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GAS CHROMATOGRAPHIC DETERMINATION OF SOME CHLOROETHYL PHTHALIMIDE COMPOUNDS*

J. F. GATES CLARKE, Jr., J. MINN and N. P. CARLSON
Hercules Incorporated, Hercules Research Center, Wilmington, Del. 19899 (U.S.A.)
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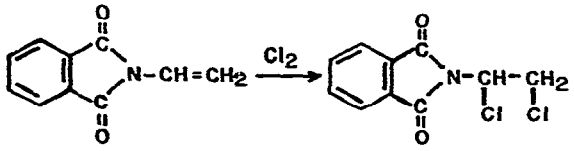
SUMMARY

The use of small-bore glass columns packed with low liquid-phase-loaded inert supports has provided the capability for the separation and quantitative determination of a series of chloroethyl phthalimides. Compounds such as N-(2-chlorovinyl) and N-(1,2-dichloroethyl) phthalimide have been measured with a relative standard deviation of no more than 1.4%. The N-(1-chloroethyl) phthalimide compound is not stable even in this inert system, but it can be stabilized by the room temperature preparation of the N-(1-ethoxyethyl) phthalimide derivative. Methods of standards preparation, calibration, and analysis of N-(1,2-dichloroethyl) phthalimide reaction mixtures are presented.

INTRODUCTION

N-(1,2-Dichloroethyl) phthalimide (N-DCEP) (II), an intermediate in the preparation of Torak® dialifor insecticide, O,O-diethyl-S-(2-chloro-1-phthalimidoethyl)phosphorodithioate, is prepared by chlorinating N-vinyl phthalimide (N-VP) (I), at temperatures below 25°. During the course of this reaction other side reactions



I II

occur to form N-(2-chlorovinyl) phthalimide (N-2CVP), N-(1-chloroethyl) phthalimide (N-1CEP), and N-(1,2,2-trichloroethyl) phthalimide (N-TCEP). Small amounts of phthalimide (PI) and N-(2-chloroethyl) phthalimide (N-2CEP) can also be formed although their contribution to the whole is small.

Other than some spectroscopic data, no information regarding the analysis of

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such a mixture could be found in the literature. The need for a rapid quantitative method easily applied in a quality or process control environment led to the investigation of gas chromatography as the method of choice. A complication encountered during the development of this procedure was the thermal instability of the N-1CEP compound, which easily loses hydrogen chloride to form N-VP. This problem was overcome by formation of thermally stable N-(1-ethoxyethyl) phthalimide (N-1EEP)[1].

EXPERIMENTAL

Apparatus

A Hewlett-Packard Model 5711 gas chromatograph equipped with a dual flame ionization detector (FID) and a Model 7123A recorder was used. Another FID instrument can be substituted, but provision must be made for direct on-column introduction of the sample. For this work, the instrument is not equipped with a heated injection port; if a heated inlet be used, the temperature must be maintained no more than 10–20° above the column temperature. Peak areas and retention data were measured with a data acquisition and computer system developed within Hercules Incorporated.

Reagents

Chromosorb W-HP (80–100 mesh) and the liquid phases Silicone Oil DC 200 (12,500 cs) and QF-1 (Silicone Fluid FS-1265) were purchased from Analabs (North Haven, Conn., U.S.A.). Other reagents used, with the exception of ethyl alcohol, which was USP 200 proof, were reagent grade.

Column and chromatographic conditions

A 1.8 m × 1.8 mm I.D. (3 mm O.D.) borosilicate coiled glass tube was packed under vacuum and mild vibration with about 1.5 g of the mixed liquid-phase packing. The column packing was prepared on a rotary evaporator, sieved, and was nominally 1.5% each of the liquid phases on the solid support (3.0% total mixed liquid phase). The column was operated at 140° isothermal with a nitrogen carrier flow-rate of 30 ml/min. The FID was operated with 30 ml/min hydrogen and 240 ml/min air at a temperature of 300°. Injection of samples is on-column with no heated injection port zone.

CALIBRATION

Standards

The internal standard, eicosane (n-C_{20}), was purchased in 99+% purity from Chemical Samples (Columbus, Ohio, U.S.A.). A 30 mg/ml stock solution was prepared. PI and N-VP were purchased from Matheson, Coleman and Bell (East Rutherford, N.J., U.S.A.) and the Borden Chemical Division of Borden (Philadelphia, Pa., U.S.A.) respectively. N-2CEP was purchased from Aldrich (Milwaukee, Wisc., U.S.A.) (S37,266-8) and recrystallized from water–ethanol (1:10) (m.p. 78.5–80.5°; Cl theory 16.91%, found 16.65%). The other chloroethyl and alkoxyethyl phthalimide standards were prepared as detailed below.

N-(1-Chloroethyl) phthalimide

Over a period of 78 min, 22 g (0.6 mole) of HCl was added to a stirred solution of 69.2 g (0.4 mole) of N-VP in 200 ml of benzene. No attempt was made to cool the mixture, which increased in temperature from an initial 25° to 40°. After standing overnight, the reaction was stripped on a rotary evaporator. The nonvolatiles were recrystallized from benzene and then from hexane to obtain a white crystalline solid, m.p. 112–114° (Lit. 110–111°, ref. 1). Theory for $C_{10}H_8O_2NCl$: 57.29 C, 3.84 H, 6.68 N, 16.91 Cl. Found: 58.02 C, 3.81 H, 7.28 N, 16.15 Cl.

N-(1-Ethoxyethyl) phthalimide

A 5.0-g sample of N-1CEP was stirred overnight at room temperature with 125 ml of ethyl alcohol. After stripping on a rotary evaporator, the 4.4 g of oil isolated was passed through a 15 cm × 1.8 cm I.D. column of silica gel (Woelm, Eschwege, G.F.R.) with 230 ml of benzene. Upon solvent removal, 3.3 g of a white crystalline solid were isolated, m.p. 65–68°. (Lit. 63.5–64.5°, ref. 1). Theory for $C_{12}H_{13}O_3N$: 65.27 C, 5.80 H, 6.33 N. Found: 65.74 C, 5.98 H, 6.39 N.

N-(2-Chlorovinyl) phthalimide

A 24.4-g (0.1 mole) sample of N-DCEP was refluxed for 2 h with 100 ml of N,N-dimethylformamide. After cooling to room temperature, the mixture was poured into 200 ml of ice water. Following filtration, the filter cake was recrystallized from 200 ml of hexane to obtain 6.5 g of yellow crystals, m.p. 97–100°. A second recrystallization from hexane gave yellow crystals, m.p. 100–102°. (Lit. 101.5–102.5°, ref. 2). Theory for $C_{10}H_6O_2NCl$: 57.85 C, 2.91 H, 6.74 N, 17.07 Cl. Found: 58.50 C, 3.16 H, 6.92 N, 17.50 Cl.

N-(1-Ethoxy-2-chloroethyl) phthalimide (N-1E2CEP)

A 24.4-g (0.1 mole) sample of N-DCEP was refluxed for 20 h with 200 ml (3.4 moles) of ethanol and then stripped with a rotary evaporator, steam bath and water aspirator for 30 min to get 23.0 g of a dark brown oil. The dark brown oil was dissolved in 50 ml of benzene and purified by passing it through a 20 cm × 2.5 cm I.D. column of silica gel (Woelm), 200 ml of benzene being used to develop the column. The first 200 ml of eluate were stripped to yield 15 g of a yellow solid. Recrystallization from hexane gave 9 g of a white crystalline compound, m.p. 69–71° (Lit. = 73–74°, ref. 1). Theory for $C_{12}H_{12}O_3NCl$: 56.81 C, 4.76 H, 5.52 N, 13.97 Cl. Found: 57.24 C, 4.60 H, 5.71 N, 13.56 Cl.

N-(1,2,2-Trichloroethyl) phthalimide

Over a period of 35 min, 8 g (0.11 mole) of chlorine was added to 20.8 g (0.1 mole) N-2CVP in 200 ml of benzene. No attempt was made to cool the reaction temperature which increased from an initial temperature of 22 to 35°. The product solution was stripped with a rotary evaporator, steam bath, and water aspirator for 0.5 h to get 27.0 g of stripped product. Recrystallization from 125 g of isopropyl acetate yielded 20.7 g of a white solid, m.p. 169–172°. A second recrystallization from hexane gave white crystals, m.p. 169–170°. Theory for $C_{10}H_6O_2NCl_3$: 43.12 C, 2.17 H, 5.02 N, 38.18 Cl. Found: 43.77 C, 2.23 H, 5.15 N, 37.78 Cl.

N-(1,2-Dichloroethyl) phthalimide

To 150 g (0.87 mole) of N-VP in 200 g of N,N-dimethylformamide were added 60 g (0.85 mole) of chlorine over a 1-h period at 18–21°. A wet-ice bath was used to control the temperature. The product solution was stripped on a rotary evaporator for 15 min with a steam bath and water aspirator, followed by a steam bath and vacuum pump for 0.5 h to yield 222.5 g of stripped product. This was recrystallized from an equal weight of isopropanol and then recrystallized from an equal weight of isopropyl acetate plus 10 g of Darco KB charcoal to decolorize it. Obtained: 91.5 g white crystals, m.p. 93–96°. Recrystallization of a small amount of these white crystals from hexane gave white crystals melting at 95–97° (Lit. 94.5–95.5°, ref. 1). Theory for $C_{10}H_7O_2NCl_2$: 49.21 C, 2.89 H, 5.73 N, 29.05 Cl. Found: 49.88 C, 3.03 H, 5.86 N, 29.42 Cl.

Calibration procedure

All calibration standards were checked for "gas chromatographic purity" before use as standards. About 1 mg/ml of each standard was prepared individually in chloroform and 1- to 2-μl aliquots were chromatographed under the conditions of analysis. All peaks detected were measured and the purity of each component, PF_c, calculated as

$$PF_c = \frac{A_c}{A_t}$$

where A_c is the area of the component of interest and A_t is the total area of all peaks in the chromatogram exclusive of solvent. No impurities were detected in any of the chloroethyl phthalimide standards that would interfere with the calibration of one in the presence of another.

Each standard component, in the approximate concentration expected in the sample, was weighed into a small 17-ml screw-cap vial and to it were added 10 ml of ethanol and a few drops of chloroform to aid in dissolution. N-1EEP was used as a secondary standard for the N-1CEP calibration. A 2.0-ml aliquot of the standard eicosane solution (about 60 mg of eicosane) was transferred to a 50-ml volumetric

TABLE I

CALIBRATION AND RETENTION DATA — CHLOROETHYL PHTHALIMIDE SYSTEM

Compound	*Abbreviation*	*Relative retention*	*Kováts' index*	*Typical response factor*
N-Vinyl phthalimide	N-VP	0.14	1568	1.25
Phthalimide	PI	0.17	1621	3.07
N-(1-Chloroethyl) phthalimide	N-1CEP	0.27	1728	1.65
N-(1-Ethoxyethyl) phthalimide	N-1EEP			1.73
N-(2-Chlorovinyl) phthalimide	N-2CVP	0.37	1795	1.92
N-(2-Chloroethyl) phthalimide	N-2CEP	0.38	1802	—
N-(1,2-Dichloroethyl) phthalimide	N-DCEP	0.48	1849	2.23
N-(1-Ethoxy-2-chloroethyl) phthalimide	N-1E2CEP	0.63	1905	2.14
N-(1,2,2-Trichloroethyl) phthalimide	N-TCEP	0.67	1920	2.54
Eicosane (internal standard)	C_{20}	1.00	2000	1.00

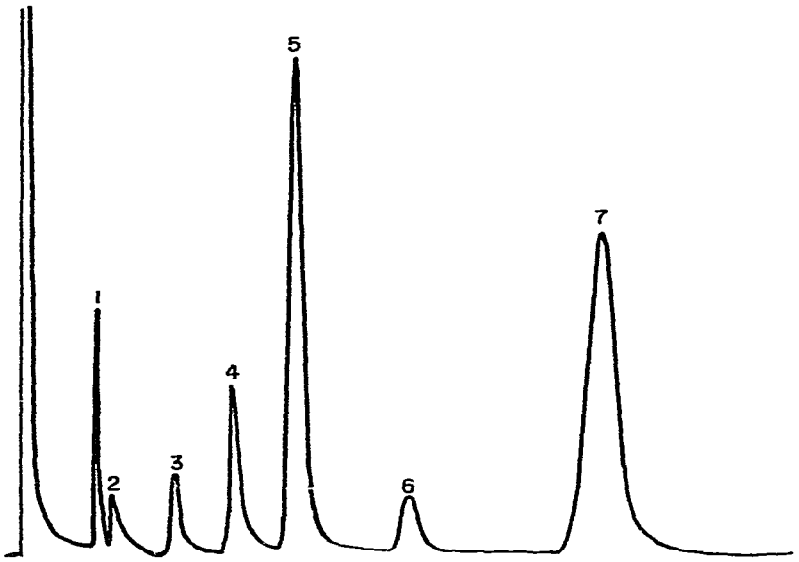


Fig. 1. Gas chromatogram of some chloroethyl phthalimide standards. 1 = N-VP (6.0%); 2 = PI (4.9%); 3 = N-1EEP (4.6%); 4 = N-2CVP (14.2%); 5 = N-DCEP (59.2%); 6 = N-TCEP (11.0%); 7 = *n*-eicosane (internal standard).

flask followed by a quantitative transfer of the standard mixture in the vial. The solution was made to volume with chloroform. A 1-μl aliquot of the final solution was chromatographed. Retention data of all standards used are presented in Table I. A gas chromatogram of a standard mixture is shown in Fig. 1.

Except for N-1CEP, the FID response factor, F_c, for each standard component *versus* eicosane was computed from eqn. 1

$$F_c = \frac{A_{IS} \times W_c \times PF_c}{A_c \times W_{IS}} \quad (1)$$

where W_c and W_{IS} are the weights of a standard compound and of the internal standard, respectively, and A_c and A_{IS} are their chromatographic peak areas. As the calibration for N-1CEP was indirect through the alkoxyl derivative, conversion of the N-1EEP factor obtained with eqn. 1 to that for N-1CEP was made by application of the ratios of their molecular weights: $F_{\text{N-1CEP}} = F_{\text{N-1EEP}} \times 0.956$. A set of typical response factors is presented in Table I.

ANALYTICAL PROCEDURES

Reaction mixtures

About 500 mg of the benzene reaction mixture solution were weighed into a 17-ml screw-cap vial, and 10 ml of absolute ethanol were added. After thorough mixing, the sample was allowed to stand at room temperature for 20 min. The reaction mixture was quantitatively transferred with chloroform to a 50-ml volumetric flask, which contained 2.0 ml of the stock internal standard solution, and then made to

volume with chloroform. A 1-μl aliquot of the final solution was injected directly onto the chromatographic column.

Solid samples

To avoid sampling errors, solid samples were gently warmed on a steam bath until a uniform melt was obtained. About 250 mg were transferred to a tared 17-ml screw-cap vial. The sample was cooled and the sample weight obtained. About 0.5 ml of chloroform was added to dissolve the sample, followed by 10 ml of absolute ethanol. After 20 min at room temperature, the reaction mixture was transferred to a 50-ml volumetric flask, made to volume with chloroform, and a 1-μl aliquot chromatographed as above.

The weight percentages of the individual components, Wt_c (%), were then calculated with eqn. 2 and the appropriate response factors

$$Wt_c\,(\%) = \frac{F_c \times A_c \times Wt_{IS} \times 100}{A_{IS} \times Wt_s} \tag{2}$$

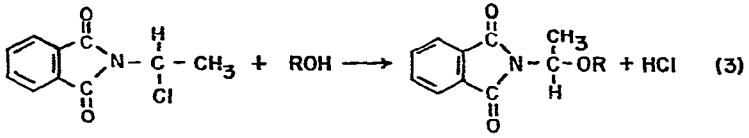
where Wt_s is the sample weight, and the other symbols have the same meaning as in eqn. 1.

Fig. 2. Gas chromatogram of N-1CEP. (A) Before reaction with ethyl alcohol. (B) After reaction with ethyl alcohol to form the N-1EEP derivative. 1 = PI contaminant; 2 = N-1EEP. Concentrations of N-1CEP before and after derivative formation were equivalent.

RESULTS AND DISCUSSION

The availability of an all-glass chromatographic system, the heart of which is a small-bore glass column packed with a low-loaded inert support, has provided a ready means of analyzing many materials too thermally labile and/or nonvolatile for easy application of gas chromatography. In this system, this combination allows for operation at a column temperature just above or even below the melting point of several of the compounds being determined. Further inertness is provided by direct on-column injection of the sample and connection of the column exit to just below the flame detector jet.

Under these favorable conditions, most of the chlorinated ethyl phthalimides are stable to gas chromatographic analysis even up to about 180°. An exception, however, is the N-1CEP compound, which shows considerable decomposition, principally to N-VP (Fig. 2A) through loss of HCl. As measurement of the N-1CEP even in small amounts is important to the determination of product quality, a way had to be found to stabilize the compound before gas chromatography. The lability



N-1CEP III

of the α-chlorine is well known and its reaction with alcohols (eqn. 3) to form 1-alkoxy-derivatives (III) has been demonstrated by Kato and Yoshida[1]. These derivatives proved to be quite stable under our gas chromatographic operating conditions.

TABLE II

RECOVERY OF N-1CEP FROM ADD-BACK EXPERIMENTS

Sample	*N-1CEP (%, w/w)*				
	Added	*Found*		*Recovery (%)*	
		Laboratory 1	*Laboratory 2*	*Laboratory 1*	*Laboratory 2*
Control	0	0.8	0.8	—	—
1	0.5	1.3	1.3	100	100
2	1.0	1.8	1.7	100	90

TABLE III

EFFECT OF TIME ON REACTION MIXTURE ANALYSIS AFTER QUENCHING WITH CHLOROFORM

Compound	*Weight per cent*					
	0.33 h	*2 h*	*4 h*	*6.5 h*	*24.5 h*	*28 h*
N-1CEP	1.2	1.2	1.2	1.2	1.2	1.2
N-2CVP	7.3	7.5	7.3	7.3	7.4	7.4
N-DCEP	27.9	28.6	27.9	28.4	28.1	28.2
N-TCEP	1.6	1.6	1.6	1.6	1.6	1.6

TABLE IV
STATISTICAL DATA — N-DCEP DETERMINATION
Sample 1: four determinations; sample 2: three determinations.

Compound	*Sample 1*			*Sample 2*			*Pooled — Samples 1 and 2*			
	Mean wt. %	*Per cent relative standard deviation (% s)*	*(Confidence interval)/2 at 95%*	*Mean wt. %*	*Per cent relative standard deviation (% s)*	*(Confidence interval)/2 at 95%*	*Mean wt. %*	*Degrees of freedom*	*Per cent relative standard deviation (% s)*	*(Confidence interval)/2 at 95%*
N-VP	1.30	0.73	0.03	1.31	1.17	0.07	1.30	5	0.93	0.03
PI	1.80	4.07	0.24	1.93	4.43	0.40	1.85	5	4.22	0.20
N-1CEP	2.51	1.54	0.12	2.45	1.87	0.22	2.48	5	1.68	0.11
N-2CVP	19.88	1.39	0.90	20.09	1.31	1.24	19.97	5	1.36	0.69
N-DCEP	69.40	0.44	0.99	70.91	0.31	1.04	70.05	5	0.39	0.70
N-TCEP	1.76	2.35	0.13	0.13	4.34	1.35	1.75	5	3.29	0.15

In our work, a number of alcohols from methyl to *n*-decyl were investigated as possible derivatizing agents, but because of either long elution times or interference with other sample components, ethanol appeared to be the best choice. Furthermore, excess ethanol eluted early with the sample solvent, causing no interference with components eluting early in the chromatogram. A comparison of chromatograms of N-1CEP before and after derivatization is shown in Figs. 2A and B, respectively.

The retention time of N-1EEP, confirmed after preparation and isolation of the known compound, was unfortunately identical to that for the N-1CEP so that it was difficult to determine if complete reaction in a sample had been achieved. Reaction completeness was determined through add-back experiments. First the level of N-1CEP was measured (after derivatization) in a typical laboratory-produced reaction mixture. Small known amounts of N-1CEP were then added to the sample and the analysis was redone. Results of analyses from two different laboratories are shown in Table II. Further assumption of reaction completeness was indicated when no further change was observed in the chromatographic pattern after 20 min and up to 2 h standing at room temperature.

The α-chlorine on the N-DCEP product is also labile, and the effect of ethanol on this species and on product analyses was studied. Fortunately, this reaction is much slower and the N-(1-ethoxy-2-chloroethyl)phthalimide (N-1E2CEP) reaction product does not appear until after some 2 h at room temperature. To ensure minimal reaction and therefore a longer delay time between derivative formation and analysis, the reaction is quenched by dilution with chloroform after a 20-min reaction period. Typical analysis data for a sample run under the finalized procedure are given in Table III. Essentially no change has occurred in the analytical results even after the quenched reaction solution has stood for more than 24 h.

Statistical data for the analysis of a laboratory chlorination reaction mixture are presented in Table IV. Two separate samplings of the mixture were made and the statistical parameters for each sampling as well as for the pooled data were calculated. The per cent relative standard deviations (% s) at the 95% confidence interval were obtained for each impurity as well as for product N-DCEP. The % s values for all components except for PI and N-TCEP are less than 2%, which is excellent, considering the labile nature of these compounds. The value for PI of 4.22% is somewhat high, but considering the tailed nature of the peak (Fig. 1) and the concentration level, the value was certainly acceptable for these analyses. The N-TCEP statistical calculations suffer again from the low concentration present and the resultant difficulty in measuring a low broad peak. Computer enhancement (sharpening) of the peak through data compression alleviates the problem somewhat but the point of peak entry selected can still provide some scatter in the data.

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