SEARCH FOR NEW DRUGS

SYNTHESIS OF PYRIDO[3′,2′ : 4,5]PYRROLO- AND PYRIDO[3′,2′ : 4,5]THIENO[3,2-d]PYRIMIDINE DERIVATIVES USING THE THORPE – ZIEGLER CYCLIZATION REACTION

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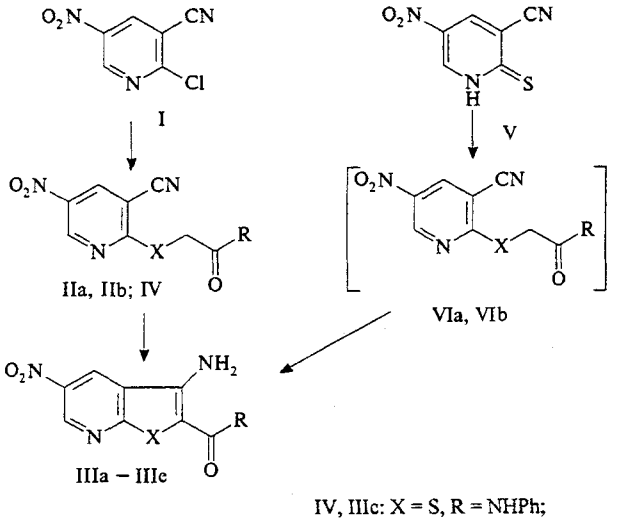
The Thorpe – Ziegler reaction is a most universal method for the synthesis of 3-aminopyrroles and 3-aminothiophenes, as well as various heterostructures containing ring fragments of these heterocycles [1 – 3].

Previously we have demonstrated that 5-nitro-2-chloro-3-cyanopyridine (I) is a convenient initial compound for obtaining functionally disubstituted 3-cyanopyridines (IIa, IIb) that readily enter into a cyclization process in the presence of basic agents with the formation of 5-nitro-3-cyano-2-ethoxycarbonylpyrrolo- and thieno[2, 3-b]pyridines (IIIa, IIIb) [4]. Similar syntheses of pyrrolo- and thieno[2,3-b]pyridines in other systems were also described [3, 5].



IIa, IIIa: X = NMe, R = OEt;
IIb, IIIb: X = S, R = OEt;
IV, IIIc: X = S, R = NHPh;
IVa, IIId: X = S, R = 4-BrC_6H_4;
IVb, IIIe: X = S, R = 4-MeC_6H_4.

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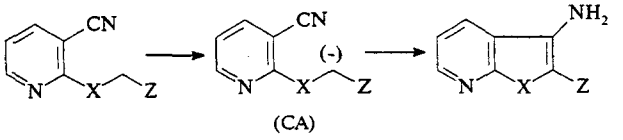
An alternative possibility of obtaining compounds of type III is based on the S-alkylation of pyridinethiones (V), followed by the intramolecular cyclization process. Both methods were employed in this work. In particular, interaction of chloropyridine I with thioglycolic acid anilide in the presence of potassium carbonate leads to an intermediate IV that is readily cyclized with a high yield into 3-amino-5-nitro-2-phenylaminocarbonylpyrrolo[2,3-b]pyridine (IIIc). In contrast, no such intermediates (VIa, VIb) can be isolated during the synthesis of bicyclic compounds (IIId, IIe) by interaction between pyridinethione V with 4-bromo- and 4-methylphenacyl bromides, since the thiophene ring is closed in the alkylation step.

According to present notions [6], the rate of the cyclization process is determined by the concentration of a carbanion (CA) formed under the action of a base. Therefore, the cyclization rate depends on the electron-donor effect of a substituent group Z:



The variation of activity in the series of substituents Z is determined by their electronegativities; according to [6], the order is as follows:

$$NO_2 > ArCO > CN > COOR > CONH_2 > H.$$

Substituents of the ArCO type significantly facilitate the cyclization process as compared to the case of amide group. This fact explains the above-mentioned isolation of stable in-

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termediate IV and the spontaneous cyclization of intermediates VIa, VIb under the process conditions studied.

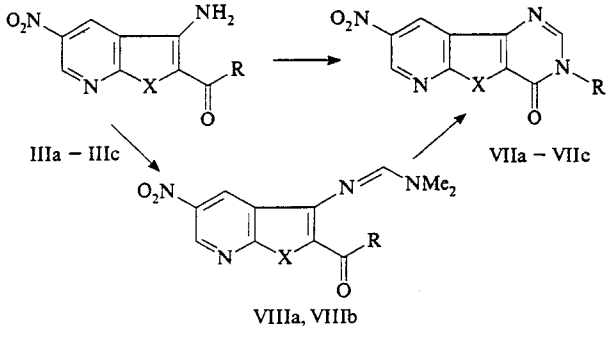
The resulting bicyclic compounds have certain features determining possibilities of their subsequent use in the synthesis.

The former method is most widely used in practice, because it involves readily available halogenocarbonyl or related compounds. First, the presence of functional substituents in the neighboring positions of a five-membered heterocycle provides the possibility of further annelation. Second, the nitro group in position 5 can be converted into various groups of other types, thus markedly extending the circle of synthesized compounds.

In this work, we have performed cyclization of pyrimidines with the participation of carbonyl-containing substituents and amino group in positions 2 and 3 of the pyrrole and thiophene cycles. Heating compound IIIc with orthoformic ester in the presence of acetic anhydride leads to the formation of 8-nitro-3-phenylpyrido[3′,2′ : 4,5]thieno[3,2-d]pyrimidin-4-(3H)-one (VIIc).

Another approach to the synthesis of tricyclic compounds of this series was based on the use of dimethylformamide diethyl acetal, whose condensation with compounds IIIa and IIIb led to amidine derivatives VIIIa and VIIIb.

The closure of pyrimidine ring was achieved by interaction of the amidine derivatives VIIIa, VIIIb with benzyl- or methylamine, which led to 3-methyl-8-nitropyrido-[3′,2′ : 4,5]thieno[3,2-d]pyrimidin-4(3H)-one (VIIb) and benzyl-5-methyl-8-nitro-5H-pyrido[3′,2′ : 4,5]pyrrolo[3,2-d]pyrimidin-4(3H)-one (VIIa).



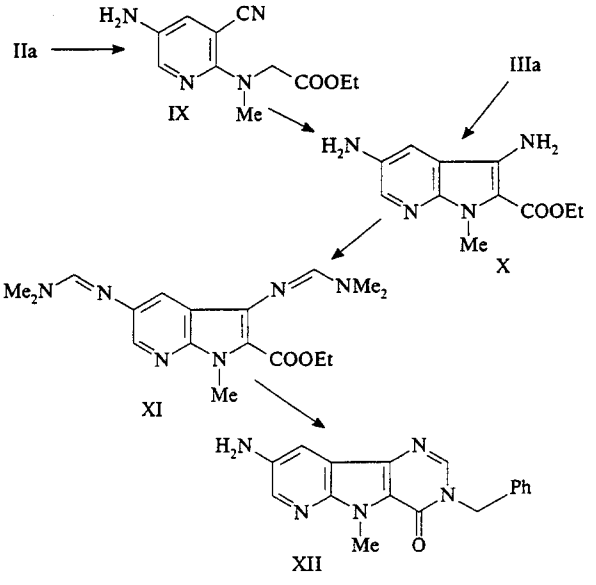
VIIa: X = NMe, R = CH_2Ph;
VIIb: X = S, R = Me;
VIIc: X = S, R = Ph;
VIIIa: X = NMe, R = OEt;
VIIIb: X = S, R = OEt.

The above considerations along with the data cited indicate that the structure of side chains involved in the Thorpe – Ziegler cyclization reaction determines to a considerable degree the rate and efficiency of the process of five-member heterocycle formation. As for the dependence of the heterocyclization on the structure of other fragments of the molecule involved, for example, on the presence or absence of the nitro group in the pyridine ring of compounds such as V or VI, the question is not as clear.

According to the general notions, it is obvious that the electron-acceptor effect of the nitro group not only stabilizes the anion centers of carbanions, but increases the electrophilic character of the cyano group as well, which must lead to an increase in the cyclization rate. In order to verify this conclusion, the nitro group in a previously synthesized compound IIa [4] was reduced by interaction with tin(II) chloride in hydrochloric acid. Heating the resulting amino derivative IX with sodium ethylate led to a high yield of 3,5-diamino-1-methyl-2-pyrrolo[2,3-b]pyridine (IIIa). Spectroscopic investigation showed complete identity of the compounds obtained by different methods.

Thus, replacing the nitro group by the amino group under the conditions studied had no significant effect on the Thorpe – Ziegler cyclization; as will be shown below, nor did this substitution affect the subsequent closure of the pyrimidine ring.

In the next stage, we have obtained the amidine derivative XI. The presence of two amino groups in compound X allows the condensation of dimethylformamide diethyl acetal in both the third and fifth positions with the formation of the bisamidine product XI.



Then compound XI entered into reaction with benzylamine to form 8-amino-3-benzyl-5-methyl-5H-pyrido[3′,2′ : 4,5]pyrrolo[3,2-d] pyrimidin-4(3H)-one (XII). The formamidine fragment in the β-position of the pyridine cycle transforms into an amino group, which is probably accompanied by the liberation of N,N-dimethyl-N′-benzylformamide.

EXPERIMENTAL CHEMICAL PART

The mass spectra of the synthesized compounds were obtained on a Varian MAT-112 spectrometer operating at an ionization voltage of 50 eV and an ionization chamber temperature of 140°C. The ^1H NMR spectra were measured on a Varian Unity+400 spectrometer using TMS as internal standard. The IR absorption spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer. The melting temperatures were determined using a Boetius type heating stage. The data of elemental analysis agreed with the results of analytical calculations based on the empirical formulas. The physicochemical properties of the synthesized compounds are listed in Table 1.

5-Nitro-2-(N-phenylaminocarbonylmethylthio)-3-cyanopyridine (IV). To a solution of 5 g (27 mmole) of 5-nitro-2-chloro-3-cyanopyridine (I) [7] in 50 ml of ethanol was added 5.85 g (35 mmole) of thioglycolic acid anilide and 2.87 g (35 mmole) of sodium acetate and the mixture was stirred for 1 h at room temperature. The precipitate was filtered and washed with water; M^+ 314.

3-Amino-5-nitro-2-(N-phenylaminocarbonyl)thieno-[2,3-b]pyridine (IIIc). To a solution of 2 g (6.4 mmole) of compound IV in 30 ml of boiling ethanol was added a catalytic amount of sodium ethylate in ethanol. The mixture was cooled and the precipitate filtered and washed with water; M^+, 314.

3-Amino-2-(4-bromobenzoyl)-5-nitrothieno[2,3-b]pyridine (IIId). To a solution of 2 g (11 mmole) of 5-nitro-3-cyanopyridine-2-thione (V) in 20 ml of DMF was added 3.34 g (12 mmole) of 4-bromophenacyl bromide and 2.28 g (165 mmole) K_2CO_3 and the mixture was boiled with stirring for 5 h. Upon cooling, the precipitate was filtered and washed with water; M^+, 378.

3-Amino-2-(4-methylbenzoyl)-5-nitrothieno[2,3-b]pyridine (IIIe). Compound IIIe was obtained similarly to compound IIId by the alkylation of thione V with 4-methylphenacyl bromide; M^+, 313.

3-(Dimethylaminomethylamino)-1-methyl-5-nitro-2-ethoxycarbonyl-1H-pyrrolo[2,3-b]pyridine (VIIIa). To a solution of 1.93 g (7.2 mmole) of compound IIIa in 30 ml of toluene was added 1.225 g (8.3 mmole) DMF acetal and the mixture was boiled with stirring for 5 h. Upon cooling, the precipitate was filtered; M^+, 319.

3-(Dimethylaminomethylamino)-5-nitro-2-ethoxycarbonylthieno[2,3-b]pyridine (VIIIb). Compound VIIIb was obtained from compound IIIb using a procedure similar to that for compound VIIIa; M^+, 322.

3-Benzyl-5-methyl-8-nitro-5H-pyrido[3',2' : 4,5]pyrrolo[3,2-d] pyrimidin-4(3H)-one (VIIa). To a solution of 0.07 g (0.22 mmole) of compound VIIIa in 10 ml of toluene was added 0.047 g (0.44 mmole) benzylamine and the mixture was boiled with stirring for 6 h. Then the solvent was evaporated and the residue triturated with water. The precipitate was filtered and washed with ethanol; M^+, 335.

3-Methyl-8-nitropyrido[3',2' : 4,5]thieno[3,2-d]pyrimidin-4(3H)-one (VIIb). A solution of 1.00 g (3.1 mmole) of compound VIIIb in 15 ml of a 15 % solution of methylamine in methanol was heated in an autoclave for 15 h at 120°C. Upon cooling, the precipitate was filtered; M^+, 262.

8-Nitro-3-phenylpyrido[3',2' : 4,5]thieno[3,2-d]pyrimidin-4(3H)-one (VIIc). To a solution of 1 g (3.2 mmole) of compound IIIc in 8 ml of acetic anhydride was added 3.17 g (19.2 mmole) of triethyl orthoformate, and the mixture was boiled for 1.5 h. Upon cooling, the precipitate was filtered; M^+, 324.

5-Amino-3-cyano-2-(N-ethoxycarbonylmethyl-N-methylamino)pyridine (IX). To a mixture of 2.43g (13 mmole) of $SnCl_2 \cdot 2H_2O$ and 3.2 ml of concentrated hydrochloric acid was added with stirring 0.83 g (3.79 mmole) of compound IIa at a temperature of 5 – 7°C. The deposit dissolved in 10 min, after which the stirring was continued for 2 h. The precipitate was filtered, dissolved in water, and alkalized to pH 9 – 10. The precipitate was filtered to obtain the target compound; M^+, 234.

TABLE 1. Physicochemical Properties of the Synthesized Compounds

Compound	Empirical formula	M.p., °C	Yield, %	IR spectrum (ν_{max}, cm^{-1})
IV	$C_{14}H_{10}N_4O_3S$	228 – 230	94	1590 (C=C), 2225 (C≡N), 1680(C=O), 3380 (NH)
IIIc	$C_{14}H_{10}N_4O_3S$	> 260	97	1590 (C=C), 1665 (C=O), 3310, 3420 (NH_2)
IIId	$C_{14}H_8N_3O_3SBr$	254 – 256	82	1590 (C=C), 1670 (C=O), 3280, 3340 (NH_2)
IIIe	$C_{15}H_{11}N_3O_3S$	258 – 259	77.5	1590 (C=C), 1670 (C=O), 3295, 3440 (NH_2)
VIIa	$C_{17}H_{13}N_5O_3$	227 – 228	74.6	1590 (C=C), 1680 (C=O)
VIIb	$C_{10}H_6N_4O_3S$	> 260	78	1590 (C=C), 1675 (C=O)
VIIc	$C_{15}H_8N_4O_3S$	> 260	80	1590 (C=C), 1670 (C=O)
VIIIa	$C_{14}H_{17}N_5O_4$	148 – 149	87	1580 (C=C), 1700 (C=O)
VIIIb	$C_{13}H_{14}N_4O_4S$	161 – 163	90	1580 (C=C), 1720 (C=O)
IX	$C_{11}H_{14}N_4O_2$	171 – 172	73.5	1590 (C=C), 2210 (C≡N), 3340, 3420 (NH_2)
X	$C_{11}H_{14}N_4O_2$	142 – 144	91	1590 (C=C), 1660 (C=O), 3320, 3400 (NH_2)
XI	$C_{17}H_{24}N_6O_2$	228 – 230	85	1590 (C=C), 1680 (C=O)
XII	$C_{17}H_{15}N_5O$	195 – 196	67.2	1590 (C=C), 1650 (C=O), 3340 (NH_2)

3,5-Diamino-1-methyl-2-ethoxycarbonyl-1H-pyrrolo [2,3-b]pyridine (X). Obtained from compound IIIa similarly to compound IX; mass spectrum (*M*/*z*): M^+, 234; ^{1}H NMR spectrum, DMSO-d_6 (δ, ppm): 1.32 (t, 3H, $CH_2\underline{CH_3}$), 3.73 (s, 3H, $\underline{NCH_3}$), 4.28 (q, 2H, $\underline{CH_2}CH_3$), 5.60 (bs, 4H, 3-NH_2, 5-NH_2), 7.33 (d, 1H, $^4J_{H^4,H^6}$ 2.5 Hz, 4-CH), 7.98 (d, 1H, 6-CH).

3,5-Bis(dimethylaminomethyleneamino)-1-methyl-2-ethoxycarbonyl-1H-pyrrolo[2,3-b]pyridine (XI). Obtained from compound X similarly to compound VIIIa. After stirring the reaction mixture for 4 h, the solvent was evaporated and the residue triturated with hexane; mass spectrum (*M*/*z*): M^+, 344; ^{1}H NMR spectrum, DMSO-d_6 (δ, ppm): 1.25 (t, 3H, $CH_2\underline{CH_3}$), 2.93, 2.98 (bs, 3H, $N(CHC_3)_2$), 2.99 (bs, 6H, $N(CH_3)_2$), 3.88 (s, 3H, $N\underline{CH_3}$), 4.19 (q, 2H, $\underline{CH_2}CH_3$), 7.66, 7.82 (bs, 1H, 3,5-$\underline{CH}$=$N(CH_3)_2$), 7.41 (d, 1H, $^4J_{H^4,H^6}$ 2.4 Hz, 4-CH), 8.10 (d, 1H, 6-CH).

8-Amino-3-benzyl-5-methyl-5H-pyrido[3′,2′ : 4,5]pyrrolo[3,2-d] pyrimidin-4(3H)-one (XII). Obtained from compound XI similarly to compound VIIa by boiling the reaction mixture with stirring for 4 h; M^+, 305.

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