PYRIDO[2,3-d]PYRIMIDINES. 7.* REACTIONS OF 1,3-DIMETHYL-5,7-DICHLORO-6-NITROPYRIDO-[2,3-d]PYRIMIDINE-2,4-DIONE WITH AMINES. SYNTHESIS OF DERIVATIVES OF TRIAZOLO-(4′,5′:4,5)PYRIDO[2,3-d]PYRIMIDINE

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The reaction of 5,7-dichloro-6-nitropyrido[2,3-d]-pyrimidine-2,4-dione with amines gave products of the substitution of one or two chlorine atoms by amino groups. The catalytic reduction of 6-nitro-5,7-disubstituted pyrido[2,3-d]pyrimidines with hydrogen over palladium oxide on carbon leads to 5,6-diamino- and 5,6,7-triaminopyridopyrimidines, the reaction of which with amyl nitrite in acetic acid gives triazolo-(4′,5′:4,5)pyrido[2,3-d]pyrimidines.

The aminopyrido[2,3-d]pyrimidines possess a significant diuretic and antibacterial activity [2, 3]. During work [4, 5] on the synthesis of amino derivatives of pyrido[2,3-d]pyrimidines and the investigation of their reactivity, undertaken to search for biologically active substances, we have investigated the reaction of 5,7-dichloro-6-nitropyrido[2,3-d]pyrimidine-2,4-dione I [1] with amines (butylamine, 1-ethyl-2-aminomethylpyrorolidine), which leads to the substitution of the chlorine atom in position 5. The structure of compounds IIa, b as 5-amino and not as 7-amino derivatives was proven on the example of the pyridopyrimidine IIa by comparing it with the isomeric 1,3-dimethyl-5-chloro-6-nitro-7-butyl-aminopyrido[2,3-d]pyrimidine-2,4-dione III [5].

The compounds IIa and III have the same elemental composition, but differ in their physicochemical and spectral characteristics. The PMR spectrum of compound IIa contains a signal of the proton of the 5-NH group at 10.14 ppm, while the spectrum of compound III contains a signal of the proton of the 7-NH group at 6.75 ppm. The signals disappear in deuteration. The IR spectrum of compound IIa shows a moderate band of NH vibrations at C(5) at 3130 cm^{-1}, while the IR spectrum of compound III contains a strong band of the NH group at C(7) at 3385 cm^{-1}.

The reaction of compound I with an excess of 25% aqueous methylamine or with butylamine gives products of the complete substitution of the chlorine atoms IVa, b. The PMR spectrum of compound IVb contains signals of the protons of NH at C(7) in the region of 8.40 ppm and of NH at C(5) at 10.56 ppm.

The treatment of compound IIa with N-methylpiperazine and acetylhydrazine leads to the derivatives Va, b. The conditions of the synthesis and the physicochemical characteristics of the products, II, IV, V, and VII are presented in Table.

The catalytic reduction of the nitro group of compounds IIa and VI (described in [1]) by hydrogen over palladium oxide on carbon leads to the 5,6-diamino derivatives VIIa, b. Compound VIIa was obtained as the hydrochloride. The 5,6,7-triaminopyridopyrimidines VIIc, d were obtained from compounds Va and IVb in the same way.

As expected, the PMR spectra of compounds VIIa-d show a shift of the signals of the 5-NH and 7-NH protons to the stronger field by 2.0-2.5 ppm in comparison with the chemical shifts of the corresponding signals of the NH protons of the initial 6-nitro derivatives. Thus, for compound VIId the signals of the protons of the NH groups at C(5) and C(7) appear in the region of 8.20 and 5.75 ppm, respectively.

*For communication 6 see [1].

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TABLE 1. Synthesis and Physicochemical Characteristics of Compounds IIa, b, IVa, b, Va, b, and VIIa-d

Compound	Empirical formula	Reaction conditions			mp, °C**	Yield %
		reagent	solvent*	t, h		
IIa	$C_{13}H_{16}N_5O_4Cl$	Butylamine	A	4	132...134	89
IIb	$C_{16}H_{21}N_6O_4Cl \cdot HCl$	1-Ethyl-2-aminomethylpyrrolidine	A	2	220...222	79
IVa	$C_{11}H_{12}N_6O_4$	25% Methylamine	A	4	274...276	79
IVb	$C_{17}H_{26}N_6O_4$	Butylamine	A	7	92...93	81
Va	$C_{18}H_{27}N_7O_4$	N-Methylpiperazine	B	1	107...108	63
Vb	$C_{15}H_{21}N_7O_5$	Acetylhydrazine	C	2	168...169,5	90
VIIa	$C_{13}H_{19}N_5O_2 \cdot HCl$	H_2, 5% PdO/C	D	1	192...194	65,5
VIIb	$C_{13}H_{19}N_5O_3$	» »	D	1	179...181	70
VIIc	$C_{18}H_{29}N_7O_2$	» »	D	2	143...154	97
VIId	$C_{17}H_{28}N_6O_2$	» »	D	1	119...120	73

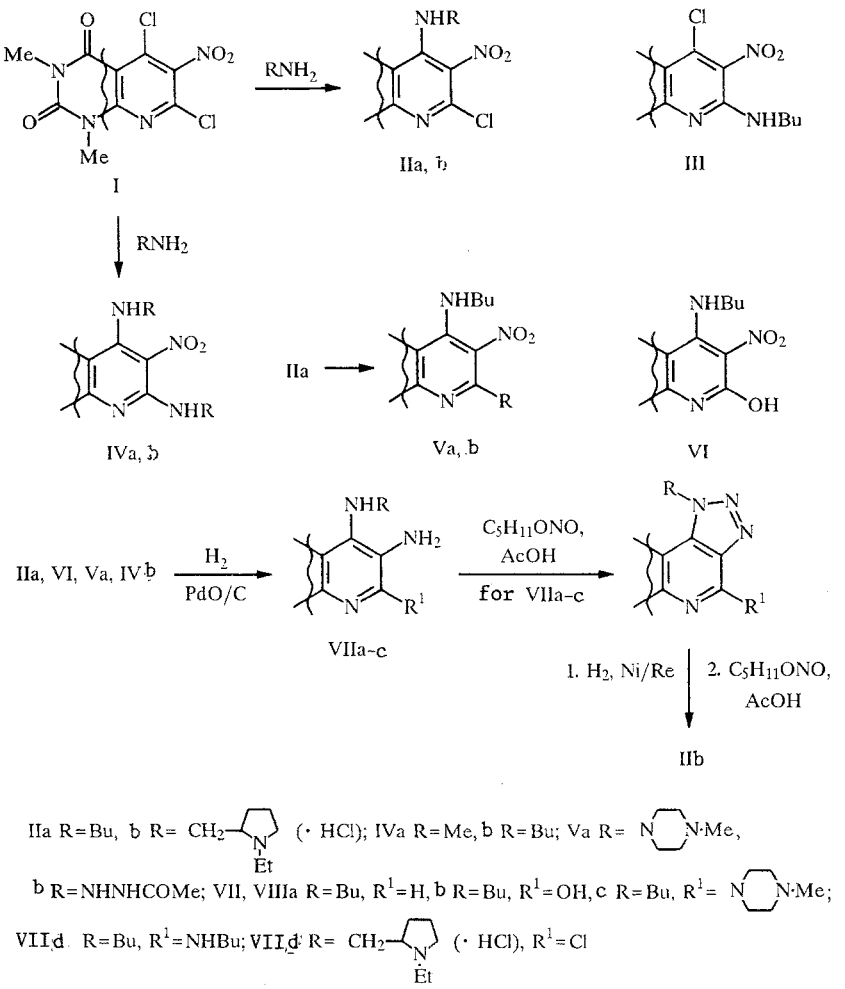
*A chloroform; B ethanol; C DMF; D methanol.

**Compounds IIa, b, IVb, and VIIa, b crystallize from ethanol, Vb from methanol, IVa from AcOH, Va from ether.

TABLE 2. IR and PMR Spectra of Compounds IIa, b, IVa, b, Va, b, d, VIIa-d, and VIIIa-d

Compound	IR spectra (KBr), cm^{-1}	PMR spectrum, δ, ppm (SSCC, J, Hz, in $CDCl_3$)
IIa	1655, 1720, 3130	0,93 (3H, t, J = 6); 1,2...1,8 (4H, m), 3,08 (2H, m); 3,40 (3H, s); 3,69 (3H, s); 10,14 (1H, br.s)
IIb (·HCl)	1660, 1713, 3107	1,38 (3H, t, J = 8); 1,9...2,4 (4H, m); 2,9 (2H, q, J = 8); 3,34 (3H, s); 3,55 (3H, s); 3,65...4,0 (5H, m); 10,55 (1H, t, J = 8)
IVa	1347, 1540, 1653, 1708, 3140, 3400	2,80 (3H, d, J = 5); 3,08 (3H, d, J = 5); 3,35 (3H, s); 3,56 (3H, s)
IVb	1327, 1556, 1638, 1700, 3120, 3353	0,8...1,1 (6H, m); 1,2...2,0 (8H, m); 2,8...3,1 (2H, m); 3,39 (3H, s); 3,60 (3H, s); 3,6...4,0 (2H, m); 8,38 (1H, br.s); 10,57 (1H, br.s)
Va	1353, 1520, 1653, 1700, 3160	0,86 (3H, t, J = 6); 1,2...1,8 (4H, m); 2,3 (3H, s); 2,40...2,75 (8H, m); 3,05...3,30 (2H, m); 3,32 (3H, s); 3,49 (3H, s); 10,6 (1H, br.s)
Vb	1373, 1513, 1642, 1702, 3140, 3327	0,82 (3H, t, J = 6); 1,1...1,8 (4H, m); 2,07 (3H, s); 2,8...3,0 (2H, m); 3,33 (3H, s); 3,47 (3H, s); 8,13 (1H, br.s); 9,73 (1H, br.s); 10,5 (1H, br.s)
VIIa* (·HCl)	1667, 1727, 3120, 3220, 3313	0,9 (3H, t, J = 6); 1,2...1,7 (4H, m); 3,20 (3H, s); 3,42 (3H, s); 3,65...3,95 (2H, m); 8,32 (1H, s)
VIIb*	1667, 1704, 3300, 3414	0,86 (3H, t, J = 6); 1,1...1,7 (4H, m); 3,20 (3H, s); 3,42 (3H, s); 3,53 (2H, m); 4,50 (2H, br.s); 8,50 (1H, br.s)
VIIc	1653, 1680, 3287, 3304, 3400	0,85 (3H, t, J = 6); 1,20...1,65 (4H, m); 2,32 (3H, s); 2,43...2,70 (8H, m); 3,12...3,35 (2H, m); 3,35 (3H, s); 3,53 (3H, s); 8,13 (1H, br.s)
VIId	1660, 1673, 3245, 3347, 3380, 3420	0,9 (6H, t, J = 6); 1,1...1,8 (8H, m); 2,3...2,7 (2H, m); 3,1...3,6 (2H, m); 3,36 (3H, s); 3,55 (3H, s); 5,72 (1H, br.s); 8,20 (1H, br.s)
VIIIa	1667, 1713	0,91 (3H, t, J = 7); 1,14...1,50 (2H, m); 1,7...2,0 (2H, m); 3,51 (3H, s); 3,82 (3H, s); 5,31 (2H, t, J = 7); 9,34 (1H, s)
VIIIb*	1680, 1700, 3567	0,84 (3H, t, J = 6); 1,10...1,35 (2H, m); 1,5...1,9 (2H, m); 3,22 (3H, s); 3,49 (3H, s); 5,04 (2H, t, J = 6)
VIIIc	1667, 1708	0,85 (3H, t, J = 6); 1,0...1,4 (2H, m); 1,6...1,9 (2H, m); 2,37 (3H, s); 2,45...2,75 (8H, m); 3,40 (3H, s); 3,62 (3H, s); 5,24 (2H, t, J = 6)
Vd	1667, 1720	0,6...1,2 (5H, m); 1,9...2,5 (4H, m); 1,43 (3H, t, J = 6); 3,05 (2H, q, J = 6); 3,43 (3H, s); 3,76 (3H, s)

*The PMR spectra were recorded in DMSO-D_6.



IIa R=Bu, b R= CH_2-(N-Et) (· HCl); IVa R=Me, b R=Bu; Va R= N(N-Me),

b R=NHNHCOMe; VII, VIIIa R=Bu, R^1=H, b R=Bu, R^1=OH, c R=Bu, R^1= N(N-Me);

VIId R=Bu, R^1=NHBu; VIIe R= CH_2-(N-Et) (· HCl), R^1=Cl

The reaction of compounds VIIa-c with amyl nitrite in acetic acid leads to triazolo(4′,5′:4,5)pyrido[2,3-d]pyrimidines VIIIa-c with yields of 70-97%. The catalytic reduction of compound IIb with hydrogen over Raney nickel, followed by the treatment of the 6-amino derivative formed without separating it from the reaction mixture with amyl nitrite leads to the triazolopyridopyrimidine VIIId as the hydrochloride.

The IR, PMR, and mass-spectrometric data of compounds VIIIa-d are in agreement with their structures. Thus the IR spectrum of the substance VIIIb contains an OH band at 3567 cm^{-1}. The PMR spectrum of compound VIIIa contains a signal from the proton at C(4) with 9.34 ppm, which is missing for the 4-substituted VIIIb-d. In the mass spectra of compounds VIIIB, c the peaks of the molecular ions $M^{+\cdot}$ 304 and 386 correspond to the calculated values.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer, using KBr tablets. The mass spectra were obtained on a Varian MAT-311A spectrometer with direct injection of the sample into the ion source. The PMR spectra were recorded on a Tesla BS-497 spectrometer (100 MHz) with HMDS as the internal standard. The progress of the reactions was followed by TLC on Silufol UV-254 plates. The elemental analysis data for C, H, Cl, and N corresponded to the calculated values.

General Procedure for the Preparation of Compounds IIA, b, IVa, b, and Va, b (Table 1). A solution (suspension) of 10 mmole of compound I or IIa in 30 ml chloroform (ethanol, DMF) is treated with a nucleophilic reagent; the reaction mass is brought to boiling (to 80°C when using DMF) and kept for 1-7 h. The molar ratio of the reagent and the starting substance is 1.5 for the synthesis of compounds IIa, b; 8 for IVa; 3.5 for IVb and Va, and 2.0 for Vb. The solvent is then stripped in vacuum to dryness (in the isolation of compound IIa half of the solvent is removed). The residue is treated with 10-20 ml ether, cooled to 0-5°C, and stirred for 1 h; the precipitate formed is filtered off and recrystallized.

General Procedure for the Preparation of Compounds VIIa-d. A suspension of 1.5 mmole of compound IIa (or

VI, Va, IVb) in 50 ml methanol is hydrogenated over 0.5 g of 5% PdO/C for 1 h. The catalyst is filtered off, the solvent is removed under vacuum, and the residue ground with ether (see Table 1).

1-Butyl-5,6-dimethyl-6,7,8,9-tetrahydrotriazolo-(4′,5′:4,5)pyrido[2,3-d]pyrimidine-7,9-dione (VIIIa, $C_{13}H_{16}N_6O_2$). A solution of 0.5 g (1.6 mmole) of compound VIIa in 4 ml AcOH is treated with 0.5 ml (5 mnmole) amyl nitrite. The reaction mixture is stirred for 0.5 h and diluted with 10 ml water; 0.39 g (85%) of compound VIIIa is filtered off, mp 139-141°C (from ether).

1-Butyl-4-hydoxy-6,8-dimethyl-6,7,8,9-tetrahydrotriazolo(4′,5′:4,5)pyrido[2,3-d]pyrimidine-7,9-dione (VIIIb, $C_{13}H_{16}N_6O_3$) is obtained in the same way as VIIIa from compound VIIb with a yield of 70%, mp 226-228°C (from acetone); **1-butyl-4-N-(1-methylpiperazinyl-4)-6,8-dimethyl-6,7,8,9-tetrahydrotriazolo(4′,5′:4,5)pyrido[2,3-d]pyrimidine-7,9,dione (VIIIc, $C_{18}H_{26}N_8O_2$)** is obtained from VIIc with a yield of 97%, mp 200-202°C (from ether).

1-[1′-Ethyl-2-pyrrolidinyl]methyl-4-chloro-6,8-dimethyl-6,7,8,9-tetrahydrotriazolo(4′,5′:4,5)pyrido[2,3-d]-pyrimidine-7,9-dione (VIIId, $C_{16}H_{20}N_7O_2Cl \cdot HCl$). A suspension of 1.8 g (4.2 mmole) of compound IIb in 100 ml methanol is treated with 1 g Raney nickel and reduced with hydrogen for 2 h. The catalyst is filtered off and the methanol stripped off in vacuum; the residue is treated with 5 ml AcOH and 1 ml (10 mmole) amyl nitrite, stirred for 0.5 h, diluted with 30 ml water, neutralized with ammonia to pH 7, and extracted with chloroform (5 × 5 ml). After drying of the extract over $CaCl_2$ and stripping of the solvent the residue is ground in ether. The yield is 0.6 g (35%) of compound VIIId with respect to IIb, mp 205°C (decomposes, from a chloroform–ether mixture).

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