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The Quantitation of Phenyl-2-Propanone Using High-Performance Liquid Chromatography

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ABSTRACT: A method using high-performance liquid chromatography (HPLC) has been developed for the rapid, selective, and accurate quantitation of phenyl-2-propanone (P-2-P). A Perkin-Elmer HS/5 C18 column is utilized with a water, methanol, phosphoric acid mobile phase to achieve separation of clandestinely manufactured P-2-P from precursor chemicals and reaction by-products. Absorbance ratio and relative retention time data for some of the more common by-products and precursors are presented.

KEYWORDS: forensic science, phenyl-2-propanone, chromatographic analysis, laboratories, clandestine laboratories, precursor chemicals, high-performance liquid chromatography, absorbance ratio

Phenyl-2-propanone (P-2-P) has been, and apparently remains, a much sought-after commodity by illicit drug manufacturers across the United States. P-2-P, a nonpsychoactive substance, is used as the primary precursor in the illegal manufacturing of amphetamine and methamphetamine [*1*]. For this reason, in 1980 it was placed in Schedule II of the Controlled Substances Act, under which the maximum penalty for possession with intent to distribute, could be 20 years imprisonment and a $1 million fine [*2*].

Law enforcement officers submit two types of P-2-P samples to forensic science laboratories for analysis—samples which have been purchased and those which have been seized. The analysis of purchased samples is usually rather straightforward, since many are found to contain relatively pure P-2-P. Samples seized from clandestine laboratories, on the other hand, are expected not to be as "clean" as those purchased. Many seizures consist of laboratory glassware containing crude reaction mixtures, making the identification and quantitation of P-2-P extremely difficult. The situation can be even more complex if the laboratory operator followed, or attempted to follow, more than one synthetic route. Many clandestine laboratory operators, who in the past had been producing only methamphetamine, have now taken to synthesizing P-2-P either alone or in combination with methamphetamine [*3*]. This has led to an increase in submission of P-2-P exhibits to the Drug Enforcement Administration's (DEA) laboratory system during the past few years. DEA records show a rise of 76% nationwide for this past year alone! This trend has created a greater need for suitable methods dealing with the forensic analysis of P-2-P.

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The analysis of liquid samples seized at clandestine laboratories can be very simple or extremely complicated and difficult. The identification of pure solvents normally presents no problems; it is the examination of unknown chemical reaction mixtures that often becomes a time-consuming and cumbersome affair. At the present time, no method is reported in the open literature for the quantitation of illicitly manufactured P-2-P. High-performance liquid chromatography (HPLC) appears to be a logical way to determine P-2-P in complex mixtures. Reported here is an isocratic reverse phase HPLC system, using a 5-micron C18 column and a phosphate-buffered water/methanol mobile phase, with ultraviolet (UV) detection. This method separates P-2-P from common precursor chemicals and reaction by-products. This allows for the rapid, selective, and accurate quantitation of clandestinely manufactured P-2-P. In addition, absorbance ratio and relative retention time data, for some of the more common P-2-P precursor chemicals and by-products, are presented. These dual parameters provide a check on peak purity and also enhance the specificity of the analysis [*4,5*].

Experimental Procedure

The chromatographic system consisted of a Series 4 liquid chromatograph (Perkin-Elmer, Norwalk, CT), an ISS-100 autosampler (Perkin-Elmer), two Model LC-90 variable UV detectors fitted with 8-μL flowcells, and a 4.6- by 125-mm stainless steel column prepacked with 5-micron C18 packing material (Perkin-Elmer HS/5 C18). Two Model LCI-100 laboratory computing integrators (Perkin-Elmer) were used for data handling.

The mobile phase used was 37% methanol and 63% phosphate buffer solution. The buffer solution consisted of 590-parts distilled water and 10-parts phosphoric acid with the pH adjusted to 3.5 with 2*N* sodium hydroxide. This solution was filtered and degassed by passing it through a 0.45-μm filter (Rainin Instruments Co., Woburn, Massachusetts). The mobile phase was mixed internally from two solvent reservoirs, one containing pure methanol, the other containing the phosphate buffer solution. A flow rate of 2.0 mL/min was used.

The methanol used was distilled in glass, Omnisolv (MCB, Cincinnati, Ohio). All other chemicals were of reagent grade. Standard P-2-P was obtained from Mallinkrodt, Inc. (no longer available). All other drug and chemical standards employed were of USP/NF quality.

Standard and sample solutions were prepared by weighing a minimum of 200 mg material into an appropriate volumetric flask followed by dilution with methanol until a final concentration of approximately 0.5 mg/mL for the compound of interest was obtained. Injection volume was 10 μL for all determinations.

P-2-P was quantitated by comparing average peak area measurements of sample versus standard, based on dual injections of each, using UV detection at 220 nm. The accuracy of the method was checked by quantitating five separate weighings of a synthetic sample consisting of 75% P-2-P, 15% phenylacetic acid, and 10% methanol. The precision of the chromatographic response was examined by making six quantitative determinations of a single sample solution. The absorbance ratio data for P-2-P were obtained by measuring the peak area response of more than 30 injections of standard and sample material using 1 variable UV detector set at 220 nm, in series with another set at 254 nm.

Results and Discussion

Representative chromatograms of standard P-2-P and a prepared sample solution are shown in Figs. 1 and 2, respectively. Quantitative determinations were based on peak area measurements of the UV response at 220 nm. The relationship of detector response with P-2-P concentration was found to be linear over the range of 0.05 to 1.00 mg/mL. The relative standard deviation of the chromatographic response was found to be 2.2%, while the

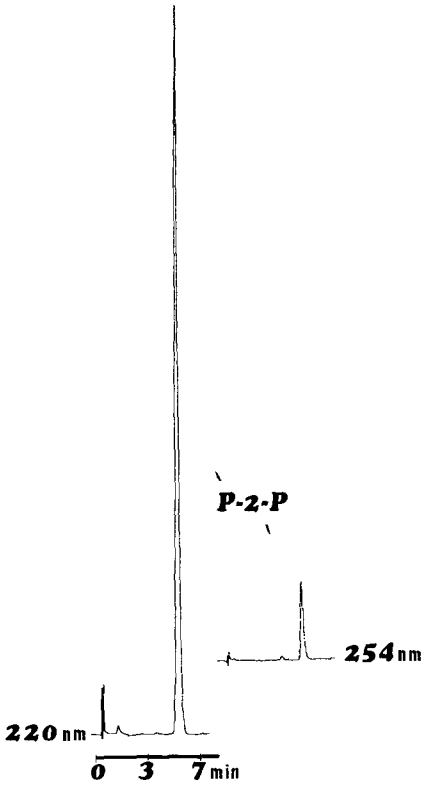

FIG. 1—*Liquid chromatogram of standard P-2-P detection by UV absorbance at 220 and 254 nm.*

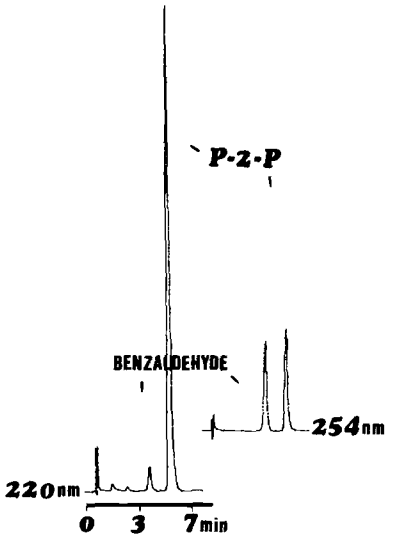

FIG. 2—*Liquid chromatogram of a P-2-P exhibit: detection by UV absorbance at 220 (×2) and 254 nm.*

percentage of error for the accuracy determination was found to be 1.8%, with a relative standard deviation of 1.9%.

The purity of the P-2-P response of all samples analyzed was checked by comparing the 220:254-nm absorbance ratio for each to that of standard material. These ratios were found to be in good agreement. The mean value for the 220:254-nm absorbance ratio determination of P-2-P was 9.63, with a relative standard deviation of 1.4%.

The relative retention times and the 220:254-nm absorbance ratios of the various chemicals and compounds that were examined are presented in Table 1. The values were remeasured after six weeks. The average long-term reproducibility of the relative retention times was 2.0%, while the average variability of the absorbance ratios was 2.5%. In general, a sample injection should be followed by a standard injection to obtain close matches for relative retention time and absorbance ratio values.

During the past year, over 50 alleged P-2-P exhibits have been analyzed using this procedure. Some were found to contain only P-2-P, while others contained P-2-P mixed with any number of unknown compounds. In all cases, however, quantitation of P-2-P was possible. Some samples seized from clandestine laboratories were found to contain pure precursor chemicals such as phenylacetic acid and phenyl-2-propanol. Each of these exhibits was analyzed using this procedure, and their relative retention times and absorbance ratios were compared to standard material. Identities were confirmed by infrared spectrophotometry or gas chromatography/mass spectrometry (GC/MS). One particularly complex sample that was analyzed is shown in Fig. 3. Relative retention time and absorbance ratio data indicated the presence of P-2-P, phenyl-2-propanol, and either methamphetamine or amphetamine. The presence of P-2-P and phenyl-2-propanol was confirmed by GC/MS. The presence of methamphetamine, after suitable extraction and isolation, was confirmed by Fourier transform infrared spectrophotometry.

Benzaldehyde can be used as a primary precursor in the synthesis of P-2-P via the "phenyl-2-nitropropene route" [3] and as such could be present in samples seized at laboratories where this particular procedure was used. Benzaldehyde is commonly found, however, in many exhibits of P-2-P which are obviously unrelated to this synthetic route. It is usually present in very small amounts, possibly a result of mixed mechanisms involving photochemical decomposition or free radical formation or both, all with respect to the ketone, P-2-P.

TABLE 1—*Relative retention data and 220:254-nm absorbance ratios for phenyl-2-propanone and some related precursor chemicals and reaction by-products.*

Compound	RRT(P-2-P)	220:254
Nitroethane	0.23	76.5
Amphetamine	0.28	2.1
Methamphetamine	0.28	2.2
Phenylacetic acid	0.66	9.5
Chloroacetone	0.74	0.6
Benzoic acid	0.74	9.8
Benzaldehyde	0.76	0.14
Phenylacetonitrile	0.87	1.3
P-2-P	1.00(6 min)	9.6
Phenyl-2-propanol	1.39	4.5
Benzene	1.59	0.2
α-Acetylphenylacetonitrile	1.93	0.8
1,3-Diphenylacetone	[a]	...
Allylbenzene	[a]	...
α-Methylstyrene	[a]	...

[a]Retention time greater than 1 h.

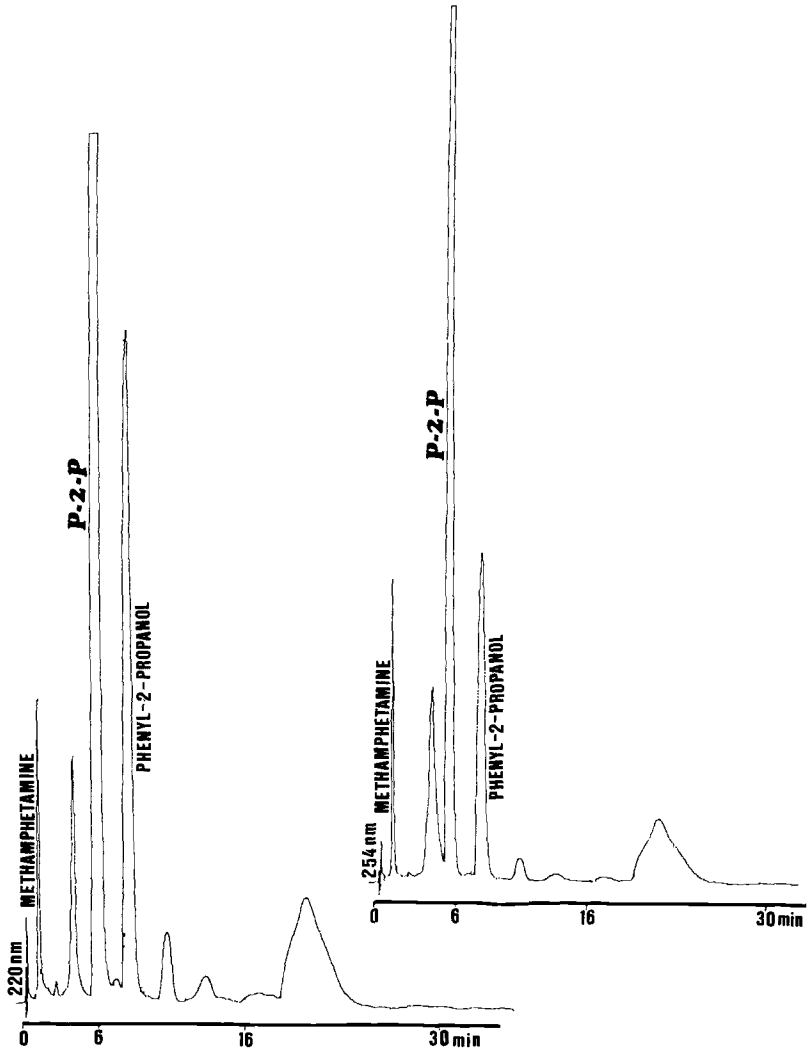

FIG. 3—*Liquid chromatogram of a multicomponent P-2-P exhibit; detection by UV absorbance at 220 (×2) and 254 nm.*

The sample chromatogram shown in Fig. 2 is of a high-purity P-2-P exhibit in which the presence of a small amount of benzaldehyde was confirmed by GC/MS analysis. A small amount of benzaldehyde in a sample consisting primarily of P-2-P yields a response at 254 nm for benzaldehyde that is almost equal to that of the P-2-P. This is due to the fact that benzaldehyde exhibits a strong response at 254 nm, compared to a relatively weak response by P-2-P. Benzaldehyde is known to readily autoxidize to benzoic acid [*6*]. Several samples analyzed during this study were found to contain benzoic acid in combination with benzaldehyde and P-2-P.

Conclusion

An isocratic reverse-phase HPLC system, using a 5-micron C18 column with a phosphate buffered water/methanol mobile phase, has been developed for the rapid, selective, and

accurate quantitation of P-2-P. The quantitative determination of P-2-P in complex mixtures, such as samples seized at clandestine laboratories, can be readily accomplished through the use of the described procedure. Absorbance ratio data are presented which can aid in the qualitative identification of P-2-P precursor chemicals and related by-products, when combined with the parameter of relative retention time.

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