A CONTRIBUTION TO THE CHEMICAL-PHARMACODYNAMIC RELATIONSHIPS OF ATROPINE AND HOMATROPINE.*

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INTRODUCTION.

The structure of the atropine molecule and the relation of its chemical structure to the pharmacological effects of the alkaloid are perhaps better known than those of most other pharmacological agents. While the medicinal use of various members of the Belladonna family goes back to remote antiquity the discovery of their active principles is of a comparatively recent date. Atropine was discovered in 1831 by Mein who isolated it from the root of *Datura*.[1] The same substance in pure form was independently and almost simultaneously obtained by Geiger and Hesse.[2] These latter investigators gave some of their base to Liebig for analysis and Liebig gave the empirical constitution of the substance $C_{17}H_{23}NO_3$.[3] This formula was confirmed by Planta[4] and is the accepted empirical formula for atropine at the present day. The chemical structure of this alkaloid has been elucidated beginning with the interesting observations of Kraut[5] and Lossen[6] and by eminent chemists after them. Kraut and Lossen found that atropine on hydrolysis with hydrochloric acid or sodium hydroxide is broken into a base, called tropine, and an acid, named tropic acid; while on hydrolyzing with baryta water the decomposition products are tropine and atropic acid which differs from tropic acid by one molecule of water. Following these observations the work on the chemical structure of tropine, tropic acid and related compounds was continued especially by Merling,[7] Wilstätter[8] and Ladenburg[9] until the present accurate conception of the atropine molecule was attained. The culmination of the various studies on the subject may be said to be the synthesis of atropine by Ladenburg in 1879.[9] This achievement is the first instance of an artificial synthesis of a natural alkaloid in the laboratory.

The pharmacological properties of atropine and its decomposition products have been investigated by a number of authors. Fraser[10] studied the properties of tropine and tropic acid as compared with atropine itself. He found that while atropine is a powerful mydriatic, tropine itself has very little effect on the pupil of the eye. The same results were obtained by Hellmann;[11] Buchheim also studied the pharmacological properties of tropine as compared with atropine and found that tropine itself is practically inert both as regards its effect on the eye and the vagus inhibition of the heart.

Following the chemical studies of Ladenburg who decomposed atropine into the base tropine and tropic acid and could synthesize atropine by combining tropine with tropic acid again, that author prepared a number of other combinations of tropine with various acid radicals to which he gave the collective name of *tropeines*. Thus one of his preparations was salicyl tropeine, another phthalyl tropeine and still another oxytoluyl tropeine. This last compound which is a combination of tropeine with mandelic acid he named *homatropine*. The properties of this new synthetic alkaloid were examined for him by the physiologists Völckers and Quinke[12]

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who found it to be a very powerful mydriatic and superior to atropine in that the mydriasis was of a shorter duration. The drug very quickly came into widespread use by ophthalmologists and is to-day perhaps the most important mydriatic in clinical practice.

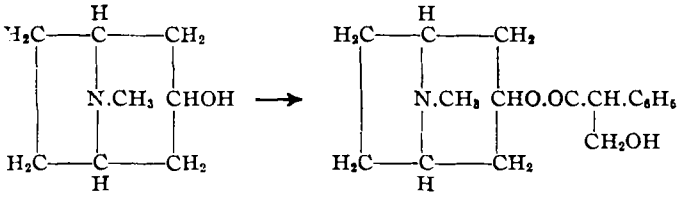
While the pharmacology of atropine is very well known the pharmacodynamics of homatropine have received very little attention. It is a matter of common knowledge that perhaps the most characteristic effect of atropine is its selective action on the myoneural junctions of the bulbo-sacral autonomic or parasympathetic nervous system, which junctions this alkaloid depresses or paralyzes. Thus the mydriasis produced by atropine is due to a paralysis of the myoneural junctions or endings of the oculomotor nerve; the inhibition of intestinal peristalsis produced by it is due to the depression of the vagus terminals in the intestinal walls; the loss of inhibition of the heart rate, produced by the same drug, is due to the paralysis of the vagus terminals in the heart, etc. Furthermore it is well known that this peculiar and selective action of atropine is due to the effect of the atropine molecule *as a whole*, that is, it is produced by the chemical combination of the base tropine with the tropic acid. Tropine alone or tropic acid alone does not exhibit these pharmacological properties. It has been generally assumed that homatropine, being a tropine and therefore closely related to a tropine chemically, produces its pharmacological effects in the same way as atropine; that it produces mydriasis through the paralysis of the oculomotorural nerve endings, etc. An examination of the literature on the pharmacology of homatropine, however, fails to bring evidence in support of this view. In the first place, very little experimental work on the pharmacology of homatropine has been done altogether. In the second place, what experimental evidence there is, points to properties possessed by homatropine which are quite different from those of atropine. Thus, for instance, de Schweinitz and Hare[13] noted that after the administration of homatropine the pulse instead of becoming more rapid is actually slowed and the same observation has been made by other authors. Even the few experiments made by Zulick[14] to clear up this point have not served to elucidate the pharmacodynamics of homatropine—indeed, have only served to complicate the subject.

The present author originally became interested in the pharmacological effects of homatropine through a study of mandelic acid. This acid is closely related and indeed is made from benzaldehyde and inasmuch as the author has already shown[15] that benzaldehyde exhibits the peculiar antispasmodic properties of benzyl alcohol and certain benzyl esters, it was thought that the mandelic radical in homatropine might play a rôle in its pharmacological action. Accordingly, an extensive study was begun of homatropine on the one hand and its decomposition products on the other. To analyze further the chemical and physiological relationships of homatropine, comparative studies of homatropine were made with those of atropine itself and a number of related derivatives. The effects of these were studied on the heart, eye, various smooth muscle viscera, etc., and are described hereafter.

CHEMICAL STRUCTURE.

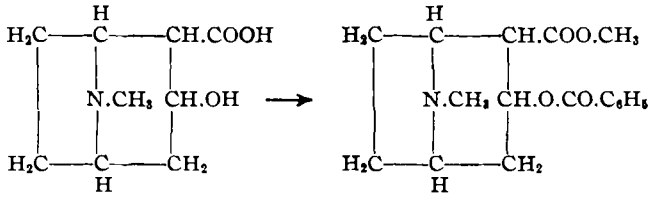
The chemical structure of atropine and homatropine is at present very completely established. The following formulas convey graphically the various chemical relationships. It will be seen that atropine consists of a combination of

tropine and tropic acid. Tropine itself may be regarded as the combination of pyrimidine and pyridine nuclei, that is, of a five-membered and six-membered aromatic ring with a nitrogen atom common to both. As is well known tropine is very closely related to the base ecgonine and the formulas in Fig. 2 reveal the close relationship between the important alkaloids, atropine and cocaine.



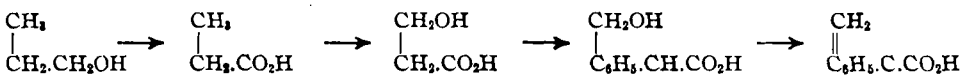
Tropine. Tropine tropate = Atropine.

Fig. 1.



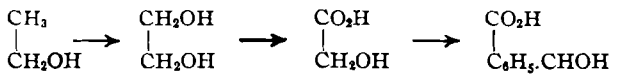
Ecgonine. Cocaine.

Fig. 2.



Propyl alcohol. Propionic acid. β-Hydroxypropionic acid (hydracrylic acid). α-Phenylhydracrylic acid (tropic acid). α-Phenylacrylic acid (atropic acid).

Fig. 3.



Ethyl alcohol. Glycol. Glycolic acid (hydroxyacetic acid). Phenyl-glycolic acid (mandelic acid).

Fig. 4.

The structure of tropic acid is shown by Fig. 3. Starting with propyl alcohol we note the structure of propionic acid, of β-hydroxypropionic acid or hydracrylic acid and of tropic acid which is simply an α-phenylhydracrylic acid. Atropic acid is derived from tropic acid by abstraction of a molecule of water. Fig. 4 shows the structure of mandelic acid. Starting with ethyl alcohol we pass to glycol and from this to glycolic acid. Mandelic acid is phenylglycolic acid. It is important to bear the chemical structure of these compounds in mind in order to appreciate the pharmacological properties of the same as described above.

EFFECT OF ATROPINE AND HOMATROPINE ON THE VAGUS.

The effect of atropine on the heart is familiar to all. When a small dose of atropine sulphate is injected intravenously in a dog the myoneural junctions of the vagus in the heart are completely paralyzed so that stimulation of the vagus nerve electrically or otherwise fails to slow the heart action. Simultaneously with the paralysis of the vagus terminals and consequent loss of normal inhibitory impulses to the heart, the rate is accelerated and the blood pressure rises to a moderate degree. One milligram of atropine sulphate is generally sufficient to produce complete paralysis of the vagus terminal in the heart of a medium-sized dog as is well known to every student of physiology and pharmacology. If a similar experiment is performed with the use of homatropine, however, a different picture is obtained. The author has given numerous injections of homatropine to dogs and other animals and studied the effects of the same on the vagus and the heart. In the first place, after injecting a small dose (1 to 3 mg.) of homatropine it was noted that practically no effect on the vagus was produced at all as shown by electrical stimulation of the nerve. It requires from six to ten times as much homatropine as atropine to be injected before paralysis of the vagus terminals in the heart is produced so that the heart can no longer be inhibited by electrical

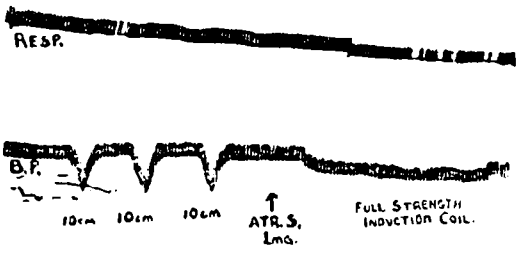


Fig. 5.—Dog 12 kilos, paraldehyde anesthesia. Effect of atropine, 1 mg., on electrical stimulation of the vagus. Upper curve respiration, lower curve blood pressure.

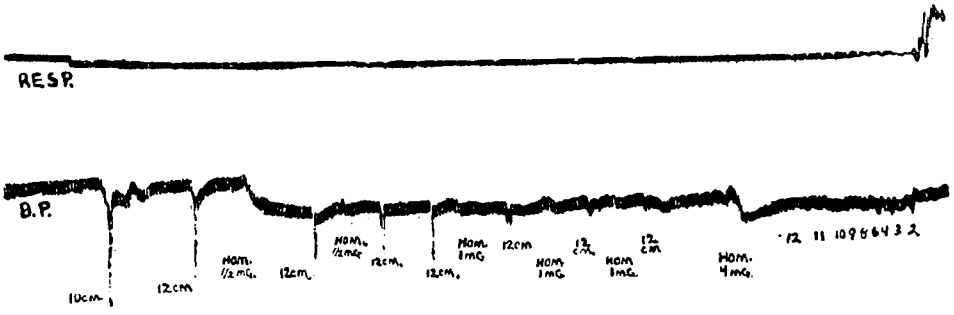


Fig. 6.—Dog 10 kilos, paraldehyde anesthesia. The effect of homatropine hydrochloride on electrical stimulation of vagus. Upper curve respiration, lower curve blood pressure.

stimulation of the vagus nerve trunk. Figs. 5 and 6 illustrate well the difference in action between atropine and homatropine in the inhibitory apparatus of the heart in dogs. In these experiments the vagus response was first tested with an induction coil and the amount of energy required to produce the first definite inhibition of the heart was determined. A small dose of atropine was injected and the depressant effect on the inhibitory mechanism was studied with the same induction coil. The amount of atropine required to produce complete paralysis, so that even a maximum stimulation produced no effect, was then determined.

Fig. 5 illustrates a vagus experiment on a dog weighing 12 kilos. The vagi having been dissected out, the electrode of an induction coil was applied to them and the point at which the first response to stimulation occurred was noted. In this experiment such a point was when the secondary coil was 10 cm. distant from the primary. One milligram of atropine sulphate was then injected intravenously. Almost immediately afterwards complete paralysis of the vagus endings occurred so that even the full strength of the induction coil failed to produce inhibition of the heart.

Exactly similar experiments were made with homatropine. As is seen in Fig. 6 it took eight times as much homatropine to completely paralyze the vagus apparatus of the heart. In this experiment a dog weighing 10 kilos was prepared in the same way as in the previous experiment and the vagus was found to be even more sensitive than in the previous dog, the first response to stimulation occurring at the distance of 12 cm. from the primary coil. It required a total of 8 mg. of homatropine in divided doses to produce paralysis of the vagus endings.

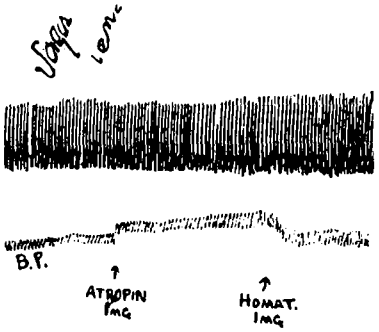


Fig. 7.—Blood pressure and respiratory tracings of dog weighing 10 kilos. Ether anesthesia. One mg. of atropine sulphate produces rise in blood pressure. One mg. of homatropine hydrobromide produces fall in blood pressure.

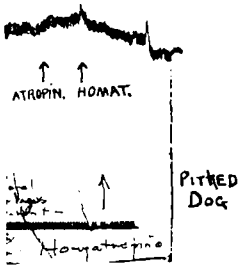


Fig. 8.—Dog, 8 kilos, paraldehyde anesthesia, decerebration. One mg. of atropine produces rise in blood pressure. One mg. of homatropine produces fall in blood pressure.

In the second place simultaneously with the effect on the inhibitory response of the vagus a very interesting phenomenon was noted. Whereas injections of atropine in moderate doses ordinarily produce a slight rise in blood pressure due to loss of normal heart inhibition, it was noted that after injections of even small doses of homatropine a fall in pressure was produced. Fig. 7 is an illustration of such an experiment. It will be noted that after injecting 1 mg. of atropine in this dog inhibition was paralyzed and as a consequence the blood pressure was slightly increased. On injecting 1 mg. of homatropine, however, a decided fall in pressure occurred in the same animal. This fall in blood pressure was not explainable by a central effect on the brain as the same phenomenon and the same difference between atropine and homatropine were observed in decerebrated animals as illustrated in Fig. 8.

In the third place inspection of the splanchnic viscera in the course of the above experiments revealed, in every case when homotropine was injected, a marked

vaso-dilatation of the abdominal viscera. No such effect was noted after injections of ordinary doses of atropine.

These observations at once point to a difference in action between atropine and homatropine on the vagus mechanism of the heart. A careful examination of the literature on homatropine showed that a number of older observers were not entirely ignorant of this difference in action between atropine and homatropine on the heart. Thus it was already mentioned that de Schweinitz and Hare noted a slowing of the pulse after the administration of homatropine instead of the acceleration usually observed after atropine injections. Bertheau[16] in his study of homatropine noted a slowing of the pulse and stated that excitation of the vagus nerve in animals did not indicate a paralysis of the vagus terminals after homatropine injections. The same author also remarks that homatropine has but little effect in checking the secretions of sweat. Tweedy and Ringer[17] also mentioned the fact that homatropine produces a slowing of the pulse in man and is not effective in checking the secretion of sweat glands. They moreover made experiments with frogs' hearts and noted that homatropine does not antagonize the effects of muscarine on the heart. All these observations led the author to suspect that the action of homatropine is not completely explainable by its effects on the parasympathetic nervous system and to surmise that it might possibly exert an action directly on the muscle cells. Accordingly further experiments were undertaken to decide this point.

COMPARISON OF ATROPINE AND HOMATROPINE ON ISOLATED ORGANS.

Atropine is generally regarded as a powerful antispasmodic and it has been used as such clinically. While its relaxing properties on smooth muscle organs are quite striking they are by no means uniform, for on smooth muscle viscera the antispasmodic effect of atropine varies not only with the dose of the drug but also with the organ studied. Thus, for instance, the author has already shown in another paper that in the case of the isolated ureter small doses of atropine are actually stimulating and not sedative to the contractions and the tonus of the organ.[18] In the present investigation a comparative study of atropine and homatropine was undertaken on excised muscle of various viscera. The following organs were examined: uterus, urinary, bladder, ureters, stomach, intestines, gall bladder and bronchi. The organs were obtained from various animals, namely, dogs, cats, rabbits, guinea pigs, rats, mice; on a few occasions human tissue was procured from the surgical operating room in cases where extirpation of gall bladder and other organs was performed. The action of drugs on the tissues was studied in the ordinary way by suspending the same in oxygenated Locke's solution at body temperature and introducing the chemicals into the solution.

On comparing the effects of homatropine with atropine it was found that while in the case of some organs, especially the intestines, both of the alkaloids acted as very powerful depressant or antispasmodics, in the case of other organs the intensity and rapidity of action was different for the two drugs. Thus, for instance, in the case of the ureter small doses of atropine produced no inhibition of contractions and indeed actually tended to stimulate the same, whereas homatropine acted as an immediate depressant or relaxant, causing cessation of the contractions and lowering of the tonus. Similar results were obtained in the case of the urinary bladder.

In the case of the uterus, by treating the same preparations or two exactly similar preparations with small doses of atropine and homatropine it was quite evident that the antispasmodic or relaxant effect was much greater in the case of homatropine. Whereas in such cases atropine produced a gradual relaxation of the muscle, the effect of homatropine was much more rapid and the relaxation came on abruptly.

In the case of the intestines the difference between the two alkaloids was very slight, inasmuch as atropine in very small doses produces rapid relaxation of the intestinal tonus and inhibition of its contractions. The intestinal effect was studied in this connection not only in excised preparations but also *in situ* in cats and rabbits. It was noted that after injections of minute doses of either atropine or homatropine intravenously, immediate cessation of peristalsis occurred, but in the case of homatropine this was accompanied by a marked *dilatation* of the splanchnic vessels which did not occur in the case of atropine.

The effects of the two drugs were also studied after previous stimulation of the preparations with parasympathetic poisons such as pilocarpine, physostigmine and muscarine. On comparing the results obtained it appeared that these parasympathetic drugs antagonized the effects of atropine much more than those

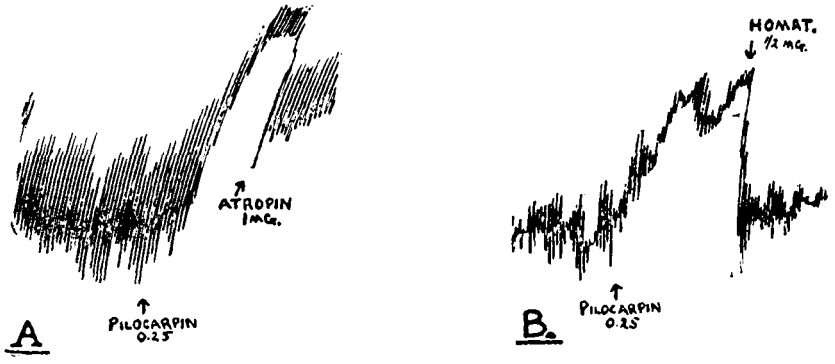


Fig. 9.—Small intestine of cat. A, the effect of pilocarpine and atropine. B, effect of pilocarpine and homatropine.

of homatropine. In other words, after previous construction of smooth muscle preparations with one of the parasympathetic drugs relaxation was produced much more promptly and with smaller doses of homatropine than by the use of atropine. All these observations tended to support the view that homatropine produced relaxation of smooth muscle not exactly through the same mechanism as atropine did. This view was further strengthened by experiments with certain other esters of mandelic acid.

EFFECT OF SOME OTHER MANDELIC ESTERS.

Three other mandelates besides tropine mandelate or homatropine have been introduced into therapeutic practice. These are antipyrine mandelate, known as tussol, eucaine mandelate, extensively employed under the name of euphthalmine, and a combination of phenetidine with mandelic acid, marketed under the name of amygdophenine. The author was unable to obtain a sample of amygdophenine but did procure specimens of tussol and euphthalmine. The action of these was

studied on various smooth muscle preparations and compared with those of antipyrine and eucaine themselves. The results obtained are illustrated in the subjoined figures and were most remarkable. It was found that whereas solutions of antipyrine or of eucaine themselves when administered in moderate doses produced

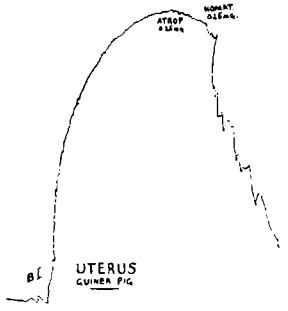


Fig. 10.—Uterus of guinea pig. Stimulation with histamine (B-I) followed by atropine, 0.25 mg., and homatropine, 0.25 mg.

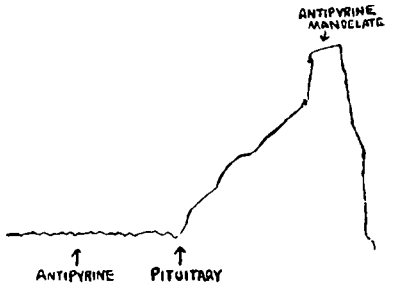


Fig. 11.—Uterus of guinea pig. Effect of antipyrine, pituitary and antipyrine mandelate.

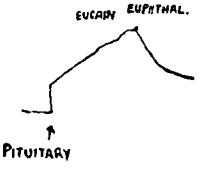


Fig. 12.—Uterus of guinea pig. Contracted by pituitary extract. Eucaine has no effect. Euphthalmine (eucaine mandelate) produces relaxation.

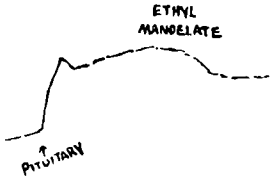


Fig. 13.—Strip of intestinal muscle of cat contracted by pilocarpine hydrochloride, 1 mg., and relaxed by 5 mg. of ethyl mandelate in 40 cc of Locke's solution.

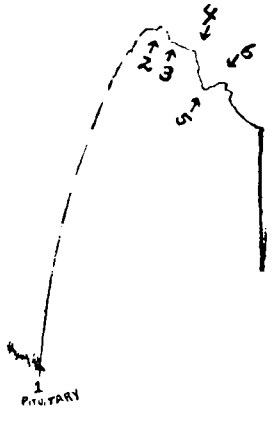


Fig. 14.—Uterus of guinea pig. Fifty cc of Locke's solution. 1, effect of pituitary extract; 2, effect of sodium tropate, 3 mg.; 3, effect of tropine hydrochloride, 3 mg.; 4, effect of atropine sulphate, 2 mg.; 5, effect of pituitary extract, 0.25 cc; 6, effect of homatropine hydrobromide, 2 mg.

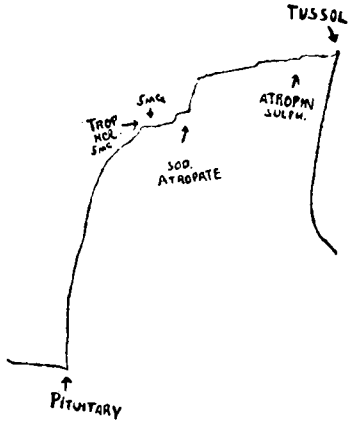


Fig. 15.—Uterus of guinea pig. Contracted by pituitary fluid. Tropine hydrochloride has no effect. Sodium atropate has no effect. Atropine sulphate has no effect. Tussol (antipyrine mandelate) produces no relaxation.

no antispasmodic or sedative effect on the muscle preparations, the introduction of even small doses of the mandelic esters of the same was followed by an immediate and abrupt relaxation, comparable very much to the powerful relaxing effects produced by the alkaloid papaverine.

The author was fortunate in securing a specimen of pure ethyl mandelate (Kahlbaum). Experiments with this simple ester also revealed that it was a powerful relaxant of smooth muscle. The above experiments with various mandelic acid esters obviously indicated that the mandelic acid radical plays an important rôle in their antispasmodic influence on smooth muscle preparations. Figs. 9–13 serve to illustrate the findings just described.

Fig. 9 illustrates an experiment on two segments of the small intestine of a cat. At A the intestine is stimulated by 0.25 gram of pilocarpine hydrochloride and afterwards treated with 1 mg. of atropine sulphate. At B intestine is stimulated with the same quantity of pilocarpine hydrochloride and afterwards with 0.5 mg. of homatropine hydrochloride. It will be noted that the homatropine produces the greater relaxation.

In Fig. 10 an experiment on the isolated uterus of a virgin guinea pig was performed. This was first stimulated to powerful contraction by a small dose of histamine which brought the uterus into a state of tonic contraction. At the height of the contraction 0.25 mg. of atropine sulphate was introduced into the solution and was followed by practically no effect. The same quantity of homatropine solution was then introduced and as will be noted was followed by an immediate and rapid relaxation of the organs.

In Fig. 11 another uterine preparation from a guinea pig was treated with antipyrine without previously being stimulated by an oxytocic and showed no change. It was then contracted with a few drops of pituitary liquid and at the height of its contraction 5 mg. of antipyrine mandelate caused immediate relaxation and fall of the tonus below the original level.

Fig. 12 illustrates an experiment in which a uterus was first contracted with pituitary and then treated with a solution of eucaine (5 mg.). No effect was produced. On adding, however, the same quantity of eucaine mandelate (euphthalmine) relaxation occurred.

Fig. 13 shows a curve traced by a bit of circular muscle of cat's intestine. This was stimulated to contraction by 1 mg. of pilocarpine in 50 cc of Locke, and was relaxed by the introduction of 5 mg. of ethyl mandelate in the same solution.

EFFECT OF SOME DECOMPOSITION PRODUCTS.

In order to analyze still further the rôle played by mandelic acid in the action of homatropine, experiments were undertaken with the "Bausteine," or decomposition products of homatropine, on the one hand, and of atropine on the other. In other words, an examination was made of the individual properties of tropine in the form of a simple salt, such as tropine hydrochloride; of tropic acid in the form of sodium tropate; and of mandelic acid in the form of simple salts such as those of sodium and potassium.

It was found that tropine itself when administered in the form of tropine hydrochloride produces very little effect on the tonus or contractions of smooth muscle. Tropic acid itself in the form of its simple salts such as sodium tropate was also found to be very little active in this respect. Moderate quantities of sodium tropate produced no effect on smooth muscle while very large doses of the same only occasionally produced a very slight relaxation of the tonus of a uterus previously brought into a state of maximum contraction by a powerful stimulant

such as pituitary extract. Neither did atropic acid in the form of sodium atropate produce any effect on the behavior of isolated smooth muscle preparations.

On testing the properties of sodium mandelate, however, a very different result was obtained. It was seen at once that sodium mandelate produced a relaxation of tonus and inhibition of the rhythmic contractions of smooth muscle. This was found to be true of preparations from all kinds of organs.

Simple mixtures of sodium tropate with tropine hydrochloride did not produce the same effect as atropine; in other words, it was evident that the action of the atropine molecule was due to an intimate chemical combination of the two components. Simple mixtures of tropine hydrochloride with sodium mandelate, on the contrary, did produce relaxation of smooth muscle preparations. As a result of all these experiments with the components of atropine and homatropine it seemed plausible to assume that the mandelic acid played an important rôle in the antispasmodic properties of homatropine. It was therefore of especial interest to inquire whether that held true for the mydriatic action of homatropine. Accordingly some experiments were carried out to clear up this question.

Fig. 14 shows a uterus of a guinea pig brought into powerful contraction by a drop of pituitary fluid at 1. At 2, 3 mg. of sodium tropate were introduced without any effect; at 3, 3 mg. of tropine hydrochloride, without any effect. At 4, 2 mg. of atropine sulphate produced a slight relaxation. The uterus was stimulated at 5 by a second dose of pituitary. At 6, 2 mg. of homatropine hydrochloride were introduced and this was followed by rapid and marked relaxation of the preparation. In Fig. 15 the uterine horn of a guinea pig was stimulated with pituitary extract. The dose was repeated with the same results. Ten mg. of sodium atropate produced no relaxation and indeed were followed by further contraction of the uterus. Two mg. of atropine sulphate produced no relaxation. Finally 5 mg. of antipyrine mandelate produced an immediate fall of the lever.

ANALYSIS OF HOMATROPINE MYDRIASIS.

The mydriasis produced by homatropine has been studied clinically by many authors, beginning with Völckers and Quincke who first demonstrated it for Ladenburg. The effects of homatropine on the eye were investigated by Bertheau, Tweedy and Ringer, Oliver,[19] Reily,[20] Jackson,[21] Schell,[22] Ziem,[23] Vossius[24] and others. It was established that homatropine produces satisfactory mydriasis but must be used in about double the concentration of atropine and that the mydriasis is of much shorter duration, a circumstance which is clinically usually very desirable. It is also generally conceded that atropine paralyzes accommodation much more quickly and in weaker dilutions than homatropine.

The effect of light in relation to atropine and homatropine has been noted by various authors. Ordinarily exposure to a bright light produces a reflex contraction of the iris. This reflex contraction fails to appear after instillation of full therapeutic doses of atropine. The explanation of this phenomenon is found in the paralysis of the occulomotor nerve terminals supplying the circular muscle of the iris, so that the reflex arc is incomplete and cannot respond to the stimulation of light. When the reaction of the pupil to light is tested after instillation of homatropine, however, this reflex myosis or contraction of the pupil is generally not completely obliterated unless very strong solutions of the alkaloid are employed or weaker solutions repeatedly instilled, for a protracted period of time. The

present author has repeatedly instilled solutions of atropine sulphate (1–1000) and of homatropine (1–500) into the conjunctival sacs of cats and rabbits and found that while the atropine completely obliterated the light reflex, the homatropinized animals still responded with a distinct contraction to the pupil on exposure to a bright light. This difference in the action of the two alkaloids would seem to speak in favor of a different mechanism in the two cases as regards the production of mydriasis. If homatropine were to produce relaxation of the constrictor pupilae by a direct action on the muscle cells without affecting the parasympathetic nerve terminals, then it is easily conceivable how a strong stimulation by light would still produce a contraction of the pupil by reflex stimulation of these nerve terminals. On the other hand, if a drug like atropine completely paralyzes the parasympathetic nerve endings, then no degree of intensity or light stimulation will be able to produce a myosis through a reflex stimulation, no more than the strongest electric stimulation may be able to inhibit the heart action after the vagus nerve terminals in the heart have been paralyzed by atropine.

In order to ascertain further the mechanism of pupillary dilatation produced by homatropine, experiments were made by the author with tropine hydrochloride, sodium tropate, sodium atropate and various mandelic esters. The author was able to confirm the results by Fraser and other earlier investigators with tropine on the eye. Instillation of solutions of tropine hydrochloride into the eyes of cats and rabbits failed to produce mydriasis. Experiments made on excised frogs' eyes gave the same results, tropine hydrochloride produced neither mydriasis nor myosis of the eye.

Tropic acid in the form of its sodium salt was also found to have practically no effect on the pupils of both rabbits and cats and on excised frogs' eyes. On the other hand experiments with ethyl mandelate made by instilling solutions of the same (2 percent) into the eyes of cats and rabbits were found to produce a distinct dilatation. Finally a solution of sodium mandelate was prepared and the same was tested on intact animals and on excised frogs' eyes and it was found that this drug produced a distinct though mild mydriasis or dilatation of the pupil. Thus, for instance, a 4 percent solution of sodium mandelate instilled into rabbits' eyes was followed by a distinct dilatation. A 10 percent solution of the same salt produced a more striking effect.

In conclusion, the action of homatropine and the various related compounds mentioned above were studied on the eye by a new method which, so far as the author is aware, has not been described. The author studied the effects of the various drugs on the *excised* circular muscle of the iris. The eyes of cats, rabbits, dogs and pigs were used in this connection, the cat's eye being the most suitable. The circular muscle of the iris was carefully dissected out, care being taken not to injure it by pulling or tearing, and a suspension preparation was made in the same way as other smooth muscle preparations are studied. When such a preparation is carefully made and the muscle lever is delicately balanced, the iris writes a horizontal line on the hymograph, sometimes exhibiting small rhythmic contractions. The response of the muscle to drugs is then studied by introducing solutions of the same into the suspension chamber. In this way it was found that the muscle contracted after pilocarpine and eserine and relaxed to atropine and homatropine. On studying the effects of tropine, tropic acid, and mandelic acid it was found

that whereas sodium tropate and tropine hydrochloride produced no effect, sodium mandelate and other mandelic esters produced a relaxation of such iris muscle preparations. Furthermore, it was found in some instances that after contracting such preparations with pilocarpine and relaxing the same with atropine on subsequent addition of homatropine an even greater relaxation of the muscle could be produced.

In Fig. 16, the isolated circular muscle of the iris of the cat was suspended in oxygenated Locke's solution. On the addition of 2 mg. of pilocarpine in 50 cc of Locke contraction occurred. One mg. of atropine failed to relax the preparation. The addition of 1 mg. of homatropine, however, produced a marked and rapid relaxation.

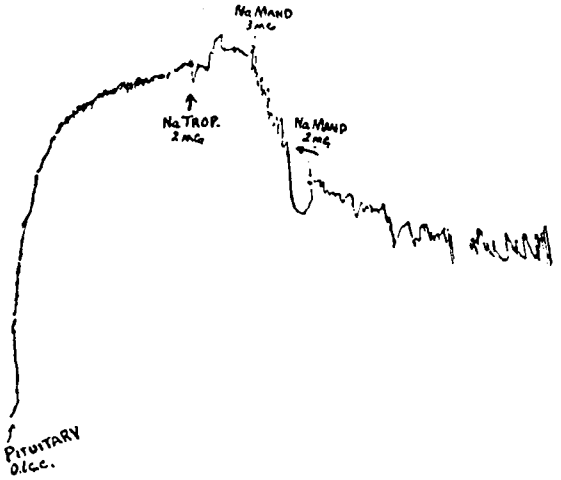


Fig. 16.—Uterus of guinea pig. Contraction after 0.1 cc of pituitary fluid. Sodium tropate, 2 mg., has no effect. Sodium mandelate, 3 mg., produces relaxation.

Fig. 17.—Isolated circular muscle of the iris from a cat. Pilocarpine, 2 mg., in 40 cc of Locke produces contraction. Atropine sulphate, 0.25 mg., has little effect. Homatropine hydrobromide, 0.25 mg., produces relaxation.

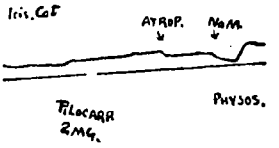


Fig. 18.—Iris preparation same as above. Contraction after pilocarpine, slight relaxation by atropine, greater relaxation by sodium mandelate and second contraction after physostigmine.

In Fig. 17 the circular muscle of the iris of a cat was first stimulated by pilocarpine and this contraction was antagonized by 1 mg. of atropine sulphate. On addition of 5 mg. of sodium mandelate a much more marked relaxation occurred than after the atropine. The fact that the preparation was not injured by the mandelate is indicated by a subsequent response to physostigmine.

DISCUSSION.

The analysis of the results of the various experiments by the author enumerated above justified the formulation of some plausible generalizations and the drawing of certain conclusions. It is evident, in as far as the effect on the viscera is

concerned, that the antispasmodic effect of atropine on smooth muscle is due to a specific and peculiar action of the atropine molecule as a whole on the myoneural junctions of the parasympathetic nervous system, because neither tropine (tropine hydrochloride) nor tropic acid (sodium tropate), nor simple mechanical mixtures of the two produce any such effect. Very different, however, are the properties of homatropine in this respect. While large doses of homatropine do paralyze the vagus endings on the heart and for the production of such paralysis the homatropine molecule as a whole is necessary, the inhibitory and tonus lowering properties of homatropine on smooth muscle can in a measure be produced by one of its component nuclei, namely, by the mandelic acid radicle. Thus the vaso-

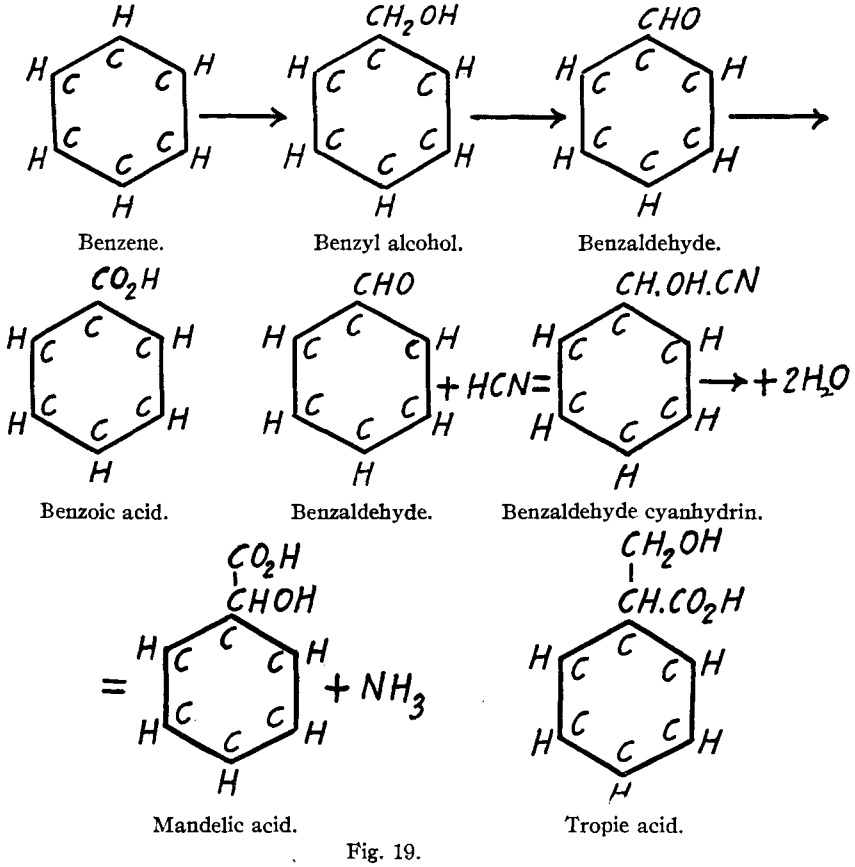


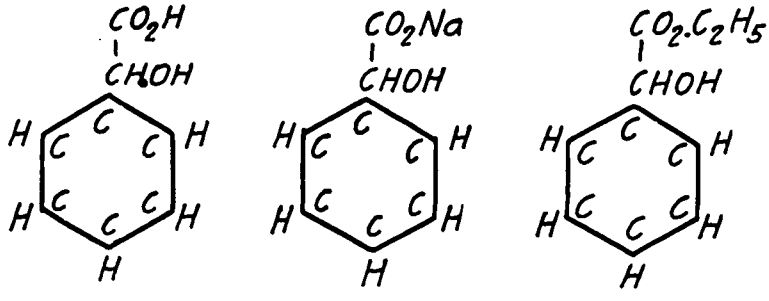
Fig. 19.

dilatation and consequent fall in blood pressure, and the relaxation of uterine, intestinal, vesical and other smooth muscle preparations are produced by various esters of mandelic acid and also by the simple sodium and potassium salts of mandelic acid. The conclusion is therefore justifiable that this property of homatropine in relation to smooth muscle is inherent to a great extent in its mandelic component.

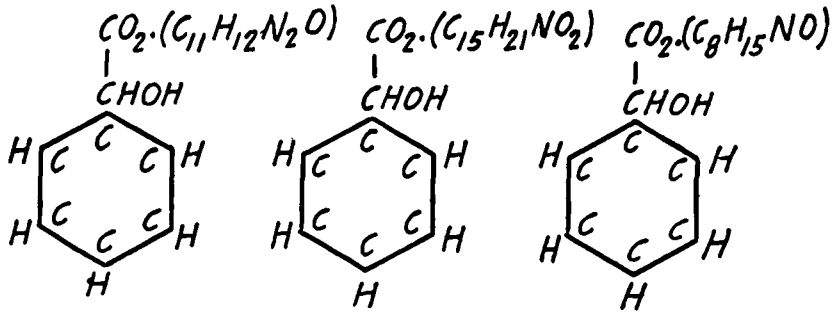
A careful examination of the action of homatropine as compared with atropine especially in regard to their antagonism to various parasympathetic pressor drugs, such as muscarine, pilocarpine and physostigmine, would seem to indicate that the muscle effect of homatropine is not exerted through the parasympathetic

terminal apparatus. The behavior of other mandelic esters and of sodium and potassium mandelates renders this view even more conclusive. Neither is there any evidence as far as the author is aware, pointing to the true sympathetic nervous mechanism as being responsible for the antispasmodic effects of these substances. All the evidence on hand seems to speak in favor of the action being very much the same as that of the alkaloid papaverine and also of certain benzyl esters and benzyl alcohol, which the author has shown to act in the same way as papaverine. [18,19] This action is probably exerted *directly on the muscle cell.*

The interesting properties of various mandelates described above are not altogether unexpected in view of the remarkable properties of various benzyl compounds which have been discovered by the author. The subjoined structural



Mandelic acid. Sodium mandelate. Ethyl mandelate.



Antipyrine mandelate (tussol). Eucaine mandelate (euphthalmine). Tropine mandelate (homatropine).

Fig. 20.

formulas will serve to show the closer relationship of mandelic acid to benzaldehyde which has already been investigated by the author and shown to act as an antispasmodic (Fig. 18). It will be seen that mandelic acid is prepared from benzaldehyde by first treating with hydrocyanic acid and thus forming benzaldehyde cyanhydrin. Fig. 20 exhibits the structural formulas of sodium mandelate, ethyl mandelate and other mandelic esters. Fig. 19 also indicates the structure of tropic acid and the comparison of this formula with that of mandelic acid will reveal at once that mandelic acid is much more closely related to benzaldehyde and benzyl alcohol than tropic acid is.

In view of the above considerations it would seem probable that the mydriatic action of homatropine is produced in part at least by a direct action on the muscle of the iris without the mediation of the parasympathetic terminal nervous appara-

tus. This is further corroborated by the difference in the response to light stimulation which has already been described and also by the experiments on isolated iris muscle shown by the author.

This peculiar action of homatropine on smooth muscle is supported by the careful observations of clinical ophthalmologists. It has been noted by Jackson and others that instillation of homatropine into the conjunctional sac is followed by a hyperemia of the conjunctival and corneal vessels. This is not regarded as due to an irritant effect of the drug but rather in the nature of a true hyperemia or vaso-dilatation. To quote literally from the excellent paper of E. Jackson we read, "there is hyperemia of the eye due to enlargement of minute vessels that form a rosy zone around the cornea, the straight vessels and the deep vessels of the sclerotic. This is not due to water or to acid. I believe it to be due to a specific influence of the drug on the vessels." This careful observation of a keen clinician is in perfect agreement with the experimental results obtained with atropine which has been found by the author to be a vaso-dilator due to its antispasmodic or relaxing effect on the muscle of the vessel walls.

SUMMARY.

1. A comparative study of the pharmacological properties of atropine and homatropine and their products of decomposition was made on the circulation, the eye, and all kinds of smooth muscle viscera.

2. While small doses of atropine completely paralyze the vagus terminals in the heart, and through a loss of normal vagus inhibition this generally causes a rise in blood pressure, equivalent and even larger doses of homatropine fail to paralyze these vagus endings, and cause a fall in blood pressure due to a marked vaso-dilatation.

3. Homatropine as compared with atropine is a more powerful drug in respect to the inhibition of contractions and lowering of the tonus of smooth muscle preparations.

4. Of the components of atropine, neither tropine, nor tropic acid alone, or a simple mixture of their salts produces the characteristic effects of atropine on smooth muscle.

5. Of the components of the homatropine molecule, mandelic acid in the form of simple salts or esters exhibits the characteristic effects of homatropine on smooth muscle.

6. As a conclusion from the data obtained it would seem that the property of relaxing smooth muscle and especially of producing mydriasis resides chiefly in the mandelic component of the homatropine molecule, and is probably produced through a direct action on the muscle cells.

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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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