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PURINES, PYRIMIDINES, AND CONDENSED SYSTEMS BASED ON THESE COMPOUNDS.

12.* 1,3-DIMETHYLPYRIMIDO[4,5-d]PYRIMIDINE-2,4-(1H,3H)DIONE: THE FIRST CASE OF REGIOSELECTIVE AMINATION OF CONDENSED PYRIMIDINES IN POSITION 2

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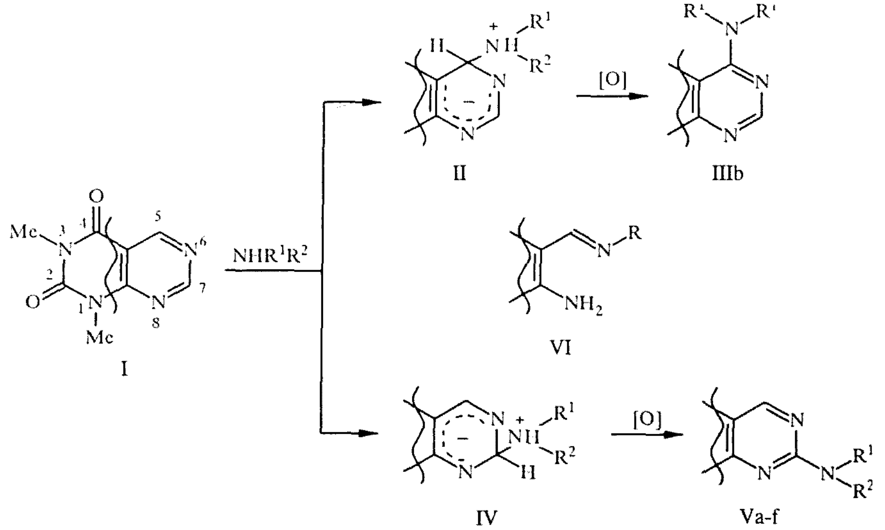
1,3-Dimethylpyrimido[4,5-d]pyrimidine-2,4-(1H,3H)dione (I) reacts with alkylamines in liquid ammonia in the presence of an oxidizing agent such as $KMnO_4$ or $Ag(C_5H_5N)_2MnO_4$, giving 7-amino derivatives; but the interaction of (I) with methylamine gives a mixture of isomeric alkylaminated products. Subsequent hydrolysis of the 7-piperidino derivative in an alkaline medium and then in an acidic medium gives 4-methylamino-2-piperidinopyrimidine with quantitative yield.

It is known that condensed pyrimidines (quinazoline, pteridine) are aminated by alkali metal amides, ammonia, or alkylamines in the presence of an oxidizer, with the amination proceeding exclusively at position 4 [2-4]. Pyrimidine itself and some of its 4- and 5-substituted derivatives, in most cases, also give 6- and 4-aminopyrimidines, respectively [2, 5, 6]. There is very little replacement of hydrogen in position 2, and such replacement is possible only under conditions of kinetic control [7].

We have found that 1,3-dimethylpyrimido[4,5-d]pyrimidine-2,4-(1H,3H)dione [I] undergoes oxidative amination primarily at position 7, corresponding to position 2 in the pyrimidine molecule. By the action of alkylamines or liquid ammonia on compound I in the presence of an oxidizer such as $KMnO_4$ or $Ag(C_5H_5N)_2MnO_4$, 7-amino derivatives V are formed with good yields.



NR^{1}R^2: a) NH_2, b) NHMe, c) NHEt, d) NHBu-t, e) piperidino; f) morpholino

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*For Communication 11, see [1].

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TABLE 1. Synthesis of 7-Alkylamino-1,3-dimethylpyrimido[4,5-d]pyrimidine-2,4-(1H,3H)diones (V)

Compound	Empirical formula	Reaction conditions			R_f*	mp, °C	Yield, %
		amine	oxidant	temperature, °C			
Va	$C_8H_9N_5O_2$	NH_3	$KMnO_4$	-78...-75	0,07	323...324	79
Vb, IIIb	$C_9H_{11}N_5O_2$	$MeNH_2$	KMnO4	-75...-70	0,09	—	90†²
Vc	$C_{10}H_{13}N_5O_2$	$EtNH_2$	$KMnO_4$	-10	0,17	202...205	78
Vd	$C_{12}H_{17}N_5O_2$	*t*-$BuNH_2$	$Ag(C_5H_5N)_2MnO_4$	7...10	0,39	234...236	51
Ve	$C_{13}H_{17}N_5O_2$	Piperidine	$Ag(C_5H_5N)_2MnO_4$	5...10	0,43	180...181,5	75
Vf	$C_{12}H_{15}N_5O_3$	Morpholine	$Ag(C_5H_5N)_2MnO_4$	7...10	0,28	226...228	83

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*TLC on Al_2O_3, chloroform eluent, development by iodine vapor. For original compound I, $R_f = 0.67$.

†Total yield of mixture of compounds IIIb and Vb.

TABLE 2. Physicochemical Properties of 7-Alkylamino-1,3-dimethylpyrimido-[4,5-d]pyrimidine-2,4-(1H,3H)diones (V)

Compound	PMR spectrum ($CDCl_3$), δ, ppm*					IR spectrum ($CHCl_3$), ν, cm^{-1}†		UV spectrum (CH_3OH), λ_{max}, nm (and log ε)
	N(1)—Me (3H, s)	N(3)—Me (3H, s)	5-H (1H, s)	NH	other signals	C=O	N—H	
I	3,48	3,70	9,29	—	9,14 (1H, s, 7-H)	1666, 1724	—	—
Va	3,21	3,40	8,67	7,53 (2H, s)	—	1677, 1719	3170, 3384	232 (5,54), 259 (4,97), 274 (5,14), 315 (5,17)
Vc	3,41	3,59	8,85	6,24 (1H, m)	1,29 (3H, t, *J* = 5 Hz, C—CH_3), 3,56 (2H, q, *J* = 5 Hz, N—CH_2—C)	1663, 1714	3444	215 (5,38), 231 (5,43), 272 (5,20), 310 (5,08)
Vd	3,40	3,59	8,84	5,94 (1H, br.s)	1,51 (9H, s, *t*-Bu)	1662, 1713	3429	214 (5,21), 231 (5,31), 271 (5,10), 309 (5,00)
Ve	3,39	3,54	8,86	—	1,69 (6H, m, β- and γ-CH_2 piperidino), 3,90 (4H, m, α-CH_2 piperidino,	1664, 1714	—	215 (5,34), 233 (5,35), 279 (5,32), 318 (5,11)
Vf	3,41	3,55	8,91	—	3,47 (4H, m, $N(CH_2)_2$ morpholino), 3,97 (4H, m, $O(CH_2)_2$ morpholino)	1672, 1720	—	216 (5,30), 235 (5,32), 276 (5,25), 314 (5,11)

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*Spectrum of compound Va was obtained in DMSO-d_6.

†Spectra of compounds Va,f were obtained in white mineral oil.

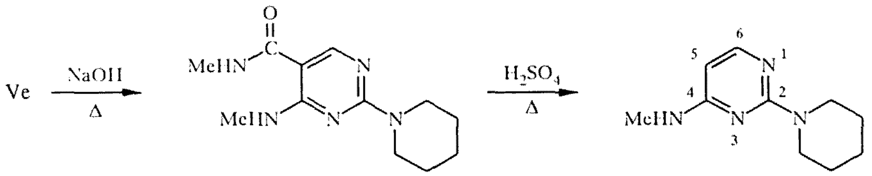
In theory, a nucleophile may attack either the $C_{(7)}$ or $C_{(5)}$ atom of the original molecule. For example, it had been reported previously [8] that refluxing of the pyrimidouracil I with primary alkylamines RNH_2 leads to breakdown of the pyrimidine ring of compound I and the formation of azomethines VI. It is obvious that the initial stage of such a conversion must be the addition of the nucleophile to position 5. A quantum-mechanical calculation (HMO method) shows that in the original molecule, the positive π-charge on the $C_{(7)}$ atom (+0.198) is somewhat greater than on the $C_{(5)}$ atom (+0.183). At the same time, the energy of nucleophilic localization for the σ-complex II (2.80 β) is smaller than for the σ-complex IV

(2.87 β); i.e., the latter complex is less stable. Evidently, the reactivities of positions 5 and 7 are commensurate, and nucleophilic attack in position 7 is more probable under conditions of kinetic control.

Thus, it would be logical to expect the formation of a mixture of isomeric products of alkylamination III and V. However, we found such a mixture only in experiments with methylamine; in all other cases, we recovered a single product of nucleophilic substitution at the $C_{(7)}$ atom, having the structure V.

Evidence in favor of substitution at position 7 is provided by certain PMR spectroscopic data on the compounds we obtained. In the spectrum of the original pyrimidouracil I there are two singlets of N-methyl groups (δ 3.48 and 3.70), and also two singlets of aromatic protons 7-H (δ 9.14) and 5-H (δ 9.29 ppm). We determined the spin–spin coupling constants of the $C_{(5)}$ and $C_{(7)}$ nuclei with the corresponding protons $J_{C(5),H^1} = 187.5$ and $J_{C(7),H^1} = 206.4$ Hz. The difference between the values of these constants enables us to establish the site of entry of the substituent into the pyrimidine ring. Thus, in the PMR spectra of the amination products Vc-f, the singlet of the sole aromatic proton lies in the region δ 8.84-8.91 ppm, with $J_{C,H^1} = 183.4$ Hz, so that this signal can be assigned to the 5-H proton. The compounds V have monotypical IR and UV spectra (Table 2).

For final proof of the structure of V, compound Ve was subjected to the action of a 5% NaOH solution, with heating. From this reaction, we recovered the derivative of pyrimidine-5-carboxylic acid VII. It should be noted that in this particular case, the opening of the uracil ring in alkaline media that is characteristic for xanthines and lumazines [9, 10] proceeds only with great difficulty. Acid hydrolysis of the amide VII with subsequent decarboxylation affords 2-piperidino-4-methylaminopyrimidine (VIII). In the PMR spectrum of this compound, along with the signals of protons of the methylamino and piperidino groups, there are two doublets with equal intensity in the region δ 5.61 and 7.85 ppm (J = 5.7 Hz), corresponding to the aromatic protons 5-H and 6-H of the pyrimidine VIII. Obviously, in the case of 5-substitution, the PMR spectrum of the analogous product would contain two unsplit signals of the aromatic protons.



VII

VIII

As indicated above, by the action of methylamine on the pyrimidouracil I in the presence of $KMnO_4$, we obtained a mixture of two substances that we were not able to separate by fractional crystallization or by chromatography. In the PMR spectrum of this product there was a double set of signals of N-methyl groups of the uracil ring, aromatic protons, and amine residue; on the basis of these data we have concluded that the isomeric compounds IIIb and Vb were formed. A comparison of the chemical shifts of the NH proton (δ 5.94-6.24) and the 5-H proton (δ 8.84-8.85) in compounds Vc, d with the chemical shifts of the analogous protons in the PMR spectrum of the mixture that was obtained – δ 5.58 (1.36 H), 6.32 (3.65 H), 8.84 (3.65 H), and 8.97 (1.39 H) – enabled us to assign the more intense signals to the product of 7-substitution and to calculate the ratio of isomers in the mixture IIIb:Vb = 1:2.6. One of the probable reasons for the absence of the product of nucleophilic substitution at the $C_{(5)}$ atom in all of the other cases is the steric hindrance at this position.

Thus, we have observed for the first time a regioselective nucleophilic replacement of a hydrogen atom in position 2 of condensed pyrimidines.

EXPERIMENTAL

IR spectra were recorded on an IKS-40 instrument, UV spectra on a Specord 40-M spectrometer in methanol solution. PMR spectra were registered on a Bruker WH-90 instrument (internal standard TMS; compounds Va, c-f and VII) and a Unity-300 instrument (compound VIII). The course of the reaction and the individuality of the compounds that were obtained were monitored by TLC on Al_2O_3 (Brockman activity 3-4), chloroform eluent, development by iodine vapor.

Elemental analyses of the synthesized compounds for C, H, and N matched the calculated values.

7-Alkylamino-1,3-dimethylpyrimido[4,5-d]pyrimidine-2,4-(1H,3H)dione (V; general method of preparation). A suspension of 0.2 g (1 mmole) of compound I and 3 ml of the appropriate amine was stirred for 5-10 min at the corresponding temperature (see Table 1). Then 1.3 mmoles of oxidizing agent was added, and the mixture was stirred for 1.5-2 h at the same temperature. The course of the reaction was monitored by TLC on Al_2O_3 (chloroform eluent). Next, the amine was driven off, and the dry residue was extracted with 50 ml of boiling chloroform (in the case of compound Va, 3 × 50 ml). The solvent was driven off, and the residue was recrystallized from ethanol. The yields, reaction conditions, and physico-chemical characteristics of the compounds V are given in Tables 1 and 2.

Methylamide of 4-Methylamino-2-piperidinopyrimidine-5-carboxylic Acid (VII, $C_{12}H_{19}N_5O$). A 0.28-g quantity (1 mmole) of compound Ve was dissolved in a minimum quantity of boiling ethanol and rapidly poured into 100 ml of a 5% NaOH solution. The resulting suspension was refluxed for 3 h and then cooled. The white, fibrous precipitate was filtered off and thoroughly washed with water. This was followed by recrystallization from aqueous ethanol. Yield 100%; white fibers, mp 182-184°C. IR spectrum (in white mineral oil), cm^{-1}: 1630 (C═O), 3322, 3348 (NH). PMR spectrum ($CDCl_3$), δ, ppm: 1.63 (6H, m, piperidino β- and γ-CH_2); 2.90 (3H, d, J_{NH,CH_3} = 4.9 Hz, $\underline{CH_3}$-NH); 2.96 (3H, d, J_{NH,CH_3} = 4.9 Hz, $\underline{CH_3}$-NHCO); 3.79 (4H, m, piperidino α-CH_2); 5.83 (1H, br.s, NH); 8.10 (1H, s, 4-H); 8.44 (1H, br.s, NHCO).

4-Methylamino-2-piperidinopyrimidine (VIII, $C_{10}H_{16}N_4$). A solution of 0.5 g (2 mmoles) of compound VII in 5 ml of 50% H_2SO_4 was boiled for 3 h. After cooling, the solution was neutralized with concentrated NH_4OH, and the oil that separated was extracted with chloroform (3 × 30 ml). The extract was concentrated and passed through a column with Al_2O_3 (chloroform eluent), taking the first colorless fraction. The substance VIII is a cream-colored oil, perchlorate mp 182-184°C. PMR spectrum ($CDCl_3$), δ, ppm: 1.57 (6H, m, piperidino β- and γ-CH_2); 2.86 (3H, d, J = 5.4 Hz, CH_3–N); 3.69 (4H, m, piperidino α-CH_2); 4.65 (1H, br.s, NH); 5.60 (1H, d, J = 5.7 Hz, 5-H); 7.85 (1H, d, J = 5.7 Hz, 6-H).

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