solvent, such as chloroform, benzene, even at their boiling points, and in alcohol, provided the alcohol is reasonably free from water. In the case of the former solvents it is essential that no water will condense in the vessel during evaporation. Such solutions may be safely evaporated to dryness and the dry alkaloid subjected to low heat with impunity.

Hyoscyamine and atropine are unstable in water alone or in aqueous alkaline solution even in the cold, and heat materially hastens the process of hydrolysis. Ammonia appears to exert much less activity as a hydrolytic agent than has been supposed.

REFERENCES.

(1) *Annalen*, 6, 67 (1833); 5, 43, 6, 44, 7, 269 (1833).
Dunstan and Chaston, *Pharm. J.*, iii, 14, 623 (1883–4); iii, 16, 237, 238, 777 (1885); iii, 20, 461 (1889).
Dunstan and Brown, *Trans. Chem. Soc.*, 75, 72 (1899); 79, 71 (1901).
Andrews, *Trans. Chem. Soc.*, 99, 1871 (1911).
Bourcet, *Bull. des Sciences Pharmacologique*, 32, 1585–8 (1925).
(2) "Plant Alkaloids," Henry, Second Edition, pp. 62, 4, 5, 7 (1924).
(3) Will and Bredig, *Berichte*, 21, 2797 (1888).
(4) Gadamer, *Arch. Pharm.*, 239, 294 (1901).
(5) Dott, *Pharm. J.*, 107, 286 (1921).
(6) J. C. Munch, Unpublished Manuscript.
(7) Palkin, Murray and Watkins, *Ind. Eng. Chem.*, 17, 612 (1925).
(8) Contrary to Findings by Bodnar and Ferenczy, *Arch. der Pharm.*, 98, 566–570 (1925).
(9) *Loc. cit.* (4).
(10) *Loc. cit.* (7).

ONE REASON WHY MANY ALKALOIDAL ASSAYS COME LOW.

NOTES ON THE ASSAY OF HYOSCYAMUS.

BY ALBIN STIKAROFSKY.

I read with much delight W. F. Reindollar's article on "A Note on the Assay of Tincture of Hyoscyamus" in the September[1] number of the JOURNAL, because of my own interesting experience.

A sample of Hyoscyamus, assayed by the writer according to the U. S. P. method, was found to contain 0.078 per cent of alkaloids. Check analyses were run in three other disinterested laboratories.

Laboratory No. 1 (U. D. Co.), 0.0782; 0.0758; 0.0790
Laboratory No. 2 (Consulting chemist), 0.048; 0.050
Laboratory No. 3 (Consulting chemist), 0.078
Laboratory No. 4 (Manufacturing chemist), 0.053.

Surely, a director of a laboratory must be (?) pleasantly impressed when the submitted figures differ so widely.

Of course, it was now up to the writer to determine, for his own satisfaction, who was right in this "Tower of Babel." As I suspected overheating to be responsible for these losses, a fourth portion of the drug was assayed, allowing the dry alkaloidal residue to remain five minutes longer on the steam-bath. This time the estimated alkaloidal per cent was 0.0478. Thus checking reports of Laboratories No. 2 and No. 4.

[1] JOUR. A. PH. A., September 1925, p. 789.

Because the alkaloids are shaken out of an ammoniacal liquid, there was the possibility of occluding some ammonia, which would give high figures if the residue were not sufficiently heated to drive it off. So the once titrated alkaloid was again shaken out from an ammoniacal solution and heated just enough to get rid of the chloroform. The result again was 0.0478, proving that occluded ammonia was not the cause, but that prolonged heating was responsible for the low results.

It remained to be found how far the dwindling down of alkaloids would proceed upon further heating of the alkaloidal residue on the water-bath. The following results speak for themselves:

Time of heating dry alkaloid.	Results.
Two minutes	0.0730%
Three minutes	0.0672%
Five minutes	0.0478%
Fifteen minutes	0.0450%

All determinations were made in the same beaker, which had an average bottom thickness of 1.753 mm., because it had been found that the rate of dissipation of alkaloids depends on the thickness of the bottom of the beaker as well as the time of exposure to heat.

Correspondence elicited the information that Laboratory No. 4 followed the practice of placing the beakers in an inclined position on the water-bath, in order to facilitate the evaporation of the chloroform. Now, an inclined beaker exposes dry alkaloidal residue to heat as fast as the surface of the chloroform recedes—a thing that should always be guarded against. The analyst expected a more rapid evaporation from an inclined beaker and gave no thought to what else might happen.

Laboratory No. 2 questioned the uniformity of the sample, but their ash determinations and ours checked very well. They also remarked naively that every sample of Hyoscyamus examined in their laboratory during the past year was found to be below the U. S. P. requirement.

Now, I want to ask what show any young but careful analyst has—I am not talking about myself now, for I am neither young nor careful—as compared with these "established" chemists, whose names appear so often in scientific journals. Is their fame a natural outgrowth of conscientious work and accomplishment, or do not many of us become victims of cleverly concealed advertisements in professional journals? Had it not been for the careful and conscientious work of Laboratory No. 3 and their good reputation, I certainly would have been by this time looking for another job, or would have left of my own accord, because of disgust and distrust in my own ability.

I suppose a few hints on alkaloidal assay work ought to follow now. In the "Proceedings of the Pennsylvania Pharmaceutical Association" of 1918, Mr. G. E. Ewe has so well epitomized my own experience that I can do no better than reiterate his conclusions:

> 1. Before drawing off the final shakeouts with chloroform, it is absolutely necessary to rinse the stem of the funnel free from acid in order to prevent the introduction of an error due to increased amount of acid in the titration. For the same reason it is essential to have the stem free from alkali.
>
> 2. After drawing off an alkaloidal solution through the stem of the separatory funnel it is best to draw off a little of the next portion of the solvent used in

the next extraction and to combine it with the bulk, thus washing down any residue that may have dried on the inside wall.

3. The greatest losses of alkaloids are apt to occur during the final evaporation. Only water-baths should be used in the evaporation and under no circumstances should *dry alkaloids* be exposed to the heat of the water-bath. A stream of compressed air directed in the beaker while on the water-bath facilitates the evaporation greatly. For volumetric determinations 250-cc. beakers are best. For gravimetric assays usually smaller sizes are to be preferred.

4. It is of utmost importance to keep the beakers in a level position while on the water-bath, and to remove them while still about 3 cc. of the solvent remain. This residual solvent should be blown out with a jet of air. Use as little heat as possible in the manipulation of alkaloids.

The writer wishes to express his thanks and appreciation for valuable suggestions to Mr. E. C. Merrill, Chief Chemist of the United Drug Company, under whose direction the work was carried out.

THE DETERMINATION OF CINCHOPHEN IN TABLETS.*

BY L. E. WARREN.

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Cinchophen was introduced into medicine under the name of atophan. The substance was described in "New and Nonofficial Remedies" under the name of atophan and in the United States Pharmacopœia IX, under the name of phenylcinchoninic acid. During the World War the Federal Trade Commission invented the name "cinchophen" and that designation was adopted by the Council on Pharmacy and Chemistry of the American Medical Association for "New and Nonofficial Remedies." Later the name was included in the United States Pharmacopœia X. In therapy cinchophen finds application in the treatment of gout and certain forms of rheumatism. In pharmacy it is usually marketed in the form of tablets, but occasionally it is found in mixtures with acetylsalicylic acid and perhaps other substances. In the manufacture of tablets various excipients and lubricants are employed, such as starch, starch paste, acacia, talc, lycopodium, calcium carbonate, stearic acid and petrolatum.

The U. S. Pharmacopœia provides an assay for determining the purity of cinchophen, but the literature is singularly bare of references to the determination of the substance in mixtures, such as in tablets or pills. Because of this it was deemed worth while to consider methods for the analysis and examination of cinchophen in preparations. Rabak[1] extracted cinchophen from its mixtures with milk sugar by boiling with absolute alcohol. He filtered and determined the acidity of the filtrate by adding an excess of 0.1 *N* alkali and titrating back with 0.1 *N* acid, using phenolphthalein as indicator. He also tried titrating directly to the color with 0.1 *N* alkali and obtained equally good results. He suggested the use of boiling absolute alcohol as a solvent for the extraction of cinchophen from tablets, but he did not try the method on market tablet material.

* Scientific Section, A. PH. A., Philadelphia meeting, 1926.

[1] *J. Assoc. Official Agr. Chem*, 7, 34 (1923). *Ibid.*, 8 (1924).