THIOHYDROXIMIC ESTERS

I. S-DIETHYLAMINOETHYL ESTERS OF THIOHYDROXIMIC ACIDS AND THEIR DERIVATIVES

V. E. Krivenchuk and V. E. Petrun'kin

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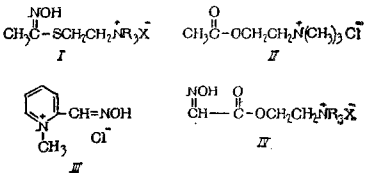
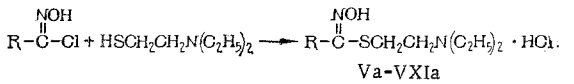
Thiohydroximic esters constitute a relatively little-studied group of organic compounds. In particular, aminoalkyl esters of thiohydroximic acids have not been described in the literature. Meanwhile, such compounds may present interest as physiologically active substances, especially as cholinesterase reactivators where cholinesterase has been inactivated by organic phosphorus insecticides. While hydroxamic acids and oximes have been widely studied as cholinesterase reactivators [1], the esters of hydroximic acids have not attracted the attention of investigators. There are data from a study of ethyl benzhydroxymate, $C_6H_5C(=NOH)OC_2H_5$, but its activity was very slight, even by comparison with benzhydroxamic acid [2]. We have not found data in the literature with respect to S-esters of thiohydroximic acids as cholinesterase reactivators. However, we think that this type of compound presents considerable interest, since reactivators of type I, which is structurally similar to acetylcholine (II), can be obtained in this series.



Effective reactivators which have found practical use, for example, 2-pyridoxal methochloride (2-PAM) (III), contain a quaternary nitrogen atom separated from the oxime group by a chain of two carbon atoms as the acetylcholine structure fragment. Reactivators of type IV, which are obtained in the series of esters and amides of oximinoacetic acid [3, 4], have a greater similarity to acetylcholine.

However, among the cholinesterase reactivators which have been described, those which are structurally closest to acetylcholine are the S-esters of thiohydroximic acids of type I which we first prepared [5]. Precisely this structural similarity of the reactivator to acetylcholine may ensure optimum conditions for fixing the reactivator on the active surface of the cholinesterase and effecting the reactivation process.

The thiohydroximic esters were prepared by the reaction of hydroximyl chlorides* with 2-diethylaminoethanethiol.



The starting hydroximyl chlorides were prepared by chlorinating the aldoximes [7, 8] dissolved in chloroform, methanol, or a mixture of chloroform and ether. Thereupon the oximes of anisic and salicylic

*This name is given in conformity with the nomenclature of [6] for organic compounds. In many works, compounds of this type are mistakenly called hydroxamyl chlorides.

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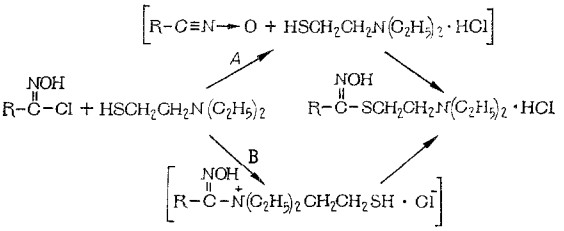
TABLE 1. Thiohydroximic Esters: a) Hydrochlorides; b) Free Bases; c) Methiodides

Compound	R	Yield (%)	Mp (in deg)	Found (%)				Empirical formula	Calc. (%)			
				C	H	halogen	S		C	H	halogen	S
Va	CH_3	47	164—165	42,53	8,58	Cl 15,47	14,09	$C_6H_{18}N_2OS \cdot HCl$	42,38	8,44	Cl 15,63	14,14
Vb		70	78—78,5	51,49	9,77	—	17,10	$C_9H_{16}N_2OS$	50,49	9,53	—	16,85
Vc		95	179—180,5	32,78	6,43	I 38,01	9,60	$C_9H_{21}IN_2OS$	32,56	6,37	I 38,23	9,65
VIa	C_2H_5	52	137—139	45,13	8,92	Cl 15,49	14,02	$C_9H_{20}OS \cdot HCl$	44,89	8,79	Cl 14,72	13,31
VIc		69	114—115,5	34,40	6,88	I 38,26	9,67	$C_{10}H_{23}IN_2OS$	34,67	6,69	I 36,64	9,25
VIIa	$CH_3CH_2CH_2$	81	143—144	47,17	9,18	Cl 13,85	12,53	$C_{10}H_{22}N_2OS \cdot HCl$	47,13	9,09	Cl 13,91	12,58
VIIc		47,5	99—100	36,70	6,43	I 35,75	9,03	$C_{11}H_{25}IN_2OS$	36,66	6,99	I 35,22	8,90
VIIIa	$(CH_3)_2CH$	81,5	130—131	47,27	8,95	Cl 13,93	12,80	$C_{10}H_{22}N_2OS \cdot HCl$	47,13	9,09	Cl 13,91	12,58
IXa	$(CH_3)_2CHCH_2$	78	136—138	48,76	9,35	Cl 13,13	11,88	$C_{11}H_{24}N_2OS \cdot HCl$	49,15	9,37	Cl 13,19	11,92
Xa	C_6H_5	70	134—135	54,74	7,37	Cl 12,10	10,71	$C_{13}H_{20}N_2OS \cdot HCl$	54,05	7,32	Cl 12,27	11,10
Xb		79,5	129—130	61,67	7,96	—	12,52	$C_{13}H_{20}N_2OS$	61,87	7,99	—	12,71
Xc		90	178—179,5 (dec.)	43,60	6,21	I 32,05	7,99	$C_{14}H_{23}IN_2OS$	42,64	5,88	I 32,19	8,13
XIa	p-BrC_6H_4	68,7	147—147,5	43,13	5,66	Cl 9,57, 21,43	8,57	$C_{13}H_{19}BrN_2OS \cdot HCl$	42,45	5,48	Cl 9,64 Br 21,73	8,71
XIb		62	107—108	47,99	6,06	Br 23,75	9,72	$C_{13}H_{19}BrN_2OS$	47,13	5,78	Br 24,15	9,67
XIc		78	171—173	35,69	5,10	Br 16,80; I 26,57	6,74	$C_{14}H_{22}BrIN_2OS$	35,52	4,68	Br 16,89 I 26,81	6,77
XIIa	o-$NO_2C_6H_4$	82	222—224 (dec.)	47,21	6,31	Cl 10,55	9,55	$C_{13}H_{19}N_3O_3S \cdot HCl$	46,77	6,04	Cl 10,62	9,60
XIIb		64	140—141	52,76	6,67	—	10,91	$C_{13}H_{19}N_3O_3S$	52,49	6,43	—	10,77
XIIc		68	178—179	38,74	5,21	I 28,48	7,18	$C_{14}H_{22}IN_3O_3S$	38,26	5,04	I 28,89	7,30
XIIIa	м-$NO_2C_6H_4$	66	107—108	46,85	6,40	Cl 10,51	9,50	$C_{13}H_{19}N_3O_3S \cdot HCl$	46,77	6,04	Cl 10,62	9,60
XIIIb		67,5	93	53,24	6,75	—	10,69	$C_{13}H_{19}N_3O_3$	52,49	6,43	—	10,77
XIIIc		74	167—168	38,69	5,30	I 28,98	7,32	$C_{14}H_{22}IN_3O_3$	38,26	5,04	I 28,89	7,30
XIVa	p-$NO_2C_6H_4$	83,5	149—151	46,86	6,34	Cl 10,58	9,56	$C_{13}H_{19}N_3O_3S \cdot HCl$	46,77	6,04	Cl 10,62	9,60
XIVb		64	100—101	52,84	6,60	—	10,40	$C_{13}H_{19}N_3O_3S$	52,49	6,43	—	10,77
XIVc		68	160—161	38,89	5,45	I 28,64	7,24	$C_{14}H_{22}IN_3O_3S$	38,26	5,04	I 28,89	7,30
XVa	3-Cl-4-$CH_3OC_6H_3$	59,5	143—144	48,18	6,63	Cl 19,44	8,74	$C_{14}H_{21}Cl_4N_2O_2S \cdot HCl$	47,57	6,27	Cl 20,06	9,07
XVb		55	Viscous mass	53,48	6,70	Cl 10,90	10,07	$C_{14}H_{21}ClN_2O_2S$	53,07	6,68	Cl 11,19	10,12
XVc		92	130—132	39,09	5,26	Cl 17,78; I 28,18	7,13	$C_{15}H_{24}ClIN_2O_2S$	39,24	5,26	Cl 7,72 I 27,66	6,98
XVIa	2-HO-3,5-$Cl_2C_6H_2$	72	186—188	42,15	5,28	Cl 28,18	8,43	$C_{13}H_{18}Cl_2N_2O_2S \cdot HCl$	41,78	5,12	Cl 28,44	8,58
XVIb		98	169—171	46,20	5,28	Cl 20,89	9,46	$C_{13}H_{18}Cl_2N_2O_2S$	46,29	5,38	Cl 21,03	9,50
XVIc		87	120—122	35,89	4,87	Cl 14,40; I 25,86	6,50	$C_{14}H_{21}Cl_2IN_2O_2S$	35,09	4,41	Cl 14,18; I 26,09	6,69

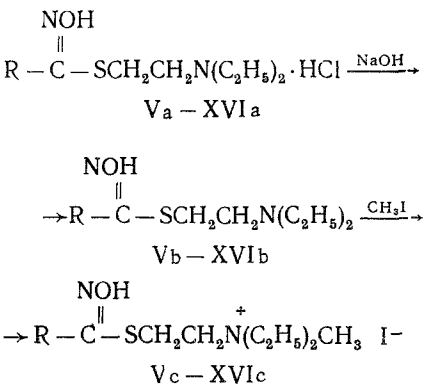
aldehydes were chlorinated to form 5-chloro-4-methoxybenzhydroximyl chloride and 3,5-dichloro-2-hydroxybenzhydroximylchloride [9].

The hydroximyl chlorides reacted very easily with 2-diethylaminoethanethiol to form the corresponding thiohydroximic esters in the form of the hydrochlorides. Apropos the mechanism of this reaction, the suggestion has been made in the literature that a nitrile oxide is formed from the hydroximyl chloride in the first stage under the action of the base, and that the thiol then adds to this compound [10-12]. In the case of the compounds which we have synthesized this can be represented by scheme A.



Along with this mechanism, it may also be suggested that in the first stage of the reaction a quaternary hydroximylammonium derivative is formed (scheme B), which then rearranges to the thiohydroximic ester hydrochloride. In the case of reaction of an aminothiol with a hydroximyl chloride, that is, when the basic group and the thiol group are present in the same molecule, occurrence of reaction by route B seems more probable to us.

The thiohydroximic ester hydrochlorides are crystalline substances which are usually readily soluble in water. Upon the action of one equivalent of alkali on aqueous solutions of the hydrochlorides, the bases are liberated; these are insoluble in water and have limited solubility in organic solvents. The quaternary derivatives were prepared by alkylating the bases dissolved in alcohol, nitromethane, or dimethylformamide (see Table 1).



According to data obtained by [13], the hydrochlorides of S-diethylaminoethyl esters of thiohydroximic acids exert a definite medicinal effect in intoxication of animals by O,O-dimethyl-O-(2,2-dichlorovinyl) phosphate (DDVP) and reactivate the cholinesterase of various organs.

EXPERIMENTAL

Hydrochloride of S-diethylaminoethyl Benzthiohydroximate (Xa). Benzaldoxime (6 g) was dissolved in 20 ml of chloroform, the mixture was cooled in ice and salt, and chlorine was passed in until the gain in weight was 3.5 g. The reaction mixture was allowed to stand for 30-40 min in the cooling mixture. Dry air was passed through the solution for 40 min to remove hydrogen chloride. A solution of 5.6 g of diethylaminoethanethiol [14] in 30 ml of ether was added in 2 to 5 ml portions to the benzhydroximyl chloride solution, with cooling and stirring. A precipitate separated in the form of a viscous mass which crystallized over the course of 20-30 min. The reaction mixture was allowed to sit in a refrigerator until the following day. The precipitate was filtered off, washed with chloroform, and dried in a vacuum desiccator. The yield was 8.5 g, mp 132-134°. After recrystallization from absolute alcohol, the mp was 134-135°.

Compounds Va-XVIa were prepared under analogous conditions.

S-Diethylaminoethyl Benzthiohydroximate (Xb). Method I. Compound Xa (2.88 g) was dissolved in 10 ml of water, and a solution of 0.6 g of potassium hydroxide in 3 ml of water was added. The precipitate which separated was filtered off, washed with water, and dried in a vacuum desiccator. The yield was 2 g, a white powder which was difficultly soluble in alcohol or chloroform, mp 129-130° (from chloroform).

Compounds Vb-XIVb were prepared similarly.

Method II. Sodium hydroxide (2 g) was dissolved in 40 ml of alcohol, the solution was cooled in ice, and 6.5 g of 2-diethylaminoethanethiol was added; to this solution was added by drops a solution of benzhydroximyl chloride which had been prepared by chlorinating 6 g of benzaldoxime. The precipitate was filtered off, washed with alcohol and then with water, and was dried in a vacuum desiccator. The yield was 7.2 g (57%), a white, finely crystalline powder, mp 131-132°, identical to the substance obtained by method I.

S-Diethylaminoethyl Benzthiohydroximate Methiodide (Xc). Compound Xb (0.5 g) was dissolved by warming (to about 40°) in a mixture of 10 ml of absolute ethanol and 7 ml of nitromethane, methyl iodide (0.91 g) was added, and the mixture was allowed to stand for 24 h at room temperature in a dark place. Dry petroleum ether (3 ml) was added to the reaction mixture, and it was cooled to −10 to −15°. The precipitate was filtered off, washed with a mixture of absolute alcohol and petroleum ether (1:2), and dried in a vacuum desiccator. The yield was 0.7 g, consisting of thin, transparent, rectangular plates, mp 178-179.5° (dec.).

Compounds Vc-XVc were prepared under similar conditions. To prepare XVIc, the starting base was dissolved in dimethylformamide.

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