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σ-COMPLEXES IN THE PYRIMIDINE SERIES. 14*. DIHYDROPYRIMIDINE ANALOGS OF ACYCLONUCLEOSIDES. SYNTHESIS OF 2,3-DIHYDROXYPROPYL DERIVATIVES OF 4-ARYL-6-METHYL-5-NITRO-1,4(3,4)-DIHYDROPYRIMIDIN-2-ONES

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Methods have been developed for the synthesis of 5-nitro-1,4- and 5-nitro-3,4-dihydropyrimidin-2-one analogs of acyclonucleosides containing a 2,3-dihydroxypropyl fragment in positions 1 and 3 respectively of the dihydropyrimidine ring.

Keywords: anionic σ-complexes, acyclonucleosides, nitrodihydropyrimidinones, allylation.

In recent years compounds possessing a wide spectrum of biological action have been found in the hydrogenated pyrimidine series [2]. In particular derivatives of 3,4-dihydroquinazolin-2-one have been described which are nonnucleoside inhibitors of reverse transcriptase [3-5]. From the anionic σ-complexes of 5-nitropyrimidine we have obtained [6] 5-nitro-2,5- and 5-nitro-1,6-dihydropyrimidine analogs of acyclonucleosides, which at a lower cytotoxicity possess activity against HIV-1 comparable with the activity of azidothymidine [6,7]. On the basis of these data it may be assumed that the hydrogenated pyrimidine fragment participates in the antiviral action. In the present work, which continues investigation of dihydropyrimidine analogs of acyclonucleosides, approaches have been developed for the synthesis of 2,3-dihydroxypropyl derivatives of 4-aryl-6-methyl-5-nitro-1,4-dihydropyrimidin-2-ones. Choice of the latter as the heterocyclic fragment is also due to the fact that these compounds display the properties of modulators of cellular calcium [8,9] and are aza-analogs of 4-aryl-1,4-dihydropyrimidines, potentiators of antiviral and anticancer preparations [10-13].

We showed previously that methylation of 4-aryl-2-methoxy-5-nitro-1,4-dihydropyrimidines is effected at a nitrogen atom of the pyrimidine ring [14,15]. It is possible to consider this reaction as a model for the synthesis of dihydropyrimidine analogs of nucleosides containing an acyclic substituent in positions 1 and 3 of the heterocycle.

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* For Part 13 see [1].

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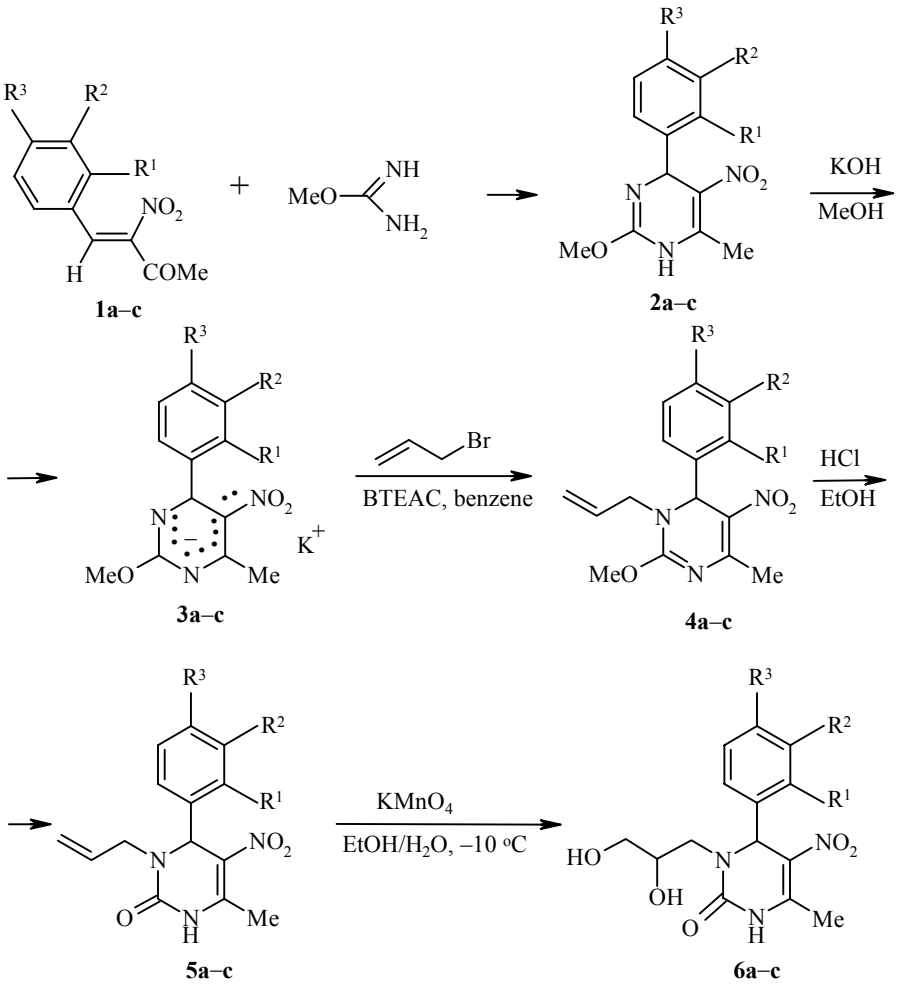
4-Aryl-2-methoxy-6-methyl-5-nitro-1,4-dihydropyrimidines **2a-c**, synthesized from 1-arylidene-1-nitro-2-propanones **1a-c**, form stable anionic σ-complexes **3a-c** in alkaline media. On interacting these complexes with allyl bromide in benzene in the presence of benzyltriethylammonium chloride (BTEAC) $N_{(3)}$-allyl-4-aryl-6-methyl-5-nitro-3,4-dihydropyrimidines **4a-c** were obtained, which are converted in acidic medium into $N_{(3)}$-allyl-3,4-dihydropyrimidin-2(1H)ones **5a-c** (Table 1). The singlet form of the signal of the geminal proton of the pyrimidine ring in the ^{1}H NMR spectra of these compounds (Table 2) unequivocally proves the position of the allyl substituent. Selective oxidation of the double bond of the allyl fragment in compounds **5a-c** leads to 4-aryl-$N_{(3)}$-(2,3-dihydroxypropyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1H)-ones **6a-c**.



1a–c, **2a–c**, **3a–c**, **4a–c**, **5a–c**, **6a–c**

1–6 a R^1 = Cl, R^2 = R^3 = H; **b** R^1 = H, R^2 = R^3 = OMe; **c** R^1 = H, R^2 + R^3 = –OCH_2O–

This is confirmed by the disappearance from the IR spectra of compounds **6a-c** of absorption bands for the stretching vibrations of the allyl group double bond (Table 1) and by the presence of absorption bands at 3600-3700 cm^{-1} corresponding to the stretching vibrations of hydroxyl groups. The presence of two singlet signals at 5.66-6.52 ppm in the ^{1}H NMR spectra of compounds **6a-c** (Table 2), corresponding to the geminal proton, indicates that the carbacyclonucleosides were isolated as a mixture of two diastereomers. However the close values of the chemical shifts do not permit specific assignments to be made.

With the aim of obtaining $N_{(1)}$-allyl derivatives of 4-aryl-5-nitro-1,4-dihydropyrimidin-2-one the interaction has been studied of 6-methyl-5-nitro-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**7**) with allyl bromide in DMSO in the presence of sodium hydride. However nucleophilic attack occurred at the $N_{(3)}$ atom

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (ethanol)	IR spectrum* (KBr), ν, cm^{-1}	UV spectrum (CH_3OH), λ_{max}, nm (log ε)	Yield, %
		C	H	N				
5a	$C_{14}H_{14}ClN_3O_3$	55.12 / 54.64	4.82 / 4.59	13.70 / 13.65	147-149	1681, 1637, 3412	239 (3.78); 341 (3.76)	86
5b	$C_{16}H_{19}N_3O_5$	57.98 / 57.65	5.84 / 5.75	12.84 / 12.61	167-169	1693, 1643, 3418	236 (3.94); 340 (3.8)	83
5c	$C_{15}H_{15}N_3O_5$	56.13 / 56.78	4.80 / 4.76	13.35 / 13.24	160-162	1681, 1643, 3412	240 (4.1); 340 (4.0)	84
6a	$C_{14}H_{16}ClN_3O_5$	49.94 / 49.20	5.04 / 4.72	12.36 / 12.30	Oil	1681, 3418, 3600, 3687	240 (3.8); 342 (3.79)	9
6b	$C_{16}H_{21}N_3O_7$	52.80 / 52.31	5.94 / 5.76	11.21 / 11.44	Oil	1681, 3412, 3600, 3675	236 (3.9); 340 (3.87)	15
6c	$C_{15}H_{17}N_3O_7$	52.00 / 51.28	4.92 / 4.88	12.01 / 11.96	186-189	1690, 3412, 3606, 3687	240 (4.05); 342 (3.98)	12
8	$C_{17}H_{19}N_3O_3$	65.19 / 65.16	6.09 / 6.11	13.67 / 13.41	165-168	1681, 1631, 3412	344 (4.05)	9
9a	$C_{14}H_{14}ClN_3O_3$	54.91 / 54.64	4.62 / 4.59	13.86 / 13.65	175-177	1681, 1631, 3431	230 (3.8); 344 (3.76)	42
9b	$C_{16}H_{19}N_3O_5$	57.94 / 57.65	6.01 / 5.75	12.97 / 12.61	205-206	1689, 1637, 3418	230 (3.9); 342 (3.8)	34
9c	$C_{15}H_{15}N_3O_5$	57.59 / 56.78	4.74 / 4.76	13.31 / 13.24	192-195	1693, 1618, 3418	239 (4.05); 346 (3.9)	40
10a	$C_{14}H_{16}ClN_3O_5$	49.35 / 49.20	4.79 / 4.72	12.72 / 12.30	108-112	1675, 3431, 3606, 3681	345 (3.8)	12
10b	$C_{16}H_{21}N_3O_7$	52.41 / 52.31	5.73 / 5.76	11.48 / 11.44	137-139	1675, 3425, 3600, 3694	238 (3.96); 342 (3.9)	9
10c	$C_{15}H_{17}N_3O_7$	51.34 / 51.28	4.89 / 4.88	11.95 / 11.96	132-135	1672, 3425, 3600, 3686	234 (3.95); 346 (3.89)	14

* Bands at 1672-1693, 1618-1643, 3412-3431, and 3600-3687 cm^{-1} correspond to the absorption of C=O, $CH=CH_2$, NH, and OH groups respectively.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

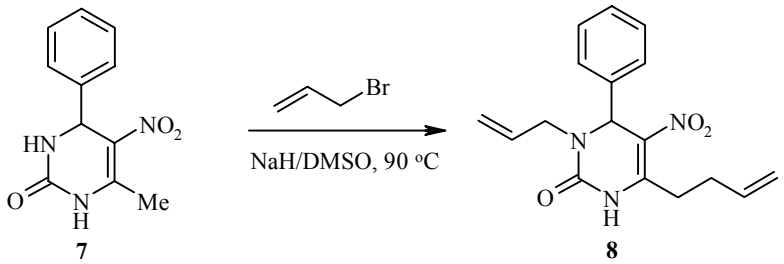
Com-pound	Chemical shifts, δ, ppm (coupling constants, *J*, Hz)*				
	N–H	H-4	CH_3, s	N–CH_2	Other signals
2a	5.74, br. s*^{2}	5.93 (d*^{2}, *J* = 2.2)	2.58*^{2}	—	3.95 s*^{2} (OCH_3)
2c	5.74, br. s*^{2}; 6.25, s*^{3}	5.78 (d*^{2}, *J* = 2.4); 5.84, s*^{3}	2.58*^{2}, 2.51*^{3}	—	3.97 s*^{2}, 3.85 s*^{3} (OCH_3); 5.90 s (CH_2)
3a	—	6.28, s	2.53	—	3.98 s (OCH_3)
3b	—	5.96, s	2.44	—	4.03 s (OCH_3)
3c	—	5.81, s	2.50	—	6.00 (CH_2); 4.00 s (OCH_3)
4a	—	6.25, s	2.60	5.19, m	5.66 s (CH); 3.98 s (OCH_3); 4.08-3.57 m (=CH_2)
4b	—	5.66, s	2.58		5.26 m (CH+NCH_2); 3.99 s, 3.86 s (OCH_3); 4.25-3.47 m (=CH_2)
4c	—	5.62, s	2.57		5.94 s (CH_2); 5.25 m (CH+NCH_2); 3.98 s (OCH_3); 4.25-3.51m (=CH_2)
5a	9.50, s	6.14, s	2.59	5.26, m	5.71 m (CH); 4.39-3.35 m (=CH_2)
5b	8.71, s	5.63, s	2.56	5.28, m	5.72 m (CH); 3.88 s (OCH_3); 4.54-3.32 m (=CH_2)
5c	9.64, s	5.57, s	2.56	5.30, m	5.98 s (CH_2); 5.73 m (CH); 4.54-3.29 m (=CH_2)
6a	8.92, s	6.52, s; 5.96, s	2.56	5.64, m	4.23 m (C<u>H</u>OH); 4.50–3.38 m (C<u>H_2</u>OH)
6b	8.92, s	5.98, s; 5.75, s	2.53	5.58, d; 5.03, d	4.29 m (C<u>H</u>OH); 3.97 s (OCH_3); 4.20-3.38 m (C<u>H_2</u>OH)
6c	8.84, s	5.71, s; 5.66, s	2.55	5.44, dd; 5.17, dd	5.98 s (CH_2); 4.42 m (C<u>H</u>OH); 4.20-3.29 m (C<u>H_2</u>OH)
8	8.97, s	5.63, s	—		5.73 s (CH); 5.30-5.00 m (CH+NCH_2); 4.56-3.25 m (=CH_2); 2.50 m (CH_2)
9a	6.08 (d; *J* = 3.3)	6.14 (d, *J* = 3.3)	2.76	5.23, m	5.85 m (CH); 4.46 m (=CH_2)
9b	6.91 (d, *J* = 3.4)	5.72 (d, *J* = 3.4)	2.61	5.20, m	5.87 m (CH); 4.63 m (=CH_2); 3.84 s, 3.82 s (OCH_3)
9c	6.05 (d, *J* = 3.0)	5.68 (d, *J* = 3.0)	2.63	5.23, m	5.96 s (CH_2); 5.93 m (CH); 4.47 m (=CH_2)
10a	7.97, br. s; 7.74, br. s	3.76, m	1.65, 1.63	5.65, m	4.24 m (C<u>H</u>OH); 4.50-3.37 m (C<u>H_2</u>OH)
10b	7.34, br. s; 7.32, br. s	3.71, m	1.64, 1.63	5.48, d, 5.03, d	4.39 m (C<u>H</u>OH); 3.88 s, 3.87 s (OCH_3); 4.20-3.34 m (C<u>H_2</u>OH)
10c	7.33, br. s; 7.20, br. s	3.92, m	1.63, 1.62	5.42, dd, 5.07, dd	6.15 s, 6.14 s (CH_2); 4.47 m (C<u>H</u>OH); 4.20-3.33 m (C<u>H_2</u>OH)

* The ^{1}H NMR spectra of compounds **2a,c, 4a-c,** and **8** were obtained in $CDCl_3$, and of the remaining compounds in DMSO-d_6; the signals of the aromatic protons resonate at 6.92-7.54 ppm.

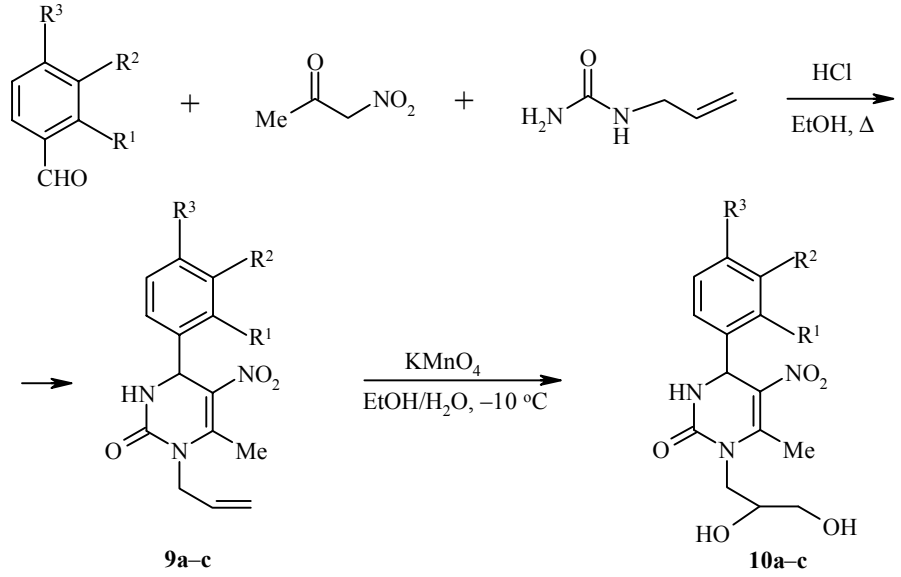
*^{2} Signals of the 3,4-dihydro tautomeric form.

*^{3} Signals of the 1,4-dihydro tautomeric form.

and the methyl group forming 3-allyl-6-(3-butenyl)-5-nitro-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**8**), the structure of which was demonstrated by spectral data (Tables 1 and 2).



For the purpose-directed introduction of an allyl fragment into position 1 of the dihydropyrimidin-2-one ring a three-component cyclocondensation of the appropriate aromatic aldehyde, nitroacetone, and N-allylurea in acid medium was used. This led to $N_{(1)}$-allyl-4-aryl-6-methyl-5-nitro-1,4-dihydropyrimidin-2(3H)-one **9a-c**. The structures of these compounds were confirmed by their spectral characteristics.



9, **10 a** R^1 = Cl, R^2 = R^3 = H; **b** R^1 = H, R^2 = R^3 = OMe; **c** R^1 = H, R^2 + R^3 = –OCH_2O–

In the ^{1}H NMR spectra the signal of the geminal proton of the pyrimidine ring was displayed as a doublet due to coupling with the proton on the nitrogen atom (Table 2). On interacting these compounds with $KMnO_4$ a selective oxidation occurs of the double bond of the allyl fragment with the formation of 4-aryl-$N_{(1)}$-(2,3-dihydroxypropyl)-6-methyl-5-nitro-1,4-dihydropyrimidin-2(3H)-ones **10a-c**. The double set of signals in the ^{1}H NMR spectra of these compounds (Table 2) indicates that in this case also the carbacyclonucleosides are isolated as a mixture of two diastereomers. It is interesting to note that the signals corresponding to the geminal proton and the methyl group protons in compounds **10a-c** were displaced significantly towards high field compared with the signals of the initial compounds.

A new type of acyclonucleoside, containing a 5-nitrodihydropyrimidin-2-one fragment as the heterocyclic base, has therefore been synthesized. The methods thereby developed enable selective introduction of a dihydroxyalkyl substituent into positions 1 and 3 of the pyrimidine ring.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a VXR-300 (300 MHz) spectrometer, internal standard was TMS. The IR spectra were obtained on a Specord M-80 instrument, and the UV spectra on a Specord M-40 instrument. A check on the course of reactions and the homogeneity of compounds was effected by TLC on Silufol UV 254 plates in the solvent system chloroform–methanol, 50:1, visualization was in UV light.

Nitroacetone, 1-arylidene-1-nitro-2-propanones **1a-c**, 5-nitro-1,4-dihydropyrimidine **2b** (Found, %: C 54.63; H 5.80; N 13.71. $C_{14}H_{17}N_3O_5$. Calculated, %: C 54.7; H 5.60; N 13.80), and 5-nitrodihydropyrimidin-2-one **7** were obtained as described in [16,17,15,14] respectively.

2-Methoxy-6-methyl-5-nitro-4-(2-chlorophenyl)-1,4-dihydropyrimidine (2a). A mixture of 1-(2-chlorobenzylidene)-1-nitro-2-propanone (0.78 g, 3.46 mmol) and free O-methylisourea (0.30 g, 4.0 mmol) was triturated without solvent for 2 h, then treated with chloroform (100 ml), the mixture dried over $MgSO_4$, evaporated to dryness, and product **2a** was isolated from the residue by column chromatography on silica gel (eluent chloroform). Yield 0.32 g (28%); mp 145-146°C (ethanol). Found, %: C 51.24; H 4.59; N 14.81. $C_{12}H_{12}ClN_3O_3$. Calculated, %: C 51.16; H 4.29; N 14.92.

2-Methoxy-6-methyl-4-(3,4-methylenedioxyphenyl)-5-nitro-1,4-dihydropyrimidine (2c) was obtained analogously from 3,4-methylenedioxybenzylidene-1-nitro-2-propanone. Yield 17%. Oil. Found, %: C 52.73; H 4.42; N 14.10. $C_{13}H_{13}N_3O_5$. Calculated, %: C 53.61; H 4.50; N 14.43.

Potassium 4-(2-Chlorophenyl)-2-methoxy-6-methyl-5-nitro-4H-pyrimidinide (3a). Finely powdered potassium hydroxide (0.04 g, 0.71 mmol) was added with stirring to a solution of dihydropyrimidine **2a** (0.20 g, 0.71 mmol) in dry methanol (5 ml). After 1 h 30 min the reaction mixture was evaporated to 1/5 initial volume and the **anionic σ-complex 3a** precipitated with ether (200 ml). Yield 0.19 g (83%).

Anionic σ-Complexes 3b (79% yield) and **3c** (84% yield) were obtained analogously from compounds **2b** and **2c**. Complexes **3a-c** did not have sharp melting points and melted above 300°C. Due to incomplete combustion of these compounds it was not possible to determine data on their elemental composition.

3-Allyl-4-(2-chlorophenyl)-2-methoxy-6-methyl-5-nitro-3,4-dihydropyrimidine (4a). Allyl bromide (0.28 ml, 3.3 mmol) was added with stirring to a suspension of σ-complex **3a** (0.48 g, 1.50 mmol) and BTEAC (0.36 g, 1.6 mmol) in dry benzene (10 ml). After 20 h the solid was filtered off, the solvent was evaporated in vacuum, and product **4a** was isolated from the residue by column chromatography on silica gel (eluent chloroform).

3-Allyl-4-aryl-2-methoxy-6-methyl-5-nitro-3,4-dihydropyrimidines 4b,c were obtained analogously from anionic σ-complexes **3b,c** respectively.

3-Allyl-4-(2-chlorophenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1H)-one (5a). Conc. HCl (0.1 ml) was added to a solution of 3,4-dihydropyrimidine **4a** (0.34 g, 1.10 mmol) in methanol (25 ml). After 4 h the reaction mixture was evaporated to dryness, and the residue dissolved in chloroform (120 ml). The solution was washed with water to neutral reaction, and dried over $MgSO_4$. The solvent was evaporated in vacuum, and the residue crystallized from ethanol.

3-Allyl-4-aryl-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1H)-ones 5b,c were obtained analogously from **4b,c** respectively.

3-Allyl-6-(3-butenyl)-5-nitro-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (8). An 80% suspension of sodium hydride (0.37 g, 12.3 mmol) was added in portions in a stream of argon with stirring to a solution of compound **7** (1.0 g, 4.2 mmol) in DMSO (20 ml). After 2h, after complete evolution of hydrogen, allyl bromide (1.9 ml, 21.0 mmol) was added. The reaction mixture was stirred at 90°C for 2 h, diluted with water (200 ml), and extracted with ethyl acetate (350 ml). The extract was dried over $MgSO_4$, the solvent removed to dryness in a waterpump vacuum, and product **8** was isolated from the residue by column chromatography on silica gel (eluent chloroform).

1-Allyl-4-(2-chlorophenyl)-6-methyl-5-nitro-1,4-dihydropyrimidin-2(3*H*)-one (9a). Conc. HCl (1.0 ml) was added with stirring to a mixture of 2-chlorobenzaldehyde (0.37 ml, 3.3 mmol), nitroacetone (0.34 g, 3.3 mmol), and N-allylurea (0.66 g, 6.6 mmol) in absolute ethanol (75 ml). The reaction mixture was boiled for 6 h, the precipitated solid product **9a** was filtered off, and dried.

1-Allyl-4-aryl-6-methyl-5-nitro-1,4-dihydropyrimidin-2-ones (9b,c) were obtained analogously from the corresponding substituted benzaldehydes.

General Procedure for Obtaining 2,3-Dihydroxypropyl Derivatives of Dihydropyrimidin-2-ones 6a-c and 10a-c. A mixture of $KMnO_4$ (0.55 g, 3.5 mmol) and $MgSO_4 \cdot 7H_2O$ (0.86 g, 3.56 mmol) in water (60 ml) was added with stirring during 30 min to a solution of the appropriate N-allyl derivative **5a-c** (or **9a-c**) (3.5 mmol) in ethanol (50 ml) cooled to -10°C. After 4 h the solid was filtered off, the filtrate was evaporated to dryness, and product **6** or **10** was isolated from the residue by column chromatography on silica gel (eluent chloroform–methanol, 10:1).

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