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Original Scientific Paper

Hydropyrimidines. II. Observations on Selective Hydrogenation of Some Hydroxypyrimidines

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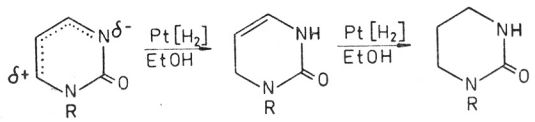
Contrary to the generally accepted principle that selective reduction of pyrimidines occurs at the $\Delta^{5,6}$ position, the partial hydrogenation of 2-hydroxypyrimidine (I) over Adams' catalyst in ethanol was shown to afford 3,6-dihydro-2-hydroxypyrimidine (II). Upon subsequent reduction 3,4,5,6-tetrahydro-2-hydroxypyrimidine (III) was obtained.

In order to ascertain the structure of the dihydro compound structurally unambiguous 1-methyl-2-oxopyrimidine (IV) was subjected to the same partial hydrogenation. The NMR spectra of so obtained dihydro-1-methyl-2-oxopyrimidine (V) and the corresponding tetrahydro derivative VI, in particular the chemical shifts of their methyl groups ($\tau\tau$ 7.08 and 7.06 resp.), complied with the requirements for a 3,6-dihydro compound.

4-Hydroxypyrimidine (IX) did not react with hydrogen under the above mentioned conditions. However, very slow reduction to 1,2,3,6-tetrahydro-4-hydroxypyrimidine (X) occured with rhodium on carbon as catalyst. On the other hand rhodium on carbon was shown to be very active for reduction of 3-methyl-4-oxopyrimidine (XII) yielding 1,2,3,6-tetrahydro-3-methyl-4-hydroxypyrimidine (XIII). In this series the isolation of dihydro derivatives failed.

In spite of wide investigations of amino-, hydroxy- and hydropyrimidines, it was not easy to correlate the published data of the reduction-oxidation processes of these compounds. The reduction of pyrimidines to the chemically very sensitive hydropyrimidines could influence the structures of ribonucleic and desoxyribonucleic acids and consequently the biological and genetic courses. The present study of hydroderivatives of 2- and 4-hydroxypyrimidines was initiated with the hope that the results would bring additional light into chemistry and metabolism of the heterocyclic components of polynucleotides, particularly with regards to 2,4-dihydroxypyrimidine (uracil)*.



* The substituted pyrimidines are named without regard to keto-enol tautomerism, *i.e.* the nomenclature does not reflect the actual state of the molecule.

To our knowledge the data of electrochemical[1], polarographic[2] and catalytic[3-6] reductions of halo-, hydroxy- and thio-pyrimidines indicate that preferentially the $\Delta^{5,6}$ position undergoes hydrogenation and other chemical reactions. Consequently, it could be expected that the partial hydrogenation of 2-hydroxypyrimidine (I) would give 5,6-dihydro-2-hydroxypyrimidine as suggested by Fox and Praag[5] for the intermediate which was not isolated, but showed in UV an absorption band at 260 mμ. The results presented in this paper were not in accord with their presumption and indicated an exceptional course of hydrogenation when performed in ethanol using platinum as catalyst. The *p*K values, listed in Table I, and the values given for the chemical shifts (NMR spectrum, Figure 1) refered towards 3,6- or 3,4-dihydro-2-hydroxypyrimidine (II), having an absorption at 248 mμ, log ε 3.368.

TABLE I

Compound	pK_k	C 10^{-3} *M*	pK_a	C 10^{-3} *M*
II	2.73	4.49	11.22	4.66
III	2.71	4.65	11.18	4.97
Urea	—	—	11.25	4.76
I	3.05 (2.24)[7]	4.53 100	9.21 (9.17)[7]	4.8 10

The *p*K-values of the dihydro derivative II corresponded to the value of urea as well as of 3,4,5,6-tetrahydro-2-hydroxypyrimidine (III) but not of 2-hydroxypyrimidine, to which these values should be closer if a 5,6-dihydro structure would have been present.

The NMR spectrum of dihydro derivative II (Figure 1) clearly showed the signals related to ABC_2 pattern with tau values 3.8, 5.8 and 5.95. These three bands with relative intensities 1:1:2 were consistent with the protons in 4,5 and 6 positions of compound II.

However, these experiments still left unanswered the question whether the hydrogenation of compound I takes the course of a "1,2" or a "1,4 addition". Namely, the addition at 3 and 6 or at 3 and 4 positions gives the same hydropyrimidine. To clarify this point the hydrogenation procedure was applied to 1-methyl-2-oxopyrimidine (IV) because of its undoubtful arrangement of double bonds. The partially hydrogenated compound IV showed the NMR spectrum with the same chemical shifts, relative intensities of signals and spin coupling constants for protons at 4,5 and 6 position as for 3,6-dihydropyrimidine II (Table II). In addition the chemical shifts of methyl

TABLE II

Results from NMR measurements

Compound	Chemical shift, τ				Coupling const.		
	4-H	5-H	6-H	CH_3	$J_{4,5}$	$J_{5,6}$	$J_{4,6}$
II	3.82(6)	5.08(6)	5.95(4)	—	8.0	3.5	1.8
V	3.83(6)	5.08(4)	5.94(4)	7.08	8.0	3.5	1.8

Figures in brackets denote the number of line of multiplets. Spin coupling constants, *J*, are given in *c.p.s.*.

groups of dihydro- V (τ 7.08) and 3,4,5,6-tetrahydropyrimidine VI (τ 7.06)[8] were of the same magnitude and differed from that one shown in the NMR spectrum of methylpyrimidine IV (τ 6.36)[8].

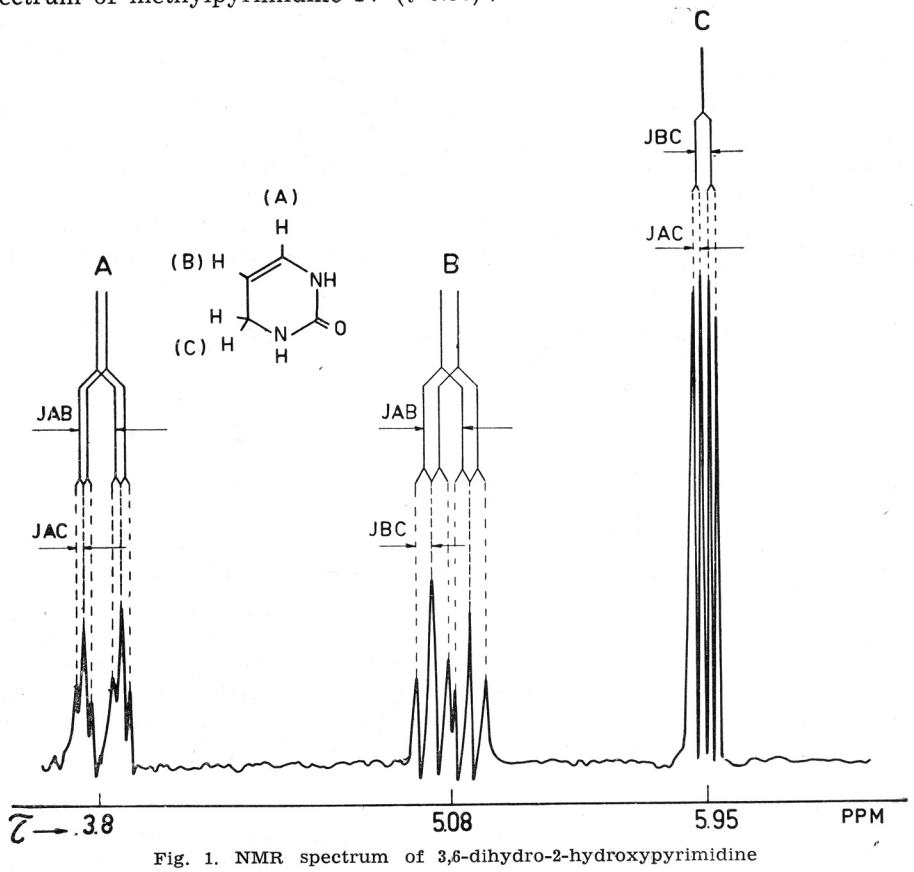
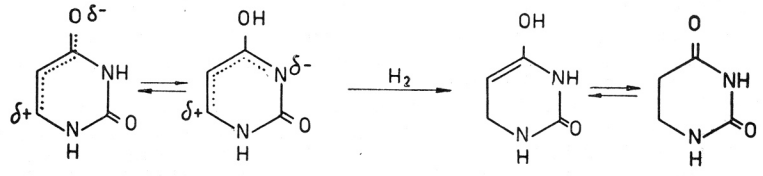


Fig. 1. NMR spectrum of 3,6-dihydro-2-hydroxypyrimidine

Although there was thought to be little if any 3,4,5,6-tetrahydro-1-methyl-2-hydroxypyrimidine (VI) present as contaminant, our results indicated that the reduction proceeded *via* 3,6-dihydro-1-methyl-2-hydroxypyrimidine (V). The alternative "1,2 addition" at the $\Delta^{3,4}$ posion is ruled out.

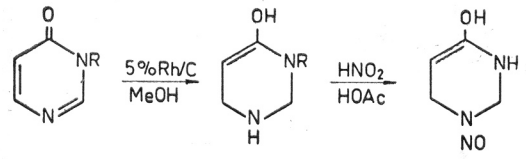
The above conclusions are put to practical use by studying the course of hydrogenation of uracil (VII)[9]. Namely in this case the course of "1,4 addition" could produce 5,6-dihydrouracil (VIII) as well as "1,2 addition".



VII VIII

Complete catalytic hydrogenation of II and IV yielded tetrahydroderivatives III and VI, previously prepared from 4-thiouracil and its 1-methyl--derivative[5] respectively.

The procedure used for hydrogenation of 2-hydroxypyrimidines failed in the case of 4-hydroxypyrimidines. In an attempt to prepare its hydroderivatives unchanged starting material was obtained. However, a slow reduction took place in the presence of catalytic amounts of rhodium on carbon. In such hydrogenation 4-hydroxypyrimidine (IX) was converted into 1,2,3,6-tetrahydro-2-hydroxypyrimidine (X). Dihydroderivative could not be isolated indicating concurrent reductions. Compound X, treated with 10 per cent hydrochloric acid or 5 per cent sodium hydroxide was degraded to β-alanine. With nitrous acid XI yielded 1-nitroso-1,2,3,6-tetrahydro-4-hydroxypyrimidine (XI).



IX R=H X R=H XI

XII R=CH_3 XIII R=CH_3

The hydrogenation of 3-methyl-4-oxopyrimidine (XII) over rhodium on carbon proceeded to 1,2,3,6-tetrahydro-3-methyl-4-hydroxypyrimidine (XIII) at a surprisingly rapid rate. This finding did not agree with the conclusion[1] stating that —N—CO—C=C— grouping as part of a ring could not be reduced catalytically. The hydrolytic treatment of compound XIII with acid or base yielded β-alanine, methylamine and formaldehyde, thus confirming at the same time the 3 position of the methyl group.

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. The UV spectra were measured in 95% ethanol on Perkin-Elmer model 137-UV spectrophotometer with automatic gain control. The IR-absorption bands were recorded, unless otherwise stated, in potassium bromide plates on a Perkin-Elmer infracord model 137 and reported in wavelengths followed by relative intensities in brackets. The *p*K's values were determined by potentiometric micro-titrations in water with 0.1 *N* solution of sodium hydroxide and 0.1 *N* solution of hydrochloric acid. The *p*H values were not corrected. 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 side-band method. Values given for the chemical shifts, τ, were in parts per milion, tetramethylsilane taken as zero.

2-Hydroxypyrimidine (I)

2-Amino-pyrimidine (10 g., 0.105 mmole) treated with 10 *N* sodium hydroxide (100 ml.) was converted into 2-hydroxypyrimidine according to the procedure of Brown[10]. The procedure for isolation of the product was modified. The mixture was refluxed for 12 hours and then left in the refrigerator overnight. The crystals were separated, filtered off, washed with a small amount of anhydrous ethanol, and then dissolved in redistilled water (1 l.). 2-Hydroxypyrimidine was isolated after the solution was passed through a column of Amberlite IRC-50. Yield 7 g. (70%). The compound was recrystallized from ethanol, colorless needles, m.p. 179—180° (Brown[10] reported m.p. 178—180°, yield 66%; Hunt *et al.*[11] m.p. 179—181°).

3,6-Dihydro-2-hydroxypyrimidine (II)

To reduced Adams' catalyst (200 mg.) in ethanol (10 ml.) the solution of 2-hydroxypyrimidine (960 mg., 10 mmole) in ethanol (60 ml.) was added. The mixture was shaken with hydrogen about 35 minutes until one equivalent has been consumed. The platinum was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue crystallized upon standing, m.p. 145—148° (extended). The crystallization from absolute ethanol yielded 610 mg. (62%), m.p. 152—154° with softening at 120°. Further crystallization from absolute ethanol gave the analytical sample as colorless prisms, m.p. 156—157°

Anal. $C_4H_6N_2O$ (98.10) calc'd.: C 48.97; H 6.17; N 28.56%
found: C 49.16; H 5.94; N 28.73%

UV spectrum: $\lambda\lambda_{max}$ 203 mμ, log ε 3.372; 248 mμ, log ε 3.368; λ_{min} 216.5 mμ, log ε 2.895. IR spectrum: 3.07(s), 3.23(m), 3.45(m), 6.0(s), 6.68(s), 6.92(m), 7.27(w), 7.72(s), 8.15(w), 8.32(m), 8.72(m), 9.49(vw), 9.70(w), 10.22(vw), 10.86(vw), 11.37(w), 11.86(w), 12.7(w) μ.

The NMR spectrum with τ values and spin coupling constants, *J*, are represented in Figure 1 and Table II respectively.

3,4,5,6-Tetrahydro-2-hydroxypyrimidine (III)

a) by cyclization. — Following the procedure for the preparation of 2-imidazolidone[12] propylendiamine (2.0 g., 27 mmole) was heated with urea (1.6 g.) and water (0.8 ml.). The residue was sublimed at 120°/0.02 mm, yield 2.2 g. (80%), m.p. 263—264°. The m.p. remained unchanged after crystallization from absolute ethanol. (Fox and Praag[5] reported m.p. 258—259°, for the compound obtained by reduction of 4-thiouracil).

b) by reduction. — 3,6-Dihydro-2-hydroxypyrimidine (30 mg., 0.3 mmole) in ethanol (7 ml.) was hydrogenated over platinum oxide (8 mg.) under the same condition as described for compound II. Recrystallized from absolute ethanol, yield 25 mg. (82%), m.p. 263—264°, undepressed on admixture with the sample obtained by cyclization. IR spectra of both sample were superimposable.

3,6-Dihydro-1-methyl-2-hydroxypyrimidine (V)

1-Methyl-2-oxopyrimidine[13] (110 mg., 1.0 mmole) in ethanol (20 ml.) was hydrogenated over Adams' catalyst (20 mg.). In the course of about 30 minutes one mole of hydrogen was absorbed. The colorless needles separated quantitatively. Recrystallization from ethylacetate-hexane yielded 47 mg. (44.6%), m.p. 108—114° (extended). Further crystallization gave a sample with m.p. 120—121°. For analysis it was sublimed at $60°/5 \cdot 10^{-4}$ mm.

Anal $C_5H_8N_2O$ (112.13) calc'd.: C 53.55; H 7.19; N 24.99%
found: C 53.83; H 7.01; N 24.81%

UV spectrum: $\lambda\lambda_{max}$ 202 mμ, log ε 3.695; 250 mμ, log ε 3.362; λ_{min} 222.5 mμ, log ε 2.983. IR spectrum: 3.05(m), 3.25(m), 3.4(m), 6.06(s), 6.65(s), 6.95(m), 7.2(m), 7.74(m), 7.97(m), 8.3(m), 9.15(m), 9.75(w), 11.3(w), 12.95(m), 13.3(m), 14.25(m) μ.

3,4,5,6-Tetrahydro-1-methyl-2-hydroxypyrimidine (VI)

1-Methyl-2-hydroxypyrimidine[13] (110 mg., 1.0 mmole) in ethanol (20 ml.) was hydrogenated over platinum oxide (40 mg.) until two molecular equivalents were consumed (about 75 minutes). The crystalline product separated quantitatively, m.p. 88—90.5°. For analysis it was recrystallized from ether-hexane as colorless needles, m.p. 94—96° (Fox and Praag[5] reported m.p. 86—89°).

Anal. $C_5H_{10}N_2O$ (114.15) calc'd.: C 52.61; H 8.83; N 24.54%
found: C 52.50; H 8.66; N 24.78%

UV spectrum: λ_{max} 194 mμ, log ε 3.735. IR spectrum: 2.94(s), 3.24(s), 3.39(s), 6.04(s), 6.54(s), 6.85(s), 7.14(s), 7.42(m), 7.62(s), 7.88(m), 8.34(m), 9.06(m), 9.34(m), 10.07(w), 13.13(m) μ.

1,2,3,6-Tetrahydro-4-hydroxypyrimidine (X)

4-Hydroxypyrimidine (200 mg., 2 mmole), prepared from 2-thiouracil according to the procedure of Brown[14], was dissolved in anhydrous methanol (15 ml.) and 5 per cent rhodium on carbon catalyst (100 mg.) was added. The mixture was shaken with hydrogen under pressure of 65 *psi* until the fluorescence of starting material disappeared (about 13 hours). The catalyst was filtered off and the filtrate evaporated to a crystalline residue, m.p. 83—88°. It was recrystallized from ethylacetate as colorless prisms, m.p. 88—90°, yield 164 mg. (82%). Further recrystallization from ethylacetate and sublimation at $110°/10^{-3}$ mm afforded the analytically pure sample, m.p. 91—92°.

Anal. $C_4H_6N_2O$ (100.12) calc'd.: C 47.98; H 8.05; N 27.98%
found: C 47.66; H 8.14; N 27.83%

UV spectrum: λ_{max} 204 mμ, log ε 3.449. IR spectrum: 2.95(s), 3.15(s), 3.32(s), 3.42(s), 3.5(m), 6.1(s), 6.75(s), 6.85(s), 7.12(s), 7.32(s), 7.52(w), 7.65(s), 8.15(m), 8.27(w), 8.8(m), 8.95(w), 9.5(m), 9.9(s), 10.4(m), 11.05(s), 11.55(s), 12.1(m), 12.8(m), 13.5(w) μ.

1,2,3,6-Tetrahydro-1-nitroso-4-hydroxypyrimidine (XI)

To the solution of 1,2,3,6-tetrahydro-4-hydroxypyrimidine (45 mg., 0.45 mmole) in water (1 ml.) sodium nitrite (40 mg., 0.57 mmole) and acetic acid (0.1 ml.) were added. The mixture was left at room temperature for 2 hours, diluted with water and passed through a column of Amberlite IRC-50. The eluate was evaporated under reduced pressure. The oily residue solidified after standing. It was extracted with methylenechloride. Evaporation of the extract to dryness yielded 42 mg. (80%) of crystalline product, m.p. 93—95°. For analysis it was recrystallized from methylenechloride-hexane as colorless prisms, m.p. 95—96°.

Anal. $C_4H_7N_3O_2$ (129.12) calc'd.: C 37.21; H 5.46; N 32.55%
found: C 37.48; H 5.18; N 32.71%

UV spectrum: λ_{max} 230.5 mμ log ε 3.937 and shoulder λ 203.5 mμ, log ε 3.635. IR spectrum: 3.1(m), 3.2(m), 3.45(w), 5.85(s), 6.0(s), 6.75(m), 6.85(m), 6.95(m), 7.05(s), 7.2(m), 7.5(s), 7.55(s), 7.68(s), 7.8(s), 7.95(m), 8.25(s), 8.45(m), 8.7(s), 9.28(s), 9.48(w), 9.75(m), 10.1(m), 10.75(w), 12.45(w), 12.95(s), 14.75(m) μ.

Hydrolysis of 1,2,3,6-tetrahydro-4-hydroxypyrimidine

a) with sodium hydroxide. — 1,2,3,6-Tetrahydro-4-hydroxypyrimidine (30 mg., 0.3 mmole) in 5 per cent sodium hydroxide (2 ml.) was refluxed for 90 minutes in an inert atmosphere. Evolved ammonia was absorbed in 10 per cent hydrochloric acid and isolated as ammonium chloride. The mixture was acidified with 10 per cent hydrochloric acid (2 ml.) and evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol-ether, yield 21 mg. (66%), m.p. 120—121°, undepressed on admixture with an authentic sample of β-alanine hydrochloride. The IR spectra of both sample were superimposable.

b) with hydrochloric acid. — 1,2,3,6-Tetrahydro-4-hydroxypyrimidine (30 mg., 0.3 mmole) in 10 per cent hydrochloric acid (2 ml.) was refluxed for 1 hour. The mixture was evaporated to dryness. Ammonium chloride, one undefined by-product and β-alanine separated by fractional crystallization from ethanol-ether. β-Alanine hydrochloride (31 mg., 83%), m.p. 119—121° was isolated.

1,2,3,6-Tetrahydro-3-methyl-4-hydroxypyrimidine (XIII)

3-Methyl-4-oxopyrimidine[13] (110 mg., 1 mmole) was hydrogenated over 5 per cent rhodium on carbon catalyst (55 mg.) in ethanol (20 ml.) until two molecular equivalents of hydrogen were absorbed (2.5 hours). The colorless oil, which separated quantitatively, was distilled at $65°/5 \cdot 10^{-4}$ mm.

Anal. $C_5H_{10}N_2O$ (114.15) calc'd.: C 52.61; H 8.83; N 24.54%
found: C 52.67; H 8.54; N 24.39%

IR spectrum (neat): 2.79(m), 2.94(m), 3.35(m), 6.13(s), 6.64(s), 7.12(m), 7.3(s), 7.73(s), 8.1(m), 8.64(w), 9.76(m), 10.04(m), 10.72(w), 11.54(m), 13.44(w) μ.

Hydrolysis of 1,2,3,6-tetrahydro-3-methyl-4-hydroxypyrimidine

a) with sodium hydroxide. — 1,2,3,6-Tetrahydro-3-methyl-4-hydroxypyrimidine (40 mg., 0.35 mmole) was refluxed with a 5 per cent aqueous sodium hydroxide solution (3 ml.). The volatile material was collected in 10 per cent hydrochloric acid, isolated quantitatively and identified as methylamine hydrochloride, m.p. 226° (recrystallized from ethanol-hexane), undepressed with an authentic sample. IR spectra of both sample were superimposable. β-Alanine hydrochloride (39 mg., 91%), m.p. 120—121° was isolated and identified as described before.

b) with hydrochloric acid. — Tetrahydropyrimidine XIII (38 mg., 0.33 mmole) was treated with 10 per cent hydrochloric acid (2 ml.) as described for compound X. Formaldehyde was isolated by means of dimedone (m.p. 187°). The excess of dimedone was extracted with chloroform and β-alanine hydrochloride was separated by fractional crystallization from absolute ethanol-ether.

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IZVOD

Hidropirimidini. II. Prilog poznavanju selektivnog hidriranja nekih hidroksipirimidina

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Suprotno zaključku da selektivna redukcija pirimidina nastupa kod $\Delta^{5,6}$ pozicije, parcijalno katalitičko hidriranje 2-hidroksipirimidina (I) u etanolu (Pt kao katalizator) daje 3,6-dihidro-2-hidroksipirimidin (II). Daljnje hidriranje tvari II pod istim uslovima vodi do 3,4,5,6-tetrahidro-2-hidroksipirimidina (III).

Da bi se utvrdila struktura dihidro spoja parcijalno se hidrirao strukturno nedvojbeni 1-metil-2-oksopirimidin (IV). NMR spektar tako dobivenog dihidro-1--metil-2-oksopirimidina, kao i odgovarajućeg tetrahidro derivata, a posebno kemijski pomaci njihovih metilnih skupina (ττ 7.08 odnosno 7.06) odgovaraju podacima za 3,6-dihidro spoj.

4-Hidroksipirimidin (IX) pod navedenim uslovima nije moguće reducirati. Međutim, vrlo polagana redukcija do 1,2,3,6-tetrahidro-4-hidroksipirimidina (X) slijedi pored rodija na ugljenu kao katalizatora. Rodij na ugljenu se pokazao kao vrlo aktivan kod redukcije 3-metil-4-oksopirimidina (XII). Takva redukcija daje 1,2,3,6-tetrahidro-4-hidroksipirimidin (XIII), što se opet protivi tvrdnjama da sistem N—CO—C=C— nije moguće reducirati ako je dio jednog cikličkog sistema.

Hidroliza tvari XIII daje β-alanin, metilamin i formaldehid što potvrđuje njenu strukturu sa metilnom skupinom u poziciji 3.

INSTITUT »RUĐER BOŠKOVIĆ«
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