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TETRAHYDROZOLINE—CENTRAL NERVOUS SYSTEM DEPRESSANT VETERINARY COMPOSITIONS AND METHOD OF USING SAME

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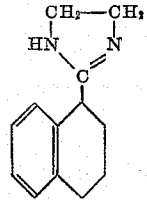
No Drawing. Application August 25, 1955
Serial No. 530,618

7 Claims. (Cl. 167—52)

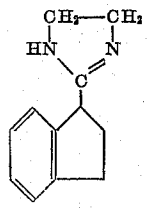
This invention is concerned with certain processes for inducing sleep and anesthesia, and for relieving pain. It is also concerned with valuable medicinal compositions useful for their hypnotic and anesthetic properties. In particular, these compositions comprise certain combinations of tetrahydrozoline with a central nervous system depressant. The process involves administration of a central nervous system depressant with tetrahydrozoline either as a separate dosage or as a combined dosage form containing both materials.

It has now been found that, in general tetrahydrozoline has a potentiating effect on drugs that depress the central nervous system. Drugs which depress the central nervous system are generally classified as sedatives or hypnotics, and anesthetics. A prolonged duration of the central nervous system depression is observed when tetrahydrozoline is administered with such a drug. In particular this effect has been observed with the barbiturates, the acetylenic carbinols, the water soluble esters of pregnanolones, the pharmacologically useful forms of chloral, morphine, and its acid addition salts.

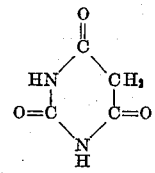
Tetrahydrozoline whose systematic name is 2-(1,2,3,4,-tetrahydronaphthyl) - imidazoline has the following structure

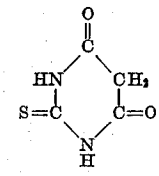


and is the subject of U. S. Patent 2,731,471 to Martin E. Synerholm et al. As indicated in this application, tetrahydrozoline and its next lower homolog whose formula is given below are themselves potent pressor materials. They are most commonly used as aqueous isotonic solutions of their hydrochloride salts, but other salts are also useful. When the term tetrahydrozoline is used, it is to be understood that it refers either to the above free base or its salts.



The barbiturates referred to above are a group of derivatives, mostly the 5-substituted alkyl derivatives, of barbituric or 2-thiobarbituric acid. The formulas of these two materials are given below.



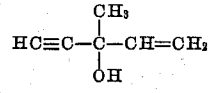


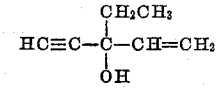
The barbiturates have been widely used as hypnotics and anesthetics for over 50 years. Their use as well as that of morphine is summarized in a number of texts such as Burger, "Medical Chemistry," vol. I., Interscience Publishers, Inc., New York, 1951, chaps. IX and XI, and Goodman and Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, 1941, chap. 12.

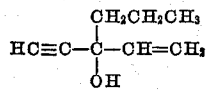
The acetylenic carbinols referred to above are a much newer group of hypnotic agents which are described in the following copending patent applications.

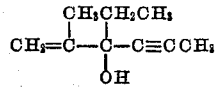
Bavley and Harfenist	Serial No. 286,012	Filed May 3, 1952, now abandoned.
Do	Serial No. 296,744	Filed July 1, 1952, now abandoned.
Do	Serial No. 296,745	Filed July 1, 1952, now abandoned.
Bavley, Harfenist and McLamore.	Serial No. 317,348	Filed October 28, 1952.
Do	Serial No. 329,088	Filed December 31, 1952, now patent No. 2,750,428.
Bavley and McLamore	Serial No. 349,938	Filed April 20, 1953, now patent No. 2,746,400.

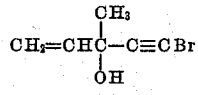
Compounds of this type are tertiary alcohols embodying as a common structural feature a lower alkyl group, a lower alkenyl group, and a lower alkynyl group each attached to the carbon atom which bears the hydroxyl group. A few examples of compounds of this sort are given below.

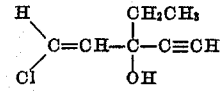




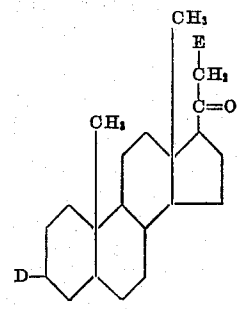








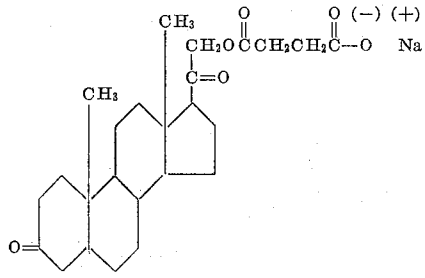
The water soluble esters of pregnenolones comprise a new class of hormonally inactive steroid anesthetics which are the subject of United States Patent 2,708,651. These steroid anesthetics are water soluble derivatives in the pregnane and allopregnane series of steroids and have the following structural formula



wherein D and/or E are ionic ester groups of a variety of types including metal and amine salts of hemisuccinates, hemimalonates, hemi-adipates, and hemiglutarates, etc. D and/or E may also be quaternary and acid addi-

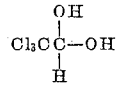
tion salts of certain amino acid esters such as dimethylaminoacetates, β-piperidinopropionates, β-diethylaminoethyl carbonates, β-diethylaminoethyl carbamates, etc.

Hydroxydione sodium, a preferred member of this series, has the following structural formula:

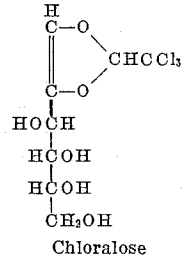


Other salts of hydroxydione which have also proven useful include the triethylamine salt, the methylamine salt, the diethylamine salt, the dimethylbenzylamine salt, the ammonium salt and the potassium salt.

Chloral, or trichloroacetaldehyde, was one of the earliest useful hypnotics discovered. It has been widely used both in the forms of its hydrate and as its condensation product with glucose known as chloralose.



Chloral hydrate



Chloralose

Thus, when the term a pharmacologically useful form of chloral is used what is meant is either chloral itself, its hydrate, α-chloralose, or other useful forms of this well known hypnotic. Chloral, in its various useful forms, has various disadvantages which can be minimized by reducing its dosage and using a potentiating agent with it. For example, its bitter taste can be more readily masked in the smaller doses required when tetrahydrozoline is used with it.

Morphine is an alkaloid obtained from the opium poppy, *Papaver somniferum*. It has been used as a central depressant for centuries. By appropriate adjustment of the dosage employed, a wide variation in the degree of central depression can be obtained ranging from simple analgesia to sedation, and euphoric sleep. Morphine is commonly used as the free base, either purified or as a mixture with the alkaloids that occur with it, and as its acid addition salts such as the sulfate and hydrochloride.

The novel potentiating ability that tetrahydrozoline has for the central depressants of the above types has been demonstrated with a number of specific agents. The anesthetic and hypnotic activity of pentobarbital, 2-chlorovinyl ethynyl ethyl carbinol, hydroxydione sodium and α-chloralose is prolonged by tetrahydrozoline. Tetrahydrozoline also has the ability to increase the analgesic activity of morphine, thus reducing the dose of the analgesic that must be administered to obtain a given level of relief from pain, or when the customary dosage is administered, a prolonged effect is observed.

The great value of the compositions of this invention resides in their ability to yield a pharmacological effect equal to or greater than a much larger dose of the central

depressant alone which is contained therein. Thus, by use of lower dosages of the barbiturate or morphine the deleterious side effects of these materials can be minimized.

The potentiating agent, tetrahydrozoline, used in this invention of itself has little hypnotic effect and no analgesic activity in animals. The combined effect of tetrahydrozoline with the barbiturates, the acetylenic carbinols, the water soluble esters of pregnenolone, the pharmacologically useful forms of chloral, and morphine is thus much greater than would be expeected by a mere additive process. A synergistic effect is obtained.

In making use of this novel potentiating ability of tetrahydrozoline, it may be administered as a separate dosage when the hypnotic or analgesic is applied, or it may be administered simultaneously with the hypnotic or analgesic in one of the valuable compositions of this invention. Thus, in describing the valuable processes of this invention, when we say that the tetrahydrozoline and the central depressant under consideration are administered at substantially the same time, it is meant that the two materials are administered in such a fashion that their periods of pharmacological effectiveness overlap.

The compositions of this invention comprise tetrahydrozoline along with the central depressant and an acceptable pharmaceutical carrier therefor. The choice of carrier is determined by the route of administration, the solubility of the tetrahydrozoline and of the central depressant under consideration, and by standard pharmaceutical practices. Excipients such as starch and milk sugar may be used to prepare tablets for oral administration. Elixirs containing flavoring and sweetening agents may also be used. For injection the compositions may be administered as a finely divided suspension in a solvent, or as an aqueous solution. It is generally advisable in the latter case to employ an isotonic solution of glucose or sodium chloride as the solvent. A preservative such as chlorobutanol may also be used. The compositions may be administered by various routes, oral, parenteral, or rectal.

In general, the tetrahydrozoline is present in the composition in an amount by weight less than the amount by weight of the central depressant employed. Considerable variation in the sensitivity to tetrahydrozoline among various species of animals is observed. For example, the rat is fairly insensitive to the potentiating effect of tetrahydrozoline. In the example of morphine potentiation by tetrahydrozoline in the rat, the weight of the tetrahydrozoline actually exceeded that of the morphine. However, this is an unusual case. In the experiment with chloralose anesthesia in the cat, a weight ratio actually in excess of 450 parts of chloralose to one part of tetrahydrozoline was found effective.

The potentiating effect of tetrahydrozoline on the hypnotic activity of a barbiturate and an acetylenic carbinol was measured by comparing the sleeping times of mice that were treated with the sedative and tetrahydrozoline separately with the sleeping times of mice treated with the two drugs in combination. In the barbituate series, sodium pentobarbital (sodium 5-ethyl-5-(1-methylbutyl) barbiturate) was selected as the test drug. Five groups of ten mice were used in this experiment. One group was treated intraperitoneally with tetrahydrozoline only. These mice did not fall asleep. To the remaining groups of mice, sodium pentobarbital was administered orally at a given dosage level. One of these groups was then maintained as a pentobarbital control group and the remaining groups were treated intraperitoneally with tetrahydrozoline at various dosage levels. The average sleeping time for each group of animals was then observed. A substantially longer duration of sleep was observed with those treated with combinations of the two drugs. In a similar experiment in which an acetylenic carbinol, 2-chlorovinyl ethynyl ethyl carbinol, was used as the test drug in groups of mice tested with the carbinol alone

and in combination with tetrahydrozoline, a marked synergistic or potentiating behavior was observed.

A similar type of experiment was employed to study the synergistic effect of hydroxydione sodium and tetrahydrozoline. Both rats and monkeys were used as test animals. With rats the tetrahydrozoline was administered at three different dosage levels by the oral, subcutaneous and intraperitoneal routes. The highest dosage employed was the maximum tolerated dose (LD_0) by each route. A fixed dosage of hydroxydione sodium equivalent to twice its median anesthetic dose (AD_{50}) was administered from 15 to 120 minutes after treatment with tetrahydrozoline and the duration of anesthesia for the various groups of rats was observed. Control groups of rats were maintained that received hydroxydione sodium only. The length of time permitted to elapse between treatment with tetrahydrozoline and hydroxydione sodium depended upon the route by which the tetrahydrozoline was administered. The pharmacological effect of tetrahydrozoline sets in much more rapidly when it is administered intraperitoneally than it does when the drug is administered orally. The object in doing this was to administer the tetrahydrozoline in such a fashion that the duration of its effectiveness coincided with that of the central depressant employed. This is an essential feature of the process of the instant invention regardless of the central depressant employed.

A similar type of experiment was used to test tetrahydrozoline as an adjunct to hydroxydione anesthesia in monkeys. In this experiment graded doses of both materials were administered, the tetrahydrozoline orally and the hydroxydione sodium intravenously.

Although tetrahydrozoline and hydroxydione sodium can be administered as a combination dosage, this is not a preferred embodiment of this invention. Hydroxydione sodium is most advantageously administered intravenously while it is preferred to administer tetrahydrozoline by the oral route.

The potentiating effect of tetrahydrozoline on chloralose was observed using the cat as an experimental animal. Tetrahydrozoline, 150 mcg./kg. in two divided doses, was administered following an intravenous dose of 70 mg./kg. of chloralose. The animal slept for 26 hours following medication. In control experiments, the above dose of tetrahydrozoline alone was without hypnotic effect and the chloralose at a dosage of 70 mg./kg. caused the animal to sleep about three to four hours.

For the measurement of the potentiation of morphine by tetrahydrozoline, the radiant heat method for producing a standardized pain was used in which a beam of light of constant intensity was focused on the blackened tail of a rat. The light intensity was adjusted so that normal rats would withdraw their tails in less than 10 seconds. In treated rats, failure to withdraw the tail in 15 seconds was taken as evidence of analgesia. Combinations of tetrahydrozoline with morphine were thus found to be much more effective analgesics than morphine is alone.

The following examples are given by way of illustration and are not to be considered as placing any limitation on this invention. In fact, many variations are possible without departing from the spirit and scope thereof.

EXAMPLE I

Four groups of ten albino Swiss mice were treated orally with 50 mg./kg. of sodium pentobarbital. One of these groups was retained as a control and the others were treated respectively with 5, 10 and 20 mg./kg. of tetrahydrozoline intraperitoneally. A fifth group was treated with 20 mg./kg. of tetrahydrozoline alone. The time of onset and duration of anesthesia was recorded. The loss and regaining of the righting reflex was taken as the beginning and end of anesthesia. The results of this experiment are given in the accompanying table.

Effect of tetrahydrozoline on pentobarital anesthesia

Pentobarbital (mg./kg.)	Tetrahydrozoline (mg./kg.)	No. anesthesized/No. injected	Average Onset (min.)	Anesthesia Average Duration (min.)
50	0	6/10	10	29±3
50	5	5/10	8	49±9
50	10	4/10	12	52±16
50	20	8/10	11	53±6
0	20	0/10	none	none

The figure given under duration of anesthesia is the mean value ± Standard Error in this measurement. It will be noted that very substantial prolongation of anesthesia occurred at the 5 mg. level of tetrahydrozoline dosage. When administered alone, tetrahydrozoline at a level of 20 mg./kg., did not induce sleep.

EXAMPLE II

Three groups of mice were treated respectively with 100 mg./kg. of β-chlorovinyl ethynyl ethyl cabinol, 25 mg./kg. of tetrahydrozoline, and with both materials in the above dosage. The group treated with β-chlorovinyl ethynyl ethyl carbinol had an average sleeping time of 24 minutes. Those treated with tetrahydrozoline alone did not sleep, and those treated with both materials had an average sleeping time of 139 minutes.

EXAMPLE III

The potentiating effect of tetrahydrozoline on morphine was measured in the rat. Analgesic activity was determined by the radiant heat method. Using a beam of light of constant intensity (330 mc./cm.²/sec.) focused on the rat's tail which was blackened. Normal animals withdrew their tails within ten seconds under these test conditions. The failure of treated animals to withdraw their tails in 15 seconds was taken as evidence of analgesic action. Morphine and tetrahydrozoline were each given alone and together in varying dosages and the median effective doses (ED_{50}) of morphine alone and in the combinations were calculated according to the method of Litchfield and Wilcoxon, J. Pharm. and Exptl. Therapeutics, 96, 99 (1940). The results of this experiment are set forth in the accompanying table. At a dosage of 10 mg./kg., tetrahydrozoline reduced the median effective dose of morphine by about 35% and at a dosage at 20 mg./kg. tetrahydrozoline effected a reduction of about 60%.

Effect of tetrahydrozoline on morphine analgesia in rats

Morphine (mg./kg.)	Tetrahydrozoline (mg./kg.)	No. analgesic/No. tested	ED_{50} (19/20 confidence limits)
0.625	0	2/20	
1.25	0	11/26	
2.5	0	20/29	2.0 (1.3–2.9).
5.0	0	11/16	
10.0	0	10/10	
0.625	10	2/10	
1.25	10	7/10	
2.5	10	11/18	1.3 (1.1–1.87).
5.0	10	10/10	
0.625	20	9/20	
1.25	20	8/10	
2.5	20	12/18	0.75 (0.49–1.16).
0.0	10	0/10	
0.0	20	0/10	no analgesia observed.

EXAMPLE IV

Nine groups of five male albino rats weighing 50–60 grams each were used in one experiment testing tetrahydrozoline-hydroxydione synergism. Three groups were treated with graded doses of tetrahydrozoline by the oral route, three groups by the subcutaneous route and three by the intraperitoneal route. The highest dose of tetrahydrozoline employed by each route was the highest dose that could be given without toxic effect, i. e., the LD_0. In order to be sure that the periods of pharmacological

effectiveness would overlap, the tetrahydrozoline was administered an arbitrary period of time prior to treatment with the hydroxydione sodium. The periods chosen were 15 minutes following the intraperitoneal administration of tetrahydrozoline, 30 minutes following the subcutaneous administration of tetrahydrozoline, and 120 minutes following the oral administration of tetrahydrozoline. The same dose, 50 mg./kg., of hydroxydione sodium was used with each group of animals.

Effect of tetrahydrozoline on hydroxydione, sodium anesthesia in rats

No. of rats	Tetrahydrozoline		Hydroxydione, Sodium		Duration of Anesthesia (min.)
	Dosage (mg./kg.)	Route	Dosage (mg./kg.)	Time of treatment (min.)	
5	260	Oral	59	120	74.0
5	200	Oral	50	120	94.6
5	100	Oral	50	120	92.2
5	180	Subcu	50	30	115.0
5	140	Subcu	50	30	120.6
5	80	Subcu	50	30	87.5
5	56	Intraper	50	15	151.0
5	40	Intraper	50	15	87.2
5	20	Intraper	50	15	74.5
10	0		50		46.3

Although intraperitoneal administration of tetrahydrozoline is the most effective, it is apparent that dramatic increases in the duration of anesthesia are observed by each route tested. The duration of anesthesia resulting from the intravenous administration of 50 mg./kg. of hydroxydione sodium was approximately doubled by the administration of 40 mg./kg. of tetrahydrozoline intraperitoneally; 80 mg./kg. of tetrahydrozoline subcutaneously; or 100 mg./kg. of tetrahydrozoline orally.

EXAMPLE V

Six groups of monkeys were selected for additional testing of tetrahydrozoline as an adjunct to hydroxydione anesthesia. The number of monkeys in each group varied from one to eight. Three of these groups were then treated with 5 mg./kg. of tetrahydrozoline orally followed in two hours by doses of hydroxydione sodium varying from 50 to 100 mg./kg. The other three groups of monkeys each received 25 mg./kg. of hydroxydione sodium intravenously preceded at a two hour interval by oral doses of tetrahydrozoline varying from 2.0 to 5.0 mg./kg. Lower dosages of tetrahydrozoline gave variable results. Three control groups of monkeys were maintained which received 25, 50 and 100 mg./kg. of hydroxydione sodium respectively and no tetrahydrozoline. The time of onset, and duration of anesthesia were recorded. The results are tabulated below.

No. of Monkeys	Tetrahydrozoline (mg./kg.)	Hydroxydione, Sodium (mg./kg.)	Anesthesia	
			Onset (min.)	Duration (min.)
1	5.0	100	6.0	205
1	5.0	75	7.0	192
1	5.0	50	10.0	106
8	5.0	25	10.4	57.5
2	2.5	25	9.0	52.0
1	2.0	25	10.0	17.0
6	none	25	hypnosis only	
3	none	50	7.8	45.0
1	none	100	3.0	90.0

It is apparent that a remarkable synergistic effect is obtained with the above combinations. An intravenous dose of 25 mg./kg. of hydroxydione sodium is not an anesthetic dose for a monkey. However, when 5.0 mg./kg. of tetrahydrozoline is administered orally previous to the above dosage, anesthesia lasting 57.5 min. results. Similarly 5.0 mg./kg. of tetrahydrozoline administered orally 2 hours prior to treatment with 50 and 100 mg./kg. doses of hydroxydione sodium more than doubles the duration of anesthesia resulting from this dosage of the anesthetic.

EXAMPLE VI

Sodium pentobarbital, 1.5 g., and 0.3 g. of tetrahydrozoline were thoroughly blended with an appropriate quantity of starch and the resulting homogeneous dry mixture used to fill 100 gelatin capsules with equal portions of the total batch.

EXAMPLE VII

A homogeneous mixture of the following materials was prepared:

	Grams
2-chlorovinyl ethynyl ethyl carbinol	15.0
Tetrahydrozoline	0.1
Polyethyleneglycol 400 (Carbide and Carbon Chemical Corp.)	6.0

The carbinol and glycol are miscible liquid materials. The tetrahydrozoline is a solid which was thoroughly mixed with the combined liquid ingredients to form a homogeneous mixture. The mixture was then subdivided and used to fill 100 gelatin capsules with equal portions of the total batch.

EXAMPLE VIII

The following materials in the amounts given were placed in each of a group of sterile vials.

	Mg.
Tetrahydrozoline hydrochloride	1
Morphine sulfate	5
Na_2HPO_4	15
Citric acid	9

When 1 ml. of sterile water was added to each of these vials, solutions suitable for parenteral injection were obtained.

EXAMPLE IX

A solution of 5 milligrams of tetrahydrozoline and 25 mg. of hydroxydione sodium in 1 ml. of sterile water was prepared. This solution was then suitable for intravenous administration to an adult *Macaca rhesus* monkey at a dosage of 1 ml. per kilogram of body weight.

EXAMPLE X

A female cat weighing 3.1 kg. was treated with a dose of 70 mg./kg. of chloralose intravenously. This was followed at intervals of 14 minutes and 39 minutes respectively with 50 mcg./kg. and 100 mcg./kg. of tetrahydrozoline intravenously. The animal slept for approximately 26 hours after which time it was revived by application of an electric heating pad. When a similar dose of tetrahydrozoline was administered without the chloralose no hypnotic effect was observed. An identical dose of chloralose alone produced an anesthetic effect lasting from three to four hours.

EXAMPLE XI

A composition was prepared consisting of 150 milligrams of chloral hydrate and 1 mg. of tetrahydrozoline homogeneously blended with an appropriate quantity of starch. The dry mixture was transferred to a gelatin capsule in which form it was suitable for oral administration.

What is claimed is:

1. A therapeutic composition comprising the active ingredients tetrahydrozoline and a central nervous system depressant selected from the group consisting of the 5-substituted alkyl derivatives of barbituric acid and 2-thiobarbituric acid, a tertiary acetylenic carbinol, a water soluble ester of a pregnanolone, chloral, chloral hydrate, chloralose, morphine, and an acid addition salt of morphine.

2. A therapeutic composition as claimed in claim 1 wherein the central nervous system depressant is a tertiary acetylenic carbinol.

3. A therapeutic composition as claimed in claim 1 wherein the central nervous system depressant is sodium pentobarbital.

4. A therapeutic composition as claimed in claim 1 wherein the central nervous system depressant is a water soluble ester of a pregnanolone.

5. A therapeutic composition as claimed in claim 1 wherein the central nervous system depressant is chloral hydrate.

6. A therapeutic composition as claimed in claim 1 wherein the central nervous system depressant is an acid addition salt of morphine.

7. A process which comprises administering tetrahydrozoline to an animal at the same time that there is administered a central nervous system depressant selected from the group consisting of the 5-substituted alkyl derivatives of barbituric acid and 2-thiobarbituric acid, a tertiary acetylenic carbinol, a water soluble ester of pregnanolone, chloral, chloral hydrate, chloralose, morphine, and an acid addition salt of morphine, so that the periods of pharmacological effectiveness of the two materials overlap.

No references cited.