# United States Patent [19]

**Adams et al.**

[11] **3,862,321**

[45] **Jan. 21, 1975**


[54] **ACYL XYLIDIDE LOCAL ANAESTHETICS**


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[22] Filed: **Mar. 4, 1974**

[21] Appl. No.: **447,680**

**Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 164,022, July 19, 1971, Pat. No. 3,812,147, which is a continuation-in-part of Ser. No. 100,777, Dec. 22, 1970, abandoned.

[52] **U.S. Cl.** ..... **424/274,** 424/324

[51] **Int. Cl.** ..... **A61k 27/00**

[58] **Field of Search** ..... 424/274, 324



[56] **References Cited**

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[57] **ABSTRACT**

The 2-alkyl-2-alkylamino-2′,6′-acetoxylidide compounds are useful as long lasting local anaesthetics.

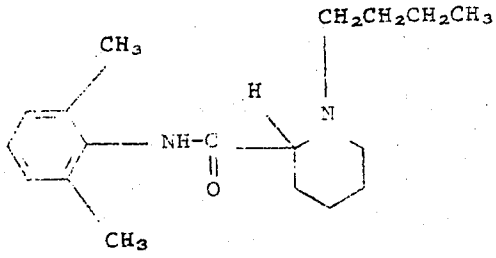

**16 Claims, No Drawings**

# ACYL XYLIDIDE LOCAL ANAESTHETICS

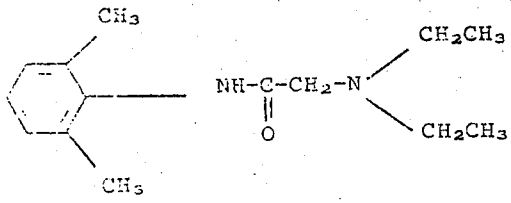
This application is a continuation-in-part of our U.S. application Ser. No. 164,022, filed July 19, 1971, now U.S. Pat. No. 3,812,247, which in turn is a continuation-in-part of our U.S. application Ser. No. 100,777, filed Dec. 22, 1970, now abandoned.

The present invention relates to 2-alkyl-2-alkylamino-2',6'-acetoxylidide local anaesthetic compounds.

Two acylxylidide local anaesthetic compounds which are commercially available are N-n-butylpipecolyl-2,6-xylidide or bupivacaine sold under the trademark "Marcaine" having the structural formula



and diethylaminoaceto-2,6-xylidide or ω-diethylamino-2,6-dimethyl-acetanilide or lidocaine sold under the trademark "Xylocaine" having the structural formula

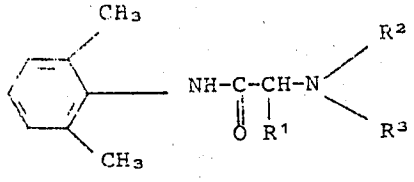


However, while bupivacaine or Marcaine is a long lasting local anaesthetic, it has the drawback of being irritating to tissue and while lidocaine or Xylocaine is not irritating to tissue, it has the drawback of not being a long lasting local anaesthetic.

Other local anaesthetics which are commercially available include α-propylaminopropiono-2-toluidide or prilocaine sold under the trademark "Citanest"; α-pyrrolidinoaceto-2,6-xylidide or pyrrocaine sold under the trademarks "Endocaine" and "Dynacaine"; and N-methylpipecolyl-2,6-xylidide or mepivacaine sold under the trademark "Carbocaine." However, these local anaesthetics are of short action.

It is, therefore, the principal object of the present invention to provide compounds which generally have the combined properties of long lasting local anaesthetic effect or high local anaesthetic activity, a satisfactory low level of tissue irritation and a satisfactory low acute toxicity.

The compounds of the present invention are the 2-alkyl-2-alkylamino-2',6'-acetoxylidide local anaesthetic compounds having the structural formula

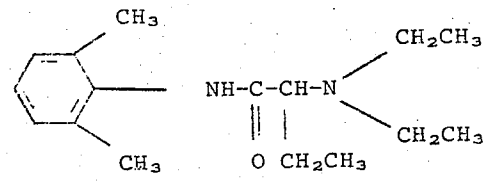


wherein $R^1$ is ethyl, propyl or butyl; $R^2$ and $R^3$ may be the same or different alkyl radicals and are methyl,

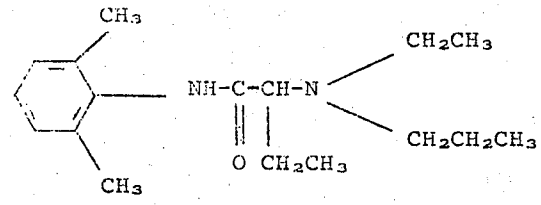


ethyl, propyl or butyl; $R^2$ together with $R^3$ is tetramethylene; the number of carbon atoms in $R^1$, $R^2$, and $R^3$ is totally at least six; or the pharmaceutically acceptable salts thereof. These compounds are racemic compounds and hence the local anaesthetic ∂- or l-optical isomers are included within the scope of the present invention.

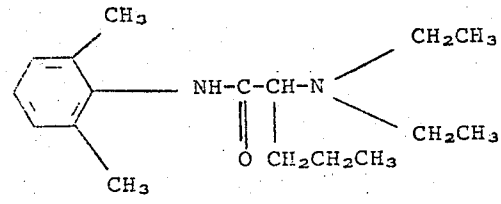
Representative compounds include the following: 2-diethylamino-2',6'-n-butyroxylidide, which can be alternatively named 2-ethyl-2-diethylamino-2',6'-acetoxylidide, having the formula



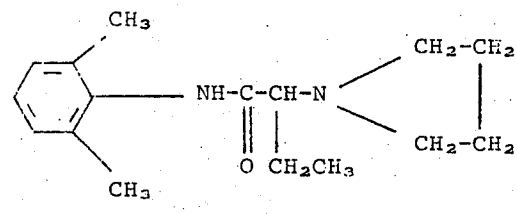
2-(N-ethyl-n-propylamino)-2',6'-n-butyroxylidide, which can be alternatively named 2-ethyl-2(N-ethyl-n-propylamino)-2',6'-acetoxylidide, having the structural formula



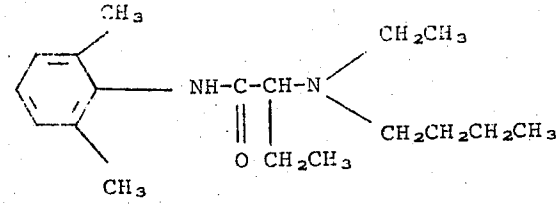
2-diethylamino-2',6'-n-valeroxylidide, which can be alternatively named 2-n-propyl-2-diethylamino-2',6'-acetoxylidide, having the structural formula



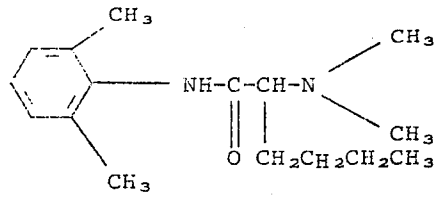
2-pyrrolidino-2',6'-n-butyroxylidide, which can be alternatively named 2-ethyl-2-pyrrolidino-2',6'-acetoxylidide, having the structural formula



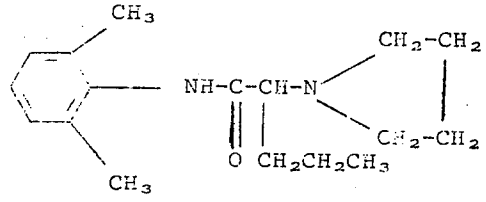
2-(N-ethyl-n-butylamino)-2',6'-n-butyroxylidide, which can be alternatively named 2-ethyl-2-(N-ethyl-n-butylamino)-2',6'-acetoxylidide, having the structural formula



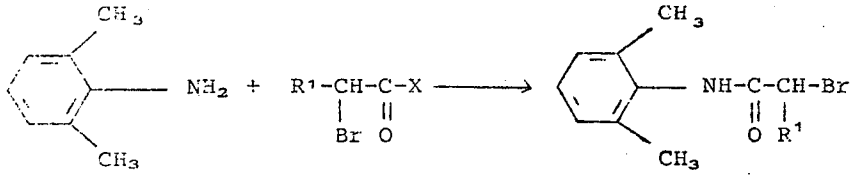
2-dimethylamino-2',6'-caproylxylidide, which can be alternatively named 2-n-butyl-2-dimethylamino-2',6'-acetoxylidide, having the structural formula

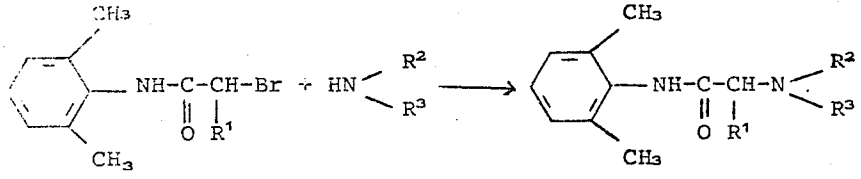


and 2-pyrrolidino-2',6'-n-valeroxylidide, which can be alternatively named 2-n-propyl-2-pyrrolidino-2',6'-acetoxylidide, having the structural formula



The compounds of the invention can be prepared in accordance with the following partial class reactions:





where $R^1$, $R^2$ and $R^3$ are as stated above and X is a bromine or a chlorine atom. More detailed and other procedures of preparation are give in the representative examples hereinafter.

The racemic compounds may be resolved into their ∂ - and l-optical isomers by treatment with l- and ∂ - tartaric acid.

The compounds of the invention are useful as local anaesthetics in the conventional manner and employing conventional dosages thereof. These bases may be conventionally used in the form of solutions of their pharmaceutically acceptable salts, e.g., the hydrochlorides, tartrates and citrates.

The invention will be further illustrated by the following examples:

## EXAMPLE 1

This example illustrates the preparation of 2-diethylamino-2',6'-n-butyroxylidide or α-(diethylamino)-n-butyro-2,6-xylidide.

(α-Bromo-n-butyryl chloride) — Redistilled thionyl chloride (2.40 moles) was added to α-bromo-n-butyric acid (1.20 moles) in a 1,000 ml. flask attached to a reflux condenser and drying tube. The mixture was heated to reflux for 5 hours. Excess thionyl chloride was distilled off with the bath temperature up to 120°C. The reaction mixture was kept at 25°–30°C. for 1 hour at water pump vacuum, whereafter the bath temperature was raised slowly to 80°C., at which point the α-bromo-n-butyryl chloride started distilling; bp. 48°–50°C.; yield: 1.10 moles (92%). A product sufficiently pure for the following reaction was obtained by omitting the vacuum distillation and allowing a stream of dry argon (or nitrogen) to pass through the α-bromo-n-butyryl chloride at 80°–100°C. for 1.5–2 hours after the main bulk of thionyl chloride had been distilled off.

(α-Bromo-n-butyryl-2,6-xylidide) — α-Bromo-n-butyryl chloride (1.005 moles) was added to a cold mixture (5°–10°C.) of 2,6-xylidine (0.92 mole) and glacial acetic acid (814 ml.) in a 4 liter bottle, quickly mixed, and quickly followed by a cold solution of sodium acetate trihydrate (315.6 g.) in water (1,610 ml.). The bottle was closed and shaken for 30 minutes. The precipitate was filtered and washed several times by slurrying in water to remove the acetic acid as efficiently as possible. It was then dried in air or in vacuum; m.p. 198°–200°C.; yield: 0.74 mole (80%). Calculated for $C_{12}H_{16}BrNO$: C 53.3, H 5.97, Br 29.6. Found: C 53.3, H 5.79, Br 29.7.

[α-(Diethylamino)-n-butyro-2,6-xylidide] — α-Bromo-n-butyryl-2,6-xylidide (0.0148 mole), diethylamine (0.0444 mole), and anhydrous benzene (25 ml.) were heated at 100°C. for 15 hours in a pressure vessel. After cooling, the diethylammonium bromide was filtered off and the benzene solution extracted with three 25 ml. portions of 1 M hydrochloric acid. The acid extract was washed with 25 ml. of ether and brought up to pH 10 with 7 M sodium hydroxide and extracted with four 25 ml. portions of ether. The ether extract was dried over anhydrous sodium sulfate, filtered and the ether evaporated under vacuum giving α-(diethylamino)-n-butyro-2,6-xylidide (0.00499 mole, 33.7%) as a waxy solid. This was converted to its hydrochloride salt with ethereal hydrogen chloride, and the salt was recrystallized three times from a mixture of absolute ethanol and ether; m.p. 224.5°–226°C. (decomp.). Calculated for $C_{16}H_{27}ClN_2O$: C 64.3, H 9.11, N 9.37. Found: C 64.4, H 9.12, N 9.39. I.r. (KBr disc, hydrochloride) μ3175 (s, NH amide), 2980 and

2938 (shoulder) (s, $CH_3$ and $CH_2$), 2577 (s, $NH^+$), 2490 (s, $NH^+$), 1685 (s, amide I), 1599 (w, Ph), **1530** (s, amide II), 1479 (s), 1232 (s, amide III), 787 (s, Ph 3 adjacent hydrogens out of plane) $cm^{-1}$. N.m.r. ($CDCl_3$, base), δ1.10 (t, 9H, $CH_2—C\underline{H}_3$), 1.60–2.10 (m, 2H, $CHC\underline{H}_2CH_3$), 2.18 (s, 6H, Ph $—CH_3$), 2.68 (q, 4H, $N—CH_2C\underline{H}_3$), 3.25 (t, 1H, COCH), 6.98 (s, 3H, Ph), 8.73 (s broad, 1H, NHCO). A gas chromatographic analysis of the compound showed the presence of one single peak.

## EXAMPLE 2

This example illustrates the preparation of 2-(N-ethyl-n-propylamino)-2′,6′-butyroxylidide or α-(N-ethyl-n-propylamino)-n-butyro-2,6-xylidide.

(α-Bromo-n-butyryl-2,6-xylidide) — This compound was prepared as described in Example 1.

(α-Iodo-n-butyryl-2,6-xylidide) — α-Bromo-n-butyryl-2,6-xylidide (224.7 g., 0.832 mole), powdered potassium iodide (191.2 g., 1.15 moles) and anhydrous methanol (1,200 ml.) were mixed in a 3,000 ml. flask equipped with reflux condenser, mechanical stirrer and heating mantle. After refluxing for 3 hours, the mixture was allowed to cool for 30 minutes with continued stirring, transferred with stirring to a beaker containing 2.5 liters distilled water and left for 1 hour. The precipitate was filtered and pressed as dry as possible. It was then transferred back to the beaker and carefully stirred with circa 1.5 liters distilled water and filtered again. This procedure was repeated until the filtrate was free from bromide and iodide ion. The precipitate was then dried in air and/or in a desiccator. Yield: 243 g. mp 220°–222°C. (decomp.).

The obtained preparation was almost colorless. Recrystallized from 95% ethanol the product melted at 223.5°C. under decomposition.

The uncrystallized product contains some of the bromo compound but was sufficiently pure for the following step.

[α-(n-propylamino)-n-butyro-2,6-xylidide] — Method a. n-propylamine (67.9 g., 1.15 moles) and α-iodo-n-butyryl-2,6-xylidide (121.5 g., 0.383 mole) were mixed with anhydrous benzene (1,220 ml.) in a flask equipped with reflux condenser, mechanical stirrer and heating mantle and refluxed for 8 hours. The light yellow solution was filtered from a yellow precipitate which was washed thoroughly with ether. The precipitate (no C=O band in ir) was discarded. The filtrate and washings were combined and evaporated leaving a yellow residue (143.4 g.).

The residue was treated with 380 ml. 1 M hydrochloric acid. An insoluble solid was filtered off and washed with ether. The acid filtrate was extracted with ether and an additional precipitated solid was filtered off and combined with the primarily obtained insoluble solid. The weight of the combined solid fractions was 156.2 g. (I). The acid filtrate (II) was washed with four additional portions of ether. The solid fraction I was refluxed with anhydrous benzene, filtered, and washed with hot benzene and ether. The combined benzene and ether extracts from these operations contained 6.8 g. residue and was discarded. The solid fraction I and the acid solution II were combined and based out with 7 M NaOH and the freed base was extracted into ether. After drying over anhydrous sodium sulfate the ether extract was filtered and evaporated yielding 93 g. of a partly solidifying maroon-colored residue.

This residue was dissolved in 80 ml. of ether in a separatory funnel and equilibrated with 200 ml. phosphate buffer so that the pH at equilibrium was 7.3. Keeping the pH at 7.3 the buffer solution was extracted three more times with 80 ml. portions of ether.

The ether extracts yielded 79.2 g. of a base that contained mainly the desired compound and which was sufficiently pure for the next step.

From the buffer solution 6.3 g. of an oil could be obtained on raising the pH to 11 and extracting with ether. This fraction contained mainly the β-substituted isomer, and was discarded.

Method b. α-Bromo-n-butyryl-2,6-xylidide (63.1 millimoles), n-propylamine (254 millimoles), sodium iodide (63.1 millimoles), and absolute ethanol (180 ml.) were refluxed for 6.5 hours. The alcohol was evaporated in vacuo and the residue was mixed with 0.5 M HCl (200 ml.). The suspension was washed with two 100 ml. portions of ether, the pH adjusted to 11 with 7 M NaOH and the mixture extracted three times with 100 ml. portions of ether. After drying over anhydrous sodium sulfate the ether was evaporated leaving a residue of the amine. Yield: 51.0 millimoles (81%). The hydrochloride hydrate was prepared from the base with ethereal hydrogen chloride and addition of water. Recrystallized from ethanol/ether it melted at 199°–199.5°C. Calculated for the base ($C_{15}H_{24}N_2O$): C 72.5, H 9.74, N 11.3. Found: C 72.5, H 9.81, N 11.2.

[α-(N-ethyl-n-propylamino)-n-butyro-2,6-xylidide]— α-(n-propylamino)-n-butyro-2,6-xylidide (0.243 mole) and freshly distilled diethyl sulfate (1.6 moles) were mixed in a flask equipped with reflux condenser, drying tube and stirrer. The mixture was stirred for 5 hours at 90°C. After cooling, water (110 ml.) was added with stirring for 15 minutes followed by 4 M HCl (110 ml.). The solution was washed with ether (3×100 ml.) and made alkaline with 7 M NaOH to pH 10–11. The freed base was taken up in ether (3×100 ml.); the extracts were dried over sodium sulfate, filtered and evaporated. The residue was dissolved in absolute ether (200 ml.) and the hydrochloride prepared by addition of ethereal hydrogen chloride. The precipitate was filtered, washed with ether, and recrystallized twice from absolute ethanol/ether and from isopropanol/isopropylether; m.p. 203°–203.5°C.; yield: 0.126 mole (52%). Calculated for $C_{18}H_{31}ClN_2O$: C 65.3, H 9.34, Cl 11.3. Found: C 65.2, H 9.29, Cl 11.3. I.r. (KBr disc, hydrochloride) μ3175 (s, amide NH), 2970 and 2940 (s, $CH_3$ and $CH_2$), 2580 (s, $NH^+$), 2505 (s, $NH^+$), 1680 (s, amide I), 1595 (w, Ph), 1531 (s, amide II), 1474 (s), 1227 (s, amide III), 778 (s, Ph 3 adjacent hydrogens out of plane) $cm^{-1}$. N.m.r. ($CDCl_3$, base) δ1.06 (t, $CH_2C\underline{H}_3$), 1.26 (t, $CH_2C\underline{H}_3$) [9H for the two triplets], 1.58–2.48 (m, 4H, $C\underline{H}_2CH_3$), 2.53 (s, 6H, $PhCH_3$), 2.82–3.30 (m, 4H, $NCH_2$), 3.72 (t, 1H, COCH), 7.98 (s, 3H, Ph). A gas chromatographic analysis showed one single peak.

## EXAMPLE 3

The racemic compound of Example 2 was resolved into the ∂- and l- optical isomers by the following procedure:

The racemate of α-(N-ethyl-n-propylamino)-n-butyro-2,6-xylidide base (9.73 g., 0.3519 mole) was dissolved in a mixture of l-tartaric acid (5.28 g., 0.3519 mole) and 19.5 ml. water by gentle heating. After filtering, the solution was cooled and left at 4°C. The crys-

tals formed were filtered cold. The mother liquor was concentrated to about half its volume and a second crop was obtained. The combined crops (I) were recrystallized repeatedly from water until constant optical rotation was obtained $[\alpha]_D^{25} = -8.3°$. The mother liquor was made alkaline with 7M sodium hydroxide and extracted with ether. The ether was evaporated and 3.18 g. (0.0115 mole) residual base was obtained which was dissolved in a solution of -tartaric acid (1.73 g., 0.0115 mole) in 6.4 ml. water with heating. From the cold solution (4°C.) crystals (II) were obtained which were recrystallized repeatedly from water until constant rotation was obtained, $[\alpha]_D^{25} = +8.6°$. The bases were liberated from the two tartrates with sodium hydroxide in water. The bases from (I) and (II) had specific rotation of +34.1° and −32.8°, respectively. The rotation of their hydrochlorides were +6.2° and −6.2°, respectively, after recrystallization from abs. ethanol - ether. Their melting points were identical, 184°–185°C.

The racemic compounds of Examples 1 and 4–8 can be resolved into the ∂- and l- optical isomers thereof by a procedure similar to the one of Example 3.

## EXAMPLE 4

This example illustrates the preparation of 2-diethylamino-2′,6′-n-valeroxylidide.

2-Bromo-2′,6′-n-valeroxylidide — In a 2 liter bottle were mixed 2,6-xylidine (0.347 mole) and glacial acetic acid (310 ml.). The mixture was cooled to 12°C. and 2-bromo-n-valeryl chloride (0.349 mole) was added rapidly. After quick mixing a precooled (5°C.) solution of sodium acetate trihydrate (85 g.) in water (340 ml.) was immediately added and the mixture was shaken for circa 30 minutes. The solid was filtered and washed carefully and repeatedly with water until the filtrate was free from bromide. After drying in a desiccator over potassium hydroxide flakes the solid (0.345 mole) melted at 189°–190.5°C. After recrystallization from 95% ethanol the melting point of the colorless crystals was 190°–190.5°C. Yield: 65–78%. Calculated for $C_{13}H_{18}BrNO$: C 54.9, H 6.38, Br 28.1. Found: C 54.9, H 6.33, Br 28.2.

2-Diethylamino-2′,6′-n-valeroxylidide — A mixture of 2-bromo-2′,6′-n-valeroxylidide (0.176 mole), diethylamine (0.528 mole), and benzene (125 ml.) was placed in a pressure vessel and heated to 100°C. for 35 hours. After cooling, the dark brown content was filtered and the solid (23.2 g. of diethylammonium bromide) washed carefully with benzene. The filtrate was extracted with 4N hydrochloric acid (3×50 ml.), the acid extract washed with ether (3×50 ml.), and based out with 7N sodium hydroxide under cooling and stirring and in the presence of ether (100 ml.). After two further extractions with ether (2×50 ml.) the combined ether extracts were dried ($Na_2SO_4$) and the ether evaporated leaving 16.5 g. of residue. The hydrochloride was prepared from the residue by dissolving it in ether and adding ethereal hydrogen chloride. The hydrochloride was recrystallized from abs. ethanol: ether (3:5) twice, m.p. 205°–206°C. Calculated for $C_{17}H_{29}ClN_2O$: C 65.3, H 9.34, N 8.95. Found: C 65.2, H 9.49, N 9.15. Only one distinct peak was obtained on gas chromatography of the salt. I.r. (KBr disc, hydrochloride): 3170 (mw, NH amide); 2968 and 2930 (m, $CH_3$ and $CH_2$); 2560 (m, $NH^+$); 1677 (s, amide I); 1593 (w, Ph); 1528 (s, amide II); 1472 and 1433 (ms); 1230 (mw, amide III); 775 (m, 3 adjacent Ph hydrogens out of plane.

## EXAMPLE 5

This example illustrates the preparation of 2-pyrrolidino-2′,6′-n-butyroxylidide.

2-Pyrrolidino-2′,6′-n-butyroxylidide — A mixture of 2-bromo-2′,6′-butyroxylidide (0.0463 mole), pyrrolidine (0.13 g. mole) and benzene (100 ml.) was refluxed for 21 hrs. The solvent and excess pyrrolidine were evaporated in vacuo leaving a partly solidifying residue that was dissolved in 1 N hydrochloric acid (125 ml.). The acid solution was washed with ether (2×50 ml.) whereafter it was made alkaline with 7 N sodium hydroxide and extracted with ether (3×50 ml.). The ether extract was dried ($Na_2SO_4$) and the solvent evaporated in vacuo. The hydrochloride was prepared by dissolving the residue in ether and adding a sufficient amount of gaseous hydrogen chloride; yield 0.0414 mole. After two recrystallizations from 95% ethanol: ethyl acetate (1:1) the colorless crystals melted at 238°–240°C. Calculated for $C_{16}H_{25}N_2OCl$: C 64.7, H 8.49, Cl 11.9. Found: C 64.9, H 8.59, Cl 12.1. I.r. (KBr disc, hydrochloride): 3450 (m, broad); 3175 (ms, amide NH); 2965 and 2927 (ms, $CH_3$ and $CH_2$); 2670, 2630, and 2600 (ms); 2475 (mw, $NH^+$); 1680 (s, amide I); 1529 (w, Ph); 1525 (s, amide II); 1469 (ms); 1227 (m, amide III); 781 (ms, 3 adjacent Ph hydrogens out of plane).

## EXAMPLE 6

This example illustrates the preparation of 2-(N-ethyl-n-butylamino)-2′,6′-n-butyroxylidide.

2-n-Butylamino-2′,6′-butyroxylidide — A mixture of 2-iodo-2′,6′-butyroxylidide (0.0315 mole), n-butylamine (0.0945 mole) and anhydrous benzene (100 ml.) was refluxed for 5 hrs. After cooling, the benzene and excess n-butylamine were evaporated in vacuum. The residue was taken up in 1 N hydrochloric acid, washed with ether (3×25 ml.), filtered, made alkaline to a pH of 9 with 7 N sodium hydroxide and extracted with ether (4×25 ml.). The ether extract was dried ($Na_2SO_4$) and the ether was then evaporated in vacuo leaving a colorless oil (0.0153 mole). (This oil is sufficiently pure for the ethylation step described below.) A hydrochloride was prepared from the oily base in anhydrous ether by addition of an ethereal hydrogen chloride solution. The formed product was not crystallizing readily from a number of solvents. On dissolving in water, crystals appeared on standing. The formed hydrochloride hydrate was recrystallized from aqueous ethyl acetate, m.p. 92°–95°C. Calculated for $C_{16}H_{27}ClN_2O \cdot H_2O$: $H_2O$ 5.71. Found: 5.73 (Karl Fischer). A sample was dried at high vacuum and elevated temperature. Calculated for $C_{16}H_{27}ClN_2O$: C 64.3, H 9.11, Cl 11.9. Found: C 64.1, H 9.26, Cl 11.8.

2-(N-ethyl-n-butylamino)-2′,6′-n-butyroxylidide — A mixture of 2-n-butylamino-2′,6′-butyroxylidide [the oily unpurified base (0.0153 mole) mentioned above] and diethyl sulfate (0.0996 mole) was heated at 90°C. for 5 hrs. After cooling, the clear amber-colored solution was mixed with 10 ml. of water, stirred for 15 min. and mixed with 10 ml. of 4 N hydrochloric acid. The acid solution was washed with ether allowing the phases to separate completely, the upper ether layer being discarded each time. The pH was adjusted to 11 with 7 N sodium hydroxide and the separating base taken up in ether (4 × 30 ml.). After drying ($Na_2SO_4$) the ether was evaporated leaving a residue of crude base (0.0395 mole). The hydrochloride was prepared by dissolving

the residue in anhydrous ether and adding ethereal hydrogen chloride to the solution. Recrystallized from abs. alcohol: ether, colorless crystals were obtained melting at 202.5°–204.5°C. Calculated for $C_{18}H_{31}ClN_2O$: C 66.1, H 9.56, Cl 10.8. Found: C 66.1, H 9.71, Cl 11.1. I.R. (KBr disc, hydrochloride): 3160 (ms, amide NH); 2960 (s) and 2890 (ms)($CH_3$ and $CH_2$); 2615–2595 (m, broad); 2505 (m, $NH^+$); 1680 (s, amide I); 1594 (w, Ph); 1530 (s, amide II); 1470 (s); 1228 (m, amide III); 781 (m, 3 adjacent Ph hydrogens out of plane).

## EXAMPLE 7

This example illustrates the preparation of 2-dimethylamino-2',6'-caproylxylidide.

2-Bromo-2',6'-caproylxylidide — A mixture of 2,6-xylidine (0.125 mole) and glacial acetic acid (115 ml.) was cooled to 10°C. in a 1 liter bottle and 2-bromocaproyl bromide (0.136 mole) was added and mixed rapidly. As fast as possible this was followed by a cool (50°C.) solution of sodium acetate trihydrate (45 g.) in water (190 ml.). The mixture was shaken for 45 min. and filtered. The precipitate was washed carefully and repeatedly with water until free from bromide ions. It was then dried in a desiccator over potassium hydroxide flakes and recrystallized from methanol: water (approx. 15:1) twice; m.p. 167°–169°C. Yield: 67%. This material was sufficiently pure for the subsequent reaction. The pure compound (one further recrystallization) had a m.p. of 168.5°–169°C. Calculated for $C_{14}H_{20}BrNO$: C 56.4, H 6.76, Br 26.8. Found: C 56.2, H 6.40, Br 25.9.

2-Dimethylamino-2',6'-caproylxylidide — A mixture of 2-bromo-2',6'-caproylxylidide (0.110 mole), dimethylamine (0.356 mole) and benzene 177 ml.) were heated in a pressure vessel for 22 hrs. at 100°C. After cooling the reaction mixture was filtered. The weight of the obtained dimethylammonium bromide indicated that 97% of the bromo compound had reacted. The filtrate was extracted with 4 N hydrochloric acid (1×50+2×25 ml.), the acid solution based out to pH 11 with 7 N sodium hydroxide and extracted with ether (3×50 ml.). The combined ether extracts were dried ($Na_2SO_4$) and evaporated in vacuo. From the residue the hydrochloride was prepared with ethereal hydrogen chloride. It was recrystallized from abs. alcohol: ether (1:8) twice, yielding colorless crystals (0.0992 mole) melting at 193.5°–194.5°C. Calculated for $C_{16}H_{27}ClN_2O$: C 64.3, H 9.10, N 9.37, Cl 11.9. Found: C 64.2, H 9.04, N 9.52, Cl 12.0. I.r. (KBr disc, hydrochloride): 3185 (m, amide NH); 2950 and 2920 (ms-m, $CH_3$ and $CH_2$); 2450 (ms, NH+); 1682 (s, amide I); 1591 (w, Ph); 1530 (s, amide II), 1470 (s); 1236 (mw, amide III); 776 (m, 3 adjacent Ph hydrogens out of plane).

## EXAMPLE 8

This example illustrates the preparation of 2-pyrrolidino-2',6'-n-valeroxylidide.

2-Iodo-2',6'-n-valeroxylidide — A mixture of 2-bromo-2',6'-n-valeroxylidide (0.137 mole), potassium iodide (0.274 mole) and dry methanol (375 ml.) was refluxed under stirring for 3 hrs. After cooling, 1 liter of water was added to the yellow-colored reaction mixture and it was left with stirring for 15 min. The precipitate was filtered, washed repeatedly with water until the filtrate was free of halogenides, and dried. After recrystallization from 95% ethanol it melted at 196.5°–197.5°C.; yield 0.105 mole of a product sufficiently pure for the next synthetic step. Another recrystallization brought the m.p. to 197°–198°C. Calculated for $C_{13}H_{18}INO$: C 47.1, H 5.48, I38.3. Found: C 47.3, H 5.36, I 38.2.

2-Pyrrolidino-2',6'-n-valeroxylidide — A mixture of 2-iodo-2',6'-n-valeroxylidide (0.0754 mole), pyrrolidine (0.226 mole) and benzene (65 ml.) was heated in a pressure vessel for 24 hrs. at 100°C. After cooling, the benzene and excess pyrrolidine were evaporated in vacuo. The residue was stirred with water (150 ml.) for 30 min. and filtered. To the filtrate 7 N sodium hydroxide was added (pH 11) with stirring and after 30 min. the solid base was filtered, washed carefully and repeatedly with water and dried in vacuo. The crude base (14 g.) was recrystallized from aqueous ethanol to constant m.p. (126°–127.5°C.); yield 4.9 g. From the mother liquors another 2.7 g. were obtained. Total yield: 37%. Calculated for $C_{17}H_{26}N_2O$: C 74.4, H 9.55, N 10.2. Found: C 74.1, H, 9.66, N 10.4. Ir. (KBr disc, base): 3210 (s, NH amide); 2933 (s), 2915 (ms) ($CH_3$ and $CH_2$); 1645 (s, amide I); 1593 (w, Ph); 1529 (s, amide II): 1478 and 1465 (ms); 770 (s, 3 adjacent Ph hydrogens out of plane).

## EXAMPLE 9

This example illustrates pharmaceutical compositions.

Solutions containing 0.25, 0.50, 0.75 and 1.0% 2-(N-ethylpropylamino)-2',6'-butyroxylidide hydrochloride without added vasoconstrictor. pH 3.5–4.5.

| Component | Amount (g) 0.25 % | 0.50 % | 0.75 % | 1.0 % |
|---|---|---|---|---|
| 2-(N-Ethylpropylamino)-2',6'-butyroxylidide, hydrochloride | 2.50 | 5.00 | 7.50 | 10.00 |
| Sodium chloride USP XVIII | 8.53 | 8.07 | 7.70 | 7.10 |
| Hydrochloric acid, 2N | If necessary to adjust pH | | | |
| Sodium hydroxide, 2N | do. | | | |
| Water for injection, USP XVIII | Sufficient amount to make 1000 ml. | | | |

The active ingredient of the solutions above can be replaced by 2-diethylamino-2',6'-n-valeroxylidide hydrochloride.

## EXAMPLE 10

This example illustrates pharmaceutical compositions.

Solutions containing 0.25, 0.50, 0.75 and 1.0% 2-(N-ethyl-propylamino)-2',6'-butyroxylidide hydrochloride with epinephrine 1:200,000. pH 3.5–4.5

| Component | Amount (g) 0.25% | 0.50% | 0.75% | 1.0% |
|---|---|---|---|---|
| 2-(N-Ethylpropylamino)-2',6'-butyroxylidide, hydrochloride | 2.50 | 5.00 | 7.50 | 10.00 |

—Continued

| Component | Amount (g) 0.25% | 0.50% | 0.75% | 1.0% |
|---|---|---|---|---|
| Sodium chloride, USP XVIII | 8.53 | 8.07 | 7.70 | 7.10 |
| Epinephrine, USP XVIII | 0.0050 | 0.0050 | 0.0050 | 0.0050 |
| Sodium metabisulfite | 0.50 | 0.50 | 0.50 | 0.50 |
| Sodium hydroxide, 2N | If necessary to adjust pH | | | |
| Hydrochloride acid, 2N | | | do. | |
| Water for injection, USP XVIII | Sufficient amount to make 1000 ml. | | | |

The active ingredient of the solutions above can be replaced by 2-diethylamino-2',6'-n-valeroxylidide hydrochloride.

In the tables presented below the following code designations have been used:

A is 2-diethylamino-2',6'-n-butyroxylidide.

B is 2-(N-ethyl-n-propylamino)-2',6'-n-butyroxylidide.

C is the ∂-optical isomer of the racemic compound B.

D is the l-optical isomer of the racemic compound B.

E is 2-diethylamino-2', 6'-n-valeroxylidide.

F is 2-pyrrolidino-2',6'-n-butyroxylidide.

G is 2-(N-ethyl-n-butylamino)-2',6'-n-butyroxylidide.

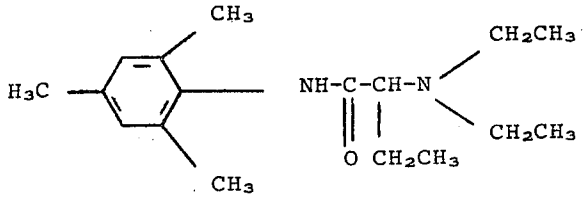
H is 2-dimethylamino-2',6'-caproylxylidide.

I is 2-pyrrolidino-2',6'-n-valeroxylidide.

X is the prior art compound N-n-butylpipecolyl-2,6-xylidide, i.e., bupivacaine or Marcaine.

Y is the prior art compound diethylaminoaceto-2,6-xylidide, i.e., lidocaine or Xylocaine.

Z is the prior art compound α-(diethylamino)-n-butyromesidide having the following structural formula:



Tables I through V contain comparative data on the duration of several of these local anaesthetic compounds, Table VI contains comparative data on the degree of tissue irritation of several of these local anaesthetic compounds, Tables VII and VIII contain comparative data on the acute toxicity of several of these local anaesthetic compounds, Tables IX through XI contain data on clinical trials of Compound B in man, and Table XII contains comparative tissue distribution data of two of these local anaesthetic compounds in a representative animal species.

TABLE I

Rat Sciatic Nerve Blocks*
Duration in Minutes ± Standard Deviation

| % Conc. as Base | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 0.125 | 156 ± 32 | 156 ± 41 | 81 ± 22 | 111 ± 5 | 117 ± 11 | 96 ± 5 | 131 ± 16 | 96 ± 22 |
| 0.25 | 235 ± 12 | 222 ± 54 | 96 ± 16 | 148 ± 19 | 123 ± 19 | 116 ± 9 | 179 ± 18 | 117 ± 11 |
| 0.5 | 297 ± 6 | 279 ± 16 | 114 ± 23 | 160 ± 27 | 140 ± 12 | 135 ± 18 | 236 ± 38** | 126 ± 13 |
| 1.0 | 308 ± 5 | 313 ± | 97 ± 6 | 191 ± 57 | 179 ± 27 | 178 ± 18 | 3 days | 146 ± 19 |
| 2.0 | — | — | 172 ± 37 | 287 ± 86 | 268 ± 36 | 180 ± 43** | — | 280 ± 42** |

| % Conc. as Base | X | Y | Z |
|---|---|---|---|
| 0.125 | 121 ± 32 | — | 101 ± 15 |
| 0.25 | 175 ± 16 | 102 ± 15 | 114 ± 14 |
| 0.5 | 212 ± 34 | 123 ± 10 | 118 ± 15 |
| 1.0 | 213 | 162 ± 39 | 126 ± 21 |
| 2.0 | — | 185 ± 23 | 146 ± 18 |

All solutions contained 1:100,000 epinephrine.
*Test method given in Truant, A.P.: Arch. Int. Pharmacodyn. 115: 483–497 (1958), which is incorporated by reference herein.
**Some animals blocked >12 hrs.

TABLE II

Guinea Pig Intradermal Wheals*
Duration in Minutes ± Standard Deviation

| % Conc. as Base | A | B | X | Y | Z |
|---|---|---|---|---|---|
| 0.125 | — | — | 156 ± 11 | — | — |
| 0.25 | 95 ± 8 | 154 ± 15 | 182 ± 4 | 78 ± 9 | 96 ± 12 |
| 0.5 | 110 ± 4 | 174 ± 12 | 252 ± 5 | 110 ± 13 | 101 ± 12 |
| 1.0 | 169 ± 8 | 232 ± 11 | 314 ± 10 | 117 ± 6 | 117 ± 14 |
| 2.0 | — | — | — | 121 ± 12 | 166 ± 19 |

All solutions contained 1:100,000 epinephrine.
*Test method given in Bulbring, E. and Wajda, I.: J. Pharmacol. Exp. Therap. 85: 73–84 (1945), which is incorporated by reference herein.

TABLE III

Peridural Anaesthesia in the Cat*
Duration of Block of Support of Weight
in Minutes ± Standard Deviation

| % Conc. as Base | A | B | X | Y |
|---|---|---|---|---|
| 0.5 | — | 209 ± 23 | 136 ± 30 | — |
| 1.0 | 143 ± 24 | 308 ± 21 | 296 ± 77** | — |
| 2.0 | 236 ± 26 | — | — | 88 ± 10 |

All solutions contained 1:100,000 epinephrine.
*Test method given in Duce, B. R., Zelechowski, K., Camougis, G. and Smith, E. R.: Brit. J. Anaesth. 41: 579–587 (1969), which is incorporated by reference herein.
**Toxic effects observed at this concentration.

TABLE IV

Peridural Anaesthesia in the Guinea Pig*
Duration of Block of Support of Weight
in Minutes ± Standard Deviation

| % Conc. as Base | E | G | X | Y |
|---|---|---|---|---|
| 0.25 | 39 ± 7 | 46 ± 8 | 38 ± 7 | 10 |
| 0.5 | 55 ± 7 | 101 ± 21 | 59 ± 12 | 14 ± 2 |
| 1.0 | 68 ± 5 | ** | 89 ± 8 | 21 ± 6 |

All solutions contained 1:100,000 epinephrine.
*Test method given in Tan and Snow, Am. J. Vet. Res., 29, 487 (1968), which is incorporated by reference herein.
**Three animals died 5 minutes post-injection and one animal did not recover from block.

TABLE V

Peridural Anaesthesia in the Dog*
Duration of Block of Support of Weight in Minutes

| % Conc. as Base | E | X | Y |
|---|---|---|---|
| 0.5 | — | 304 | — |
| 1.0 | 417 | — | — |
| 2.0 | — | — | 137 |

All solutions contained 1:100,000 epinephrine.
*Test method given in Lebeaux, MI.: Brit. J. Anaesth. 45:549–588 (1973) which is incorporated by reference herein.

TABLE VI

Irritation Studies: Rabbit Intradermal Wheals*
Irritation Index

| % Conc. as Base | A | B | X | Y | Z |
|---|---|---|---|---|---|
| 0.5 | 2.2 | 1.6 | 5.3 | 0 | 3.1 |
| 1.0 | 2.7 | 4.4 | 6.3 | 0 | 4.4 |
| 2.0 | 8.2 | 7.5 | 9.0 | 2.0 | 10.0 |

Solutions did not contain epinephrine.
*Test method given in Truant, A.P.: Arch. Int. Pharmacodyn. 115: 483–497 (1958), which is incorporated by reference herein.

TABLE VII

Acute Toxicity in Female Mice

| Compound | $LD_{50}$ and 95% Fieller Confidence Limits:mg/kg as Base Intraperitoneal | Intravenous |
|---|---|---|
| A | 54(46–117) | 9.4(8.2–11) |
| B | 62(53–82) | 5.8(5.1–6.5) |
| C | — | 15.9(14.0–18.6) |
| D | — | 6(5.4–6.7) |
| E | 51(41–58) | — |
| G | 37(28–49) | — |
| H | — | 11.3(9.2–13.9) |
| X | 40(28–56) | 6.4(5.5–7.3) |
| Y | 102(73–142) | 25(22–33) |
| Z | 93(81–110) | 9.4(8.3–10.6) |

Solutions did not contain epinephrine.

TABLE VIII

Acute Subcutaneous Toxicity in Male and Female Rats
$LD_{50}$ and 95% Fieller Confidence Limits:mg/kg as Base

| Sex | A | B | X |
|---|---|---|---|
| Male | — | 136(102–172) | 71(53–90) |
| Female | 94(73–120) | 124(98–160) | 74(58–98) |

Solutions contained 1:200,000 epinephrine.

TABLE IX

Peridural Anesthesia in Man. Compound B.
Epinephrine 1:200,000. Onset and duration times in minutes ± S.D.

| Concn. % | Volume ml. | Dose mg. | Sensory Onset Initial | Sensory Onset Complete | Motor Onset Initial | Motor Onset Complete | Complete Return Sensory | Complete Return Motor | Number of patients* |
|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 20 | 100 | 4.6±1.1 | 17.1±3.8 | 10.5±2.5 | 17.4±2.3 | 189.7±51.0 | 147.8±31.6 | 10–16 |
| 0.5 | 30 | 150 | 4.7±0.8 | 15.8±4.1 | 10.8±5.4 | 18.7±4.6 | 242.1±43.2 | 165.0±31.5 | 4–7 |
| 0.75 | 20 | 150 | 4.4±0.9 | 16.3±2.0 | 10.3±1.8 | 17.6±2.1 | 256.4±52.2 | 181.6±39.2 | 7–8 |
| 0.75 | 30 | 225 | 4.7±0.8 | 15.8±3.4 | 9.8±2.1 | 14.5±2.7 | 243.5±28.1 | 195.5±31.3 | 11–12 |
| 1.0 | 20 | 200 | 4.4±1.1 | 18.4±3.3 | 9.9±2.6 | 17.5±3.2 | 285.7±53.0 | 220.3±57.8 | 16–21 |
| 1.0 | 30 | 300 | 4.0±0.6 | 16.7±3.1 | 9.8±2.1 | 17.0±5.1 | 319.4±62.8 | 261.3±66.3 | 20–23 |

*Number of patients: The range indicates incompleteness of data

TABLE X

Intracestal Blocks in Man. Compound B.
Epinephrine 1:200. Onset and duration times in minutes ± S.D.

| Concn. % | Volume ml. | Dose mg. | Sensory Onset Initial | Sensory Onset Complete | Complete Return (sensory) Initial | Complete Return (sensory) Complete | Number of Patients |
|---|---|---|---|---|---|---|---|
| 0.25 | 60 | 150 | 3.4±0.7 | 6.8±5.0 | 348.0±77.7 | 723.0±113 | 10 |
| 0.5 | 30 | 150 | 3.6±1.4 | 14.3±12.0 | 366.8±87.0 | 590.5±115.5 | 11 |
| 0.5 | 60 | 300 | 3.4±0.8 | 5.7±1.3 | 432.0±161 | 790.5±106 | 10 |

TABLE XI

Brachial Plexus Blocks in Man. Compound B.
Epinephrine 1:200,000. Onset and duration times in minutes ± S.D.

| Concn. % | Volume ml. | Dose mg. | Sensory Onset Initial | Sensory Onset Complete | Motor Onset Initial | Motor Onset Complete | Complete Return Sensory | Complete Return Motor | Number of Patients |
|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 20 | 100 | 3.7±1.4 | 9.1±3.1 | 3.1±1.7 | 10.3±4.2 | 606.7±135 | 571.7±173 | 6–8 |
| 0.5 | 30 | 150 | 3.2±2.1 | 7.2±2.4 | 2.9±0.6 | 8.6±2.1 | 516.0±155 | 475.7±140 | 7–10 |

TABLE XII

A. Tissue Distribution of B and of X in the Guinea Pig:

| Tissue | Drug Concentration (μg/gm) B | X |
|---|---|---|
| Blood | 2.6 | 3.7 |
| Brain | 3.5 | 13.1 |
| Heart | 4.7 | 14.4 |
| Fat | 20.2 | 16.3 |
| Muscle | 2.1 | 4.8 |

B Tissue-to-Blood Ratios of B and of X in the Guinea Pig:

| Tissue | (μg/gm Tissue) (μg/ml Blood) B | X |
|---|---|---|
| Brain | 1.3 | 3.5 |
| Heart | 1.8 | 3.9 |
| Fat | 7.8 | 4.4 |
| Muscle | 0.8 | 1.3 |

Methods as described by J. Keenaghan and R. Boyes in J. P. E. T. –180: 454–463 (1972).

Irritation indices reported in Table VI are determined in the following manner:

Wheals are made on the shaved backs of albino rabbits by intradermal injection of aqueous solutions of the agents. Twenty-four hours later each wheal is graded for: presence and severity of erythema, presence and severity of edema, and presence or absence of necrotic tissue in the wheal. The grading is done on an arbitrary numerical scale, and a mean "irritation index" is calculated for all wheals at a given concentration.

The test method employed for the acute toxicity studies reported in Tables VII and VIII was as follows:

Sexually mature male or female animals are used.

Animals are divided into groups of 10 and dosed with drug solution or vehicle. After being dosed, animals are observed at intervals for several hours for overt effects and fatalities. Survivors are housed as groups according to dose level and checked once daily for the duration of the study in order to determine whether or not delayed fatalities occur.

$LD_{50}$'s and 95% Fieller confidence limits (or 95% approximate limits) are calculated by the Minimum Logic Chi Square Method of Berkson, J. Am. Stat. Assoc. 48-:565 (1953).

Surgical procedures have been performed in patients to whom compound B was administered either epidurally (Table IX), intracostally (Table X), or in the brachial plexus region (Table XI). Particularly noteworthy were the surprisingly short onset times obtained, the satisfactory depth and length of anesthesia and the complete absence of systemic as well as local side effects. An unexpected beneficiary effect of muscle relaxation was observed which facilitated the surgical procedures, e.g., in abdominal operations.

The comparative data presented in Tables I–VIII above establish that the racemic compounds of the invention generally are appreciably longer lasting local anaesthetics, particularly at use concentrations of 1% or 2%, than are the comparative homologous compounds Y and Z and yet they have a satisfactory low level of tissue irritation and a satisfactory low acute toxicity.

The local anesthetic compositions of the invention illustrated above, therefore, comprise as the active ingredient thereof a 2-alkyl-2-alkylamino-2′,6′-acetoxylidide local anesthetic compound of the invention or a pharmaceutically acceptable salt thereof in a conventional amount (e.g., a concentration of 0.1%–2.0% by weight of the carrier) sufficient to provide local anesthetic effect together with a usual nontoxic pharmaceutically acceptable carrier, such as water, water-ethanol, dextrose solutions, saline solutions and blends thereof. In addition, such herein exemplified local anesthetic compositions may contain a vasoconstrictor, as is well known in the art, such as epinephrine, norepinephrine, phenylephrine and levonorephrine, in conventional amounts (e.g., 1:100,000–1:200,000).

The local anesthetic compositions may be prepared in the usual manner by dissolving the local anesthetic compound of the invention and a vasoconstrictor, when present, in the liquid carrier.

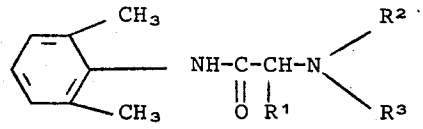
Application of the local anesthetic compositions to animals, including humans, is accomplished, as exemplified above, in the usual manner, e.g., by infiltration or injection, using conventional total dosages (e.g., 50–450 mg).

The above Compound B, i.e., 2-(N-ethyl-n-propylamino)-2′,6′-n-butyroxylidide (also called W–19053 or etidocaine or "Duranest"), not only possesses the above-mentioned combination of properties, but is further characterized by the properties of rapid onset of action and low toxicity in humans as shown by clinical studies, for example, those reported in the two articles appearing at pages 407–413 and 482–494 in Anesthesia and Analgesia . . . Current Researches, Vol. 52, No. 3, May–June, 1973, the one appearing in Brit. J. Anaesth., 45:1010–1012 (1973), and those set forth above in Tables IX through XI which were reported or disclosed in our Belgian convention Pat. No. 776,656 issued on June 14, 1972. (The entire disclosures in these three articles and Belgian patent are hereby incorporated by reference herein.)

The data of Table XII also demonstrates the more favorable tissue distribution of Compound B compared to the prior art Compound X, i.e., bupivacaine.

What is claimed is:

1. A local anesthetic composition comprising (a) as its active ingredient a compound having the structural formula



wherein $R^1$ is ethyl, propyl or butyl; $R^2$ and $R^3$ are each separately selected from the group consisting of methyl, ethyl, propyl and butyl; $R^2$ together with $R^3$ is tetramethylene; the total sum of carbon atoms in $R^1$, $R^2$ and $R^3$ is at least six; or a pharmaceutically acceptable salt thereof in an effective amount sufficient to provide local anesthetic effect, together with (b) a nontoxic pharmaceutically acceptable carrier.

**2.** The composition as defined by claim **1** wherein the active ingredient is 2-diethylamino-2',6'-n-butyroxylidide.

**3.** The composition as defined by claim **1** wherein the active ingredient is 2-(N-ethyl-n-propylamino)-2',6'-n-butyroxylidide.

**4.** The composition as defined by claim **1** wherein the active ingredient is 2-diethylamino-2',6'-n-valeroxylidide.

**5.** The composition as defined by claim **1** wherein the active ingredient is 2-pyrrolidino-2',6'-n-butyroxylidide.

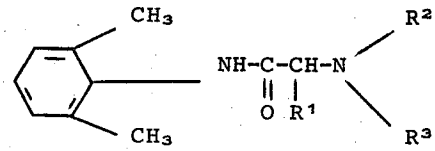
**6.** The composition as defined by claim **1** wherein the active ingredient is 2-(N-ethyl-n-butylamino)-2',6'-n-butyroxylidide.

**7.** The composition as defined by claim **1** wherein the active ingredient is 2-dimethylamino-2',6'-caproylxylidide.

**8.** The composition as defined by claim **1** wherein the active ingredient is 2-pyrrolidino-2',6'-n-valeroxylidide.



**9.** A method of inducing local anesthesia in animals, which comprises applying to the area of the body to be anesthetized a locally anesthetizing amount of a compound having the structural formula



wherein $R^1$ is ethyl, propyl or butyl; $R^2$ and $R^3$ are each separately selected from the group consisting of methyl, ethyl, propyl and butyl; $R^2$ together with $R^3$ is tetramethylene; the total sum of carbon atoms in $R^1$, $R^2$ and $R^3$ is at least six; or a pharmaceutically acceptable salt thereof.

**10.** The method as defined by claim **9** wherein said compound is 2-diethylamino-2',6'-n-butyroxylidide.

**11.** The method as defined by claim **9** wherein said compound is 2-(N-ethyl-n-propylamino)-2',6'-n-butyroxylidide.

**12.** The method as defined by claim **9** wherein said compound is 2-diethylamino-2',6'-n-valeroxylidide.

**13.** The method as defined by claim **9** wherein said compound is 2-pyrrolidino-2',6'-n-butyroxylidide.

**14.** The method as defined by claim **9** wherein said compound is 2-(N-ethyl-n-butylamino)-2',6'-butyroxylidide.

**15.** The method as defined by claim **9** wherein said compound is 2-dimethylamino-2',6'-caproylxylidide.

**16.** The method as defined by claim **9** wherein said compound is 2-pyrrolidino-2',6'-n-valeroxylidide.

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# UNITED STATES PATENT OFFICE

# CERTIFICATE OF CORRECTION

Patent No. 3,862,321 Dated January 21, 1975

Inventor(s) Adams et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 3, line 49, "give" should read -- given --. Col. 5, line 7, "N-$CH_2CH_3$" should read -- N-$CH_2CH_3$ --. Col. 7, line 9, " -tartaric acid" should read -- ∂-tartaric acid --. Cols. 11 and 12, Table I, under the caption "G", "3 days" should read -- >3 days --; bottom of Table II, second line of footnote, "85:73-84" should read -- 85:78-84 --. Cols. 13 and 14, Table IX, the figures in the last line appearing under the caption "Motor" are illegible and should therefore read -- 261.3±66.3 --.

Signed and sealed this 1st day of April 1975.

(SEAL)
Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents
and Trademarks