ACETYLATION OF 6-ALKYL-5-ETHOXYCARBONYL-2-HYDROXY-4-METHYL-DIHYDROPYRIMIDINES AND THEIR 2-MERCAPTO ANALOGS

A. M. Buzueva

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A number of 6-alkyl- and 6-aryl-5-ethoxycarbonyl-2-hydroxy-4-methyldihydropyrimidines and their 2-mercapto analogs and the acetyl derivatives of these compounds have been synthesized. In each case, two isomeric acetyl derivatives were obtained, probably the 1- and 3-acetyl compounds.

Some pyridine derivatives are stimulators of the growth of microorganisms and viruses [1, 2] and others are inhibitors [3]. The introduction of an acetyl group into the pyridine ring enhances the inhibiting action [4]. The influence of hydrogenated derivatives of primidine and their N-acetyl derivatives on the growth of microorganisms has been studied comparatively little; with this aim, we have synthesized a number of dihydropyrimidines and their N-acetyl derivatives. The influence of the compounds synthesized on the rate of growth of rat liver regenerators and on the growth of a number of microorganisms has been studied in the biological testing laboratory of the Institute of the Chemistry of Natural Compounds, AS USSR.

The synthesis of the initial 6-alkyl- and 6-aryl-5-ethoxycarbonyl-2-hydroxy-4-methyldihydropyrimidines and their 2-mercapto analogs (I–V) (see Table 1) was carried out by a method described previously [5–8].

There is little information on the acetylation of hydrogenated derivatives of monohydroxy- and monomercaptopyrimidines [9, 10]. It is considered [9] that both mono- and di-N-acetyl derivatives may be obtained, depending on the degree of hydrogenation of the compounds and their tendency to undergo tautomeric conversions. In the acetylation of the dihydropyrimidines I, III, and IV with an excess of acetic anhydride, we obtained monoacetyl derivatives (see Table 2). We were unable to obtain N-acetyl derivatives of compounds II and V under these conditions.

When 5-ethoxycarbonyl-2-hydroxy-4, 6-dimethyldihydropyrimidine was acetylated with an excess of acetic anhydride, two isomeric monoacetyl derivatives (VIa and VIb) were isolated. The saponification of both compounds with alkali yielded the starting material. In the acetylation of III it was impossible to isolate individual substances; they were separated chromatographically.

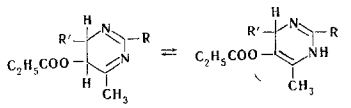
Apparently 1-acetyl and 3-acetyl derivatives are obtained, since the possibility of the formation of the two isomers is similar (although there is information in the literature that the probability of the formation of the 3-acetyl derivatives is greater [10]).

EXPERIMENTAL

5-Ethoxycarbonyl-2-hydroxy-6-isopropyl-4-methyldihydropyrimidine (I). A mixture of 7.2 g (0.1 mole) of isobutyraldehyde, 6 g (0.1 mole) of urea, and 19.5 g (0.15 mole) of acetoacetic ester in 50 ml of absolute ethanol, with the addition of 16 drops of hydrochloric acid as catalyst, was boiled for 6 hr. After 1 day, the colorless precipitate was separated off and purified by three crystallizations from (1 : 2) or 50% acetic acid (1 : 15). Compound I is sparingly soluble in water and is soluble on heating in methanol, ethanol, acetic acid, and dioxane.

5-Ethoxycarbonyl-2-hydroxy-4-methyl-6-styryldihydropyrimidine (II). A mixture of 2.22 g (0.01 mole) of cinnamaldehyde, 0.6 g (0.01 mole) of urea, and 1.95 g (0.015 mole) of acetoacetic ester in glacial acetic acid (18 ml) was left at room teperature for 48 hr. It was not necessary to add hydrochloric acid as catalyst. After 24 hr, a voluminous yellow precipitate deposited, and this was purified by crystallization from butanol (1 : 25). Colorless crystals, sparingly soluble in water, soluble on heating in alcohols, dioxane, and acetic acid. In the cold

Table 1

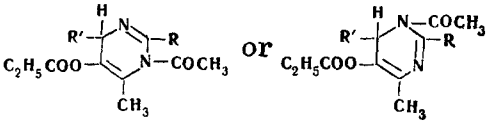


Compound	R	R′	MP °C	Empirical formula	Found, %			Calculated, %			R_f**	Yield, %
					C	H	N	C	H	N		
I	OH	*i*-C_3H_7	198	$C_{11}H_{18}N_2O_3$	58.63 58.75	8.14 8.15	12.56 12.65	58.40	8.02	12.37	0.62	32.4
II*	OH	$C_6H_5CH{=}CH$									0.78	
III	SH	CH_3	193—194	$C_9H_{14}N_2O_2S$	50.90 50.26	7.16 7.08	13.02 13.22	50.46	6.83	13.08	0.69	21.5
IV	SH	*i*-C_3H_7	165—166	$C_{11}H_{18}N_2O_2S$	54.22 54.18	7.84 7.76	11.86 11.93	54.54	7.52	11.56	0.71	20.5
V	SH	$C_6H_5CH{=}CH$	182—182.5	$C_{16}H_{18}N_2O_2S$	63.36 63.48	5.93 6.03	9.18 9.04	63.57	5.96	9.27	0.56	78.1

*Compound II has been synthesized previously.

**Thin-layer chromatography on alumina in the benzene–methanol (9 : 1) system.

Table 2



Compound	R	R′	Mp, °C	Empirical formula	Found, %			Calculated, %			R_f*	Yield, %
					C	H	N	C	H	N		
VIa	OH	CH_3	136.5—137.5	$C_{11}H_{16}N_2O_4$	54.78 54.84	6.93 6.88	11.58 11.52	55.00	6.66	11.66	0.45	32.6
VIb	OH	CH_3	163.5—164.5	$C_{11}H_{16}N_2O_4$	54.88 54.76	6.80 6.96	11.60 11.54	55.00	6.66	11.66	0.60	26.0
VII	OH	i-C_3H_7	173 —173.5	$C_{13}H_{20}N_2O_4$	57.74 57.90	8.02 7.94	10.54 10.48	58.19	7.51	10.44	0.56	70.8
VIII	SH	CH_3	178.5—179.5	$C_{11}H_{16}N_2O_3S$	51.24 51.18	6.38 6.44	10.82 10.96	51.56	6.24	10.93	a) 0.66 b) 0.80	42
IX	SH	i-C_3H_7	162 —163	$C_{13}H_{20}N_2O_3S$	54.74 54.68	6.80 6.71	9.88 9.96	54.85	7.03	9.85	0.64	62.2

*Thin-layer chromatography on alumina in the benzene—methanol (9 : 1) system.

it adds bromine quantitatively, and it decolorizes a solution of potassium permanganate.

5-Ethoxycarbonyl-2-mercapto-4, 6-dimethyldihydropyrimidine (III). a) A mixture of 22 g (0.5 mole) of acetaldehyde, 38 g (0.5 mole) of thiourea, 99.5 g (0.75 mole) of acetoacetic ester, 180 ml of absolute ethanol, and 20 drops of hydrochloric acid was boiled for 9 hrs and was left at room temperature for 48 hr. A yellow crystalline precipitate separated; it was purified by three crystallizations from methanol (1:22) or ethanol (1:50). Light yellow crystals sparingly soluble in water and soluble on heating in alcohols, dioxane, and acetic acid.

b) A mixture of 22 g (0.5 mole) of acetaldehyde, 38 g (0.5 mole) of thiourea. 87.5 g (0.65 mole) of acetoacetic ester, and 20 drops of concentrated hydrochloric acid was boiled in 100 ml of glacial acetic for 8 hr. After cooling, the reaction mixture was poured into 500 ml of water, whereupon a yellow precipitate of III deposited.

5-Ethoxycarbonyl-6-isopropyl-2-mercapto-4-methyldihydropyrimidine (IV). a) A mixture of 7.2 g (0.1 mole) of isobutyraldehyde, 7.6 g (0.1 mole) of thiourea, 19.5 g (0.15 mole) of acetoacetic ester, 40 ml of absolute ethanol (or 40 ml of dioxane), and 10 drops of hydrochloric acid was boiled for 8 hr. After 48 hr, the lemon-yellow precipitate was separated off and recrystallized from 80% acetic acid (1 : 10) or from absolute ethanol (1 : 5).

b) The same amounts of starting materials were boiled in 30 ml of glacial acetic acid for 6 hr. After 48 hr, the precipitate of IV was separated off.

Yellow crystals comparatively readily soluble in methanol and ethanol and more sparingly soluble in acetic acid, benzene, and toluene.

5-Ethoxycarbonyl-2-mercapto-4-methyl-6-styryldihydropyrimidine (V). A mixture of 2.2 g (0.01 mole) of cinnamaldehyde, 0.7 g (0.01 mole) of thiourea, 1.95 g (0.015 mole) of acetoacetic ester, and 18 ml of glacial acetic acid was left at room temperature for 48 hr. The lemon-yellow precipitate was purified by crystallization from butanol (1 : 10). Colorless crystals, sparingly soluble in water, soluble in alcohols on heating and in acetic acid. In the cold, V decolorizes bromine water and potassium permanganate solution.

N-Acetyl-5-ethoxycarbonyl-2-hydroxy-4, 6-dimethyldihydropyrimidines (VIa and VIb). A mixture of 3.98 g (0.02 mole) of 5-ethoxycarbonyl-2-hydroxy-4, 6-dimethyldihydropyrimidine and 40 ml of acetic anhydride was boiled for 6 hr. Then it was cooled and poured into 250 ml. of water. On rubbing the walls of the flask with a glass rod, a colorless crystalline precipitate separated. On the following day, 1.58 g of VIa was filtered off. Colorless crystals, mp 136.5–137.5° C (from methanol or 30% ethanol). The aqueous filtrate was left for a further 24 hr, whereupon a precipitate of VIb (1.3 g) with mp 163.5 164.5° C separated. The saponification of both N-acetyl derivatives with 10% alkali yielded the starting material, mp 197–198° C.

N-Acetyl-5-ethoxycarbonyl-2-hydroxy-6-isopropyl-4-methyldihydropyrimidine (VII). A mixture of 2.2 g (0.01 mole) of 5-ethoxycarbonyl-2-hydroxy-6-isopropyl-4-methyldihydropyrimidine and 18 ml of acetic anhydride was boiled for 4 hr, cooled, and poured into 80 ml of water. After 24 hr, the grayish crystalline precipitate was separated off. Yield 1.7 g. It was purified by crystallization from ethanol (1 : 40). Colorless crystals, sparingly soluble in water, soluble in alcohols on heating and in acetic acid.

N-Acetyl-5-ethoxycarbonyl-2-mercapto-4, 6-dimethyldihydropyrimidine (VIII). A mixture of 4.28 g (0.02 mole) of 5-ethoxycarbonyl-2-mercapto-4, 6-dimethyldihydropyrimidine and 40 ml of acetic anhydride was boiled for 6 hr. The liquid was left at room temperature for 48 hr, and then the precipitate that had deposited (3.2 g) was purified by crystallization from ethanol (1 : 7), mp 178.5–17.95° C. Colorless acicular crystals sparingly soluble in water and soluble in alcohols and acetic acid. Chromatography of the material yielded two substances with R_f 0.66 and 0.80.

N-Acetyl-5-ethoxycarbonyl-6-isopropyl-2-mercapto-4-methyldihydropyrimidine (IX). A mixture of 2.42 g (0.01 mole) of 5-ethoxycarbonyl-6-isopropyl-2-mercapto-4-methyldihydropyrimidine and 20 ml of acetic anhydride was boiled for 4 hr. After cooling, the mixture was poured into 70 ml of water. The light yellow precipitate (1.6 g) was purified by crystallization from 70% acetic acid (1 : 12). Light yellow crystals, readily soluble in alcohols and more sparingly soluble in water.

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