HARMINE, THE ALKALOID OF CAAPI

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Of numerous American Indian habits, the use of caapi is perhaps attended by more fanciful tales than other traditional practices. Villavicencio[1] was apparently the first man to record its peculiar properties after he learned of it from the Indians. Other early descriptions were made by Spruce,[2] Martius,[3] Orton,[4] Crevaux,[5] Bayón,[6] and Koch-Grünberg.[7] The same subject was mentioned or reviewed by Perrot,[8] Perrot and Raymond-Hamet,[9] Rusby,[10] Michiels and Clinquart,[11] Rouhier,[12] Lewin,[13] Sachs,[14] Critchley,[15] and Costa and Faria.[16] Briefly, caapi is a woody climber known botanically as *Banisteria Caapi*, family Malpighiaceae, and grown in the North-western regions of South America. Several tribes of the American Indians, particularly the Tucános, Turianas, Guahibos, Zaparos, Augutéros, and Mazánes, make a decoction of the stems of caapi, and use it during their feasts and festivities. After a few drinks of the decoction, the Indian appears pale and trembling, and suddenly bursts into perspiration, seizes his arms, and exhibits his fierceness. The excitatory stage lasts for about ten minutes, and the subject then sinks into one of exhaustion. It is said[2] that following the drinking of the decoction, the Indian experiences a feeling of vertigo and buoyancy, and sees beautiful lakes, woods laden with fruits, birds of brilliant plumage, and the like. Soon the scene changes: he sees savage beasts preparing to seize him, and other horrors. It is at this moment that he breaks out in fury.

The decoction of caapi is also drunk by the Indian medicine-man when called on to adjudicate in a controversy, to disclose the plans of an enemy, to give proper information to an embassy, to detect the approach of strangers, to ascertain if wives are unfaithful, and to determine who has bewitched a sick man. Certain Indians employ the plant as a cure for beri-beri.

The most outstanding feature of caapi seems to be its ability to produce visual hallucinations and dreams in men. The Caucasians who took this preparation apparently confirmed the Indians' claims. Thus, Villavicencio[1] experienced an aerial

voyage, in which he saw the most beautiful sights, and Spruce[2] quoted a Brazilian friend as saying that once when he took a full dose of caapi he saw all the marvels that he had read about in the *Arabian Nights* pass rapidly before his eyes as in a panorama; the final sensations and sights were horrible, as usual. Cardenas[17] made seven observations on men, including himself, with the decoction in various doses. All the subjects appeared to have optical illusions of different degrees. No excitement was recorded in any case.

FIG. 1.—Map showing the habitat of *Banisteria Caapi*.

The "liana" caapi attains a height of 3 to 4 metres, and attaches itself to the trunks of large trees. It is indigenous to Venezuela, Colombia, Ecuador, Brazil, Peru, and Bolivia as shown in Figure 1. The vernacular name differs among the different tribes of Indians, The natives of Brazil. Venezuela, Bolivia, and part of Colombia call it caapi; those of Ecuador and Peru name it ayahuasca (meaning dead man's vine); and those of Southern Colombia designate it as yajé. To Spruce[2] goes the credit of its first description and identification as *Banisteria Caapi*. Other botanical and pharmacognostical investigations have been made by Clinquart,[18] Perrot and Raymond-Hamet,[9] and Costa and Faria.[16]

The isolation of an alkaloid was first successfully undertaken in 1923 by Cardenas[17] who named it *telepathine*, but did not give any analytical data. Two years later Villalba,[19] based upon the work of Albarracin,[20] announced the crystallisation of two alkaloids, *yajeine* and *yajeinine*. The former is said to be present to the extent of 1·5 per cent. of the dried plant, to melt at 206° C.,

and to have an empirical formula of $C_{14}H_8ON_3$. Little is known about yajeinine. Michiels and Clinquart[11] also recognised yajeine. Lewin[13] obtained *banisterine*, m.pt. 256° to 257° C., having an empirical formula of $C_{13}H_{12}ON_2$, and reported an extensive pharmacological investigation with the base. Clinical trials were made with banisterine in mental diseases by Beringer[21] and Schuster.[22] Almost simultaneously, Wolfes and Rumpf[23] and Elger[24] first suspected the identity of *harmine* with banisterine and yajeine, respectively. The former arrived at the conclusion through the nitrate, and the latter by direct analysis. Further evidence of identity was furnished by Brückl[25] and Dalmer[26] by physical examination. Gunn,[27] Kreitmair,[28] and Beringer and Wilmanns[29] demonstrated the very close resemblance in pharmacological action and clinical effects between harmine and banisterine. On the other hand, Raymond-Hamet[30] conceded the identity of telepathine, yajeine, and banisterine, but expressed the desire for additional work before pronouncing the identity of the forementioned alkaloids with harmine. It is probably true that the evidence heretofore presented should be further strengthened.

In 1931, the Field Museum of Natural History, Chicago, offered to us for study a quantity of twigs, leaves, and roots of caapi, and also a quantity of the decoction just as used by the Indians. The material was collected near Iquitos by the Museum's botanical expedition to Peru. Mr. Williams[31] has already given full descriptions of the specimens in question.

An alkaloid was easily isolated from both the decoction and the dried plant. Six salts were prepared. Analytical results conform to the empirical formula $C_{13}H_{12}ON_2$. In warm-blooded animals, the alkaloid in the form of hydrochloride caused violent convulsions.

Coincidentally, a sample of the seeds of *Peganum harmala* was available in our crude drug collection, so that it was possible to isolate harmine and compare it side by side with the alkaloid of caapi. After studies by combustion analyses, mixed melting-points of the derivatives, ultraviolet absorption spectra, intravenous injection into mice and monkeys for toxicity, and symptomatology, respectively, there remains no shadow of doubt that the alkaloid of caapi is harmine, and that the names telepathine, yajeine, and banisterine can be dispensed with from scientific literature. In confirmation with several previous reports, the present investigation should terminate all the mysteries surrounding the Indian plant caapi as recorded by the early travellers of South America. Incidentally, our observation on the detoxification of harmine by sodium amytal may

have a therapeutic bearing, that is, perhaps harmine poisoning can be best treated with this barbituric acid derivative.

Experimental

Banisteria Caapi. The decoction was made alkaline with ammonium hydroxide, and the alkaloid was extracted and exhausted with an ether-chloroform mixture (4 : 1). Upon the evaporation of the volatile solvents, the residue was dissolved in ethyl alcohol and recrystallised several times.

A quantity of 721 gm. of the pulverised root and lower stems was thoroughly percolated with ethyl alcohol. The extract was evaporated to a syrup under reduced pressure, treated with 1 per cent. hydrochloric acid, followed by ammonium hydroxide. The alkaloid, in the form of a brownish precipitate, was extracted repeatedly with an ether-chloroform mixture and purified in ethyl alcohol as with the decoction. The yield of the base was 2·934 gm. When assayed according to the United States Pharmacopœia X method for belladonna leaf, the dried roots showed an average of 1·87 per cent. of alkaloid, a figure not far from that reported by Seit and Putt.[32] There was very little alkaloid obtained from the branches and upper stems and leaves of the plant. Out of 273 gm. of powdered leaves, only 20 mgm., and out of 141 gm. of the branches and stems, only 5 mgm. of the crude alkaloid were isolated.

Peganum harmala.—Our sample assayed 6·87 per cent. of total alkaloids by the United States Pharmacopœia X method. The separation of harmine from the alcoholic extract by the salting out process described by Henry[33] proved satisfactory. The purification was carried out as usual. Harmaline was also obtained as a by-product, but not investigated.

TABLE I

Melting-point comparisons

Compound	Melting-point °C. corrected	
	Banisteria Caapi	*Peganum harmala*
Base (Harmine)	266	266 to 266·5
Hydrochloride	269·5 to 270·5	270 to 270·5
Hydrobromide	278 (sinters at 268)	280 (sinters at 268)
Sulphate	247 (sinters at 235)	247 to 248 (sinters at 236)
Oxalate	215 to 216	216 to 216·5
Flavianate	259·5 to 260	260
Platinichloride	264 to 266	266 to 266·5

TABLE II

COMBUSTION ANALYSES

Alkaloid (harmine) of	Composition per cent.		
	C	H	N
Banisteria caapi	73·53	5·72	13·20
	73·67	5·66	13·35
Peganum harmala	73·66	5·60	13·20
	73·85	5·71	13·27
Theoretical for $C_{13}H_{12}ON_2$ ..	73·55	5·70	13·21

The Derivatives.—The hydrochloride, hydrobromide, sulphate, oxalate, flavianate, and platinichloride of the alkaloid of caapi,

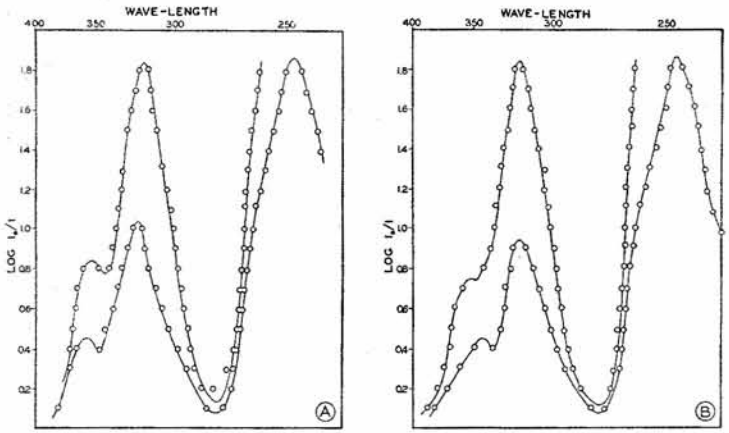

FIG. 2.—Absorption spectra of the alkaloid of caapi and harmine.

A. The hydrochloride of the alkaloid isolated from *Banisteria Caapi*, 1 : 40,000 in water (0·0025 per cent.). The upper curve was made with a cell of 0·5 cm. thickness, and the lower with one of 1·0 cm. thickness.

B. Harmine hydrochloride from *Peganum harmala*, 1 : 40,000 in water (0·0025 per cent.). The upper curve was made with a cell of 0·5 cm. thickness, and the lower with one of 1·0 cm. thickness.

and of harmine from *Peganum harmala*, were respectively prepared by standard procedures. Their melting-points are listed in Table I. No depression of mixed melting-points could be detected

between corresponding salts. Aqueous solutions of the compounds all exhibited a blue fluorescence.

The Analysis.—When subjected to combustion analyses, the results of the two alkaloids bear a very close relationship, as shown in Table II. They all conform to the empirical formula $C_{13}H_{12}ON_2$.

The Spectrogram.—Professor Wallace R. Brode, Department of Chemistry, Ohio State University, Columbus, kindly measured the absorption spectra for us. These solutions were given to him without any hint that they might have the same absorption. Figure 2 shows very definitely the identical occurrence of maxima and minima.

TABLE III

TOXICITY IN WHITE MICE BY INTRAVENOUS INJECTION

Harmine hydrochloride from	Dose	No. of mice died / No. of mice used	LD50 ± Standard error
	mgm. per kgm.		mgm. per kgm.
Banisteria Caapi ..	36·7	0/5	42·65 ± 1·61
	38·6	2/5	
	40·6	2/5	
	42·8	3/5	
	44·9	2/5	
	47·3	2/2	
Peganum harmala ..	36·7	0/5	43·44 ± 1·45
	38·6	2/5	
	40·6	0/5	
	42·8	2/5	
	44·9	3/5	
	47·3	2/2	

The Toxicity.—By intravenous injection of a 0·2 per cent. solution into starved white mice, the median lethal dose (LD50) of the hydrochloride of each alkaloid was determined and computed according to Bliss's formula.[34] The difference between the figures as given in Table III was not significant when a *t* test was applied.

Monkeys receiving harmine hydrochloride in doses of 2 to 3 mgm. per kgm. showed trembling of the body and unsteady gait, and tended to stay in the same corner of the cage. Doses of 5 mgm. per kgm. caused arching of back, stiffening of legs, trembling and shaking all over the body, and clonic convulsions. Recovery was usually prompt and complete. Almost identical

effects were observed with the same doses of the alkaloid of caapi in the same group of animals.

TABLE IV

DETOXIFICATION OF HARMINE BY SODIUM AMYTAL IN WHITE MICE

Harmine hydrochloride (Subcutaneous)	Sodium amytal (Intraperitoneal)	No. of mice died / No. of mice used	LD50 ± Standard error
mgm. per kgm.	mgm. per kgm.		mgm. per kgm.
152	—	1/5	202·4 ± 10·8
174	—	0/5	
200	—	2/5	
230	—	4/5	
264	—	5/5	
303	—	5/5	
379	100	0/5	595·5 ± 64·6
436	100	1/5	
500	100	2/5	
574	100	2/5	
659	100	3/5	

TABLE V

DETOXIFICATION OF HARMINE BY SODIUM AMYTAL IN NEW ZEALAND RED RABBITS

Harmine hydrochloride (Subcutaneous)	Sodium amytal (Intraperitoneal)	No. of rabbits died / No. of rabbits used	LD50 ± Standard error
mgm. per kgm.	mgm. per kgm.		mgm. per kgm.
66	—	1/5	78·91 ± 6·75
76	—	2/2	
87	—	2/5	
100	—	4/5	
116	—	5/5	
132	—	5/5	
180 (2·3 LD50)	80	2/3	
270 (3·4 LD50)	80	1/3	
360 (4·5 LD50)	60	2/3	
450 (5·7 LD50)	60	1/1	
395 (5 LD50)	80	1/1	
475 (6 LD50)	80	0/1	
850 (7 LD50)	80	1/1	
630 (8 LD50)	80	1/1	

Detoxification of Harmine by a Barbiturate.—In view of the fact that harmine is a convulsant in higher mammals and that

sodium amytal has proved to be an efficient antidote against strychnine,[35] dendrobine[36] and picrotoxin and coriamyrtin,[37] experiments were designed to demonstrate any possible antagonism between harmine and sodium amytal. In Table IV it should be noted that the LD50 of harmine (2 per cent.) in mice by subcutaneous injection was found to be 202·4 ± 10·8 mgm. per kgm.; but if sodium amytal in the dosage of 100 mgm. per kgm. was administered intraperitoneally following harmine the LD50 of the latter was raised to 595·5 ± 64·6. In other words, the barbituric acid derivative almost detoxified three median lethal doses of harmine. Similarly, in rabbits, as illustrated in Table V, the LD50 of harmine (2 per cent.) by subcutaneous injection was determined to be 78·91 ± 6·75; but when sodium amytal was injected intraperitoneally after harmine, one rabbit survived 6, one 4·5, two 3·4, and one 2·3 median lethal doses. Although the antidotal action is not as great as against strychnine, picrotoxin, and coriamyrtin, it is definite and unmistakable.

Summary

The alkaloid of *Banisteria Caapi* is harmine, proved directly with the harmine of *Peganum harmala*, by analyses, preparation of derivatives, absorption spectra, toxicity in mice, and symptomatology in monkeys.

The previously proposed names of telepathine, yajeine, and banisterine, for the same alkaloid should, therefore, be dismissed.

In mice and rabbits a limited detoxification of harmine by sodium amytal has been demonstrated.

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