

In order to determine the PH of a 1% solution of atropine hydrochloride, a known weight of pure atropine was dissolved in the theoretical volume of $\frac{N}{10}$ hydrochloric acid and made up to 1 percent strength. The PH of the solution was found to be 3.75.

This corresponds to a distinct blue color with brom-phenol blue, and is reasonably close to the end-point of the morphine titration given above. It is again evident the cochineal is an unsuitable indicator for this titration, and that brom-phenol blue should be used, finishing with a distinct blue color.

A commercial sample of atropine sulphate had in 1% solution PH = 5.9, showing that it contained an excess of atropine over the sulphuric acid.

SUMMARY.

On theoretical grounds and as the result of practical experiments it has been shown that the indicators ordinarily employed for the titration of the alkaloids, morphine, quinine, and atropine, are not the most suitable for the titrations.

From measurement of the hydrogen ion concentration of the solutions of the pure hydrochlorides it was found that brom-phenol blue is a better indicator to use for morphine, atropine, and the neutral salts of quinine. For the acid salts of quinine, methyl red is the most suitable indicator.

THE STRUCTURAL RELATIONS AMONG OPIUM, BERBERIS, CORYDALIS, AND HYDRASTIS ALKALOIDS.

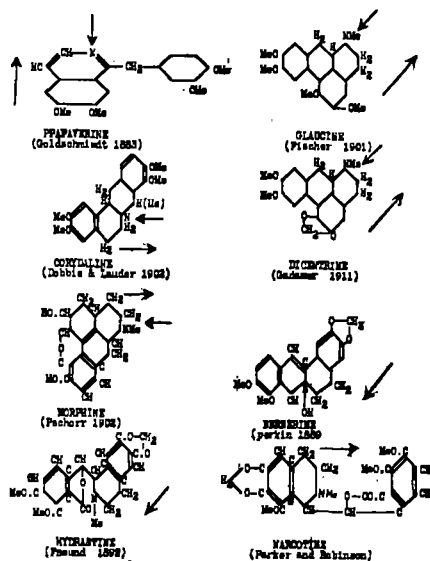
BY INGO W. D. HACKH.*

This paper has a twofold purpose: first, to discuss some striking relations in structure of a number of important alkaloids which enables a systematic classification; second, to point the way to synthetic preparation of these alkaloids.

The rapid rise and success of synthetic organic chemistry has come mainly by an application of the structure theory, for once the structure is established, it remains only a matter of time until some synthetic method for the preparation of the compound is discovered. The painstaking investigations of a number of workers have established, with some certainty, the structure of many alkaloids, a number of which contain the isoquinoline nucleus. The structure formulas of the more important isoquinoline alkaloids are shown on the following page. All these structure formulas are taken from one of the larger reference books, yet they illustrate the random method of the present system of notation. Thus the formulas for hydrastine and narcotine are printed completely—showing every atom; the other six structure formulas are incomplete in varying degrees through absence of symbols or double bonds. It is small wonder that this inconsistent way of representing the structures of organic compounds clouds the understanding and bewilders the student while it remains forever a mystery to the layman. Small progress can be made if the notation is not precise and complete. On looking over these same structure formulas, there appears to be no relationship among these alkaloids, even though the reader's knowledge supplies all the missing double bonds and symbols. The isoquinoline group, when hunted for, is found in each case, either standing on its head or inclined at various angles. With the use of

* College of Physicians and Surgeons, San Francisco, Cal.

structure symbols, a simpler and more precise notation,¹ and bringing the structure symbols of all these compounds into the same relative position of the isoquinoline group, a close connection among these structures at once becomes apparent. The shift necessary to bring the structures into the same position is indicated by the arrow.

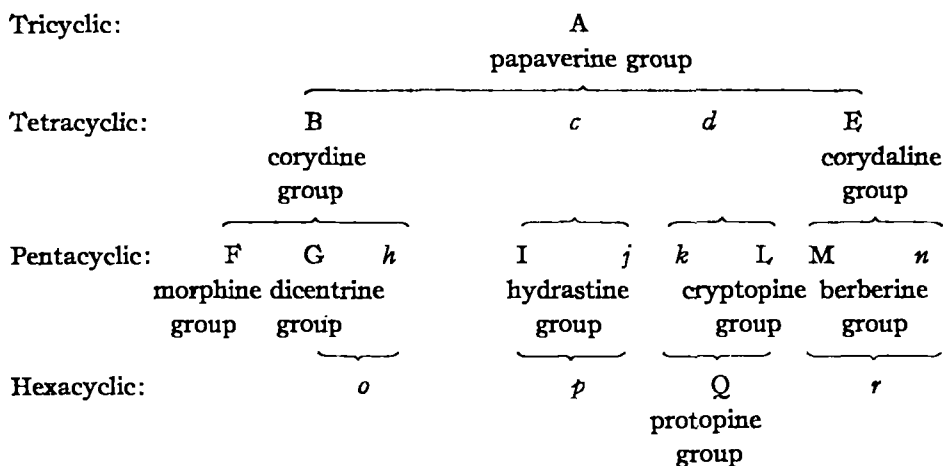


According to the structure of these alkaloids, established at different times by different investigators, it is possible to arrange them into nine groups which have definite relationship. By bringing these nine groups into a logical system, it also becomes possible to predict the existence of additional nine groups. The remarkable genetic relationship of the alkaloids of opium, berberis, corydalis, and hydrastis might furthermore be of benefit in construction of structure for the little known alkaloids of other medicinal plants; such as Glaucium, Eschscholtzia, Coptis, Bicuculla, Dicentra, Jateorrhiza, Anamirta, and Xanthoxylum, which are known to have alkaloids of a similar nature. If theoretical considerations lead to the assumption of nine different ring systems, and none of these ring systems has yet been found, it is a safe guess that future investigations will reveal alkaloids belonging to these groups.

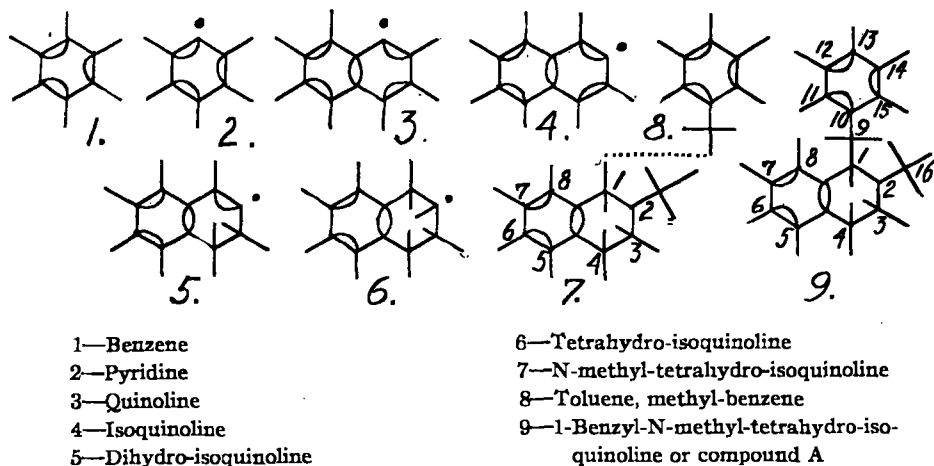
The relation of these eighteen groups is shown in the diagram at the top of the following page.

Capital letters indicate those groups of which one or more compounds are known, while small letters indicate those ring systems which at present have unknown alkaloids. The simplest group is A, the papaverine group, to which belong the alkaloids, papaverine, paperoline, laudanosine, etc., and as all the alka-

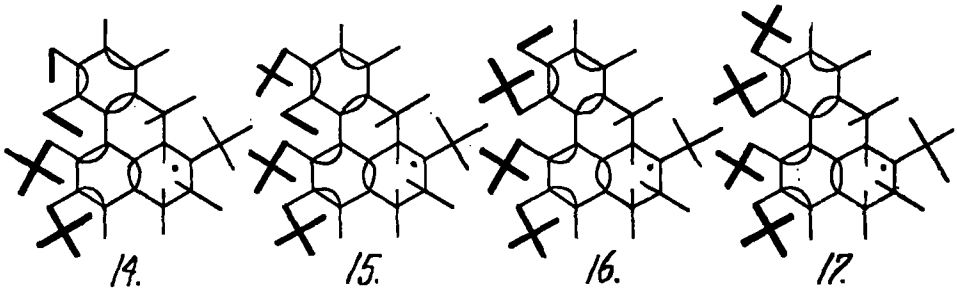
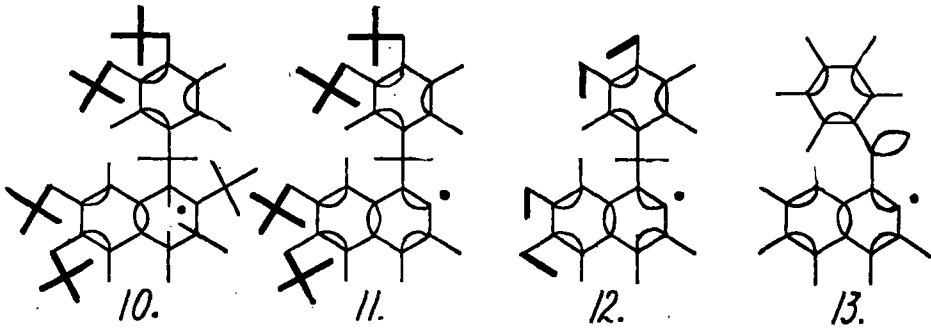
¹ *Canadian Chem. Journ.*, 2, 135 1918; *Science*, 48, 333, 1918; *Chem. Eng.*, 26, 377, 1918; *Chem. News.*, 118, 289, 1919 and 121, 85, 1920; *Chem. Age* (London), 3, 392, 1920; *Jour. A. Ph. A.*, 9, 392, 1920.



loids contain either hydroxy groups (-OH) or methoxy groups (-OCH₃), the hydrocarbon from which they are derived will be spoken of as the parent substance and designated by the group letters.

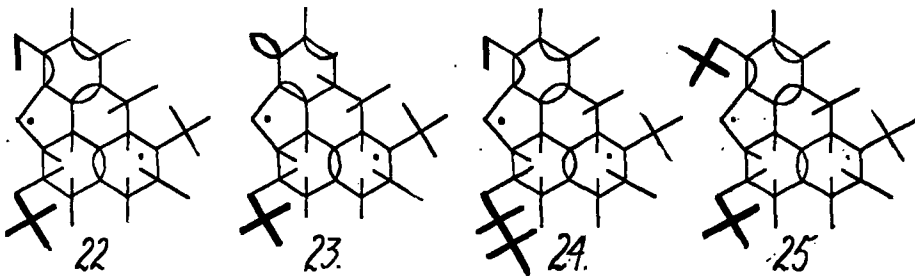
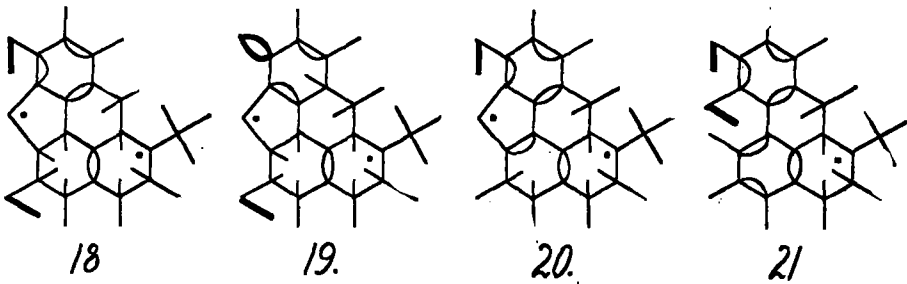


The parent substance A is chemically 1-benzyl-N-methyl-trihydro-isoquinoline. Quinoline (3) is a condensation of benzene (1) and pyridine (2). Isoquinoline (4) differs in the position of the N atom, and as it is an unsaturated hydrocarbon containing five double bonds, it can be gradually saturated. Thus, dihydro-isoquinoline is (5), and tetrahydro-isoquinoline (6). Replacing the hydrogen attached to nitrogen by a methyl group N-methyl-trihydro-isoquinoline (7) is formed. Methylbenzene or toluene (8) gives the benzyl radical when its methyl-carbon atom is attached to another group. Thus, if the methyl-carbon atom of 8 is attached to the first carbon atom of 7, the parent substance A which contains three rings results, *i. e.*, a tricyclic compound.



10—Laudanosine
11—Papaverine
12—Papaveroline
13—Papaveraldine

14—Corytuberine
15—Corydine
16—Isocorydine
17—Glaucine



18—Morphine
19—Morphine (quinoid form)
20—Apomorphine (ether form)
21—Apomorphine (carbinol form)

22—Codeine
23—Codeine (quinoid form)
24—Dionine
25—Thebaine

Laudanosine (10) contains four methoxy groups attached to the carbon atoms numbered 6, 7, 12, and 13. Papaverine (11) is unsaturated laudanosine, and paperoline (12) differs from papaverine by having hydroxy groups instead of methoxy groups, while papaveraldine (13) has the keto group in position 9.

The substance B is derived from A by the formation of a fourth ring brought about by connecting the eighth and eleventh carbon atom. To group B belong corydine (15), isocorydine (16), corytuberine (14), and glaucine (17).

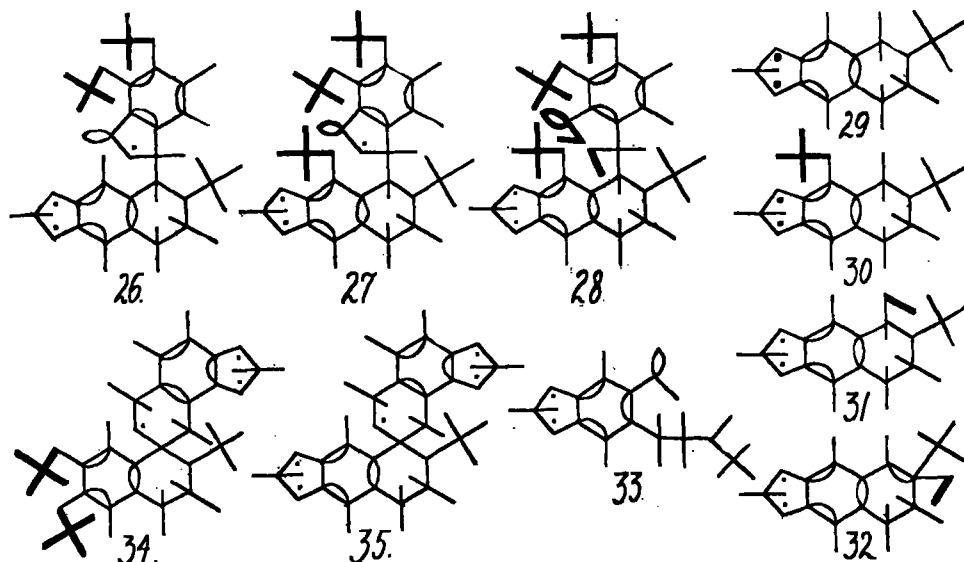
The substance *c* is derived from A by connecting the ninth and eleventh carbon atom of A with a -COO- group, thus forming a fourth pentatomic ring which is also present in the hydrastine group.

The substance *d* is derived from A by connecting the first and eleventh carbon atom of A by a -COO- group, thus forming a hexatomic ring, which is also present in the cryptopine and protopine groups.

The substance E is derived from A by connecting the fifteenth and sixteenth carbon atom of A, thus forming a hexatomic ring. To this group belong corydaline (36) and dehydrocorydaline (37).

The substance F is derived from B by connecting the seventh and twelfth carbon atom by an oxygen atom. Morphine (18) is then 6, 13-dihydroxy- of B, codeine (22) is 6-hydroxy-13-methoxy of B, dionine (24) is 6-hydroxy-13-ethoxy- of B, thebaine (25) is 6, 13-dimethoxy- of B.

The substance G is derived from B by the formation of a methylene-dioxy ether. Thus the -O.CH₂.O- group can be attached to the sixth and seventh carbon atom. Dicentrine (39) is 12, 13-dimethoxy- compound of G, while bulbo-carpine (38) is the 12-hydroxy-13-methoxy compound of G.



26—Hydrastine

27—Narcotine

28—Narceine

29—Hydro-hydrastinine

30—Hydro-cotarnine

31—Hydrastinine, carbinol form

32—Hydrastinine, ammonium form

33—Hydrastinine, aldehyde form

34—Cryptopine

35—Protopine

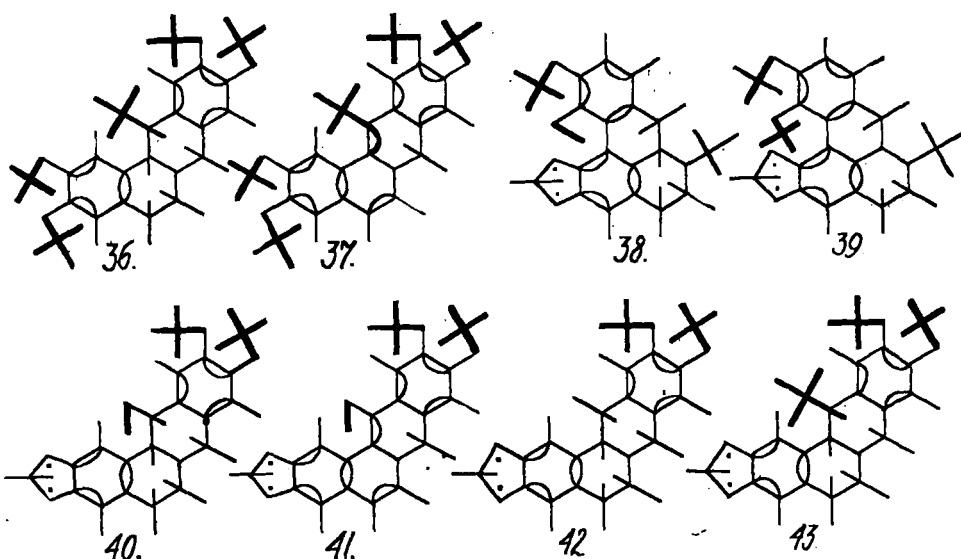
The substance *h* is derived from B by attaching the methylene-dioxy group to the twelfth and thirteenth carbon atom.

The substance I is derived from *c* by attaching the methylene-dioxy group to the sixth and seventh carbon atom. Hydrastine (26) is then 12, 13-dimethoxy-compound of I, and narcotine (27) is 8, 12, 13-trimethoxy compound of I.

The substance *j* is derived from *c* by attaching the methylene-dioxy group to the twelfth and thirteenth carbon atom.

The substance *k* is derived from *d* by attaching the methylene-dioxy group to the sixth and seventh carbon atom.

The substance L is derived from *d* by attaching the methylene-dioxy group to the twelfth and thirteenth carbon atom. Cryptopine (34) is 6,7-dimethoxy compound of L.



36—Corydaline

37—Dehydrocorydaline

38—Bulbocapnine

39—Dicentrine

40—Dihydroberberine

41—Berberine

42—Canadine

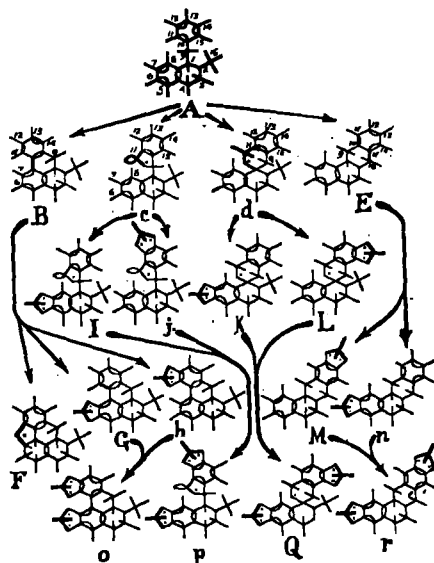
43—Artarine

The substance M is derived from E by attaching the methylene-dioxy group to the sixth and seventh carbon atom. Canadine (42) is 12, 13-dimethoxy-compound of M; berberine (41) is 9-hydroxy-12, 13-dimethoxy-compound of M; artarine (43) is the 9-methyl-12, 13-dimethoxy-compound of M.

The substance *n* is derived from E by attaching the methylene-dioxy group to the twelfth and thirteenth carbon atom.

The substance *o* is derived from G or *h* by attaching the methylene-dioxy group either to the 12th, and 13th, or to the 6th and 7th carbon atom; likewise *p* is derived from I or *j*.

In a similar way substance Q is derived from *k* or L, and finally the substance *r* from M or *n*. Protopine (35) is the substance Q.



It will be noticed that from the tricyclic compound A (papaverine group) there are derived four tetracyclic compounds (B, c, d and E), the additional ring being formed between the carbon atoms numbered 8-11, 9-11, 1-11, and 15-16, respectively. Alkaloids containing the structural system B and E are known, while the derivatives of c and d are found in the groups I, L, and Q. The unknown alkaloids, that is, the hydroxy and methoxy compounds, are given in the table.

Substitution usually takes place in the preferred positions 6.7- and 12.13-, whether it be by the hydroxy, methoxy, or ethoxy group. From each tetracyclic compound (B, c, d, E) there are two pentacyclic compounds derived by attaching the methylene-dioxy group, which forms the fifth ring, either in the 6.7- or 12.13- position; thus, G and M are 6.7- derivative while I and L are the 12.13- derivatives—these four types justify the prediction of h, j, k, and n.

Finally Q, the only hexacyclic compound of the series, has a methylene-dioxy group in both positions and indicates the possibility of the compounds o and p.

Some of the possible isomers are indicated in the attached list and it is highly probable that alkaloids corresponding to these formulas will be isolated. It contributes to the plausibility of this genetic relationship among important alkaloids, that the structures used in this paper have been established by independent workers; e. g., Goldschmidt, Fischer, Dobbie, Lauder, Pschorr, Freund, Parker, Robinson, Perkin, etc., etc., and thus the system of alkaloids might aid in the selection of the more probable form of a structure. In this connection it appears that the structure formula for morphine as given by Pschorr is the correct formula and more plausible than those given by Freund and others.

Systematic list of alkaloids derived and related to Compound A.

Derivatives of compound A = $C_{17}H_{19}N$:

$C_{17}H_{19}O_4N$ = 6.7.12.13-tetrahydroxy derivative

$C_{18}H_{21}O_4N$ = 6.7.12-trihydroxy-13-methoxy derivative

- 6.7.13-trihydroxy-12-methoxy derivative
 6.12.13-trihydroxy-7-methoxy derivative
 7.12.13-trihydroxy-6-methoxy derivative
 $C_{19}H_{23}O_4N$ = 6.7-dihydroxy-12.13-dimethoxy derivative
 6.12-dihydroxy-7.13-dimethoxy derivative
 6.13-dihydroxy-7.12-dimethoxy derivative
 7.12-dihydroxy-6.13-dimethoxy derivative
 7.13-dihydroxy-6.12-dimethoxy derivative
 12.13-dihydroxy-6.7-dimethoxy derivative
 $C_{20}H_{25}O_4N$ = 6-hydroxy-7.12.13-trimethoxy derivative
 7-hydroxy-6.12.13-trimethoxy derivative
 12-hydroxy-6.7.13-trimethoxy derivative
 13-hydroxy-6.7.12-trimethoxy derivative
 $C_{21}H_{27}O_4N$ = 6.7.12.13-tetramethoxy derivative = laudanosine
 Derivatives of unsaturated compound A = $C_{16}H_{14}N$:
 $C_{16}H_{14}O_4N$ = 6.7.12.13-tetrahydroxy derivative = paperoline
 $C_{17}H_{16}O_4N$ = trihydroxy-methoxy derivatives (4 compounds)
 $C_{18}H_{17}O_4N$ = dihydroxy-dimethoxy derivatives (6 compounds)
 $C_{19}H_{19}O_4N$ = hydroxy-trimethoxy derivatives (4 compounds)
 $C_{20}H_{21}O_4N$ = 6.7.12.13-tetramethoxy derivative = papaverine
 Derivatives of compound B = $C_{17}H_{17}N$:
 $C_{17}H_{17}O_4N$ = 6.7.12.13-tetrahydroxy derivative (1 compound)
 $C_{18}H_{19}O_4N$ = trihydroxy-methoxy derivatives (4 compounds)
 $C_{19}H_{21}O_4N$ = dihydroxy-dimethoxy derivatives = corytuberine and 5 isomers
 $C_{20}H_{23}O_4N$ = hydroxy-trimethoxy derivatives = corydine and 3 isomers
 $C_{21}H_{25}O_4N$ = 6.7.12.13-tetramethoxy derivative = glaucine
 Derivatives of compound C = $C_{18}H_{17}O_2N$:
 $C_{18}H_{17}O_6N$ = tetrahydroxy derivative (1 compound)
 $C_{19}H_{19}O_6N$ = trihydroxy-methoxy derivatives (4 compounds)
 $C_{20}H_{21}O_6N$ = dihydroxy-dimethoxy derivatives (6 compounds)
 $C_{21}H_{23}O_6N$ = hydroxy-trimethoxy derivatives (4 compounds)
 $C_{22}H_{25}O_6N$ = tetramethoxy derivative (1 compound)
 Derivatives of compound d = $C_{18}H_{19}ON$:
 $C_{18}H_{19}O_5N$ = tetrahydroxy derivative (1 compound)
 $C_{19}H_{21}O_5N$ = trihydroxy-methoxy derivative (4 compounds)
 $C_{20}H_{23}O_5N$ = dihydroxy-dimethoxy derivative (6 compounds)
 $C_{21}H_{25}O_5N$ = hydroxy-trimethoxy derivative (4 compounds)
 $C_{22}H_{27}O_5N$ = tetramethoxy derivative (1 compound)
 Derivatives of compound E = $C_{17}H_{17}N$:
 $C_{17}H_{17}O_4N$ = tetrahydroxy derivative (1 compound)
 $C_{18}H_{19}O_4N$ = trihydroxy-methoxy derivative (4 compounds)
 $C_{19}H_{21}O_4N$ = dihydroxy-dimethoxy derivative (6 compounds)
 $C_{20}H_{23}O_4N$ = hydroxy-trimethoxy derivative (4 compounds)
 $C_{21}H_{25}O_4N$ = tetramethoxy derivative (1 compound)
 $C_{22}H_{27}O_4N$ = 9-methyl-tetramethoxy derivative = corydaline
 Derivatives of compound F = $C_{17}H_{19}ON$:
 $C_{17}H_{19}O_3N$ = 6.13-dihydroxy derivative = morphine
 $C_{18}H_{21}O_3N$ = 6-hydroxy-13-methoxy derivative = codeine
 13-hydroxy-6-methoxy derivative = iso-codeine
 $C_{19}H_{23}O_3N$ = 6.13-dimethoxy derivative = thebaine
 6-hydroxy-13-ethoxy derivative = dionine
 13-hydroxy-6-ethoxy derivative = iso-dionine
 Derivatives of compound G = $C_{18}H_{17}O_2N$:
 $C_{18}H_{17}O_4N$ = 12.13-dihydroxy derivative (1 compound)
 $C_{19}H_{19}O_4N$ = 12-hydroxy-13 methoxy derivative = bulbocapnine

- $C_{20}H_{21}O_4N$ = 12.13-dimethoxy derivative = dicentrine
 Derivatives of compound *h* = $C_{19}H_{17}O_2N$:
 Similar to those of compound G
 Derivatives of compound I = $C_{11}H_{11}O_4N$:
 $C_{19}H_{17}O_4N$ = 12.13-dihydroxy derivative (1 compound)
 $C_{20}H_{19}O_6N$ = hydroxy-methoxy derivative (2 compounds)
 $C_{21}H_{21}O_6N$ = 12.13-dimethoxy derivative = hydrastine
 Derivatives of compound *j* = $C_{19}H_{17}O_4N$:
 Similar to those of compound I
 Derivatives of compound *k* = $C_{19}H_{19}O_2N$:
 Similar to those of compound L
 Derivatives of compound L = $C_{19}H_{19}O_3N$:
 $C_{19}H_{19}O_4N$ = dihydroxy derivative (1 compound)
 $C_{20}H_{21}O_4N$ = hydroxy-methoxy derivative (2 compounds)
 $C_{21}H_{23}O_6N$ = 12.13-dimethoxy derivative = cryptopine
 Derivatives of compound M = $C_{18}H_{18}O_2N$:
 $C_{18}H_{18}O_4N$ = 9.12.13-trihydroxy derivative (1 compound)
 $C_{19}H_{18}O_5N$ = dihydroxy-methoxy derivatives (3 compounds)
 $C_{20}H_{17}O_4N$ = 9-hydroxy-12.13-methoxy derivative = berberine
 $C_{21}H_{19}O_6N$ = 9.12.13-trimethoxy derivative (1 compound)
 Derivatives of compound *n* = $C_{18}H_{18}O_2N$:
 Similar to those of compound M
 Derivatives of compound *o* = $C_{19}H_{17}O_4N$:
 No hydroxy or methoxy derivatives possible
 Derivatives of compound *p* = $C_{20}H_{17}O_6N$:
 No hydroxy or methoxy derivatives possible
 Derivatives of compound *q* = $C_{20}H_{19}O_6N$ (protopine):
 No hydroxy or methoxy derivatives possible
 Derivatives of compound *r* = $C_{17}H_{15}O_4N$:
 No hydroxy or methoxy derivatives possible

THE EXTRACTION OF LICORICE.*

BY WILBUR L. SCOVILLE.

Licorice is one of the troublesome drugs from which to make galenical preparations. Its use chiefly as a flavoring agent, and the fact that its flavoring principle, glycyrrhizin, is easily soluble in water, and supposedly more soluble in alkaline solutions, have led to the general application of weak ammonia solutions as a menstruum.

But licorice root contains a large amount of soluble matter of an albuminoid character which is dissolved by the ammoniacal menstruum, and which is prone to mould or sour in the extract form, or to precipitate or even gelatinize from solution. Some samples of licorice root contain so much of this extraneous matter that it cannot be held in solution in fluidextract strength. Obviously this reflects upon the present U. S. P. process and menstruum.

The use of an alcoholic menstruum would easily solve that part of the problem, but such would be an unwarranted expense if other means can be found to satisfactorily extract and hold the flavoring principles.

At the New York meeting of the American Pharmaceutical Association Dr. Anthony Armentano recommended boiling water as the most satisfactory men-

* Read before Scientific Section, A. Ph. A., New Orleans Meeting, 1921.