REFERENCES

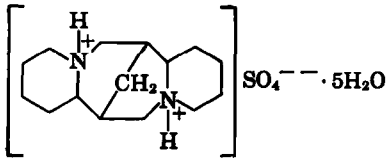
(1) Goodman, L., and Gilman, A., "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1956, p. 587.
(2) Staininer, C., and Capiere, C., *J. Pharm. Belg.*, **8**, 3(1954).
(3) Kolsek, J., *Z. Anal. Chem.*, **140**, 186(1953).
(4) Kurada, G., and Tamamura, S., *Yakkyoku*, **7**, 1193 (1956).
(5) Jung, Z., *Cesk. Farm.*, **6**, 299(1957).
(6) Sakal, E. H., and Merrill, E. J., THIS JOURNAL, **43**, 709(1954).
(7) Klohs, M. W., *J. Am. Chem. Soc.*, **76**, 1381(1954).
(8) Schlitter, E., and Schwarz, H., *Helv. Chim. Acta*, **33**, 1463(1950).

Quantitative Determination of Sparteine Sulfate

By PAUL TURI and DAN GROSSMAN

Official compendia fail to include assay methods for pharmaceutical preparations of sparteine sulfate. A direct acidimetric titration method for sparteine sulfate and an indirect titration of the sparteine base, obtained by distillation from a solution of sparteine sulfate, were investigated in a comparative study. The accuracy and applicability of both methods are evaluated.

SPARTEINE, an alkaloid of *Cytisus scoparius* L. (syn. *Sarothamnus scoparius*, Koch), *Lupinus luteus* L. and other plants of the *Leguminosae*, has been known as a medicinal agent for more than 70 years (1).



Sparteine had been formerly recommended in tachycardia, functional palpitation of the heart, and as a diuretic agent.

"The National Formulary," 8th ed., 1946, monograph (2) for sparteine sulfate (the last official U. S. compendium to list this drug) fails to include a method of assay. Recent interest in sparteine sulfate as an adjunct in induction of labor (3) prompted an evaluation of the known quantitative assay procedures.

In a survey of several suggested methods Higuchi and Bodin (4) list four methods for the determination of sparteine sulfate: (*a*) a colorimetric assay through the Reineckate salt, (*b*) an acid dye procedure (assaying colorimetrically a chloroform extract of the compound formed with acid methyl orange), (*c*) a polarographic method, and (*d*) a gravimetric determination through the silicotungstate salt.

The official method in the "Pharmacopoea Helvetica V" (5) for sparteine sulfate assay is a direct acidimetric titration. This procedure is based on the principle that mineral acid salts of very weak nitrogen bases in aqueous solution can be titrated directly with strong alkaline titrants to the phenolphthalein red end point, since the liberated weak base does not interfere with the indicator (6).

Our objective was to select a simple and rapid method with satisfactory accuracy. The direct titration method requires only a single step; therefore its advantages are obvious. To increase the specificity of the analysis, we adapted another titration technique which included a separation step. The principle of distillation of the alkaloid base and back titration of volatile alkaloids was utilized.

The scope of this study is a comparison between the two acidimetric titration methods: *method I*, sparteine sulfate is titrated directly with 0.1 *N* sodium hydroxide solution; and *method II*, sparteine sulfate salt is converted to the base, distilled with steam into a measured volume of acid, and the excess acid is back-titrated.

EXPERIMENTAL

Reagents and Test Solutions

Sparteine sulfate: a commercial sample of sparteine sulfate, N.F. VIII, was used in this study without further purification m.p. 136° dec., $[\alpha]_D^{25} = -21.5°$ (c = 4 in water); 0.1 *N* NaOH; 0.1 *N* HCl; methyl orange T.S.; phenolphthalein T.S.; hydrogen peroxide T.S.; 0.1 *N* H_2SO_4; sulfuric acid, diluted; 0.1 *N* $KMnO_4$; 50% NaOH: 10 Gm. of NaOH (U.S.P. XVI) dissolved in 10 ml. of water. Volumetric and test solutions meet U.S.P. XVI specifications.

Analytical Procedures

Sample A.—Approximately 1.0 Gm. of sparteine sulfate ($C_{15}H_{26}N_2 \cdot H_2SO_4 \cdot 5H_2O$, mol. wt. 422.53), accurately weighed, was dissolved in water in a 25-ml. volumetric flask, and the volume was adjusted to mark at 20° (stock solution).

Method I: 5.0 ml. of the stock solution was transferred into an Erlenmeyer flask, one drop of

TABLE I.—COMPARATIVE ASSAY RESULTS FOR SPARTEINE SULFATE

Sample No.	Sample Type	Method I %	Method I d_a	Method II %	Method II d_a
1	A	100.43	0.13	99.68	−0.60
2	A	100.43	0.13	98.84	−1.44
3	A	100.35	0.05	100.88	0.60
4	B	101.00	0.70	101.50	1.22
5	B	100.00	−0.30	102.50	2.22
6	B	99.00	−1.30	100.00	−0.28
7	B	99.50	−0.80	101.50	1.22
8	B	100.50	0.20	99.00	−1.28
9	B	101.50	1.20	98.60	−1.68

Received August 6, 1962, from the Analytical Research Department, Sandoz Pharmaceuticals, Hanover, N. J.
Accepted for publication November 6, 1962.

TABLE II.—STATISTICAL DATA OF SPARTEINE SULFATE ASSAYS

	Method I	Method II
Average Assay Result, %	100.30	100.28
Probable Error,[a] %	0.50	0.93

[a] Probable error was calculated from the following formula 7)

$$r = 0.6745 \sqrt{\frac{\Sigma d a^2}{n - 1}}$$ (n = number of assays)

TABLE III.—ASSAY RESULTS FOR PEROXIDE-TREATED SPARTEINE SULFATE SOLUTIONS

Sample No.	Sample Type	Method I, %	Method II, %
1	C	100.14	90.08
2	C	98.66	89.05

phenolphthalein T.S. was added, and the solution was titrated with 0.1 *N* NaOH to the appearance of the red color. 1 ml. 0.1 *N* NaOH = 42.253 mg. $C_{15}H_{26}N_2 \cdot H_2SO_4 \cdot 5H_2O$.

Method II: 5.0 ml. of the stock solution was transferred into a 300-ml. Kjeldahl flask. A few glass beads, 75 ml. water, and 2 ml. of 50% NaOH were added, and the flask was connected immediately to a condenser fitted with a delivery tube extending below the surface of 15.0 ml. 0.1 *N* HCl in a receiver. Two drops of methyl orange T.S. was added to the receiver as the indicator.[1] About 65 ml. of the distillate was collected in the receiver, followed by a residual titration of the excess acid with 0.1 *N* NaOH. Each ml. of 0.1 *N* HCl is equivalent to 21.1265 mg. $C_{15}H_{26}N_2 \cdot H_2SO_4 \cdot 5H_2O$.

Sample B.—An ampul solution of sparteine sulfate (containing 150 mg. of $C_{15}H_{26}N_2 \cdot H_2SO_4 \cdot 5H_2O$ and 4.5 mg. sodium chloride in 1.0 ml. of water) has been assayed by the two methods in a similar manner to that described above. Experimental results are summarized in Tables I and II.

Degradation Studies

To investigate the effects of degradation products on the two titration methods, the following experiment was performed.

Sample C.—4.0 Gm. sparteine sulfate was dissolved in about 80 ml. of distilled water. Seven milliliters of hydrogen peroxide T.S. and exactly 3.0 ml. of 0.1 *N* H_2SO_4 were added, and this colorless mixture was boiled for 1 hour. The solution was cooled to room temperature. A definite yellow coloration indicated presence of degradation products. Following the addition of exactly 3.0 ml. of 0.1 *N* NaOH, the solution was quantitatively transferred into a 100-ml. volumetric flask and brought up with water to volume (at 20°).[2] Five-milliliter aliquots of the peroxide-treated sparteine sulfate solution was assayed by both methods described above. Assay results are reported in Table III.

RESULTS AND DISCUSSION

The assay series performed on sparteine sulfate solutions (*Samples A* and *B*) facilitated an evaluation of the reproducibility and accuracy of the investigated methods.

As shown in Tables I and II, the averages of nine parallel determinations are very close; the difference of the average percentages is only 0.02%. The probable error is less than 1% for both methods, and only 0.5% for the direct titration procedure (*method I.*)

Solutions of sparteine sulfate exposed to high temperatures (100–160°) for a prolonged period showed insignificant degradation or no degradation. Earlier reported experiments (8) indicate a number of different oxidation products which could be formed by treating sparteine with a variety of oxidizing agents. Our results, reported in Table III, indicate that under the described experimental conditions degradation products develop which do not affect the direct titration method. By the distillation technique (*method II*), an anticipated decrease in alkaloid content appears.

CONCLUSIONS

Our experimental data led us to conclude that the method of choice for pure sparteine sulfate substance or for pharmaceutical preparations containing no interferring ingredients is the direct titration method. In the presence of interferring substances (incorporated in the pharmaceutical formula or developed by degradation), the distillation technique offers the advantage of separating the sparteine base from the nonvolatile ingredients and can be used for quantitative determinations with satisfactory accuracy.

REFERENCES

(1) Sollmann, T., "A Manual of Pharmacology," 8th ed., W. B. Saunders Co., Philadelphia, Pa., 1957, pp. 469–470.

(2) "The National Formulary," 8th ed., Mack Printing Co., Easton, Pa., 1946, p. 496.

(3) Gary, M. J., and Plentl, A. A., *Obstet. Gynecol.*, **11**, 204(1958).

(4) Higuchi, T., and Bodin, J. L., "Alkaloids and Other Basic Nitrogenous Compounds," (Higuchi, T., and Brochmann-Hanssen, E., "Pharmaceutical Analysis") Interscience Publishers, New York, N. Y., 1961, pp. 313–543.

(5) "Pharmacopoea Helvetica," Editio Quinta, (Deutsche Ausgabe), Druck und Verlag von Staempfli and Cie., Bern, 1933, pp. 869–871.

(6) Haedicke, M., and Kuntze, M., *Pharmazie*, **15**, 51 (1960).

(7) Crumpler, T. B., and Yoe, J. H., "Chemical Computations and Errors," John Wiley and Sons, Inc., New York, N. Y., 1940, pp. 170–191.

(8) Leonard, J. N., "Lupin Alkaloids," (Manske, R. H. F., and Holmes, H. L., "The Alkaloids," Vol. III.), Academic Press, Inc., Publishers, New York, N. Y., 1953, p. 157.

[1] More recent work indicates that a sharper end point can be obtained by using four drops of bromocresol green-methyl orange mixed indicator (0.2% BCG + 0.02% MO) to the appearance of a light green color.

[2] A 5-ml. aliquot of this solution was acidified with 1 ml. of diluted sulfuric acid, and one drop of 0.1 *N* $KMnO_4$ solution added. A slight pink color indicated absence of hydrogen peroxide.