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LXV.—*On the Relation between the Absorption Spectra and the Chemical Structure of Corydaline, Berberine, and other Alkaloids.*

By James J. Dobbie, M.A., D.Sc., and Alexander Lauder, B.Sc.

In a paper read before the Society in December, 1901 (Trans., 1902, **81**, 145), we communicated the results of our investigation on the constitution of corydaline, and showed that this alkaloid is closely related to berberine. We have since been engaged in the spectroscopic

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examination of these two alkaloids and their decomposition products, and we now propose to lay the results of this supplementary investigation before the Society, with the object mainly of showing that the spectroscopic method might, with advantage, be generally employed in such researches.

In a paper communicated to the Royal Society eighteen years ago by Professor Hartley (*Phil. Trans.*, 1885, Part II, 471), it is shown that the principal alkaloids give highly characteristic absorption spectra which can be used for their identification and for ascertaining their purity. It is further shown that alkaloids closely related to one another, like quinine and quinidine, cinchonine and cinchonidine, morphine and codeine, give very similar spectra. At the time at which this paper was published, however, little progress had been made with the investigation of the alkaloids, and it was not possible, therefore, to trace any close connection between their structure and their spectra.

The constitution of the principal members of the group of alkaloids to which corydaline and berberine belong, namely, papaverine, hydrastine, narcotine, and narceine, has now been definitely determined, and the examination of this group furnishes a good basis for the study of the relationship between the absorption spectra and the constitution of the alkaloids.

Since papaverine is, in some respects, more simply constituted than the other members of the group, it will be convenient to consider each of the others with reference to it. According to Goldschmiedt, the structure of papaverine is represented by the following formula:

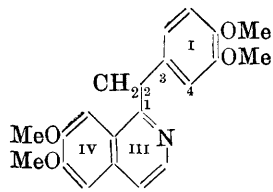

FIG. 1.

A graphic representation of the absorption spectra of papaverine is given in Fig. 8, p. 616. The spectra show two absorption bands, the first lying between $^1/\lambda$ 2998 ($\lambda = 3335$) and $^1/\lambda$ 3295 ($\lambda = 3035$), and the second between $^1/\lambda$ 3956 ($\lambda = 2528$) and $^1/\lambda$ 4555 ($\lambda = 2195$).

Hydrastine differs structurally from papaverine in the following particulars: (i) The *iso*quinoline nucleus is partially reduced. (ii) The two methoxyl radicles of the *iso*quinoline nucleus are replaced by a dioxymethylene group. (iii) A methyl group is attached to the nitrogen atom. (iv) A carbonyl group is attached to the carbon atom (4), and through the medium of an oxygen atom is also linked to carbon atom

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(2), which has only one atom of hydrogen attached to it. From this comparison, it is obvious that the two substances differ considerably in their constitution. On comparing the curve of the absorption spectra of hydrastine with that of papaverine (Figs. 10 and 8, pp. 617 and 616), it will be seen that there is a correspondingly wide difference between them; hydrastine exhibits slightly less general absorption than papaverine, and shows only one absorption band which is wider and much more persistent than either of the absorption bands of papaverine. Narcotine only differs from hydrastine in containing an additional methoxyl group attached to ring IV, and the two alkaloids give practically identical absorption spectra (Figs. 11 and 10, p. 617). Assuming the constitution of corydaline, as determined by us, to be correct, it is represented by the second of the following formulæ:

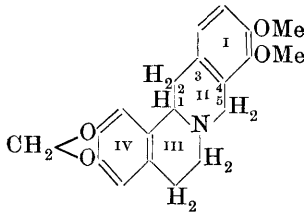

FIG. 2.—Tetrahydroberberine.

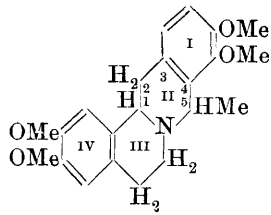

FIG. 3.—Corydaline.

On comparing this formula with that of papaverine, the differences will be seen to consist in the partial reduction of the *iso*quinoline nucleus and in the presence of carbon atom (5), which, with its associated methyl group, is linked on the one hand to carbon atom (4), and on the other to the nitrogen atom, thus forming a fourth closed chain in the molecule. Here, again, the difference between the absorption spectra and those of papaverine is very marked. The amount of general absorption is less, and there is only one absorption band, which is, however, better defined and more persistent than the papaverine bands (Figs. 8 and 12, pp. 616 and 618).

In discussing the relations between corydaline and berberine, it is to be remembered that corydaline corresponds to tetrahydroberberine, and berberine to dehydrocorydaline. The constitutional connection between corydaline and tetrahydroberberine is undoubtedly very close (Trans., 1902, **81**, 145), as a comparison of the formulæ (Figs. 2 and 3, above) will show, and between the spectra of the two substances there is also a very close relation (Figs. 12 and 13, p. 618), the only difference being that the general absorption of tetrahydroberberine is slightly greater than that of corydaline.

When papaverine is reduced to tetrahydropapaverine, it is brought structurally very near to corydaline. A comparison of the formulæ of the two substances shows that the former substance differs from the

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latter in the absence of carbon atom (5) of ring II with its associated hydrogen atom and methyl group. The spectra of the two compounds are almost identical (Figs. 9 and 12, pp. 616 and 618). Viewing corydaline as derived from tetrahydropapaverine by the addition of CH_2 forming a fourth closed chain in the molecule, it might have been anticipated that the difference between the absorption spectra of the two substances would be greater than is found to be the case. It should be noted, however, that ring II in corydaline is a reduced ring, and would not therefore exert the same influence on the absorption spectra as the formation of a pyridine ring. It might be expected to produce an effect comparable with that produced by the substitution of a dioxymethylene for two methoxyl groups, which, we shall show later, is slight in compounds of high molecular weight (Hartley, Trans., 1885, **47**, 691 ; Hartley and Dobbie, Trans., 1900, **77**, 846).

Narceine is the extreme member of this group. It has two benzene nuclei, but no pyridine ring, and in other particulars differs considerably in constitution from papaverine. The absence of any absorption band differentiates the spectra widely from those of the other members of the group (Fig. 29, p. 609).

We have shown (Dobbie and Lauder, *loc. cit.*) that corydaline and berberine give rise to a parallel series of derivatives. The absorption spectra of the corresponding derivatives are related to one another in the same way as the spectra of the parent substances. When corydaline is acted on with mild oxidising agents, four atoms of hydrogen are removed, and a yellow substance is obtained, which stands in the same relation to corydaline as berberine to tetrahydroberberine (Trans., 1902, **81**, 145).

Oxidation with dilute nitric acid converts corydaline and berberine respectively into the dibasic corydic and berberidic acids:

$$C_{13}H_6(CH_3)(OCH_3)_2\cdot N(CO_2H)_2,$$
Corydic acid.

$$C_{13}H_7(CH_2O_2)\cdot N(CO_2H)_2,$$
Berberidic acid.

whilst oxidation with permanganate gives rise, amongst other products, to corydaldine in the former case, and to ω-aminoethylpiperonylcarboxylic anhydride in the latter. The corresponding derivatives differ structurally from one another in the same way as corydaline and tetrahydroberberine, excepting that, in the case of corydaldine and ω-aminoethylpiperonylcarboxylic anhydride, ring II having disappeared, the difference between the two compounds is confined to the replacement of the two methoxyl groups of the former by dioxymethylene in the latter. The spectra of the corresponding derivatives (Figs. 16 and 17, and 20 and 21, pp. 620 and 622) exhibit the same close relationship as those of the

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alkaloids themselves. The general absorption of the berberine derivatives is, however, always slightly greater than that of the corresponding corydaline derivatives. This is probably due to the influence of the dioxymethylene group, and the correctness of this inference is supported by the fact that piperonylic acid, $C_6H_3(CH_2O_2)\cdot CO_2H$, shows slightly greater general absorption than veratric acid, $C_6H_3(OCH_3)_2\cdot CO_2H$ (Figs. 18 and 19, p. 621).

Whilst the spectra of corydaldine and ω-aminoethylpiperonylcarb-

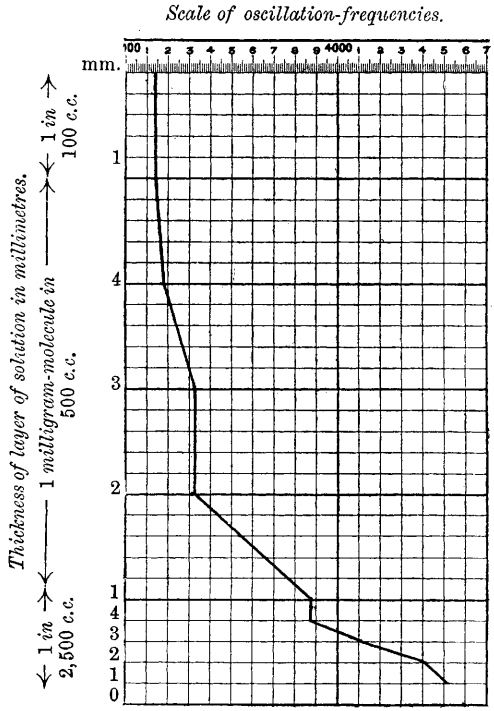

FIG. 29.—*Narceine*, $C_{23}H_{27}O_8N + 3H_2O$. (*In alcoholic solution.*)

oxylic anhydride approach one another closely, they differ widely from those of cotarnine and hydrastinine (Figs. 20, 21, and 22, pp. 622 and 623), the corresponding oxidation products of narcotine and hydrastine respectively. The difference finds a sufficient explanation in the fact that whilst all four substances are nearly related, the chain containing the nitrogen atom, which is closed in the two former, is open in the two latter. When, however, hydrastinine is oxidised by means of an aqueous solution of potassium hydroxide, the open chain is closed, and

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oxyhydrastinine (Figs. 6 and 7, below), the absorption spectra of which are almost identical with those of corydaldine and ω-aminoethylpiperonylcarboxylic anhydride, is produced (Figs. 20, 21, and 23). The relationship between these compounds is shown by the following formulæ:*

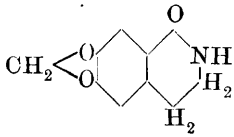

FIG. 4.—ω-Aminoethylpiperonylcarboxylic anhydride.

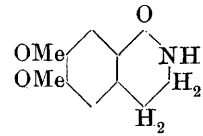

FIG. 5.—Corydaldine.

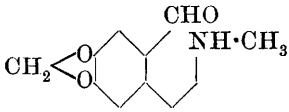

FIG. 6.—Hydrastinine.

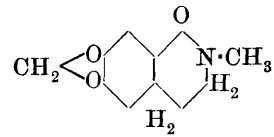

FIG. 7.—Oxyhydrastinine.

Again, when the pyridine ring of cotarnine and hydrastinine is closed by the conversion of these substances into their salts or by their reduction to hydro-derivatives, the changes of structure are reproduced in a striking manner in the spectra. As, however, additional points of considerable interest have arisen in connection with the study of these compounds, we postpone the further discussion of them to a future paper.

We proceed now to consider more fully the influence of specific differences of constitution on the spectra, and to indicate how the relationships established may be used in the study of alkaloids of unknown constitution.

It is now known that many alkaloids which possess the same formula are stereoisomerides. Alkaloids which are related in this way give, like other stereoisomerides, identical spectra (Hartley and Dobbie, Trans., 1900, **77**, 498 and 509). Illustrations of this are afforded by *d*-corydaline and *i*-corydaline (Fig. 12), narcotine and gnoscopine (Fig. 11), tetrahydroberberine and canadine (Fig. 13). Quinidine (conquinine) and cinchonidine also give absorption spectra identical with those of quinine and cinchonine respectively, of which substances they are probably stereoisomeric forms (Figs. 24 and 25, p. 624). This relationship might sometimes be used to assist the investigation of cases of suspected stereoisomerism. Where, for example, two compounds of

* Since the above was written, we have found that cotarnine and hydrastinine in alcoholic solution do not possess the constitution commonly assigned to them. This, however, in no way affects the above argument, since there is an important constitutional difference between oxycotarnine and oxyhydrastinine on the one hand, and cotarnine and hydrastinine on the other, whatever formulæ be accepted for the two latter.

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the same formula are known, one active and the other inactive, it may be inferred that they are not optical isomerides if they have different absorption spectra.

A case in point is afforded by canadine and papaverine, which possess the same molecular formulæ but give widely different absorption spectra. Even if it were not known otherwise that these two substances are structurally different, this might be inferred from the differences in their absorption spectra (Figs. 8 and 13, pp. 616 and 618). Canadine has long been regarded as a stereoisomeride of tetrahydroberberine This question might have been decided by a comparison of the spectra of the two substances, and with this end in view we had already undertaken their comparison, when Gadamer (*Arch. Pharm.*, 1901, **239**, 648) published an account of the resolution of tetrahydroberberine into its active components, and showed that one of them was identical with canadine. The result of the spectroscopic examination points to the same conclusion (Fig. 13, p. 618).

According to Gadamer (*Arch. Pharm.*, 1902, **240**, 19), inactive corydaline exists in two modifications, one melting at 134—135°, and the other at 158—159°. The latter of these only can be resolved into *d*- and *i*-corydalines.* The inactive modification of lower melting point which cannot be resolved, might either be a structural or a stereoisomeric modification of corydaline. The fact that its spectra are identical with those of natural corydaline (Fig. 12) affords strong presumption in favour of the view that the two are structurally identical.

Homologous alkaloids give practically identical spectra. It has been shown from the examination of many homologous substances that the replacement of an atom of hydrogen by a methyl group produces very little effect on the spectra even when the compounds are of low molecular weight (Hartley, *Phil. Trans.*, 1879, Part I, 257). The effect is still less noticeable when the replacement occurs in substances of high molecular weight, such as the alkaloids.

Codeine and morphine (Fig. 26, p. 612) were examined by Hartley (*Phil. Trans.*, 1885, Pt. II, 471), and his curves show clearly the relation between these two compounds. We have examined numerous other cases of homologous alkaloids, and find that they all give practically identical spectra. The curves of corybulbine, $C_{21}H_{25}O_4N$ (Fig. 27, p. 625), and corydaline, $C_{22}H_{27}O_4N$ (Fig. 12), and those of quinine, $C_{20}H_{24}O_2N_2$, and cupreine, $C_{19}H_{22}O_2N_2$ (Fig. 24), may be referred to as examples. When, therefore, the formulæ of two alkaloids differ by CH_2, it may

* In 1901, we succeeded in resolving *i*-corydaline into its optically active forms, and in separating out the dextro- but not the lævo-modification. We supposed that we had effected the resolution of ordinary corydaline, but the specimen of *i*-corydaline with which we worked may have become, unknown to us, transformed into the modification of higher melting point since described by Gadamer.

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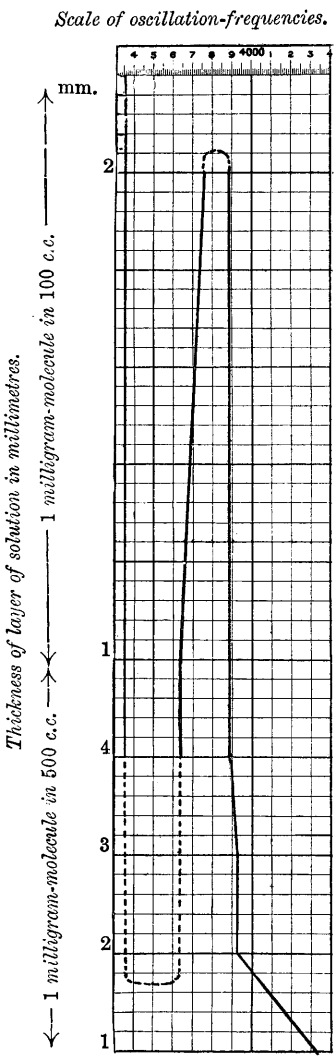

FIG. 26.—*Morphine*, $C_{17}H_{19}O_3N + H_2O$.
(*In alcoholic solution.*)
The curve of codeine is identical with this (*See also Hartley*, loc. cit.).

be inferred with certainty, if they give dissimilar spectra, that they are not homologous. On the other hand, it cannot be inferred with certainty that two substances which differ by CH_2, and have very similar spectra, are really homologous, because the difference in the formulæ may be due to other slight structural differences.

The formula of bulbocapnine, $C_{19}H_{19}O_4N$, differs from that of papaverine, $C_{20}H_{21}O_4N$, and of tetrahydroberberine, $C_{20}H_{21}O_4N$, by CH_2, but the wide difference between the spectra of all three substances (Figs. 28, 8, and 13) renders it highly improbable that bulbocapnine is homologously related to either of the others. What is known of the chemistry of bulbocapnine entirely bears out this conclusion (Gadamer and Ziegenbein, *Arch. Pharm.*, 1902, **240**, 81).

Many minor modifications of structure in alkaloids are unaccompanied by any marked difference in the spectra even where the same modifications would produce an appreciable effect on the spectra of compounds of low molecular weight. Corydaline, tetrahydroberberine, and their derivatives afford instances in which the replacement of $2OCH_3$ by CH_2O_2 does not markedly alter the spectra, and narcotine and hydrastine furnish an example in which the introduction of an additional methoxyl group is unaccompanied by any considerable effect.

The case of cinchotenine and cinchonine may be quoted as another instance. In cinchotenine the side chain $\cdot CH{:}CH_2$ of cinchonine is oxidised to a carboxyl group without the spectra being appreciably affected. The resemblance between

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the two series of spectra is so close that it would at once suggest a near structural relation of the substances, even if we knew nothing of their chemistry.

The reduction of closed chain compounds is accompanied by a complete change in the character of the spectra (Hartley, Trans., 1885, **47**, 691, and Hartley and Dobbie, Trans., 1900, **77**, 846). Good illustrations of this are afforded by the widely different spectra of berberine and tetrahydroberberine (Figs. 15 and 13), dehydrocorydaline and corydaline (Figs. 14 and 12), papaverine and tetrahydropapaverine (Figs. 8 and 9). There are, however, cases in which partial reduction produces very little change. Hydroquinine, $C_{20}H_{26}O_2N_2$, is unquestionably very closely related to quinine, $C_{20}H_{24}O_2N_2$, from which its formula only differs in containing two more atoms of hydrogen. The difference between the spectra of the two substances is hardly perceptible, and it is highly probable, therefore, that the addition of the two atoms of hydrogen is unaccompanied by any important change of structure. The change probably consists in the reduction of the side chain.

From the examination of a large number of alkaloids,* we believe it may be laid down as a general rule that those which agree closely in structure give similar absorption spectra, whilst those which differ in essential points of structure give dissimilar spectra.

This principle has already been recognised and applied in previous investigations, but it is probably capable of a more extended application in the case of the alkaloids than in that of any other group of substances. This is due to the fact that most of these compounds have a high molecular weight, and changes may be effected in their molecules without alteration of the spectra which, in substances of lower molecular weight, would be attended by wide differences. Thus, the essential identity of constitution subsisting between two alkaloids can often be detected by the spectroscope in spite of differences of structure which, in substances of lower molecular weight, would give rise to spectra so dissimilar that no close chemical relationship between them could be suspected. An example of this is afforded by the absorption spectra of piperonylic and veratric acids, from which no safe conclusion could be drawn as to the relationship of the two substances, whereas a comparison of the absorption spectra of corydaline and tetrahydroberberine, between which the same difference exists, leaves no doubt as to the essential similarity of their structure. Again, cinchonine and cinchotenine give

* We have made an independent examination of more than thirty alkaloids, including quinine, cinchonine, cinchonidine, cinchonamine, homocinchonidine, quinidine, cupreine, hydroquinine, strychnine, brucine, papaverine, narcotine, gnoscopine, narceine, morphine, codeine, thebaine, laudanine, laudanosine, cryptopine, protopine, hydrastine, canadine, berberine, corydaline, bulbocapnine, corybulbine, corytuberine, and chelidonine.

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practically identical spectra, whereas styrolene and benzoic acid, which differ in the same way, give very different spectra. If, therefore, an alkaloid of unknown constitution is found to give spectra closely resembling those of an alkaloid of known constitution, it may with great probability be inferred that the two only differ in the details of their structure.

The study of absorption spectra is thus of real practical value in the investigation of the alkaloids, and we believe that, if systematically used in the manner we have indicated, it might often be the means of saving much time and labour in their chemical investigation, especially in dealing with a large number of closely related compounds such as the lesser known alkaloids of the cinchona bark.

Experimental.

For the specimens of the opium alkaloids, including gnoscopine, we are indebted to the kindness of Messrs. T. and H. Smith, of Edinburgh, and for the specimens of oxyhydrastinine and ω-aminoethylpiperonylcarboxylic anhydride, to Professor W. H. Perkin, jun. The specimens of inactive and artificial corydaline, corybulbine, tetrahydroberberine, tetrahydropapaverine, dehydrocorydaline, corydic and berberidic acids, corydaldine, and hydrastinine were prepared in the College laboratory, and our best thanks are due to Messrs. C. K. Tinkler, K. S. Caldwell, and Ed. Jones for assisting in the preparation of some of these substances, and to Mr. C. P. Finn for assisting in photographing the spectra. The remaining alkaloids were obtained by purchase. In every case the specimens were tested as to their purity, and, where necessary, subjected to purification.

Whenever possible, specimens were obtained from at least two distinct sources, and several independent examinations were made of each specimen.

The method adopted in photographing the spectra and in representing them graphically is that employed in the paper on isatin and carbostyril (Trans., 1899, **75**, 640), and fully described in earlier papers by Hartley. In every case, equimolecular solutions were employed. Starting with 1 mill.-mol. in 100 c.c., layers of 5—1 mm. were successively photographed; the solution was then diluted to five times its volume (so that 1 mill.-mol. was then contained in 500 c.c.) and the solution photographed as before. The dilution was continued until the whole spectrum was transmitted. In drawing the curves, the ordinate representing thickness of layer is reduced at each dilution to 1/5 of its former size. Each vertical scale division represents, therefore, an equal number of molecules in solution. The abscissæ are reciprocals of wave-lengths. Owing to the slight

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solubility of some of the substances examined, it was not always possible to get a solution of 1/100, and thicker layers of a more dilute solution had to be employed. In such cases, for convenience of reference, we have, in drawing the curves, plotted 25 mm. of a solution of 1/500 as equivalent to 5 mm. of a solution of 1/100. Except in the case of hydrastine, all the curves are drawn to the same scale. The position of the transmitted portions of the spectra and of the absorption band have been marked on one of the curves (Fig. 9, p. 616).

The tables of measurements from which the curves were drawn will be included in the next report of the committee of the British Association appointed to investigate the relation between the chemical constitution and the absorption spectra of organic substances.

We may remark that it is difficult by means of curves to give a proper representation of the plates, it being found impracticable to represent adequately differences of intensity as well as extent of absorption upon which the similarity or difference between two plates often to a large extent depends.

By far the most satisfactory comparison is that which is made by the actual inspection of the photographs. When reasonable care is taken to work under similar conditions, the results are remarkably constant. We have never discovered any discrepancy between the photographs of the same preparation, even when taken by different operators at wide intervals of time. Professor Hartley having worked with constant weights and not with molecular quantities of the alkaloids, we have found it necessary, for purposes of comparison, to repeat the examination of a few of the alkaloids which he had previously examined. In so far as it is possible in such cases to compare the results, they show remarkably close agreement.

We gladly avail ourselves of this opportunity to express our thanks to Professor Hartley for lending us the apparatus used in the spectroscopic examination of the alkaloids, as well as for much valuable assistance during the course of the investigation.

UNIVERSITY COLLEGE OF NORTH WALES,
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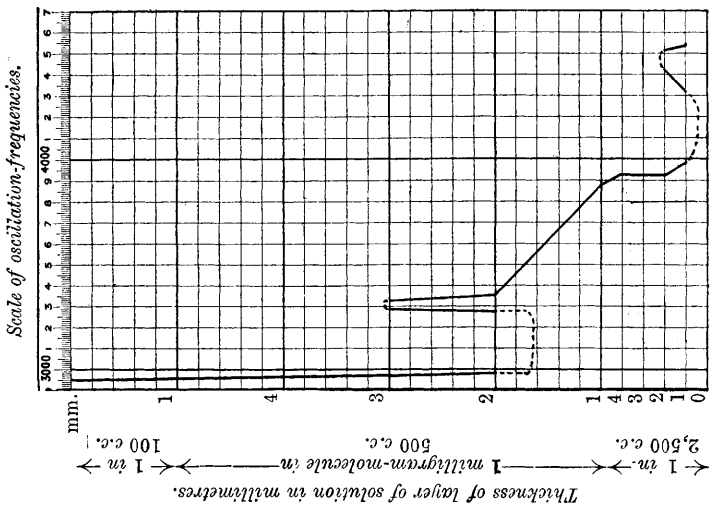

FIG. 8.—*Papaverine*, $C_{20}H_{21}O_4N$.
(*In alcoholic solution.*)
[*Cf.* Hartley, *Phil. Trans.*, 1885, Pt. II., 471.]

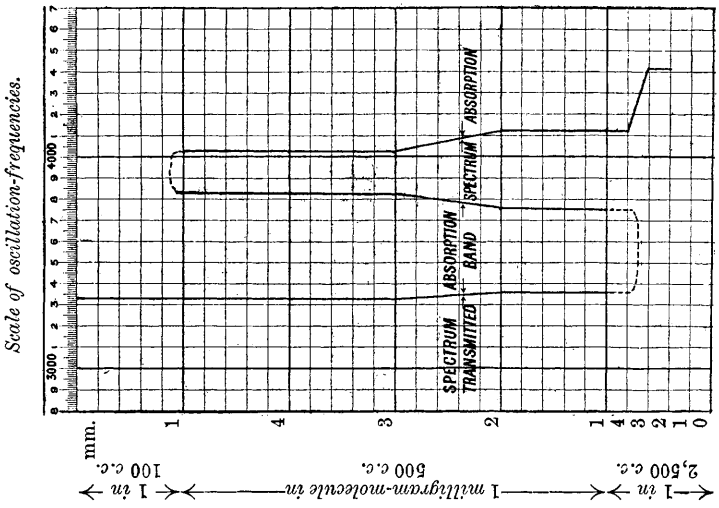

FIG. 9.—*Tetrahydropapaverine*, $C_{20}H_{25}O_4N$.
(*In alcoholic solution.*)

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FIG. 11.—*Narcotine*, $C_{22}H_{23}O_7N$.
(*In alcoholic solution.*)
(*See also Hartley*, loc. cit.)
The curve of gnoscopine is identical with this.

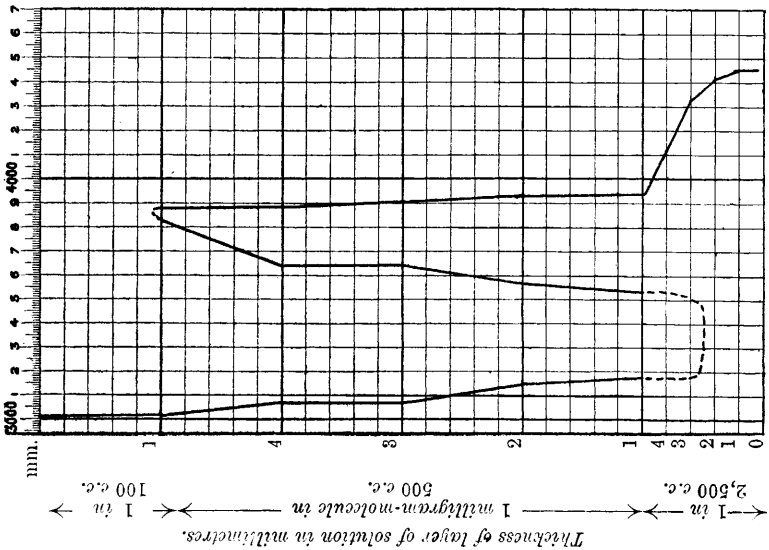

FIG. 10.—*Hydrastine*, $C_{21}H_{21}O_6N$.
(*In alcoholic solution.*)

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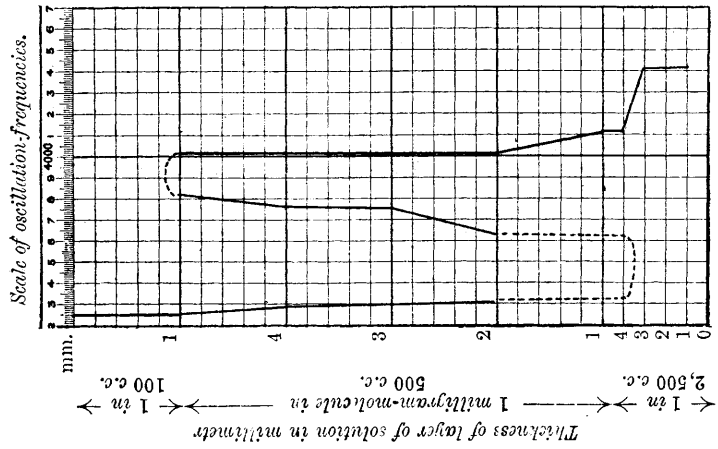

FIG. 13.—*Tetrahydroberberine*, $C_{20}H_{21}O_4N$. (*In alcoholic solution.*) *The curve of canadine is identical with this.*

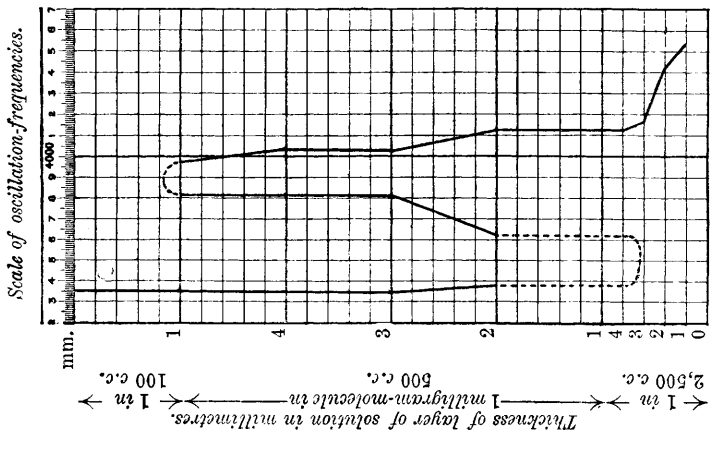

FIG. 12.—*Corydaline*, $C_{22}H_{27}O_4N$. *The curves of artificial corydaline and of i-corydaline are identical with this.* (*In alcoholic solution.*)

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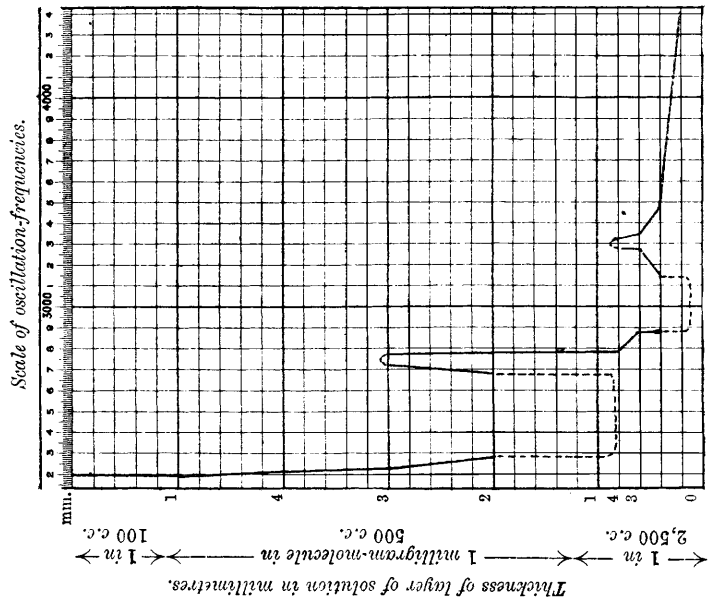

FIG. 14.—*Dehydrocorydaline nitrate*, $C_{22}H_{23}O_4N{\cdot}HNO_3 + 2H_2O$. (*In aqueous solution.*)

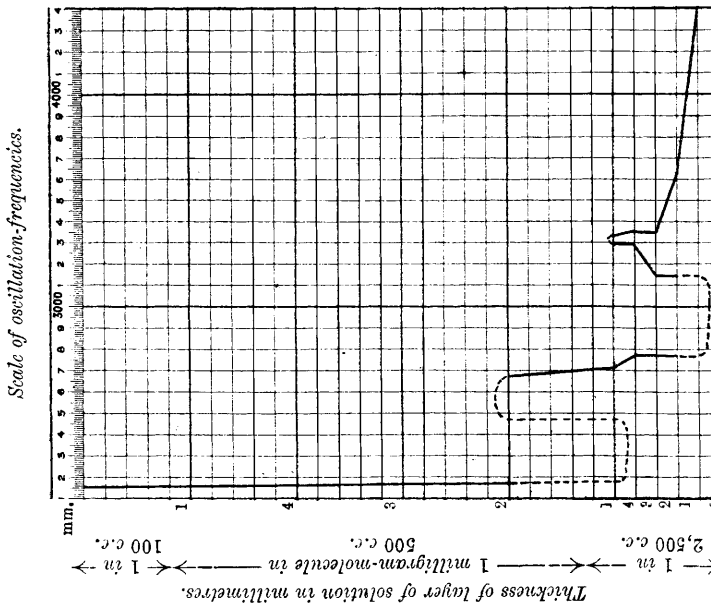

FIG. 15.—*Berberine nitrate*, $C_{20}H_{17}O_4N{\cdot}HNO_3$. (*In aqueous solution.*)

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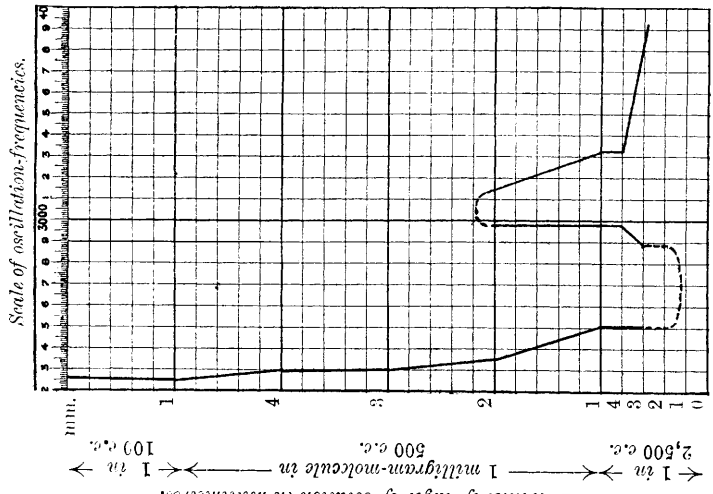

FIG. 17.—*Berberidic acid*, $C_{13}H_7N(CH_2O_2)(CO_2H)_2$. (*In aqueous solution.*)

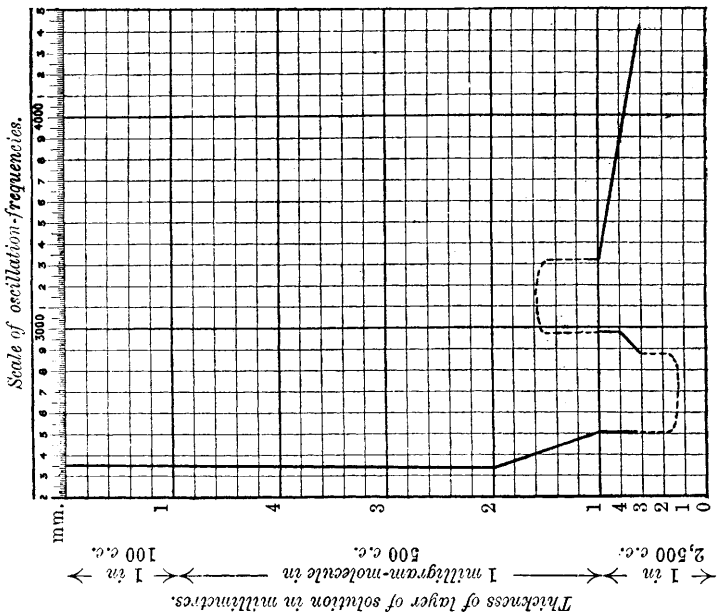

FIG. 16.—*Corydic acid*, $C_{14}H_9N(OCH_3)_2(CO_2H)_2 + \frac{1}{2}H_2O$. (*In aqueous solution.*)

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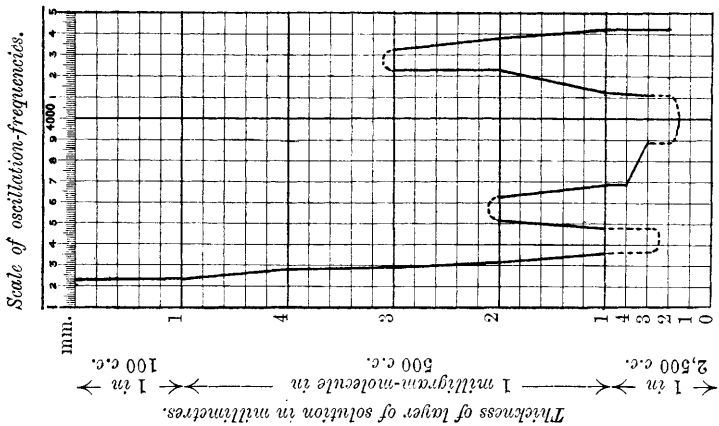

FIG. 18.—*Veratric acid*, $C_6H_3(OCH_3)_2CO_2H + 2H_2O$. (*In alcoholic solution.*)

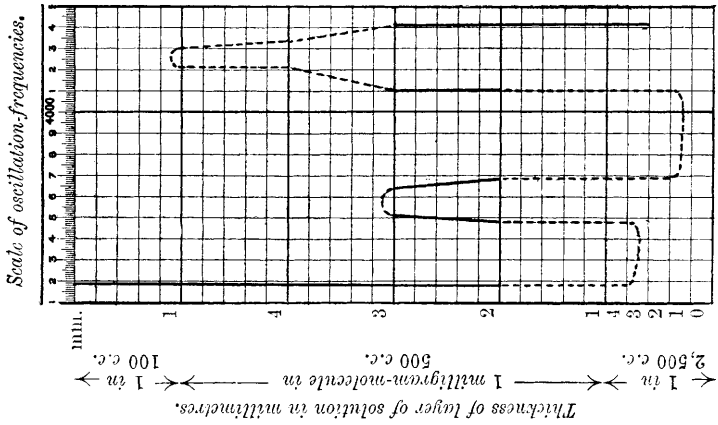

FIG. 19.—*Piperonylic acid*, $C_6H_3(CH_2O_2)CO_2H$. (*In alcoholic solution.*)

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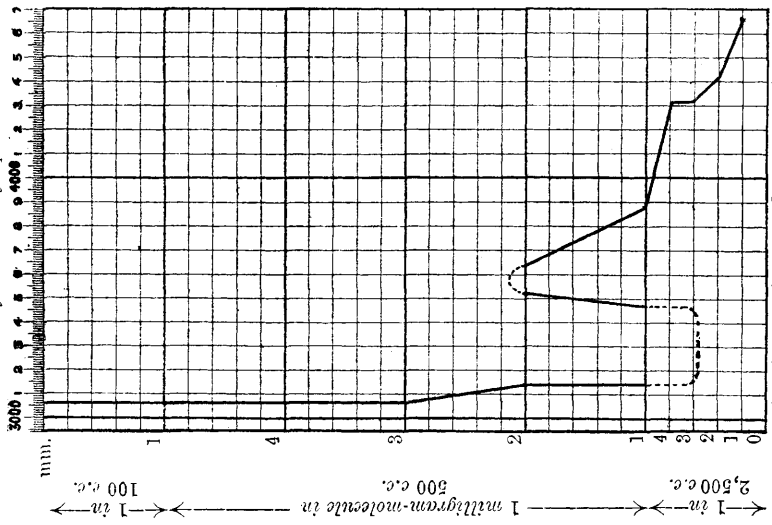

FIG. 21.—*ω-Aminoethylpiperonylcarboxylic anhydride*, $C_9H_7ON(CH_2O_2)$. (*In alcoholic solution.*)

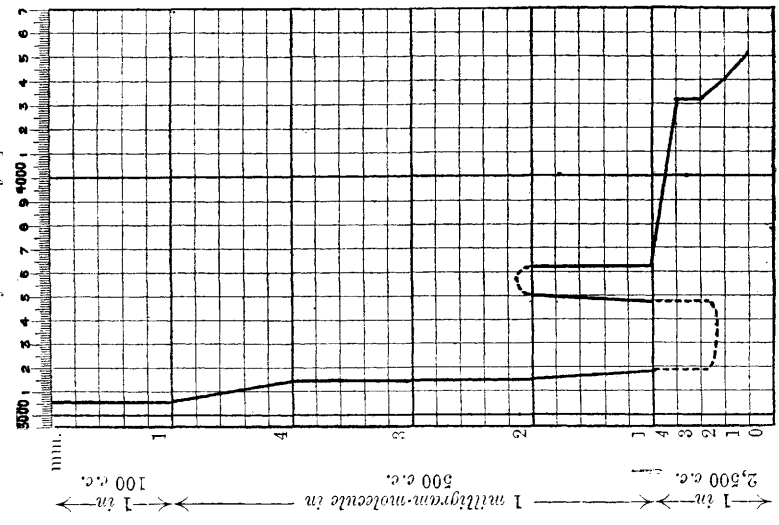

FIG. 20.—*Corydaldine*, $C_9H_7ON(OCH_3)_2$. (*In aqueous solution.*)

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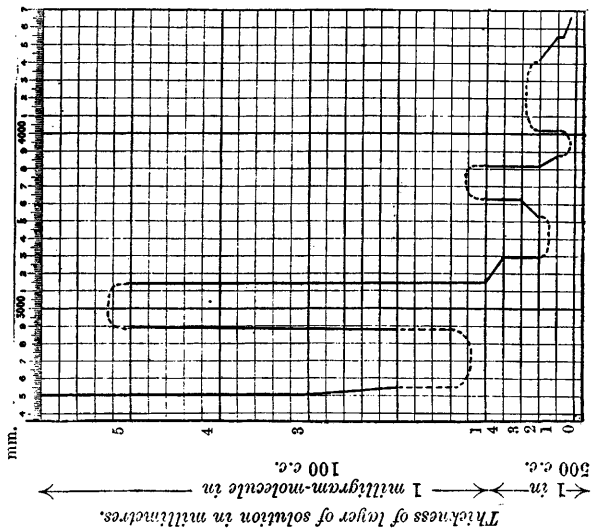

FIG. 22.—*Hydrastinine*, $C_{11}H_{13}O_2N$.
(*In alcoholic solution.*)

NOTE.—*The scale in this case is only one-fifth of the scale on which the other curves are drawn.*

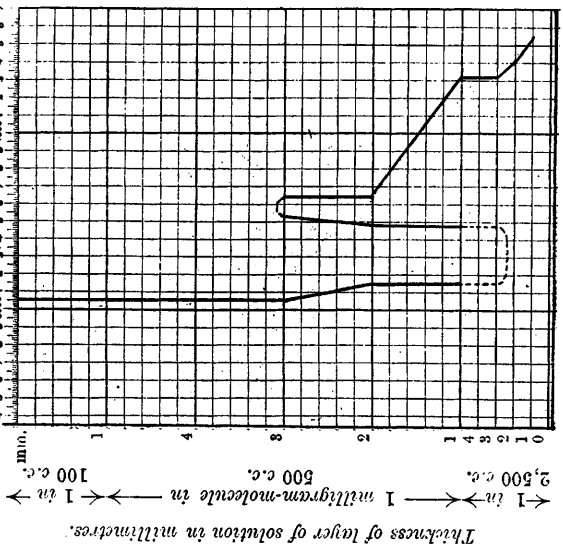

FIG. 23.—*Oxyhydrastinine*, $C_{10}H_9ON(CH_3O_2)$.
(*In alcoholic solution.*)

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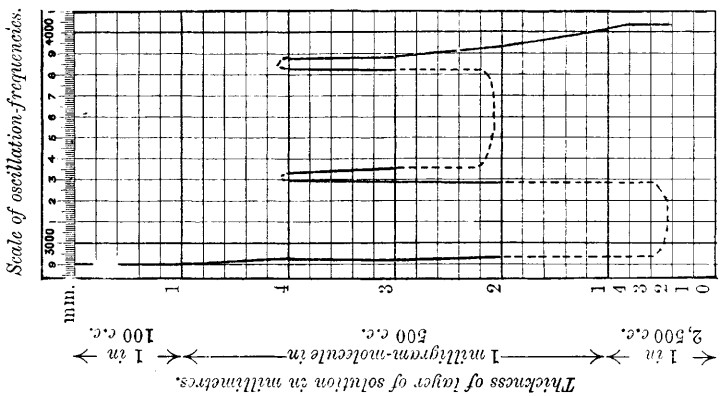

FIG. 24.—*Quinine*, $C_{20}H_{24}O_2N_2$.
(*In alcoholic solution.*)
(*See also Hartley*, loc. cit.)
The curves of quinidine and cupreine are identical with those of quinine.

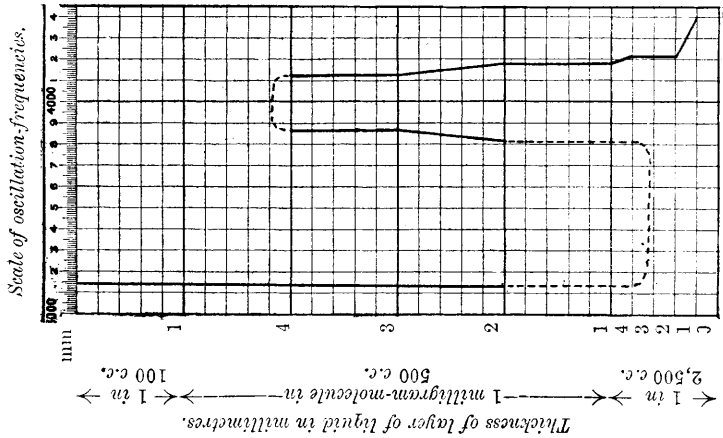

FIG. 25.—*Cinchonine*, $C_{19}H_{22}O_2N$.
(*In alcoholic solution.*)
(*See also Hartley*, loc. cit.)
The curve of cinchonidine is identical with this.

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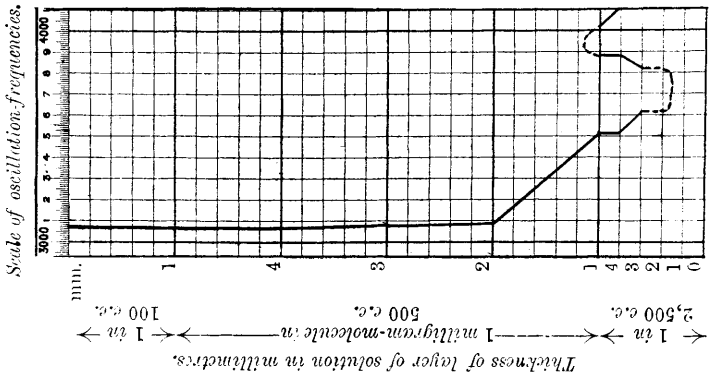

FIG. 28.—*Bulbocapnine*, $C_{19}H_{19}O_4N$. (*In alcoholic solution.*)

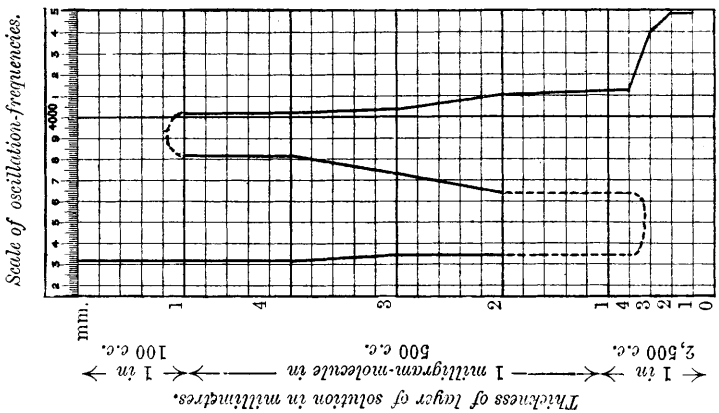

FIG. 27.—*Corybulbine*, $C_{21}H_{25}O_4N$. (*In alcoholic solution.*)