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SYNTHESIS AND REACTIONS OF 2-SUBSTITUTED 1-PHENYL-4-OXO-1,4-DIHYDROPYRIDO-[2,3-*d*]PYRIMIDINES

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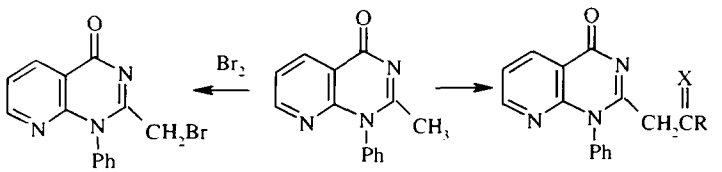
2-Methyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-d]pyrimidine was acylated by succinic and trifluoroacetic anhydrides and also underwent the Claisen reaction with diethyl oxalate and ethyl oxanilate to give acyl derivatives at the methyl group, which, according to UV, IR, and ^{1}H NMR spectra, exist as enaminocarbonyl and iminoenol tautomers with intramolecular hydrogen bonds.

Keywords: 1,4-dihydropyrido[2,3-*d*]pyrimidines, Claisen reaction, enaminocarbonyl-iminoenol tautomers.

It has been shown previously that a methyl group in position 2 of 1-aryl-2-methyl(2,7-dimethyl)-4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidines possesses considerable CH acidity and is able to be acylated comparatively easily [1, 2]. The objective of the present work was to continue the study of analogous reactions to investigate the properties of the compounds obtained. It was found that 2-methyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]-pyrimidine (**1**) was acylated on heating with succinic and trifluoroacetic anhydrides to give 2-(4-carboxy-2-oxobutyl)- (**2a**) and 2-(3,3,3-trifluoroacetonyl)-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidines (**2b**).



3 **1** **2a-e**

2a R = $HOCOCH_2CH_2$; **2b** R = CF_3; **2c** R = C_6H_5NH; **2d** R = CH_3OCO;
2e R = C_6H_5NHCO; **2a,b,d,e** X = O; **2c** X = S

However the reactions of compound **1** with chloroacetyl- and β-bromopropionyl chlorides on heating in benzene in the presence of triethylamine or pyridine, and also with oxalyl chloride under the same conditions with cooling, were unsuccessful. In the last case resinification was observed. Compound **1** underwent condensation with phenylthiourea on boiling in xylene with evolution of ammonia and formation of 2-(N-phenylthiocarbamoylmethyl)- 4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidine (**2c**).

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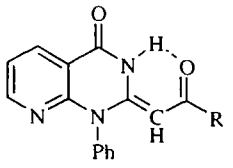
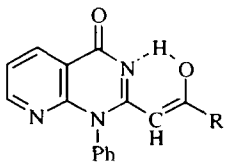
Compound **1** underwent the ester condensation reaction with diethyl oxalate and ethyl oxanilate in the presence of sodium methoxide in methanol to give the corresponding 2-methoxalylmethyl-(**2d**) and 4-oxo-2-(N-phenyloxamoylmethyl)-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidines (**2e**). In the synthesis of **2d** transesterification was observed along with the basic reaction. Compound **1** did not react with N-ethoxalylpiperidine under these conditions.

Bromination of compound **1** gave 2-bromomethyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidine (**2**) in 35% yield. The hydrobromide of the starting material **1** was also isolated from the reaction mixture.

The ^{1}H NMR and IR spectra of compounds **2a-e** (Table 2) confirm their proposed structures. There is no signal for a methyl group in the ^{1}H NMR spectrum of compound **3**, but there is a methylene singlet at 5.93 ppm. Signals for the protons of a CH_2 group at $C_{(2)}$ of pyrimidine are absent from the ^{1}H NMR spectra of compounds **2a-e** but there are signals in the 4.37-5.47 ppm region corresponding to an ethylene proton and in the 10.37-14.00 ppm region for the proton of a chelate ring which shows that these compounds exist in enaminocarbonyl (A) and iminoenol (B) forms with strong intramolecular hydrogen bonds of the chelate type.



A



B

The UV spectra of 2-acetonyl(phenacyl)-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidines, which are similar in structure to compounds **2a-e**, have been studied previously [2]. These spectra have a maximum at 315 nm ascribed to form A and a second maximum at longer wavelength – 317 nm – ascribed to the alternative imino-enol tautomer with a conjugated chain of maximum length. The UV spectrum of compound has only one maximum at 317 nm with a shoulder at 340 nm, which confirms the suggestion that compound **2a** exists predominantly in form A. Its UV spectrum is similar with that of the 2-N-phenylcarbamoylmethyl derivative for which the tautomer of form A is characteristic [2, 3].

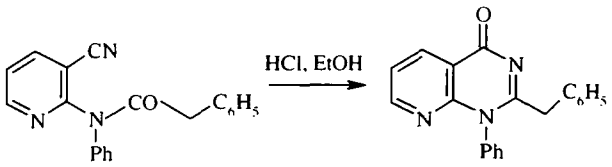
2-Benzyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidine (**5**) was prepared by cyclization of 2-(N-phenylacetylanilino)nicotinonitrile to determine if it existed as the enamine tautomer.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
2a	$C_{18}H_{14}N_4O_4$	63.1 / 64.0	4.6 / 4.4	12.8 / 12.5	215-217	0.65	60
2b	$C_{16}H_{10}F_4N_4O_2$	---	---	13.0 / 12.6	205-207	0.58	45
2c	$C_{21}H_{16}N_4OS$	---	---	15.3 / 15.0	241-243	0.82	68
2d	$C_{17}H_{13}N_3O_4$	62.9 / 63.2	4.2 / 4.0	13.4 / 13.0	257-259	0.73	75
2e	$C_{22}H_{16}N_4O_4$	68.3 / 68.8	4.5 / 4.2	15.0 / 14.6	228-230	0.70	71
3	$C_{14}H_{10}BrN_3O$	---		13.5 / 13.2	190-192		35
4	$C_{20}H_{15}N_3O$	77.0 / 76.7	5.3 / 4.8	13.6 / 13.4	67-69	- -	73
5	$C_{20}H_{14}N_4O$	77.2 / 76.7	5.0 / 4.8	13.5 / 13.4	154-156	0.56	89

TABLE 2. Spectroscopic Characteristics of the Compounds Synthesized

Compound	^{1}H NMR spectra, ppm					IR spectra, ν, cm^{-1}		UV spectra, λ_{max}, nm (log ε)
	CH_2	=CH, s	Ph	Py, m	O···H···N	CO	OH, NH	
2a	2.38	4.37	7.37	8.57	14.00 (s)	1610, 1650, 1720	3360, 3000	313 (4.17), 340 sh, 340 (4.00)
2b		4.79	7.66	8.56	13.50 (br. s)	1640, 1650	3200	—
2c		4.87	7.01	8.43	10.37 (s)	1650, 1680	3190	375 (4.24)
2d	—	5.27	7.25	8.36	13.9 (s)	1680, 1720	—	—
2e		5.43	7.47	8.60	13.97 (s)	1660, 1690	3310	280 (4.44), 365 (4.38)
3	5.93 (s)	—	7.27	8.66	—	1645	—	318 (3.43)
4						1670	2240 (CN)	
5	4.05 (s)		7.50	8.90		1660		309 (3.92)



4 **5**

The ^{1}H NMR spectrum of **5** in $CDCl_3$, recorded over the temperature range from -32 to +40°C, contained signals for protons of the CH_2 group at 4.05 ppm, but no signals for the =CH– and NH groups were observed. Bands for a secondary amino group were absent in the IR spectrum of this compound. The UV spectra of compounds **1**,**3**,**5**, and also of 2-benzyl-7-methyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidine [4], are similar to one another and have a single maximum within the range 306-318 nm. The data cited indicate that the enamine form is not characteristic for compound **5**.

EXPERIMENTAL

IR spectra were recorded with a UR-20 instrument in CCl_4 (C = 0.05 M) for compound **5** and in nujol mulls for other compounds. UV spectra of ethanol solutions ($C = 1 \cdot 10^{-5}$ M) were recorded with SF-16 instrument. ^{1}H NMR spectra of $CDCl_3$ solution (compounds **2b**, **2d**, and **5**) or DMSO-d_6 (all other compounds) were recorded on a PC-60 spectrometer with HMDS as internal standard. TLC was carried out with Silufol UV-254 plates (benzene–butanol, 1:1).

2-(4-Carboxy-2-oxobutyl)-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidine (2a). A mixture of compound **1** (2.37 g, 0.01 mol) and succinic anhydride (6 g, 0.02 mol) was heated at 160°C for 4 h on a metal bath. After cooling, the mixture was treated with $NaHCO_3$ solution, the solution was filtered and neutralized with 10% HCl. The precipitate was separated and recrystallized from ethanol.

4-Oxo-1-phenyl-2-(3,3,3-trifluoroacetonyl)-1,4-dihydropyrido[2,3-*d*]pyrimidine (2b). Trifluoroacetic anhydride (1.23 g, 0.01 mol) was added with cooling to a solution of compound **1** (2.37 g, 0.01 mol) in pyridine (50 ml). The mixture was kept for 1 h and then diluted with water. The substance which separated was filtered off and recrystallized from ethanol.

4-Oxo-1-phenyl-2-(N-phenylthiocarbamoylmethyl)-1,4-dihydropyrido[2,3-*d*]pyrimidine (2c). A solution of compound **1** (2.37 g, 0.01 mol) and phenylthiourea (1.52 g, 0.01 mol) in *p*-xylene was boiled for 8 h. The solvent was steam distilled. The residue was treated with hot water, dried, and recrystallized from a 1:1 butanol–xylene mixture.

2-Methoxalylmethyl- and 4-Oxo-1-phenyl-2-(N-phenyloxamoylmethyl)-1,4-dihydropyrido[2,3-*d*]-pyrimidine (2d,e). A solution of compound **1** (2.37 g, 0.01 mol), diethyl oxalate (or ethyl oxaminate) (0.01 mol), and sodium methoxide (0.54 g, 0.01 mol) in dry methanol (50 ml) was boiled for 2 h, cooled, the precipitate was separated, washed with water, and recrystallized from ethanol (**2d**) or butanol (**2e**).

2-Bromomethyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidine (3). Compound **1** (2.37 g, 0.01 mol) was dissolved in glacial acetic acid (25 ml) and bromine (0.8 g, 0.01 mol) in acetic acid (10 ml) was added. The mixture was kept at 20°C for 1 h. The precipitate of **1** hydrobromide was filtered off. The filtrate was diluted with water and treated with 10% NaOH solution. The precipitate was filtered off and recrystallized from ethanol.

2-Benzyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-*d*]pyrimidine (5). Dry hydrogen chloride was passed through a solution of compound **4** (3.17 g, 0.01 mol) in anhydrous ethanol (70 ml) for 2 h, the mixture was then boiled for 1 h, and cooled. The precipitate was filtered off, treated with sodium acetate solution, and recrystallized from ethanol.

REFERENCES

1. N. I. Shramm and M. E. Kon'shin, *Khim. Geterotsikl. Soedin.*, No. 1, 114 (1985).
2. L. M. Demina, M. Yu. Gavrilov, M. I. Vakhrin, and M. E. Kon'shin, *Khim. Geterotsikl. Soedin.*, No. 10, 1397 (1991).
3. A. B. Deyanov, M. Yu. Gavrilov, and M. E. Kon'shin, *Khim. Geterotsikl. Soedin.*, No. 4, 535 (1992).
4. L. M. Demina, M. Yu. Gavrilov and M. E. Kon'shin, *Izv. Vuzov. Khim. Khim. Tekhnologiya.* **33**, 21 (1990).