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PURINES, PYRIMIDINES, AND CONDENSED SYSTEMS BASED ON THEM. 17*. REACTIONS OF 6,8-DIMETHYL-3-CHLOROPYRIMIDO-[4,5-*c*]PYRIDAZIN-5,7(6H,8H)DIONE WITH C-NUCLEOPHILES

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6,8-Dimethyl-3-chloropyrimido-[4,5-c]pyridazin-5,7(6H,8H)dione reacts with malonodinitrile, cyanoacetic ester, and nitromethane in the presence of bases to give products of nucleophilic substitution of the chlorine atom. The products containing the cyanoacetic ester and nitromethane residues exist exclusively in the chelated methylidene form in $CHCl_3$ and DMSO solutions. Reactions of pyridazinouracil with methylmagnesium chloride and butyllithium gave products of nucleophilic addition at $C_{(4)}$.

Keywords: 6,8-dimethyl-3-chloropyrimido[4,5-*c*]pyridazin-5,7(6H,8H)dione, CH-acids, organometallic compounds, C-nucleophiles, nucleophilic substitution.

Products of nucleophilic substitution of the chlorine atom and the hydrogen atom at position 7 were formed when 1,3-dimethyl-6-chlorolumazine reacted with alkylamines and carbanions of CH-acids [2, 3]. The object of the present work was to study the reactivity of an isomer of 1,3-dimethyl-6-chlorolumazine – pyridazinouracil **1** – relative to C-nucleophiles. Organometallic compounds and some CH-acids (malonic and cyanoacetic esters, malonodinitrile, nitromethane, etc.) were chosen as examples. Sodium methoxide, diethylamine or potassium amide were used to ionize the CH-acids.

We found that when pyridazinouracil **1** was heated with malonodinitrile and cyanoacetic ester in the presence sodium methoxide/methanol the products of nucleophilic substitution of the chlorine atom with the residues of the CH-acids, **2a-c**, were formed exclusively. Under the same conditions no reactions occurred with ethyl malonate and 1,3-dimethylbarbituric acid even on prolonged boiling. The character of the reaction of pyridazinouracil **1** with CH-acids in the presence of diethylamine was no different. Thus when an excess of methyl cyanoacetate, ethyl cyanoacetate, or malonodinitrile was used the salts **3a-c** were formed, from which compounds **2a-c** were obtained by acidification.

No clear dependence between the CH-acidity of the nucleophile [4] and the results of the reaction was observed. Evidently both the possibility of forming the carbanion and its nucleophilicity are important. For example, in the case of malonodinitrile (pK_a 11.2) the yields of compounds **2a** and **3a** were 82 and 43% respectively, whereas for the less acidic cyanoacetic esters ($pK_a \sim 12$) the yield did not exceed 32%. Attempts to

* For Comunication 16, see [1].

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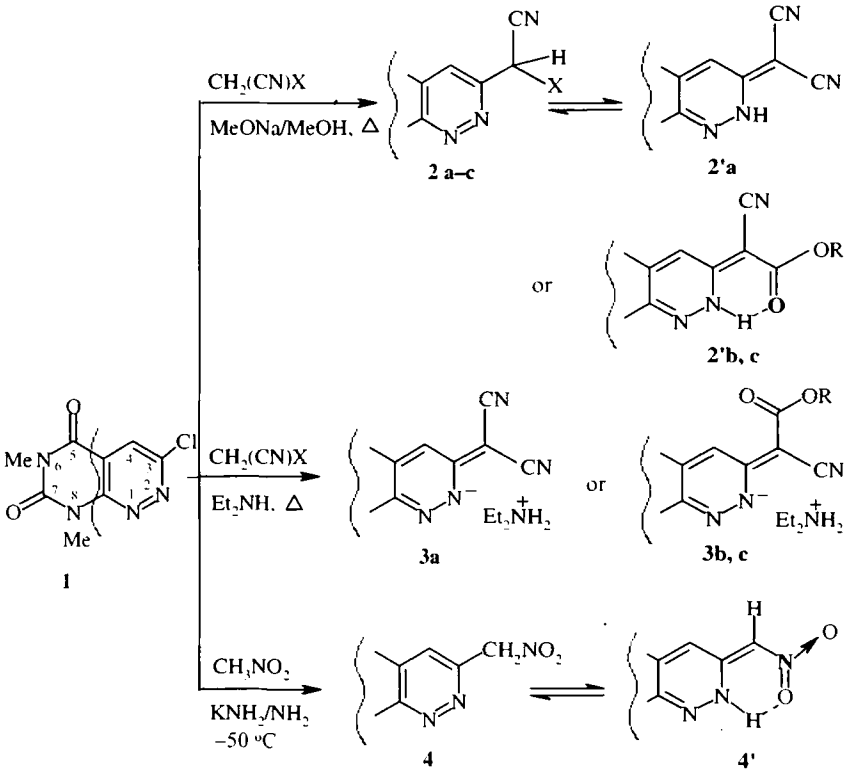
carry out analogous reactions with ethyl acetoacetate, acetylacetone (pK_a 9.0), and nitromethane (pK_a 10.2), which form less nucleophilic anions, were not successful: no reaction occurred at all at room temperature while considerable resinification was observed on prolonged heating. However reaction of the pyridazinouracil **1** with nitromethane is possible in liquid ammonia in the presence of potassium amide to give a 79% yield of the 3-nitromethyl derivative **4**. Some characteristics of the compounds synthesized are given in Tables 1-3.



2, 3a X = CN, **b** X = CO_2Me, **c** X = CO_2Et;
2, 3b R = Me, **c** R = Et

Since methyl–methylidene tautomerism is possible for compounds **2** and **4** we also examined the question as to which of the two tautomeric structures, **2** or **2'**, **4** or **4'**, was preferred.

In the IR spectra of compounds **2** and **4** the C≡N (2150-2200 cm^{-1}) and C=O (1645 cm^{-1}) stretching frequencies are significantly lowered which indicates that they are included in a conjugated chain, which is only possible for the methylidene form **2'**. In the same way in the ^1H NMR spectra of compounds **2** and **4** in DMSO-d_6 the signal for a methyne proton is absent, which corresponds to an aromatic structure. In the cases of compounds **2b**, **2c**, and **4** the chelated forms **2'b,c** and **4** apparently exist as indicated by the weak field shift of the NH proton signal (δ 13-14 ppm).

Methyl–methylidene tautomerism is very sensitive to the solvent [5-7]. Compounds **2a** and **4** are practically insoluble in chloroform, therefore the ^1H NMR spectrum in $CDCl_3$ was successfully obtained only for **2b,c**. However, as in DMSO-d_6, the signal of the methyne proton was absent, but the signal for the 4-H proton was split into a doublet (J = 1.5-2.3 Hz) by spin-spin interaction with the NH proton. Thus compounds **2b** and **2c** exist in the methylidene form in chloroform solution as well. The UV spectra of the synthesized compounds confirm this conclusion (Table 2). Compounds **2-4** are brightly colored, the colors of the chelated compounds **2'b,c** being noticeably deeper than that of the dicyanomethyl derivative **2'a** for which formation of a chelate structure is impossible (the difference in λ_{max} for the long wave absorption bands is 65-100 nm). The values of λ_{max} for compounds **2b,c** in $CHCl_3$ and DMSO solutions are close to the same. In methanol a hypsochromic shift of the

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	^{1}H NMR spectrum, δ, ppm						Yield, %
		C	H	N		DMSO-d_6			$CDCl_3$			
						N-Me	4-H	NH	N-Me	4-H	NH	
2a	$C_{11}H_8N_6O_2$	51.8 / 51.6	3.3 / 3.1	32.7 / 32.8	>300	3.20; 3.51	8.51					82
2b	$C_{12}H_{11}N_5O_4$	49.5 / 49.8	3.7 / 3.8	24.4 / 24.2	260-262	3.28; 3.49	7.96	13.92	3.44; 3.53	8.39 d (J = 2.33 Hz)	14	11
2c	$C_{13}H_{13}N_5O_4$	51.6 / 51.5	4.1 / 4.3	23.3 / 23.1	221-224	3.29; 3.40	7.93	13.92	3.44; 3.52	8.38 d (J = 1.52 Hz)	14.02	15
3a	$C_{15}H_{10}N_4O_2$	54.9 / 54.7	5.8 / 5.8	29.6 / 29.8	232-235	3.26; 3.57	7.23		3.44; 3.62	7.96		43
3b	$C_{16}H_{22}N_6O_4$	53.0 / 53.0	6.2 / 6.1	23.4 / 23.2	240-242	3.25; 3.56	8.54		3.44; 3.56	8.54		32
3c	$C_{17}H_{24}N_6O_4$	54.1 / 54.3	6.2 / 6.4	22.1 / 22.3	202-205	3.28; 3.61	8.77		3.44; 3.59	8.74		19
4	$C_9H_9N_5O_4$	43.3 / 43.0	3.8 / 3.6	27.7 / 27.9	229-230 (dec.)	3.22; 3.36	8.66	13.23				79

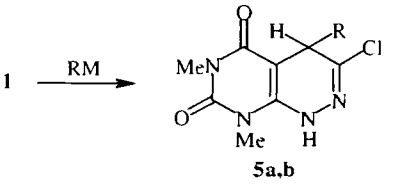
TABLE 2. IR and UV Spectra of the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}			UV spectrum					
	C=O	C≡N	NH	MeOH		$CHCl_3$		DMSO	
				λ_{max}, nm	log ε	λ_{max}, nm	log ε	λ_{max}, nm	log ε
2a	1660, 1730	2180	3300-600	430	3.92			430	5.02
2b	1687, 1731, 1759	2200	3200-3500	495	3.32	540	4.56	530	4.23
2c	1687, 1731, 1759	2200	3350-3400	495	3.54	538	4.69	530	4.30
3a	1685, 1720	2150, 2180	3250-600	530	3.07	570	5.40	550	4.30
3b	1640, 1690, 1725	2160	3200-3600	490	3.43	550	4.60	540	4.26
3c	1645, 1690, 1720	2160	3200-600	500	3.41	550	4.35	540	3.76
4	1694, 1731		3300-3500	418	2.95			430	4.43

absorption maximum by 30-50 nm and a small hypochromic effect were observed. Apparently the protonic solvent facilitates the prototropic transition and the concentration of the methyl form is slightly increased. For compounds **2b,c** and the corresponding salts **3b,c** $\Delta\lambda_{max}$ did not exceed 5-10 nm in any of the solvents, whereas for the dicyanomethyl derivatives **2a** and **3a** transition to the anion was accompanied by a strong bathochromic shift ($\Delta\lambda_{max}$ 100-120 nm).

In the ^{1}H NMR spectrum of the salt **3a** the expected strong field shift of the 4-H signal by ~1.3 ppm in comparison with the unionized molecule **2a** was observed. However in the salts **3b,c** the 4H proton signals was somewhat unexpectedly shifted by 0.7-0.8 ppm to weak field in comparison with the analogous signals in the spectra of compounds **2b,c**. In these cases it is probable that a conformation occurs, reflected in the structures of **3b,c**, in which the 4-H proton is deshielded by the carbonyl group.

The pyridazinouracil **1** reacts rather differently with organometallic compounds. For example, reactions with equimolar amounts of methylmagnesium chloride or butyl-lithium gave the products of nucleophilic addition **5a,b** in 58 and 21% yields respectively.



5a,b

5a R = Me, **b** R = Bu

The ^{1}H NMR spectrum of compound **5a** has a doublet for the 4-CH_3 group (1.34 ppm), a quartet for the methyne proton 4-H (3.84 ppm), and a broad NH signal which disappears on deuteration (8.32 ppm). These results are the first examples of the reaction of azinouracils with organometallic compounds (see [8]).

The reason for the dual reactivity of the pyridazinouracil **1** with respect to C-nucleophiles, as in the case 1,3-dimethyl-6-chlorolumazine, is the insufficient mobility of the chlorine atom which is caused by the electron donor effect of the pyrrole type nitrogen atom at position 8. Under conditions of kinetic control, the nucleophile attacks the more electron deficient [1] atom $C_{(4)}$, whereas on heating the thermodynamically more stable products of nucleophilic substitution of the atom $Cl_{(3)}$ are formed. It is also probable that position 4 in molecule **1** is partially shielded by the carbonyl group $C_{(5)}$=O, so that the more bulky CH-acids react with difficulty with the pyridazinouracil **1** at room temperature.

EXPERIMENTAL

IR spectra of nujol mulls were recorded with UR-20 and Specord IR-71 spectrometers. ^{1}H NMR spectra were recorded with a Bruker-250 spectrometer. Melting points were measured with a PTP apparatus in sealed capillaries. Progress of reactions and purity of compounds synthesized were monitored by TLC on Brockman Al_2O_3 (activity 3-4) with chloroform as eluent and detection with iodine vapor.

6,8-Dimethyl-3-chloropyrimido[4,5-*c*]pyridazin-5,7(6H,8H)-dione **1** starting material was prepared by a known method [9].

(2,3,5,6,7,8-Hexahydro-5,7-dioxo-6,8-dimethylpyrimido[4,5-*c*]pyridazin-3-yliden)malonodinitrile (2a). **A.** Malonodinitrile (132 mg, 1.67 mmol) was added with stirring to a solution of sodium (46 mg, 2 mmol) in methanol (2 ml). After 3 min the pyridazinouracil **1** (227 mg, 1 mmol) was added. The reaction mixture was heated to boiling, the solution became dark red and the starting material dissolved. After 5-7 min a yellow precipitate appeared. The mixture was cooled, the residue was filtered off, washed with alcohol and ether, and recrystallized from water. Yield 210 mg (82%).

B. Compound **2a** was obtained by acidification of salt **3a** with dilute HCl.

Methyl (2,3,5,6,7,8-Hexahydro-6,8-dimethyl-5,7-dioxopyrimido[4,5-*c*]pyridazin-3-ylidene)cyanoacetate (2b). A. The reaction was carried out analogously to the preceding experiment, using methyl cyanoacetate as the CH-acid. The mixture was boiled for 20 min (much tar!). It was cooled for a day in a refrigerator. The residue was filtered off, acidified with conc. HCl (3 drops), and evaporated to dryness. The residue was treated with water (4-5 ml), the clear red precipitate was filtered off and recrystallized from dilute acetic acid (1:1). Yield 32 mg (11%).

B. Compound **2b** was obtained by acidification of salt **3b** with dilute HCl.

Ethyl (2,3,5,6,7,8-Hexahydro-6,8-dimethyl-5,7-dioxopyrimido[4,5-*c*]pyridazin-3-ylidene)cyanoacetate (2c). A. Compound **2c** was obtained analogously to compound **2b** from pyridazinouracil **1** and ethyl cyanoacetate.

B. Compound **2c** was obtained by acidification of salt **3c** with dilute HCl.

Diethylammonium Salt of (2,3,5,6,7,8-Hexahydro-6,8-dimethyl-5,7-dioxopyrimido[4,5-*c*]pyridazin-3-yliden)malonodinitrile (3a). Pyridazinouracil **1** (227 mg, 1 mmol) was added to a solution of malonodinitrile (165 mg, 2.5 mmol) in diethylamine (5 ml). The solution turned red. The reaction mixture was boiled for 5 min. A red precipitate deposited. After cooling, the reaction product was filtered off, washed with ethanol and ether, and recrystallized from isopropanol. Yield 140 mg (43%).

Diethylammonium Salt of Methyl (2,3,5,6,7,8-Hexahydro-6,8-dimethyl-5,7-dioxopyrimido[4,5-*c*]-pyridazin-3-ylidene)cyanoacetate (3b) was obtained analogously to compound **3a** using methyl cyanoacetate (0.25 ml, 2.5 mmol) as the CH-acid. The reaction mixture was boiled for 3 h, then left overnight. The red precipitate was filtered off, washed with ethanol and ether, and recrystallized from isopropanol. Yield 113 mg (32%).

Diethylammonium Salt of Ethyl (2,3,5,6,7,8-Hexahydro-6,8-dimethyl-5,7-dioxopyrimido[4,5-*c*]-pyridazin-3-ylidene)cyanoacetate (3c) was obtained analogously to compound **3a** using ethyl cyanoacetate (0.25 ml, 2.5 mmol) as the CH-acid. The reaction mixture was boiled for 3 h, then left overnight. The red precipitate was filtered off, washed with ethanol and ether, and recrystallized from isopropanol. Yield 73 mg (19%).

(2,3,5,6,7,8-Hexahydro-6,8-dimethyl-5,7-dioxopyrimido[4,5-*c*]pyridazin-3-ylidene)nitromethane (4). Nitromethane (0.8 ml, 1.5 mmol) was added to a solution of potassium (60 mg, 1.5 mmol) in liquid ammonia at -50 to -40°C. After 10 min pyridazinouracil **1** (100 mg, 0.44 mmol) was added. The reaction mixture was stirred at this temperature for 1 h during which it developed an orange color. Cooling was ceased and the ammonia evaporated freely. The dry residue was extracted with chloroform (15 ml) (to remove unreacted starting material – 20 mg was recovered). The product which did not dissolve in chloroform was treated with acetic acid (10 ml). The deep orange solution was evaporated to dryness, treated with water (7 ml), and filtered. The mustard yellow residue was washed with water, alcohol, and ether. Yield 70 mg (79%).

3-Chloro-4,6,8-trimethyl-1,4-dihydropyrimido[4,5-*c*]pyridazin-5,7(6H,8H)-dione (5a). The reaction was carried out under nitrogen. A 3 M solution of methylmagnesium chloride in hexane (0.6 ml, 2 mmol) was added dropwise to a stirred solution compound **1** (227 mg, 1 mmol) in diethyl ether (50 ml). After 30 min ether was evaporated under reduced pressure. The solution was neutralized with saturated NH_4Cl solution and extracted with chloroform (3 × 15 ml). The extracts were concentrated and passed through an Al_2O_3 column (eluent chloroform). The fraction with R_f 0.2 was collected to give compound **5a** (145 mg, 58%) as a colorless oil. IR spectrum: 1600, 1620 (ring), 1690, 1715 (C=O), 2800-3400 cm^{-1} (ac. NH). ^1H NMR spectrum ($CDCl_3$): 1.35 (3H, d, J = 6.83 Hz, C–Me); 3.45 (3H, s, 8-Me); 3.45 (3H, s, 6-Me); 3.83 (1H, q, J = 6.83 Hz, 4-H); 8.32 ppm (1H, br.s, disappeared after deuteration, NH).

4-Butyl-3-chloro-6,8-dimethyl-1,4-dihydropyrimido[4,5-*c*]pyridazin-5,7(6H,8H)-dione (5b). The reaction was carried out in an inert atmosphere (a stream of nitrogen). The reaction was cooled with a mixture of liquid nitrogen and isobutanol. A 1.6 M solution of butyllithium in hexane (1.4 ml, 2.1 mmol) was added with stirring to a solution of compound **1** (400 mg, 1.76 mmol) in a 4:4:1 mixture of diethyl ether, THF, and hexane (70 ml), cooled to -100°C. The mixture was stirred for 4 h at this temperature, the cooling bath was then removed, and the reaction mixture warmed to room temperature. The reaction mixture was treated with saturated aqueous solution of NH_4Cl to pH 7-8. The organic layer was separated, evaporated, and passed through an Al_2O_3 column (eluent chloroform). The fraction with R_f 0.15 was collected to give compound **5b** (60 mg, 21%) as a colorless oil. IR spectrum: 1605, 1620 (ring), 1695, 1720 (C=O), 2800-3400 cm^{-1} (ac. NH). ^1H NMR spectrum ($CDCl_3$): 0.83 (3H, t, J = 7.05 Hz, $CH_2CH_2CH_2\underline{Me}$); 1.24 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}Me$); 1.7 (2H, m, $\underline{CH_2}CH_2CH_2Me$); 3.29 (3H, s, 8-Me); 3.44 (3H, s, 6-Me); 3.88 (1H, t, J = 4.72 Hz, 4-H); 8.98 ppm (1H, br. s, disappeared on deuteration, NH).

REFERENCES

1. A. V. Gulevskaya, D. V. Besedin, and A. F. Pozharskii, *Izv. Akad. Nauk , Ser. Khim.*, 1161 (1999).
2. A. V. Gulevskaya, A. F. Pozharskii, A. I. Chernyshev, and V. V. Kuz'menko, *Khim. Geterotsikl. Soedin.*, No. 9, 1202 (1992).
3. A. V. Gulevskaya and A. F. Pozharskii, *Zh. Org. Khim.*, **32**, 455 (1996).
4. I. I. Beletskaya, *Chemistry of Carbanions* [in Russian], Znanie, Moscow (1978), p.64.
5. L. H. Klemm, D. R. Muchiri, and J. N. Louris, *J. Heterocycl. Chem.*, **21**, 1135 (1984).
6. L. H. Klemm, D. R. Muchiri, M. Anderson, W. Salbador and J. Ford, *J. Heterocycl. Chem.*, **31**, 261 (1994).
7. H. Gunter, *Introductory Course in NMR Spectroscopy* [Russian translation], Mir, Moscow (1984), p. 393.
8. A. V. Gulevskaya and A. F. Pozharskii, *Targets in Heterocyclic Systems. Chemistry and Properties.* **2**, 101 (1998).
9. S. Nishigaki, M. Ichiba, and K. Senga, *J. Org. Chem.*, **48**, 1628 (1983).