of a lubricant on the dissolution rate of a mass compressed at a given force was demonstrated for particles of 80/100-mesh size fraction. It is conceivable that a given weight of a lubricant may be distributed differently when blended with particles of different sizes and that different distributions may influence the dissolution of the compressed mass.

The dissolution rates of disks compressed at 1135 kg of 40/60-, 80/100-, and 140/200-mesh size fractions of salicylic acid containing 0.1–5% talc are shown in Fig. 6. The presence of talc in a concentration as great as 5% and the use of three size fractions of salicylic acid did not significantly alter the dissolution rates of the compressed disks. Similar results with talc were obtained from disks composed of aspirin (Fig. 7) and of an equimolar mixture of aspirin and salicylic acid (Figs. 8 and 9). The use of three size fractions of aspirin and an equimolar mixture of aspirin and salicylic acid with concentrations of talc from 0.1 to 5% did not alter the dissolution rates.

The dissolution rates of disks compressed at 1135 kg of 40/60-, 80/100-, and 140/200-mesh size fractions of salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid containing 0.1–5% magnesium stearate are shown in Figs. 6–9. As observed with talc, the dissolution rate, when using magnesium stearate, was independent of the size of the particles used to prepare the compressed disks.

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Recommendations to Eliminate Subjective Olfactory Methods from Compendial Identification Tests

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Abstract □ Substitution of IR and UV absorption spectroscopy and use of the various test papers listed in the compendia provide satisfactory means of identifying drugs and other substances that presently require subjective odor identification.

Keyphrases □ Compendial odor identification tests—substitution of IR and UV spectroscopic methods recommended □ IR spectroscopy—recommended as substitute for compendial odor identification tests □ UV spectroscopy—recommended as substitute for compendial odor identification tests

Many identification tests in USP XIX (1) and NF XIV (2) monographs rely on detection of odors produced either by the test substance itself or by its reaction products. Olfactory methods are inherently undesirable, both because of the possible toxic nature of the inhaled substances and because all such tests are markedly and unpredictably influenced by such subjective and idiosyncratic factors as the experience and discriminatory powers of the analyst, sensory fatigue, and the presence of masking odors.

Compounding the subjective nature of such olfactory testing, a varied terminology is used to describe the odors actually produced. Tables I and II list the various terms used in USP XIX and NF XIV, respectively.

For many drug substances, the IR spectrum is distinctive and can be compared to a curve in the literature. Final identification is made by comparing the unknown spectrum with a curve obtained from a reference standard prepared similarly and run under the same conditions and, preferably, on the same instrument. One advantage of the IR spectrophotometer is the ease with which it handles samples in the solid, liquid, or gaseous state. Commercial test papers or those described in the compendia (USP XIX, p. 760) are also useful for confirming the identity of several gases evolved in monograph identity tests.

Table I—USP XIX Odor Identification Tests

Compound	Odor Description	Identification Test Odor
	Drugs	
Acetic acid	Recognizable	Ethyl acetate
Aluminum acetate solution	Recognizable	Ethyl acetate
Aluminum sulfate[a]	Not perceptible	Ammonia
Aspirin	Perceptible	Acetic acid, ethyl acetate
Busulfan	Perceptible	Methanesulfonic acid
Carbachol	Perceptible	Amine odor
Chloral hydrate	Recognizable	Chloroform
	Disagreeable	Phenyl isocyanide (poisonous)
Cocaine hydrochloride	Aromatic	Methyl benzoate
Cortisone acetate	Perceptible	Ethyl acetate
Ether[b,c]	Not perceptible	Foreign odor
Gelatin[c,d]	Disagreeable	Free from any
Glycerin[d]	Pungent vapor	Acrolein
Helium[c,e]	Discernible	No appreciable odor
Isoniazid	Perceptible	Pyridine
Methenamine mandelate	Liberated or evolved	Ammonia, almond odor of benzaldehyde
Methylprednisolone acetate	Perceptible	Ethyl acetate
Oxygen[c,e]	Discernible	No appreciable odor
Paraldehyde	Pungent	Acetaldehyde
Phentolamine mesylate	Recognizable	Sulfur dioxide
Potassium acetate	Recognizable	Ethyl acetate
Potassium chloride	Recognizable	Chlorine
Primidone	Evolved	Ammonia
Pyrazinamide	Perceptible	Ammonia
Sodium aminosalicylates[c,f]	Not perceptible	Hydrogen sulfide or sulfur dioxide
	Perceptible	Amyl alcohol
Sodium chloride	Recognizable	Chlorine
Sulfacetamide sodium	Perceptible	Acetamide
Precipitated sulfur	Recognizable	Sulfur dioxide
Thiopentyl sodium	Evolved and recognizable	Hydrogen sulfide
Trichloroacetic acid	Formation	Chloroform
	Disagreeable	Phenyl isocyanide (poisonous)
Zinc acetate	Recognizable	Ethyl acetate
Zinc chloride[a]	Recognizable and perceptible	Chlorine
	Pharmaceutical Ingredients	
Amaranth	Perceptible	Sulfur dioxide
Cellulose acetate phthalate	Perceptible	Ethyl acetate
Chlorobutanol	Disagreeable	Phenyl isocyanide (toxic)
Nitrogen[c,e]	Discernible	No appreciable odor
Propylene glycol	Evolved	Fruity odor, no sharp acrid odor of acrolein
Sodium acetate	Recognizable	Ethyl acetate
Sodium bisulfite	Recognizable Pungent	Sulfur dioxide

[a] Listed in monograph under Ammonium Salts. [b] Listed in monograph under Foreign Odor. [c] No recommendations for testing this compound. [d] Listed in monograph under Odor and Water-Insoluble Substances. [e] Listed in monograph under Odor. [f] Listed in monograph under Hydrogen Sulfide and Sulfur Dioxide.

By a combination of simple test reactions and UV and IR spectrophotometric identification, many olfactory tests in the compendial monographs can be eliminated. Judicious use of one or several such techniques is generally adequate for confirming the presence of all major functional groups to demonstrate that the molecule is intact and to provide specific "fingerprint" identification of the substance.

This paper reports the results of a survey of compendial monographs that specify olfactory tests. In every case, IR spectroscopy, alone or in combination with UV spectroscopy or one or more simple chemical tests, provided a superior, more specific method of identification. Typical spectra are shown in Figs. 1–7.

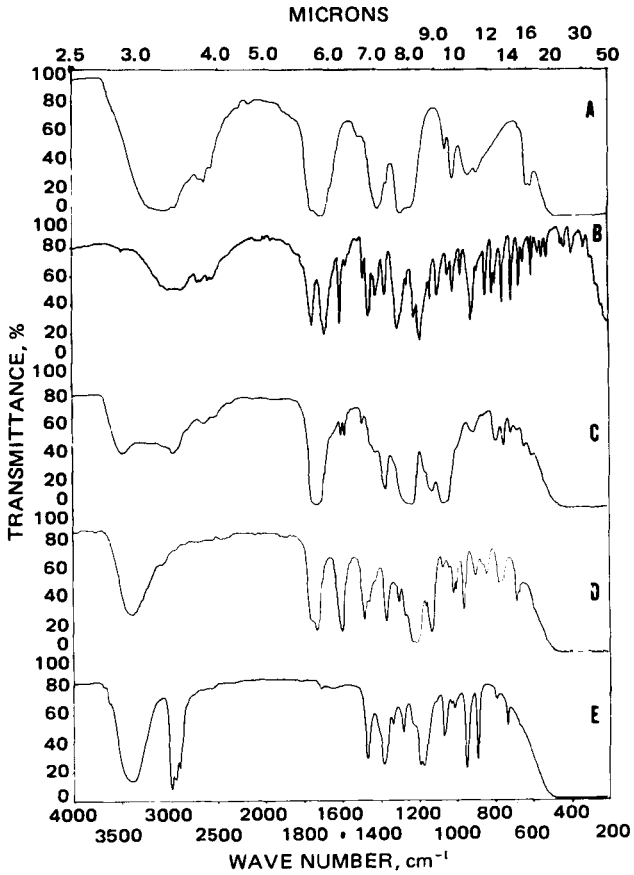

Figure 1—*IR spectra of acetic acid (A), aspirin (B), cellulose acetate phthalate (C), resorcinol monoacetate (D), and amylene hydrate (E).*

EXPERIMENTAL

IR absorption spectra were obtained as potassium bromide disks, as mineral oil[1] USP mulls, as melts on a sodium chloride plate, neat between polished sodium chloride crystals, or in a 10-cm gas cell by the following procedures.

For the potassium bromide disk preparation, usually 1–2 mg of sample was mixed thoroughly with 200 mg of potassium bromide in a 65-mm o.d. agate mortar with a pestle for 2 min. The mixture was placed in a potassium bromide die (13 mm), the plunger was inserted, and the assembly was placed in a press. The die was connected to a vacuum pump and evacuated. Then the assembly was pressed for 2 min at 9080 kg (20,000 lb). The vacuum was disconnected, the pressure was released, the disk was removed, and the IR spectrum was obtained.

For a melt, the sample was placed on a sodium chloride crystal, heated to the temperature required to melt the compound, and then cooled to room temperature. The crystal was placed in a demountable IR cell, and the IR spectrum was obtained.

For neat samples, a few drops of sample were placed on a sodium chloride crystal, a second sodium chloride crystal was placed on top of the sample, and the sample was gently squeezed to a uniform layer. The crystals were placed in a demountable IR cell, and the IR spectrum was obtained.

For mulls, about 10–15 mg of the sample was placed in a 65-mm agate mortar, a few drops of mineral oil USP were added, and a portion of the mixture was ground for 2 min. The mixture was then removed to a sodium chloride crystal, a second sodium chloride crystal was placed on top of the mull, and the crystals were squeezed gently to distribute the material evenly between them. The crystals were placed in a demountable IR cell, and the IR spectrum was obtained.

For gases, the materials needed to generate vapor were placed in a 10-ml glass-stoppered erlenmeyer flask, the stopper was inserted, and the flask was shaken for several minutes. Then the stopper was removed,

[1] Nujol.

Table II—NF XIV Odor Identification Tests

Compound	Odor Description	Identification Test Odor
	Drugs	
Alum, ammonium	Evolved	Ammonia
Alum, potassium	Evolved	No ammonia
Aminosalicylic acid[a,b]	Perceptible	Amyl alcohol
	Not percepitble	Hydrogen sulfide or sulfur dioxide
Ammonium chloride	Recognizable	Ammonia, chlorine
Amobarbital	Evolved	Ammonia
Amyl nitrite	Perceptible	Amyl valerate
Aspirin capsules	Perceptible	Acetic acid, ethyl acetate
Benzocaine	Recognizable	Alcohol
Betamethasone acetate	Perceptible	Ethyl acetate
Calcium aminosalicylate[a,b]	Perceptible	Amyl alcohol
	Not perceptible	Hydrogen sulfide or sulfur dioxide
Cetylpyridinium chloride	Perceptible	Pyridine
Chloral betaine	Recognizable	Chloroform
Chlorothiazide sodium for injection	Recognizable	Sulfur dioxide
	Pungent	
Cocaine	Aromatic	Methyl benzoate
Dehydrocholic acid[b,c]	—	Odorless
Digitalis[b]	—	Odor slight when dry, peculiar and characteristic when moistened
Ethamivan	—	Typical amine odor develops
Ethyl chloride[b,d]	Not perceptible	Foreign odor, acetaldehyde
Fluroxene[b,e]	Not perceptible	Foreign odor
Ichthammol[e]	Evolved	Ammonia
Sulfurated lime solution	Evolved	Hydrogen sulfide
Menadione sodium bisulfite	Recognizable	Sulfur dioxide
Methacholine chloride[b]	Perceptible	Ethyl acetate
		Trimethylamine
Methenamine	Recognizable	Formaldehyde
	Evolved	Ammonia
Methoxyflurane	Evolved	Hydrofluoric acid
Methylprednisolone acetate suspension	Perceptible	Ethyl acetate
Plantago seed[b,f]	—	Nearly odorless
Potassium aminosalicylate[a,b]	Perceptible	Amyl alcohol
	Not perceptible	Hydrogen sulfide or sulfur dioxide
Rauwolfia serpentina[b,g]	—	Odor indistinct, reminiscent of stored white potatoes
Resorcinol monoacetate	Recognizable	Ethyl acetate
Senna[b,h]	—	Odor is characteristic
Sodium hypochlorite solution	Evolved	Chlorine
Sublimed sulfur	Recognizable	Sulfur dioxide
Terpin hydrate	Aromatic	Strong aromatic
Vinyl ether[b]	Perceptible	Alcohol
	Not perceptible	No foreign odor
	Pharmaceutical Ingredients	
Amylene hydrate	Recognizable	Ethyl acetate
Benzyl alcohol	Noticeable	Benzaldehyde
Cardamon seed[b,i]	Aromatic	Aromatic
	Not perceptible	No foreign odor
Chloroform[b,j]	Evolved	Faint vinous or ether odor
Cinnamon[b,k]	Aromatic	Characteristically aromatic
Eriodictyon[b,l]	Aromatic	Aromatic
Ethyl acetate[m]	—	Acetous odor produced; does not resemble that of pineapple or banana
Paraffin	Evolved	Hydrogen sulfide
Peppermint[b]	Aromatic	Aromatic characteristic odor
Phenylmercuric acetate	Evolved	Nitrobenzene, ethyl acetate
Phenylmercuric nitrate	Evolved	Nitrobenzene
Sodium metabisulfite	Recognizable	Pungent odor
Sodium propionate	Recognizable	Propionic acid
Sulfurated potash	Evolved	Hydrogen sulfide
Spearmint[b]	Aromatic	Aromatic and characteristic
Tartaric acid	—	Resembling burning sugar
Vanilla[b]	Aromatic	Characteristic, agreeably fragrant and aromatic

[a] Listed in monograph under Hydrogen Sulfide and Sulfur Dioxide, *etc.* [b] No recommendations for testing this compound. [c] Listed in monograph under Odor on Boiling. [d] Listed in monograph under Nonvolatile Residue and Odor and under Alcohol. [e] Listed in monograph under Foreign Odor. [f] Listed in monograph under Odor and Taste. [g] Listed in monograph under Unground Rauwolfia serpentina Root. [h] Listed in monograph under Unground Alexandria Senna. [i] Listed in monograph under Unground Cardamon Seed. [j] Listed in monograph under Odorous and Chlorinated Decomposition Products and under Foreign Odor. [k] Listed in monograph under Unground Cinnamon. [l] Listed in monograph under Unground Eriodictyon. [m] Listed in monograph under Butyl or Amyl Derivatives.

and the vapors were quickly withdrawn into a 50-ml hypodermic syringe (without an attached needle). Care was taken not to touch the materials in the flask. The vapors were injected into an evacuated 10-ml gas cell[2], modified by inserting 20-gauge needles fitted with removable polytef plugs into the rubber septums in the entrance ports. This technique permitted easy injection with a syringe into the gas cell.

RESULTS AND DISCUSSION

Fifteen analysts in this laboratory were requested to identify nine different odors listed in identification tests of the compendial monographs. These odors, with the possible exception of amyl valerate, were those of compounds to which analysts are normally exposed in their training or laboratory experience. As shown in Table III, in four of the nine identification tests, fewer than half of the analysts identified the correct compound.

Tables I and II list some drugs for which the compendia require olfactory testing. Because of possible toxicity or irritation to many chemists, as well as their unfamiliarity with the odors of these compounds, the staff was not subjected to additional tests of these materials.

Examples are listed below to demonstrate the ease with which drugs can be identified without the possible exposure to dangerous malodorous compounds involved in subjective testing.

Tests Involving the Odor of Ethyl Acetate—In at least 15 monographs of the USP and NF, production of the odor of ethyl acetate is specified as an identification test (Tables I and II). In some cases, the intent of the test is to confirm the presence of the acetate anion of an inorganic salt, *e.g.*, aluminum acetate solution and sodium, potassium, and zinc acetates.

In other monographs, confirmation of the presence of an acetyl group in an organic substance is sought, *e.g.*, acetic acid, aspirin, resorcinol monoacetate, cellulose acetate phthalate, and various steroidal acetates. In both categories, the IR spectrum of the compendial substance provides a more suitable test; the acetate anion or acetyl group is readily confirmed by characteristic carbonyl absorption. The spectrum as a whole is uniquely characteristic for each substance. Figure 1A shows the IR spectrum of acetic acid, taken neat; it is distinct from that of other carboxylic acids.

Aspirin—Figure 1B shows the characteristic IR spectrum of aspirin. At present, there is no indication that aspirin exists in polymorphic states (3). In identifying the steroidal acetates, however, great care must be taken in preparing the potassium bromide disks since polymorphism for this class of compounds is well documented (4). Both sample and standard must be treated with identical solvents, heating conditions, halide matrix, pressure, and time.

A satisfactory test for aspirin capsules involves extracting the contents with chloroform, removing the solvent, and obtaining the IR spectrum of a potassium bromide disk of the dried extract.

If a separate test for acetate in organic salts is desired, the test described in USP XIX (p. 615) should be used. Ferric chloride TS is added to a solution of the salt, producing a deep-red color which is destroyed by addition of a mineral acid.

[2] Barnes-Econo-Gas-Cell part 0026-006, Barnes Engineering Co., Stamford, Conn.

Table III—Attempted Olfactory Identification of Various Odors by 15 Analysts

Compound (Odor)	Correct Identification	
	Number	%
Dilute acetic acid	10/15	67
Amyl alcohol	11/15	73
Amyl valerate	1/15	7
Ethyl acetate	7/15	47
Ethyl alcohol	12/15	80
Hydrogen sulfide	15/15	100
Methyl benzoate	4/15	26
Sulfur dioxide	6/15	40
No perceptible odor (water)	14/15	93

Cellulose Acetate Phthalate—USP XIX identification test A for cellulose acetate phthalate requires the generation of ethyl acetate, which is recognizable by its characteristic odor. A satisfactory characteristic identification of this product involves dissolving about 0.1 g of sample in 3 ml of acetone and pouring the solution onto a clean sodium chloride crystal; a glossy clear film is deposited as the acetone evaporates. An IR spectrum (Fig. 1C) of this film is satisfactory and characteristic for this material. This test eliminates the need for identification test B and satisfies the requirement of a glossy clear film in identification test C.

Resorcinol Monoacetate—The IR spectrum (Fig. 1D) of a neat solution of resorcinol monoacetate between sodium chloride crystals is a satisfactory and characteristic identity test for this drug. Likewise, the IR spectrum (Fig. 1E) of amylene hydrate neat between sodium chloride crystals is a satisfactory and characteristic identification for this alcohol.

Phenylmercuric Acetate—NF XIV identification tests A and B for phenylmercuric acetate require the evolution of nitrobenzene and ethyl acetate, both of which have characteristic odors. The UV spectrum (Fig. 2) of phenylmercuric acetate (approximately 0.75 mg/ml of 95% ethanol) is a characteristic curve of the phenyl moiety of the molecule and satisfies the identification requirement of test A.

To 100 mg of phenylmercuric acetate in a 10-ml erlenmeyer flask with a glass stopper, 500 ml of sulfuric acid and 1 ml of alcohol are added. The flask is then warmed with the stopper in place. The headspace vapors are removed with a 50-ml syringe and injected into a gas cell. The IR spectrum (Fig. 3C), which is characteristic of ethyl acetate vapor, is obtained.

Phenylmercuric Nitrate—NF XIV identification test A for phenylmercuric nitrate requires heating the compound with sulfuric acid; a vapor with the characteristic odor of nitrobenzene is evolved.

The IR spectrum (Fig. 4A) of a potassium bromide disk of phenylmercuric nitrate is a satisfactory and characteristic identification test.

Ethyl Acetate—Paradoxically, in the NF XIV monograph for ethyl acetate, its odor is not utilized; instead, it is burned and an "acetous" odor is produced. The IR spectrum of ethyl acetate itself (Fig. 4B, obtained neat) is, of course, characteristic and satisfactory for identification.

Tests Involving Ammonia—Numerous monographs rely on the generation of the odor of ammonia as an identification test; in other monographs, the *absence* of the odor of ammonia is a requirement. In all such cases, the red-to-blue transformation of moistened litmus paper (or the absence of this change) is a more sensitive and less subjective criterion for the evolution of ammonia.

Several of these monographs already specify that the IR and UV spectra be obtained, *e.g.*, primidone and pyrazinamide in USP XIX and benzocaine in NF XIV. Since these tests are satisfactory and unambiguous, the test for ammonia may be considered superfluous.

Methenamine—The NF XIV identification test for methenamine requires the identification of the odors of formaldehyde and ammonia. Although the test also confirms the presence of formaldehyde by stating that it darkens paper moistened with silver ammonium nitrate TS, the test does not confirm the presence of ammonia by moistened red litmus paper.

The IR spectrum of a potassium bromide disk of methenamine, described under IR absorption in the monograph, is a satisfactory identity test and eliminates the need for the present identification test.

Methenamine Mandelate—A similar case is methenamine mandelate in USP XIX. Identification test A requires dissolving about 0.5 g of methenamine mandelate in water, adding diluted sulfuric acid, and heating the solution. The evolved formaldehyde vapor turns silver-ammonia-nitrate TS paper brown and has a characteristic odor. An excess of sodium hydroxide added to the warm mixture liberates ammonia, which turns moistened red litmus paper blue.

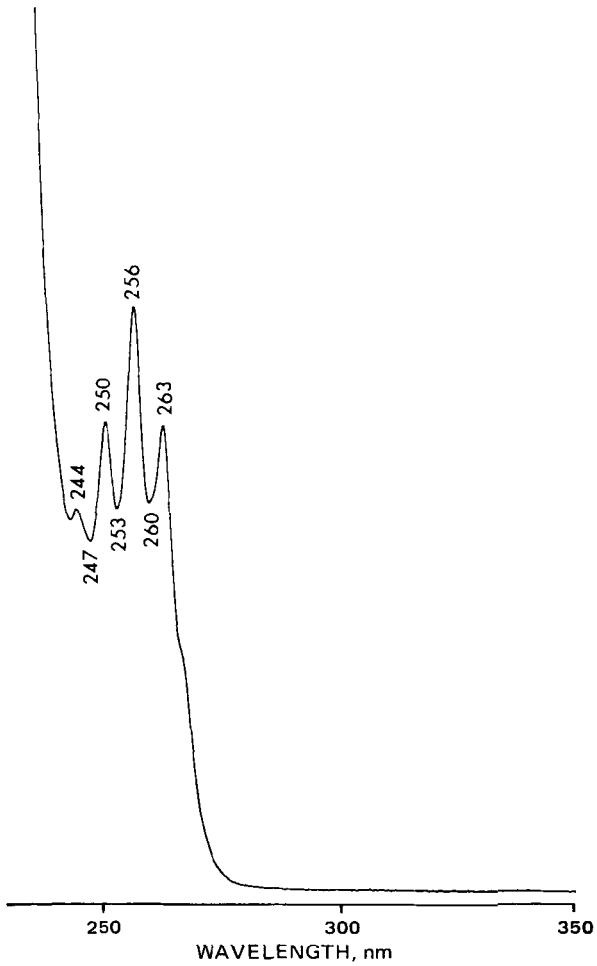

Figure 2—*UV spectrum of phenylmercuric acetate.*

In identification test B, 0.1 g of methenamine mandelate is dissolved in water, and potassium dichromate TS is added; the almond odor of benzaldehyde is evolved. An IR spectrum of a potassium bromide disk of methenamine mandelate (Fig. 4C) gives a satisfactory and characteristic identification curve.

Tests Involving Sulfur Dioxide—Seven monographs in USP XIX and NF XIV contain identity tests that depend on the detection of the odor of evolved sulfur dioxide; in two other monographs, the *absence* of sulfur dioxide is a requirement. Moistened starch iodate paper, which turns blue in the presence of sulfur dioxide, is used as a supplementary test in some cases.

It is suggested that the use of this indicator paper alone is sufficient to test for sulfur dioxide; for some of these monographs (*e.g.*, phentolamine mesylate, chlorothiazide sodium for injection, and menadione sodium bisulfite), a combination of IR and UV spectrophotometry, after suitable sample preparation, provides a much more specific means of identification.

Tests Involving Hydrogen Sulfide—The odor of hydrogen sulfide, although perhaps universally recognizable, is disagreeable and toxic. The detection of either its presence or absence is a requirement in several monographs. The darkening of moistened lead acetate paper is given as an additional test in most of these monographs; it is suggested that the olfactory test be eliminated.

Tests Involving Chlorine—For identification methods requiring the detection of the odor of chlorine (*e.g.*, potassium chloride USP, sodium chloride USP, zinc chloride USP, ammonium chloride NF, and sodium hypochlorite NF), it is recommended that only the test with starch iodide paper (which turns blue) and silver nitrate TS (which forms a white precipitate, insoluble in nitric acid but soluble in excess ammonia TS) be used.

Busulfan—The busulfan identification test in USP XIX involves dissolving busulfan in water, adding sodium hydroxide, and heating; a characteristic odor of methanesulfonic acid is perceptible. Preparation of a potassium bromide disk of busulfan and IR examination produce a

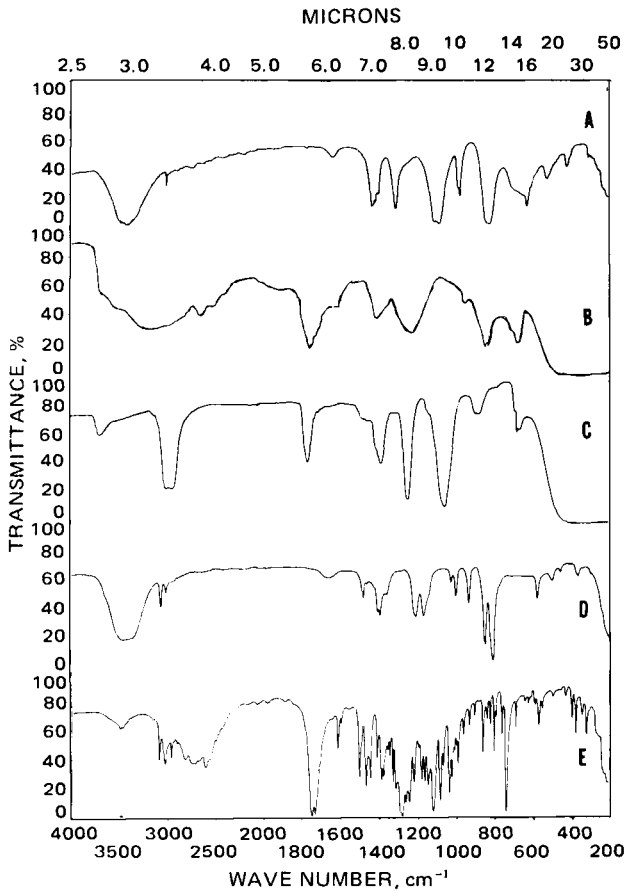

Figure 3—*IR spectra of chloral hydrate (A), trichloroacetic acid (B), ethyl acetate vapor (C), chlorobutanol (D), and cocaine hydrochloride (E).*

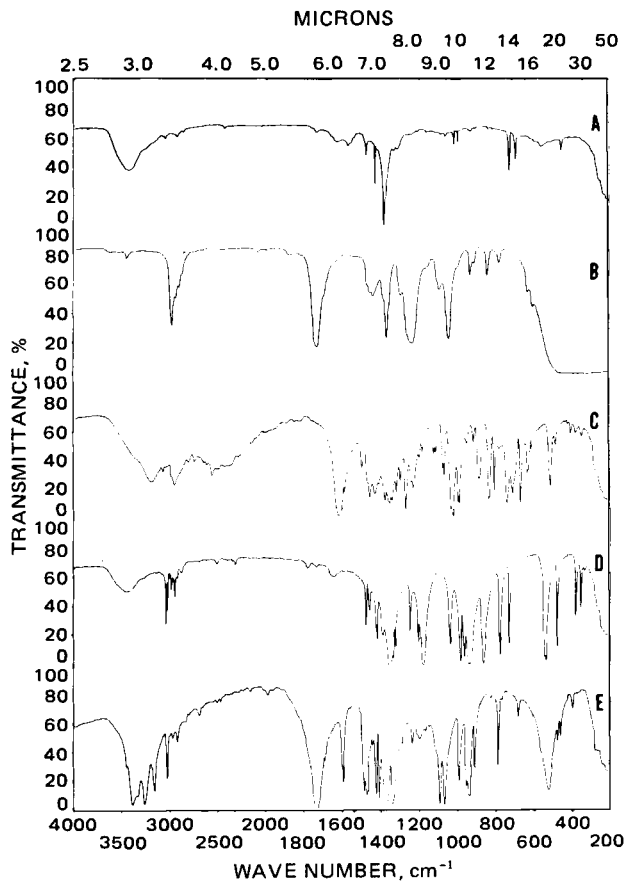

Figure 4—*IR spectra of phenylmercuric nitrate (A), ethyl acetate (B), methenamine mandelate (C), busulfan (D), and carbachol (E).*

characteristic spectrum (Fig. 4D). (Busulfan is an antineoplastic and should be handled with caution.)

Carbachol—In USP XIX identification test B for carbachol, 0.5 g of carbachol is boiled with alcoholic potassium hydroxide. A white precipitate is formed, and an amine odor is perceptible when the mixture cools. The IR spectrum of a potassium bromide disk of carbachol (Fig. 4E) gives a characteristic spectral curve and also eliminates the need for identification test A listed in the monograph.

Chloral Hydrate—USP XIX identification tests A and B for chloral hydrate require treating the drug with a sodium hydroxide solution to produce chloroform, which is recognizable by its odor. When chloral hydrate is warmed with a few drops of aniline and sodium hydroxide solution, the mixture has the intensely disagreeable odor of phenyl isocyanide (caution: poisonous).

The IR spectrum of a potassium bromide disk (Fig. 3A) gives a characteristic spectrum of chloral hydrate, thus eliminating the need for the two subjective olfactory tests. Although no chloral hydrate polymorphs have been detected in this laboratory, Kuhnert *et al.* (5) reported the presence of two polymorphic forms.

Trichloroacetic Acid—The USP XIX identification test for trichloroacetic acid requires heating the solution with an alkali hydroxide to form an alkali carbonate and chloroform. Addition of a few drops of aniline to the heated mixture also produces the disagreeable odor of phenyl isocyanide. The IR spectrum of a few crystals of trichloroacetic acid melted between sodium chloride crystals (Fig. 3B) is uniquely different from other aliphatic organic acids, giving a characteristic and satisfactory curve for identification of trichloroacetic acid.

Chlorobutanol—USP XIX identification test B for chlorobutanol requires heating the chemical with sodium hydroxide TS, mixing, and adding a few drops of aniline. Again, the disagreeable odor of phenyl isocyanide is produced.

An IR spectrum of a potassium bromide disk of chlorobutanol (Fig. 3D) gives a satisfactory and characteristic identity test.

Cocaine Hydrochloride—USP XIX identification test A for cocaine hydrochloride requires heating the drug with sulfuric acid at 100° and then cautiously mixing with a small volume of water. The mixture has the odor of methyl benzoate and, on cooling, yields crystals of benzoic acid.

An IR spectrum of a potassium bromide disk of cocaine hydrochloride (Fig. 3E) is very characteristic of this compound and also eliminates the need for identification tests A, B, and C of the monograph.

Glycerin—In the USP XIX identification test for glycerin, a few drops are heated with about 0.5 g of potassium bisulfate; pungent odors of acrolein are evolved.

Examination of a few drops of glycerin neat between two sodium chloride crystals in an IR spectrophotometer gives a characteristic IR spectrum (Fig. 5A).

Isoniazid—In USP XIX identification test A for isoniazid, a small amount of sample is mixed with about 0.5 g of anhydrous sodium carbonate. The mixture is then heated in a test tube over a small flame to produce an odor of pyridine.

An isoniazid mineral oil mull between sodium chloride plates gives a characteristic IR spectrum which can be used to identify isoniazid (Fig. 5B).

Cetylpyridinium Chloride—NF XIV identification test A for cetylpyridinium chloride involves a pyridine odor generated when the substance is heated to melting and browning. In the pyridine test, about 1 g of cetylpyridinium chloride is dissolved in sodium hydroxide solution without heating, and the odor of pyridine is *not* immediately perceptible. The IR and UV absorption tests in the monograph for cetylpyridinium chloride satisfy the identification requirement; the odor test is not needed.

Paraldehyde—In the USP XIX identification test, paraldehyde is heated with a small quantity of dilute sulfuric acid; the pungent odor of acetaldehyde is produced. A few drops of paraldehyde between potassium bromide crystals examined in an IR spectrophotometer produce a characteristic spectrum adequate for identification (Fig. 5C).

Sulfacetamide Sodium—USP XIX identification test B for sulfacetamide sodium requires converting the drug to sulfacetamide and heating until it boils, producing an oily liquid which has a characteristic odor. An IR spectrum obtained from a potassium bromide disk of either

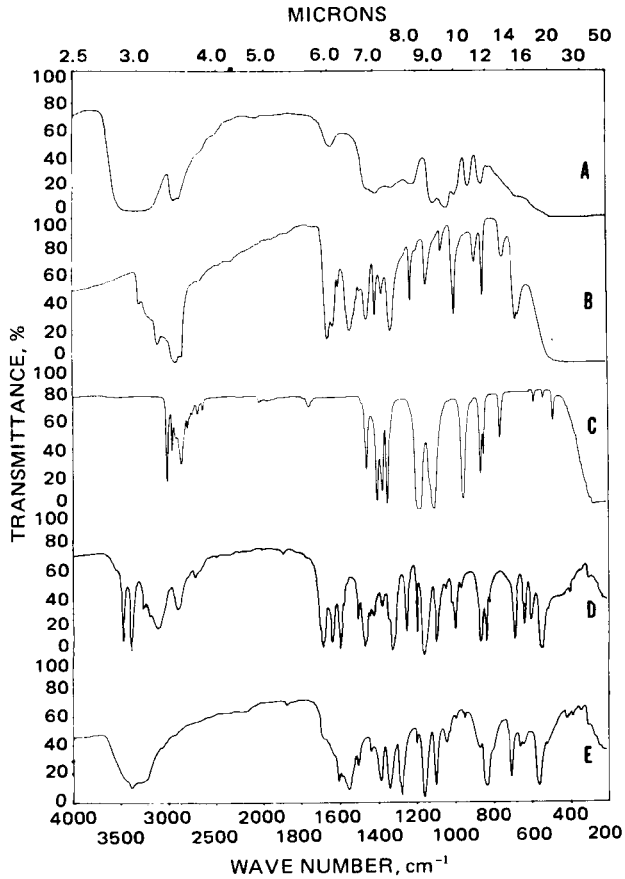

Figure 5—*IR spectra of glycerin (A), isoniazid (B), paraldehyde (C), sulfacetamide (D), and sulfacetamide sodium (E).*

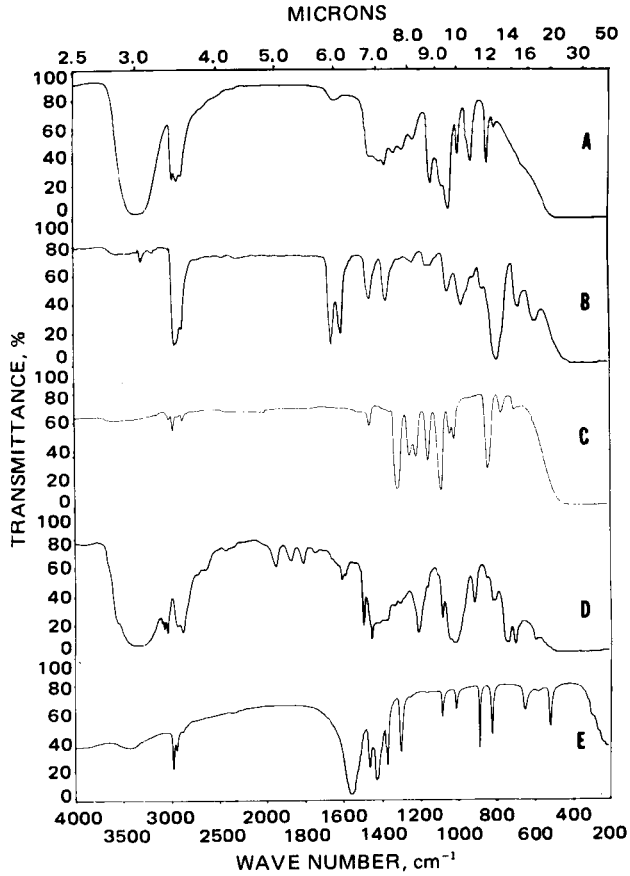

Figure 6—*IR spectra of propylene glycol (A), amyl nitrite mixture (B), methoxyflurane (C), benzyl alcohol (D), and sodium propionate (E).*

sulfacetamide produced in identification test A (Fig. 5D) or sulfacetamide sodium itself (Fig. 5E) is characteristic and satisfactory as an identification test. In a study by Yang and Guillory (6) on polymorphism in sulfonamides using various solvents, polymorphism was not detected for sulfacetamide.

Propylene Glycol—In the USP XIX identification test for propylene glycol, the viscous liquid is heated with 1 g of potassium bisulfate, producing a fruity odor. When propylene glycol is heated to dryness, no odor of acrolein is perceptible. The IR spectrum of propylene glycol (Fig. 6A) run neat between sodium chloride crystals is a satisfactory and characteristic identification for propylene glycol.

Amyl Nitrite—In the NF XIV identification test for amyl nitrite, a few drops of water and sulfuric acid are added to amyl nitrite and the product is diluted with water; the odor of amyl valerate is perceptible.

The following procedure is recommended to replace the odor identification. An amyl nitrite braided cover ampul is placed in a 10-ml glass-stoppered erlenmeyer flask and crushed with a glass rod; the flask is stoppered and shaken. The vapors are removed with a 50-ml syringe (no needle) and injected into a 10-cm IR gas cell fitted with sodium chloride windows. The vapors give a very specific and characteristic IR spectrum of amyl nitrite mixture (Fig. 6B). IR spectra of samples of this product from two different manufacturers were identical.

Chloral Betaine—In the NF XIV identification test for chloral betaine, a few milliliters of sodium hydroxide TS is added to the drug; chloroform, recognizable by its odor, is formed. The IR absorption test described in the monograph is satisfactory for characterizing chloral betaine; the odor test is not needed.

Cocaine—NF XIV identification test A for cocaine requires heating about 0.1 g of the alkaloid with 1 ml of sulfuric acid at 100° for approximately 5 min and then cautiously mixing with a few milliliters of water; the aromatic odor of methyl benzoate is produced. Identification test D (IR) in the monograph is satisfactory for characterizing cocaine, and identification test A is not needed.

Ethamivan—NF XIV identification test B for ethamivan requires the evolution of vapors that have a typical amine odor and turn red litmus blue. However, both the IR and UV absorption tests in the monograph are satisfactory for characterizing ethamivan. Therefore, identification test B should be eliminated.

Methoxyflurane—In NF XIV identification test B for methoxyflurane, the drug is heated with sulfuric acid and hydrofluoric acid is evolved. A 10-cm gas cell can be filled with methoxyflurane vapor, and an IR spectrum (Fig. 6C) is obtained that is distinctive from the spectra of chloroform, trichloroethylene, and halothane. This IR spectrum can be used to identify methoxyflurane when compared to the spectrum of NF methoxyflurane reference standard similarly measured.

Terpin Hydrate—The NF XIV identification test for terpin hydrate requires addition of a few drops of sulfuric acid to a hot solution of terpin hydrate; the liquid develops a strong aromatic odor. The IR absorption procedure described in the monograph for terpin hydrate is a satisfactory and characteristic test.

Benzyl Alcohol—The NF XIV identification test for benzyl alcohol requires treating a few drops of the alcohol with a solution of potassium permanganate; the odor of benzaldehyde is noticeable. The IR spectrum of benzyl alcohol (Fig. 6D) neat between two sodium chloride plates provides a satisfactory and characteristic identification.

Sodium Propionate—In NF XIV identification test C for sodium propionate, the salt is warmed with sulfuric acid to evolve propionic acid,

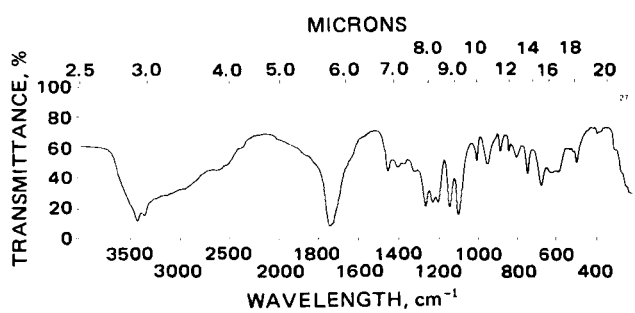

Figure 7—*IR spectrum of tartaric acid.*

recognizable by its odor. The IR spectrum (Fig. 6E) of a potassium bromide disk of sodium propionate is a satisfactory and characteristic test for this salt. It is suggested that identification test A for sodium remain in the monograph.

Tartaric Acid—In NF XIV identification test B for tartaric acid, the acid is ignited, emitting an odor resembling that of burnt sugar. The IR spectrum (Fig. 7) of a potassium bromide disk of tartaric acid is a satisfactory and characteristic test for this acid.

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NOTES

Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IX: Acetaminophen Prodrug

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Received July 19, 1976, from the *Division of Drug Information and Technology, College of Pharmacy, University of Kentucky, Lexington, KY 40506* and *INTERx Research Corporation, Lawrence, Kans.* Accepted for publication June 29, 1977.

Abstract □ The synthesis, hydrolysis rate, and bioavailability of 1-(*p*-acetaminophenoxy)-1-ethoxyethane, an acetaminophen prodrug, are described. The prodrug is less soluble than acetaminophen and stable at neutral pH. However, in an acidic environment, the compound cleaves rapidly, generating acetaminophen. When both the prodrug and acetaminophen were administered to dogs in equivalent amounts, the blood acetaminophen levels were comparable.

Keyphrases □ Prodrugs—of acetaminophen, synthesis, hydrolysis rate, and bioavailability studied, dogs □ Acetaminophen prodrug—1-(*p*-acetaminophenoxy)-1-ethoxyethane synthesized, hydrolysis rate and bioavailability studied, dogs □ 1-(*p*-Acetaminophenoxy)-1-ethoxyethane—acetaminophen prodrug synthesized, hydrolysis rate and bioavailability studied, dogs □ Hydrolysis rate—acetaminophen prodrug studied, dogs □ Bioavailability—acetaminophen prodrug studied, dogs □ Analgesics—acetaminophen, prodrug synthesized, hydrolysis rate and bioavailability studied, dogs

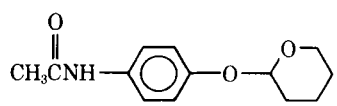
Acetaminophen, a well-known analgesic–antipyretic drug, is widely used in oral dosage forms. The drug, however, is unpleasantly bitter, and attempts made to formulate it in an acceptable chewable dosage form intended especially for pediatric use have apparently not been very successful.

Repta and Hack (1) were successful in masking the bitterness of acetaminophen *via* derivation of the hydroxy group to form 2-(*p*-acetaminophenoxy)tetrahydropyran (I). Prodrug I was stable at neutral pH (pH of the saliva) but hydrolyzed in the gastric juice. This paper reports the synthesis, hydrolysis rate, and absorption of another acetaminophen prodrug where the hydroxy group was transiently blocked using ethyl vinyl ether. This prodrug, 1-(*p*-acetaminophenoxy)-1-ethoxyethane (II), has an advantage over the corresponding tetrahydropyran derivative (I) in that it reverts to acetaminophen 10 times faster. Therefore, the possibility that the prodrug might be absorbed as such is greatly minimized.

EXPERIMENTAL

Synthesis of II (2)—To a suspension containing 4 g of acetaminophen (0.26 mole) in freshly distilled ethyl acetate were added 30 ml (~0.4 mole) of freshly distilled ethyl vinyl ether and 0.2 ml of 0.4% *p*-toluenesulfonic acid in benzene. The suspension was stirred magnetically at room temperature until all suspended material was dissolved and a clear colorless solution was obtained, usually within 2–4 hr.

At the completion of the reaction, 0.2 ml of 0.4% pyridine in benzene was added. The solution obtained was transferred to a rotary evaporator,



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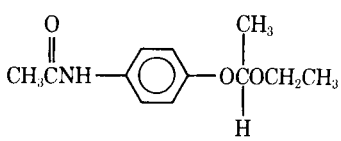

II