This invention relates to novel composition and method of potentiating ataractic, analgesic, hypnotic, and myorelaxing drugs. This invention 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 potentiating according to the method of the invention the following can be mentioned: Barbiturates in general, such as 5-phenyl-5-ethyl-barbituric ("Phenobarbital") and 5-ethyl-5-(1-methylbutyl)-barbituric acids ("Pentobarbital"); Opium alkaloids, such as morphine and total extracts of opium alkaloids ("Pantopon"); Anagastic-spasmolytic drugs, such as 1-alkyl-4-phenyl-piperidine-4-alkyl carbonate and derivatives thereof ("Pethidine"); Ataractics such as "Meprobamate" (2-n-propyl-1,3-propanediol-dicarbamate), and "Penaglycodol" 2-p-chlorophenyl-3-methyl-2,3-butandiol; 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-triodo-ethylate ("Galamine") and similar compounds; Myorelaxing drugs, such as "Methocarbamol" (3-o-methoxyphenoxo-2-hydroxypropyl-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: a. (p-chlorophenyl)-a-phenyl-4-pyridyl-carbinol; and the nontoxic, pharmacologically acceptable salts thereof. a-(p-chlorophenyl)-a-phenyl-4-pyridyl-carbinol' have 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 a. (p-chlorophenyl)-a-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-triodoethylene and 3-o-methoxy-phenoxo-2-hydroxypropyl-carbamate, and their derivatives, and a. (p-chlorophenyl)-a-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 carbonate, 6-dimethylamino-4,4-diphenyl-3-heptanone and 2-p-chlorophenyl-3-methyl-2,3-butanediol, which comprises administering internally, for combined physiological action with said drug, a suitable dosage of a-(p-chlorophenyl)-a-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-[diethylamino-ethyl-hydroxy]-1,2,3-benzene-triodoethylene and 3-o-methoxy-phenoxo-2-hydroxypropyl-carbamate, and their derivatives, which comprises administering internally, for combined physiological action with said myorelaxing drug, a suitable dosage of a-(p-chlorophenyl)-a-phenyl-4-pyridyl-carbinol.

The potentiating compound of the instant invention may be prepared by a number of different chemical processes, for example by reduction 4-p-chlorobenzoylpyridine 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 as 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 hereinafore, 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 mgs. 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 mgs., the daily dose being liable to vary from about 20 to about 100 mgs. The amount of the 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>
<thead>
<tr>
<th>Sr. No.</th>
<th>Syndrome or painful affection under treatment</th>
<th>Treated cases, number</th>
<th>Drug to be potentiated</th>
<th>Potentiating compound</th>
<th>Dosage, mgs.</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Intestinal sepsis</td>
<td>4</td>
<td>3-phényl-1-ethylbarbiturate sed (orally)</td>
<td>100 (daily)</td>
<td>α-[[chloro-2-phenyl-2 (1)- pyridyl]- carbine]</td>
<td>20 (daily)</td>
</tr>
<tr>
<td>2.</td>
<td>Epileptic seizures</td>
<td>7</td>
<td>do</td>
<td>do</td>
<td>do</td>
<td>Clinical pattern nearly unchanged.</td>
</tr>
<tr>
<td>3.</td>
<td>Patients needing narcosis before surgical operations</td>
<td>20</td>
<td>Opium alkaloids (orally)</td>
<td>20-30 (daily)</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>4.</td>
<td>Patients having been subjected to very painful surgical operations</td>
<td>15</td>
<td>6-methyl-4-phenyl-piperidino-4-ethyl carboline hydricarbochlorine (intramuscularly)</td>
<td>10 (single dose)</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>5.</td>
<td>Patients having been subjected to very painful surgical operations on the skeleton</td>
<td>20</td>
<td>6-methyl-4-ethyl-piperidino-4-ethyl carboline hydricarbonchlorine (intramuscularly)</td>
<td>20 (single dose)</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>6.</td>
<td>do</td>
<td>10</td>
<td>6-methyl-4-ethyl carboline hydricarbonchlorine (intramuscularly)</td>
<td>20 (single dose)</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>7.</td>
<td>do</td>
<td>10</td>
<td>5-methyl-1-ethylcarboline sed (orally)</td>
<td>20 (single dose)</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>8.</td>
<td>Patients having been subjected to very painful surgical operations on the skeleton (Control group)</td>
<td>10</td>
<td>None</td>
<td>20 (single dose)</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>9.</td>
<td>do</td>
<td>10</td>
<td>Tri-crotonaline hydroxy 2,2,3-amino-tricarbonylic (an acute-like drug (intramuscularly)</td>
<td>20 (single dose)</td>
<td>do</td>
<td>do</td>
</tr>
</tbody>
</table>

The skeletal-muscle relaxing action of the potentiated curare-like drug has an intensity which is 5 times that afforded by the curare-like drug administered alone. A marked improvement in the general condition, accompanied by diminution of the hallucinations, delusions of grandeur and delusions. The patients, yet after the first few days of treatment, needed no restraining means and became accessible to permissive psychotherapy. Very remarkable improvements in the 80% of the treated cases. A notable reduction of anxiety, restlessness and muscular strain was observed, yet within the first week of treatment. The painful headaches and equal derangements, characteristic of these, were rapidly disappeared. The routine dosage of "Diphorganon" alone is from 500 to 1,000 mgs. daily. Very remarkable improvement in the 80% of the treated cases. Disappearance of the social derangements and painful headaches ("tail-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 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 \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl-carbinoil.

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-potentiating myorelaxing drug respectively, was measured in mice.

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

Table 2

<table>
<thead>
<tr>
<th>Number of animals</th>
<th>Mgm./Kg.</th>
<th>Minutes</th>
<th>Number of animals without Pr.</th>
<th>Mgm./Kg.</th>
<th>Minutes</th>
<th>Number of animals without Pr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>250</td>
<td>0</td>
<td>250</td>
<td>10</td>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>30</td>
<td>250</td>
<td>0</td>
<td>250</td>
<td>10</td>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>50</td>
<td>250</td>
<td>0</td>
<td>250</td>
<td>10</td>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>70</td>
<td>250</td>
<td>0</td>
<td>250</td>
<td>10</td>
<td>0</td>
<td>250</td>
</tr>
</tbody>
</table>

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-potentiating drug gives time 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 \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl-carbinoil 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-\( \alpha \)-propyl-1-3-propanediol-carbamate, 6-dimethylamino-4,4-diphenyl-3-heptanone, and 2-p-chlorophenyl-3-methyl-2,3-butanediol, and the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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 tria(ethylamino-ethyl-hydroxy)-1,2,3-benzene triiodoethylethyl and 3-0-methoxy-phenoxy-2-hydroxypyrrol-carbamate, and their derivatives, and the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil which is normally inactive and 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-\( \alpha \)-propyl-1-3-propanediol-carbamate, 6-dimethylamino-4,4-diphenyl-3-heptanone and 2-p-chlorophenyl-3-methyl-2,3-butanediol, which comprises administering internally the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil, 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 tria(ethylamino-ethyl-hydroxy)-1,2,3-benzene triiodoethylethyl and 3-o-methoxy-phenoxy-2-hydroxypyrrol-carbamate, and their derivatives, which comprises administering internally the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil, for combined physiological action with said drug.

5. A medicinal preparation comprising a barbiturate, and the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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 \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil which is normally inactive and capable of increasing the hypnotic effect of said drug.

7. A medicinal preparation comprising a neurotropic drug consisting of 1-alkyl-4-phenyl-piperidine-4-alkyl carbonate, and the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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-\( \alpha \)-propyl-1-3-propanediol-di-carbamate, and the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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 \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil which is 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 \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil which is capable of increasing the effectiveness of said neurotropic drug.

11. A medicinal preparation comprising the muscle-relaxing drug tris(ethylamino-ethyl-hydroxy)-1,2,3-benzene triiodoethylethyl, and the normally inactive tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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 \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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 \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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 internally the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil for combined physiological action with said hypnotic drug.

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

16. The method of enhancing the effectiveness of the ataractic drug 2-methyl-2-\( \alpha \)-propyl-1-3-propanediol-di-carbamate, which comprises administering internally the tertiary alcohol \( \alpha \)-[p(chlorophenyl)-\( \alpha \)-phenyl]-4-pyridyl carbinoil 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-(p-chlorophenyl)-(a-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-(p-chlorophenyl)-(a-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 triolofethalate, which comprises administering internally the tertiary alcohol -(p-chlorophenyl)-(a-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 3-0-methoxy-phenoxy-2-hydroxypropyl-carbamate, which comprises administering internally the tertiary alcohol-(p-chlorophenyl)-(a-phenyl)-4-pyridyl carbinol for combined physiological action with said muscle-relaxing drug.

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