color, intensifying on cooling, indicates the presence of methyl alcohol.

This test is as simple to carry out as is the U. S. P. method using fuchsin-sulfurous acid T.S. and, in addition, eliminates the need for freshly prepared solutions. Furthermore, chromotropic acid is readily available and at a price which makes the cost per test almost negligible.

Chromotropic Acid and Methanol in Whisky.—In order to determine whether whisky contains interfering substances, the tests above were repeated, using whisky in the place of 50% ethanol. The same order of sensitivity was observed, again detecting 0.016 milligrams of methanol. Pure whisky gave negative results.

CONCLUSIONS

1. The U. S. P. test for methanol in whisky gives a positive reaction with ethanol even though no methanol is present.

2. Chromotropic acid is specific and extremely sensitive to formaldehyde and may be employed in detecting methanol in amounts as little as 0.016 milligrams. Ethanol and whisky do not interfere with this test.

3. The chromotropic acid method is dependable as a specific test for methanol, it is easily carried out and it may be applied to samples as small as 0.02 cc. of a 1:1000 solution of methanol.

REFERENCES

(1) Pharmacopœia of the United States of America. Eleventh revision, page 355.

(2) Shriner and Fuson, "The Systematic Identification of Organic Compounds," (Second edition), John Wiley and Sons, New York (1940), page 62.

(3) Eegriwe, *Z., anal. Chem.*, 110 (1937), 22–25; through *Chem. Abstr.*, 31 (1937), 8442.

(4) Feigl, "Qualitative Analysis by Spot Tests." Translated by Matthews, Nordemann Publishing Company, New York, (1939), pages 327–329.

The following scientists have been honored by France by portrayal on postage stamps: Marcelin Berthelot, pioneer in organic synthesis; Claude Bernard, physiologist; Louis Pasteur, Pierre Curie and Marie Curie, discoverers of polonium and radium; Leon Calmette, research worker in tuberculosis.

Determination of Unsaturates in Cyclopropane*

By Frederick K. Bell and John C. Krantz, Jr.†

The quantitative determination of the amount of unsaturated hydrocarbons present in cyclopropane as impurity presents an interesting and difficult problem. In the preparation of cyclopropane the formation of some unsaturated hydrocarbons is to be expected especially since the chemical procedure involves the transition from a straight chain to a closed ring structure.

There is evidence to indicate that certain of these unsaturated compounds predispose the patient to pulmonary edema, therefore, it is important both to the manufacturer and to the patient that suitable methods be available for determining the efficiency of purification methods employed before this anesthetic gas is used.

Cyclopropane or trimethylene, is the simplest possible cyclic hydrocarbon and it is the least stable of the cyclic hydrocarbons, the stability increasing markedly in passing to the tetra or the pentamethylene ring. It is not surprising then that cyclopropane displays in its chemical reactivity many of the properties ascribed to straight chain unsaturated hydrocarbons, for with simple rupture of the cyclopropane ring the unsaturated hydrocarbon, propene, results.

There are three unsaturated hydrocarbons which are most likely to occur in the preparation of cyclopropane: (1) propene, or methylethene, which is the straight chain isomer of cyclopropane; (2) propadiene, C_3H_4, which contains two double bonds and has a boiling point very near to that of cyclopropane; (3) propyne, or methyl acetylene, which is isomeric with propadiene and contains one triple bond. Reactions typical of these compounds such as the ease of hydrogenation and halogenation, oxidation by potassium permanganate and addition of hydriodic acid are all displayed to some extent by cyclopropane and at the present time no specific reaction has been discovered

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which can be used for the quantitative separation of cyclopropane and unsaturated hydrocarbons.

The potassium permanganate method was selected and introduced into the U. S. P. monograph for cyclopropane. In this method one liter of the gas to be examined is passed, under closely specified conditions, through 50 cc. of hundredth-normal potassium permanganate which has been cooled and is maintained at approximately 0° C. To be sure, under these conditions the efficiency of the absorption of unsaturates could not be expected to be high, but it was hoped that by using dilute and cold permanganate solution the oxidation of the cyclopropane could be practically eliminated so that the results finally obtained would bear a simple and direct relation to the amount of unsaturates present in the liter gas sample.

After the passage of the gas through the permanganate solution, the latter is promptly transferred to a suitable flask and 50 cc. of hundredth-normal oxalic acid are added. The mixture is heated to 80° C. and then titrated with hundredth-normal potassium permanganate in the presence of sulfuric acid. This titer is a measure of the quantity of unsaturates present and the Pharmacopœia requires that it shall not exceed 10 cc.

EXPERIMENTAL

Owing to time restrictions, an extensive study of the permanganate test could not be completed. The results that were obtained indicated that the method had considerable merit although it was recognized that the reproducibility of results was not entirely satisfactory. We have recently completed a more comprehensive examination of the present pharmacopœial test with and without certain modifications. In this work we have had the coöperation of various manufacturers of cyclopropane through one of whom we also obtained an especially purified sample which we have designated as C.P. Several commercial samples of cyclopropane were examined as well as some special ones showing a high value for unsaturates. Nearly 200 analyses were carried out.

In the following table a summary of the results obtained by the pharmacopœial method are shown. Average values are indicated.

It is seen at once that the reproducibility of results is not only of low order but also appears to vary with the particular gas sample being analyzed and this suggested that at least one important variable of the system was not under control. In this connection we directed our attention to a consideration of the ultimate fate of the cyclopropane dissolved in the cold permanganate solution. After the passage of the liter-gas sample through this cold solution it is probable that nearly 20 cc. of cyclopropane are dissolved therein.

Table I

Sample	Cc. *N*/100 $KMnO_4$ Titer	Deviation
A	4.2	0.36
B	18.5	0.65
C	4.7	0.18
D	4.7	0.34
E (C.P.)	3.0	0.42

In a second series of experiments we have modified the pharmacopœial method in the following manner. The cold permanganate solution through which the cyclopropane sample has been bubbled is added in small portions to a mixture of 50 cc. of hundredth-normal oxalic acid and 5 cc. of sulfuric acid which has been heated to 90° C. After each addition of the permanganate the mixture is shaken for a few seconds until it becomes colorless. After the complete transfer of the permanganate solution the mixture, which then has a temperature of 55 to 60° C., is titrated with hundredth-normal permanganate. The average values obtained by this modified method are as follows:

Table II

Sample	Cc. *N*/100 $KMnO_4$ Titer	Deviation
B	18.4	0.6
C	4.2	0.21
D	3.7	0.37
E (C.P.)	1.8	0.23
F	12.4	0.45

CONCLUSIONS

The results show a slight improvement of reproducibility as shown by a general decrease in the average deviation. In the modified procedure, there is also a general decrease in the magnitude of the permanganate titer which is especially marked in the case of the C.P. cyclopropane (sample E) where the value has dropped from 3 cc. to 1.8 cc. Although the modified procedure does not produce any marked improvement in the accuracy of the method, it is believed to be desirable since it attempts to further standardize the procedure particularly at the point where the source of the difficulty most likely occurs.

Either the pharmacopœial method or the modified form may be regarded as ade-

quate with regard to the present cyclopropane market and methods of production. Any marked change in these factors would undoubtedly call for an immediate review of the method. Therefore, it is clearly indicated that further studies should be undertaken.

Detection of Quinicine and Cinchonicine*

By J. W. Millar and S. J. Dean

The presence of quinicine (quinotoxin) and cinchonicine (cinchotoxin) in preparations containing quinine and cinchonine has frequently been questioned. A number of tests have been proposed, some of which are not satisfactory. This study was undertaken to obtain satisfactory tests for these substances and to determine in each case the minimum concentration in which detection can be made in aqueous and in alcoholic solutions, also when they are present with the unchanged parent alkaloid.

EXPERIMENTAL

Preparation of Cinchonicine and Quinicine.—Employing the method used by Biddle (1), ten grams of cinchonine, ten grams of glacial acetic acid and one hundred and thirty cc. of water were heated to boiling for thirty-five hours. The cooled brownish red solution was treated with an excess of sodium hydroxide and the light brown oil which separated was extracted with ether. The ether solution was dried with calcium carbide. Any unchanged cinchonine, which is insoluble in dry ether, is precipitated when the solution is dried.

The excess of ether was evaporated and the cinchonine dissolved in alcohol or water.

Quinicine was prepared from quinine in a similar manner.

Diazo-Benzene Sulfonic Acid Reagent.—Biddle (2) makes use of this reagent for the identification of cinchonicine and quinicine.

Procedure: two cc. of a freshly prepared saturated aqueous solution of diazobenzene sulfonic acid rendered alkaline with a few drops of sodium hydroxide is added to ten cc. of a solution of quinicine. The color produced varies from a light pink to a reddish violet according to the amount of quinicine present. The color must appear within five minutes. The minimum concentration of quinicine in aqueous solutions yielding distinctive tests was found to be 1 part in 12,500.

Alcoholic solutions reduce the sensitivity of the test to 1 part in 2500.

To determine the delicacy of this test in the presence of soluble salts of quinine, saturated solutions of the hydrobromide, hydrochloride and sulfate containing known amounts of quinicine were used.

The minimum concentration of quinicine yielding satisfactory tests was 1 part in 6250.

Tests performed with cinchonicine and diazobenzene sulfonic acid in the same manner in aqueous solution, yielded distinctive tests in dilutions of 1 part in 6250.

In alcoholic solution, the sensitivity was 1 part in 3000.

With saturated solutions of salts of cinchonine, the sensitivity of the test was 1 part in 3500.

Dinitro Thiophene Reagent.—Biddle (3) also made use of this reagent for the identification of quinicine and cinchonicine.

It is prepared by dissolving dinitro thiophene in pure nitro benzene (1:200).

To two cc. of the reagent is added a few drops of alcohol and then the alcoholic or ethereal solution of the substance to be tested.

The color produced varies from a light orange to a deep purple-red according to the amount of toxin present. The solution tested must be neutral and the test is unreliable in the presence of salts of quinine or cinchonine.

The minimum concentration of quinicine yielding distinctive tests was 1 part in 2700. In the presence of quinine alkaloid the sensitivity was 1 part in 480.

With cinchonicine, tested in the same manner, the minimum concentration yielding distinctive tests was 1 part in 1740, and in the presence of cinchonine alkaloid the sensitivity was 1 part in 600.

Lipkin's Test.—Lipkin (4) describes the following test to differentiate between quinine and quinicine:

"To 5 cc. of the solution to be tested is added 2–3 drops of a 0.5% aqueous solution of Congo Red. Bromine water is added until a yellow color is obtained; ammonia added immediately and the solution extracted with chloroform. Quinine yields a green color in the chloroform extract and quinicine a red color."

Tests were made replacing Congo Red in the above test with other indicators, *viz.*, brom-phenol blue, brom-cresol green, methyl red, thymol blue, phenol red, brom-thymol blue, brom-cresol purple, and with each indicator the resulting color was the same for quinicine and no color change for cinchonicine.

The same test was made on quinicine and cinchonicine omitting the indicator; the same results were obtained.

It is suggested that this test (no indicator being used) may be used for the differentiation of quinicine and cinchonicine.

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* A contribution from the laboratories of the College of Pharmacy, University of California, Medical Center, San Francisco, California.