3. The structure of bis[6-(1-adamantyl)-3-cyanopyrid-2-yl] disulfide has been confirmed by an x-ray structural examination.

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CONDENSED PYRIDINES. COMMUNICATION 4.*

THE MICHAEL REACTION IN THE SYNTHESIS OF SUBSTITUTED 3-CYANOPYRIDINE-2(1H)-THIONES

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The only report of the use of the Michael reaction in the synthesis of substituted 3-cyanopyridine-2(1H)-thiones is in the preparation of 4,6-diaryl-3-cyanopyridine-2(1H)-thiones [2, 3]. These were obtained by reacting chalcones with cyanothioacetamide (I), to give, depending on the reaction conditions and the catalyst used, either substituted 3-cyanopyridine-2(1H)-thiones [2], or their hydrogenated analogs [3].

We here describe an examination of the reaction of arylidenemalononitriles (II) with (I), or arylidenecyanoacetamides (III) with malononitrile (IV), and ethyl cyanoacetate (V), and of arylidene derivatives of ethyl cyanoacetate (VI) with (I). Some new reactions of the Michael adducts formed have been observed. For example, in the reaction of (I) with (II) in the presence of an organic base, the previously unknown thioamides of 3-aryl-2,4,4-tricyano-2-butenoic acid (VII) were obtained via the Michael adduct (VIII). The formation of (VIII) was confirmed by the fact that the reaction between (III) and (IV) also gave the thioamide (VII).

We have shown that the thioamides (VII) react with ketones (IX) containing a methyl or methylene group in the α position to give pyridinethiones (X). The reaction appears to proceed via the formation of the Michael adducts followed by elimination of malononitrile (IV) and intramolecular cyclization of the intermediate (XI).

*For communication 3, see [1].

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TABLE 1. Thioamides of 3-Aryl-2,4,4-tricyano-2-butenoic Acid (VII)

Compound	Yield,%	mp, °C (from ethanol)	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm			Empirical formula	Found/Calculated %				
			CN	NH_2	Ar (J, Hz)	NH_2 (s)	CH (s)		C	H	Hal	N	S
(VIIa)	94	176–179	2190, 2174 sh	3204, 3320, 3400, 3440	7,2 m	6,87	4,24	$C_{13}H_8N_4S$	61,64 / 61,89	3,11 / 3,20		22,04 / 22,21	12,83 / 12,71
(VIIb)	74	167–168	2184, 2148sh	3210, 3330, 3450	7,2 m	6,88	4,29	$C_{13}H_7FN_4S$	57,84 / 57,77	2,85 / 2,61	7,04 / 7,03	20,53 / 20,73	11,60 / 11,86
(VIIc)	76	185–186	2192, 2148 sh	3228, 3325, 3386, 3450	7,38 d, 7,20 d (5,8)	6,89	4,32	$C_{13}H_7ClN_4S$	54,31 / 54,45	2,33 / 2,46	12,23 / 12,36	19,65 / 19,54	10,90 / 11,18
(VIId)	83	182–183	2190, 2146 sh	3228, 3327, 3354, 3393	7,47 d, 7,09 d (5,9)	6,89	4,30	$C_{13}H_7BrN_4S$	47,03 / 47,15	2,08 / 2,13	23,95 / 24,13	17,03 / 16,92	9,33 / 9,68

TABLE 2. 3-Cyanopyridine-2(1H)-thiones (X) and (XII)

Compound	Yield, %	mp, °C (from AcOH)	IR spectrum, ν, cm^{-1} (CN)	PMR spectrum, δ, ppm				Empirical formula	Found/Calculated, %			
				NH(s)	Ar	R^1(s)	R^2(s)		C	H	N	S
(Xa)*	58	273–275 dec.	2218									
(Xb)	67	269	2232	13,90	7,48 d, 7,34 d (J=5,7 Hz)	6,72	2,40	$C_{13}H_9FN_2S$	63,84 / 63,92	3,52 / 3,71	11,30 / 11,47	12,88 / 13,12
(Xc)	54	267–270 dec.	2223	13,90	7,38 m	1,74	2,40	$C_{14}H_{12}N_2S$	70,08 / 69,97	4,93 / 5,03	11,37 / 11,66	13,30 / 13,34
(Xd)	63	200–202	2215	14,10	7,30 7,56 **	7,04	**	$C_{18}H_{11}FN_2S$	70,30 / 70,57	3,53 / 3,62	9,19 / 9,14	10,15 / 10,47
(Xe)	72	261–263	2228	13,98	7,68 d 7,25 d (J=5,8 Hz)	2,74 t, 1,61 m	2,08 t	$C_{16}H_{13}BrN_2S$	55,53 / 55,66	3,62 / 3,79	8,00 / 8,11	9,20 / 9,29
(Xf)	53	270–271 dec	2236	13,94	7,63 d, 7,44 d (J=5,9 Hz)	1,86	2,38	$C_{15}H_{11}ClN_2OS$	59,62 / 59,50	3,38 / 3,66	9,37 / 9,25	10,50 / 10,59
(XIIa)	74	269–272	2215, 2170 sh	13,70	7,40 d, 7,22 d (J=5,8 Hz)			$C_{13}H_6ClN_3OS$	54,03 / 54,27	2,23 / 2,10	14,56 / 14,60	11,26 / 11,14
(XIIb)	78	280	2216, 2185	13,52	7,47 d, 7,08 d (J=5,7 Hz)			$C_{13}H_6BrN_3OS$	47,22 / 47,01	1,94 / 1,82	12,48 / 12,65	9,57 / 9,65
(XIIc)	73	280–282	2218	13,68	7,71 d 7,42 d (J=5,7 Hz)		7,93	$C_{13}H_7BrN_4S$	47,24 / 47,15	2,01 / 2,13	17,08 / 16,92	9,53 / 9,68

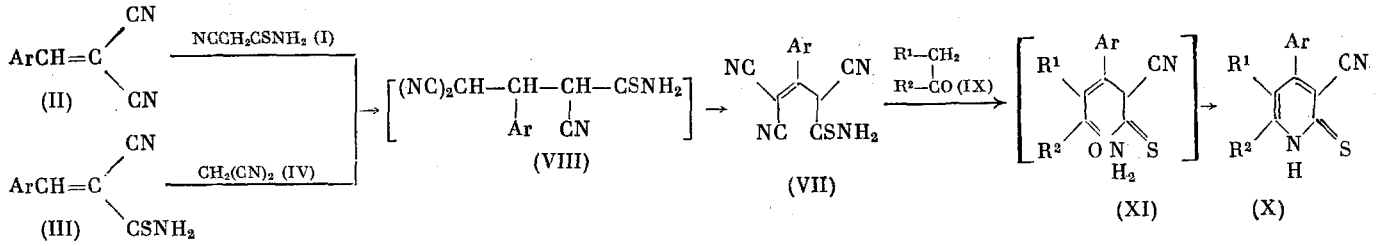
*(Xa) was identical with 6-methyl-4-phenyl-3-cyanopyridine-2(1H)-thione obtained as described in [2].

TABLE 3. Mass Spectra of 3-Cyanopyridine-2(1H)-thiones (Xa, c, d)

Compound	Mol. wt.	m/z (intensity, %)	W_M, %
(Xa)	226	229(1), 228(7), 227(22), 226(100), 225(71), 224(3), 211(7) 194(7), 193(6), 192(5), 191(3), 182(8), 167(3), 166(7), 165(3), 164(3), 141(3), 140(9), 139(5), 128(4), 127(3), 115(3), 114(3), 113(7), 112(3), 102(3), 77(4), 76(3), 51(8), 39(5)	38,3
(Xc)	240	243(1), 242(8), 241(22), 240(100), 239(85), 225(1), 224(2), 213(3), 212(7), 211(5), 207(3), 206(2), 205(6), 181(3), 180(3), 179(4), 177(3), 168(2), 153(3), 152(4), 151(4), 141(3), 140(8), 127(3), 119(4), 112(4), 77(5), 76(3), 39(3)	42,4
(Xd)	306	309(3), 308(9), 307(26), 306(100), 305(47), 274(2), 273(4), 272(7), 270(4), 262(7), 247(3), 246(5), 245(7), 226(4), 140(7), 95(4), 77(3), 51(3)	56,3

The thioamide IR spectrum contains absorption bands of the thioamide group in the region 3204-3450 (νNH_2) and 1618-1648 cm^{-1} (δNH_2), and also high-intensity valence vibration bands of the nitrile group in the region 2184-2190 cm^{-1}, with the shoulder located at 2140-2148 cm^{-1}. It should be noted also that within the PMR spectra the proton signal for the CH group of these compounds is mixed in the strong polar region (δ 4.24-4.32 ppm) as compared to the position of the proton signal of the methylene group of cyanothioacetamides (I) in Table 1.

The structures of the pyridinethiones (X) were confirmed by their elemental analyses and their IR and PMR spectra (Table 2). We have also examined the behavior of the pyridinethiones (Xa, c, d) under electron impact. It was found that the intensities of the molecular ions of these compounds are at a maximum, but the stability to electron impact (W_M) is



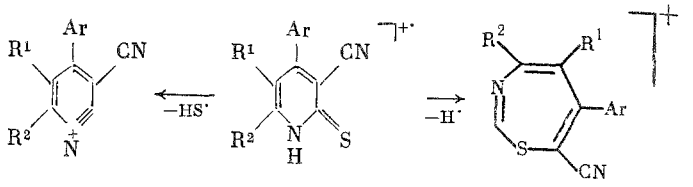
(II), (III), (VII): Ar = C_6H_5 (a); Ar = 4-F·C_6H_4(b); Ar = 4-ClC_6H_4 (c); Ar = 4-BrC_6H_4 (d).

(IX): R^1 = H, R^2 = CH_3 (a); R^1 = R^2 = CH_3 (б); R^1 — R^2 = $(CH_2)_4$ (c); R^1 = CH_3CO, R^2 = CH_3 (d); R^1 = H, R^2 = 4-FC_6H_4 (e);

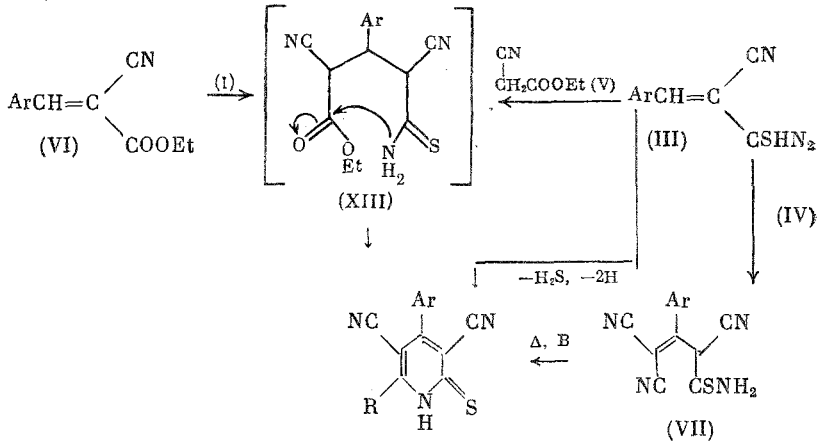
(X): R^1 = H, R^2 = CH_3, Ar = C_6H_5 (a); R^1 = H, R^2 = CH_3, Ar = 4-FC_6H_4 (b); R^1 = R^2 = CH_3, Ar = C_6H_5 (c); R^1 = H, R^2 = 4-FC_6H_4, Ar = C_6H_5 (d); R^1 — R^2 = $(CH_2)_4$, Ar = 4-BrC_6H_4 (e); R^1 = CH_3CO, R^2 = CH_3, Ar = 4-ClC_6H_4 (f).

insufficiently great, falling within the range 38.3-56.3. The principal mode of fragmentation of the ions of these compounds involves cleavage of the H· radical to give the stable 1,3-thiazepine structure, which is isoelectronic with the cycloheptatrienyl cation, as noted previously in the case of phenyl sulfides [4] and aromatic sulfur compounds [5]. Another breakdown mode of the molecular ions is elimination of the HS· radical, as shown by the presence in the mass spectra of peaks with m/z 193, 207, and 273 for (Xa, c, and d), respectively (Table 3).

The reaction of arylidene derivatives of ethyl cyanoacetate (VI) with (I) or of the arylidenecyanothioacetamides (III) with ethyl cyanoacetate (V) gives better than 70% yields of the 3,5-dicyanopyridinethiones (XII). In this case also, it appears that the first stage in the reaction is the formation of the Michael adducts (XIII), which we have been unable to isolate as a result of their rapid cyclization to the pyridinethiones (XII). These pyridinethiones were also obtained by reacting (III) with (I), and in addition 6-amino-4-(4-bromophenyl)-3,5-dicyanopyridine-2(1H)-thione (XIIc) was synthesized by another route, namely, cyclization of the thioamide (VIId) in ethanol in the presence of piperidine.

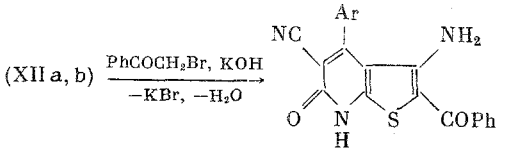


(X a, b, d)



(VI): Ar = 4-ClC_6H_4 (a); Ar = 4-BrC_6H_4 (b); (XII): Ar = 4-ClC_6H_4, R = OH(a); Ar = 4-BrC_6H_4, R = OH(b); Ar = 4-BrC_6H_4, R = NH_2 (c); B — piperidine.

The spectral properties of the pyridinethiones (XII), which confirm their structures, are given in Table 2. Their structures were also confirmed by the formation of 3-amino-4-aryl-2-benzoyl-5-cyanothieno[2,3-b]pyridin-6(7H)-ones (XIV) when (XIIa, b) were reacted with phenacyl bromide



(XIV): Ar = 4-ClC_6H_4 (a); Ar = 4-BrC_6H_4 (b).

EXPERIMENTAL

The IR spectra of the compounds were obtained on a Perkin—Elmer 457 spectrometer in KBr disks. PMR spectra were recorded on Varian FT-80A (80 MHz) and Bruker XL-90H (90 MHz) instruments, in DMSO-d_6 relative to TMS. Mass spectra were obtained on an MKh-1310 mass spectrometer with direct introduction of the sample into the ion source. The ionization chamber temperature was 150°C, ionizing voltage 70 eV, and emission current 100 μA. The purity of the compounds was checked by TLC on Silufol UV-254 plates in the system ethyl methyl ketone—hexane, 3:5.

Thioamides of 3-Aryl-2,4,4-tricyano-3-butenoic Acid (VIIa-d). a) To a mixture of 10 mmoles of (II) and 10 mmoles of (I) in 25-30 ml of ethanol was added 0.5 ml of triethylamine or piperidine at 25°C, and the mixture stirred for 4-6 h. The solid was then filtered off, and washed with ethanol, hexane, or isobutanol.

b) A mixture of 10 mmoles of (III), 10 mmoles of (IV), and 0.5 ml of triethylamine in 25-30 ml of ethanol was stirred for 4-6 h at 25°C, the solid filtered off, washed with ethanol and hexane, and recrystallized. Compounds (VIIa-d), obtained by methods a) and b), were identical with respect to their melting points and IR and PMR spectra; data for (VIIa-d) are given in Table 1.

3-Cyanopyridine-2(1H)-thiones (Xa-f). A mixture of 10 mmoles of the thioamide (VII), 10-20 mmoles of the ketone (IX), 0.4-0.8 ml of piperidine, and 25-30 ml of benzene was boiled with stirring for 3-4 h, and the hot mixture filtered, the filtrate cooled, and the solid which separated filtered off, washed with benzene and hexane, and recrystallized from acetic acid. Data for (Xa-f) are given in Table 2.

4-Aryl-6-hydroxy-3,5-dicyanopyridine-2(1H)thiones (XIIa, b). a) A mixture of 10 mmoles of (VI), 10 mmoles of (I), 0.3-0.5 ml of piperidine, and 20-25 ml of ethanol was stirred for 24-48 h at 25°C, acidified with 2 ml of conc. HCl, and the solid filtered off, washed with ethanol and hexane, and recrystallized from acetic acid.

b) A mixture of 10 mmoles of (III), 10 mmoles of (V), 0.3-0.5 ml of piperidine, and 20-25 ml of ethanol was stirred for 24-48 h at 25°C, then worked up as in a) above. The pyridinethiones (XIIa, b) obtained by methods a) and b) were identical; data for them are given in Table 2.

6-Amino-4-(4-bromophenyl)-3,5-dicyanopyridine-2(1H)-thione (XIIc). a) A mixture of 10 mmoles of (IIId), 10 mmoles of (I), 0.5 ml of piperidine, and 25 ml of ethanol was stirred for 2 h at 25°C, boiled for 2 h, cooled, acidified with 2 ml of conc. HCl, and the solid filtered off and recrystallized from acetic acid.

b) A mixture of 5 mmole of (VIId), 1 ml of triethylamine, and 30 ml of ethanol was boiled for 5 h, cooled, acidified with 3 ml of glacial acetic acid, and the solid filtered off and recrystallized from acetic acid. The pyridinethiones (XII c) obtained by methods a) and b) were identical; data for them are given in Table 2.

3-Amino-2-benzoyl-4-(4-chlorophenyl)-5-cyanothieno[2,3-b]pyridin-6(7H)-one (XIVa). To a suspension of 2.88 g (10 mmoles) of (XIIa) in 30 ml of DMF was added dropwise with stirring 5.6 ml of 10% KOH solution, followed after 5 min by 1.99 g (10 mmoles) of phenacyl bromide. The mixture was stirred for 20 min, a further 5 ml of 10% KOH added, stirring continued for 2 h at 25°C, 10 ml of 15% HCl added, and the solid filtered off, washed with ethanol and hexane, and recrystallized from ethanol to give 3.27 g (81%) of (XIVa), mp 265°C. IR spectrum (KBr, ν, cm^{-1}): 1658, 3312, 3485 (NH_2), 2228 (CN). Found: C 62.02; H 3.12; Cl 8.63; N 10.64; S 8.03%. $C_{21}H_{12}ClN_3O_2S$. Calculated: C 62.15; H 2.98; Cl 8.74; N 10.53; S 7.90%.

3-Amino-2-benzoyl-4-(4-bromophenyl)-5-cyanothieno[2,3-b]pyridin-6(7H)-one (XIVb). Obtained similarly, from (XIIb), yield 83%, mp 216-217°C (from ethanol). IR spectrum (KBr, ν, cm^{-1}): 1653, 3310, 3480 (NH_2), 2230 (CN). Found: C 56.15; H 2.54; Br 17.64; N 9.16; S 7.03%. $C_{21}H_{12}BrN_3O_2S$. Calculated: C 56.01; H 2.69; Br 17.74; N 9.33; S 7.12%.

CONCLUSIONS

1. The reaction of arylidenemalononitriles with cyanothioacetamide, or of arylidenecyanothioacetamides with malonodinitrile affords thioamides of 3-aryl-2,4,4-tricyano-2-butenoic acid, which condense with ketones carrying a methyl or methylene group in the α position to give 3-cyanopyridine-2(1H)-thiones.

2. Arylidene derivatives of ethyl cyanoacetate react with cyanothioacetamide to give 4-aryl-6-hydroxy-3,5-dicyanopyridine-2(1H)-thiones, which then react with phenacyl bromide to give 3-amino-4-aryl-2-benzoyl-5-cyanothieno[2,3-b]pyridin-6(7H)-ones.

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