bulk density. This is patently not true. However, its flow potential, as a relative measure, does improve as measured by the mentioned procedures.

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GLC Analysis of the Trimethylsilyl Derivative of 2,4-Dihydroxy-3,3-dimethylbutyric Acid γ-Lactone in Pantothenyl Alcohol

Keyphrases □ Pantothenyl alcohol—analysis □ 2,4-Dihydroxy-3,3-dimethylbutyric acid γ-lactone—determination in pantothenyl alcohol □ GLC—analysis

Sir:

The production of *d*-pantothenyl alcohol involves the reaction between 2,4-dihydroxy-3,3-dimethylbutyric acid γ-lactone (*l*-lactone) and 2-amino-*l*-propanol (1). For manufacturing purposes, it became desirable to know the amount of residual lactone present in *d*-pantothenyl alcohol. Initial attempts to quantitate the lactone content utilized a TLC method supplied by the manufacturer[1] (2). However, the method was not completely satisfactory.

The relative volatility of the lactone (sublimes) (3) favored the investigation of GLC as a means of analysis. The initial work involved injecting pyridine solutions of known amounts of *l*-lactone and the internal standard (2,6-dimethylphenol) directly onto the GLC columns. The resulting plot of concentration *versus* peak height ratio gave a negative *y*-intercept, which suggests irreversible adsorption of the lactone. In addition, analysis of a sample of pantothenyl alcohol produced an extraneous interfering peak, which we assumed to result from thermal degradation of the polyalcohol.

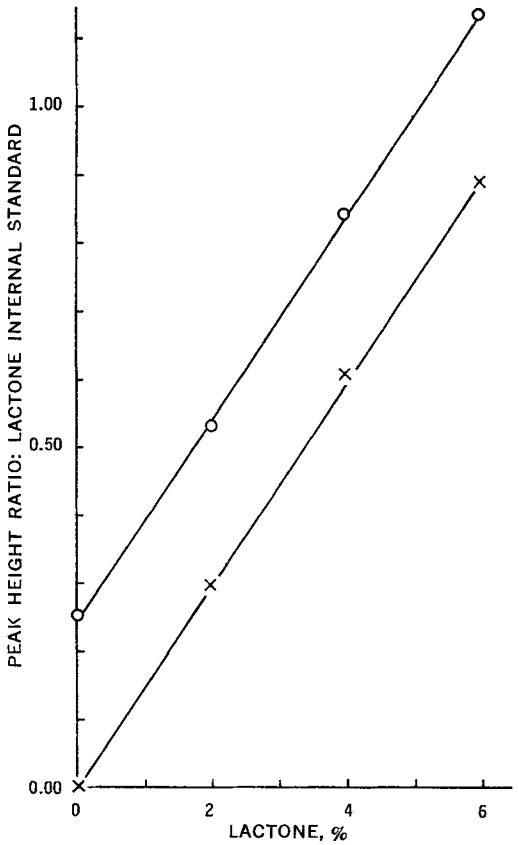

Figure 1—*Key:* ○, *lactone added to* d-*pantothenyl alcohol; and* ×, *lactone standards.*

In an attempt to obtain a suitable chromatographic moiety, the trimethylsilyl ether derivatives of known amounts of *l*-lactone were prepared and subsequently analyzed. 2,6-Dimethylphenol was used as the internal standard. The preparation of the silyl ethers is discussed. The resulting curve of concentration *versus* peak height ratio passed through the origin and was linear, as indicated in Fig. 1.

A series of samples was run in which known amounts of *l*-lactone were added to a sample of pantothenyl alcohol, and the percent recovery was determined using the recommended procedure. In Fig. 1, the slope of the curve for *l*-lactone added to panthenol is essentially the same as the slope of the curve obtained in the standard calibration method. This indicates that the recovery is linear and essentially 100% relative to the normal calibration procedure.

An indication of the precision was determined by assaying three aliquots of a given sample of panthenol. The mean percent lactone was found to be 2.88% w/w with a standard deviation of ±0.03% w/w. The 2.88% is within our specifications for the sample of panthenol studied. The method cannot be used for resolving the *l*- and *d*-isomers of the lactone.

Basically, the method consists of weighing exactly 100 mg. of pantothenyl alcohol into a suitable vial and smearing the sample around the lower inside portion of the vial with a glass rod. A 50-μl. aliquot of internal standard solution, prepared by dissolving 1.00 g. of

[1] Hoffmann-La Roche.

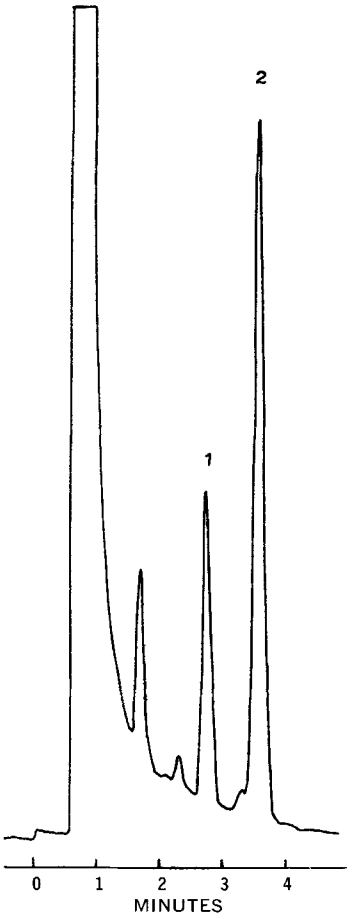

Figure 2—*Key: 1, lactone derivative* (R_T = *2.7 min.*); *and 2, internal standard* (R_T = *3.6 min.*).

2,6-dimethylphenol[2] in 10 ml. of benzene (A.R. grade), and 1 ml. (1 ampul) of Sil-Prep[3] reagent is added to the vial which is then stoppered, and the contents are shaken vigorously for at least 30 sec. Simultaneously, 2 and 6% w/w (in terms of pantothenyl alcohol) lactone standards are prepared by pipeting 0.2 ml. of the *l*-lactone standard solution, which is prepared by dissolving 100 mg. of *l*-lactone[4] in dichloromethane (A.R. grade) and diluting to 10.0 ml., into one vial and 0.60 ml. into a second vial. The solvent is evaporated from each sample by using a steady stream of dry air.

A 50-μl. aliquot of internal standard solution and 1 ml. (1 ampul) of Sil-Prep are added to each standard. The vials are stoppered, and the contents are shaken vigorously for at least 30 sec.

Each sample is chromatographed by injecting approximately 0.5 μl. of the specific sample into a GLC unit[5] containing a 1.8 m. × 0.32 cm. (6 ft. × 0.125 in.) column packed with 5% SE-30 on 80/100 mesh Chromosorb G (AW-DMCS), and a hydrogen flame-ionization detector. The column temperature is maintained at 170° and the injection port temperature at 180°. Helium is used as the carrier gas at a flow rate of 15 ml./min. The detector temperature could not be independently adjusted, but the design of the unit is such that the temperature is equal to or up to 50° in excess of the column temperature. Figure 2 shows an example of a typical chromatograph.

(1) U. S. pat. 2,413,077.
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(3) "The Merck Index," 8th ed., Merck & Co., Inc., Rahway, N. J., 1968, pp. 780, 781.

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[2] Eastman Kodak.
[3] Sil-Prep is available from Applied Science Laboratories and is a 9:3:1 mixture of pyridine–hexamethyldisilazane–trimethylchlorosilane.
[4] Supplied by the manufacturer of pantothenyl alcohol. We assumed 100% purity for the lactone.
[5] Perkin-Elmer model 800.