United States Patent [19]

Campen, Jr.

[11] **3,860,393**

[45] **Jan. 14, 1975**

[54] **AUTOMATED SYSTEM FOR IDENTIFYING TRACES OF ORGANIC CHEMICAL COMPOUNDS IN AQUEOUS SOLUTIONS**

[75] Inventor: **Charles F. Campen, Jr.**, Arcadia, Calif.

[73] Assignee: **California Institute of Technology**, Pasadena, Calif.

[22] Filed: **Feb. 22, 1972**

[21] Appl. No.: **227,977**

[52] **U.S. Cl.** ..... **23/230 R**, 23/230 M, 23/232 C, 23/253 R, 23/254 R, 23/255 R, 73/23.1, 235/151.13

[51] **Int. Cl.** **G01n 33/00**, G01n 31/08

[58] **Field of Search** .. 23/230 R, 230 B, 253, 232 C, 23/254; 73/23.1; 235/151.13

[56] **References Cited**

UNITED STATES PATENTS

3,403,978 10/1968 Favre ..... 23/232 X

OTHER PUBLICATIONS

Vestergaard, "Automatic Multiple-Column Chromatography with Computer Calculation of Data," Technicon Symposia Automation in Analytical Chemistry, 1965, Vol. 1, pp. 615–619.

Primary Examiner—Morris O. Wolk
Assistant Examiner—R. E. Serwin
Attorney, Agent, or Firm—Lindenberg, Freilich, Wasserman, Rosen & Fernandez

[57] **ABSTRACT**

An automated system wherein, under computer control, traces of organic chemical compounds in aqueous solutions are separated into a plurality of families of compounds. Several of the families are separated as separate extracts, dissolved in organic solvents. The volume of solvent, containing each extract, is greatly reduced in a separate pre-GC unit, to increase the ratio of extract to solvent volume. The output of each pre-GC unit is supplied to a separate gas chromatograph (GC). The elution times of the peaks, exiting the various GC's, are used in the selection of peaks of interest by the computer based on the comparison of the extract types and the elution times with elution times of known compounds. Peaks of interest from any of the several GC's are supplied one at a time to an absorption cell of a single IR spectrometer through a peak storage unit, which is designed to hold each peak of interest in one of its holding columns until the spectrometer is ready to receive the peak. Compounds are identified by the computer based on their extract types, elution times and the spectral data from the spectrometer.

6 Claims, 6 Drawing Figures

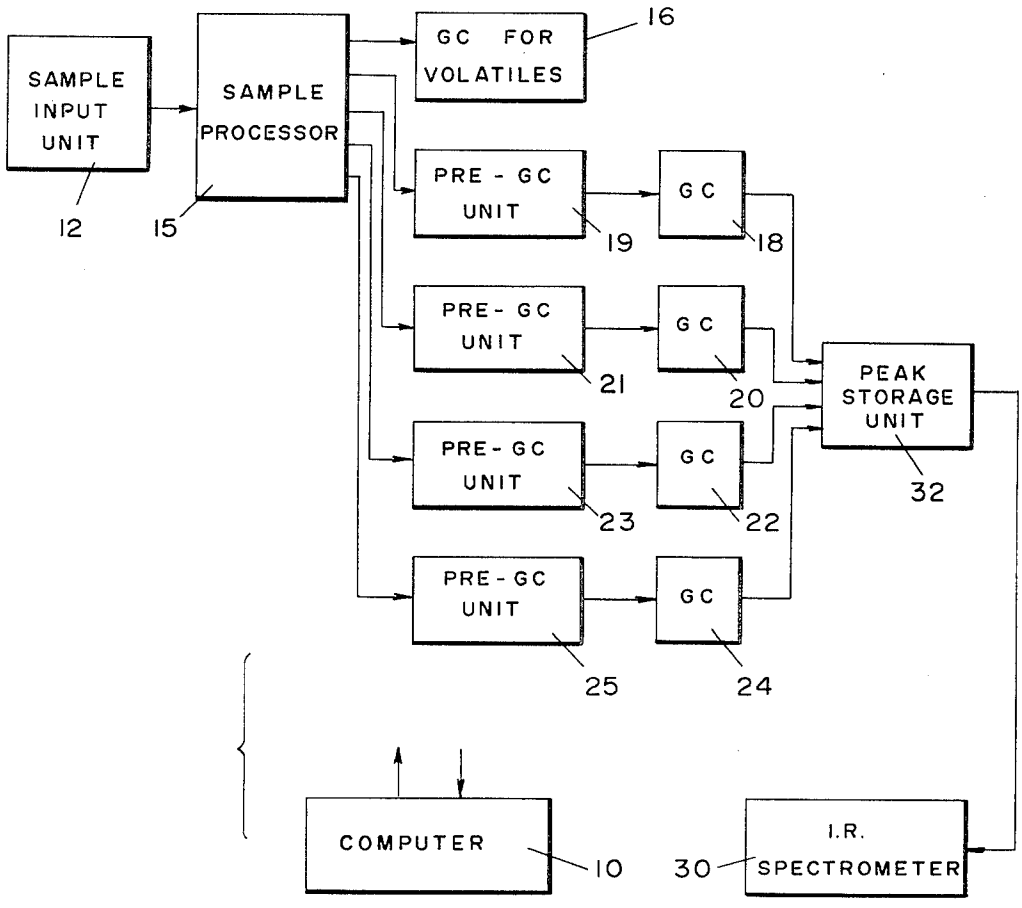


FIG. 2a

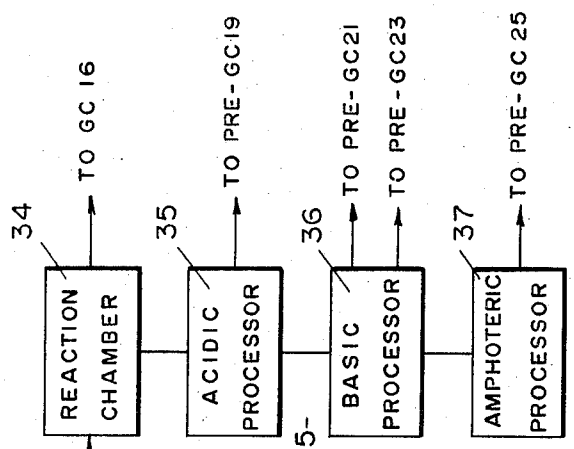
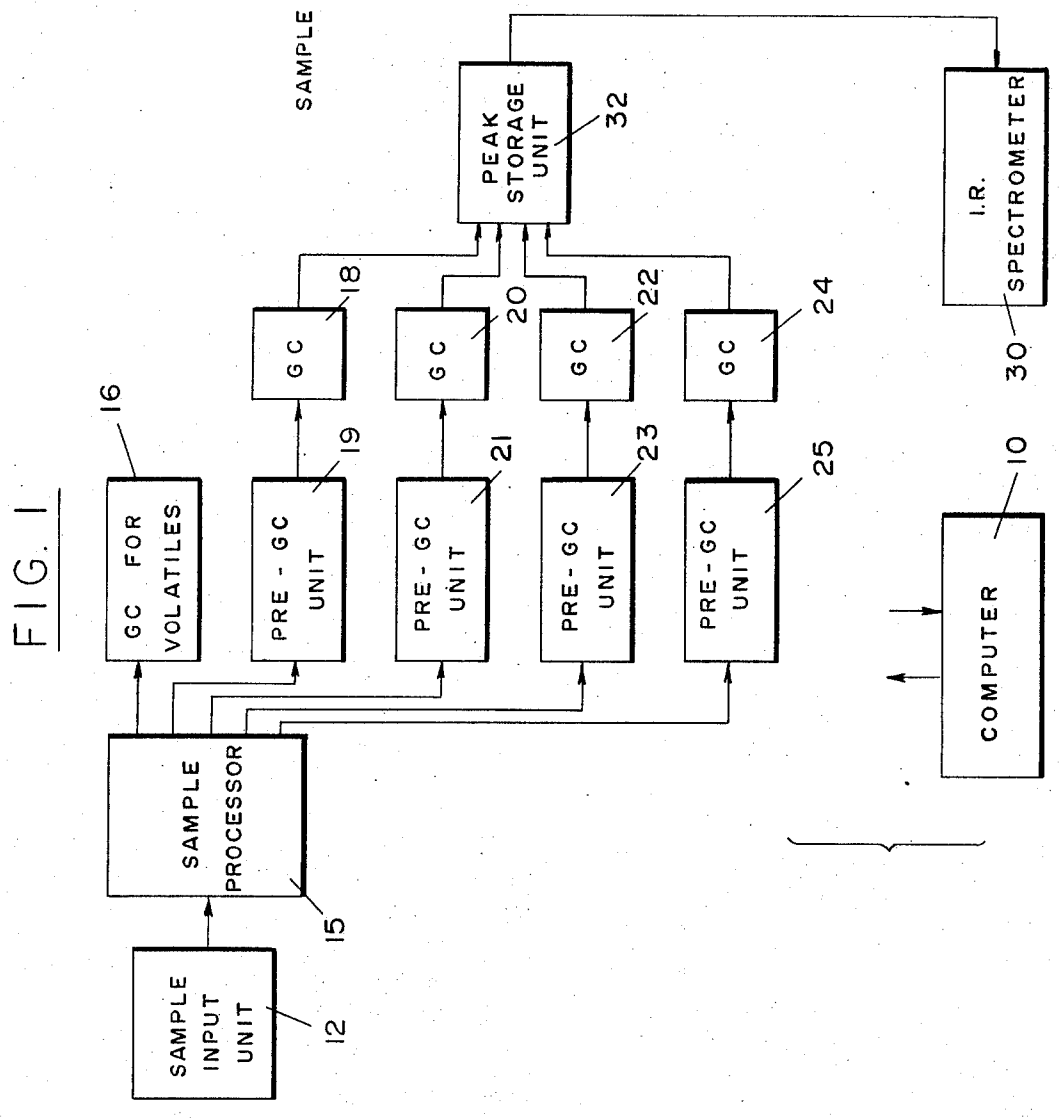

34
TO GC 16
35
TO PRE-GC19
36
TO PRE-GC21
TO PRE-GC23
37
TO PRE-GC 25
REACTION CHAMBER
ACIDIC PROCESSOR
BASIC PROCESSOR
AMPHOTERIC PROCESSOR
-15-
SAMPLE

FIG. 1


PEAK STORAGE UNIT
32
I.R. SPECTROMETER
30
GC
18
20
22
24
16
GC FOR VOLATILES
PRE-GC UNIT
19
21
23
25
COMPUTER
10
SAMPLE PROCESSOR
15
SAMPLE INPUT UNIT
12

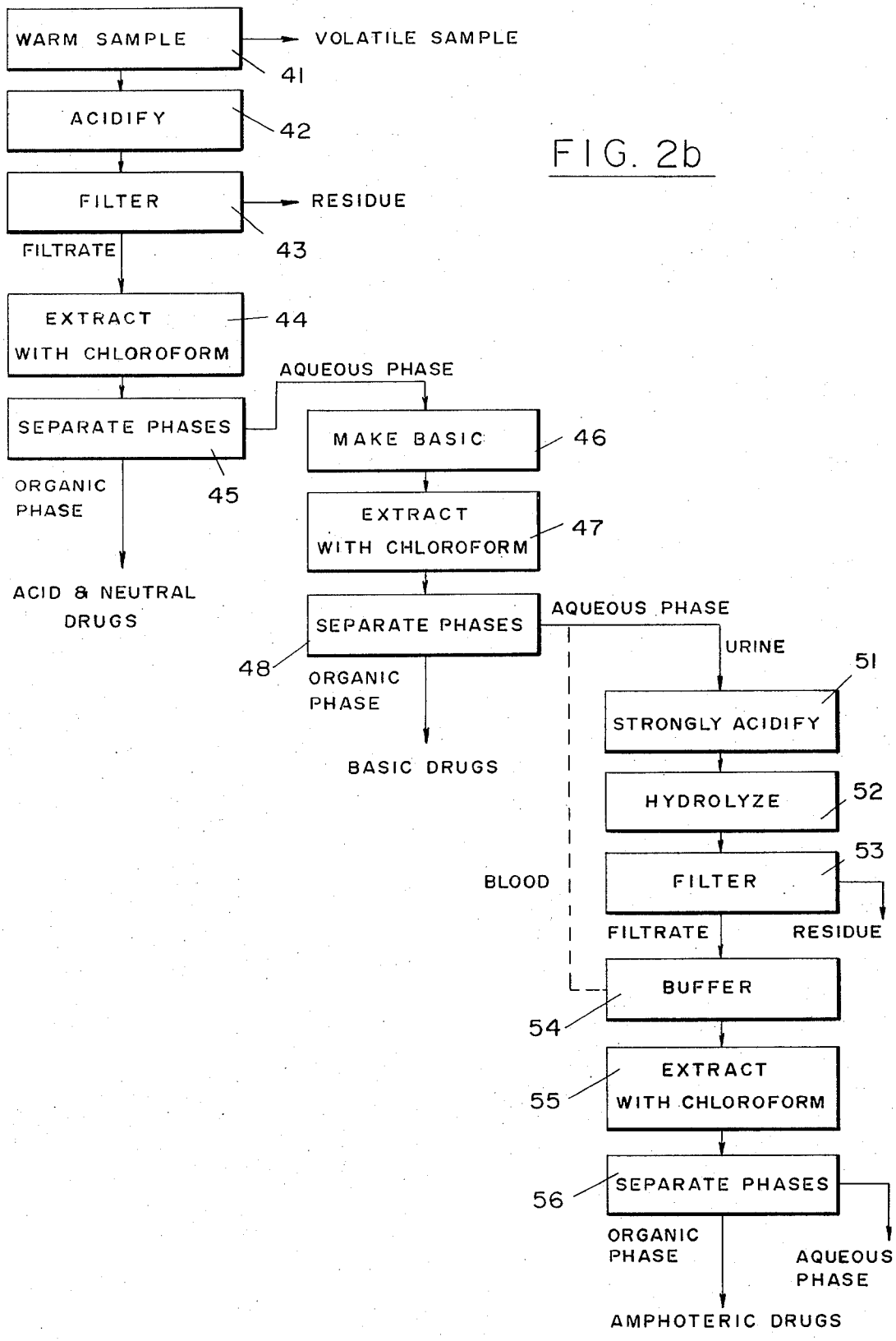

WARM SAMPLE
VOLATILE SAMPLE
41
ACIDIFY
42
FILTER
RESIDUE
43
FILTRATE
EXTRACT WITH CHLOROFORM
44
AQUEOUS PHASE
SEPARATE PHASES
45
MAKE BASIC
46
ORGANIC PHASE
EXTRACT WITH CHLOROFORM
47
ACID & NEUTRAL DRUGS
SEPARATE PHASES
AQUEOUS PHASE
48
URINE
51
ORGANIC PHASE
STRONGLY ACIDIFY
BASIC DRUGS
HYDROLYZE
52
53
BLOOD
FILTER
FILTRATE
RESIDUE
BUFFER
54
EXTRACT WITH CHLOROFORM
55
56
SEPARATE PHASES
ORGANIC PHASE
AQUEOUS PHASE
AMPHOTERIC DRUGS

FIG. 2b

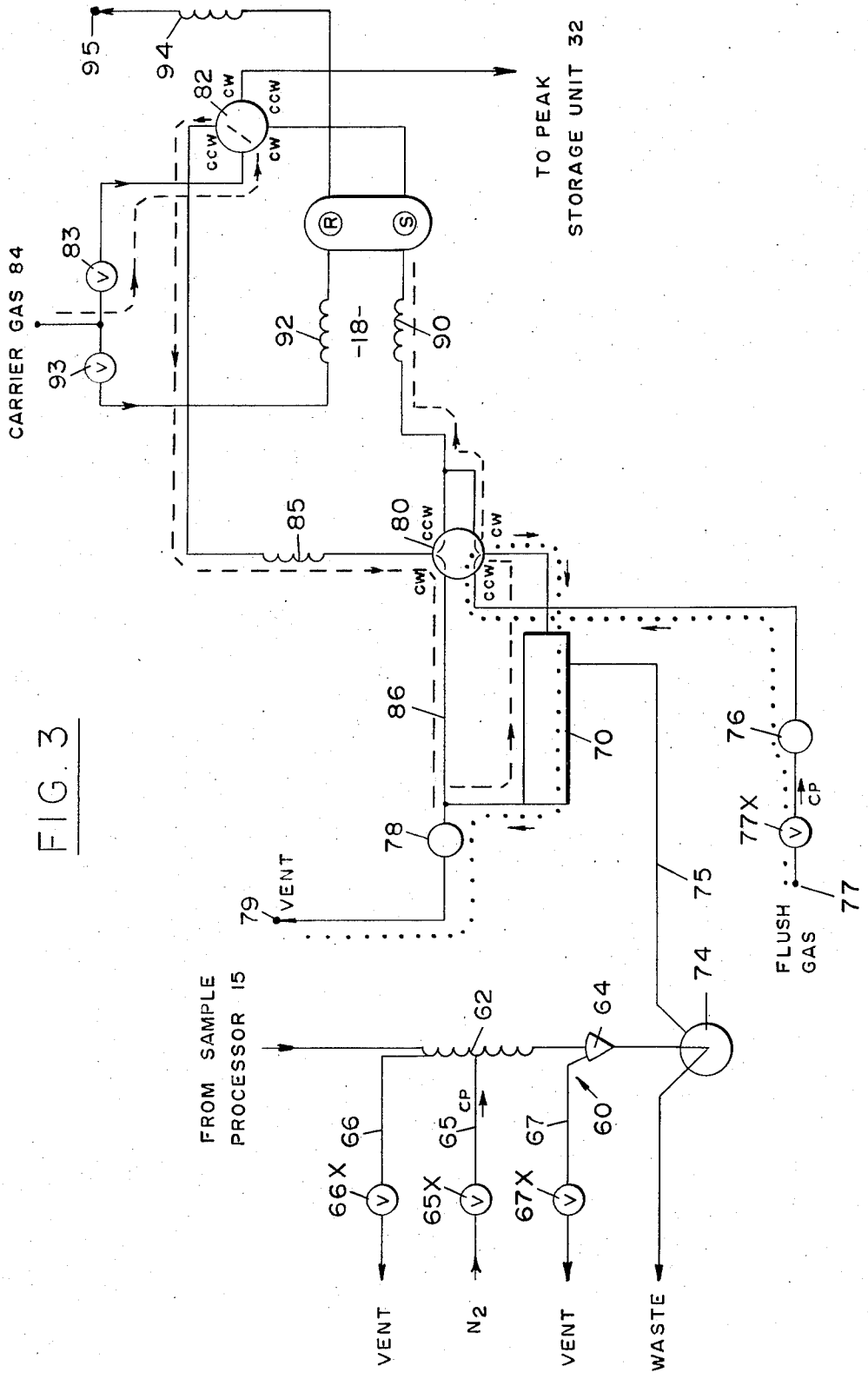

95
94
82
CW
CCW
CCW
CW
TO PEAK
STORAGE UNIT 32
CARRIER GAS 84
83
93
R
S
92
-18-
90
85
80
CCW
CW
CW
CCW
86
70
76
CP
77X
78
VENT
79
75
FLUSH
GAS
77
FROM SAMPLE
PROCESSOR 15
62
64
74
66
65
CP
67
60
66X
65X
67X
VENT
N2
VENT
WASTE

FIG. 3

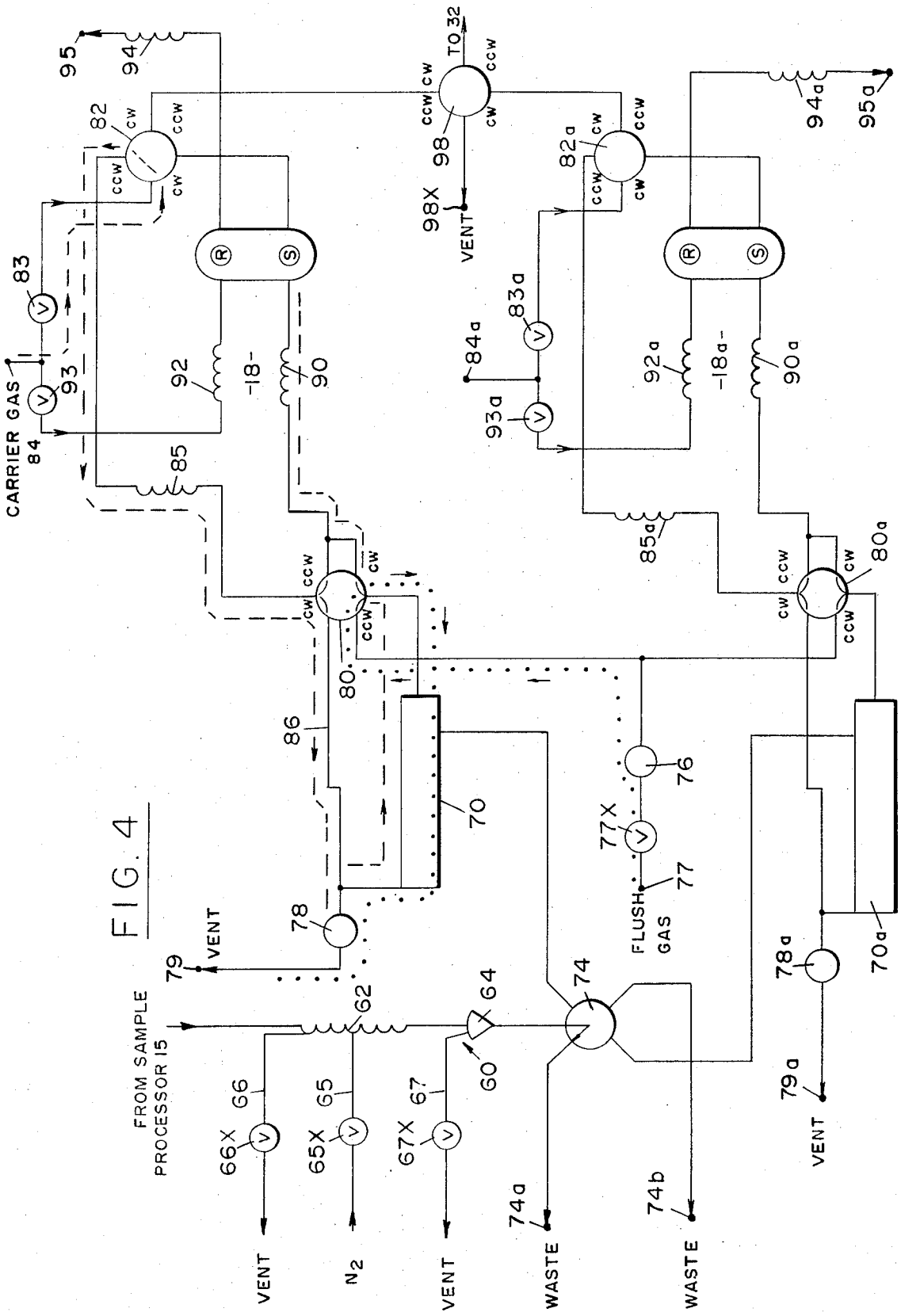
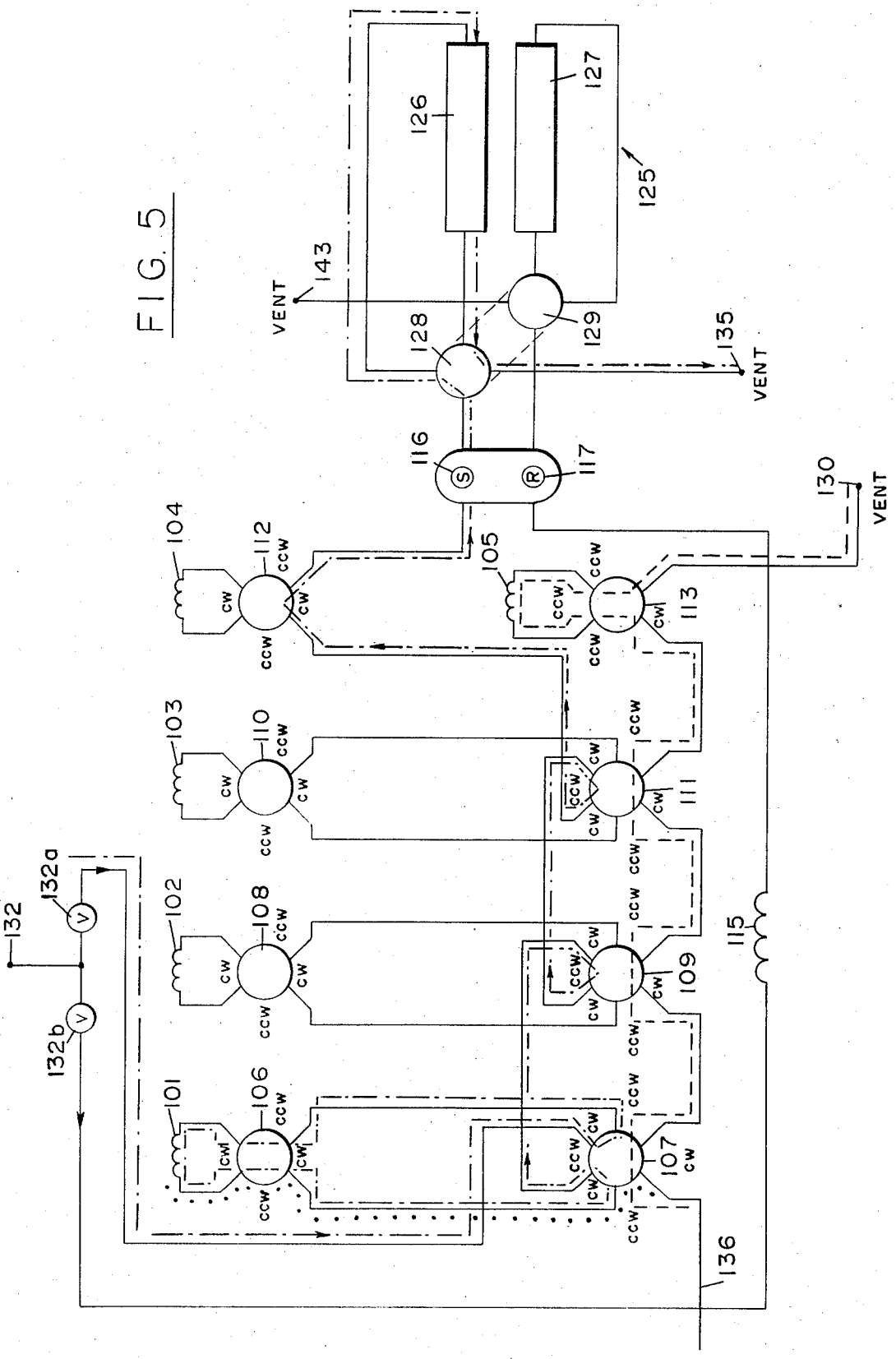

95
94
82
cw
ccw
ccw
cw
83
CARRIER GAS
84
93
92
-18-
90
85
R
S
TO 32
ccw
cw
98
98X
VENT
82a
83a
84a
93a
92a
-18a-
90a
85a
94a
95a
80
80a
86
70
70a
76
77X
77
FLUSH GAS
78
78a
79
79a
VENT
62
64
60
74
74a
74b
WASTE
WASTE
FROM SAMPLE PROCESSOR 15
66
66X
65
65X
67
67X
VENT
N2
VENT

FIG. 4

FIG. 5


126
127
125
143
VENT
128
129
135
VENT
116
S
R
117
130
VENT
104
112
105
113
103
110
111
102
108
109
115
132a
132
132b
101
106
107
136
cw
ccw

AUTOMATED SYSTEM FOR IDENTIFYING TRACES OF ORGANIC CHEMICAL COMPOUNDS IN AQUEOUS SOLUTIONS

ORIGIN OF THE INVENTION

The invention described herein was made in the performance of work under a NASA contract and is subject to the provisions of Section 305 of the National Aeronautics and Space Act of 1958, Public Law 85–568 (72 Stat. 435; 42 USC 2457).

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is generally directed to an automated chemical analysis system, and, more particularly, to an automated system for identifying vestigal organic chemical compounds in aqueous solutions. 2. Description of the Prior Art

Methods traditionally utilized for determination of the presence and amount of very small quantities (on the order of a few parts per million by weight) of specific organic chemical compounds in aqueous solutions in the presence of large amounts of numerous other compounds generally involve manual procedures for separation of the desired compounds from the parent solution with subsequent manual application of conventional analytical techniques. For example, the procedures which have been in use for years and are still generally in use in clinical and forensic toxicological laboratories to determine the presence of small proportions of drugs or organic poisons in blood or urine samples and to identify them are described briefly. First, the sample is placed in a suitable container of volume greater than three to 10 times the sample volume and is acidified by manual addition of a suitable reagent. Then, three to 10 times volume of a suitable solvent which is immiscible with water, such as chloroform, is manually added to the container. The container is stoppered and agitated either manually or by being placed in a mechanism for this purpose.

After a suitable period of agitation, the mixture of sample and solvent, if an emulsion should form, is passed into centrifuge tubes and centrifuged to break the emulsion. If no emulsion is formed, the centrifugation is omitted. The solvent and sample mixture is then poured into a chemist's separatory funnel and the two immiscible phases are manually separated. The solvent which now contains the class of organic compounds extractable from aqueous solutions in acidic condition is filtered to remove any residual solid matter and transferred to a container suitable for evaporation of the solvent.

This container is placed in a holder over a source of heat and under a stream of gas, such as nitrogen, and the solvent allowed to evaporate, leaving the material which was extracted from the sample deposited on the walls of the evaporation container. This material is manually redissolved in a small quantity (on the border of a milliliter) of a suitable solvent. A suitable aliquot of this solution is withdrawn by means of a syringe or similar implement. This aliquot is then injected into a gas-liquid chromatograph whose operating characteristics have been selected and adjusted to match the nature of the class of organic compounds extractable in this step.

Conventional chromatographic instruments currently in use for analysis purposes can accept only limited amounts of solvents with the injection of the extract, typically 1 to 10 microliters. Hence, only a small portion of the original extract can be analyzed. The aliquot, upon injection is volatilized and is forced by flow of carrier gas to transit the gas chromatograph plumbing. The solvent and the various types of organic compounds of this class transit the chromatograph at rates depending on their interaction with the stationary phase of the chromatograph. The solvent vapors generally emerge first followed at intervals by the vapors of the different types of extracts. A detector at the exit of the gas chromatograph provides an indication that material other than carrier gas is exiting. For a given set of gas chromatograph parameters the time elapsing between injection and exit (elution time) is a characteristic of specific organic compounds. That is, only a limited number of types would exit at any specified time after injection.

If only presumptive determination of the nature and amounts of the extract is required, the elution times and detector response may be recorded for comparison with a reference file of elution times for various organic compounds. However, if identification is required, it is necessary to collect the fractions of the original aliquot as they exit so that they may be subjected to further analysis. For this purpose the gas chromatograph exit is filtered with a valve for diverting the vapors to a collection vessel which is cooled to a temperature sufficient to condense the extract fraction but not the carrier gas. As each fraction exits the gas chromatograph, the valve is manually activated to divert the fraction to the collection vessel. A separate collection vessel is used for each fraction. The instrument generally used for analysis and identification of the fraction is an infrared (IR) absorption spectrophotometer. Mass spectrometers, though available and capable of equivalent analysis are, because of their complexity and high cost, not available to the majority of laboratories.

To prepare the fraction for examination in the IR spectrophotometer, the fraction is redissolved in an appropriate solent, mixed with a small amount of potassium bromide powder, the solvent evaporated and the vestigal fraction and potassium bromide placed in a die where it is made into a solid pellet, which can be manually inserted in the sample holder of the infrared spectrometer. The potassium bromide, being transparent over the range of wavelengths of interest, the chart recordings, made by operating the spectrometer, represent the absorption spectrum of the fraction. This recording may be manually compared with a reference file of similar recordings to ascertain the identify of the material. Once this is accomplished the calibration of the gas chromatograph detector for that material may be utilized for calculation of the amount which exited the chromatograph.

The aqueous residuum of the initial extraction is reextracted at a strongly basic pH and the aforementioned process repeated. The residuum of this may be again reextracted under different conditions to isolate additional classes of organic chemicals and the analysis process is repeated. Three such extraction conditions are generally sufficient to isolate most of the materials of interest to clinical and forensic toxicologists. Many of these operations are done in parallel in order to reduce the time and manpower required. However, because of the large number of manual operations and the existence of only semi-automatic apparatus, the cost

and the time required for such analysis are high. Furthermore, due to inevitable human error the analysis is always subject to uncertainty, particularly with increased work load.

The number of samples and the number of drugs requiring identification is constantly on the increase, thereby increasing the work load of the laboratories as well as the total identification cost. This is particularly the case in forensic toxicology laboratories, which, due to the present wide spread use of drugs, are called upon to analyze large volumes of specimens for the presence of narcotics, dangerous drugs and alcohol, all of which are referred to herein as drugs. Although various techniques have been suggested to improve the state of the art and achieve increased efficiency and reliability as well as high flexibility, none of the prior art systems either in use or those described in the literature has attained the following goals:

1. reduction in turnaround time for drug analysis,
2. reduction of the cost of drug analysis,
3. increased reliability of the analysis and increased confidence in the resulting data, and
4. high degree of flexibility to accommodate identification of many types of drugs.

With the advent of an increased awareness of the effects of pollution on the environment there is an urgent need for a system of and method for analyzing large numbers of samples for the presence of traces of organic chemical compounds or constituents, such as pesticides and manufacturing by-products. Current practices in these areas generally involve manual analysis for one compound at a time. The ability to simultaneously determine the presence of a large number of traces of organic compounds would provide a significant advance in the knowledge of the effects of pollution. Furthermore, any system which can automatically identify organic chemical compounds speedily and at a relatively low cost and high degree of flexibility would permit studies not possible heretofore except in a very limited sense. For example, such a system may be used to determine the vitamin budget of children. The vitamin needs of each individual vary and those of children vary widely. Routine analysis of the vitamin usage in a clinical environment would be of immense value. Such routine analysis could only be performed if a system were available which is capable of speedily and relatively cheaply but yet accurately analyzing and identifying organic chemical compounds.

OBJECTS AND SUMMARY OF THE INVENTION

It is a primary object of the present invention to provide a new automated system for identifying organic chemical compounds.

Another object of the present invention is to provide a new automated system which is capable of analyzing and identifying traces of organic chemical compounds of different types present in aqueous solutions at reduced time and cost as compared with the state of the art.

A further object of the present invention is to provide a new automated system capable of simultaneous analysis of an aqueous solution for many traces of organic chemical compounds of different types with a high degree of reliability.

Yet another object of the present invention is to provide a novel system for identifying traces of organic chemical compounds automatically and reliably based on known properties of a repertoire of compounds, at reduced turnaround time.

Yet a further object of the invention is to provide a new method of analyzing drugs of different classes simultaneously at reduced analysis cost and turnaround time.

These and other objects of the invention are achieved by providing a computer-controlled system in which a sample containing trace quantities of organic chemical compounds is automatically processed in a series of automatic steps in a sample processor to provide a plurality of solvents each containing organic chemical compounds of a different family. As used herein the term family refers to a group of organic chemical compounds based on the manner in which they are separated from other compounds in the processor.

The organic chemical compounds which can be identified by the present invention include those compounds which are extractable by means of organic solvents into families and which are separable chromatographically. The system is directed to identify traces of such compounds present in aqueous solutions in parts per million. In order to simplify the following description, the traces of such organic chemical compounds will be referred to as drugs. The term drug should be regarded broadly rather than in the conventional sense in which it is generally employed.

Briefly in the processor the drugs are separated by the sequence of steps into the following five families:

1. volatile drugs
2. acidic and some neutral drugs
3. basic relatively volatile drugs
4. basic relatively non-volatile drugs, and
5. amphoteric drugs.

For each family the system includes a separate gas chromatograph (GC). The family of volatile drugs are supplied directly from the processor to its GC, Each of the other four families is supplied to its GC as an extract, dissolved in its appropriate solvent, through a novel pre-GC unit. As each solvent-solute is produced it is transferred to the pre-GC unit wherein the solvent volume is reduced substantially to an amount compatible with the GC capability to handle the remanant unit without substantial extract loss. Thus the ratio of extract to solvent which is supplied to the GC is increased by a very large factor, thereby greatly increasing the system's sensitivity. As is appreciated by those familiar with the art, a GC separates the constituents of an extract by causing each to exit the GC at different times. The time elapsed from injection to exit is herein called elution time. The elution times provide presumptive determination of the nature of the constituents.

The exit of a constituent of an extract from the GC is monitored with a detector which provides an electrical signal proportional to the concentration of the constituent in the portion of the GC carrier gas stream passing the detector in any instant. This electrical signal is generally recorded on a strip chart recorder, providing a record of concentration versus time. The integral of the detector electrical signal which is represented by the area under the curve recording concentration versus time in indicative of the quantities of the various constituents. Thereafter when reference is made to the transfer of a peak, it is intended to refer to the transfer of a quantity of the constituent as represented by the area under its peak.

The electrical outputs of each of the detectors for each of the GC's, i.e., the elution times are sent to the computer wherein properties including elution times of many drugs in a repertoire of drugs, are stored. The computer decides whether the elution times received from the various GC's are of interest, namely relate to drugs to be identified. If the elution time of any of the peaks received from the GC's which analyze the extracts of families 2 – 5 are of interest the peak is transferred to an absorption cell of an IR spectrometer for spectral analysis. The spectral data, elution time of any peak, and the type of extract from which it was derived are used in the computer for final drug identification. If the elution time provided by any of the GC's which analyze the drug families 2 – 5 do not match any in the repertoire, the peak is normally vented out rather than being supplied to the spectrometer. The information as to what peaks were vented is recorded for the operator's use. At the operator's discretion the computer can be instructed to transfer any specific peak to the IR spectrometer.

In the present invention all of the GC's operate in parallel each analyzing the drugs of a different group. Of the four GC's which analyze families 2 – 5 and whose peaks may be supplied to the spectrometer, the rate at which these GC's may produce peaks is greater than the scan rate of the spectrometer. That is the time between successive potential peaks of interest, e.g., 10 seconds, is less than the scan time, e.g. 1.5 minutes, of the spectrometer. In order to insure that each peak of interest is spectrally analyzed, a separate spectrometer could be associated with each GC, for a total of four spectrometers. Such an arrangement would greatly increase the overall system cost since each spectrometer is very expensive. In accordance with the present invention, a novel peak storage unit is incorporated between the outputs of the GC's and the absorption cell of the spectrometer. The storage unit enables all the peaks of interest to be analyzed by a single spectrometer thereby greatly reducing system cost.

This system will be utilized to generate its reference files. This will be accomplished by placing samples containing groups of known drugs in the sample processor and instructing the computer to store all the measured data and associate that with the appropriate drug names as given it by the operator.

The novel features of the invention are set forth with particularity in the appended claims. The invention will best be understood from the following description when read in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a single block diagram of the present invention;

FIGS. **2***a* and **2***b* are diagrams useful in explaining the sample processor, shown in FIG. **1**;

FIGS. **3** and **4** are schematic diagrams of two embodiments of a novel pre-GC unit; and

FIG. **5** is a schematic diagram of a novel peak storage unit.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Attention is first directed to FIG. **1** which is a simplified block diagram of the present invention. The drug identification system of the present invention is fully automatic and is under the control of computer **10** which controls the sub-systems to perform the various steps to be described hereafter. The computer receives signals from some of the subsystems and identifies drugs in samples supplied to the system, based on previously stored data pertaining to all the drugs in the repertoire of drugs to be identified. The computer in addition to performing the control and decision making functions also serves as the data output unit of the system.

The input sample is supplied from a sample input unit **12** to a sample processor **15** which will be described later in connection with FIGS. **2***a* and **2***b*. Briefly, the function of processor **15** is to extract the various drugs from the sample and divide them into the following five families: (1) volatile drugs, (2) acidic and some neutral drugs, (3) basic relatively volatile drugs, (4) basic relatively non-volatile drugs, and (5) amphoteric drugs. The latter may be referred to as the family of neutral drugs. The family of volatile drugs is separated from the sample by heating it in the processor and transferring a head-space sample to a GC **16.** The elution times from GC **16** are computed by the computer for comparison with elution times of known volatile drugs, stored in the computer for identification purposes.

Each of the other families of drugs is separated in the processor **15** in the form of an extract dissolved in its appropriate solent. For explanatory purposes, it is assumed that the solvent carrying the extract of the acidic and some of the neutral drugs is supplied to GC **18** through a pre-GC unit **19,** the solvent containing the basic relatively volatile drugs is supplied to GC **20** through pre-GC **21,** the solvent containing the extract of the basic relatively non-volatile drugs is supplied to GC **22** through a pre-GC unit **23,** and the solvent containing the extract of the neutral drugs is supplied to GC **24** through pre-GC unit **25.** The four GC's **18, 20, 22** and **24** are identical to one another and, similarly, the four pre-GC units **19, 21, 23,** and **25** are also identical to one another.

The function of each pre-GC unit, one embodiment of which will be explained hereafter in detail, is to greatly reduce the volume of the solvent containing the extract, without any substantial loss of extract. Consequently, the ratio of extract to solvent which is supplied to the GC is greatly increased thereby, significantly increasing the system's sensitivity. This feature is unlike any of the prior art systems or techniques. In the prior art, in the extraction, the extract is finally dissolved in a solvent of a few hundred microliters (μl). Since a typical GC is capable of receiving only several microliters (μl), the reduction in volume is achieved by removing by means of a syringe or like device several microliters from the few hundred microliters of solvent containing the extract. As a result, the few microliters which are supplied to the GC do not contain all of the extract in the larger solvent volume, but only a fraction thereof. The fraction of extract which is actually supplied to the GC is equal to the volume supplied to the GC divided by the total solvent volume containing the extract. In the present invention, however, substantially all of the extract is supplied to the GC since the pre-GC unit reduces the solvent volume without substantially reducing the amount of extract.

In the present invention, as each extract is produced by the processor, it is supplied to the GC through the pre-GC unit. Consequently, the GC's operate in paral-

lel. As a result simultaneous peaks of interest may be provided by several of the GC's. This problem may be solved by associating a separate IR spectrometer with each of the GC's **18, 20, 22** and **24.** This, however, would greatly increase the system's cost which is most undesirable. Furthermore, each GC may occasionally produce individual peaks of interest within very short time intervals, e.g. 10 seconds, which is considerably less than the time required for a conventional IR spectrometer to scan each of the peaks of interest. Typically the minimum scanning time of a peak by a conventional IR spectrometer is in the range of 1.5 minutes. The problem is further complicated due to the possibility of the production of overlapping peaks by any of the four GC's. The use of four separate rapid-scanning infrared spectrometers or mass spectrometers would greatly resolve these problems. However, since the cost of each rapid scanning infrared spectrometer or mass spectrometer is very high, the need for four such devices would increase the system cost beyond the budget of most if not all potential users of the system.

This cost problem is eliminated in the present invention by incorporating a single, relatively inexpensive IR spectrometer **30** which is connected to the outputs of GC's **18, 20, 22** and **24** through a peak storage unit **32.** Briefly, unit **32,** which will be described hereafter in detail, temporarily stores each peak of interest produced by any of the four GC's until the IR spectrometer is ready to receive the peak in its absorption cell. Thus, in operation, when any of the four GC's produces a peak of interest, as determined by the computer, the computer transfers the peak from the GC to the peak storage unit **32** and stores it in one of its holding columns. Then, when the IR spectrometer **30** is ready to receive a new peak, a peak, stored in one of the holding columns **32,** is transferred to the spectrometer's absorption cell. The GC's are coupled to the storage unit so that even when simultaneous peaks are produced by different GC's the peaks can be stored in separate holding columns. The storage unit can also be used to separate overlapping peaks of interest from one another for subsequent supply to the single IR spectrometer.

The spectrometer produces a spectral analysis of the peak and supplies the results to the computer. The computer, is thus supplied with information concerning the extract type, the elution time of the peak of interest from the GC producing the peak, as well as, with the spectral analysis of the peak which is received from the spectrometer. Each constituent or drug is identified, based on the comparison of its extract type, its elution time, and its spectral data with the elution times and spectral data of all of the known drugs for each extract type in the drug repertoire.

Attention is now directed to FIGS. **2***a* and **2***b* in conjunction with which the sample processor **15** and the steps performed in it will be described in more detail. FIG. **2***a* is a more detailed block diagram of the processor and FIG. **2***b* is a flow diagram, outlining the steps performed in the processor under computer control. As seen from FIG. **2***a*, the processor **15** includes a reaction chamber **34** to which the original input sample is supplied. Therein the sample is warmed so the family of volatile drugs is removed therefrom as a headspace sample, which is supplied to GC **16** for chromatographic separation. The sample is then transferred to an acidic processor **35** wherein the family of acidic and some of the neutral drugs are separated from the sample. This family is supplied to pre-GC unit **19** in the form of an extract dissolved in an appropriate solvent. The remainder of the sample in the form of an aqueous solution is then supplied to a basic processor **36** wherein the families of the relatively volatile and relatively non-volatile drugs are extracted and are respectively supplied in an appropriate solvent to pre-GC's **21** and **23.** The remainder of the sample is then supplied to an amphoteric processor **37,** wherein the family of amphoteric drugs is extracted and supplied to pre-GC **25.**

In the first step which is performed in the processor on the input sample, the sample is warmed in the reaction chamber **34** as represented by block **41** in FIG. **2***b*. As a result, the family of volatile drugs is extractable in the form of a headspace sample which is supplied to GC **16.** Then an acidification step **42** is performed. In it, the pH of the sample is adjusted by the addition of proper reagents. The pH is adjusted to a value of between 1 and 3. Thereafter, the residual solids from the sample and any precipitates produced as a result of the acidification step are removed as a residue by a filtering step **43.** An appropriate organic solvent, i.e., chloroform, which is immiscible with water is then added in an extraction step **44** to the filtrate. As is appreciated, the family of acidic drugs and some of the neutral drugs are dissolved in the organic solvent. Then a phase separation step **45** is performed in which the solvent in which the particular family of drugs is dissolved is separated from the aqueous phase. The organic solvent which now contains the acidic and some of the neutral drugs such as barbiturates, aspirin, diazepam and meprobamate is supplied to pre-GC **19** and the aqueous phase is supplied to the basic processor **36.**

Therein, steps **46** through **48** are performed. First, the pH of the aqueous phase is adjusted to between **10** and **12,** making the aqueous phase basic, as represented by step **46.** This is followed by the addition of an appropriate organic solvent, such as chloroform, to extract the basic relatively volatile and relatively non-volatile drugs which dissolve in the organic solvent. The extraction is represented by step **47.** This step is followed by phase separation step **48** in which the aqueous phase is separated from the organic solvent containing the families of basic drugs. Various techniques may be employed to separate the relatively volatile basic drugs from the relatively non-volatile basic drugs. This can be done simply by dividing the quantity of volume of the organic solvent containing all the basic drugs which is separated from the aqueous phase step in **48** into two equal parts and supply each to a different one of the pre-GC's **21** and **23.**

The aqueous phase which now contains the family of residual neutral, amphoteric and, in the case of urine, conjugated drugs is transferred to the neutral processor **37** wherein the series of steps which is performed depends on whether the original sample is urine or blood. In case of urine, the aqueous phase is strongly acidified in step **51** followed by a hydrolyzing step **52** which is in turn followed by a filtering step **53.** Therein any precipitates are removed. The filtrate is buffered ina buffering step **54** by adjusting its pH to a value between 7 and 8.5. If the sample is blood, steps **51** through **53** are eliminated and the aqueous phase, received from the basic processor **36** following step **48** is directly buffered in step **54.** Thereafter, a proper organic solvent, such as chloroform, is added in step **55** to dissolve the neu-

tral drugs therein. This is followed by a phase separation step **56** wherein the aqueous phase is separated from the solvent containing the family of neutral or conjugated drugs such as morphine, dextromethorphan and dextropropoxyphene which is supplied to the pre-GC **25.**

From the foregoing it is thus seen that in the sample processor **115,** once a sample is received a series of steps is performed under the control of computer **10,** resulting in the sequential separation of the drugs into the various families hereinbefore referred to. As each family is separated (except the volatile drugs) it is supplied to its appropriate pre-GC unit and therefrom to its GC for chromatographic separation. As previously pointed out, the function of each pre-GC unit is to greatly increase the ratio of extract to solvent volume which is supplied to the GC by significantly reducing the solvent volume without any substantial loss of extract.

One embodiment of such a pre-GC unit is shown in FIG. **3** to which reference is made herein. The pre-GC unit which for explanatory purposes is assumed to be pre-GC unit **19** includes a concentrator **60** in the form of a helical tube **62** which is connected at its top to the sample processor **15** to receive therefrom the extract of the family of the acidic and some of the neutral drugs dissolved in its appropriate solvent. The bottom end of the helical tube is directed to a funnel **64.** A flushing gas, i.e., nitrogen (N_2), enters via line **65** through a valve **65***x* at the center of the helical tube **62.** The function of valve **65***x* is to control the flow rate of the flushing gas in the tube. Some of the flushing gas flows upwardly in a direction counter to the solvent flow, while some of the gas co-flows with the solvent towards funnel **64.** The tube is provided with heaters which are adjusted to just compensate for the heat of evaporation of the solvent so that the temperature of the drugs plus the solvent is not raised significantly. As a result, only solvent is basically evaporated by the flushing characteristics of the flushing gas.

The collector funnel **64** acts as a chamber so that the flushing nitrogen gas could leave it without having high velocity flow over the relatively small volume of solvent plus extract. At the top end of the helical tube **62,** the velocity flow of the nitrogen is significantly higher than that at the bottom. However, at the top the solvent volume is significantly greater and therefore the greater flow velocity presents no problem. In FIG. **3,** line **65** represents the input line for the flushing gas and lines **66** and **67** the venting lines through which the nitrogen flushing gas containing the evaporated solvent exits. Valves **66***x* and **67***x* are incorporated to control the pressure in the tube **62.**

The pre-GC unit also includes a pre-column unit **70.** After the solvent passes through the concentrator **60** in which its volume as compared with the extract is reduced significantly, it is transferred to the pre-column **70** via valve **74** and line **75.** In FIG. **3** it is assumed that the extract with the solvent of reduced volume enters the pre-column **70** from the right towards the left end of the pre-column. Once the extract is in the pre-column and valve **74** is closed, valves **76** and a venting valve **78** are opened. Also, multiport valve **80** is positioned so that flush gas entering the valve **76** from port **77** through a valve **77***x* is passed through valve **80** into the pre-column **70** from the right. The temperature of the pre-column is selected to enhance the vaporization process of the solvent in the pre-column and to permit the drug to be retained in the pre-column. The solvent vapor is vented through valve **78** and a vent port **79.**

After the solvent vaporization is completed and the volume of the solvent is again greatly reduced so that the total volume of solvent plus extract is only a few microliters, a volume which is typically insertable into a GC, valves **76** and **78** are closed. Valve **80** and a valve **82** are positioned to enable carrier gas passing through a valve **83,** from a port **84** to flow through valve **82,** a pre-heating column **85,** valve **80** and line **86** into the pre-column from the left hand side. The temperature of the pre-column is raised sufficiently to volatilize the drugs. The carrier gas thus flushes the extract out of the pre-column in a direction opposite to that in which it entered the pre-column. The now vaporized extract is forced through valve **80** into a separation column **90** of GC **18.**

In FIG. **3** the direction of flow of the flush gas from port **77** is indicated by dotted lines and the direction of flow of the carrier gas which forces the extract into column **90** is indicated by dashed lines. Also, the legent CW near the valves indicates a connection between the adjacent parts in one valve position and the legend CCW indicates a connection in another valve position.

As shown in FIG. **3,** GC **18** is a dual-column GC, including the separation column **90** and a balancing column **92** which is also supplied with the carrier gas from port **84** through a valve **93.** Columns **90** and **92** have associated therewith detectors designated S (for Sample) and R (for Reference). The carrier gas exiting balancing column **92** passes past detector R and is vented through another balancing column **94** and a vent port **95.** The function of valves **83** and **93** is to maintain a balanced flow through both detectors.

The electrical output of detector S is supplied to computer **10** wherein the elution (or retention) times of the various constituents of the extract forced into the separation column **90** are computed. These elution times are compared with elution times of known drugs of the drug repertoire belonging to the same family of drugs. If a computed elution time indicates that the constituent, producing the particular elution time, is of interest the peak from the detector S is passed through valve **82** to the IR spectrometer **30** through the peak storage unit **32.** If, however, the computed elution time indicates that the peak producing it is not of interest, valve **82** and other valves, which will be described hereafter and which form part of the peak storage unit **32,** are used to vent the peak which is not of interest.

In order to reduce the turn around time and thereby increase the samples which may be analyzed in any given period, in a preferred embodiment of the present invention certain of the parts shown in FIG. **3** are duplicated. Such an arrangement is shown in FIG. **4** to which reference is made herein in which elements shown in FIG. **3** are designated by like numerals and duplicate identical parts are designated by the same numerals followed by the suffix *a.* Thus, as seen from FIG. **4** in a preferred embodiment two pre-columns designated **70** and **70***a* are employed as well as two identical dual-column GC's, designated therein by numerals **18** and **18***a.*

In such an arrangement, once the solvent with the dissolved extract is forced into one of the pre-columns for subsequent supply to its associated GC, the other pre-column and GC are cleansed to prepare them to

receive a solvent containing an extract from a succeeding sample to be analyzed. Basically a wash solution passes through the tube **62** and funnel **64** and exits througoh valve **74** to one of the waste ports **74***a* or **74***b*. Then some of the wash solution passes through valve **74** to the pre-column being cleansed and exits via one of the ports **79** or **79***a*. The cleansing of the GC is done by backflushing its separating column with carrier gas which is vented through valve **98** and vent port **98***x*. As seen from FIG. **4** valve **98** is also used to route the peak from GC **18** or GC **18***a* to the peak storage unit **32.**

Attention is now directed to FIG. **5** which is a schematic diagram of the novel peak storage unit **32** and of an absorption cell of IR spectrometer **30.** As shown in FIG. **5,** the novel peak storage unit **32** consists of three holding columns **101, 102** and **103** and two pressure balancing columns **104,** and **105.** Unit **32** also includes valves **106** through **113,** a balancing column **115** and a pair of detectors **116** and **117.** Valves **82** and **82***a* which are respectively associated with GC's **18** and **18***a* are connected to the peak storage unit **32** through a valve **98** (FIG. **4**).

In FIG. **5** the absorption cell of the IR spectrometer is designated by numeral **125.** It is shown comprising an IR sample cell **126** and an IR reference cell **127.** Cell **126** is connected to the output of detector **116** through a valve **128** and cell **127** is connected to the output of detector **117** through a valve **129.**

In operation, when a peak passes through a detector S of GC **18** through valves **82** and **98,** (or through detector S of GC **18***a*, through valves **82***a* and **98**) toward the peak storage unit **32,** its elution time is computed either in the GC's associated circuitry or in the computer. If, based on the computation, a decision is made that the peak is not of interest valves **107, 109, 111** and **113** are activated so as to direct the peak through these valves toward a vent port **130.** If, however, a decision is made that the peak is of interest and should be analyzed in the spectrometer, valves **106** and **107** are activated to direct the peak and temporarily hold it in holding column **101.** If a peak is already held in column **101,** the two valves associated with any of the other holding columns are activated to direct the peak thereto. Then, when the absorption cell **125** is ready to receive the peak for spectral analysis a carrier gas from port **132** and controlled by valve **132***a* is directed through valves **107** and **106** to force the peak stored in column **101** out of the column and through valves **109, 111, 112,** to the detector **116** and through valve **128** to the sample cell **126.** The carrier gas from port **132** is also directed through a valve **132***b* to the reference cell **127** through the balancing column **115,** detector **117** and valve **129.** The function of valves **132***a* and **132***b* is to maintain a balanced flow through detectors **116** and **117.**

The direction of flow of a peak which is not of interest towards vent port **130** is indicated in FIG. **5** by dashed lines while the direction of flow of the peak of interest into column **101** is indicated by dotted lines. Furthermore, the direction of flow of the peak of interest from a holding column to the sample cell **126** is indicated by dashed-dot lines. As seen from these lines a peak is flushed out of a holding column in a direction opposite to the direction in which it was inserted into the column.

After the spectral analysis of a peak is completed, carrier gas from port **132** is passed through the various valves to flush out the peak from the sample cell **126** through valve **128** and vent port **135.** It should be noted that the flushing of a peak from the sample cell is done in the same direction that the peak was inserted therein. In FIG. **5** vent port **143** is used to vent out the carrier gas passing through the reference cell **127,** the carrier gas reaching vent port **143** through valve **129.**

As previously pointed out, the incorporation of the peak storage units **32** in the system is most significant since it enables a single relatively slow scanning IR spectrometer to analyze peaks of interest which are produced within a time interval, i.e., 10 seconds which is a fraction of the total scanning time per peak which is typically over 1 minute. Basically, the peak storage unit **32** holds the peaks of interest in the various holding columns until the spectral analysis of the peak in the sample cell **126** is completed and the cell is available to receive a subsequent peak of interest. Although in FIG. **5** the peak storage unit **32** is shown including only three holding columns **101, 102** and **103,** it should be appreciated that any number of holding columns may be included therein, depending upon the expected rate of production of peaks of interest and the length of time it takes the IR spectrometer to complete the scanning of a peak.

In practice, the outputs of all the valves **98** associated with all the GC's **18, 20, 22** and **24** are manifolded together in line **136** which serves as the common input line of the peaks' storage unit **32** from the four GC's shown in FIG. **1.** Preferably the manifolding is done through additional valves and by-pass lines so that if several peaks of interest are provided simultaneously by several GC's these valves and lines are used as a delay arrangement to supply the peaks to line **136** one after another rather than together. Thus, even though the peaks are simultaneously produced their storage in the unit **32** is sequential in different holding columns. The storage unit **32** provides a satisfactory solution to the presence of overlapping peaks from a single GC. If a decision is made that the leading peak (or the trailing peak) of the overlapping peaks is of interest, it can be stored in one of the holding columns and the rest can be vented. Also the overlapping peaks can be stored in one of the holding columns and the rest can be vented. Also the overlapping peaks can be stored in one of the holding columns and the decision which part should be vented and which should be supplied to the spectrometer may be made when the overlapping peaks exit the holding column to the absorption cell of the IR spectrometer.

Herebefore the invention has been described in conjunction with a drug identification system. As previously pointed out the term drug is intended to include all organic chemical compounds and not be limited to drugs in the conventional sense. The system can be used to separate and identify traces of organic chemical compounds in aqueous solutions. Also the system can be used to separate and identify other than organic chemical compounds, such as inorganic chemical compounds, organo-metallic compounds and others. The only primary requirement is that the compounds be extractable into distinct families, anad that the compounds in each extract be of the type which are separable chromatographically then depending on the class of compounds which is to be identified in appropriate spectral analysis device is employed.

Although particular embodiments of the invention have been described and illustrated herein, it is recognized that modifications and variations may readily occur to those skilled in the art. For example although gas chromatographs have been described, it is appreciated that the system may be modified to employ liquid-liquid chromatography and other than an IR spectrometer. Consequently, it is intended that the claims be interpreted to cover such modifications and equivalents.

What is claimed is:

1. An automated chemical compound identification system comprising:

a sample processor means for extracting chemical compounds from a sample supplied thereto into a plurality of families of chemical compounds contained in said sample in a controlled sequence of steps, at least N of said families being dissolved as extracts in appropriate solvents, N being at least two;

first means including N chromatograhic columns, each being responsive to a different one of said N families for separating the compounds in the family from one another and for providing chromatographic data for each compound to be identified;

computer means including means controlling the sequence of steps in said sample processor means and said first means including means for storing chromatographic and spectral data of each of a plurality of known chemical compounds defining a compound repertoire, means for comparing the chromatographic data provided by said first means for each compound separated in any of said N columns to be identified with the chromatographic data of said known compounds for selecting unidentified compounds of interest;

a single spectrometer; and

compound storage means connected to said N chromatographic columns and said spectrometer, said compound storage means comprising a plurality of holding columns for transferring to said spectrometer any compound of interest received from any of said N chromatographic columns for spectral analysis and for holding any compound of interest received from any of said N chromatographic columns when another compound of interest is being analyzed by said spectrometer, the time of analysis of a compound by said single spectrometer is greater than the expected shortest time between the successive exits of two compounds of interest from any two of saids N chromatographic columns, with the spectral data of each compound provided by said spectrometer being supplied to said computer means to identify a compound based on at least its spectral data from said spectrometer.

2. A system according to claim 1 wherein said N chromatographic columns are gas chromatographs and said single spectrometer is an infrared spectrometer.

3. A method of automatically identifying traces of chemical compounds in an aqueous solution, the steps comprising:

automatically separating the compounds into a plurality of families of compounds, at least N of said families being dissolved as separate extracts in selected solvents, N being an integer not less than two;

separately chromatograhically separating each family extract dissolved in a solvent into its compound in separate chromatographs;

automatically selecting of the compounds which have been chromatographically separated by each chromatograph, compounds of interest;

spectrographically analyzing each compound of interest in a single spectrometer to obtain spectral data therefor; and

while the spectrometer analyzes a compound of interest, temporarily storing any compound of interest which subsequently exited any of said chromatographs until said spectrometer is ready to receive the subsequent compound of interest for spectral analysis.

4. An automated drug identification system comprising:

computer means for storing chromatographic and spectral data for each of a plurality of known drugs, for identifying unknown drugs based on the comparison of their chromatograhic and spectral data derived in said system with the data stored therein, and for controlling the separation of said drugs from a sample containing unknown drugs and the acquisition of their chromatographic and spectral data;

sample processor means controlled by said computer means for extracting unknown drugs from a sample supplied thereto into a plurality of families of unknown drugs in a sequence of steps controlled by said computer means, said families including at least N families which are dissolved as separate extracts in preselected solvents, N being an integer not less than two;

at least N chromatographs, each receiving a solvent containing the dissolved extract of a different family of drugs for separating the unknown drugs in the family and for providing chromatographic data for each drug, said computer means utilizing the chromatographic data provided for the unknown drugs for selecting therefrom drugs of interest;

spectrometer means for receiving each selected drug of interest for spectral analysis and for providing to said computer means spectral data for each drug supplied thereto; and

storage means coupled to each separate chromatograph and to said spectrometer means for temporarily storing only each drug of interest exiting any of said chromatographs for subsequent supply to said spectrometer means, said storage means includes a plurality of holding columns and control valves which are controlled by said computer means to transfer only a drug of interest exiting any of said N chromatographs for temporary storage in one of said holding columns and for transferring a drug stored in one of said holding columns to said spectrometer means when the latter is ready to receive a drug for spectral analysis, the time of analysis of a drug by said spectrometer being greater than the expected time between the successive exit of two drugs of interest from any two of said chromatographs.

5. A system according to claim 4 further including vent means for venting a drug which exits any one of said chromatographs and which is determined by said computer means not to be of interest so as to inhibit said drug from subsequent entry to said spectrometer means through said storage means.

6. A system according to claim 5 wherein each of said N chromatographs is a gas chromatograph and said spectrometer is an infrared spectrometer.

* * * * *

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,860,393 Dated January 14, 1975

Inventor(s) Charles F. Campen, Jr.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Under the heading entitled "Abstract", line 1, insert --is disclosed-- after "system".

Column 1
line 17, delete "2." and instead insert it on the next line before "Description of the Prior Art".
line 58, delete "border" and instead insert --order--.

Column 2
line 27, delete "filtered" and instead insert --fitted--.
line 42, delete "solent" and instead insert --solvent--.

Column 3
line 38, after "and" insert --a--.

Column 4
line 63, delete "in" and insert --is--.

Column 6
line 28, delete "solent" and instead insert --solvent--.
line 33, after "pre-GC" insert --unit--

Column 8
line 62, delete "ina" and instead insert --in a--.

Column 9
line 8, delete "115" and instead insert --15--.

Column 10
line 22, delete "legent" and instead insert --legend--.

Column 11
line 4, delete "througoh" and instead insert --through--.

Column 12
line 63, delete "anad" and instead insert --and--.

Column 13
Claim 1, line 28, after "means" (first occurrence), insert --and--.
line 52, delete "saids" and instead insert --said--.

Column 14
Claim 3, line 2, change "compound" to --compounds--.

Signed and Sealed this

twenty-ninth Day of *July 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks

FORM PO-1050 (10-69)

USCOMM-DC 60376-P69
U.S. GOVERNMENT PRINTING OFFICE : 869-930