

IX.—Occurrence of *Hyoscyamine* in the *Hyoscyamus muticus* of India.

By WYNDHAM R. DUNSTAN, F.R.S., and HAROLD BROWN, Assistant Chemist in the Laboratories of the Imperial Institute.

Hyoscyamus muticus is a species of henbane which occurs in certain districts of India, and has long been used in Indian medical practice, as a particularly virulent drug. The nature of its alkaloid, however, has never been determined.

The following account of the plant is abbreviated from that given in Hooker's *Flora Indica*.

H. muticus is found in the West Punjab, in Scinde, and in Cabul, westward to Egypt.

Cauline leaves, petioled, ovate or oblong, entire or toothed, lower flowers pedicelled, calyx striate, pubescent, teeth short, triangular, not acute in fruit, corolla 1 to $1\frac{1}{2}$ inches, lurid yellow or nearly white. Stem, 1 to 3 feet. Leaves, 4 to 7 inches, pubescent, or somewhat woolly, petiole $\frac{1}{4}$ to 3 inches. Lower pedicles in fruit, $\frac{1}{4}$ to 1 inch. Calyx, $\frac{2}{3}$ inch, in fruit, 1 by $\frac{1}{2}$ inch, funnel-shaped, ribbed, somewhat reticulate, villous, or ultimately glabrous; teeth short, triangular, not spreading. Capsule, $\frac{1}{4}$ inch in diameter. Seed, $\frac{1}{24}$ inch in diameter.

The medicinal effects of this drug appear to resemble those of ordinary henbane; when administered in comparatively large doses, it acts as a powerful excitant, leading to what have been described as paroxysms of mania, whence the synonym *Hyoscyamus insanus*. There is some reason to believe that it has been employed in the preparation of certain extremely potent kinds of the Persian "Benj" and in some varieties of the Indian "Bhang," which, however, is usually prepared from Indian hemp. Since there is at present a considerable demand for atropaceous drugs and their alkaloids, it seemed desirable to examine

that of water. It gave a mass of acicular crystals on being cooled to about -20° . The oil gave no crystalline compound with sodic bisulphite, nor could evidence be obtained of methyl salicylate. It gave a semi-solid mass on treatment with a concentrated solution of caustic soda. It is readily soluble in dilute caustic soda, and reprecipitated by acids apparently unaltered. It is slightly soluble in water, its aqueous solution gives a purple-blue coloration with ferric chloride. The volatile oil is evidently a phenol.

"There are several volatile oils having somewhat similar properties to those above described, but the quantity of oil obtained was too small to admit of the further examination which its peculiarity appears to deserve."

the alkaloid of this plant, which is fairly abundant in the districts of India in which it is found, and might possibly prove to be worth exporting.

Extraction and Estimation of the Alkaloid.

The sample, which weighed nearly two pounds, was collected in Scinde, at the instance of the Reporter on Economic Products to the Government of India, and consisted of both stems and leaves of the plant; these were separated as far as possible, but there remained a mixture of fine stems and broken leaf.

Total weight, 900 grams...	{	300 grams leaf.
		310 „ stem.
		290 „ mixture of leaf and stem.

These three portions were extracted separately, in order to determine the proportion of alkaloid in each.

The material was air-dried at a low temperature, finely powdered, and then exhausted by percolation with cold alcohol, the percolate being evaporated under reduced pressure until nearly the whole of the alcohol had been removed. The semi-solid residue was then extracted with dilute hydrochloric acid (0.5 per cent.), gently warmed, and well shaken; after subsidence, the acid liquid was poured off and the treatment repeated until the alkaloid was completely removed. The acid solution, after filtration, was shaken with small quantities of chloroform in order to remove the chlorophyll, then made slightly alkaline by the addition of dilute ammonia, and the alkaloid extracted by successive shakings of the alkaline liquid with chloroform; on distilling off the chloroform under reduced pressure, a gummy, alkaloidal residue was obtained having a slight odour recalling that of pyridine.

A small quantity of alkaloid remained in the alkaline liquid, and could not be removed by agitation with chloroform; it was, however, subsequently isolated and examined.

By percolation with cold alcohol, the following percentages of alkaloid were found.

In the plant (stem and leaf), 680 grams yielded 0.7 gram of alkaloid, or 0.1 per cent. (nearly pure).

In the stem only, 310 grams yielded 0.46 gram of alkaloid (nearly pure), which is 0.15 per cent.

In the broken leaf and fine stems, 250 grams yielded 0.14 gram of alkaloid (nearly pure), which equals 0.056 per cent.

Examination of the Alkaloid.

In order to identify the alkaloid or alkaloids present, the impure amorphous residues were converted into the aurichloride, which was

74 DUNSTAN AND BROWN : OCCURRENCE OF HYOSCYAMINE

examined by fractional crystallisation, as described in a previous paper on the alkaloids of *Scopola Carniolica* (Dunstan and Chaston, *Ph. J.*, [iii], 20, 461); this was obtained as a yellow, pulverulent precipitate, which was recrystallised from hot water acidified with hydrochloric acid. The alkaloid from the mixed stem and leaf yielded two large fractions of auric chloride melting at 154—156° and, after recrystallising, at 157—158°, which is very near the melting point of hyoscyamine aurichloride. From the mother liquors, containing the excess of auric chloride, two very small fractions of crystals were obtained melting at 149—150° and 140—145° respectively; these were too small to be dealt with separately.

The alkaloid from the stem yielded three main fractions of aurichloride all melting between 154° and 156°. On recrystallising once, three fractions melting at 158°, 157·5° and 154—156° were obtained; by concentrating the mother liquors from these, two small fractions melting at 150—155° and 145—150° were obtained, and, finally, a few crystals melting at 141—145°. The fractions of similar melting points were combined and recrystallised from dilute acid until a constant melting point was attained. In the case of the fractions of higher melting point, two or three recrystallisations sufficed, whereas the lower fractions required the operation to be repeated at least six times before a constant melting point was obtained; by this means, practically the whole of the aurichloride originally taken was obtained in shining leaflets melting at 159·5°. There only remained two small fractions melting at 157—158° and the two lowest fractions, at 140—145°, which were too small to be separately dealt with, and were consequently retained and afterwards combined with a fraction of similar melting point.

It is, therefore, proved that nearly the whole of the aurichloride is that of hyoscyamine, which melts at 160° (Ladenburg).

The small quantity of alkaloid which remained in the alkaline liquid and was not removed by agitation with chloroform was isolated in the following manner (Dunstan and Ransom, *Ph. J.*, [iii], 14, 623). The chloroform and alcohol present were removed by distillation under reduced pressure, the liquid was acidified, and the whole of the alkaloid precipitated by adding a solution of iodine in potassium iodide; the alkaloidal periodide was collected, washed, and then decomposed by a small quantity of a solution of sodium thiosulphate, the liquid made alkaline with dilute ammonia, and the alkaloid extracted with chloroform. The small quantity of alkaloid thus obtained was converted into the aurichloride, but this could not be recrystallised and was mixed with the lowest melting fractions (above referred to) for further treatment.

Analysis of the Aurichloride.

The pure aurichloride melting at 159.5° , was analysed, the gold, chlorine, and alkaloid, being directly determined. A weighed quantity of the salt was dissolved in water, the gold precipitated as sulphide, ignited, and weighed as metal. After the hydrogen sulphide had been removed from the filtrate by passing a current of air, it was exactly neutralised with soda, and the chlorine determined by titration with centinormal silver nitrate. The filtrate from the silver chloride was concentrated in a vacuum over sulphuric acid, then made alkaline with dilute ammonia, and the alkaloid removed by agitation with chloroform, and the residue obtained on distilling off the chloroform was dried in a vacuum over sulphuric acid until its weight was constant.

I. 0.0636 aurichloride gave 0.0201 Au, and required 42.2 c.c. N/100 AgNO_3 (1 c.c. = 0.0003416 Cl). Au = 31.60; Cl = 22.66.

II. 0.0424 aurichloride gave 0.0134 Au, and required 27.8 c.c. N/100 AgNO_3 . Au = 31.60; Cl = 22.40.

The two solutions containing the alkaloid from both the above determinations were mixed, and the total amount of alkaloid estimated.

0.106 aurichloride gave 0.0491 alkaloid = 46.32 per cent.

	Gold.	Chlorine.	Alkaloid.
Found	31.60, 31.60	22.66, 22.40	46.32
Calculated for $\text{C}_{17}\text{H}_{23}\text{NO}_3, \text{HAuCl}_4$	31.34	22.54	45.95

Another specimen of aurichloride yielded, on ignition, 31.25 per cent. of gold.

From more of the pure aurichloride, the alkaloid was regenerated by the method above described, and after recrystallisation from a mixture of dry chloroform and petroleum, it was obtained in long, silky needles. These were dissolved in absolute alcohol, and the specific rotatory power determined. The solution was levorotatory.

$$\alpha = 31'. \quad l = 1 \text{ dm.} \quad c = 2.04. \quad t = 19^{\circ}.$$

$$\text{whence } [\alpha]_D = \frac{100 \times 31}{2.04 \times 60} = -25.32^{\circ}.$$

Other observers have recorded numbers lying between 20° and 21° .

Hyoscyamus muticus as a Commercial Source of Pure Hyoscyamine.

Having thus ascertained that the alkaloid in *Hyoscyamus muticus* is chiefly, if not entirely, hyoscyamine, experiments were made to extract the crystalline alkaloid direct from the plant. For this purpose,

about $1\frac{1}{2}$ lbs. of the plant, both stem and leaf, was finely powdered and the alkaloid extracted by the method already described; in this way, 0.7 gram of impure alkaloid was obtained as a coloured, gummy residue, which could not be crystallised either from ether or from dilute alcohol. By dissolving in dry chloroform, however, and gradually adding light petroleum, the colouring matter was precipitated, together with a little of the alkaloid, and a nearly colourless solution was obtained, from which, on adding more petroleum and allowing it to stand, groups of small needles were gradually deposited. Several fractions of the crystalline base were thus obtained, and were recrystallised in the same manner. Finally, pure hyoscyamine was obtained in colourless, silky needles melting at 105° .

Absence of other Mydriatic Alkaloids.—The small quantity of alkaloid precipitated along with the colouring matter by the first additions of petroleum to the solution in chloroform was also examined. The precipitate was extracted with very dilute hydrochloric acid, the solution filtered, and aurichloride added, when a yellow precipitate was produced which quickly aggregated to a resinous mass (fraction A); this was removed, and on adding more of the reagent to the filtrate a yellow, pulverulent precipitate was obtained, which did not aggregate on standing (fraction B). These two fractions were recrystallised separately from dilute acid; from fraction A, two crops of crystals were obtained melting at 154 — 155° and 156 — 158° respectively; and from fraction B, crystals were obtained melting at 157 — 158° . The mother liquors from all these were concentrated in a vacuum, and thus a few crystals melting at 146 — 149° were separated.

All fractions of aurichloride insufficient for separate recrystallisation which had been obtained in the various experiments made were finally combined into two groups according to their melting points, 155 — 158° and 140 — 145° respectively. These were recrystallised as before and virtually the whole of the gold salt was found to melt constantly at 159.5° . A very small fraction melted at 158 — 159° , and another from 150 — 155° , but these were too minute for further recrystallisation. The following are the melting points of the aurichlorides of the chief mydriatic alkaloids: atropine, 136 — 138° , hyoscyamine, 159 — 160° ; scopolamine or hyoscine, 198 — 199° .

There is, therefore, no evidence of the existence in this sample of *Hyoscyamus muticus* of any mydriatic alkaloid than hyoscyamine. We believe that the plant will prove to be an important source of this alkaloid, since it can be isolated from it with far less difficulty than from ordinary henbane (*Hyoscyamus niger*), which also contains the alkaloid hyoscine, and often atropine in addition.

It should, however, be remembered that the nature of the alkaloids contained in atropaceous plants appears to vary with age, mode of culti-

vation, and other circumstances. Thus, in belladonna, the proportion of hyoscyamine to atropine fluctuates widely with the age of the plant. It is, therefore, desirable that other specimens of *Hyoscyamus muticus* should be examined, in order to ascertain whether hyoscyamine is invariably the only alkaloidal constituent.

It will be convenient to summarise here our present information as to the occurrence of hyoscyamine in various plants.

Hyoscyamus niger and *albus* (hyoscyamine and scopolamine).

Hyoscyamus muticus (hyoscyamine).

Atropa belladonna (atropine, hyoscyamine, and a little scopolamine).

Datura stramonium " " "

Duboisia myoporoides (hyoscyamine and a little scopolamine).

Scopola carniolica (hyoscyamine).

Scopola japonica (atropine, hyoscyamine, and scopolamine).

Lactuca sativa and *virosa* (hyoscyamine).

The following percentages of total alkaloid have been recorded.

	<i>Atropa belladonna.</i>	<i>Datura stramonium.</i>	<i>Hyoscyamus niger.</i>		<i>Hyoscyamus muticus.</i>
			Biennial.	Annual.	
Roots.	0·21—0·41	0·15	0·155—0·173	—	—
Leaves	0·30—0·90	{ 0·12—0·20 { (av. = 0·49)	{ 1st yr. 0·039—0·069 2nd ,, 0·045—0·068	leaves } 0·064—0·070 and tops }	stem } 0·1 and leaf }
Seeds..	—	0·16—0·37	0·058—0·1	—	—
Stem .	—	—	—	—	0·46
Entire herb.	—	—	—	0·03	—

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SCIENTIFIC DEPARTMENT,
IMPERIAL INSTITUTE, LONDON.
