NEW SYNTHESIS OF 2-AMINO-4-OXOPYRIDO[3,2-*e*]-1,3-THIAZINES AND 1-ALKYL(ARYL)PYRIDO[3,2-*e*]-2-THIOURACILS

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Addition reactions of 2-chloronicotinoyl isothiocyanate with primary and secondary amines and subsequent cyclization of intermediate thioureas represent new synthesis of pyrido[3,2-*e*]thiouracil and pyrido[3,2-*e*]-thiazine derivatives. 2-Amino-4-oxopyrido[3,2-*e*]-1,3-thiazines are formed upon heating the reaction components in ethanol, whereas 1-alkyl(aryl)pyrido[3,2-*e*]-2-thiouracils are products of alkali-catalyzed reaction. In reaction with primary amines the corresponding thioureas were isolated as intermediates, whereas secondary amines reacted directly to give the pyridothiazine derivatives. Structure of the synthesized compounds was confirmed by their ^{13}C NMR and mass spectra; also the IR and ^{1}H NMR spectra are in accord with the suggested formulae.

In our preceding paper we described the synthesis of 2-substituted 6-phenyl-4*H*-1,3-thiazin-4-ones starting from 3-chloro-3-phenylpropenoyl isothiocyanate[1]. Similar syntheses of 2-amino-4*H*-1,3-thiazin-4-ones and thiouracils by reaction of *β*-chloroacryloyl isothiocyanates with amines were studied by Schroth and coworkers[2]. These 1,3-thiazine and pyrimidine systems are very interesting both from the chemical and biochemical point of view[3-5].

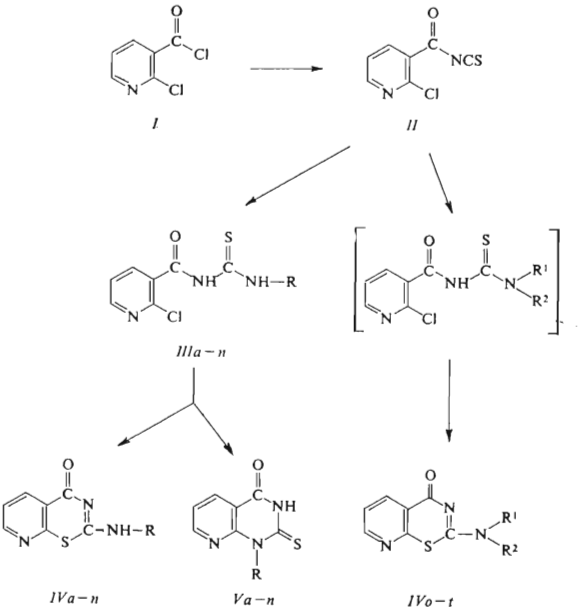
In our search for biologically active compounds we tried to introduce a pyridine nucleus into the thiazine and pyrimidine heterocycles, making use of the previous results.

Such compounds are described in several papers[6-12]. The pyrido[3,2-*e*]thiouracil derivatives were synthesized by cyclization of 2-aminonicotinic acid, its amide or ester, with acetic anhydride, methyl isothiocyanate, *etc.*[6-8]. Stanovnik and Tišler[9] carried out the cyclization in the presence of N-ethoxycarbonyl-N'-2-pyridylthiourea, prepared from 2-aminopyridine and ethoxycarbonyl isothiocyanate whereas Noda and coworkers[10] obtained pyrido[3,2-*e*]thiouracils by reaction of 2-halogenonicotinamides with aryl isothiocyanates. Pyrido[3,2-*e*]thiazine derivatives were synthesized by reaction of 2-mercapto- or 2-chloronicotinic acid with carbodiimides or by condensation of ethyl 2-chloronicotinate with the corresponding thioureas[13-14].

Our present synthesis starts from 2-chloronicotinoyl isothiocyanate (*II*)prepared from 2-chloronicotinoyl chloride (*I*) and ammonium thiocyanate in acetone. The

compound *II* reacted with amines to give thioureas *III* which were cyclized to 2-amino-4-oxopyrido[3,2-*e*]-1,3-thiazines *IV* or pyrido[3,2-*e*]-2-thiouracils *V*, depending on the reaction conditions (Scheme 1). Reaction of compound *II* with ammonia and aliphatic amines in acetone or chloroform led to the thioureas *IIIa*–*IIIe*, reaction with aromatic amines afforded well crystallizable products *IIIf*–*IIIn* (Table I).

Because of ambidental character of the thiocarbamoyl group —CSN< in the thioureas *IIIa*–*IIIn*, the 2-pyridine chlorine atom may be substituted either by the



In formulae *III*–*V*: *a*, R = H; *b*, R = CH_3; *c*, R = C_2H_5; *d*, R = C_6H_{11}; *e*, R = $C_6H_5CH_2$; *f*, R = C_6H_5; *g*, R = *p*-$CH_3C_6H_4$; *h*, R = *o*-CH_3—C_6H_4; *i*, R = *p*-CH_3—O—C_6H_4; *j*, R = *p*-Br—C_6H_4; *k*, *p*-NO_2—C_6H_4; *l*, R = *m*-NO_2—C_6H_4; *m*, R = *p*-$(CH_3)_2NC_6H_4$; *n*, R = v-naphtyl; *o*, $R^1 = R^2 = (CH_2)_5$; *p*, $R^1 = R^2 = (CH_2)_4O$; *r*, $R^1 = R^2 = C_2H_5$; *s*, $R^1 = R^2 = C_6H_5$; *t*, $R^1 = CH_3$; $R^2 = C_6H_5$.

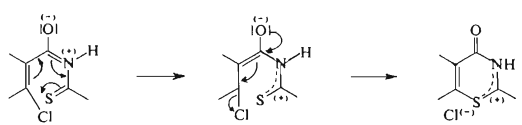
SCHEME 1

sulfur atom under formation of pyridothiazines *IVa–IVn*, or by the nitrogen atom, giving rise to pyridothiouracils *Va–Vn*.

TABLE I
Properties of N-substituted-N'-(2-chloronicotinoyl)thioureas *IIIa–IIIn* and *IIIr*

Compound	Formula (mol.wt.)	M.p., °C solvent	Yield %	Calculated/Found		
				% C	% H	% N
IIIa	$C_7H_6ClN_3OS$ (215·7)	107 acetone–water	30	38·98 39·02	2·80 2·71	19·48 19·25
IIIb	$C_8H_8ClN_3OS$ (229·7)	96–97 acetone–water	27	41·83 41·80	3·51 3·91	18·29 18·30
IIIc	$C_9H_{10}ClN_3OS$ (243·7)	98 acetone–water	28	44·35 44·55	4·13 3·98	17·24 17·48
IIId	$C_{13}H_{16}ClN_3OS$ (297·8)	137 ethanol–water	21	52·38 52·00	5·37 5·39	14·10 14·00
IIIe	$C_{14}H_{12}ClN_3OS$ (305·8)	140–142 acetone–water	56	54·99 55·00	3·95 3·70	13·74 13·70
IIIf	$C_{13}H_{10}ClN_3OS$ (291·7)	122–123 ethanol–water	85	53·51 53·60	3·45 3·50	14·40 14·50
IIIg	$C_{14}H_{12}ClN_3OS$ (305·7)	131–132 ethanol–water	60	54·99 55·00	3·95 4·01	13·74 13·50
IIIh	$C_{14}H_{12}ClN_3OS$ (305·8)	154–155 ethanol–water	63	54·99 54·80	3·95 4·17	13·74 13·70
IIIi	$C_{14}H_{12}ClN_3O_2S$ (321·8)	154–155 acetone–water	73	52·25 52·30	3·75 3·60	13·04 13·10
IIIj	$C_{13}H_9BrClN_3OS$ (370·7)	160–161 acetone–water	82	42·12 42·16	2·44 2·51	11·33 11·30
IIIk	$C_{13}H_9ClN_4O_3S$ (336·8)	190–191 acetone–water	81	46·36 46·50	2·69 2·85	16·63 16·61
IIIl	$C_{13}H_9ClN_4O_3S$ (336·8)	196–197 acetone–water	83	46·36 46·50	2·69 2·85	16·63 16·61
IIIm	$C_{15}H_{15}ClN_4OS$ (334·8)	150–151 ethanol–water	76	53·80 54·02	4·51 4·70	16·73 16·81
IIIn	$C_{17}H_{12}ClN_3OS$ (339·8)	131–132 ethanol–water	59	60·03 60·15	3·59 3·35	12·36 12·30
IIIr	$C_{11}H_{14}ClN_3OS$ (271·8)	102–103 acetone–water	48	48·71 48·70	5·19 5·12	15·46 15·50

Compounds *IIIa–IIIn* were cyclized by four hours' reflux in toluene or by two hours' boil in ethanol to give the corresponding pyridothiazines *IVa–IVn* (Table II and III). These derivatives were formed also directly in the reaction of II with secondary amines (N-methylaniline, morpholine, piperidine, diphenylamine), except diethylamine which afforded also the intermediate thiourea *IIIr*. On the other hand, reaction in an alkaline medium (triethylamine, 1M-NaOH, lithium hydride in dimethylformamide, or a 1 : 1 methanol–ammonia mixture) led to the corresponding pyridothiouracils *Va–Vn* (Scheme 1), well soluble in chloroform. The obtained pyridothiazine and pyridothiouracil derivatives are not interconverted by Dimroth rearrangement in an acidic, neutral or basic medium. Mechanism of reaction of similar β-chlorovinyl-carbonyl systems Cl—C=C—C=O was studied by Schroth and collaborators[2]. These authors assume a pericyclic process in which the chlorine atom substition is an electrocyclic reaction or an intramolecular polar cycloaddition[15–18] (Scheme 2).



SCHEME 2

The amine – imine tautomerism in N-substituted 2-amino-6-phenyl-4*H*-1,3-thiazin-4-ones was investigated by Imrich and Kristian[1] by means of IR spectra. The N-monosubstituted derivatives *IVa–IVn* can exist in two tautomeric forms. Therefore, their carbonyl vibrations, ν(C=O), can be observed in the region 1 630 to 1 670 cm^{-1}, according to the structure and solvent whereas the N,N-disubstituted pyridothiazines *IVo–IVt*, which can exist only in the amino form, absorb at 1 630 cm^{-1}. The strong absorption bands due to ν(C=N) are situated at 1480 to 1520 cm^{-1}. In the case of pyridothiouracils *Va–Vn* whose —NH—CO— grouping in the thiouracil system corresponds to the imino form of 2-aminothiazines, the carbonyl band of all derivatives is markedly shifted to higher frequencies (1680 to 1 710 cm^{-1}). Compound *IVg* was methylated to give the 3-N-methyl derivative *VI* whereas methylation of the compound *Vg* afforded the S-methyl derivative *VII* (Scheme 3). As expected[1], methylation of the compounds *IVg* and *Vg* changed the conjugation in the thiazine and thiouracil ring, causing a shift of ν(C=O) bands to higher and lower frequencies, respectively (for *VI* ν(C=O) ~ 1 670 cm^{-1}, for *VII* ν(C=O) ~ 1 650 cm^{-1}). A characteristic feature of the prepared heterocycles is that in the UV spectra the compounds *V* show a marked bathochromic shift of the long-wave maximum relative to compounds *IV*.

TABLE II

Spectral data for N-substituted-N′-(2-chloronicotinoyl)thioureas *IIIa*—*IIIn* and *IIIr*

Compound	IR cm^{-1} ($CHCl_3$)			^1H NMR (ppm δ)[a]		UV nm
	ν(C=O) ν(NH—C=S)	ν(NH) free	(νNH) assoc.	H_γ—H_β[b] H_γ	NH	λ_{max}/log ε
IIIa	1 680 1 500	3 400	3 270 3 200	8·52—7·43 7·87	11·18	222/5·13
IIIb	1 675 1 510	3 400	3 283 3 250	8·50—7·31 7·90	10·50	235/5·09
IIIc	1 676 1 488	3 380	3 200 3 122	8·53—7·37 7·97	9·70 10·33	236/4·81
IIId	1 680 1 495	3 395	3 250 3 200	9·76—7·81	9·75 11·12	240/5·03
IIIe	1 70 1 510	3 400	3 250 3 198	8·47—7·30 7·85	10·80 11·40	245/4·18
IIIf[c]	1 673 1 506	3 386	3 242 3 180	8·55—7·40 8·07	9·62 12·20	250/4·28
IIIg	1 670 1 500	3 390	3 233 3 172	8·51—7·40 7·95	11·51 12·30	223/3·14
IIIh	1 674 1 502	3 385	3 240 3 174	8·50—7·40 7·9	11·67 12·25	230/4·16
IIIi	1 675 1 510	3 400	3 219 3 190	8·62—7·45 8·12	11·53	240/4·03
IIIj	1 677 1 502	3 400	3 240 3 170	8·50—7·37 7·93	11·75 12·50	260/4·13
IIIk	1 680 1 505	3 385	3 174 3 135	8·68—7·75 8·00	12·25 12·50	—
IIIl	1 682 1 506	3 388	3 194 3 130	8·77—7·80 8·22	12·52	244/4·11
IIIm	1 671 1 520	3 389	3 238 3 182	8·47—7·42 7·92	12·12	—
IIIn	1 670 1 502	3 390	3 245 3 178	8·52—7·42 8·00	11·80 12·53	—
IIIr	1 700 1 500	3 385	3 240 3 130	8·60—7·50 8·00	9·70	—

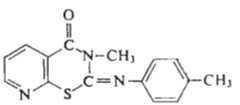
[a] Compounds *IIIa*—*IIIe*, *IIIg* and *IIIr* were measured in C^2HCl_3, compounds *IIIf*, *IIIh*—*IIIn* in C^2HCl_3–hexadeuteriodimethyl sulfoxide; [b] pyridine ring protons; [c] mass spectra, *m*/*z* (rel. int., %): 305 (2), 270 (55), 269 (100), 149 (34·2), 138 (64·2), 132 (56·5), 120 (16·8), 106 (20·4), 91 (22·3), 76 (14·4), 36 (65·7).

TABLE III

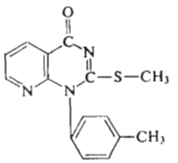
Properties of 2-amino-4-oxopyrido[3,2-*e*]-1,3-thiazines *IVa*–*IVt*

Compound	Formula (mol. wt.)	M.p., °C solvent[a]	Yield %	Calculated/Found		
				% C	% H	% N
IVa	$C_7H_5N_3OS$ (179·2)	175 DMF–H_2O	43	46·91 47·01	2·81 2·85	23·44 23·51
IVb	$C_8H_7N_3OS$ (193·2)	148 DMSO–H_2O	41	49·73 49·63	3·65 3·66	21·75 21·80
IVc	$C_9H_9N_3OS$ (207·2)	194 DMF–H_2O	48	52·16 52·10	4·38 4·44	20·27 20·30
IVd	$C_{13}H_{15}N_3OS$ (261·4)	121 DMF–H_2O	41	59·74 59·68	5·78 5·75	16·07 16·02
IVe	$C_{14}H_{11}N_3OS$ (269·3)	179 DMF–H_2O	69	62·43 62·55	4·12 4·01	15·60 15·81
IVf	$C_{13}H_9N_3OS$ (255·3)	190 DMSO–H_2O	68	61·16 62·03	3·55 3·61	16·45 16·40
IVg	$C_{14}H_{11}N_3OS$ (269·3)	164 DMSO–H_2O	60	62·43 62·40	4·12 4·00	15·60 16·03
IVh	$C_{14}H_{11}N_3OS$ (269·3)	173 DMF–H_2O	58	62·43 62·66	4·12 4·30	15·60 15·83
IVi	$C_{14}H_{11}N_3O_2S$ (285·3)	193–194 DMF–H_2O	58	58·93 58·74	3·88 3·96	14·73 14·80
IVj	$C_{13}H_8BrN_3OS$ (334·2)	202 DMF–H_2O	61	46·72 46·88	2·41 2·55	12·57 12·61
IVk	$C_{13}H_8N_4O_3S$ (300·3)	309 DMF–H_2O	63	52·00 52·03	2·68 2·88	18·66 18·77
IVl	$C_{13}H_8N_4O_3S$ (300·3)	310 DMF–H_2O	64	52·00 5·20	2·68 2·83	18·66 18·56
IVm	$C_{15}H_{14}N_4OS$ (298·4)	204 DMF–H_2O	63	60·38 60·31	4·73 4·81	18·78 18·80
IVn	$C_{17}H_{11}N_3OS$ (305·4)	260 DMF–H_2O	66	66·87 66·91	3·63 3·71	13·76 14·02
IVo	$C_{11}H_{13}N_3OS$ (235·3)	202 $CHCl_3$–PE	42	56·15 56·11	5·57 5·60	17·86 17·80
IVp	$C_{14}H_{11}N_3OS$ (269·3)	256 $CHCl_3$–PE	56	62·43 62·55	4·12 4·11	15·60 15·70
IVr	$C_{19}H_{13}N_3OS$ (331·4)	268 $CHCl_3$–PE	46	68·86 69·02	3·95 4·01	12·68 13·63
IVs	$C_{12}H_{13}N_3OS$ (247·3)	187 $CHCl_3$–PE	35	58·27 58·00	5·30 5·10	16·99 16·85
IVt	$C_{11}H_{11}N_3O_2S$ (249·3)	212 $CHCl_3$–PE	38	53·00 53·10	4·45 4·51	16·85 16·90

DMF dimethylformamide, DMSO dimethyl sulfoxide, PE light petroleum.



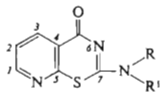
VI



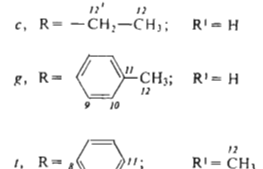
VII

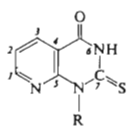
SCHEME 3

The ^{1}H NMR spectra of the pyridothiazines *IV* and pyridothiouracils *V* exhibit three multiplets at δ 7·5–9·12, typical for pyridine ring protons, together with signals of 2-alkyl or 2-aryl substituents. Because of rapid chemical exchange, the N—H proton signal was observed only in the spectra of some derivatives (*IVg*, *h* and *Vm*) (Table IV and VI). The N-methyl singlet of *VI* is at δ 3·5 whereas the S-methyl singlet of *VII* is situated at δ 2·6 (Scheme 3). The pyridothiazine and pyridothiouracil systems of the synthesized compounds were distinguished by the ^{13}C NMR spectra of several selected representatives: *IIIg*, *IVc*, *IVg*, *IVt*, *Vc* and *Vg*. The signals were assigned

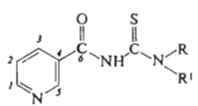


IVc, *IVg*, *IVt*





Vc, *Vg*



IIIg

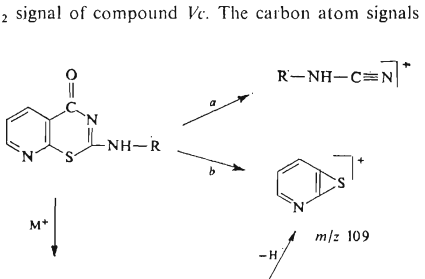
by the off resonance method. First, we determined the ^{13}C chemical shifts of the thiocarbonyl carbon atoms, present only in the pyridothiouracils *V*. It is known[8,9] that the signal of this carbon is shifted downfield relative to that of the carbonyl carbon.

TABLE IV

Spectral data for 2-amino-4-oxopyrido[3,2-*e*]-1,3-thiazines *IVa*—*IVt*

Compound	IR cm^{-1}, (KBr)		^1H NMR (ppm δ)[a]		UV nm
	ν(C=O)	ν(C=N)	$H_\alpha - H_\gamma$ H_β[b]	NH	λ_{max}/log ε
IVa	1 620[c] 1 625	1 509	9·12—8·68 7·50	12·40	222/5·48
IVb	1 600 1 630[c]	1 505	9·02—8·62 7·65	—	228/4·08
IVc	1 625	1 505	8·76—8·51 7·30	—	221/5·54 315/3·39
IVd	1 660	1 500	8·87—8·63 7·32	—	326/5·43
IVe	1 670	1 520	8·80—8·58 7·45	—	235/3·40
IVf[d]	1 648[c] 1 625	1 520	8·50—8·42 7·25	—	237/4·31
IVg[e]	1 635	1 505	8·52—8·45 7·35	12·55	248/3·70
IVh	1 640	1 520	9·85—8·60 7·42	12·57	230/3·33
IVi[f]	1 635	1 510	8·81—8·65 8·68	—	246/3·83
IVj	1 640	1 495	8·75—8·60 8·31	—	245/3·46
IVk	1 630	1 525	8·87—8·76	12·50	230/4·18
IVl	1 630	1 520	8·87—8·75	—	230/3·46
IVm	1 645[c] 1 630	1 500	8·75—8·61 7·57	—	224/3·16
IVn	1 660[c] 1 630	1 510	8·67—8·57 7·55	—	225/3·12
IVo	1 630[c]	1 505	8·51—8·42 7·25	—	256/4·73
IVp	1 638[c]	1 495	8·63—8·53 7·38	—	262/4·19
IVr	1 639[c]	1 486	8·93—8·62 7·56	—	260/4·32
IVs	1 629[c]	1 495	8·74—8·55 7·45	—	255/4·13
IVt	1 635[c]	1 508	8·62—8·52 7·40	—	254/4·03

In the spectra of *Vc* and *Vg* the respective signals at 167·89 ppm and 177·58 ppm are due to the thiocarbonyl carbon atoms whereas the signals of the corresponding carbonyl carbon atoms are at 161·92 ppm and 158·80 ppm, respectively. The thiourea *IIIg* exhibits a C=S carbon signal at 178·29 ppm and a signal due to the carbonyl carbon at 166·28 ppm. Compound *IVi* serves as a good model of a pyridothiazine skeleton since its synthesis cannot lead to a thiouracil derivative. Due to conjugation with the carbonyl group, the C=N carbon signal is shifted downfield (168·02 ppm) relative to the carbonyl carbon signal (163·46 ppm). Analogous values are found also in the spectra of pyridothiazines *IVc* and *IVg* (δ(CN) 173·61 and 173·91 ppm, respectively; δ(C=O) 164·72 and 164·95 ppm, respectively). In the case of the compound *IVi* the CH_3 signal is obscured by the dimethyl sulfoxide multiplet; the same was observed for the CH_2 signal of compound *Vc*. The carbon atom signals are listed in Table VII.



IVf, $M^+ = 255$; *IVg*, $M^+ = 269$; *IVi*, $M^+ = 285$

SCHEME 4

The pyridothiazine and pyridothiouracil structures were confirmed also by mass spectra of selected compounds. Mass spectra of the pyridothiazines *IVf*, *IVg* and *IVi* show that the molecular ions, M^+ are the most abundant. On the other hand, the

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[a] In deuteriochloroform–hexadeuteriodimethyl sulfoxide; [b] pyridine ring protons; [c] in chloroform; [d] mass spectrum, *m/z* (rel. int., %): 255 (94), 138 (100), 118 (61), 105 (31), 77 (41), 41 (31); [e] mass spectrum, *m/z* (rel. int., %): 269 (100), 137 (34·2), 132 (39·5), 109 (36), 105 (27·2), 91 (36·8), 77 (16·8), 41 (18·5); [f] mass spectrum, *m/z* (rel. int., %): 285 (100), 270 (11·9), 148 (95·2), 137 (45·2), 109 (16), 41 (18·57), 39 (17).

thiourea *IIIg* shows only a very weak molecular ion peak $M^+ = 305$. During the measurement the compound loses hydrogen chloride and is cyclized to the corresponding heterocyclic compound *IVg*. This is manifested by the presence of the fragment ion $[M\text{-}HCl]^+$ which represents a base peak. Further fragmentation

TABLE V
Properties of 1-alkyl(aryl)pyrido[3,2-*e*]-2-thiouracils *Va*–*Vn*

Compound	Formula (mol. wt.)	M.p., °C (chloroform–solvent)	Yield %	Calculated/Found		
				% C	% H	% N
Va	$C_7H_5N_3OS$ (179·2)	286 light petroleum	40	46·91 46·80	2·81 2·77	23·44 23·36
Vb	$C_8H_7N_3OS$ (193·2)	276–278 ether	41	49·73 49·50	3·65 2·61	21·75 21·66
Vc	$C_9H_9N_3OS$ (207·3)	209 ether	47	52·16 52·11	4·38 4·32	20·27 20·30
Vd	$C_{13}H_{15}N_3OS$ (261·4)	201 pentane	43	59·74 59·60	5·78 6·00	16·08 16·00
Ve	$C_{14}H_{11}N_3OS$ (269·3)	214 light petroleum	67	62·43 62·59	4·12 4·12	15·60 15·61
Vf	$C_{13}H_9N_3OS$ (255·3)	210–212 light petroleum	68	61·16 61·20	3·55 3·43	16·46 16·50
Vg	$C_{14}H_{11}N_3OS$ (269·3)	267 light petroleum	60	62·43 62·50	4·12 4·10	15·60 15·66
Vh	$C_{14}H_{11}N_3OS$ (269·3)	210 ether	38	62·43 62·50	4·12 4·15	15·60 14·68
Vi	$C_{14}H_{11}N_3O_2S$ (285·3)	246 ether	57	58·93 58·70	3·88 3·90	14·73 14·83
Vj	$C_{13}H_8BrN_3OS$ (334·2)	270 heptane	61	46·72 46·80	2·41 2·49	12·57 12·76
Vk	$C_{13}H_8N_4O_3S$ (300·3)	347 ether	63	52·00 52·13	2·68 2·60	18·66 18·50
Vl	$C_{13}H_8N_4O_3S$ (300·3)	259 ether	54	52·00 51·90	2·68 2·61	18·66 18·40
Vm	$C_{15}H_{14}N_4OS$ (298·4)	286 ether	63	60·38 60·41	4·73 4·77	18·78 18·80
Vn	$C_{17}H_{11}N_3OS$ (205·4)	316 light petroleum	66	66·87 66·60	3·63 3·70	13·76 13·80

TABLE VI

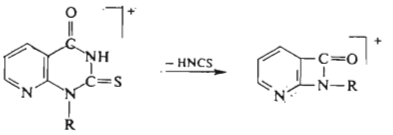
Spectral data for 1-alkyl(aryl)pyrido[3,2-*e*]-2-thiouracils *Va*—*Vn*

Compound	IR cm^{-1}		^1H NMR (ppm, δ)[a]		UV nm
	ν(C=O)	ν(NHC=S)	$H_\alpha - H_\gamma$[b] H_β	NH	λ_{max}/log ε
Va	1 690	1 500 1 400	9·12—8·68 7·50	12·01	254/3·01
Vb	1 710	1 450	9·12—9·62 7·65	—	293/5·19
Vc	1 710	1 440	8·76—8·51 7·30	—	313/3·14
Vd	1 696	1 496	8·87—8·63 7·32	—	296/3·20
Ve	1 685	1 460	8·80—8·58 7·45	—	293/3·40
Vf	1 703	1 448	8·50—8·42 7·25	—	270/3·38
Vg[c]	1 710	1 450	8·52—8·45 7·35	12·55	294/3·47
Vh	1 700	1 440	8·85—8·60 7·42	11·57	280/3·40
Vi[d]	1 690	1 440	9·81—8·65 8·68	—	280/3·41
Vj	1 680	1 430	8·75—8·60 8·31	—	281/3·51
Vk	1 715	1 460	8·87—8·70 8.21	— —	277/3·46
Vl	1 695	1 450	8·87—8·73 8·10	—	274/3·42
Vm	1 700	1 450	8·75—8·61 7·57	12·55	280/3·29
Vn	1 710	1 460	8·70—8·57 7·55	—	292/3·38

[a] Compounds *Va*—*Vd* in C^2HCl_3, compounds *Ve*—*Vn* in C^2HCl_3–hexadeuteriodimethyl sulfoxide; [b] pyridine ring protons; [c] mass spectrum, *m*/*z* (rel. int., %): 269 (72), 268 (100), 210 (10), 182 (18), 134 (11), 119 (18·5), 91 (21·4), 65 (14), 59 (22·9), 44 (22·6); [d] mass spectrum, *m*/*z* (rel. int., %): 285 (100), 226 (51), 198 (43), 142 (31), 119 (31), 107 (28), 59 (31), 15 (20·3).

proceeds according to Scheme 4 valid for the pyridothiazines *IV*. Mass spectra of compounds *IV* exhibit also doubly charged positive fragments of half the *m/z* value. The decompositions of the molecular ions, depicted in Scheme 4, confirms unequivocally their structure.

Mass spectra of pyridothiouracils *Vg*, *Vi* exhibit again characteristic strong molecular ion peaks, which represent the base peaks. The fragment ions $[M\text{-}HNCS]^+$ are typical for the structure *V* (Scheme 5).



Vg, $M^+ = 269$; *Vi*, $M^+ = 285$ *Vg*, *m/z* 210; *Vi*, *m/z* 226

SCHEME 5

EXPERIMENTAL

2-Chloronicotinoyl chloride (*I*) was prepared according to ref.[19] in 55% yield, m.p. 21°C. IR spectrum ($CHCl_3$), cm^{-1}: ν(C=O) 1 780, ν(C=N) 1 575, ν(C—Cl) 880. ^1H NMR spectrum (C^2HCl_3), δ: 8·56–8·37 m (H_α and H_γ), 7·46 q ($H\beta$).

TABLE VII

Chemical shifts in ^{13}C NMR spectra (ppm, internal standard tetramethylsilane)

C-atom	*IIIg*	*IVc*	*IVg*	*IVt*	*Vc*	*Vg*
1	151·42	143·07	142·70	153·04	152·89	153·37
2	123·11	114·03	113·27	123·85	123·33	123·17
3	138·69	142·55	142·10	137·36	137·51	137·46
4	123·10	131·28	130·90	119·17	120·27	120·12
5	146·28	152·48	149·72	154·92	154·91	154·86
6	166·28	164·72	164·95	163·46	161·92	158·80
7	178·29	173·61	173·91	168·02	167·89	177·58
8	135·11	—	134·52	140·82	—	134·21
9	124·27	—	119·63	128·18	—	121·68
10	129·34	—	128·89	130·28	—	129·53
11	131·03	—	132·69	129·64	—	128·88
12	20·77	14·89	19·83	—	13·73	20·45
12	—	34·08	—	—	37·40	—

2-Chloronicotinoyl Isothiocyanate (*II*)

A solution of 2-chloronicotinoyl chloride (0·01 mol) in acetone (10 ml) was added to a stirred solution of NH_4SCN (0·01 mol) in acetone (10 ml). After stirring for 5 min at 40°C, the separated ammonium chloride was filtered off, the filtrate was taken down and the remaining crude 2-chloronicotinoyl isothiocyanate was used directly in further preparations. The product *II* was a yellow liquid which turned dark and polymerized even in a refrigerator. IR spectrum ($CHCl_3$), cm^{-1}: ν(C=O) 1700, ν(NCS) 1948, ν(C=N) 1575. ^1H NMR spectrum (C^2HCl_3), δ: 8·68–8·62 m ($H_\alpha + H_\gamma$); 7·68, d (H_β).

N-Alkyl(aryl)-N'-2-chloronicotinoylthioureas *IIIa–IIIn*

A solution of alkyl- or arylamine (0·01 mol) in acetone (15 ml) was slowly added to a solution of an equivalent amount of the isothiocyanate *II* in acetone. After stirring for 30 min at 20°C, the mixture was poured into ice-cold water. The precipitate was filtered, dissolved in chloroform, treated with charcoal and the product was crystallized from chloroform–light petroleum or aqueous ethanol. The N-alkylthioureas *IIIa–IIId* crystallized only with difficulty (Table I).

N-Diethyl-N'-2-chloronicotinoylthiourea (*IIIr*)

A solution of diethylamine (0·01 mol) in acetone (15 ml) was added to an equimolar amount of the isothiocyanate *II* in acetone. The mixture was stirred for 30 min at room temperature and poured into cold water. The precipitate was filtered and crystallized from aqueous ethanol (1 : 1) (Table I).

2-(N-Monosubstituted)amino-4-oxopyrido[3,2-*e*]-1,3-thiazines *IVa–IVn*

The thiourea *IIIa–IIIn* (5 mmol) in ethanol (30 ml) was refluxed for 2 h in ethanol (20 ml) or for 4 h in toluene (30 ml). After cooling, the separated product was filtered, the filtrate was concentrated, affording another portion of the product. The combined portions were washed with light petroleum and crystallized from a suitable solvent (Table III).

2-(N,N-Disubstituted)amino-4-oxopyrido[3,2-*e*]-1,3-thiazines IVo–*IVt*

A solution of the secondary amine (0·01 mol) in acetone (15 ml) was slowly added to an equimolar amount of the isothiocyanate *II* in acetone. After stirring for 30 min, the mixture was briefly boiled and poured into a four-fold excess of ice-cold water.The precipitate was filtered, dissolved in an appropriate solvent, purified with charcoal and crystallizad from aqueous ethanol (Table III).

1-Alkyl(aryl)pyrido[3,2-*e*]-2-thiouracils *Va–Vn*

A solution of the corresponding thiourea *III* in dimethylformamide (15 ml) was added in the course of 5 min to a stirred suspension of lithium hydride (1 mmol) in dimethylformamide (35 ml). The mixture was stirred at room temperature until it became homogeneous and the solution was poured into ice-cold water. The crude products were crystallized from chloroform–ligh petroleum (1 : 2) (Table V).

2-(*p*-Tolylimino)-3-methyl-4-oxopyrido[3,2-*e*]-1,3-thiazine (*VI*)

The thiazine *IVg* (2 mmol) was added at room temperature to a suspension of lithium hydride (2 mmol) in dimethylformamide (20 ml) and the mixture was stirred to homogenity (about 1 h). Methyl iodide (2 mmol) was added and the stirring was continued for 1 h. The mixture was poured into cold water and the precipitate was collected on filter, washed with water and crystallized from aqueous ethanol (1 : 1), affording the product, melting at 153–155°C. Yield 78%.

For $C_{15}H_{13}N_3OS$ (283·1) calculated: 63·60% C, 4·59% H, 14·84% N; found: 63·81% C, 4·61% H, 14·92% N. IR spectrum ($CHCl_3$), cm^{-1}: ν(C=O) 1 674, ν(C=N) 1 573. ^1H NMR spectrum (C^2HCl_3), δ: 2·37, s (CH_3), 3·5, s (—N—CH_3), 6·8—7·4, m (H_β), 9·55, m, (H_α, H_γ).

1-(*p*-Tolyl)-2-S-methylpyrido[3,2-*e*]thiouracil (*VII*)

The 2-thiouracil *Vg* (2 mmol) was added at room temperature to a suspension of lithium hydride (2 mmol) in dimethylformamide (20 ml). The mixture was stirred until it became homogeneous (about 40 min), methyl iodide (2 mmol) was added and the stirring was continued for 1 h. Pouring into ice-cold water precipitated the S-methyl product which was filtered, washed with water and crystallized from aqueous ethanol (1 : 1); m.p. 253—255°C. Yield 82%. For $C_{15}H_{13}N_3OS$ (283·1) calculated: 63·60% C, 4·59% H, 14·84% N; found: 63·72% C, 4·66% H, 14·73% N. IR spectrum ($CHCl_3$), cm^{-1}: ν(C=O) 1645, ν(C=N) 1 490. ^1H NMR spectrum (C^2HCl_3), δ: 2·5, s (CH_3); 2·6, s (S—CH_3); 7·2—7·5, m (Hν, and C_6H_4); 8·55, m, (H_α, H_γ).

Spectral Measurements

The IR absorption spectra were taken in chloroform or KBr pellets in the region 400—5 000 cm^{-1} on a Specord 75 IR (Zeiss) instrument, calibrated with a polystyrene film. UV spectra were measured in methanol in 1 cm cells on a Perkin–Elmer 402 spectrophotometer. ^1H NMR spectra were obtained with an 80 MHz Tesla BS 497 spectrometer and ^{13}C NMR spectra with a 100 MHz Tesla BS 567A or JEOL FX 100 instruments in deuteriochloroform–hexadeuteriodimethyl sulfoxide mixtures with tetramethylsilane as internal standard. Mass spectra were measured on an MS-902S spectrometer (AEI, Manchester); ionization energy 70 eV, direct inlet.

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