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PROCESS OF ALLEVIATING DIARRHEA WITH OPTICAL ISOMERS OF PIPERIDYL METHADONE

Richard Baltzly, Tuckahoe, and John C. Seed, Scarsdale, N.Y., assignors to Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y., a corporation of New York

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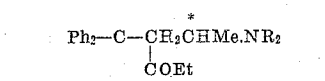
The present invention relates to the separation of piperidyl methadone into its optical isomers, and the discovery of novel therapeutic properties associated with the resolved isomers which are not possessed to any degree by the racemic mixture.

In common with many other alkaloids, the natural analgesic, morphine, has several types of physiological action. Of these, at least two have been utilized by medicine. The most prominent utility of morphine is as an analgesic, but a second use known for ages is to check diarrhea. This action is of a special character and unusually desirable. Most spasmolytics have some constipating effect; this is, however, due to general inhibition of intestinal motility. As a consequence, although the intestinal contents are retained, digestion is interfered with since the churning and mixing actions of the intestine are repressed. The atropine-like spasmolytics also produce marked dryness of the mouth, blurring of vision and inhibition of urination in doses that inhibit intestinal activity.

Morphine, however, has the hitherto unique property of suppressing only the propulsive action of the intestine while allowing the churning muscular contractions to continue. As a consequence, opiates tend to inhibit diarrhea without interfering with digestion.

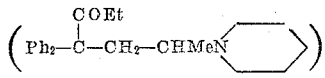
Unfortunately, since morphine is a notorious habit-forming drug, its use for the above purpose is greatly restricted.

The amidone or methadone type of synthetic analgesic have the formula:



wherein R represents lower alkyl groups. It will be observed that the carbon atom marked with the asterisk is asymmetric, wherefore, each of these compounds normally exists as a pair of optical antipodes. Where such a pair of antipodes possesses physiological action, it is commonly found that one of the isomers has appreciably more activity than the other, but both as a rule have the same type of activity. Thus, in the ephedrine-ψ-ephedrine family, *l*-ephedrine is about five times as active as *d*-ephedrine and about 10 times as active as *d*-ψ-ephedrine. Similarly, *l*-epinephrine is about ten times as strong a pressor agent as *d*-epinephrine. All, however, are pressors of essentially the same sort. Among many natural alkaloids, of course, such generalizations are incomplete since one antipode is unkown.

In the case of piperidyl methadone



we have discovered a most usual exception to the rule discussed above. It has been observed clinically that, whereas, 10 mg. of the *l*-isomer intramuscularly produces

analgesia equivalent to that of 10 mg. of morphine, the *d*-isomer in doses up to 40 mg. produces no effect distinguishable from that of placeboes. This indicates that the analgesic activity resides entirely or substantially in the *l*-isomer. Freed of the *d*-isomer, the *l*-isomer, by injection, is twice as potent as the *dl* mixture, and appears to produce fewer side effects.

On the other hand 40 mg. of the *d*-isomer by mouth every four hours has been effective in controlling diarrhea in patients. The fact that the *l* and *d*-isomers are qualitatively different in animals lends support to the belief that the *d*-isomer will be free of narcotic addiction liability in man. The *d*-isomer in doses of 2 mg./kg., I.V., causes only respiratory stimulation in the dog, whereas, the *l*-isomer in like doses causes the respiratory depression typical of addicting, narcotic-type analgesics. In the mouse, although both compounds are capable of suppressing spinal reflexes, the *d*-isomer is roughly 1/24 as potent as the *l*, and gives a dose response curve quite different from that of morphine and other addicting narcotics.

Thus, whereas neither the *l*-isomer nor the unresolved *dl* drug can be used to suppress diarrhea due to the danger of habituation and addiction, the dextro-isomer is highly effective and shows promise of a freedom from side effects. It thus opens up for the first time the possibility of obtaining an effective nonnarcotic agent for the control of diarrhea which does so by inhibiting propulsive activity without interfering with normal churning activity so essential to proper digestion. At the same time, the *l*-isomer shows promise of being a superior analgesic of the narcotic type.

The resolution of the *d-l* mixture can be accomplished by conventional methods—somewhat complicated by the reluctance of this family of compounds to crystallize. The *d*-isomer is conveniently separated as the *d*-acid tartrate. From the mother liquors, which are enriched in the *l*-isomer, that antipode can be obtained as the *l*-acid tartrate, the *l*-acid malate or as the hydrochloride. Separation of the *l*-acid tartrate is the most efficient, but since the *l*-tartaric acid is expensive and difficult to obtain, we prefer to crystallize the *l*-hydrochloride. This technique using the *d*-base-*d*-tartrate and the *l*-base hydrochloride has the further advantage of giving directly those salts that are to be employed therapeutically.

EXAMPLE 1

D-piperidyl methadone d-acid tartrate

Fifty g. (⅛ mole) of *d-l*-piperidyl methadone hydrochloride monohydrate was dissolved in warm water, cooled and basified with conc. ammonium hydroxide solution. The precipitated oil was taken into a mixture of ether and petroleum ether, washed with water and dried briefly over potassium carbonate. The solution was then decanted, evaporated to small volume, and added to a solution of 22 g. (0.145 mole) of *d*-tartaric acid in 1 l. of acetone. Anhydrous ether (about 500 cc.) was added to incipient turbidity and the solution was seeded and stirred mechanically overnight. In the morning the supernatant solution was decanted from the separated crystals which were washed with acetone. The washings were added to the mother-liquors and 10 g. of *d*-enriched base (from previous operations) together with 4.5 g. of *d*-tartaric acid was added. From this mixture a second crop of *d*-tartrate was obtained. The combined salts were recrystallized from acetone giving 18 g. (0.036 mole) of pure *d*-tartrate which melts at 182–183° C.

The *d*-hydrochloride was obtained from the *d*-tartrate by conventional procedures. It crystallizes from acetone-ether mixture and melts at 178–179° C.

$[\alpha]_d^{30°} = +93.8° \pm 0.2°$ (4% solution in 95% ethanol)

EXAMPLE 2

L-piperidyl methadone l-acid tartrate

The mother liquors from the crude crops of *d*-base-*d*-tartrate (Example 1) were evaporated. The residue was dissolved in water and the solution was basified with ammonia. The bases, taken into ether-hexane, dried and evaporated, were added to a solution of 22 g. of *l*-tartaric acid in 1 l. of acetone. The solution was seeded with *l*-tartrate and stirred overnight. The precipitated salt weighted 29 g. (0.058 mole).

The *l*-base *l*-acid tartrate melts at 182–183° after recrystallization from acetone.

The *l*-hydrochloride prepared from the *l*-tartrate melts at 178–179°.

$[\alpha]_D^{30°} = -93° \pm 0.3°$ (4% in 95% ethanol)

EXAMPLE 3

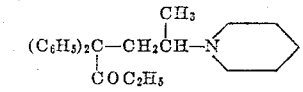
L-piperidyl methadone hydrochloride from l-enriched material

On hundred g. (0.22 mole) of *l*-enriched base from the separation of *d*-tartrate crops, was disssolved in 500 cc. of acetone. About 500 cc. of dry ether was added and the base was neutralized by passing in a current of hydrogen chloride gas. Seeds of *l*-hydrochloride were added and the solution was allowed to stand overnight. There was obtained 37 g. of *l*-hydrochloride melting at 175.5–177°. Recrystallization from acetone-ether rendered this material completely pure.

The *l*-malate can be obtained in acetone-ether solution from *l*-enriched material after seeding. It melts at 127.5–128.5° and can be recrystallized from acetone-ether. The yield obtained through it, however, is not superior to that with the hydrochloride.

What we claim is:

1. A process for the alleviation of diarrhea which comprises the administration to a person suffering from diarrhea of a compound selected from the class consisting of the optically isomeric free base and the acid addition salts thereof, said free base having the formula:



2. A process for the allevation of diarrhea which comprises the administration to a person suffering from diarrhea of *d*-piperidyl methadone.

3. A process for the alleviation of diarrhea which comprises the administration to a person suffering from diarrhea of *d*-piperidyl methadone *d*-acid tartrate.

4. A process for the alleviation of diarrhea which comprises the administration to a person suffering from diarrhea of *d*-piperidyl methadone hydrochloride.

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