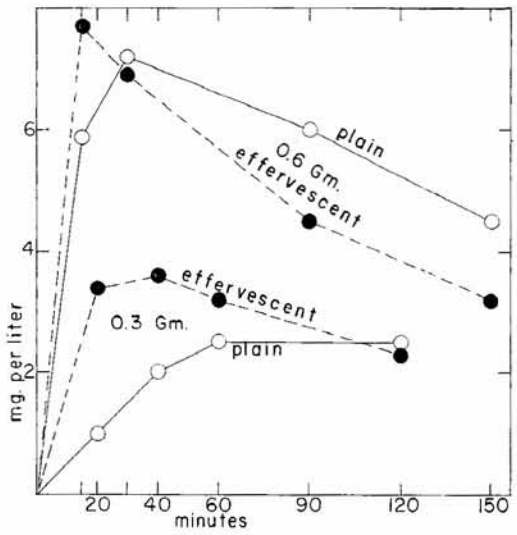


Fig. 2.—Plasma levels of N-acetyl-*p*-aminophenol after oral administration with and without effervescent base.

(3) and Lolli and Smith (4) who used fewer subjects and made initial observations at thirty minutes. The results with N-acetyl-*p*-aminophenol suggest that the faster absorption observed with an alkaline effervescent vehicle may be a more general phenomenon.

SUMMARY

The addition of an effervescent base to preparations containing either acetylsalicylic acid or N-acetyl-*p*-aminophenol results initially in appreciably higher plasma levels after oral administration to human subjects.

REFERENCES

(1) Brodie, B., and B. Axelrod, J., *J. Pharmacol. Exptl. Therap.*, **94**, 22(1948).
(2) Brodie, B. B., Udenfriend, S., and Coburn, A. F., *ibid.*, **80**, 114(1944).
(3) Lester, D., Lolli, G., and Greenberg, L. A., *ibid.*, **87**, 329(1946).
(4) Lolli, G., and Smith, R., *New Engl. J. Med.*, **235**, 80 (1946).

The Pharmacologic Action of Indole Compounds*

By C. E. POWELL, E. E. SWANSON, and K. K. CHEN

The pharmacologic action of serotonin (I), cinobufotenine (II), tryptamine (III), gramine (IV), and β-(N-methyl-N-β-hydroxyethylaminoethyl) indole has been studied and the results on anesthetized cats, pithed dogs, anesthetized chickens, the cat's uterus *in situ*, and the isolated uterus of the rabbit, guinea pig, and rat are reported.

THE CHEMICAL CONSTITUTION and pharmacologic action of indole amines have been investigated by numerous workers. In 1933, one of us (K. K. C.) (1), reported the results of a study on pressor amines related to ephedrine and tryptamine, including cinobufotenine, a constituent of the Chinese toad poison Ch'an Su. Chen and associates (2) had shown this substance to be an indole amine having a stimulating action on isolated smooth muscle, as well as a pressor value in cats, equal to one-tenth that of epinephrine. Later, Jensen and Chen (3) identified the amine as the betaine of 3-(β-dimethylaminoethyl)-5-hydroxy indole.

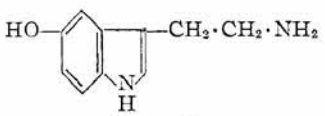
Recently, several investigators have isolated 5-hydroxytryptamine from various mammalian and amphibian tissues. Rapport, *et al.* (4–6), obtained a crystalline vasoconstrictor substance from beef serum which they named serotonin. This was found to have an indole ring conforming to the structure of 5-hydroxytryptamine. Erspamer (7) extracted a pharmacologically active substance called enteramine from the posterior salivary glands of octopoda. This substance was identified by chemical means as being 5-hydroxytryptamine (8). Further, Hamlin and Fisher (9), and Speeter, *et al.* (10), synthesized 5-hydroxytryptamine and showed it to be identical with natural serotonin. More recently, Dalgliesh (11), working with extracts of small intestines of horses, separated one fraction which contained 5-hydroxytryptamine.

Pharmacological investigations with serotonin have been reported by Page (12), Freyburger, *et al.* (13), and Reid and Rand (14). In general, their results showed that isolated muscle preparations responded to serotonin with contraction or spasmogenic action. In anesthetized and cord transectioned dogs serotonin usually had a pressor action; however, in anesthetized cats the response was primarily depressor. Further studies by Page and McCubbin (15) on the blood pressure of dogs showed that pressor response to

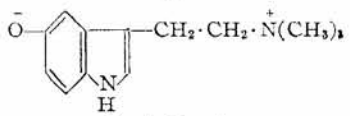
* Received November 4, 1954, from the Lilly Research Laboratories, Indianapolis 6, Ind.
The authors are indebted to Dr. M. E. Speeter, Upjohn Company, for the supply of serotonin; and to Dr. J. Mills, of our Organic Division, for the supply of β-(N-methyl-N-β-hydroxyethylaminoethyl) indole. We also wish to acknowledge the invaluable assistance of Dr. H. M. Lee, Messrs. Lester LeCompte, Jr. and James Waddell.

cinobufotenine and serotonin was reduced following antimetabolites. Also the pressor response of both serotonin and cinobufotenine in pithed cats was blocked by an antimetabolite, 2,3-dimethyl-5-aminoindole. Twarog and Page (16) discovered that the hearts of *Venus mercenaria* were sensitive to cinobufotenine and tryptamine in a concentration of 10^{-7}. On the retractor muscle of *Mytilus edulis*, cinobufotenine was found to be a weaker stimulant than serotonin. Reid (17) has recently studied the pharmacologic action of tryptamine. His results confirmed the pressor action in cats and dogs and the stimulating action on isolated uterine strips.

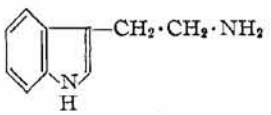
Since there is a renewed interest in compounds that have an indole nucleus, we were prompted to carry out additional pharmacologic experiments with cinobufotenine in comparison with serotonin. Also, because of their similar chemical structure, tryptamine, gramine, and a heretofore unreported compound, β-(N-methyl-N-β-hydroxyethylaminoethyl) indole, have been included in this report. Preliminary pharmacological results of gramine have been previously published from this laboratory (18). In anesthetized cats small doses had a pressor action, whereas large doses (20–40 mg. intravenously) acted as a depressor. Isolated uterine strips were stimulated. The following formulas show the close structural relationship among the five compounds. Both serotonin (I) and cinobufotenine (II) have an OH in the 5-position, whereas the new compound, β-(N-methyl-N-β-hydroxyethylaminoethyl) indole (V) has the OH group on the side chain. Tryptamine (III) and gramine (IV) are different in that they have no OH group.



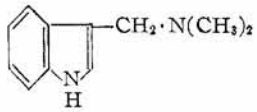
Serotonin
(I)



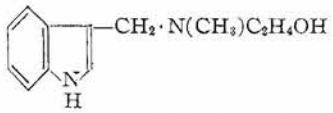
Cinobufotenine
(II)



Tryptamine
(III)



Gramine
(IV)



β-(N-Methyl-N-β-hydroxyethyl-aminoethyl) indole
(V)

EXPERIMENTAL

For pharmacological experiments, cinobufotenine was used as flavianate; tryptamine, as hydrochloride; compound (V), as the base; gramine, as hydrobromide; and serotonin, as creatinine sulfate. Because of the difference of potencies, their stock solutions varied from 0.04, 0.01, 0.5, 1.0 to 0.1%, respectively. To effect a clear solution of compound (V), tartaric acid (0.1%) was added. All solutions appeared to be stable for two days, at which time fresh solutions were made.

For determination of the activity of the five indole amines on blood pressure, respiration, and intact uterus, a total of 50 cats under phenobarbital anesthesia (180–200 mg. per Kg. intraperitoneally) were employed. Ten of them were postpartum twenty-four hours or less, and 40, adult young female cats. The uterine action of postpartum cats was recorded through a balloon inserted directly into the uterus and connected to a recording tambour, and the system filled with approximately 5 cc. of air. Action on the normal uterus was recorded through a pulley system attached to a recording lever. Blood pressure was determined from the carotid artery through a mercury manometer. Respiratory movements were registered from a tracheal cannula attached to a tambour. The test solutions were injected into the femoral vein. In addition the blood pressure response to serotonin and cinobufotenine was evaluated in 14 dogs and 3 cats, all decerebrated and pithed by Elliot's method (19).

Since cinobufotenine flavianate is a quaternary ammonium salt, it was tested for its ganglionic action. Two cats under phenobarbital anesthesia were arranged for recording the movements of the nictitating membrane by the method described by Chen, *et al.* (20). The superior cervical ganglion was crushed, and 30 μg. per Kg. doses were injected intra-arterially.

The blood-pressure action of serotonin, cinobufotenine, tryptamine, and gramine was also studied in 12 adult New Hampshire roosters, weighing 1.5–2.7 Kg. The fowls were anesthetized with sodium phenobarbital (180 mg./Kg. intravenously) and blood pressure recorded from the ischiatic artery through a mercury manometer similar to the method described in U. S. P. XIV (21). Injections of the compounds were made into the crural vein.

Action of the five indole compounds was determined on the isolated uterus and small intestines of

rabbits and guinea pigs, and the isolated uterus of rats. All tissues were immersed in Tyrode's solution kept at 37.5°. Sixteen strips of uterus and 20 strips of small intestines from 9 normal rabbits, and 7 strips of uterus and 14 strips of small intestines from 9 guinea pigs were used in this study. In addition 8 strips of uterus from 6 normal rats were used.

RESULTS

Blood Pressure, Respiration, and Intact Uterus of Cats.—Since there appeared to be no significant differences in the blood pressure, respiration, and intact-uterus responses between postpartum and normal female cats to the indole amines, results of all tests on each compound were combined. Quantitative comparison between compounds was unsatisfactory because of changes in sensitivity of the blood-pressure responses following repeated and alternate doses. Thus, unless otherwise stated, the following data only refer to qualitative differences. Doses that induced minimum responses were adopted.

From Table I it may be noted that the blood pressure of anesthetized cats responded more consistently to cinobufotenine and tryptamine than to compound (V), gramine, and serotonin. Twenty-seven doses (50–250 μg.) of cinobufotenine caused a prompt rise of blood pressure with only short duration of action, similar to that observed with epinephrine. The amplitude of respiration was briefly depressed and on recovery the rate increased slightly prior to normal recovery, particularly with doses of 200 and 250 μg. These changes may be reflex in nature. The intact uterus of both postpartum and normal cats was relaxed by cinobufotenine. In this respect the toad venom base is similar to epinephrine.

Tryptamine was found to be less potent than cinobufotenine on the blood pressure and intact uterus of cats. In 9 animals, 14 doses of 0.5–4 mg. by vein consistently had a pressor action, occasionally preceded by a depressor action. Duration of pressor action was somewhat greater with tryptamine than with cinobufotenine. In contrast to cinobufotenine, tryptamine exerted a weak stimulating action on the uterus. The amplitude of respiration was slightly reduced following injection, with prompt recovery. The blood pressure effect of compound (V) was also inconsistent. Two 10-mg. doses had a prolonged pressor action; two other 10-mg. doses, a depressor-pressor action; and one 20-mg. dose, a depressor response. With each dose the amplitude of respiration was briefly decreased, and following the 20-mg. dose artificial respiration was required to restore normal breathing. Only a very slight stimulation of the uterus was noted. Gramine also had an inconsistent action on the blood pressure, as previously reported (18). In three cats, one 5-mg. dose, one 10-mg. dose, and one 30-mg. dose raised the pressure, whereas depressor responses occurred in 4 cats with a 20-mg., 30-mg., 40-mg., and three 50-mg. doses. Two 10-mg. doses were ineffective. As with the other four compounds, the amplitude of respiration was decreased following injection, but promptly returned to normal following a brief period of increased rate. Serotonin also caused inconsistent response of the anesthetized cat's blood pressure. Of a total of 30 doses (12.5 μg. to 1 mg.) injected intravenously into 14 animals, 20 (250, 100, 50, and 25 μg.) caused a depressor response; 2 (200 and 50 μg.), a depressor-pressor response; and 8 (1 mg., 250, 100, 50, and 25 μg.), a pressor response. One 12.5-μg. dose was inactive. Similar to the action of the other four compounds, amplitude of respiration was initially decreased, followed by a brief increase in rate before recovery to normal. On both the postpartum and the normal uterus, serotonin induced contractions of a varying degree, depending on the size of the dose. Figure 1 illustrates the blood pressure and uterus response to 100-μg. doses of serotonin and cinobufotenine given intravenously to an adult young female cat. By comparison, serotonin was found to be consistently more effective in increasing the activity of the cat's uterus *in situ* than the other four compounds, whereas cinobufotenine exerted the strongest action upon the blood pressure of anesthetized cats.

Evaluation of Pressor Action in Pithed Dogs and Cats.—The results of the studies on the blood pressure response to serotonin and cinobufotenine are shown in Table II. Calculated as the geometric mean from 5 pithed dogs, 1 mg. of serotonin had an epinephrine equivalent of 0.709 ± 0.136 μg. By the same method of calculation in 5 pithed dogs, 1 mg. of cinobufotenine had an epinephrine equivalent of 177.5 ± 28.2 μg. Serotonin was given following cinobufotenine to 4 pithed dogs and found to have an epinephrine equivalent of 0.372 ± 0.109 μg., indicating that cinobufotenine preceding serotonin reduced its pressor action. In 3 pithed cats, 1 mg. of cinobufotenine was found to have an epinephrine equivalent of 184.1 ± 33.5 μg., which was close to the figure for pithed dogs. Serotonin in pithed cats, regardless of dose, produced only a slight pressor action, followed by a depressor response.

Ganglionic Action of Cinobufotenine.—The study of the action of cinobufotenine on the nictitating membrane of cats brought the following results:

TABLE I.—ACTION OF INDOLE COMPOUNDS IN ANESTHETIZED CATS

Compound		No. of Animals	No. of Doses	Dose Range	Response		
Name	No.				Blood pressure	Respiration	Uterus
Serotonin	(I)	14	30	12.5 μg. to 1.0 mg.	Inconsistent	Depressed	Contraction
Cinobufotenine	(II)	17	27	50.0 μg. to 250.0 μg.	Pressor	Depressed	Relaxed
Tryptamine	(III)	9	14	0.5 mg. to 4.0 mg.	Pressor	Depressed	Slight contraction
Gramine	(IV)	7	11	5.0 mg. to 30.0 mg.	Inconsistent	Depressed	Slight contraction
β-(N-Methyl-N-β-hydroxyethylaminoethyl) indole	(V)	3	5	5.0 mg. to 20.0 mg.	Inconsistent	Depressed	Slight contraction

TABLE II.—PRESSOR ACTIVITY OF SEROTONIN AND CINOBUFOTENINE IN PITHED DOGS AND CATS

Compound	Animal	No. of Animals	Mean Epinephrine Equivalent for 1 mg. of Indole Amine
Serotonin (I)	Dog	5	0.709 ± 0.136 μg.
Cinobufotenine (II)	Dog	5	177.500 ± 28.190 μg.
	Cat	3	184.100 ± 33.450 μg.
Serotonin (I) after Cinobufotenine (II)	Dog	4	0.372 ± 0.109 μg.

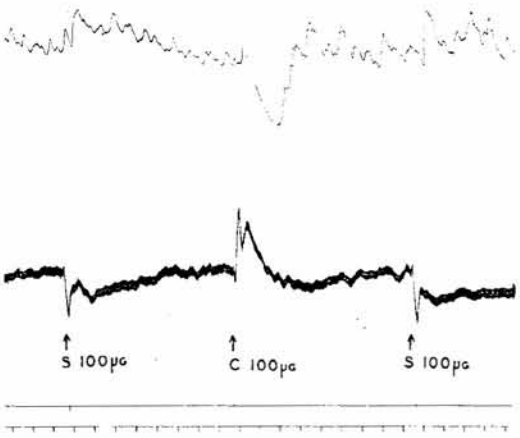


Fig. 1.—Action of serotonin and cinobufotenine on the cat's uterus and blood pressure. Cat, female, 2.3 Kg., phenobarbital sodium anesthesia, 190 mg./Kg. intraperitoneally. The curves from top to bottom are: uterus, blood pressure, base line, and time in minutes. Note that cinobufotenine (C) relaxes the uterus and raises the blood pressure, whereas serotonin (S) has the opposite effect in that it stimulates the uterus and lowers the blood pressure.

Immediately after a 1.25-mg. dose intra-arterially of hexamethonium, the contraction caused by a 30 μg./Kg. dose of cinobufotenine by the same route was partially blocked; however, subsequent doses of cinobufotenine stimulated the nictitating membrane to the same level as before treatment with the blocking agent. After crushing the cervical ganglion and repeating the intra-arterial administration, the response of the nictitating membrane to the same dose of 30 μg./Kg. of cinobufotenine was so greatly reduced that it could be said to have been abolished. At this stage 1.5 μg./Kg. doses of epinephrine were still effective, indicating that cinobufotenine exerted its action mainly through the superior cervical ganglion.

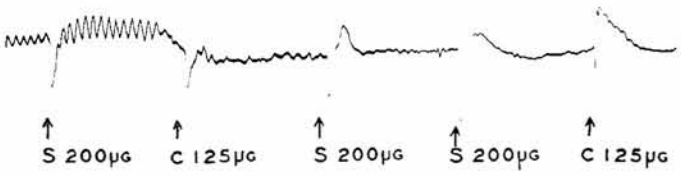


Fig. 2.—Action of serotonin and cinobufotenine on the blood pressure of a chicken. White New Hampshire rooster, 1.9 Kg., phenobarbital sodium anesthesia, 180 mg./Kg. intravenously. Note that separated doses of serotonin (S) lower the blood pressure, whereas cinobufotenine (C) reverses the depressor response after the initial dose.

Blood Pressure in Chickens.—In 6 chickens, 49 doses of cinobufotenine, ranging from 2.5 to 250 μg., induced inconsistent responses. Depressor action occurred with initial injections, but after two or three 125-μg. doses alternated with serotonin, the responses were reversed and became pressor, as shown in Fig. 2. Serotonin had a more consistent action on the chicken's blood pressure than cinobufotenine. Fifty-nine doses, ranging from 10 to 250 μg., in 7 chickens resulted in a depressor response. Gramine was found to have a pressor action with 2-mg. doses, but tryptamine, a depressor action with 0.25-mg. doses.

Isolated Muscle Preparations of Guinea Pig, Rabbit, and Rat.—The study of the effect of the five indole compounds upon isolated smooth muscle preparations may be summarized as follows: Dilutions of cinobufotenine from 1:100,000 to 1:500,000, and serotonin from 1:50,000 to 1:200,000 caused contractions of the isolated rabbit's uterus. The response to repeated doses was not quantitative as the uterus became more rhythmic following each exposure. Doses of ergotamine tartrate, up to 10 times the amount required to inhibit epinephrine activity, failed to arrest contractions induced by cinobufotenine and serotonin. Tryptamine, compound (V), and gramine also produced contractions of the isolated rabbit's uterus. Initial dilutions of 1:10,000 to 1:100,000 of each compound stimulated the uterus but repeated dilutions were less effective. Compound (V) was the least active on the isolated rabbit's uterus, requiring 1:10,000 dilutions to effect contraction.

All five indole amines contracted the isolated guinea pig's uterus. Dilutions of cinobufotenine ranging from 1:100,000 to 1:300,000 consistently induced graded responses of the uterus. Serotonin was more potent since dilutions up to 1:1,000,000 induced contractions of the muscle. When compared on the same strip of uterus, serotonin was found to be five times as active as cinobufotenine. No antagonism or potentiation was observed when serotonin and cinobufotenine were given simultaneously in a half-and-half combination. Tryptamine, compound (V), and gramine were less potent on the isolated guinea pig's uterus. Dilutions of 1:20,000 were necessary to produce definite contractions. On the isolated rat's uterus 1:100,000 to 1:1,000,000 dilutions of cinobufotenine and serotonin caused spasmogenic responses, whereas with compound (V) and gramine, dilutions of 1:10,000 and 1:20,000 only increased the rhythmic movements. Tryptamine definitely stimulated the uterus in 1:100,000 dilutions. As in other isolated smooth muscle preparations, repeated doses of this

substance were less effective than the initial dose.

Each of the five indole amines caused contraction of the isolated rabbit's ileum. Cinobufotenine was found to be the most potent compound. Dilutions of 1:2,000,000 and 1:4,000,000 produced sharp contractions of the ileum, whereas serotonin was ineffective with dilutions weaker than 1:400,000. Repeated doses of serotonin following removal of the poisoned Tyrode's solution induced only a slight decrease in height of response. However, if doses were repeated following the period of stimulation without changing the poisoned solution, no response occurred. Comparison of dose-response revealed that cinobufotenine was more than 20 times as active as serotonin on the rabbit's ileum. It was also observed that cinobufotenine had a blocking action on serotonin responses. A 1:100,000 dilution of serotonin did not block a 1:4,000,000 dilution of cinobufotenine, but conversely 1:10,000,000 and 1:20,000,000 dilutions of cinobufotenine blocked a 1:200,000 dilution of serotonin (Fig. 3). Tryptamine and compound (V) were also less potent on the isolated rabbit's ileum. Dilutions of 1:10,000 to 1:500,000 were required to cause contraction. Gramine was less consistent in its action. Five dilutions of 1:10,000 and 1:5,000 on four strips of ileum only slightly increased the amplitude, followed by a decrease. On two separate strips a 1:15,000 and 1:50,000 dilution briefly reduced the amplitude.

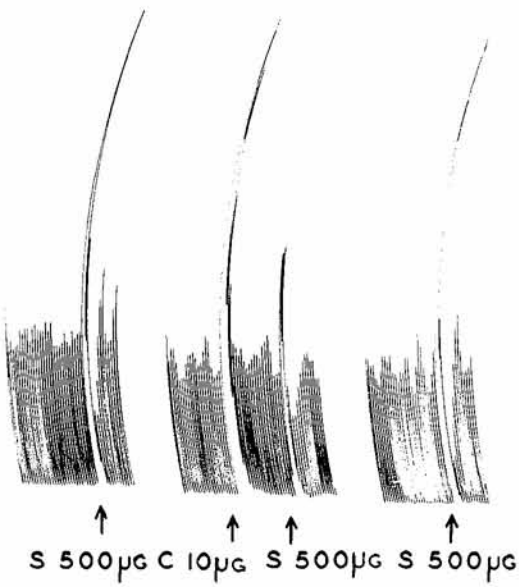


Fig. 3.—Action of serotonin and cinobufotenine on isolated small intestines of rabbits. A strip of rabbit's small intestine was suspended in Tyrode's solution at 37.5°C. Note the sharp contraction caused by both serotonin (S) and cinobufotenine (C). Further, the response to serotonin is reduced when it is added to the cinobufotenine solution. Following the wash-out the muscle responds to serotonin in the usual manner.

Action of the five indole amines was determined on the isolated ileum of guinea pigs. All five compounds contracted the gut to a various degree. As in other smooth muscle preparations, serotonin and cinobufotenine were the most potent. When compared on the same strip, a 1:3,000,000 dilution of serotonin had the same activity as a 1:2,500,000 dilution of cinobufotenine. Dilutions of 1:100,000 and 1:200,000 of ergotamine tartrate inhibited contractions caused by 1:2,000,000 dilutions of cinobufotenine, and 1:2,500,000 dilutions of serotonin. Although tryptamine, gramine, and compound (V) were active on the isolated guinea pig's ileum, more concentrated solutions, 1:10,000 to 1:100,000, were required to cause definite stimulation which could be blocked by ergotamine tartrate.

DISCUSSION

The results of these experiments show that of the five indole amines studied cinobufotenine differs in its pharmacological action from serotonin, tryptamine, gramine, and β-(N-methyl-N-β-hydroxyethylaminoethyl) indole. In pithed dogs and cats it has a consistent pressor action, confirming our previous observation. In pithed dogs serotonin is only $^1/_{268}$ as active as cinobufotenine in raising blood pressure. It has also been shown that cinobufotenine reduces by 50 per cent the pressor action of serotonin in the pithed dog when given in alternate doses. In the pithed cat, cinobufotenine is consistently pressor in its action whereas serotonin is primarily depressor. It is of additional interest that, when tested in the chicken's blood pressure, the initial depressor action of cinobufotenine becomes pressor when the substance is alternated with serotonin. The ganglionic action of cinobufotenine has been elucidated in cats by the nictitating membrane preparation.

Cinobufotenine has a relaxing action on the normal cat's uterus in the same manner as epinephrine, whereas the other four compounds induce a slight stimulating response. On the isolated small intestines of the rabbit, cinobufotenine blocks the stimulating action of serotonin.

SUMMARY

1. The action of five indole amines (serotonin, cinobufotenine, tryptamine, gramine, and β-(N-methyl-N-β-hydroxyethylaminoethyl) indole) has been studied.

2. Both cinobufotenine and tryptamine have a pressor action in anesthetized cats. The other three products have an inconsistent effect on blood pressure. Cinobufotenine has a ganglionic stimulating action.

3. While serotonin raises blood pressure in pithed dogs it is only $^1/_{268}$ as potent as cinobufotenine. If cinobufotenine and serotonin are alternately injected into these animals, the former reduces the pressor action of the latter; but not vice versa.

4. In anesthetized chickens a single injection of serotonin, cinobufotenine, or tryptamine is

followed by a fall of blood pressure. Gramine, on the other hand, raises the blood pressure. Upon repeated injections in fowls, the depressor action of cinobufotenine is reversed to pressor.

5. Cinobufotenine relaxes the cat's uterus *in situ*, but the other four indole derivatives contract the same organ to various degrees, serotonin being the most active.

6. A single application of any of the five indole amines stimulates the isolated uterus of the rabbit, the guinea pig, or the rat. Similarly, all five compounds contract the isolated ileum of the rabbit and the guinea pig.

REFERENCES

(1) Chen, K. K., and Chen, A. L., THIS JOURNAL, **22**, 813(1933).
(2) Chen, K. K., Chen, A. L., and Jensen, H., *J. Pharmacol. Exptl. Therap.*, **43**, 13(1931).
(3) Jensen, H., and Chen, K. K., *J. Biol. Chem.*, **116**, 87 (1936).
(4) Rapport, M. M., Green, A. A., and Page, I. H., *Science*, **108**, 329(1948).
(5) Rapport, M. M., Green, A. A., and Page, I. H., *J. Biol. Chem.*, **176**, 1243(1948).
(6) Rapport, M. M., *ibid.*, **180**, 961(1949).
(7) Erspamer, V., *Arch. Sci. Biol. Napoli*, **31**, 86(1946).
(8) Erspamer, V., and Asero, B., *Nature*, **169**, 800(1952).
(9) Hamlin, K. E., and Fisher, F. E., *J. Am. Chem. Soc.* **73**, 5007(1951).
(10) Speeter, M. E., Heingelmann, R. V., and Weisblat, D. I., *ibid.*, **75**, 5514(1951).
(11) Dalgliesh, C. E., Toh, C. C., and Work, T. S., *J. Physiol.*, **120**, 298(1953).
(12) Page, I. H., *J. Pharmacol. Exptl. Therap.*, **105**, 58 (1952).
(13) Freyburger, W. A., Graham, B. F., Rapport, M. M., Seay, P. H., Grovier, W. M., Swoop, O. F., and Vander Brook, M. J., *ibid.*, **105**, 80(1952).
(14) Reid, G., and Rand, M., *Nature*, **169**, 801(1952).
(15) Page, I. H., and McCubbin, J. W., *Am. J. Physiol.*, **174**, 436(1953).
(16) Twarog, B. M., and Page, I. H., *ibid.*, **175**, 157(1953).
(17) Reid, G., *Austral. J. Exptl. Biol. Med. Sci.*, **29**, 101 (1951).
(18) Powell, C. E., and Chen, K. K., *Proc. Soc. Exptl. Biol. Med.*, **58**, 1(1945).
(19) Elliot, T. R., *J. Physiol.*, **44**, 374(1912).
(20) Chen, G., Portman, R., and Wickel, A., *J. Pharmacol. Exptl. Therap.*, **103**, 330(1951).
(21) United States Pharmacopeia, 14th rev., Mack Publishing Company, Easton, Pa., 1950, p. 475.

Some Biological Effects of the Flavonoids*

By J. J. WILLAMAN

There are known at present at least 137 natural flavonoids, occurring in at least 62 families, 153 genera, and 277 species of plants. About 33 different types of physiological and biochemical activities have been reported for one or another of 30 of these flavonoids. This paper summarizes these activities and what is known about the relation of structure to such activities. It is suggested that this is a fruitful field for further research.

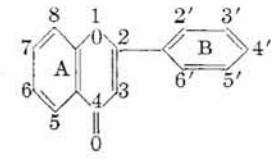
THE PURPOSE of this article is to collect the scattered evidence for the biological activities of the various flavonoids in the hope that the diversity and importance of some of their activities will stimulate further scrutiny of this class of compounds. The literature reveals that at least 33 different manifestations of activity of one or another of the flavonoids have been reported. These activities are listed in Table I. No attempt is made here to evaluate or to review critically these published findings.

REVIEW

Probably the first record of physiological activity was that of Koike in 1931 (26) on the diuretic effect of seven flavonoids. During the next fifteen years a few reports of other effects appeared. From 1947 on there has been considerable activity in this field. Rutin was developed as a commercial drug, then its quercetin moiety was also shown to be active in correcting capillary fault (21). Quercitrin and, to a lesser extent, quercetin were shown to have an antiviral effect (13). Most dramatic of all, the dread subterranean clover disease of Australia, causing sterility in sheep, was proved to be due to the estrogenic effect of genistein and formonetin (formononetin) (5).

To keep the scope of this review within reasonable limits, it will be confined largely to the aglycones themselves and will not deal with their glycosides.

For convenience, the skeleton of the flavonoids is given below, since it will be necessary frequently to refer to position numbers. The structure given is for the flavones. In the flavanones the 2,3 double bond is missing, with a hydrogen at 2 and two hydrogens or their equivalent on 3. In the isoflavones ring B is attached at 3. In the chalcones the pyrone is open, the oxygen at 1 becoming an OH.



About 30 flavonoid aglycones have been reported as having various activities on organisms, tissues, and enzymes or effects on physiological functions. Table II lists these, together with the kinds of activities established for each.

It will be noted in Table I that the types of activity are extremely diverse. Furthermore, different flavonoids may have opposite effects: depress or stimulate the heart; decrease or increase blood

* Received December 20, 1954, from the Eastern Regional Research Laboratory, Agricultural Research Service, United States Department of Agriculture, Philadelphia 18, Pa.