is related to *Strychnos diaboli* Sandw. *Capparis sola*, which is considered as a very important component of curare by the Javas, on several tests showed a positive paralyzing action. Most of the other plants used by the Java Indians showed the presence of alkaloids, but they did not produce the paralyzing action, and none was very toxic.

CONCLUSIONS AND SUMMARY.

It has been found in regard to Tecuna and Java curare that five species of *Strychnos* possess alkaloids which cause a curare-like action in frogs. These species are *Strychnos* cf. *Peckii*, *Strychnos* sp. nov. (related to *Strychnos diaboli*), *Strychnos Jobertiana*, *Strychnos Castelnœana* and *Strychnos toxifera*. The extracts of two Menispermaceous plants, namely, *Chondodendron limaciifolium* and *Telitoxicum minutiflorum*, were found to be highly toxic, but the curare paralyzing action remains to be studied further. *Capparis sola*, a member of *Capparidaceæ*, has been found to contain alkaloids of curare-like action. It is an interesting plant and to our knowledge it has not been reported previously to contain alkaloids with such an action. Many other plants, as used by the Tecunas and Javas, have been eliminated as not being of interest to the problem of alkaloids of curare-like action. The interesting spp. of *Strychnos*, and *Capparis sola*, as well as plants of the *Menispermaceæ*, will be given further chemical and pharmacological study.

ACKNOWLEDGMENTS.

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REFERENCES.

(1) King, *J. Chem. Soc.*, 1381 (1935); *Ibid.*, 1272 (1936); *Ibid.*, 1472 (1937).
(2) King, *Nature*, 135, 469 (1935).
(3) King, *Chemistry & Industry*, 54, 739 (1935).
(4) West, *Proc. Roy. Soc. Med.*, 28, 41 (1935).
(5) West, *Arch. intern. pharmacodynamie*, 56, 81 (1937).
(6) West, *J. Physiol.*, 91, 437 (1938).
(7) Wieland, Kunz and Sonderhoff, *Ann.*, 527, 160 (1937).
(8) Späth and others, *Ber.*, 61, 1698 (1928); 67, 55 (1934).
(9) Friese, *Pharm. Ztg.*, 82, 577 (1937); 81, 818 (1936); 81, 241 (1936); 78, 852 (1933).
(10) Hauschild, *Arch., exptl. Path, Pharmakol.*, 175, 14 (1934); 174, 742 (1934).
(11) Santesson, *Acta Med. Scand.*, 75, 1 (1931).
(12) Krukoff, B. A., and Smith, A. C., *Bull. Torrey Botan. Club*, 64, 401 (1937).

ERYTHRINA ALKALOIDS. II. A REVIEW, AND NEW DATA ON THE ALKALOIDS OF SPECIES OF THE GENUS ERYTHRINA.*

BY KARL FOLKERS[1] AND KLAUS UNNA.[1]

Subsequent to the isolation of erythroidine from the seeds of *Erythrina americana* Mill. (1), and the developments which included the demonstration that this new alkaloid can cause a curare-like action, it was of considerable interest to make an examination of other species of the genus *Erythrina*. For the beginning of this

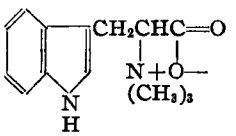
*,[1] From the Research Laboratories of Merck & Co., Inc., and the Merck Institute of Therapeutic Research, Rahway, New Jersey.

study, it was desirable to clarify certain information already existing in the literature concerning the species of this genus. It was at once apparent that there exists much confusion in the names of the plants that have been studied. Consequently, in the following brief review of the papers, which are concerned with the alkaloids of various species of *Erythrina*, the plant name used by the investigators is quoted, but following in parenthesis, when necessary, is the scientific name by which the plant is now known. By this notation, various isolated studies on the same plant may be more readily correlated. The corrections of names are made on the basis of the assumption that each investigator had the plant of which he wrote properly identified. Actually, it is probable that in certain cases he did not.

It is more expedient to review in one section at this time, certain past references to the alkaloids of the *Erythrina* species rather than to discuss them in the somewhat separated future papers from this laboratory, which will describe the studies that are now in progress on many species of *Erythrina*.

HISTORICAL REVIEW.

Greshoff discovered (2, 3), in the seeds of *Erythrina Hypaphorus* Boerl. (*Erythrina subumbrans* (Hassk.) Merr.), the alkaloid, hypaphorine, which was later proved by van Romburgh and Barger (4, 5) to be the betaine of tryptophane.



It has been claimed (3, 6, 7) that the seeds of *Erythrina subumbrans* contained a poisonous alkaloid of unknown nature. This unknown and not isolated alkaloid was not identical with hypaphorine, since the latter, examined by Plugge (8), has but little pharmacological activity.

The seeds of *Erythrina variegata* L. var. *orientalis* (L.) Merr. were examined by Maranon and Santos (9). They found about 2.5% of hypaphorine to be present, but do not mention the presence of other alkaloids. Chopra and Ghosh (10) claimed that the bark of *Erythrina indica* Lam. (*Erythrina variegata* var. *orientalis*) contained 0.05% of amorphous alkaloids, for which they did not observe any particular pharmacological activity. The leaves and the bark of the same species have been used to make extracts for use as anodynes, febrifuges and vermicides (11). In this case, the leaves were extracted with petroleum ether to yield a white neutral solid of m. p. 83° which was not a phytosterol or a glucoside. Ether and alcohol extracted an alkaloid of m. p. 117°, although it was best isolated by percolation of the leaves with a one per cent hydrochloric acid solution followed by precipitation as the bismuth iodide salt.

The bark and wood of *Erythrina Corallodendrum* L. were said by Bochefontaine and Rey to contain a narcotic-like principle (12, 13). Simon (14) has studied the pharmacological actions of extracts of bark of *Erythrina Corallodendrum*.[1]

Stenotropis Berteroi Hassk. (*Erythrina poianthes* Brot.) was said to contain an unknown toxic alkaloid in the bark, which was ether soluble, and formed a crystalline sulfate (3, 6, 7). It was called "erythrinine," and was examined pharmacologically by Plugge in the form of an amorphous acetate (15), under the name of "erythrine."

The curare-like action of extracts of various parts of *Erythrina crista-galli* L. has been recognized (16, 17).

[1] The materials on which Bochefontaine and Rey, and more recently Simon, have made their studies, were from Brazil. As far as it is now known, *Erythrina Corallodendrum* is not found in that country, but is limited to the West Indies. The name of *Erythrina Corallodendrum* has been applied erroneously in the past to several distinct species of *Erythrina*. It seems doubtful that it will ever be possible to trace back the identity of the plant on which Bochefontaine and Rey have made their studies. The studies of Simon were probably made with *Erythrina crista-galli* L.

Erythrina mulungu Mart. was said to contain a narcotic-like alkaloid (18).

The seeds of *Erythina Zeyheri* Harv. (19) were said to contain an alkaloid for which the name "erythrine" was suggested, but later, Holmes (20) recommended "zeyherine."

Other references to species of *Erythrina* which concern fatty oils, sterols, dyestuffs, etc., may be found in the literature.

COMMENT ON HISTORICAL REVIEW.

It is evident from the above review that many people have recognized the presence of alkaloids in various species of *Erythrina*. Of these, one alkaloid, hypaphorine, has been isolated from *Erythrina subumbrans* (2, 3) and *Erythrina variegata* var. *orientalis* (9) and has been characterized and its constitution shown (4, 5). Only one of the physiologically active alkaloids, erythroidine, has been isolated in pure form, characterized, and assigned an empirical formula, $C_{16}H_{19}NO_3$ (1). It was obtained from *Erythrina americana*. All others were so poorly defined that they cannot be recognized as chemical individuals, and still others have been assumed to be present because of the toxicity of crude preparations of various parts of the plants.

Apart from the knowledge that extracts of *Erythrina americana* would produce a curare-like action (21, 22),[1] such activity has been reported and proved for *Erythrina crista-galli* (16, 17).

All other investigators who worked with crude extracts differ widely in their observations and interpretations of the effects of the alkaloids obtained from various species of *Erythrina*. Bochefontaine and Rey (12, 13) found a sedative and hypnotic effect, observable also in humans. Simon (14) working with a bark infusion reported a depression of motor activity and sensibility, both of central origin. Plugge (15), in his investigations, found that "erythrine" acts in a similar way as cytisin and is quite different from a curare-like action.

NEW DATA.

Before attempting the isolation of alkaloids from various species of *Erythrina*, other than *Erythrina americana*, it was considered desirable to ascertain by a pharmacological test if other species contained alkaloids of curare-like action. For this purpose, the following method was used.

Analytical Procedure.—A sample of 1 to 100 Gm. of seeds was ground to 40 mesh and extracted with petroleum ether in a small Soxhlet extraction apparatus for 3 hours to remove the fatty oil. The seed powder was then extracted with ethanol for 6 to 20 hours to remove the alkaloids together with other alcohol extractives. The alcohol extract was filtered, distilled and all residual alcohol removed by pumping out at 2-mm. pressure and 25° C. The alcohol extractives were dissolved in a given volume of water, and this solution, or a dilution, was injected intralymphatically into frogs and the threshold dose for curare action was determined by application of an electrical stimulation to the sciatic nerve. The aqueous solutions showed positive reactions with Valser's and Scheibler's reagents. From this threshold dose, a paralysis potency value for the seed was calculated. This value is defined as the number of Gm. of frog paralyzed by one Gm. of seed. Thus, if the alcohol extractives of 2.0 Gm. of seed were dissolved in 5 ml. of water, and the

[1] Other references to the pharmacological actions of extracts of *Erythrina americana* are quoted in Lehman's papers.

threshold dose in frogs was 0.05 ml. per Kg., then the paralysis potency value would be 50,000.

In Table I, there are summarized the data obtained on certain species of *Erythrina*.

DISCUSSION OF NEW DATA.

Of the species of the genus *Erythrina* which have been included in our research, twenty-six are listed in Table I. Those unidentified specifically and indicated by collectors' numbers only, await botanical identification, but it is expected that they will be fully named later. The data show the presence of alkaloids of curare-like action in frogs in all twenty-six of the species. The demonstration of this fact is new for twenty-four of the species, two having been recognized before (*Erythrina americana* and *Erythrina crista-galli*). These species are from North and South America, Asia, Africa and Australia, all from the tropics and subtropics. Thus, these alkaloids occur widely spread in nature, both geographically and in the various sections of the genus. It has been convenient to study first the seeds, although the presence of such active alkaloids has also been demonstrated in the bark of *Erythrina velutina* Willd. (Krukoff 7912), *Erythrina Berteroana* Urb. (Walsingham 9133) and others.

TABLE I.—DATA ON SPECIES OF ERYTHRINA.

Name of Plant.	Collectors' Names and Specimen Numbers.[1]		Amount Gm. Seeds.	Fatty Fraction %.	Ethanol Extractives %.	Water Added Ml.	Threshold Dose Ml./Kg.	Paralysis Potency Value Gm. Frog/1 Gm. Seed.
E. herbacea L.	Brazol	9144	2.4440	18.1	12.6[2]	4.0	0.02	82,000
E. herbacea L.	(Unknown)	9125[3]	1.4607	14.5	11.6	1.0	0.05	13,700
E. flabelliformis Kearn.	(Unknown)	9126[3]	1.7170	14.7	10.7	1.0	0.02	29,100
E. flabelliformis Kearn.	Marshall	9138[4]	5.1071	15.6	17.0	10.0	0.04	49,000
E. flabelliformis Kearn.	Marshall	9138[5]	4.9701	14.4	15.0	10.0	0.04	50,300
E. neglecta Kruk. & Mold.	Benitez	9159	5.5003	11.9	15.3	19.0	0.50	6,900
E. neglecta Kruk. & Mold.	Armstrong	9178	1.8816	10.6	19.3	5.0	0.50	5,300
E. Berteroana Urb.	(Unknown)	9130[3]	1.4885	9.7	14.5	1.0	0.20	3,360
E. Berteroana Urb.	Otero	9166	2.0709	9.7	17.1	5.0	0.30	8,000
E. sandwicensis Deg.	L. W. Bryan	9136	10.0000	(15.0)	17.3	8.0	0.02	40,000
E. crista-galli L.	Diddell	9132	10.0000	14.8	26.2	8.0	0.05	16,000
E. subumbrans (Hassk.) Merr.	From Buitenzorg	9151	6.5000	12.5	23.2	11.5	0.05	35,400
E. fusca Lour.	Canicoza	9153	10.8400	7.5	5.3	5.0	0.05	9,200
E. Poeppigiana (Walp.) Cook.	From Buitenzorg	9150	5.844	10.0	12.5	6.0	0.02	51,400
E. Poeppigiana (Walp.) Cook.	From Buitenzorg	9150	2.1877	12.0	17.8	2.2	0.02	50,300
					1.2[6]	0.5	5.00	45
E. variegata L.	From Buitenzorg	9148	4.8590	11.1	11.3	4.0	2.00	410
E. variegata L. var. *orientalis* (L.) Merr.	Haigh	9172	10.0251	9.9	14.9	20.0	4.00	500
E. variegata L. var. *orientalis* (L.) Merr.	Otero	9131	10.4372	11.7	11.4	20.0	8.00	240

E. variegata L. var. *orientalis* (L.) Merr.	(Unknown)	9129[3]	9.880	11.5	10.4	9.0	2.00	450
E. variegata L. var. *orientalis* (L.) Merr.	Canicoza	9152	10.1945	9.9	10.5	20.0	8.00	240
E. hondurensis Standl.	Chickering	9157/ 133[3]	1.6001	12.8	11.1	1.0	0.20	3,100
E. americana Mill. (?)	Purpus	9145	1.7779	16.5	14.9	1.0	0.30	1,870
E. americana Mill.	Conzatti	9135/ 5383	1.1656	13.0	16.5	7.0	0.60	10,000
E. Folkersii Kruk. & Mold.	Kinloch	9167	2.3793	16.5	14.5	2.0	0.20	4,200
E. caffra Thunb. (hort. var.; fl. orange)	Robertshaw	9175	2.3790	9.3	13.5	2.0	0.10	8,300
E. vespertilio Benth.	Trist	9180	2.9395	8.1	11.9	1.5	0.20	2,500
E. abyssinica Lam.	Ross	9179	2.1826	11.0	16.8	5.0	0.05	46,000
E. species	Montealegre	9193	2.1990	13.6	18.1	5.0	0.20	11,400
E. velutina Willd.	Krug	9196	2.3590	8.0	17.5	5.0	0.50	4,200
E. falcata Benth.	Thays	9188	2.0290	6.4	20.8	5.0	0.06	41,000
E. glauca Willd. (?)	Campos Porto	9199	9.4133	8.8	18.2	37.0	0.10	39,400
E. glauca Willd.	Dugand	9203	10.5960	6.7	11.8	25.0	0.04	59,000
E. species	Gomez Parente	9169	3.3470	10.2	12.7	2.0	0.01	60,000
E. rubrinervia H. B. K.	Jaramillo	9181	2.1378	18.7	12.6	5.0	0.08	29,300
E. Dominguezii Hassler	Schulz	9197/ 1569	2.0443	8.2	20.9	5.0	0.05	49,000
E. senegalensis DC.	Bur. Affair Econ. Fr. Guin.	9202	50.0000	9.2	19.1	100.0	0.10	20,000
E. acanthocarpa E. Mey.	Everitt	9198	100.0000	17.9	19.8	200.0	0.03	66,600
E. edulis Triana	Jaramillo	9182	3.7667	1.5	5.1	5.0	8.0	165

[1] The numbers of the specimens were assigned by Mr. B. A. Krukoff to the botanical specimens taken from the same plants as the seeds. These botanical specimens are deposited with the New York Botanical Garden.

[2] The ethanol extractives were 12.5% after 10 hours, and 12.6% after 16 hours.

[3] These were old seeds.

[4,5] There was no observable difference between the red seeds (4) and the buff-colored seeds (5).

[6] This 1.2% represents a continued extraction of 6 hours.

The numerical value of the paralysis potency has only limited quantitative significance as to the amount of the active alkaloids which are present. Various factors such as sampling, slight selective losses of alkaloids into the fatty oil fraction, relative potencies, relative amounts of alkaloids, etc., affect these values, and these factors must be remembered when comparing values. The influence of other ethanol extractives upon the action of the alkaloids, and mutual alkaloid synergism, in the pharmacological test must be considered also.

Although hypaphorine is present in many of the species, and was therefore present in the aqueous test solution, it is not responsible for any of the curare-like action, because it causes a hyperexcitability in frogs as Plugge found, and as has been confirmed in this laboratory. Further-

more, it may be calculated for the seeds of *Erythrina crista-galli*, which contain about three per cent of hypaphorine, that about 2 mg. of hypaphorine were present in the threshold dose of 0.05 ml./Kg. Thus the amount of 2 mg./Kg. was decidedly below the minimum responsive dose of approximately 250 mg. /Kg. of hypaphorine as found by Plugge, and in our experiments.

It is noteworthy that the paralysis potency of *Erythrina variegata* var. *orientalis* was next to the lowest of all. Thus, it is not surprising that the slight potency of this widespread and well-known species has received so little recognition in the past.

These results, and the recent studies on the clinical use of curare and erythroidine hydrochloride in the muscular rigidity and spasms of spastic paralysis, and dystonia musculorum deformans (23) have encouraged a continued chemical and pharmacological study of the active alkaloids of species of *Erythrina* in the interest of the therapeutics of these diseases. Several new active alkaloids, related to erythroidine, have already been isolated and characterized, and others are being newly characterized from various species of *Erythrina*. Hypaphorine has been newly isolated from most of the species. The chemistry and pharmacology of these new alkaloids will be described in future papers.

Because of the classical curare, the research for alkaloids which paralyze the nerve-endings of voluntary muscles has been primarily concerned with plants of the genus *Strychnos*, and of the *Menispermaceæ* (25 to 31 incl.), and recently a plant, *Capparis sola* Macbr., of the *Capparidaceæ* (32). The genus *Erythrina* now seems to occupy a place in this field.

SUMMARY.

The literature on the alkaloids of species of *Erythrina* has been briefly reviewed. New data have been presented which have shown for the first time the presence of alkaloidal substances in twenty-four species of *Erythrina*, which can cause a curare-like action in frogs.

ACKNOWLEDGMENT.

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REFERENCES.

(1) Folkers, K., and Major, R. T., *J. Am. Chem. Soc.*, 59, 1580 (1937).
(2) Greshoff, M., *Mededeelingen uit's Lands. Plantentuin*, 7, 29 (1890).
(3) Greshoff, M., *Ibid.*, 25, 54 (1898).
(4) van Romburgh, P., *Akad. Wetensch. Amsterdam Wisk. Natk. Afd.*, 13, 1177 (1911).
(5) van Romburgh, P., and Barger, G., *J. Chem. Soc.*, 2068 (1911).
(6) Greshoff, M., *Ber.*, 23, 3540 (1890).
(7) Greshoff, M., *Ber. deut. pharm. Ges.*, 9, 215 (1899).
(8) Plugge, P. C., *Arch. exptl. Path. Pharmakol.*, 32, 313 (1893).
(9) Maranon, J., and Santos, J. K., *Philippine J. Sci.*, 48, 563 (1932).
(10) Chopra, R. N., and Ghosh, S., *Indian Med. Record*, 55, 77 (1935).
(11) Chakravarti, S. N., Sitaraman, M. L., and Venkatasubban, A., *J. Annamalai Univ.*, 2, 238 (1933).
(12) Bochefontaine, A., and Rey, P., *Gaz. Med. Paris* (6), 3, 196 (1881).
(13) Rey, P., *Journal de Therapeutique*, 10, 843 (1883).
(14) Simon, I., *Arch. farmacol. sper.*, 59, 193 (1935).
(15) Plugge, P. C., *Arch. exptl. Path. Pharmakol.*, 33, 46 (1894).
(16) Cicardo, V. H., and Hug, E., *Rev. soc. argentina biol.*, 13, 121 (1937).
(17) Cicardo, V. H., and Hug, E., *Compt. rend. soc. biol.*, 126, 154 (1937).
(18) Christy, Quoted in Wehmer, C., "Die Pflanzenstoffe," 2nd Edition, page 573, G. Fischer, Jena (1929).

(19) Watt, J. M., and Breyer-Brandwijk, M. G., "The Medicinal and Poisonous Plants of Southern Africa," pages 77–78, Livingstone, Edinburgh (1932).
(20) Langham, E., and Holmes, E. M., Quoted in *Pharm. J.*, 134, 25 (1910). (See reference 19, page 80.)
(21) Lehman, A. J., *Proc. Soc. Exptl. Biol. Med.*, 33, 501 (1936).
(22) Lehman, A. J., *J. Pharmacol.*, 60, 69 (1937).
(23) Burman, M. S., Private communication.
(24) Boehm, R., "Handbuch Exp. Pharmakologie," 2, 179, Springer, Berlin (1920).
(25) West, R., *Proc. Roy. Soc. Med.*, 28, 41 (1935).
(26) West, R., *Arch. intern. pharmacodynamie*, 56, 81 (1937).
(27) West, R., *J. Physiol.*, 91, 437 (1938).
(28) King, H., *J. Chem. Soc.*, 1381 (1935).
(29) King, H., *Ibid.*, 1276 (1936).
(30) King, H., *Ibid.*, 1472 (1937).
(31) Krukoff, B. A., and Smith, A. C., *Bull. Torrey Botan. Club*, 64, 401 (1937).
(32) Folkers, K., JOUR. A. PH. A., 27, 689 (1938).

SOCIALIZED MEDICINE IN TAMPA, FLORIDA.*

BY FRANK L. CONIGLIO.[1]

In the latter part of the last century, there was a tremendous influx of emigrants to this section, mostly Italians, Spaniards and Cubans. Coming from the familiar institutions of their former homes, to this land whose customs and language were foreign to them, they found themselves among a strange people. The first great necessity felt by these newly arrived people was that of associating together for mutual protection, which gave rise to the present-day Mutual Aid Societies. At the beginning the membership of each organization was small, but in a few years it increased greatly.

The original purpose of these organizations was to secure medical aid and financial support for the individual in time of sickness. Later, however, others were added making these societies recreational and cultural as well. But, we are concerned primarily with the sick benefit division, which brings in for discussion the doctor, the pharmacist and other members of the medical professions.

BENEFITS.

The following is a generalized idea of the benefits obtained in accordance with specified weekly or monthly dues, usually beginning with the sum of twenty-five cents. (1) Each member gets medical treatment both at home or at the hospitals, including operations and medicine. (2) A specified weekly income during the period of sickness and convalescence, usually two dollars a day. (3) For a small weekly payment of from five to ten cents a week, death insurance is acquired, paying the family the sum of two hundred and fifty dollars in cash. However, this death benefit provision is optional and need not be purchased with the health insurance.

For a Rate of Sixty-Five Cents a Week.—(1) Two dollars a day in case of sickness (after being a member for eight weeks).
(2) Medical assistance after the payment of the first receipt.

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[1] Pharmacist, West Tampa, Fla.