Scientific article
UDC 547.853.3:547-327

AMINOLYSIS OF HEXAHYDROCHROMENO[4,3-D]PYRIMIDINE-2,5-DIONES

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Keywords: *hexahydrochromeno[4,3-d]pyrimidinones, hydrazine hydrate, carbohydrazides*

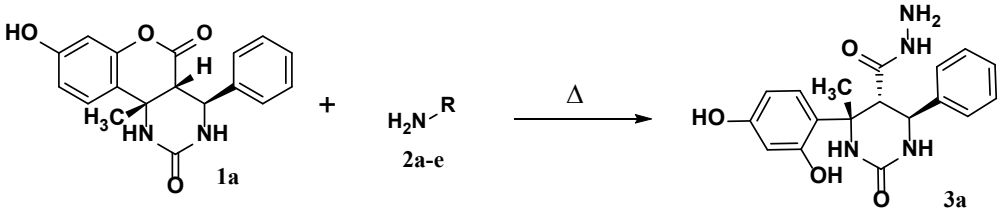
Abstract. *The paper concerns with the study of the (4R*,4aS*,10bR*)-chromeno[4,3-d]pyrimidine-2,5-diones aminolysis. According to the research results, a lactone cycle opening reaction is possible only when treating the chromanes with hydrazine hydrate.*

For citation:
Chirkova, Zh.V., Makarova, E.S., Uryadova, A.M., Filimonov, S.I., Shalabanova, M.S. & Ivanovsky, S.A. (2024) Aminolysis of hexahydrochromeno[4,3-d]pyrimidine-2,5-diones, *From Chemistry Towards Technology Step-By-Step,* 5(1), pp. 114-121 [online]. Available at: http://chemintech.ru/index.php/tor/issue/view/2024-5-1

Introduction

Substituted hydrazides are important biologically active structures in pharmacology [1-4]. They are used as antibacterial [5-11], neuroleptic drugs [12-14], etc. However, they are especially appreciated for their antitubercular action as one of the few pharmacophores capable for inhibiting the action of pathogenic microorganisms [15-19]. A number of new hydrazide derivatives also showed antiproliferative activity comparable to ibuprofen [20-24]. Moreover, hydrazides and pyrimidine hydrazides are very interesting in terms of preparation of more complex compounds. Noteworthy, hydrazine fragment-containing molecules are relatively rare in nature, but they have been isolated from plants [3, 4], marine organisms [1], and microorganisms. These compounds possess structural diversity and biological activity, although the enzymes involved in N-N bond formation have not yet been described in the scientific literature.

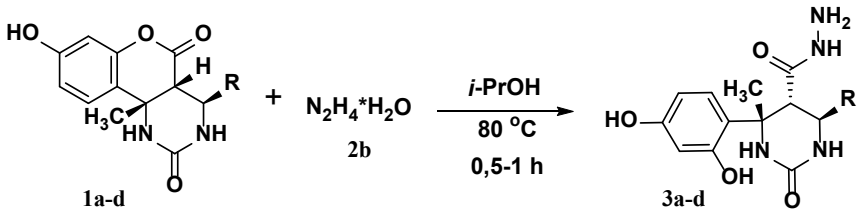
We investigated the aminolysis reaction of the lactone cycle of hydrazides and pyrimidine hydrazides to study the chemical properties of hexahydrochromeno[4,3-d]pyrimidine-2,5-diones. We used structure **1a** interacting with various aminating agents **2** (ammonia, aliphatic amines, hydrazine hydrate, phenylhydrazine) as a model compound. These studies continue earlier studies of pyrimidines interaction with various reagents [27].



2: R = -H (**a**), R = -NH_2*H_2O (**b**), R = -NH-Ph (**c**), R = -C_6H_{11} (**d**); R = -CH_2-C_6H_5 (**e**)

The interaction of reagents **1a** and **2** was performed in various solvents (ethanol, isopropyl alcohol, DMFA, toluene) at temperatures 78–150 °C without the use of specific catalysts. The formation of target products was not registered with ammonia **2a**, amines **2d,e** and phenylhydrazine **2c** at prolonged heating at temperatures up to 100 °C; at 130–150 °C osmosis of the initial compounds was observed. We obtained the target carbohydrazide **3a** only with hydrazine hydrate **2b** using isopropyl alcohol as a solvent at 80 °C. The aminolysis of hexahydrochromeno[4,3-*d*]pyrimidine-2,5-diones **1** proceeded similarly to the previously studied aminolysis of the corresponding pyrimidine thiourea derivatives [28].

Diastereomerically pure (4*R**,4a*S**,10b*R**)-chromeno[4,3-*d*]pyrimidines **1a-d** obtained according to the method of [29] were used as objects of further investigation. As a rule, syntheses with hydrazine hydrate **2b** proceeded in heterophase, and were completed rather quickly within 0.5-1.0 h. Isopropyl alcohol was chosen as the solvent because the target product was insoluble in it even at boiling. The progress of the reaction was monitored by TLC by disappearance of the substrate **1** stain. The yield of the target carbohydrazides **3a-d** reached 91–98%.



1, **3**: R = C_6H_5 (**a**), R = 4-Cl-C_6H_4 (**b**), R = 4-MeO-C_6H_4 (**c**), R = 3-NO_2-C_6H_4 (**d**)

Table 1 summarizes the reaction conditions and yields for compounds **3a-d**.

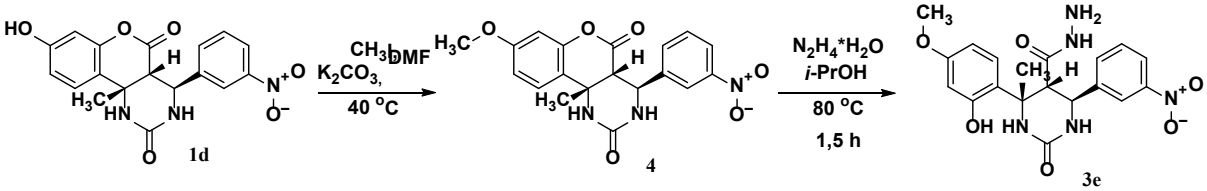
Table 1. Reaction time and yield of pyrimidinone-5-carbohydrazides **3a-d**

No.	**1**	R	Reaction time, min	Yield **3**, %.
1	**a**	C_6H_5	40	91
2	**b**	4-Cl-C_6H_4	35	98
3	**c**	4-MeO-C_6H_4	40	92
4	**d**	3-NO_2-C_6H_4	55	98

The structure of the synthesized compounds **3a-d** was confirmed by a combination of IR and NMR spectroscopy data (including two-dimensional correlation NOESY) and mass spectrometry. We observed significant changes in the valence vibrations of the hydroxyl groups on the IR spectra compared to the condensed chromanes (in carbohydrazide they are practically absent due to the formation of hydrogen bonds). Also visually we observed disappearing of band of the lactone carboxyl group of the initial chromeno[4,3-*d*]pyrimidines **1**, and the appearing of amide group band instead. Molecular ion was usually not observed in the

electron impact mass spectra for compounds **3a-d**. However, only the fragmentation ion $[M\text{-}NH_2NH_2]^+$ was detected with low intensity.

Intra- and intermolecular hydrogen bonds observed in ^{1}H NMR spectra were the characteristic features of the products **3a-d**. It was observed in the exchange processes of hydrogen atoms of OH- and NH-groups with deuterated solvent water. This made it difficult to accurately integrate the "acidic protons" and identify the products. To reduce this effect, compound **1d** was methylated with methyl iodide according to the known procedure [29] to give the corresponding product **4**. This product was then treated with hydrazine hydrate under the above conditions. The structure of product **3e** was determined on the basis of two-dimensional correlation NOESY spectroscopy data (Fig. 1).



The key signals confirming the acyclic structure of carbohydrazides **3a-e** are the cross-peaks of the C(5)H proton with the proton of the amide NH-group, 4-CH_3/3-NH, H(6)/1-NH. The values of CCCV $J_{C(5)H,C(6)H}$ in ^{1}H NMR spectra were practically unchanged compared to the analogous data of the original chromanes, and ranged 10.5-11.0 Hz [29]. The observed symmetric C(5)H/C(4)CH_3 cross-peak in the NOESY spectrum indicates the retention of the spatial configuration of the original (4R*,4aS*,10bR*)-chromeno[4,3-d]pyrimidines **1** in the obtained hydrazides 3.

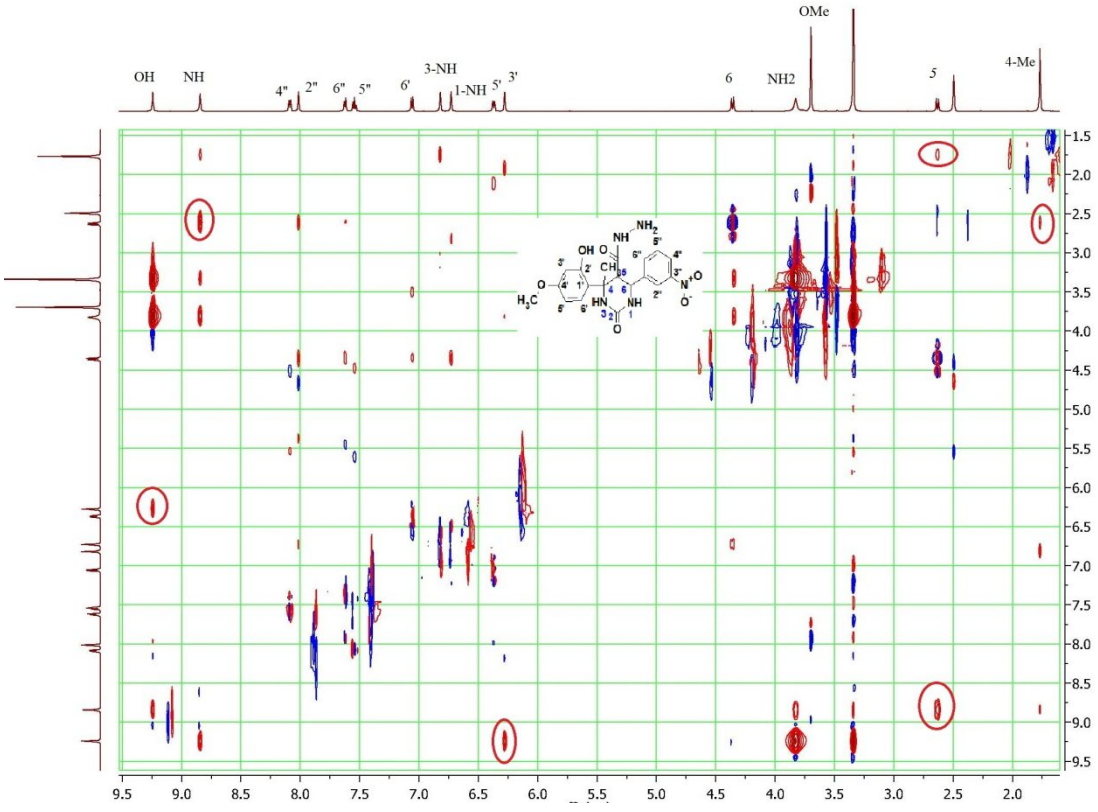


Fig. 1. NOESY spectrum fragment of compound **3e**

Hence, we have found that aminolysis of (4*R**,4*aS**,10*bR**)-hexahydrochromeno[4,3-d]pyrimidine-2,5-diones and the methylated nitro derivative of chromeno[4,3-d]pyrimidine-2,5-dione occurs only in the presence of hydrazine hydrate; it causes the formation of substituted (4*R**,5*S**,6*R**)-2-oxohexahydropyrimidine-5-carbohydrazides, the structure of which was confirmed by a set of spectral methods.

The study was performed within the framework of the State assignment of Yaroslavl State Pedagogical University named after K.D. Ushinsky for 2024 from the Ministry of Education of the Russian Federation on the issue "Development of a new drug for the treatment of neurodegenerative diseases based on a monoamine oxidase inhibitor" (registry entry number 720000F.99.1.BN62AAA12000).

Experimental part

We recorded IR spectra in reflected light on a Spectrum Two PerkinElmer FT-IR spectrometer at 700-4000 cm^{-1}. We recorded the NMR spectra on an apparatus "Bruker DRX-400" for DMSO-d_6 solutions at 30 °C. As reference for the chemical shifts we used the signals of the residual solvent protons in ^1H NMR (δ_H = 2.50 ppm) and ^{13}C NMR (δ_C = 39.5 ppm). We used tetramethylsilane signal (IOC RAS, Moscow, Russia) as a marker. Then we recorded mass spectra on a FINNIGAN MAT.INCOS 50 mass spectrometer at an ionization voltage of 70 eV and a temperature of 100–220 °C in the ionization chamber (IOC RAS, Moscow, Russia). We conducted elemental analysis in analytical laboratory INEOS RAS, Moscow, Russia on analyzer "PerkinElmer 2400"; melting and boiling points were determined on apparatus BüchiM-560.

Methods of synthesis and physicochemical characteristics of compounds **1** and **4** are described in [29].

We added 0.05 mL (1 mmol) of hydrazine hydrate **2b** to a suspension of 0.5 mmol of chromeno[4,3-*d*]pyrimidines **1a-d**, **4** in 3 mL isopropyl alcohol and heated at boiling point for 0.5-1.5 h. Then the precipitate was filtered off and washed with methylene chloride. It was dried on air.

(4*R,5*S**,6*R**)-4-(2,4-Dihydroxyphenyl)-4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carbohydrazide (3a).** Yield 326 mg (91%), T.melt. 253–256 °C. IR spectrum, ν/cm^{-1}: 3509, 3417, 3398, 3335 (OH), 3282 (NH), 1650, 1615, 1511 (Ar), 1225, 1169. NMR spectrum ^1H (400 MHz, δ, ppm., *J*/Hz): 1.73 (s, 3 H, C(4)CH_3), 2.60 (d, 1 H, C(5)H, *J* = 10.5), 3.78 (br.s., 2H, NH_2), 4.25 (d, 1 H, C(6)H, *J* = 10.5), 6.16 (m, 2 H, C(3',5')H), 6.36 (br.s., 1 H, N(1)H), 6.57 (br.s., 1 H, N(3)H), 6.97 (d, 1 H, C(6′)H, *J* = 8.6), 7.12 - 7.27(m, 5 H, Ph), 8.77 (br.s., 1 H, CONH), 9.09 (br.s., 2 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm.): 27.68, 53.89, 55.10, 57.87, 103.74, 105.19, 120.42, 126.87, 127.67, 127.90 (2 C), 129.28 (2 C), 141.83, 155.89, 156.16, 157.13, 167.84. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 356[*M*]$^+$(4), 324 [*M*-NH_2-NH_2]$^+$ (25), 309 (32), 189 (24), 187(100), 177(60), 148 (55), 136 (16), 132 (59), 106 (38), 104 (61), 91 (14), 77 (64). Found (%): C, 60.29; H, 5.63; N, 15.67. $C_{18}H_{20}N_4O_4$. Calculated (%): C, 60.66; H, 5.66; N, 15.72.

(4*R,5*S**,6*R**)-4-(2,4-Dihydroxyphenyl)-4-methyl-2-oxo-6-(4-chlorophenyl)hexahydropyrimidine-5-carbohydrazide (3b).** Yield 384 mg (98%), T.melt. 297–300 °C. IR spectrum,

ν/cm^{-1}: 3418, 3330 (OH), 3245 (NH), 1671 1662, 1638, 1519 (Ar), 1234, 1172, 1132. NMR spectrum ^{1}H (400 MHz, δ, ppm., *J*/Hz): 1.74 (s, 3 H, C(4)Me), 2.54 (d, 1 H, C(5)H, *J* = 10.7), 3.82 (br.s., 2 H, NH_2), 4.23 (d, 1 H, C(6)H, *J* = 10.7), 6.16 (m, 2 H, C(3',5')H), 6.50 (s, 1 H, N(1)H), 6.65 (s, 1 H, N(3)H), 6.93 (d, 1 H, C(6′)H, *J* = 8.7), 7.19 (d, 2 H, C(2'',6'')H, *J* = 8.3), 7.30 (d, 2 H, C(3'',5'')H, *J* = 8.3), 8.79 (s, 1 H, CONH), 8.99 (br.s., 1 H, OH), 9.12 (br.s., 1 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm.): 25.49, 53.32, 55.07, 57.87, 103.73, 105.21, 120.29, 127.79 (2 C), 129.28, 129.81 (2 C), 131.69, 140.58, 155.28, 156.13, 157.16, 167.61. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 358 [*M*-NH_2-NH_2]$^+$ (7), 223 (16), 221 (35), 177 (55), 166 (28), 148 (51), 138 (34), 111 (24), 102 (28), 91 (25), 77 (50). Found (%): C, 55.18; H, 4.87; N, 14.29. $C_{18}H_{19}ClN_4O_4$. Calculated (%): C, 55.32; H, 4.90; N, 14.34.

(4*R,5*S**,6*R**)-4-(2,4-Dihydroxyphenyl)-4-methyl-6-(4-methoxy-phenyl)-2-oxohexa hydropyrimidine-5-carbohydrazide (3c).** Yield 357 mg (92%), T.melt. 252–254 °C. IR spectrum, ν/cm^{-1}: 3392, 3312 (OH), 3216 (NH), 1662, 1622, 1511 (Ar), 1249, 1175. NMR spectrum ^{1}H (400 MHz, δ, ppm., *J*/Hz): 1.73 (s, 3 H, C(4)Me), 2.54 (d, 1 H, C(5)H, *J* = 10.0), 3.70 (s, 3 H, C(4'')OCH_3), 3.78 (br.s., 2 H, NH_2), 4.19 (d, 1 H, C(6)H, *J* = 10.0), 6.12-6.19 (m, 2 H, C(3',5')H), 6.27 (br.s., 1 H, N(1)H), 6.55 (br.s., 1 H, N(3)H), 6.79 (d, 1 H, C(6′)H, *J* = 8.5), 6.95 (d, 2 H, C(2'',6'')H, *J* = 8.5), 7.09 (d, 2 H, C(3'',5'')H, *J* = 8.5), 8.76 (br.s., 1 H, CONH), protons of two OH-groups are not observed due to rapid deuteronomy. NMR spectrum ^{13}C (100 MHz, δ, ppm.): 25.51, 53.23, 54.98, 55.16, 57.86, 103.74, 105.18, 113.21 (2 C), 120.47, 128.96 (2 C), 129.33, 133.46, 155.37, 156.18, 157.13, 158.38, 167.92. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 354 [*M*-NH_2-NH_2]$^+$ (60), 217 (64), 204 (19), 177 (38), 162 (27), 148 (28), 135 (51), 121 (18), 110 (15). Found (%): C, 58.91; H, 5.71; N, 14.44. $C_{19}H_{22}N_4O_5$. Calculated (%): C, 59.06; H, 5.74; N, 14.50.

(4*R,5*S**,6*R**)-4-(2,4-Dihydroxyphenyl)-4-methyl-6-(3-nitrophenyl)-2-oxohexahydro pyrimidine-5-carbohydrazide (3d).** Yield 350 mg (98%), T.melt. 205–208 °C. IR spectrum, ν/cm^{-1}: 3452, 3329 (OH), 3237 (NH), 1669, 1639, 1527 (Ar), 1220, 1134. NMR spectrum ^{1}H (400 MHz, δ, ppm., *J*/Hz): 1.75 (s, 3 H, C(4)Me), 2.61 (d, 1 H, C(5)H, *J* = 11.0), 3.80 (br.s., 2 H, NH_2), 4.36 (d, 1 H, C(6)H, *J* = 11.0), 6.13 - 6.22 (m, 2 H, C(3',5')H), 6.67 (s, 1 H, N(1)H), 6.73 (s, 1 H, N(3)H), 6.90 (d, 1 H, C(6′)H, *J* = 8.3), 7.55 (tr, 1 H, C(5'')H, *J* = 8.4), 7.64 (d, 1 H, C(6'')H, *J* = 8.4), 8.02 (d, 1 H, C(2'')H, *J* = 1.5), 8.09 (dd, 1 H, C(4'')H, *J* = 1.5, 8.3), 8.80 (s, 1 H, CONH), 9.15 (br.s., 1 H, OH). Protons of one OH-group are not observed due to rapid deuteronomy. NMR spectrum ^{13}C (100 MHz, δ, ppm.): 25.48, 53.51, 55.16, 57.95, 105.27, 110.63, 120.08, 122.37, 122.58, 129.26, 129.41, 135.06, 143.86, 147.35, 155.27, 156.16, 157.26, 167.36. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 369 [*M*-NH_2-NH_2]$^+$ (1), 352 (11), 221 (100), 177 (75), 148 (42), 140 (23), 111 (14), 77 (16). Found (%): C, 53.67; H, 4.75; N, 17.40. $C_{18}H_{19}N_5O_6$. Calculated (%): C, 53.86; H, 4.77; N, 17.45.

(4*R,5*S**,6*R**)-4-(4-Hydroxy-2-methoxyphenyl)-4-methyl-6-(3-nitrophenyl)-2-oxohexa hydropyrimidine-5-carbohydrazide (3e).** Yield 145 mg (70%), T.melt. 260–262 °C. NMR spectrum ^{1}H (400 MHz, δ, ppm., *J*/Hz): 1.77 (s, 3 H, C(4)Me), 2.68 (d, 1 H, C(5)H, *J* = 11.0), 3.70 (s, 2 H, NH_2), 4.38 (d, 1 H, C(6)H, *J* = 11.0), 6.29 (d, 1 H, C(3')H, *J* = 2.5), 6.37 (dd, 1 H, C(5')H, *J* = 8.7, 2.5), 6.67 (s, 1 H, N(1)H), 6.75 (s, 1 H, N(3)H), 7.08 (d, 1 H, C(6′)H, *J* = 8.7), 7.55 (tr, 1 H, C(5'')H, *J* = 7.9), 7.64 (d, 1 H, C(6'')H, *J* = 7.7), 8.03 (d, 1 H, C(2'')H, *J* = 2.3),

8.09 (dd, 1 H, C(4'')H, J = 2.3, 8.2), 8.86 (s, 1 H, CONH), 9.21 (s, 1 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm): 27.46, 53.54, 54.82, 55.08, 57.93, 102.35, 103.38, 121.88, 122.43, 122.59, 129.42, 129.47, 135.07, 143.77, 147.36, 155.25, 156.31, 159.19, 167.25. Mass spectrum (EI, 70 eV), m/z (I_{rel}, %): 383 $[M\text{-}NH_2\text{-}NH_2]^+$ (13), 232 (100),191(33), 177 (37), 166 (21), 150 (19), 147 (18), 105 (14),102 (18), 77 (13). Found (%): C, 54.78; H, 5.18; N, 16.78. $C_{19}H_{21}N_5O_6$. Calculated (%): C, 54.94; H, 5.10; N, 16.86.

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Received 04.03.2024
Approved after reviewing 12.03.2024
Accepted 14.03.2024