THE OPTICAL IDENTIFICATION OF ALKALOIDS.*

BY GEORGE L. KEENAN.

Although the immersion method for the identification of crystalline substances has been discussed by many workers, those who are not familiar with the polarizing microscope may be interested in the procedure followed in the optical study of alkaloids. The value of the optical-crystallographic constants of crystalline substances in the identification of minerals has long been recognized by mineralogists. More recently these constants have been found to be useful in the identification of synthetic substances, both inorganic and organic, as shown by Wright (1), Wherry (2, 3) and Keenan (4, 5, 6). A few alkaloids have been referred to in some of the papers cited, but several additional ones are included here.

In order to study the crystalline alkaloids to best advantage, a microscope with a revolving stage and equipped with nicol prisms which can be adjusted so that their vibration planes are exactly "horizontal" (right and left) and "vertical" (forward and backward) is essential. An ocular with crosshairs in positions corresponding with these vibration planes must be used. A 4-millimeter and an 8- or 16-millimeter objective completes the necessary equipment. The microscope should also have a slit in the body tube for the insertion of a selenite plate and it should be provided with a substage condenser and diaphragm. The immersion media required are oily liquids of known refractive index (previously determined on a refractometer), these liquids most conveniently consisting of mixtures of mineral oil (n = 1.49), monochloronaphthalene (n = 1.66), and occasionally methylene iodide (n = 1.74). These oils are usually mixed in such proportions that each differs in n from the next by 0.005.

The study of crystalline substances with the polarizing microscope will show that all such substances can be classified optically into two groups—singly refractive (isotropic) and doubly refractive (anisotropic). If they are singly refractive, they will exhibit no change but will remain dark when the microscope stage is revolved with the nicols crossed. Doubly refractive substances, on the other hand, will appear alternately bright and dark under the same conditions. The common alkaloids and their salts are doubly refractive.

In order to determine the refractive indices by this method, the plan is to immerse the finely powdered crystalline alkaloid in successive liquids of known refractive index and match the index of the crystal fragments against that of the liquid. In determining the refractive index, advantage is taken of the fact that the greater the difference in refractive index of object and mounting medium, the greater the visibility of the former. Conversely, the smaller this difference, the weaker the relief of the object in the menstruum.

Being doubly refractive, all of the alkaloids have at least two refractive index values that may be useful for determinative work. To be sure, in making a complete description of a new substance, it is advisable to determine certain additional optical constants, but it is not necessary to consider these here.

The following procedure has been found to be convenient in the optical study of alkaloids:

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* Scientific Section, A. Ph. A., Diamond Anniversary meeting, St. Louis, 1927.

Mount a minute quantity of the finely powdered crystalline material in a drop of oily liquid on a microscopical slide and apply the cover-glass. Examine the preparation in ordinary light, noting any significant characteristics, such as habit. The material usually consists of grains of various sizes and shapes, many of them extinguishing sharply when the stage is revolved with nicols crossed, others remaining bright.

In determinative work, pay particular attention to fragments which extinguish sharply. Place one of these grains in an extinction position (crossed nicols), and remove the upper nicol, leaving the polarizer in place. Such a crystal will then exhibit one of three phenomena:

1. The contour or outline will have completely disappeared;

2. The fragment will brighten, *i. e.*, the light will converge toward its center, when the microscope tube is moved slightly upward with the fine adjustment screw, indicating that the refractive index of the fragment (in the crystallographic direction which lies parallel to the plane of the polarizer) is higher than that of the liquid;

3. The light will pass out of the fragment and into the liquid (diverge) when the tube is raised, showing the liquid to possess a higher refractive index than that of the crystal fragment in that crystallographic direction.

Then revolve the microscope stage to a position 90° from the first, thereby placing the fragment in another extinction position, and repeat the observations just described. If the refractive index of the crystal fragment has been matched against that of the liquid, *i. e.*, all outline of the fragment has disappeared when lying in one or the other position, one of its indices may have been determined.

The identification of many of the alkaloids is simple when this method is used, whereas their determination, particularly in mixtures, is often laborious and difficult when chemical methods are used. In view of the marked difference in the optical properties of the alkaloids and their salts already studied, it has seemed worth while to continue the work on all those which can be obtained in a crystalline form for study by this method. It will be of interest at this time, however, to indicate how certain common alkaloids can be differentiated by means of their refractive indices. The following table and directions illustrate how such data can be arranged and used in determinative work.

Mount a small portion of the finely powdered material in the first of the oily liquids indicated in the left-hand column of the table and examine it between crossed nicols. Select a well-defined crystal and bring it to an extinction position. Now remove the upper nicol (analyzer) and partially close the diaphragm. If one of the eight substances listed is represented, it will match in refractive index one of the liquids indicated in the left-hand column, in one crystallographic direction. In case the crystal is matched, its outline will be invisible, indicating that its refractive index in the crystallographic direction lying parallel to the plane of the polarizer is identical with that of the immersion liquid. If the first liquid chosen does not match the crystal when this lies in the extinction position first selected, revolve the stage 90°, to bring the crystal to another extinction position, try the next liquid, and so on. Ultimately a liquid which matches the crystal in one direction will be found.

Another preparation of the same alkaloid is made in one of the liquids given in the table in line with the index already determined. Repeat the procedure until matching occurs, the crystal then lying in a crystallographic direction 90° from that in which the other index was determined.

In this manner the two significant indices of the substance are determined, and the alkaloid is thus differentiated from the others listed.

When the material consists of rods or needles, the determination of the refractive indices is simpler than when it consisted of irregular fragments. Morphine sulphate, for example, crystallizes in needles. When one of these is so oriented that it is parallel to the vibration plane of the polarizer (parallel to one cross-hair, which should be ascertained in advance), it will be found to match liquid 1.545. If another portion of this alkaloid is mounted in liquid 1.632 and one of the rods oriented at right angles to the vibration direction of the lower nicol, matching will occur in this crystallographic direction.

DETERMINATIVE TABLE OF ALKALOIDS.

Refractive index.	Remarks.	Alkaloid.
1.535	Always shown crosswise on rods; confirm by immersing in liquid 1.686	Brucine sulphate
1.545	Shown lengthwise on rods; confirm by immersing in liquid 1.632	Morphine sulphate
1.555	Usually shown on every fragment in one extinction position; confirm by mounting in liquid 1.595	Atropine
1.560	Shown on fragments extinguishing sharply with crossed nicols; confirm by immersing in liquid 1.610	Heroin
1.560	Shown lengthwise on rods; confirm by mounting in liquid 1.660	Codeine sulphate
1.580	Shown on fragments extinguishing sharply with crossed nicols; confirm by immersing in liquid 1.645	Morphine
1.600	Shown crosswise on rods, many of them slightly curved; confirm by mounting in liquid 1.685	Quinine sulphate
1.600	Found on thin, flaky plates; confirm by mounting in liquid 1.620	Cocaine hydrochloride

The polarizing microscope can be practically applied to the qualitative analysis of mixtures of alkaloids and the immersion method of identification is one of the quickest and most convenient ones to apply to this group of substances. Such a method, of course, requires practice, and, in the hands of the beginner, close attention to details of manipulation. Once the technic is acquired, however, it is a simple matter to determine the refractive indices of a substance, these, fortunately, being the most readily obtained of all the optical constants and the most useful in analytical work.

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FOOD, DRUG AND INSECTICIDE ADMINISTRATION,
U. S. DEPARTMENT OF AGRICULTURE,
WASHINGTON, D. C.

A PRESCRIPTION INCOMPATIBILITY THAT HAS BECOME A CLASSIC.*

BY EDWARD KREMERS.

In the April number of the *American Druggist*, the editor of this well-known journal comments editorially on "The Mysterious Affair at Styles," a detective story by Agatha Cristie. Commenting upon the plot under the caption "Murder by pharmaceutical incompatibility," the editor makes the following statement: "The pharmacist will be interested in learning that the murder in this mysterious affair was accomplished by the introduction into a tonic containing strychnine of a bromide which precipitated out the strychnine from the mixture leaving sufficient strychnine in the last dose to prove fatal. The criminals would have escaped detection but for the trouble they took to direct suspicion against an innocent member of the household. The detective in the case quotes from the pages of the "Art of Dispensing," one of the best books on the subject prepared by that admirable editor and accomplished pharmacist, the late Peter MacEwan. The item quoted follows:

"The following prescription has become famous in textbooks:

Strychnine[1] Sulph.	gr. i.
Potassii Bromid[1]	dram vii.
Aqua[1] qs.[1]	oz. viii.
Fiat mistura.	

"This solution deposits in a few hours the greater part of the strychnine salt as an insoluble bromide in transparent crystals. A lady in England lost her life by taking a similar mixture. The precipitated strychnine collected at the bottom, and in taking the last dose she swallowed nearly all of it.

"The patient is taking a tonic containing strychnine but no bromide. She, however, does occasionally take a bromide sleeping powder. The villain in the case, a member of the household, adds one of these powders to the tonic, thus precipitating the strychnine, and bringing about the death of the patient."

The author's source of information having been quoted in its entirety, no further comment on this aspect of the subject is necessary. The first line of Mr. MacEwan's comment, however, seems worth requoting, *viz.:* "The following prescription has become famous in textbooks."

This prescription which has become famous in textbooks is given space in "Remington's Practice of Pharmacy." In the fourth edition of 1905, the author

* Read before Section on Practical Pharmacy and Dispensing, St. Louis meeting, 1927.

[1] The typographical errors are not those of Mr. MacEwan. (Edition of 1901, p. 368.)