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.

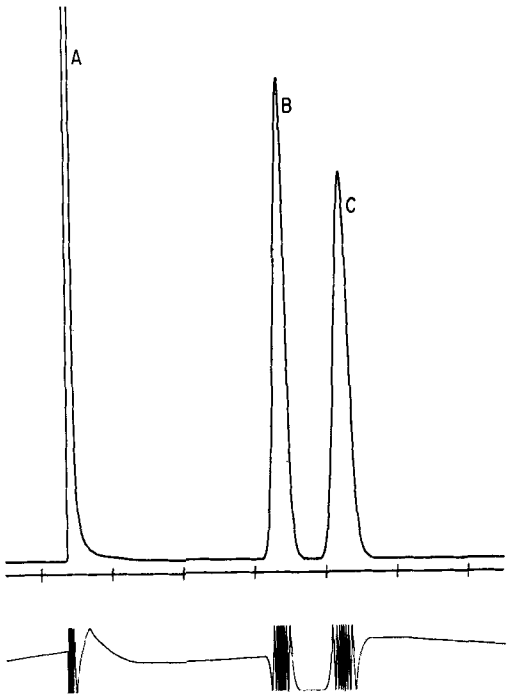

Fig. 2—Typical chromatogram. A = Solvent, B = Terpin, C = 3-tert-Butylphenol.

REFERENCES

(1) Polyanskii, N. G., Markevich, S. M., Safronenko, E. D., Buzlanova, M. M., *Trudy Komiss. Anal. Chim. Akad. Nauk SSSR*, **13**, 93 (1963); through *Anal. Abstr.*, **11**, [2210], June 1964.
(2) Buzlanova, M. M., Kozhikhova, N. A., Polyanskii, N. G., *Zh. Anal. Khim.*, **18**, 1125(1963); through *Anal. Abstr.*, **11** (4920), November, 1964.
(3) Robinson, W. T., *Anal. Chem.*, **33**, 1030(1961).
(4) Platt, H., and James, A. E., *J. Assoc. Offic. Agr. Chemists*, **44**, 666(1955).
(5) Milos, C., *ibid.*, **42**, 459(1959).
(6) "Official Methods of Analysis," 10th ed., Assoc. of Offic. Agr. Chem., Washington, D. C., 1965, p. 537.
(7) Kurlansik, L., Damon C., and Salim, E. F., *J. Pharm. Sci.*, **56**, 1160(1967).

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

Received July 7, 1967, from the Drug Standards Laboratory, American Pharmaceutical Association Foundation, Washington, DC 20037
Accepted for publication October 19, 1967.
* Present address: Philips-Roxane Laboratories, Columbus OH 43216

resorcinol diacetate (RDA) and disodium resorcinate. Recently, investigators have synthesized the monoacetate by acetylation of resorcinol with ketene (4, 5).

A survey of the literature indicated an almost total absence of methods of analysis for RMA. Brud and Daniewski (6) have effected a thin-layer chromatographic separation of resorcinol, RMA, and RDA on the product of RMA synthesis and quantitatively determined each component. It was felt that gas chromatography could be employed for determination of RMA but initial chromatograms of commercial RMA were characterized by the presence of three components which persisted throughout variations in chromatographic conditions. An early report (1) which indicated that RMA could be prepared from resorcinol and RDA and the analysis of Brud and Daniewski (6) offered the suggestion that resorcinol monoacetate is not a pure compound but rather an equilibrium mixture consisting of resorcinol and its mono- and diacetates. The following study has been undertaken in support of this theory.

EXPERIMENTAL

Standards—*Resorcinol*—USP grade material was recrystallized twice from 1,1,1-trichloroethane, m.p. 110.5–111.0°.

Resorcinol Monoacetate—Prepared according to the method of Chattaway (2). The RMA so obtained was not chemically pure when examined by GLC and further purification was necessitated. About 30 Gm. of the product was transferred to a separator containing 25 ml. of ethylene glycol. After mixing, 45 ml. of water was added, and the contents shaken and extracted with 25 ml. of chloroform. The chloroform wash was discarded. To the separator was added 50 ml. of water and the solution extracted with two 25-ml. portions of chloroform. Evaporation of the combined chloroform extracts *in vacuo* resulted in a slightly yellow, viscous liquid; density 1.234; n_D^{20} 1.5349 [lit. (4) 1.5328]. The product was observed to yield only one peak chromatographically.

Resorcinol Diacetate—Matheson, Coleman and Bell RDA was purified by alternate washings with cold 5% sodium hydroxide solution and water until the material was chromatographically pure; density 1.185; n_D^{20} 1.5029 [lit. (4) 1.5034].

Equilibrium Studies—About 5 ml. of resorcinol monoacetate standard was placed in a test tube and heated in an oil bath at the specified temperature. At varying time intervals, a 0.1-ml. aliquot was diluted to 25.0 ml. with a mixture of chloroform–methanol (20:1). A 4-μl. portion of this solution was injected into an F & M model 810 dual-column gas chromatograph equipped with a dual-flame ionization detector and a Minneapolis Honeywell recorder. The columns were stainless steel (6 ft. × 1/8 in.) packed with 10% SE-30 on Diatoport S, 60–80 mesh (prepared by F & M Scientific Company). Chromatographic conditions: column temperature, 105°; injection port temperature, 110°; detector temperature, 110°; helium flow, 83 ml./min.; hydrogen, 66 ml./min.; air, 450 ml./min.

RESULTS AND DISCUSSION

The appearance of three distinct peaks by gas chromatographic injection of commercial RMA dissolved in chloroform indicated impure material or degradation of the compound on the column. RMA was subjected to thin-layer chromatography by application on a silica gel strip (Eastman Chromagram, type K301R2) and development of the chromatogram in a solvent system consisting of chloroform–hexane–acetone (50:75:10). Visualization with iodine vapor disclosed the presence of three spots that were identified as the suspected resorcinol, RMA, and RDA by R_f values corresponding to reference compounds chromatogrammed on the same thin-layer strip. This confirmed the composition of commercial RMA to be a mixture but it was not certain that the samples tested were simply below expected quality.

Equilibrium studies were conducted whereby RMA standard was exposed to constant heat at selected temperatures to note the production of GLC peaks corresponding to resorcinol and the diacetate and a simultaneous reduction in the height (in actuality the area) of the original single RMA peak. Experimentation at each temperature was continued to a point at which the reduction of the RMA peak was no longer significant and it was assumed that equilibrium had been attained. Equilibrium concentrations of resorcinol, RMA, and RDA at experimental temperatures are recorded in Table I. Quantitative determination of each constituent observed chromatographically was based on a comparison of peak area to a calibration curve prepared for each standard using the same instrument parameters. Data obtained from these investigations were used to calculate thermodynamic values included in Table II. Substantiation of experimental equilibria has been obtained by a graphical representation of log K *versus* reciprocal

Table I—Equilibrium Between Resorcinol, Resorcinol Monoacetate, and Resorcinol Diacetate at Various Temperatures

Temp., °C.	Concn., moles/L. Resorcinol	RMA	RDA
150	2.14	5.51	0.83
190	2.67	5.26	0.72
	2.67	5.26	0.72
240	2.85	4.94	0.86
264	3.04	4.73	0.93
283	3.63	4.48	0.80
	3.51	4.53	0.81

Table II—Thermodynamic Values Calculated from Equilibrium Studies on Resorcinol Monoacetate

Temp., °C.	$K_c \times 10^2$	ΔH_R, cal./mole	ΔF, cal./mole	ΔS, cal./deg./mole
150	23.5	3069	1218	4.37
190	30.9	3069	1085	4.29
240	40.6	3069	918	4.19
264	50.8	3069	724	4.37
283	56.3	3069	636	4.38

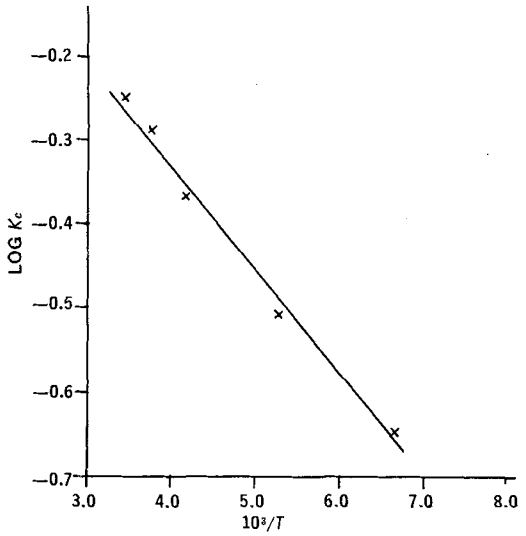

Fig. 1—Effect of temperature on equilibrium constants of RMA.

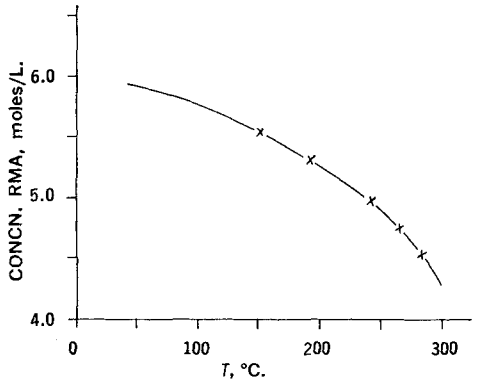

Fig. 2—Influence of temperature on equilibrium concentrations of RMA.

temperature to yield a linear relationship as shown in Fig. 1 and by the converse reaction of resorcinol and RDA to form the monoacetate at selected temperatures. The influence of temperature on equilibrium concentrations of RMA is plotted in Fig. 2.

Commercially available RMA has been characterized as a mixture whose composition can vary depending on the method of manufacture, purification, and age. Nevertheless, analysis can be achieved by gas chromatography to accurately determine the percentage content of each major constituent. An accurately weighed quantity of RMA is diluted to volume with chloroform–methanol (20:1) and a sample injected into the instrument. A typical resultant chromatogram is shown in Fig. 3. The percentage of RMA is calculated by correlation of the peak area to the calibration curve prepared for use in the equilibrium studies. In a similar manner is is possible to obtain the quantities of resorcinol and RDA. Total analyses of three commercial samples have been investigated and the recoveries summarized in Table III.

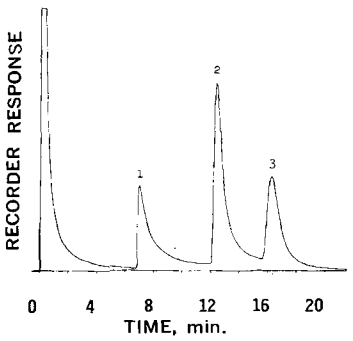

Fig. 3—Chromatogram of a chloroform–methanol solution of commercial RMA on a 10% SE-30 column. Key: 1, resorcinol; 2, RMA; 3, RDA.

TABLE III—COMPOSITION OF COMMERCIAL RESORCINOL MONOACETATE SAMPLES ANALYZED BY GAS CHROMATOGRAPHY

	Recoveries, %		
	Resorcinol	RMA	RDA
Sample A	19.5	61.7	18.9
	19.6	61.8	18.6
Sample B[a]	19.1	60.9	20.0
	18.6	61.8	19.6
Sample C[a]	20.2	63.7	16.1
	20.3	64.1	15.7

[a] NF material.

Quantitative analysis of RMA has been attempted by formation of trimethylsilyl (TMS) ethers by the method of Brobst and Lott (7) and other conventional procedures. A GLC chromatogram of the reaction mixture would represent TMS derivatives of resorcinol and RMA and unreacted RDA. Inspection of chromatograms prepared subsequent to etherification indicated the presence of two peaks instead of the expected three. Supporting investigations on standard materials have shown that the TMS ethers of resorcinol and RMA are eluted simultaneously as a single peak and that this approach is not feasible as a specific assay for RMA in the presence of resorcinol.

REFERENCES

(1) Prager, B., *et al.* (eds.), "Beilstein's Handbuch der organischen Chemie," vol. 6, Springer-Verlag OHG, Berlin, Germany, 1923, p. 816.
(2) Chattaway, F. D., *J. Chem. Soc.*, **1931**, 2495.
(3) Israelstam, S. S., and Simpson, J. D. M., *J. S. African Chem. Inst.*, **9**, 92(1956).
(4) Nodzu, R., and Isoshima, T., *Bull. Inst. Chem. Research Kyoto University*, **32**, 139(1954).
(5) Isoshima, T., *J. Chem. Soc. Japan*, **77**, 429(1956).
(6) Brud, W., and Daniewski, W., *Chem. Anal.*, **9**, 267 (1964); through *Chem. Abstr.*, **64**, 1357(1966).
(7) Brobst, K. M., and Lott, C. E., Jr., *Cereal Chem.*, **43**, 35(1966).

Keyphrases

Resorcinol monoacetate composition
Resorcinol, resorcinol mono- and diacetate combination—confirmed
Equilibrium studies
TLC—separation
GLC—analysis