

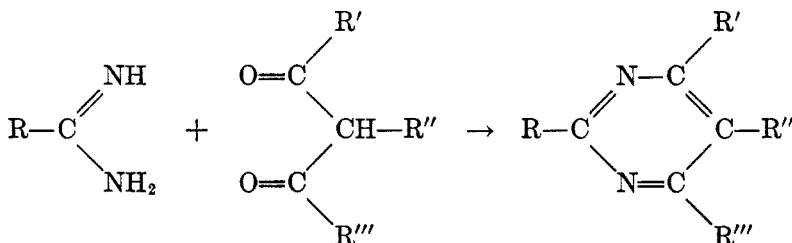
A STUDY OF THE SYNTHESIS OF VINYL PYRIMIDINES¹

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Since the preparation and characterization of vinylpyrimidines seemed a problem of possible practical and theoretical interest, an investigation aimed toward this end was considered desirable. Although to date no monomeric vinylpyrimidine has been isolated, the results appear of some significance and are therefore reported here at this time.

It would appear that the direct condensation of 2- or 4-methylpyrimidine with formaldehyde might be a logical approach. Since these simple methylpyrimidines are difficult to prepare and work with, an alternative approach was chosen involving direct synthesis of a pyrimidine ring system containing a vinyl group or a group easily transformable to a vinyl group.

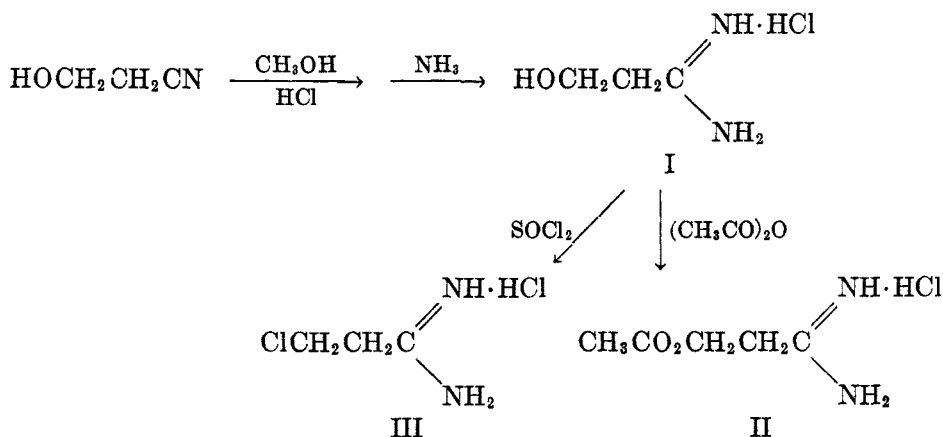


Such a classical pyrimidine synthesis, in which any one of the R groups could be vinyl (or β -chloroethyl, β -hydroxyethyl or β -acetoxyethyl), the remainder preferably hydrogen or alkyl, might present a rather direct approach to a vinylpyrimidine. Experiments on the approach in which R is the potential vinyl group were most thoroughly investigated, since the starting materials seemed the most readily available.

The first objective was the synthesis of the desired amidines, acrylamidine or 3-hydroxy-, 3-chloro- or 3-acetoxy-propionamidine. Of these, only the hydroxy compound could be prepared from the corresponding nitrile, ethylene cyanohydrin, by the usual amidine preparation of Pinner and Klein (1). The 3-acetoxy and 3-chloro derivatives were prepared from the 3-hydroxypropionamidine.

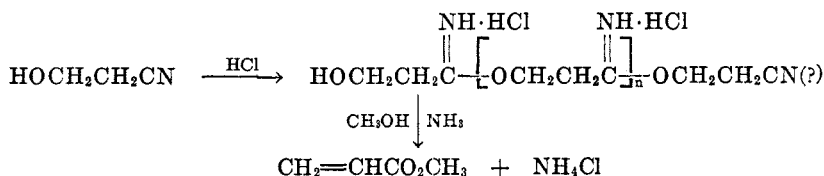
¹ Abstracted from a Ph.D. thesis presented to the Graduate School of the University of Notre Dame.

² General Tire and Rubber Company Fellow, 1946-1947; American Cyanamid Company Fellow, 1947-1948.

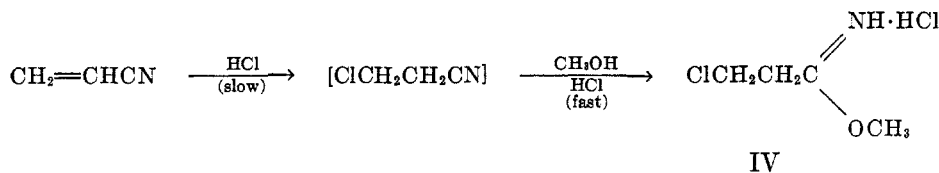


These amidine hydrochlorides were all extremely hygroscopic and difficult to handle and purify.

Incidentally, attempts were made to prepare a polyimidic ester from ethylene cyanohydrin by omitting methanol, relying on the hydroxyl group already present in the nitrile. The evidence indicated that the polyimidic ester was formed but decomposition with methanolic ammonia proceeded to methyl acrylate and ammonium chloride.



On treatment of acrylonitrile with two equivalents of hydrogen chloride in methanol, methyl 3-chloropropionimidate hydrochloride was formed in nearly quantitative yield.



When only one equivalent of hydrogen chloride was used, only half the theoretical amount of IV was obtained. In either case, the reaction required several days. When 3-chloropropionitrile was used as starting material, the reaction required only one equivalent of hydrogen chloride and proceeded to completion within two hours. From these data, which indicate a rather remarkable difference in the reactivity of the nitrile group in acrylonitrile and 3-chloropropionitrile, it appears that conjugation of the nitrile triple bond with the carbon-carbon

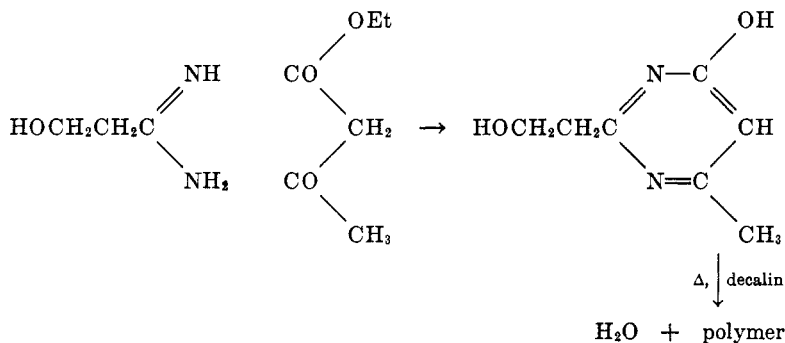
double bond (a) decreases its reactivity toward addition, and (b) allows 1,4-addition to occur.

Treatment of the imidate IV with ammonia produced an amorphous polymeric product and ammonium chloride; it seems evident that the chlorine atom is too reactive, presumably undergoing replacement both by ammonia and by any amidine which may be formed. It was, however, possible to convert the imidate IV to 3-chloropropionamide by cautious hydrolysis.

Attempts to convert 3-acetoxypropionitrile to the imidate and thence to the amidine failed, apparently due to the ready transesterification with methanol, converting the latter to methyl acetate, the former to ethylene cyanohydrin.

The condensation of 3-hydroxypropionamidine with acetylacetone was investigated under various conditions. The reaction mixtures, which presumably contained 2-(2-hydroxyethyl)-4,6-dimethylpyrimidine, were difficult to purify. On distillation or under various dehydrating conditions, the product formed a clear viscous tan resin. It seems likely that the desired 2-vinylpyrimidine was actually formed but that the lability toward polymerization, evident in 2-vinylpyridine (2), is accentuated to such an extent that efforts to inhibit it by addition of inhibitors such as hydroquinone and picric acid were unsuccessful.

It was possible to isolate 2-(2-hydroxyethyl)-4-hydroxy-6-methylpyrimidine by condensing I with acetoacetic ester. The lability of the product was indicated by its quantitative conversion to polymer with evolution of just one equivalent of water on refluxing in decalin.



EXPERIMENTAL³

3-Hydroxypropionamidine hydrochloride (I). Hydrogen chloride (76.7 g., 2.1 moles) was bubbled into a stirred mixture of 142 g. (2.0 moles) of redistilled ethylene cyanohydrin, 64 g. (2.0 moles) of absolute methanol, and 250 ml. of ether, held at 0°. With efficient stirring, the absorption was completed in one hour. The stirrer was raised so that it agitated only the upper ether layer and the mixture was stirred at 0° for three days, during which the lower layer completely solidified. After washing with dry ether, the solid cake was dissolved in 500 ml. of absolute methanol and this solution was poured into a solution of 51 g. (3.1 moles) of ammonia in 500 ml. of methanol maintained at 0°. After stirring the clear solution for one hour, it was evaporated to dryness at about 20 mm. leaving a white residue, 200–225 g. (80–90%). The crude product was purified by dissolving in dry isopropyl alcohol and filtering to remove ammonium chloride, followed by precipitation with three

³ Combustion analyses by Micro-Tech Laboratories, Skokie, Ill.

volumes of ether. After drying *in vacuo* over phosphorus pentoxide, the hygroscopic white solid melted at 84–85.5°.

Anal. Calc'd for $C_5H_9ClN_2O$: Cl, 28.46. Found: Cl, 28.49 (by titration).

The product was insoluble in benzene, toluene, ether, dioxane, acetone, chloroform, carbon tetrachloride, and petroleum ether. It was readily soluble in water, methanol, and ethanol. It failed to give crystalline salts with picric, picramic, picrolonic, benzoic, tartaric, 3,5-dinitrobenzoic, oxalic, or sulfuric acids. It did not form crystalline complexes with cupric acetate, zinc chloride, mercuric chloride, or auric chloride.

3-Acetoxypropionamide hydrochloride (II). The crude hydroxyamide (I, 205 g.) was dissolved in 250 ml. of boiling glacial acetic acid and filtered free of undissolved ammonium chloride. The solution was heated to boiling, the flame removed, and 306 g. of acetic anhydride was added in portions so as to maintain boiling. After an hour of refluxing, 250 ml. of acetic acid was removed by distillation at about 40 mm. The cooled residue was added dropwise to 1 liter of acetone. The brown precipitate was dried *in vacuo* over phosphorus pentoxide (m.p. 94–96°) and then recrystallized from absolute ethanol, m.p. 102–103°.

Anal. Calc'd for $C_6H_{11}ClN_2O_2$: C, 36.31; H, 6.66; N, 16.82; Cl, 21.28.

Found: C, 37.10; H, 6.84; N, 16.31; Cl, 21.30.

The *picrate* melted at 171.6–172.0° after four recrystallizations from ethanol.

Anal. Calc'd for $C_{11}H_{13}N_3O_6$: C, 36.77; H, 3.65.

Found: C, 37.44; H, 3.80.

3-Chloropropionitrile was prepared by reaction of thionyl chloride with ethylene cyanohydrin at 50–60° in 60% yield, and by reaction of acrylonitrile and hydrogen chloride without solvent at reflux for twelve hours in 40% yield. The use of ether as a solvent greatly promoted the latter reaction, so that a yield of 80–85% was obtained in three hours at room temperature, b.p. 70–72° (15 mm.). [lit. (3), 65–66.5° (11 mm.).]

Methyl-3-chloropropionimide hydrochloride (IV). A. *From 3-chloropropionitrile.* Dry hydrogen chloride was passed into a stirred solution of 74 g. (0.82 mole) of 3-chloropropionitrile, 27.2 g. (0.82 mole) of methanol, and 200 ml. of dry ether maintained at 0–5°. Thirty minutes was required to add 30 g. (0.12 mole) of hydrogen chloride. Within two hours at 0°, the reaction mixture had set to a crystalline magma, which was filtered, the product washed with ether, and dried *in vacuo* over phosphorus pentoxide, m.p. 93–94°; yield, 120 g. (93%).

B. *From acrylonitrile.* A total of 219 g. (6.0 moles) of hydrogen chloride was bubbled into 159.2 g. (3.0 moles) of acrylonitrile, 96.0 g. (3.0 moles) of methanol, and 400 ml. of dry ether kept at 0–5°. Crystals began to separate after about six hours but it required two days at 0° for the mixture to solidify. The crystals were collected, washed with ether and dried, m.p. 93–94°; yield, 406 g. (86%).

Anal. Calc'd for $C_4H_5ClNO \cdot HCl$; Ionizable chloride, 22.44; Total chlorine, 44.87.

Found: Ionizable chloride, 23.28; Total chlorine, 44.58 (by titration).

When only 110 g. of hydrogen chloride was added, a 44% yield of the imide was obtained, m.p. 93–94°.

Hydrolysis to *3-chloropropionamide* was accomplished in aqueous solution at room temperature overnight. The amide was isolated by neutralizing with sodium carbonate and extracting the aqueous solution continuously with ether for ten hours. Evaporation and recrystallization from benzene gave a 65% yield, m.p. 102° [lit. (4), m.p. 102–102.5°].

3-Chloropropionamide hydrochloride. A. *From methyl 3-chloropropionimide hydrochloride.* Numerous attempts to effect the conversion of methyl 3-chloropropionimide hydrochloride to the amidine by treatment with ammonia yielded only ammonium chloride and intractable gummy solids, evidently polymeric.

B. *From 3-hydroxypropionamide hydrochloride.* During half an hour, 169 g. (1.42 moles) of thionyl chloride was added to a stirred suspension of 93 g. (0.75 mole) of purified hydroxyamide hydrochloride in 500 ml. of toluene. After standing overnight, the mixture was warmed for half an hour and the toluene was decanted from the dark brown solid. The solid was purified by dissolving in 300 ml. of hot isopropyl alcohol, treating with 10

g. of Norit, filtering, and evaporating. The dark brown hygroscopic solid, 100 g. (93%), melted from 90–95°.

Anal. Calc'd for $C_3H_5Cl_2N_2$: Cl, 49.58. Found: Cl, 48.87.

Condensation of 3-hydroxypropionamidine hydrochloride with acetylacetone. Numerous experiments were carried out in an effort to effect this condensation so that a pure product might be obtained. The method most nearly successful seemed to be the use of sodium methoxide in methanol as a condensing agent.

Sodium methoxide (10.8 g.) was dissolved in 100 ml. of methanol and 20 g. of acetylacetone and 24.5 g. of crude 3-hydroxypropionamidine hydrochloride were added. After refluxing for two hours, the mixture was filtered and the alcoholic solution, which had a strong ammoniacal odor, was immersed in a bath maintained at 50° and the volatile components were removed under 10 mm. pressure. After two days, a yellow, semisolid hygroscopic residue remained which was soluble in water, methanol, ethanol, isopropyl alcohol, Methyl Cellosolve, acetic acid, and pyridine, but completely insoluble in ether, acetone, chloroform, benzene, carbon tetrachloride, and dioxane. Once dissolved, it could be recovered as solid only by evaporation to dryness; attempts to precipitate with a miscible non-solvent always gave two liquid phases. A wide variety of attempts to prepare solid derivatives failed.

Attempted distillation at atmospheric pressure gave a few drops of yellow oil, b.p. 190–210°, and a red, resinous residue, soluble only in water and aqueous acids. Distillation at 0.03 mm. pressure gave about 5 ml. of yellow oil, b.p. 95–100° (0.03 mm.), and 15 g. of polymeric residue. The yellow oil (impure 2-vinyl-4,6-dimethylpyrimidine?) decolorized permanganate and bromine in carbon tetrachloride, but no crystalline derivative could be obtained and, on attempted redistillation, it resinified.

A similar yellow oil was obtained in better yield by pyrolysis of the crude product over copper turnings at 350°.

Condensation of 3-hydroxypropionamidine hydrochloride with acetoacetic ester. Equivalent quantities of the two reagents (2.0 moles) in 95% ethanol containing (2.0 moles) of sodium methoxide were refluxed for twenty-four hours. The alcoholic filtrate was concentrated to half volume and cooled at 0° for five hours. The yield of white solid was 140 g. (45.6%). Recrystallization from 95% ethanol yielded 110 g. (37%), of 2-(2-hydroxyethyl)-4-hydroxy-6-methylpyrimidine, m.p. 163–165°. Repeated recrystallization from pyridine did not raise the melting point.

Anal. Calc'd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.18.

Found: C, 55.88; H, 6.67; N, 18.04.

A 15.4-g. sample (0.1 mole) was dehydrated by refluxing in 150 ml. of decalin containing 1.0 g. of trinitrotoluene. Water was no longer evolved after one hour; exactly 1.8 ml., or just one equivalent, was collected. The decalin solution contained a red resin, insoluble in water, alcohols, and all other common solvents.

Miscellaneous experiments. An attempt was made to condense 2-chlorovinyl methyl ketone (5) with acetamidine in ethanol. The principal product on attempted distillation was a hard insoluble residue.

An attempt was made to condense 3-ethoxyacrolein diethyl acetal (6) with acetamidine in ethanol. Some dark brown oil was recovered by extraction but it could not be induced to form a picrate, characteristic of 2-methylpyrimidine (7).

SUMMARY

Of four related nitriles, acrylonitrile, 3-hydroxy-, 3-chloro- and 3-acetoxypropionitriles, only the 3-hydroxy compound could be converted to an amidine by the usual procedure.

3-Hydroxypropionamidine hydrochloride has been successfully converted to the 3-acetoxy and 3-chloro derivatives.

Acrylonitrile, or better 3-chloropropionitrile, have been converted to methyl 3-chloropropionimidate hydrochloride, but attempts to convert this material to the amidine by treatment with ammonia produced only intractable resins.

3-Hydroxypropionamidine hydrochloride has been condensed with acetoacetic ester to give 2-(2-hydroxyethyl)-4-hydroxy-6-methylpyrimidine, which was readily dehydrated to a polymeric resin. Condensation with acetylacetone gave a product, presumably 2-(2-hydroxyethyl)-4,6-dimethylpyrimidine, not satisfactorily characterized but readily converted to polymeric resin.

NOTRE DAME, INDIANA

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