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3,755,416

NORACYMETHADOL CARBAMATES

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5 Claims

ABSTRACT OF THE DISCLOSURE

Noracymethadol carbamates, analgesically active and useful in treatment of heroin addiction.

BACKGROUND OF THE INVENTION

Methadon (systematically named as *dl*-4,4-diphenyl-6-dimethylamino-3-heptanone) is analgesically active with a low addiction liability. The compound, therefore, became a candidate for use in the treatment of heroin addiction since it afforded the possibility of repressing the symptoms accompanying the withdrawal of heroin from persons addicted thereto. An addict in the process of withdrawing from heroin is able to do so by taking a daily dose of methadon and still perform useful work and earn a living although he may become addicted to methadon in the process. Furthermore, the addict in order to support his or her habit, need no longer resort to armed robbery, burglary or prostitution. Methadon is orally active and the daily cost for an addict has been in the neighborhood of \$1–\$1.50 as compared to the daily cost of heroin which is said to be from \$20–\$60 day.

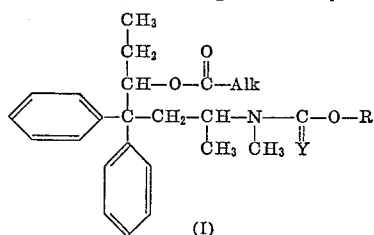
Methadon, however, does suffer from one drawback as a heroin treatment drug in that it can be "main-lined" as is heroin and is more addictive, in that it produces more euphoria, when administered by this route than when taken orally. Secondly, it would be desirable to have a compound capable of substituting for heroin in an addict which would have a somewhat longer duration of action than methadon so that it would not be necessary for the addict to report daily to the maintenance clinic in order to receive his medication.

Methadon was discovered in Germany during World War II and has been marketed as an analgesic since the conclusion of hostilities in most countries of the world. The reduction products of methadon are alcohols known as methadols and the acyl derivatives of the alcohol group are known as acymethadols. Both the methadols and acymethadols are active analgesics. The nor derivatives of methadon (by nor is meant compounds which have a methylamino in place of a dimethylamino group in methadon) are unstable but the nor derivatives of the methadols and acymethadols are quite stable. The noracymethadols are described in U.S. Pat. 3,021,360 issued Feb. 13, 1962.

It is an object of this invention to provide analgesically-active substances having the ability to suppress heroin withdrawal symptoms by the oral route and having a prolonged effect compared to those compounds presently useful for such purpose.

SUMMARY

In fulfillment of the above and other objects this invention provides compounds represented by the formula:



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wherein Alk is methyl or ethyl, Y is O or S, and R is C₁–C₅ alkyl or phenyl. Groups illustrative of R when it is C₁–C₅ alkyl include the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, 2-pentyl, n-amyl, isoamyl, 3-pentyl, 3-methyl-2-butyl, 2-methyl-2-butyl and the like.

Compounds represented by the above formula include the following:

- 10 t-butyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl) carbamate
- neopentyl N-methyl-N-(1-methyl-3,3-diphenyl-4-propionyloxy-n-hexyl) carbamate
- 15 sec-amyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl) carbamate
- n-propyl N-methyl-N-(1-methyl-3,3-diphenyl-4-propionyloxy-n-hexyl) carbamate.

It will be noted that the compounds represented by the above formula possess two asymmetric carbon atoms. Accordingly, four different forms of each compound are possible, these consisting of two diastereoisomeric pairs, each of which can be resolved into dextro- and levorotatory isomers. Since it is not possible at present to assign an absolute spatial configuration to the diastereoisomeric pairs, they have been arbitrarily designated as the α - and β -isomers, the designation α - having been given to that diastereoisomeric pair or more properly, racemic pair, which has the lower solubility.

Both α and β diastereoisomeric pairs have utility in this invention in that both are analgesically active. With the α -*dl* pair, the *l*-isomer has the analgesic activity, the *d*-isomer being analgesically inactive. While it is preferable to employ the pure α -*l*-isomer as an analgesic or for use in treatment of heroin withdrawal symptoms, the unresolved α -*dl* or diastereoisomeric pair is useful for the same purposes in accordance with its analgesic content, the analgesic content being one-half that of the pure active *l*-isomer.

With the β -*dl* diastereoisomeric pair, the β -*l* isomer is the more active analgetically. As with the α -*dl* pair, the unresolved racemate is useful as an analgesic and in the alleviation of heroin withdrawal symptoms.

As previously stated, the compounds represented by the above formula have analgesic action as measured by the method of Robbins, J. Am. Pharm. Assoc. (Sci. Ed.) 44 497 (1955). According to this procedure, which is modified from the method of Davies et al., Brit. J. Pharmacol. 1 255 (1946), rats are divided into groups of four and appropriate concentrations of the analgesic under test are administered to the rats, one dose level per group of rats. One group of rats is used as a control group and are administered orally the medium used for administration of the analgesic itself. Analgesic activity in the administered compounds is measured by an increase in reaction time to a painful stimulus over the reaction time of the control group of rats to the same stimulus. In this instance, the painful stimulus consists of heat, the rat's tail being grasped between the thumb and forefinger of the operator equidistant between the sides of an electrically-heated rod.

Table 1 below gives the results of testing representative compounds of this invention as analgesics by the above method. In the table, column 1 is the Y substituent for the formula at the head of the table, column 2 the R substituent, column 3 the oral dose in mg./kg., column 4 the time of peak analgesic action, this time being that at which the analgesic response is measured, and column 5 the prolongation time in seconds for the response of the treated group to the painful stimulus over the response time of the control group.

TABLE 1

$$\begin{array}{c}
 \text{C}_2\text{H}_5 \\
 | \\
 \text{CH}-\text{O}-\text{CO}-\text{CH}_3 \\
 | \\
 (\text{C}_6\text{H}_5)_2\text{C}=\text{CH}-\text{CH}_2-\text{CH}-\text{N}-\text{C}-\text{O}-\text{R} \\
 | \quad | \quad | \\
 \text{CH}_3 \quad \text{CH}_3 \quad \text{Y}
 \end{array}$$

Y	R	Oral dose, mg./kg.	Peak analgesic action	Prolongation time in secs.
O	Ethyl (α -dl).....	10.0	3 m.	13.3
	Ethyl (α -d).....	5.0	3 m.	~6.5
	Ethyl (α -l).....	2.0	3 hr.	~2.0
	Ethyl (α -dl).....	20	4 m.	(i)
	Ethyl (α -l).....	5.0	4 hr.	Max.
	Ethyl (β -dl).....	2.5	4 hr.	~9.5
	Ethyl (β -d).....	20	4 hr.	13.7
	Ethyl (β -l).....	10	4 hr.	3.9
	Isopropyl (α -dl).....	20	3 m.	7.65
	Phenyl (α -dl).....	20	3 hr.	3.0
S	sec-Butyl (α -dl).....	20	3 hr.	21.9
	n-Butyl (α -dl).....	20	3 m.	16.3
	Ethyl (α -dl).....	20	3 hr.	9.55

¹ Inactive.

Other compounds coming within the scope of this invention have a comparable analgesic activity although the dose required to give a 6.5 second prolongation time may be somewhat higher than those recorded in the table above. In addition, the time of peak analgesic action will vary somewhat from compound to compound; for some compounds, the time of peak analgesic action is about 3 hours and for others about 4 hours.

The compounds of this invention also demonstrate their analgesic action in the mouse writhing assay described by Koster et al., Fed. Proc. Soc. Exptl. Biol. 18 412 (1969).

The compounds of this invention are relatively non-toxic in that their analgesically effective dose is low compared to the dose at which toxic signs appear. Table 2 which follows records the lethal dose for 50% of rats (LD₅₀) for α -dl-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate. In the table, column 1 gives the route of administration of the compound and column 2, the LD₅₀ determined from the mortality rate among groups of rats at various dose levels.

TABLE 2

Toxicity of α -dl-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate

Route:	LD ₅₀
Oral	116.6±6.7
Intraperitoneal	130.4±15.7
Subcutaneous	656.4±43.4

Since the compounds of this invention are effective analgesically by the oral route, this route of administration is preferred. For oral administration, the compound may be placed in empty telescoping gelatin capsules, either with or without conventional pharmaceutical extending media. The compounds can also be mixed with various excipients, binders, etc. and compressed into tablets. Additionally, it is also possible to administer the compounds orally in a suspension, usually in saline with about 1% of a surface-active agent such as polyoxyethylene sorbitan monooleate. The compounds can also be administered intraperitoneally or subcutaneously as an aqueous suspension of the type illustrated above. The compounds are not soluble in water and they do not form salts which might be water soluble. Hence the compounds are not suitable for intravenous injection and thus cannot be self-administered as can methadon. It is, of course, an advantage accruing to the compounds of this invention that they cannot be self-administered and are therefore not subject to street abuse as is methadon.

A second advantage of the compounds of this invention is their comparatively long duration of action which, in some instances, is greater than six hours.

The compounds of this invention are white crystalline solids. They are prepared in general by acylating nor-

acetylmethadol or its propionic acid analogue. The preparation of these starting materials is set forth in U.S. Pat. 3,021,360. The acylating agent is preferably a chlorocarbonate such as ethyl chlorocarbonate, n-butyl chlorocarbonate or the like. The preparation of a compound of this invention is illustrated by the following specific example.

EXAMPLE 1

 α -l-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate

Eight grams of α -l-noracetylmethadol free base obtained from the corresponding hydrochloride salt were dissolved in a mixture of 10 ml. of pyridine and 100 ml. of benzene. The mixture was cooled to about 0° C. 2.4 g. of ethyl chlorocarbonate in 20 ml. of benzene were added slowly with stirring to the chilled solution containing the α -l-noracetylmethadol. After the addition had been completed, stirring was continued for about 2 more hours at about 0° C. The reaction mixture was then poured into water. The organic layer was washed with successive portions of dilute aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. The organic layer was dried and the solvent removed by evaporation in vacuo leaving as a residue about 8 g. of a yellow oil. Chromatography of this oil over silica gel using a 1:10 ethyl acetate-benzene solvent yielded about 6 g. of a colorless oil which crystallized from hexane. This crystalline product α -l-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate melted at about 89-90° C. after recrystallization from hexane: $[\alpha]_D^{25} = -35.31^\circ$ (c.=1 in ethanol). Analysis, Calc.: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.72; H, 8.19; N, 3.41.

Other compounds which are prepared by the process of the above example include the following:

α -dl-Ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate. M.P.=82-3° C. Anal., Calc.: C, 72.96; H, 8.08; N, 3.40. Found: C, 73.16; H, 8.29; N, 3.21.

β -dl-Ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate. M.P.=95-6° C. Anal., Calc.: C, 72.96; H, 8.08; N, 3.40. Found: C, 73.13; H, 8.33; N, 3.68.

α -dl-n-Butyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate. Oil. Anal., Calc.: C, 73.77; H, 8.48; N, 3.19. Found: C, 74.04; H, 8.23; N, 2.99.

α -dl-sec-Butyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate. M.P.=61-2° C. Anal., Calc.: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.98; H, 8.29; N, 3.05.

Compounds represented by the above formula in which Y is S are prepared by reacting α -dl-noracetylmethadol or α -l-noracetylmethadol or their propionyl or β -dl or β -l analogues with thiophosgene to yield an intermediate thiocarbamyl chloride, reaction of which with an alcohol or phenol, R-OH, produces the desired thiocarbamate. α -dl-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)thiocarbamate synthesized by this procedure, is a high boiling oil having the following analysis: Calc.: N, 3.28; S, 7.50. Found: N, 3.09; S, 7.49.

All compounds described above have NMR spectra consistent with their assigned structure.

The starting noracetylmethadol can be prepared by an alternate procedure in addition to that set forth in U.S. Pat. 3,021,360. This procedure is illustrated below.

EXAMPLE 2

 α -l-Noracetylmethadol

30 g. of α -l-acetylmethadol hydrochloride were converted to the free base and the free base mixed with 15.6 g. of diethyl azodicarboxylate in 200 ml. of n-hexane. The mixture was allowed to stand at ambient temperature overnight. The solvent was then removed in vacuo and the residual oil dissolved in 200 ml. of 1 N aqueous hydro-

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chloric acid. Ethanol was added to effect complete solution. The mixture was heated for about 4 hours at about 100° C. The reaction mixture was then cooled and extracted with ether. The ether layer was separated and discarded. The aqueous layer was made basic with dilute ammonium hydroxide and α -*l*-noracetylmethadol free base prepared in the above reaction was extracted into ether. The aqueous basic layer was again extracted with ether and the ether layers combined. The ether layers were then washed with water and dried. Removal of the solvent in vacuo yielded about 30 g. of an oil. The oil was dissolved in ether and the ethereal solution saturated with dry gaseous hydrogen chloride. The hydrochloride salt of α -*l*-noracetylmethadol thus prepared was separated by filtration and crystallized from an ethyl acetate-ether solvent mixture.

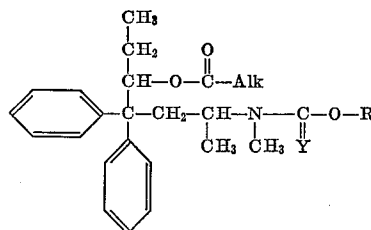
Although the preparation of the carbamate derivatives of noracymethadols has been illustrated above with reference to a pure, analgesically-active optical isomer, the same preparative method is employed for racemic (α -*dl* or β -*dl*) mixtures. The pure optically active noracymethadols which are utilized as starting materials in the above reaction are, however, not usually prepared from the noracymethadols themselves but the separation into optical antipodes is begun at an early step in the preparation of the noracymethadols. The procedure which is preferably utilized for the preparation of the pure optical isomers of noracymethadol carbamates is conveniently initiated with the separation of 2,2-diphenyl-4-dimethylaminopentanone nitrile into its *d*- and *l*-isomers. The racemic form of 2,2-diphenyl-4-dimethylaminopentanone nitrile is readily converted to methadon by a well known series of reactions and this same series of reactions is applied to the preparation of the optically active *d*-methadon and *l*-methadon. Reduction of *d*-methadon in a stereospecific reaction using low-pressure hydrogenation and a platinum catalyst yields the pure isomer, α -*l*-methadol. Acylation of this latter compound yields α -*l*-acymethadol. The α -*l*-acymethadol is converted to the corresponding nor derivative by treatment with diethyl azodicarboxylate as illustrated above in Example 2. A stereospecific reduction of *l*-methadon with sodium in ethanol yields the pure

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optical isomer, β -*l*-methadol. Acylation of this alcohol followed by treatment with diethyl azodicarboxylate yields an analgesically active isomer, specifically, β -*l*-noracetylmethadol or β -*l*-norpropionylmethadol.

I claim:

1. A compound represented by the formula



wherein Y is O or S, Alk is methyl or ethyl and R is C₁-C₃ alkyl or phenyl.

2. A compound according to claim 1, said compound being α -*dl*-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate.

3. A compound according to claim 1, said compound being β -*dl*-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate.

4. A compound according to claim 1, said compound being α -*l*-ethyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate.

5. A compound according to claim 1, said compound being α -*dl*-sec-butyl N-methyl-N-(1-methyl-3,3-diphenyl-4-acetoxy-n-hexyl)carbamate.

References Cited

UNITED STATES PATENTS

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