[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

STUDIES ON CONDENSED PYRIMIDINE SYSTEMS. VIII (1). THE 5,6-DIHYDROFURO[2,3-*d*]PYRIMIDINE RING SYSTEM

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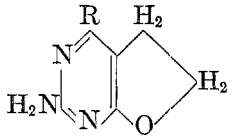
In view of the growth inhibitory properties of various condensed pyrimidines on a number of biological systems (2–5) the syntheses of such compounds are being studied in this laboratory.

This paper is mainly a study of the cyclodehydration of 4-hydroxy-5-β-hydroxyethylpyrimidines to the hitherto unknown dihydrofuropyrimidine ring system. Several 5-β-hydroxyethylpyrimidines have been previously synthesized from lactones (6–9) which react similarly to the parent β-hydroxyethyl ester or acid in condensing with urea and thiourea. In this work is described the preparation of several lactones by treatment of the appropriate β-keto or β-cyanoester (as the sodium salt) with ethylene oxide (10, 11), followed by condensation of the lactone with guanidine and subsequent cyclodehydration of the resulting 4-hydroxy-5-β-hydroxyethylpyrimidine to give the dihydrofuropyrimidine. Beginning with ethyl acetoacetate, ethyl benzoylacetate, and ethyl cyanoacetate the following compounds were obtained:



I R = CH_3
II R = C_6H_5
III R = NH_2

Ethyl sodiooxaloacetate did not react with ethylene oxide. Although Cope (11) has reported the isolation of stable lactones prepared from ethyl cyanoacetate and higher molecular weight aliphatic epoxides, we were unable to isolate α-cyano-γ-butyrolactone which decomposed during attempted isolation liberating large amounts of hydrogen cyanide. The desired pyrimidine was obtained, however, by treatment of the sodium salt of the lactone, as formed, with guanidine hydrochloride.

An attempted preparation of 2-amino-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine by reduction of the corresponding 5-acetic acid (prepared by the condensation of diethyl α-acetylsuccinate with guanidine) with lithium aluminum hydride was unsuccessful and no reduction product could be isolated.

As would be expected, the cyclodehydration of the 4-hydroxy-5-β-hydroxyethylpyrimidines results in the loss of alkali solubility in the products and profound changes in their ultraviolet spectra. The spectra of compounds I and II are almost completely devoid of the alkaline shift characteristic of their immediate precursors and aminohydroxypyrimidines[2] in general. The spectrum

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[2] Unpublished work in this laboratory.

of compound III resembles closely that characteristic of the simple 2-amino-4 alkylaminopyrimidines[2] (*p*H 1.0, abs. max. at 235–250 mμ, 268–278 mμ; *p*H-11.0, 235–245 mμ, 280–290 mμ) indicating elimination of contributions due to ionic (hydroxyl) oxygen.

The cyclodehydration of 2-amino-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine to form I was effected in quantitative yields with concentrated sulfuric acid and thionyl chloride and in lesser yield with concentrated hydrochloric acid. The reaction with thionyl chloride probably proceeds through the 4-hydroxy-4-β-chloroethylpyrimidine[3] and the ease of cyclization of this compound is undoubtedly due to the uniquely favorable conditions for an internal SN_2 reaction, namely the presence of (12) a negatively charged oxygen able to displace the chloride or the chlorosulfite ions to form a five-membered strainless ring.

The action of phosphorus oxychloride upon 2-amino-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine resulted at first in the formation of the dihydrofuran in 50–80% yield. Experimentally this necessitated the removal of the solvent by distillation under reduced pressure after the initially observed reaction had subsided. Continuance of the reaction under reflux conditions for 30 minutes gave a 0–5% yield of dihydrofuran and a 30–40% yield of "chloropyrimidine" (soluble in chloroform). A reaction time of 3.5 hours resulted in virtually complete destruction of the pyrimidine structure leaving but several milligrams of a dichloropyrimidine (13). The yields and the nature of the products of any particular run varied with different samples of phosphorus oxychloride.[4] The analysis and spectra of different batches of "chloropyrimidine" indicate their composition to be mixtures of 2-amino-4-chloro-5-β-chloroethyl-6-methylpyrimidine and 2-amino-4-chloro-5-β-hydroxyethyl-6-methylpyrimidine. That the latter compound is the nuclear and not the side chain chloropyrimidine is supported by its alkali insolubility, solubility in chloroform, and its spectrum which closely resembles that of 2-amino-4-chloro-6-methylpyrimidine. The only observable difference between the spectra of the mono- and dichloro-pyrimidines is an additional alkaline absorption maximum in the spectrum of the monochloropyrimidine. A sample of the monochloropyrimidine was cyclized to the dihydrofuran in 30% yield in acetic acid indicating that the internal SN_2 cyclization mechanism can operate when the chlorine and oxygen atoms are interchanged with respect to positions in the nucleus and side chain.

The attempted bromination of the dihydrofuran ring (I) at room temperature in carbon tetrachloride and in trifluoroacetic acid resulted in oxidative degradation, only unreacted starting material being recovered. The compound was also unreactive towards palladium in water under conditions of dehydrogenation but was extensively decomposed in acetic acid by the same catalyst.

[3] The conversion of hydroxypyrimidines to chloropyrimidines using thionyl chloride has been repeatedly attempted unsuccessfully in this laboratory.

[4] Unpublished results in this laboratory on the use of phosphorus oxychloride as a cyclizing reagent for other condensed pyrimidine systems indicate a similar variance in yield and nature of products with different samples of reagent.

Treatment of III with nitrous acid resulted in extreme decomposition but I and II underwent replacement of the amino by an hydroxyl group. That this deaminative hydrolysis did not occur in mineral acids but did occur in glacial acetic acid indicates that the free base rather than the salt is the active entity towards nitrous acid. The extreme water solubility of the product obtained from I made its isolation in the presence of sodium acetate rather difficult. The conversion of the sodium acetate into sodium chloride by treatment with hydrochloric acid resulted unexpectedly in the cleavage of the furan ring to a compound the spectrum of which resembled that of uracil (14) rather than 2-amino-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine and the analysis of which supports the structure 2,4-dihydroxy-5-β-chloroethyl-6-methylpyrimidine. The isolation of this compound from hydrochloric acid is rather surprising in view of the instability of 2-amino-4-hydroxy-5-β-chloroethyl (or β-chlorosulfite ester)-6-methylpyrimidine in thionyl chloride. Furthermore I is unaffected by hydrochloric acid. The presence of an hydroxyl group in the 2-position and the resulting uracil type of structure apparently stabilizes the open chain structure with respect to acid reagents. Treatment with alcoholic potassium hydroxide caused extreme degradation of the compound.

EXPERIMENTAL

2-Amino-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine. α-Acetyl-γ-butyrolactone (10) (12.8 g.) was added to a solution of guanidine (from 2.3 g. of sodium and 9.6 g. of guanidine hydrochloride) in 300 ml. of absolute ethanol. The mixture was refluxed for two hours and evaporated to dryness under reduced pressure. The residue was dissolved in 500 ml. of 1 *N* sodium hydroxide, treated with Darco, filtered hot, and acidified with acetic acid causing the precipitation of 5.5 g. (33%) of a white solid of m.p. 265–270° (d.) A 24% over-all yield (based on acetoacetic ester) was obtained by not isolating the lactone, and condensing it as its sodium salt with guanidine hydrochloride.

Anal. Calc'd for $C_7H_{11}N_3O_2$: C, 49.7; H, 6.51; N, 24.8.
Found: C, 49.8; H, 6.37; N, 24.4.

Ultraviolet absorption spectrum: ε, 8,100 (*p*H 1.0) at 263 mμ; minimum at 245 mμ; ε, 8,500, 7,600 (*p*H 11.0) at 232 mμ and 276 mμ; minimum at 254 mμ.

2-Amino-4-hydroxy-5-β-hydroxyethyl-6-phenylpyrimidine. α-Phenyl-γ-butyrolactone (b.p. 204–205°/11 mm.) was prepared in 21% yield by the method used for acetylbutyrolactone (10) and condensed with guanidine as described above to give the pyrimidine, m.p. 305–310°, in 60% yield.

Anal. Calc'd for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.62; N, 18.2.
Found: C, 62.0; H, 5.63; N, 17.8.

Ultraviolet absorption spectrum: ε, 10,000 (*p*H 1.0) at 275 mμ; minimum at 252 mμ; ε, 7,400 (*p*H 11.0) at 285 mμ; minimum at 260 mμ.

2,4-Diamino-5-β-hydroxyethyl-6-hydroxypyrimidine. The attempted hydrolysis (ice-cold) of the sodium salt of α-cyano-γ-butyrolactone, prepared by the method developed by Cope (11), resulted in the liberation of large amounts of hydrogen cyanide. The condensation was therefore accomplished by the addition of a molecular equivalent of guanidine hydrochloride to the alcoholic solution of the sodium salt of the cyanolactone, followed by a four-hour reflux of the mixture to give a 58% over-all yield of a solid. Crystallization from water gave white crystals, m.p. 298–300° (d.).

Anal. Calc'd for $C_6H_{10}N_4O_2$: C, 42.3; H, 5.93; N, 32.9.
Found: C, 42.2; H, 6.17; N, 32.2.

Ultraviolet absorption spectrum: ϵ, 16,000 (*p*H 1.0) at 270 mμ; ϵ, 5,100, 10,200 (*p*H 11.0) at 240 mμ and 270 mμ; minimum at 249 mμ.

2-Amino-4-methyl-5,6-dihydrofuro[2,3-d]pyrimidine. (a) *Cyclization with sulfuric acid.* A suspension of 2-amino-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine (2.0 g.) in 25 ml. of concentrated sulfuric acid was heated on a steam-bath for one hour with occasional shaking until solution occurred. The mixture was then poured onto ice, diluted, and made alkaline with 17 *N* sodium hydroxide, causing the precipitation of a solid 1.8 g. (100%). The product was dissolved in 20 ml. of acetic acid, treated with Darco, and filtered into hot dilute ammonia causing the precipitation of a white solid which had no melting point but decomposed slowly on being heated.

Anal. Calc'd for $C_7H_9N_3O$: C, 55.5; H, 5.96; N, 27.8.
Found: C, 55.7; H, 6.12; N, 28.2.

Ultraviolet absorption spectrum: ϵ, 5,900 (*p*H 1.0) at 282 mμ; minimum at 250 mμ; ϵ, 8,100, 5,700 (*p*H 11.0) at 233 mμ and 275 mμ; minimum at 255 mμ.

(b) *Other reagents.* A one-hour reflux in concentrated hydrochloric acid (2.0 g. in 50 ml.) gave a 20% yield while cold thionyl chloride (2.0 g. in 40 ml.) gave a quantitative yield of furopyrimidine. Thionyl chloride gave a 65% yield with the sodium salt of the pyrimidine.

Reaction of 2-amino-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine with phosphorus oxychloride. The pyrimidine (6.0 g.) was added to 50 ml. of phosphorus oxychloride. After about one minute a vigorous reaction occurred and the pyrimidine dissolved. Removal of the solvent by distillation under reduced pressure left a white solid which was treated with 100 ml. of chloroform to effect partial solution. The mixture was hydrolyzed with ice-cold dilute ammonium hydroxide and the layers were separated and filtered separately to recover the dihydrofuran (4.1 g., 76%). Dilution of the chloroform fraction with petroleum ether (b.p. 30–60°) did not cause the formation of a precipitate.

The same reaction mixture refluxed for one-half hour and worked up as above gave 2.0 g. of "chloropyrimidine" (m.p. 195–198°, crystallized from ether) and 0.3 g. of dihydrofuran. A particular batch of "chloropyrimidine" corresponding to 2-amino-4-chloro-5-β-hydroxyethyl-6-methylpyrimidine melted at 189–192°. Both products had the "mousy" odor characteristic of nuclear chloropyrimidines.

Anal. Calc'd for $C_7H_{10}ClN_3O$: C, 44.7; H, 5.32; Cl, 18.9; N, 22.3.
Found: C, 42.6; H, 4.63; Cl, 22.4; N, 22.0.
Found for "chloropyrimidine": C, 39.3; H, 3.91; Cl, 28.0; N, 18.9.

Ultraviolet absorption spectrum: ϵ, 5,100 (*p*H 1.0) at 310 mμ; minimum at 256 mμ; ϵ, 14,000, 4,400 (*p*H 11.0) at 232 mμ and 278 mμ; minimum at 258 mμ.

Ultraviolet absorption spectrum of "chloropyrimidine": ϵ, 5,900 (*p*H 1.0) at 310 mμ; minimum at 260 mμ; ϵ, 18,000, 4,700 (*p*H 11.0) at 235 mμ and 298 mμ; minimum at 260 mμ.

Ultraviolet absorption spectrum of 2-amino-4-chloro-6-methylpyrimidine: ϵ, 6,600 (*p*H 1.0) at 303 mμ; minimum at 247 mμ; ϵ, 5,300 (*p*H 11.0) at 290 mμ; minimum at 255 mμ.

A solution of 0.5 g. of the chloropyrimidine in 40 ml. of acetic acid was refluxed for one hour resulting in the isolation of 150 mg. (30%) of the dihydrofuran.

2-Amino-4-chloro-5-β-chloroethyl-6-methylpyrimidine. A mixture of 2.0 g. of I in 40 ml. of phosphorus oxychloride was refluxed for 3,5 hours. The mixture was then concentrated to a syrup under reduced pressure and 20 ml. of chloroform were added to dissolve the syrup. The chloroform solution was slowly added to ice-cold dilute ammonium hydroxide and 100 ml. of ether was added to effect extraction of the product. The organic layer was separated, dried over magnesium sulfate, and concentrated to 20 ml. Then 200 ml. of petroleum ether (b.p. 30–60°) was added to precipitate 0.3 g. of a light yellow solid. The substance was soluble in dilute hydrochloric acid but insoluble in dilute sodium hydroxide and gave a positive halogen test with boiling silver nitrate. The substance was treated with Darco in chloroform from which it was obtained as a white solid having a strong mouse-like odor characteristic of chloropyrimidines and a melting range of 165–190°.

Anal. Calc'd for $C_7H_8Cl_2N_3$: C, 40.8; H, 4.37; Cl, 34.4; N, 20.4.
Found: C, 38.3; H, 4.58; Cl, 32.5; N, 20.2.

A carbonaceous residue amounting to about 6% of the sample was left uncombusted but most of this material was burned in an open flame leaving some white ash. This would raise the carbon figure closer to the theoretical value.

Ultraviolet absorption spectrum: ϵ, 5,000 (*p*H 1.0) at 310 mμ; minimum at 235 mμ; ϵ, 3,800 (*p*H 11.0) at 295 mμ; minimum at 262 mμ.

2-Amino-4-phenyl-5,6-dihydrofuro[2,3-d]pyrimidine. The compound was prepared in quantitative yield from the appropriate hydroxyethylpyrimidine with concentrated sulfuric acid as described above and was crystallized from ethanol to give white crystals, m.p. 188–190°.

Anal. Calc'd for $C_{12}H_{11}N_3O$: C, 67.7; H, 5.16; N, 19.7.

Found: C, 67.6; H, 5.45; N, 20.2.

Ultraviolet absorption spectrum: ϵ, 11,000 (*p*H 1.0) at 298 mμ; minimum at 255 mμ; ϵ, 19,000, 7,200 (*p*H 11.0) at 238 mμ and 308 mμ; minimum at 273 mμ.

2,4-Diamino-5,6-dihydrofuro[2,3-d]pyrimidine. The compound was prepared in 57% yield from the hydroxyethylpyrimidine by the use of concentrated sulfuric acid as described above. Purification was accomplished by solution in boiling water and treatment with Darco. Upon cooling there separated an amorphous white solid, m.p. 265–270° (d.)

Anal. Calc'd for $C_6H_6N_4O$: C, 47.3; H, 5.31; N, 36.8.

Found: C, 47.4; H, 5.12; N, 35.2.

Ultraviolet absorption spectrum: ϵ, 7,300, 12,800 (*p*H 1.0) at 235 mμ and 282 mμ; minimum at 258 mμ; ϵ, 6,400, 8,200 (*p*H 11.0) at 235 mμ and 270 mμ; minimum at 253 mμ.

2-Amino-4-hydroxy-6-methyl-5-pyrimidylacetic acid. Diethylacetosuccinate was condensed with guanidine as described above to give the pyrimidine in 47% yield. The product was crystallized from water as white crystals, m.p. 315–320° (d.).

Anal. Calc'd for $C_7H_9N_4O_3$: C, 45.8; H, 4.42; N, 22.9.

Found: C, 45.9; H, 4.51; N, 22.3.

Ultraviolet absorption spectrum: ϵ, 8,100 (*p*H 1.0) at 263 mμ; minimum at 242 mμ; ϵ, 8,300, 7,000, (*p*H 11.0) at 234 mμ and 278 mμ; minimum at 252 mμ.

2-Hydroxy-4-phenyl-5,6-dihydrofuro[2,3-d]pyrimidine. Sodium nitrite (5.0 g.) was added to a previously cooled solution of 5.0 g. of II in 30 ml. of acetic acid. The mixture was occasionally shaken and cooled in an ice-bath for 30 minutes after which it was heated on a steam-bath for 30 minutes and poured into 200 ml. of water. The solid was dissolved in 100 ml. of 2 *N* sodium hydroxide, filtered, and reprecipitated with acetic acid to give 1.5 g. (30%) of a tan solid which was crystallized from anhydrous ethanol as small hard crystals, m.p. 265–270°.

Anal. Calc'd for $C_{12}H_{10}N_2O_2$: C, 67.3; H, 4.67; N, 13.1.

Found: C, 67.1; H, 4.88; N, 13.0.

Ultraviolet absorption spectrum: ϵ, 12,000 (*p*H 1.0) at 315 mμ; minimum at 275 mμ; ϵ, 18,000, 9,000 (*p*H 11.0) at 235 mμ and 310 mμ; minimum at 270 mμ.

2,4-Dihydroxy-5-β-chloroethyl-6-methylpyrimidine. Sodium nitrite (5.0 g.) was added to a previously cooled solution of 10 g. of I in 30 ml. of acetic acid. The mixture was treated as above and hydrolyzed but no solid formed. Concentrated hydrochloric acid (100 ml.) was added and the mixture was evaporated to dryness on the steam-bath under reduced pressure, leaving a white residue which was extracted with 250 ml. of boiling absolute ethanol. Upon cooling 2.2 g. of white flaky crystals, m.p. 265–270°, separated out of solution. The compound did not give a test for ionic chlorine.

Anal. Calc'd for $C_7H_9ClN_2O_2$: C, 44.4; H, 4.76; Cl, 18.8; N, 14.8.

Found: C, 45.1; H, 5.28; Cl, 17.1; N, 14.9.

Ultraviolet absorption spectrum: ϵ, 14,000 (*p*H 1.0) at 268 mμ; minimum at 235 mμ; ϵ, 6,100 (*p*H 11.0) at 283 mμ; minimum at 250 mμ.

Oxidative bromination of I. To 75 ml. of carbon tetrachloride was added 0.95 g. of bromine and 2.0 g. of I. The mixture was shaken for 30 minutes in sunlight at which time the color of the solution was a faint yellow. The reaction mixture was poured into 200 ml. of petroleum ether (b.p. 30–60°) and the solid filtered off and leeched with 200 ml. of water

leaving 1.1 g. of starting compound. A similar experiment in trifluoroacetic acid (four hours in sunlight) gave 0.6 g. of starting compound.

Attempted dehydrogenation of I. A mixture of 2.0 g. of I, 2.0 g. of potassium carbonate, 2.0 g. of maleic acid, and a palladium catalyst (0.5 ml. of 33% palladium chloride solution hydrogenated with 1.0 g. Darco) in 50 ml. of water was refluxed for 68 hours. The mixture was diluted to 300 ml. with water and was filtered. The insoluble material was washed with ml. of 1 *N* hydrochloric acid and the combined filtrate was made alkaline with saturated sodium hydroxide to give 1.0 g. of starting material as a white precipitate.

A 19-hour reflux of a mixture of 2.0 g. of I, 2.0 g. of maleic acid, and a palladium catalyst in 50 ml. of acetic acid resulted in the recovery of a few milligrams of starting material as the only insoluble product.

SUMMARY

1. The cyclodehydration of 2-amino-4-hydroxy-5-β-hydroxyethylpyrimidines by various acidic reagents results in the formation of the 5,6-dihydrofuro-[2,3-*d*]pyrimidine ring system.

2. Phosphorus oxychloride effects first cyclization, then cleavage of the furan ring.

3. 2-Amino-4-chloro-5-β-hydroxyethyl-6-methylpyrimidine undergoes cyclization in acetic acid but its isomer 2-amino-4-hydroxy-5-β-chloroethyl-6-methylpyrimidine, which is probably formed in thionyl chloride, cyclizes spontaneously.

4. The presence of an hydroxyl group in the 2-position of the pyrimidine ring stabilizes the 4-hydroxy-5-β-chloroethyl structure towards hydrochloric acid.

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