Determination of Acetylsalicylic Acid and Barbiturate Combinations by Differentiating Nonaqueous Titration

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Acetylsalicylic acid and barbiturate mixtures are determined by differentiating nonaqueous titration. The titration solvent is methyl isobutyl ketone, the titrant is sodium methoxide in benzene–methanol, and the electrode system consists of the glass-calomel or antimony-calomel electrode pair. Satisfactory end points were realized when the acetylsalicylic acid-to-barbiturate ratio was as high as 14 to 1. Tetrabutylammonium hydroxide proved unsuitable as a differentiating titrant. Differentiation was not possible when dimethylformamide was the titration solvent. The barbiturates studied included phenobarbital, amobarbital, barbital, allylisobutylbarbituric acid, pentobarbital, and secobarbital.

A VARIETY of techniques have been proposed for the analysis of acetylsalicylic acid and barbiturates when used individually. These methods involve titrimetry, chromatography, colorimetry, and spectrophotometry. They have been reviewed by Zimmer and Huyck (1) and Connors (2). Titrimetric procedures in aqueous and nonaqueous media have been reviewed by Ashworth (3).

Since acetylsalicylic acid and the barbiturates are weakly acidic and since they differ significantly in their ionization constants, it seems appropriate that a suitable differentiating titration procedure can be developed by the proper selection of titration solvent, titrant, and electrode system. It was the purpose of this study to develop such a procedure.

A number of solvents have been employed in differentiating acids and bases. These have included acetone (4, 5), methyl ethyl ketone (6–8), methyl isobutyl ketone (9, 10), acetonitrile (11), isopropanol (8), *tert*-butyl alcohol (12, 13), nitrobenzene (14), dimethylformamide (10, 13), *N,N*-dimethyl fatty amides (15), pyridine (5, 13, 16), and ethylenediamine (17).

In the present report combinations of acetylsalicylic acid with a variety of barbiturates are determined by differentiating nonaqueous titration. The titration solvent is methyl isobutyl ketone and the titrant is sodium methoxide in benzene–methanol. Titration is effected potentiometrically using a glass-calomel or antimony-calomel electrode system.

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EXPERIMENTAL

Apparatus.—All titrations were performed potentiometrically with a Fisher titrimeter, model 35. The following electrodes were employed: glass electrode (Beckman No. 40495), sleeve-type calomel electrode (Beckman No. 41240), antimony electrode (Beckman No. 39027), and silver-silver chloride electrode (Beckman No. 41236). The calomel electrode was used as such unless otherwise indicated.

Reagents and Solutions.—Acetylsalicylic acid U.S.P. (Mallinckrodt) was dried at 60° for 4 hr. Analysis by U.S.P. assay indicated a purity of better than 99.5%. Phenobarbital U.S.P. (Mallinckrodt) was recrystallized from diluted ethanol and dried at 100° for 2 hr., m.p. 176–178°. Analysis by U.S.P. assay indicated a purity of better than 99.0%. Amobarbital was recrystallized from diluted alcohol and dried at 105° for 4 hr., m.p. 156–158°. Analysis by U.S.P. assay indicated a purity of better than 99.0%. Allylisobutylbarbituric acid was dried at 105° for 2 hr., m.p. 138°. Analysis by N.F. X method indicated a purity of better than 99.5%. Other chemicals and all solvents used in this study were reagent grade and were employed without further purification.

Tenth normal sodium methoxide in benzene–methanol (10:1) was prepared and standardized as described by Fritz and Lisicki (18).

Differentiating Titration of Acetylsalicylic Acid and Phenobarbital.—About 0.70 meq. of acetylsalicylic acid and 0.70 meq. phenobarbital, accurately weighed, were dissolved in 70 ml. of solvent in a 150-ml. beaker. The solution, magnetically stirred, was titrated potentiometrically with 0.1 *N* sodium methoxide solution, using a sleeve-type calomel and glass electrode system. A blank titration was performed. Titration curves were obtained by plotting potential reading (mv.) *versus* volume (ml.) of titrant. The exact end point was determined by plotting $\Delta E/\Delta v$ *versus* ml. The titration solvents in this study included dimethylformamide, acetonitrile, acetone, methyl ethyl ketone, methyl isobutyl ketone, isopropanol, and *tert*-butyl alcohol.

TABLE I.—DIFFERENTIATING TITRATION OF ACETYLSALICYLIC ACID AND PHENOBARBITAL IN VARIOUS SOLVENTS

Curve Ref.[a]	Solvent	Recovery, % Acetylsalicylic Acid	Recovery, % Phenobarbital
1	Dimethylformamide	One End Point[b]	
2	Acetonitrile	99.25 ± 0.56[c]	100.49 ± 0.95
3	Acetone	100.82 ± 0.91	99.32 ± 0.82
4	Methyl ethyl ketone	101.15 ± 0.70	98.78 ± 0.62
5	Methyl isobutyl ketone	100.35 ± 0.54	99.89 ± 0.69
6	Isopropanol	100.64 ± 0.92	100.58 ± 0.62
7	*tert*-Butyl alcohol	101.72 ± 0.48	99.03 ± 0.90

[a] Numbers correspond to curves in Fig. 1. [b] Corresponds to total acetylsalicylic acid and phenobarbital. [c] Standard deviation based on at least 4 determinations.

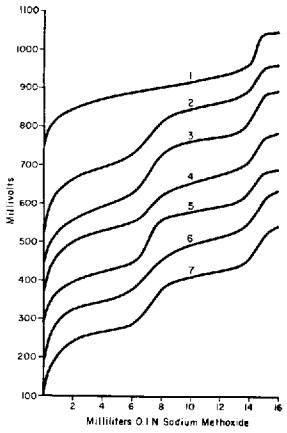

Fig. 1.—Typical curves for differentiating titration of acetylsalicylic acid and phenobarbital in various solvents. The titrant was 0.1 *N* sodium methoxide in benzene–methanol (10:1). The numbers above the curves correspond to those in Table I.

Electrode Systems.—About 0.60 meq. of acetylsalicylic acid and 0.40 meq. of phenobarbital, accurately weighed, were dissolved in 50 ml. of methyl isobutyl ketone. Three electrode pairs were employed, glass-calomel, antimony-calomel, and glass-silver-silver chloride. The sleeve-type calomel electrode was used as such or was modified by replacing the aqueous saturated potassium chloride solution in the bridge with a saturated solution of potassium chloride in methanol or with a saturated solution of potassium chloride in methyl isobutyl ketone.

Variation of Acetylsalicylic Acid-to-Phenobarbital Ratio.—A series of differentiating titrations was performed in which the milliequivalent ratio of acetylsalicylic acid to phenobarbital was varied from 1 to 1 to greater than 30 to 1. Calculated amounts of acetylsalicylic acid and phenobarbital to give the desired milliequivalent ratio of components were accurately weighed and dissolved in 70 ml. of methyl isobutyl ketone. The solution was titrated potentiometrically with 0.1 *N* sodium methoxide using the glass-calomel or antimony-calomel electrode system. The calomel electrode was employed without modification.

Analysis of Acetylsalicylic Acid Combinations with Various Barbiturates.—Accurately weighed quantities of acetylsalicylic acid and one of a number of barbiturates were dissolved in 50 ml. of methyl isobutyl ketone in a 150-ml. beaker. The solution was titrated potentiometrically with 0.1 *N* sodium methoxide using a glass-calomel or antimony-calomel electrode system. The calomel electrode was used without modification.

RESULTS AND DISCUSSION

Although acetylsalicylic acid and phenobarbital, as individual components, can be readily determined by titration in nonaqueous media, the titrimetric analysis of mixtures of these compounds has not been reported. Since the pKa of acetylsalicylic acid is 3.49 and the pKa of phenobarbital is 7.54, the differentiating titration of mixtures in a number of solvents is readily accomplished. The solvents examined in this investigation are listed in Table I, and typical titration curves are shown in Fig. 1. Titrations were effected potentiometrically with 0.1 *N* sodium methoxide in benzene–methanol using a glass-calomel electrode system. Basic solvents such as dimethylformamide, while excellent for the individual components, do not permit differentiation in the case of mixtures. Figure 1, curve 1, indicates a single end point corresponding to the total acid present when titration is performed in dimethylformamide. In preliminary studies similar results were obtained with ethylenediamine, butylamine, and pyridine.

TABLE II.—EFFECT OF ELECTRODE COMBINATION ON DIFFERENTIATING TITRATION OF ACETYLSALICYLIC ACID AND PHENOBARBITAL

Curve Ref.[a]	Electrode Combination	Electrolyte Bridge in Calomel Electrode	Recovery, % Acetylsalicylic Acid	Recovery, % Phenobarbital
1	Antimony-calomel	Sat. KCl in water	100.32[c]	101.09
2	Antimony-calomel	Sat. KCl in methanol	98.97	100.29
3	Antimony-calomel	Sat. KCl in MIK[b]	100.42	98.32
4	Glass-calomel	Sat. KCl in water	99.83	98.69
5	Glass-calomel	Sat. KCl in methanol	99.78	100.81
6	Glass-calomel	Sat. KCl in MIK	100.35	100.46
7	Glass-silver-silver chloride		101.70	99.77

[a] Numbers correspond to curves in Fig. 2. [b] Methyl isobutyl ketone. [c] Average of at least 3 determinations.

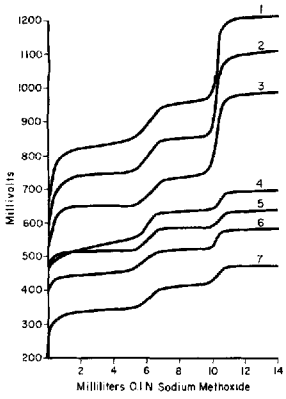

Fig. 2.—Effect of electrode combination on sensitivity of differentiating titration of acetylsalicylic acid and phenobarbital dissolved in methyl isobutyl ketone. The numbers above the curves correspond to those in Table II.

It is apparent that acetylsalicylic acid and phenobarbital are leveled to the same strength in these solvents and this precludes their differentiation. Acetonitrile and the ketones and alcohols listed in Table I did permit satisfactory differentiation. The curves in Fig. 1 show two distinct inflections, the first corresponding to the acetylsalicylic acid content and the second representing the phenobarbital end point. Methyl isobutyl ketone consistently produced the greater potential breaks for both end points when comparison is made with the other solvents tested. (See Fig. 1, curve 5.) Bruss and Wyld (9) found methyl isobutyl ketone an excellent solvent for differentiating acids or bases because of the large potential range which it affords.

Methyl isobutyl ketone was used as the titration solvent for subsequent studies reported in this investigation. The effect of electrode combination on the resolution of acetylsalicylic acid and phenobarbital mixtures was explored. The electrode systems and their modifications are listed in Table II. Typical titration curves are shown in Fig. 2. The most satisfactory results were realized with the antimony–calomel electrode pair. A comparison of the titration curves indicates that for acetylsalicylic acid the potential break was doubled and for phenobarbital the potential break was increased about ninefold when the antimony-calomel electrode pair replaced the glass-calomel electrode system. Little or no effect was noted when the supporting electrolyte in the calomel electrode was modified. In preliminary studies a number of other electrode systems were tested. The platinum-calomel and glass-antimony pairs gave poorly defined and unpredictable potential breaks corresponding to the first end point, although the second end point

Table III.—Effect of Acetylsalicylic Acid-to-Phenobarbital Ratio on Sensitivity of Differentiating Titration

Curve Ref.[a]	Amt. Weighed, meq. Acetylsalicylic Acid	Amt. Weighed, meq. Phenobarbital	Recovery, % Glass-Calomel Electrodes: Acetylsalicylic Acid	Glass-Calomel Electrodes: Phenobarbital	Antimony-Calomel Electrodes: Acetylsalicylic Acid	Antimony-Calomel Electrodes: Phenobarbital
1	1.00	1.00	100.46 ± 0.63[b]	100.06 + 0.88	100.35 ± 0.54	99.89 ± 0.69
2	1.00	0.75	99.42 ± 0.78	99.98 ± 0.39	100.14 ± 0.63	98.99 ± 0.46
3	1.00	0.40	99.18 ± 0.47	101.23 ± 0.49	100.97 ± 0.49	101.02 ± 0.66
4	1.00	0.30	99.04 ± 0.81	99.51 ± 0.62	99.77 ± 0.28	100.80 ± 0.34
5	1.00	0.25	100.93 ± 0.94	98.38 ± 0.48	98.62 ± 0.21	101.06 ± 0.29
6	1.00	0.20	98.75 ± 0.72	99.83 ± 0.79	101.78 ± 0.42	99.79 ± 0.50
7	1.00	0.15	101.82 ± 0.66	99.89 ± 0.96	99.97 ± 0.28	98.90 ± 0.63
8	1.00	0.10	One end point[c]		98.96 ± 0.48	101.85 ± 0.31
9	1.00	0.07	One end point		101.25 ± 0.67	99.06 ± 0.97
10	1.00	0.03	One end point		One end point	

[a] Numbers correspond to curves in Figs. 3 and 4. [b] Standard deviation based on at least 4 determinations. [c] Corresponds to acetylsalicylic acid plus phenobarbital.

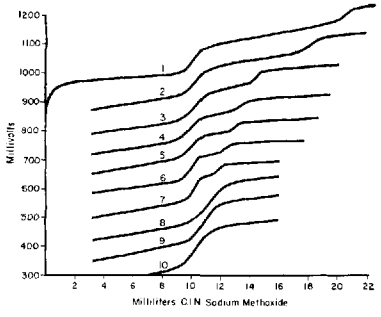

Fig. 3.—Effect of acetylsalicylic acid-to-phenobarbital ratio on sensitivity of differentiating titration of acetylsalicylic acid and phenobarbital dissolved in methyl isobutyl ketone. The glass-calomel electrode system was employed. The numbers above the curves correspond to those in Table III.

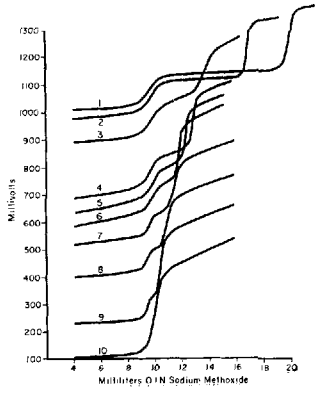

Fig. 4.—Effect of acetylsalicylic acid-to-phenobarbital ratio on sensitivity of differentiating titration of acetylsalicylic acid and phenobarbital dissolved in methyl isobutyl ketone. The antimony-calomel electrode system was employed. The numbers above the curves correspond to those in Table III.

TABLE IV.—DIFFERENTIATING TITRATION OF ACETYLSALICYLIC ACID AND BARBITURATE COMBINATIONS

Mixture	pKa	Amt. Weighed, meq.	Glass-Calomel Electrodes $\left(\frac{\Delta E}{\Delta v}\right)_{max.}$	Glass-Calomel Electrodes Recovery, %	Antimony-Calomel Electrodes $\left(\frac{\Delta E}{\Delta v}\right)_{max.}$	Antimony-Calomel Electrodes Recovery, %
Acetylsalicylic acid	3.49(21)[a]	0.50	80	99.81 ± 0.63 (*10*)[b]	80	99.72 ± 0.57 (*10*)
Allylisobutylbarbituric acid	7.68(22)	0.25	140	100.14 ± 0.55 (*10*)	250	100.28 ± 0.68 (*10*)
Acetylsalicylic acid	...	0.50	60	99.81 ± 0.62 (*9*)	65	100.32 ± 0.75 (*9*)
Amobarbital	8.02(23)	0.33	75	100.13 ± 0.56 (*9*)	150	98.90 ± 0.48 (*9*)
Acetylsalicylic acid	...	0.40	80	99.40 ± 0.44 (*4*)	80	99.32 ± 0.48 (*4*)
Barbital	8.06(23)	0.40	50	100.48 ± 0.60 (*4*)	340	98.84 ± 0.62 (*4*)
Acetylsalicylic acid	...	0.60	85	99.38 ± 0.49 (*5*)	95	100.40 ± 0.37 (*5*)
Pentobarbital	8.17(23)	0.30	60	98.97 ± 0.50 (*5*)	300	99.86 ± 0.62 (*5*)
Acetylsalicylic acid	...	0.50	60	99.82 ± 0.47 (*10*)	90	100.91 ± 0.56 (*10*)
Phenobarbital	7.54(23)	0.33	55	100.09 ± 0.73 (*10*)	520	100.34 ± 0.71 (*10*)
Acetylsalicylic acid	...	0.50	70	98.93 ± 0.53 (*4*)	85	99.88 ± 0.49 (*5*)
Secobarbital	8.08(22)	0.40	60	101.08 ± 0.62 (*4*)	110	100.09 ± 0.82 (*5*)

[a] Literature reference. [b] Standard deviation based on the number of determinations indicated in parenthesis.

representing total acid was satisfactory. Discernible end points were not obtained with the glass-platinum or antimony-platinum electrode systems.

Since in dosage forms there is usually a considerably greater amount of acetylsalicylic acid than phenobarbital, the effect of varying the ratio of concentrations of the components on the sensitivity of the differentiating titration was studied. The data for a series of titrations in which the milliequivalent ratio of acetylsalicylic acid to phenobarbital was varied from 1 to 1 to about 30 to 1 are reported in Table III. Typical titration curves are shown in Figs. 3 and 4. In one series of titrations (Fig. 3) the glass-calomel electrode pair was used, while in a second series of titrations (Fig. 4) the antimony-calomel electrode system was employed. With the glass-calomel electrodes two inflections in the titration curve were obtained when the milliequivalent ratio of acetylsalicylic acid to phenobarbital was not greater than about 7 to 1. When the ratio was greater than this, only one end point corresponding to the total acid was realized. The family of curves in Fig. 3 demonstrates clearly the effect of the ratio on the resolution of the two end points. With the antimony-calomel electrode pair the acetylsalicylic acid end point is well defined when the ratio of components was as high as 14 to 1. In Fig. 4, curve 9, two end points are clearly defined. However, in curve 10, only one end point is discernible. In general, both inflections in the curves shown in Fig. 4 are more satisfactory than those in Fig. 3.

Tetrabutylammonium hydroxide has been shown (4, 8, 9, 19, 20) to be extremely useful as a titrant for determining weak acids. This titrant in benzene–methanol (10:1) was prepared and standardized as described by Cundiff and Markunas (19). Some preliminary studies were conducted to evaluate this titrant in differentiating mixtures of acetylsalicylic acid and phenobarbital. Methyl isobutyl ketone was used as the titration solvent. In all cases only a single end point was obtained corresponding to the total acid present. When the individual components were titrated excellent results were obtained with distinct and reproducible end points. The unsuccessful differentiation with this titrant cannot be explained at this time.

The proposed procedures were applied to combinations of acetylsalicylic acid with a variety of barbiturates. The data are reported in Table IV. All titrations were performed with sodium methoxide as the titrant and methyl isobutyl ketone as the titration solvent. Both the glass-calomel and the antimony-calomel electrode pairs were employed. The maximum potential change per unit volume of titrant added is shown for each combination. While excellent results were obtained for all combinations, the antimony-calomel electrode system produced greater potential changes for the barbiturate end point than did the glass-calomel electrode pair.

The proposed procedures make possible the simple and accurate determination of combinations of acetylsalicylic acid and a variety of barbiturates without preliminary extraction of the components. The technique is applicable even when there is a disproportionate concentration of the acetylsalicylic acid which is the usual situation when these combinations are used therapeutically.

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