Pyrimidines. XXI. 1-(Tetrahydro-2-furyl)pyrimidines (1)

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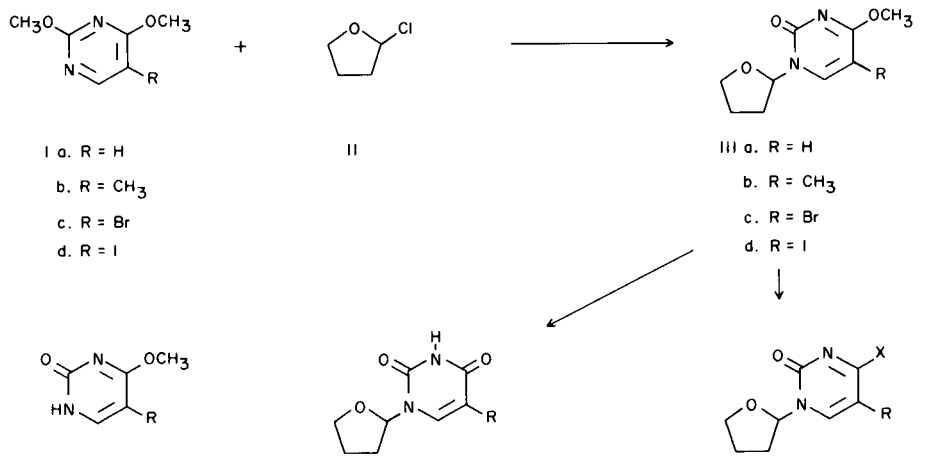
A number of 1-(tetrahydro-2-furyl)uracils, cytosines and related compounds were synthesized by a modified Hilbert-Johnson method from 2-chlorotetrahydrofuran and the corresponding 2,4-dimethoxypyrimidines. The relative stability in acid of tetrahydrofuryl and tetrahydropyranyl moieties in compounds of this type was discussed. 2-Oxo-4-methoxy-1,2-dihydropyrimidine, a compound which has been erroneously reported, has now been prepared and its structure confirmed by conversion into cytosine.

In connection with the synthetic investigation of 1-(tetrahydro-2-pyranyl)cytosine and related compounds (2), preparation of the corresponding 1-(tetrahydro-2-furyl)-pyrimidines has also been studied in our laboratory. The biological importance of pyranyl and furyl ring systems in naturally occurring compounds and antitumor agents has already been discussed (2). Compounds of this type may also contribute toward a better understanding of the mechanism of inhibition of nucleoside phosphorylases (3).

Although 1-(tetrahydro-2-pyranyl)-2-oxo-4-methoxy-1,2-dihydropyrimidine (2) was readily obtained by the treatment of 2,4-dimethoxypyrimidine (Ia) (4) with 2-chlorotetrahydropyran (5), treatment of Ia with 2-chloro-tetrahydrofuran (II) (6) under the same reaction conditions failed to yield 1-(tetrahydro-2-furyl)-2-oxo-4-methoxy-1,2-dihydropyrimidine (IIa). This perhaps can be attributed to the extreme lability of the tetrahydrofuryl moiety in the acidic environment. In a modified experiment, when freshly prepared II was stirred with Ia in the presence of anhydrous sodium carbonate, the desired product IIIa was obtained in good yield.

During the preparation of IIIa, if the hydrogen chloride



Ia. R = H
b. R = CH_3
c. R = Br
d. R = I

II

IIIa. R = H
b. R = CH_3
c. R = Br
d. R = I

IVa. R = H
b. R = I

Va. R = H
b. R = CH_3
c. R = Br
d. R = I

VIa. R = H, X = NH_2
b. R = H, X = $NHCH_3$
c. R = H, X = NHOH
d. R = CH_3, X = NH_2
e. R = CH_3, X = $NHCH_3$
f. R = CH_3, X = NHOH
g. R = Br, X = NH_2
h. R = I, X = NH_2

produced during the reaction was not properly neutralized, an insoluble product was formed. Elemental analysis and spectral study of this compound, m.p. 206-208°, suggested its structure to be 2-oxo-4-methoxy-1,2-dihydropyrimidine (IVa). Although Chi and Chen (7) claimed the preparation of IVa, m.p. 132-134° (without complete analysis), by the treatment of 2-ethylthio-4-methoxypyrimidine with hydrogen peroxide in ethanol, their results could not be duplicated in this laboratory. Treatment of our product, m.p. 206-208°, with methanolic ammonia at 100° readily yielded cytosine, thus confirming the structure of this product as IVa.

Conversion of compound IIIa to 1-(tetrahydro-2-furyl)-uracil (Va) was carried out in dilute hydrochloric acid. Since the tetrahydrofuryl ring is readily cleaved in acid, the course of this conversion was followed by noting the shift of the major ultraviolet absorption peak (from 275 to 263 mμ at *p*H 1) of the reaction solution. The solution was worked up immediately when the maximum absorption of 263 mμ was reached. Prolonged standing of the reaction mixture yielded uracil. In a later experiment, it was found that compound Va can be prepared in good yield by warming IIIa in dilute sodium hydroxide.

Preparation of 1-(tetrahydro-2-furyl)cytosine (VIa) from IIIa was readily accomplished with methanolic ammonia. The corresponding 4-methylamino (VIb) and 4-hydroxyamino (VIc) derivatives were obtained by treating IIIa with aqueous methylamine and hydroxylamine, respectively.

Substitution of a methyl group at the 5-position of a pyrimidine ring strengthens the linkage between the 1-(tetrahydro-2-furyl) and the pyrimidine moieties. Thus 1-(tetrahydro-2-furyl)-2-oxo-4-methoxy-5-methyl-1,2-dihydropyrimidine (IIIb) was readily obtained from 2,4-dimethoxy-5-methylpyrimidine (Ib) (8,9) and II. Conversion of IIIb to the 1-substituted thymine Vb in acid media did not require uv monitoring of the reaction since the product Vb precipitated from the acidic reaction mixture. Compound Vb can also be obtained by the treatment of IIIb with dilute base. The corresponding 4-amino derivatives, VId-f, were prepared in a fashion similar to that used for the preparation of VIa-c.

In contrast to the foregoing, substitution of a halogen atom at the 5-position of a pyrimidine ring further weakens the tetrahydrofuran-pyrimidine linkage in acid solution. Although 1-(tetrahydro-2-furyl)-2-oxo-4-methoxy-5-bromo-1,2-dihydropyrimidine (IIIc) and the corresponding 5-iodo derivative (IIId) were prepared from II and the appropriate 5-halo-substituted pyrimidines Ic and Id, respectively, attempts to prepare the 1-substituted uracil derivatives, Vc and Vd, in acidic media only resulted in the isolation of 5-bromo- and 5-iodouracil. Base treatment of Ic and Id, on the other hand, gave the desired products Vc and Vd without difficulty. The corresponding cytosine derivatives, VIg and VIh, were accordingly prepared.

A by-product was also obtained during the preparation of IIId. This compound was identified as 2-oxo-4-methoxy-5-iodo-1,2-dihydropyrimidine (IVb) by elemental analysis, spectral examination, and its conversion to the known 5-iodocytosine (10) with ammonia.

EXPERIMENTAL (11)

1-(Tetrahydro-2-furyl)-2-oxo-4-methoxy-1,2-dihydropyrimidine (IIIa).

A moderate stream of dry hydrogen chloride was passed through a solution (cooled in an ice bath) of 10 g. of 2,3-dihydrofuran (6) in 80 ml. of dry dichloromethane for 15 minutes. To the solution was added 20 g. of anhydrous sodium carbonate. The mixture was stirred for 5 minutes and 20 g. of 2,4-dimethoxypyrimidine (Ia) (4) was added in one portion. The mixture was then stirred for an additional 15 minutes after which the ice bath was removed. Stirring was continued for 20 hours at room temperature. The reaction mixture was then filtered and the filtrate concentrated to a clear oil by means of a rotary flash evaporator. The oil was triturated with warm petroleum ether (b.p. 35-60°). The solvent was decanted and the residue was covered with 100 ml. of anhydrous ether. The mixture was triturated for 5 minutes by means of a glass rod and then allowed to stand at 5° for 2 hours. The resulting crystalline solid was collected by filtration, washed with petroleum ether and dried in a vacuum desiccator over phosphorus pentoxide to give 24 g. (86% yield) of IIIa, m.p. 68-70°. An analytical sample was obtained by recrystallization from ether, m.p. 74-75°; λ max (*p*H 1) 275 mμ (ε, 7,900); λ max (*p*H 11) 273 mμ (ε, 7,900).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.20; H, 6.17; N, 14.54.

2-Oxo-4-methoxy-1,2-dihydropyrimidine (IVa).

At a moderate rate, dry hydrogen chloride was passed through a cooled solution of 50 g. of 2,3-dihydrofuran (6) in 400 ml. of dry dichloromethane for 15 minutes. Approximately 26 g. of hydrogen chloride was absorbed. To the solution was added, at 0°, 50 g. of anhydrous sodium carbonate. The mixture was stirred for 5 minutes and filtered. To the cold filtrate was added, with stirring, 110 g. of 2,4-dimethoxypyrimidine (Ia) (4). After stirring for another 30 minutes, the cooling bath was removed and the mixture was allowed to stir for 20 hours at room temperature. The precipitated solid, which had formed during this time, was collected by filtration and washed with dichloromethane. The product was dried at 80° to give 25 g. of white solid, m.p. 203-205°. One recrystallization from methanol yielded an analytical sample, m.p. 206-208°; λ max (*p*H 1) 267 mμ (ε, 4,700); λ max (*p*H 11) 275 mμ (ε, 5,400).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.40; H, 5.06; N, 22.40.

This product, when treated with excess methanolic ammonia at 100° in a sealed container, gave cytosine in almost quantitative yield.

1-(Tetrahydro-2-furyl)uracil (Va).

Method A.

A solution of 6 g. of IIIa in 40 ml. of water containing 2 ml. of concentrated hydrochloric acid was allowed to stand at 3° for 12 hours. During this time the major absorption maxima had undergone a hypsochromic shift to 263 mμ. The solution was then carefully neutralized with 2 *N* sodium hydroxide solution. The

resulting solution was then evaporated to dryness *in vacuo*. The solid mass was then boiled with 160 ml. of dry ethyl acetate. The insoluble solid (sodium chloride) was removed by filtration and the volume of the filtrate was concentrated to 50 ml. On cooling, the desired product Va was collected by filtration and recrystallized from ethyl acetate to give 3 g. (54% yield) of analytically pure product, m.p. 103-104°; λ max (*p*H 1) 263 mμ (ε, 10,800), λ max (*p*H 11) 225 mμ (ε, 6,500) and 263 mμ (ε, 8,000).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 53.09; H, 5.29; N, 15.61.

Method B.

A mixture of 3 g. of IIIa and 30 ml. of 2 *N* sodium hydroxide was warmed at 80-90° for 10 minutes. It was then allowed to cool slowly to room temperature. After the solution was kept at room temperature for 20 minutes, it was carefully neutralized with 1 *N* hydrochloric acid at $< 15°$. The resulting solution was then evaporated to dryness *in vacuo* at $<15°$, and the residue extracted with ethyl acetate and worked up as described in the previous method to give 2.1 g. (70% yield) of Va. The product was found to be identical with that obtained by Method A.

1-(Tetrahydro-2-furyl)cytosine (VIa).

A mixture of 10 g. of IIIa and 200 ml. of methanolic ammonia (methanol saturated with ammonia at 0°) was heated at 100° for 12 hours in a sealed container. The reaction mixture was then evaporated to dryness under reduced pressure, and the semi-crystalline residue was triturated with 100 ml. of warm ethyl acetate. After cooling, the crystalline mass was collected by filtration. One recrystallization from ethyl acetate containing a trace of methanol gave 4 g. (43% yield) of analytically pure VIa, m.p. 193-194°; λ max (*p*H 1) 280 mμ (ε, 14,800); λ max (*p*H 11) 231 (ε, 7,800) and 271 mμ (ε, 10,000).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.17; H, 5.97; N, 23.46.

1-(Tetrahydro-2-furyl)-2-oxo-4-methylamino-1,2-dihydropyrimidine (VIb).

A mixture of 10 g. of IIIa, 40 ml. of 35% aqueous methylamine and 50 ml. of water was stirred at room temperature for 2 hours. The solution was then evaporated to dryness *in vacuo* and the residue triturated with ether. The resulting crystalline mass was isolated by filtration to give, after drying at 70° for 16 hours, 7.5 g. (75% yield) of a white solid, m.p. 123-125°. One recrystallization from benzene gave 5.4 g. (54% yield) of analytically pure VIb, m.p. 130-131°; λ max (*p*H 1) 281 mμ (ε, 15,800); λ max 234 (ε, 9,400) and 271 mμ (ε, 11,900).

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.59; H, 6.67; N, 21.72.

1-(Tetrahydro-2-furyl)-2-oxo-4-hydroxyamino-1,2-dihydropyrimidine (VIc).

Hydroxylamine hydrochloride (7.2 g.) was dissolved in 50 ml. of water. The solution was adjusted to *p*H 7 by means of 4 *N* sodium hydroxide. To this neutral solution was added 5 g. of IIIa and the mixture was refluxed for 1 hour. The hot reaction solution was then evaporated to dryness by means of a rotary evaporator and the crystalline residue triturated with 50 ml. of cold water. The resulting crystalline solid was recrystallized from 100 ml. of water to give 3 g. (60% yield) of analytically pure product, m.p. 173-175°; λ max (*p*H 1) 281 mμ (ε, 14,400); λ max (*p*H 11) 239 mμ (ε, 11,600).

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.76; H, 5.90; N, 21.06.

1-(Tetrahydro-2-furyl)-2-oxo-4-methoxy-5-methyl-1,2-dihydropyrimidine (IIIb).

This compound was prepared from 20 g. of 2,3-dihydrofuran, 40 g. of sodium carbonate and 44.2 g. of 2,4-dimethoxy-5-methylpyrimidine (7) in a similar fashion to that used for the preparation of IIIa. The product was recrystallized from a mixture of hexane and acetone to give 24 g. (40% yield) of IIIb, m.p. 99-100°. Further recrystallization from the same solvent pair raised its m.p. to 100-101°; λ max (*p*H 1) 279 mμ (ε, 6,900); λ max (*p*H 11) 279 mμ (ε, 7,100).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.22; H, 6.97; N, 13.66.

1-(Tetrahydro-2-furyl)thymine (Vb).

Method A.

To a solution of 5 g. of IIIb in 50 ml.of water was added 5 ml. of concentrated hydrochloric acid. The solution was stirred for 4 hours and the precipitate was collected by filtration. The solid was recrystallized from water to give 2.3 g. (50% yield) of analytically pure Vb, m.p. 183-185°. λ max (*p*H 1) 268 mμ (ε, 10,400); λ max (*p*H 11) 225 (ε, 7,800) and 267 mμ (ε, 8,200).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.08; H, 6.21; N, 14.55.

Method B.

A mixture of 2 g. of IIIb and 20 ml. of 2 *N* sodium hydroxide was gently boiled for 10 minutes and then allowed to cool to room temperature. The solution was then acidified with glacial acetic acid to *p*H 6 and cooled. The resulting precipitate was collected by filtration and washed with water, acetone, and dried at 80° to give 0.9 g. (48% yield) of Vb, which was identical with that prepared by Method A.

1-(Tetrahydro-2-furyl)-5-methylcytosine (VId).

This compound was prepared from 6 g. of IIIb and 180 ml. of methanolic ammonia in a similar fashion to that used for the preparation of VIa. The product was recrystallized from acetonitrile to give 4 g. (72% yield) of analytically pure product, m.p. 217-219°; λ max (*p*H 1) 288 mμ (ε, 12,600); λ max (*p*H 11) 230 (ε, 7,500) and 278 mμ (ε, 8,800).

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.51; H, 6.57; N, 21.85.

1-(Tetrahydro-2-furyl)-2-oxo-4-methylamino-5-methyl-1,2-dihydropyrimidine (VIe).

This compound was prepared from 10 g. of IIIb and 150 ml. of 35% aqueous methylamine in a fashion similar to that used for the preparation of VIb. Recrystallization from a mixture of benzene and methanol gave 9.2 g. (93% yield) of white crystals, m.p. 173-174°; λ max (*p*H 1) 286 mμ (ε, 11,600); λ max (*p*H 11) 233 mμ (ε, 6,700) and 276 mμ (ε, 8,500).

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 58.00; H, 7.36; N, 20.20.

1-(Tetrahydro-2-furyl)-2-oxo-4-hydroxyamino-5-methyl-1,2-dihydropyrimidine (VIf).

This compound was prepared from 13.2 g. of hydroxylamine hydrochloride and 10 g. of IIIb in a similar fashion to that used for the preparation of VIc. Recrystallization from water gave 7 g. (70% yield) of VIf, m.p. 170-172°; λ max (*p*H 1) 285 mμ (ε, 13,800); λ max (*p*H 11) 240 mμ (ε, 10,400).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.90. Found: C, 51.36; H, 6.36; N, 19.81.

1-(Tetrahydro-2-furyl)-2-oxo-4-methoxy-5-bromo-1,2-dihydropyrimidine (IIIc).

This compound was prepared from 12 g. of 2,3-dihydrofuran, 30 g. of sodium carbonate and 25 g. of 2,4-dimethoxy-5-bromopyrimidine (Ic) (12) in a similar fashion to that used for the preparation of IIIa. The product was recrystallized from water to give 9.8 g. (31% yield) of IIIc, m.p. 110-111°; λ max (*p*H 1) 289 mμ (ε, 5,400); λ max (*p*H 11) 289 mμ (ε, 5,200).

Anal. Calcd. for $C_9H_{11}BrN_2O_3$: C, 39.29; H, 4.03; N, 10.18. Found: C, 39.50; H, 3.97; N, 10.33.

1-(Tetrahydro-2-furyl)-5-bromouracil (Vc).

This compound, m.p. 205-207°, was prepared from 1.5 g. of IIIc by essentially the same procedure as used for the preparation of Vb. After recrystallization of the crude product from a mixture of ethanol and water, a yield of 70% of Vc was obtained; λ max (*p*H 1) 280 mμ (ε, 8,900); λ max (*p*H 11) 276 mμ (ε, 6,500).

Anal. Calcd. for $C_8H_9BrN_2O_3$: C, 36.80; H, 3.47; N, 10.73. Found: C, 37.08; H, 3.38; N, 10.78.

1-(Tetrahydro-2-furyl)-5-bromocytosine (VIg).

This compound was prepared from 7 g. of IIIc and 200 ml. of methanolic ammonia by a similar procedure as used for the preparation of VIa. Recrystallization from water gave 3.5 g. (53% yield) of VIg, m.p. 192-193°; λ max (*p*H 1) 300 mμ (ε, 11,200); λ max (*p*H 11) 286 mμ (ε, 7,800).

Anal. Calcd. for $C_8H_{10}BrN_3O_2$: C, 36.94; H, 3.87; N, 16.16. Found: C, 36.84; H, 4.09; N, 16.04.

1-(Tetrahydro-2-furyl)-2-oxo-4-methoxy-5-iodo-1,2-dihydropyrimidine (IIId) and 2-Oxo-4-methoxy-5-iodo-1,2-dihydropyrimidine (IVb).

From 20 g. of 2,3-dihydrofuran, 30 g. of sodium carbonate and 70 g. of 2,4-dimethoxy-5-iodopyrimidine (Id) (13) was obtained, in a similar fashion to that used for the preparation of IIIa, 40 g. of a solid material. This material, which contained a mixture of IIId and IVb, was dissolved in 200 ml. of cold ethyl acetate. The solution was then boiled for a few minutes and a precipitate began to separate. After the mixture was boiled for 15 minutes, the insoluble material was collected by filtration and washed with hot ethyl acetate. The yield of 2-oxo-4-methoxy-5-iodo-1,2-dihydropyrimidine (IVb) after recrystallization from acetonitrile was 4.6 g., m.p. 228-229°; λ max (*p*H 1) 227 mμ (ε, 18,200) and 290 mμ (ε, 3,900); λ max (*p*H 11) 234 mμ (ε, 17,600) and 291 mμ (ε, 5,500).

Anal. Calcd. for $C_5H_5IN_2O_2$: C, 23.83; H, 2.00; N, 11.12. Found: C, 23.88; H, 2.01; N, 11.28.

This product, when treated with excess methanolic ammonia at 100° in a sealed container, gave 5-iodocytosine (10) in almost quantitative yield.

The filtrate and ethyl acetate washings were combined and evaporated to dryness under reduced pressure, and the residue recrystallized from 1000 ml. of water to give 29.2 g. of IIId, m.p. 141-143°. One more recrystallization from the same solvent yielded a sample of analytical purity, m.p. 145-146°; λ max (*p*H 1) 227 mμ (ε, 16,400) and 295 mμ (ε, 5,800); λ max (*p*H 11) 230 (ε, 14,800) and 295 mμ (ε, 5,800).

Anal. Calcd. for $C_9H_{11}IN_2O_3$: C, 33.56; H, 3.44; N, 8.70. Found: C, 33.23; H, 3.56; N, 9.06.

1-(Tetrahydro-2-furyl)-5-iodouracil (Vd).

This compound m.p. 209-211°, was prepared from 1.0 g. of IIId by a similar procedure as used for the preparation of Vb. A yield of 94% was obtained after the crude product was recrystallized from a mixture of ethanol and water; λ max (*p*H 1) 289 mμ (ε, 7,400); λ max (*p*H 11) 279 mμ (ε, 5,600).

Anal. Calcd. for $C_8H_9IN_2O_3$: C, 31.19; H, 2.94; N, 9.11. Found: C, 31.22; H, 2.96; N, 8.80.

1-(Tetrahydro-2-furyl)-5-iodocytosine (VIh).

This compound was prepared from 8 g. of IIId and 180 ml. of methanolic ammonia by a similar procedure as used for the preparation of VIa. Recrystallization from water gave 3.2 g. (42% yield) of VIh, m.p. 187-189°; λ max (*p*H 1) 308 mμ (ε, 8,900); λ max (*p*H 11) 277 mμ (ε, 10,400) and 294 mμ (ε, 5,200).

Anal. Calcd. for $C_8H_{10}IN_3O_2$: C, 31.29; H, 3.28; N, 13.68. Found: C, 31.00; H, 3.48; N, 13.20.

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