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Keyphrases

Vitamin (multiple) dosage forms
α-Tocopheryl acetate—analysis
GLC—analysis
Mass spectrometry—identity

Determination of Terpin Hydrate by Gas-Liquid Chromatography

By ERNEST J. KUBIAK

A gas chromatographic procedure has been developed for the quantitative determination of terpin hydrate. The procedure may be applied to any of the NF dosage forms containing this compound. The terpin hydrate is extracted with chloroform from a saturated sodium chloride solution and chromatographed as intact terpin on a hydrogenated castor oil column. Degradation products of terpin hydrate, other terpenes, and formulation excipients do not interfere. The method is specific, rapid, and accurate. A coefficient of variation of less than 1 percent was determined from replicate analyses.

METHODS FOR THE ANALYSIS of terpin hydrate, which have been proposed and described in the literature, include precipitation with mercury salts (1, 2), esterification with 3,5-dinitrobenzoyl chloride (3), and spectrophotometric determinations (4, 5). These methods lack specificity. They do not distinguish terpin hydrate from its decomposition products, and are not satisfactory for many formulations.

A method for the determination of terpin hydrate is presented in "Official Methods of Analysis"(6). In this procedure terpin hydrate is converted by acid dehydration to a mixture of terpenes which is reacted with molybdo-phosphotungstic acid to produce a blue reduction product which is measured spectrophotometrically. Any mixture of terpenes, treated similarly, will result in comparable color formulations.

The gas chromatographic (GLC) procedure presented in this paper is specific for the intact terpin molecule. Degradation products, other terpenes, and formulation excipients do not interfere with the quantitation of terpin hydrate by the procedure described.

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After this manuscript was submitted, a paper by L. Kurlansik, C. Damon, and E. F. Salim was published on the gas chromatographic determination of terpin hydrate (7).

METHOD

Reagents—(*a*) *Internal Standard Solution*—Prepare a chloroform solution containing 5.5 mg. of 3-tert-butylphenol per ml. of chloroform. (*b*) *Reference Preparation*—Dry terpin hydrate NF ($C_{10}H_{20}O_2 \cdot H_2O$) at 60° in vacuum at 10 mm. mercury for 3 hr. Determine any residual moisture in the terpin hydrate reference material by Karl Fischer, and use on the completely anhydrous basis for preparation of the reference solution. Transfer an accurately weighed portion of the anhydrous terpin ($C_{10}H_{20}O_2$), approximately 158 mg., into a 200-ml. volumetric flask. Add exactly 25.0 ml. of the internal standard solution and dilute to volume with chloroform.

Sample Preparation—Transfer an accurately measured portion of the formulation containing approximately 170 mg. of terpin hydrate NF ($C_{10}H_{20}O_2 \cdot H_2O$) into a 250-ml. separator. Add about 80 ml. of saturated sodium chloride solution and mix. Extract the terpin hydrate with two successive 50-ml. portions of chloroform. Collect the chloroform extracts in a 200-ml. volumetric flask, add exactly 25.0 ml. of the internal standard preparation, and dilute to volume with chloroform.

Chromatography—Chromatograph aliquots of the sample and reference preparation. Under typical circumstances the following instrument conditions were found to be satisfactory.

Chromatograph—F & M 402 with flame ionization detector. Column—Glass 3 mm. i.d. × 1.2 meters, 5% hydrogenated castor oil[1] on 80–100 mesh

[1] Castorwax, the Baker Castor Oil Co., Bayonne, N. J.

Diatoport-S, operated isothermally at 140°. Sample volume—8 μl. Carrier gas—Helium at about 60 ml./min. Attenuation—10 × 64.

Calculations—Calculate the quantity, in mg., of $C_{10}H_{20}O_2 \cdot H_2O$ in each ml. of the formulation taken by the formula:

$$\frac{R_1}{R_2} \times \frac{C}{D} \times F$$

in which,

R_1 = Sample terpin peak area / Internal standard peak area

R_2 = Reference terpin peak area / Internal standard peak area

C = Weight in milligrams of anhydrous terpin ($C_{10}H_{20}O_2$) in the reference preparation

D = The milliliters of the formulation in the sample preparation

F = 1.1045 = the factor for converting anhydrous terpin ($C_{10}H_{20}O_2$) to terpin hydrate NF ($C_{10}H_{20}O_2 \cdot H_2O$)

RESULTS AND DISCUSSION

In the proposed procedure, time-consuming distillation and the conversion of terpin to a mixture of terpenes by acid dehydration are avoided. Terpin hydrate is quantitatively extracted with chloroform from a saturated salt solution; a partition coefficient of $K > 100$ was determined for this system.

Based on replicate determinations, the procedure described gave an average recovery of 100.8% with a coefficient of variation of 0.75% (Table I). Three NF dosage forms manufactured by various pharmaceutical companies, were assayed for terpin hydrate (Table II). Except for one lot which showed evidence of decomposition, the results were in good agreement with the label requirements.

The procedure is specific for anhydrous terpin. The infrared spectra of a GLC fraction showed terpin hydrate chromatographed with a loss of water but without rearrangement or decomposition.

The accuracy of the procedure is dependent on the careful preparation of the reference anhydrous terpin. Terpin hydrate sublimes at 60° in vacuum with the possibility of incomplete dehydration. Therefore, the dried terpin reference material should be corrected for residual moisture, as determined by the Karl Fischer procedure, and used on the anhydrous basis for preparation of the reference solution.

The ratio of the areas of terpin to the internal standard, *3-tert*-butylphenol, *versus* the amount of terpin hydrate in the sample is linear for injected quantities between 0–75 mcg. of terpin hydrate.

Anticipated acid dehydration products and closely

Table I—Replicate Analyses of Terpin Hydrate Elixir NF

Terpin Hydrate, mg./ml.		
17.27	Theory	= 17.00
17.10	$\bar{x}$	= 17.14
17.20	σ	= 0.13
16.89	Coefficient of variation	= 0.75
17.16		%
17.15		
17.19		

Table II—Determination of Terpin Hydrate in NF Dosage Forms

Type of Formulation	Lot	Terpin Hydrate, mg/ml. Found	% Label[a] Found
Terpin hydrate elixir NF	1	16.93	99.6
	2	16.95	99.7
	3	17.27	101.6
	4	17.10	100.6
Terpin hydrate and codeine elixir NF	5	16.99	99.9
	6	17.11	100.6
	7	17.14	100.8
	8	16.88	99.3
	9	17.27	101.6
Terpin hydrate and dextromethorphan hydrobromide elixir NF	10	17.13	100.8
	11	17.07	100.4
	12	17.24	101.4
	13	17.07	100.4
	14	15.87[b]	93.4
	14	15.97[b]	93.9

[a] All dosage forms labeled 17.00 mg./ml. [b] Degradation products noted in chromatogram.

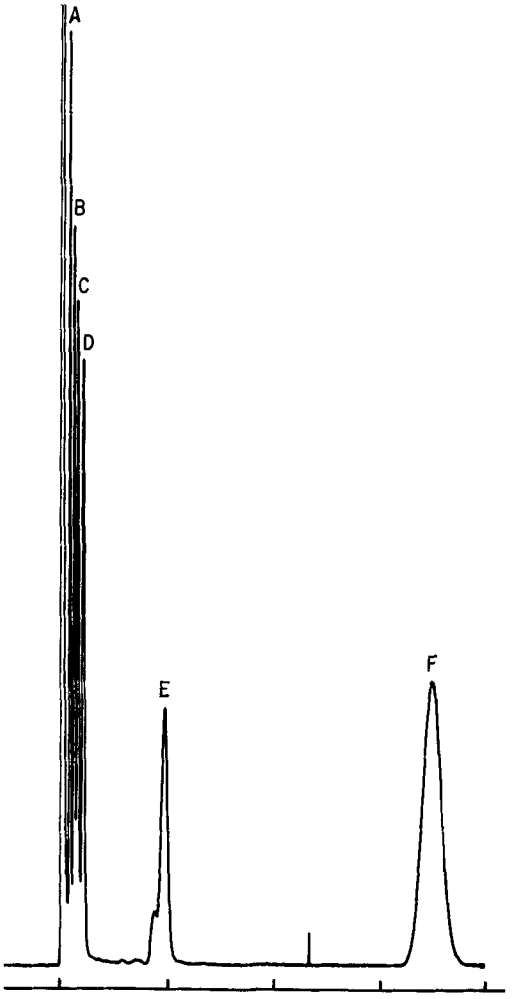

Fig. 1—Chromatogram of a terpene mixture. A = α-Pinene, B = β-Pinene, C = α-Terpinene and Limonene, D = γ-Terpinene, E = α-Terpineol, and F = Terpin.

TABLE III—RELATIVE RETENTION TIMES OF SOME TERPENES

		R.R.T.[a]
A	α-Pinene	0.11
B	β-Pinene	0.14
C	α-Terpinene and Limonene	0.18 0.19
D	γ-Terpinene	0.23
E	α-Terpineol	1.00
F	Terpin	3.89

[a] Retention time relative to terpineol.

associated compounds are completely separated (Fig. 1), having retention times much less than that of terpin (Table III). Figure 2 is a chromatogram showing the separation of terpin and the internal standard, 3-tert-butylphenol.

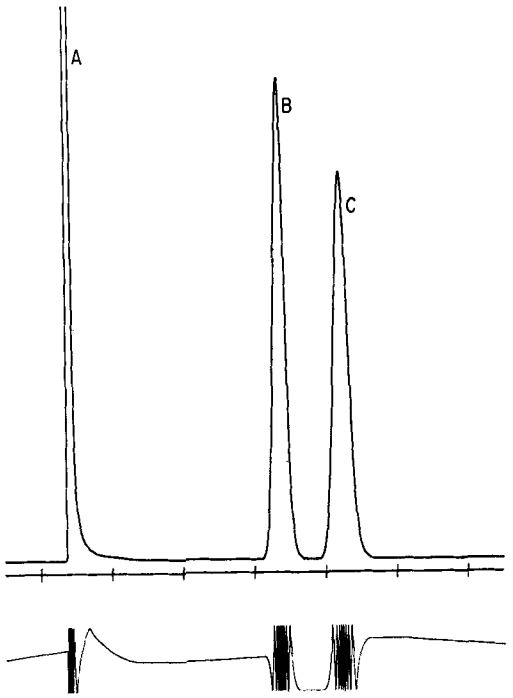

Fig. 2—Typical chromatogram. A = Solvent, B = Terpin, C = 3-tert-Butylphenol.

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Keyphrases

Terpin hydrate formulations—analysis
GLC—analysis
IR spectrophotometry—structure
Terpenes—relative retention times

Observations Concerning a Gas Chromatography Study of Resorcinol Monoacetate

By LEON KURLANSIK and EDWARD F. SALIM*

Initial investigations to develop a gas chromatographic assay for resorcinol monoacetate indicated that commercial material was not a single substance but a three-component mixture. A resorcinol monoacetate standard has been prepared and studies conducted at elevated temperatures to evaluate the conversion of resorcinol monoacetate to a mixture which includes resorcinol and resorcinol diacetate. Thermodynamic values have been calculated from experimental data. Characterization of the composition of commercial resorcinol monoacetate has been demonstrated by gas chromatography.

THE SYNTHESIS of resorcinol monoacetate (RMA) was first reported in 1899 (1). In 1931 Chattaway (2) prepared the compound by reacting resorcinol and acetic anhydride in sodium hydroxide solution and published physical constants for the material. Israelstam and Simpson (3) produced RMA by a modification of Chattaway's method and by the reaction of

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