

Determination of Codeine in Terpin Hydrate and Codeine Elixir

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Ion exchange chromatography and non-aqueous titrimetry are applied to the analysis of codeine in terpin hydrate and codeine elixir. The method is simple and accurate.

ALTHOUGH terpin hydrate and codeine elixir has been official for many years, it has been only recently that an assay procedure (1) has been included in the monograph. The assay involves the extraction of the alkaloid from the elixir with chloroform, followed by titration with perchloric acid in dioxane using methanolic methyl red as the indicator. The Association of Official Agricultural Chemists (2) recognizes a spectrophotometric procedure for both the terpin hydrate and codeine in the elixir. It is based on a report by Milos (3). The codeine is determined by measuring the absorbance of an aqueous solution of the hydrochloride salt at 285 $m\mu$. Interfering substances are removed by ether extraction.

In a recent paper (4) Milos extracted the codeine from the elixir as the *p*-toluenesulfonic acid complex on a column of chromatographic siliceous earth.¹ The complex was eluted with chloroform-acetic acid solution and passed through a second column of chromatographic siliceous earth containing NaHCO_3 as the stationary phase. The codeine in the eluate was determined spectrophotometrically at 278 $m\mu$.

Ion-exchange resins have been employed in the determination of alkaloids and alkaloidal salts. These have been noted in a previous paper (5). The analysis of alkaloids and their salts by nonaqueous titration and by ion-exchange chromatography has been extensively reviewed by Higuchi and Bodin (6). Kucharsky and Safarik (7) have thoroughly reviewed the literature on the determination of alkaloids by titration in nonaqueous media.

In the present paper the techniques of ion-exchange chromatography and nonaqueous titrimetry are applied to the analysis of codeine in the elixir of terpin hydrate and codeine.

EXPERIMENTAL

Preparation of the Ion-Exchange Column.—The strongly acidic cation-exchange resin Dowex 50-X8 (200-400 mesh) was used in this study. The chromatographic column was prepared as described in an earlier paper (5). Five grams of resin was added to the tube as a slurry in water. The column was washed with 250 ml. of distilled water, 50 ml. of 2 *N* HCl, and distilled water until the eluate gave a negative test with AgNO_3 T.S. The column was ready for use.

Assay Procedure.—Exactly 20 ml. of terpin hydrate and codeine elixir² was transferred by pipet to a 150-ml. beaker. About 40 ml. of ethanol was added to reduce the viscosity of the elixir and permit a more rapid flow rate through the column. The solution was passed through the resin column. The beaker was rinsed several times with small amounts

of ethanol and the washings were added to the column. The column was washed with an additional 50 to 75 ml. of ethanol.

The codeine was eluted from the column with 10% ammonia in ethanol prepared by diluting stronger ammonia water with ethanol. A total of 100 ml. of eluate was collected. The solution was evaporated to dryness by gentle aeration by directing a fine stream of air above the surface of the liquid. The residue was dissolved in ethanol and the solution was evaporated to dryness. This procedure was repeated.

The codeine content of the residue was determined by dissolving in 30 ml. of glacial acetic acid and titrating visually with 0.01 *N* perchloric acid in acetic acid. The indicator for the titration was 0.2% methyl violet in glacial acetic acid. The exact indicator color change was noted by using indicator solution in conjunction with a potentiometric titration. The color change corresponding to the graphic end point was from violet to dark blue. A blank determination was performed with each series of titrations, and any necessary corrections were made.

Comparison was made with the N.F. XII assay procedure (1).

RESULTS AND DISCUSSION

On the basis of 10 consecutive determinations the proposed procedure gave an average per cent recovery (based on labeled amount) of 99.66 with a standard deviation of ± 1.17 . By the N.F. method the per cent recovery was 98.04 with a standard deviation of ± 1.64 .

The proposed assay for codeine in terpin hydrate and codeine elixir is simple, rapid, and accurate. The codeine is extracted from the elixir by passage through a sulfonic acid ion-exchange resin. This obviates the tedious and time-consuming solvent extraction procedure. The codeine is readily eluted from the column by displacement with the stronger base ammonia. The codeine is recovered from the eluate by aeration which removes the ammonia, ethanol, and any water which may be present. The codeine is then titrated in glacial acetic acid with acetous perchloric acid using methyl violet as the indicator. This technique produces a much sharper and more readily detectable end point than the official method. Considerable difficulty was experienced in end point detection when the official assay procedure was performed. In addition, lower results were obtained with a higher standard deviation.

REFERENCES

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¹ Marketed as Celite 545 by Johns-Manville, New York, N. Y.

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