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A PHARMACOLOGICAL EXAMINATION OF BENZALDEHYDE AND MANDELIC ACID.*

BY DAVID I. MACHT.†

INTRODUCTION.

About five years ago the author first published his studies on the relationship between the chemical structure of the opium alkaloids and their pharmacological action on smooth muscle.[1] He showed that in this respect the principal alkaloids of opium can be sharply divided into two groups, the pyridine-phenanthrene group of which morphine is the principal member and the benzyl-isoquinolin group of which papaverine is the principal representative. It was further shown that a peculiar and characteristic property of papaverine as a relaxant of smooth muscle was due to the benzyl nucleus of its molecule. As a result of this pharmacodynamic analysis the discovery of the remarkable antispasmodic properties of the benzyl esters, benzyl benzoate, benzyl acetate, etc., followed. Almost simultaneously with the publication of the author's studies concerning benzyl esters the author also announced the discovery of the local anesthetic properties of benzyl alcohol.[2] The pharmacological and therapeutic properties of the benzyl esters and benzyl alcohol have been described in various publications by the author himself and by other investigators. A very good summary of the work to date appeared in Merck's "Jahresberichte" for 1921.

In connection with the study of benzyl esters and benzyl alcohol it was logical to inquire into the pharmacological and physiological effects of benzaldehyde. A preliminary communication on the subject by the author appeared some time ago.[3] In the present paper it is proposed to report more fully the author's investigations on the subject.

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CHEMISTRY.

Benzaldehyde, $C_6H_5.CHO$, is a constituent of a number of natural volatile oils. It occurs in various amounts in a number of plants, especially those belonging to the family of *rosaceae* and more particularly in the species *prunus*. Thus it is found in the cherry laurel or *prunus laurocerasus*, in *prunus persica* or peach kernels, in *prunus serotina*, in *prunus puddum*, *prunus cerasus*, *prunus domestica* and *prunus spinosa*. Benzaldehyde is an important constituent of *amygdala amara* or bitter almond. It is also found in small quantities in some species of *cinnamomum*, *genista*, *myristica*, in the *balsam* of *tolu* and in *benzoinum*. Perhaps the most important natural source of benzaldehyde is oil of bitter almonds. As is well known benzaldehyde is formed from the glucoside amygdalin by the action of the enzyme emulsin, each molecule of amygdalin by yielding one molecule of hydrocyanic acid and one molecule of benzaldehyde, with two molecules of dextrose.

Benzaldehyde was first prepared by Liebig and Wöhler in 1837 who ascertained its composition and studied its relation to benzoic acid. Having been first isolated from the oil of bitter almonds it was originally designated pharmaceutically as *oleum amygdalarum aethereum sine acido prussico*. Benzaldehyde can be prepared (*a*) from bitter almond oil, and (*b*) from toluene. The artificial benzaldehyde can be prepared from toluene in two ways; in one case the toluene is first converted into benzyl chloride, this is heated with barium nitrate and water while passing a current of carbon dioxide through the mixture. The benzyl nitrate resulting decomposes with the formation of benzaldehyde and oxides of nitrogen. Another method is to convert toluene into benzal chloride which can be transformed directly into benzal glycol, $C_6H_5CH(OH)_2$. On treating the benzal glycol with caustic soda or milk of lime or with water under pressure benzaldehyde is directly formed.

Benzaldehyde is a colorless or yellowish, strongly refractive liquid. It possesses the odor peculiar to oil of bitter almonds and a burning aromatic taste. Its specific gravity is about 1.045 at 25 degrees C. and its boiling point is 178–182 degrees C. It is optically inactive. It is sparingly soluble in water, the solution being about 1–300 but is readily soluble in most organic solvents and also in oils. When exposed to oxygen it is readily oxidized to benzoic acid. In the pharmacological experiments performed in this investigation a solution of 1–500 or 0.2% was easily prepared and used.

PHARMACOLOGICAL PROPERTIES.

Inasmuch as the benzyl esters, such as benzyl benzoate and benzyl acetate, are most remarkable for their antispasmodic action on smooth muscle and inasmuch as the most striking characteristic of benzyl alcohol is its local anesthetic property, it was interesting to inquire into the pharmacological behavior of benzaldehyde from these two points of view. Furthermore the author has called attention elsewhere to the fact that benzyl alcohol in addition to its striking local anesthetic effect possesses also to quite a marked degree antiseptic properties as indicated by its action on a number of bacteria.[4] It was therefore of interest also to inquire into the possible antiseptic properties of benzaldehyde.

Effect on Smooth Muscle.—Experiments were made on the isolated muscle preparations from the uterus, intestines, stomach, urinary bladder, gall bladder,

ureters, vas deferens, seminal vesicles, uterus, bronchi and arteries taken from various animals, namely, dog, cat, rat, rabbit, mouse, guinea pig, pig, frog and in a few cases experiments were also made on the isolated muscle from human tissue obtained from the surgical operating room. All these experiments indicated that benzaldehyde is a marked antispasmodic exerting the same effect as the benzyl esters already studied by the author. In these experiments *in vitro* the author

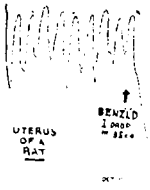

Fig. 1.—Uterus of rat. One drop of benzaldehyde in 35 cc of Locke produces marked relaxation.

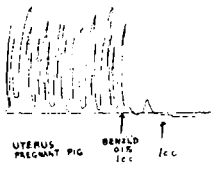

Fig. 2.—Uterus of pregnant pig. One cc of 0.1% solution of benzaldehyde in 50 cc of Locke's solution produces inhibition of contraction.

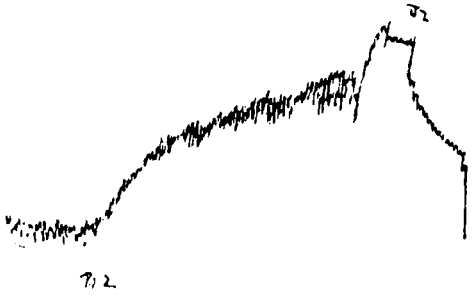

Fig. 3.—Jejunum of guinea pig stimulated by 1 mg. of pilocarpine hydrochloride and relaxed by 1 drop of benzaldehyde in 50 cc of Locke's solution.

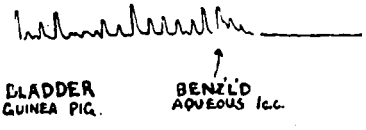

Fig. 4.—Urinary bladder of guinea pig. Inhibition produced by 1 cc of 0.1% solution of benzaldehyde in 30 cc of Locke.

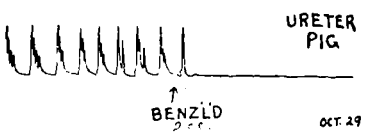

Fig. 5.—Ureter of pig. In 30 cc of Locke's solution effect of 2 cc of 0.2% benzaldehyde.

used for the most part a solution of benzaldehyde in water or in physiological sodium chloride, 1–500. The results obtained are illustrated by the subjoined figures.

Fig. 1 shows the effect of benzaldehyde on the contractions of a horn of a uterus of a rat. The preparation was suspended in 35 cc of Locke's solution; one small drop of benzaldehyde was introduced into the chamber. Note marked relaxation and inhibition of contraction.

Fig. 2 shows the effect of benzaldehyde on a bit of uterus from a pregnant sow. In this case 1 cc of a 0.1% solution of benzaldehyde was sufficient to produce a marked relaxation and inhibition of contraction.

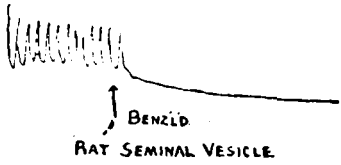

Fig. 6.—Seminal vesicle of rat. Relaxation produced by 1 cc of 0.2% solution of benzaldehyde in 30 cc of Locke.

Fig. 3 shows the effect of 1 drop of benzaldehyde introduced into a chamber containing 50 cc of Locke's solution in which a short loop of jejunum from a guinea-pig was suspended. Notice relaxation.

Fig. 4 shows the effect of benzaldehyde on the isolated bladder of a guinea pig. One cc of a saturated solution of benzaldehyde in 35 cc of Locke's solution produced inhibition.

Fig. 5 shows the effect of 2 cc of 0.2% solution of benzaldehyde on the contractions of the ureter of a pig.

Fig. 6 shows the effect of 1 cc of 0.2% solution of benzaldehyde on the contractions and tonus on the seminal vesicle of a rat.

In experiments with benzaldehyde *in vitro* it is important to bear in mind that dilute solutions of it very rapidly oxidize, forming benzoic acid, and this increase in the hydrogen-ion concentration of the solution sometimes produces anomalous results. The experiments must be made with solutions of benzaldehyde *freshly prepared* immediately before the experiment.

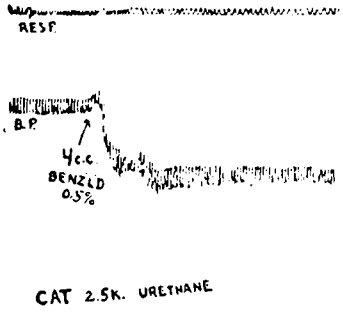

Fig. 7.—Effect of benzaldehyde on the respiration and blood pressure of cat. Upper curve indicates respiration, lower curve indicates blood pressure.

The effect on various organs *in situ* was also studied to some extent, especially on the intestines and blood pressure. In these experiments again care must be taken to discount the anomalous effects produced by oxidized solutions of benzaldehyde and it must be furthermore borne in mind that the sedative effects of benzaldehyde as well as those of the benzyl esters come on slowly and run parallel to the hydrolysis or decomposition of those compounds in the body. After injecting solutions of emulsions of benzaldehyde in rabbits and other animals a marked paresis or relaxation of the intestines and the urinary bladder with marked vaso-dilatation of the splanchnic vessels is noted at the expiration of ten or more minutes after injection and sometimes earlier. Fig. 7 is a striking illustration of the effect of benzaldehyde on the blood pressure. In this experiment a cat weighing 2.5 kilos was anesthetized with urethane. Note the effect of injection intravenously of 4 cc of a 0.5% solution of benzaldehyde, as manifested by a fall in blood pressure and showing of the respiration.

Anesthetic Effect.—The anesthetic action of benzaldehyde can be readily demonstrated by all of the common methods employed in experimental pharmacology. The author studied pure benzaldehyde itself and also aqueous solutions of the strength of 1–500. Pure benzaldehyde can be shown to produce blocking of nerve impulses in the sciatic nerves of cats and dogs paralyzing the ascending or sensory fibers before the descending or motor fibers of the nerve trunk. Conduction anesthesia was also found by the author to take place by applying even weak solutions of benzaldehyde, 1–500, to the sciatic nerves of frogs.

The dilute solutions of benzaldehyde were studied for anesthesia on the eyes of rabbits and dogs and on the skin of frogs. The author found on instilling a solution of 1–500 into the conjunctival sac that complete anesthesia occurred at the end of two minutes and lasted for some ten to fifteen minutes. Together with the anesthesia of the cornea considerable irritation of the conjunctiva occurred, due probably to the gradual oxidation of the benzaldehyde with the formation of benzoic acid.

The anesthetic action on frogs' skin was strikingly demonstrated by the well-known method employed in pharmacological laboratories. Frogs were suspended with the brain destroyed but the spinal cord intact. The response of the legs on dipping in a dilute solution of sulphuric acid or hydrochloric acid was determined. One of the legs was then immersed for periods varying from one to two to five minutes in solutions of benzaldehyde of 1–500. On subsequent testing with the same chemical stimuli, that is, solutions of acids, no reflex contraction of the leg could be elicited, thus indicating an anesthesia or paralysis of the sensory nerve endings. This anesthetic effect persisted for half an hour and longer. As a result of the various experiments on anesthesia there was no doubt that benzaldehyde exerted a local anesthetic action very much like benzyl alcohol with the sole difference that while benzyl alcohol is fairly stable when kept free from alkalis, as shown by Macht and Scholl,[4] benzaldehyde rapidly oxidizes to benzoic acid and is therefore unsuitable for practical use as a local anesthetic, especially on mucous surfaces such as those of the eye.

ANTISEPTIC ACTION.

The author in collaboration with Drs. Satani and Schwartz[5] has already called attention to the antiseptic and germicidal properties of benzyl alcohol, for *B. coli;* staphylococcus, and gonococcus. It was interesting to inquire into whether benzaldehyde exhibited similar effects. Accordingly a series of bacteriological experiments were carried out for the author by Miss J. H. Hill.

In testing the drug, the benzaldehyde was diluted with cottonseed oil. It was found that pure benzaldehyde diluted with an equal part of oil killed *B. coli* in less than one minute. Benzaldehyde one part mixed with parts of oil also killed the bacteria in one minute. A dilution of one in a hundred killed an enormous number of the organisms in one hour, and destroyed all of them within three hours.

It is thus evident that benzaldehyde possesses distinct germicidal properties.

TOXICOLOGY.

The toxicity of benzaldehyde is very similar to that of benzyl benzoate, benzyl alcohol and benzyl succinate[6] which have already been studied by the author. In other words the toxicology of benzaldehyde is very low. Experiments on rats show that the lethal dose of pure benzaldehyde was about 0.5 cc per 100 grams weight of the animal when injected subcutaneously. The same dose injected intraperitoneally produced marked poisoning but was occasionally recovered from. In dogs 1 cc pure benzaldehyde injected intravenously or subcutaneously produced a slight slowing of the respiration but otherwise no deleterious result. On administering pure benzaldehyde mixed with a little water to dogs by stomach tube 2 cc of pure benzaldehyde per kilo produced no effect with the exception of a slight slowing of the respiration. On intravenous injection the author has been able to administer to rabbits a solution of benzaldehyde in normal saline of 0.2% strength in doses as high as 20 cc per kilo weight of the animal without dangerous results. Intravenous injection of such aqueous or saline solutions in dogs were given even in larger doses without any harm, the only results noted in anesthetized animals being a lowering of the blood pressure, a slight slowing of the respiration and an inhibition of the intestinal contractions with vaso-dilatation of the splanchnic vessels.

When very large doses of benzaldehyde are injected into animals the most important toxic effects are exerted on the medulla. Respiration is slowed and after very large doses is paralyzed. The heart is very little affected by benzaldehyde, after intravenous or other injections in the intact animal. On the isolated frog's heart benzaldehyde acts as a muscular depressant.

EXAMINATION OF MANDELIC ACID.

Closely related to benzaldehyde and occurring to some extent in nature is mandelic acid. Mandelic acid is chemically *phenylglycolic* acid with the formula $C_6H_5.CHOH.CO_2H$. The relation of this acid to benzaldehyde is very close and it can be prepared from the latter by first treating benzaldehyde with hydrocyanic acid, forming benzaldehyde cyanhydrin. This on treatment with water forms ammonia and phenylglycolic acid.

Mandelic acid is a colorless substance which crystallizes in platelets melting at 115–118° C. It is freely soluble in water, alcohol and ether and easily forms salts or esters. On oxidation it is transformed into benzoic acid. According to Schulze and Graebe[7] mandelic acid in the body is metabolized and excreted as hippuric acid.

Owing to the close relationship of mandelic acid to benzaldehyde it was interesting to inquire into its pharmacological properties which, so far as the author is aware, have never been investigated. For this purpose sodium and potassium mandelates were employed and later the ester ethyl mandelate and some more complex esters were also experimented with. It was found that ethyl mandelate and to a somewhat lesser degree sodium and potassium mandelates exhibited the characteristic antispasmodic properties of the benzyl esters, benzyl alcohol and benzaldehyde, on smooth muscle. Ethyl mandelate and sodium mandelate were found to relax smooth muscle preparations and in blood-pressure experiments they were found to lower the blood pressure through a marked vasodilatation of the splanchnic vessels, and also to produce broncho-dilatation. These antispasmodic properties are exhibited in even a higher degree in certain more complex esters of mandelic acid and are of great pharmacological interest. The author is conducting an investigation with a number of these bodies and the results of the work are to be published in a separate paper. Suffice it to say that the pharmacological properties of mandelic acid shed a new light on the physiological effects of the well-known mydriatic, homatropine, as demonstrated by the author elsewhere. (Fig. 8.)

Fig. 8.—Jejunum of rabbit. Stimulation with 1 mg. of pilocarpine hydrochloride in 40 cc of Locke and relaxation of the same on introduction of 5 mg. of sodium mandelate.

DISCUSSION.

An analysis of the data obtained from the pharmacological study of benzaldehyde reveals the fact that this substance can no longer be regarded as a mere aromatic or flavoring agent. While the toxicity of benzaldehyde is comparatively very low it exhibits certain very striking pharmacodynamic effects, the most important of which are of a threefold nature. The substance possesses important

antispasmodic, local anesthetic and *antiseptic* properties all of which are exhibited not only by pure benzaldehyde but even by weak solutions of it in alcohol, oil or water. These characteristic effects of benzaldehyde considered in connection with the similar properties of benzyl alcohol and certain benzyl esters such as benzyl benzoate and benzyl acetate throw a new light on certain well-established empirical therapeutic uses of old drugs. A good example of such an empirical practice is the use of benzoinum in the form of a simple or compound tincture of benzoin. These preparations have long ago been found useful as sedatives in sore throat and also as antipruritics in cases of skin irritation. With the rise of modern pharmacology there was a tendency on the part of some writers to taboo these empirical usages without any further experimentation and to ascribe the beneficial effects of benzoin, if any, to psychic suggestion or in the case of inhalation to the beneficent effects of steam. In view of the present investigation a rational basis for the empirical use of benzoin is found. The author has made mixtures of water with tincture of benzoin in proportions of 1 to 10 and even weaker concentrations, and distilled these mixtures collecting the distillate through a condenser. On testing the distillate he was able to show that there is a sufficient amount of benzyl alcohol and benzaldehyde present in the fluid obtained to demonstrate a definite anesthetic effect on frog skin. Again bearing in mind the anesthetic and also antiseptic properties of benzyl alcohol and benzaldehyde and related compounds the use of such in lotions for itching and burning of the skin is evidently also justified on pharmacological grounds.

It has been found that a combination of antipyrine with mandelic acid in the form of an ester, antipyrine mandelate, or *tussol*, is beneficial in certain cases of whooping cough. Such a therapeutic effect with such an ester would seem to be a plausible one in view of the experiments by the author with benzyl benzoate in the same clinical condition.[8] The above experiments with benzaldehyde suggest, furthermore, an improvement in the therapeutic practice in the case of inhalations and other applications of benzyl compounds in that such preparations can be rendered more efficient by fortifying them with an addition of benzaldehyde or benzyl alcohol.

SUMMARY.

1. A pharmacological study of benzaldehyde showed that while the substance is of low toxicity it exhibits three important physiological effects.

2. Benzaldehyde was found to relax the tonus and inhibit contractions of smooth muscle.

3. Benzaldehyde was found to possess definite local anesthetic properties.

4. Benzaldehyde was found to exhibit a distinct antiseptic effect on bacteria.

5. Mandelic acid closely related to benzaldehyde chemically was found to possess distinct antispasmodic properties as exhibited by a study of its salts and esters.

6. The interesting properties of benzaldehyde and mandelic acid shed light on the beneficent results obtained by the empirical use of certain natural drugs containing benzyl compounds.

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COMPOSITION OF NECTANDRA COTO, RUSBY NOV. PRELIMINARY REPORT.

BY HARVEY A. SEIL.

Previous investigators have shown[1] that true coto bark contains cotoin, cotoin methyl ethers, phenyl coumalin, protocotoin, methyl-protocotoin, ethereal oil and tannin. The chemical constitution of cotoin and its derivatives has been carefully studied and can be briefly outlined as follows:

Cotoin—$C_6H_5.CO.C_6H_2(OH)_2.OCH_3$. Melting point, 130° C.

Hydrocotoin
(Cotoin monomethyl ether)—$C_6H_5.CO.C_6H_2(OH)(OCH_3)_2$. Melting point, 98° C.

Methyl-hydrocotoin
(Cotoin dimethyl ether)—$C_6H_5.CO.C_6H_2(O.CH_3)_3$. Melting point, 113° C.

These are all methyl ethers of a substituted benzophenone, or better, of benzoylphloroglucin.

Protocotoin—$(CH_3O)_2HO.C_6H_2.CO.C_6H_3\left\langle {}^{O}_{O} \right\rangle CH_2$. Melting point, 141–2° C.

Methyl-protocotoin—$(CH_3O)_3.C_6H_2.CO.C_6H_3\left\langle {}^{O}_{O} \right\rangle CH_2$. Melting point, 134–5° C.

Protocotoin and methyl-protocotoin are derivatives of 1,3,5-trioxybenzoprotocatechone and are the methylene ethers of hydrocotoin and methyl-hydrocotoin.

Phenyl coumalin—C_6H_5—C : C H . C H.
                    ‖   Melting point, 68° C.
        O —CO—CH

Cotoin, the main constituent of the bark, occurs in pale yellow prisms or plates melting at 130° C. It is sparingly soluble in cold water, more readily in hot. It is easily soluble in the ordinary organic solvents but difficulty soluble in petroleum ether. It dissolves readily in alkali, with a yellow color. It reduces silver solution in the cold and Fehling's solution hot. Ferric chloride added to an alcoholic solution gives a brown-black coloration. A drop of concentrated nitric acid to a solution of cotoin in glacial acetic acid gives a blood-red color.

Nectandra Coto RUSBY.

The sample of coto under investigation was kindly furnished by Dr. Henry H. Rusby who personally collected the bark in his recent exploration with the H. K. Mulford expedition. The bark was ground to about 20 mesh with considerable difficulty since it was very resinous and continually clogged the mill.

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[1] Ciamician and Silber, *Ber.*, 24, 2977; 26, 2340; 27, 419; 28, 1549. *Pollak-Monatsch.*, 22, 996. Jobst and Hesse, *Annalen*, 199, 17.