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NOTE ON THE SEPARATION OF STRYCHNINE AND BRUCINE.

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(*Read at the Meeting, June 7, 1905.*)

As a preliminary to the investigation of Gordin's method for the separation of strychnine and brucine, and the determination of the former in presence of the latter, it appeared desirable to investigate Keller's method, of which that of Gordin is a modification. It is the account of this preliminary investigation which I have the honour to submit to the Society. Keller's method is as follows:

"0.2 to 0.4 gram of the dry mixture of alkaloids is dissolved in 10 c.c. of 10 per cent. sulphuric acid by heating on the water-bath. After complete cooling, 1 c.c. of nitric acid S.G. 1.40 to 1.42 is added, and the mixture shaken. The strychnine sulphate, which usually separates from the solution, is redissolved on addition of the nitric acid, and at the same time the red brucine-nitric acid coloration is developed. After allowing the mixture to stand for an hour to an hour and a half, in order to complete the destruction of the brucine, 40 grams of chloroform, an equal quantity of ether, and 10 c.c. of 10 per cent. ammonia are added, and the whole shaken. Forty grams of the extract are filtered into a tared flask, from which the mixture of chloroform and ether are distilled. The residual strychnine is dried at 95° to 100° C. and weighed." It has been stated that this process "only returns about 96 per cent. of the alkaloid," but on experimenting with a mixture of strychnine and brucine the results were found to be too high—*e.g.*, 0.2486 gram strychnine with 0.19 gram brucine gave 0.2498 gram residue = 100.48 per cent. It should be mentioned that the acid solution was extracted three times with the solvent mixture, the latter washed with ammonia solution (which separates more easily than water), and the whole of the solvent distilled.

Brucine similarly treated left a small residue (probably due to some impurity in the alkaloid used, as it gave no reaction for brucine), but not enough to account for the error in the strychnine determination described above.

E.g., 0.412 gram brucine gave a residue of 0.002 gram = 0.5 per cent. A number of experiments were then made, using strychnine only.

Using caustic soda solution to precipitate the alkaloid and to wash the solvent, 0.2434 gram strychnine gave 0.2473 gram residue = 101.6 per cent.

A large excess of caustic soda was then tried—viz., 30 c.c. of 10 per cent. solution—with the result that 0.4617 gram strychnine gave 0.4629 gram residue = 100.23 per cent.

Discarding the nitric acid, and dissolving the strychnine in sulphuric acid, extracting, and washing the solvent with ammonia solution, 0.2776 gram strychnine gave 0.2795 gram residue = 100.7 per cent.

Washing the solvent twice with ammonia solution, S.G. 0.959, 0.3311 gram gave 0.3358 gram residue = 101.4 per cent.

On filtering the solvent after washing with ammonia the same result was obtained—viz., 101.4 per cent.

Drying the solvent with calcium chloride, 0.2909 gram strychnine gave 0.2948 gram residue = 101.3 per cent., but the residue contained a trace of chloride.

An experiment was made with strychnine recrystallized from alcohol and dried at 50° C. till it ceased to lose weight; 0.3068 gram gave 0.3097 gram residue = 100.9 per cent.

Using chloroform only as a solvent without treatment with acid, 0.3677 gram gave 0.3710 = 100.9 per cent. after drying for twelve hours at 100° C., and this was not reduced by further drying at 110° C.

A similar experiment, using ether (purified by washing with chromic acid, sodium bisulphite, and caustic soda, and then by distilling); 0.3802 gram gave 0.3831 gram residue = 100.7 per cent.

A similar experiment, using a mixture of ether and chloroform, 0.2364 gram gave 0.2384 gram residue = 100.8 per cent.

On the other hand, dissolving strychnine in alcohol, then distilling off the latter, produced no alteration in the weight; also redissolving the residue from the ether or chloroform extractions in alcohol, and distilling off has little or no effect on the result.

A mixture of benzene and amyl alcohol (which is an excellent solvent for cinchona alkaloids) was tried as a solvent, but proved unsatisfactory, the residue after distilling being a brown resinous body with strongly-marked odour, and the results being very high—e.g., 0.3217 gram gave 0.3365 gram residue = 104.6 per cent.

As these results do not bear out the statement that Keller's method only returns about 96 per cent. of the alkaloid, some experiments were made to ascertain the effect of temperature on the reaction.

0.1612 gram strychnine with 0.2017 gram brucine, left in contact with the nitric acid for three and a half hours at 21° C., gave only 0.1456 gram residue, or 90.32 per cent.

0.2256 gram strychnine with 0.1785 gram brucine, left in contact with the nitric acid for seventeen hours at 21° C., gave only 0.1821 residue, or 80.7 per cent.

0.2412 gram strychnine with 0.1452 gram brucine, left in contact with the nitric acid for seventeen hours at 0° C., gave 0.2420 gram residue, or 100.3 per cent.

0.3436 gram strychnine with 0.1273 gram brucine, left in contact with the nitric acid for two hours at 0° C., gave 0.3460 gram residue = 100.7 per cent., almost exactly the result obtained by dissolving strychnine in the chloroform and ether mixture, and then distilling without any treatment with acid.

It appears, therefore, that at a sufficiently low temperature brucine can be completely destroyed in the presence of strychnine without injury to the latter, and that the defects of Keller's method are simply those attendant on the use of chloroform and ether as a solvent.

I feel that I owe some apology to the Society for submitting an account of this investigation at so early a stage, but as I may be unable to go further into the matter for some time, I offer these results in the hope that they may prove of some assistance (however slight) to others whose work lies in the same direction.

I have to express my indebtedness to Mr. G. E. Shaw, B.Sc., F.I.C., etc., late senior assistant in the analytical laboratory of my firm, for his valuable help in carrying out the analyses described.

DISCUSSION.

Mr. CHAPMAN, who had read the paper in the author's absence, added that Mr. Howard had been good enough to undertake this matter in connection with the Council's investigation scheme. The object had been to ascertain whether Keller's method could be modified with advantage, as had been stated to be the case by Gordin, who had published a modification of Keller's method, involving the omission of the nitric acid and the substitution for it of a further quantity of much stronger sulphuric acid. The method as modified by Gordin gave, it was claimed, exact results, whereas Keller's method was stated to yield only 96 per cent. of the total strychnine present. Mr. Howard's results, however, went to show that Keller's method was capable of giving not 96 per cent. of the strychnine, but, if anything, rather more than the actual quantity present, and consequently that its modification for the reasons given by Gordin was not necessary.

The PRESIDENT (Mr. Bevan) said this seemed to be one of those cases in which very strict observance of time and temperature conditions was essential.

Mr. F. C. J. BIRD said that the method laid down in the British Pharmacopœia for the determination of strychnine in preparations of nux vomica was not described in very full detail, a good deal being left to the judgment of the worker. As a matter of fact, the method was hedged around by conditions, not stated in the text, which it was absolutely necessary to observe in order to get correct results. In a recent case in his own experience several samples of nux vomica preparations had been condemned by certain analysts as containing excessive amounts of strychnine, whereas on further analysis they had been found to contain the correct amount only. Such errors were due simply to want of knowledge of the particular conditions under which the Pharmacopœia process gave correct results. In the precipitation of the strychnine by ferrocyanide of potassium the prescribed strength of sulphuric acid must be strictly observed, and a certain definite amount of wash-water (at 70° F) used, a correction being made for the amount of strychnine ferrocyanide dissolved by the wash-water. The temperature of the wash-water was also a most important factor. He had himself found that the same sample of a preparation of nux vomica yielded very different results when examined in summer and in winter respectively, the difference being due almost entirely to the variation in the temperature of the wash-water. At low temperatures—*e.g.*, in winter-time—brucine ferrocyanide was

THE ANALYST.

precipitated with the strychnine ferrocyanide, and came out in the final weighing as strychnine, making the result too high. In order, therefore, that the Pharmacopœia process might be properly understood, it was necessary that more detailed instructions should be given with regard to it. The method in which the brucine was destroyed by means of nitric acid was a very promising one, and Mr. Howard had placed it on a sound basis in showing that at 0° C. it gave practically the exact amount of strychnine present. As a member of the committee of reference appointed by the Pharmacopœia Committee of the General Medical Council, he could assure Mr. Howard that his results would be welcomed and greatly appreciated by those who were endeavouring to raise the analytical processes of the Pharmacopœia to that high level of accuracy and reliability on which it was most desirable that they should be placed.