Analysis of Binary Mixtures of Pharmaceutical Amines by the Acid Dye Technique

FUMI MATSUI and W. N. FRENCH

Abstract □ A general procedure using the acid dye technique is described for the direct analysis of certain binary mixtures of pharmaceutical amines without prior separation. Benzene (or benzene containing a small amount of isoamyl alcohol) is used to extract selectively the ion-pair formed between the amine and an indicator dye from a suitably buffered aqueous phase. The less-polar amine of the binary mixture is determined using bromcresol purple, while the total of both amines is determined with bromthymol blue. The amount of the more-polar amine is calculated by difference. Specific combinations examined include diphenhydramine–ephedrine, prochlorperazine–amphetamine, promazine–phenmetrazine, promethazine–ephedrine, promethazine–codeine, diphenhydramine–codeine, and diphenylpyraline–codeine. Recoveries for simulated mixtures average 99.76%, with an average coefficient of variation of 0.85 for an individual determination. The method has some limitations in accuracy for binary mixtures containing a large proportion of the less-polar amine. The scope of the technique is demonstrated by application to several commercially available dosage forms.

Keyphrases □ Amine binary mixtures—analysis □ Bromthymol blue—total amine determination □ Bromcresol purple—less-polar amine determination □ Colorimetric analysis—spectrophotometer

The acid dye technique is a general procedure for the quantitative analysis of a variety of pharmaceutical amines. In practice, a buffered aqueous solution containing the amine and a suitable indicator dye is shaken with an organic solvent, and the concentration of the resulting ion-pair in the organic phase is determined spectrophotometrically. Most amines exhibit a high sensitivity while acidic, neutral, and weakly basic compounds, as well as the commonly used excipients, do not interfere. Specific compounds for which methods have been described in the recent literature include thiamine in tablets (1), methapyraline in cough syrups (2), atropine in tablets and elixirs (3), procaine in parenteral preparations (4), ephedrine in tablets (5), imipramine and related compounds in tablets (6), and trifluoperazine in tablets (7). Automated procedures have been described for drugs such as propoxyphene (8), propoxyphene and other amines (9), and for several pharmaceutical amines and quaternary compounds (10). The technique also has been combined with quantitative TLC for the determination of amines in mixtures after separation on the chromatoplate (11).

The majority of publications describe the use of chloroform as the organic solvent. However, for most compounds, benzene is equally good and, in certain cases, has some advantages. With benzene, the experimental technique is simplified since the extraction can be carried out in a centrifuge tube and the organic layer can be clarified by centrifugation and decanted directly into a cell. The use of chloroform sometimes leads to emulsion formation and difficulties in reproducibility when extractions are carried out in a separator.

Table I—Photometric Solvents, Dye Solutions, and Buffers Required for Analysis

Mixture Code	With BCP: Percent IAA in Benzene[a]	With BCP: BCP Concn.[b]	With BCP: Buffer pH	With BTB: Percent IAA in Benzene[a]	With BTB: BTB Concn.[c]	With BTB: Buffer pH
A	0.5	37	5	1.0	40	6
B	0	35	6	0.5	45	6
C	0	35	4	0	45	6
D	0.5	35	4	0.5	42.5	6
E	0	35	4	0	45	6
F	0	37.5	5	0	42.5	6
G	0	37.5	6	0	42.5	6

[a] Percent by volume of isoamyl alcohol (IAA) in benzene. [b] Milligrams/100 ml. in solvent pH 6. [c] Milligrams/100 ml. in solvent pH 8.

Chloroform may be considered as a broad-spectrum solvent for the acid dye technique, since similar sensitivities are realized for different types of amines with a number of indicator dyes. Benzene, on the other hand, may be considered more selective because varying degrees of sensitivity are evident, depending on factors such as the polarity of the amine and type of indicator dye. Sensitivities may range from zero to values approaching those realized by the use of chloroform.

Most pharmaceutical amines fall into two general categories in terms of their sensitivity with different indicator dyes when benzene is used as the photometric solvent. The first category includes relatively polar compounds such as monophenyl amines, dibasic amines, and many alkaloids (*e.g.*, ephedrine, amphetamine, phenmetrazine, chlorpheniramine, and codeine); the second category includes the relatively nonpolar amines such as the diphenylmethane derivatives and compounds that are relatively free from polar structural configurations (*e.g.*, most phenothiazine derivatives, diphenylmethane amine drugs, and compounds such as dextromethorphan and propoxyphene). In general, amines in the more-polar category exhibit good sensitivity only with bromthymol blue (BTB) and little or no sensitivity with bromcresol purple (BCP); amines in the less-polar category display good sensitivity with both BCP and BTB.

Thus, by proper selection of experimental conditions including the choice of indicator dye, binary mixtures containing one amine in each category are amenable to analysis without prior separation. The less-polar amine can be determined with BCP, while the total of

Table II—Concentration of Sample and Reference Solutions[a]

Mixture Code	Components	Stock Sample Soln.	Detn. with BCP: Ref. Soln.	Detn. with BCP: Dil. Sample Solution	Detn. with BTB: Ref. Soln.[b]	Detn. with BTB: Dil. Sample Solution
A	Diphenhydramine HCl	20	2.0	2.0	2.0	1.2
	Ephedrine sulfate	10	—	1.0	2.0	0.6
B	Prochlorperazine[c]	2.5	2.5	2.5	2.5	0.7
	Amphetamine sulfate	5	—	5.0	2.0	1.4
C	Promazine HCl	10	2.0	2.0	2.0	1.0
	Phenmetrazine HCl	10	—	2.0	1.6	1.0
D	Promethazine HCl	10	1.6	1.6	1.6	1.0
	Ephedrine HCl	10	—	1.6	2.0	1.0
E	Promethazine HCl	10	1.6	1.5	2.0	1.0
	Codeine phosphate	20	—	3.0	2.5	2.0
F	Diphenhydramine HCl	32	2.0	1.6	2.0	1.6
	Codeine phosphate	8.0	—	0.4	2.5	0.4
G	Diphenylpyraline HCl	8.0	2.0	1.6	2.0	0.6
	Codeine phosphate	32	—	6.4	2.5	2.4

[a] Milligrams/100 ml. in 1% v/v HCl. [b] Each reference compound in separate reference solutions. [c] Present as the maleate.

both amines is determined with BTB. The amount of the more-polar amine is determined by difference. An investigation of the scope of this concept of analysis was carried out in the present study.

EXPERIMENTAL

Reagents—*Buffer Solutions*—McIlvaine buffers were prepared by mixing appropriate volumes of 0.1 *M* citric acid and 0.2 *M* disodium phosphate.

Bromcresol Purple Dye Solution—BCP (acid form)[1] was dissolved in buffer of pH 6 to give the required concentration (Table I).

Bromthymol Blue Dye Solution—BTB (acid form)[2] was dissolved in buffer of pH 8 to give the required concentration (Table I).

Photometric Solvents—Benzene AR, benzene AR containing 0.5% by volume of isoamyl alcohol AR, or benzene AR containing 1% by volume of isoamyl alcohol AR was used.

Hydrochloric Acid (1% v/v)—Concentrated HCl, diluted 1:100, was used.

Reference Solutions—Appropriate quantities of reference standards were dissolved in 1% v/v HCl to provide the desired concentrations (Table II).

Sample Solutions—Twenty tablets were weighed and finely powdered, or the contents of 20 capsules were combined and weighed. An accurately weighed aliquot of powder containing the weight of drug indicated in Table II was transferred to a 100-ml. volumetic flask. About 80 ml. of 1% v/v HCl was added, and the flask was shaken mechanically for 1 hr. Then 1% v/v HCl was added to volume, and the solution was mixed and filtered, if necessary, through Whatman No. 1 filter paper (the first few milliliters of filtrate were discarded) to give the stock sample solution. Appropriate aliquots of this stock sample solution were diluted with 1% v/v HCl to provide the desired concentrations (Table II).

Assay **Procedure**—The less-polar amine (upper entry for each amine pair in Tables III and IV) in each binary mixture was determined directly with BCP by carrying the appropriate reference solution and diluted sample solution through the following procedure.

Five milliliters of diluted sample solution or reference solution was pipeted into a 42-ml. centrifuge tube,[3] followed by 5 ml. of the appropriate buffer solution, 5 ml. of the appropriate dye solutions, and 10 ml. of the appropriate photometric solvent (as specified in Table I). The tube was shaken for 60 sec. (or alternatively tumbled end-over-end at 100 r.p.m. for 5 min. in a mechanical device designed to process 15 tubes simultaneously) and then centrifuged to effect complete separation and clarification of the organic layer (about 2 min.). The supernatant was decanted directly into a clean dry cell, and its absorbance was measured[4] at 410 nm. against a reagent blank prepared in a similar manner but with 5 ml. of 1% v/v HCl in place of the sample solution.

Comparison of the absorbance values for the reference and sample determination thus gave the amount of less-polar amine in the sample.

The more-polar amine (lower entry for each amine pair listed in Tables III and IV) in each binary mixture was determined indirectly with BTB by carrying the diluted sample solution and separate reference solutions of each amine through the described assay procedure. From the absorbance observed for the reference solution containing the less-polar amine and the amount of this material in the sample as determined by direct analysis with BCP, its absorbance contribution to the total observed for the sample solution with BTB was calculated; hence the absorbance of the more-polar amine was determined by difference. Comparison of this absorbance with the reference solution absorbance then gave the amount of more-polar drug in the sample.

RESULTS AND DISCUSSION

Development of optimum conditions for the acid dye technique involves proper selection of experimental parameters of buffer pH, kind and concentration of indicator dye, and kind of extracting photometric solvent. For application of the technique to binary mixtures of amines, conditions also must be such that the less-polar amine can be determined with BCP without interference from the more-polar amine. Variables examined for the development of the present procedure were the following:

Choice of Buffer pH—The pH of the aqueous phase should be such that any excess dye remains in this phase, thus giving a minimum blank, while formation of the ion-pair in the organic phase

Table III—Analysis of Simulated Mixtures

Mixture Code	Components	Relative Amounts (by wt.)	Recovery, %	CV[a]
A	Diphenhydramine HCl	2	100.9	0.5
	Ephedrine sulfate	1	99.4	1.0
B	Prochlorperazine[b]	1	101.8	0.7
	Amphetamine sulfate	2	98.3	0.5
C	Promazine HCl	1	100.1	1.1
	Phenmetrazine HCl	1	98.3	0.9
D	Promethazine HCl	1	99.0	0.4
	Ephedrine HCl	1	100.3	1.5
E	Promethazine HCl	1	100.1	0.8
	Codeine phosphate	2	99.2	0.5
F	Diphenhydramine HCl	4	101.0	1.3
	Codeine phosphate	1	96.9	1.3
G	Diphenylpyraline HCl	1	102.0	0.5
	Codeine phosphate	4	99.3	0.9

[a] Coefficient of variation based on six determinations. [b] Present as the maleate.

[1] Fisher Scientific.
[2] Fisher Certified Reagent ACS.
[3] Cat. No. 15846, Wilkens-Anderson Co., Chicago, Ill.
[4] Beckman DU-2 spectrophotometer.

Table IV—Analysis of Pharmaceutical Formulations

Product	Components	Label Claim, mg.	Assay Value— Label, %	CV[a]
A	Diphenhydramine HCl	50	95.7	0.8
	Ephedrine sulfate	25	99.5	1.1
B	Prochlorperazine[b]	2.5	102.0	1.5
	Amphetamine sulfate	5	98.9	1.0
C	Promazine HCl	25	95.0	0.6
	Phenmetrazine HCl	25	94.9	0.5
D	Promethazine HCl	25	93.6[c]	0.8
	Ephedrine HCl	25	93.4	0.7

[a] Coefficient of variation based on six determinations. [b] Present as the maleate salt. [c] Assay value of 94.9% of label claim (CV = 0.5) obtained by direct UV absorbance.

is at a maximum, thus giving optimum sensitivity. In practice, the optimum pH values for minimum blank and maximum sensitivity do not always coincide, although for most compounds the variation in sensitivity over several pH units is not appreciable. Table V shows the magnitude of variation encountered for the compounds studied.

With the majority of compounds studied, absorptivities are greater with BTB when buffer pH values are less than 6. However, at these low pH values, the blank is considerable and may be quite variable. This is particularly so when isoamyl alcohol in benzene is used, as in the assay of ephedrine where this photometric solvent is required to enhance the sensitivity. Therefore, a buffer of at least pH 6 is recommended for all analyses. With BCP in the buffer range of pH 3–6, blanks are minimal and reproducible over the entire range while changes in sensitivity are characteristic for the individual amine.

In dealing with mixtures of amines, the determining factor in the selection of buffer pH for the direct analysis of the less-polar amine with BCP is the elimination of any response by the more-polar amine. Most of the polar amines have no response (at the concentrations usually encountered) so the choice of pH is not critical. However, some materials, such as amphetamine, do have a significant sensitivity with BCP at higher pH values (Table VI). Therefore, for example, to eliminate any possibility of interference in the assay of prochlorperazine–amphetamine mixtures (in which the amount of amphetamine in a dosage form is double the amount of prochlorperazine), a buffer of pH 5 was chosen for the direct determination of prochlorperazine with BCP.

In the assay partition system (consisting of 5 ml. sample solution, 5 ml. buffer solution, 5 ml. of buffered dye solution, and 10 ml. of photometric solvent as described in the *Experimental* section), the actual pH of the aqueous phase is lower than the pH of the buffer quoted in Tables I and V because of the influence of the acidic sample solvent. When using BCP made up in a solution of pH 6 along with buffers of pH 4, 5, or 6, the pH in the partition system is 3.3, 3.8, or 4.3, respectively, while with BTB made up in a solution of pH 8 along with buffers of pH 6, 7, or 8, the pH is 5.1, 6.9, or 7.0, respectively. Although it is possible to use one dye–buffer reagent rather than a separate indicator dye solution and buffer solution for

Table VI—Effect of Buffer pH on Absorbance Exhibited by Amphetamine with BCP Using Benzene as the Photometric Solvent

Micrograms of Amphetamine Sulfate in 5-ml. Sample Aliquot for Assay	Absorbance— Buffer pH 5	Buffer pH 6	Buffer pH 7
250	0.003	0.004	0.013
375	0.003	0.006	0.016
500	0.003	0.007	0.018

routine analysis, it is preferable to utilize separate solutions during method development or for the analysis of a variety of compounds. In this way, a fixed stock of dye solution can be used for a series of experiments and only the buffer solution need be changed to obtain optimum conditions.

Choice of Sample and Dye Solvents—The use of dilute acid (1% v/v HCl in the present case) is considered essential for sample dissolution since many amine salts, even though completely soluble in water when in the pure state, are not completely extracted from a powdered tablet mixture with water alone. The use of water alone for the preparation of the dye solution has the disadvantage that many dyes, especially in the acid form, have a low solubility. The use of 0.01 N NaOH overcomes the solubility problem and is satisfactory, providing a good quality dye is available. However, the quality of dye often varies from batch to batch, even from the same manufacturer, giving rise to blanks which are high (*e.g.*, >0.025 absorbance unit) and variable. Prewashing a solution of dye in 0.01 N NaOH with photometric solvent does not overcome the problem. However, if the dye is dissolved in a suitable buffer, prewashing with photometric solvent often reduces the blank to a low and reproducible level (*e.g.*, <0.015 absorbance unit). With some batches of dye, an inordinately large volume of photometric solvent may be required in the prewash to reduce the blank. In such cases, recrystallization of the dye is preferable. This may be readily accomplished by heating about 2 g. of dye with 50 ml. of glacial acetic acid to effect almost complete dissolution, adding a few drops of acetone to clarify the solution, filtering through Whatman No. 2 filter paper, and allowing to crystallize. The residue may then be washed with cold benzene and air dried.

Choice of Dye and Dye Concentration—Although the ion-pair is usually a 1:1 molar ratio of dye to drug in an organic solvent, a higher ratio of dye is required in the partition system used during analysis to achieve maximum absorbance in the organic phase. Typical curves showing the effect of increasing dye concentration on absorbance with a fixed concentration of drug (the relative position of the curves is arbitrary with respect to absorbance) are shown in Fig. 1. Three general types of curve are exemplified in this figure. The first represents relatively less-polar compounds, such as promazine or prochlorperazine with BTB, for which the absorbance increases sharply until a molar ratio of between 2:1 and 4:1 is reached and then becomes independent of dye concentration. The

Table V—Effect of Buffer pH on Absorptivity Values

Drug	Absorptivity[a] With BCP pH 3	pH 4	pH 5	pH 6	With BTB pH 5	pH 6	pH 7	pH 8
Diphenhydramine HCl	57.1	58.9	58.9	56.3	66.9	67.1	66.2	64.5
Diphenylpyraline HCl	—	65.2	64.6	63.7	62.3	61.8	62.2	61.4
Promazine HCl	68.3	68.0	66.9	65.1	—	62.1	61.4	61.0
Promethazine HCl	68.5	67.3	64.4	58.6	—	61.1	60.7	59.2
Prochlorperazine maleate	23.8	30.1	31.4	32.0	—	33.7	32.5	31.6
Phenmetrazine HCl	—	—	—	—	—	75.3	71.3	63.6
Codeine phosphate	—	—	—	—	—	40.2	38.6	34.9
Ephedrine base	—	—	—	—	81.4	80.5	76.4	70.2
Amphetamine sulfate	—	—	—	—	59.8	58.2	52.2	—

[a] Calculated as absorbance/grams/liter based on theoretical weight in 10 ml. of photometric extracting solvent.

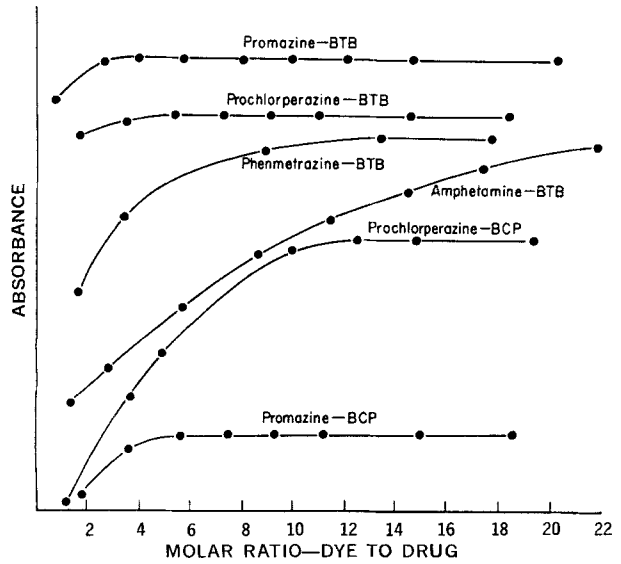

Figure 1—*Effect of dye concentration on absorbance of various drugs (as determined by varying the amount of dye with a fixed concentration of drug).*

second represents more-polar compounds, such as phenmetrazine, for which a molar ratio of 12:1 is required before the absorbance becomes independent of dye concentration. The third represents still more-polar compounds, such as amphetamine, for which the absorbance continuously increases with an increasing ratio of dye to drug.

Under the experimental conditions given in Tables I and II, the concentration of BTB used in the analysis of each amine pair is sufficient to ensure minimal variations in the assay through the effect of variations in molar ratio of dye to drug. For all compounds examined, Beer's law is followed over the concentration range of practical interest. Typical curves are shown in Fig. 2. Even for the amphetamine–BTB system, in which the absorbance varies continuously with a change in dye-to-drug ratio (but using a fixed concentration of drug), Beer's law is followed, providing a fixed concentration of dye is used. Therefore, it is imperative in such a system that the same stock dye solution be used throughout a sequence of analyses.

Choice of Photometric Solvent—With benzene alone as the photometric extracting solvent, many more-polar amines exhibit a much lower sensitivity on a molar basis than the less-polar amines. Inclusion of 0.5–1.0% isoamyl alcohol by volume, however, usually enhances the absorptivity of the more-polar amine to a level comparable to that of the less-polar amine (the absorptivity of the less-polar amine is usually not changed significantly by the inclusion of isoamyl alcohol when using BTB, but there may be some enhancement when using BCP).

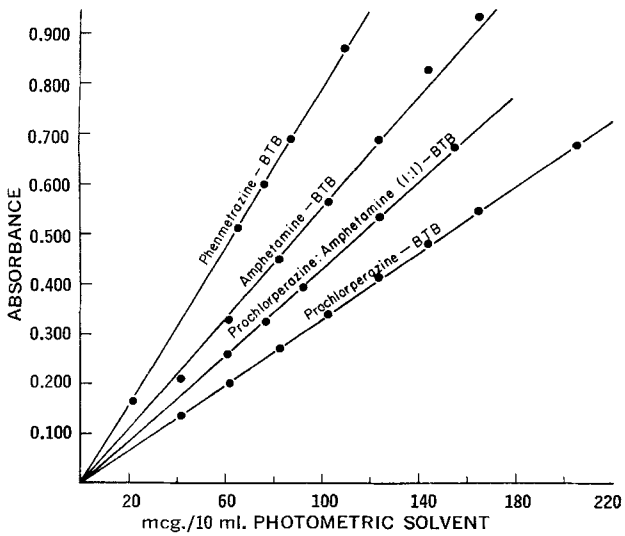

Figure 2—*Relationship of drug concentration and absorbance.*

With ephedrine, for example, the absorbance is increased by 25 and 50% by the addition of 0.5 and 1.0% by volume of isoamyl alcohol; with amphetamine the absorbance is increased 100% by the presence of 1% by volume of isoamyl alcohol. Nevertheless, some precautions must be observed with the use of isoamyl alcohol when dealing with mixtures of amines. With Mixture A (Table I), for example, 0.5% isoamyl alcohol in benzene is used for the determination of diphenhydramine with BCP to increase its sensitivity. Use of isoamyl alcohol is possible in this case since ephedrine causes no interference. With Mixture F, by comparison, benzene alone is used for the determination of diphenhydramine with BCP because of the possibility of interference by codeine. For the determination of both components of Mixture A with BTB, 1% by volume of isoamyl alcohol is included to enhance the sensitivity of ephedrine. By doing so, the sensitivity of ephedrine becomes comparable to that of diphenhydramine, thus minimizing the error that may occur when the amount of ephedrine is obtained by difference.

Analysis of Simulated Mixtures and Commercial Samples—The specific mixtures listed in Table III represent those containing amine pairs in the weight ratio that may be found in commercial formulations. The upper entry for each amine pair falls into the category of a relatively less-polar amine that exhibits good sensitivity with both BCP and BTB. The lower entry for each amine pair falls into the category of a relatively polar amine that exhibits good sensitivity only with BTB. The amount of the less-polar amine (upper entry) is determined directly by analysis with BCP, while the total amount of both amines is determined with BTB. The amount of the more-polar amine (lower entry) is determined by difference.

The analytical results given in Table III demonstrate that the overall accuracy and precision of the method are satisfactory for this type of assay, although a somewhat lower recovery is realized for codeine phosphate in admixture with four times its weight of diphenhydramine hydrochloride (Mixture F). This is not unexpected because the amount of diphenhydramine is obtained directly with BCP whereas the amount of codeine is obtained by difference. Any error in the determination of diphenhydramine would therefore be enhanced in the determination of codeine. The error is even greater if the more-polar compound has a lower sensitivity. In this particular case, an overestimation of 1% with BCP would mean an overcalculation of about 0.005 unit in the absorbance contributed by diphenhydramine in the BTB determination. This would then give an underestimation of 0.005 unit in the absorbance calculated for codeine and would lead to an underestimation in the assay of codeine of about 6.25%. Therefore, the procedure has limitations in accuracy for mixtures with large amounts of the less-polar amine relative to those of the more-polar amine. The optimum situation is that involving a 1:1 weight ratio of the two amines with each having an equal sensitivity, such as Mixture D in Table III. If the sensitivities are not equal, an increase in the proportion of the less sensitive compound (Mixture E) is desirable to maintain precision.

The results of analysis of four commercially available formulations are shown in Table IV. The absolute composition of each formulation was not determined by a secondary method except for the amount of promethazine in Product D. In that case, the assay values of the acid dye technique and those of direct UV measurement agree to within 1.3%. Coupled with the results of application of the method to simulated mixtures, as shown in Table III, the assay values and reproducibility shown in Table IV give an indication of the applicability to dosage forms containing binary mixtures of certain types of pharmaceutical amines.

Application of the technique to an expectorant containing liquid extract of ipecacuanha in addition to the combination of promethazine and codeine did not enable a complete analysis to be carried out. The amount of promethazine could be determined directly by using BCP without interference by codeine or emetine, the major alkaloid component of ipecacuanha. With BTB, emetine formed an ion-pair extractable into benzene, thus interfering with the determination of codeine. Nevertheless, the procedure is of value in determining one component directly in such multicomponent formulations.

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Specificity of Spectrophotometric Determination of Ephedrine and Other Phenalkanolamine Drugs as Benzaldehydes after Periodate Oxidation

LESTER CHAFETZ

Abstract □ Determination of ephedrine and other phenalkanolamine drugs by spectrophotometry of benzaldehydes extracted after periodate oxidation was critically examined with respect to specificity. It is shown that the compounds must have the general structure: Ar—CHOH—CH(NHR)—R′, that Ar cannot be *o*-dihydroxyphenyl (catecholamines do not interfere), that the amine function must be basic and sterically unhindered, and that there is no mutual interference by phenolic compounds and benzaldehyde-forming drugs. It is demonstrated that *N*-acetylephedrine, as an example of an acylated phenalkanolamine, does not react with periodate under the assay conditions. The carbonyl compound analogs of ephedrine and phenylpropanolamine, *i.e.*, ephedrone and α-aminopropiophenone, respectively, are oxidized to benzoic acid by periodate and do not interfere in the assay for the amino-alcohols. A method for the determination of phenylephrine and phenylpropanolamine in the same solution is presented, where solvent extraction of the periodate oxidation products affords their differentiation. Because the structural requirements for periodate oxidation are so confining, the procedure affords very high selectivity for phenalkanolamine drugs together with greater sensitivity and facility than are provided by most extant methods for this important group of compounds.

Keyphrases □ Phenalkanolamines—determination □ Periodate oxidation—phenalkanolamines to benzaldehydes □ Specificity, periodate oxidation—phenalkanolamine determination □ UV spectrophotometry—analysis

UV spectrophotometric determination of benzaldehyde or substituted benzaldehydes formed by periodate oxidation of ephedrine and other drugs with vicinal hydroxyl and amine functions has provided simple and sensitive assay methods for them in dosage forms and in biological fluids. Ephedrine HCl, in dilute acid solution, exhibits a benzenoid UV spectrum with a molar absorptivity, ε, of about 190 l./mole cm. at its 258.5 nm. maximum: oxidation of it to benzaldehyde affords an ε-value of about 14,400 at its maximum at about 241 nm. in hydrocarbon solvents, about a 75-fold gain in sensitivity. Although the literature on this reaction provides abundant implications on its specificity, it has not been critically reviewed from this standpoint. The purpose of this article is to provide a synthesis of the relevant literature and of previously unreported observations from these laboratories on the specificity of the method.

Periodate oxidations are among the most elegant reactions used in organic chemistry, because they are often quantitative within minutes at room temperature in aqueous media. The extent of the reaction can be measured easily by titration of excess oxidant or determination of any of the reaction products. Malaprade (1) introduced periodic acid as a reagent for the oxidation of 1,2-glycols in 1928. Its use in structure determination and as a selective analytical reagent was reviewed by Jackson (2), Dyer (3), and Bunton (4).

Nicolet and Shinn (5) first reported the use of periodate for oxidation of ethanolamine derivatives. They found that ethanolamines with primary or secondary amine functions were rapidly and quantitatively cleaved to aldehydes and ammonia or a primary amine, while attack on compounds with tertiary amine or acylated amine functions was extremely slow. Wickstrøm (6) studied the rate of periodate oxidation of ephedrine as a function of pH, titrating excess oxidant iodometrically. He found that periodate consumption was too slow to measure at pH 3.0, very slow at pH 6.0, and stoichiometric within 10 min. at pH 7.5 or higher. Overconsumption of periodate, *i.e.*, further oxidation of the aldehyde reaction products, was negligible except at very high pH. [The oxidation potential of the reagent is irrelevant in this reaction. Periodate is a very strong oxidizing agent in acid solution, with the potential of the periodate–iodate couple estimated at −1.6 v. In alkaline solution, however, the potential is only about −0.7 v. (7). Moreover, other oxidizing reagents of comparable redox potentials do not selectively cleave glycols and ethanolamines.] Wickstrøm (6) showed that the ephedrine reaction products are benzaldehyde, acetaldehyde, and methylamine (Scheme