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### ACKNOWLEDGMENTS

We thank Douglas W. Litke for technical assistance.

# Digitonin Derivatives of Low Toxicity: Potential Solubilizers for Lipophilic Compounds

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Received October 18, 1982, from the *Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224.* Accepted for publication January 10, 1983.

**Abstract** □ Digitoxin was modified by condensation with propylene oxide or with 1,4-butanediol diglycidyl ether in aqueous alkali, yielding products in which some of the $CH_2OH$ groups of digitonin were converted to $CH_2OCH_2CHOHCH_3$ or to $CH_2OCH_2CHOHCH_2O(CH_2)_4O$-$CH_2CHOHCH_2OH$ groups, respectively. These modified digitonins were very soluble in water and chloroform and effectively solubilized lipophilic compounds into aqueous solutions; *e.g.*, 2 mg of vitamin A or 0.6 mg of cholecalciferol could be dissolved per 1 mL of 5% aqueous solutions of modified digitonins. Compared with the toxicity of digitonin ($LD_{50}$ 4 mg/kg iv), the toxicity of modified digitonin was greatly reduced: doses of 500 mg/kg by intravenous infusion were not lethal for mice.

**Keyphrases** □ Digitonin—derivatives, potential use as solubilizers, lipophilic drugs, comparative toxicity □ Solubilizers—digitonin derivatives, potential use with lipophilic drugs □ Lipophilic drugs—potential use of digitonin derivatives as solubilizers, comparative toxicity

Solubilizing agents are widely used both in pharmacy and pharmacology, and there is a constant need for new compounds that have low toxicity and do not functionally interfere with biomolecules (1, 2). Saponins, which are steroid glycosides, have some of the desirable properties (3). Two saponins, tomatin and digitonin, are readily available. Commercial preparations of tomatin have reasonable purity but are expensive, whereas for digitonin, which is rather widely used, the situation is reversed (4). The commercial preparation of digitonin is an extract of saponins from seeds of *Digitalis purperea*, further purified by treatment with cholesterol, which precipitates digitonin and related compounds. Such preparations are described as containing digitonin (40%), digalonin (15%), desglucodigitonin (25%), gitonin (15%), tigonin (3%), and dig d′ (2%) (5). The content of digitonin in commercial preparations is given as 70–80% (6). In most applications, the mixture is used. Despite its complexity, this mixture has unique properties and has been used extensively in biochemical pharmacology (7–9). Digitonin, on the other hand, even in the pure state, has some undesirable properties—its solubility in water is low and variable depending on the sample used (7) and on whether the digitonin sample had been previously treated with solvents (10). Furthermore, digitonin forms a complex with cholesterol, a process which is bound to have toxic and denaturating effects. In this work the aim was to modify the digitonin mixture chemically to overcome these defects; attempts were also made to make the necessary chemical modifications simple and easy to perform even with large quantities of material.

## EXPERIMENTAL

**Synthesis of Digitonin Derivative 2**—Digitonin[1] (1 g, 0.8 mmol) was suspended in a solution of sodium hydroxide (200 mg) in water (6.5 mL), and propylene oxide (1 mL, 15 mmol) was added. The mixture was then stirred at 60°C for 1 h and at room temperature overnight. The clear solution was then neutralized by hydrochloric acid and dialyzed for 1 d against distilled water. Dialysis tubing from regenerated cellulose[2] was used with a nominal molecular weight cutoff of 8000–12,000. Freeze-drying of the contents of dialysis tubing gave derivative 2 as a solid foam-like material (1 g).

The solubility of derivative 2 in water was ~21 g/100 mL at room temperature. This compound tended to occlude solvents and thus, elemental analysis could not be used to estimate the degree of substitution of derivative 2. Field-desorption mass spectrometry[3] was used for that purpose; analysis of the relative intensities of peaks (mass of digitonin derivative plus sodium ion) gave the following distribution at the molecular weight: unsubstituted (36%), monosubstituted (36%), disubstituted (19%), trisubstituted (6%), tetrasubstituted (2%), and pentasubstituted (1%). Thus, the average degree of substitution is ~1.4.

**Synthesis of Digitonin Derivative 3**—The same procedure as above using 1,4-butanediol diglycidyl ether[4] in place of propylene oxide yielded 6.9 g of derivative 3 from 8 g of digitonin. The solubility of derivative 3 in water at room temperature was 11 g/100 mL.

To estimate the degree of substitution in derivative 3, the compound was exhaustively methylated and then analyzed for the content of carbon and methoxy groups. Derivative 3 (1 g, ~1 mmol) was dissolved in dimethylformamide (10 mL), sodium hydride (0.4 g) was slowly added, and then the mixture was stirred at room temperature for 30 min. The viscous mixture was then cooled to 0°C, methyl iodide (4.5 g) was added in a dropwise manner, and stirring was continued for another 12 h. Methanol was added, and the mixture was dialyzed against water and freeze-dried. Product 4 was a white powder (0.92 g) which was hygroscopic; completion of methylation was established by absence of absorption in the region of the hydroxyl stretching vibration (3100–3600 $cm^{-1}$) in the IR spectrum[5]. Compound 4 was repeatedly dissolved in water and evaporated

[1] Sigma Chemical Co., St. Louis, Mo.
[2] A. H. Thomas Co., Philadelphia, Pa.
[3] NIHLB assembly, Bethesda, Md.
[4] Aldrich Chemical Co., Philadelphia, Pa.
[5] Beckman infrared spectrophotometer IR12.



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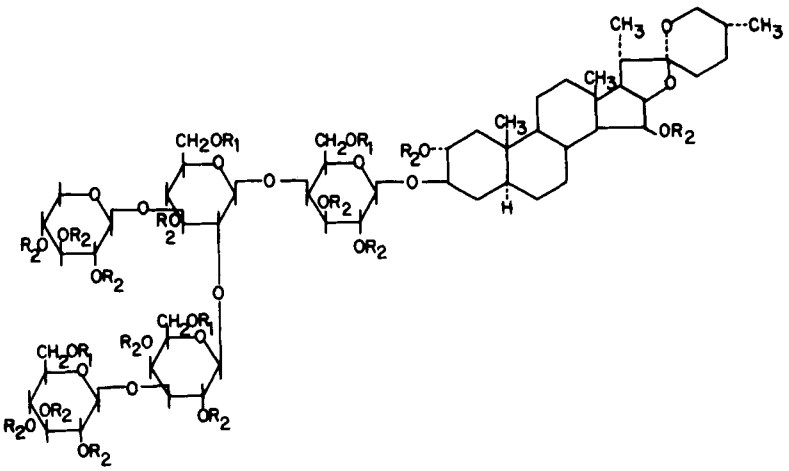

DIGITONIN $R_1$ = H, $R_2$ = H
DERIVATIVE 2, $R_1$ = —$CH_2$—CHOH—$CH_3$ or H; $R_2$ = H
DERIVATIVE 3, $R_1$ = —$CH_2$—CHOH—$CH_2$—O—$CH_2$—$CH_2$—$CH_2$—$CH_2$—O—$CH_2$—CHOH—$CH_2$OH or H; $R_2$ = H
DERIVATIVE 4, $R_1$ = —$CH_2$—CH($OCH_3$)—$CH_2$—O—$CH_2$—$CH_2$—$CH_2$—$CH_2$—O—$CH_2$—CH($OCH_3$)—$CH_2$—O—$CH_3$ or $CH_3$; $R_2$ = $CH_3$

to dryness *in vacuo* to eliminate all traces of organic solvents, and was then analyzed for carbon content and for content of methoxy groups (Zeissel method). In two separate preparations of product 4, these values were found to be 33.1 and 35.8% for methoxyl and 50.0 and 56.3% for carbon, respectively. From the ratio of methoxyl to carbon contents, the average degree of substitution was calculated to be ~1.

Control experiments, in which only digitonin or only 1,4-butanediol diglycidyl ether was treated with aqueous alkali, were performed with the following results. From self-condensation of digitonin, <1% of the water-soluble material could be isolated. If the products of self-condensation of digitonin were dissolved in 50% aqueous dimethylformamide, <1% was nondialyzable. The products of self-condensation of 1,4-butanediol diglycidyl ether were water soluble, but >97% was dialyzable.

**Measurement of Micellar Space in Aqueous Solutions of Derivatives 2 and 3**—The method (11, 12) is based on the color change of iodine that takes place when micelles are formed in the aqueous solution of iodine (30 mg/L). The absorbancy[6] at 385 nm, which is proportional to the micellar space, was measured as the function of concentration of derivatives 2 and 3 in solution.

**Molecular Weight Determination by Vapor Pressure Osmometry**—Chloroform (used as a solvent) was purified by washing with solutions of sulfuric acid, sodium hydroxide, and water, then dried and redistilled. The vapor pressure osmometer[7] was used for measurements; the osmometer was calibrated using pentaerythrityl tetrastearate (mol. wt. 1202) and polystyrene standard ($\overline{M}_w$:$\overline{M}_n$ = 1.04; $\overline{M}_w$ 9000). All measurements were performed at 29.9°C.

**Precipitation of Digitonin and its Derivatives by Cholesterol**—To a solution of a saponin (10 mg) in absolute ethanol (1 mL) was added a solution of cholesterol (40 mg) in ethanol (95%, 6.0 mL). The mixture was heated at 60°C for 10 min allowed to stand for 1 h and then the product was removed by filtration to give 41, 6, and 0 mg for digitonin and derivatives 2 and 3, respectively.

**Binding of Cholesterol–Digitonin Derivatives by Equilibrium Dialysis**—Dialysis tubing[2] was washed extensively with boiling water and with ethanol; dialyses were performed in ethanol (95%). The solution of digitonin derivative (1 mL) was placed inside of the dialysis tubing, and 2 mL of a solution of [$^{14}$C]cholesterol[8] was placed outside. After equilibration for 6 d, the concentration of radioactivity inside and outside of the dialysis bag was measured by liquid scintillation counting[9].

**Solubilizing Effects of Digitonin Derivatives**—Excess lipophilic compound (1.2 mL) was introduced into a stoppered polyethylene test tube containing phosphate-buffered isotonic saline (1 mL) without or with derivative 2 or 3 (50 mg). After equilibration by rotation overnight at 20–22°C, the suspension was centrifuged and the clear supernatant was used to measure spectrophotometrically[5] the concentration of the solubilized lipophilic compound.

**Effects of Digitonin and its Derivatives on Cells in Culture**—Friend erythroleukemia cells grown in Eagle's minimal essential medium with 10% calf serum were used (12) for the *in vitro* studies.

**Toxicity of Digitonin Derivatives**—Female C57B1/6J mice, ~9 weeks of age, were used for the experiments. The solution in phosphate-buffered saline was infused by peristaltic pump (0.12 mL/h) into the tail veins of animals for ~20 h. Five animals were used per group; these were followed for 3 weeks after treatment.

## RESULTS AND DISCUSSION

Digitonin contains 17 hydroxyl groups; four of the groups are primary. Epoxides, which were used in the derivatization of digitonin, are known to react approximately one order of magnitude faster with primary hydroxyls than with secondary ones (13, 14); consequently, structures 2 and 3 are suggested for the products of the condensations of digitonin with propylene oxide or 1,4-butanediol diglycidyl ether, respectively. The average degree of substitution was found to be 1.4 and 1.0 for derivatives 2 and 3, respectively.

Since the commercial digitonin that was used in the condensation contains several other saponins, these were also derivatized. On the other hand, it was established that derivatives 2 and 3 were not contaminated with products of self-condensation reactions of either digitonin or epoxides. Derivatives 2 and 3, in spite of being mixtures, had uniform solubility properties. Digitonin dissolves in water only slightly, whereas derivatives 2 and 3 give solutions both in water and chloroform.

Derivatives 2 and 3 were found to be self-associated in aqueous solutions; that followed from the inability of these derivatives to dialyze. Self-association was also apparent from the concentration dependence of nonpolar (*i.e.*, micellar) space in aqueous solutions of derivatives 2 and 3. This space is relatively small when only nonassociated species of am-

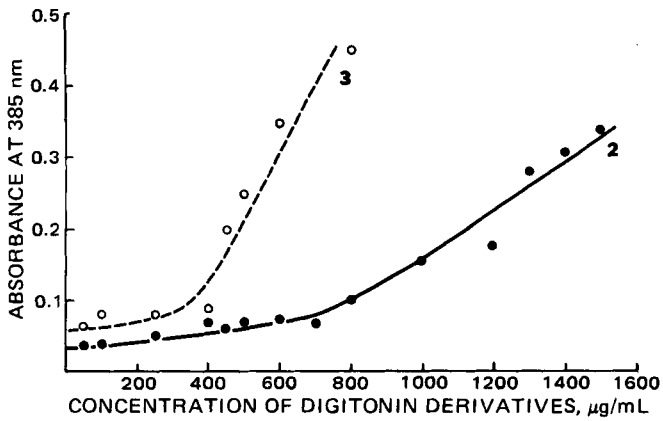


**Figure 1**—*Dependence of the absorbance at 385 nm of an aqueous solution of iodine (30 mg/L) on the concentration of derivatives 2 (●) and 3 (○). The absorbance at this wavelength is proportional to the concentration of iodine in nonpolar surroundings and, thus, to the amount of micelles present.*

[6] Cary 14 M recording ultraviolet spectrophotometer.
[7] Hitachi model 117.
[8] New England Nuclear, Boston, Mass.
[9] Beckman LS-250 Liquid Scintillation System.

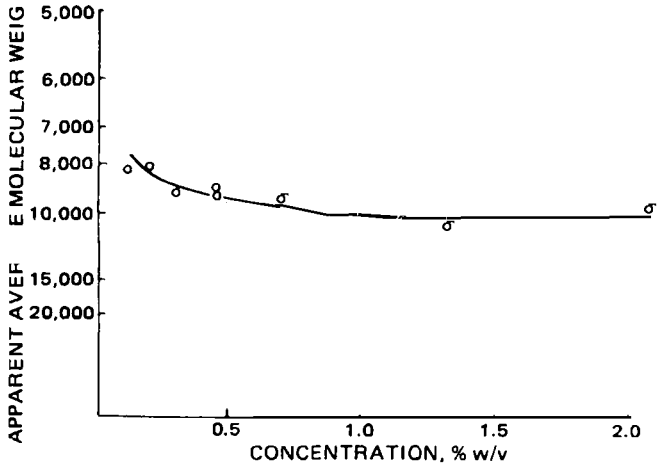


**Figure 2**—*Concentration dependence of apparent average molecular weight of derivative 3 as measured in chloroform by vapor pressure osmometry.*

phiphile are present in solution, but becomes prominent when the higher-order self-associated species (micelles) began to be formed; this occurred at concentrations of 700 μg/mL for derivative 2 and 300 μg/mL for derivative 3 (Fig. 1). Derivative 3 was also found to be strongly self-associated in chloroform solutions. Results of the concentration dependence of apparent molecular weight, as measured by vapor pressure osmometry, are in Fig. 2. Even at 0.1%, the measured molecular weight of derivative 3 is five to six times higher than that calculated for the monosubstituted product.

Digitonin forms insoluble complexes with cholesterol. The substitution of digitonin by epoxides apparently suppresses this complexation. Under the experimental conditions, when digitonin formed a precipitate with cholesterol in a relative amount of 100, derivatives 2 and 3 formed a precipitate in relative amounts of only 15 and 0, respectively.

Derivatives 2 and 3 did not permeate through the dialysis membrane; consequently, equilibrium dialysis could be used to study the potential interaction of cholesterol with derivative 3 in ethanol solutions, in which soluble complexes may be formed. The equilibrium concentrations of cholesterol found inside the dialysis tubing, which contained increasing amounts of derivative 3, were within experimental error and equal to those found in solutions outside the tubing, where there was no digitonin derivative present (Table I). Consequently, no complex formation was detected by this method.

The solubility of drugs and related compounds is of considerable theoretical and practical importance in the pharmaceutical sciences (1, 2, 15, 16), and development of effective solubilizing agents presents a useful complement to the development of new drugs. Derivatives 2 and 3 are very potent solubilizers of lipophilic compounds. Results of solubilization experiments are given in Table II; the solubility of some of the compounds in water was increased by two to three orders of magnitude even at moderate solubilizer concentrations. Derivative 3 seems to be a more potent solubilizer of vitamin A than any cyclodextrin or polymethionine sulfoxide previously tested (17, 18).

Although the mass spectra showed that compound 2 contained some unsubstituted digitonin, its presence could not be detected through the insolubility of digitonin in water or chloroform. Perhaps this behavior may be explained by a strong self-association of derivative 2. These self-associated species apparently have not only the capacity to complex and dissolve various lipophilic compounds, but also the contaminating digitonin.

**Table I—Equilibrium Dialysis in the Cholesterol–Derivative 3 System**

| Conc. of Derivative 3[a], mg/mL | Distribution of [$^{14}$C]Cholesterol, cpm/mL[b] | |
|---|---|---|
| | Inside of Dialysis Tubing | Outside of Dialysis Tubing |
| 0 | 13,820 | 13,940 |
| 2 | 13,980 | 14,020 |
| 10 | 14,380 | 14,920 |
| 50 | 14,940 | 14,680 |

[a] Inside the dialysis tubing. [b] Corrected for background counts.

**Table II—Solubilization of Nonpolar Compounds by Derivatives of Digitonin in Phosphate-Buffered Isotonic Saline**

| Compound | Solubilization, μg/mL | | |
|---|---|---|---|
| | No Agent | Derivative 2[a] | Derivative 3[a] |
| β-Ionone | 7.3 | 2050 | 1820 |
| Retinol | <4 | 1600 | 2500 |
| β-Carotene | 0 | 11 | 11 |
| *trans*-β-Carotene | 0 | 5 | 8 |
| Cholecalciferol | 0.2 | 190 | 640 |
| Naphthalene | <0.5 | 850 | 1035 |
| Anthracene | 0 | 69 | 84 |
| 2,3-Benzanthracene | 0 | 60 | 59 |

[a] 5% solutions.

The toxicity of derivatives 2 and 3 to cells grown in culture was tested by effects of these compounds on the growth curves of murine erythroleukemic cells for a 5-d growth period. A concentration of 0.1 mg/mL of derivative 3 added to the serum-supplemented medium allowed growth and cell division, whereas addition of 0.01 mg/mL of digitonin led to cell destruction. The onset of cell damage was also considerably slower for derivative 3 than for digitonin. When cells were treated with 0.1 mg/mL of digitonin in the absence of serum, even 30 min of treatment affected the cell growth that occurred later in serum-supplemented medium, whereas with derivative 3 at least 4 h of treatment was necessary to change the later growth (Fig. 3).

The toxicity of derivative 3 to animals was tested using intravenous infusions of derivative 3 into the tail veins of mice. Doses of 1000–2000 mg/kg of derivative 3 resulted in death, but doses of 500 mg/kg were without lethal effects.

When administered perorally, digitonin is toxic to mice (19) but nontoxic to rats (>50 mg/kg) (3), which tolerate even repeated applications (150 mg/kg/d) (19). Digitonin is also nontoxic to monkeys in amounts up to 0.4% in food (19). On the other hand, in all parenteral applications digitonin is rather toxic, producing acute inflammation when injected intramuscularly or subcutaneously (800-μg dose). This inflammation may be inhibited by anti-inflammatory drugs (20). Digitonin also has hemolytic effects (4). For digitonin given intravenously, the $LD_{50}$ was found to be 4 mg/kg in rats (3). Since mice tolerated doses of 500 mg/kg iv by infusion of derivative 3, it is obvious that toxicity of digitonin was de-

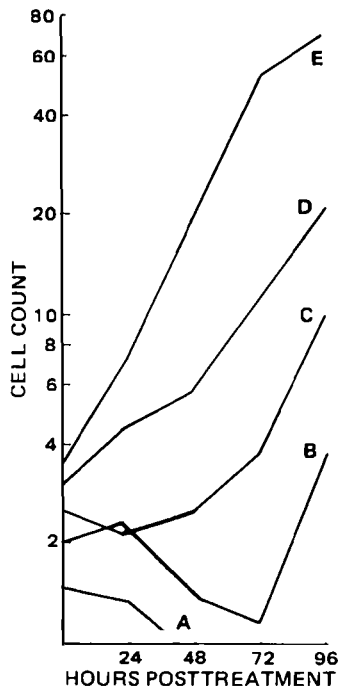


**Figure 3**—*Effects of treatment by digitonin and derivative 3 on the* in vitro *growth of Friend erythroleukemia cells. Cells were treated with 0.1 mg/mL of the compound in serum-free medium for the times indicated; thereafter, the cells were diluted into serum-supplemented medium. Key: (A) digitonin, 2 h; (B) digitonin, 1 h; (C) derivative 3, 4 h; (D) derivative 3, 2 h; (E) control.*

creased by at least two orders of magnitude on substitution by epoxides. Since the pharmacokinetics of parenterally applied lipophilic drugs are very strongly affected by their relative water solubility (21), derivatives 2 and 3 may be useful in modifying the effects of lipophilic drugs.

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## ACKNOWLEDGMENTS


The authors appreciate the interest and help of Dr. Henry M. Fales who arranged for the mass spectra measurements and interpreted the results. For vapor pressure osmometry we thank Dr. K. Solc. The first attempts to synthesize derivative 3 were made by Dr. J. Zjawiony in this laboratory. For performance of cell culture experiments and for the equilibrium dialysis experiment we thank Mrs. B. A. Hughes.


# Stability of the 6,14-*endo*-Ethanotetrahydrooripavine Analgesics: Acid-Catalyzed Rearrangement of Buprenorphine


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Received March 15, 1982, from the *National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, KY 40583.* Accepted for publication September 23, 1982



**Abstract** □ Buprenorphine (I), a member of the 6,14-*endo*-ethanotetrahydrooripavine series of analgesics, undergoes an acid-catalyzed rearrangement reaction when exposed to acid and heat. The product was shown by $^1$H-NMR and GC–MS to have undergone overall elimination of a molecule of methanol with concurrent formation of a tetrahydrofuran ring at C(6)–C(7) of I. Short-term stability studies across a wide range of pH and temperature conditions indicate that I is stable in aqueous solution at pH > 3 for 24 h at 36–38°C. Under the more extreme conditions of the autoclave, significant loss of I occurred. Long-term stability studies (10 weeks) of I in aqueous solution (pH 1 and pH 5) at 0–4°C and 26–28°C indicate only minor conversion (4%) to the rearrangement product. Eight other 6,14-*endo*-ethanotetrahydrooripavine derivatives were subjected to extremes of acid (pH 0) and temperature (autoclave) to determine if similar rearrangement reactions occur. GC–MS indicated that hydrolysis products were produced whose spectra were consistent with the proposed rearrangement structures.



**Keyphrases** □ Buprenorphine—6,14-*endo*-ethanotetrahydrooripavine analgesics, stability, acid-catalyzed structural rearrangement □ Analgesics—6,14-*endo*-ethanotetrahydrooripavine series, buprenorphine, stability, acid-catalyzed structural rearrangement □ Stability—buprenorphine and other 6,14-*endo*-ethanotetrahydrooripavine analgesics, acid-catalyzed structural rearrangement


The 6,14-*endo*-ethanotetrahydrooripavine series of analgesics contains numerous potent narcotic agonist and antagonist derivatives including buprenorphine (I), diprenorphine (V), and etorphine (VI). These substances are highly lipophilic (1) and display limited solubility at physiological pH; however, at lower pH values their solubilities increase substantially. Members of the closely related 6,14-*endo*-ethanotetrahydrothebaine series of analgesics have been shown to undergo acid-catalyzed rearrangement under vigorous conditions (2). However, it was not apparent whether a similar rearrangement would be observed for the 6,14-*endo*-ethanotetrahydrooripavine series. Consequently, a study was made of the stability of I under a variety of conditions involving exposure to acid and heat. A rearrangement product of I was identified by mass spectrometry and $^1$H-NMR. Evidence was obtained by GC–MS for the presence of similar rearrangement products from other 6,14-*endo*-ethanotetrahydrooripavine derivatives following acid hydrolysis.

## EXPERIMENTAL

**Materials**—Compounds I–IX[1] (Table I) were used as received. Their structural identity and purity were confirmed by TLC and GC–MS. Tri-Sil Z[2], obtained in 1-mL sealed glass ampules, was used as supplied. All other chemicals were reagent-grade quality.

**Instrumentation**—GC was conducted on a gas chromatograph[3] equipped with a flame-ionization detector. The stationary liquid phase, 3% OV-210[4], was coated on 100–120 mesh Gas Chrom Q[5] and packed into a 0.36-m × 2-mm i.d. silanized glass column. The temperatures were:

[1] Reckitt and Coleman, Hull, England.
[2] Pierce, Rockford, Ill.
[3] Model 2700; Varian Associates, Palo Alto, Calif.
[4] Applied Science, State College, Pa.
[5] Supelco Inc., Bellefonte, Pa.


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