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REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED THIENO[2,3-*b*]PYRIMIDINES AND PYRIDO[3′,2′:4,5]THIENOPYRIMIDINES AND THEIR [3,2-d]SELENOPHENO ANALOGS FROM 3-CYANOPYRIDINE-2(1H)-THIONES, 3-CYANO-PYRIDINE-2(1H)-SELENONES, AND N-CYANOCHLORACETAMIDINE

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3-Cyanopyridine-2(1H)-thiones and 3-cyano-2(1H)-selenones undergo heteroannelation with N-cyano-chloracetamidine to give thieno[2,3-b]pyridines, selenopheno[2,3-b]pyridines, 2,4-diaminopyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidines, and 2,4-diaminopyrido[3′,2′:4,5]selenopheno[3,2-d]pyrimidines, which were converted to compounds containing triazine, aminopyrimidine, and pyrimidinedione rings.

N-Cyanochloracetamidine (I) was first obtained in 1963 by Huffman and Schaefer [1] but only a few reports concerning the synthetic use of this compound have appeared. Del Corona [2] and Sendai [3] have used this compound as an alkylating agent, while Harris [4, 5] used the cyanoamidine group for closure of the triazine ring with retention of the chlorine atom. On the other hand, reactions affecting both functional moieties and the methyl group have not been described. Such reactions could lead to fused heterocyclic compounds not readily available by other methods.

We have developed a new method for the regioselective synthesis of substituted thienopyridines, selenophenopyridines, pyridothienopyrimidines, and pyridoselenophenopyrimidines based on the reaction of N-cyanochloracetamidine I with substituted 3-cyanopyridine-2(1H)-thiones (IIa)-(IIj) and 3-cyanopyridine-2(1H)-selenones (IIIb) and (IIIf). This reaction proceeds regioselectively in DMF in the presence of excess KOH to give the corresponding 3-aminothieno- and 3-amino-selenopheno[2,3-*b*]pyridines (IVa)-(IVj), (Vb), and (Vf) (method A)

Products IV and V are yellow crystalline compounds with UV luminescence. The physicochemical indices of these compounds are given in Table 1.

The regioselectivity of the reaction of II and III with I is a consequence of two consecutive reactions, namely, nucleophilic substitution and the Thorpe–Ziegler reaction. The regioselective alkylation of the pyridinethiolates formed under the reaction conditions proceeds initially at the sulfur atom to give pyridines (VI), which was confirmed by isolation of these products from the reaction mixture when insufficient KOH was used. The structure of VI was indicated by elemental analysis as well as IR and PMR spectroscopy (Table 2). These products are readily cyclized to give thienopyridines IV in DMF in the presence of catalytic amounts of base (method B). Products VI could not be isolated in the case of pyridinethiolates having basic substituents (quinuclidine derivative IIg and pyridylthione IIj) due to the formation of IVg and IVj. This failure is attributed to the catalytic action of the basic substituent. Analogously, alkylated selenones could not be isolated, probably due to the enhanced CH-acidity of the methylene group in going from the $-S-CH_2-$ group to $-Se-CH_2-$.

The finding of two IR bands for the nitrile group for IV and V at 2200-2180 and 2140-2150 cm^{-1} was unexpected. These bands probably characterize the cyanoamidine group [1].

We also obtained a compound with two trifluoromethyl groups, namely, IVk. The synthesis of this compound was carried out *in situ* in light of the lability of the corresponding pyridinethione IIk

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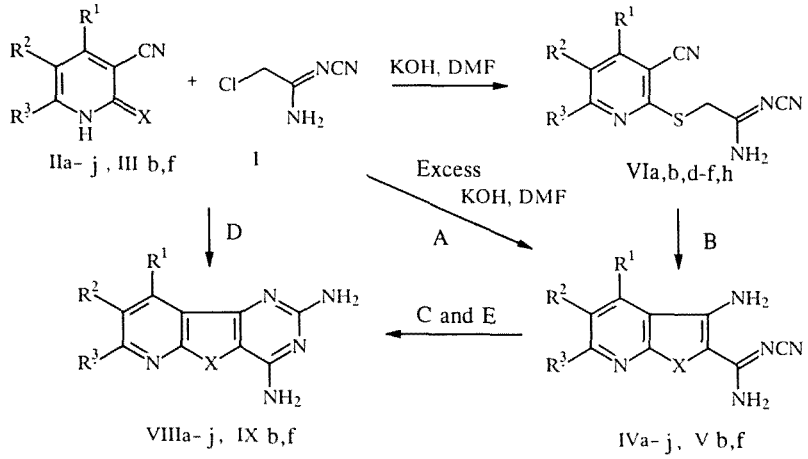
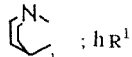
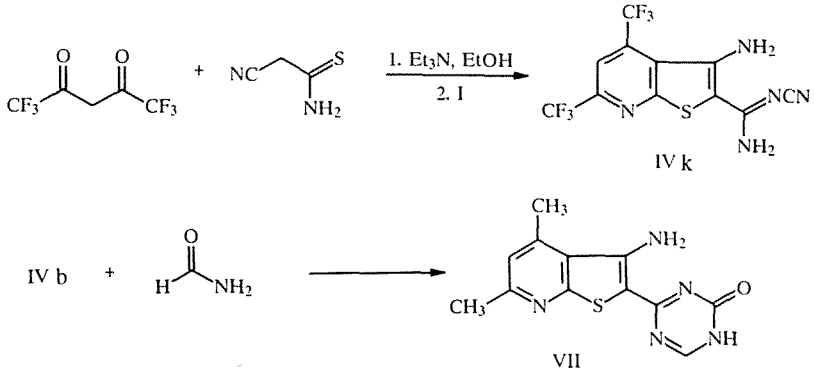


II, IV, VIII: X = S; III, V, IX: X = Se; II—VI, VIII, IX: a $R^1 = R^2 = H$, $R^3 = CH_3$; b $R^1 = R^3 = CH_3$, $R^2 = H$; c $R^1 = R^2 = H$, $R^3 = Ph$; d $R^1 = R^3 = Ph$, $R^2 = H$; e $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$, $R^3 = 4\text{-}CH_3C_6H_4$; f $R^1 = CF_3$, $R^2 = H$, $R^3 = Ph$; g $R^1 = H$, $R^2R^3 =$  ; h $R^1 = 4\text{-}ClC_6H_4$, $R^2R^3 = (CH_2)_4$; i $R^1 = 4\text{-}BrC_6H_4$, $R^2R^3 = (CH_2)_4$; j $R^1 = 3\text{-Py}$, $R^2R^3 = (CH_2)_4$

3-Aminothieno[2,3-*b*]pyridines IV and 3-aminoselenopheno[2,3-*b*]pyridines V have two functional groups, namely, amino and cyanoamidine groups, and, thus, may undergo reactions either at one or both of these groups.

Thienopyridine IVb reacts with formamidine upon heating at the cyanoamidine group to give a product containing a triazine ring (VII):



Heating of thienopyridines IV and selenophenopyridines V with sodium ethylate in ethanol gives closure of the pyrimidine ring to give substituted 2,4-diaminopyrido[3′,2′:4,5]thieno- (VIII) and 2,4-diaminopyrido[3′,2′:4,5]seleno-pheno[3,2-*d*]pyrimidines (IX) (method C). Thus, pyridothieno- and pyridoselenophenopyrimidines were obtained from all thieno- (IV) and selenophenopyridines (V) with the exception of di(trifluoromethyl) derivative IVk. Products VIII and IX are colorless or slightly yellow compounds, which sublime upon heating. Their structure was supported by elemental analysis and spectral methods (Table 3).

Since the formation of thienopyridines IV and their cyclization to give VIII occur under analogous conditions, these two reactions may be carried out in a single stage, as demonstrated for dimethyl derivative VIIIb (method D).

IR spectroscopy is especially convenient for monitoring these reactions. Thus, VI has two nitrile group bands: a band with medium intensity at 2225-2214 cm^{-1} for the 3-CN group and strong band at 2192-2170 cm^{-1} for the amidine CN group. The former band disappears upon closure of the thiophene ring, while the latter is shifted to 2200-2180 cm^{-1}, indicating enhanced conjugation of the amidine CN group. Furthermore, a new band appears at 2140-2150 cm^{-1}. Both these bands disappear in tricyclic products VIII.

The PMR signals for the NH_2 groups are also characteristic. The amino group in VI appears as a broad singlet at 8.6-8.7 ppm. The signals for the amidine NH_2 group protons in 3-aminothieno- (IV) and 3-aminoselenophenopyridines (V) are found at 8.0-8.2 ppm, while the signal for the 3-amino group is found for several compounds at 6.0-7.8 ppm. Both signals appear as poorly resolved doublets. These signals are shifted upfield upon closure of the pyrimidine ring and appear at 6.9-7.1 (4-NH_2) and 5.2-6.1 ppm (2-NH_2). The assignment of the signals for the NH_2 group protons in VIII was made by comparison with the PMR spectra of substituted aminopyridines [6].

TABLE 1. Indices for Thienopyridines IV and Selenophenopyridines V

Compound	Chemical formula	mp, °C	IRspectrum, ν, cm^{-1}	PMR spectrum, chemical shifts, ppm, coupling constant (J), H_2					yield%
				R^1	R^2	R^3	3-NH_2	NH_2 side-chain	
1	2	3	4	5	6	7	8	9	10
IVa	$C_{10}H_9N_5S$	253...254	3425, 3380, 3276, 3148 (NH_2); 2180, 2150 (CN); 1642, 1608,1582 (C=N)	8,36 d, J = 9	7,32 d, J = 9	2,57 s	7,66 br.s	8,01 br.s	92 84*
IVb	$C_{11}H_{11}N_5S$	269...270	3456, 3384, 3308, 3168 (NH_2); 2188, 2140(CN); 1654, 1598 (C=N)	2,72 s	7,06 s	2,50 s	7,23, 7,27 2s	8,06 br.s	88 96*
IVc	$C_{15}H_{11}N_5S$	275...276	3456, 3388, 3288, 3208 (NH_2); 2186, 2156 (CN); 1626, 1570 (C=N)	8,59 d, J = 8	8,08 d, J = 8	7,46...7,58m(3H, *м*-andp-H_{Ph}), 8,15...8,21 m (2H, *o*-H_{Ph})	7,75 br.s	8,10 br.s	96
IVd	$C_{21}H_{15}N_5S$	242...244	3485, 3330, 3200 (NH_2); 2180, 2145 (CN); 1668, 1640, 1590 (C=N)	7,45...7,65 m[*2]	7,80 s	7,45...7,65 m (*м*- and p-H_{Ph})[*2], 8,17...8,28 m (*o*-H_{Ph})[*2]	8,17...8,28 m (*o*-H_{Ph})[*2]	6,26, 6,28 2s	8,17...8, 28*[2]
IVe	$C_{22}H_{16}ClN_5S$	244...247	3490, 3300, 3200 (NH_2); 2185, 2145 (CN); 1632, 1600, 1570 (C=N)	7,57...7,80, AA'BB'	7,77 s	2,38 s (CH_3), 7,34, 8,14, AA'XX'	6,30, 6,33 2s	8,20 br.s	91 80*
IVf	$C_{16}H_{10}F_3N_5S$	244...245	3500, 3420, 3292, 3148 (NH_2); 2194, 2170 (CN); 1650, 1638, 1600, 1582 (C=N)	–	8,30 s	7,50...7,60 m (*м*- and p-H_{Ph}), 8,20...8,35 m (*o*-H_{Ph})	7,07 s	8,45 br.s	93 78*
IVg	$C_{14}H_{14}N_6S$	301...302	3392, 3276 (NH_2); 2182, 2142 (CN); 1644, 1616, 1604 (C=N)	8,65 s	1,80, 2,22, 3,16, 3,71 4 m (CH_2), 3,2...3,4 (CH)[*2]		7,87 br.s	8,18 br.s	85

IVh	$C_{19}H_{16}ClN_5S$	264...265	3480, 3300, 3160 (NH_2); 2185, 2150 (CN); 1652, 1596, 1588 (C=N)	7,40, 7,64, AA'BB'	1,60...1,73, 1,73...1,87 2 m ($2CH_2$), 2,31 t, J = 6,5 (5-CH_2), 2,98 t, J = 6,5 (6-CH_2)		5,96, 5,98 2s	8,05 br.s	88 86*
IVi	$C_{19}H_{16}BrN_5S$	275...276	3480, 3312, 3156 (NH_2); 2182, 2150 (CN); 1652, 1594 (C=N)	7,32, 7,78, AA'BB'	1,60...1,74, 1,74...1,90 2 m ($2CH_2$), 2,30 t, J = 6,5 (5-CH_2), 2,98 t, J = 6,5 (6-CH_2)		5,98 br.s	8,06 br.s	98
IVj	$C_{18}H_{16}N_6S$	246...247	3488, 3312, 3156 (NH_2); 2182, 1592 (CN); 1654, 1592 (C=N)	*3	1,60...1,74, 1,74...1,86 2 m ($2CH_2$), 2,44 t, J = 6 (5-CH_2), 3,01 t, J = 6 (6-CH_2)		5,91 br.s	8,10 br.s	89
IVk	$C_{11}H_5F_6N_5S$	244...245	3504, 3452, 3312, 3184 (NH_2); 2198, 2160 (CN); 1658, 1614 (C=N)	–	8,22 s	–	7,08 br.s	8,70 br.s	57
Vb	$C_{11}H_{11}N_5Se$	237...239	3420, 3296, 3176 (NH_2); 2180, 2130 (CN); 1644, 1594, 1574 (C=N)	2,72 s	7,08 s	2,50 s	7,43 br.s	7,90 br.s	53
Vf	$C_{16}H_{10}F_3N_5Se$	228...229	3400, 3200 (NH_2); 2186, 2140 (CN); 1668, 1614, 1582 (C=N)	–	8,30 s	7,52...7,60 m (*m*- and p-H_{Ph}), 8,22...8,28 m (*o*-H_{Ph})	7,21 br.s	8,36 br.s	67

*Method B.

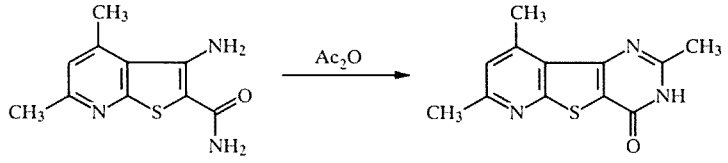
*2Signal is superimposed by the signal of the protons of another fragment.

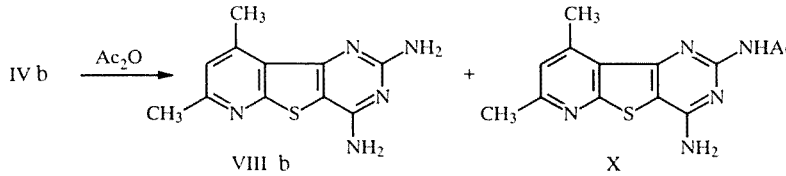
*3Signals of the pyridine substituent: 7.62 d.d, J_1 = 8, J_2 = 5 Hz (5'-H), 7.86 d.t, J_1 = 8, J_2 = 2 Hz (4'-H), 8.58 d, J = 2 Hz (2'-H), 8.77 d.d, J = 5, J_2 = 2 Hz (6'-H).

The methyl groups in VIIIb give rise to singlets at 2.55 and 2.90 ppm. These signals were assigned to the methyl groups at $C_{(7)}$ and $C_{(9)}$, respectively, on the basis of correlation with the spectrum of monomethyl derivative VIIIa. This assignment is opposite to that adopted for dimethylpyridinethione IIb [7], indicating considerable screening of substituent R^1 in VIII and IX. The R^1 group produces significant steric hindrance as seen by examination of the Stewart–Briegleb models. The difference in the melting points of VIIIa and VIIIb is probably related to this circumstance (Table 3).

The closure of the pyrimidine ring in IV may be carried out not only under base catalysis conditions but also under acid catalysis conditions (method E). Thus, stirring a suspension of thienopyridine IVb in hydrochloric acid at room temperature over 0.5 h leads to the quantitative formation of VIIIb (Table 3). Bistrifluoromethyl derivative VIIIk, which could not be synthesized under base catalysis conditions, was also obtained using acid catalysis.

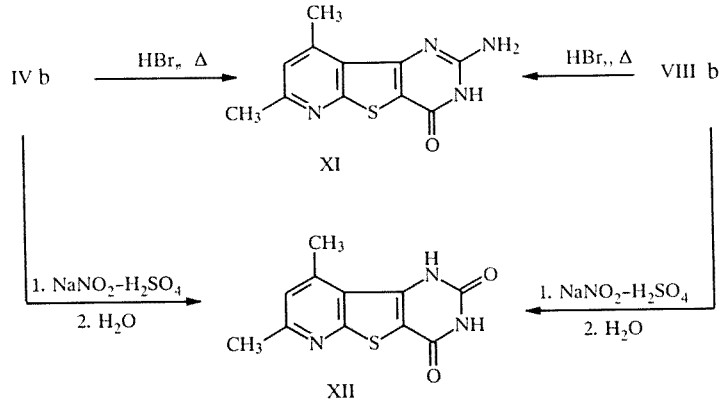
Tornetta et al. [7] have described the reaction of 3-aminothieno[2,3-*b*]pyridines possessing an amide group with acetic anhydride, leading to closure of the pyrimidine ring [7]. In the case of the analogous compound, IVb, which has a cyanoamidine substituent, this closure proceeds differently:





This reaction gives a mixture of VIIIb and X. Direct acylation of VIIIb also gave X.

Hydrolysis of one of the amino groups occurs upon the cyclization of IVb under more vigorous acid catalysis conditions (heating with HBr or the use of concentrated sulfuric acid) to give product XI.



Both amino groups may be converted to keto groups (XII) by the diazotization of IVb or VIIIb with one equivalent of $NaNO_2$ in H_2SO_4 and subsequent hydrolysis.

Thus, new methods for the regioselective synthesis of various substituted thieno- and selenopheno[2,3-*b*]pyridines and pyrido[3′,2′:4,5]thieno- and pyrido[3′,2′:4,5]selenopheno[3,2-*d*]pyrimidines have been developed starting from N-cyanochloracetamidine I and also 3-cyanopyridine-2(1H)-thiones II and 3-cyanopyridine-2(1H)-selenones III.

TABLE 2. Characteristics of Pyridine VI

Compound	Chemical formula	mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, chemical shifts, ppm, coupling constants (J), Hz yield, %					Yield, %
				R^1	R^2	R^3	CH_2	NH_2	
VIa	$C_{10}H_9N_5S$	191...192	3312, 3168 (NH_2); 2224, 2186 (CN); 1662, 1588 (C=N)	8,13 d, J = 8	7,23 d, J = 8	2,54 s	4,22 br.s	8,57 br.s	80
VIb	$C_{11}H_{11}N_5S$	195...197	3308, 3164 (NH_2); 2224, 2186 (CN); 1600, 1586 (C=N)	2,42 s	7,14 s	2,50 s	4,22 br.s	8,58 br.s	53
VId	$C_{21}H_{15}N_5S$	204...205	3390, 3330, 3170 (NH_2); 2220, 2180 (CN); 1660, 1640, 1570 (C=N)	7,50...7,67 m (*м*- and *n*-H_{Ph})*, 7,72...7,80 m (*o*-H_{Ph})	7,98 s	7,50...7,67 m (*м*-and p-H_{Ph}), 8,25...8,35 m (*o*-H_{Ph})	4,38 br.s	8,70 br.s	48
VIe	$C_{22}H_{16}ClN_5S$	203...206	3390, 3320, 3150 (NH_2); 2215, 2190 (CN); 1665, 1635, 1595, 1575 (C=N)	7,69, 7,79, AA'BB'	7,95 s	2,40 s (CH_3), 7,34, 8,20, AA'XX' (Ar)	4,38 br.s	8,69 br.s	31
VIf	$C_{16}H_{10}F_3N_5S$	201...202	3388, 3330, 3148 (NH_2); 2230, 2220 (CN); 1664, 1645, 1588, 1576 (C=N)	–	8,30 s	7,50...7,70 m (*м*-and p-H_{Ph}), 8,25...8,40 m (*o*-H_{Ph})	4,42 br.s	8,74 br.s	56
VIh	$C_{19}H_{16}ClN_5S$	206...207	3420, 3320, 3160 (NH_2); 2220, 2180 (CN); 1663, 1630, 1580 (C=N)	7,43, 7,61, AA'BB'	1,60...1,73, 1,73...1,87 2 m ($2CH_2$), 2,35 t, J = 6 (5-CH_2), 2,95 t, J = 6 (6-CH_2)		4,23 br.s	8,58 br.s	46

*Signals overlapped by the signals of the protons of another fragment.

EXPERIMENTAL

The melting points were determined on a Koeffler block. The IR spectra were taken on a Specord M-80 spectrometer for KBr pellets. The PMR spectra were taken on a Bruker WM-250 spectrometer for DMSO-d_6 solutions. The ^{13}C NMR spectra were taken on a Bruker WM-300 spectrometer for DMSO-d_6 solutions. The mass spectra were taken on a Varian MAT CH-6 mass spectrometer at 70 eV. The elemental analysis for C, H, and N was carried out on a Perkin–Elmer C,H,N-analyzer.

The elemental analysis data of the compounds synthesized correspond to the calculated values.

The indices for IV-VI, VIII, and IX are given in Tables 1-3.

3-Cyanopyridine-2(1H)-thiones II and 3-cyanopyridine-2(1H)-selenones III were obtained using reported procedures [8-10], while N-cyanochloracetamidine was obtained as described by Huffman and Schaefer [1].

3-Amino-2-aminocyanoiminomethyl-4-R^1-5-R^2-6-R^3-thieno- (IVa)-(IVj) and 3-Amino-2-aminocyano-iminoethyl-4-R^1-5-R^2-6-R^3-selenopheno[2,3-*b*]pyridines (Vb) and (Vf). Method A. A sample of 3 mmoles KOH introduced as a 10% aqueous solution was added to a solution of 3 mmoles pyridinethione II or selenone III in 20 ml DMF and stirred for 5 min at room temperature. Then, 3.1 mmoles N-cyanochloracetamidine I was added and the mixture was stirred for an additional 5 min. An additional 6 mmoles KOH introduced as a 10% aqueous solution was added and the mixture was stirred for 0.5 h. The product was precipitated by the addition of water, filtered, washed with cold ethanol, and recrystallized from acetonitrile.

IVb: ^{13}C NMR spectrum, ppm: 10.3 (4-CH_3), 14.2 (6-CH_3), 106.3 ($C_{(2)}$), 112.5 ($C_{(5)}$), 112.9 (CN), 120.6 ($C_{(3a)}$), 135.5 ($C_{(6)}$), 139.7 ($C_{(4)}$), 150.0 ($C_{(3)}$), 155.4 ($C_{(7a)}$). Mass spectrum, *m/e* (intensity, %): 247 (12.7), 246 (33.8), 245 (100, M^+), 228 (38.6, $M^+ - NH_3$), 203 (46, $M^+ - H_2NCH$).

IVd: Mass spectrum, *m/e*: 370, 369 (M^+), 327 ($M^+ - H_2NCH$).

2-(2-Amino-2-cyanoiminoethylthio)-3-cyano-4-R^1-5-R^2-6-R^3-pyridines (VIa), (VIb), (VId)-(VIf), (VIh). A sample of 2.8 mmoles KOH (10% aqueous solution) was added to a solution of 3 mmoles pyridinethione II in 20 ml DMF and stirred for 5 min at room temperature. Then, 3 mmoles acetamidine I was added and the mixture was stirred for an additional 5 min. The product was precipitated by the addition of water, filtered, washed with cold ethanol, and dried in the air.

VIb: ^{13}C NMR spectrum, ppm: 9.9 (4-CH_3), 14.4 (6-CH_3), 21.7 (CH_2), 94.1 (N–C=N), 105.2 ($C_{(3)}$), 111.2 ($C_{(5)}$), 112.6 (3-CN), 143.0 ($C_{(6)}$), 151.9 ($C_{(4)}$), 155.8 ($C_{(2)}$), 163.5 (–C(=N–)NH_2). Mass spectrum, *m/e* (intensity, %): 247 (6.1), 246 (15.6), 245 (100, M^+), 228 (22.2, $M^+ - NH_3$), 212 (41.8, $M^+ - SH$), 203 (23.4, $M^+ - H_2NCN$).

VId: Mass spectrum, *m/e*: 370, 369 (M^+), 352 ($M^+ - NH_3$), 336 ($M^+ - SH$), 327 ($M^+ - H_2NCN$).

3-Amino-2-aminocyanoiminomethyl-4-R^1-5-R^2-6-R^3-thieno[2,3-*b*]pyridines (IVa), (IVb), (IVd)-(IVf), (IVh). Method B. A sample of 0.5 mmole KOH (10% aqueous solution) was added to a solution of 1 mmole cyanopyridine VI in 10 ml DMF. After maintaining the mixture obtained for 0.5 h at room temperature, the product was precipitated by the addition of water and treated as indicated in Method A.

3-Amino-2-aminocyanoiminomethyl-4,6-di(trifluoromethyl)thieno[2,3-*b*]pyridine (IVk). A sample of 5 mmoles hexafluoroacetylacetone was added rapidly to a solution of 5 mmoles cyanothioacetamide and 5 mmole Et_3N in 20 ml absolute ethanol. The reaction mixture was maintained for 12 h at 20°C. Then, 5.1 mmoles acetamidine I was added and the mixture was maintained for 20 min at 40°C. The product precipitated upon cooling the solution was treated as described for other IV.

3-Amino-4,6-dimethyl-2-(1,3,5-triazin-2-on-4-yl)thieno[2,3-*b*]pyridine (VII). A solution of 1 mmole thienopyridine IVb in 6 ml formamide was maintained for 1 h at 80°C. The precipitate obtained upon cooling was treated as in the case of IV, mp >340°C. IR spectrum, cm^{-1}: 3332, 3164 (NH_2, NH), 1688 (C=O), 1645, 1680 (C=N). PMR spectrum, ppm: 2.58 (3H, s, 6-CH_3), 2.88 (3H, s, 4-CH_3), 7.22 (1H, s, 5-H), 7.58 (2H, s, 3-NH_2), 9.44 (1H, d, J = 6.5 Hz, triazine ring CH), 10.52, 1H, d, J = 6.5 Hz, triazine ring NH). Mass spectrum, *m/e* (intensity, %): 246 (9.3), 245 (51, $M^+ - CO$), 232 (14.7), 230 (100, $M^+ - HNCO$). Product VII was obtained in 93% yield.

2,4-Diamino-7-R^1-8-R^2-9-R^3-pyrido[3′,2′:4,5]thieno- (VIIIa)-(VIIIj) and 2,4-Diamino-7-R^1-8-R^2-9-R^3-pyrido[3′, 2′:4,5]selenopheno[3,2-*d*]pyrimidines (IXb) and (IXf). Method C. A sample of 1 mmole thienopyridine IV or selenopheno-pyridine V was added to 3 mmoles Na in 20 ml ethanol. The mixture was heated at reflux for 6 h and then cooled. The precipitated product was treated as in the case of IV.

VIIIb: ^{13}C NMR spectrum, ppm: 18.7 (7-CH_3), 23.9 (9-CH_3), 101.2 ($C_{(4a)}$), 121.8 ($C_{(8)}$), 123.6 ($C_{(9a)}$), 146.2 ($C_{(7)}$), 157.1 ($C_{(9)}$), 158.5 and 158.7 ($C_{(2)}$ and $C_{(9b)}$), 161.7 and 161.9 ($C_{(4)}$ and $C_{(5a)}$). Mass spectrum, *m/e* (intensity, %): 247 (30.2), 246 (41.5), 245 (100, M^+), 228 ($M^+ - NH_3$), 203 (41.1, $M^+ - H_2NCN$).

VIIId: Mass spectrum, *m/e*: 369 (M^+), 368 ($M^+ - H$).

TABLE 3. Characteristics of Pyridothieno(selenopheno)pyrimidines VII and IX

Compound	Chemical formula	mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, chemical shifts, ppm, coupling constants (J), Hz					Yield, %
				R^1	R^2	R^3	2-NH_2	4-NH_2	
1	2	3	4	5	6	7	8	9	10
VIIIa	$C_{10}H_9N_5S$	>340	3472, 3316, 3164 (NH_2); 1652, 1620, 1573 (C=N)	8,25 d, J = 8	7,36 d, J = 8	2,62 s	6,14 br.s	7,05 br.s	76
VIIIb	$C_{11}H_{11}N_5S$	298...299	3464, 3424, 3328, 3204 (NH_2); 1618, 1590, 1568 (C=N)	2,90 s	7,12 s	2,55 s	5,96 br.s	6,92 br.s	93 70* 91*2
VIIIc	$C_{15}H_{11}N_5S$	324...325	3436, 3348, 3100 (NH_2); 1666, 1608, 1570, 1562 (C=N)	8,43 d, J = 8	8,09 d, J = 8	7,44...7,60 m (*м*- and p-H_{Ph}), 8,18...8,22 m (*o*-H_{Ph})	6,17 br.s	7,11 br.s	84
VIIId	$C_{21}H_{15}N_5S$	278...279	3400, 3140 (NH_2); 1660, 1640, 1595, 1565 (C=N)	7,45...7,60 m (*м*- and p-H_{Ph})*3, 7,72...7,78 m (*o*-H_{Ph})	7,85 s	7,45...7,60 m (*м*- and p-H_{Ph})*3, 8,23...8,30 m (*o*-H_{Ph})	5,53 s	7,03 s	64
VIIIe	$C_{22}H_{16}ClN_5S$	276...277	3400, 3200 (NH_2); 1635, 1570 (C=N)	7,53, 7,77, AA'BB'	7,84 s	2,40 s (CH_3), 7,35, 8,17, AA'XX'	5,64 br.s	7,03 br.s	63
VIIIf	$C_{16}H_{10}F_3N_5S$	261...262	3400, 3352, 3108 (NH_2); 1616, 1566 (C=N)	–	8,30 s	7,55...7,65 m (*м*- and p-H_{Ph}), 8,25...8,34 m (*o*-H_{Ph})	6,06 s	7,20 s	42
VIIIg	$C_{14}H_{14}N_6S$	>340	3420, 3336, 3172 (NH_2); 1666, 1638, 1558 (C=N)	7,89 s	1,62, 2,00, 2,58, 3,17 4 m (CH_2), 3,2...3,4 (CH)*3		6,12 s	7,06 s	84

TABLE 3. (Continued)

1	2	3	4	5	6	7	8	9	10
VIII h	$C_{19}H_{16}ClN_5S$	271...272	3456, 3332, 3200 (NH_2); 1650, 1630, 1562 (C=N)	7,25, 7,46, AA'BB'	1,60...1,75, 1,77...1,90 2 m ($2CH_2$), 2,41 t, J = 6,5 (8-CH_2), 3,03 t, J = 6,5 (7-CH_2)		5,24 br.s	6,89 br.s	67
VIII i	$C_{19}H_{16}BrN_5S$	295...296	3456, 3332, 3212 (NH_2); 1650, 1630, 1560 (C=N)	7,17, 7,60, AA'BB'	1,60...1,75, 1,75...1,90 2 m ($2CH_2$), 2,39 t, J = 6 (8-CH_2), 3,02 t, J = 6 (7-CH_2)		5,25 br.s	6,90 br.s	71
VIII j	$C_{18}H_{16}N_6S$	314...316	3460, 3324, 3108 (NH_2); 1664, 1606, 1560 (C=N)	*4	1,65...1,77, 1,77...1,92 2 m ($2CH_2$), 2,46 t, J = 6 (8-CH_2), 3,04 t, J = 6 (7-CH_2)		5,22 br.s	6,93 br.s	85
VIII k	$C_{11}H_5F_6N_5S$	249...250	3560, 3452, 3324, 3168 (NH_2); 1658, 1604, 1562 (C=N)	–	8,20 s	–	6,18 br.s	7,37 br.s	74
IX b	$C_{11}H_{11}N_5Se$	288...289	3492, 3340, 3132 (NH_2); 1664, 1614, 1585, 1564 (C=N)	2,88 s	7,11 s	2,52 s	5,90 br.s	6,78 br.s	76
IX f	$C_{16}H_{10}F_3N_5Se$	289...290	3416, 3140 (NH_2); 1640, 1610, 1562 (C=N)	–	8,30 s	7,54...7,64 m (*m*-and p-H_{Ph}), 8,25...8,30 m (*o*-H_{Ph})	5,96 br.s	7,10 br.s	63

*Method D.

*2Method E.

*3The signal is overlapped by the signal of protons of another fragment.

*4Signals of the pyridyl fragment: 7.47 d.d, J_1 = 8, J_2 = 5 Hz (5'-H), 7.70 d.t, J_1 = 8, J_2 = 2 Hz (4'-H), 8.41 d, J = 2 Hz (2'-H), 8.61 d.d, J_1 = 5, J_2 = 2 Hz (6'-H).

2,4-Diamino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (VIIIb). Method D. A sample of 1 mmole aqueous KOH was added to a solution of 1 mmole pyridinethione IIb in 20 ml ethanol and the mixture was stirred for 10 min at room temperature. Then, 1.1 mmole N-cyanochloracetamidine I was added and the mixture was maintained at room temperature for 20 min. Then, a solution of 3 mmoles EtONa in ethanol was added and the mixture was heated at reflux for 2 h. The product was isolated as in the case of IV.

Method E. A mixture of 1 mmole thienopyridine IVb, 5 ml 5% hydrochloric acid, and 5 ml water was stirred at room temperature for 0.5 h, poured into water, and neutralized by the addition of sodium carbonate. The precipitate formed was filtered off and subsequently treated as described for IV.

2,4-Diamino-7,9-di(trifluoromethyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (VIIIk). A sample of 10 ml 35% hydrochloric acid was added to a solution of 2 mmoles thienopyridine IVk in 20 ml methanol. The mixture was heated at reflux and then maintained for 12 h at 20°C. Water was added and the mixture was neutralized by adding sodium carbonate. The product was isolated as indicated for VI.

Reaction of thienopyridine IVb with acetic anhydride. Thienopyridine IVb was heated with excess acetic anhydride at reflux for 6 h. The reaction mixture was evaporated on a rotary evaporator and the residue was analyzed without additional purification. PMR spectral analysis indicated that the product consisted of 70% VIIIb and 30% X.

2-Acetylamino-4-amino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (X). A mixture of 1 mmole pyridothienopyrimidine VIIIb and excess acetic anhydride (6 ml) was heated a reflux for 48 h without access to atmospheric moisture. The reaction mixture was evaporated on a rotary evaporator to dryness. The residue was washed with ethanol and dried in the air, mp >340°C. IR spectrum, cm^{-1}: 3332, 3184, (NH_2, NH), 1670 (C=O), 1645, 1578 (C=N). PMR spectrum, ppm: 2.29 (3H, s, $COCH_3$), 2.58 (3H, s, 7-CH_3), 2.90 (3H, s, 9-CH_3), 7.23 (1H, s, 8-H), 7.44 (2H, br.s, 4-NH_2), 9.90 (1H, br.s, NHCO). The yield of X was 97%.

2-Amino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimid-4-one (XI). A mixture of 1 mmole thienopyridine IVb and 15 ml 48% hydrobromic acid was heated at reflux for 2 h, poured into water, and neutralized by the addition of sodium carbonate. The precipitate formed was filtered off, washed with water and ethanol, and dried in the air, mp >340°C. IR spectrum, cm^{-1}: 3392, 3320, 3188 (NH_2, NH), 1690 (C=O), 1648, 1578 (C=N). PMR spectrum, ppm: 2.55 (3H, s, 7-CH_3), 2.88 (3H, s, 9-CH_3), 6.57 (2H, s, 2-NH_2), 7.16 (1H, s, 8-H), 11.30 (1H, br.s, NH). Mass spectrum, *m/e* (intensity, %): 248 (5.4), 247 (19.4), 246 (100, M^+), 203 (15.5, M^+ −HNCO). The yield of XI was 62%.

Product XI was obtained analogously from pyridothienopyrimidine VIIIb in 83% yield. The IR spectrum of this sample was identical to the IR spectrum of the product obtained from thienopyridine IVb.

7,9-Dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-2,4-dione (XII). A solution of 1 mmole $NaNO_2$ in 10 ml sulfuric acid was added slowly with stirring to a suspension of 1 mmole thienopyridine IVb in 5 ml concentrated sulfuric acid at 0°C. The reaction mixture was stirred for 0.5 h at 0°C, poured onto ice, and neutralized by the addition of sodium carbonate at 20°C. The precipitate formed was filtered off, washed with water and acetone, dried in the air, and washed with boiling acetonitrile to remove traces of the starting thienopyridine, mp >340°C. IR spectrum, cm^{-1}: 3420, 3324, 3092 (NH), 1675, 1640 (C=O), 1616, 1595, 1562, 1550, 1530. PMR spectrum, ppm: 2.56 (3H, s, 7-CH_3), 2.86 (3H, s, 9-CH_3), 7.18 (1H, s, 8-H), 7.50 (1H, br.s, NH). Mass spectrum, *m/e* (intensity, %): 249 (6.3), 248 (16.1), 247 (100, M^+), 205 (20.6), 204 (57.7, M^+ −HNCO). The yield of XII was 53%.

Product XII was obtained analogously also from pyridothienopyrimidine VIIIb in 61% yield. The IR spectrum of this sample was identical to the spectrum of the sample synthesized from thienopyridine IVb.

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