g. of benzaldehyde, 20 g. of acetophenone and 50 ml. of acetone-free methanol was then added dropwise with stirring over 15 min. The reaction mixture was heated at 55–60° with stirring for an additional 1.5 hr., during which colorless solid precipitated. The mixture was cooled, filtered, and the precipitate was washed with methanol, water, again with methanol, and then ether. Upon drying, 49 g. of colorless solid was obtained, m.p. 244–248°, recrystallized from a large volume of acetone and also from benzene, m.p. 253–255°, (lit.[8] m.p. 249°). Infrared analysis showed significant absorption bands at 4.50 μ and 6.12 μ.

Anal. Calcd. for $C_{31}H_{23}ON$: C, 87.50; H, 5.45. Found: C, 87.67; H, 5.51.

Molecular weight. Calcd.[8] for $C_{31}H_{23}ON$: 425. Found: 427.

Hydrolysis of $C_{31}H_{23}ON$ to the corresponding amide. Ten grams of $C_{31}H_{23}ON$ was added portionwise with stirring to 200 g. of concentrated sulfuric acid at room temperature. Stirring was continued until all the solid dissolved. After standing at room temperature for 4 hr., the solution was poured with stirring into 2 l. water, solid precipitating. The mixture was filtered and the solid washed with water. Upon drying, 8.7 g. of colorless solid was obtained, m.p. 169–173° (dec.), recrystallized from acetone, m.p. 194–196 (dec.).

Anal. Calcd. for $C_{31}H_{25}O_2N$: C, 83.94; H, 5.68. Found: C, 83.88; H, 5.82.

Reaction of 2-thiophenaldehyde, acetophenone and sodium cyanide. A mixture of 3 g. of sodium cyanide and 30 ml. of acetone-free methanol was heated to 55–60° with stirring, 10 g. of acetophenone was added, and then 4 g. of 2-thiophenaldehyde over 5 min. with stirring. The reaction mixture was heated at 55–60° for an additional hour, cooled, filtered, and the solid washed with methanol, water, a second time with methanol, and dried. The colorless solid, 2.3 g., melted at 198–204°, recrystallized from acetone, m.p. 205–207°. Infrared analysis showed significant absorption peaks at 4.50 μ and 6.13 μ.

Anal. Calcd. for $C_{27}H_{19}S_2ON$: C, 74.13; H, 4.38. Found: C, 74.16; H, 4.46.

Reaction of benzaldehyde, methyl-p-tolyl ketone and sodium cyanide. In a similar manner, 53 g. of benzaldehyde was added over 20 min. at 55–60° to a mixture of 30 g. sodium cyanide, 400 ml. acetone-free methanol, 25 ml. water, and 90 g. of methyl-*p*-tolyl ketone. After stirring at 55–60° for 2 hr., the mixture was cooled, filtered, and solid washed with methanol, water, methanol, ether, and then dried. The colorless solid, 52.5 g., melted at 253–257°, recrystallized from dioxane, m.p. 263–266°. Infrared analysis showed significant absorption bands at 4.48 μ and 5.91 μ.

Anal. Calcd. for $C_{33}H_{29}O_2N$: C, 84.04; H, 6.20. Found: C, 84.16; H, 6.24.

Reaction of p-methoxybenzaldehyde, acetophenone and sodium cyanide. In like manner, the addition of 20 g. of *p*-methoxybenzaldehyde over 10 min. at 60–65° to 20 g. sodium cyanide, 200 ml. acetone-free methanol and 35 g. acetophenone produced 10.5 g. of colorless solid, m.p. 252–255°, recrystallized from acetic acid, m.p. 258–260°. Infrared analysis showed significant absorption bands at 2.95 μ, 3.06 μ, and 5.98 μ.

Anal. Calcd. for $C_{33}H_{29}O_4N$: C, 78.70; H, 5.80; N, 2.78. Found: C, 78.52; H, 5.94; N, 2.81.

Reaction of p-methoxybenzaldehyde, methyl-p-tolyl ketone and sodium cyanide. Similarly, the addition of 20 g. of *p*-methoxybenzaldehyde over 10 min. at 60–65° to a mixture of 20 g. sodium cyanide, 200 ml. acetone-free methanol and 40 g. methyl-*p*-tolyl ketone yielded 8.5 g. of solid, m.p. 231–233°, recrystallized from dioxane, m.p. 233–235°. Infrared analysis showed significant absorption bands at 2 95 μ, 3.05 μ, and 5.99 μ.

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Anal. Calcd for $C_{35}H_{33}O_4N$: C, 79.07; H, 6.26; N, 2.63. Found: C, 78.82; H, 6.62; N, 2.67.

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Quaternary Hydroxamic Acids Derived from Pyridine[1]

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Within the past few years several publications have appeared[3–12] in which hydroxamic acids and oximes have been described and tested as protecting cholinesterase (or alternatively reactivating it) from the inhibiting effects of such substances as tetraethyl pyrophosphate, di-isopropyl phosphorofluoridate and isopropyl methylphosphonofluoridate. It has been shown that while the hydroxamic acids exhibit little toxicity of their own to enzyme preparations, the oximes which are more potent prophylactically and therapeutically manifest inhibiting properties of their own.[13] Some of the most effective compounds described to date are nicotin- and picolinhydroxamic acids and their methiodides, and in particular pyridine-2-aldoxime methiodide.[14–25] It seemed of interest to determine

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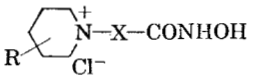
TABLE I

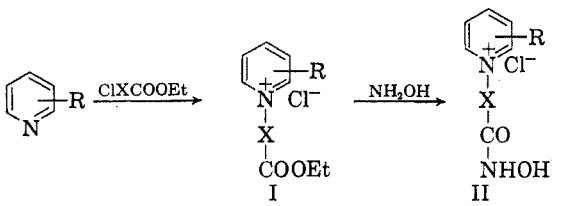
QUATERNARY HYDROXAMIC ACIDS DERIVED FROM PYRIDINE



Compound[a]	R	X	Yield, %[b]	M.P., °C.	Analyses Found C	Found H	Calcd. C	Calcd. H	Formula
N-Carbhydroxamidomethyl pyridinium chloride	H	CH_2	58	186	44.26	4.68	44.57	4.81	$C_7H_9ClN_2O_2$
N-Carbhydroxamidomethyl-2-picolinium chloride	2-CH_3	CH_2	66	170	47.43	5.55	47.41	5.47	$C_8H_{11}ClN_2O_2$
N-Carbhydroxamidomethyl-3-picolinium chloride	3-CH_3	CH_2	64	190	47.63	5.51	47.41	5.47	$C_8H_{11}ClN_2O_2$
N-Carbhydroxamidomethyl-4-picolinium chloride	4-CH_3	CH_2	70	188	47.21	5.40	47.41	5.47	$C_8H_{11}ClN_2O_2$
N-Carbhydroxamidomethyl-2,3-lutidinium chloride	2,3-$(CH_3)_2$	CH_2	84	205	49.66	6.38	49.88	6.05	$C_9H_{13}ClN_2O_2$
N-Carbhydroxamidomethyl-2,4-lutidinium chloride	2,4-$(CH_3)_2$	CH_2	76	188	50.14	5.92	49.88	6.05	$C_9H_{13}ClN_2O_2$
N-Carbhydroxamidomethyl-3,5-lutidinium chloride	3,5-$(CH_3)_2$	CH_2	81	191	49.71	5.82	49.88	6.05	$C_9H_{13}ClN_2O_2$
N-Carbhydroxamidomethyl-3-ethyl-4-picolinium chloride	3-C_2H_5,4-CH_3	CH_2	63	147	52.15	6.32	52.08	6.56	$C_{10}H_{15}ClN_2O_2$
N-Carbhydroxamidomethyl-4-(3′-hydroxypropyl)pyridinium chloride	4-($HOCH_2CH_2CH_2$)	CH_2	79	153	48.35	6.02	48.68	6.13	$C_{10}H_{15}ClN_2O_3$
N-(2′-Carbhydroxamidoethyl)pyridinium chloride	H	CH_2·CH_2	25	151	47.55	5.62	47.41	5.47	$C_8H_{11}ClN_2O_2$
N-(1′-Carbhydroxamidoethyl)pyridinium chloride	H	$CH(CH_3)$	84	158	47.73	6.09	47.41	5.47	$C_8H_{11}ClN_2O_2$
N-(1′-Carbhydroxamidoethyl)-4-picolinium chloride	4-CH_3	$CH(CH_3)$	91	206	49.75	6.24	49.88	6.05	$C_9H_{13}ClN_2O_2$
N-(1′-Carbhydroxamidoethyl)-3,5-lutidinium chloride	3,5-$(CH_3)_2$	$CH(CH_3)$	51	218	52.20	6.25	52.08	6.56	$C_{10}H_{15}ClN_2O_2$

[a] These names have been used as conforming to standard rules of nomenclature. [b] Yield based on the amount of base ester–chloride.

whether or not the activity displayed by these pyridine compounds was retained when the hydroxamic acid residue was attached through the nitrogen atom, and a series of compounds have been prepared rom pyridine and its homologs, utilizing the following sequence of reactions:



I II

R = H, alkyl or substituted alkyl
X = —CH_2—, —CH_2CH_2—, or —$CH(CH_3)$—

Treatment of the appropriate base with the ethyl ester of α- or β-chloroaliphatic acids gave rise to substituted carbethoxyalkyl pyridinium chlorides (I). The ease of this reaction depends entirely on the nature of the reactants and in some cases proceeds very slowly. The reaction was carried out at a relatively low temperature in view of the fact that alkyl β-chloropropionates can be dehydrohalogenated by certain tertiary bases[26,27]; however, since this work was completed a paper has appeared describing the formation of a base ester–chloride from ethyl-β-chloropropionate and pyridine by refluxing in ethanol.[28] The base ester–chlorides are extremely hygroscopic solids which are difficult to purify. They were reacted with hydroxylamine in methyl alcohol to give the corresponding hydroxamic acid (II) in good yield as colorless crystalline solids. The hydroxamic acids prepared in this fashion are listed in Table I.

These compounds were found to be very effective in preventing and reversing some of the physiological effects of cholinesterase inhibition, presumably by protecting, or reactivating the cholinesterase. The precise results of the biological testing of these compounds will be published elsewhere.[29]

EXPERIMENTAL[30]

Base ester–chlorides (I). The appropriate base[31] was mixed with an equivalent amount of the ethyl chloroacylate and an equal volume of ether added. If after standing at room temperature for 2 days little product had separated, then the mixture was heated under reflux for several days, ether being added if any was lost. The total time depended on the nature of the reactants.[32] No attempt was made to obtain the maximum possible yield and the reaction was terminated as soon as sufficient product had separated. The product was rapidly filtered through a sintered funnel, washed with ether, and dried in a vacuum desiccator. The base ester–chlorides obtained in this fashion were sufficiently pure for the subsequent reaction and as they are very hygroscopic, recrystallization is a tedious and wasteful procedure. These compounds form adducts with mercuric chloride from an aqueous solution. Most of them were obtained as oils which could not be crystallized; however, the adducts of *N*-carbethoxymethyl pyridinium chloride, m.p. 124–125° (Kruger[33], gives 124–125°); *N*-carbethoxymethyl-3-picolinium chloride, m.p. 149–151°; *N*-carbethoxymethyl-4-picolinium chloride, m.p. 104°; and *N*-carbethoxymethyl-2,3-lutidinium chloride, m.p. 95–98° were obtained and recrystallized from water.

Hydroxamic acids. A solution of hydroxylamine was prepared by mixing hot methanolic solutions of hydroxylamine hydrochloride (0.15 mole) and sodium methoxide (0.15 mole). The mixture was filtered under suction into a flask containing the base ester–chloride (0.1 mole) in methanol (40 ml.). The flask was stoppered and kept at 0° for 4 days. The solution was decanted from small amounts of solid that had separated and then concentrated under vacuum until crystallization of the hydroxamic acid commenced; ether was then added to precipitate the product which was finally recrystallized from ethanol. Data for these compounds are given in Table I.

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Pyrolysis of *N*-Phenylthiocarbamylethylenediamine and Related Materials

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Imidazolines are formed readily from monoacyl- or diacylethylenediamines[2] by heating the materials

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