819. What is the assumed constitution of the salts of the alkaloids?

820. Describe the treatment in cases of poisoning by alkaloids. 821. Give the process for the preparation of Hydrochlorate of Morphine. In what form does morphine occur in opium?

822. How is Acetate of Morphine prepared?

823. What plan is adopted for preventing the decomposition of the official solutions of morphine?

824. Mention the analytical reactions of morphine.

825. In addition to the reactions of morphine, what test may be employed in searching for opium in a liquid or semifluid material?

826. How is Apomorphine prepared, and what are its properties?

827. Describe the relation of morphine to codeine.

QUININE, OR QUINIA.

Formula C₂₀H₂₄N₂O₂,3H₂O. Molecular weight 378.

Source.—Quinine (Quinina, U. S. P.) and other similar alkaloids exist in cinchona-bark as kinates. In the yellow bark (Cinchona Flava, U. S. P., from Cinchona calisaya) chiefly quinine is present; in the pale bark (Cinchona Pallida Cortex, B. P., chiefly from C. officinalis) other alkaloids are more frequently found; in the red bark (Cinchona Rubra, U. S. P.) these alkaloids occur in irregular proportions; they occur also in various species of Remijia, the cuprea barks.

Under Cinchona the United States Pharmacopoeia recognizes "the bark of any species of Cinchona containing at least 3 per cent. of

its peculiar alkaloids."

Extraction of the Mixed Alkaloids.—Take 750 grains of finely powdered bark. Make it into a paste with milk of lime (slaked lime about 400 grains and water about 4 ounces). Dry the mixture over a water-bath. Powder the residue and place the whole in a cylindrical percolator. Pour in 31 fluidounces of chloroform. When, after standing, packing is complete, allow percolation to commence and to proceed slowly. After a time pour 32 fluidounces more chloroform into the percolator. When percolation has ceased transfer the percolate to a retort, and add nearly half an ounce of water and enough dilute sulphuric acid to make the mixture acid to test-paper. Recover the chloroform by distilling from a water-bath, and allow the residue to cool; filter. To the filtrate, which contains the alkaloids as acid sulphates, add ammonia in slight excess. Collect the precipitated alkaloids on a filter, wash, and dry in the air or over a dish of sulphuric acid covered by a bell-jar. (For the separation of alkaloids see Index, "Dr. Vrij's process," an operation which should not be attempted at this stage of study.)

Process for Sulphate.—Sulphate of quinine (Quininæ Sulphas. U. S. P.) may be prepared by treating the yellow bark with dilute hydrochloric acid, precipitating the resulting solution of hydrochlorate of quinine by soda, and redissolving the precipitated quinine in the proper proportion of hot dilute sulphuric acid. This, the common commercial sulphate, crystallizes out on cooling in silky acicular crystals, one molecule containing two atoms of quinine (2C₂₀H₂₄N₂O₂).

one of sulphuric acid (H₂SO₄) and seven of water of crystallization (7H₂O).

In the process of the former United States Pharmacopæia (1870) lime was used instead of soda, the precipitated quinine dissolved in boiling alcohol, the latter recovered by distillation, the residual quinine neutralized by diluted sulphuric acid, the solution treated with animal charcoal, filtered while hot, set aside to crystallize, and recrystallized if necessary.

Sulphate of quinine, the common or so-called disulphate ($C_{20}H_{24}N_2O_{2}$), H_2SO_4 , $8H_2O$, is only slightly soluble in water; on the addition of dilute sulphuric acid the so-called neutral sulphate, or soluble sulphate (Quininæ Bisulphas, U. S. P.; $C_{20}H_{24}N_2O_2$, H_2SO_4 , $7H_2O$), is formed, which is freely soluble. The latter salt may be obtained in large rectangular prisms.* An acid sulphate ($C_{20}H_{24}N_2O_2$, $2H_2SO_4$, $2H_2O_2$), as $2H_2O_2$, $2H_2O_3$, $2H_$

7H₂O) also exists.

The ordinary disulphate of quinine is more soluble in alcohol or alcoholic liquids than in water. The citrate of iron and quinine (Ferri et Quininæ Citras, U. S. P.) is the well-known scale compound. It is made by dissolving ferric hydrate, prepared from ferric sulphate, and quinine, prepared from the sulphate, in solution of citric acid; the liquid, evaporated to a syrupy consistence and dried in thin layers on glass plates, yields the usual greenish-yellow scales (vide p. 152).

scales (vide p. 152).

Quininæ Valerianas, U. S. P., may be made by dissolving precipitated quinine in warm aqueous solution of valerianic acid and setting aside to crystallize. Its formula is Coople, N.O. C. H. O. H.O.

aside to crystallize. Its formula is $C_{20}H_{24}N_2O_2$, $C_5H_{10}O_2$, H_2O .

Basic Citrate of Quinine has the formula $(C_{20}H_{24}N_2O_2)_2$, $H_3C_6H_5O_7$, $5H_2O$. Other citrates contain three molecules of quinine to two of citric acid, and one of quinine to one of citric acid.

Quininæ Hydrobromas, U. S. P., has the formula C₂₀H₂₄N₂O₂, HBr,-

Quininæ Hydrochloras, U. S. P., has the formula $C_{20}H_{24}N_2O_2$, $HCl_{24}O_2$.

REACTIONS.

First Analytical Reaction.—To a solution of quinine or its salts in acidulated water add fresh chlorine-water, shake, and then add solution of ammonia; a green coloration (thalleiochin, or dalleiochin) is produced. Bromine-water or bromine vapor may be used instead of chlorine, excess being avoided.

^{*} We do not know whether or not these sulphates are ordinary sulphates, the hydrogen of the acid going over to the quinine molecule, nor whether or not the quinine molecule is univalent or bivalent; hence we cannot say whether the common sulphate or the soluble sulphate is, in constitution, the neutral sulphate. In the above paragraph the names disulphate, neutral sulphate, acid sulphate, indicate nothing more than that the first sulphate contains in one molecule two atoms (chemical atoms) of quinine to one of sulphuric acid, the second one of each, and the third two of acid to one of quinine.

Second Analytical Reaction.—Repeat the foregoing reaction, but precede the addition of solution of ammonia by that of solution of ferrocyanide of potassium; an evanescent red coloration is produced (Livonius and Vogel).

Third Analytical Reaction.—To an aqueous solution of a soluble salt of quinine add solution of oxalate of ammonium; a white crystalline precipitate of oxalate of quinine falls. It is soluble in acids. If the solution to be tested be made from ordinary sulphate of quinine, excess of the latter should be added to water very faintly acidulated with sulphuric acid, and the undissolved crystals removed by filtration.

Fourth Analytical Reaction.—A saturated aqueous solution of any neutral salt of quinine is made by dissolving so much of the salt in hot water as that some shall separate when the mixture has cooled to about 60° F. After standing for some time, filter. Evaporate to one-fifth. To the filtrate waterwashed ether is added until a distinct layer of ether remains undissolved, and then ammonia in slight excess. After agitation and rest for fifteen minutes all quinine precipitated by the ammonia will have dissolved.

Note.—In the case of quinidine salts well-defined crystals will appear at the junction of the aqueous and ethereal layers, especially after standing. In the case of cinchonidine salts a thick layer of small crystals makes its appearance at once, whilst in the case of cinchonine salts the undissolved alkaloid is enough to make the ethereal layer nearly solid.

Fifth Analytical Reaction.—Formation of Iodo-sulphate of Quinine. Dissolve sulphate of quinine in weak spirit of wine slightly acidulated with sulphuric acid, and add an alcoholic solution of iodine; a black precipitate forms. Allow the precipitate to settle, pour away the fluid, wash once or twice with alcohol, and then boil with alcohol; on cooling, minute crystals separate having the optical properties of the mineral tourmaline. This iodo-sulphate is sometimes termed Herapathite, from the name of one of the chemists who discovered it (in 1852). Under the name of iodide of hydriodate of quinine, Bouchardat described and used it in 1845. It is so slightly soluble in alcohol that by its means quinine can be separated from its admixture with the other cinchona alkaloids. According to Jörgensen, it has the formula $4C_{20}H_{24}N_2O_{23}3H_2SO_4,2HI,I_4,xH_2O$

Sixth Analytical Reaction.—Prepare a saturated solution of ordinary sulphate of quinine in water at about 60° F., and add to 5 volumes of that solution 7 volumes of solution of ammonia (sp. gr. 0.96). The alkaloid which at first precipitates redissolves upon slight agitation if the sulphate of quinine is

free from anything but traces of other cinchona alkaloids. If, however, more than traces of quinidine, cinchonidine, and cinchonine salts be present a permanent precipitate remains. This is Kerner's method of testing sulphate of quinine for other cinchona alkaloids. It turns upon the fact that the solubility of the sulphates of the cinchona alkaloids in water is in the opposite order to the solubility of the alkaloids themselves in solution of ammonia.

Other Characters.—Concentrated sulphuric acid dissolves quinine with production of only a faint yellow color, which distinguishes it from salicin.—Quinine and its salts, heated on platinum foil, burn entirely away.—Most salts of quinine when in solution have a beautiful blue fluorescence. They twist the ray of polarized light to the left. Quinine is soluble in alcohol, ether, benzol, and chloroform. Ordinary quinine sulphate is insoluble in chloroform, and but slightly soluble in water. Its solubility in chloroform is increased by the presence in solution of quinidine and cinchonine sulphates (Prescott), and its solubility in water is decreased by the presence in solution of ammonium sulphate (Carles). The slight solubility of its sulphate and iodo-sulphate in water distinguishes quinine from the other cinchona alkaloids, including the "amorphous alkaloid," or "quinoidine." (See "Paul's test" in Index.)

Quinidine (C20H24N2O2, the Conquinine or Conchinine of Hesse) is an isomer of quinine. Its salts are fluorescent, and give thalleioquin with chlorine- or bromine-water and ammonia. They twist the ray of polarized light to the right. Quinidine is insoluble in water and sparingly soluble in ether (see Quinine, 4th Analytical Reaction). It is soluble in alcohol, benzol, and chloroform. It is less soluble than quinine in ammonia, 5 volumes of a saturated aqueous solution of its ordinary sulphate requiring 60 to 80 volumes of ammonia solution (sp. gr. 0.96). Its sulphate (Quinidinæ Sulphas, U. S. P.; $2C_{20}H_{24}N_2O_2$, H_2SO_4 , $2H_2O$) is more soluble in water and chloroform than the sulphate of quinine. Tartrate of quinidine is soluble in water. The hydriodate is insoluble in water and weak spirit, and occurs as sandy crystals. The hydriodates of the other cinchona alkaloids, though more soluble than quinidine hydriodate. are sometimes precipitated from neutral concentrated solutions as amorphous or semi-liquid precipitates. These, however, are soluble in weak spirit. "If 0.5 gm. each of sulphate of quinidine and of iodide of potassium (not alkaline to test-paper) be agitated with 10 c.c. of water at about 60° C. (140° F.), the mixture then macerated at 15° C. (59° F.) for half an hour, with frequent stirring, and filtered, the addition to the filtrate of a drop or two of water of ammonia should not cause more than a slight turbidity (abs. of more than small proportions of cinchonine, cinchonidine, or quinine)."-U. S. P.

Cinchonidine (C20H24N2O).-When perfectly pure, salts of cinchonidine do not give thalleioquin and are not fluorescent. Even good commercial salts, however, nearly always give both reactions. Salts of cinchonidine twist the polarized ray to the left. Cinchonidine is insoluble in water and nearly so in ether (see Quinine, 4th Analytical Reaction). It is soluble in alcohol, benzol, and chloroform. It is less soluble in ammonia solution than quinine, five volumes of a saturated aqueous solution of cinchonidine sulphate requiring about 80 volumes of ammonia solution (sp. gr. 0.96). It is true that cinchonidine is dissolved as readily as quinine if excess of strong ammonia is quickly mixed with the solution of a salt of cinchonidine; but from such a solution cinchonidine soon crystallizes, while quinine remains dissolved for many hours. Sulphate (Cinchonidinæ Sulphas, U. S. P. $(C_{20}H_{24}N_2O)_2, H_2SO_4, 3H_2O)$ and hydriodate of cinchonidine are soluble in water, but the sulphate, like quinine sulphate, is insoluble in chloroform. Tartrate of cinchonidine is insoluble in water, and in this form cinchonidine is usually separated from neutral solutions containing the other cinchona alkaloids except quinine.

Cinchonine $(C_{20}H_{24}N_2O)$ (Cinchonina, U. S. P.) is an isomer of einchonidine. When quite pure its salts are not fluorescent and do not give thalleioquin. As in the case of cinchonidine, even good commercial specimens of cinchonia salts nearly always give both reactions. Cinchonia salts twist the polarized ray to the right. Cinchonine is insoluble in water and nearly so in ether (see Quinine, 4th Analytical Reaction). It is soluble in chloroform, benzol, and alcohol. Chloroform containing one-fourth of its weight of 95-per cent. alcohol dissolves cinchonine much more readily than either alcohol or chloroform alone. Cinchonine is insoluble in ammonia solution. Sulphate (Cinchoninæ Sulphas, U. S. P.) (C₂₀H₂₄N₂O)₂,H₂SO₄,2H₂O, tartrate, and hydriodate of cinchonine, are soluble in water, and the sulphate, like sulphate of quinidine, is soluble in chloroform. In mixtures of cinchona alkaloids this alkaloid is precipitated by alkali after the others have been successively removed by ether, tartrate of sodium, and iodide of potassium.

Constitution of the Cinchona Alkaloids.—This is not yet clear, though great advances have been made. In the course of the investigations derivatives of quinoline, more or less resembling quinine, have been obtained—namely, kairine, kairoline, and thalline; antipyrin also. Acetanilide, or "antifebrin," has, too, been found to possess even greater antipyretic powers than the derivatives just mentioned. See also p. 504.

"Quinoidine" or the "Amorphous Alkaloid" (Chinoidin, U. S. P.).—Cinchona-barks generally contain some alkaloid isomeric with quinine, which, like quinine, is soluble in ether, but the ordinary sulphate and iodo-sulphate of which are not crystalline and are soluble. These salts are semisolid, resinous-looking substances. The iodo-sulphate is used in Dr. Vrij's method for the separation of mixed alkaloids (see Index). Quinoidine is usually obtained along with quinine, etc. from the mixed alkaloids by ether, and

remains in the mother-liquor, from which it is precipitated by an alkali. If quinoidine be triturated with boiling water, the liquid, after filtration, should be clear and colorless, and should remain so on the addition of an alkali (abs. of alkaloidal salts). On ignition, quinoidine should not leave more than 0.7 per cent. of ash.

Cinchovatine occurs in a particular variety of cinchona-bark. Quinicine and Cinchonicine are alkaloids produced by the action of heat on quinine or quinidine and on cinchonine or cinchonidine respectively. They also are isomers—Hesse says polymers—of the parent alkaloids. Both yield ordinary salts. Quiniretin is the name given to the brown or reddish-brown indifferent substance into which quinine in aqueous solution is converted when exposed to much light.

Quinamine $(C_{20}H_{26}N_2O_2)$ is a fifth cinchona alkaloid obtained by Hesse in 1872 from the bark of Cinchona succirubra. Its solution is not fluorescent and does not give thalleioquin. The same chemist announces the presence in cinchona of a sixth alkaloid, cinchamidine $(C_{20}H_{26}N_2O)$.

Cupreine, C₁₉H₁₂N₂O₂, is an alkaloid discovered by Paul and Coronley in the bark of a Remijia (allied to Cinchona), and termed cuprea-bark. It closely resembles quinine, but it is sparingly soluble in ether. The alkaloid at first termed homoquine or ultraquinine seem to have been a mixture of cupreine and quinine. Hydroquinine, C₂₀H₂₈N₂O₂, whose molecule contains two more atoms of hydrogen than are present in that of quinine, is an alkaloid associated with quinine, in minute amount, in cinchona-bark. It remains in the mother-liquor when quinine sulphate is crystallized from an acid solution. Its therapeutic action is similar to that of quinine. It was discovered by Hesse.

STRYCHNINE, OR STRYCHNIA.

Formula C21H22N2O2. Molecular weight 334.

Source.—This alkaloid (Strychnina, U. S. P.) exists, to the extent of 0.2 to 0.5 per cent., in the seed of Strychnos Nux Vomica (Nux Vomica, U. S. P.), also (Shenstone) in minute quantity in the bark of the Nux Vomica tree (false Angustura-bark), and to 1.0 or 1.5 per cent. in St. Ignatius's bean (Strychnos Ignatia) (Ignatia, U. S. P.), chiefly in combination with strychnic or igasuric acic, or, after slight fermentation when moistened, with lactic acid. Crow also found it in the bark of S. Ignatia.

Process.—According to the British official process for its preparation, the nuts, disintegrated by subjection to steam, and, after drying, grinding in a coffee-mill, are exhausted with spirit, the latter removed by distillation, the extract dissolved in water, coloring and acid matters precipitated by acetate of lead, the filtered liquid evaporated to a small bulk, the strychnine precipitated by ammonia, the precipitate washed, dried, and exhausted with spirit, the spirit recovered by dis-

tillation and the residual liquid set aside to crystallize. Crystals of strychnine having formed, the mother-liquor (which contains the brucine of the seeds) is poured away, and the crystals of strychnine washed with spirit (to remove any brucine) and recrystatlized.

In the U.S.P. (1870) process the rasped Nux Vomica is exhausted by very dilute hydrochloric acid, milk of lime added to the evaporated decoction to decompose the hydrochlorate of strychnine, the precipitated and dried mixture of strychnine and lime treated with diluted alcohol to remove brucine, and then with strong, hot alcohol to dissolve out strychnine; the alcohol having been recovered by distillation, the residual impure strychnine is dissolved in very dilute sulphuric acid, the solution decolorized by animal charcoal, evaporated, and set aside to crystallize, the crystals of sulphate of strychnine (Strychninæ Sulphas, U. S. P.; (C21H22N2O2)2H2SO4,7H2O; Coleman, 6H2O) redissolved in water, ammonia added to precipitate pure strychnine, and the latter dried. It is soluble in about 40 parts of water. The citrate $(C_{21}H_{22}N_2O_2)_2C_6H_8O_7,4H_2O$ (or $2H_2O$) at common temperatures dissolves in 45 parts of water and 115 parts of alcohol.

Properties.—Strychnine occurs "in right square octahedrons or prisms, colorless and inodorous; sparingly soluble in water, but communicating to it its intensely bitter taste; soluble in boiling rectified spirit and in chloroform, but not in absolute alcohol or in

REACTIONS.

First Analytical Reaction.—Place a minute particle of strychnine on a white plate, and near to it a small fragment of red chromate of potassium; to each add one drop of concentrated sulphuric acid; after waiting a minute or so for the chromate to fairly tinge the acid, draw the latter, by a glass rod, over the strychnine spot; a beautiful purple color is produced, quickly fading into a yellowish-red. The following oxidizing agents may be used in the place of the chromate: puce-colored oxide of lead, fragments of black oxide of manganese, ferridcyanide of potassium, or permanganate of potassium.

This reaction is highly characteristic: a minute fragment dissolved in much dilute alcohol-or, better, chloroform-and one drop of the liquid evaporated to dryness on a porcelain crucible-lid or other white surface, yields a residue which immediately gives the purple color on

being oxidized in the manner directed.

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Other Reactions.—Strong sulphuric acid does not decompose strychnine even at the temperature of boiling water, a fact of which advantage is taken in separating strychnine from other organic matter for purposes of toxicological analysis. Sulphocyanide of potassium produces, even in dilute solutions of strychnine, a white precipitate. which under the microscope is seen to consist of tufts of acicular crystals. Strong nitric acid does not color strychnine in the cold, and on heating only turns it yellow.

The Physiological Test.—A small frog placed in an ounce of water to which $\frac{1}{100}$ of a grain of a salt (acetate) of strychnine is added is in two or three hours seized with tetanic spasms on the slightest touch, and dies shortly afterward.

Strychnine has an intensely bitter taste. Cold water dissolves only 2000 part, yet this solution, even when largely diluted, is distinctly bitter. Alcohol is a somewhat better solvent. The salts of the alkaloid are more soluble. The Liquor Strychniae, B. P., contains four grains of strychnine to the ounce, the solvent being three parts water, one part spirit, and a few minims (6 per ounce) of hydrochloric acid (rather more than sufficient to form hydrochlorate of strychnine). A syrup of Phosphates of Iron, Quinine, and Strychnine is official (Syrupus Ferri, Quininæ, et Strychninæ Phosphatum). It contains 1 part of strychnine in 2500.

Brucine, or Brucia (C23H26N2O4,4H2O), is an alkaloid accompanying strychnine in Nux Vomica and St. Ignatius's bean to the extent of about 0.5 per cent. It is readily distinguished by the intense red color produced when nitric acid is added to it. Igasurine, once supposed to be a third alkaloid of nux vomica, has been shown by Shenstone to be only a mixture of brucine and

Curarine (C10H15N), the active principle of the arrow-poison termed urari, ourari, wourali, or woorara, prepared from a Strychnos, resembles strychnine in giving color by oxidation, but the color is more stable. Iodide or platino-cyanide of potassium does not with curarine afford precipitates which crystallize from alcohol like those of strychnine. Curarine also is soluble in water. Unlike strychnine, curarine is reddened by sulphuric acid; it, also, is not dissolved out by ether from an acid or alkaline liquid. Curari appears to vary much in strength and quality. It is probably a mixture of vegetable extracts.

Distinction of Brucine from Morphine.—The red coloration produced by the action of nitric acid on brucine is distinguished from that yielded by morphine by the action of reducing agents (such as stannous chloride, hyposulphite of sodium, sulphydrate of sodium), which decolorize the morphine red, but change that of the brucine to

violet and green (Cotton).

Distinction of Free Alkaloids or their Salts from Each Other .-This is accomplished by remembering the appearance and other physical characters of the substances as met with in pharmacy, the effect of heat, the action of such solvents as water, alcohol, and ether, the influence of strong and diluted acids, strong and weak alkalies, oxidizing agents, chlorine-water and ammonia, and other reagents. (See annexed Tables, I. and II.)

QUESTIONS AND EXERCISES.

828. What alkaloids are more or less characteristic of the different varieties of cinchona-bark? In what form do they occur? 829. By what method is Disulphate of Quinine obtained?

830. Give the characters of disulphate of quinine.

831. Describe the tests for quinine.

832. How is the adulteration of disulphate of quinine by salicin detected?

833. Show how the sulphates of quinine or cinchonine may be proved to be present in commercial quinine.

834. How are cinchonine and quinine distinguished from morphine?

835. Whence is strychnine obtained?

836. Describe the official process for the isolation of strychnine.

837. Give the characters of strychnine.

838. Enumerate the tests for strychnine, and describe their mode of application.

839. By what reagent is brucine distinguished from strychnine?

840. Distinguish between brucine and morphine.

841. By what general methods would you distinguish common alkaloids from each other?

Analytical Exercises.—Analyze small quantities of alkaloids, their salts, and various "scale" compounds by aid of the annexed Tables, I. and II.

ALKALOIDS OF LESS FREQUENT OCCURRENCE.

Aconitine, Aconitina, or Aconitia is an alkaloid obtained from aconite (Aconitum Napellus) leaves (Aconiti Folia, B. P.) and root (Aconitum, U. S. P.). The alkaloid itself is only slightly soluble in water; it occurs in the plant in combination with a vegetable acid, forming a soluble salt.

Process.—The process for the preparation of Aconitine, B. P., consists in dissolving out the natural salt of the alkaloid from the root by rectified spirit, recovering the latter by distillation, mixing the residue with water, filtering, precipitating the aconitine by ammonia, drying the precipitate and digesting it in ether (in which some of the accompanying impurities are insoluble), recovering the ether by distillation, dissolving the dry residue in the retort in water acidulated by sulphuric acid, again precipitating the alkaloid by ammonia and finally washing and driving.

nia, and finally washing and drying.

Properties.—Aconitine usually occurs as a white powder, but has been obtained and studied in the crystalline state by Groves, Wright, Williams, and others. It is very slightly soluble in cold water, more so in hot, and is much more soluble in alcohol and ether. It is one of the most violent poisons known. "When rubbed on the skin it causes a tingling sensation, followed by prolonged numbness."

The thousandth part of a grain on the tip of the tongue produces, after a minute or so, a characteristic tingling sensation and numbness; larger quantities rubbed into the skin cause numbness and loss of feeling. Sulphuric acid turns it to a yellowish, and afterward dirty-violet, color.

BIBLIOTECA*

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