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SYNTHESIS OF 2,6-DIAMINO-3,5-DICYANO-4-ETHYL-4H-THIOPYRAN AND ITS RECYCLIZATION TO 6-AMINO-3,5-DICYANO-4-ETHYLPYRIDINE-2(1H)-THIONE

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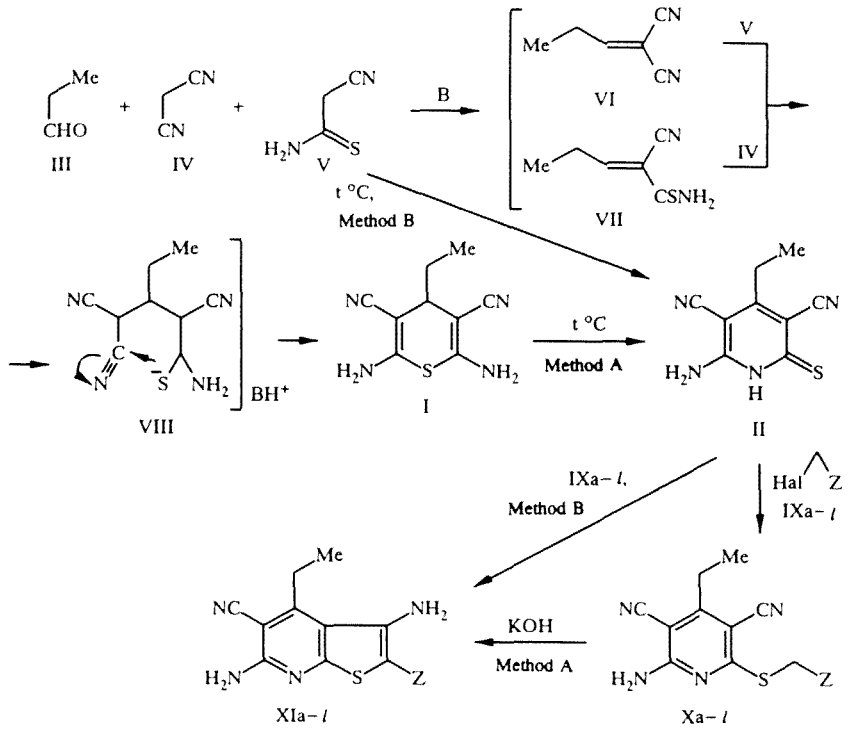
The triple condensation of propionaldehyde, malononitrile, and cyanothioacetamide gives 2,6-diamino-3,5-dicyano-4-ethyl-4H-thiopyran, which recyclizes to give 6-amino-3,5-dicyano-4-ethylpyridine-2(1H)-thione. This thione was used to synthesize substituted 2-alkylthiopyridines and the corresponding thieno[2,3-b]pyridines.

Alkyl-substituted 3-cyanopyridine-2(1H)-thiones, 3-cyano-2(1H)-pyridones, and their derivatives have been used as intermediates in the synthesis of various central nervous system depressants [1], drugs for the treatment of allergic disease [2] and cardiac insufficiency [3], as well as antifungal and antibacterial drugs [4]. However, the methods for the synthesis of such compounds are limited [5]. We have developed methods for the preparation of previously unreported 2,6-diamino-3,5-dicyano-4-ethyl-4H-thiopyran (I) and 6-amino-3,5-dicyano-4-ethylpyridine-2(1H)-thione (II), whose mechanism is given in the following scheme.



B = Piperidine, morpholine, N-methylmorpholine. IX—XI a Hal = Cl, Z = $CONH_2$; b Cl, 4-BrC_6H_4NHCO; c Cl, C_6H_4NHCO; d Br, 4-BrC_6H_4CO; e Cl, CN; f Cl, COOEt; g Br, C_6H_5CO; h Br, 4-$CH_3C_6H_4CO$; i Cl, $COOCH_2Ph$; j Br, 3,4-$Cl_2C_6H_3CO$; k Cl, COOPr; l Br, 2-thenoyl

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TABLE 1. Indices of Compounds Synthesized

Compound	mp, °C, crystallization solvent	Found, %				Chemical formula	Calculated, %				Yield, % (method A/B)
		C	H	N	S		C	H	N	S	
Xa	202...205, AcOH	50,49	4,18	26,48	12,21	$C_{11}H_{11}N_5OS$	50,56	4,24	26,56	12,77	74
Xb	245...247, AcOH	48,95	3,33	18,77	7,62	$C_{17}H_{14}BrN_5OS$	49,05	3,39	16,82	7,70	85
Xc	230...232, AcOH	60,45	4,39	20,71	9,45	$C_{17}H_{15}N_5OS$	60,52	4,48	20,76	9,50	83
Xd	203...205, AcOH	50,79	3,21	13,89	7,91	$C_{17}H_{13}BrN_4OS$	50,88	3,27	13,96	7,99	77
Xe	198...200, AcOH	54,17	3,66	28,69	13,12	$C_{11}H_9N_5S$	54,31	3,73	28,79	13,18	69
Xf	152...154, ethanol	53,71	4,79	19,26	10,95	$C_{13}H_{14}N_4O_2S$	53,78	4,86	19,30	11,04	70
Xg	220...222, AcOH	63,26	4,31	17,29	9,89	$C_{17}H_{14}N_4OS$	63,34	4,38	17,38	9,95	81
Xh	234...236, 1-butanol	64,18	4,71	16,58	9,49	$C_{18}H_{16}N_4OS$	64,26	4,79	16,65	9,53	84
Xi	145...147, ethanol	61,29	4,51	15,83	9,05	$C_{18}H_{16}N_4O_2S$	61,35	4,58	15,90	9,10	80
Xj	223...225*, 1-butanol	52,14	3,04	14,27	8,13	$C_{17}H_{12}Cl_2N_4OS$	52,18	3,09	14,32	8,19	93
Xk	130...132, 1-butanol	55,19	5,24	18,37	10,48	$C_{14}H_{16}N_4O_2S$	55,25	5,30	18,41	10,53	80
Xl	224...226, 1-butanol	54,72	3,75	17,22	19,41	$C_{15}H_{12}N_4OS_2$	54,86	3,68	17,06	19,53	70
XIa	278...280, AcOH	50,48	4,20	26,50	12,25	$C_{11}H_{11}N_5OS$	50,56	4,24	26,56	12,27	81/84
XIb	276...278, AcOH	48,89	3,41	16,75	7,65	$C_{17}H_{14}BrN_5OS$	49,05	3,39	16,82	7,70	72/75
XIc	293...295, AcOH	60,60	4,33	20,82	9,41	$C_{17}H_{15}N_5OS$	60,52	4,48	20,76	9,50	74/76
XId	252...254, AcOH	50,78	3,31	13,88	7,90	$C_{17}H_{13}BrN_4OS$	50,88	3,27	13,96	7,99	78/88
XIe	285...287*, AcOH	54,21	3,61	28,84	13,22	$C_{11}H_9N_5S$	54,31	3,73	28,79	13,18	70/68
XIf	159...162, AcOH	53,62	4,77	19,41	11,13	$C_{13}H_{14}N_4O_2S$	53,78	4,86	19,30	11,04	66/71
XIg	232...234, AcOH	63,47	4,22	17,43	9,81	$C_{17}H_{14}N_4OS$	63,34	4,38	17,38	9,95	64/60
XIh	255...257, 1-butanol	64,13	4,64	16,72	9,67	$C_{18}H_{16}N_4OS$	64,26	4,79	16,65	9,53	72/68
XIi	211...213, 1-butanol	61,45	4,64	15,84	8,92	$C_{18}H_{16}N_4O_2S$	61,35	4,58	15,90	9,10	82/80
XIj	228...230, AcOH	52,29	3,15	14,44	8,01	$C_{17}H_{12}Cl_2N_4OS$	52,18	3,09	14,32	8,19	69/66
XIk	219...221*, AcOH	55,11	5,21	18,55	10,60	$C_{14}H_{16}N_4O_2S$	55,25	5,30	18,41	10,53	78/81
XIl	272...274*, AcOH	54,95	3,73	16,92	19,48	$C_{15}H_{12}N_4OS_2$	54,86	3,68	17,06	19,53	79/83

*Compound sublimates.

TABLE 2. IR and PMR Spectral Data for Pyridines Xa-X*l* and Thieno[2,3-*b*]pyridines XIa-XI*l*

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm				
	NH_2	C=O	C ≡ N	6-NH_2, s	CH_3, t	CH_2, q	S—CH_2, s, 3-NH_2, s	Z
Xa	3210...3365	1710	2190	7,93	1,20	2,71	3,84	7,23 s, 7,48 s
Xb	3213...3485	1680	2190	7,93	1,20	2,70	4,12	10,23 s, 7,53 s
Xc	3215, 3310, 3420	1640	2205	7,95	1,21	2,73	4,13	10,08 s, 7,06...7,59 m
Xd	3220, 3303, 3400	1704	2220, 2235	7,82	1,22	2,72	4,92	8,00 d, 7,77 d
Xe	3170, 3296, 3332		2222, 2250	8,14	1,22	2,73	4,30	
Xf	3225, 3330, 3423	1730	2218, 2227	7,89	1,20*	2,70	4,14*	1,20* t, 4,14* m
Xg	3220, 3342, 3425	1715	2230	7,85	1,22	2,71	4,98	8,06 m, 7,64 m
Xh	3215, 3340, 3432	1675	2218	7,72	1,21	2,71	4,90	2,34 s, 7,94 d, 7,36 d
Xi	3240, 3334, 3420	1724	2220, 2228	7,92	1,20	2,70	4,25	7,35 s, 5,17 s
XJ	3233, 3330, 3424	1695	2118, 2235	7,83	1,22	2,71	4,93	7,88...8,25 m
Xk	3255, 3352, 3440	1740	2230	7,87	1,20	2,70	4,15	4,03 t, 1,57 m, 0,84 t
X*l*	3225, 3314, 3400	1680	2220, 2235	7,84	1,22	2,73	4,90	7,31 m, 8,14 m
XIa	3180, 3355	1690	2215	7,71	1,27	3,11	6,93	7,02 s
XIb	3165, 3224, 3400	1692	2190	7.30	1.26	3,13	7,14	9,42 s, 7,66 d, 7,47 d
XIc	3210, 3333, 3454, 3481	1620	2220	7,64	1,30	3,01	7,10	9,30 s, 7,30 m
XId	3300, 3435, 3480	1660	2218	8,31	1,28	3,16	7,55	7,68 m
XIe	3148, 3225		2190	7,37	1,21	3,11	6,46	
XIf	3234, 3350, 3415, 3463	1655	2223	7,33	1,27 m*	3,11	6,87	1,27* m, 4,23 q
XIg	3150, 3295, 3412	1648	2194	8,27	1,27	3,14	7,52	7,63 m
XIh	3215, 3340, 3440	1648	2230	8,18	1,25	3,12	7,29	2,33 s, 7,48 m
XIi	3210, 3364, 3482	1650	2212	7,36*	1,24	3,07	6,91	5,25 s, 7,36* m
XIj	3213, 3315, 3390, 3496	1650	2220	8,25	1,27	3,14	7,45	7,70...7,84 m
XIk	3210, 3315, 3440, 3422	1654	2220	7,32	1,24	3,10	6,86	4,12 t, 1,65 m, 0,91 t
XI*l*	3155, 3270, 3450	1650	2200	8,35	1,27	3,14	7,50	7,23 t, 7,87 m

*Signals overlap.

The reaction of equimolar amounts of propionaldehyde (III), malononitrile (IV), and cyanothioacetamide (V) in ethanol at 25°C leads to the Knoevenagel condensation of C—H acids IV and V with aldehyde III to give substituted acrylonitriles VI and VII, which then undergo the Michael reaction with thioamide V or, correspondingly, with nitrile IV. The adduct formed (VIII) undergoes intramolecular cyclization to give thiopyran I, which is stable in the crystalline state and in ethanolic solution at room temperature. Heating the reaction mixture at reflux leads to opening of the thiopyran ring and formation of pyridinethione II (method A), which was also obtained in a single operation by heating a mixture of starting reagents III, IV, and V in ethanol at reflux in the presence of N-methylmorpholine (method B). This result indicates, in our opinion, that thione II is the product of thermodynamic control, while thiopyran is the product of kinetic control [6]. Similar behavior has been found for aryl derivatives of 4H-thiopyridines and 4H-selenopyridines [7, 8].

Pyridinethione II in basic media in DMF reacts with alkyl halides (IX) to give sulfides (X), which then undergo the Thorpe—Ziegler reaction to give substituted thienopyridines (XI) (method A). Products XI may also be obtained in one step from thione II and halides IX in the presence of two equivalents of KOH (method B). The formation of products XI indicates the regioselectivity of the alkylation at the sulfur atom. The structure of the products was supported by their spectral data. The IR spectra of these compounds show stretching bands for conjugated nitrile groups at 2190-2240 cm^{-1} and for amino groups at 3215-3420 cm^{-1}. The most characteristic PMR signals for pyran I and pyridines II, X, and XI are the signals for the protons of the ethyl group at δ 0.87-1.26 ppm (3H, t, CH_3) and 2.70-3.14 ppm (2H, q, CH_2), amino group at δ 6.81-7.93 ppm (2H, br.s, NH_2), and alkylthio group in the corresponding regions (Table 2).

EXPERIMENTAL

The IR spectra were taken on an IKS-29 spectrometer for Vaseline mulls. The PMR spectra were taken on a Bruker WP-100SY spectrometer at 100 MHz in DMSO-d_6 with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with 3:5 acetone—heptane as the eluent. The spots were developed with iodine vapor.

2,6-Diamino-3,5-dicyano-4-ethyl-4H-thiopyran (I). A mixture of 10 mmoles propionaldehyde (III), 10 mmoles malononitrile (IV), 10 mmoles cyanothioacetamide (V), and three drops of organic base (B) in 20 ml ethanol was stirred for 4 h at 20°C. The precipitate formed was separated and washed with ethanol and hexane to give yellow crystalline thiopyran in 61% yield, mp 150-152°C (ethanol). IR spectrum, ν, cm^{-1}: 2185 sh (CN), 3200-3425 (NH_2), 1648 (δNH_2). PMR spectrum, δ, ppm: 6.81 (4H, br.s, $2NH_2$), 2.91 (1H, t, 4-H), 1.51 (2H, m, CH_2), 0.87 (3H, t, CH_3). Found: C, 52.30; H, 4.72; N, 27.29; S, 15.69%. Calculated for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16; S, 15.54%.

6-Amino-3,5-dicyano-4-ethylpyridine-2(1H)-thione (II). A. Three drops of an organic base (B) were added to a suspension of thiopyran I in 15 ml ethanol and the reaction mixture was heated at reflux for 1 h. After cooling to room temperature, the mixture was brought to pH 4-5 by adding 10% hydrochloric acid and left for 24 h. The precipitate formed was filtered off and washed with ethanol and hexane to give thione II in 69% yield, mp 285-287°C (ethanol). IR spectrum, ν, cm^{-1}: 3285-3370 (NH_2), 2218 sh (CN). PMR spectrum, δ, ppm: 12.73 (1H, br.s, NH), 7.81 (2H, s, NH_2), 2.65 (2H, q, CH_2), 1.21 (3H, t, CH_3). Found: C, 52.85; H, 3.88; N, 27.47, S, 15.68%. Calculated for $C_9H_8N_4S$: 52.92; H, 3.95; N, 27.43; S, 15.70%.

B. A suspension of 10 mmoles aldehyde III, 10 mmoles dinitrile IV, and 10 mmoles thioamide V in 15 ml ethanol in the presence of three drops of base (B) was heated at reflux for 1 h. After cooling to 20°C, the reaction mixture was brought to pH 4-5 by adding 10% aqueous hydrochloric acid with stirring and left stand for 24 h. The precipitate formed was filtered off and washed consecutively with ethanol and hexane to give thione II in 60% yield, which was identical in its melting point and PMR spectrum to the sample obtained by method A.

6-Amino-2-*Z*-methylthio-3,5-dicyano-4-ethylpyridines (Xa-X*l*). A sample of 5.6 ml (10 mmoles) 10% aqueous KOH was added with stirring to a suspension of 10 mmoles thione II in 8 ml DMF at 20°C. After 1 min, 10 mmoles alkyl halide (IX) was added. The reaction mixture was then stirred for 3 h and diluted with 10 ml water. The precipitate formed was filtered off and washed consecutively with water, ethanol, and hexane to give pyridines (Xa-X*l*), whose indices are given in Tables 1 and 2.

3,6-Diamino-2-*Z*-5-cyano-4-ethylthieno[2,3-*b*]pyridines (XIa-XI*l*). A. A sample of 5.6 ml (10 mmoles) 10% aqueous KOH was added with stirring to a suspension of 10 mmoles 2-alkylthiopyridine X in 10 ml DMF at 20°C and stirred for 4 h.

The reaction mixture was then diluted with 10 ml water. The precipitate formed was filtered off and washed with water, ethanol, and hexane to give XIa-XI*l*, whose indices are given in Tables 1 and 2.

B. A sample of 5.6 ml (10 mmoles) 10% aqueous KOH was added with stirring to a suspension of 10 mmoles thione II in 10 ml DMF. After 1 min, 10 mmoles alkyl halide (IX) was added. The reaction mixture was then stirred for 3 h. Then, an additional 5.6 ml (10 mmoles) 10% aqueous KOH was added and stirring was continued for an additional 4 h. The mixture was diluted with 10 ml water. The precipitate formed was separated and washed consecutively with water, ethanol, and hexane to give XIa-XI*l*, which proved identical in their melting point and IR spectra to the product samples obtained using method A.

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