very stable in aqueous solutions. The toxicity of the latter compound is about 0.3 mg. per one Gm. rat.

REFERENCES.

(1) Ger. Patent No. 193,661.
(2) Reynolds, *J. Chem. Soc.*, 61, 253 (1891).
(3) Sollman, Manual of Pharmacology, 1936, page 743.

SULFOMORPHID; AND THE PURPLE FLUORESCENCE TEST, A NEW DERIVATIVE TEST FOR MORPHINE.*

BY CHARLES C. FULTON.[1]

The product resulting from heating morphine in sulfuric acid was known to the early students of morphine chemistry as "sulphomorphid." Perhaps they had noted the loss of amine properties, and assumed that the nitrogen had in some way gone to the amide form. What actually happens (in addition to dehydration) is doubtless sulfonation, with formation of an inner salt (1). Modern texts either say nothing about the specific action of sulfuric acid, or, apparently losing sight of the actual nature of the usual product, say that apomorphine is formed. There probably is partial conversion to apomorphine with *diluted* sulfuric acid (5 plus 3, for example), but with the usual concentrated acid *no* apomorphine is formed under any circumstances.

True enough, the product may be regarded as a derivative of apomorphine, as well as a derivative of morphine. The derivative first formed with concentrated acid, at temperatures below 60° C., is probably identical with apomorphine-sulfonic-acid, as obtained and described by Kitasato and Goto (1, 2). But this is not apomorphine, any more than sulfanilic acid is aniline. Nor is there anything to indicate that apomorphine is formed first and then sulfonated. On the contrary, sulfonation, with formation of an inner salt, probably occurs first, almost coincident with solution; but dehydration begins simultaneously, and it is difficult, if not impossible, to separate these effects. Without any heating, at room temperature or even below, the transformation begins at once in concentrated acid; it is made complete within a few minutes by warming to 40–50° C. (3). As the acid is diluted its power to dehydrate seems to outlast, for a time, and to some extent, its power to sulfonate, so that a partial conversion to apomorphine, as appears from qualitative tests, may be obtained by heating. However, the unqualified assertion of many texts, that apomorphine is the resultant product, is little better than entirely erroneous, particularly as concentrated sulfuric acid seems to be the reagent meant.

OBTAINING INSOLUBLE CRYSTALLINE SULFOMORPHID.

Place some dry morphine or its salt in a dry test-tube; dissolve in a little pure concentrated sulfuric acid, taking care to get all the morphine in the tube into solution. Stand in a beaker of water at about 40° C. for 7 or 8 minutes. Dilute with 1 cc. water for every 0.1 cc. sulfuric acid.

* Scientific Section, A. PH. A.

[1] Associate Chemist, Alcohol Tax Unit Laboratory, U. S. Internal Revenue Bureau, 710 Main Post Office Bldg., Saint Paul, Minnesota.

Cool the diluted solution. Test a few drops with Wagner's and Mayer's reagents and phosphomolybdic acid. These and similar reagents give no precipitate. Let the solution stand an hour or longer; if necessary cool with ice and rub the inside of the tube to induce crystallization. A crystalline precipitate forms; it is white, and under the microscope is seen to consist of needles or transparent rods, often in rosettes. These crystals are easily obtained from 1 mg. of morphine, treated as described.

The time for warming stated is close to the optimum, but anywhere from 4 to 20 minutes at 40° will do. At 20°, the same change takes close to 45 minutes at least, with 1 to 2 hours to be preferred.

COLOR REACTIONS.

If sufficient precipitate is obtained, it can be filtered, washed with a little cold water and dried. The color reactions of the product are like those of apomorphine, with some differences, notably in the solubilities of the oxidation product.

HNO_3—red-purple, changing to red, then to orange.
Froehde's reagent—green.
Flückiger's reagent—red.
Marquis' reagent—purple changing to very dark green.

In the presence of chloride, concentrated sulfuric acid containing arsenate produces a beautiful purple, soon changing to dark green.

Very characteristic reactions are the fluorescence developed by ammonia, the colors of the oxidation product, and the ortho-diphenol colors obtained with a little iron; however, these tests are easily obtained without any necessity of isolating the derivative.

INSOLUBLE SULFOMORPHID.

Summarizing, this compound is:

(*a*) Not very soluble in cold water or cold dilute acid, crystallizing out in white, microscopically transparent needles or prisms; quite soluble in alkali, ammonia or Na_2CO_3 solution;

(*b*) Unlike apomorphine in that it does not precipitate with alkaloidal reagents;

(*c*) Like apomorphine in being an ortho-diphenol, and in giving similar, though not identical color reactions.

SOLUBLE SULFOMORPHID.

If the solution in concentrated sulfuric acid is heated further, a new change begins at 60–70° C., and is complete with heating to about 90°. The compound no longer crystallizes out of cold dilute acid, and some differences in the color reactions also signalize the change, which is probably a further sulfonation. This second product is the one known, in solution at least, to the earlier chemists, and which they named "sulphomorphid;" despite that the formula they attributed to it corresponded to apomorphine sulfate and not to a sulfonic acid. When they referred Husemann's test, and other reactions for which such treatment was prescribed as heating the morphine in concentrated sulfuric acid at 100° for half an hour, to "sulphomorphid," there can be no doubt as to the compound actually meant.

Soluble sulfomorphid is also formed by increasing the time of treatment, instead

of the temperature. Standing over night at 20°, or warming an hour or more at 40°, in concentrated acid, effects complete conversion to this compound.

When conversion is made by raising the temperature steadily, the compound undergoes no further change until about 140° is reached, when the solution becomes dark olive-green.

CODEINE AND DIONINE.

Codeine is changed similarly to morphine, only the derivative first formed (sulfocodid or apocodeine-sulfonic acid) is a monophenol, since the methyl group is not displaced by heating to 50°. With continued heating there is a change at 60–70° corresponding to the morphine change at the same temperature; then there is a further change at about 100° which consists in the loss of the methyl group. Thereafter the codeine and morphine reactions are the same.

Dionine reacts like codeine, save that it begins to lose the ethyl group at about 70° instead of 100°; with heating above 80° it reacts the same as morphine.

THE PURPLE FLUORESCENCE TEST FOR MORPHINE.

Dissolve a little dry morphine or its salt in a test-tube in 0.5 cc. of pure concentrated sulfuric acid. Warm in a water-bath at 40° C. for about 7 or 8 minutes. Dilute with 5 cc. water, then add 6 cc. of concentrated ammonium hydroxide, and mix. Do not cool. The solution becomes brown, and gradually a strong and beautiful purple fluorescence develops, very conspicuous on looking obliquely down the tube against a dark background. This fluorescence is noticeable within a few minutes with the optimum amount of morphine, about half a milligram, but it requires at least two or three hours to develop fully, when the tube stands at room temperature. Warming at 40–60° will hasten its development somewhat. With standing over night, or warming for an hour or so, fluorescence is perceptible in the test made with 0.025 mg. of morphine, and could hardly be missed with 0.05 mg. The developed fluorescence remains on dilution with water, and is permanent. In great dilution it finally appears bluish in a nearly colorless solution.

The test, with the quantities of reagents, etc., as given, will yield a much better fluorescence with an ordinary small amount of morphine, 0.1 to 1 mg., than with a larger amount. This will occasion little difficulty, as the order of sensitivity of this test is the same as Pellagri's and other related tests, and the amount of morphine that will normally be taken for such a sensitive test will give close to the maximum reaction. About 0.5 mg. is recommended.

Codeine, treated as above described, shows a little bluish fluorescence in a greenish yellow solution; but this reaction is quite weak, does not resemble the morphine test, and can hardly be considered a test. Pseudomorphine, so far as observed, gives no fluorescence. Apomorphine as such gives no fluorescence; being insoluble in ammonia it collects as a brown precipitate. However, apomorphine after warming in sulfuric acid solution, treated, that is, the same as morphine, gives the test like morphine. Heroine, of course, also gives this test.

SUMMARY.

1. The crystalline derivative of morphine, discovered by the writer (3), which is formed by warming the morphine in concentrated sulfuric acid at about 40° C.,

is probably identical with apomorphine-sulfonic-acid as prepared and described by Kitasato and Goto (1, 2).

2. With further heating in the concentrated acid the compound undergoes another change, probably a further sulfonation. This second compound is the "sulphomorphid" of early investigators of morphine chemistry.

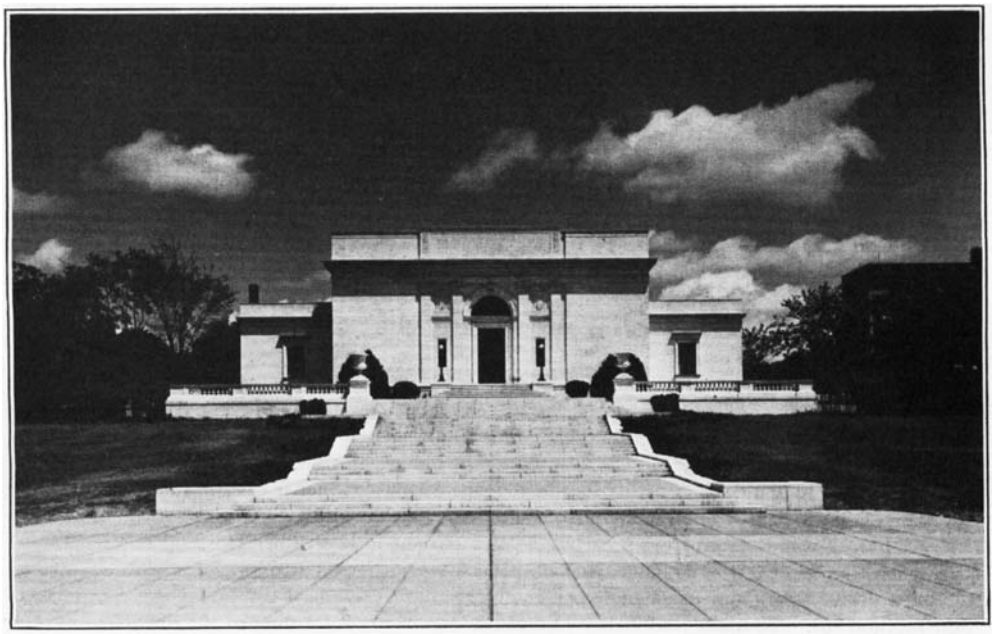
3. A new derivative test for morphine is given, the purple fluorescence test, which is based on conversion of the morphine to insoluble sulfomorphid (apomorphine-sulfonic-acid).

REFERENCES.

(1) *Chemical Abstracts*, 25, 1532 (1931); Zenjiro Kitasato and Kakuji Goto, "Sulfonation of Alkaloids," *Ber.*, 63B, 2696 (1930).

(2) Small, Lyndon F., and Lutz, Robert E., "Chemistry of the Opium Alkaloids," Public Health Service, U. S. Treasury Department, 1932. (Citing Kitasato and Goto.)

(3) Fulton, Charles C., "Some New and Improved Tests for Morphine and Related Alkaloids," *J. Lab. Clin. Med.*, 13, 8, 750 (1928).



AMERICAN INSTITUTE OF PHARMACY, Washington, D. C., designed by John Russell Pope.

The AMERICAN INSTITUTE OF PHARMACY is dedicated to those who have given of their thought and endeavor to the improvement of public health and to the further advancement of Science in Pharmacy.

"Unconsciously the spirit of the design—its elegant simplicity, the richness of its landscape setting, its thorough appropriateness instantly impress artist and layman alike."—CHARLES MOORE, *Chairman*, National Commission of Fine Arts.