3-Oxo-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid Anilide (VIIb). A mixture of 2.78 g (10 mmole) of anilide IIc, 0.72 g (12 mmole) of urea, and 30 ml of ethylene glycol was refluxed, after which it was cooled, and the resulting precipitate was recrystallized.

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PYRIDO[2,3-d]PYRIMIDINES

3.* SYNTHESIS AND PROPERTIES OF 7-CHLORO- AND 6-NITRO-7-CHLOROPYRIDO[2,3-d]PYRIMIDINE-2,4,5-TRIONES

O. A. Burova, I. D. Bystryakova, N. M. Smirnova, and T. S. Safonova

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7-Chloropyridopyrimidine was obtained by diazotization of 1,3-dimethyl-7-amino-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione in HCl, and its nitration and reactions with nucleophilic reagents were studied. An imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine derivative was synthesized.

Pyrido[2,3-d]pyrimidine derivatives have a broad spectrum of biological properties, including the manifestation of anticancer [2], diuretic [3], and antifolic [4] activity.

The aim of the present research was to develop methods for obtaining 7-chloro- and 6-nitro-7-chloropyrido[2,3-d]pyrimidine-2,4,5-triones, investigate their reactions with nucleophilic agents, and study their biological activity.

The reaction of 1,3-dimethyl-7-amino-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione (I) with sodium nitrite in 35% HCl at 0-5°C leads to 7-chloropyridopyrimidine II. Compound II is nitrated by a blend in concentrated H_2SO_4 at 80°C to give 6-nitro derivative III.

7-Chloropyridopyrimidines II and III react with nucleophilic agents such as amines, sodium azide, and sodium butoxide to give the corresponding 7-substituted pyrido[2,3-d]pyrimidines IV and V (Table 1).

Refluxing II and III in dry DMF leads to 7-dimethylamino derivatives IVb and Vd (see [5, 6]).

Absorption bands of an NH group attached to the $C_{(7)}$ atom (3300-3375 cm^{-1}) and of an 8-NH group at 3100 cm^{-1} are present in the IR spectra of IVa and Va-c. Signals of an NH proton attached to the $C_{(7)}$ atom at 8.45-9.11 ppm and of an 8-NH proton at 10.5-12.5 ppm are present in the PMR spectra (Table 2).

Refluxing 6-nitro-7-butylamino derivative Vb with thionyl chloride in the presence of a catalytic amount of DMF gave 5-chloro derivative VI, the IR spectrum of which contains bands of stretching vibrations of the carbonyl groups of a pyrimidine ring at 1667 and 1702 cm^{-1} and of an NH bond at 3385 cm^{-1}; a signal of an NH proton attached to the $C_{(7)}$ atom is observed in the PMR spectrum at 6.75 ppm, while a signal of a proton attached to the $N_{(8)}$ atom at 10-15 ppm is absent.

The reaction of Vc with $SOCl_2$ at 20°C leads to 7-(2-chloroethyl)aminopyridopyrimidine Ve (26%) and derivative VII (59%). Derivative VII was obtained in quantitative yield when Vc was refluxed with thionyl chloride in chloroform or when it was heated at 140°C with polyphosphoric acid. Signals of labile protons of the NH group attached to the $C_{(7)}$ atom at 9.06 ppm and of the 8-NH group at 14.43 ppm are observed in the PMR spectrum of Ve. The band of $N_{(8)}$—H vibrations at 3100 cm^{-1} is absent in the IR spectrum of VII, and an intense band at 3333 cm^{-1}, which is characteristic for $C_{(7)}$—NH vibrations, is observed.

*See [1] for Communication 2.

Novokuznetsk Scientific-Research Institute of Pharmaceutical Chemistry, Novokuznetsk 654034.

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TABLE 1. Synthesis and Physicochemical Properties of IVa-e and Va-d

Compound	Empirical formula	Reaction conditions				mp,** °C	m/z (I/I_{max}, %)	Yield, %
		reagent	t, h	T, °C	solvent*			
IV a	$C_9H_{11}N_5O_3$	$NH_2NH_2 \cdot H_2O$	1	100	B	276...277,5	M+ 337 (100), 238 (32), 207 (17), 163 (18), 150 (14), 122 (9), 80 (20), 68 (20), 58 (12), 42 (9)	85
IV b	$C_{11}H_{14}N_4O_3$	DMF	1	100	A	208...209	M+· 250 (100)	97
IV c	$C_{13}H_{17}N_3O_4$	C_4H_9ONa	3	120	B	126...129	M+· 279 (34), 236 (30), 224 (30), 223 (100), 195 (39), 138 (20), 111 (21), 82 (26), 69 (18), 40 (21)	61
IV d	$C_9H_8N_6O_3$	NaN_3	1	115	C	154 (dec.)	M+· 248 (100)	80
IV e	$C_{14}H_{19}N_5O_3$	—***	1	110	B	200	M+· 305 (18), 236 (14), 235 (100), 82 (11), 71 (10), 70 (29), 58 (10), 56 (12), 43 (34), 42 (34)	95
V a	$C_{10}H_{11}N_5O_5$	25% CH_3NH_2	1	70	A	272...274	—	96
V b	$C_{13}H_{17}N_5O_5$	$C_4H_9NH_2$	1	80...90	A	172...174	[M+1] 324 (54)	76
V c	$C_{11}H_{13}N_5O_6$	$H_2NCH_2CH_2OH$	1	90...100	B	211...213	M+· 311 (36), 281 (17), 280 (100), 267 (16), 264 (21), 252 (28), 234 (17), 222 (60), 207 (23), 82 (17)	92
V d	$C_{11}H_{13}N_5O_5$	DMF	0,5	100	A	212...214	M+· 295 (100)	92

*Symbols: A) DMF, B) N-ethylpyrrolidone, C) DMSO.

**The compounds were crystallized: IVa and Va,c from DMF, IVb,c and Vb from acetone, IVe from alcohol, Vd from AcOH, and IVd from DMSO.

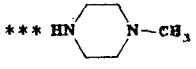
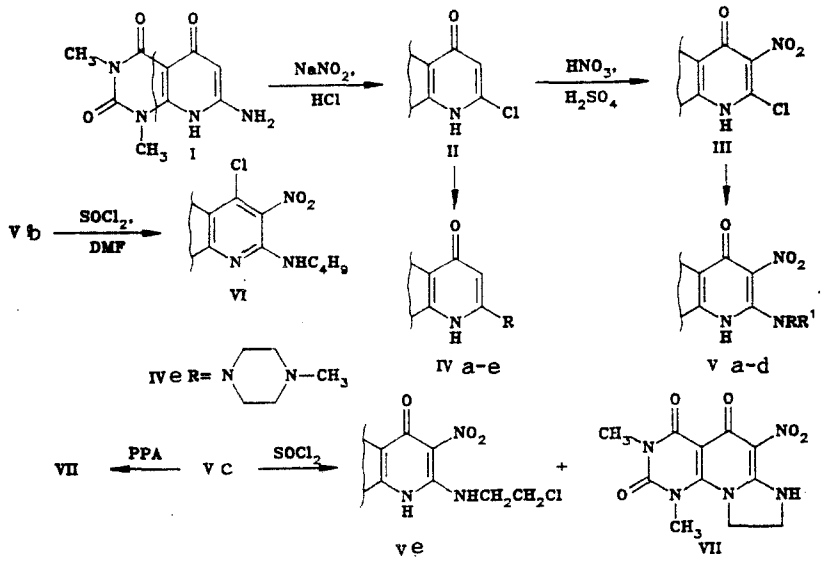
*** 

TABLE 2. IR and PMR Spectra of II-VII

Compound	IR spectrum, ν, cm^{-1}	3 PMR spectrum (in $CDCl_3$).* δ, ppm (SSCC, J, Hz)
II	1673, 1705 (CO); 3117 (NH)	3,40 (3H, s); 3,61 (3H, s); 6,62 (1H, s); 12,30 (1H, s)
III	1671, 1729 (CO); 1360, 1540 (NO_2)	3,41 (3H, s); 3,62 (3H, s); 13,10 (1H, s)
IV a	1673, 1693 (CO); 3413, 3360 (NH_2); 3100 (NH)	3,18 (3H, s); 3,39 (3H, s); 4,38 (2H, br.s); 5,87 (1H, s); 8,45 (1H, s)
IV b	1660, 1671, 1700 (CO)	3,10 (6H, s); 3,34 (3H, s); 3,50 (3H, s); 5,63 (1H, s); 11,86 (1H, s)
IV c	1673, 1709 (CO); 3100 (NH)	0,94 (3H, t, J=7); 1,20...1,90 (4H, m); 3,37 (3H, s); 3,55 (3H, s); 4,28 (2H, t, J=7); 5,84 (1H, s); 11,89 (1H, s)
IV d	3100 (NH); 2147 (N_3)	3,39 (3H, s); 3,60 (3H, s); 6,03 (1H, s); 12,23 (1H, s)
IV e	1653, 1667, 1693 (CO)	2,26 (3H, s); 2,40 (4H, t, J=5); 3,31 (3H, s); 3,48 (3H, s); 3,60 (4H, t, J=5); 5,74 (1H, s); 11,82 (1H, s)
V a	1653, 1667, 1711 (CO); 3367 (NH); 1347, 1527 (NO_2)	3,07 (3H, d, J=5); 3,24 (3H, s); 3,48 (3H, s); 8,83 (1H, br.. s); 12,34 (1H, s)
V b	1667, 1740 (CO); 3387 (NH); 1335, 1540 (NO_2)	0,83 (3H, t, J=6); 1,00...1,80 (4H, m); 2,85... 3,50 (2H, m); 3,10 (3H, s); 3,40 (3H, s); 8,93 (1H, t, J=6); 12,20 (1H, s)
V c	1653, 1667, 1700 (CO); 3360 (NH); 3440 (OH)	3,13 (3H, s); 3,34 (3H, s); 3,78 (4H, m)
V d	1660, 1673, 1712 (CO); 1343, 1527 (NO_2)	3,10 (6H, s); 3,36 (3H, s); 3,53 (3H, s); 13,27 (1H, s)
V e	1653, 1720 (CO); 3380 (NH); 1340, 1521 (NO_2)	3,40 (3H, s); 3,58 (3H, s); 3,74 (2H, t, J=5); 3,95 (2H, t, J=5); 9,06 (1H, s); 14,43 (1H, s)
VI	1667, 1702 (CO); 3385 (NH); 1361, 1524 (NO_2)	0,94 (3H, t, J=6); 1,20...1,80 (4H, m); 3,40... 3,75 (2H, m); 3,41 (3H, s); 3,64 (3H, s); 6,75 (1H, s)
VII	1640, 1683, 1720 (CO); 3333 (NH)	3,13 (3H, s); 3,62 (3H, s); 3,96 (2H, t, J=9); 4,87 (2H, t, J=9)

*The spectra of IVa-c were recorded in d_6-DMSO, while the spectra of Va,b were recorded in d_7-DMF.



IV a R=$NHNH_2$; b R=$N(CH_3)_2$; c R=OC_4H_9; d R=N_3; V a R=H, R^1=CH_3; b R=H, R^1=C_4H_9; c R=H, R^1=CH_2CH_2OH; d R=R^1=CH_3

In the PMR spectrum the signals of the methylene groups of the imidazole ring of VII are recorded as triplets at 3.96 and 4.87 ppm with spin-spin coupling constant (SSCC) J = 9 Hz.

The inhibiting action of the synthesized compounds with respect to dihydrofolatereductase was studied. The activity of the enzyme was evaluated by colorimetry [7]. Compound III inhibits dihydrofolatereductase completely at a concentration of 10^{-5} mole and causes 57% inhibition at a concentration of 10^{-6} mole.

Pyridopyrimidines Vc, d displayed weak diuretic activity. The diurnal diuresis in experiments with female rats in the case of administration of Vc, d was 148% and 122%, respectively, as compared with a control [8].

Compounds with pronounced antibacterial activity were not found among the investigated pyrido[2,3-d]pyrimidones II, III, and IVa,d. Weak bacteriostatic activity was displayed by IVa,d: they retarded the growth of Gram-positive (*Staphylococcus aureus* 209P, *Streptococcus* 284, and *B. anthracoid* 1312) and Gram-negative (*Proteus vulgaris* 5) microorganisms in concentrations of 50 μg/ml.

As a result of preliminary testing of the biological activity of IV in the All-Union Science Center for the Safety of Medicinals, it was observed that it displays a weakly expressed antistaphylococcic and cardiotropic effect.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Specord IR-75 spectrometer. The PMR spectra were obtained with a Tesla BS-497 spectrometer (100 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with a Varian MAT-311A spectrometer with direct introduction of the samples into the ion source.

The results of elementary analysis of the synthesized compounds for C, H, Cl, and N were in agreement with the calculated values.

1,3-Dimethyl-7-chloro-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione (II, $C_9H_8N_3O_3Cl$). A 10-g (99 mmole) sample of $NaNO_2$] was added in portions at 0-5°C to a solution of 5 g (22.5 mmole) of I in 220 ml of 35% HCl, and the mixture was stirred at this temperature for 1 h. The resulting precipitate was removed by filtration and washed with water until the wash water had pH 7. This procedure gave 2.92 g (54%) of II with mp 190-192°C (from acetone) and $M^{+\cdot}$ 241.

1,3-Dimethyl-6-nitro-7-chloro-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione (III, $C_9H_7N_4O_5Cl$). A 0.3-ml sample of a blend (6.9 mmole of HNO_3) was added to a solution of 1 g (4.1 mmole) of II in 6 ml of concentrated H_2SO_4, and the mixture was stirred for 1 h at 70-80°C. It was then poured into 30 ml of water cooled to 5°C, and the resulting precipitate was removed by filtration and washed with water until the wash water had pH 7. This procedure gave 1.1 g (92%) of III with mp 171-173°C (from acetone).

General Method for Obtaining IVa-e and Va-d. A 15-50-mmole sample of the nucleophilic agent (see Table 1) was added to a solution of 10 mmole of II or III in 10-15 ml of DMF (or N-ethylpyrrolidone or DMSO), and the mixture was maintained at 70-120°C for 0.5-3 h. It was then cooled to 10-15°C (or diluted with 10-30 ml of water in the preparation of IVa, b, d, e and Va, b, d), and the resulting precipitate was removed by filtration and washed with 20 ml of water (20 ml of alcohol in the case of Vc). In the isolation of IVc the reaction mass was neutralized to pH 7 with 35% HCl.

1,3-Dimethyl-6-nitro-7-(2-chloroethyl)amino-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione (Ve, $C_{11}H_{12}N_5O_5Cl$) and 1,3-Dimethyl-6-nitro-8,9-dihydro-7H-imidazo[1′,2′:1,6]pyrido[2,3-d]pyrimidine-2,4,5-trione (VII, $C_{11}H_{11}N_5O_5$). A. A suspension of 2 g (6.4 mmole) of Vc in 30 ml of $SOCl_2$ was allowed to stand at 20°C for 2 days. The resulting precipitate was removed by filtration and washed with 20 ml of water to give 1.1 g (59%) of VII with mp > 360°C.

The mother liquor remaining after removal of VII by filtration was added in portions to 60 ml of water, and Ve was removed by filtration and washed with water until the wash water had pH 7. This procedure gave 0.6 g (28%) of a product with mp 211-213°C (dec., from acetone).

B. A suspension of 2 g (6.43 mmole) of Vc and 0.9 g (7.68 mmole) of $SOCl_2$ in 20 ml of chloroform was refluxed for 8 h, after which it was cooled to 20°C and filtered to give 1.9 g (quantitative yield) of VII.

C. A suspension of 2 g (6.43 mmole) of Vc and 20 g of polyphosphoric acid containing 86% P_2O_5 was heated with stirring to 140°C and maintained at this temperature for 0.5 h. It was then cooled to 20°C, diluted with 50 ml of water, and neutralized to pH 7 with ammonia. Filtration gave 1.9 g (quantitative yield) of VII.

1,3-Dimethyl-5-chloro-6-nitro-7-butylaminopyrido[2,3-d]pyrimidine-2,4-dione (VI, $C_{13}H_{16}N_5O_4Cl$). One drop of DMF was added to a suspension of 0.4 g (1.24 mmole) of Vb in 4 ml of $SOCl_2$, and the mixture was refluxed for 2 h. It was then cooled and poured into 20 ml of water, and the resulting precipitate was removed by filtration to give 0.2 g (47%) of VI. After purification with a column (2.5 × 60 cm) packed with silica gel L 100/250 (elution with chloroform), the product had mp 143-145°C.

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4-TRIFLUOROMETIIYLPYRIMIDINES

I. I. Gerus, S. I. Vdovenko, M. G. Gorbunova, and V. P. Kukhar'

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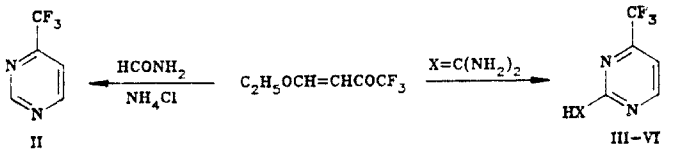
It is shown that β-alkoxyvinyl trifluoromethyl ketones are convenient reagents for the synthesis of 4-trifluoromethylpyrimidines that contain a hydrogen atom or hydroxy, mercapto, and amino groups in the 2 position. The NMR, IR, and UV spectra of the synthesized compounds were studied. The absorption bands in the IR spectra of some of the 4-trifluoromethylpyrimidines were assigned empirically.

4-Trifluoromethyl-substituted pyrimidines are of interest as potential physiologically active substances: among them are known antibacterial [1, 2] and antidiabetic compounds and herbicides [3]. Pyrimidines that contain a trifluoromethyl group in the 4 position and an alkyl group in the 6 position have traditionally been synthesized from the corresponding β-diketones [2, 3]. The multistep character of the synthesis of 5- and 6-unsubstituted 4-trifluoromethylpyrimidines is due to the difficulty in obtaining trifluoroacetylacetaldehyde, which has not yet been described in the literature. We recently proposed that the accessible β-alkoxyvinyl trifluoromethyl ketones be used for the synthesis of trifluoromethyl-containing heterocycles [4].

The aim of the present research was to synthesize 4-trifluoromethylpyrimidines by means of β-ethoxyvinyl trifluoromethyl ketone (I) and study the physicochemical properties of the heterocycles obtained.



III X=O; IV X=S; V X=NH; VI X=$NSO_2C_6H_4NHCOCH_3$-4

Pyrimidine II with a trifluoromethyl group in the 4 position was obtained in low yield by heating butenone I with ammonium chloride in formamide. Pyrimidine II is a volatile liquid with a characteristic odor. In its PMR spectrum (Table 1) the signal of the 5-H proton has the form of a doublet of doublets as a result of spin-spin coupling (SSC) with the other two protons of the pyrimidine ring, although the proton in the 2 position shows up in the form of a broad singlet (rather than a doublet) with a spin-spin coupling constant (SSCC) of 1.5 Hz.

The reaction of butenone I with gem-diamino compounds leads to 4-trifluoromethylpyrimidines containing diverse functional groups in the 2 position. Heating butenone I with urea at 120-130°C gives pyrimidine III, the yield of which increases from 35 to 75% when the reaction is carried out in the presence of hydrochloric acid for 2 days at 20°C. Compound III is a colorless crystalline substance that is only slightly soluble in water and low-polarity organic solvents.

Institute of Bioorganic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660.

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