[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

THE PREPARATION AND PROPERTIES OF SOME ω-(N,N-DIALKYLAMINO)ALKYL 2-THENOATE HYDROCHLORIDES

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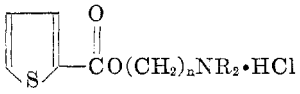
As a continuation of our studies (1, 2) directed toward the synthesis of sulfur containing compounds of medicinal interest, the present investigation of a number of ω-(N,N-dialkylamino)alkyl 2-thenoate hydrochlorides (I) was undertaken.

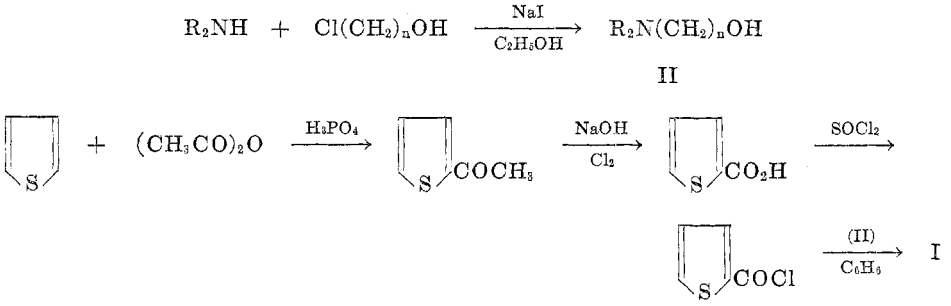


I

Representative compounds in which the secondary amino groups were morpholino and piperidino have been prepared. In these compounds the intermediate alkyl chain, between the ester group and the amino nitrogen, was varied between two and four methylene carbon atoms and included one branched chain group of three carbon atoms.

Several investigators (3, 4, 5) have reported the synthesis of certain basic esters of thenoic acids which possessed local anesthetic properties but in no case was a systematic study made of the pharmacological effects resulting from the variation of the intermediate chain length, nor have the morpholinoalkyl or piperidinoalkyl derivatives of 2-thenoic acid been reported. Therefore it seemed of interest to study the correlation of activity of these compounds with their structures.

The ω-(N,N-dialkylamino)alkyl 2-thenoate hydrochlorides of the present investigation were prepared by the following sequence of reactions:



The N-(ω-hydroxyalkyl)amines were prepared by the reaction of a two molar excess of the secondary amine with the corresponding chlorohydrin in dry ethanol, following the procedure employed by Clinton and his co-workers (6).

By the interaction of thiophene with acetic anhydride according to the method of Hartough (7) and treatment of the 2-acetylthiophene produced with chlorine

gas in an aqueous sodium hydroxide solution (8) a good yield of 2-thenoic acid was obtained. This product was converted to 2-thenoyl chloride by reaction with a slight excess of thionyl chloride in dry benzene.

The ω-(N,N-dialkylamino)alkyl 2-thenoate hydrochlorides were obtained in excellent yields from the corresponding N-(ω-hydroxyalkyl)amines by treatment with 2-thenoyl chloride using dry benzene as a diluent.

The essential data and properties of the ω-(N,N-dialkylamino)alkyl 2-thenoate hydrochlorides which have been prepared for the first time are shown in Table I.

Pharmacological results. The pharmacological studies showed the ω-(N,N-dialkylamino)alkyl 2-thenoate hydrochlorides to be comparable to procaine in the intradermal wheal test in guinea pigs. Toxicities were low, especially in

TABLE I

ω-(N,N-DIALKYLAMINO)ALKYL 2-THENOATE HYDROCHLORIDES $C_4H_3S\text{-}CO_2(CH_2)_n\text{-}N(R)(R)\cdot HCl$

2-THENOATE HYDROCHLORIDES[a]	YIELD, %	M.P., °C.	FORMULA	NITROGEN	
				Calc'd	Found
β-Piperidinoethyl	87	181.5–182.5	$C_{12}H_{18}ClNO_2S$	5.08	5.18
α-Methyl-β-piperidinoethyl	91.5	173.5–174.5	$C_{13}H_{20}ClNO_2S$	4.83	4.72
γ-Piperidinopropyl	89	169.5–171	$C_{13}H_{20}ClNO_2S$	4.83	4.78
δ-Piperidinobutyl	94	152.5–154	$C_{14}H_{22}ClNO_2S$	4.62	4.60
β-Morpholinoethyl	83.5	209–210.5	$C_{11}H_{16}ClNO_3S$	5.05	4.93
α-Methyl-β-morpholinoethyl	84.5	197–198.5	$C_{12}H_{18}ClNO_3S$	4.81	4.84
γ-Morpholinopropyl	86	190–190.5	$C_{12}H_{18}ClNO_3S$	4.81	4.74
δ-Morpholinobutyl	79	110–112	$C_{13}H_{20}ClNO_3S$	4.58	4.51

[a] Crystallized from absolute ethanol.

the morpholino compounds. Preliminary nerve block tests indicate an absence of activity. A single compound, namely, 4-morpholinobutyl 2-thenoate hydrochloride, was unusual in that it was found to be devoid of activity in both tests.

Aknowledgement. The authors wish to express their appreciation to Abbott Laboratories for the preliminary pharmacological results reported here.

EXPERIMENTAL

2-Thenoyl chloride. A solution of 64 g. (0.5 mole) of 2-thenoic acid and 95 g. (0.8 mole) of thionyl chloride in 100 ml. of dry benzene was heated at its reflux temperature for four hours on a steam-bath. The benzene and excess thionyl chloride were removed with a water aspirator. The resulting straw-colored liquid was fractionated under a vacuum using a column 30 cm. in height and 12 mm. in diameter packed with ⅛″ glass helices, to yield 54 g. (0.34 mole, 74%) of a clear liquid boiling at 85°/14 mm. The reported (9) boiling point is 190° at atmospheric pressure.

N-(ω-Hydroxyalkyl)-piperidines and -morpholines. These compounds were prepared in yields of 63 to 86% by the interaction of the appropriate secondary amine with the cor-

responding polymethylene chlorohydrin in alcoholic sodium iodide solution according to a previously described procedure (6).

ω-(N,N-Dialkylamino)alkyl 2-thenoate hydrochlorides. A solution of 0.030 mole of N-(ω-hydroxyalkyl)amine in 25 ml. of dry benzene was treated with 5 g. (0.034 mole) of 2-thenoyl chloride in a 100-ml. flask fitted with a reflux condensor. A vigorous reaction took place immediately upon addition of the 2-thenoyl chloride with the evolution of heat and the formation of a white crystalline product. After the initial spontaneous reaction had subsided, the reaction mixture was heated at reflux temperature on a steam-bath for 15 minutes to complete the reaction. The product, in a fairly pure condition, was removed from the reaction mixture by filtration and was recrystallized once from absolute ethanol.

SUMMARY

1. A series of eight ω-(N,N-dialkylamino)alkyl 2-thenoate hydrochlorides have been prepared for the first time and some of their properties were determined.

2. The results of testing these compounds for pharmacological activity are reported.

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