Sensitive Ultraviolet Spectrophotometric Determination of Some Phenethanolamine Drugs

By LESTER CHAFETZ

The ultraviolet determination of phenylpropanolamine as benzaldehyde after periodate oxidation reported (12) was the basis of a study using a modified procedure for the assay of other phenethanolamine derivative drugs in dosage forms. Quantitative recoveries of aryl aldehyde after periodate oxidation of ephedrine, phenylpropanolamine, phenyramidol, and phenylephrine were demonstrated.

THE UTILITY of ephedrine, phenylpropanolamine, phenylephrine, and other compounds which may be considered phenethanolamine derivatives has led to the publication of a large number of methods for their determination in pharmaceutical dosage forms and other environments (1). Among the methods described for the nonphenolic members of the group are titrations of the base function (2), gravimetric determination *via* the hydrochloride salt (3) or tetraphenylboron salt (4), condensation with chromogens (5), dye-complex colorimetry (6), and absorption spectrometry (7). The monophenolic members of the group have also been determined by methods depending on the presence of that group; among these are bromination (8), coupling with a diazonium salt (9) or 4-aminoantipyrine (10), and the Millon reaction (11). Many other assay methods have been reported for this chemical class, attesting both to their importance and the limitations of sensitivity and selectivity which must be reckoned with in solving each analytical problem.

One of the more selective analytical procedures for a phenethanolamine drug was that described by Heimlich and his co-workers (12) in 1961. They determined phenylpropanolamine in urine by oxidizing the drug to benzaldehyde with periodate and measuring the ether extracted aldehyde spectrophotometrically. The possible application of the periodate oxidation procedure to the assay of ephedrine and related drugs in dosage forms led to the modifications and extensions reported here. The availability of a series of phenethanolaminoheterocyclic compounds synthesized in these laboratories (13) afforded an opportunity to test the procedure on analogs of differing base strength. The chemical structures of the compounds are described in Table I.

EXPERIMENTAL

Reagents.—Two per cent sodium metaperiodate, concentrated hydrochloric acid, approximately 0.05 *N* hydrochloric acid, 0.05 *N* sodium hydroxide, hexane (Phillips high purity grade or equivalent), chloroform A.C.S., and saturated sodium bicarbonate were employed.

Equipment.—A Beckman DU spectrophotometer or equivalent instrument equipped for ultraviolet measurements, Bausch and Lomb spectronic 505 or equivalent recording ultraviolet spectrophotometer (optional), and standard volumetric laboratory glassware were used.

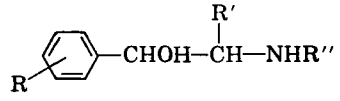
Estimation of Phenethanolamines as Benzaldehyde.—Transfer 5.0 ml. of an approximately 0.12 *M* solution of the nonphenolic phenethanolamine salt to a glass-stoppered tube of about 40-ml. capacity. Add 1.0 ml. of saturated sodium bicarbonate and 0.5 ml. of 2% sodium metaperiodate, and shake 10 minutes. Add 1–2 drops of concentrated hydrochloric acid. (The acid serves to convert amines which are not oxidized by periodate to their nonextractable salts.) Shake the mixture for 30 seconds with exactly 20.0 ml. of hexane, and filter the hexane layer through Whatman No. 1 paper. Determine the absorbance of the hexane extract at 242 mμ *versus* hexane in a 1-cm. silica cell or scan the ultraviolet spectrum in a recording instrument.

Estimation of Phenylephrine as *m*-Hydroxybenzaldehyde.—Transfer 5.0 ml. of an approximately 0.11 *M* solution of phenylephrine hydrochloride to a 60-ml. separator. Add 1.0 ml. of saturated sodium bicarbonate and 0.5 ml. of 2% sodium metaperiodate, and shake mechanically 10 minutes. Add 1–2 drops of concentrated hydrochloric acid. Extract the solution with five 5-ml. volumes of chloroform, and collect the extracts through cotton in a 25.0-ml. volumetric flask. Adjust the solution to the mark, and shake 15.0 ml. with exactly 10.0 ml. of 0.05 *N* sodium hydroxide. Filter the alkali extract through Whatman No. 1 paper, and determine its absorbance at 237 mμ in a 1-cm. cell against 0.05 *N* alkali or scan its spectrum.

RESULTS

Quantitation.—All of the phenethanolamines in Table I gave quantitative amounts of aryl aldehyde, except for the pyrimidine and *s*-triazine derivatives. Unoxidized fenyripol was recovered practically quantitatively and identified by its ultraviolet spectrum. Since the phenethanolamine derivative furnishes an equimolar quantity of aryl aldehyde, a close approximation of the extent of conversion can be made by comparing log molar extinction coefficients of the oxidized phenethanol-

TABLE I.—STRUCTURE OF PHENETHANOLAMINES STUDIED



Compd.	R	R′	R″
Ephedrine	H	CH_3	CH_3
Phenylpropanolamine	H	CH_3	H
Phenylephrine	*m*-OH	H	CH_3
Phenyramidol	H	H	2-Pyridyl
Fenyripol	H	H	2-Pyrimidyl
2-(β-Hydroxyphenethylamino)-*s*-triazine	H	H	2-*s*-Triazinyl

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TABLE II.—SPECTRAL DATA OBTAINED AFTER PERIODATE OXIDATION OF PHENETHANOLAMINES

Compd.	Solvent	λ max.	log ε	$E_{1cm.}^{1\%}$ as HCl salt	
Ephedrine	Hexane	242 mμ	4.15	716.1	
Phenylpropanolamine	Hexane	242	4.14	735.9	
Phenyramidol	Hexane	242	4.15	564	
Benzaldehyde	Hexane	242	4.15	...	(14)
Phenylephrine	Chloroform	257	3.95	441	
		315	3.43	131.8	
	0.05 *N* alkali	237	4.33	1073	
		267*s*	3.84	338	
m-Hydroxybenzaldehyde	Chloroform	...	...	...	
	0.05 *N* alkali	237	4.38		(15)
		267	3.79		
		357	3.41		

TABLE III.—PRECISION OF ABSORPTIVITY VALUES OBTAINED WITH EPHEDRINE HYDROCHLORIDE

Trial	$E_{1cm.}^{1\%}$ value
1	701.7
2	715.3
3	727.3
4	713.0
5	698.3
6	722.2
7	730.7

Mean = 716.1; S.D. = 11.1 units = 1.56%

amines with those of the aryl aldehydes. The absorptivity values ($E_{1cm.}^{1\%}$) of the phenethanolamines as aldehydes are listed in Table II, furnishing another indication of the sensitivity of the analytical method.

To test the feasibility of employing absorptivity values in dosage form assays, the periodate oxidation of ephedrine hydrochloride was replicated over a period of several days. The precision obtained is shown in Table III.

Assays of Ephedrine in Dosage Forms.—The assay procedure was applied to the determination of ephedrine hydrochloride in tablets declaring 1/4 gr. (16.2 mg.) of the drug along with aminophylline, pentobarbital sodium, ethyl aminobenzoate, and aluminum hydroxide, as well as excipients (starch, stearic acid, iron oxide, talc, calcium carbonate, gelatin). A weighed quantity of pulverized tablet representing about 2 mg. of declared ephedrine hydrochloride was shaken with exactly 100.0 ml. of distilled water for 10 minutes in a glass-stoppered 250-ml. conical flask. The mixture was filtered through Whatman No. 1 paper and the first 10–15 ml. filtrate discarded. A 5.0-ml. aliquot was run through the procedure. A scan of the spectrum of the hexane extract showed the characteristic spectrum of benzaldehyde. Using the mean absorptivity value of 716.1, a recovery of 16.5 mg. of ephedrine hydrochloride was obtained, which represents 101.8% of the declared amount. Potassium iodide in a similar formulation interferred with the direct determination of ephedrine by reducing periodate.

Assay of Phenylephrine Hydrochloride in a Dosage Form.—Phenylephrine hydrochloride was assayed in a commercial tablet declaring 2.5 mg. of the drug and 5.0 mg. prophenpyridamine maleate, 194.4 mg. salicylamide, 129.6 mg. of acetophenetidin, 97.2 mg. of aluminum hydroxide, and excipients (starch, talc, magnesium stearate, methyl cellulose, colorant). A quantity of pulverized tablet equivalent to 2 mg. of phenylephrine hydrochloride was shaken mechanically for 10 minutes with exactly 100.0 ml. of 0.05 *N* sulfuric acid and about 25 ml. of chloroform. The acid layer was filtered through paper and two 5.0-ml. aliquots of filtrate were treated as described in the phenylephrine procedure above, omitting addition of periodate for one used as the blank. Using the absorptivity value of 1073, a result of 2.41 mg. of phenylephrine hydrochloride, corresponding to 96.5% of the declared amount, was obtained. A scan of the spectrum showed it to be *m*-hydroxybenzaldehyde.

DISCUSSION

Periodate cleaves carbon-carbon bonds of vic-glycols, α-aminoalcohols where the amine is primary or secondary, and α-hydroxyketones (16). The reaction does not distinguish between *threo* and *erythro* isomers, although the observation that *cis* glycols cleave faster than *trans* (17) with periodate and the use of a difference in cleavage rate of *threo* and *erythro* α-aminoalcohols by lead tetra-acetate (18) suggests that a rate difference might be used as a basis for an analytical method in periodate reactions. The failure of the reaction to proceed with the pyrimidine and *s*-triazine analogs of phenyramidol suggests that the availability of electrons on the exocyclic nitrogen is a factor in the reaction.

Although the data given by Heimlich, *et al.* (12), show a quantitative extraction of benzaldehyde by ether, hexane has advantages in the procedure, since it dissolves compounds having a narrower range of polarity and fewer interferences are possible. Addition of acid before extraction eliminates interference from amine bases. It has been found that iodide causes difficulties, but this and similar interferences might be removed by rational separation techniques (19). The general procedure appears to be applicable with little or no modification to the assays of ephedrine, racephedrine, and phenylpropanolamine and their preparations in the compendia official in the United States.

The sensitivity afforded by the procedure is adequate for its use in dosage form assay. It could be increased by manipulating the volumes employed or by derivatization of the aryl aldehyde formed in a manner analogous to that of McChesney and his co-workers (20).

SUMMARY

Periodate oxidation of phenethanolamine drugs followed by ultraviolet spectrophotometry of the aryl aldehyde formed was shown to be quantitative. It affords a convenient, sensitive, and selective means for the assay of ephedrine in dosage forms,

and it appears applicable to the determination of phenylpropanolamine, phenyramidol, and phenylephrine.

The limitations in selectivity of the periodate procedure and interferences in the method are discussed.

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Book Notices

Annual Review of Pharmacology. Edited by WINDSOR C. CUTTING, ROBERT H. DREISHBACH, and HENRY W. ELLIOTT. Annual Reviews, Inc., Palo Alto, Calif., 1963. vi + 486 pp. 22 × 14½ cm. Price $8.50.

The 1963 edition of this respected series presents sections entitled enzymes as primary targets of drugs, metabolic fate, drugs in lipid metabolism, interactions of drugs with endocrines, drugs and nerve conduction, effects of drugs on behavior, electrolyte and mineral metabolism, cellular effects of anticancer drugs, as well as others. Also included is a prefatory chapter by Henry H. Dale on pharmacology during the past 60 years. Cumulative indexes of authors and chapter titles for volumes 1 through 3 are appended.

British Pharmacopoeia. General Medical Council. Pharmaceutical Press, 17 Bloomsbury Square, London, 1963. xxviii + 1210 pp. 13½ × 22 cm. Price $22.50.

The General Medical Council of England has released the tenth edition of the British Pharmacopoeia which contains nearly 1000 monographs —some 211 of which did not appear in the previous edition. Additionally, the monographs for this edition employ the metric system throughout. This edition also includes 278 pages of appendices which give reagent specifications and information on nonaqueous titration, the oxygen flask method, chromatographic analysis, infrared absorption spectra, biological assays, and other useful information and procedures. The edition will become official on January 1, 1964.

Biochemical Systematics. By R. E. ALSTON and B. L. TURNER. Prentice-Hall, Inc., Englewood Cliffs, N. J., 1963. xii + 404 pp. 14½ × 22½ cm. Price $13.25.

By integrating data from biochemistry, plant chemistry, plant genetics, and systematics, the authors present a work oriented towards botanical systematics in what appears to be an unprecedented effort. The book is organized around major groups of chemical constituents rather than taxonomic systems of categories and the authors indicate that they do not now feel that available chemical correlations justify the construction of a phylogenetic tree. The main body of the book is devoted to the examination of the chemical nature of specific groups of plant constituents with a view to their actual and potential contributions to systematics.

Essentials of Biological Chemistry. By JAMES L. FAIRLEY and GORDON L. KILGOUR. Reinhold Publishing Corp., 430 Park Ave., New York 22, N. Y., 1963. xiii + 287 pp. 14½ × 22¼ cm. Price $7.50.

An undergraduate text book designed for an introductory course in biochemistry is presented for students who require some familiarity with biochemical principles in their chosen fields. Emphasis is placed on relating chemical structure to biological function. The volume pares the basics to a minimum and builds this foundation with materials in considerable depth. The volume gets progressively more complex beginning with the organic chemistry of the cellular constituents and working towards basic metabolic reaction sequences.

The Dictionary of Chemical Names. By W. E. FLOOD. Philosophical Library, Inc., 15 East 40th St., New York 16, N. Y., 1963. xxi + 238 pp. 13 × 20 cm. Price $7.50.

A glossary of the origin and history of chemical names is presented. An introductory section describes the development of the main branches of chemistry and the evolution of systematic nomenclature. The principal glossary is composed of two parts—one dealing with the chemical elements and the other dealing with chemical compounds, minerals, and other substances of chemical interest. An appendix provides brief biographical notes on about 50 of the more prominent chemists referred to in the glossary's text.