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Extraction Procedures for Some Common Drugs in Clinical and Forensic Toxicology

There are many reports in the literature which deal with general screening methods for drugs in both clinical patients and postmortem specimens [1-13]. Much attention has been given to the clinical aspects where urgent identification and quantitation of unknown drugs are required. Of prime importance in this work is the selection of a suitable extraction technique. The number of available drugs has increased enormously since the more popular extraction methods were described, when at that time most overdoses involved acidic drugs (salicylates and barbiturates). These extraction systems have not been adequately evaluated with many of the more modern and predominantly basic drugs.

Although the literature contains references to numerous solvent systems [14-19], each may only be specific for a particular group of drugs. Relatively few of these systems are suitable for screening procedures, the most common being chloroform or ether. Recently, it has been suggested that *n*-butyl chloride may also be suitable [8], but the evidence to support this is not yet complete. Several important studies [5,11] have reported the extraction efficiency of a large number of drugs from aqueous solutions.

We have continued and expanded these surveys and have examined the back-extraction process, which is the efficiency of the drug extraction from organic solutions into acid or alkali media.

In an attempt to find an extraction procedure suitable for drug screening work, we have studied the distribution of 86 drugs by three, and in some cases four, systems. In addition we have studied the gas liquid chromatography (GLC) properties of these drugs and have included a list of suitable temperatures for their detection on an OV-17 column. The incorporation of ultraviolet spectroscopy (UV) proved to be an asset in the identification of drugs in the aqueous solutions.

Materials and Methods

Apparatus

Ultraviolet spectra were recorded in a 1-cm cell on a Unicam SP 800 recording spectrophotometer, scanning from 450 to 220 nm. A Hewlett-Packard series 5700A gas chromatograph equipped with a flame ionization detector was used. The column was a 4-ft by 1/4-in. (1.2-m by 6.35-mm) OD glass-coiled tube, packed with a 3% OV 17

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(Supelco) on gas chrom Q 80/100 mesh (Supelco). The instrument settings were as follows: injection port temperature, 300°C (572°F); detector temperature, 300°C; nitrogen carrier gas flow rate, 60 ml/min; hydrogen flow rate, 60 ml/min; and air flow rate, 240 ml/min. In this work the oven temperature was set at temperatures varying from 100 to 290°C (212 to 554°F). In screening for unknown drugs a temperature program was used starting at 150°C (302°F) for 2 min and then increasing 8 deg/min to 290°C (554°F). This temperature was then held isothermally for 8 min.

Reagents and Standards

Reagents used were 1M HCl, 1.8M H₂SO₄, 0.45M NaOH, chloroform, ether, and sodium carbonate. All reagents were of analytical grade, manufactured by British drug houses.

All the drugs investigated were as the free acid or base, made up to an accurate concentration of 5 to 10 mg in 10 ml of ethanol. Reference standards were made up by diluting 1 ml of this stock solution to 50 ml, the final concentration being 10 to 20 µg/ml.

Procedures

The extraction procedures used to study the drug distributions are outlined in Figs. 1 to 3. For some of the more volatile compounds a slight modification of the extraction technique of Ramsey and Campbell [20] was used (Fig. 4).

Explanation of Tables

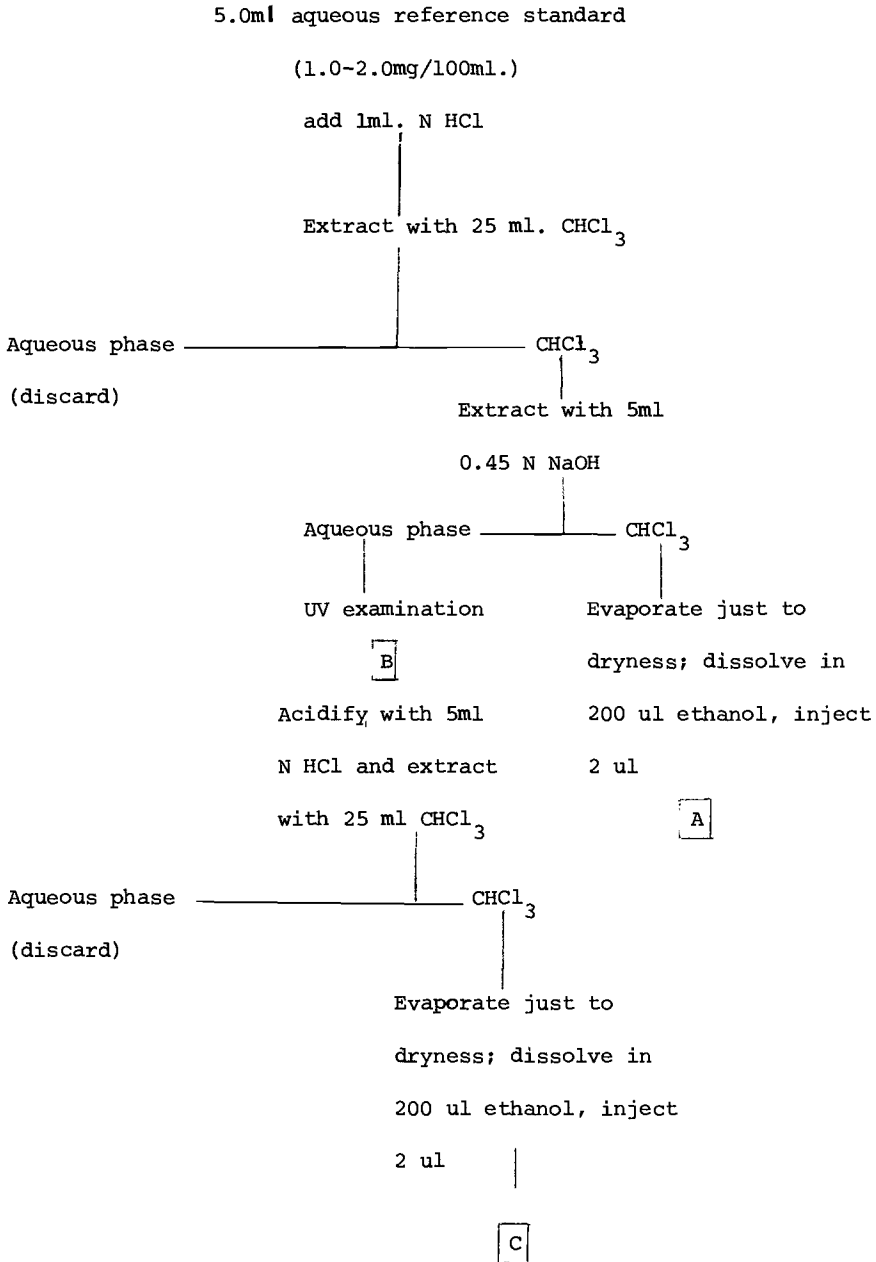
The results obtained from an examination of the behavior of each drug under the extraction procedures outlined in Figs. 1-3 are shown in Table 1, in which the distribution, relative recoveries, and most suitable method of extraction have been recorded.

In Table 1, the columns A to I refer to the fractions shown in Figs. 1-3, and the following symbols have been used. For columns B, E, and H (UV): A positive sign (+) refers to the ultraviolet spectrum which was easily recognized as that of the particular drug under investigation; that is, the absorbance was greater than 0.4. If the absorbance was less than 0.4, a negative sign (-) was included in the table. For columns A, C, D, F, G, and I (GLC): The recovery levels were determined by GLC. A triple positive sign (+++) indicates greater than 75% recovery, a double positive sign (++) indicates greater than 50% but less than 75% recovery, a single positive sign (+) indicates greater than 10% but less than 50% recovery, and a negative sign (-) indicates less than 10% recovery.

The most suitable method (Fig. 1,2,3, or 4) for maximum recoveries is shown in column J.

In Table 2 a positive sign (+) designates that the drug can be satisfactorily analyzed by GLC (first column) or UV (fourth column). The remaining columns refer to the GLC properties of the drugs. The retention time of each drug was related to one of the following reference standards at the temperatures used. Amphetamine, 1.7 min at 100°C (212°F); nicotine, 2.4 min at 125°C (257°F); phenacetin, 8.1 min at 150°C (302°F); glutethimide, 5.7 min at 175°C (347°F); methaqualone, 7.9 min at 200°C (392°F); codeine, 5.8 min at 225°C (437°F); codeine, 2.7 min at 250°C (482°F); nitrazepam, 3.7 min at 275°C (527°F); and strychnine, 5.0 min at 290°C (554°F).

Some of the more volatile drugs were successfully extracted by a rapid extraction technique (Fig. 4). The results are shown in Table 3 in which the symbols (referring to gas chromatographic detection) have the same meaning as those in Table 1.



- A = Contains neutral drugs and chloroform-soluble basic hydrochlorides
- B = Contains acidic drugs
- C = Contains acidic drugs

FIG. 1—Flow chart for the extraction procedure using HCl/chloroform.

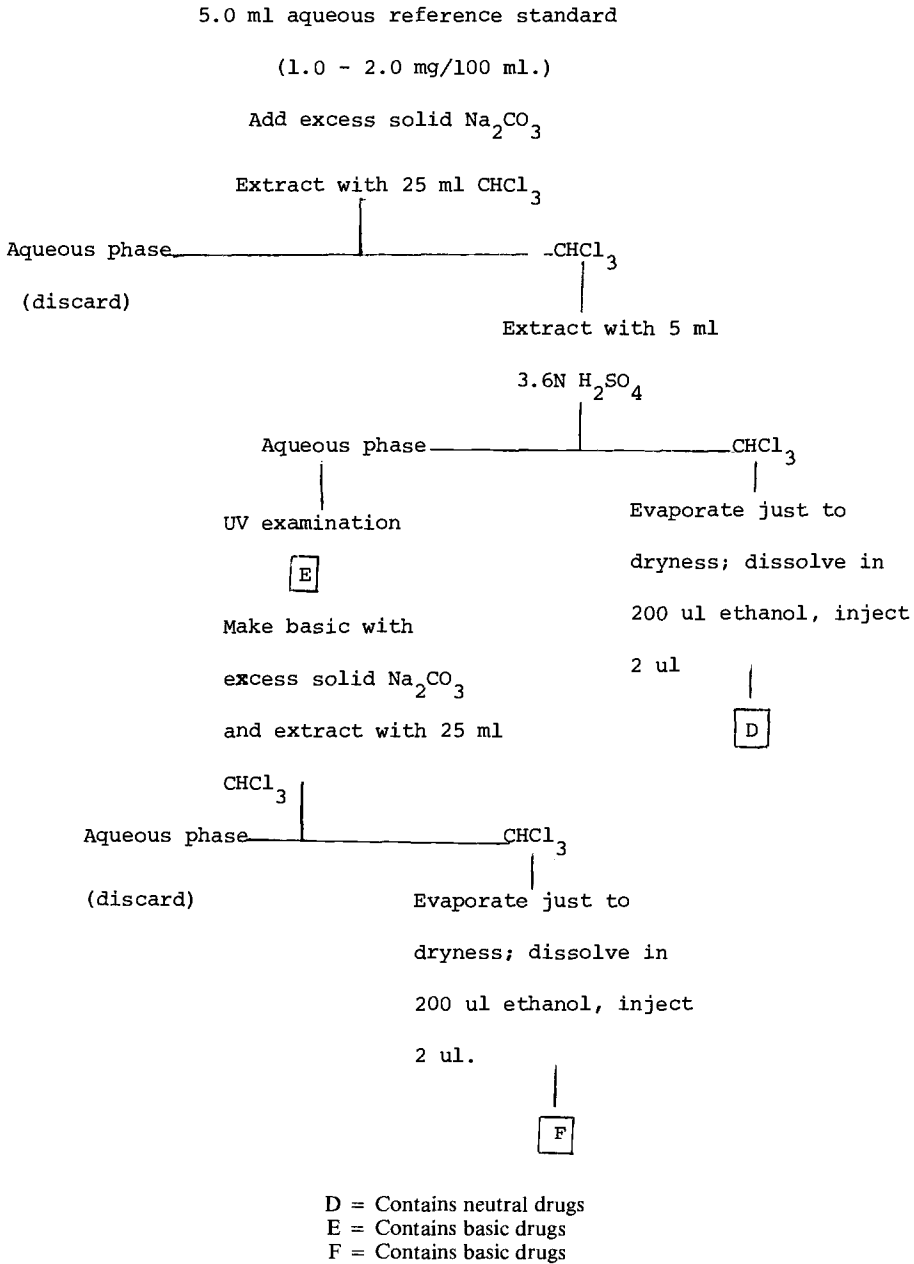


FIG. 2—Flow chart for the extraction procedure using Na_2CO_3 /chloroform.

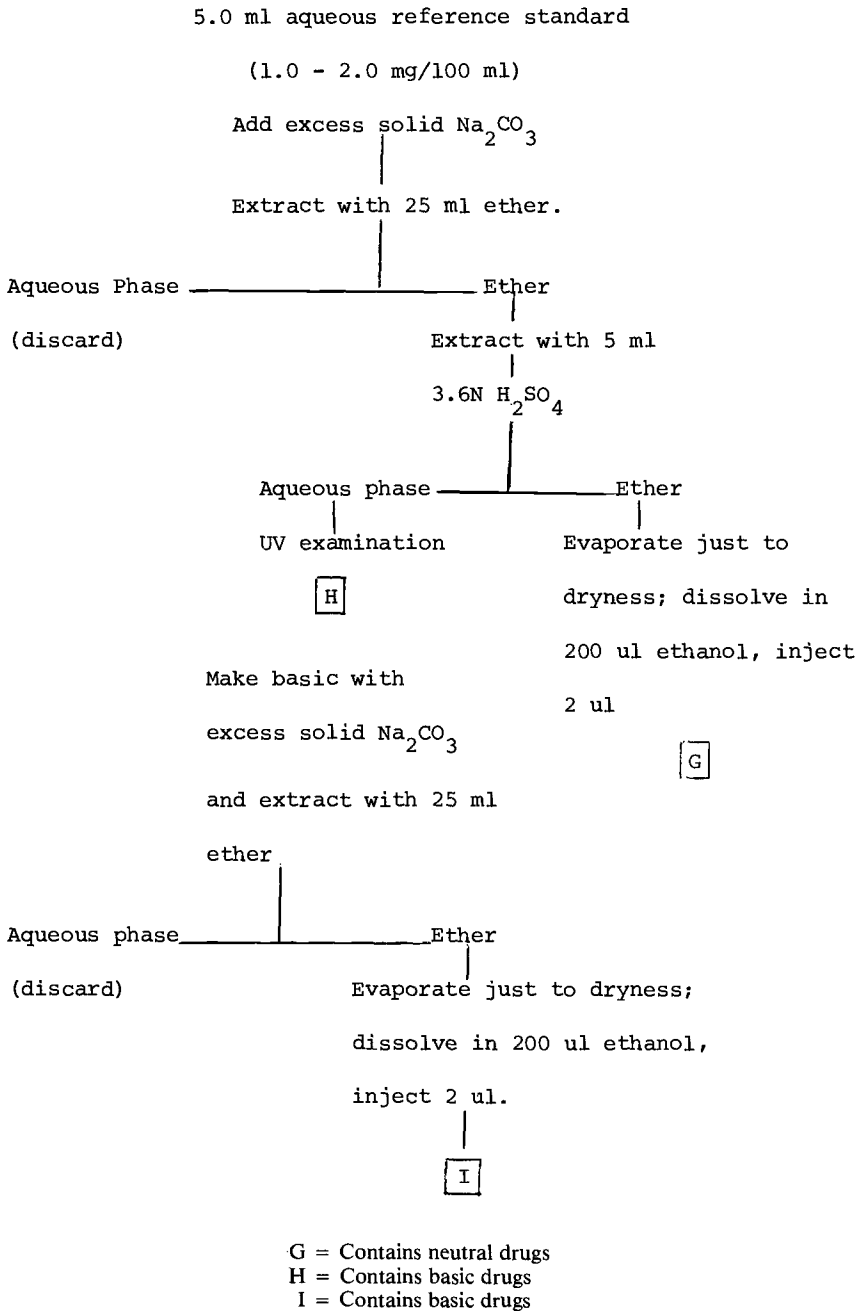


FIG. 3—Flow chart for the extraction procedure using Na_2CO_3 /ether.

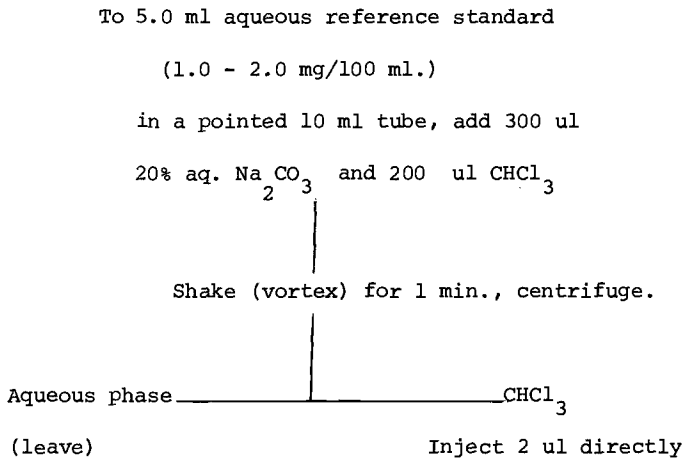


FIG. 4—Flow chart for the rapid extraction procedure.

TABLE 1—Distribution of drugs for the three extraction procedures.

Drug	HCl/CHCl ₃			Na ₂ CO ₃ /CHCl ₃			Na ₂ CO ₃ /Ether			J
	A	B	C	D	E	F	G	H	I	
Acetaminophen	-	-	-	+	-	+	-	-	-	2
Alprenolol	+	-	-	-	-	++	-	-	+++	3
Amitriptyline	+++	-	-	+	+	+	-	+	+++	1,3
Amobarbital	-	+	+++	++	-	-	+++	-	-	1
Amphetamine #	-	-	-	-	-	+	-	-	+	4
Atropine	-	-	-	-	-	+++	-	-	+++	3
Aspirin	*	+	*	*	-	*	*	-	*	1
Butobarbital	-	+	+++	+	-	-	++	-	-	1
Caffeine	+++	-	-	++	-	+	-	+	++	1
Carbamazepine	+++	-	-	+++	-	-	+++	-	-	1
Carbromal	+	-	-	++	-	-	++	-	-	3
Chlorcyclizine	+++	-	-	-	+	+++	-	+	+++	3
Chlordiazepoxide	-	-	-	-	-	++	-	+	++	3
Chloroquine	-	-	-	-	+	+++	-	+	+	2
Chlorphentermine #	-	-	-	-	-	-	-	-	+	4
Chlorpromazine	+++	-	-	++	+	+	-	+	++	1
Chlorpropamide	-	-	++	-	-	-	-	-	-	1
Cholesterol	+++	-	-	+++	-	-	+++	-	-	3
Cocaine	-	-	-	-	+	++	-	+	++	3
Codeine	-	-	-	-	-	++	-	-	++	2
Desipramine	+	-	-	-	+	+++	-	+	+++	3
Dextromoramide	+++	-	-	+++	-	+	-	-	+++	3
Dextropropoxyphene	+++	-	-	+	-	+	-	-	++	1
Diazepam	+++	-	-	+++	-	-	+	+	+++	1,3
Dibenzepin	++	-	-	-	+	+++	-	+	+++	3
Dichloralphenazone	+++	-	-	+	-	+	-	+	+++	3
Diethylpropion #	+	-	-	-	+	+	-	+	+	4
Dihydroergotoxine	*	-	*	*	-	*	*	-	*	Nil
Diphenylhydantoin	-	-	+++	+++	-	-	+++	-	-	1
Diphenhydramine	++	-	-	-	-	++	-	-	+++	3
Doxepin	++	-	-	+	+	++	-	+	+++	3
Ethosuximide #	-	-	++	+	-	-	-	-	-	1
Fenfluramine #	-	-	-	-	-	+	-	-	+	4
Fluphenazine	-	-	-	-	+	+	-	+	++	3
Furosemide	*	+	*	*	-	*	*	-	*	1
Glutethimide	+++	-	-	+++	-	-	+++	-	-	1,3
Imipramine	+++	-	-	+	-	+	-	-	+++	1,3
Iproniazid	-	-	-	-	-	+	-	-	++	3

TABLE 1—Distribution of drugs for the three extraction procedures—Continued.

Drug	HCl/CHCl ₃			Na ₂ CO ₃ /CHCl ₃			Na ₂ CO ₃ /Ether			J
	A	B	C	D	E	F	G	H	I	
Isocarboxazid	++	-	+	+++	-	-	+	-	+	2
Levorphanol	-	-	-	-	-	+++	-	-	+++	3
Medazepam	+++	-	-	+	+	++	-	+	+++	3
Mephobarbital	-	+	+++	++	-	-	+++	-	-	1
Meprobamate	+++	-	-	+++	-	-	+++	-	-	3
Metaraminol	*	-	*	*	-	*	*	-	*	Nil
Methadone	+++	-	-	++	-	+	-	-	++	1
Methamphetamine #	-	-	-	-	-	+	-	-	+	4
Methaqualone	+++	-	-	+++	-	-	+	+	++	1,2
Methoin	+++	-	-	+++	-	-	+++	-	-	1,2,3
Methylphenidate	++	-	-	-	-	+++	-	-	+++	4,3
Methyprylon	+++	-	-	++	-	-	+++	-	+	3
Morphine	-	-	-	-	-	-	-	-	-	Nil
Nicotine #	-	-	-	-	+	-	-	+	+	4
Nikethamide	-	-	-	-	+	++	-	+	++	3
Nitrazepam	+	-	-	+	+	++	-	+	+++	3
Nortriptyline	+++	-	-	-	-	++	-	+	+++	1,3
Orphenadrine	+++	-	-	-	-	+	-	-	+++	3
Oxazepam	+	-	-	++	+	+	++	+	+	2
Oxprenolol	-	-	-	-	-	+++	-	-	+++	3
Oxyphenbutazone	*	+	*	*	-	*	*	-	*	1
Oxyphencyclimine	+++	-	-	+++	-	-	++	-	-	2
Pentazocine	++	-	-	-	-	+++	-	-	+++	3
Pentobarbital	-	+	+++	++	-	-	+++	-	-	1
Pethidine	++	-	-	-	-	++	-	-	+++	4,3
Phenacetin	++	-	-	+++	-	-	+++	-	-	3
Phenelzine	-	-	-	-	-	-	-	-	-	4
Pheniramine	-	-	-	-	+	+++	-	+	+++	4,3
Phenmetrazine	-	-	-	-	-	-	-	-	++	4,3
Phenobarbital	-	+	+++	-	-	-	-	-	-	1
Phentermine	-	-	-	-	-	+	-	-	+	4
Phenylbutazone	-	+	+++	++	-	-	++	-	-	1
Primidone	+	-	-	++	-	+	+	-	+	2
Promazine	+++	-	-	+	+	+	-	+	++	1
Protriptyline	+	-	-	-	+	++	-	+	+++	3
Quinidine	-	-	-	-	-	++	-	+	+++	3
Quinine	-	-	-	-	+	++	-	+	+++	3
Salicylamide	-	+	+++	-	-	-	+	-	-	1
Salicylic acid	*	+	*	*	-	*	*	-	*	1
Scopolamine	-	-	-	-	-	++	-	-	+++	3
Secobarbital	-	+	+++	++	-	-	+++	-	-	1
Strychnine	++	-	-	-	+	+++	-	+	+++	3
Theophylline	-	+	+	-	-	-	-	-	-	1
Thioridazine	+++	-	-	+++	-	-	-	+	++	2
Tranlycypromine #	-	-	-	-	-	-	-	-	-	4
Trifluoperazine	++	-	-	-	+	+++	-	+	+++	2
Trimipramine	+++	-	-	++	+	+	-	+	+++	3
Yohimbine	+++	-	-	+++	-	-	+++	-	+	3

A = Initial chloroform extract after back extraction with NaOH.
 B = UV identification of the NaOH fraction.
 C = Chloroform extract of acidified NaOH fraction.
 D = Initial chloroform extract after back extraction with H₂SO₄.
 E = UV identification of the H₂SO₄ fraction.
 F = Chloroform extract of H₂SO₄ fraction made basic.
 G = Initial ether extract after back extraction with H₂SO₄.
 H = UV identification of the H₂SO₄ fraction.
 I = Ether extract of H₂SO₄ fraction made basic.
 J = The most suitable method for maximum recoveries.
 1 = HCl/chloroform extraction procedure.
 2 = Na₂CO₃/chloroform extraction procedure.
 3 = Na₂CO₃/ether extraction procedure.
 4 = Rapid extraction technique.
 - = Less than 10% recovery.
 + = 10 to 50% recovery.
 ++ = 50 to 75% recovery.
 +++ = Greater than 75% recovery.
 # = Possibly volatile.
 * = Cannot be detected by GLC using an OV 17 column.
 + = On columns B, E, and H, refer to an identifiable UV pattern of the drug at the concentration used in the extractions (50 100 µg).

TABLE 2—Gas liquid chromatography (GLC) and ultraviolet spectroscopy (UV) properties.

Drug	GLC	Temperature °C	R _{RT}	UV
Amphetamine	+	100	1.00	—
Phentermine	+	100	1.13	—
Methamphetamine	+	100	1.23	—
Fenfluramine	+	100	1.32	—
Tranlycypromine	+	100	2.00	—
Nicotine	+	100	4.00	—
Chlorphentermine	+	100	4.09	—
Ethosuximide	+	125	0.74	—
Nicotine	+	125	1.00	—
Phenmetrazine	+	125	2.03	—
Diethylpropion	+	125	2.04	+
Salicylamide	+	125	3.31	+
Iproniazid	+	125	5.38	—
Nikethamide	+	150	0.38	+
Methyprylon	+	150	0.40	—
Iproniazid	+	150	0.46	—
Butobarbital	+	150	0.68	+
Pethidine	+	150	0.81	—
Amobarbital	+	150	0.81	+
Methylphenidate	+	150	0.88	—
Phenacetin	+	150	1.00	—
Alprenolol	+	150	1.13	—
Carbromal	+	175	0.20	—
Pentobarbital	+	175	0.52	+
Alprenolol	+	175	0.63	—
Secobarbital	+	175	0.63	+
Oxyphencylimine	+	175	0.64	—
Acetaminophen	+	175	0.65	—
Pheniramine	+	175	0.67	+
Chlorpropamide	+	175	0.77	—
Glutethimide	+	175	1.00	—
Methoin	+	175	1.00	—
Hexobarbital	+	175	1.02	+
Oxprenolol	+	175	1.03	—
Orphenadrine	+	175	1.07	—
Caffeine	+	175	1.18	+
Mephobarbital	+	175	1.23	+
Phenobarbital	+	175	1.90	+
Isocarboxazid	+	200	0.47	—
Phenobarbital	+	200	0.50	+
Phenelzine	+	200	0.57	—
Methadone	+	200	0.62	—
Dextropropoxyphene	+	200	0.71	—
Amitriptyline	+	200	0.79	+
Trimipramine	+	200	0.82	+
Atropine	+	200	0.91	—
Imipramine	+	200	0.91	—
Nortriptyline	+	200	0.93	+
Doxepin	+	200	0.94	+
Levorphanol	+	200	0.97	—
Methaqualone	+	200	1.00	+
Cocaine	+	200	1.00	+
Levorphanol	+	225	0.50	—
Methaqualone	+	225	0.51	+
Phentazocine	+	225	0.53	—
Desipramine	+	225	0.54	+
Protriptyline	+	225	0.59	+
Medazepam	+	225	0.65	+
Promazine	+	225	0.75	+

TABLE 2—*Gas liquid chromatography (GLC) and ultraviolet spectroscopy (UV) properties—Continued.*

Drug	GLC	Temperature, °C	R _{RT}	UV
Scopolamine	+	225	0.79	—
Oxazepam	+	225	0.94	+
Codeine	+	225	1.00	—
Phenylbutazone	+	225	1.01	+
Primidone	+	225	1.02	—
Carbamazepine	+	225	1.12	—
Chlorpromazine	+	225	1.17	+
Codeine	+	250	1.00	—
Diphenylhydantoin	+	250	1.14	—
Morphine	+	250	1.20	—
Dibenzepin	+	250	1.21	+
Diazepam	+	250	1.23	+
Yohimbine	+	250	1.82	—
Quinine	+	250	3.38	+
Cholesterol	+	275	0.87	—
Quinine	+	275	0.87	+
Quinidine	+	275	0.87	+
Nitrazepam	+	275	1.00	+
Dextromoramide	+	275	1.07	—
Fluphenazine	+	275	1.24	+
Chlordiazepoxide	+	275	1.29	+
Strychnine	+	275	2.42	+
Thioridazine	+	290	0.73	+
Strychnine	+	290	1.00	+
Aspirin	—	—	—	+
Dihydroergotoxine	—	—	—	—
Furosemide	—	—	—	+
Metaraminol	—	—	—	—
Oxyphenbutazone	—	—	—	+
Salicylic Acid	—	—	—	+

TABLE 3—*Recovery of drugs using the rapid extraction procedure.*

Amphetamine	+++	Nikethimide	+++
Chlorphentermine	+++	Pethidine	+++
Diethypropion	+++	Phenelzine	+++
Fenfluramine	+++	Pheniramine	+++
Methylamphetamine	+++	Phenmetrazine	+++
Methylphenidate	+++	Phentermine	+++
Nicotine	+++	Tranlycypromine	+++

Results and Discussion

The work outlined in this paper is primarily a study of the distribution of drugs between aqueous and organic phases. Therefore, instead of the more common practice of using two or three solvent extractions only one was used. When urgency is an important factor, such as in cases involving a possible overdose, the slightly lower recoveries from a single extraction would be compensated by the time saved in multiple extractions and solvent evaporation.

The use of excess sodium carbonate in the initial steps of the extractions (Figs. 2 and 3) was found to be a reliable method by which a constant and easily reproducible pH of

approximately 10 could be obtained. Ether and chloroform appear to offer advantages over most of the other solvents in that they are relatively polar, volatile, and largely immiscible with water.

We have studied the distribution of 86 drugs by three solvent systems:

1. HCl/chloroform, back extracted with 0.45M NaOH (Fig. 1),
2. Na₂CO₃/chloroform, back extracted with 1.8M H₂SO₄ (Fig. 2), and
3. Na₂CO₃/ether, back extracted with 1.8M H₂SO₄ (Fig. 3).

The results from this investigation have enabled each system to be evaluated according to the efficiency of the drug recovery from either aqueous or organic solutions. The extraction procedure outlined in Fig. 1 (HCl/chloroform) has proved satisfactory for the extraction of acidic drugs. For most basic drugs the Na₂CO₃/ether procedure (Fig. 2) proved more efficient than the Na₂CO₃/chloroform procedure (Fig. 3). Equally good recoveries of many bases, however, could be obtained when these were extracted as their chloroform-soluble hydrochlorides. (Fig. 1). Although chloroform-soluble hydrochlorides have been discussed by previous authors [5], few methods rely on this technique as the primary means of extraction [7]. Our preliminary observations dealing with clinical samples indicate that this method may be useful when dealing with certain basic drugs in biological fluids. The behavior of organic solutions of some of the drugs to sulfuric acid was interesting. While Tompsett [5] has reported that methaqualone is extracted from acidic (HCl), neutral, or alkaline (NaOH) solutions into chloroform, we have observed that the sulfate of methaqualone is soluble in chloroform but almost insoluble in ether. Similarly we have found that the sulfates of diazepam, dextromoramide, and thioridazine were very soluble in chloroform but were insoluble in ether. For these drugs the choice of solvent (either chloroform or ether) and acids (HCl or H₂SO₄) can be varied, enabling the drug to be recovered from either the aqueous or the organic phase.

It is possible that the apparent low recoveries of some drugs (Table 1) could be attributed to their volatility rather than their extraction properties. In this case another extraction procedure based on the method of Ramsey and Campbell [20], in which no evaporation is necessary, proved more successful. The results are shown in Table 3.

Although barbiturates are classified as acidic drugs, those which have been examined, with the exception of phenobarbital, can be extracted from sodium carbonate solution at a pH of approximately 10. It was observed that only the medium- and fast-acting barbiturates were extracted into ether or chloroform at this pH.

Yohimbine and oxyphencyclimine could not be extracted into acid from either ether or chloroform. Although these drugs were expected to have basic properties, they behaved as neutral substances and it would seem desirable to consider them in this category in the future.

Of the drugs we examined, neither morphine, metamamol, nor dihydroergotoxine could be detected in any fraction either because of extraction difficulties or because of the lack of response on the GLC system used.

The classical methods of extracting drugs from biological fluids and tissues usually incorporate preliminary protein precipitation (tungstate or ammonium sulfate techniques) prior to extraction with organic solvents. Jackson has noted that direct extraction methods have been used in certain cases but are not recommended as a general procedure [2,4]. In our opinion the application of direct extraction procedures warrants further investigation. We have applied two direct extraction procedures (Figs. 1 and 3) to clinical and postmortem specimens and the preliminary results, in comparison with the protein precipitation techniques, were very encouraging even when the drug concentration was at a therapeutic level.

Acid hydrolysis, prior to extraction, has lead to significantly greater recoveries of

many of the basic drugs, although it is not suitable for some heat and acid labile drugs; thus, this procedure should be omitted in preliminary drug identification.

The procedures outlined in this paper provide efficient and rapid extraction techniques which may be useful in clinical and forensic drug screening.

Summary

The results of four extraction systems for 86 drugs are reported. These systems were investigated with the view to obtaining a rapid, reliable, and efficient extraction technique in clinical and forensic toxicology.

Acknowledgment

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