



Australian Government



NATIONAL
ARCHIVES
OF AUSTRALIA

Your story, our history

These copies are provided for research or study purposes. Before making use of the material for other purposes (for example publication) you should familiarise yourself with any copyright obligations.

NAA: A13882, 9023/1943B

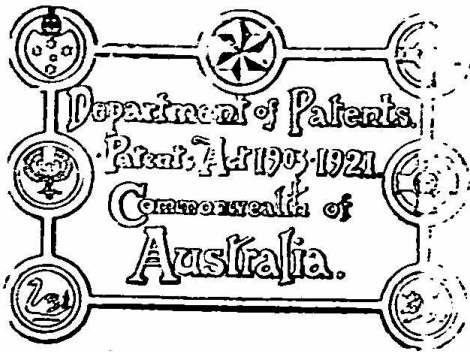
Series number: A13882

Control symbol: 9023/1943B

Barcode: 201379593

Number of pages: 5

[Patent No - 1943009023] - Improvements in or relating to the extraction and recovery of alkaloids



Application Date : 19th Apr., 1943. No. 9023/43.

<i>Applicant (Assignee of Actual Inventors)</i>	ELLIOTTS & AUSTRALIAN DRUG PTY. LIMITED.
<i>Actual Inventors</i>	HANS SPITZER and FREDERICK CHARLES BENNETT, of New South Wales.
<i>Application and Provisional Specification</i>	Accepted, 12th May, 1943.
<i>Complete Specification after Provisional Specification</i>	Lodged, 14th January, 1944.
<i>Complete Specification</i>	Accepted, 4th December, 1944.
<i>Acceptance Advertised (Sec. 50)</i>28th March, 1946.....

Class 09.6.

No drawing.

COMPLETE SPECIFICATION.

“Improvements in or relating to the extraction and recovery of alkaloids.”

We, ELLIOTTS & AUSTRALIAN DRUG PTY. LIMITED, a Company duly incorporated under the Companies Act of the State of New South Wales, carrying on business as Wholesale Druggists and Manufacturers, at 20-22 O'Connell Street, Sydney, New South Wales and Commonwealth of Australia, hereby declare this invention and the manner in which it is to be performed, to be fully described and ascertained in and by the following statement:—

This invention has relevance to the extraction and recovery of alkaloids as alkaloidal salts and to the salts recovered through such extraction. In such extraction and recovery raw plant alkaloid containing materials are selected and treated. As instances of some of such plants which may be treated for recovery therefrom of their alkaloid content the following may be mentioned: *Alstonia constricta* (Mollis), *Cinchona ledgeriana*, *Atropa belladonna*, and

Duboisia myoporoides. It is to be understood, however, that the invention is not confined to treatment of these mentioned plants but is also applicable to other alkaloidal vegetable materials.

Existing methods of alkaloidal extraction and recovery are open to objection in several respects, for example, they usually involve the necessity in one stage or another of the process to extract the free alkaloidal bases from an alkaline medium with an immiscible solvent. Only in rare individual cases is it possible to extract alkaloids from an aqueous solution of an acidity greater than pH equal 7 but this applies only to alkaloids of a very weak basic nature such as Caffeine the salts of which are hydrolysed to a great extent in aqueous solution. In practically all cases of alkaloid recovery it is therefore necessary to liberate the alkaloidal bases from their salts by an alkaline reagent and to express them in this state to

the atmosphere while the alkaloid recovery by shaking-out with immiscible solvents is carried out. This treatment of the free alkaloidal bases is in many cases conducive to their partial destruction or molecular arrangement, particularly in cases where the alkaloids are sensitive to oxidation, or where saponification or hydrolysis may be brought about by the influence of alkalis, or where the molecular structure is unstable except in acid solutions.

The shaking-out process with immiscible solvents is furthermore by its nature one which requires frequent repetition if effective transfer from the aqueous into the non-aqueous phase is to be achieved. Theoretically quantitative alkaloidal extraction can never be achieved and a certain amount of the alkaloid, depending upon its partition-coefficient in the aqueous and immiscible solvent phase respectively is of necessity lost.

The physical laws governing the shaking-out method with immiscible solvents require in many cases that a relatively concentrated aqueous phase be subjected to this treatment if anything like economic usage of the solvent is desired, and the aqueous extracts, containing the alkaloids have therefore in many cases to be concentrated by evaporation. This treatment besides being costly is also conducive to destruction or molecular alteration of the alkaloidal substances.

The present invention has been devised to overcome disadvantages of recovery of alkaloids by present methods of treatment by the provision of improved methods of alkaloidal extraction and recovery, and if desired purification, such improved methods for such purposes, in comparison to known methods, being performable in a simpler, cheaper, and more rapid manner and which also do not involve any treatment which would be detrimental to the alkaloids which it is desired to recover.

Broadly, the invention has relevance to a method of extracting and recovering alkaloid salt or salts of the character mentioned herein. Such method consists in treating a substance containing said salt or salts to obtain an acid or neutral aqueous or aqueous alcoholic solution thereof. Said solution is treated with a water immiscible phenol so as to bring the aqueous or aqueous alcoholic and the phenolic phases into intimate contact with each other and to transfer the alka-

loid salt or salts into the phenolic phase. Both phases are then separated and the said alkaloid salt or salts are recovered from the phenolic phase.

By experiments carried out in connection with the invention it has been ascertained:—

(1) That a phenol, which is immiscible with water, say a cresol or a xylenol or a mixture thereof, is capable of application in the extraction of the beforementioned alkaloid salts from the said acid or neutral aqueous or aqueous alcoholic solution of the said alkaloid salts, and

(2) That a phenol, which is immiscible with water, say a cresol or a xylenol or a mixture thereof, is capable of application in the taking up of the salts of alkaloid bases with resultant formation of a homogeneous phase.

Prior to this invention these facts were not known, neither could they be expected or foretold ordinarily, as alkaloid salts have generally been found to be insoluble in organic solvents which are immiscible with water. It was known, however, that phenols could dissolve a number of alkaloid bases. In such cases the phenols acted as non-aqueous solvents, similar to other known solvents used for dissolving such bases, for instance chloroform, benzene, ether and other. It is to be noted that the present invention is differentiated from prior practice in the use of phenols in that by such invention the solubility of alkaloid salts in phenols is recognised and achieved and not the solubility of alkaloid bases in phenols.

Through such experiments it has been determined that the entrance of the said alkaloid salts into the phenolic phase is not accompanied by any partition-coefficient phenomena, and that it proceeds very rapidly, and in the cases of salts of quinine, strychnine, atropine, hyoscamine, hyoscyne or the like, it may be effected quantitatively. From such experiments it has also been observed:—

(1) That alkaloid salts can be taken up by phenols from acidic aqueous solutions without the usual partition-co-efficient phenomena, and

(2) That water or dilute aqueous acid will not extract the alkaloids or alkaloid salts from the phenolic phase.

It is thus assumed that the alkaloid salts are taken up by the phenols chemically rather than in physical solution. A relatively small volume of the phenol used usually suffices to take up all of the alkaloid salts extractable from the said prepared solution thereof. The said solution need not be concentrated or made alkaline prior to treatment with said phenolic substances.

If desired the solution extract may be purified prior to phenolic treatment thereof, by shaking out with a water immiscible solvent, say ether, chloroform, petrolether or the like, the said solvent being capable of taking up unwanted matters in the extract without affecting the alkaloids of the extract.

Generally, by the experiments before-mentioned, it has been determined that salts of different alkaloids are taken up by phenols with varying degrees of efficiency from acid aqueous solutions thereof. Such variation enables the separation or partial separation of mixtures of alkaloid salts such as occur in extracts of alkaloid drugs.

Said aqueous or aqueous alcoholic solution may be prepared in any of the conventional ways suitable for the preparation of such solution. For instance, it may be made by extracting a vegetable drug, carrying alkaloid constituents, with an aqueous or aqueous alcoholic solution of a pH from 1.0 to 6.8; or by extracting a vegetable drug, carrying alkaloid constituents, with alcohol, or a mixture of water and alcohol, removing all or part of the alcohol by evaporation, and treating the extract residue with an aqueous or aqueous alcoholic solution of a pH from 1.0 to 6.8; or by dissolving one or a mixture of alkaloid basis or alkaloid salts in an aqueous or aqueous alcoholic solution of a pH from 1.0 to 6.8.

The treatment of said solution with a water immiscible phenol may consist in bringing the two phases into intimate contact with each other. This is achievable in various ways, say by shaking a closed vessel containing the two phases; or by agitating the mixture with a stirrer or similar device; or by circulating one phase through the other by gravity flow or mechanical means which will result in intimately contacting the surfaces of the two immiscible phases with each other.

Extraction steps for the alkaloid salts according to the invention may be stated as follows:—

(1) Treatment of the alkaloid salts solution with a water immiscible phenol, this consisting of a cresol or a mixture of isomeric cresols; or a xylenol or a mixture of isomeric xylenols; or a mixture of cresols and xylenols, and

(2) Separation of the aqueous or aqueous alcoholic phase from the phenolic phase derived from the combination of such phases from Step 1, and recovery of the phenolic phase.

Similarly, recovery steps for the alkaloid salts according to the invention may be stated as follows:—

(1) Dilution in suitable proportions of the phenolic phase with a solvent or a mixture of solvents miscible with each other and with the phenol or phenols used, but the solvent or solvents being immiscible with water, being preferred as such solvent or as one constituent of a mixture of solvents mentioned.

(2) Shaking out the solvent diluted phenolic phase with an aqueous phase, the pH of which lies between 1.0 and 7.0:

(3) Separation of the said aqueous phase from the said solvent diluted phenolic phase and recovery of the said aqueous phase.

As alternative recovery steps for the alkaloid salts according to the invention the following may be mentioned:—

(1) Precipitation of the alkaloid salt or salts contained in the phenolic phase, by mixing in suitable proportions the phenolic phase with a solvent, or a mixture of solvents, which is or are miscible with the phenol or phenols used and with each other, but all of which are immiscible with water, the solvent or one of its constituents, if a mixture thereof is used, being ether.

(2) Recovery of the precipitated alkaloid salt or salts by decanting the phenol solvent mixture and by washing the precipitate with the diluent solvent or mixture of solvents used, or with another solvent or mixture of solvents having similar general characteristics.

(3) Subjecting the decanted phenol solvent mixture to recovery steps described under headings (2) and (3) of the above-mentioned first main recovery steps.

The following may be given as simple examples for the practising of the invention:—

EXAMPLE 1.

5 An alcoholic extract of *Alstonia* bark from *Alstonia constricta* (Mollis) was vacuum evaporated to give an alcohol free extract. Dilute sulphuric acid was then added to this in the aqueous acidic phase
10 and that a solution of extract in such amount that all alkaloidal constituents were dissolved a pH value lying substantially between 1.0 and 6.5 resulted. The resulting acid aqueous extract was then treated
15 with a phenol, namely, cresylic acid, which was added in the proportion of from one tenth to one twentieth volumes of cresylic acid to one volume of extract. This mixture was then shaken out to give an
20 aqueous residue (exhausted of alkaloids) and a cresylic alkaloid sulphate solution. Ether and water were then added to this solution in the proportions of from 3 to 7 volumes of ether and from 2 to 3 volumes
25 of water, to one volume of phenolic phase. This mixture was then shaken out, giving a cresylic acid ether residue on the one hand, and an aqueous alkaloid sulphate solution on the other. The desired alkaloid
30 sulphate was then obtained by vacuum evaporation.

EXAMPLE 2.

An alcoholic extract of *Duboisia myoporoides* was vacuum evaporated and the
35 residue exhaustively extracted with a weak sulphuric acid solution. The acid aqueous extract was diluted so as to result in a solution containing approximately 0.25% sulphuric acid and then treated with a
40 phenol, namely cresylic acid, in the proportion of one tenth volume of cresylic acid to one volume of extract. This mixture was then shaken out to give an aqueous residue and a cresylic alkaloid sulphate solution.
45 The aqueous residue contained one fraction of the alkaloids, but was exhausted in respect to the alkaloids of the hyoscyamine-hyoscyne-group. It was rendered alkaline by addition of sodium carbonate
50 and again treated with cresylic acid in successive quantities in the proportion of one twentieth volume to one volume of extract. This mixture was then shaken out to give an aqueous residue, exhausted of
55 alkaloids, and a cresylic alkaloid solution.

Said two cresylic alkaloid sulphate solutions were separately treated for recovery of their alkaloid content. The cresylic solution from the first stage of extraction was treated with three to five volumes of
5 ether and with one half to three-fourths of one volume of water to one volume of phenolic phase. This mixture was then shaken out, giving a cresylic acid ether residue on the one hand, and an aqueous
10 solution of alkaloid sulphate on the other. Said aqueous solution was then saturated with potassium carbonate, and the liberated alkaloids were collected by decantation. They were then recrystallised from benzene
15 and were found to be a mixture of hyoscyamine with atropine and hyoscyne.

The cresylic solution from the second stage of extraction was treated with six to
20 eight volumes of ether and one to two volumes of dilute sulphuric acid to one volume of phenolic phase. This mixture was then shaken out, giving a cresylic acid ether residue on the one hand and an acid
25 aqueous solution of alkaloid sulphates on the other. Said aqueous solution was saturated with potassium carbonate and the liberated alkaloids, which remained liquid, were collected by separating in a
30 separating funnel. They were subjected to the Vitali Test and proved to contain no atropine, hyoscyamine or hyoscyne.

An effective separation of the alkaloids of the group hyoscyamine, atropine, hyoscyne from other alkaloids contained in
35 extracts of *Duboisia myoporoides* had been effected by the treatment described.

Having now fully described and ascertained our said invention and the manner in which it is to be performed, we declare
40 that what we claim is:—

1. Method of extracting and recovering alkaloid salt or salts of the character herein mentioned consisting in treating a substance containing said salt or salts to obtain
45 an acid or neutral aqueous or aqueous alcoholic solution thereof, treating said solution with a water immiscible phenol or phenols so as to bring the aqueous or aqueous alcoholic and the phenolic phases into intimate
50 contact with each other and to transfer the alkaloid salt or salts into the phenolic phase, separating both phases, and recovering the said alkaloid salt or salts from said phenolic phase.

2. Method of extracting and recovering alkaloid salt or salts herein mentioned, consisting in treating a substance containing said salt or salts to obtain an acid or neutral aqueous or aqueous alcoholic solution thereof, treating said solution with a water immiscible phenol or phenols consisting of a cresol or a mixture of isomeric cresols, or a xylenol or a mixture of isomeric xylenols, or a mixture of cresols and xylenols to take up the alkaloid salt or salts, and separating both phases to recover the phenolic phase from which the said salt or salts is or are recovered.

3. Method of extracting and recovering alkaloid salt or salts according to Claim 4, in which the solution extract is purified prior to phenolic treatment thereof by shaking out with a water immiscible solvent, the said solvent being capable of taking up unwanted matters in said extract.

4. Recovering alkaloid salt or salts from the phenolic phase prepared by operation of the method according to Claim 1, in which dilution is first effected of the phenolic phase with a solvent or a mixture of solvents miscible with each other and with the phenol or phenols used, the said solvent or solvents not being miscible with water, subsequently treating by shaking out the solvent diluted phenolic phase with an aqueous phase whose pH lies between 1.0 and 7.0, and subsequently separating the said aqueous phase from the said solvent diluted phenolic phase and recovering the aqueous phase.

5. Recovering alkaloid salt or salts from the phenolic phase prepared by operation of the method according to Claim 1, in

which precipitation of said salt or salts is effected from said phase by mixing said phase with a solvent or a mixture of solvents which is or are miscible with the phenol or phenols used and with each other, but all of which are immiscible with water, the solvent or one of its constituents, if a mixture thereof is used, being ether, subsequently recovering the precipitated salt or salts by decanting the phenol solvent mixture and by washing the precipitate with the diluent solvent or mixture of solvents used, or with another solvent or solvents having similar general characteristics, subsequently subjecting the decanted phenol solvent mixture to recovery steps by shaking it out with an aqueous phase whose pH lies between 1.0 and 7.0, and subsequently separating the said aqueous phase from said decanted phenol solvent mixture and recovering the said aqueous phase.

6. Method of extracting and recovering alkaloid salt or salts according to either of the Examples 1 herein referred to.

7. An alkaloid salt or salts obtained by carrying out any of the methods for the extraction and recovery of said salt or salts according to any of the Claims 1 to 6 hereof.

8. Method for the extraction and recovery of alkaloid salt or salts substantially as herein described.

Dated this 13th day of January, 1944.

ELLIOTTS & AUSTRALIAN DRUG PTY.
LIMITED,

By its Patent Attorneys,
SPRISON & FERGUSON.

Witness—A. Roberts.