Identification and Differentiation of Organic Medicinal Agents I

Local Anesthetics

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Ten local anesthetics have been identified and differentiated by utilizing their reactions with styphnic, picric, chloroplatinic, and picrolonic acids, ammonium reinecate, and methyliodide. The resulting derivatives, infrared spectra, and photomicrographs are presented and discussed. Of the 47 derivatives prepared, 37 have not been reported previously.

MUCH HAS BEEN published concerning the techniques which have been used for the qualitative characterization of this class of chemically important drugs. Several of the local anesthetics are described in the official pharmaceutical compendia (B.P., U.S.P., and N.F.) which, together with their individual physical properties, includes various color, precipitation, and derivatization reactions. Local anesthetics have been characterized through derivatization and melting point data (1–16), infrared and ultraviolet spectroscopy (14, 17–19), photomicrography (20–27), paper chromatography (28–34), gas-liquid chromatography (35), less specific color and precipitation reactions (20–22, 36–39, 40–45), vacuum microsublimation (46), solubilities (47, 48), and paper electrophoresis (49).

The widespread acceptance of local anesthetics by the medical and dental professions and the general public has resulted in their appearance on the market in many different dosage forms, both alone and in combination with other local anesthetics and/or drugs. Although they are seldom the cause of poisoning, their facile acquisition without prescription by the public and the variety of local anesthetics currently available have made their qualitative identification a matter of considerable importance. The intent of this investigation was to devise a comprehensive series of several physical reference criteria to enable the positive identification of these compounds. Those used were derivatization, infrared spectroscopy, and photomicrography.

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EXPERIMENTAL

Apparatus

Fisher-Johns melting point apparatus (calibrated with melting point reference standards), Beckman IR-5A infrared spectrophotometer equipped with NaCl optics, and a Bausch & Lomb biological microscope equipped with an Olympus PM-8 35-mm. microphotographic camera.

Local Anesthetics

The 10 local anesthetics studied were the commercially available salts of benoxinate, butethamine, cyclomethycaine, dibucaine, dimethisoquin, hexylcaine, lidocaine, naepaine, proparacaine, and tetracaine.

Reagents and Solutions

Acetous perchloric acid, 0.05 *N* (standardized against potassium acid phthalate, primary standard); crystal violet indicator solution (0.5% in glacial acetic acid); 10% aqueous solution of sodium hydroxide; saturated ethanolic solution of styphnic acid; 2% aqueous solution of Reinecke salt; 2.5% aqueous solution of sodium tetraphenylboron; 25% aqueous solution of chloroplatinic acid; aqueous solutions of lidocaine HCl, 0.5 and 1.0%; hexylcaine HCl, 0.5%; tetracaine HCl, 0.1, 0.5, and 1.0%; butethamine HCl, 0.5 and 1.0%; naepaine HCl, 0.5 and 1.0%; dimethisoquin HCl, 0.5 and 1.0%; cyclomethycaine sulfate, 0.25 and 1%; benoxinate HCl, 0.25, 0.5, and 1.0%; proparacaine HCl, 1%; dibucaine HCl, 0.25 and 1.0%; aqueous Reinecke salt solutions, 0.1, 0.25, and 0.5%; aqueous and alcoholic picric acid solutions 0.25, and 0.5% and 1%, respectively; aqueous alcoholic styphnic acid solutions, 0.16, 0.32, and 0.64% and 0.5 and 1.0%, respectively; aqueous potassium permanganate solutions, 0.5 and 1.0%; aqueous chloroplatinic acid solutions, 0.35, 0.5, and 1.0%; alcoholic picrolonic acid (reagent grade) solutions, 0.5 and 1.0%.

Formation of Derivatives.—All derivatives were dried *in vacuo* over phosphorus pentoxide for 24 hr. prior to determining their respective melting points on a Fisher-Johns melting point apparatus.

Styphnates.—(*a*) The styphnates were prepared according to the procedure as outlined by Wild (50). The crystalline styphnates were recrystallized from 95% ethanol.

(*b*) The equivalent weight of each derivative was determined by dissolving about 1 meq. of the styphnate in 5 ml. of acetone and 45 ml. of glacial acetic acid, adding 2 drops of crystal violet indicator solution, and titrating with 0.05 *N* acetous perchloric acid to a blue end point for dibucaine, lidocaine, naepaine, butethamine, and benoxinate styphnates, a turquoise end point for cyclomethycaine and tetracaine styphnates, and a green end point for dimethisoquin styphnate.

The equivalent weights as determined by the foregoing procedure gave excellent agreement with the theoretical values. These together with the elemental analysis (C, H, and N) confirmed the purity of the styphnates.

Reineckates.—(*a*) The reineckates were prepared according to the following modified procedure of Chatten and Levi (51).

To 250 mg. of the local anesthetic salt dissolved in 10 ml. of water, excess Reinecke salt solution (2%) was added with constant stirring. The resulting precipitated mass was allowed to stand 10 min. at room temperature. The amorphous or crystalline precipitate was then filtered off and washed with cold water until the filtrate was clear; recrystallization was carried out by suspending or dissolving the washed precipitate in approximately 5 ml. of ethanol (95%), adding sufficient acetone to solubilize it if it had not already dissolved, and then adding water dropwise with agitation until a permanent turbidity was produced. The vessel was then cooled and the resulting crystalline material filtered off.

Experimental analysis (C, H, N, and Cr) confirmed the purity and identity of the reineckates.

Tetraphenylborates.—(*a*) The procedure used by Koehler and Feldmann (8) was followed with slight modifications. To 250 mg. of the local anesthetic salt dissolved in 5 ml. of water, a slight excess of 2.5% sodium tetraphenylborate solution was added slowly with concomitant stirring and allowed to stand for 20 min. The precipitate was then filtered off, washed with water until the filtrate was clear, and recrystallized from the following solvent systems by adding water dropwise with agitation until the solution became turbid, and then cooling. The tetraphenylborates of lidocaine, tetracaine, and naepaine were recrystallized from ethanol–water; hexylcaine tetraphenylborate was recrystallized from methanol–water; cyclomethycaine, dibucaine, benoxinate, and proparacaine tetraphenylborates were recrystallized from ethanol–methanol–water; dimethisoquin tetraphenylborate was recrystallized from methanol–acetone–water, while the butethamine derivative was washed well with cold water only.

(*b*) The equivalent weights were determined by the nonaqueous titration procedure for local anesthetic tetraphenylborates as outlined by Chatten *et al.* (14) and gave excellent agreement with the theoretical values. Cyclomethylcaine, dibucaine, and lidocaine tetraphenylborates were titrated to a blue end point, while the remaining seven were titrated to a green end point.

The foregoing results together with the elemental analysis (C, H, and N) confirmed the purity and identity of the tetraphenylborates.

Chloroplatinates.—The method presented by Wild (50) was adapted to local anesthetics as follows.

To 250 mg. of the local anesthetic salt dissolved in 5 ml. of water, a slight excess of the chloroplatinic acid solution (25%) was added with stirring. All but naepaine, butethamine, benoxinate, and proparacaine chloroplatinates were prepared in this manner. These were prepared as follows. To the local anesthetic salt dissolved in 5 ml. of absolute methanol, a slight excess of chloroplatinic acid, also dissolved in 5 ml. of absolute methanol, was added with stirring. The mixture was allowed to stand 20 min. in an ice bath, and the fine crystalline precipitate filtered and purified. Those derivatives prepared in absolute methanol were washed well with cold methanol. The chloroplatinates of cyclomethycaine, tetracaine, and hexylcaine were washed well with water, while those of dibucaine, lidocaine, and dimethisoquin were recrystallized from ethanol (95%).

Elemental analyses (C, H, and N) confirmed the purity and identity of the chloroplatinates.

Methiodides.—The general procedure for the preparation of methiodides of local anesthetics outlined by Jensen *et al.* (52) was modified slightly as follows.

To 250 mg. of the local anesthetic salt dissolved in approximately 10 ml. of water in a separator, a slight excess of 10% sodium hydroxide solution was added and shaken well. The free base was extracted with three 5-ml. portions of ether, and after the combined ethereal extracts were dried with anhydrous sodium sulfate, a slight excess of methyl iodide was added and the solution refluxed for 5 min. After cooling, the crystalline derivative was filtered off and washed well with ether. Dibucaine methiodide was recrystallized from acetone–ether, while the remaining six methiodides were recrystallized from isopropanol.

Elemental analyses (C, H, and N) confirmed the purity and identity of the methiodides.

Infrared Spectra.—The infrared spectra of the compounds were measured by the potassium bromide pellet technique.

Photomicrographs.—To 1 drop of an aqueous solution of each of the local anesthetic salts placed on a microscope slide, 1 drop of a reagent solution was added, mixed well, and covered with a cover glass.

DISCUSSION

Formation of Derivatives.—All compounds prepared are presented in Table I together with their melting ranges and previously reported literature values.

Styphnates.—A review of the literature has revealed that relatively few styphnates have been reported for these compounds. In general, however, they proved to be highly desirable derivatives for characterizing these drugs since they were easily prepared and purified and had melting ranges which did not overlap.

Both the elemental analyses and nonaqueous titrations verified that, in each instance, the 1:1 derivative had formed.

Brandstatter-Kuhnert and Grimm (15) were unsuccessful in preparing crystalline dibucaine styphnate. In the present work, it was necessary to evaporate the reaction mixture to approximately one-half of its original volume and then refrigerate, after which crystals separated with scratching.

TABLE I.—MELTING RANGES OF DERIVATIVES OF LOCAL ANESTHETICS

Local Anesthetic	Styphnate	Reineckate	Tetraphenylborate	Chloroplatinate	Methiodide
Benoxinate	74.0– 76.5	129.0–132.0	118.5–120.0	186.0–189.0	139.5–140.5
Butethamine	172.0–173.0	155.0–156.5	76.5–79.0 [90–98(8)] [91.5–108 14)]	210.5–215.0	
Cyclomethycaine	100.0–101.0	152.0–155.0	132.5–135.0 [154–158(8)]	86.0– 91.0	180.5–184.5
Dibucaine	109.5–110.5	102.0–104.0	142.5–144.5	169.5–171.5	114.0–115 [114 (52)]
Dimethisoquin	125.5–127.0	137.5–140.5	133.5–135.0	145.5–149.0	182.5–183.5
Hexylcaine	164.5–165.5	145.0–147.5	64.0– 68.0	84.0– 88.0	
Lidocaine	227.0–228.0 [119 –204 (15)]	179.0–181.5	137.0–139.5	193.0–197.0	151.5–152.0
Naepaine	139.5–140.5	157.5–159.0	116.0–118.0 [110.5–112.5 (14)] [72–76(8)]	210.5–215	
Proparacaine	151.0–158.0	138.0–140.0	131.5–132.0 [143–147(8)]	195.5–198.5	145.0–147.5
Tetracaine	146.5–147.5 [143–147(15)]	139.5–144.0	126.5–128.0 [135–137(8)] [119–120(14)]	128.5–130.5	146.5–148.0

Only two structurally similar local anesthetics, benoxinate and proparacaine, failed to yield satisfactory derivatives. By the procedures used in this investigation, it was not possible to prepare benoxinate styphnate as a well-defined crystalline derivative from either absolute methanol or ethanol (95%), with or without the aid of water. After evaporating the reaction mixture to one-half volume and cooling overnight, a mixture of pale orange and scarlet hard globules separated. Another attempt resulted in a yellowish product (m.p. 92.0–99.5°) after recrystallizing from methanol which on elemental analysis proved to be ill-defined. One batch, prepared in 95% ethanol, was obtained from the reaction solution by adding water and cooling. The bright orange crystalline product, after recrystallizing from aqueous ethanol, melted between 74.0–76.5°.

Anal.—Calcd. for $C_{23}H_{31}N_5O_{11}$: C, 49.91; H, 5.65; N, 12.65. Found: C, 48.12; H, 5.31; N, 13.10.

Similar results were noted for proparacaine styphnate. This derivative was more readily preparable than benoxinate styphnate, separating almost immediately on cooling from the reaction solution as hard well-defined bright yellow crystalline globular hemispheres. After six recrystallizations from ethanol (95%), the melting range was still consistently broad (151.0–158.0°).

Anal.—Calcd. for $C_{22}H_{29}N_5O_{11}$: C, 48.94; H, 5.42; N, 12.98. Found: C, 46.79; H, 5.43; N, 12.85.

Reineckates.—Under the weakly acidic conditions used in this investigation (pH 5–6), the anhydrous monoreineckates were formed and were recrystallized at room temperature. Reasonably sharp decomposition ranges were observed with some overlap between certain derivatives, a situation necessitating the preparation of other derivatives for positive identification.

Tetraphenylborates.—Butethamine represented an apparent anomaly within this series, since it could not be recrystallized from any of the solvent systems utilized for the remaining tetraphenylborates. When titrated in nonaqueous media, recoveries were consistently low (averaging 97.5%), and the compound underwent spontaneous photodecomposition in air. These phenomena are in agreement with previous reports (14).

The observed melting ranges for these derivatives differed markedly from literature values in that they were higher than those reported by Chatten *et al.* (14) and lower than those of Koehler and Feldmann (8). Such discrepancies do not invalidate them as reliable derivatives since the results obtained in this laboratory were entirely reproducible and gave well-defined crystalline compounds having an exact 1:1 stoichiometric composition.

Chloroplatinates.—The stoichiometric relationship involved in these derivatives depends upon whether the drug is mono- or dibasic. In the following second equation, $H_2N—NH^+$ refers to a monoprotonated dibasic local anesthetic cation.

Monobasic

$$2[R_3NH]^+Cl^- + H_2[PtCl_6] \rightarrow [R_3NH]^{++}[PtCl_6]^= + 2HCl$$

Dibasic

$$\left[\begin{array}{c} H_2N-NH \\ | \quad | \\ R \quad R_2 \end{array}\right]^+ Cl^- + H_2[PtCl_6] \rightarrow \left[\begin{array}{c} H_3N-NH \\ | \quad | \\ R \quad R_2 \end{array}\right]^{++} [PtCl_6]^= + HCl$$

The chloroplatinates prepared for this series have not yet been reported in the literature. Generally,

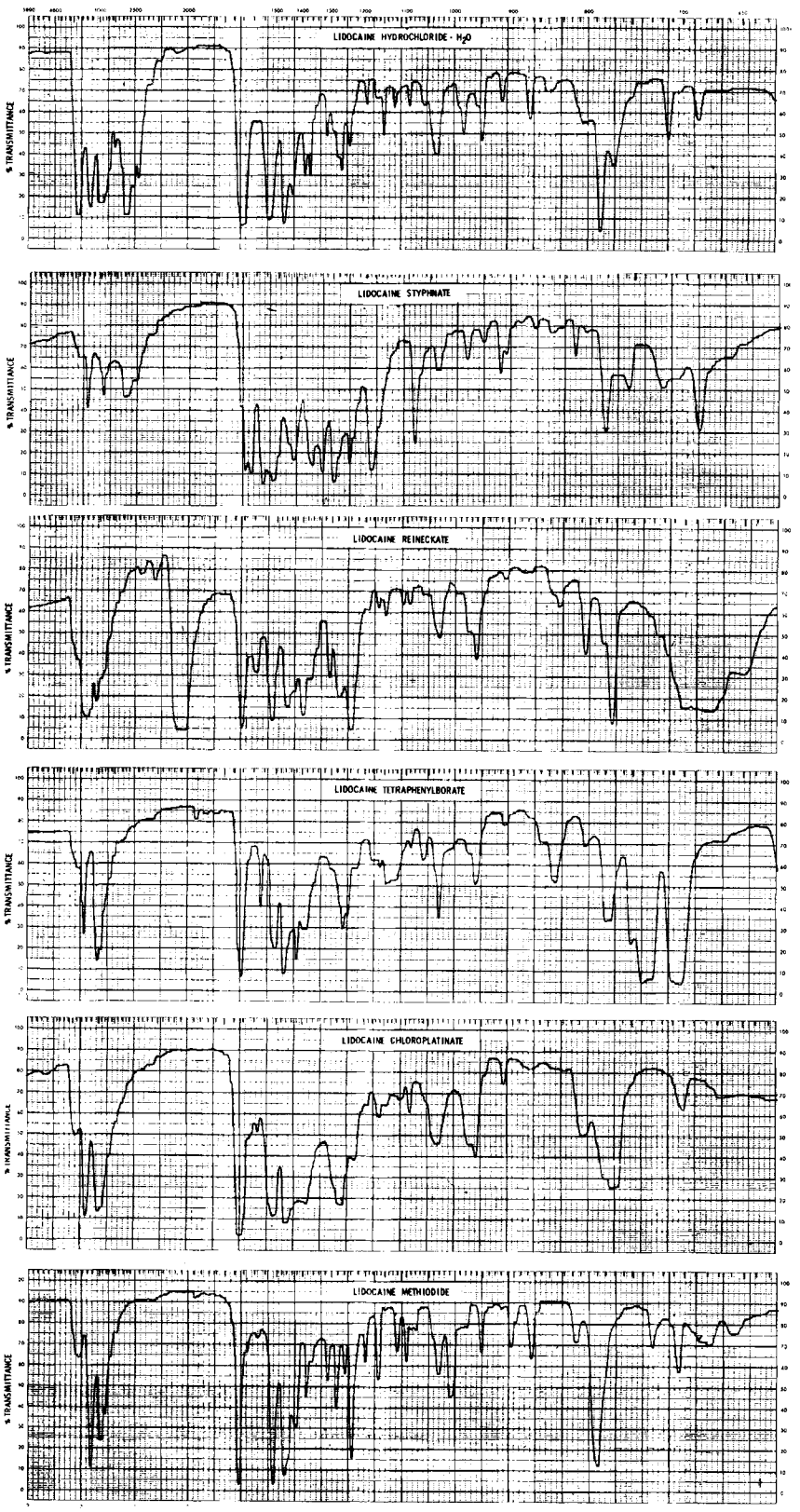

Fig. 1.—Infrared spectra of lidocaine salt and derivatives.

an aqueous solution of the acid salt of a local anesthetic, when mixed with an aqueous solution of chloroplatinic acid, yielded a well-defined, sparingly soluble derivative. Purification was a problem, since several derivatives were adaptable to recrystallization, while others, being just sparingly soluble, were only thoroughly washed.

The four dibasic local anesthetics (naepaine, butethamine, benoxinate, and proparacaine) formed monochloroplatinates which decomposed in hot epichlorhydrin, were only slightly soluble in absolute methanol, and practically insoluble in ethanol (95%). When prepared from aqueous solutions, several anomalous properties were observed, the most obvious one being their lack of the expected characteristic orange of chloroplatinates. Under these conditions, the benoxinate derivative precipitated as a dark amber lumpy mass which, when collected on filter paper, decomposed to an oil of the same color and eventually hardened. The proparacaine derivative precipitated from aqueous solution initially as a pale orange solid (m.p. 193.0–197.0°) but changed to a dull buff color when washed with water (m.p. 193.5–197.5°). These four local anesthetics gave satisfactory derivatives, however, when precipitated from absolute methanol solutions.

Methiodides.—In each instance, the elemental analyses were satisfactory, indicating the formation of well-defined 1:1 tetraalkylammonium salts.

Infrared Spectroscopy.—In addition to the preparation of derivatives and the determination of their attendant melting points, the infrared spectra of these compounds were determined to provide further parameters for differentiating these local anesthetics.

The spectra of the commercially available salts, *i.e.*, hydrochlorides and cyclomethycaine sulfate, can be found in many well known sources such as the "National Formulary" (53) and other publications (14). Therefore, they will not be reproduced in this paper.

In the interest of brevity, lidocaine hydrochloride has been chosen as the prototype, and its infrared spectra will be compared with those of the styphnate, reineckate, tetraphenylborate, chloroplatinate, and methiodide of lidocaine in Fig. 1.

There is a strong absorption band at 3400 cm.$^{-1}$ in the lidocaine hydrochloride spectra resulting from the mole of water present. This band is absent in the remaining spectra as anticipated since elemental analysis showed them to be anhydrous.

The styphnates retain the same weak to medium absorption bands throughout the 3450–3120 cm.$^{-1}$ region due to NH stretching vibrations, although they appear to be slightly shifted. Many other bands which are common to the hydrochloride are retained in the styphnate spectra of lidocaine. Minor shifts have occurred and some splitting of peaks.

In general, the reineckate spectra are less detailed than are the spectra of the hydrochlorides of the parent compounds, an observation which has been attributed to the damping effect of the heavy atoms of the inorganic anion (51). Broad, intense bands occur throughout the 3500–2500 cm.$^{-1}$ and 700 cm.$^{-1}$ regions. The fact that such absorption was also evident in the spectrum of ammonium reineckate suggests that the reineckate anion is largely responsible for this. A broad, intense band arising

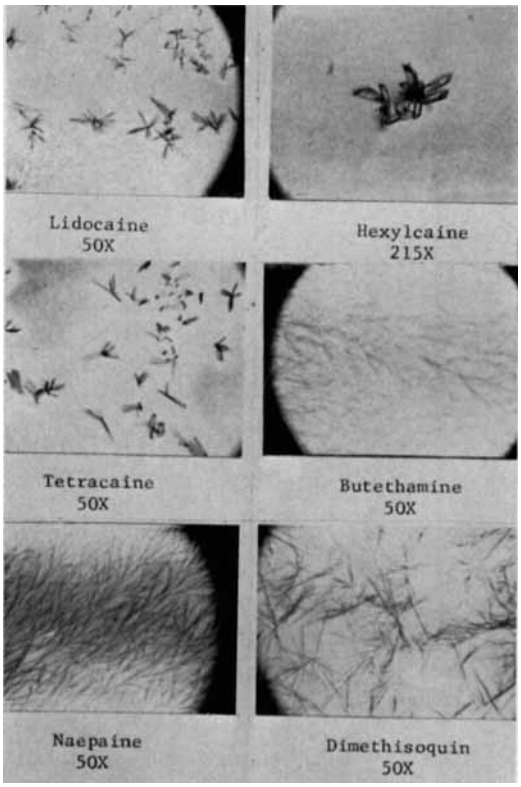

Fig. 2.—Photomicrographs of styphnates.

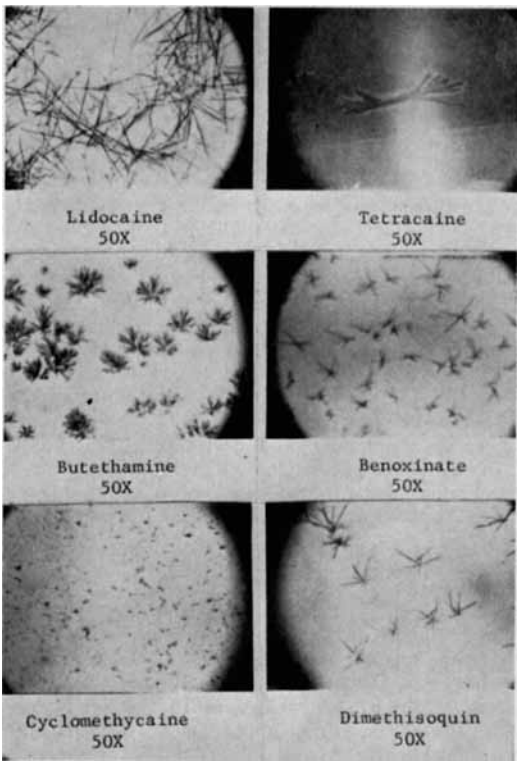

Fig. 3.—Photomicrographs of picrates.

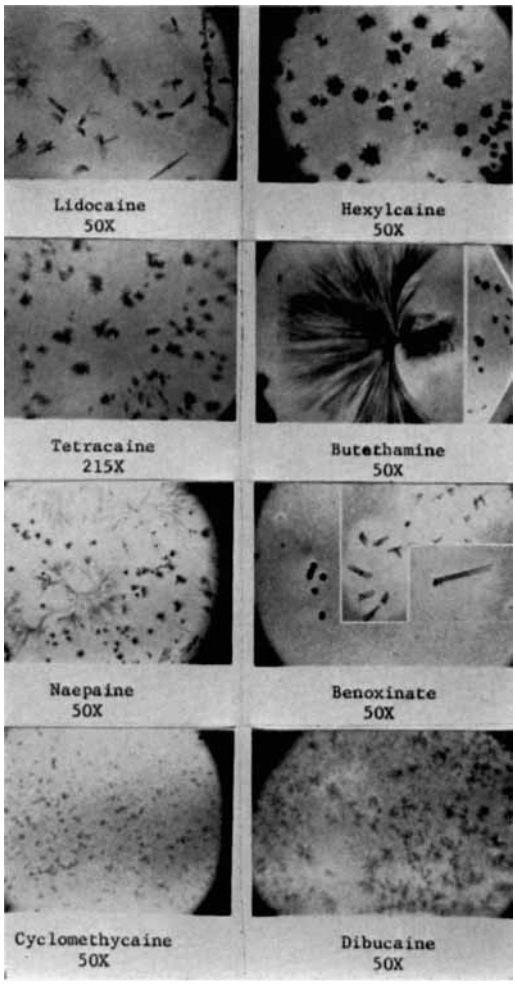

Fig. 4.—Photomicrographs of reineckates.

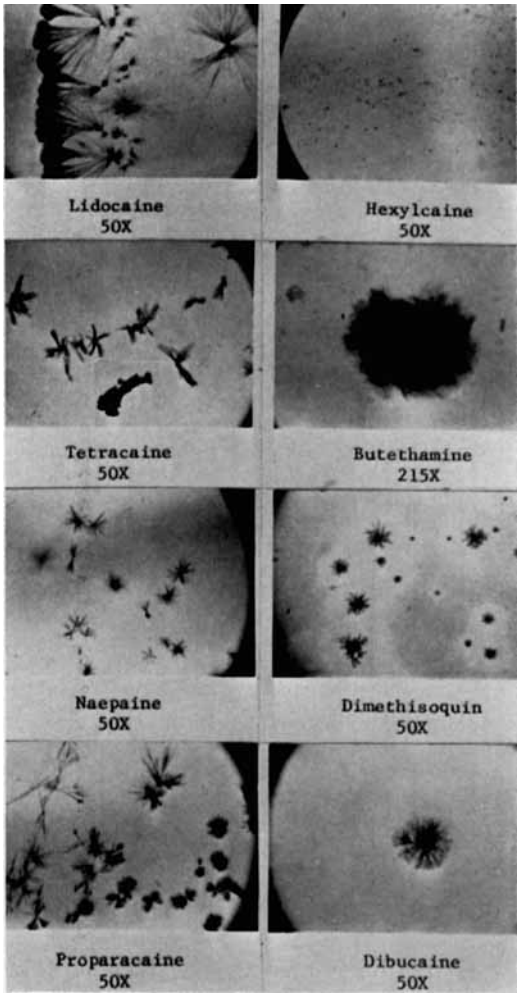

Fig. 5.—Photomicrographs of chloroplatinates.

from the isothiocyanate grouping centering on 2150 cm.$^{-1}$ is apparently lowered from the expected ester carbonyl absorption frequencies by derivatization and is frequently slightly broader than that observed in the corresponding mineral acid spectra. Medium to strong, probably aromatic, and aliphatic C—N and C—O stretching bands are observed at about 1265 and 1170 cm.$^{-1}$. The 8–10 μ region seems to be specific for these derivatives and is of value for their qualitative identification.

In the spectrum of sodium tetraphenylborate, the TPB anion exhibited characteristic bands due to the monosubstituted phenyl and boronaryl groups with two intense broad bands in the 750–700 cm.$^{-1}$ region (out-of-plane CH bending vibrations of the phenyl groups). Chatten *et al.* (14) have reported bands for local anesthetic TPB's around 3500 cm.$^{-1}$ and have attributed them to the N—H bond establishing the ionic forces of attraction between the organic cation and the inorganic anion. Characteristic aromatic and aliphatic CH stretching vibrations are found, frequently in the form of a doublet throughout the 300 cm.$^{-1}$ region. Medium absorption about 2750–2500 cm.$^{-1}$ is characteristic in the spectra of the mineral acid salts of these local anesthetics; similar absorption is absent from the corresponding TPB spectra. This phenomenon has been observed for similar local anesthetic TPB's previously reported (14).

In spite of common characteristics, the spectra are sufficiently characteristic to enable the differentiation of the TPB's, especially in the 8–16 μ range. The spectra of tetracaine, naepaine, butethamine, and dibucaine TPB's were identical with those published by Chatten *et al.* (14).

Upon examination of the spectra of the chloroplatinates, the absence of the broad band or group of relatively sharp bands in the 2750–2450 cm.$^{-1}$ region so prominent in the corresponding mineral acid salt spectra (NH^+ stretching vibrations, overtones, and combinations) is immediately evident. In its stead, broad absorption in the 3100–2300 cm.$^{-1}$ region is seen as a result of aromatic and aliphatic CH stretching vibrations in the higher frequencies and NH^+ stretching vibrations, overtones, and combinations on the lower frequency side. A medium to strong absorption band about 300 cm.$^{-1}$ in width at 3450 cm.$^{-1}$ is common to all the spectra (present as a shoulder in the spectrum of dibucaine chloroplatinate). This band is usually present

TABLE II.—MICROCHEMICAL TESTS WITH PICROLONIC ACID AND POTASSIUM PERMANGANATE

Anesthetic	Description of Microcrystals: Picrolonates	Permanganates
Benoxinate	Clusters of dark green twisted "seaweed" type crystals	Not characteristic
Butethamine	Individual crystal clusters of flat pale greenish-yellow plane and bent blades with square ends	Fernlike formations
Cyclomethycaine	Not characteristic	Not characteristic
Dibucaine	Not characteristic	Not characteristic
Dimethisoquin	Pale yellow rhomboid prisms	Not characteristic
Hexylcaine	Dark green four- or five-pointed star-shaped crystals	Minute fragmentary flat plates and prisms
Lidocaine	Not characteristic	Not characteristic
Naepaine	Pale yellow elongated radiated flat prisms joined centrally to form rosettes	Flat, usually elongated plates and blades with ragged peripheries
Proparacaine	Not characteristic	Not characteristic
Tetracaine	Not characteristic	Individual clusters of radiating leafy curved blades with irregular peripheries

TABLE III.—LOCAL ANESTHETICS CHARACTERIZED BY MICROCRYSTALLOGRAPHY[a]

Local Anesthetic	Styphnic Acid	Picric Acid	Ammonium Reineckate	Chloroplatinic Acid	Picrolonic Acid	Potassium Permanganate
Lidocaine	1.0–0.64 (*5*)	1.0–1.0[b] (*1*)	0.5 –0.5 (*3*)	1.0–1.0 (*5*)	...	...
Hexylcaine	0.5–0.32 (*1.5*)	...	0.5 –0.5 (*4*)	0.5–0.25 (*10*)	0.5–0.5[b] (*2*)	0.5–0.5 (*5*)
Tetracaine	1.0–0.64 (*5*)	1.0 –1.0[b] (*4*)	0.1 –0.1 (*5*)	1.0–1.0 (*10*)	...	0.5–0.5 (*1*)
Butethamine	0.5–0.32 (*3*)	0.5 –0.5 (*1*)	0.5 –0.5 (*8*)	0.5–0.5 (*20*)	1.0–1.0[b] (*2*)	1.0–1.0 (*1/4*)
Naepaine	0.5–0.5[b] (*5*)	...	0.5 –0.5 (*2*)	1.0–1.0 (*1*)	0.5–1.0[b] (*5*)	0.5–0.5 (*5*)
Benoxinate	...	1.0 –1.0[b] (*15*)	0.25–0.25 (*10*)	...	0.5–1.0[b] (*15*)	...
Cyclomethycaine	...	0.25–0.25 (*2*)	0.25–0.25 (*5*)	...	...	1.0–1.0 (*5*)
Dimethisoquin	1.0–1.0[b] (*1*)	1.0 –1.0[b] (*2*)	...	1.0–0.5 (*5*)	1.0–1.0[b] (*5*)	0.5–0 5 (*5*)
Proparacaine	...	...	...	1.0–0.5 (*4*)	1.0–1.0[b] (*2*)	...
Dibucaine	...	...	0.25–0.25 (*3*)	1.0–0.25 (*15*)	...	...

[a] Local anesthetic concentration (%)–reagent concentration (%); numbers in parentheses denote time in minutes when picture was taken. [b] Ethanol (95%) solution.

either as a characteristic doublet or singlet in the spectra of those compounds having a free primary or secondary amino group, but with the chloroplatinates, these characteristics are fused into one relatively broad band at the same frequency, probably because these groups are protonated.

The spectra of the methiodides are highly characteristic for all seven of the local anesthetics. Examination of these spectra reveals the common similarities which have been discussed for the previous four derivatives in the 3450–3100 cm.$^{-1}$ region (NH stretching vibrations), 3050–2800 cm.$^{-1}$ (aromatic and aliphatic CH stretching vibrations), and about 1700 cm.$^{-1}$ (carbonyl stretching frequency).

It will be seen from inspection of Fig. 1 that, while certain similarities in the absorption patterns in the higher frequencies do exist, the spectra are specific and constitute an excellent technique for quickly differentiating qualitatively these local anesthetics.

Photomicrography.—For many years, a broad variety of nitrogenous pharmaceutical bases have been characterized qualitatively by photomicrography, and this technique has again proved of value in the present work. The photomicrographs were taken at two magnifications, 50 or 215×, and only those which are characteristic have been reproduced in Figs. 2–5.

It is not intended that the crystalline habits of these compounds be used as a sole criterion of identification, but rather as an adjunct to the other physical methods previously presented (melting points and the infrared spectra of selected derivatives). None of the reagents employed gave characteristic crystals with all of the local anesthetics.

Picrolonic acid was not a particularly successful reagent. However, no characteristic picrolonates have previously been reported, and they are therefore described in Table II together with the permanganates.

The microcrystals formed with potassium permanganate were the least satisfactory. Only six of the 10 local anesthetics studied gave crystalline

formations, of which only four were truly specific. In each instance, the crystals were a purple permanganate color initially, but soon changed to various shades of brown.

The condition under which the characteristic microcrystals formed are summarized in Table III. All solutions are aqueous unless otherwise indicated.

SUMMARY

1. A series of physical criteria, by which 10 of the newer local anesthetics currently in use can be positively identified and differentiated, has been presented.

2. Forty-seven derivatives of these drugs have been prepared in a systematic manner, of which 37 have not been reported to date in the literature (Table I). Benoxinate styphnate was the only derivative prepared which was considered unreliable.

3. The infrared spectra of these derivatives have been obtained as a further aid in their qualitative differentiation, and representative specimens are included in Fig. 1.

4. A series of photomicrographs has been included in Figs. 2–5 along with a summary of the conditions under which they were formed (Table III).

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