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α-[(p-CHLOROPHENYL)-α-PHENYL]-4-PYRIDYL CARBINOL AS A POTENTIATING AGENT

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This invention relates to novel composition and method of potentiating ataractic, analgesic, hypnotic, and myorelaxing drugs.

This application is a continuation-in-part of application Serial No. 687,375, filed October 1, 1957, now abandoned. It is a primary object of the present invention to provide compounds capable of potentiating the action of ataractic, analgesic, hypnotic and myorelaxing drugs, thus making it possible to reduce the dosage of these drugs as routinely administered in the therapeutic practice; the advantages thus achieved need hardly be outlined since it is known in the medical art how dangerous those drugs are, due to their inherent toxicity. Furthermore, treatments very often must be continued for long periods of time and thus, give rise to the danger of chronic toxicity. Another important object of the present invention is to provide nontoxic potentiating compounds for the above listed drugs. The potentiating compounds of the invention not only are such as to exhibit no unpleasant side effects when administered in conjunction with any of the ataractic, analgesic, hypnotic and myorelaxing drugs referred to above, but also are themselves inert and harmless substances if administered alone.

Among the ataractic, analgesic, hypnotic, and myorelaxing drugs liable to be potentiated according to the method of this invention the following can be mentioned:

Barbiturates in general, such as 5-phenyl-5-ethyl-barbituric ("Phenobarbital") and 5-ethyl-5-(1-methyl-butyl)-barbituric acids ("Pentobarbital");

Opium alkaloids, such as morphine and total extracts of opium alkaloids ("Pantopon");

Analgesic-spasmolytic drugs, such as 1-alkyl-4-phenyl-piperidine-4-alkyl carbonate and derivatives thereof ("Pethidine");

Ataraxics such as "Meprobamate" (2-n-propyl-1,3-propanediol-dicarbamate), and "Fenaglycodol" 2-p-chlorophenyl-3-methyl-2,3-butanediol;

Analgesics of the "Methadone" class, such as 6-dimethylamino-4, 4-diphenyl-3-heptanone and derivatives thereof;

Skeletal-muscle relaxing, curare-like drugs, such as tris-[diethylamino - ethyl-hydroxy]-1,2,3-benzene-triiodoethylate ["Gallamine"] and similar compounds;

Myorelaxing drugs, such as "Methocarbamol" (3-o-methoxyphenoxy-2-hydroxypropl-carbamate), and derivatives thereof.

Illustrative of the potentiating compounds which may be used in performing the method and in forming the compositions according to the present invention are: α - [(-p-chlorophenyl)-α-phenyl]-4-pyridyl - carbinol; and the nontoxic, pharmacologically acceptable salts thereof.

α-[P-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol have

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proven to be valuable as an agent capable of potentiating the action of analgesics, tranquilizers, sedatives and hypnotics and, in general, the neurotropic drugs acting on the nervous central system. The above identified compound has also shown a marked potentiating action towards skeletal-muscle loosening, curarelike drugs, and myorelaxing drugs in general.

Thus, according to the invention, we provide a medicinal preparation comprising a centrally acting drug selected from the group consisting of barbiturates, opium alkaloids, 1-methyl-4-phenyl-piperidine-4-ethyl carbonate, 2 - methyl-2-n-propyl-1,3 - propanediol-dicarbamate, 6-dimethylamino-4,4-diphenyl-3-heptanone and 2-p-chlorophenyl-3-methyl - 2,3-butanediol, and α - [(p-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol, which acts as a potentiating compound capable of substantially increasing the effectiveness of the centrally acting drug.

Also, according to the invention, we provide a medicinal preparation comprising a myorelaxing drug selected from the group comprising tris-[diethylamino-ethyl-hydroxy] - 1,2,3-benzene triiodoethylate and 3-o-methoxyphenoxy-2-hydroxy-propyl-carbamate, and their derivatives, and α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl - carbinol, which acts as a potentiating compound capable of substantially increasing the myorelaxing effectiveness of said myorelaxing drug.

Our invention provides, moreover, a method of potentiating the ataractic, analgesic and hypnotic effect of a centrally acting drug selected from the group consisting of barbiturates, opium alkaloids, 2-methyl-2-n-propyl-1,3, propanediol dicarbamate, 1-alkyl-1-phenyl-piperidine-4-alkyl carbonates, 6 - dimethylamino-4,4-diphenyl-3-heptanone and 2-p-chlorophenyl-3-methyl-3,3 - butanediol, which comprises administering internally, for combined physiological action with said drug, a suitable dosage of α[(p-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol.

According to our said invention, a method is also provided for potentiating the myorelaxing effect of a muscle-relaxing drug selected from the group comprising tris-[diethylaminoethyl - hydroxy]-1,2,3-benzene triiodoethylate and 3-o-methoxy-phenoxy-2-hydroxpropyl - carbamate, and their derivatives, which comprises administering internally, for combined physiological action with said myorelaxing drug, a suitable dosage of α-[-p-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol.

The potentiating compound of the instant invention may be prepared by a number of different chemical processes, for example by refluxing 4-p-chlorobenzoyl pyridine with an organic magnesium compound of the structure X—Mg—R wherein X is an atom of a halogen having an atomic weight higher than 19 and R is a member selected from the group consisting of an alkyl radical having not more than 5 carbon atoms, a phenyl radical, and a phenylalkyl radical having not more than 11 carbon atoms, as disclosed in our application for Letters Patent of the United States Serial No. 687,375, filed October 1, 1957, of which this application is a continuation-in-part.

In the practical use of the potentiating compound of the invention it has been found expedient to administer the potentiating compound first, and in general from 30 minutes to 1 hour before administering the drug whose

effect it is desired to potentiate. Specially made clinical tests have shown, however, that the potentiating effect obtained by simultaneously administering the potentiating compound and the drug to be potentiated is virtually the same obtained by administering the potentiating compound first.

Thus, the compositions of this invention may be advantageously employed in multiple doses and in timed delay tablets and the like. Due to the relative insolubility of the potentiating compound of the invention in aqueous media they do not lend themselves to administration by injections so that the preferred form of administration ought to be one permitting the diffusion of the potentiating compound through the organism without the intermediary of liquid media. Thus, administration by tablets and suppositories is preferred but this is not, of course, the only form of administration, since any other form which does not require solubilization of the potentiating compound is equally well adapted to the purpose.

As has been outlined hereinbefore, the potentiating compound of the invention is itself harmless and an inert substance since the product is tolerated by animals (mice) in doses up to 3 gms. per kgm. body weight (acute toxicity), and for 40 days at the daily dose of 50 mgms. per kgm. body weight. The latter dose is at least 100 times the dosage required in order that an appreciable potentiating effect might be observed in the same animals.

Clinical tests have been carried out on human beings by administering the potentiating compound of the invention alone; no alteration in the morbid pattern of the patients thus treated has ever been observed.

Generally speaking, the selected potentiating compound will be used in single doses of from about 10 to about 20 mgms., the daily dose being liable to vary from about 20 to about 100 mgms. The amount of potentiating compound will, of course, vary widely depending on the drug to be potentiated, the potentiating effect desired and the nature of the disease being treated.

Also, the amount of the selected drug to be potentiated will vary widely depending on the physiological effect to be achieved. Generally speaking, it is desirable to employ from about the standard effective therapeutic dose of the selected drug to about one-third the standard dose.

The following Table 1 reports practical examples of modes of practicing the method of the invention and making the medical preparations therefor.

Table 1

Ex. No.	Syndrome or painful affection under treatment	Treated cases, number	Drug to be potentiated	Dosage, mgms.	Potentiating compound	Dosage, mgms.	Observations
1	Insomnia, nightmares.	4	5-phenyl 5-ethyl barbituric acid (orally).	100 (daily)	α-[(p-chlorophenyl)-α-phenyl] 4-pyridyl-carbinol.	20 (daily)	Normal sleep, for all 4 patients, of prolonged duration as compared with that obtained with the barbiturate alone.
2	Epileptic seizures	7	do	do	do	do	Clinical pattern nearly unaltered.
3	Patients needing narcosis before surgical operations.	20	Opium alkaloids (intramuscularly). + sodium tiopental (intravenously).	20 / 50 (single dose).	do	20 (single dose).	A strong potentiating action towards the opium alkaloids is observed. The potentiating compound has been administered after the opium alkaloids and before the tiopental. Very intensive anaesthetic effect.
4	Patients having been subjected to very painful surgical operations.	19	1-methyl-4-phenyl piperidino-4-ethyl carbonate hydrochloride (intramuscularly).	50 (single dose).	do	20	The analgesic effect of the drug appears to be markedly potentiated and lasts from 6 to 16 hrs.
5	Patients having been subjected to very painful surgical operations on the skeleton.	15	6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride (intramuscularly).	10 (single dose).	do	20 (single dose).	The potentiated analgesic effect lasted from 10 hrs. to 22 hrs. and permitted the patients to rest the night immediately following the operation.
6	do	50	5-phenyl-5-ethyl-barbituric acid (orally).	30 (single dose).	do	do	48 patients out of the 50 treated brilliantly responded to the treatment. The two nonresponsive cases were due to particular psychic conditions of the patients who successively become inmates of a Psychiatric Hospital.
7	do	10	5-ethyl-5-(1-methyl-butyl)-barbituric acid-(orally).	100	do	20	A very sound sleep, lasting from 12 hrs. to a maximum of 22 hrs. is observed.
8	Patients having been subjected to very painful surgical operations on the skeleton (Control group).	10	None	Nil	do	20	Clinical pattern unaltered. Neither pharmacological action nor unpleasant side effects are observed.
9	Patients needing a myorelaxing treatment during progress of surgical operations.	15	Tris-[diethylamino-hydroxy]-1,2,3-benzene triiodoethylate (a curare-like drug) (intramuscularly).	20 (single dose).	do	20	The skeletal-muscle relaxing action of the potentiated curare-like drug has an intensity which is 3 times that afforded by the curare-like drug administered alone.
10	Acute schizophrenia.	5	Reserpine alkaloids (orally).	2 to 5 (daily)	do	40	A marked improvement in the general conditions, accompanied by attenuation of the hallucinations, delirious fantasies and restlessness. The patients, yet after the first few days of treatment needed no restraining means and became accessible to persuasive psychotherapy.
11	Catatonic schizophrenia.	3					
12	Chronic schizophrenia.	4					
13	Neuroses such as anxiety neuroses, hypochondrias, neurosthenic states with insomnia, neurasthenic states with neurovegetative troubles.	25	2-methyl-2-n-propyl-1,3-propanediol-dicarbomate ("Meprobamate") (orally).	600 to 800 (daily).	do	20 to 40 (daily).	Very remarkable improvements in the 80% of the treated cases. A notable reduction of anxiety, restlessness and muscular strains was observed yet within the first week of treament. The painful headaches and sexual derangements, characteristic of these, neuroses, rapidly disappeared. The routine dosage of "Meprobamate" alone is from 800 to 1,600 mgms. daily.
14	Obsessional neuroses.	12	do	do	do	20 to 40	Very remarkable improvements in the 80% of the treated cases. Disappearance of the sexual derangements and painful headaches ("nail-in-the-head" feeling). Substantial relief from anxiety states.

It is believed that the casuistry reported hereinbefore (199 cases) is sufficient to illustrate the best mode of practicing the process of the invention, being it understood that the above examples are merely illustrative and that it is not desired to be limited except as set forth in the claims appended to this specification.

With particular respect to the potentiating effect shown by the potentiating compounds of the invention towards the typical myorelaxing activity of "Methocarbamol" (3-o-methoxy-phenoxy-2-hydroxypropyl-carbamate), the preliminary pharmacological experiments have given outstandingly encouraging results. The potentiating compound used in these experiments was α[(p-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol.

In the course of one set of experiments, the length of time, during which the righting reflex was absent following the administration of a potentiated and a non-potentiated myorelaxing drug respectively, was measured in mice.

Several groups of mice, each group comprising 10 animals, were injected with different doses of methocarbamol, alone and potentiated with [α(p-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol.

Table 2

Lack of righting reflex (r.r.), in minutes, methocarbamol alone, nonpotentiated				Lack of righting reflex (r.r.), in minutes, methocarbamol, potentiated with 60 mgm. of potentiating compound			
Number of animals	Mgm./kg.	Minutes	Number of animals without r.r.	Mgm./kg.	Minutes	Number of animals without r.r.	Number of animals
10	250	0	0	250	48	10	10
10	325	27	3	325	146	10	10
10	350	50	10	400	(1)	10	10
10	400	70	10	-----	----	----	----
10	500	95	10	-----	----	----	----

[1] More than 4 hours.

The data tabulated above show that the righting reflex (r.r.) is absent for a relatively great length of time, when the myorelaxing drug is potentiated, whereas the non-potentiated drug give times of absence of righting reflex which are considerably shorter.

These preliminary pharmacological data are believed to be a sufficient showing of the potentiating effect of α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol towards the myorelaxing activity of Methocarbamol.

What is claimed is:

1. A medicinal preparation comprising a centrally acting drug selected from the group consisting of barbiturates, opium alkaloids, 1-alkyl-4-phenyl-piperidine-4-alkyl carbonates, 2-methyl-2-n-propyl-1,3-propanediol-dicarbamate, 6-dimethylamino-4,4-diphenyl - 3 - heptanone, and 2-p-chlorophenyl-3-methyl-2,3-butanediol, and the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is normally inactive and capable of substantially increasing the effectiveness of the selected centrally acting drug.

2. A medicinal preparation comprising a muscle relaxing drug selected from the group consisting of tris-(diethylamino-ethyl-hydroxy)-1,2,3-benzene triiodoethylate and 3-o-methoxy-phenoxy-2-hydroxypropyl - carbamate, and their derivatives, and the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is a normally inactive compound capable of substantially increasing the myorelaxing effectiveness of said muscle-relaxing drug.

3. The method of enhancing the ataractic, analgesic and hypnotic effect of a centrally acting drug selected from the group consisting of barbiturates, opium alkaloids, 1-alkyl-4-phenyl-piperidine-4-alkyl carbonates, 2-methyl-2-n-propyl - 1,3 - propanediol - dicarbamate, 6-dimethylamino-4,4-diphenyl-3-heptanone and 2-p-chlorophenyl-3-methyl-2,3-butanediol, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol, for combined physiological action with said drug.

4. The method of enhancing the muscle-relaxing effect of a muscle relaxing drug selected from the group comprising tris-(diethylamino-ethyl-hydroxy)-1,2,3 - benzene triiodoethylate and 3-o-methoxy-phenoxy-2-hydroxy-propyl-carbamate, and their derivatives, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol, for combined physiological action with said muscle-relaxing drug.

5. A medicinal preparation comprising a barbiturate, and the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is normally inactive and capable of increasing the effectiveness of said barbiturate.

6. A medicinal preparation comprising a hypnotic drug consisting of opium alkaloids, and the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is normally inactive and capable of increasing the hypnotic effect of said drug.

7. A medicinal preparation comprising a neurotropic drug consisting of a 1-alkyl-4-phenyl-piperidine-4-alkyl carbonate, and the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is normally inactive and capable of increasing the effectiveness of said neurotropic drug.

8. A medicinal preparation comprising the neurotropic drug 2-methyl-2-n-propyl-1,3 - propanediol - dicarbamate, and the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is normally inactive and capable of increasing the effectiveness of said neurotropic drug.

9. A medicinal preparation comprising the analgesic drug 6-dimethylamino-4,4-diphenyl-3-heptanone, and the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is normally inactive and capable of increasing the effectiveness of said analgesic drug.

10. A medicinal preparation comprising the neurotropic drug 2-p-chlorophenyl-3-methyl-2,3-butanediol, and the normally inactive tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is capable of increasing the effectiveness of said neurotropic drug.

11. A medicinal preparation comprising the muscle-relaxing drug tris-(diethylamino-ethyl - hydroxy) - 1,2,3-benzene-tri-iodoethylate, and the normally inactive tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is capable of increasing the effectiveness of said drug.

12. A medicinal preparation comprising the muscle-relaxing drug 3-o-methoxy-phenoxy-2-hydroxy-propyl-carbamate, and the normally inactive tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol which is capable of increasing the effectiveness of said drug.

13. The method of enhancing the hypnotic effect of a hypnotic barbiturate, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol for combined physiological action with the barbiturate.

14. The method of enhancing the effectiveness of an hypnotic drug consisting of opium alkaloids, which comprises administering interally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol for combined physiological action with said hypnotic drug.

15. The method of enhancing the effectiveness of an analgesic and spamolytic drug consisting of a 1-alkyl-4-phenyl-piperidine-4-alkyl-carbonate, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol for combined physiological action with said drug.

16. The method of enhancing the effectiveness of the ataractic drug 2-methyl-2-n-propyl-1,3-propane-diol-dicarbamate, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl-carbinol for combined physiological action with said drug.

17. The method of enhancing the effectiveness of the analgesic drug 6-dimethylamino-4,4,diphenyl - 3 -hepta-

none, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol for combined physiological action with said analgesic drug.

18. The method of enhancing the effectiveness of the ataractic drug 2-p-chlorophenyl-3-methyl-2,3 butanediol, which comprises administering internally the tertiary alcohol-α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol for combined physiological action with said ataractic drug.

19. The method of enhancing the effectiveness of the muscle-relaxing drug tris-(diethylaminoethyl-hydroxy)-1,2,3-benzene triiodoethylate, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl)-α-phenyl]-4-pyridyl carbinol for combined physiological action with said muscle-relaxing drug.

20. The method of enhancing the effectiveness of the muscle-relaxing drug 3-o-methoxy-phenoxy-2-hydroxypropyl-carbamate, which comprises administering internally the tertiary alcohol α-[(p-chlorophenyl-α-phenyl]-4-pyridyl carbinol for combined physiological action with said muscle-relaxing drug.

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