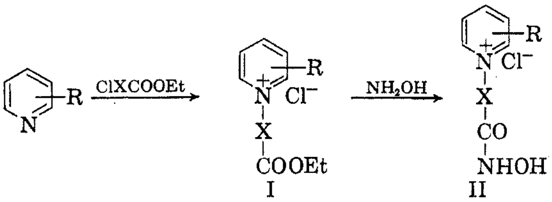
whether or not the activity displayed by these pyridine compounds was retained when the hydroxamic acid residue was attached through the nitrogen atom, and a series of compounds have been prepared from pyridine and its homologs, utilizing the following sequence of reactions:



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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(18) H. Kewitz, I. B. Wilson, and D. Nachmansohn, *Arch. Biochem. Biophys.*, **60**, 261 (1956).

(18) H. Kewitz, I. B. Wilson, and D. Nachmansohn, *Arch. Biochem. Biophys.*, **64**, 456 (1956).

(19) I. B. Wilson, *Biochim. et Biophys. Acta*, **27**, 196 (1958).

(20) D. R. Davies and A. L. Green, *Biochem J.*, **63**, 529 (1956).

(21) F. Hobbiger, *Brit. J. Pharmacol.*, **12**, 438 (1957).

(22) B. M. Askew, *Brit. J. Pharmacol.*, **12**, 336 (1957).

(23) H. Kewitz, *Arch. Biochem. Biophys.*, **66**, 263 (1957).

(24) H. Kewitz and D. Nachmansohn, *Arch. Biochem. Biophys.*, **66**, 271 (1957).

(25) H. Kewitz, *Klin. Wochschr.*, **35**, 550 (1957).

(26) C. S. Marvel, J. Dec, H. G. Cooke, and J. C. Cowan, *J. Am. Chem. Soc.*, **62**, 3495 (1940).

(27) C. Moureu, M. Murat, and L. Tampier, *Ann. chim. (Paris)*, [9] **15**, 221 (1921).

(28) S. A. Heininger, *J. Org. Chem.*, **22**, 704 (1957).

(29) W. C. Stewart and D. G. Coe, unpublished work.

(30) Melting points are uncorrected.

(31) The gift of several of the pyridine bases used in this work by the Ansul Chemical Co. is gratefully acknowledged.

(32) Ethyl chloroacetate reacts fairly rapidly at room temperature with pyridine, 2-, 3-, and 4-picoline, also 4-(3′-hydroxypropyl)-pyridine. All of the lutidines and any of the reactions involving ethyl α- or β-chloropropionate require heating; 2:6-lutidine gave no signs of reaction with ethyl chloroacetate even after standing for several months.

(33) M. Kruger, *J. prakt. Chem.*, **43** (2), 274 (1891).

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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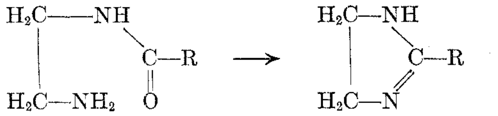
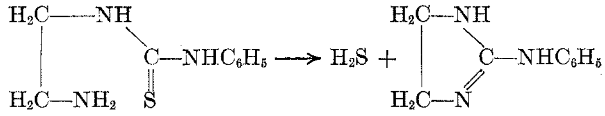
(1) To whom inquiries for reprints should be addressed.

(2) K. Hofmann, *The Chemistry of Heterocyclic Compounds. Part I. Imidazole and Its Derivatives*, Interscience Publishers, New York, 1953, p. 214.



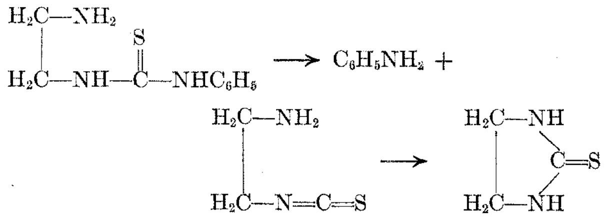
with selected reagents. In somewhat similar manner, Forssel[3] prepared 2-substituted 2-imidazolines from thioamides and ethylenediamine.

It seemed reasonable, therefore, to expect *N*-phenylthiocarbamylethylenediamine to eliminate hydrogen sulfide on heating to give 2-anilinoimidazoline. These substituted ethylenediamines are readily available by the process recently described.[4] It had been observed that these materials evolved hydrogen sulfide above the melting points. The expected reaction follows.



It was verified that this reaction did occur to an appreciable extent (about 20%). The hydrogen sulfide was precipitated as copper sulfide. The 2-anilinoimidazoline was isolated in quantity reasonably equivalent to the hydrogen sulfide. The 2-anilinoimidazoline and its picrate proved to be identical with the same products synthesized from the methyl thioether of ethylenethiourea and aniline.

The major reaction, however, was different. A liquid evolved during the pyrolysis proved to be aniline. The bulk of the residue was ethylenethiourea, about equivalent in quantity to the aniline. It thus appears that initially there might be an elimination of aniline to give an intermediate isothiocyanate which intramolecularly reacts to give ethylenethiourea. This decomposition of ureas above the melting points is not unexpected for it has been shown repeatedly[5] that substituted ureas and thioureas are thermally unstable.



Similar results were obtained when the phenyl group was replaced by *n*-butyl and *n*-heptyl groups, respectively. The major reaction was the elimination of the amine and the formation of ethylenethiourea. The minor reaction was the elimination of hydrogen sulfide accompanied by imidazoline formation. The 2-alkylimidazolines were synthesized[6] and they and their picrates proved identical with those obtained from pyrolysis.

Attempts were made to prepare the benzoyl derivatives of each of the three mentioned imidazolines. All three materials proved to be *N,N'*-dibenzoylethylenediamine. This reaction is in line with the known[7] reactions of 2-alkylimidazolines.

N-Phenylcarbamylethylenediamine decomposed similarly to give a series of parallel products. Aniline was obtained in abundance and a small amount of ethyleneurea was recovered. However, the bulk of the residue was a white solid melting above 300°. This has not been identified but probably is a low polymer formed by the reaction of the hypothetical intermediate, $H_2NCH_2CH_2NCO$, to give a linear polymer as well as the cyclic urea.

It was interesting to observe the pyrolysis of *N,N'*-bis-phenylthiocarbamylethylenediamine, for a number of possible reactions might be encountered. Amongst the products obtained were hydrogen sulfide, aniline, *N,N'*-diphenylthiourea, and ethylenethiourea. It appeared, therefore, that in part the pyrolysis might have eliminated phenyl isothiocyanate and thus formed *N*-phenylcarbamylethylenediamine. This latter material would decompose according to the earlier comments in this research. Lastly, the aniline and the phenyl isothiocyanate would unite to give the diphenylthiourea.

EXPERIMENTAL[8]

N-Phenylthiocarbamylethylenediamine. This material was prepared[4] using benzene as the solvent. The yield was 165% of the quantity anticipated on the basis of random distribution.

Pyrolysis of N-phenylthiocarbamylethylenediamine. A 500 cc. Claisen flask was partially filled with 168 g. (0.87 mole) of the amine. The flask was placed in an oil bath maintained at 155° and a slow flow of nitrogen was introduced. A heavy evolution of hydrogen sulfide resulted and the gas was trapped reasonably effectively by copper sulfate solution. After 90 min. the reaction appeared complete and the flask was gradually evacuated until at the end of 1 hr. the vacuum was 10 mm.

The distillate thus obtained weighed 60 g. (0.65 mole), boiled at 182–184°, and was identified as aniline by converting a portion to phenylthiourea.

The residue in the pyrolysis flask weighed 101 g. It was washed several times with ethanol and yielded 61 g. (0.60 mole) of a granular solid, m.p. 203–204°, which was identified as ethylenethiourea.

The balance of the residue was mainly 2-anilinoimidazoline. The alcoholic filtrate from above was evaporated to a low volume and was cooled to give an abundant precipitate. This was filtered and washed with cold alcohol. The solid was dissolved in dilute hydrochloric acid, treated with charcoal, and was recovered by making the solution strongly basic. The 2-anilinoimidazoline thus obtained was a white solid, recrystallized from water, m.p. 137–138°. Additional yield was obtained by working up the filtrate from this isolation. Even though the recovery was not quantitative, the yield was 9 g.

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(3) Ref. 2, p. 216.

(4) O. Stoutland, L. Helgen, and C. Agre, *J. Org. Chem.*, **24**, 818 (1959).

(5) J. Saunders and R. Slocombe, *Chem. Revs.*, **43**, 211 (1948).

(6) *Chem. Abstr.*, 24, P732 (1930); British Patent **310,534**.

(7) Ref. 2, p. 221.

(8) All melting points are uncorrected.

Anal. Calcd. for $C_9H_{11}N_3$: N, 26.0; equiv. wt., 161. Found: N, 26.2; equiv. wt., 163.

Treatment of the 2-anilinoimidazoline in alcohol with picric acid gave a picrate, recrystallized from alcohol, m.p. 201–202°. A mixed melting point with the authentic synthetic material was unchanged.

Anal. Calcd. for $C_{15}H_{15}N_6O_7$: N, 21.6. Found: N, 21.6.

The copper sulfide was recovered and weighed 14 g., equivalent to 4.6 g. hydrogen sulfide.

2-Anilinoimidazoline. This material was made by a modification of the process of Aspinall and Bianco.[9] A mixture of 12 g. of aniline, 16 g. of the methyl thioether of ethylenethiourea,[10] and 28 ml. of ethanol was refluxed for 2 days. The volatile material was removed by heating on a steam bath followed by evacuation for a few minutes. There remained a yellow, viscous oil which dissolved in dilute acid. Addition of base to the cold, filtered solution liberated an oil which solidified. The product, 1.8 g., is 2-anilinoimidazoline, m.p. 138–139° when recrystallized from water. The reported[6] value is 122°. Treatment of an alcohol solution with picric acid gave the picrate, recrystallized from alcohol, m.p. 201–203°.

Treatment of 2-anilinoimidazoline with benzoyl chloride in aqueous alkali gave *N,N'*-dibenzoylethylenediamine, m.p. 250° from alcohol.

Acknowledgment. The authors thank the Research Corporation for the generous grant under which this research was conducted.

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(9) S. Aspinall and E. Bianco, *J. Am. Chem. Soc.*, **73**, 602 (1951).

(10) A. McKay, M. Buchanan, and G. Grant, *J. Am. Chem. Soc.*, **71**, 766 (1949).

Formation of a Cyclic Ester from the Reaction of Di-*n*-butyltin Dichloride with Ethylene Glycol

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Received January 2, 1959

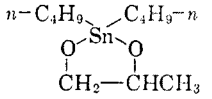
Recently, Ramsden and Banks[2] reported that the product formed from the reaction of di-*n*-butyltin dichloride with ethylene glycol in the presence of sodium hydroxide has the linear structure I.

$$HOCH_2CH_2OSn(C_4H_9\text{-}n)_2OCH_2CH_2OSn(C_4H_9\text{-}n)_2OCH_2CH_2OH$$

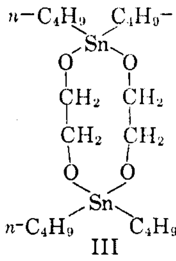
I

We have repeated this reaction and the resulting product has been found by means of its elemental analysis, melting point, and infrared spectrum to be identical to the compound obtained in this laboratory from the treatment of di-*n*-butyltin oxide with ethylene glycol. Our results of the investigation of the structure of this product do not support structure I, however. The following evidence shows that the product is a cyclic tin ester which should be formulated as III.

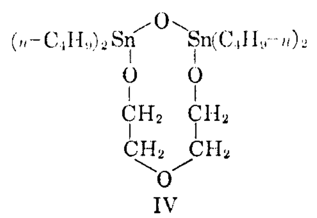
When equimolar amounts of ethylene glycol and di-*n*-butyltin oxide were heated under reflux in benzene, an equimolar amount of water was evolved and a crystalline product separated from the resulting solution. This solid was found consistently to have the molecular formula $C_{20}H_{44}O_4Sn_2$ from numerous elemental analyses[3] and from the determination of its molecular weight by three different methods. The infrared spectrum of the compound in the O—H stretching region was particularly interesting. The spectrum in chloroform solution displayed a broad, medium intense band at 3250 cm.$^{-1}$ which could be indicative of the presence of bonded O—H.[4] However, in carbon disulfide solution this band was completely absent. The identical behavior was observed with di-*n*-butyltin methyldioxolane (II).[5] In contrast, this band was not observed with di-*n*-butyltin dichloride in chloroform. These observations indicate that the band is not due to the presence of a hydroxyl group but, rather, may be due to hydrogen bonding involving the hydrogen of the chloroform and the oxygen of the glycol derivative. Tests for the presence of active hydrogen with methylmagnesium iodide and with lithium aluminum hydride were negative and, hence, provided additional proof of the absence of the hydroxyl function. These facts demonstrate that the product is a cyclic tin ester whose structure must be either III or IV. Structure IV is precluded, however, since the compound is very rapidly hydrolyzed in boiling aqueous ethanol



II



III



IV

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(1) Department of Chemistry, Boston College, Chestnut Hill, Mass.

(2) H. E. Ramsden and C. K. Banks, U. S. Patent 2,789,994 (Apr. 23, 1957).

(3) Ramsden and Banks (ref. 2) reported 36.95% Sn for their compound. Our Sn values were always significantly higher. *Cfr.* experimental section of this paper.

(4) Dr. Ramsden has kindly pointed out (private communication to J. B.) that although a hydroxyl group attached to tin is not always detectable by infrared, a hydroxyl bonded to carbon as in structure I should be observable.

(5) First prepared and characterized by Ramsden and Banks (ref. 2). Investigation of the structure of II in this laboratory supports their findings.