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Determination of chloropyridine isomers by gas chromatography and high-performance liquid chromatography in chlorpyrifos process development[a]

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ABSTRACT

Vapour phase chlorination of pyridine yields pentachloropyridine, and selective reduction of pentachloropyridine gives 2,3,5,6-tetrachloropyridine, both being important industrial intermediates. Various other isomeric chloropyridines may be formed during the chlorination reaction, and gas and high-performance liquid chromatographic methods are described for the separation and determination of chloropyridine isomers obtained during the vapour phase chlorination of pyridine. The methods have been successfully tested on the process development of the insecticide chlorpyrifos.

INTRODUCTION

Chlorination of pyridine in the vapour phase yields pentachloropyridine (PCP) and selective reduction of PCP gives 2,3,5,6-tetrachloropyridine (TCP), both being important intermediates in industry. A variety of other isomeric chloropyridines are obtained during this chlorination reaction and sensitive, precise and rapid methods are essential for their separation and determination and also for controlling the reaction pathways during the vapour-phase chlorination of pyridine.

Various spectroscopic methods have been published [1–9] for the determination of some of the chloropyridines. Meikle and Williams [10] reported the separation of 2,3,5,6-TCP, 2,3,6-trichloropyridine (TCP) and 2,6-dichloropyridine (DCP) isomers by column chromatography using alumina as stationary phase. A review on the application of gas chromatography (GC) to non-halogenated pyridine derivatives has been published [11]. GC retention ratios of a few chloropyridines have been determined [12]. However, these methods are either not complete or are tedious and time consuming. We have previously reported the GC determination of PCP [13] and the high-performance liquid chromatographic (HPLC) determination of TCP isomers [14], but only a few isomers were studied. We report here GC and HPLC methods for the separation and determination of pyridine and nine isomeric chloropyridines

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obtained during the vapour-phase chlorination of pyridine. The procedures have been successfully applied to monitoring the reactions in the manufacture of the insecticide chlorpyrifos from pyridine.

EXPERIMENTAL

Materials

All the chloropyridine isomers employed were obtained from Fluka (Buchs, Switzerland) and from Aldrich (Gillingham, U.K.). Liquid phases and supports employed for GC were procured from Analabs (North Haven, CT, U.S.A.). Acenaphthene used as an internal standard was obtained from Fluka. All other chemicals and solvents were of analytical-reagent grade. Doubly distilled water from an all-glass apparatus was used wherever necessary. A Zorbax Sil column for HPLC was purchased from Shimadzu (Kyoto, Japan). HPLC-grade solvents were used for all HPLC experiments.

Preparation of standard mixtures

Standard mixtures were prepared in the same proportions as expected in reaction mixtures. Standard mixtures of various compositions were prepared.

Determination of chloropyridines by GC

A Hewlett-Packard 5840 A gas chromatograph with a flame ionization detector connected to a microprocessor was used for all the experiments. The following conditions were employed for GC: injection port temperature, 300°C; detector temperature, 300°C; stationary phase, 15% diethylene glycol succinate (DEGS) coated on Chromosorb W AW (80–100 mesh); column, stainless-steel (8 ft. × 1/8 in. I.D.): column temperature, programmed from 100°C (held for 1 min) to 200°C at 10°C/min; chart speed, 1 cm/min; attenuation, 14; carrier gas, nitrogen; flow-rate, 35 ml/min; injection volume, 1 μl.

Determination of chloropyridines by HPLC

A Shimadzu Model LC-6A HPLC system, equipped with a Model LC-6A pump, a Rheodyne 7125 injection valve with a 20-μl sample loop, a Model SPD-6AV variable-wavelength UV spectrophotometric detector, a Model CR 3A data processor and a Chromatopac recorder, was used. A Zorbax Sil silica column (25 cm × 4.6 mm I.D.) was used with *n*-hexane–chloroform (97:3, v/v) as the mobile phase at a flow-rate of 1 ml/min.

RESULTS AND DISCUSSION

The separation of chloropyridine isomers was studied on various stationary phases of different polarities. Polar stationary phases were found to be more selective for these compounds, and DEGA and DEGS were examined in more detail. The resolution of the analytes was similar on the two stationary phases. Relative retention times and relative response factors with respect to acenaphthene (internal standard) are given in Table I. It can be seen from the relative retention time data that all the chloropyridine isomers are separated except 2,3- and 2,6-DCP and 2,3,5-TCP, which

TABLE I

RELATIVE RETENTION TIMES (RRT) AND RELATIVE RESPONSE FACTORS (RRF) OF CHLOROPYRIDINE ISOMERS BY GC

Compound	DEGA				DEGS			
	RRT	S.D. (n = 3)	RRF	S.D. (n = 3)	RRT	S.D. (n = 3)	RRF	S.D. (n = 3)
Pyridine	0.24	0.004	4.29	0.038	0.22	0.004	4.50	0.042
2-Chloropyridine	0.45	0.005	1.41	0.025	0.40	0.004	1.45	0.016
3-Chloropyridine	0.33	0.004	2.25	0.022	0.30	0.004	2.45	0.028
3,5-DCP	0.41	0.005	2.02	0.015	0.35	0.004	2.04	0.017
2,5-DCP	0.50	0.004	1.34	0.020	0.47	0.005	1.74	0.021
2,6-DCP + 2,3-DCP + 2,3,5-TCP	0.58	0.005	2.25	0.032	0.53	0.005	2.33	0.030
2,3,5,6-TCP	0.75	0.006	2.12	0.018	0.72	0.006	2.50	0.025
PCP	0.91	0.005	2.66	0.026	0.90	0.006	2.72	0.022
Acenaphthene (internal standard)	1.00	–	1.00	–	1.00	–	1.00	–

eluted as a single peak. The results in Table I show that the response factors for all the chloropyridines are >1, which indicates that the detector response is poor.

Synthetic mixtures of various compositions were prepared and analysed by GC and a typical chromatogram is shown in Fig. 1. Additional synthetic mixtures were analysed using the response factors to evaluate the efficacy of the method. The results

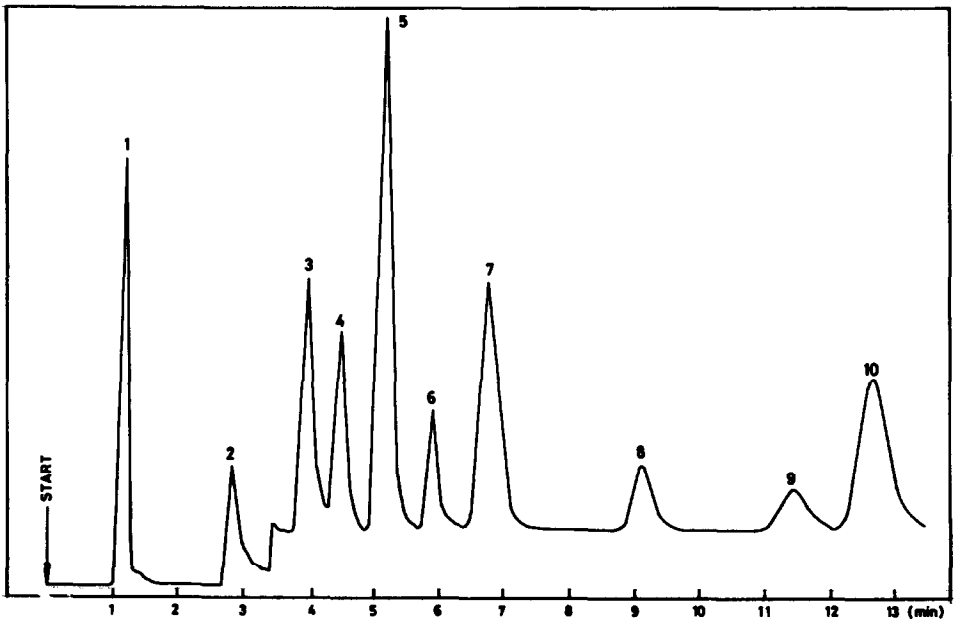

Fig. 1. Separation of a standard mixture of chloropyridine isomers by GC. Peaks: 1, solvent; 2, pyridine; 3, 3-chloropyridine; 4, 3,5-DCP; 5, 2-chloropyridine; 6, 2,5-DCP; 7, 2,6-DCP + 2,3-DCP + 2,3,5-TCP; 8, 2,3,5,6-TCP; 9, PCP; 10, acenaphthene (internal standard).

TABLE II

RESULTS OF ANALYSIS OF STANDARD MIXTURES OF CHLOROPYRIDINES BY GC

Compound	Mixture No.			
	1	2	3	4
Pyridine				
Taken (%)	2.48	1.35	0.92	0.66
Found (%)	2.50	1.36	0.91	0.67
Standard deviation (%, n = 3)	0.024	0.010	0.008	0.006
2-Chloropyridine				
Taken (%)	2.30	1.38	1.10	0.68
Found (%)	2.34	1.40	1.11	0.68
Standard deviation (%, n = 3)	0.020	0.011	0.011	0.008
3-Chloropyridine				
Taken (%)	2.45	1.32	0.88	0.74
Found (%)	2.42	1.31	0.89	0.73
Standard deviation (%, n = 3)	0.026	0.012	0.010	0.008
3,5-DCP				
Taken (%)	2.38	1.08	0.92	0.80
Found (%)	2.42	1.09	0.92	0.81
Standard deviation (%, n = 3)	0.020	0.011	0.009	0.010
2,5-DCP				
Taken (%)	2.38	1.29	1.11	0.69
Found (%)	2.41	1.29	1.10	0.70
Standard deviation (%, n = 3)	0.019	0.012	0.009	0.007
2,6-DCP + 2,3-DCP + 2,3,5-TCP				
Taken (%)	7.39	3.72	3.21	2.21
Found (%)	7.41	3.74	3.32	2.18
Standard deviation (%, n = 3)	0.033	0.026	0.030	0.023
2,3,5,6-TCP				
Taken (%)	0.80	6.20	4.93	3.14
Found (%)	0.81	6.25	4.95	3.12
Standard deviation (%, n = 3)	0.010	0.046	0.042	0.028
PCP				
Taken (%)	79.82	83.66	86.93	91.08
Found (%)	79.53	83.52	87.14	90.99
Standard deviation (%, n = 3)	0.387	0.044	0.422	0.406

obtained are given in Table II together with the standard deviations (σ). The experimental values agree with the true values within the limits of experimental error.

As 2,3- and 2,6-DCP and 2,3,5-TCP could not be resolved by GC, HPLC of the analytes was investigated. A typical chromatogram is shown in Fig. 2 and relative retention times of the compounds with respect to pyridine and the response factors are given in Table III. All the chloropyridine isomers were resolved. Various solvent systems were tried as mobile phases in both normal- and reversed-phase modes. In the reversed-phase mode, water and acetonitrile and water and methanol in various proportions were tried as eluents, but the resolution of isomers was poor. Gradient

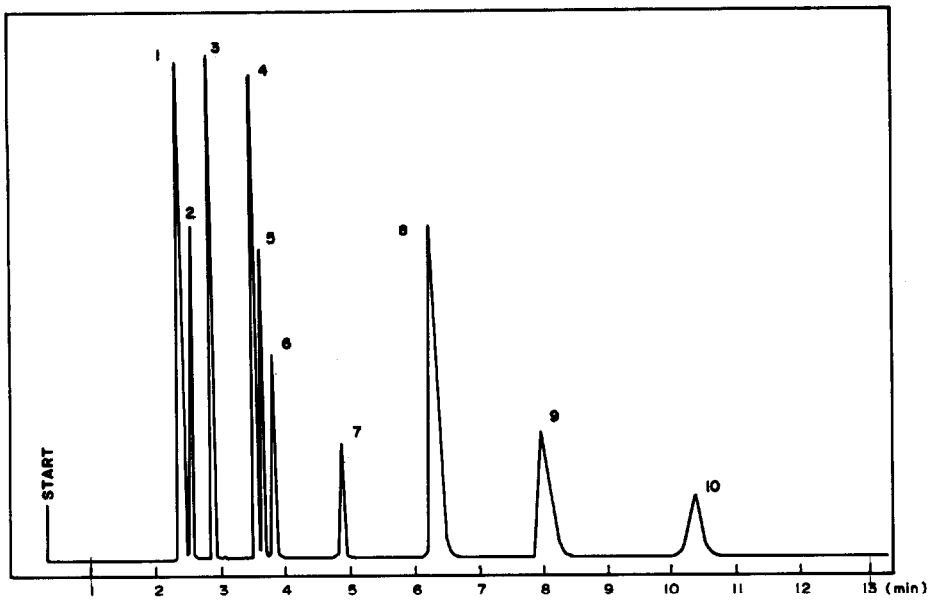

Fig. 2. Separation of standard mixture of chloropyridine isomers by HPLC. Peaks: 1, PCP; 2, 2,3,5,6-TCP; 3, 2,3,5-TCP; 4, 3,5-DCP; 5, 2,5-DCP; 6, 2,6-DCP; 7, 2,3-DCP; 8, 2-chloropyridine; 9, 3-chloropyridine; 10, pyridine.

elution in the normal-phase mode using a mixture of *n*-hexane and chloroform as eluent and changing the proportion of chloroform from 0.1 to 30% in 30 min was tried. 2,3,5-TCP and 3,5-DCP were not resolved. The optimum separation was obtained with *n*-hexane–chloroform (97:3, v/v) in the normal-phase mode utilising a Zorbax Sil column.

Pyridine is a base, and the basicity of the pyridine ring and the nature of the substituents affect the retention behaviour. Chlorine is electron-withdrawing in nature

TABLE III

RELATIVE RETENTION TIMES AND RESPONSE FACTORS OF CHLOROPYRIDINE ISOMERS BY HPLC

Compound	RRT	S.D. (n = 3)	RF	S.D. (n = 3)
Pyridine	1.00	–	2.36	0.039
2-Chloropyridine	0.59	0.010	1.92	0.022
3-Chloropyridine	0.76	0.012	2.03	0.019
2,3-DCP	0.45	0.009	1.45	0.020
2,6-DCP	0.35	0.008	1.38	0.016
2,5-DCP	0.33	0.010	1.77	0.018
3,5-DCP	0.32	0.008	1.68	0.016
2,3,5-TCP	0.26	0.007	1.52	0.021
2,3,5,6-TCP	0.22	0.007	1.90	0.022
PCP	0.21	0.008	1.55	0.018

TABLE IV

ANALYSIS OF CHLOROPYRIDINE STANDARD MIXTURES BY HPLC

Compound	Mixture No.			
	1	2	3	4
Pyridine				
Taken (%)	2.48	1.35	0.92	0.66
Found (%)	2.45	1.36	0.91	0.008
Standard deviation (%, $n = 3$)	0.030	0.021	0.010	0.008
2-Chloropyridine				
Taken (%)	2.30	1.38	1.10	0.68
Found (%)	2.33	1.39	1.12	0.66
Standard deviation (%, $n = 3$)	0.024	0.014	0.008	0.007
3-Chloropyridine				
Taken (%)	2.45	1.32	0.88	0.74
Found (%)	2.49	1.35	0.87	0.73
Standard deviation (%, $n = 3$)	0.025	0.020	0.011	0.009
2,6-DCP				
Taken (%)	2.51	1.16	1.05	0.81
Found (%)	2.53	1.14	1.07	0.82
Standard deviation (%, $n = 3$)	0.022	0.009	0.010	0.008
3,5-DCP				
Taken (%)	2.38	1.08	0.92	0.80
Found (%)	2.36	1.08	0.90	0.81
Standard deviation (%, $n = 3$)	0.020	0.012	0.009	0.006
2,3-DCP				
Taken (%)	2.35	1.21	1.14	0.71
Found (%)	2.32	1.19	1.16	0.69
Standard deviation (%, $n = 3$)	0.018	0.011	0.009	0.005
2,5-DCP				
Taken (%)	2.35	1.21	1.14	0.71
Found (%)	2.32	1.19	1.16	0.69
Standard deviation (%, $n = 3$)	0.018	0.011	0.009	0.005
2,3,5-TCP				
Taken (%)	2.53	1.35	1.02	0.69
Found (%)	2.49	1.38	1.00	0.68
Standard deviation (%, $n = 3$)	0.026	0.012	0.008	0.010
2,3,5,6-TCP				
Taken (%)	0.80	6.20	4.93	3.14
Found (%)	0.80	6.22	4.88	3.18
Standard deviation (%, $n = 3$)	0.006	0.044	0.037	0.028
PCP				
Taken (%)	79.82	83.66	86.93	91.08
Found (%)	79.68	83.42	87.07	91.29
Standard deviation (%, $n = 3$)	0.289	0.350	0.285	0.262

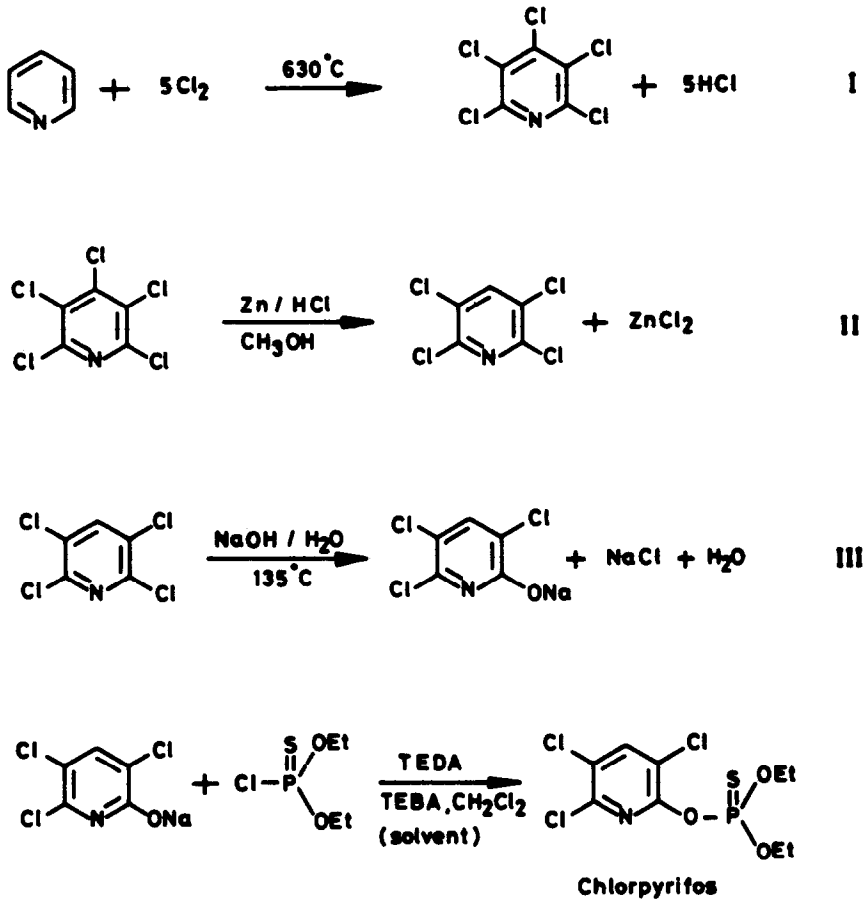

Fig. 3. Manufacture of chlorpyrifos from pyridine.

and hence substitution of chlorine in the pyridine ring reduces the basicity and, therefore, the polarity is also reduced. This may be the reason for the lowest retention being shown by pentachloropyridine in the normal-phase mode. Pyridine, which is the most polar of the compounds investigated, had the longest retention time in HPLC; the order of elution in GC was the reverse of that in HPLC.

The validity of the HPLC procedure was checked by analysing additional synthetic mixtures and using the response factors. Quantitative determinations were carried out by internal normalization. The results obtained are given in Table IV. These results demonstrate that both the accuracy and the precision of the procedure are acceptable.

Process stream samples obtained at the end of the first and second steps during chlorpyrifos process development were analysed using the developed procedures. The method of preparation of chlorpyrifos from pyridine is shown in Fig. 3. Results of the analysis of typical reaction mixtures by GC are given in Table V and those by HPLC in

TABLE V

RESULTS OF THE ANALYSIS OF TYPICAL REACTION MIXTURES IN CHLORPYRIFOS PROCESS DEVELOPMENT BY GC

Compound	Mixture No.			
	First step		Second step	
	1	2	1	2
Pyridine				
Found (%)	0.77	0.52	–	–
Standard deviation (%, $n = 3$)	0.009	0.005	–	–
2-Chloropyridine				
Found (%)	1.61	0.76	0.89	0.34
Standard deviation (%, $n = 3$)	0.016	0.008	0.009	0.008
2,6-DCP + 2,3-DCP + 2,3,5-TCP				
Found (%)	2.15	1.45	1.00	0.58
Standard deviation (%, $n = 3$)	0.023	0.012	0.012	0.010
2,3,5,6-TCP				
Found (%)	2.32	1.11	83.09	87.12
Standard deviation (%, $n = 3$)	0.037	0.018	0.424	0.377
PCP				
Found (%)	88.50	92.37	8.14	5.80
Standard deviation (%, $n = 3$)	0.041	0.455	0.081	0.052

TABLE VI

RESULTS OF THE ANALYSIS OF TYPICAL REACTION MIXTURES IN CHLORPYRIFOS PROCESS DEVELOPMENT BY HPLC

Compound	Mixture No.			
	First step		Second step	
	1	2	1	2
Pyridine				
Found (%)	0.75	0.54	–	–
Standard deviation (%, $n = 3$)	0.010	0.007	–	–
2-Chloropyridine				
Found (%)	1.58	0.54	0.66	0.35
Standard deviation (%, $n = 3$)	0.015	0.006	0.006	0.004
2,6-DCP				
Found (%)	1.50	0.79	0.80	0.36
Standard deviation (%, $n = 3$)	0.010	0.008	0.007	0.004
2,3-DCP				
Found (%)	0.46	0.55	0.25	0.18
Standard deviation (%, $n = 3$)	0.004	0.005	0.006	0.005
2,3,5-TCP				
Found (%)	0	0	0	0
2,3,5,6-TCP				
Found (%)	2.40	1.04	83.89	87.12
Standard deviation (%, $n = 3$)	0.025	0.021	0.244	0.266
PCP				
Found (%)	90.17	93.69	8.14	5.66
Standard deviation (%, $n = 3$)	0.312	0.268	0.075	0.047

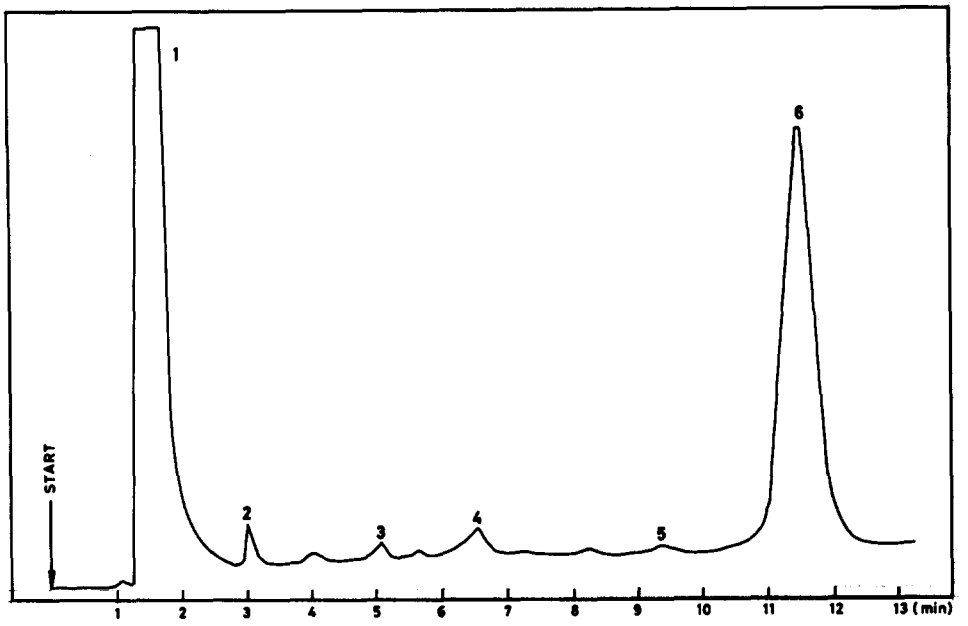

Fig. 4. GC of process stream sample obtained after vapour-phase chlorination of pyridine. Peaks: 1, solvent (toluene); 2, pyridine; 3, 2-chloropyridine; 4, 2,6-DCP; 2,3-DCP and 2,3,5-TCP; 5, 2,3,5,6-TCP; 6, PCP.

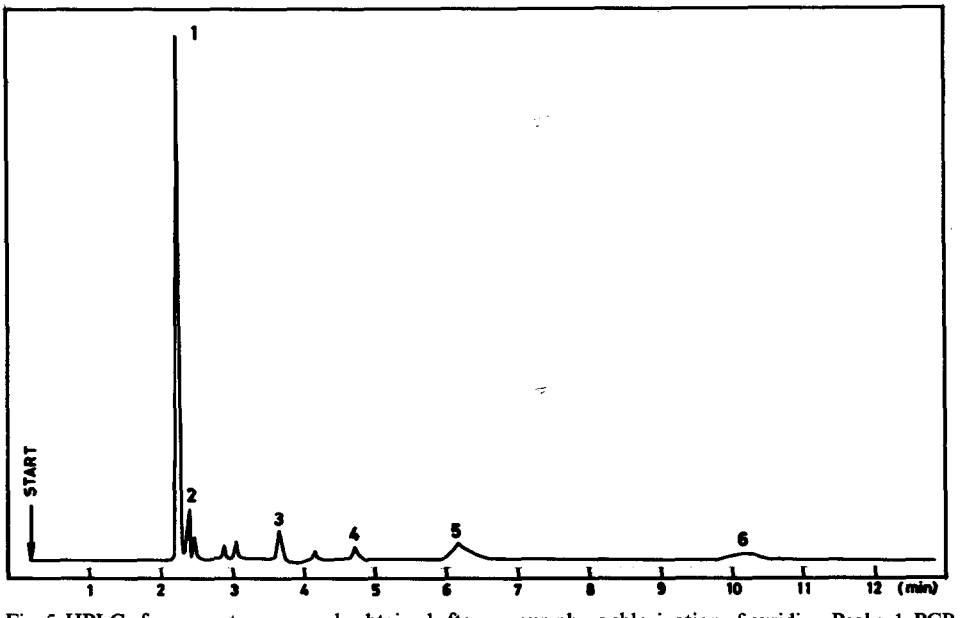

Fig. 5. HPLC of process stream sample obtained after vapour-phase chlorination of pyridine. Peaks: 1, PCP; 2, 2,3,5,6-TCP; 3, 2,6-DCP; 4, 2,3-DCP; 5, 2-chloropyridine; 6, pyridine.

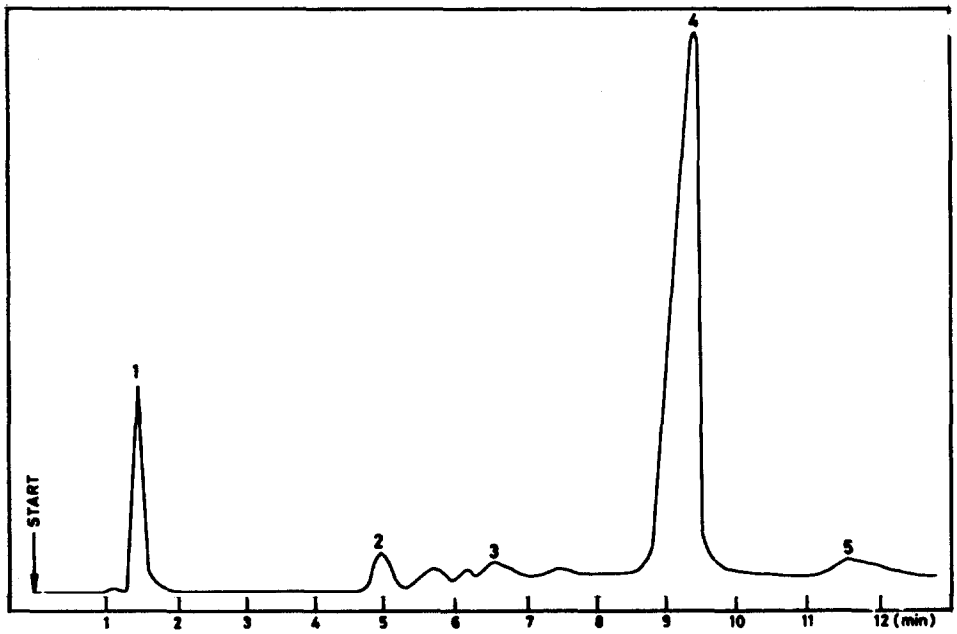

Fig. 6. GC of process stream sample collected after reduction of PCP. Peaks: 1, solvent; 2, 2-chloropyridine; 3, 2,6-DCP, 2,3-DCP and 2,3,5-TCP; 4, 2,3,5,6-TCP; 5, PCP.

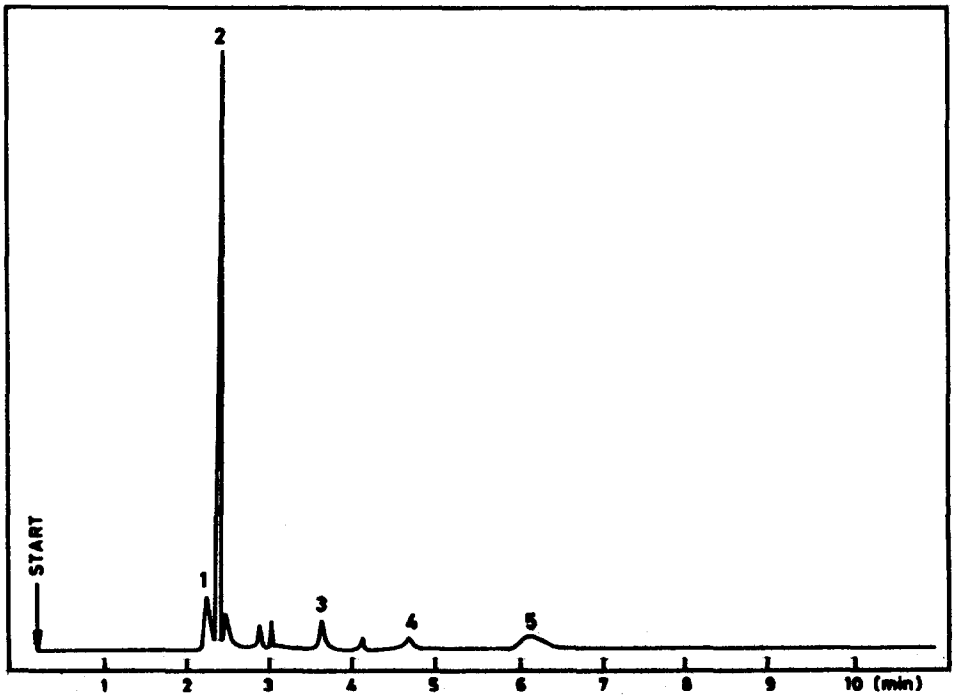

Fig. 7. HPLC of process stream sample collected after reduction of PCP. Peaks: 1, PCP; 2, 2,3,5,6-TCP; 3, 2,6-DCP; 4, 2,3-DCP; 5, 2-chloropyridine.

Table VI. Typical chromatograms showing the separation of process stream samples are shown in Figs. 4–7. It is seen from Fig. 4 (GC) that peak 1 is due to the solvent and peaks 2, 3, 4, 5 and 6 were identified as pyridine, 2-chloropyridine, mixture of 2,3- and 2,6-DCP and 2,3,5-TCP, 2,3,5,6-TCP and PCP, respectively, by comparison with authentic samples.

It can be observed from Fig. 5 that for the same reaction mixture using HPLC the peaks identified were PCP, 2,3,5,6-TCP, 2,6-DCP, 2,3-DCP, 2-chloropyridine and pyridine, respectively. The peak which was thought to be a mixture of 2,3- and 2,6-DCP and 2,3,5-TCP by GC was resolved into two peaks, *i.e.*, 2,3- and 2,6-DCP; 2,3,5-TCP formation was not observed.

It can be observed from Figs. 6 and 7 and Table VI that pyridine is absent in the reaction mixtures obtained at the end of the second step of the chlorpyrifos process. Amounts of the components present in the reaction mixtures were calculated and are presented in Tables V and VI together with the standard deviations. Unidentified peaks in the reaction mixtures were analysed by GC–mass spectrometry and the results have been published elsewhere [13]. The values of σ obtained show that the procedures developed are precise, and the agreement between the experimental and true values (Tables II and IV) show that the methods are accurate. It was found that the values of σ were slightly higher for reaction streams in comparison with those of standard mixtures. This may be due to the crude nature of the reaction mixtures.

CONCLUSIONS

GC and HPLC methods have been developed for the determination of chloropyridine isomers formed during high-temperature chlorination of pyridine. 2,3- and 2,6-DCP and 2,3,5-TCP could not be separated by GC, whereas all the isomers were resolved by HPLC. The relationship between the structure and chromatographic behaviour of the analytes has been discussed. It is concluded that better resolution is obtained by HPLC and it is more accurate than the GC method.

The procedures were utilized in the separation and determination of the components of reaction mixtures obtained during the high-temperature chlorination of pyridine and the reduction of pentachloropyridine in chlorpyrifos process development.

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