a dimer of I. Further structural confirmation was obtained by NMR. Formation of II is catalyzed by titanium dioxide.

Keyphrases □ Tetrabis(*tert*-butyl)stilbenequinone—analysis, isolation from polyethylene closures, synthesis from butylated hydroxytoluene catalyzed by titanium dioxide □ Butylated hydroxytoluene—conversion to tetrabis(*tert*-butyl)stilbenequinone in polyethylene closures, catalyzed by titanium dioxide □ Polyethylene—drug packaging, discoloration, butylated hydroxytoluene conversion to tetrabis(*tert*-butyl)stilbenequinone catalyzed by titanium dioxide □ Titanium dioxide—in polyethylene closures, catalysis of butylated hydroxytoluene discoloration reaction

Polymers are widely used in industry as packaging materials for food and drugs. As they age, they undergo oxidation *via* a free radical mechanism initiated by heat, light, or radiation. One result is scission or branching in the polymer chain, leading to eventual degradation in the mechanical properties of the polymer.

Antioxidants are added to the polymer in small amounts to prevent degradation. These substances can inhibit free radical formation and may become degraded instead of the polymer. Some antioxidants can convert to colored substances.

The oxidation products of antioxidants have been linked to the discoloration of polyethylene (1). An oxidation product of I caused a marked yellow discoloration of clear polyethylene (2). This colored compound was 3,3′,5,5′-tetrabis(*tert*-butyl)stilbenequinone (II). It has been isolated from cooking oil to which I was added (3). The corresponding yellowing of pigmented polyethylene caused by I has not been reported. The pigment, titanium dioxide, is used extensively as an opacifier for food and drug packaging.

This work was undertaken to isolate and identify the yellow discoloration product in titanium dioxide-pigmented polyethylene in which I is the antioxidant and to evaluate the titanium dioxide role in the discoloration reaction.

EXPERIMENTAL

Closures—Commercially available, opaque, ophthalmic, 15-mm closures, consisting of polyethylene with 1.5% titanium dioxide as the pigment and I as the antioxidant, were used. Each closure weighed ~0.2922 g with a specific gravity of 0.931.

Extraction—Extraction was performed using a soxhlet extractor under defined reproducible conditions.

Separation and Purification of II—*Column Chromatography*—The silica gel column was purged with hexane, toluene, and chloroform. The yellow band was removed using hexane and concentrated by blowing nitrogen on it at room temperature.

TLC—Hexane–toluene (80:20, v/v) was used as the developing medium on silica gel 60 F 254, 25-mm glass plates. On separation, the yellow band was scraped off and reeluted for further purification.

Spectrophotometry—A spectrophotometer was used to determine spectra in the visible and UV regions. IR spectrophotometric analysis was performed with a beam condenser in conjunction with an ultramicro liquid cell.

Mass Spectrometry—A mass spectrometer with a single-focusing magnetic mass analyzer was used. Temperature programming was such that spectra were obtained rapidly at increasing temperatures. All samples were analyzed at 70 ev.

NMR—An NMR spectrometer analyzed the sample in deuterated chloroform with tetramethylsilane as the internal marker. The sample was run at ambient temperature at 100.1 MHz in the Fourier transfer mode using a computer. Chemical shift was expressed as δ (delta) in parts per million.

GLC—GLC analysis was at 200° using a 3.08-m column (0.64 cm in diameter) with 10% SE-30 on 90–100-mesh packing. Nitrogen was the carrier gas with a flow rate of 60 ml/min.

Quantification—The amount of I injected *versus* response was generated using the gas chromatograph. Twelve solutions of I in acetone ranging from 1.0×10^{-5} to 12.0×10^{-5} g were prepared by linear stepwise dilution to quantify I in the 250–500-ppm region. Chloroform was unsuitable because both spectral and analytical grades produced a response at the same retention time as I around or below 9.0×10^{-8} g. With identical extraction conditions, the amount of I extracted per hour from nondiscolored caps was determined.

RESULTS AND DISCUSSION

At room temperature, the yellow material was slightly soluble in chloroform. A total of 913 closures, weighing 266.7786 g, was placed in this solvent. After the extraction procedure, they weighed 265.0773 g, a difference of 1.7013 g. A 10-μl injection of the concentrated crude extract into the gas chromatograph revealed 29 distinct substances.

Spectrophotometric examination of an aliquot of the extract showed major absorption bands at 418 and 442 nm and two minor absorption bands at 396 and 218–233 nm.

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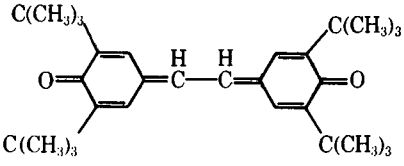
Column chromatography separated the extract into a yellow band and a white polymeric band.

After 10 TLC separations for purification, the yellow substance exhibited an IR spectrum identical to that obtained by Bohn and Campbell (4).

Mass spectra were obtained at various temperatures. Below 110°, poor fragmentation occurred. Above 160°, the compound disintegrated. The ideal conditions for obtaining mass spectra were 110–160° and 70 ev. The mass spectrum obtained was similar to that obtained previously (2).

The NMR spectrum was similar to that reported for II (6). Values of 1.30 and 1.33 ppm resulted from *tert*-butyl groups. Peaks at 6.90 and 7.52 ppm were due to the aromatic CH's. Peaks at 7.08 and 7.18 ppm were due to the olefinic CH's.

Based on the IR, mass, and NMR spectra, the yellow substance was assigned a quinoid structure with empirical formula $C_{30}H_{42}O_2$. Based on these spectral data, the structure of the isolated compound is:



II

For quantification, 334.7895 g of discolored caps was extracted. The amount of I still present after discoloration was 47.7 ppm. After purification, 2.5 mg or 7.46 ppm of II was obtained.

Synthesis of Authentic Yellow Compound—The synthesis of the authentic yellow compound was carried out by a literature method (7). Compound I was put in an oven at 100° for 2 weeks. The yellow material obtained was purified by column chromatography and TLC. The isolation and purification procedures were identical to those used for II extracted from the closures.

IR and mass spectra were recorded. The sample was smeared with mineral oil and sandwiched between two salt blocks to obtain the IR spectrum, which was similar to that obtained for II. The mass spectrum was similar to that obtained for the unknown yellow substance.

The mass spectrum exhibited base peaks at *m/e* 435, 436, and 57. This compound was identical to that isolated from the polyethylene closures.

Synthesis of Yellow Compound by Catalytic Action of Titanium Dioxide—3,3′,5,5′-Tetrabis(*tert*-butyl)stilbenequinone was obtained by adding 1.5 g of rutile titanium dioxide powder to 100 g of I. Yellowing was obtained within 24 hr at 100° in an oven. The yellow compound was purified by the methods used for II and identified by IR and mass spectral analyses. The IR and mass spectra were similar to those reported previously (2, 4, 7). Under identical conditions but without titanium dioxide, discoloration of I to form II only occurred after 2 weeks.

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Dihydroquinidine Contamination of Quinidine Raw Materials and Dosage Forms: Rapid Estimation by High-Performance Liquid Chromatography

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Abstract □ Dihydroquinidine is a commonly encountered contaminant in quinidine raw materials. The USP allows 0–20% dihydroquinidine in quinidine products, but the assays used to quantitate dihydroquinidine have been lengthy or have required sophisticated equipment. The present method separates dihydroquinidine from quinidine and provides rapid, precise quantitation of both dihydroquinidine and quinidine. The clinical importance of dihydroquinidine contamination of quinidine dosage forms remains unanswered.

Keyphrases □ Hydroquinidine—analysis, high-performance liquid chromatography, as contaminant in quinidine raw materials and dosage forms □ Quinidine—analysis, high-performance liquid chromatography, hydroquinidine contamination in raw materials and dosage forms □ High-performance liquid chromatography—analysis, hydroquinidine contamination of quinidine raw materials and dosage forms

Quinidine raw materials and dosage forms routinely contain dihydroquinidine as a contaminant. The amount of the dihydro derivative varies from 0 to 25% (1), although dosage form dihydroquinidine content is limited to 20% by the USP (2). Many methods reported for quinidine quantitation do not separate the dihydroquinidine contaminant from quinidine. Previous methods for dihydroquinidine quantitation in dosage forms and raw materials include TLC (3), NMR (4), chemical-ionization mass spectrometry (5), and normal phase high-performance liquid chromatography (HPLC) (3). These methods are time consuming or tedious or require expensive equipment. The described HPLC method separates the dihydroquinidine contaminant from quinidine and allows rapid, precise quantitation of both compounds.

EXPERIMENTAL

Apparatus—The high-performance liquid chromatograph was equipped with a multiwavelength UV detector[1] and a microparticulate C-18 column[2]. A filter[3] with a 1.2-μm pore size was used for solution filtration prior to injection.

[1] Model 711 solvent delivery system with a Spectromonitor II detector, Laboratory Data Control, Riviera Beach, Fla.
[2] Waters Associates, Milford, Mass.
[3] Millipore Corp., Bedford, Mass.

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