men view the use of alcohol in medicine very much as the U. S. Navy and would prefer to adopt a similar policy at the present time to protect the profession against the abuse of a certain class of practitioners. Furthermore, there can be no doubt that medical men in general are satisfied with the liquor permits permissible under the regulations of the Volstead Enforcement Act and are acting in good faith in using such permits. Supporters of the Volstead Act have no desire to curb the power given to medical men to issue prescriptions for alleged legitimate purposes under permits and if it becomes necessary to make more stringent regulations, the physicians have no one to blame but those in their own ranks who have abused this privilege. In the meanwhile the preponderance of evidence points to the fact that the best medical men condemn the prescription of whisky for patients and are not taking out permits for its use.

In conclusion we may say that the sobering of a nation is like the sobering of an individual. There may be relapses and back-sliding. Many hardly seem to realize the seriousness of the violation of the prohibition law. Regardless of what we feel, it is the law of the land and the violating of it is dangerous. It breeds a contempt not only for the enforcement of this law but also for other laws.

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THE IDENTIFICATION OF SOME LOCAL ANESTHETICS.*

BY L. E. WARREN.

During the last quarter of a century many organic substances have come into use in medicine because they possess the power of causing temporary loss of sensation when applied to the mucous surfaces, or by injection into the tissues. These substances are known as local anesthetics. Some are alkaloids occurring in nature, such as cocaine and tropacocaine, but most of them are synthetic bases whose physical and chemical properties resemble those of the naturally occurring alkaloids. The longest known of the local anesthetics is cocaine. Together with other bases this occurs in *Erythroxylon coca* and other species of *Erythroxylon*, shrubs, native to the Andean region of South America. Although cocaine was isolated in 1860[1] it was not until 1884[2] that its local anesthetic properties were sufficiently recognized to be made of practical value. Its use soon became widespread and for some years it remained the only known local anesthetic in practical use. However, cocaine was found to be distinctly poisonous, it produced undesirable side effects, such as mydriasis, cloudiness of the cornea and habit formation, and its salts were not stable in solution.

Tropacocaine was first found in coca leaves from Java.[3] It was found to be less poisonous than cocaine and to possess greater local anesthetic action,[4] without the objectionable mydriatic properties of cocaine. Further, the solutions of its salts were also less prone to decompose. It may be made synthetically by benzoylating pseudo-tropine.

Organic chemists, after working out the constitution of cocaine, attempted to build up a synthetic substitute for it which would be less toxic and perhaps cheaper. One of the first successful ones was α-eucaine.[5] This was found to be less toxic

* Scientific Section, A. Ph. A., Cleveland meeting, 1922.

than cocaine, cheaper and its solutions were stable on being heated. It had the disadvantage of causing pain and irritation when injected. Because of this it was superseded by β-eucaine, benzoyl-vinyl diacetone-alkamine hydrochloride.[6] This was found to be less toxic than α-eucaine. The salt of β-eucaine which is most used is the lactate because of its greater solubility than the hydrochloride.

After the advent of β-eucaine a great number of substances having local anesthetic properties were worked out by organic chemists. Many of them were more faulty than cocaine in their chemical and pharmacologic properties so that they never came into extensive use. Others were found to have some special advantages and their use became more or less general. Holocaine (phenacaine),[7] orthoform,[8] acoine,[9] nirvanin,[10] anesthesine (benzocaine),[11] alypin,[12] novocaine (procaine),[13] cycloform,[14] propaesin,[15] subcutin[16] and stovaine[17] came in quick succession. Apothesine[18] and butyn[19] were developed recently, while the anesthetic properties of saligenin[20] were only recently discovered although the substance had been known to plant chemists for many years.* Some of these have been widely used, each for some real or fancied advantage, and several have been dignified by admission into the pharmacopœias. Most of them have been described in "New and Nonofficial Remedies" at one time or another.

The synthetic local anesthetics resemble cocaine more or less in their structural relationships and they are, therefore, subject to about the same incompatibilities. In general they are precipitated by the usual alkaloidal reagents; consequently their separation in admixture is difficult. Fortunately they are rarely found together in medicine so that the analyst is usually required only to identify or determine but one at a time.

So far as the writer knows no systematic attempt has been reported heretofore to apply practically all of the commonly used alkaloidal reagents to all of the local anesthetics in common use. In these studies this has been done and the results tabulated for comparison. By this method some reactions have been observed which appear not to have been previously reported.

The literature on the chemical identification of local anesthetics is quite considerable, but is widely scattered. On that account no attempt is made here to review it systematically. The most comprehensive paper on the subject with which the writer is familiar is that by Hankin.[21] He recorded his observations on a large number of tests, and Saporetti[22] and Gadamer[23] are two others who have added much to the literature concerning tests for the local anesthetics. So far as practicable the work of these investigators has been repeated by the writer. In these studies but little attention has been paid to acoine, cycloform, α-eucaine, subcutin or nirvanin, substances which were not available because they are no longer used in medicine—at least not to any extent in this country.

Several of the local anesthetics are described in "New and Nonofficial Remedies." Several more that were formerly described in this work have been omitted because they were no longer available on the American market. Most of the observations recorded in this paper were made while preparing or revising the

* Recently benzyl alcohol and saligenin have been introduced as local anesthetics. Because of their relations to the alcohols they do not give many of the reactions for alkaloids. Benzyl alcohol is not included in these studies and but few tests were made on saligenin.

descriptions and tests for the identity and purity of the several substances for "New and Nonofficial Remedies."

The alkaloidal solutions used in this work unless otherwise stated were prepared by dissolving 1 Gm. of the substance in 50 cc of water, *i. e.*, they were approximately 2 per cent. in strength. Substances which were practically insoluble in water, such as benzocaine, orthoform and propaesin, were made soluble by suspending 1 Gm. in 50 cc of water and adding just sufficient hydrochloric acid with shaking to produce solution. Care was taken to avoid an excess of acid. The reagent solutions used, unless otherwise stated, were the test solutions described in the U. S. Pharmacopœia. The nonofficial test solutions were approximately 10 per cent. in strength.

The precipitation tests were made by adding a few drops of the reagent to about 1 cc of the alkaloidal solution with agitation. If no precipitate formed or if the precipitate at first formed had been dissolved, a few drops more of the reagent were added with further agitation. This was repeated until it became evident either that no precipitate would form, or that the one formed either was permanent or had been dissolved by an excess of the reagent. Since most alkaloidal precipitates are amorphous when first thrown down but may become crystalline on standing, about 10 minutes were allowed after the precipitation had taken place before recording the observation to determine whether or not the precipitate would become crystalline. In a few cases crystallization did not invariably begin within 10 minutes and a longer time was allowed. These exceptions are mentioned in the description of the test. The results obtained in over 400 tests are recorded in the tables.

By a comparison of the tabulated reactions it is possible to identify each of the substances studied. However, since there is such a large number of reactions to be compared a simplified scheme has been worked out to aid in the rapid identification of the substances in question. This consists first in applying the diazo-reaction by means of which the anesthetics are divided into two groups—*i. e.*, (1) those which respond to the reaction and (2) those which do not. The diazo group (A) includes benzocaine, butyn, orthoform, phenacaine, procaine and propaesin. The other group (B) includes alypin, apothesine, β-eucaine, cocaine, quinine and urea hydrochloride, stovaine and tropacocaine. The second step consists in testing the solutions with a list of seven reagents in succession. By tabulating the results obtained it is possible to identify any of the local anesthetics mentioned since no two give exactly parallel reactions. The findings for the entire series of tests are given in Table I, while Table II comprises the simplified scheme of identification. Some of the reactions require more explanation than can be given in the tables and these are given later in the form of comments. In addition to the precipitation tests several special tests were applied. For the sake of uniformity and completeness the results are included in the tables. These tests are given herewith:

Diazo Reaction.—To 5 cc of a 2 per cent. solution of the substance add 2 drops of diluted hydrochloric acid, 2 drops of 10 per cent. sodium nitrite solution and mix with a solution of 0.2 Gm. of β-naphthol in 10 cc of 10 per cent. sodium hydroxide solution. Certain of the local anesthetics give a deep red solution or scarlet precipitate.

Mercurous Chloride Test.—Mix intimately about 0.1 Gm. of the substance with 0.1 Gm.

of mercurous chloride and moisten the mixture with alcohol. With certain of the local anesthetics a darkening of the mixture takes place.

Sodium Hypochlorite Test.—To about 1 cc of the alkaloidal solution add a few drops of sodium hypochlorite solution. If a flesh-colored precipitate be given, add 2 cc of ether, shake the mixture and observe the color of the solvent. Several of the local anesthetics give precipitates more or less approaching to flesh-color and when shaken with ether the solvent is colored more or less approaching a burgundy red.

In addition to the results obtained by the experimental work considerable information concerning the physical properties of the local anesthetics was collected from the literature. As this kind of information is often of great value to the analyst it is included in the tables and comments. Specific credit cannot be given in each instance to the numerous workers whose results have been drawn upon for this collation.

Nearly all of the local anesthetics in solution give precipitates with potassium mercuric iodide solution, picric acid solution and phosphotungstic acid solution. These reagents, therefore, are of but little use in aiding in the differentiation between the several substances. Iodine is another reagent which gives precipitates with most of these substances. (The benzocaine precipitate with iodine solution is distinctive and this compound will be described later.) Certain other reagent solutions precipitate only a few of the substances; *e. g.*, tannic acid test solution precipitates only alypin and butyn; potassium sulphocyanate solution only butyn and phenacaine; potassium sodium tartrate only benzocaine, propaesin and quinine and urea hydrochloride.

Potassium permanganate solution is of considerable value in differentiating between the several substances. Apothesine, benzocaine, butyn, phenacaine, orthoform, and quinine and urea hydrochloride are reduced at once. Alypin, β-eucaine, cocaine, stovaine, and tropacocaine retain their color for some time. Cocaine precipitates with potassium permanganate, if the solution be not too dilute, in the form of violet crystals which occur in microscopically characteristic rhomboidal plates, often with an indentation at one corner. Alypin forms violet-red crystals but they are much less stable than the cocaine compound. Tropacocaine forms thick, short, violet-red prisms which are about as stable as the cocaine permanganate but which cannot be mistaken microscopically for that compound. The precipitates with β-eucaine and stovaine are amorphous.

Recently potassium citrate solution was suggested as an alkaloidal reagent by Toplis.[24] This has been applied to the local anesthetics and has proved useful. Benzocaine, butyn, orthoform, phenacaine, propaesin, quinine and urea hydrochloride and stovaine are precipitated. Some of the precipitates are crystalline as may be seen by consulting Table I.

Potassium iodide solution precipitates alypin, butyn, phenacaine, and tropacocaine. The character of the several precipitates is of importance and is described under the comments on the individual substances.

Potassium sodium tartrate produces white, crystalline precipitates with benzocaine, propaesin and quinine and urea hydrochloride.

The synthetic local anesthetics differ from cocaine and quinine and urea hydrochloride in being optically inactive. So far as the writer has been able to ascertain from the literature this rule holds good. All of the substances tested in these studies except the two mentioned were optically inactive. Since cocaine

has such pronounced optical properties it might be expected that tropacocaine might also be optically active, but such is not the case.

COMMENTS.

Alypin.—Alypin is benzoxy-2-dimethylamino-methyl-1-dimethylaminobutane. It is a white, crystalline powder; odorless; taste bitter; hygroscopic. Alypin is soluble in water, alcohol and chloroform; insoluble in ether. It melts at 169° C. Alypin gives a cream-white precipitate with tannic acid solution but the precipitate is soluble in excess of the reagent. Of the other substances tested only butyn behaved in a similar way. Alypin is distinguished from butyn by its failure to give the diazo-reaction. Alypin gives a white precipitate with potassium iodide. Butyn, phenacaine and tropacocaine react similarly. Alypin is distinguished from phenacaine and tropacocaine, however, by its failure to precipitate with sodium nitroprusside solution. It differs from benzocaine, butyn, orthoform, phenacaine, propaesin, quinine and urea hydrochloride and stovaine in not giving a precipitate with potasssium citrate. Alypin gives a violet, crystalline precipitate with potassium permanganate solution but the precipitate is not so stable as that with cocaine or tropacocaine.

Apothesine.—Apothesine is the hydrochloride of diethyl-amino-propyl cinnamate. It occurs in white, odorless masses which are composed of minute, colorless needles. It is soluble in water, alcohol and chloroform; insoluble in ether. Its taste is slightly bitter. It gives precipitates with potassium mercuric iodide solution, bromine water (soluble in hot water), sodium bicarbonate (soluble in excess), sodium borate, sodium salicylate, sodium nitroprusside, gold chloride (lemon-yellow), platinum chloride (yellow crystals) and palladium chloride (salmon). It is distinguished from other local anesthetics tested by the character of its precipitate with sodium nitroprusside. Of the others tested only butyn, phenacaine and tropacocaine give precipitates with this reagent. Of these butyn alone gives an amorphous precipitate which is yellowish-white in color and of a resin-like consistency. The apothesine precipitate is not resin-like and is of a salmon color. Butyn base and apothesine base are liquid; phenacaine base melts at 116-7° C., while tropacocaine base melts at 49° C. A color reaction for apothesine which appears to be characteristic is that with Marquis' reagent. About 0.01 Gm. of apothesine is treated with a few drops of sulphuric acid containing a trace of formaldehyde. The mixture is colorless at first but soon a pale brownish rose color develops which gradually changes to an intense mahogany brown. The isolated base responds to the test fully as well as the hydrochloride. It is believed that this reaction has not been described previously.

Benzocaine.—Benzocaine is ethyl amino-benzoate. It is a white, crystalline, odorless powder almost insoluble in water but soluble in very dilute hydrochloric acid. The most characteristic tests for benzocaine are with iodine test solution and mercuric chloride solution. With iodine solution benzocaine produces beautiful, iridescent crystals. The precipitate is slow to form and is aided by gentle shaking of the test-tube. In absence of confirmatory tests the precipitate might be mistaken for herepathite. With mercuric chloride test solution benzocaine forms beautiful, colorless needles on standing. This reaction takes place slowly and is best observed after the mixed solutions have stood for 30 minutes. Of the other substances tested several (cocaine, quinine and urea, and tropacocaine) gave white, crystalline precipitates with mercuric chloride but none gave such long, slender needles as were obtained with benzocaine. It is believed that this reaction has not been described previously. Benzocaine gives the diazo-reaction but this does not distinguish it from butyn, orthoform, phenacaine, procaine or propaesin, each of which responds to the test. However, three of these substances may be distinguished from benzocaine by the physical properties of their separated bases. Butyn base is liquid at ordinary temperatures, procaine base melts at about 58 to 60° C. and phenacaine base at 116 to 117° C. The melting point of benzocaine is 90 to 91° C., and that of propaesin 73° C. Propaesin is not precipitated by mercuric chloride. Orthoform is not precipitated by potassium sodium tartrate (as is benzocaine). Quinine and urea hydrochloride is precipitated by potassium sodium tartrate (as well as benzocaine) but this substance is readily distinguished from benzocaine by its failure to give the diazo-reaction and by its strong fluorescence in very dilute sulphuric acid. Benzocaine does not darken with mercurous chloride and alcohol (difference from alypin, apothesine, cocaine, procaine, quinine and urea hydrochloride, stovaine and tropacocaine).

Cocaine Hydrochloride.—Cocaine hydrochloride, methyl benzoyl ecgonine hydrochloride,

is official in the U. S. Pharmacopœia. It occurs in white, crystalline masses; odorless; permanent in the air. It is soluble in water, alcohol and chloroform; insoluble in ether. Cocaine hydrochloride is precipitated by mercuric chloride, sodium carbonate, sodium bicarbonate, potassium permanganate and Fehling's solution. It is darkened by mercurous chloride and alcohol (*difference from β-eucaine*). Its precipitate with potassium permanganate occurs in violet, rhomboidal plates which frequently have an indentation at one corner and which are more stable than the permanganates of the other local anesthetics. It is distinguished from alypin by its failure to precipitate with potassium iodide, tannic acid solution or sodium borate; from benzocaine by its failure to precipitate with potassium bismuth iodide or potassium sodium tartrate or to give the diazo-reaction; and by its precipitation with potassium cadmium iodide and by its positive reaction with mercurous chloride and alcohol; from β-eucaine by its precipitation with sodium bicarbonate and mercuric chloride and by its positive reaction with mercurous chloride and alcohol; from apothesine by its failure to precipitate with sodium salicylate, sodium nitroprusside, sodium borate or potassium ferricyanide; from phenacaine by its failure to precipitate with potassium iodide, sodium nitroprusside, potassium citrate, sodium borate or potassium sulphocyanate; from butyn by its failure to precipitate with potassium iodide, sodium salicylate, sodium nitroprusside, tannic acid, potassium citrate, sodium borate or potassium sulphocyanate; from orthoform by its precipitation with potassium mercuric iodide, pieric acid, sodium carbonate and potassium cadmium iodide and by its failure to precipitate with potassium citrate or to give the diazo-reaction. Further, it does not reduce chromic acid, potassium permanganate or gold chloride as does orthoform. Cocaine is distinguished from procaine by its precipitation with sodium bicarbonate or chromic acid (after adding hydrochloric acid), by its failure to give the diazo-reaction or to reduce potassium permanganate immediately; from quinine and urea hydrochloride by its failure to precipitate with sodium salicylate, potassium citrate, potassium ferricyanide or sodium borate; from propaesin by its precipitation with mercuric chloride, chromic acid (after adding hydrochloric acid), potassium cadmium iodide or sodium borate and by its failure to precipitate with potassium tartrate, potassium citrate or sodium borate; from stovaine by its precipitation with chromic acid (after the addition of hydrochloric acid) and by its failure to precipitate with potassium citrate or sodium borate; and from tropacocaine by its failure to precipitate with potassium iodide, sodium nitroprusside, potassium bismuth iodide, sodium borate or potassium ferricyanide, and by its precipitation with sodium bicarbonate.

β-Eucaine Lactate.—β-Eucaine is trimethyl-benzoyl-oxy-piperidine. It is official in the U. S. Pharmacopœia in the form of its chloride. β-Eucaine lactate is a white, crystalline powder; odorless; permanent in the air. It is soluble in water, alcohol and chloroform, but only slightly soluble in ether. β-Eucaine lactate is precipitated by sodium salicylate, bromine water, chromic acid, gold chloride and Fehling's solution. It is distinguished from cocaine by its failure to precipitate with mercuric chloride and sodium bicarbonate, by its precipitation with sodium salicylate, by its optical inactivity, and by the fact that it does not darken with the mercurous chloride and alcohol test; from phenacaine by its failure to precipitate with mercuric chloride, sodium bicarbonate, sodium nitroprusside, potassium iodide, potassium citrate, sodium borate, and potassium ferricyanide; from procaine by its failure to precipitate with mercuric chloride or to give the diazo-reaction and by its precipitation with chromic acid and sodium salicylate. β-Eucaine is distinguished from stovaine by its precipitation with chromic acid, sodium salicylate and potassium dichromate and by its failure to precipitate with mercuric chloride, sodium bicarbonate or potassium citrate; from tropacocaine by its failure to precipitate with potassium iodide, mercuric chloride, sodium nitroprusside, sodium borate or potassium ferricyanide.

Butyn.—This is *p*-aminobenzoyl-γ-dinormalbutylaminopropanol sulphate. It is a white, hygroscopic solid; very soluble in water; soluble in alcohol and chloroform; insoluble in ether. Butyn gives a white, curdy precipitate with potassium iodide solution. Of the other substances tested alypin, phenacaine and tropacocaine only give precipitates with this reagent. The alypin precipitate is crystalline, the tropacocaine precipitate is in the form of glistening white scales and the phenacaine precipitate does not form curds. Consequently this test is, in a sense, distinctive for butyn. Attempts to determine butyn by collecting the butyn-iodide compound and weighing it were not satisfactory. This is due to the fact that the precipitate is appreciably soluble in water. Butyn gives white, amorphous precipitates with potassium sulphocyanate, potassium citrate and mercuric chloride solutions. It gives crystalline precipitates with chromic

TABLE I.—REACTIONS OF SOME LOCAL ANESTHETICS.

Reagent.	Alypin.	Benzocaine (anesthesine).	Apothesine.	β-Eucaine lactate.	Butyn.	Cocaine hydrochloride.	Phenacaine (holocaine hydrochloride).	Orthoform.	Procaine.	Quinine and urea hydrochloride.	Stovaine.	Tropacocaine-hydrochloride.	Propaesin.
Iodine and potassium iodide	Brown	Brown iridescent crystals	Red-brown	Brown precipitate; sol. on boiling	Drab	Brown	Brown	Brown; slow to form; then reduction	Brown	Brown	Brown	Brown	Brown
Potassium mercuric iodide	White; curdy	....	White	White	White	White	White; curdy	....	White	White	White to cream	White	White
Potassium iodide	White; cryst.	....	....	....	White; curdy	....	White	....	....	....	....	White glistening scales	....
Mercuric chloride	White; amorphous	Beautiful colorless needles on standing	White; amorphous	....	White; amorphous	White; cryst.	White	....	White; sol. in hot water	White; cryst.	White; sol. in excess	White; bulky; cryst.	....
Phosphotungstic acid	White	White	White	White	White	White	White	White	White	White	White	White	White
Picric acid	Yellow; masses; minute prisms	Yellow	Yellow; cryst.	Yellow; cryst.	Yellow; cryst.	Yellow; long needles	Yellow; cryst.	.... cryst.	Yellowish masses of needle-like prisms	Yellow	Yellow; cryst.	Yellow; minute needles	Yellow
Sodium carbonate	White	White; cryst.	White	White	White	White	White	....	White	White	White	White; amorphous	White
Sodium bicarbonate	....	White; soluble in excess	White; soluble in excess	....	White	White; colorless; slender needles	White	White; cryst.	....	White	White	....	White
Gold chloride	Pale lemon-yellow; cryst.	Brown	Lemon-yellow	Lemon-yellow	Brown	Pale lemon-yellow; like fern fronds	Canary-yellow	Dirty, dark green	Brown	Orange-yellow	Yellow; cryst.	Yellow; pinnate prisms	Yellowish brown
Platinum chloride + HCl	Salmon; aggregate of minute prisms	Pale yellow; cryst.	Yellow; cryst	Crystalline needles	Pale orange, amorphous	Yellow plumose needles	Drab	....	Yellow	Pale yellow	....	Pale salmon; cryst.	Yellow; cryst.
Palladium chloride	Salmon	Yellowish white; gelatinous	Salmon	....	Yellowish brown	....	Salmon	Pale yellow cryst.	Brownish orange	Salmon	....	Salmon; fern-like cryst.	Salmon, flocculent
Chromic acid	....	....	Orange	Yellow large crystals	Orange-yellow cryst.	Add HCl; orange; cryst.	Orange-yellow	Blackens instantly	....	Orange	....	Yellow; fern-like	....
Bromine water	Yellow; sol. in hot water; reappears on cooling	White; partly soluble in hot water	Yellow; sol. in hot water	Pale yellow; sol. on heating	White	Yellow; sol. on heating	Yellowish brown; sol. on heating	Yellowish green; orange on boiling	Yellow; sol. in hot water	Yellow; sol. in hot water	Orange	Yellow; sol. on heating	White

Potassium cadmium iodide	White	....	White	White	White	White	White	....	Drab	Cream	White	White; cryst.; very bulky	....
Potassium zinc iodide	....	....	Pale yellow; beautiful needles	....	White	Pale yellow	Yellowish white	....	....	....	Yellow cloud	White; cryst.; bulky	....
Sodium salicylate	....	White	White; amorphous	White; cryst.	White	....	White	....	....	Cream-white	....	....	White; cryst.
Sodium nitroprusside	....	....	Pale salmon; amorphous	....	Yellowish white; resin-like	....	Pale salmon; cryst.	....	....	....	....	Colorless; cryst.	....
Fehling's solution	White	White; cryst.	White	White	White	White; large prisms	White	Green; sol. in excess	White	White; curdy	White	White	White; cryst.
Potassium sodium tartrate	....	White; cryst.	....	....	....	....	....	....	....	White; cryst.	....	....	White; cryst.
Sodium hypochlorite	White	Flesh-colored precipitate	Cream-white; curdy	White	Flesh-colored; cryst.	White; amorphous	Flesh-colored; becoming violet	Grayish brown	Flesh-colored	Cream-white; curdy; becoming cryst.	White; amorphous	White; cryst.	Flesh-colored
Potassium dichromate	Orange; cryst.	Darkens on standing	Yellow precipitate	Orange	Orange-yellow	Orange-red	Yellow	Black; reduces instantly	....	Orange	....	Orange-red; cryst.	....
Potassium permanganate	Violet; cryst. soon decomp.	Decomposes instantly	Decolorizes at once	Does not decomp. at once	Decomposes instantly	Violet minute cryst.	Reduces at once	Reduces at once	Decomposes immediately	Reduces instantly	Reduces slowly	Violet; cryst.	Reduces instantly
Tannic acid	Cream-white; sol. in excess	....	....	....	Cream-white; sol. in excess	curdy;	....	....	....	....	....	....	....
Potassium citrate	....	White; cryst.	....	....	White; amorphous	....	White; amorphous	White; cryst.	....	White; cryst.	White; amorphous	....	White; cryst.
Potassium chromate	Yellow; cryst.; slow to form	Orange; cryst.	Greenish yellow cloud	....	Orange-yellow; cryst.; reduces on standing	Add HCl; orange precipitate	Yellow	Black; reduces instantly	....	Yellow; cryst.	Yellow	....	Orange; cryst.
Potassium bismuth iodide	White	Orange; cryst.	Orange	....	White cryst.	....	Orange	....	....	Orange	....	Bulky white; cryst.	Orange
Sodium borate	White	White; cryst.	White	....	White	....	White	....	....	White	White	White; amorphous	White; cryst.
Potassium ferricyanide	....	....	Lemon-yellow; oily	....	Brownish yellow oil	....	Brownish yellow	....	....	Pale yellow; sol. in excess	....	Needle-like; cryst.	....
Mercurous chloride	Darkens	No change	Darkens	No change	No change	Blackens	No change	No change	Blackens	Darkens	Darkens	Darkens	No change
Diazo-reaction	White precip.; dissolves on standing	Dark ruby-red color	White precip. dissolves on standing	White precip. soon dissolves	Red	White precip. soon dissolves	Scarlet	Dark red color	Scarlet precipitate	White; dissolves on standing	No color	Yellow	Scarlet
Potassium sulphocyanate	....	....	....	....	White; amorphous	....	White rosettes	....	....	....	....	....	....

acid, potassium zinc iodide, sodium hypochlorite and potassium dichromate solutions. Since butyn is a sulphate it gives a precipitate with barium chloride solution thus differing from other local anesthetics in common use. Butyn is distinguished from alypin by its precipitation with sodium bicarbonate, from apothesine by its precipitation with potassium iodide, potassium citrate, sodium borate, potassium ferricyanide, and potassium sulphocyanate; from cocaine by its precipitation with sodium nitroprusside, potassium citrate and sodium borate; from phenacaine by its precipitation with tannic acid; from orthoform by its precipitation with potassium iodide, picric acid and mercuric chloride; from procaine by its precipitation with potassium iodide, sodium bicarbonate and sodium nitroprusside, and from stovaine by its precipitation with potassium iodide and sodium salicylate.

Orthoform.—Orthoform is *m*-amino-*p*-hydroxy benzoate. It is a white, odorless powder; almost insoluble in water, but soluble in dilute hydrochloric acid. Its insolubility in water distinguishes it from the other local anesthetics tested except benzocaine and propaesin. It is soluble in ether, thus differing from most of the other local anesthetics, except benzocaine and propaesin. No precipitate is given with picric acid. This distinguishes it from most other local anesthetics except saligenin. It is not precipitated by potassium mercuric iodide. It reduces chromic acid instantly; also potassium chromate and potassium dichromate, thus differing from all of the other substances tested. It gives a white, crystalline precipitate with potassium citrate. It gives the diazo-reaction, forming an intensely dark red solution. Orthoform (solid) gives an intensely black color with nitric acid which gradually changes to a rich, mahogany brown. Under the same conditions saligenin gives a yellowish brown color and phenacaine slowly becomes brown, but none other of the substances tested gave reactions at all simulating the reaction with orthoform. Orthoform reduces potassium permanganate instantly but it does not darken with mercurous chloride and alcohol.

Phenacaine.—Phenaciane is ethenyl-*p*-diethoxy-diphenyl amidine hydrochloride. It is soluble in about 50 parts of water; soluble in alcohol and chloroform; insoluble in ether. Phenacaine is precipitated by potassium sulphocyanate in the form of white rosettes, a reaction which is distinctive and which appears not to have been noted previously. It also gives precipitates with potassium iodide, sodium nitroprusside, potassium citrate and mercuric chloride. Phenacaine is distinguished from the other members of the diazo-group of local anesthetics by its failure to precipitate with potassium sodium tartrate. None of the members of the non-diazo-group are precipitated by potassium sulphocyanate, and only quinine and urea hydrochloride with potassium sodium tartrate. Phenacaine is precipitated by a larger number of reagents than is any other of the synthetic anesthetics tested.

Procaine.—Procaine is *p*-amino-benzoyldiethylamino-ethanol hydrochloride. It is a white, odorless, crystalline powder; soluble in water, alcohol and chloroform; insoluble in ether. Procaine gives the diazo-reaction and a white precipitate with mercuric chloride solution which is soluble in hot water. It is not precipitated by potassium citrate solution which distinguishes it from the other alkaloids of the diazo-group. It is not precipitated by sodium bicarbonate, chromic acid, sodium salicylate or potassium dichromate. It gives a brown precipitate with gold chloride solution. It reduces potassium permanganate instantly.

Propaesin.—Propaesin is propyl-amino-benzoate. It occurs as a fine, white, odorless powder; permanent in the air. It is soluble in alcohol, ether and chloroform, but only slightly soluble in water. It is distinguished from alypin, butyn, phenacaine and tropacocaine by its failure to precipitate with potassium iodide; from benzocaine and quinine and urea hydrochloride by its failure to precipitate with mercuric chloride; from apothesine and butyn by its failure to precipitate with chromic acid; from β-eucaine by its failure to precipitate with sodium salicylate; and from cocaine by its failure to precipitate with potassium cadmium iodide.

Quinine and Urea Hydrochloride.—Quinine possesses distinct local anesthetic properties but many of its salts are too scantily soluble to be of good service in this field. By mixture with urea hydrochloride the quinine salts become much more soluble. A mixture of equimolecular proportions of quinine hydrochloride and urea hydrochloride is very soluble in water and, before the advent of so many synthetic local anesthetics, this preparation had some vogue as a local anesthetic. Quinine and urea hydrochloride occurs as a white, granular powder or in colorless, translucent prisms; odorless; taste bitter; soluble in water, alcohol and chloroform; insoluble in ether. Quinine and urea hydrochloride precipitates with potassium ferricyanide but not with

sodium nitroprusside, thus distinguishing this substance from apothesine, butyn and phenacaine which give precipitates with both reagents. Quinine and urea hydrochloride is distinguished from all of the other substances tested by its strong fluorescence when dissolved in very dilute sulphuric acid. It is optically active, the specific rotation being about $-173.7°$ in water at 21° C. It is distinguished from alypin by its failure to precipitate with potassium iodide or tannic acid; from apothesine by its failure to precipitate with sodium nitroprusside; from benzocaine by its precipitation with potassium ferricyanide and potassium mercuric iodide; from β-eucaine by its precipitation with potassium sodium tartrate, potassium citrate, sodium bicarbonate and sodium borate; from cocaine by its precipitation with potassium sodium tartrate, potassium citrate and sodium borate; from phenacaine by its failure to precipitate with potassium iodide; from procaine by its precipitation with sodium bicarbonate, potassium sodium tartrate and potassium citrate; from propaesin by its precipitation with mercuric chloride; from orthoform by its precipitation with picric acid; from stovaine by its precipitation with palladium chloride and potassium ferricyanide; and from tropacocaine by its failure to precipitate with potassium iodide and sodium nitroprusside.

TABLE II.—REACTIONS FOR THE RAPID IDENTIFICATION OF LOCAL ANESTHETICS.

	Synthetic.	Potassium sulphocyanate.	Potassium iodide.	Sodium nitroprusside	Potassium sodium tartrate.	Potassium citrate.	Potassium permanganate.	Mercuric chloride.
	Benzocaine	....	....	....	White; cryst.	White; cryst.	Decomposes instantly	Beautiful, colorless needles (Form slowly)
	Butyn	White; amorphous	White	Yellowish white; resin-like	....	White; amorphous	Decomposes instantly	White; amorphous
A Diazo-Group	Orthoform	....	....	....	....	White; cryst.	Reduces instantly	....
	Phenacaine	White; rosettes	White	Pale salmon; cryst.	....	White; amorphous	Reduces instantly	White
	Procaine	....	....	....	....	....	Decomposes instantly	White; soluble in hot water
	Propaesin	....	....	....	White; cryst.	White; cryst.	Decomposes instantly	....
	Alypin	....	White; cryst.	....	....	....	Violet; cryst.; not very stable	White; amorphous
	Apothesine	....	....	Pale salmon	....	....	Decomposes instantly	White; amorphous
B Non-Diazo-Group	β-Eucaine	....	....	....	....	....	Not decomposed at once	....
	Cocaine	....	....	....	....	....	Violet; cryst.; quite stable	White; cryst.
	Quinine and urea hydrochloride	....	....	....	White; cryst.	White; cryst.	Decomposes instantly	White; cryst.
	Stovaine	....	....	....	....	White; amorphous	Decomposes slowly	White; soluble in excess
	Tropacocaine	....	White; glistening scales	Colorless; cryst.	....	....	Violet; thick prisms	White; bulky; cryst.

Saligenin.—Saligenin is *o*-hydroxy-benzyl alcohol. It is not precipitated by any of the ordinary alkaloidal precipitants except bromine water. With this reagent it forms pale yellowish white crystals. Since saligenin is a phenolmethylol it is probable that it might be estimated by adding an excess of bromine solution and titrating the excess as is done with phenols. It slowly reduces gold chloride and instantly reduces potassium permanganate. It is optically inactive. Saligenin (solid) is instantly colored rose-red by concentrated sulphuric acid. None of the other local anesthetics tested gave this reaction. Saligenin (solid) with ferric chloride solution gives a grass-green color which is persistent.

Stovaine.—Stovaine is ethyl-dimethylamino-benzoyl-pentanol hydrochloride. Stovaine occurs as a white, crystalline, odorless powder; soluble in water, alcohol and chloroform, but insoluble in ether. Stovaine is precipitated by mercuric chloride (soluble in excess), Fehling's solution, potassium citrate and sodium borate. It is not precipitated by sodium salicylate, sodium nitroprusside or potassium sodium tartrate. Stovaine is distinguished from alypin, butyn, phenacaine and tropacocaine by its failure to precipitate with potassium iodide; from benzocaine by its failure to precipitate with palladium chloride; from apothesine and β-eucaine by its failure to precipitate with sodium salicylate; and from cocaine and quinine and urea hydrochloride by its failure to precipitate with platinum chloride. It is distinguished from orthoform by its precipitation with potassium mercuric iodide; from procaine by its precipitation with sodium bicarbonate; and from propaesin by its precipitation with mercuric chloride.

Tropacocaine.—Tropacocaine hydrochloride is distinguished from cocaine hydrochloride in being optically inactive and in giving crystalline precipitates with potassium ferricyanide, sodium nitroprusside and potassium iodide. The last mentioned precipitate occurs in glistening white scales unlike the iodide of any other local anesthetic tested. The ferricyanide and nitroprusside tests also distinguish it from alypin, benzocaine, orthoform, procaine, propaesin, saligenin and stovaine. Apothesine, butyn and phenacaine give precipitates with both these reagents; butyn and phenacaine give precipitates with potassium citrate and potassium sulphocyanate (which tropacocaine does not do) and apothesine is not precipitated by potassium iodide as is tropacocaine. Further, tropacocaine differs from cocaine in the crystalline form of its permanganate as has been noted under cocaine.

TABLE III.—PHYSICAL PROPERTIES OF THE LOCAL ANESTHETICS.

Anesthetic.	Solubility in water.	Solubility in alcohol.	Solubility in chloroform.	Solubility in ether.	Melting point.	Melting point of base.
Alypin	Soluble	Soluble	Soluble	Insoluble	169°	Liquid
Apothesine	Soluble	Soluble	Soluble	Insoluble	137°	Liquid at room temperature
Benzocaine	Slightly soluble	Soluble	Soluble	Soluble	90–91°	90–91°
β-Eucaine lactate	Soluble	Soluble	Soluble	Slightly soluble	152° 155°	91°
Butyn	Soluble	Soluble	Slowly soluble	Insoluble	98–100°	Liquid
Cocaine hydrochloride	Soluble	Soluble	Soluble	Insoluble	183–191°	96–98°
Orthoform	Nearly insoluble	Soluble	Slightly soluble	Soluble	141–143°	....
Phenacaine	Soluble	Soluble	Soluble	Insoluble	189°	116–117°
Procaine	Soluble	Soluble	Soluble	Insoluble	153–155°	58–60°
Propaesin	Almost insoluble	Soluble	Soluble	Soluble	73°	....
Quinine and urea hydrochloride	Soluble	Soluble	Soluble	Insoluble	....	....
Stovaine	Soluble	Soluble	Soluble	Insoluble	175–176°	Liquid
Tropacocaine Hydrochloride	Soluble	Soluble	Soluble	Insoluble	271–276° decomposes	49°

SUMMARY.

The usual alkaloidal reagents have been applied to 2 per cent. solutions of alypin, apothesine, benzocaine, β-eucaine, butyn, cocaine hydrochloride orthoform, phenacaine, procaine, propaesin, quinine and urea hydrochloride, stovaine, and tropacocaine hydrochloride. Observations on the optical activity of the substances studied were also made and a few color reactions were included. In a total of over 400 tests several reactions were observed which it is believed have not been reported previously. Several of these reactions are of particular value in the identification of the substances. A method for the rapid identification of certain local anesthetics has been worked out. This consists in first applying the diazo-reaction by which the substances are separated into two groups. This is followed by treating separate portions of the unknown solution, respectively, with potassium sulphocyanate, potassium iodide, sodium nitroprusside, potassium sodium tartrate, potassium citrate, potassium permanganate and mercuric chloride. In these tests no two of the substances studied give parallel reactions.

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