On the Relations between the Chemical Constitution and Pharmacological Action of Phenanthrene Alkaloids.

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It has been stated by previous writers that many phenanthrene alkaloids have a twofold action, a narcotic and a convulsant, which is due to the increase of the reflex excitability of the spinal cord. According to Dixon¹⁾ and Bernard,²⁾ who dealt with the opium alkaloids, of three phenanthrene alkaloids, morphine, codeine and thebaine, the first alkaloid has the strongest narcotic action, but the least convulsant, and the second on the contrary has a less narcotic and a more convulsant, while the last has the least narcotic, but the most convulsant. And if we consider that these three alkaloids are alike in possessing one phenanthrene-pyridine nucleus in the molecule, but differ in that morphine has two hydroxyl groups as its side chains, and thebaine two methoxys, while codeine possesses one hydroxyl and one methoxy, we may presume that both the narcotic and the convulsant actions possessed by these alkaloids have an intimate relation with the possession of the phenanthrene-pyridine nucleus and their intensities are to be influenced by the attaching side chains, the former action being increased by the hydroxyl group, and the latter by the methoxy. To know whether or not this presumption is true by experimenting on the many phenanthrene alkaloids was the chief aim of our studies. As is known, there are also many phenanthrene alkaloids containing some atomic groups other than hydroxyl and methoxy in their molecules, and to make clear their influence exerting upon the activities of the alkaloids was also our interest.

For these purposes 10 phenanthrene alkaloids shown in the following were examined.

The alkaloids containing hydroxyl groups :

Morphine.

Apomorphine.

Those containing hydroxyl and methoxy groups :

Codeine.

Dihydrocodeine.

Oxycodone.

Dihydrooxycodone.

Sinomenine.

Bulbocapnine.

Those containing methoxy groups :

Thebaine.

Domesticinmethylether.

Method. Each of the phenanthrene alkaloids to be examined was introduced into the abdominal lymph sac of a series of male frogs (*Rana japonica*), weighing about 15 grams and the intensities of the convulsant action were almost accurately determined by estimating the minimum dose just sufficient to cause convulsions. And the determination of the intensity of the narcotic was made, in the cases of the alkaloids possessing a relatively powerful narcotic action, by estimating the minimum doses sufficient to bring about a deep narcosis, in which state the animal lay quite flat on the floor, showed no spontaneous movement and no effort to turn from its back, no matter whether reflexes existed or not, while in the cases of those possessing only a weak narcotic action, by comparing the depth of the narcosis. For this reason the intensity of the narcotic action could not be given in quantity and we had to be satisfied only with arranging the substances examined in order of the intensity of their narcotic power.

The experiments were carried on during the months of April and May. The doses shown in the following description were referred to the quantity of the free substances used per 10 grams body weight of the frogs.

Experiments. **Morphine.** With 0.005 gm. frog gradually became quiet, but jumped very clumsily when stimulated, and after 2 or 3 hours it fell into a slight narcotic state, without showing noticeable change in reflexes, which increased several hours later. With an increase in the doses both actions became more marked, and the deep narcosis and marked increase of reflex excitability were caused in several hours with 0.01 gm. and in 1 or 2 hours with 0.02 gm. Such state continued comparatively long, resulting either in gradual recovery or in death. Sometimes the tetanic convulsion might be produced after a deep narcosis. With doses over 0.03 gm. usually the tetanic convulsion occurred after the deep narcosis was produced.

Codeine. With 0.001–0.002 gm. the animal showed a remarkable increase of reflex excitability and a slight narcosis, which gradually recovered, without amounting to tetanic convulsions or deep narcosis. With 0.003–0.004 gm. a deep narcosis was seen in 1 or 2 hours, but was soon concealed by convulsion due to the increase of reflex excitability.

Thebaine. A dose of 0.00003 gm. caused a slight increase in the reflex excitability; with doses of 0.00005–0.0001 gm. the animal showed in 20–30 minutes after the application the reflex excitability becoming gradually more vigorous until tetanic spasms sometimes occurred. Injection of over 0.0003 gm. caused in 20–30 minutes tetanic convulsions which were seen occasionally for more than 10 hours and during the intervals of convulsions a slight narcotic state was observed. The convulsions however gradually disappeared with increase of the narcosis resulting finally in death.

Apomorphine. With 0.002 gm. no recognizable change in reflex was seen, but gradually it caused a slowness of the spontaneous movements and then a slight narcosis after about 1 hour. Still larger doses, such as 0.003–0.004 gm., caused a deep narcosis and a marked decrease in the reflex excitability and death resulted, with the exception of only a few cases, where reflex excitability somewhat increased.

Oxycodone. With 0.0005–0.001 gm. after a preliminary uneasiness the animal gradually became quiet in about 30 minutes, this was followed by a slight narcosis and some increase of reflexes, lasting for 10 or more hours. With 0.004–0.005 gm. the reflex excitability was so increased that convulsions were produced after about 1 hour and followed by a deep narcosis, and the animal died within a few hours.

Sinomenine. With 0.001 gm. in about 1 hour, and with 0.002 gm. in 20–30 minutes after the injection the frog fell into a state of marked increased reflexes and a slight narcosis, at which time tetanus might be produced by some slight stimulation. Such a state continued for several hours, resulting in either recovery or death.

Dihydroxycodone. With 0.005–0.006 gm. an increase of reflexes and a slight narcosis were observed in about 30 minutes after the application. With a large dose (0.007 gm.) the increase of reflexes was so marked that tetanic convulsions occurred within 2 hours and the narcotic state was also deeper. Death might usually occur in 10 or more hours.

Dihydrocodeine. With 0.002–0.003 gm. an increase of reflexes was observed in 20 or 30 minutes and a slight narcosis in about 1 hour after the application, and the animals usually recovered gradually. With a dose of 0.003 gm. violent convulsions occasionally occurred without caus-

ing death. With 0.004–0.005 grm. the frog fell into a deep narcotic state within 30 minutes, and convulsions might be caused by a slight stimulation. Death took place in 10 or more hours.

Domesticinmethylether. With 0.005 grm. no noticeable change was produced. With 0.002 grm. in about 10 minutes it caused a slight narcosis which was immediately followed by the convulsant stage in which typical tetanus frequently appeared, as after strychnine. In another 10 minutes the convulsant fits diminished by degrees, and the complete narcotic state set in within a few hours.

Bulbocapnine. With a dose under 0.001 grm. no recognizable symptom was caused. With 0.002 grm. in 20–30 minutes after the application a slight narcotic state was reached with a remarkable increase in the reflexes. In another 20–30 minutes the convulsant fits suddenly set in, resulting finally in death.

The results of our experiments, as we had expected, show, that all these substances examined possess two defined actions,—a stimulant action on the cord as well as a depressant on the brain,—there being however wide differences in the intensity of both actions, and that the substances which have the greatest narcotic action have the least convulsant, while those which have the most convulsant have the least narcotic. In the following table the substances are arranged in descending order of the intensity of their convulsant action, and in ascending order of that of their narcotic one. And for the sake of convenience kinds and numbers of the atomic groups possessed by these substances are also added here.

	Minimum convulsant dose	Chemically inactive atomic groups containing etherial oxygen			Chemically active atomic groups containing oxygen			-II
		-CCH ₃	indiff. O<	$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{O} \end{array}$	alcoholic -OH	O=C<	phenolic -OH	
Thebaine	0.0003 grm.	**	*					
Domesticinmethylether	0.002 "	**		*				
Sinomenine	0.002 "	**				*	*	
Bulbocapnine	0.002 "	*		*			*	
Codeine	0.003 "	*	*		*			
Oxycodeinone	0.004 "	*	*		*	*		
Dihydrocodeine	0.004 "	*	*		*			*
Dihydroxycodeinone	0.007 "	*	*		*	*		*
Morphine	0.03 "		*		*		*	
Apomorphine							**	

As is seen in the table, thebaine and domesticinmethylether which are the most convulsant and the least narcotic have only chemically inactive atomic groups, while, on the other hand, apomorphine, which is the most narcotic and the least convulsant has only chemically active atomic groups. The other substances which are less narcotic and less convulsant have both chemically active and inactive atomic groups, and indeed the more inactive groups they possess the more convulsant and the less narcotic they are, while on the contrary, the more active groups they have, the more narcotic and the less convulsant they are.

Conclusion. It can therefore be said, that the chemical inactive atomic groups increase the convulsant action of the phenanthrene alkaloids, whereas the chemical active increase the narcotic action and that both the inactive and active groups interfere with each other, so as to decrease the property of each other. The intensity of the atomic groups in increasing the actions seems to vary with their kinds and indeed as is given in the following.

The intensity of the groups increasing the convulsant action :

The intensity of those increasing the narcotic action :

Dihydrocompounds, such as dihydrocodeine and dihydroxycodeinone, formed from phenanthrene alkaloids, such as codeine and oxycodeinone, are more narcotic and less convulsant than the latter themselves. But there is no definite relation between the alkaloids and their dihydrocompounds, as according to Loeb³⁾, Monod⁴⁾ and Kolb⁵⁾ dihydromorphine is weaker in narcotic action, but stronger in convulsant than morphine.

LITERATURE.

- (1) Dixon, cited in Dixon's Manual of Pharmacology, London 1915, 137.
- (2) Bernard, Compt. rend. d. Acad. Scien., 1864, 59, 406.
- (3) Loeb, (4) Monod and (5) Kolb, cited in Oswald's Chemische Konstitution und pharmakologische Wirkung, Berlin 1924, 569.