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ANTHELMINTIC PIPERAZINES

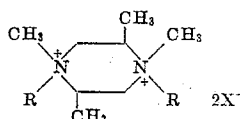
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4 Claims. (Cl. 260—268)

The subject of the present invention relates to a family of diquaternary salts derived from 2,5-dimethylpiperazine. The general formula is:



wherein X⁻ is the anion of a nontoxic acid and R is a straight chain alkyl radical having 10-12 carbon atoms inclusive.

These compounds have exceptional activity against intestinal worms and particularly against pinworms. Human pinworm infestations are extremely difficult to combat and are widespread even among highly civilized populations. The drug of choice at present is piperazine, which is inexpensive and virtually nontoxic. Its use has only one major disadvantage. The treatment extends over a long period of time, 10 days to 3 weeks, and thus involves a number of inconveniences especially as the simultaneous treatment of an entire family is generally advisable to prevent reinfection.

Such prolonged treatment with piperazine is believed to be necessary because pinworms inhabit the lower part of the intestinal tract and the drug, which is extensively absorbed, does not arrive at the site of its action in a high concentration. Against *Ascaris lumbricoides*, which dwells in the duodenum, piperazine is completely effective when given over a three-day period and removes large numbers of worms in even one dose.

Since quaternary ammonium salts of large size are not readily absorbed from the gut, it was hoped that piperazine quaternary salts might be more effective. To some extent this is true, and a family of piperazine monoquaternary salts forms the subject of a copending application. Along with the monoquaternary salts, a variety of diquaternary salts were prepared not only from piperazine but also from several C-substituted piperazines, although these compounds as the simple bases are uniformly less effective for this purpose than is piperazine.

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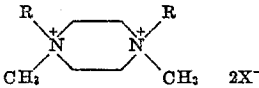
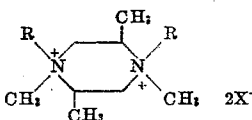
Of the C-substituted piperazines examined, the readily available 2,5-dimethylpiperazine offered derivatives of the greatest interest. In the table are shown the potencies and toxicities of some of these in comparison with those of the corresponding piperazine derivatives. Quaternary salts of both series having values for R higher or lower than those shown have only minor interest. The toxicities (LD-50) and activities were both determined on mice, the latter on mice infested with the pinworm *Syphacia obvelata* which is closely related to the human pinworm, and has been shown to be a reliable guide in these investigations (cf. Kam-Fai Chan, Am. J. Hyg. 56, 22 (1952); Paul E. Thompson and J. S. Reinertson, Exper. Parasit. 1, 384 (1952); H. W. Brown, K-F Chan and B. D. Ferrell, Exper. Parasit. 3, 45 (1954)). The dose is that given on each of two successive days and the percent of worms removed is based on the worm-burden of treated mice compared to that of control mice infected at the same time and in the same fashion.

It will be seen that in each series there is a "peaking" of the activity at some middle value of R (a very common phenomenon in biological work) and that most surprisingly the optimum value for R is higher in the 2,5-dimethylpiperazine series (R=12) than in the common piperazine series (R=10-12) despite the fact that the same figure for R gives a higher molecular weight in the former case. At the same time the toxicity to the host of the dimethylpiperazine series is appreciably less (LD-50 values higher) than in the normal series—giving a larger safety factor highly desirable in general and especially when dealing with an ailment of a nonlethal though annoying nature.

The nature of the anion, X⁻, is of only subsidiary importance, the valuable properties residing in the cation. Most frequently the iodides were first prepared and when these were of interest, the chlorides or other salts were formed. Suitable salts are (further) methosulfates, phosphates, lactates, acetates, citrates, toluene sulfonates, etc. The most convenient route is to react 2,5-dimethylpiperazine with two equivalents of RX (X being iodide, bromide or toluene sulfonate) to give an N,N'-diR-2,5-dimethylpiperazine. This is then reacted with excess methyl iodide to give a dimethiodide or with methyl-toluenesulfonate to give a dimethyl tosylate, or with methyl sulfate to give a dimethosulfate. The iodide can be converted to the chloride by treatment with silver chloride or by warming with methanolic hydrogen chloride. Other salts can be prepared from those just mentioned by conventional methods.

An alternative preparation is by treating 2,5-dimethylpiperazines with formalin and formic acid (Clarke-Eschweiler procedure) to give 1,2,4,5-tetramethylpiperazine which is then quaternized with the higher halide, usually the bromide. In general, this is less convenient since the reaction time for the quaternization step becomes inconveniently long.

COMPARISON OF ACTIVITIES OF PIPERAZINE
AND 2,5-DIMETHYLPIPERAZINE DERIVATIVES

								
R	X	LD-50, mg./kg.	Dose, mg./kg.	Percent worms removed	X	LD-50, mg./kg.	mg./kg.	Percent worms removed
C ₈ H ₁₇	I	-----	200	34	I	-----	400	100
					Cl	-----	200	33
						-----	200	45
C ₁₀ H ₂₁	I	3,700	600	100	I	3,600	500	100
			300	45			200	80
C ₁₁ H ₂₃	I	3,000	1,000	100	I	4,000	500	100
			200	70			200	96
					Cl	-----	400	100
						-----	200	99
C ₁₂ H ₂₅	I	5,500	1,500	100	I	8,000	2,500	100
			400	67			500	99
							500	92
							200	100
					Cl	8,000	200	96
							150	85
							100	60
C ₁₃ H ₂₇					I	4,000	500	82
C ₁₄ H ₂₉					I	3,700	1,200	90

A still further advantage of these diquaternary salts is that they damage the parasites irreversibly while piperazine merely paralyzes them. Usually the worms are expelled while helpless, but if any are not, they are able to continue their life normally after treatment with piperazine.

N,N'-bis-n-decyl-2,5-dimethyl piperazine

57 g. of 2,5-dimethyl piperazine, 88 g. NaHCO₃, 259 g. n-decyl bromide and 1 l. 95% ethanol were refluxed for 22 hours. Water was added to the mixture until all the salts dissolved, and the solution was concentrated in vacuo. The remaining oil was cooled and extracted twice with ether. The combined ether extracts were acidified with alcoholic hydrochloric acid and the dihydrochloride was filtered off and washed with ether. The resulting 191 g. of the dihydrochloride was suspended in water, made strongly basic with 45% NaOH, and extracted twice with benzene. The benzene extracts were evaporated in vacuo. Ether and pentane were added and the solution cooled and filtered, to give 116 g. of crystalline base, M. P. 119–121°.

N,N'-bis-decyl, N,N'-bis-methyl, 2,5-dimethyl piperazinium iodide

120 g. of N,N'-bis-n-decyl, 2,5-dimethyl piperazine was dissolved in 250 ml. of methanol and 160 g. methyl iodide was added. The vessel was kept tightly stoppered at a temperature of 40° for seven days. Most of the solvent was then evaporated in vacuo and several volumes of ether were added. The resulting crystalline solid was filtered off and dried, and then recrystallized from nitromethane until the melting point remained constant at 197–200°.

N,N'-bis decyl, N,N'-bis methyl, 2,5-dimethylpiperazinium chloride

36.3 g. of N,N'-bis decyl, N,N'-bis methyl, 2,5-dimethylpiperazinium iodide was dissolved in 100 ml. of MeOH and 21.5 g. of freshly prepared silver chloride was added with stirring. After 3 hours the mixture was filtered, and the material evaporated almost to dryness. Several volumes of ether were added; the material was filtered off and recrystallized from methanol-ether to yield 26.0 g. of pure material melting at 235–237°.

N,N'-bis-n-undecyl-2,5-dimethylpiperazine

A mixture of 100 g. of n-undecyl bromide, 22.8 g. 2,5-dimethylpiperazine, 35.7 g. of sodium bicarbonate and 600 ml. of ethanol was refluxed with stirring for 14

hours. It was then cooled and filtered. The solvent was evaporated off in vacuo, and the residue was extracted with ether twice. Dry hydrogen chloride gas was bubbled through the ether solution until it was saturated. The dihydrochloride was filtered off and washed with ether. It was then stirred with water and excess 45% NaOH to convert it to the base which was then extracted twice with benzene. The benzene was dried over K₂CO₃, and then evaporated in vacuo, leaving the base as the residue.

N,N'-bis-undecyl-N,N'-bis methyl, 2,5-dimethylpiperazinium iodide

71.5 g. of N,N'-bis-undecyl 2,5-dimethyl piperazine, dissolved in 250 ml. of acetone and 50 ml. of dry benzene, was warmed and 64 g. of methyl iodide was added. The mixture in a tightly stoppered bottle was kept at 40–50° for two weeks. Four to five volumes of ether was then added and the precipitated solid filtered off to yield 117 g. of crude crystalline residue. This, when recrystallized from nitromethane yielded material melting at 190–192°.

N,N'-bis-undecyl-N,N'-bismethyl-2,5-dimethylpiperazinium chloride

20 g. of N,N'-bis-undecyl-N,N'-bismethyl-2,5-dimethyl piperazinium iodide was dissolved in 50 ml. of absolute methanol and 17 g. of freshly prepared silver chloride was added. The mixture was stirred for 3 hours, filtered, and the filtrate evaporated almost to dryness. Several volumes of ether were added and the material was filtered off. Recrystallization from methanol-ether yielded 14 g. of solid melting at 234–236°.

N,N'-bis-n-dodecyl-2,5-dimethyl piperazine

A mixture of 57 g. of 2,5-dimethyl piperazine, 299 g. of n-dodecyl bromide, 100 g. of sodium bicarbonate and 1 l. of 95% EtOH was heated under reflux with stirring for 16 hours. The bulk of the alcohol was then evaporated in vacuo, and about 500 ml. of water was added to dissolve the salts that precipitated. The aqueous solution was brought to pH 7 with aqueous hydrochloric acid (foaming) and an additional 750 ml. of 4 N aqueous hydrochloric acid was added. The resulting precipitate of the dihydrochloride of the product was filtered off, washed with water and then with low-boiling petroleum ether. It was then suspended in benzene and converted to the base by addition of an excess of aqueous sodium hydroxide solution with efficient stirring. The product-

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base, in benzene solution, was dried over sodium hydroxide pellets, and the benzene evaporated off. The residue solidified, and was recrystallized from 1 l. of pentane (Skellysolve A) by cooling to 10° C. overnight. The crystals melted at 50–52° C., and weighed 144 g. Additional crops could be obtained from the mother liquors by partial evaporation of solvent and cooling.

N,N'-bis-dodecyl,N,N'-bis-methyl-2,5-dimethylpiperazinium iodide

50 g. of *N,N'*-bis-dodecyl-2,5-dimethylpiperazine was dissolved in 600 ml. of dry methanol and 62.5 g. of methyl iodide was added. The solution was kept tightly stoppered and warm (ca. 45–50°) for 5 days. The solution was then evaporated in vacuo to remove the solvents. Ether was added to the residue until no more material precipitated. The mixture was filtered to yield 59.5 g. of crude material. This was recrystallized until the melting point reached 196–201°.

N,N'-bis-dodecyl,N,N'-bis-methyl-2,5-dimethylpiperazinium chloride

20 g. of *N,N'*-bis-dodecyl,*N,N'*-bis-methyl-2,5-dimethylpiperazinium iodide was dissolved in 160 ml. of methanol and dry HCl gas was passed into the solution, maintained at its boiling point for ½ hour. The solution was then evaporated almost to dryness and ether added until no more material precipitated. The resulting crystals were recrystallized from methanol-ether. The yield was 14.7 g., M. P. 249–250° dec.

N,N'-bis-dodecyl,N,N'-bis-methyl-2,5-dimethylpiperazinium lactate

9.8 g. *N,N'*-bis-dodecyl-*N,N'*-bis-methyl-2,5-dimethylpiperazinium chloride was dissolved in 30 ml. absolute ethanol, and a solution of 4.03 g. sodium lactate in 30 ml. abs. ethanol was added. The mixture was cooled and 5 ml. of dry benzene was added. The sodium chloride that precipitated was filtered off after 3 hours and the filtrate was evaporated to dryness. Yield 11.3 g., M. P. 168–173°.

1,4-bis-dodecyl-1,2,4,5-tetramethylpiperazinium methanesulfonate

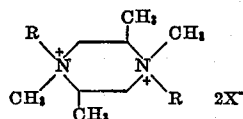
Silver methanesulfonate was prepared from equivalent

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amounts of silver oxide and methanesulfonic acid in water. One gram of 1,4-bis-dodecyl-1,2,4,5-tetramethylpiperazinium iodide dissolved in methanol was added to 650 mg. of silver methanesulfonate dissolved in 100 ml. of hot methanol. After filtration to remove silver iodide, the solvent was evaporated to leave 1.1 g. of the above-named methanesulfonate, which darkened ca. 220° and charred ca. 260° without melting.

What we claim is:

1. A compound having the formula:

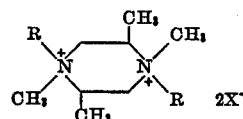


wherein R is a straight-chain alkyl radical containing 10–12 carbon atoms, and X⁻ is the anion of a nontoxic acid.

2. A 1,2,4,5-tetramethyl-1,4-bis-dodecylpiperazinium salt.

3. 1,2,4,5-tetramethyl-1,4-bis-dodecylpiperazinium chloride.

4. A process for the elimination of intestinal worms which comprises the administration of a compound having the formula



wherein R is a straight-chain alkyl radical containing 10–12 carbon atoms, and X⁻ is the anion of a nontoxic acid.

References Cited in the file of this patent

UNITED STATES PATENTS

2,755,279 Baltzly et al. July 17, 1956

OTHER REFERENCES

Smith et al.: Jour. Am. Chem. Soc., vol. 72, pp. 2969–70 (1950).