United States Patent Office

3,784,688

Patented Jan. 8, 1974



3,784,688

# ANTI-ANXIETY COMBINATION

Bernard Beer, Princeton, Donald E. Clody, Somerset, John R. Vogel, South Bound Brook, and Zola P. Horovitz, Princeton, N.J., assignors to E. R. Squibb & Sons, Inc., Princeton, N.J.

No Drawing. Filed Oct. 19, 1971, Ser. No. 190,691

Int. Cl. A61k 27/00

U.S. Cl. 424—244 1 Claim

## ABSTRACT OF THE DISCLOSURE

An anti-anxiety combination is provided having substantially no sedative side effects and comprising a chlordiazepoxide-type compound or pyrazolopyridine carboxylic acid or ester and a xanthine-type compound.

The present invention relates to an anti-anxiety combination having substantially no sedative or drowsiness side effects and which includes a chlordiazepoxide-type compound or a pyrazolopyridine carboxylic acid or ester in combination with a xanthine-type compound, such as theophylline or caffeine.

The use of benzodiazepines such as chlordiazepoxide or diazepam as tranquilizers and anti-anxiety agents is well-known in the art. These compounds have been found to have remarkable anti-anxiety properties. However, they also have been found to produce significant side effects, namely drowsiness and sedation. The use of chlodiazepoxide, for example, is therefore limited to applications where its sedative side effects will be of little or no concern. Thus, chlordiazepoxide would not be indicated for a patient in an anxious state if the patient must drive an automobile or function in any manner where he must be alert. In such cases, other anti-anxiety drugs, possibly less effective than the above mentioned benzodiabepines, would be indicated.

The use of drugs known for their stimulant properties in combinations with chloridazepoxide-type compounds has been suggested. However, such combination have not been acceptable inasmuch as many stimulants or counter-sedative drugs have been found to interfere with the anti-anxiety effects produced by the chlordiazepoxide-type compound.

It has now been found that drowsiness and other sedative side effects produced by chlordiazepoxide-type compounds can be inhibited and in many cases substantially eliminated without adversely affecting their anti-anxiety properties by employing in combination with the chlordiazepoxide-type compounds, xanthine-type compounds.

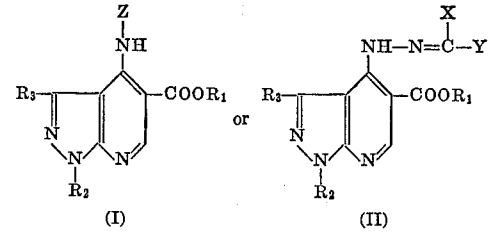
The combination of the chlordiazepoxide-type compound with the xanthine-type compound has been found to possess greater anti-anxiety properties than the chlordiazepoxide-type compound alone, without having the sedative side effects of the chlordiazepoxide-type compound.

Thus, in accordance with the present invention, chlordiazepoxide-type anti-anxiety effects can be obtained employing relatively inexpensive xanthine-type drugs in combination with relatively small amounts of the more expensive chlordiazepoxide-type compounds, without the adverse sedative side effects inherent in the use of the chlordiazepoxide compound alone.

Further, in accordance with the persent invention, anti-anxiety combinations are provided comprising pyrazolopyridine carboxylic acids or esters and a xanthine-type compound.

The pyrazolopyridine compounds which can be employed in the anti-anxiety combinations of the invention can be represented by the structures





(I) (II)

wherein $R_1$ is hydrogen, alkyl, or phenyl-lower alkyl, $R_2$ is lower alkyl, phenyl, phenyl-lower alkyl, $R_6$,$R_7$-phenyl-lower alkyl or cycloalkyl-lower alkyl, $R_3$ is hydrogen, lower alkyl, phenyl or $R_6$,$R_7$-phenyl, Z is

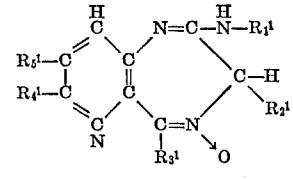
or $R^4$,$R_4$ is hydrogen, lower alkyl, lower alkanoyl or phenyl, $R_5$ is hydrogen, lower alkyl or lower alkanoyl, $R_6$ and $R_7$ each is halogen, lower alkyl or lower alkoxy, X is hydrogen, lower alkyl, hydroxy-lower alkyl, phenyl, $R_6$,$R_7$-phenyl, phenyl-lower alkyl or $R_6$,$R_7$-phenyl-lower alkyl, Y is lower alkyl, hydroxy-lower alkyl, phenyl, $R_6$,$R_7$-phenyl, phenyl-lower alkyl or $R_6$,$R_7$-phenyl-lower alkyl, and together X and Y are cyclo-lower alkyl or 5-nitrofuryl, and acid addition salts thereof.

The above-described pyrazolopyridine compounds of Formulate I and II and methods for their preparation are fully disclosed in copending U.S. patent applications Ser. No. 833,672, filed June 16, 1969, Ser. No. 42,415, filed June 1, 1970 and Ser. No. 41,568, filed May 28, 1970.

Examples of specific pyrazolopyridine compounds which can be employed herein include, but are not limited to, 1-ethyl-4-(isopropylidenehydrazino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, its ethyl ester and its ethyl ester hydrochloride salt, and 4-(butylamino)-1-ethyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid, ethyl ester. Other pyrazolopyridine compounds suitable for use herein are disclosed in the above-identified copending applications.

The chlordiazepoxide-type compounds which can be utilized in the combination of the invention have the generic formula

(III)



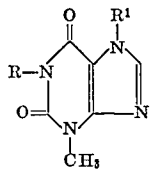
wherein $R_1^1$ represents a member of the group consisting of hydrogen, lower alkyl, lower alkenyl, hydroxy-lower alkyl and lower alkoxy-lower alkyl, $R_2^1$ represents a member of the group consisting of hydrogen and lower alkyl, $R_3^1$ represents a member of the group consisting of phenyl, halo-phenyl, nitrophenyl and lower alkoxyphenyl, $R_4^1$ and $R_5^1$ each represents a member of the group consisting of hydrogen, halogen and lower alkyl, and acid addition salts thereof.

A complete disclosure including examples and methods of preparation of chlordiazepoxide-type compounds suitable for use in the combination of the invention is set out in U.S. Pat. No. 2,893,992.

Examples of specific chlordiazepoxide-type compounds which are particularly suitable for use herein include, but are not limited to, chlordiazepoxide, that is 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide, and salts thereof.

The xanthine compounds which can be employed in the combination of the invention have the following structure:

(IV)



where R and $R^1$ are lower alkyl having from 1 to about 8 carbons such as methyl, ethyl, propyl, isopropyl, t-butyl, pentyl, hexyl, 2-methylheptyl, heptyl, octyl and the like. Examples of suitable xanthines include 1,3-dimethylxanthine, 3,7-dimethylxanthine and 1,3,7-trimethylxanthine.

In order to produce the desired anti-anxiety effects with substantially no drowsiness or sedative-side effects, the combinations of the invention should be formulated to contain a weight ratio of xanthine compound (A) and chlordiazepoxide type compound (B) or pyrazolopyridine compound (C) of within the range of from about 2:1 (A:B or C) to about 15:1 (A:B or C) and preferably from about 5:1 to about 10:1.

Preferred combinations of the present invention include theophylline or caffeine (A) and chlordiazepoxide (B) in a weight ratio (A:B) to each other ranging from 5:1 to 10:1, and theophylline or caffeine (A) and 1-ethyl-4-(isopropylidenehydrazino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, ethyl ester hydrochloride (C) in a weight ratio (A:C) to each other ranging from 5:1 to 10:1.

The combinations of the invention are useful in the alleviation of anxious states without imparting sedation or drowsiness in mammalian species, such as rats, dogs or cats. They can be formulated in various forms, such as tablet, solutions for interaperitoneal injection, or elixir. and may be administered 1 to 3 times daily to provide a dosage of active ingredients within the range of from about 0.3 mg./kg. of body weight to 10.0 mg./kg. of body weight with the preferred range being from 1.5 mg./kg. of body weight to about 5.0 mg./kg. of body weight, upon each administration.

Suitable carrier materials include, for example, water, gelatin, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical preparations can be in solid form (e.g., as tablets, dragées, suppositories, capsules); in semi-solid form (e.g., as salves) or in liquid form (e.g., as solutions, suspensions or emulsions). They may be sterilized and/or contain additives such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. The aforesaid preparations may further be compounded with other therapeutically valuable substances such as with compounds having antibacterial activity.

The test utilized in determining the activity of the combinations of this invention is described in "A Simple and Reliable Conflict Procedure for Testing Anti-Anxiety Agents," J. R. Vogel, B. Beer, and D. E. Clody; Psychopharmacologia 21: 1971, and is summarized below.

Forty naive adult male Holtzman rats (approximately 170 g.) are randomly divided into five groups and deprived of water for 48 hours prior to the test session. Food is available in the home cage at all times.

The apparatus is clear Plexiglas box (38 x 38 cm.) with a black Plexiglas compartment (10 x 10.5 cm.) attached to one wall. An opennig (5 x 7.5 cm.) leads from the large box to the small compartment. The entire apparatus has a stainless steel grid floor. A water bottle with a metal drinking tube is fitted to the outside of the small compartment, so that the tube extended 2 cm. (through a 1-cm. hole) into the box at a height of 3 cm. above the grid. A drinkometer circuit is connected between the drinking



tube and the grid floor of the apparatus, so that the subject completed the circuit whenever it licked the tube. The apparatus was placed in a quiet area of the laboratory.

Various experiments have indicated that rats lick in bursts, and that lick rate within a burst is relatively constant at about seven licks per second. Because subjects frequently extend the mouth over the tube while licking (thereby locking up the drinkometer circuit), it is difficult to measure the number of licks. To provide a reliable measure of consummatory behavior, the drinkometer was connected to a circuit that produced seven pusles per second whenever the subject was in contact with the tube. Each pulse was counted as equivalent to one lick.

Shock is administered to each subject by switching the connections to the drinking tube and grids from the drinkometer to a Grason-Stadler Shocker (Model E1064GS) set at 0.5 ma. Thus, unscrambled shock was applied between the drinking tube and grid floor.

Thirty minutes after intraperitoneal injection, each subject is placed in the apparatus. Subject is allowed to find the drinking tube and complete 20 licks before shock (available at the tube for 2 seconds) is administered. The subject controlled shock duration by withdrawing from the tube. A 3-minute times is automatically started at the termination of the first shock. During the 3-minute period, shocks are delivered following each twentieth lick. The number of shocks delivered during the 3-minute session is recorded for each subject and is a direct indication of anti-anxiety effects of the drugs administered. Because the primary interest in the effects of drugs on behavior that is suppressed by punishment, and since motivation under the deprivation conditions imposed in this procedure are maximum, non-shocked animals are not included in these experiments.

Drugs are prepared as solutions in distilled water or suspensions in agar so that each cubic centimeter contained 1 kg. of body weight dosage. All statistical comparisons were made using Mann-Whitney U test (two-tailed).

The following examples are illustrative of this invention.

## EXAMPLE 1

The effect of theophylline tht is, 1,3-dimethylxanthine (25 mg./kg.) alone, chloridazepoxide (4.0 mg./kg.) alone and a combination of theophylline and chlordiazepoxide were tested in the rat conflict procedure described above. Saline solution was employed as a control. Test results obtained are set out in Table I below.

TABLE I

| Mean No. of Shocks | |
|---|---|
| Saline | 4.0 |
| Theophylline (25 mg./kg.) | 5.75 |
| Chlordiazepoxide (4.0 mg./kg.) | 6.87 |
| Theophylline (25 mg./kg.) and chlordiazepoxide (4.0 mg./kg.) | 13.25 |

As seen from the above results, the administration to rats of the combination of theophylline and chlordiazepoxide in accordance with the present invention results in a significantly greater number of shocks taken on conflict that when either of theophylline or chloridiazepoxide is administered alone. These data indicate that the anti-anxiety effect produced by a combination of theophylline and chlordiazepoxide is significantly greater than the anti-anxiety effect produced by either alone.

## EXAMPLE 2

The effect of theophylline (25 mg./kg.) alone, 1-ethyl-4-(isopropylidenehydrazino)-1H-pyrazolo-[3,4-b]-pyridine-5-carboxylic acid, ethyl ester, hydrochloride (hereinafter referred to as pyrazolopyridine) (1 mg./kg.) alone and a combination of these two drugs in accordance with the invention were tested in the rat conflict procedure described above. Saline solution was employed as a control. Test results obtained are set out in Table II.

TABLE II

| Mean No. of Shocks | |
|---|---|
| Saline | 3.14 |
| Theophylline (25 mg./kg.) | 7.14 |
| Pyrazolopyridine (1.0 mg./kg.) | 5.3 |
| Theophylline (25 mg./kg.) and pyrazolopyridine (1.0 mg./kg.) | 11.2 |

As seen from the above results, the administration to rats of the combination of the invention results in a significantly greater number of shocks taken on conflict than when either of theophylline or pyrazolopyridine is administered alone. These data indicate that the anti-anxiety effect produced by the combination of the invention is significantly greater than the anti-anxiety effects produced by either alone.



What is claimed is:

1. A method for treating anxiety in an anxious host which comprises administering to the anxious host a composition comprising chlordiazepoxide and caffeine, wherein the weight ratio of caffeine to chlordiazepoxide is from about 2:1 to about 15:1.

**References Cited**

Chem. Abst. 71—79575p (1909).
Chem. Abst. 71—24725g (1969).
Chem. Abst. 69—50886c (1965).

STANLEY J. FRIEDMAN, Primary Examiner

U.S. Cl. X.R.

424—253