

Synthesis of 2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl Methacrylates

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Abstract—2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl methacrylates were synthesized for the first time by reaction of 5-hydroxyuracil derivatives with methacrylic anhydride. 5-Hydroxyuracil derivatives are involved in this reaction in the dioxo form.

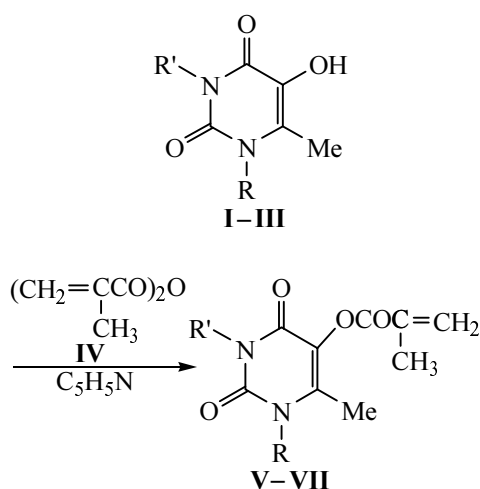
Hydroxymethyluracil is a new immunostimulant with a broad spectrum of activity; it exhibits pronounced antioxidant and hepatoprotective properties and is superior to the known immunostimulant, 6-methyluracil, in the immunomodulating activity [1–4]. In continuation of our studies on new pyrimidine derivatives which are soluble in organic solvents and are potential immunotropic, antiphlogistic, and antiradical agents, we performed reactions of 5-hydroxy-6-methyluracil (**I**), 5-hydroxy-1,3,6-trimethyluracil (**II**), and 5-hydroxy-3,6-dimethyluracil (**III**) with methacrylic anhydride (**IV**) and

isolated 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl methacrylate (**V**), 1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl methacrylate (**VI**), and 3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl methacrylate (**VII**), respectively (Scheme 1). Compounds **V–VII** are crystalline substances which are readily soluble in water and moderately soluble in alcohol and DMF. Their structure was confirmed by the analytical data and IR, UV, ¹H, and ¹³C NMR spectra, and their purity was checked by TLC.

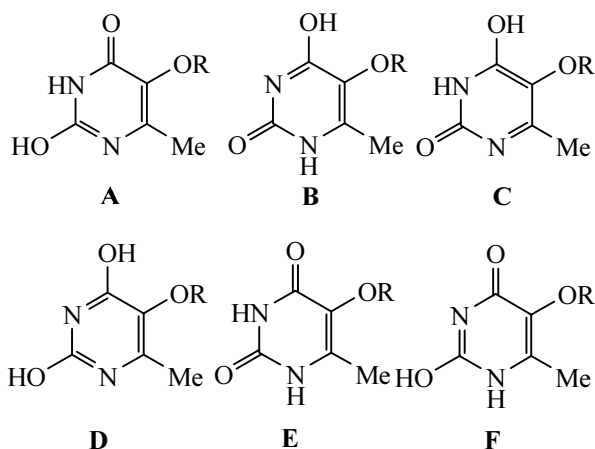
In the IR spectra of all compounds we observed absorption bands at 1620–1720 cm⁻¹ which are typical of vibrations of the pyrimidine fragment [$\nu(\text{C}=\text{O})$, $\nu(\text{=N}-\text{C}=\text{O})$] and at 1380 [$\delta_s(\text{CH}_3)$], 1160–1210 (ester), 1312 [$\nu(\text{CN})$], 840–968 [$\omega(\text{CH}_2)$], 1400–1464 [$\delta(\text{CH}_2)$], and 2856–1936 cm⁻¹ (CH₂, CH₃). The bands at 1116–1238 cm⁻¹ are typical of compounds which contain a tertiary nitrogen atom, and those in the region 3016–3252 cm⁻¹ belong to stretching vibrations of the NH groups; as shown in [5], the lower frequency corresponds to stretching vibrations of the N³-H bond. The ¹³C NMR spectra of the products contained signals typical of the uracil fragment at δ_c , ppm: 158.5 (C⁴), 151.2 (C²), 146.5 (C⁶), 116.5 (C⁵); also, signals at δ_c 12–14 (6-CH₃), 17.7 (9-CH₃), 125.0 (C¹⁰), 128.7 (C⁹), and 164.0 ppm (C⁸) were present.

On the basis of the IR, UV, and ¹³C NMR spectra Ivanov [6] showed that 5-hydroxy-6-methyluracil (**I**) can exist as six tautomers **A–F** (R = H).

Scheme 1.



I, V, R = R' = H; **II, VI**, R = R' = Me; **III, VII**, R = H, R' = Me.



I, R = H; V, R = CH₂=C(Me)CO.

The lactim–lactam equilibrium constants and the concentration of the lactim tautomer of uracil, thymine, and 5-hydroxy-6-methyluracil, calculated therefrom, are important not only for chemists but also for geneticists. According to the spontaneous mutation theory, rare lactim tautomers are capable of forming irregular pairs in the synthesis of daughter DNAs. The concentration of lactim form depends on pH. Situations are possible where pH in living cells increases as a result of various disorders. In these cases, the concentration of the lactim form should increase thus raising the probability for mutation to occur. We compared the ¹³C NMR spectrum of compound **V** with the spectra of tautomers **A–F** [R = CH₂=C(Me)CO]. The results are given in table. It is seen that the spectrum of **V** fully coincides with that of tautomer **E**, i.e., the product has the structure of 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl methacrylate.

EXPERIMENTAL

The ¹H and ¹³C NMR spectra were recorded from 1% (¹H) or 10–20% solutions (¹³C) in D₂O using a Bruker AM-300 spectrometer (300 MHz for ¹H and 75.7 MHz for ¹³C); the proton chemical shifts are given relative to HMDS. The IR spectra were obtained from samples dispersed in mineral oil or films (liquids) using a UR-20 spectrometer (Carl Zeiss, Jena) equipped with NaCl and LiF prisms. The melting points were measured on a Boetius device. The elemental compositions were determined on an M-185B CHN Analyzer. The progress of reactions and the purity of products were monitored by thin-layer chromatography on Silufol UV-254 plates (Czechia) using ethanol–aqueous ammonia (4 : 1) as eluent; spots were visualized under UV light (λ = 254 nm) or by treatment with iodine vapor. The UV spectra were recorded from 0.00001% solution using a Specord M-400 spectrophotometer (λ 200–350 nm; layer thick-ness 10 mm).

Methacrylic anhydride (IV). Methacryloyl chloride, 48.90 g (0.47 mol), was quickly added under stirring and cooling to a solution containing 90.0 g (76 ml, 1.2 mol) of anhydrous pyridine, 156 ml of anhydrous toluene, and a small amount of hydroquinone. A slight heat evolution was observed due to formation of a pyridine complex. Methacrylic acid, 40.4 g (0.475 mol, 40 ml), was added from a dropping funnel under stirring over a period of 10 min, and the mixture quickly warmed up to 50–65°C. When the addition was complete, the mixture was stirred for an additional 10 min and filtered, the solvent was distilled off from the filtrate at a bath temperature of 70°C, and the residue (72 g) was distilled under reduced

¹³C NMR spectra of possible tautomers **A–F** and isolated 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl methacrylate

Tautomer no.	C ¹² H ₃	C ¹¹ H ₃	C ²	C ⁴	C ⁵	C ⁶	C ⁸	C ⁹	C ¹⁰
VA	13.05	17.7	179.71	171.96	129.39	157.51	166.05	128.69	124.7
VB	12.06	17.7	156.74	155.81	130.69	142.75	163.72	138.44	124.7
VC	22.57	17.7	156.39	156.53	116.15	149.46	163.72	138.44	124.7
VD	18.53	17.7	157.52	163.54	131.50	154.90	166.54	134.88	124.7
VE	12.27	17.7	151.14	158.36	116.66	146.53	164.80	128.69	124.7
VF	13.09	17.7	171.22	148.34	111.37	139.87	167.95	128.69	124.7
V	12.30	17.97	151.08	158.76	116.86	143.42	164.38	128.22	123.9

pressure to obtain 60 g (83%) of methacrylic anhydride with bp 84–86°C (12 mm).

6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl methacrylate (V). A small amount (on a tip of a scalpel) of hydroquinone and 6.0 g (0.039 mol) of methacrylic anhydride (IV) were added at room temperature to a mixture of 3.6 g (0.025 mol) of 5-hydroxy-6-methyluracil and 15 ml of pyridine which was preliminarily dried over KOH and distilled over metallic sodium. The mixture was stirred for 30–50 min and was left overnight at room temperature. The precipitate (2.48 g) was filtered off, and pyridine and excess anhydride IV were distilled off from the filtrate on heating on an oil bath (180–190°C) under reduced pressure (10 mm). The residue was a yellow crystalline material which was washed with 50 ml of methanol to isolate an additional portion (3.2 g) of compound V, R_f 0.64. Overall yield 5.3 g (100%), mp 278–280°C. The product is readily soluble in methanol, ethanol, and DMF and insoluble in acetone and chloroform. IR spectrum, ν , cm^{-1} : 1620–1720 (C=O, =N–C=O), 1116–1238 (–N=), 3016–3252 (N–H), 1380 (δ_s CH₃), 1160–1210 (ester), 1312 (C–N), 840–968 (ω CH₂), 1400–1464 (δ CH₂), 2856–2936 (CH₂, CH₃). UV spectrum (water): λ_{max} 277.35 nm. ¹H NMR spectrum (CDCl₃), δ , ppm: 1.88 s (3H, C¹¹H₃), 2.0 s (3H, 6-CH₃), 5.90 s (1H, 10-H), 6.12 s (1H, 10-H), 8.50 s (1H, 1-H), 10.50 s (1H, 3-H). ¹³C NMR spectrum (CDCl₃), δ_C , ppm: 12.30 (6-CH₃), 17.97 (C¹¹), 116.80 (C⁵), 124.22 (C¹⁰), 128.22 (C⁹), 143.47 (C⁶), 151.06 (C²), 158.77 (C⁴), 164.38 (C⁸). Found, %: C 50.70; H 4.97; N 13.60. C₉H₁₀N₂O₄. Calculated, %: C 51.18; H 4.77; N 13.26.

1,3,6-Trimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl methacrylate (VI). Methacrylic anhydride (IV), 4.7 g (4 ml), was added under stirring to a mixture of 3.4 g (0.02 mol) of 1,3,6-trimethyl-5-hydroxyuracil, 15 ml of pyridine, and a small amount of hydroquinone. The mixture was stirred for 1 h at room temperature and was left overnight. Removal of the solvent left 4.65 g (97%) of compound VI as a light yellow thick liquid, R_f 0.8. IR spectrum, ν , cm^{-1} : 1620, 1650, 1670, 1740 (C=O, =N–C=O), 1130–1240 (–N=), 3350 (O–H), 1380 (δ_s CH₃), 1160–1210 (ester), 1320 (C–N), 830–960 (ω CH₂), 1400–1464 (δ CH₂), 2870–2940 (CH₂, CH₃). UV spectrum (ethanol): λ_{max} 278.20 nm. ¹H NMR spectrum (CDCl₃), δ , ppm: 1.85 s (3H, C¹¹H₃), 2.0 s (3H, 6-CH₃), 3.30 s (3H, 1-CH₃), 3.40 s (3H, 3-CH₃), 5.90 s

(1H, 10-H), 6.12 s (1H, 10-H). ¹³C NMR spectrum (CDCl₃), δ_C , ppm: 10.60 (6-CH₃), 17.70 (C¹¹), 28.20 (1-CH₃), 29.20 (3-CH₃), 115.40 (C⁵), 124.70 (C¹⁰), 128.70 (C⁹), 150.90 (C⁶), 152.20 (C²), 161.50 (C⁴), 164.50 (C⁸). Found, %: C 55.0; H 6.10; N 11.40. C₁₁H₁₄N₂O₄. Calculated, %: C 55.46; H 5.92; N 11.76.

3,6-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl methacrylate (VII). Methacrylic anhydride (IV), 5 ml, was added to a mixture of 3.2 g (0.02 mol) of 3,6-dimethyluracil and 25 ml of pyridine containing a small amount of hydroquinone, and the mixture was stirred for 1 h at room temperature and was left overnight. The crystals were filtered off, and the filtrate was evaporated to obtain 9.53 g of a liquid residue which partially crystallized on storage. The crystals were filtered off and reprecipitated from 15 ml of acetone. Yield 3.0 g (68%), mp 130–132°C, R_f 0.78. IR spectrum, ν , cm^{-1} : 1650, 1720 (C=O, =N–C=O), 1130–1230 (–N=), 3200 and 3240 (N¹–H), 1380 (δ_s CH₃), 1160–1210 (ester), 1320 (C–N), 830–980 (ω CH₂), 1464 (δ CH₂), 2880–2950 (CH₂, CH₃). UV spectrum (water): λ_{max} 272.35 nm. ¹H NMR spectrum (CDCl₃), δ , ppm: 1.88 s (3H, C¹¹H₃), 2.0 s (3H, 6-CH₃), 3.42 s (3H, 3-CH₃), 5.90 s (1H, 10-H), 6.12 s (1H, 10-H), 8.47 s (1H, 1-H). ¹³C NMR spectrum (CDCl₃), δ_C , ppm: 13.27 (6-CH₃), 17.70 (C¹¹), 28.20 (3-CH₃), 115.90 (C⁵), 124.70 (C¹⁰), 128.70 (C⁹), 146.50 (C⁶), 152.20 (C²), 161.50 (C⁴), 164.70 (C⁸). Found, %: C 53.10; H 5.60; N 12.77. C₁₀H₁₂N₂O₄. Calculated, %: C 53.57; H 5.39; N 12.49.

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