SCIENTIFIC SECTION

THE POTENCY OF ERYTHROPHLEUM ALKALOIDS.*

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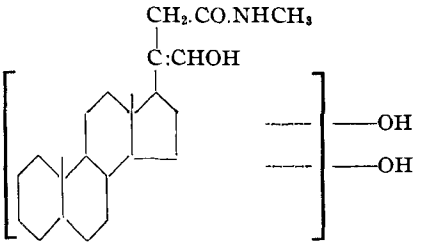
In 1875 Gallois and Hardy (1), (2) first succeeded in isolating the alkaloid erythrophleine from the African sassy bark (*Erythrophleum guineense*, family leguminoseæ). For fully sixty years erythrophleine remained the only alkaloid known to have a digitalis-like action upon the heart, although scientific investigations were made repeatedly by Harnack and Zabrocki (3), Harnack (4), Kralsheimer (5), Power and Salway (6) and Maplethorpe (7). Other species of *Erythrophleum* were also studied such as *E. couminga* by Gallois and Hardy (2), *E. laboacherii* by Petrie (8), and *E. lasianthum* by Kamerman (9), but no new alkaloid was reported. Brill and Wells (10) stated that the bark of *E. densiflorum* of the Philippine Islands yielded no alkaloidal constituents. It was not until 1935 that Dalma (11) separated four other alkaloids from the bark of *E. guineense:* Cassaine, $C_{24}H_{39}O_4N$, cassaidine, $C_{24}H_{43}O_5N$, *nor*-cassaidine, $C_{23}H_{41}O_5N$, and homophleine $C_{56}H_{88}O_9N_2$. The first three are crystalline while the last one is amorphous. Their toxicity and general action in frogs, rats and rabbits have been tested by Santi and Zweifel (12). Dalma (13) has explored the chemical structures of his new alkaloids, and has come to the conclusion that they are probably derivatives of cyclopentenophenanthrene with a side chain of methylamide coupled with a hydroxy acid. Thus, for cassaine the following formula has been suggested:



If the above structure[2] can be substantiated, it will then become clear that all the cardiac substances—glycosides, bufagins, bufotoxins and *Erythrophleum* alkaloids—have the cyclopentenophenanthrene ring system. One difference should be noted, that is, the alkaloids, unlike the glycosides, bufagins and bufotoxins, are devoid of the unsaturated lactone group which proves to be so indispensable for the cardiac action of non-alkaloidal compounds. It is also difficult to conceive how the methylamide can easily form salts with mineral acids as Dalma's new alkaloids do.

Through the courtesy of Professor Gustavo Dalma, Provincial Chemical Laboratory, Fiume, Italy, we were in possession of three alkaloids which he isolated from *Erythrophleum guineense*—cassaine, *nor*-cassaidine and homophleine. In addition, he was generous enough to supply us acetyl-cassaine, a derivative of

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[2] While this paper was in press, a private communication from Professor Dalma was received. He stated that further chemical studies, made by himself but not yet published, confirmed his assertion that cassaine was a derivative of cyclopentenophenanthrene, although it might have to be modified in order to conform to the structure of etiocholanic acid. He also mentioned that the absence of an unsaturated lactone ring had been verified.

cassaine, and two new crystalline alkaloids named coumingine and coumingaine which he obtained from *Erythrophleum coumingo*, and upon which he had not, at the time of our writing, made any publications. Cassaine, acetyl-cassaine, *nor*-cassaidine, coumingine and coumingaine were in the form of hydrochlorides while homophleine was in the form of bisulfate. As expected, they were all very soluble in water suitable for pharmacological experiments. Our data on erythrophleine sulfate have been published in a previous report (14). In the present investigation, the five new alkaloids and one derivative were subjected to assays and studies similar to those described in our preceding papers (14), (15).

The essential results are shown in Tables I, II and III and summarized in Table V. It should be noted that coumingine hydrochloride is the most potent and toxic member of the group, having an activity in cats equal to that of scillaren A. Coumingaine hydrochloride, *nor*-cassaidine hydrochloride, cassaine hydrochloride and homophleine bisulfate are all weaker than the well-known alkaloid erythrophleine sulfate. The figures for homophleine undoubtedly will be revised when, by improved methods, the alkaloid can be obtained in crystalline instead of amorphous form.

TABLE I.—CAT UNITS OF COUMINGINE, COUMINGAINE, NOR-CASSAIDINE, CASSAINE, ACETYL-CASSAINE AND HOMOPHLEINE.

Drug.	Solution.	Cat Number.	Sex.	Weight, Kg.	Fatal Dose, Mg. per Kg.
Coumingine hydrochloride	1:100,000	1808	M	2.020	0.185
		1809	F	2.408	0.128
		1810	M	1.637	0.193
		1811	M	2.889	0.152
		1812	M	2.903	0.120
		1813	M	2.538	0.112
		1814	M	2.486	0.170
		1815	M	2.600	0.148
		1816	M	2.547	0.163
		1817	M	2.210	0.110
Coumingaine hydrochloride	1:20,000	1909	M	2.448	0.587
		1910	M	1.881	0.536
		1911	F	2.195	0.569
		1912	M	1.744	0.363
		1913	M	2.321	0.515
		1914	M	2.045	0.406
		1930	M	2.403	0.450
		1931	M	2.979	0.415
		1932	M	2.452	0.348
		1937	F	1.934	0.488
nor-Cassaidine hydrochloride	1:20,000	1770	F	2.319	0.688
		1772	M	2.061	1.144
		1774	F	2.363	0.677
		1775	F	1.980	0.569
		1776	M	2.324	1.274
		1778	F	2.691	0.725
		1780	M	2.669	0.393
		1781	F	1.834	0.631
		1782	M	1.730	0.350
		1783	M	1.800	0.919
Cassaine hydrochloride	1:20,000	1764	F	2.260	1.170
		1765	F	1.929	1.298
		1766	F	2.195	2.191
		1767	F	2.083	0.806
		1768	F	2.353	1.292
		1769	M	2.583	0.964
		1771	F	2.443	0.978
		1773	M	2.888	1.118
		1777	F	2.122	0.848
		1779	F	2.640	0.922
Acetyl-cassaine hydrochloride	1:20,000	1934	F	1.890	2.053
		1935	F	1.975	1.281
		1936	M	2.512	1.330
		1938	F	2.230	2.348
		1939	M	2.905	2.077
		1940	M	1.807	1.541
		1941	M	2.234	1.759
		1942	F	2.104	2.766
		1943	F	2.026	1.478
		1969	M	2.265	2.318
Homophleine bisulfate	1:10,000	1818	M	2.340	1.487
		1819	M	2.987	2.072
		1820	F	2.065	2.300
		1821	M	1.924	2.599
		1822	M	1.981	2.655
		1823	M	2.516	1.228
		1824	M	2.406	1.444
		1825	F	1.949	1.662
		1826	M	1.680	1.667
		1829	F	2.443	1.772

TABLE II.—MINIMAL SYSTOLIC DOSES OF COUMINGINE, COUMINGAINE, CASSAINE, NOR-CASSAIDINE ACETYL-CASSAINE AND HOMOPHLEINE IN FROGS.

Drug.	Solution.	Dose, Mg. per Gm.	No. in Systolic Standstill/No. of Frogs Used.
Coumingine hydrochloride	1:2000	0.00167	0/4
		0.00208	2/8
		0.00250	6/8
		0.00292	4/4
Coumingaine hydrochloride	1:2000	0.00417	0/4
		0.00500	1/4
		0.00583	0/4
		0.00667	4/4
	1:500	0.00833	4/4
		0.01667	4/4
		0.02500	4/4
Cassaine hydrochloride	1:200	0.01667	0/8
		0.01875	3/4
		0.02083	4/4
		0.02500	3/4
		0.04167	4/4
nor-Cassaidine hydrochloride	1:200	0.01667	0/4
		0.01875	1/4
		0.02083	4/4
		0.02500	4/4
		0.04167	4/4
Acetyl-cassaine hydrochloride	1:200	0.02083	0/4
		0.02500	2/8
		0.02916	3/4
		0.06250	4/4
Homophleine bisulfate	1:200	0.02083	0/4
		0.02500	0/4
		0.03333	2/8
		0.03750	3/4
		0.04167	3/4
		0.06250	4/4

TABLE III.—EMESIS AND PERSISTENCE OF ACTION OF COUMINGINE, COUMINGAINE, NOR-CASSAIDINE, CASSAINE, ACETYL-CASSAINE AND HOMOPHLEINE IN CATS.

Drug.	Cat Number.	Sex.	Body Weight, Kg.	Initial Dose Injected Intravenously, Mg. per Kg.	Vomiting Occurred.	Final Fatal Dose (Exclusive of Initial Dose), Mg. per Kg.	Interval between Initial and Fatal Doses, Hours.
Coumingine hydrochloride	1844	F	2.051	0.060	0	0.143	5.3
	1845	F	2.606	0.070	0	0.163	5.5
	1851	M	2.593	0.080	0	0.125	5.0
	1852	M	1.986	0.080	0	0.159	5.5
	1848	F	1.973	*0.090*	+	0.116	6.7
	1854	F	1.940	*0.090*	0	0.088	23.5
	1855	M	2.537	*0.090*	+	*	...
	1849	F	1.821	0.110	+	*	...

TABLE III.—EMESIS AND PERSISTENCE OF ACTION OF COUMINGINE, COUMINGAINE, NOR-CASSAIDINE, CASSAINE, ACETYL-CASSAINE AND HOMOPHLEINE IN CATS.—(*Continued from page 11*).

Coumingaine hydrochloride	1945	M	2.848	0.100	0	**	...
	1927	M	3.166	0.150	+	0.490	2.5
	1947	F	2.345	0.150	0	**	...
	1950	F	2.337	0.150	0	**	...
	1928	M	2.400	*0.175*	+	0.478	3.5
	1951	F	2.086	*0.175*	+	**	...
	1923	F	2.293	0.200	+	0.373	5.5
	1929	F	2.162	0.200	+	0.342	23.0
	1926	M	2.837	0.250	+	0.293	21.5
	1925	M	2.564	0.300	+	0.413	22.5
nor-Cassaidine hydrochloride	1792	F	1.702	0.100	0	**	...
	1797	F	2.258	0.100	0	**	...
	1798	F	2.359	0.125	+	**	...
	1799	F	1.715	0.125	0	0.912	2.0
	1795	F	2.349	0.150	+	0.368	28.0
	1800	F	2.217	0.150	0	0.539	12.2
	1801	M	1.788	0.175	0	0.450	50.0
	1793	F	2.213	0.200	+	0.441	28.5
	1796	F	2.396	0.200	0	0.244	52.0
	1802	M	2.763	0.200	0	0.289	24.0
	1803	M	1.810	0.225	0	0.273	23.4
	1804	F	1.616	0.225	+	0.743	1.5
	1805	F	2.065	0.225	0	0.246	23.5
	1806	F	2.248	*0.250*	0	0.327	20.0
	1835	M	2.350	*0.250*	+	0.438	72.0
	1836	F	1.879	*0.250*	+	0.886	150.0
	1807	M	1.985	0.275	0	0.353	18.0
	1834	F	2.095	0.275	+	0.563	149.0
	1791	F	2.320	0.300	+	0.528	22.5
	1794	F	1.694	0.500	+	0.360	24.0
Cassaine hydrochloride	1786	M	2.810	0.300	0	0.389	26.0
	1789	F	2.306	0.300	0	1.316	1.0
	1830	F	2.695	0.350	0	0.285	48.0
	1832	M	3.174	0.350	0	0.351	72.0
	1831	F	1.871	*0.375*	+	*	...
	1833	M	2.398	*0.375*	+	*	...
	1787	M	1.590	0.400	+	1.085	5.5
	1790	M	2.140	0.400	+	0.378	24.0
	1788	F	1.948	0.500	+	**	...
	1785	M	2.704	0.600	0	***	...
	1784	F	1.786	0.800	0	0.386	24.0
Acetyl-cassaine hydrochloride	1946	M	2.759	0.200	0	0.850	2.3
	1955	M	2.417	0.250	0	2.164	3.3
	1949	F	2.905	0.300	0	1.148	5.0
	1954	M	2.943	0.300	+	0.880	22.0
	1956	M	2.493	0.300	0	**	...
	1953	M	2.762	*0.325*	+	2.190	24.0
	1957	M	2.794	*0.325*	0	**	...
	1958	F	1.861	*0.325*	+	1.478	16.8
	1952	F	2.252	0.350	+	2.527	23.5
	1948	M	2.477	0.400	+	1.053	24.0
	1944	F	2.054	0.600	+	0.842	30.0

TABLE III.—(*Continued from page 12*).

Homophleine bisulfate	1840	M	2.910	0.100	0	2.72	2.5
	1841	M	2.920	0.200	0	1.94	2.5
	1842	M	3.088	0.250	0	2.74	3.5
	1843	F	2.227	0.275	0	1.49	24.5
	1839	M	2.890	0.300	+	*	...
	1846	F	1.911	0.400	0	2.11	25.5
	1838	M	2.648	0.500	+	1.89	48.5
	1853	M	2.723	0.500	0	4.00	25.3
	1856	F	2.048	0.500	0	2.03	72.0
	1857	F	2.442	0.550	0	**	...
	1850	F	1.860	0.600	+	*	...
	1858	M	1.827	0.600	0	2.35	73.0
	1860	M	2.423	0.650	0	*	...
	1862	M	2.489	0.650	0	**	...
	1861	F	1.824	*0.675*	0	2.60	76.0
	1863	M	2.418	*0.675*	+	**	...
	1864	M	2.394	*0.675*	+	**	...
	1847	M	2.041	0.700	+	3.92	29.0
	1859	M	2.146	0.700	+	1.38	75.5
	1837	F	1.868	0.900	+	*	...

* Found dead over night or later.
** Not determined.
*** Died in 6 minutes.

TABLE IV.—LOCAL ANESTHETIC ACTION OF COUMINGINE, COUMINGAINE, CASSAINE, ACETYL-CASSAINE, NOR-CASSAIDINE AND HOMOPHLEINE.

Drug.	Concentration.	Average Duration of Anesthesia, Minutes. Guinea Pigs' Skin (Intracutaneous).	Rabbits' Cornea (Instillation).
	1:10,000	49	210+
Coumingine hydrochloride	1:50,000	26	183
	1:100,000	None	59
Coumingaine hydrochloride	1:400	460+	420+
Cassaine hydrochloride	1:400	66	176
Acetyl-cassaine hydrochloride	1:400	454+	32
nor-Cassaidine hydrochloride	1:400	82	128
Homophleine bisulfate	1:400	152	480+

TABLE V.—SUMMARY OF THE ESSENTIAL RESULTS ON ERYTHROPHLEUM ALKALOIDS.

Drug.	Cat Unit (Mean ± Probable Error), Mg. per Kg.	Frog Minimal Systolic Dose, Mg. per Gm.	Cat Minimal Emetic Dose, Mg. per Kg.
Coumingine hydrochloride	0.148 ± 0.006	0.00250	0.090
Coumingaine hydrochloride	0.468 ± 0.018	0.00667	0.175
Cassaine hydrochloride	1.153 ± 0.080	0.01875	0.375
Acetyl-cassaine hydrochloride	1.895 ± 0.105	0.02916	0.325
nor-Cassaidine hydrochloride	0.737 ± 0.057	0.02083	0.250
Homophleine bisulfate	1.889 ± 0.106	0.03750	0.675
Erythrophleine sulfate	0.374 ± 0.017	0.01100	0.300

Their potency in frogs is uniformly lower than in cats when compared with the glycosides. For example, the cat unit of both coumingine hydrochloride and scillaren A is 0.15 mg. per Kg., but the frog minimal systolic dose of the former is 0.0025 mg. per Gm. and that of the latter 0.007 mg. per Gm. (fully $3^1/_2$ times as active).

Regarding the emetic action, the newer alkaloids are more powerful than erythrophleine sulfate (Table V). The cat minimal emetic doses of *nor*-cassaidine hydrochloride, cassaine hydrochloride, homophleine bisulfate, coumingaine hydrochloride and coumingine hydrochloride are 33, 33, 36, 37 and 60 per cent of their cat units, respectively, while that of erythrophleine sulfate amounts to 81 per cent of its cat unit.

There is a peculiar phenomenon about the persistence of action of three of the *Erythrophleum* alkaloids, coumingine, cassaine and homophleine. As shown in Table III, the final fatal doses are large and lie within normal ranges (compare Table I) if they are determined 1 to 24 hours after the initial dose, but they become small if they are determined after an interval of more than 24 hours from the initial dose. As a matter of fact, 2 cats died with doses of coumingine hydrochloride smaller than its cat unit, and two others similarly died with doses of cassaine hydrochloride smaller than its cat unit, a few days after the injection. It seems that these substances become more toxic after they remain in the circulation for some time; or, in other words, the myocardium gradually accumulates coumingine, cassaine or homophleine, which exists extracardially at, and following, the time of injection.

In all instances, the action of the alkaloids upon the heart appeared promptly, contrary to that of digitoxin. For example, bradycardia occurred early during the determination of the fatal dose, and vomiting usually took place within 15 minutes after administration of adequate doses.

Acetyl-cassaine is definitely weaker in cardiac action than cassaine—approximately 64 per cent less potent in cats and 55 per cent less potent in frogs. On the other hand, its emetic action is slightly stronger than that of cassaine, being 13 per cent more efficient. These results are similar to those of acetyl-cino-bufagin when compared with cino-bufagin (16). It appears that acetylation in their molecules reduces the effect on the heart but does not diminish their emetic action.

Of the *Erythrophleum* alkaloids, cassaine causes stiffening of muscles and tonic convulsions in both frogs and cats. The convulsions in frogs cease after the destruction of the brain. The central stimulating effects of cassaine are similar to those of digitoxigenin (17) and some of the bufagins such as cino-bufagin (18). No such action was observed in cats with sublethal doses (50 per cent of the cat unit or less) of coumingine, coumingaine, *nor*-cassaidine or homophleine. Acetyl-cassaine also causes convulsions in frogs, but its central stimulating action seems to be less powerful although it will require more studies to settle this point.

When the alkaloids were placed upon the human tongue, a bitter taste was noted. In each case a 0.25 per cent solution was employed. Numbness of variable degrees was noted. The effect of cassaine hydrochloride lasted 51 minutes in one individual, that of homophleine bisulfate 44 minutes in another, that of *nor*-cassaidine hydrochloride 61 minutes in a third, that of coumingaine hydrochloride 149 minutes (average) in two others, and that of acetyl-cassaine hydrochloride 74 minutes in a sixth. The local action of coumingine on the tongue is much more intense and prolonged. Numbness and parasthesia persisted for more than $7^1/_2$ hours in one subject, and $20^1/_2$ hours in another. The following protocols may be cited for illustration:

2:21 P.M.—Subject K. K. C. received two drops of a 0.25 per cent solution of coumingine hydrochloride on the tongue. A slightly bitter taste was noted.

2:24 P.M.—Definitely bitter and acrid.

2:29 P.M.—Very pronounced bitterness and acridness.

2:34 P.M.—Bitter, numb and very acrid, reminding one of the taste of cino-bufagin.

2:42 P.M.—Marked numbness and salivation.

2:51 P.M.—Action still very pronounced.

3:06 P.M.—The tongue seemed thick; drinking water tasted like a sodium bicarbonate solution.

3:34 P.M.—Feeling better.

3:57 P.M.—Action was still there.

6:00 P.M.—Unable to taste food at dinner table.

8:30 P.M.—Effect was still present, but much weaker.

10:00 P.M.—Numbness and other peculiar sensations practically all disappeared.

Following the methods of Schmitz and Loevenhart (19) and Rose (20), these alkaloids were further tested on the rabbit's cornea by local application and in guinea pigs by intracutaneous injection. Local anesthesia was uniformly observed. Table IV shows the average duration of action in groups of 3 animals with each compound. Although their local anesthetic action is well pronounced, neither of the substances can be advocated for clinical use, because each of them produces irritating signs either by instillation into the eye or by infiltration. Furthermore, their cardiac action contributes an additional risk.

Like bufagins, bufotoxins and cardiac glycosides, the *Erythrophleum* alkaloids raise blood pressure in cats in sublethal doses, and stimulate both isolated rabbits' intestines and guinea pigs' uteri in dilute concentrations.

SUMMARY.

The potency of five natural cardiac *Erythrophleum* alkaloids and one derivative—coumingine, coumingaine, *nor*-cassaidine, homophleine, cassaine and acetyl-cassaine—has been carefully determined in cats and frogs.

Coumingine hydrochloride is the most potent member; its cat unit is approximately the same as that of scillaren A. The remaining new alkaloids, coumingaine, cassaine, *nor*-cassaidine and homophleine, are less potent than the older substance erythrophleine.

The emetic action of coumingine, coumingaine, cassaine, *nor*-cassaidine and homophleine is relatively more powerful than that of erythrophleine.

Acetyl-cassaine is less potent on the heart than cassaine, but slightly more effective in causing vomiting, Gm. for Gm.

All the newer alkaloids have a local anesthetic action upon the rabbit's cornea and the guinea pig's skin. They are bitter to the taste and produce numbness and parasthesia of the tongue in men by local application. Their irritating effects and predominant cardiac action preclude their clinical usefulness.

Like other cardiac substances, the newer *Erythrophleum* alkaloids raise blood pressure in cats, and stimulate isolated rabbits' intestines and guinea pigs' uteri. Cassaine in addition causes convulsions in frogs and cats.

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BIOTOXICOLOGY. I. METHODS.

BY JAMES C. MUNCH.*[1]

The usual methods for extraction of poisons from the viscera yield impure extracts, which often fail to give typical reactions with alkaloidal reagents. Elaborate systems of purification are required to separate the toxic principles from the fats, resins and degradation products simultaneously extracted from the tissues, and such purification is associated with significant loss of the poison.

The classical method of Stas was developed for the separation of Nicotine. Stas coagulated albuminoids with alcohol and oxalic acid, hoping to dissolve out the poison as the oxalate. After filtration from the tissues, the alcoholic solution was concentrated, and efforts made to purify the alkaloid, by making the solution alkaline with either the hydroxide, bicarbonate or carbonate. The free alkaloid was shaken out with ether, and evaporated to give the final product.

This Stas method was subsequently modified by J. and R. Otto in several particulars. Tartaric acid was used instead of oxalic, since the alkaloidal tartrates are more soluble in alcohol. The ether extraction of the acid alcoholic solution removed a large proportion of the fats, glucosides and organic acids. The aqueous solution, after evaporation of alcohol, was made alkaline with sodium bicarbonate, and the alkaloids extracted by ether. On evaporation the residue was much purer than that obtained by the Stas method.

Dragendorff macerated the minced viscera with water, acidulated with sulfuric acid to coagulate the albuminoids and to convert the alkaloids into sulfates. The aqueous solution of the alkaloidal sulfates is acidified and extracted, in turn, with petroleum ether, benzene and chloroform. The residual solution is made alkaline and extracted, seriatim, with petroleum ether, benzene, chloroform and amyl

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* Scientific Section, A. PH. A., New York meeting, August 1937.

[1] Joint communication from John Wyeth & Brother Inc., and College of Pharmacy, Temple University, Philadelphia, Pa.