[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Reaction of Cyanogen with Organic Compounds. XI. Amino Alcohols[1]

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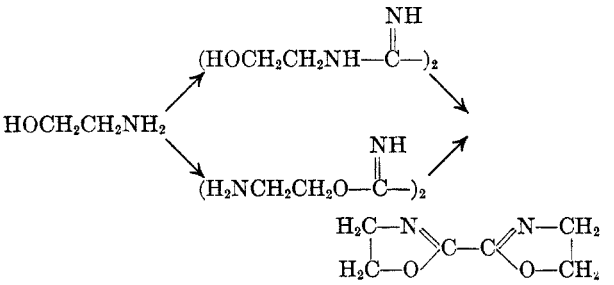
Received November 4, 1957

Amino alcohols react with cyanogen to produce oxamidines or oxaldiimidates depending upon the reaction medium. *N*-alkyl- and *N*-dialkylamino alcohols produce only diimidates. Aminoethers produce oxamidines. No evidence for the intermediate formation of cyanoformimidates or cyanoformamidines could be found.

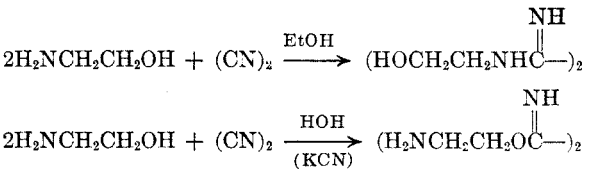
In previous papers of this series[3-5] we have discussed the reaction of cyanogen with bifunctional compounds containing NH_2 and SH groups. The commercial availability of several substituted and unsubstituted amino alcohols made these compounds attractive for an extension of this work. Furthermore, while information on the behavior of alcohols is scanty,[6,7] the indications are that conditions under which the aliphatic OH group will react with cyanogen are quite different from those required for the NH_2 group. Thus, there should be an opportunity to favor the reaction of one group over the other by controlling the conditions of the reaction. On the other hand if both groups work together, cyclic or bicyclic compounds of the oxazoline type could be formed:



In this investigation we have studied the behavior under different reaction conditions of several unsubstituted amino alcohols and of a number of compounds resulting from alkyl substitution in the NH_2 or the OH group. Results justify the following conclusions: (1) With unsubstituted amino alcohols, reaction with cyanogen can be directed by proper selection of the reaction medium, either to the NH_2 group or to the OH group. The products are oxamidines or oxaldiimidates respectively. (2) *N*-Alkylethanolamines yield oxaldiimidates regardless of the reaction medium. (3) *N*-Dialkylethanolamines and 2-alkoxyalkylamines react as would be expected of compounds in which one of the functional groups is blocked by complete substitution.

Several unsuccessful experiments with ethanolamine proved that, with the unsubstituted compounds, both the amino alcohol and the cyanogen must be completely free of carbon dioxide before a cyanogen reaction would take place. Furthermore only polar solvents would serve as reaction media; complete failure resulted from the use of a solvent like ethyl acetate. Presumably, this could be due to the necessity of dissociating the intramolecular hydrogen bond of the amino alcohol[8] before the functional groups could be attacked.

When ethanolamine in ethanol was treated with cyanogen the principal product was *sym*-bis(2-hydroxyethyl)oxamidine, but when the solvent was water, or water containing a small amount of potassium cyanide, *sym*-bis(2-aminoethyl)oxaldiimidate resulted.



The latter reaction emphasized a need, which we are presently attempting to meet, of a thorough study of the cyanogen reactions of simple alcohols, since the literature would indicate that a more potent catalyst should be required to bring both halves of cyanogen into reaction with an alcohol.[7] The effect of the potassium cyanide solution on other alkanolamines must also be investigated.

Proof of structure was especially important in this work since the oxamidine and the oxaldiimidate have the same ultimate analysis. To distinguish between the two, we have made use of the following information: (*a*) While not all oxamidines are stable as free bases, they almost always form stable, non-hygroscopic hydrochlorides.[9] (*b*) Hy-

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(3) H. M. Woodburn and R. C. O'Gee, *J. Org. Chem.*, **17**, 1235 (1952).

(4) H. M. Woodburn and B. G. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

(5) H. M. Woodburn and J. R. Fisher, *J. Org. Chem.*, **22**, 895 (1957).

(6) A. Pinner and Fr. Klein, *Ber.*, **10**, 1889 (1887).

(7) J. U. Nef, *Ann.*, **287**, 274 (1895).

(8) E. D. Bergman, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, **75**, 68 (1953).

(9) H. M. Woodburn, B. A. Morehead, and M. C. Chen, *J. Org. Chem.*, **15**, 535 (1950).

drogen sulfide reacts with oxamidines to give derivatives of dithiooxamide.[10] This is impossible with oxaldiimidates. (*c*) Oxamides can be produced by

$$(HOCH_2CH_2NHC(=NH)-)_2 + 2H_2S \longrightarrow (HOCH_2CH_2NHC(=S)-)_2 + 2NH_3$$

partial hydrolysis of oxamidines but not from oxaldiimidates.[9]

Unlike the diamines which form bicyclic compounds spontaneously when the chain length is favorable,[5] no such substances were obtained from this series and concerted efforts to produce cyclic compounds ended in failure. This was regrettable, not only because the compounds would be interesting but because they would have furnished an incontrovertible proof of structure.

The product from *N,N*-diethylethanolamine, which could only be an oxaldiimidate, confirmed the unstable nature of these compounds and their tendency to form unstable salts. On this basis the reaction products of *N*-alkylethanolamines were also deduced to be oxaldiimidates. Confirmation was obtained later in a study of the hydrogen sulfide reaction of oxamidines.[10] In the one case studied, the cyanogen reaction product was the same whether the reaction medium was ethyl ether, water, or water containing a small amount of potassium cyanide.

From 2-alkoxyethylamines we isolated stable oxamidines which in every case easily formed stable, non-hygroscopic hydrochlorides.

EXPERIMENTAL

Reagents. Cyanogen was prepared from aqueous sodium cyanide and dry copper sulfate by the method of Janz.[11] To reduce the amount of carbon dioxide in the product, the sodium cyanide (Du Pont Cyanegg) solution was treated with 10–20 ml. of a saturated solution of barium chloride and filtered before use. Hydrogen cyanide was removed by two silver nitrate scrubbing towers, water by anhydrous calcium sulfate followed by phosphorus pentoxide. Finally the cyanogen was frozen out in a trap maintained at −80° by Dry Ice and acetone. These precautions produced cyanogen in which residual carbon dioxide was too low to interfere with the reaction of unsubstituted alkanolamides.

N-Alkylethanolamines, except for *N-n*-propylethanolamine, were obtained through the courtesy of Union Carbide Corp. *N-n*-propylethanolame was prepared by the method of Biel[12] from *n*-propylamine, ethylene oxide, and hydrochloric acid. Ethanolamine, purchased from Distillation Products Industries, was fractionated immediately before use to ensure freedom from carbonate.

1-Aminopropanol-2 was purchased from Distillation Products Industries and fractionated before use. *3-Aminopropanol-1* was obtained through the courtesy of American Cyanamid Co. and fractionated before use. *2-Methoxyethylamine* and *3-methoxypropylamine* were purchased from Distillation Products Industries. They were purified by extraction from their water solutions with ether, drying, and fractionation.

2-Ethoxyethylamine and *2-propoxyethylamine* were prepared from 2-bromoethylamine hydrobromide as follows: A solution of 205 g. (1 mole) of 2-bromoethylamine hydrobromide in 500 ml. of absolute ethanol was added dropwise to a solution of 2 moles of the sodium alkoxide in 500 ml. of the anhydrous alkanol. The temperature rose to the reflux point and was maintained there for 4 hr. Sodium bromide was filtered off, the alkanol removed by distillation and the remaining liquid fractionated at atmospheric pressure. *2-Ethoxyethylamine:* b.p. 108°/758 mm., $n_D^{25°}$ 1.4070; yield 15%.[13] *2-Propoxyethylamine:* b.p. 125–126°/750 mm., $n_D^{25°}$ 1.4160; yield 14%.[14]

Method. In general cyanogenation was accomplished as follows: To provide a reasonable contact time between cyanogen and reagent, gas washing bottles with ground glass joints were used as reaction vessels. A solution of the alkanolamine in the appropriate solvent was cooled to 0° and cyanogen gas was distilled into it. In most cases removal of the Dry Ice–acetone mixture from around the cyanogen trap was sufficient to cause moderately rapid distillation. If extra heat was needed the warmth of the hand was used. The weight of cyanogen absorbed was obtained by weighing the reaction vessel before and after the cyanogenation.

Reaction of cyanogen with alkanolamines: sym-Bis(2-hydroxyethyl)oxamidine from ethanolamine. A solution of 55 g. (0.9 mole) of ethanolamine in 110 ml. of 95% ethanol was treated with 21 g. (0.43 mole) of cyanogen. At the end of the cyanogenation the mixture was orange in color. The reaction mixture was allowed to stand in an ice chest for 24 hr. during which time crystals formed.

The solid was suction-filtered and washed with ethanol. The yield of the crude product was 22 g. (29% based on cyanogen). Recrystallization from ethanol, using Norit gave white crystals; m.p. 126–127° (dec.).

Anal. Calcd. for $C_6H_{14}N_4O_2$: C, 41.3; H, 8.1; N, 32.1. Found: C, 41.2; H, 8.4; N, 31.9.

The *hydrochloride* was prepared by dissolving 0.5 g. of the free base in 25 ml. of 95% ethanol and saturating the solution with dry hydrogen chloride. A precipitate formed which was filtered off and recrystallized from 95% ethanol; m.p. 123–124° (dec.).

Anal. Calcd. for $C_6H_{16}N_4O_2Cl_2$: Cl, 28.7; N, 22.6. Found: Cl, 28.8; N, 22.5.

The *picrate* was prepared by dissolving 0.5 g. of the free base in 25 ml. of 95% ethanol and treating this solution with 25 ml. of a saturated alcoholic picric acid solution. The mixture was heated to boiling and upon cooling a yellow solid precipitated. This solid was filtered and recrystallized from ethanol; m.p. 178–180° (dec.).

Anal. Calcd. for $C_{18}H_{20}N_{10}O_{16}$: N, 22.2. Found: N, 21.8.

Details of the conversion of the oxamidine to *sym*-bis(2-hydroxyethyl)dithiooxamide by reaction with hydrogen sulfide have been reported in a previous paper.[10]

Attempts at cyclization: (*a*) A suspension of 3.4 g. (0.02 mole) of the oxamidine in 100 ml. of anhydrous carbon tetrachloride was refluxed for four hours in an apparatus fitted with a water-separating trap. At the end of this time the oxamidine had turned black but there was no evidence of dehydration as would have been indicated by the formation of two layers in the distillation trap. (*b*) To a suspension of 5 g. (0.03 mole) of the oxamidine in 100 ml. of dry benzene was added 4 g. (0.03 mole) of phosphorus pentoxide. The resulting suspension was refluxed for four hours. There was some evidence of dehydration since a portion of the pentoxide became glassy, however no product could be isolated from the reaction mixture. (*c*) To 100 ml. of dry dimethylformamide was added 3.48 g. (0.02 mole) of the oxamidine along with 2 g. of phosphorus pentoxide. The mixture was heated

(10) H. M. Woodburn, W. Platek, and E. L. Graminski, *J. Org. Chem.*, **23**, 319 (1958).

(11) G. J. Janz, *Inorganic Syntheses*, **V**, 43 (1957).

(12) J. H. Biel, *J. Am. Chem. Soc.*, **71**, 1306 (1949).

(13) L. Knorr and G. Meyer, *Ber.*, **38**, 3130 (1905).

(14) W. Traube and E. Peisner, *Ber.*, **53**, 1508 (1920).

gently at first and then to a higher temperature. As the temperature increased the mixture darkened and gave off the odor of ammonia. Diluting a portion of the mixture with ether produced only tar. It appeared that the oxamidine had completely decomposed.

sym-Bis(2-aminoethyl)oxaldiimidate from ethanolamine. (*a*) A solution of 24.4 g. (0.04 mole) of ethanolamine in 75 ml. of water containing 5 g. (0.07 mole) of potassium cyanide was treated with 19.4 g. (0.37 mole) of cyanogen. At the completion of the reaction, the mixture was extracted 5 times with 50-ml. portions of diethyl ether. Evaporation of the ether left 3 ml. of an oil which undoubtedly contained some water. A *picrate* was formed by adding 10 ml. of a saturated ethanol solution of picric acid to the oil. Yellow crystals began to form immediately. The mixture was allowed to stand for one hour and the crystals were filtered off. The solid was recrystallized from ethanol with Norit; m.p. 185–187°.

Anal. Calcd. for $C_{18}H_{20}N_{10}O_{16}$: C, 34.1; H, 3.1; N, 22.1. Found: C, 34.1; H, 3.1; N, 22.1.

(*b*) The procedure of (*a*) was repeated except that potassium cyanide was omitted. There was no difference in yield and the picrates were identical as evidenced by a mixed melting point, 185–187°.

sym-Bis(2-hydroxyethyl-2-methylethyl)oxamidine from 1-aminopropanol-2. A solution of 20 g. (0.293 mole) of 1-aminopropanol-2 in 45 ml. of ethanol was treated with 7.6 g. (0.147 mole) of cyanogen. Since there was no apparent change, the reaction mixture was protected from the atmosphere and placed in an ice chest. After 20 hr., the mixture was placed on a watch glass and the solvent was removed by evaporation hastened by blowing a stream of air over the top of the dish. The film that formed on the top of the reaction mixture had to be broken constantly to enable evaporation to continue. When the residue became viscous, it was suction filtered. The yield of crude material was 6 g. or 20% based on the amount of cyanogen used. The solid was recrystallized from absolute alcohol; m.p. 143–144° (dec.).

Anal. Calcd. for $C_8H_{18}N_4O_2$: C, 47.5; H, 8.9; N, 27.7. Found: C, 47.1; H, 9.0; N, 27.6.

All attempts to form a picrate or a hydrochloride resulted in the formation of ammonium picrate or ammonium chloride.

The reaction of 3-aminopropanol-1 with cyanogen. (*a*) Seventy-five grams (1 mole) of 3-aminopropanol-1 in 225 ml. of ethyl acetate was treated with 18 g. (0.346 mole) of cyanogen. During cyanogenation, two layers formed. The reaction mixture was placed in an ice chest for 24 hr.

At the end of this time the two layers were separated. The upper layer consisted of solvent and some 3-aminopropanol-1. To remove amino alcohol, the bottom layer was extracted 3 times with 50-ml. portions of ethyl acetate. The remaining liquid was then distilled through a 12-inch jacketed and heated column packed with glass helices. At 81.5°/9 mm. an oil began to come off which had a refractive index, n_D^{25}, 1.4720. After 12 g. of the oil had been collected the temperature began to rise steadily and a viscous liquid came off with no fractionation taking place. By treatment with methyl iodide, the liquid first obtained was proved to contain an appreciable amount of 3-aminopropanol-1.

(*b*) One-half mole (37.5 g.) of 3-aminopropanol-1 in 100 ml. of water was treated with 11.9 g. of cyanogen and the reaction mixture kept for 24 hr. in an ice chest. The water was then evaporated under 2-mm. pressure and a solid presently began to come out of solution. This was filtered and crystallized from acetone with Norit to decolorize it. The pure solid weighed 4 g.; m.p. 155–157°. A mixture with a pure sample of bis(3-hydroxypropyl)oxamide[15] showed no depression of melting point.

Anal. Calcd. for $C_8H_{16}N_2O_4$: C, 47.5; H, 7.8; N, 13.7. Found: C, 47.2; H, 8.0; N, 13.8.

(*c*) One mole of 3-aminopropanol-1 (75 g.) in 160 ml. of absolute ethanol was treated with 24.3 g. (0.467 mole) of cyanogen. The reaction mixture was allowed to stand in an ice bath for 24 hr. At the end of this time it was dark brown in color.

Preparation of the *picrate* was attempted by treating 10 ml. of the reaction mixture with 25 ml. of a saturated ethanol solution of picric acid and heating to boiling. The solution was allowed to come to room temperature and finally cooled in an ice bath. No crystals formed even after 2 days.

The *hydrochloride* was formed by saturating the remainder of the reaction mixture with dry hydrogen chloride at 0°. A solid precipitated which contained some organic material and some ammonium chloride. The solid was filtered, washed twice with ethanol, and dried in a vacuum desiccator. It was recrystallized from ethanol, however each crystallization produced a greater amount of ammonium chloride. After one recrystallization the substance melted at 145–148° (dec.).

Three grams of the impure hydrochloride was treated with an excess of *n*-butylamine. The reaction mixture was refluxed for two hours. At the end of this time, 50 ml. of water was added and a fibrous solid came out. The solid was recrystallized from petroleum ether with Norit; m.p. 85–86°. Admixture of tetra-*n*-butyloxamidine[16] gave no melting point depression. This was taken as evidence that *sym-bis(3-hydroxypropyl)oxamidine* had been formed in the reaction of 3-aminopropanol-1 with cyanogen, although we could not isolate it in the pure state.

Attempted reaction of 2-amino-2-methyl-propanol-1 with cyanogen. All attempts to find conditions favorable for a reaction between this amino alcohol and cyanogen ended in failure. Cyanogenations were performed in ethanol and diethyl ether solutions. Two moles of the amino alcohol was used for one mole of cyanogen in each run and the volume of the solvent was varied from 75 to 200 ml. Evaporation of the solvent gave only a dark, oily residue. Attempts to form a hydrochloric acid salt of the product gave quantitative yields of the hydrochloric acid salt of the starting material.

Reaction of cyanogen with N-alkylsubstituted ethanolamines: sym-Bis(2-methylaminoethyl)oxaldiimidate from *N*-methylethanolamine. A solution of 2 ml. of *N*-methylethanolamine in 6 ml. of diethyl ether was placed in a test tube and cooled to 0°. Cyanogen (0.65 g.) was distilled from a trap into the solution at a slow rate since it had been found that if the rate of cyanogenation was too rapid, the mixture would heat up considerably, darken, and yield very little product. During the passage of cyanogen, the solution turned milky and finally separated into 2 layers. Cyanogenation was continued until the solution was just saturated. By this time the mixture was dark brown. Too much or too little cyanogen rendered the reaction unsuccessful.

The lower layer solidified upon standing or scratching the walls of the test tube. The solid could not be isolated by suction filtration since when exposed to the atmosphere it darkened and formed an oil within a few minutes.

To form the more stable *hydrochloride*, 4 ml. of 95% ethanol was added to the reaction mixture and the resulting solution was slowly saturated with hydrogen chloride gas, making sure that the temperature stayed below 10° at all times. If ethanol was not added before saturating with hydrogen chloride, an oil formed, and if this was not separated quickly from the upper layer it finally resulted in the formation of ammonium chloride. With ethanol present, long needles formed, or an oil which could be induced to crystallize by placing it in a vacuum desiccator and evacuating to about 20 mm. of mercury.

(15) Prepared from oxalyl chloride and 3-aminopropanol-1.

(16) H. M. Woodburn, B. A. Morehead, and M. C. Chen, *J. Org. Chem.*, **15**, 541 (1950).

Recrystallization was carried out successfully only in absolute solvents since the crystals were quite hygroscopic. They were recrystallized from an absolute ethanol–diethyl ether pair with Norit for decolorizing. The yield of crude material was 1.5 g. (45% based on cyanogen); the melting point of the pure crystals was 165–166°.

Anal. Calcd. for $C_8H_{20}N_4Cl_2O_2$: C, 34.9; H, 7.3; N, 20.4; Cl, 25.8. Found: C, 34.6; H, 7.0; N, 20.4; Cl, 25.5.

sym-Bis(2-ethylaminoethyl)oxaldiimidate from *N*-ethylethanolamine. (*a*) With the same volume of *N*-ethylethanolamine and the same procedure described above, a 56% yield (based on cyanogen) of *sym-bis(2-ethylaminoethyl)oxaldiimidate dihydrochloride* was produced. The pure solid melted at 169–170°.

Anal. Calcd. for $C_{10}H_{24}N_4Cl_2O_2$: C, 39.6; H, 7.9; N, 18.4; Cl, 23.4. Found: C, 39.3; H, 7.7; N, 18.3; Cl, 23.8.

(*b*) A solution of 27.3 g. (0.307 mole) of *N*-ethylethanolamine in 75 ml. of water containing 5 g. (0.07 mole) of potassium cyanide was treated with 16 g. (0.307 mole) of cyanogen at a moderate rate. The reaction mixture was then extracted 6 times with 50-ml. portions of diethyl ether. The ether was evaporated and about 3 ml. of oil remained. This was dissolved in 3 ml. of ether and 3 ml. of ethanol, cooled to 0°, and saturated very slowly with dry hydrogen chloride gas. An oil came out which crystallized in a vacuum desiccator. After recrystallization from absolute ethanol–diethyl ether, the solid gave no depression of melting point when mixed with the solid obtained in (*a*). The yield was 1.5 g. or 2.2% based on cyanogen.

(*c*) The reaction was repeated exactly as in (*b*) with the exception that potassium cyanide was not used. The hydrochloride was identical to that formed in (*a*) and (*b*).

Attempted reaction of cyanogen with N-propylethanolamine. The same quantities of the amino alcohol and diethyl ether were used as above. The results of cyanogenation were similar, however the oil which formed on saturating the reaction mixture with dry hydrogen chloride was very difficult to purify. It was extremely hygroscopic and loathe to crystallize. After 4 recrystallizations from absolute ethanol–diethyl ether the solid still melted over the range 180–225°. When the temperature of the melting point block was elevated to 300° it was evident that ammonium chloride was present since the walls of the capillary tube were coated with sublimed solid. No further attempts at purification were made.

Attempted reaction of cyanogen with N-n-butylethanolamine. (*a*) The same volume of amino alcohol and ether were used as above. No layers formed during or after the reaction. When the formation of a hydrochloride was attempted, only ammonium chloride was produced.

(*b*) A solution of 4 ml. of the amino alcohol in 4 ml. of absolute ethanol was saturated with cyanogen at 0°. This mixture was treated with dry hydrogen chloride until saturated. Only ammonium chloride was produced.

(*c*) The same procedure was followed as in (*b*) except that the cyanogenation mixture was treated with 10 ml. of a saturated ethanolic solution of picric acid. The mixture was brought to a boil and allowed to cool. No crystals formed even after two days.

(*d*) A solution of 2 ml. of the amino alcohol in 6 ml. of diethyl ether was saturated with cyanogen at 0°. The reaction mixture was then treated with a saturated solution of dry hydrogen chloride in ether. A solid formed which became gummy and formed ammonium chloride after filtration.

Attempted isolation of cyanoformimidates. *N*-methyl-, *N*-ethyl-, and *N*-butylethanolamines were cyanogenated at 0° in various solvents such as ethanol, ethyl acetate, and diethyl ether in a ratio of 2 moles of the amino alcohol to 1 mole of cyanogen, with the solvent volume varying from 100 to 250 ml. After cyanogenation the solvent was distilled off at atmospheric pressure and the residue fractionated at pressures from 1–5 mm. of mercury using a 12-inch jacketed and heated column packed with glass helices. After the first fraction, which was solvent, no clean cut fractions were obtained. A steady flow of viscous liquid came off as the temperature rose. Analysis of various portions of the distillate and of picrates formed from them did not give results which coincided with calculated percentages for cyanoformimidates.

Reaction of cyanogen with N-dialkylsubstituted ethanolamine: sym-Bis(2-diethylaminoethyl)oxaldiimidate from *N*-diethylethanolamine. A solution of 41.6 g. (0.356 mole) of *N*-diethylethanolamine in 75 ml. of water containing 5 g. (0.07 mole) of potassium cyanide was treated with 18.5 g. (0.356 mole) of cyanogen. At the end of the reaction the mixture was extracted 6 times with 50-ml. portions of diethyl ether. The ether was evaporated and 50 ml. of an impure oil was obtained which decomposed rapidly even under reduced pressure. A picrate of the oil was formed by adding 250 ml. of a saturated ethanol solution of picric acid. The solid which came down was filtered off immediately. If the reaction mixture was allowed to stand or if it was heated to boiling, the solid that first come down redissolved and another crystalline material formed which was ammonium picrate. No solvent was found which was suitable for recrystallizing the picrate. Therefore the solid was placed in a large volume of ethanol, brought to a boil, and filtered while hot. This procedure removed the soluble impurities. When heated in a capillary tube, the solid contracted in volume at about 130°, finally melting at 195–198° with decomposition.

Anal. Calcd. for $C_{26}H_{36}N_{10}O_6$: C, 41.9; H, 4.8; N, 18.8. Found: C, 41.8; H, 4.6; N, 18.7.

Reaction of cyanogen with 2-alkoxyethylamines: sym-Bis(2-methoxyethyl)oxamidine from 2-methoxyethylamine. Fifty-eight grams of a 65–70% water solution of 2-methoxyethylamine (approximately 0.5 mole) was further diluted with 40 ml. of ethanol and treated with 12.8 g. (0.246 mole) of cyanogen. The reaction mixture was allowed to stand for 24 hr. in an ice chest. At the end of this time it was placed in a large watch glass and the solvent removed at room temperature by blowing air over the top of the dish.

When approximately one-half of the solvent had been removed crystals began to form. These were filtered when only a small amount of the solvent remained. They were recrystallized from diethyl ether with Norit; m.p. 73–75°. The yield of crude material was 23 g. (46% based on cyanogen). The compound appeared to decompose upon standing, since after two weeks the crystals had darkened in color.

Anal. Calcd. for $C_8H_{18}N_4O_2$: C, 47.5; H, 8.9; N, 27.7. Found: C, 47.4; H, 8.8; N, 27.4.

The *hydrochloride* was prepared by dissolving 1 g. of the free base in 5 ml. of ethanol and saturating the resulting solution with dry hydrogen chloride. The reaction mixture was cooled to 0° in an ice bath and the resulting crystals were filtered off. The hydrochloride was recrystallized from ethanol–diethyl ether. The melting point of the purified solid was 194–195° (dec.).

Anal. Calcd. for $C_8H_{20}N_4Cl_2O_2$: C, 34.9; H, 7.2; N, 20.3; Cl, 25.9. Found: C, 34.8; H, 7.1; N, 20.3; Cl, 26.2.

sym-Bis(2-ethoxyethyl)oxamidine from 2-ethoxyethylamine. Using the same conditions as above, 13.4 g. (0.149 mole) of 2-ethoxyethylamine in 32 ml. of ethanol was treated with 3.9 g. (0.075 mole) of cyanogen. The yield of crude crystals was 9 g. (52% based on cyanogen). The melting point of the solid, purified by recrystallization from ether, was 87–89°.

Anal. Calcd. for $C_{10}H_{22}N_4O_2$: C, 52.1; H, 9.5; N, 24.3. Found: C, 52.0; H, 9.4; N, 24.3.

The *hydrochloride*, prepared as above, was recrystallized from ethanol; m.p. 197–198° (dec.).

Anal. Calcd. for $C_{10}H_{24}N_4Cl_2O_2$: C, 39.6; H, 7.9; N, 18.4; Cl, 23.4. Found: C, 39.5; H, 7.7; N, 18.3; Cl, 23.7.

sym-Bis(2-propoxyethyl)oxamidine from 2-propoxyethylamine. A solution of 11.7 g. (0.136 mole) of 2-propoxyethylamine in 26 ml. of ethanol was treated with 3.5 g. (0.068 mole) of cyanogen. The yield of crude product was 6 g. (35% based on cyanogen). The solid was difficult to re-

crystallize, therefore it was converted to the hydrochloride before analysis. The hydrochloride required 5 recrystallizations from absolute ethanol before a reasonable degree of purity was achieved. The melting point was 219–220° (dec.).

Anal. Calcd. for $C_{12}H_{28}N_4Cl_2O_2$: C, 43.5; H, 8.4; N, 16.9; Cl, 21.4. Found: C, 43.3; H, 8.2; N, 16.8; Cl, 21.7.

sym-Bis(3-methoxypropyl)oxamidine from 3-methoxypropylamine. A solution of 75 g. (0.833 mole) of 3-methoxypropylamine in 175 ml. of ethanol was treated with 19 g. (0.365 mole) of cyanogen. The yield of crude crystals was 54.5 g. (64.4% based on cyanogen). After recrystallization from ethanol with Norit the solid melted at 89–91°.

Anal. Calcd. for $C_{10}H_{22}N_4O_2$: C, 52.1; H, 9.5; N, 24.3. Found: C, 52.0; H, 9.1; N, 24.6.

The *hydrochloride* prepared as above, was recrystallized from ethanol and melted at 227–228° (dec.).

Anal. Calcd. for $C_{10}H_{24}N_4Cl_2O_2$: C, 39.9; H, 7.9; N, 18.4; Cl, 23.4. Found: C, 39.7; H, 7.7; N, 18.8; Cl, 23.7.

BUFFALO 14, N. Y.

[CONTRIBUTION NO. 487 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Syntheses in the Pyrrole Series

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Received December 9, 1957

A number of pyrryl ketones and their derivatives were prepared for screening for pharmacological and chemotherapeutic activity. For comparison purposes, some other related heterocyclic compounds were also prepared. A few of the pyrryl ketones, especially 3-propionylpyrrole, were active as muscle relaxants in the anti-strychnine test in mice and cats.

Extracts of Valerian root[1] (Valeriana officinalis) have been claimed to reduce blood pressure and have some cardiac and sedative action. The finding of 2-acetylpyrrole in such extracts,[2] and also the reported hypnotic activity of 2-isobutyl pyrryl ketone[3] suggested further examination of pyrrole ketones and related compounds in order to determine the range of their biological actions.

A number of new pyrrole ketones (Table I) were prepared and tested as muscle relaxants in the anti-strychnine[4] test in mice and cats. The following previously reported pyrrole ketones were also prepared using the Grignard reaction for comparison purposes: 2- and 3-propionylpyrroles, 1-methyl-2-propionylpyrrole, 2-pyrryl isobutyl ketone, 1-(2-pyrryl)-1,3-butadione, 2-furyl 2-pyrryl ketone, 2-phenylacetylpyrrole, 2,5-dimethyl-3-propionylpyrrole, and 2,5-dimethyl-3-acetylpyrrole. Although many of the pyrrole ketones exhibited some activity as muscle relaxants, 3-propionylpyrrole[5] only (m.p. 117°), was found to be of the order of Myanesin in this test, while interestingly, 2-propionylpyrrole (m.p. 54°) was inactive.

The reduction of 3-propionylpyrrole to 3-propylpyrrole, the partial reduction to α-ethyl-3-pyrrolemethanol, and methylation to yield 1-methyl-3-propionylpyrrole eliminated anti-strychnine activity.

The heterocyclic analogs of 3-propionylpyrrole, 3-propionylfuran, 3-propionylthiophene, and also 2-propionylpyrazine, were inactive in the anti-strychnine test. During the work on the *C*-propionylpyrroles, some errors in the literature were cleared up. 2-Propionylpyrrole readily formed the phenylhydrazone (m.p. 112–114°) but failed to yield a semicarbazone; while 3-propionylpyrrole gave a semicarbazone (m.p. 181°) but failed to yield a phenylhydrazone. Previous reports[6] on the ketone derivatives of *C*-propionylpyrroles undoubtedly described mixtures of the 2 and 3 isomers.

2-Propionylpyrrole yielded a hydrazone and oxime but 3-propionylpyrrole failed to give either.

The *C*-propionylpyrroles failed to react with acetylene in liquid ammonia using sodium, potassium, or lithium to yield the acetylenic alcohols. We were unable to prepare hydantoins or substituted glycidamides using a modified Darzens' reaction[7] with chloroacetamide. The failure of the modified Darzens' reaction is probably due to the acidic pyrrole hydrogen on the nitrogen.[8]

The mixed acycloins, α-hydroxybenzyl-2-pyrryl ketone, the 4-chlorbenzyl and the 2,4-dichlorbenzyl acycloins were prepared. The presence of a high band in the ultraviolet spectrum near 290 mμ (ε 16000) of the mixed acycloins suggested the possibility of an enediol structure. However, comparison with α-pyridoin[9] which is known to be a

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