[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Further Observations on the Alcoholysis of Diethyl Diiminomalonate Monohydrochloride. Some New Pyrimidines

By S. M. McElvain and Bryce E. Tate[1]

When diethyl diiminomalonate monohydrochloride is heated in refluxing alcohol, only small amounts of diethyl malonate and carbethoxyacetamide (VII), which may be considered as direct alcoholysis products, are obtained. The principal reaction products are malondiamidine dihydrochloride (XIV), which appears at the point where ammonium chloride generally separates in other iminoester hydrochloride alcoholyses, 2-carbethoxymethyl-4,6-diethoxypyrimidine (XII), the corresponding amide XIII, and a polymeric product, the structure of which is approximated by XV. Attempts to synthesize XII and XIII were unsuccessful, but a number of new pyrimidines and intermediate amidines have been obtained and certain peculiarities of their properties are described.

In an earlier paper[2] the extraordinary stability of diethyl diiminomalonate monohydrochloride (I) to alcoholysis was noted. In a further study of the properties of this salt it has been subjected to the more drastic alcoholysis conditions of refluxing ethanol. The products obtained from this reaction are now reported.

The alcohol-insoluble salt, which separated at the point where ammonium chloride generally appears in the alcoholysis of an iminoester hydrochloride, was malondiamidine dihydrochloride (XIV); the yield of this product was 22%, based on the malonic iminoester moiety of I, but represented 44% of the available chloride ion. From the alcoholic solution was separated a product which appears to be 2-carbethoxymethyl-4,6-diethoxypyrimidine ((XII) 12.5%), the corresponding amide ((XIII), 3.6%) small amounts (1 and 1.6%) of carbethoxyacetamide (VII) and diethyl malonate (X), and a polymeric hydrochloride, indicated as XV, which represented 23% of the weight of I used in the reaction. The series of reactions (1)–(11) shown below illustrate the manner in which these products are believed to be formed.

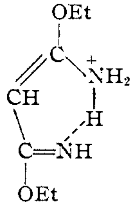
The production of the amidine salt (XIV) in such relatively large amounts, and to the exclusion of ammonium chloride, obviously requires the interaction of I or its free base (III) with ammonium chloride (reaction 10).

One source of the latter salt would be from the alcoholysis of the iminoester hydrochloride (I) to the corresponding orthoesters (V and VI). However, the relatively small amounts of reaction products, VII and X, which would originate from this reaction, indicates that the reactions (1)–(6), which involve the direct alcoholysis of I, occur to only a small extent. The principal reaction products, other than the amidine salt (XIV), are the pyrimidines XII and XIII, and the polymeric salt (XV), all of which are intermolecular condensation products of I. It is from this latter type of reaction, and from subsequent alcoholysis of such condensation products (reaction (8)), that most of the necessary ammonium chloride required for the production of the amidine salt (XIV) must come.

It is, therefore, apparent that the previously noted resistance of the monohydrochloride (I) to alcoholysis at 40° persists at the temperature of boiling alcohol. This remarkable stability of I to alcoholysis is doubtless due to the resonance of the ene-amine form of the cation of I, which may involve the open chain forms Ia and Ib or the cyclic structure Ic originally suggested.[2] This resonance has the effect of distributing the positive charge

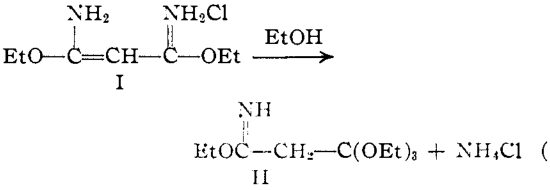
$$\mathrm{EtO\overset{^+NH_2}{\overset{\|}{C}}-CH=\overset{NH_2}{\overset{|}{C}}-OEt \longleftrightarrow EtO\overset{NH_2}{\overset{|}{C}}=CH-\overset{^+NH_2}{\overset{\|}{C}}-OEt}$$

Ia Ib

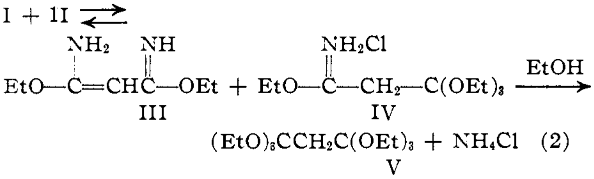


Ic

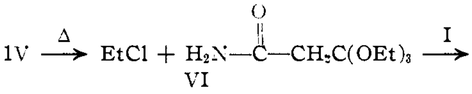
between the two nitrogen atoms so that the charge on each is about one-half that in a simple iminoester hydrochloride. Inasmuch as the latter readily undergo alcoholysis at 40° it is apparent that the rate of this reaction is related to the magnitude of the positive charge on the imino nitrogen. Thus I falls between the simple iminoester hydrochlorides and the free iminoesters, which carry no positive charge on the nitrogen and undergo no noticeable alcoholysis even in refluxing alcohol. The presence of the normal esters VII, X and XII rather than the corresponding orthoesters as reaction products indicates that any initially formed orthoesters, II, V, VI, etc., are cleaved by the hydrochloride salt (I).[3]



$$\underset{\mathrm{I}}{\mathrm{EtO-\overset{NH_2}{\overset{|}{C}}=CH-\overset{NH_2Cl}{\overset{\|}{C}}-OEt}} \xrightarrow{\mathrm{EtOH}} \underset{\mathrm{II}}{\mathrm{EtO\overset{NH}{\overset{\|}{C}}-CH_2-C(OEt)_3}} + \mathrm{NH_4Cl} \quad (1)$$



$$\mathrm{I + II} \rightleftarrows \underset{\mathrm{III}}{\mathrm{EtO-\overset{NH_2}{\overset{|}{C}}=CH\overset{NH}{\overset{\|}{C}}-OEt}} + \underset{\mathrm{IV}}{\mathrm{EtO-\overset{NH_2Cl}{\overset{\|}{C}}-CH_2-C(OEt)_3}} \xrightarrow{\mathrm{EtOH}} \underset{\mathrm{V}}{\mathrm{(EtO)_3CCH_2C(OEt)_3}} + \mathrm{NH_4Cl} \quad (2)$$



$$\mathrm{IV} \xrightarrow{\Delta} \mathrm{EtCl} + \underset{\mathrm{VI}}{\mathrm{H_2N-\overset{O}{\overset{\|}{C}}-CH_2C(OEt)_3}} \xrightarrow{\mathrm{I}}$$

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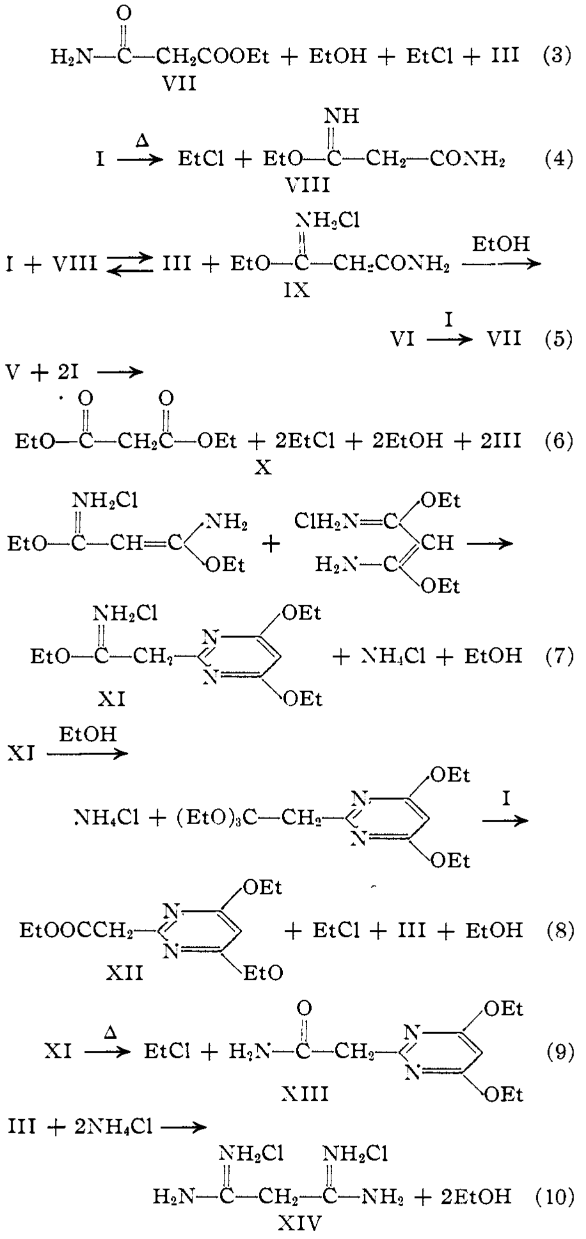
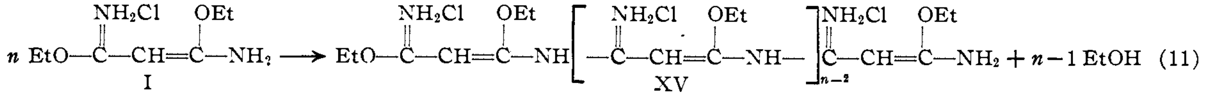
[1] E. I. du Pont de Nemours and Company Research Assistant, 1949–1950.

[2] S. M. McElvain and J. P. Schroeder, This Journal, **71**, 40 (1949).

[3] *Cf.* S. M. McElvain and B. E. Tate, *ibid.*, **73**, 2233 (1951).





$$n\ \mathrm{EtO{-}\overset{\overset{\textstyle NH_2Cl}{\|}}{C}{-}CH{=}\overset{\overset{\textstyle OEt}{|}}{C}{-}NH_2} \longrightarrow \mathrm{EtO{-}\overset{\overset{\textstyle NH_2Cl}{\|}}{C}{-}CH{=}\overset{\overset{\textstyle OEt}{|}}{C}{-}NH}\left[\mathrm{{-}\overset{\overset{\textstyle NH_2Cl}{\|}}{C}{-}CH{=}\overset{\overset{\textstyle OEt}{|}}{C}{-}NH{-}}\right]_{n-2}\mathrm{\overset{\overset{\textstyle NH_2Cl}{\|}}{C}{-}CH{=}\overset{\overset{\textstyle OEt}{|}}{C}{-}NH_2} + n-1\,\mathrm{EtOH} \quad (11)$$

I XV

The polymeric hydrochloride was obtained as a pale-green, viscous oil, which decomposed with the loss of ethyl chloride when heated. The proposed structure (XV) is a vinylog of a polyiminoester hydrochloride, which would be expected to lose ethyl chloride on heating. Linkages resulting from a linear, intermolecular loss of ammonium chloride (as in reaction (7)) are probably also present in this polymer. XV was water-soluble, ether-insoluble, and on treatment with alkali gave a non-volatile, non-crystalline free base. Alkaline hydrolysis of the latter gave ammonia and malonic acid in a molar ratio of 2:1. The formation of XV is doubtless the result of the temperature of the reaction on I, as this latter salt, when subject to pyrolysis, yielded ethyl chloride (66%), ethyl alcohol (71%) and a yellow polymeric solid, which was insoluble in all the common solvents but dissolved in boiling 10% sodium hydroxide solution. Cyanoacetamide, which might be expected to result from the pyrolysis of I,[3,4] was not an intermediate in this polymerization as it was recovered unchanged after being heated at the temperature at which I is polymerized.

The structures of the reaction products XII and XIII were assigned on the basis of chemical properties and analytical data. The ethoxyl content of XII, together with its saponification equivalent and its conversion to XIII with aqueous ammonia, definitely show the presence of two different types of ethoxyl groups. Attempts to cleave the ether-ethoxyl groups of either XII or XIII with hydrochloric, hydrobromic or hydroiodic acids resulted in complete hydrolysis to acetic acid and ammonium halide. Attempts to cleave the ether linkages in anhydrous media resulted in recovered starting material or intractable tars.

Attempts to synthesize the pyrimidine (XIII) were made but failed at the conversion of the dihydroxypyrimidine (XVII) to the diethoxypyrimidine (XIII). Carboxamidoacetamidine (XVI) reacted with malonic ester to form the dihydroxypyrimidine (XVIIa or b) in about 15% yield. The conversion of XVII to XIII could not be accomplished with aqueous silver oxide and ethyl iodide, aqueous sodium hydroxide and ethyl iodide or diethyl sulfate, alcoholic sodium ethoxide and ethyl iodide or with ketene diethyl acetal.[5] The resistance of XVII to O-ethylation, as well as its failure to melt or decompose sharply, suggests that this compound exists largely in the keto form (XVIIa).[6] Treatment of XVII with phosphorus oxychloride and dimethylaniline converted it to 2-cyanomethyl-4,6-dichloropyrimidine (XVIII). Alcoholic sodium ethoxide converted this dichloropyrimidine to a thick black oil from which no pure compound could be distilled or crystallized; XVIII was recovered after treatment with alcoholic silver carbonate.

Cyanoacetamidine (XIX) and carbethoxyacetamidine (XXI), in contrast to XVI, fail to react with malonic ester, but instead undergo self-condensation to yield products whose analyses indicate the structures XX and XXII, respectively. This behavior may be the result of the lower basicities[7] of these amidines resulting from the presence of the more negative cyano and car-

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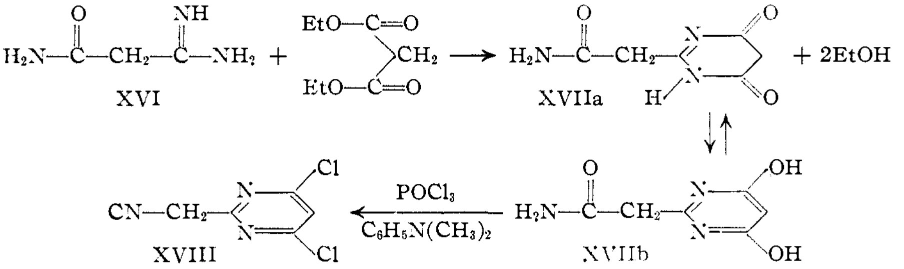
[4] R. H. Hartigan and J. B. Cloke, THIS JOURNAL, **67**, 709 (1945).

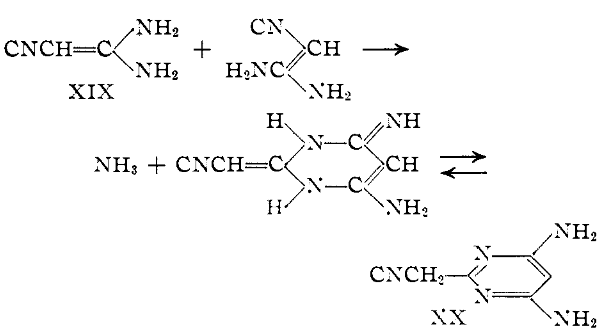
[5] S. M. McElvain and D. Kundiger, *ibid.*, **64**, 259 (1942).

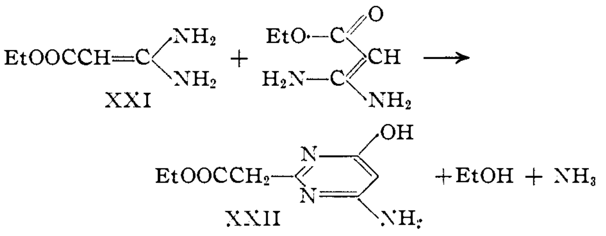
[6] M. Gates, *Chem. Revs.*, **41**, 64 (1947); B. Lythgoe, *Quart. Rev.*, **3**, 201 (1949).

[7] Another indication of the relatively low basicities of XIX and XXI was noted in their preparation by ammonolysis of the corresponding iminoesters in alcohol solution. In these reactions ammonium chloride precipitated from the alcohol solution. In the preparation of XVI and other amidines it is the amidine hydrochloride that precipitates from solution. The hydrochloride of XXI was obtained by removal of the ammonium chloride and excess ammonia from the alcoholic ammonolysis mixture and adding an equivalent of hydrochloric acid.



bethoxy groups, which causes them to exist in the ene-amine forms shown in the reactions





Experimental

Diethyl Diiminomalonate Monohydrochloride (I).—To 23.1 g. (0.1 mole) of diethyl diiminomalonate dihydrochloride[2] suspended in 100 ml. of anhydrous ethanol was added 45.2 ml. (0.1 mole) of 2.22 *N* sodium ethoxide in ethanol. The sodium chloride was removed by filtering the mixture through an alcohol-moistened pad of Filter-Cel. After the salt had been washed on the funnel three times with 30-ml. portions of ethanol the alcohol was removed from the filtrate under reduced pressure over a three-hour period. Residual solvent was removed at oil-pump pressure. The hard salt cake was covered with about 100 ml. of anhydrous ether and broken up. The large lumps were crushed and the ether was decanted. After washing a second time, the ether was removed under diminished pressure with the flask in a water-bath at 35°. The loose powder was shaken into a tared bottle. The yield was 16.3 g. (84%), m.p. 102–104°.

Anal. Calcd. for $C_7H_{15}ClN_2O_2$: Cl, 18.2. Found: Cl, 18.1.

Neutralization of the dihydrochloride with exactly 2 equivalents of alcoholic sodium ethoxide gives the free base, diethyl diiminomalonate. The earlier report[2] that neutralization of the dihydrochloride with 2 equivalents of sodium ethoxide results in ethyl cyanoiminoacetate appears to have been due to catalytic decomposition of the diethyl diiminomalonate by a slight excess of base. This base-catalyzed decomposition is demonstrated by the following experiment. Diethyl diiminomalonate, 10.50 g. (0.066 mole), and 1 ml. (0.0022 mole) of 2.22 *N* sodium ethoxide in alcohol were allowed to stand two hours at room temperature after which time the mixture was distilled. The yield of ethyl cyanoiminoacetate boiling at 105–115° (20 mm.) was 4.00 g. Extraction of the residue from the distillation with boiling ether gave 0.30 g. of additional material for a total of 4.30 g. (58%). The catalytic amount of sodium ethoxide used was necessary for the conversion since in its absence the diiminomalonate was recovered upon distillation. After two recrystallizations from ether the above ethyl cyanoiminoacetate melted at 78–81°.[2]

Pyrolysis of Diethyl Diiminomalonate Monohydrochloride (I).—In a 250-ml. distilling flask was placed 28.9 g. (0.149 mole) of diethyl diiminomalonate monohydrochloride. A 50-ml. distilling flask, used as a receiver, was connected to a Dry Ice-cooled trap protected by a calcium chloride tube. The reaction vessel was heated with a Woods metal-bath at 160–180° and the decomposition proceeded smoothly. When the reaction appeared to be over, the bath was removed and the material in the water-cooled receiver was distilled. It was found to be ethyl alcohol, b.p. 76–79°, n^{25}_D 1.3597, and amounted to 4.85 g. (71%), m.p. of α-naphthylurethan, 77–79°. The material in the cold trap was ethyl chloride, b.p. 14–15°, and amounted to 6.3 g. (66%). The odor of ammonia was noticeable in the cold trap.

The main portion of the pyrolysis mixture had not distilled and appeared to be a mixture of a glass and a yellow solid. Extraction of the mixture with boiling anhydrous ethanol removed the glassy material or converted it to the yellow solid. From the alcohol extract could be isolated only a small amount of gummy material which rapidly darkened in air, and was not further investigated. The material remaining after the hot alcohol extraction was a yellow solid which did not melt under 355°, and which was insoluble in the common solvents. It dissolved in boiling 10% sodium hydroxide to give a red solution. Vacuum sublimation of a 1.14-g. sample of the yellow solid gave 0.14 g. of a white crystalline, water-soluble material having a chloride analysis of 47.5% which did not melt but turned dark around 180–190°. Malondiamidine dihydrochloride (40.9% chlorine) behaves in this fashion when heated. The unsublimed material appeared to be the original yellow solid, little or no thermal decomposition having occurred.

The stability of cyanoacetamide under similar conditions was demonstrated by the following experiment. Ten grams of cyanoacetamide was heated in a Woods metal-bath at 170–180° for one-half hour. After the melt was cooled and recrystallized from an ethanol–ethyl acetate mixture it was found to be unchanged cyanoacetamide (8.0 g., 80% recovery), m.p. 116–119°.

Alcoholysis of Diethyl Diiminomalonate Monohydrochloride (I).—To a suspension of 165.1 g. (0.715 mole) of diethyl diiminomalonate dihydrochloride in 950 ml. of anhydrous ethanol in a 2-liter filter flask was added (with cooling) 355 ml. (0.730 mole) of 2.06 *N* sodium ethoxide in alcohol. After mixing well the suspension was filtered through an alcohol-moistened pad of Filter-Cel. The sodium chloride was washed three times with about 50-ml. portions of anhydrous ethanol. The filtrate was transferred to a 2-liter round-bottom flask and refluxed for ten hours; during this period malondiamidine dihydrochloride[8] (XIV) precipitated. After the first crop of this material (22.40 g.) had been collected by filtering the cooled reaction mixture, a second crop amounting to 5.07 g. was obtained by concentrating the filtrate under reduced pressure. The total yield of malondiamidine dihydrochloride was 27.47 g. (22.2%). The properties of this compound are similar to those of ammonium chloride, *e.g.*, it has no well defined melting or decomposition point and is rather insoluble in most organic solvents. For analysis a sample was boiled with absolute alcohol and the insoluble amidine salt was filtered from the hot alcohol. A Kjeldahl analysis showed a nitrogen content of 32.5% (calcd., 32.4%) and a Volhard determination gave a chlorine content of 41.8% (calcd., 40.9%). The malondiamidine dihydrochloride was converted to malonamide in the following manner: A small amount of the diamidine dihydrochloride was boiled with excess saturated sodium carbonate solution until the evolution of ammonia became slow. The water was then evaporated in a stream of air on the steam-bath. The remaining moist solid was mixed well with absolute alcohol and dried by boiling off the alcohol–water azeotrope. The solid mixture was then extracted with boiling absolute alcohol, the hot mixture was filtered, and the solvent evaporated to dryness in a stream of air. The remaining malonamide, after one

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(8) G. W. Kenner, *et al.*, *J. Chem. Soc.*, 575 (1943).

recrystallization from absolute alcohol, melted at 168–170.5°. The melting point of a mixture of this material and authentic malonamide was 169–171°.

Concentration of the alcohol solution from which the malondiamidine dihydrochloride had been removed was continued under reduced pressure until the mixture became sirupy. It was then washed five times with 100-ml. portions of dry ether. The insoluble polymeric oil (XV), after drying in the vacuum desiccator over potassium hydroxide and sulfuric acid, weighed 32 g. (23.0% of the weight of I in the reaction). This material could not be completely freed of the ether, since on warming under reduced pressure in an attempt to remove the ether it decomposed with the evolution of ethyl chloride. The analytical data indicate that the polymer does not have exactly the structure of XV but that some ethyl chloride has been lost from such a structure during the alcoholysis.

Anal. Calcd. for $(C_5H_9ClN_2O)_n$: OC_2H_5, 30.4; Cl, 23.9. Found: OC_2H_5, 32.9; Cl, 16.8; after standing, 14.7, 13.6.

Since the above polymeric oil could not be distilled, converted to a crystalline free base or to a crystalline picrate, it was subjected to alkaline hydrolysis. Thirty-two grams of the polymer (XV) was dissolved in 50 ml. of water and filtered. To the filtrate was added 270 ml. (0.729 mole) of 2.70 *N* sodium hydroxide. The solution was boiled under a reflux condenser equipped with a tube leading into a saturated boric acid solution. After the evolution of gaseous ammonia ceased, the water in the condenser was turned off, and the vapors allowed to distil into the boric acid until no more base distilled. Titration of the boric acid solution with standard hydrochloric acid showed that 0.256 mole of ammonia had been collected. The alkaline hydrolysis mixture was extracted with ether, and from this extract was obtained 0.167 g. of crude 2-carboxamidomethyl-4,6-diethoxypyrimidine (XIII), m.p. 137–140°, which probably was present, but not removed at the time the polymer was washed with ether. The pyrimidine (XIII) is thus shown to be quite stable to alkali. The alkaline hydrolysis mixture was neutralized with 258 ml. (0.73 mole) of 2.83 *N* hydrochloric acid (cooling). This solution was extracted with alcohol-free ether in a continuous extraction apparatus until most of the malonic acid was extracted. The ether extracts were evaporated in a stream of air, the residue was dissolved in distilled water, and the insoluble material was filtered. Removal of the water under reduced pressure at room temperature left 13.9 g. (0.134 mole or 43% of the weight of the polymer used) of crude malonic acid. After fractional crystallization from ether the acid melted at 125–130°.

The ether washings of the polymeric oil was distilled to remove the ether. The semi-solid mass remaining was filtered and washed with petroleum ether (b.p. 90–100°) leaving 2.19 g. of crude **2-carboxamidomethyl-4,6-diethoxypyrimidine** (XIII) melting at 105–125°. When the filtrate was distilled, another 0.56 g. was obtained from two of the fractions. These two crops together with the 0.167 g. of amide isolated from the polymer fraction (see above) made a total of 2.92 g. (3.6%) of crude amide. After one recrystallization from petroleum ether (90–100°) the melting point was 124–130°. Several additional recrystallizations from petroleum ether gave pure amide, m.p. 139–140°. This amide is more easily obtained in pure form by ammonolysis of the ester (XII) (see below).

Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.5; H, 6.71; N, 18.65; OC_2H_5, 40.0. Found: C, 53.8; H, 6.53; N, 18.8; OC_2H_5, 39.7.

The solution left after removal of most of the above amide was combined with the petroleum ether washings and distilled. After removal of the petroleum ether the following fractions were obtained: (a) 1.16 g. of diethyl malonate, b.p. 77–85° (8 mm.), $n^{25}{}_D$ 1.4219; (b) 1.55 g. of a mixture, the refractive index of which indicated it to be 60% (0.9 g.) 2-carbethoxymethyl-4,6-diethoxypyrimidine (XIV) and 40% (0.6 g.) diethyl malonate, b.p. 85–133° (8 mm.), $n^{25}{}_D$ 1.4425 (the total yield of diethyl malonate is thus 1.76 g. or 1.6%); (c) 10.49 g. of 2-carbethoxymethyl-4,6-diethoxypyrimidine (XII), b.p. 133–148° (8 mm.), $n^{25}{}_D$ 1.4769–1.4820, which together with the pyrimidine in fraction (b) makes a total of 11.4 g. (12.5%); (d) 0.74 g., b.p. 115–145° (0.6 mm.), $n^{25}{}_D$ 1.4991; (e) 3.99 g., b.p. 145–170° (0.6 mm.); (f) 2.68 g., b.p. 170–205° (0.6 mm.). For analysis, a fraction of **2-carbethoxymethyl-4,6-diethoxypyrimidine (XII)** boiling at 147.5–148.5° (10 mm.), $n^{25}{}_D$ 1.4809, $d^{25}{}_4$ 1.103 was taken.

Anal. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.7; H, 7.14; N, 11.02; OC_2H_5, 53.2; sapn. equiv., 254. Found: C, 56.9; H, 6.95; N, 11.3; OC_2H_5, 52.6; sapn. equiv., 257.

From fractions (d) and (e) were obtained by means of petroleum ether crystallizations 0.10 g. and 0.46 g., respectively, of very crude amide (XIII) which after several crystallizations still melted at 125–165°. From the petroleum ether-soluble fraction of (e) was obtained 0.98 g. of material which after recrystallization from ethanol melted at 54.5–55.0°. The analytical data suggested that this product might be 2-carbiminoethoxymethyl-4,6-diethoxypyrimidine, but when a hydrochloride of the material was prepared with ethereal hydrogen chloride and heated in boiling petroleum ether (b.p. 90–100°) the original material melting at 51.5–55.0° was recovered. This substance was also recovered unchanged after it had been boiled for a short period with dilute hydrochloric acid.

Anal. Calcd. for $C_{13}H_{18}N_3O_3$: C, 59.1; H, 6.87; N, 15.90; OC_2H_5, 51.2. Found: C, 58.6; H, 6.77; N, 16.08; OC_2H_5, 50.8.

In this particular experiment no carbethoxyacetamide (VII) was isolated. Oily petroleum ether-insoluble material appeared at the point where the pyrimidine amide (XIII) was being isolated, but no carbethoxyacetamide could be separated. In a similar run, however, in which the amide (XIII) was not separated before distillation of the ether-soluble material, carbethoxyacetamide distilled with the ester (XII) and crystallized from a petroleum ether solution of the ester fractions upon cooling the solution in Dry Ice. In this way carbethoxyacetamide melting at 45–47.5° was isolated in a 1.0% yield. A mixed melting point of this product and authentic carbethoxyacetamide was 48–49°.

Ammonolysis of 2-Carbethoxymethyl-4,6-diethoxypyrimidine (XII).—To 5.16 g. (0.0203 mole) of XII was added 40 ml. of concentrated ammonium hydroxide. The mixture was allowed to stand at room temperature for two weeks and was shaken frequently by hand during this period. The crystalline 2-carboxamidomethyl-4,6-diethoxypyrimidine (XIII) after filtering and drying amounted to 4.06 g. (89%). After one recrystallization from petroleum ether (b.p. 90–100°) the melting point was 138–139.5°.

Hydrolysis of 2-Carboxyamidomethyl-4,6-diethoxypyrimidine (XIII).—A mixture of 0.616 g. (0.00274 mole) of XIII and 5 ml. of 48% hydrobromic acid was refluxed for one hour. The mixture was concentrated under reduced pressure and after cooling 0.642 g. of ammonium bromide (calcd. Br, 81.7; found, 80.0) was collected by centrifuging. Distillation of the clear liquid from which the ammonium bromide had been removed was continued. Nothing remained in the pot but a small amount of ammonium bromide. The distillate was shown to contain acetic acid by the preparation of *p*-nitrobenzyl acetate, m.p. 76–78.5°.

Carboxamidoacetamidine Hydrochloride.—In a 2-liter, 3-necked, round-bottom flask equipped with a stirrer and a soda-lime tube, was placed 1 liter of a cold saturated solution of ammonia in anhydrous ethanol. To the ice-cold solution was added, with stirring, 205 g. (1.05 moles) of ethyl carbethoxyiminoacetate hydrochloride.[2] This mixture was stirred at room temperature for twenty-four hours and stood an additional twenty-four hours without stirring. The **carboxamidoacetamidine (XVI) hydrochloride** was collected on a filter and washed twice with absolute alcohol. After drying in a vacuum desiccator over potassium hydroxide and sulfuric acid, the yield of the amidine hydrochloride having a chlorine content of 25.8% was 109.9 g. By concentrating the mother liquor an additional 12.33 g. was obtained, making a total of 122.2 g. (85%). After recrystallization from absolute ethanol the melting point was 172.5–174.0°. Pinner[9] reported that this compound prepared in this way decomposed without melting at 150°.

Anal. Calcd. for $C_3H_8ClN_3O$: Cl, 25.8; N, 30.6. Found: Cl, 25.7; N, 30.6.

2-Carboxamidomethyl-4,6-dihydroxypyrimidine (XVII).—To 64.5 g. (0.469 mole) of carboxamidoacetamidine hydrochloride, 76.8 g. (0.477 mole) of diethyl malonate, and 50 ml. of absolute alcohol in a 2-liter, round-bottom, 3-

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(9) A. Pinner, *Ber.*, **28**, 479 (1895).

necked flask equipped with a stirrer and a soda-lime tube was added a solution of sodium ethoxide prepared from the reaction of 11 g. (0.48 mole) of sodium with 250 ml. of absolute alcohol. The sodium ethoxide container was rinsed with 50 ml. of absolute alcohol and this solution was added to the reaction mixture. The suspension was stirred for 12 hours at room temperature and then allowed to stand about 40 hours. The resulting solid cake was broken up, collected on a Büchner funnel, and washed with several hundred ml. of absolute alcohol. The solid material (apparently the sodium salt of the pyrimidine (XVII) mixed with sodium chloride) was dissolved in a minimum amount of water at room temperature and the solution acidified to congo red paper with concentrated hydrochloric acid. After the acidified mixture had stood one hour in an ice-bath the 2-carboxamidomethyl-4,6-dihydroxypyrimidine was collected on a filter. The yield of dry material was 7.47 g. The above alcohol filtrate was concentrated under reduced pressure; the solid was collected by filtration and dissolved in water. After acidifying the resulting solution as above a second crop of the pyrimidine was collected. When dry, it amounted to 5.60 g. making a total of 13.07 g. (16.5%). This compound did not melt or decompose sharply. A sample was prepared for analysis by several recrystallizations from hot water.

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.6; H, 4.17; N, 24.8. Found: C, 42.33; H, 4.23; N, 25.6.

Attempted O-Ethylation of 2-Carboxamidomethyl-4,6-dihydroxypyrimidine (XVII).—One gram (0.0059 mole) of XVII was suspended in 70 ml. of anhydrous alcohol in a 100-ml., 3-necked, round-bottom flask equipped with a stirrer, a Drierite-capped reflux condenser and a dropping funnel. To the stirred, boiling suspension was added through the dropping funnel 5.3 ml. (0.012 mole) of 2.28 *N* sodium ethoxide in alcohol and then 5 ml. (0.062 mole) of ethyl iodide. The mixture was refluxed for 3.75 hours and allowed to stand overnight at room temperature. The solid material in the mixture was collected by filtration and recrystallized from water. In this way 0.53 g. (53%) of unchanged pyrimidine (XVII) was recovered. The alcohol filtrate was evaporated in a stream of air on the steam-bath. The residue was boiled with petroleum ether (b.p. 90–100°) and filtered while hot. No diethoxypyrimidine (XIV) separated when the petroleum ether was cooled or concentrated. Similar attempts to ethylate XVII with aqueous sodium hydroxide and ethyl iodide or diethyl sulfate, aqueous silver oxide and ethyl iodide, and ketene acetal failed.

2-Cyanomethyl-4,6-dichloropyrimidine (XVIII).—Fifteen grams (0.089 mole) of 2-carboxamidomethyl-4,6-dihydroxypyrimidine (XVII) and 45 ml. of phosphorus oxychloride were placed in a flask which was then attached to a reflux condenser. Through the condenser was added 23 ml. of dimethylaniline. The mixture was warmed cautiously in an oil-bath which was quickly removed when the reaction began. After the initial vigorous reaction had subsided the mixture was refluxed five to ten minutes longer. The hot material was poured over 200 g. of ice and the resulting suspension was extracted once with 200 ml. of ether and six times with additional 100-ml. portions. The combined ether extracts were dried over Drierite. The ether was evaporated in a stream of air and the 2-cyanomethyl-4,6-dichloropyrimidine which was left amounted to 12.8 g. (76%). The product could also be extracted with chloroform in which it is more soluble. After recrystallization from petroleum ether (b.p. 90–100°) the colorless product melted at 97.5–99.0°.

Anal. Calcd. for $C_6H_3Cl_2N_3$: Cl, 37.7; N, 22.3. Found: Cl, 37.7; N, 22.3.

To a solution of sodium ethoxide prepared from 2.5 g. (0.109 mole) of sodium and 75 ml. of anhydrous alcohol was added 10 g. (0.053 mole) of XVIII. The solution was refluxed for six hours and the resulting hot suspension was centrifuged. The solid material (probably a mixture of sodium chloride and organic polymeric condensation products) was washed twice with hot alcohol. The alcohol fractions were combined and distilled. The black oily material remaining after removal of the alcohol did not distil under 325° (0.8 mm.).

The pyrimidine (XVIII) was recovered unchanged after it had been boiled in an alcohol suspension of an excess of dry silver carbonate.

Carbethoxyacetamidine (XXI) Hydrochloride.—In a 1-liter flask equipped with a stirrer and a soda-lime tube was placed 300 ml. of a saturated solution of ammonia in anhydrous ethanol. After the solution had been cooled in an ice-bath, 64.7 g. (0.33 mole) of ethyl carbethoxyiminoacetate hydrochloride[2] was added. The ice-bath was removed and the mixture was stirred for two hours. The ammonium chloride which was collected by filtration amounted to 14.7 g. (83%). The filtrate was concentrated at or below room temperature under reduced pressure. When the volume reached 120–150 ml., 48 ml. (0.35 mole) of 7.3 *N* alcoholic hydrogen chloride was added. The mixture was allowed to stand in the refrigerator for about one week after which time the first crop of crystals melting at 89–94° (13.0 g.) was collected. The filtrate was placed in the refrigerator for another week and then concentrated under diminished pressure. In this way a second crop of 24.9 g., m.p. 92–100°, was obtained. Upon concentrating further a third crop, m.p. 155–158° (3.28 g.) was produced. The first and second crops, which were largely carbethoxyacetamidine hydrochloride, amounted to 37.9 g. (69%). After recrystallization from an alcohol–ether mixture the melting point was 107–108°.

Anal. Calcd. for $C_5H_{11}ClN_2O_2$: Cl, 21.3; N, 16.8; OC_2H_5, 27.0. Found: Cl, 20.9; N, 16.3; OC_2H_5, 27.4.

The third crop, which after recrystallization from absolute alcohol and drying in the Fischer pistol, melted at 144.5–146° (dec.), had an analysis which indicated it was *carboxyacetamidine hydrochloride*. It was obtained in a 7.2% yield.

Anal. Calcd. for $C_3H_7ClN_2O_2$: Cl, 25.6; N, 20.2. Found: Cl, 24.9; N, 20.3.

2-Carbethoxymethyl-4-amino-6-hydroxypyrimidine (XXII).—Four hundred ml. of a saturated alcoholic ammonia solution was placed in a 2-liter, 3-necked, round-bottom flask equipped with a Hershberg stirrer and a soda-lime tube. Through the third neck was introduced 128.8 g. (0.66 mole) of ethyl carbethoxyiminoacetate hydrochloride[2] while the solution was cooled in an ice-bath. After ten minutes the ice-bath was removed and the mixture was stirred at room temperature for two hours. The precipitated ammonium chloride was filtered and washed; it amounted to 30.75 g. (87%). A Volhard analysis showed a chloride content of 66.9% (calcd. 66.4%). The filtrate was concentrated under reduced pressure and from the concentrate was isolated by means of ethanol–ethyl acetate recrystallization 14.0 g. (22%) of 2-carbethoxymethyl-4-amino-6-hydroxypyrimidine (XXII), m.p. 205–206°. After several recrystallizations from ethanol the melting point was 206.5–207°.

Anal. Calcd. for $C_8H_{11}N_3O_3$: N, 21.3; OC_2H_5, 22.8. Found: N, 21.8; OC_2H_5, 22.8.

2-Cyanomethyl-4,6-diaminopyrimidine (XX).—To 300 ml. of a cold saturated solution of ammonia in anhydrous ethanol in a 2-liter, round-bottom, 3-necked flask equipped with a stirrer and a soda-lime tube was added with cooling and stirring 35.0 g. (0.236 mole) of ethyl cyanoiminoacetate hydrochloride.[2] After removal of the ice-bath, the mixture was stirred for two hours. The precipitated ammonium chloride was collected on a filter and amounted to 8.13 g. (65%). The filtrate was distilled at atmospheric pressure in a system which was equipped with a gas trap to dispose of the ammonia evolved. After about 15 minutes solid material precipitated, but redissolved during the distillation. The solution was distilled to a volume of about 100 ml. At this time solid material had again started to precipitate. After cooling, filtering and drying, the pyrimidine (XX) amounted to 14.4 g. (82%), m.p. 200–213°. Recrystallization from water gave a product, m.p. 241.5–243° (dec.).

Anal. Calcd. for $C_6H_7N_5$: N, 46.9. Found: N, 47.0.

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