NOVEL SYNTHESIS, STRUCTURE, AND PROPERTIES OF 3-ARYL-4-THIONO-6-CYANO-7-ARYLIMINOTHIOPYRANO[2,3-d]PYRIMIDINES

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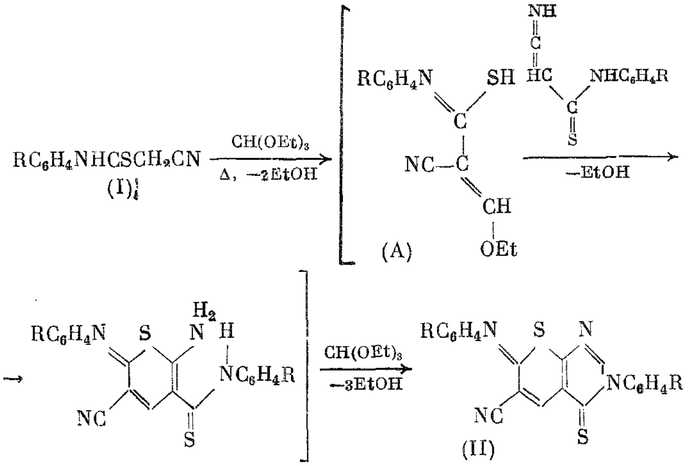
It has previously been reported [1] that cyanothioacetic acid arylamides react selectively with orthoformate ester in the presence of acetic anhydride or other catalysts to form the corresponding vinyl ethers. We have shown that these arylamides ($RC_6H_4NHCSCH_2CN$ (I), where R = H, p-CH_3, p-Cl) react with orthoformate ester at 110-120°C in the absence of catalyst and solvent forming the previously unreported 3-aryl-4-thiono-6-cyano-7-aryliminothiopyrano[2,3-d]pyrimidines II [2] and not substituted 1,5-thiazocines as erroneously reported in [1]. This reaction occurs via an intermediate 2-cyano-3-arylthiocarbamoylvinylethyl ether. In its thiol form (A), this then reacts with the ketenimine tautomer of I and orthoformate ester to give II.



Literature methods for preparing thiopyrano[2,3-d]pyrimidines have been based on the synthesis of a pyrimidine and construction of the thiopyrano ring, or, conversely, synthesis of the thiopyran ring followed by construction of the pyrimidine [3-6]. The method proposed by us is simple in operation, permits the preparation of the previously inaccessible derivatives II in one rather than nine stages [3], and can be widely recommended in a preparative mode. It should also be mentioned that II are structural analogs of folic acid, employed in medicine [7], and as compounds with potential biological activity they attract the attention of the investigator.

The structure of II was uniquely determined by x-ray analysis, NMR, and IR spectroscopy. A general view of the molecule of 3-phenyl-4-thiono-6-cyano-7-phenyliminothiopyrano[2,3-d]pyrimidine (IIa) is given in Fig. 1 obtained according to the program [8]. The thiopyrano[2,3-d]pyrimidine system is nonplanar the maximum deviation of the atoms from the mean plane of both heterocycles being 0.07 Å for the thiopyrano and 0.04 Å for the pyrimidine ring. The dihedral angle between the mean planes of these heterocycles was 5.5°. Atomic coordinates for IIa are given in Table 1.

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*Deceased.

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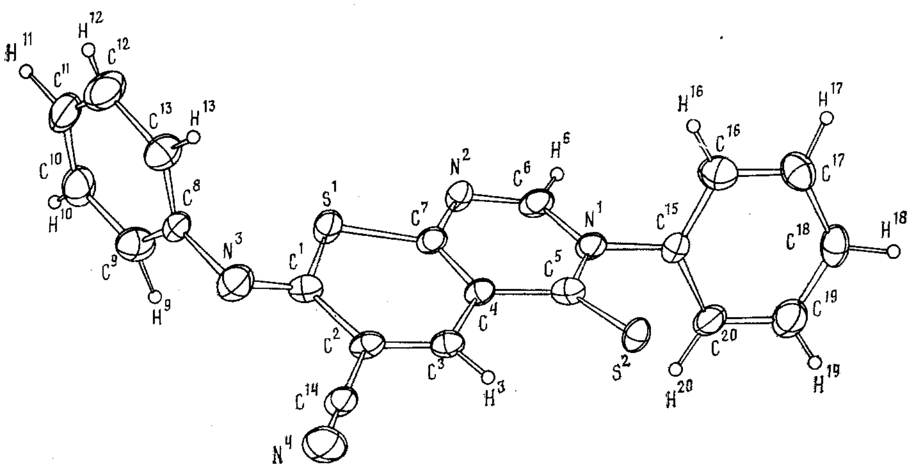

Fig. 1. General view of molecule IIa.

TABLE 1. Atomic Coordinates for IIa*

Atom	X	Y	Z	Atom	X	Y	Z
S^1	0,2850(0)	0,0740(1)	0,3658(0)	C^{14}	0,2998(1)	0,0492(4)	0,0960(2)
S^2	0,1394(0)	0,3160(1)	0,1684(1)	C^{15}	0,0923(1)	0,2993(4)	0,3475(2)
N^1	0,1405(1)	0,2473(3)	0,3417(1)	C^{16}	0,0824(1)	0,4436(4)	0,3913(2)
N^2	0,2047(1)	0,1555(4)	0,4249(2)	C^{17}	0,0362(1)	0,4919(4)	0,3979(3)
N^3	0,3531(1)	0,0376(3)	0,2485(2)	C^{18}	0,0012(1)	0,3971(5)	0,3622(3)
N^4	0,3159(1)	0,0262(4)	0,0286(2)	C^{19}	0,0123(1)	0,2510(5)	0,3187(2)
C^1	0,3097(1)	0,0621(4)	0,2581(2)	C^{20}	0,0576(1)	0,2017(4)	0,3118(2)
C^2	0,2791(1)	0,0827(4)	0,1815(2)	H^3	0,214(1)	0,153(4)	0,137(2)
C^3	0,2345(1)	0,1359(4)	0,1845(2)	H^6	0,144(1)	0,212(4)	0,471(2)
C^4	0,2097(1)	0,1719(4)	0,2646(2)	H^9	0,356(1)	−0,201(5)	0,354(3)
C^5	0,1634(1)	0,2420(4)	0,2603(2)	H^{10}	0,406(1)	−0,229(5)	0,482(3)
C^6	0,1624(1)	0,2043(4)	0,4181(2)	H^{11}	0,458(1)	−0,004(5)	0,530(3)
C^7	0,2283(1)	0,1396(4)	0,3466(2)	H^{12}	0,461(2)	0,215(6)	0,441(3)
C^8	0,3817(1)	0,0245(4)	0,3252(2)	H^{13}	0,409(1)	0,258(6)	0,317(3)
C^9	0,3823(1)	−0,1172(4)	0,3751(2)	H^{16}	0,108(1)	0,506(4)	0,412(2)
C^{10}	0,4098(1)	−0,1285(5)	0,4498(2)	H^{17}	0,030(1)	0,587(5)	0,437(2)
C^{11}	0,4375(1)	−0,0007(6)	0,4746(2)	H^{18}	−0,034(1)	0,421(5)	0,363(3)
C^{12}	0,4377(1)	0,1400(6)	0,4244(3)	H^{19}	−0,013(1)	0,195(4)	0,300(2)
C^{13}	0,4099(1)	0,1544(5)	0,3496(3)	H^{20}	0,069(1)	0,104(5)	0,277(3)

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*Bond lengths and angles can be obtained from the authors.

In the IR spectrum of IIa (Table 2) the absorption band for the C=C bond (1.372(3) Å) is influenced by the extended chain conjugation in the cyclic system and is shifted to lower frequencies. Frequencies are also quoted for C–H (0.984(4) Å), C≡N (1.130(4) Å) and C=S (1.659(2) Å) bonds.

A characteristic feature of the PMR spectrum of IIb in $CDCl_3$ is the duplicate series of signals for each kind of proton, pointing to their nonequivalence. Thus there were 2 signals for nonequivalent p-CH_3 groups (δ 2.35 and 2.42 ppm), 2 singlets for protons on sp^2 C atoms of the heterocycles (δ 8.15 and 8.80 ppm), and two overlapping AA'BB' aromatic proton systems (δ 7.0-7.5 ppm). Integral curves were as expected for equal amounts of the protons of each type. Similar PMR spectra were observed for IIa and IIc.

In structure II, one of the protons at the heterocycle sp^2 C atoms is in direct proximity to the magnetically anistropic benzene ring and, evidently, experiences its influence. In fact, exchange of the inert solvent $CDCl_3$ for $(CD_3)_2CO$ leads to the following change in the PMR spectrum of IIb: one of the low field singlets is significantly shifted to low field (δ 8.50 ppm) whereas the other is practically unaffected (δ 8.78 ppm). In the aromatic proton region the signals for one of the rings appears as a singlet (a degenerate AA'BB' system) with peak area corresponding to four protons. Similar solvent dependencies were observed in the PMR spectra of IIa and IIc.

The ^{13}C NMR spectrum of IIb was obtained using broad band proton decoupling (δ, ppm, (rel. intensity units)): 182.2 (82.2), 161.4 (36.9), 150.1 (35.7), 149.6 (177.8),

TABLE 2. IR Spectra of IIa-c (KBr, ν, cm^{-1})

Compound	ν CH	ν C≡N	ν C=C	ν C=S
(IIa)	3040	2220	1560	1020
(IIb)	3020	2220	1560	1020
(IIc)	3020	2200	1570	1010

TABLE 3. Physical Constants, Yields, and Elemental Analysis Data for IIa-c

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
(IIa)	65	235	64,4	3,0	15,0	16,7	$C_{20}H_{12}N_4S_2$	64,8	3,2	15,0	17,2
(IIb)	69	190	66,2	3,9	14,2	15,6	$C_{22}H_{16}N_4S_2$	66,0	4,0	14,0	16,0
(IIc)	56	184	54,4	2,6	12,7	14,6	$C_{20}H_{10}Cl_2N_4S_2$	54,4	2,2	12,7	14,5

146.1 (76.2), 143.6 (144.0), 140.7 (112.5), 137.8 (87.6), 135.6 (123.9), 130.7 (366.8), 130.4 (381.2), 126.6 (393.2), 124.9 (87.8), 119.0 (357.4), 115.1 (49.6), 112.7 (96.9), 21.2 (128.9), 20.9 (133.8).

The overall number of signals in the spectrum, taking into account the equivalence of o- and m-carbons in the aromatic nuclei, correspond to a molecule with 22 C atoms. Similarly in the PMR spectrum of this compound there is observed a nonequivalence in the aromatic rings and their p-CH_3 substituents. Equivalence of the C atoms of the heterocycle and nitrile group was absent. The lowest field signal at 182.2 ppm was assigned to the thiocarbonyl carbon and that at 161.4 ppm to the C=N carbon.

Experimental

3-Phenyl-4-thiono-6-cyano-7-phenyliminothiopyrano[2,3-d]pyrimidine (IIa). Cyanothioacetanilide (1 g) was heated with orthoformate ester (1 ml) for 2-3 h at 110-120°C. The unreacted reagent and alcohol produced were removed by distillation and benzene (3 ml) was added. An orange precipitate was formed slowly and was filtered off and washed with benzene to give IIa (0.72 g, 65%) with mp 235°C (from benzene). Compounds IIb and IIc were obtained similarly. The chemical composition was determined by full elemental analysis (Table 3). The presence of the exocyclic thione group was proved by iodine azide reaction and confirmed by ^{13}C NMR.

Electronic spectra of alcoholic solutions ($5 \cdot 10^{-5}$ molar) were recorded on an SF-4A spectrophotometer, PMR spectra on a Tesla BS-467 (60 MHz), and ^{13}C NMR spectra on a Bruker WP-80DS (20 MHz), relative to TMS. The molecular weight of IIa was determined ebullioscopically and by mass spectrometry on an MS-1302 (365 and 372, correspondingly). IR spectra of II were measured on an automatic, double beam UR-10 spectrophotometer for KBr tablets using a KBr prism for the range 700-400 cm^{-1}, NaCl for 1800-700 cm^{-1}, and LiF for 4000-1800 cm^{-1}.

X-Ray Analysis of IIa. Rhombic crystals, M = 371.48, a = 28.706(3), b = 8.167 (1), c = 15.059(2) Å, V = 3530.1 $Å^3$, d_{calc} = 1.40 g/cm^3, Z = 8, space group P nab. The intensities of 2384 independent reflections of type nk0-hk15 with $I > 2\sigma(I)$ were measured on a DAR-UM automatic diffractometer with CuK_α radiation (graphite monochromator) in the interval $3.1° \leq \theta \leq 67.5°$; absorption not included ($\mu(CuK_\alpha) = 27$ cm^{-1}). The structure was solved by a direct method and refined by a least square method in the block diagonal anisotropic (S, N, and C atoms) and isotropic (H atoms) approximation to R = 0.060 (see Table 1). Calculations were carried out using a complex program [9] on a BÉSM-6 computer.

Conclusions

A simple, one stage synthesis of the previously inaccessible 3-aryl-4-thione-6-cyano-7-aryliminothiopyrano[2,3-d]pyrimidines has been proposed from cyanothioacetic acid arylamides $RC_6H_4NHCSCH_2CN$ (R = H, p-CH_3, p-Cl) and orthoformate ester by heating at 110-120°C.

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CROSS-COMBINATION OF MAGNESIUM DIACETYLENIDES WITH ORGANIC HALIDES CATALYZED BY TRANSITION METALS COMPLEXES

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1,2-Disubstituted acetylenes are obtained by reacting terminal acetylenes with alkyl- and arylhalides under the influence of bimetallic (Pd-Cu) catalysts with the participation of organic and inorganic bases which act as acceptors of hydrogen halide [1-4]. The most suitable synthetic preparation method of alkylsubstituted acetylenes is the reaction between alkylhalides and the Iotsich reagent catalyzed by Cu and Co salts [5-7]. We developed the preparation of 1,4-ethynyls by cross-combination of magnesium diacetylenides with O-, N-, and S-containing allyl electrophiles in the presence of Ni complexes [8].

In order to develop the preparatory synthesis of substituted mono- and diacetylenes, including those which are function-substituted, as well as to expand the application field of cross-combination of magnesium diacetylenides with allyl electrophiles, we investigated the reactions of magnesium alkyl- and aryldiacetylenides with alkyl-, allyl-, propargyl-, and aryhalides in the presence of transition metal complexes.

It was established that magnesium diacetylenides obtained from monosubstituted alkyl- and arylacetylenes, and Et_2Mg [9] exhibit a higher activity than the corresponding Iotsich reagents in the cross-combination reaction with halides, a reaction involving both acetylene fragments attached to Mg. Ni complexes modified with Ph_3P are the most active catalysts in the cross-combination reaction of alkylhalides with Mg diacetylenides. In cases of allyl-, propargyl-, and arylhalides we used Cu and Pd compounds (THF, 40°C, 4 h) as effective catalytic systems.

With increasing R' the yield of the cross-combination products (III)-(XII) (Table 1) decreased. Besides, reagent (II) was more active than reagent (I) in reactions with alkylhalides,

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