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Original Scientific Paper

Hydropyrimidines. VII*. Covalent Hydration and Ring Opening

V. Škarić and B. Gašpert

Institute »Ruđer Bošković«, Zagreb, Croatia, Yugoslavia

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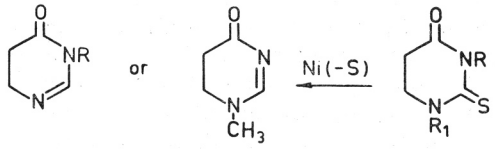
The ring opening of 5,6-dihydro-4-oxo-pyrimidine (I) and its *N*-methyl derivatives II and III has been established as the cleavage of the intermediary 2-hydroxytetrahydropyrimidines to 3-formamidopropionamide (VIII) and its *N*-methyl derivatives XIII and XIV. The formation of the 2-hydroxy intermediate is proposed as the nucleophylic addition of water to the C = N double bond of the hydropyrimidines I—III.

The rupture of 1,3-dimethyl-5,6-dihydro-2-thiouracil (VII) proceeds to 3-(*N*-methyl-formamido)-*N*-methylpropionamide (XV), most probably by reductive desulfurization *via* a carbonium ion of the mentioned type during nucleophylic addition.

The NMR spectra of formamidopropionamide are discussed.

The ring opening of dihydropyrimidine and its ring substituted derivatives has been established in several cases. Thus, the cleavage of 5,6-dihydrouracil to 1-(propionic acid)-urea has been observed in biological systems[1]. The lower homologue of thiouracil (thiohydantoin) was cleaved, during the desulfurization[2], to the corresponding 2-formamidopropionamide. 5-Formamidoimidazole-4-carboxamide ribotide was demonstrated[3] to be an intermediate in the biosynthesis of purines and corresponding nucleotides.

This prompted us to define possible pathways for opening the cyclic structures of substituted hydropyrimidines. The object of the present paper is to report the hitherto unknown ring opening of 5,6-dihydro-4-oxopyrimidines (I) and its isomeric *N*-methyl derivatives II and III[4], obtained from 5,6-dihydro-2-thiouracil (IV)[5] and the corresponding 3-methyl-(V) and 1-methyl-(VI) 2-thiopyrimidines[6].



I R=H
II. R=CH_3

III.

IV. R=R_1=H
V. R=H, R_1=CH_3
VI. R=CH_3, R_1=H
VII. R=R_1=CH_3

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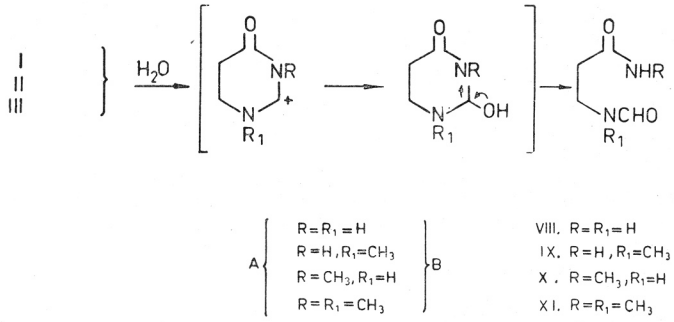
In a previous paper[4] we reported that the isomer III with a double bond at $\Delta^{2,3}$ position was not isolated because of its instability and rapid ring opening, which most probably yielded *N*-formyl derivative of 3-methylaminopropionamide. In order to elicit the manner of this ring opening to 3-(*N*-methylformamido)- propionamide (IX) we examined 5,6-dihydro-4-oxopyrimidine (I) and its 3-methyl derivative (II) with the double bond at the $\Delta^{1,2}$ position. These compounds behave in a similar way, yielding 3-formamidopropionamide (VIII) and 3-formamido-*N*-methylpropionamide (X). The formation of *N*-formyl compounds VIII and X suggests that the ring opening of 5,6-dihydro-4-oxopyrimidines I, III generally occurs through a common intermediate. Thus, the stepwise nucleophylic addition of water is envisaged to take place through a common



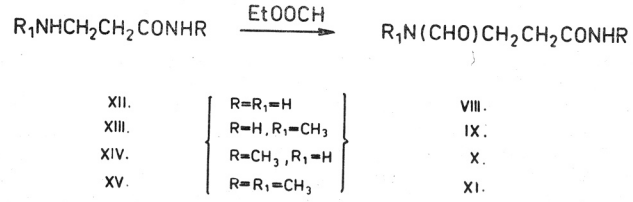
carbonium ion A, stabilized by resonance of the type $-\overset{+}{N}R=CH-NR- \longleftrightarrow \longleftrightarrow -NR-CH=\overset{+}{N}R-$.

This covalent hydration, which appears across the $\Delta^{1,2}$ as well as the $\Delta^{2,3}$ position, is completed by attachment of a hydroxyl ion. The same nucleophylic addition of water to C=N in triazanaphtalenes[7] and pteridines[8], which have stable ring structures, proceeds to equilibrium accompanied by a concurrent reversible reaction. However, the instability of intermediary 2-hydroxytetrahydropyrimidines (B) brings the reaction irreversibly to the *N*-formyl derivatives VIII—X. The presence of hydrochloric acid in catalytic amounts results in about five fold acceleration of the ring rupture of I and II.

The proposed covalent hydration for ring opening of dihydropyrimidines cannot be the pathway for the rupture of 1,3-dimethyl-5,6-dihydro-2-thiouracil (VII). The most acceptable course for the cleavage of dimethyl derivative VII to the corresponding 3-(*N*-methyl-formamido)-*N*-methylpropionamide (XI) includes hydrogenation with subsequent desulfurization *via* a carbonium ion of the mentioned type A. The rate of this transformation, recorded spectroscopically, was about five times slower than for desulfurization of 5,6-dihydro-2-thiouracil (IV).

As reported earlier[4], 1-methyl-4-oxopyrimidine showed an unexpectedly high absorption at 305 mμ during partial hydrogenation. Another example of this kind is the very slow desulfurization of 1-methyl-5,6-dihydro-2-thiouracil (VI), which is about ten times slower in comparison with compound IV. The structure of *N*-formyl derivatives VIII—XI were ascertained by an alternative preparation. Namely, the formylation of 3-aminopropionamide (XII), 3-methyl-

aminopropionamide (XIII), 3-amino-*N*-methylpropionamide (XIV) and 3-methylamino-*N*-methyl-propionamide (XV) with ethylformate yielded the correspon-



ding formamido compounds VIII—XI. The resulting 3-formamido-propionamide, and its mono- and dimethyl- derivatives were identical with the corresponding samples obtained from ring cleavage of the 4-oxo-2-thiopyrimidines IV—VII.

The results of NMR measurements of formylated 3-aminopropionamide and its *N*-methylamino and *N*-methylamido derivatives are listed in Table I. The chemical shifts and coupling constants exhibiting an AB pattern confirm the structures of these compounds. As expected, the chemical shifts of protons in the 2 and 3 positions correspond to those in positions 5 and 6 of cyclic 4-oxo-pyrimidines[4]. The appearance of the signal at very low field (τ values at 1.8 and 2.14) related to the formyl proton supports our earlier statement[4] for the ring rupture of hydropyrimidines to the formyl derivatives.

TABLE I

Results from NMR measurements of formylated 3-aminopropionamides.

Compound	Chemical shifts, τ					Coupling const. $J_{2,3}$
	2-H	3-H	CHO	amino CH_3	amido CH_3	
VIII	7.42	6.42	1.85	—	—	6.7
IX	7.29	6.22	1.85	7.0	—	6.8
X	7.45	6.42	1.85	—	7.19	6.7
XI	7.62	6.50	2.14	7.29	7.43	6.8

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. The UV spectra were measured on a *Perkin Elmer* model 137 UV spectrophotometer with automatic gain control. The IR absorption bands were recorded unless otherwise stated, in potassium bromide plates with a *Perkin Elmer* Infracord model 137 and are reported in wavelengths followed by relative intensities in brackets. The NMR spectra were taken at a frequency of 60 mC/sec. on a *Varian* model A 60 high resolution spectrometer. Solutions (8—10%) in deuterium oxide were used. The sweep was calibrated using the common modulation sideband method. Values given for the chemical shifts, τ, are in parts per milion, tetramethylsilane taken as zero.

3-Formamidopropionamide (VIII)

a) From 3-aminopropionamide. — To freshly distilled 3-aminopropionamide (XII, 360 mg., 4.05 mmole) in dioxane (5 ml.) (prepared from cyanoacetamide[9] by catalytic (PtO_2) hydrogenation and isolated according to the procedure for separation of 3-methylaminopropionamide[6]) ethylformate (5 ml.) was added. After refluxing the mixture for 2 hours and cooling overnight a crystalline precipitate was separated. Yield 281 mg. (60%), m. p. 97—101°. Further crystallization from anhydrous ethanol-

-ether gave the analytical sample as hygroscopic plates, m. p. 100—101° (M. Sekiya[10] reported m. p. 98—120°).

Anal. $C_4H_8N_2O_2$ (116.12)calc'd.: C 41.37; H 6.94; N 24.13%
found: C 41.60; H 7.24; N 24.29%

IR spectrum: 3.00 (s), 3.10 (s), 3.30 (m), 6.0 (s), 6.09 (s), 6.41 (w), 6.86 (w), 6.95 (w), 7.15 (m), 7.23 (s), 7.73 (w), 7.87 (w), 7.99 (w), 8.83 (w), 9.55 (vw), 12.10 (w) μ.

b) From 5,6-dihydro-4-oxopyrimidine[4]. — 5,6-Dihydro-4-oxopyrimidine (I, 17 mg., 0.17 mmole) in water (0.5 ml.) was left at room temperature for 3 hours. The solution was evaporated to an oil which crystallized on trituration with acetone. It was purified by chromatography on a silica gel (Camag) column using methylenechloride—methanol (5 : 1) as the eluent. These purified fractions yielded 15.9 mg. (79%). Crystallization from acetone gave a sample m. p. 100—101°, undepressed on admixture with the sample obtained by formylation of 3-aminopropionamide. The IR spectra of both samples were superimposable.

The absorption bands of 5,6-dihydro-4-oxopyrimidine in H_2O and 10^{-6} *N* NaOH at $\lambda\lambda_{max}$ 228 mμ and 258 mμ (shoulder) disappeared in 50 minutes. The absorption at λ_{max} 231 mμ disappeared in 10 minutes when the compound had been dissolved in 10^{-6} *N* HCl.

3-(N-Methylformamido)-propionamide (IX)

a) From 1-methyl-5,6-dihydro-2-thiouracil[6]. — To 1-methyl-5,6-dihydro-2-thiouracil (V, 300 mg., 2.08 mmole) in dioxane (30 ml.), deactivated W-2 Raney nickel (4.2 ml.) was added. (W-2 Raney nickel was prepared by the method of Mozingo[11] and deactivated by refluxing in acetone for 2 hours. It was assumed that 1 ml. of settled suspension previously washed with dioxane contained the equivalent of 0.6 g. of nickel). After stirring and refluxing for 40 minutes, the suspension was filtered to remove the catalyst. The filtrate was evaporated to dryness and the residual solid (115 mg.) chromatographed on a silica gel column using dioxane and dioxane-methanol as the eluents. The so purified fractions yielded 86 mg. (32%). For analysis, a sample was recrystallized from acetone (m. p. 90—92°) and then sublimed as colorless prisms at $130°/3 \cdot 10^{-2}$ mm.

Anal. $C_5H_{10}N_2O_2$ (130.15) calc'd.: C 46.14; H 7.75; N 21.53%
found: C 46.49; H 7.66; N 21.65%

IR spectrum: 3.10 (s), 3.24 (s), 3.46 (w), 5.98 (s), 6.14 (s), 6.96 (s), 7.12 (s), 7.23 (s), 8.0 (m), 8.12 (w), 8.46 (m), 8.80 (m), 9.36 (m), 10.34 (w), 10.70 (w), 13.93 (m) μ.

b) From 3-methylaminopropionamide[6]. — 3-Methylaminopropionamide (XIII, 2.1 g., 20.5 mmole) dissolved in ethylformate (21 ml.) was refluxed for 2 hours. The clear solution was evaporated to dryness. The residual solid, recrystallized from acetone, yielded 1.2 g. (45%), m. p. 90—92°, undepressed on admixture with the sample obtained by rupture of 1-methyl-5,6-dihydro-2-thiouracil. The IR spectra of both samples were superimposable.

A sample of 3-(*N*-methylformamido)-propionamide (130 mg., 1 mmole) in 10% hydrochloric acid (15 ml.) was refluxed for 1 hour. On cooling evaporation and recrystallization from isopropanol 3-methylaminopropionic acid was isolated as its hydrochloride. Yield 65 mg. (47%), m. p. 104—105° (E. Gansser[12] reported m. p. 105°).

3-Formamido-N-methylpropionamide (X)

a) From 3-amino-*N*-methylpropionamide[6]. — 3-Amino-*N*-methylpropionamide (XIV, 2.4 g., 23.6 mmole) was dissolved in ethylformate (25 ml.) and refluxed for 3 hours. The mixture was evaporated to dryness, dissolved in redistilled water (24 ml.) and passed through a column of Amberlite IRC-50 (2 ml.). The eluate was evaporated to dryness and crystallized from acetone—ether as colorless prisms. Yield 2.0 g. (65%), m. p. 57—61°. For analysis it was sublimed at 125°/0.025 mm. and then recrystallized from acetone—ether, m. p. 59—61°.

Anal. $C_5H_{10}N_2O_2$ (130.15) calc'd.: C 46.14; H 7.75; N 21.53%
found: C 46.36; H 7.80; N 21.79%

IR spectrum: 3.06 (s), 3.30 (w), 3.45 (w), 6.05 (s), 6.49 (m), 6.95 (w), 7.11 (w), 7.27 (m), 7.86 (w), 8.13 (w), 8.40 (w), 8.67 (w), 9.65 (vw) μ.

b) From 3-methyl-5,6-dihydro-4-oxopyrimidine[4]. — 3-Methyl-5,6-dihydro-4-oxopyrimidine (VI, 15 mg., 0.14 mmole) in water (0.5 ml.) was left at room temperature for 90 minutes. It was evaporated to an oil which crystallized on distillation at $130^0/10^{-2}$ mm. Yield 15 mg. (86%). A sample chromatographed on a silica gel column using methylene chloride and methylene chloride-methanol as eluents, melted at 61—63°, undepressed on admixture with the sample obtained by formylation of 3-amino-*N*-methylpropionamide. The IR spectra of both samples were superimposable.

The absorption bands of 3-methyl-5,6-dihydro-4-oxopyrimidine in H_2O and 10^{-6} *N* NaOH at λ_{max} 238 mμ, disappeared in 20 minutes. The absorption at $\lambda\lambda_{max}$ 239 mμ and 223 mμ (shoulder) disappeared in 5 minutes when the compound had been dissolved in 10^{-5} *N* HCl.

3-(N-Methylformamido)-N-methylpropionamide (XI)

a) From 1,3-dimethyl-5,6-dihydro-2-thiouracil[6]. — To 1,3-dimethyl-5,6-dihydro-2-thiouracil (VII, 475 mg., 3 mmole) in dioxane (50 ml.), deactivated W-2 Raney nickel (6 ml.), was added. The suspension was stirred and refluxed for 30 minutes. The catalyst was filtered off and the filtrate evaporated to an oily residue (360 mg.). It was chromatographed on a silica gel (5 g., Camag) column in methylene chloride-hexane. The elution with methylene chloride afforded the starting material (118 mg.) with m. p. 46—47°, undepressed on admixture with an authentic sample. Further elution with methylene chloride—methanol (50 : 1) besides a mixture (75 mg.) afforded an oily fraction (114 mg.) which on rechromatography on a silica gel column (2 g.) and elution with methylene chloride—methanol (50 : 1) yielded 89 mg. (20%) of a colorless oil. It was redistilled for analysis, b. p. $135^0/10^{-2}$ mm.

Anal. $C_6H_{12}N_2O_2$ (144.17) calc'd.: C 49.98; H 8.39; N 19.43%
found: C 49.94; H 8.60; N 19.27%

IR spectrum: 3.05 (s), 3.28 (m), 3.46 (m), 6.05 (s), 6.45 (s), 7.20 (s), 8.00 (m), 8.13 (m), 9.22 (m), 9.38 (m), 9.81 (w), 11.84 (vw), 14.42 (w) μ.

b) From 3-methylamino-*N*-methylpropionamide. — 3-Methylamino-*N*-methylpropionamide (XV, 1.1 g., 9.5 mmole) prepared from methylacrylate and methylamine (as its hydrochloride: m. p. 133—134°, Morsch[13] reported m. p. 134.5°) and passed through a column of Amberlite IRA-410, was refluxed with ethylformate (10 ml.) for 3 hours. The mixture was chromatographed on a silica gel (1.5 g., Merck) column and eluted with ethylformate. The colorless oil was collected and distilled at $135^0/10^{-2}$ mm. Yield 0.75 g (60%).

Anal. $C_6H_{12}N_2O_2$ (144.17) calc'd.: C 49.98; H 8.39; N 19.43%
found: C 50.06; H 8.55; N 19.11%

IR spectra of both samples obtained under a) and b) were superimposable.

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IZVOD

Hidropirimidini. VII. Kovalentna hidratacija i otvaranje prstena

V. Škarić i B. Gašpert

Ustanovljeno je da otvaranje prstena 5,6-dihidro-4-oksopirimidina (I) i njegovih *N*-metil derivata II i III do 3-formamidopropionamida (VIII) i njegovih *N*-metil derivata XIII i XIV slijedi kroz intermedijarne 2-hidroksitetrahidropirimidine. 2-Hidroksi intermedijer najvjerojatnije nastaje nukleofilnom adicijom vode kod C = N dvostrukog veza hidropirimidina I—III.

Cijepanje 1,3-dimetil-5,6-dihidro-2-tiouracila (VII) daje 3-(*N*-metilformamido)-*N*-metilpropionamid (XV) najvjerojatnije preko karbonium iona koji je predpostavljen i kod nukleofilne adicije.

Obrađeni su NMR spektri formamidopropionamida. Infracrveni spektri opisanih tvari zabilježeni su u detaljima.

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