SYNTHESIS OF 2-AMINO-5,7-DIMETHYL-4-OXOPYRIDO[3,4-*e*]-1,3-THIAZINES

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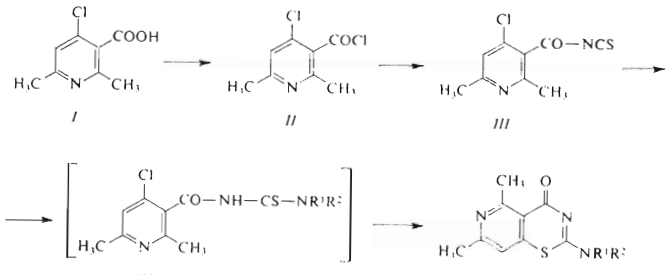
Received October 16th, 1982

New synthesis of pyrido[3,4-*e*]-1,3-thiazines consisting in reaction of 2,6-dimethyl-4-chloronicotinoyl isothiocyanate with primary or secondary amines, or with benzaldehyde phynylhydrazone, is described. High reactivity of the chlorine atom does not allow isolation of the corresponding thioureas, arising as intermediates, except in the case of the benzylamino derivative. Structure of the products was unequivocally confirmed by their spectral data (IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectra). The synthesized derivatives do not undergo the Dimroth rearrangement.

The hitherto described reactions, used for the preparation of pyrido[3,4-*e*]-1,3-thiazine derivatives, consist in the reaction of 4-chloronicotinic acid derivatives with thiourea and its N,N′-disubstituted derivatives[1,2]. The obtained pyridothiazines exhibit analgetic and intiinflammatory effects[2].

In our preceding paper we described a new synthesis of [3,2-*e*]-1,3-thiazines and pyrido[3,2-*e*]-2-thiouracils from 2-chloronicotinoyl isothiocyanate[3]. Analogically, we tried to synthesize the pyrido[3,4-*e*]-1,3-thiazine system by reaction of 4-chloro-2,6-dimethylnicotinoyl isothiocyanate with nitrogen bases. The isothiocyanate was prepared from 2,6-dimethyl-4-chloronicotinic acid[4,5] (*I*), obtained by acidification of its potassium salt to the isoelectric point (pH 4). Treatment of the acid *I* with thionyl chloride in pyridine gave the corresponding chloride *II* which upon reaction with NH_4SCN in acetone afforded 2,6-dimethyl-4-chloronicotinoyl isothiocyanate (*III*) as a yellow liquid. Since the isothiocyanate was thermally unstable, the freshly prepared crude compound was used in further reactions. It reacted with primary or secondary amines or benzaldehyde phenylhydrazone in aprotic organic solvents such as acetone, benzene or chloroform, to give the corresponding pyrido[3,4-*e*]-1,3-thiazines *V*. The reaction represents an addition – cyclization process in which the intermediate thioureas *IV* are immediately cyclized under formation of the pyridothiazines *V*. Only in the reaction with benzylamine, the corresponding thiourea *IVd* was isolated (Scheme 1). It was then converted to the pyridothiazine *Vd* as the sole product either thermally (heating in ethanol) or by treatment with lithium hydride in dimethylformamide. Since 1,3-thiazine systems are known to undergo

Dimroth rearrangement[6,7] in which the endo- and exocyclic hetero atoms (N, S) are regrouped, we tried this rearrangement also with our compounds *Va – Ve*.



In formulae IV and V:

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = C_2H_5$
c; $R^1 = H$, $R^2 = C_3H_7$
d; $R^1 = H$, $R^2 = C_6H_5CH_2$
e; $R^1 = H$, $R^2 = C_6H_5$
f; $R^1 = H$, $R^2 = 4\text{-}CH_3C_6H_4$
g; $R^1 = H$, $R^2 = 4\text{-}CH_3OC_6H_4$
h; $R^1 = H$, $R^2 = 4\text{-}BrC_6H_4$
i; $R^1 = CH_3$, $R^2 = C_6H_5$
j; $R^1 - R^2 = (CH_2)_2—O—(CH_2)_2$
k; $R^1 = R^2 = C_6H_5$
l; $R^1 = C_6H_5$, $R^2 = C_6H_5—CH=N$

SCHEME 1

Experiments, conducted in acidic, alkaline or neutral media (*p*-toluenesulfonic acid in benzene, hydrochloric acid, 1M-NaOH, aqueous-methanolic NH_4OH, reflux in toluene or with lithium hydride in dimethylformamide) were unsuccessful and resulted in recovery of the starting compounds (or their hydrochlorides).

2-Amino-1,3-thiazin-4-ones exhibit amino-imino tautomerism[8,9]. The tautomeric forms can be distinguished by the CO and CN IR stretching vibration bands which for the amino form are situated at lower wavenumbers than for the imino form[10]. Pyridothiazines *Vi – Vl* prepared from the secondary amines represent standards, which can exist exclusively in the amino form. Since the CO and CN bands in the spectra of the thiazines with an alkylamino substituent (*Vb – Ve*) are at the same position as those of the standards, we can ascribe them also the amino frorm (Table I). Contrary to the mentioned pyridothiazines (*Vb – Vd*, *Vi – Vl*), the markedly different wavenumbers of the $\nu(C{=}N)$ band and somewhat higher values of the $\nu(C{=}O)$ bands in the 2-arylaminopyridothiazine derivatives *Ve – Vh* indicate the imino form. The derivative *Va* with a free NH_2 group differs from the other alkyl(aryl)pyridothiazines *Vb*H*Vl* in substantially lower wavenumbers of the C=O and CN bands.

In comparison with the UV spectra of *Va – Vd* and *Vi – Vl*, the derivatives *Ve – Vh* show a bathochromic shift of the long-wave absorption maximum (25 nm) which can be ascribed to the presence of another aromatic ring in the molecule (Table I). The ^{1}H NMR spectra of compounds *V* exhibit a one-proton singlet of the pyridine system at δ 6·7 – 7·4, two singlets of methyl groups and signals of the alkyl or aryl substituents. Because of rapid chemical exchange, the NH signal was observed only in the spectra of some derivatives such as *Va*, *Vc* and *Vd* (Table I and II). The pyridothiazine skeleton was confirmed by the ^{13}C NMR spectrum of compound *Ve*. Since in the spectrum of this compound two signals were missing, we tried to assign

TABLE I

Properties of 2-amino-5,7-dimethyl-4-oxopyrido[3,4*e*]-1,3-thiazines

Compound	Formula (mol. wt.)	M.p., °C (chloroform–solvent)	Yield %	Calculated/Found		
				% C	% H	% N
Va[e]	$C_9H_9N_3OS$ (207·2)	115 – 117 ether	53	52·16 52·20	4·38 4·21	20·27 20·35
Vb[e]	$C_{11}H_{14}N_3OS$ (236·3)	155 light petroleum[e]	58·3	55·91 55·89	5·97 5·78	17·78 17·72
Vc	$C_{12}H_{15}N_3OS$ (249·3)	176 – 177 heptane	33	57·81 57·93	6·06 6·15	16·85 16·98
Vd[e]	$C_{16}H_{15}N_3OS$ (297·4)	187 – 188 ether	68	64·62 64·70	5·08 5·19	14·13 14·20
Ve	$C_{15}H_{13}N_3OS$ (283·4)	220 light petroleum[e]	53	63·58 63·61	4·62 4·63	14·83 14·80
Vf	$C_{16}H_{15}N_3OS$ (297·4)	213 light petroleum[e]	68·4	64·62 64·50	5·08 4·94	14·13 14·22
Vg	$C_{16}H_{15}N_3O_2S$ (313·4)	210 ether	58·8	61·32 61·33	4·82 4·80	13·41 13·32
Vh[e]	$C_{15}H_{12}BrN_3OS$ (362·3)	229 heptane	50	49·73 49·73	3·34 3·36	11·60 11·82
Vi	$C_{16}H_{15}N_3OS$ (297·4)	226 ether	67	64·62 64·60	5·08 5·13	14·13 14·11
Vj	$C_{13}H_{15}N_3O_2S$ (277·4)	208 – 209 light petroleum[e]	54·7	56·30 56·28	5·45 5·30	15·15 15·22
Vk	$C_{21}H_{17}N_3OS$ (359·5)	228 light petroleum[e]	75	70·17 70·21	4·77 4·85	11·70 11·61
Vl	$C_{22}H_{18}N_4OS$ (386·5)	244 ether	48	68·37 68·35	4·70 4·61	14·50 14·61

the signals using the "off resonance" method. The obtained results indicate that the $C_{(1)}$ and $C_{(5)}$ signals overlap each other. Also the $C_{(3)}$ signal probably coincides with that of $C_{(10)}$ or $C_{(11)}$ because in the „off resonance" spectrum these carbon atoms

TABLE II

Spectral data for 2-amino-5,7-dimethyl-4-oxopyrido[3,4-*e*]-1,3-thiazines

Compound	IR, cm^{-1}		^1H NMR (ppm, δ)[a]							UV, nm λ max/log ε
	ν(C=O) ν(C=N)[c]	ν(NH)	H_β	$CH_{3\alpha}$ $CH_{3\alpha'}$	arom.	aliphatic CH_3	aliphatic CH_2	aliphatic CH	NH	
Va	1 613 1 493	3 483	7·19	2·27 2·91	—	—	—	—	11·2	239/4·42
Vb	1 670 1 539	3 233 3 183	6·95	2·52 2·96	—	1·3	3·60	—	—	246/4·11
Vc	1 666 1 526	3 226 3 176	7·12	2·61 2·86	—	1·32 1·40	—	4·52	12·4	245/4·14
Vd	1 670 1 533	3 233 3 180	7·00	2·54 2·87	7·1—7·4	—	4·62	—	10·5	247/4·16
Ve[b]	1 679 1 626	3 363	6·76	2·45 2·95	6·9—7·4	—	—	—	—	264/4·13
Vf[c]	1 683 1 626	3 356	6·86	2·36 2·95	6·7—7·3	2·46	—	—	—	280/4·00
Vg	1 683 1 626	3 360	6·84	2·50 2·96	6·9—7·3	3·97	—	—	—	263/4·05
Vh	1 683 1 620	3 356	7·45	2·60 2·97	7·4—7·8	—	—	—	—	260/4·40
Vi	1 650 1 510	—	6·82	2·50 3·00	7·3—7·6	3·60	—	—	—	250/4·11
Vj	1 646 1 513	M	7·07	2·52 2·90	—	—	3·79	—	—	270/3·98
Vk	1 650 1 533	—	7·08	2·52 2·92	7·4—7·6	—	—	—	—	250/4·16
Vl	1 650 1 520	—	7·00	2·45 2·82	7·1—7·6	—	—	4·4	—	247/3·96

[a] Solvent: *Va*—*Vd*, *Vi*—*Vl* deuteriochloroform, *Ve*—*Vh* deuteriochloroform–hexadeuteriodimethyl sulfoxide; [b] mass spectrum *m/z* (% rel. int.): 283 (72), 166 (100), 165 (68), 138 (45), 137 (36), 118 (26), 91 (27), 77 (10); [c] mass spectrum *m/z* (% rel. int.): 297·2 (100), 166 (42·3), 165 (41·5), 138 (24·6), 137 (31·5), 132 (63·4), 105 (41·8), 91 (24), 77 (43).

do not show clear doublets. They were not distinguished even in different solvents (Table III).

In the mass spectra of compounds *Ve* and *Vf* the strong molecular ion peaks (M^+ 283 and M^+ 297, respectively) illustrate their stability. The main fragmentation pattern are shown in Scheme 2. The presence of the cyanamide fragments R—NH—C≡N is important as a proof of the pyridothiazine structure.

EXPERIMENTAL

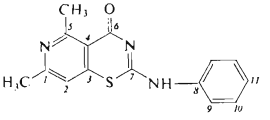
2,6-Dimethyl-4-chloronicotinic acid (*I*) was prepared by the described[4,5] procedure; its isolation was modified in the following manner: Concentrated hydrochloric acid was added dropwise to an ice-cooled solution of potassium salt of the acid *I* (50 g; 0·27 mol) in a minimum amount of water. Needles of the free acid separated at pH 4·3 (isoelectric point); m.p. 168°C, yield 94·5%. IR spectrum (KBr), cm^{-1}: ν(C=O) 1 700, ν(C=N) 1 583, ν(C—Cl) 870. ^1H NMR spectrum ($C^2H_3O^2H$), δ: 7·5, s (1 H), 2·6, s and 2·8, s (CH_3 groups).

2,6-Dimethyl-4-chloronicotinoyl Chloride (*II*)

The acid *I* (20 g; 0·16 mol) was mixed with thionyl chloride (250 ml) under cooling. The mixture was refluxed (85°C) to homogeneity (about 3 h), the excess thionyl chloride was distilled off *in vacuo* and the residue was treated with benzene (100 ml). The precipitated hydrochloride of *II* was dried and suspended in ether. Pyridine (6 g; 0·07 mol) was added with stirring and the separated pyridine hydrochloride was removed by filtration. After evaporation of benzene, the residue was distilled, b.p. 92–95°C/266 Pa, yield 12·5 g (80·5%). IR spectrum ($CHCl_3$), cm^{-1}: ν(C=O)

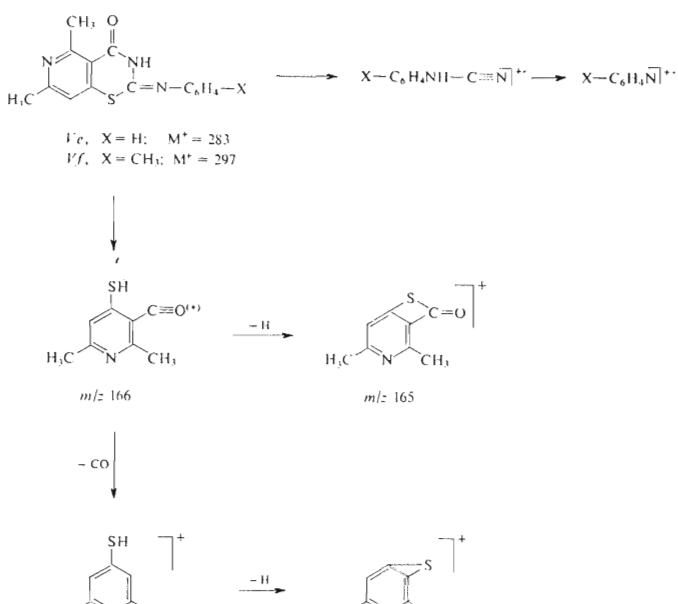
TABLE III

^{13}C NMR spectral data for 2-anilino-5,7-dimethyl-4-oxopyrido[3,4-*e*]-1,3-thiazine in hexadeuteriodimethyl sulfoxide



Atom	1	2	3	4	5	6
δ, ppm	158·92	117·27	—	114·41	158·92	160·55

Atom	7	8	9	10	11	CH_3
δ, ppm	164·77	144·24	121·30	129·16	124·55	26·38, 23·78



SCHEME 2

1 788, ν(C=N) 1 570, ν(C—Cl) 870. ^{1}H NMR spectrum (C^2HCl_3), δ: 7·4, s (1 H), 2·5 and 2·3, s (α- and α'-CH_3 groups).

2,6-Dimethyl-4-chloronicotinoyl Isothiocyanate (*III*)

A solution of NH_4SCN (0·2 g; 2·63 mmol) in acetone (15 ml) was added to a stirred solution of the chloride *II* (0·5 g; 2·19 mmol) in acetone (15 ml). After warming to 45°C for 5—10 min. the precipitated NH_4Cl was filtered off and the solvent was evaporated under diminished pressure (water pump). The crude product *III* was a reddish brown oil which decomposed even in the cold. Yield about 80%. IR spectrum, cm^{-1}: ν(NCS) 1 950, ν(C=O) 1 730, ν(C=N) 1 750. ^{1}H NMR spectrum ($CHCl_3$), δ: 7·3 s (H_β), 2·5 and 2·3, s (α- and α'-CH_3 group).

2-Amino-5,7-dimethyl-4-oxopyrido[3,4-*e*]-1,3-thiazines *Va—Vl*

A solution of the amine (0·01 mol) in acetone was added during 15 min to a solution of the isothiocyanate *III* (prepared from 0·01 mol of the chloride *II*) in acetone (15 ml). After evaporation of the acetone *in vacuo*, the formed hydrochloride was suspended in benzene (15 ml). An equimolar amount of pyridine was added, the precipitate was filtered and pyridine hydrochloride was washed out with water. The crude product was recrystallized from suitable solvent mixtures (Table I). The derivatives *Va—Ve* are stable, high-melting substances, well soluble in chloroform, dimethylformamide and dimethyl sulfoxide, insoluble in ether, light petroleum and heptane.

N-Benzyl-N′-(2,6-dimethyl-4-chloronicotinoyl)thiourea (*IV*)

A solution of benzylamine (0·01 mol) in acetone (15 ml) was slowly added to an equivalent amount of the isothiocyanate *III* in acetone under cooling with ice. The mixture was stirred at room temperature for 30 min and then poured into ice-cold water. The precipitate was crystallized from aqueous ethanol, m.p. 151—153°C; yield 69%. For $C_{16}H_{16}ClN_3OS$ (331·1) calculated: 57·65% C, 4·80% H, 12·61% N; found: 57·85% C, 4·91% H, 12·55% N. IR spectrum ($CHCl_3$), cm^{-1}: ν(C=O) 1 650, ν(NH—C=S) 1 570, ν(NH) 3 420. ^1H NMR spectrum (C^2HCl_3), δ: 6·94, s ($H_{(3)}$); 2·5 and 2·9, s (2 × CH_2); 4·75, s (CH_2 group); 8·76, broad s (NH groups).

Spectral Measurements

The IR absorption spectra were recorded on a double-beam 75 IR spectrometer (Zeiss), calibrated with a polystyrene foil, UV spectra were taken in methanol at concentrations 2·5 . 10^{-4} — 1 . . 10^{-5} mol (1 cm cells) on a Perkin–Elmer 402 spectrophotometer. The ^1H NMR spectra were measured on a Tesla BS-485 instrument (80 MHz) in deuteriochloroform or in deuteriochloroform — hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Mass spectra were taken on an MS-902 (AEI) spectrometer (70 eV, ionization chamber temperature 150°C, direct inlet). ^{13}C NMR spectrum was obtained with a Jeol FX 100/25·04 MHz instrument.

The authors are indebted to Dr J. Leško, Laboratory of Mass Spectrometry for the mass spectral measurements and to Dr M. Dandárová, Department of Organic Chemistry, Slovak Institute of Technology, Bratislava, for measurements of the ^{13}C *NMR spectra.*

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Translated by M. Tichý.