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3,532,704

ANESTHETIC BUTOXYDIMETHYLBENZAMIDES
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No Drawing. Filed Sept. 12, 1968, Ser. No. 759,505
Claims priority, application Switzerland, Oct. 20, 1967,
14,726/67

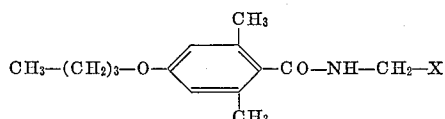
Int. Cl. C07d 29/30

U.S. Cl. 260—294

4 Claims

ABSTRACT OF THE DISCLOSURE

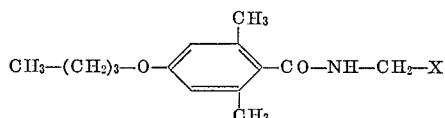
Butoxydimethylbenzamides of the formula



wherein X is N-methyl-2-piperidyl, N-methyl-3-piperidyl, or N-methylpyrrolidyl, and the salts of such butoxydimethylbenzamides with physiologically tolerated acids are effective local anesthetic agents of low toxicity.

This invention relates to anesthetic agents, and particularly to butoxydimethylbenzamides and salts thereof which have anesthetic effects.

We have found that piperidine and pyrrolidine bases of the formula



and their salts with physiologically tolerated acids are safe and effective anesthetic agents, X in the formula being N-methyl-2-piperidyl, N-methyl-3-piperidyl, or N-methylpyrrolidyl. The bases and salts are strongly neurotropic even when applied to living organisms in minute concentrations, and are therefore useful in local anesthesia, particularly as surface anesthetics. Their effects in surface anesthesia are greatly superior to those of chemically similar known anesthetics in comparable dosage.

By way of example, the hydrochloride of 1-N-methyl-2-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpiperidine (Compound I) in 2.5 millimolar solution in Tasaki-Ringer solution has the same reaction blocking effect on the isolated frog nerve as a 5 millimolar solution of the known anesthetic agent ω -diethylamino-2,6-dimethylacetanilide, (Compound IV, Lidocaine) as the hydrochloride, both solutions having a pH of 7.4.

Other properties of the above and related compounds in comparative tests are listed below. The following additional compounds are identified by Roman numerals as follows:

- (II) 1 - N - methyl - 3 - (4' - butoxy - 2',6' - dimethylbenzoylamino)-methylpiperidine
- (III) 1 - N - methyl - 3 - (4' - butoxy - 2',6' - dimethylbenzoylamino)-methylpyrrolidine
- (V) N - β - diethylaminoethyl - 2,6 - dimethyl - 4-butoxybenzamide
- (VI) N - (4' - butoxy - 2',6' - dimethylbenzoylaminoethyl)-piperidine

Compounds I, II, III are typical anesthetic agents of this invention. Compounds V and VI are known from the British Pat. 877,846 (Honkanen) and from a paper by Bonati et al. (Arch. Ital. di Scienza, Pharm. Serie III, vol. 13, April 1963, No. 2).

Toxicities were determined for Compounds I and III

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to VI by applying solutions of the several hydrochlorides in Ringer solution to mice by intravenous injection (i.v.), intramuscular injection (i.m.) or intraperitoneal injection (i.p.). The median lethal dose DL_{50} was calculated from deaths within 12 days by the method of Litchfield and Wilcoxon. Eight white mice having a weight of 18 to 24 g. were used for each set of conditions.

TABLE I

Compound:	DL_{50} , mg./kg.		
	i.v.	i.p.	i.m.
I.....	43	-----	200
III.....	26	-----	246
IV.....	25	124	174
V.....	-----	123	-----
VI.....	-----	76	-----

As is evident from Table I, the toxicity of the Compounds I and III of the invention compares favorably with the toxicity of Compound IV (Lidocaine) which is in common clinical use, and compounds V and VI are more toxic than Lidocaine.

The duration of anesthesia in rabbit corneas was determined by the method of Regnier-Hotovy by measuring the elimination of the lid closing reflex. Solutions of the hydrochlorides of the six compounds listed above in Ringer solution were instilled in the connective tissue bag at the eye and permitted to act on the cornea for two minutes. The eye was then washed with much physiological saline solution. The lid was touched with a rabbit whisker twenty times at a rate of twelve contacts per minute and the presence or absence of the reflex was observed. The results are listed in Table II. The relative effectiveness of the several compounds was calculated, assigning to Lidocaine (Compound IV) a value of 1.

TABLE II

Compound:	Concentration, percent	Anesthesia, min.	Relative effectiveness
I.....	0.125	8.3	18
II.....	0.25	16.4	-----
III.....	0.5	40	10
IV.....	1.0	55	-----
V.....	0.25	100	10
VI.....	0.5	2	1
V.....	1.0	7.6	-----
VI.....	0.5	14.5	2
VI.....	1.0	15-18	-----
VI.....	0.5	14.5	2-3
VI.....	1.0	19	-----

¹ Approximate.

The several compounds were similarly compared in tests in which the sensory nerve of rat tails was blocked by injection of 0.4 ml. of solution into the root of the tail. The injections were applied to four test animals in each test in four different locations symmetrical relative to the tail root. The blackened tail tips were exposed at a uniform distance to the focused radiation of a 500 watt spotlight.

The reaction time of untreated rats to the applied heat was 2 to 4 seconds. An extension of the reaction time to at least 30 seconds was considered indicative of anesthesia. The minimum concentration of active agent which produced anesthesia in 50% of the test animals (CE_{50}) was determined. In one series of tests, Compound IV was compared with Compounds I to III (values listed in Table III without parentheses). In another series of tests, Compound IV was compared with Compounds V and VI (values in parentheses). Because of differences in experimental technique between the two sets, their results cannot be compared directly. The values for relative effectiveness, derived from the concentration figures by assigning a value of 1 to Compound IV are not significantly affected.

TABLE III

Compound:	CE ₅₀ , percent	Relative effectiveness
I.....	0.16	2
II.....	0.26	1.2
III.....	0.22	1.4
IV.....	0.32	1
V.....	(0.17)	1
VI.....	(0.17)	1
	(0.14)	1.2

Nerve endings in the third distal region of blackened rat tails were blocked by infiltration with 0.4 ml. of the several anesthetic solutions, the infiltrated region was exposed to the afore-described electric lamp, and the minimum concentration producing anesthesia in 50% of the animals (CE₅₀) was determined in two series of tests as described with reference to Table III.

The tests performed on Compound III were incomplete. Anesthesia was obtained with Compound III in all tested animals with a 0.05% solution, the most dilute solution tested. The relative effectiveness of the compound was estimated as approximately 4 from the fact that Compound IV, under the same conditions and at a concentration of 0.125% produced anesthesia in only 50% of the test animals. Other values in Table IV were arrived at as described in connection with the preceding tests.

TABLE IV

Compound:	CE ₅₀ , percent	Relative effectiveness
I.....	0.006	4.5
II.....	0.014	2
III.....		1.4
IV.....	0.027	1
V.....	(0.18)	
VI.....	(0.07)	2.5
	(0.13)	1.4

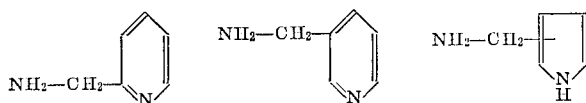
¹ Approximate.

The compounds of the invention compare favorably in their toxicity with the known anesthetic agent Lidocaine (Compound IV). The known Compounds V and VI are more toxic than Lidocaine. The anesthetic effects of the compounds of the invention are superior to Lidocaine in equal concentrations, superior in most tests to the known Compounds V and VI in equal amounts, and superior or equal under all tested conditions at equal toxicity. The superiority of the butoxydimethylbenzamides of the invention over all tested known compounds is particularly great in surface anesthesia.

The base compounds of the invention are readily prepared in good yields. The salts, whose anesthetic effects are approximately equal to those of the bases in equimolecular amounts, are obtained from the bases in a conventional manner.

In preparing a base of the invention, 4-butoxy-2,6-dimethylbenzoic acid or a reactive derivative thereof, such as the corresponding anhydride, acyl halide, or an ester, is reacted with an amine of the formula H₂N—CH₂—X, wherein X is as defined above.

4-butoxy-2,6-dimethylbenzoic acid or a reactive derivative thereof, as described above, may also be condensed with an aminomethylpyridine or an aminomethylpyrrol of one of the formulas



to the corresponding amide, whereupon the heterocyclic ring of the product is hydrogenated. Hydrogen attached

to the nitrogen atom of the ring may be replaced by methyl prior to or after hydrogenation.

The following examples describe the preparation of the compounds of the invention in more detail.

EXAMPLE 1

300 g. N-methylpyridinium-2-aldoxime iodide were suspended in a mixture of 65 ml. glacial acetic acid and 600 ml. water, and hydrogenated at a gage pressure of 1 to 2 atmospheres in the presence of a catalyst mixture of 30 g. 5% platinum on carbon and 30 g. 5% rhodium on carbon. The hydrogenation reaction was exothermic. More than 90% of the hydrogen theoretically required was consumed after about 3 hours, and more than 95% after about 8 hours.

The contents of the hydrogenation vessel were then filtered to remove the catalyst, and the filtrate was evaporated to dryness in a vacuum. The residue was dissolved in a large excess of concentrated sodium hydroxide solution, and 1-N-methyl-2-aminomethylpiperidine was extracted with ether from the alkaline medium. The compound was obtained from the dried ether extract by distillation as a liquid boiling at 101°–102° C. at 55 mm. Hg. The yield in several runs was between 89 and 105 g. (56–72%).

120.4 g. 4-butoxy-2,6-dimethylbenzoyl chloride dissolved in 150 ml. absolute chloroform were added dropwise over a period of 3 hours to a solution of 70.5 g. 1-N-methyl-2-aminomethylpiperidine in 150 ml. absolute chloroform with stirring. The temperature was held between 0° and 40° C. during the addition. Stirring was continued at room temperature for several hours, and most of the solvent was then evaporated. The residue was shaken with 400 ml. 2.5 N sodium hydroxide solution and much ethyl ether until two distinct phases were formed. The aqueous phase was discarded. The ether phase was washed with water, dried, and evaporated to remove the solvent. The residue was distilled in a high vacuum.

141.5 g. 1-N-methyl-2-(4'-butoxy - 2',6' - dimethylbenzoylamino)-methylpiperidine boiling at approximately 180° to 190° C. at 0.04 mm. were obtained (85.2% yield).

When recrystallized once or twice from low-boiling petroleum ether, the compound melted at 62°–63° C. It is insoluble in water, but dissolves readily in all commonly employed organic solvents.

The compound, which is a base, also dissolves in aqueous solutions of stoichiometric amounts of strong acids, such as hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, or fumaric acid, and the corresponding salts can be recovered from the aqueous solutions by careful vacuum evaporation. The acid oxalate, identified as having the formula C₂₂H₃₄N₂O₆, melts at 94° C. It dissolves in very small amounts of water.

The above condensation reaction is readily modified in a known manner to substitute free 4-butoxy-2,6-dimethylbenzoic acid, its anhydride, or its ethyl ester for the acyl chloride in the reaction with N-methyl-2-aminomethylpiperidine. The yields are not quite as high, and the acyl halides are therefore preferred, the bromide being as useful as the chloride.

EXAMPLE 2

36.1 g. 4-butoxy - 2,6 - dimethylbenzoyl chloride dissolved in 70 ml. chloroform were added dropwise with agitation to a solution of 33.6 g. 2-aminomethylpyridine in 180 ml. chloroform. The reaction was terminated two hours after mixing was completed. The chloroform was distilled off, and the residue was taken up in water and ether. The ether phase was repeatedly washed with water, dried, and evaporated to dryness.

The residue consist essentially of 35 g. 2-(4'-butoxy-

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2',6'-dimethylbenzoylamino)-methylpyridine (75% yield) having a melting point of 82° to 84° C. when recrystallized from petroleum ether.

18.7 g. 2-(4' - butoxy - 2',6'-dimethylbenzoylamino)-methylpyridine were hydrogenated in 75 ml. glacial acetic acid in the presence of 5 g. each of platinum-carbon and palladium-carbon catalysts at 1 to 2 atmospheres gage pressure. The calculated amount of hydrogen was absorbed quite quickly, whereupon the reaction stopped abruptly. 6.5 ml. 35% formaldehyde solution were then added to the reaction mixture and hydrogenation was resumed. The nitrogen atom in the piperidine ring was thereby methylated.

After the absorption of hydrogen stopped, the catalysts were removed from the hydrogenation mixture by suction filtration, and the filtrate was evaporated to dryness in a vacuum. The residue was taken up in 40 ml. water and mixed with 50 ml. 2 N sodium hydroxide solution to form the free base which was recovered by extraction with ether, drying and evaporation of the ether extract.

17.6 g. 1-N-methyl-2-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpiperidine (88% yield) were obtained. The compound had a melting point of 64° to 66° C. when recrystallized from petroleum ether.

EXAMPLE 3

72.2 g. 4-butoxy - 2,6 - dimethylbenzoyl chloride (0.3 mole) were dissolved in 140 ml. pure chloroform, and the solution was added dropwise with stirring to a solution of 67.2 g. 3-aminomethylpyridine (0.62 g.) in 220 ml. chloroform while the heat of reaction was absorbed in ice water. The reaction mixture was evaporated to dryness in a vacuum and further worked up as described in Example 2 to produce 72.6 g. crude 3-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpyridine (79% yield). The compound boiled at 190° to 196° C. at 0.2 mm., and it had a melting point of 73°-74° C. when recrystallized from diisopropyl ether.

A solution of 21.45 g. 3 - (4' - butoxy-2',6'-dimethylbenzoylamino)-methylpyridine in 100 ml. glacial acetic acid was hydrogenated at a gage pressure of 1-2 atmospheres in the presence of 3 g. each of platinum-carbon and palladium-carbon catalyst. After the pyridine ring had been saturated, 7.4 ml. 35% formaldehyde solution were added, and hydrogenation was resumed. The hydrogenation mixture was worked up as described in Example 2.

20.3 g. 1-N-methyl-3-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpiperidine (90% yield) were obtained.

The crude base was purified by passing its ether solution over a chromatographic column packed with aluminum oxide. The column was washed with ether, and the combined ether solutions were carefully evaporated, whereby 15.1 g. of a crystalline material were obtained (66.5% yield). The crystals sintered at 80.5° C. and melted at 81°-82° C.

The compound was identified by its equivalent weight, determined as 334.2 (calculated for $C_{20}H_{32}N_2O_2$: 332.47).

1-N-methyl - 3-(4' - butoxy - 2', 6' - dimethylbenzoylamino)-methylpiperidine is insoluble in water, but dissolves readily in aqueous solutions of strong acids and in all usual organic solvents.

EXAMPLE 4

120.4 g. 4-butoxy-2, 6-dimethylbenzoyl chloride were dissolved in 150 ml. chloroform, and the solution was stirred drop by drop into a solution of 62.8 g. 1-N-methyl-3-aminomethylpyrrolidine. The reaction mixture was stirred at ambient temperature for several hours, partly evaporated in a vacuum, and shaken with 400 ml. 2.5 N sodium hydroxide solution and much diethyl ether until two distinct phases formed. The ether phase was washed with water, dried, and evaporated, and the residue was purified by high-vacuum distillation.

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122.8 g. 1-N - methyl-3-(4' - butoxy-2', 6' - dimethylbenzoylamino)-methylpyrrolidine (77.2% yield) were obtained as a liquid boiling at approximately 185° to 200° C. at 0.03 mm. Hg. When repeatedly recrystallized from petroleum ether, the base melts at 70° to 73° C. It is soluble in all the usual organic solvents, but insoluble in water.

The salts of the base are formed by dissolving the base in stoichiometrically equivalent solutions of strong acids and evaporating the water in a vacuum. The acid oxalate melts at about 92° C., the acid fumarate at about 140° C. The salts very readily dissolve in water and also in the lower alkanols.

The same sequence of reactions, starting with 4-butoxy-2, 6-dimethylbenzoyl chloride and 1-N-methyl-2-aminomethylpyrrolidine ultimately leads to 1-N-methyl-2-(4'-butoxy - 2', 6' - dimethylbenzoylamino) - methylpyrrolidine in similar yields, and qualitative tests indicate analogy with the 3-methylpyrrolidine derivative in pharmacological properties. The cost of 1-N-methyl-2-aminomethylpyrrolidine is prohibitive at this time, and 1-N-methyl-2-(4'-butoxy-2', 6' - dimethylbenzoylamino)-methylpyrrolidine will therefore be economically unattractive until a less costly synthesis method becomes available. Similar reasons militate against preparation of the pyrrolidine derivatives of the invention by the method of Examples 2 and 3 which is readily applicable to the aminomethylpyrrols.

For the sake of convenience, the hydrochlorides of the several bases of the invention are preferred for use in injectable solutions, but other physiologically tolerated acids may be combined with the bases. Aqueous solutions containing 0.25% to 2% of the free bases in the form of the hydrochlorides and enough of a disodium phosphate/monopotassium phosphate buffer to adjust the pH to 6 have been used successfully.

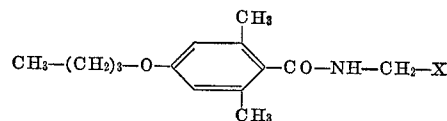
One gram of 1-(N)-methyl-2-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpiperidine or of the isomeric 3-methylpiperidine derivative requires 3.008 ml. 0.1 N hydrochloric acid solution for dissolution. The hydrochloride solutions so obtained were diluted with bidistilled water and buffer to the desired concentration. The buffered solutions were then filtered to remove dust, transferred to 1, 2, 5, or 10 ml. glass vials which were sealed and then sterilized for use in nerve blocking or infiltration anesthesia. Up to 50 ml. of solution were applied by infusion.

One gram of 1-N-methyl-3-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpyrrolidine requires 3.14 ml. 0.1 N hydrochloric acid solution for dissolution, but injectable anesthetic compositions for local anesthesia are otherwise prepared as described with reference to the piperidine bases of the invention.

The free bases may be employed in surface anesthesia, using dispersions or solutions in fatty ointments or in oily solution as is conventional in pharmacy. The salts are preferably applied to the skin or to mucous membranes in aqueous solution containing up to 5% of the active agents of the invention.

What is claimed is:

1. A substance having anesthetic effects, said substance being a piperidine or pyrrolidine base of the formula:



or a salt of said base with a physiologically tolerated acid, in said formula X being N-methyl-2-piperidyl, N-methyl-3-piperidyl, or N-methylpyrrolidyl.

2. A substance as set forth in claim 1, wherein said substance is 1-N-methyl-2-(4'-butoxy-2',6'-dimethylbenz-

oylamino)-methylpiperidine or a salt thereof with said acid.

3. A substance as set forth in claim 1, wherein said substance is 1-N-methyl-3-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpiperidine or a salt thereof with said acid.

4. A substance as set forth in claim 1, wherein said substance is 1-N-methyl-3-(4'-butoxy-2',6'-dimethylbenzoylamino)-methylpiperidine or a salt thereof with said acid.

References Cited**FOREIGN PATENTS**

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5 HENRY R. JILES, Primary Examiner

G. T. TODD, Assistant Examiner

U.S. Cl. X.R.

10 260—326.3; 424—267, 274