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SYNTHESIS OF N-METHYLMORPHOLINIUM 6-OXO-3,5-DICYANO-1,4,5,6-TETRAHYDRO-4-(SPIROCYCLOPENTANE)PYRIDINE-2-THIOLATE WITH THE MICHAEL REACTION

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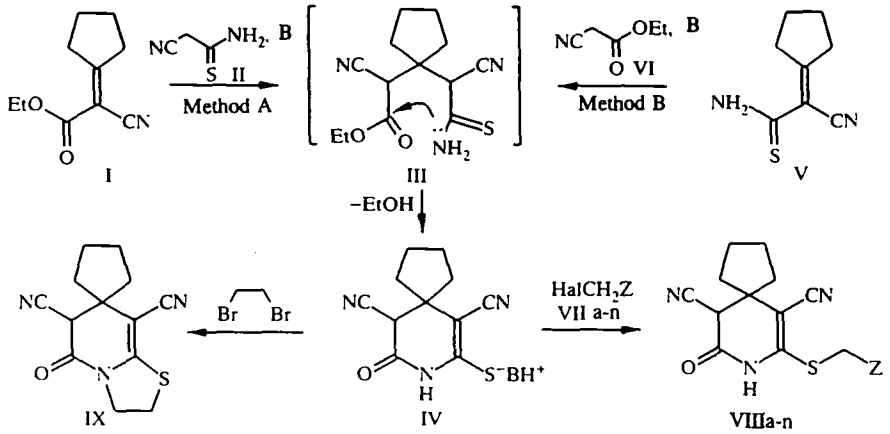
N-Methylmorpholinium 6-oxo-3,5-dicyano-1,4,5,6-tetrahydro-4-(spirocyclopentane)pyridine-2-thiolate was obtained by reaction of cyclopentylidenecyanoacetic ester with cyanothioacetamide or cyclopentylidenecyanothioacetamide with cyanoacetic ester in the presence of N-methylmorpholine; it is used in synthesis of substituted 2-alkylthiotetrahydropyridines, 5-oxo-6,8-dicyano-2,3,6,7-tetrahydro-(5H)-7-(spirocyclopentane)-thiazolo[3,2-a]pyridine, 5-allyl-2-methylthio-3,5-dicyano-4,5-dihydro-4-(spirocyclo-pentane)pyridin-6(1H)-one, and 3-amino-6-oxo-5-cyano-4,5-dihydro-4-(spirocyclopentane)-2H-pyrazolo[5,4-b]pyridin-6(7H)-one.

We recently demonstrated the possibility of synthesizing substituted 4-(spirocyclohexane)pyridine-2-thiols and -selenols by reaction of cyclohexylidenecyanoacetic ester with cyanothioacetamide [1]. In further studies of the synthesis of dihydropyridine chalcogenones, promising synthons for obtaining compounds with a broad spectrum of biological activity [2], we investigated the reaction of cyclopentylidenecyanoacetic ester (I) with cyanothioacetamide (II) in the presence of N-methylmorpholine. It was shown that this reaction takes place in the first stage like Michael addition with the formation of adduct III, whose cyclocondensation subsequently yields salt IV (method A). The latter is also obtained in the reaction of cyclopentylidenecyanothioacetamide (V) with cyanoacetic ester (VI) and N-methylmorpholine (method B). The spectral studies (see Experimental section) and chemical transformations confirm the structure of thiolate IV. Sulfides (VIIIa-n) are formed in its reaction with halides (VIIa-n), and the reaction of thiolate IV with 1,2-dibromoethane in basic medium results in the formation of substituted thiazolo[3,2-*a*]pyridine (IX).



B = N-methylmorpholine

VII, VIII a Hal = I, Z = H; b Hal = Br, Z = 3,4-$Cl_2C_6H_3CO$; c Hal = Br, Z = CH_2 = CH; d Hal = Cl, Z = $PhCH_2OCO$; e Hal = Br, Z = 2-MeC_6H_4; f Hal = I, Z = Me; g Hal = Br, Z = Et; h Hal = Br, Z = 4-MeC_6H_4; i Hal = Cl, Z = PhNHCO; j Hal = Cl, Z = Ph; k Hal = Cl, Z = EtOCO; *l* Hal = I, Z = $Me(CH_2)_4$; m Hal = Cl, Z = HOCO; n Hal = Br, Z = 2-oxo-3-chromenylcarbonyl

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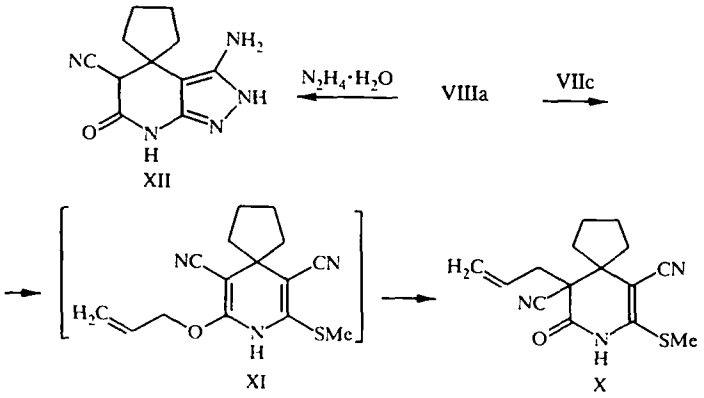
TABLE 1. Characteristics of 2-Akylthio-3,5-dicyano-4,5-dihydro-4-(spirocyclopentane)pyridin-6(1H)-ones (VIIIa-n)

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent for crystallization)	Yield, %
		C	H	N	S		
VIIIa	$C_{12}H_{13}N_3OS$	58,40 / 58,28	5,15 / 5,30	17,14 / 16,99	13,03 / 12,96	148...150 (ethanol)	86
VIIIb	$C_{19}H_{15}Cl_2N_3O_2S$	54,18 / 54,29	3,48 / 3,60	9,83 / 10,00	7,78 / 7,63	187...189 (AcOH)	80
VIIIc	$C_{14}H_{15}N_3OS$	61,62 / 61,51	5,70 / 5,53	15,18 / 15,37	11,60 / 11,73	126...127 (ethanol)	72
VIIId	$C_{20}H_{19}N_3O_3S$	63,14 / 62,97	4,88 / 5,02	10,91 / 11,02	8,62 / 8,41	101...103 (ethanol)	65
VIIIe	$C_{19}H_{19}N_3OS$	67,51 / 67,63	5,74 / 5,68	12,60 / 12,45	9,39 / 9,50	156...158 (butanol)	70
VIIIf	$C_{13}H_{15}N_3OS$	59,58 / 59,75	5,60 / 5,79	15,89 / 16,08	12,40 / 12,27	144...146 (AcOH)	81
VIIIg	$C_{14}H_{17}N_3OS$	60,89 / 61,06	6,15 / 6,22	15,33 / 15,26	11,49 / 11,64	139...141 (ethanol)	90
VIIIh	$C_{20}H_{19}N_3O_2S$	65,84 / 65,73	5,05 / 5,24	11,71 / 11,50	8,56 / 8,77	121...123 (AcOH)	68
VIIIi	$C_{19}H_{18}N_4O_2S$	62,13 / 62,28	5,08 / 4,95	15,18 / 15,29	8,60 / 8,75	174...176 (AcOH)	71
VIIIj	$C_{18}H_{17}N_3OS$	66,94 / 66,85	5,22 / 5,30	13,14 / 12,99	9,77 / 9,91	148...150 (AcOH)	70
VIIIk	$C_{15}H_{17}N_3O_3S$	56,27 / 56,41	5,20 / 5,37	13,21 / 13,16	9,84 / 10,04	95...97 (ethanol)	69
VIIIl	$C_{17}H_{23}N_3OS$	64,21 / 64,32	7,13 / 7,30	13,10 / 13,24	10,32 / 10,10	96...98 (AcOH)	68
VIIIm	$C_{13}H_{13}N_3O_3S$	53,47 / 53,60	4,33 / 4,50	14,60 / 14,42	10,85 / 11,01	72...74 (H_2O)	62
VIIIn	$C_{22}H_{17}N_3O_4S$	62,87 / 63,00	3,95 / 4,09	10,19 / 10,02	7,77 / 7,64	203...205 (AcOH)	66

This regioselectivity of the alkylation reaction was also observed previously for the homolog of N-methylmorpholinium 6-oxo-3,5-dicyano-1,4,5,6-tetrahydro-4-(spirocyclohexane)pyridine-2-thiolate salt IV [1], which corresponds to the general characteristics of the chemistry of 3-cyanopyridine-2-chalcogenones [2].



In view of the presence of two nucleophilic centers in the molecule of sulfides VIIIa-n, it was useful to investigate their subsequent alkylation. It was shown that the reaction of substituted 2-methylthio-4,5-dihydropyridin-6(1H)one VIIIa with allyl bromide VIIc in the presence of an equimolar amount of 10% aqueous solution of KOH results in the formation of 5-allyl-2-methylthio-3,5-dicyano-4,5-dihydro-4-(spirocyclopentane)pyridin-6(1H)-one (X). However, the mechanism of this reaction was not unambiguously established. It is thus possible to hypothesize that substituted dihydropyridine (XI) (not possible to separate) is initially formed in this alkylation reaction and subsequently undergoes Claisen rearrangement in the reaction conditions [3], as we previously found for allylthio(seleno)-substituted 1,4-dihydropyridines [4]. Moreover, it is known that alkylation of dihydropyridines containing a thione function can also take place at the $C_{(3)}$ atom of the pyridine nucleus [5]. Studies are continuing to clarify this problem.

TABLE 2. PMR and IR Spectral Data for Dihydropyridinones VIIIa-n

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm, SSCC (J), Hz				
	NH	CN	CONH, C=O	NH, s	5-H, s	SCH_2	$(CH_2)_4$, m	Z
VIIIa	3200	2202, 2240	1700	11,14	4,74	2,48* s	1,73	(H)*[2]
VIIIb	3480	2200, 2250	1700	11,15	4,96	4,67 s	1,76	8,07 (1H, s, Ar); 7,73 (2H,m, Ar)
VIIIc	3474	2200, 2250	1695	11,20	4,57	3,67 d, J = 7,0	1,72	5,75 (1H,m, CH); 5,16 (1H, d, J = 4,5, CH_2) and 5,02 (1H, d, CH_2)
VIIId	3212	2202, 2249	1750	11,23	4,25	4,02 s	1,66	7,36 (5H, s, Ph); 5,12 (2H, s, CH_2)
VIIIe	3200	2222, 2265	1710	11,39	4,52	4,31 q	1,68	7,18 (4H,m, Ar); 2,39 (3H, s, CH_3)
VIIIf	3210	2220, 2254	1700	11,21	4,71	3,02 q	1,76	1,22 (3H, t, CH_3)
VIIIg	3210	2205, 2244	1700	11,27	4,69	2,98 t	1,76	0,95 (3H, t, CH_3); 1,50 (2H,m, CH_2)
VIIIh	3200	2210, 2240	1680	11,16	4,60	4,76 s	1,73	2,37 (3H, s, CH_3); 7,87 (2H, d, Ar); 7,34 (2H, d, Ar)
VIIIi	3345	2217, 2250	1670, 1725	11,37	4,67	3,99 s	1,71	10,39 (1H, s, NH); 7,10...7,59 (5H,m, Ph)
VIIIj	3200	2224, 2662	1710	11,33	4,48	4,27 q, J = 12,9	1,68	7,29 (5H, s, Ph)
VIIIk	3300	2205, 2245	1650, 1770	11,22	4,56	3,93 s	1,73	4,09 (2H, q, OCH_2); (CH_3)*[3]
VIIIl	3188	2204, 2250	1700	11,20	4,66	2,99 t	1,76	0,85 (3H, t, CH_3); 1,26 (8H,m, $4CH_2$)
VIIIm	3190	2200, 2250	1695, 1730	11,21	4,61	3,92 s	1,75	-(COOH)*[4]
VIIIn	3330	2188, 2254	1700	11,11	4,88	4,62 s	1,74	8,36 (1H, s, 4-H); 7,89 (2H, d, H_{arom}); 7,66 (1H,m, H_{arom}); 7,39 (1H,m, H_{arom})

*Signal of SCH_3 group.

*[2]See signal of SCH_3 group.

*[3]The CH_3 group signal is overlapped by the signal of the $(CH_2)_4$ fragment.

*[4]Signal not observed due to deuterium exchange.

The methylthio group in compound VIIIa is substituted at the hydroazo group when it is boiled in alcohol with hydrazine hydrate. The structure of the substituted pyrazolo[5,4-*b*]pyridin-6(7H)-one XII formed is in agreement with the PMR and IR spectral data (see Experimental section).

The physicochemical studies confirm the structure of compounds VIIIa-n, IX, and X (Tables 1 and 2). Their IR spectra contain absorption bands of stretching vibrations of conjugated and unconjugated nitrile groups in the 2188-2224 and 2240-2265 cm^{-1} region, respectively. Singlet signals of the 5-H proton and NH group in the region of 4.25-4.96 and 11.11-11.39 ppm region, respectively, signals of protons of a tetramethylene fragment (8H, m), and SCH_2 and Z groups in characteristic δ regions are observed in the PMR spectra of pyridones VIIIa-n and IX.

EXPERIMENTAL

The IR spectra were made on an IKS-29 spectrophotometer in liquid petrolatum. The PMR spectra were recorded on a Bruker WP-100 SY (100 MHz) in solutions of DMSO-D_6 with TMS as internal standard. The evolution of the reaction and purity of the compounds obtained were controlled by TLC on Silufol UV-254 plates in acetone–heptane system (3:5) with iodine vapors as developer.

N-methylmorpholinium 6-Oxo-3,5-dicyano-1,4,5,6-tetrahydro-4-(spirocyclopentane)pyridine-2-thiolate (IV). A. Here 1 g (10 mmole) of cyanothioacetamide II and 2 ml (20 mmole) of N-methylmorpholine were added to a solution of 1.8 g (10 mmole) of cyclopentylidenecyanoacetic ester I in 15 ml of absolute ethanol. The mixture obtained was stirred at 20°C for 1 h. It was held at room temperature for 24 h, and then the sediment of product formed was filtered off and washed with ethanol and hexane. Yield of 2.4 g (72%), mp = 185-187°C. IR spectrum: 1680 (CONH), 2246, 2175 (C≡N), 3210 cm^{-1} (NH). PMR spectrum: 1.67 (8H, m, $4CH_2$); 2.82 (3H, s, CH_3); 3.20 (4H, m, CH_2NCH_2); 3.79 (4H, m, CH_2OCH_2); 4.13 (1H, s, 5-H); 9.46 ppm (1H, br. s, NH). Found, %: C 57.29; H 6.50; N 16.87; S 9.66. $C_{16}H_{22}N_4O_2S$. Calculated, %: C 57.46; H 6.63; N 16.75; S 9.59.

B. Here 1.1 ml (10 mmole) of cyanoacetic ester VI and 2 ml (10 mmole) of N-methylmorpholine were added to a suspension of 1.7 g (10 mmole) of cyclopentylidenecyanothioacetamide V in 15 ml of abs. ethanol at 20°C. Method A was then followed. Salt IV, identical to the sample synthesized with method A (mp, IR spectrum), was obtained.

2-Alkylthio-3,5-dicyano-4,5-dihydro-4-(spirocyclopentane)pyridin-6(1H)-ones (VIIIa-n). Here 5.6 ml (10 mmole) of 10% aqueous solution of KOH was added to a suspension of 3.3 g (10 mmole) of salt IV in 10 ml of DMF and stirred for 5 min until starting reagent IV was totally dissolved. Then the reaction mass was filtered through a fold filter into a beaker containing 10 mmole of the corresponding halide VIIa-n, stirred for 4 h, diluted with an equal volume of water, and the sediment of product VIII formed was filtered off. The characteristics of pyridones VIIIa-n obtained are reported in Tables 1 and 2.

5-Oxo-6,8-dicyano-2,3,6,7-tetrahydro-(5H)-7-(spirocyclopentane)thiazolo[3,2-*a*]pyridine (IX). Here 5.6 ml (10 mmole) of 10% aqueous solution of KOH and then 0.9 ml (10 mmole) of 1,2-dibromoethane were added to a suspension of 3.3 g (10 mmole) of salt IV in 10 ml of DMF while stirring. The reaction mass was stirred at 20°C for 1 h, then 5.6 ml (10 mmole) of 10% aqueous solution of KOH was added, stirred for 3 h, and diluted with an equal volume of water. The sediment formed was filtered off and washed with water, ethanol, and hexane. Yield of 1.7 g (66%). Mp = 96-98°C (from ethanol). IR spectrum: 1695 (C=O), 2200, 2250 cm^{-1} (C≡N). PMR spectrum: 1.76 (8H, m, $4CH_2$); 3.39 (2H, t, CH_2S); 4.14 (2H, m CH_2N); 4.74 ppm (1H, s, 6-H). Found, %: C 60.06; H 4.89; N 16.38; S 12.42. $C_{13}H_{13}N_3OS$. Calculated, %: C 60.21; H 5.05; N 16.20; S 12.36.

5-Allyl-2-methylthio-3,5-dicyano-4,5-dihydro-4-(spirocyclopentane)pyridin-6(1H)-one (X). Here 5.6 ml (10 mmole) of 10% aqueous solution of KOH was added to a solution of 2.5 g (10 mmole) of pyridone VIIIa in 12 ml of DMF while stirring at 20°C, and 0.9 ml (10 mmole) of allyl bromide (VIIb) was added after 1 min and stirred for 3 h. The reaction mixture was diluted with 10 ml of water, the sediment of the product formed was filtered off and washed with water, ethanol, and hexane. Yield of 2 g (70%). Mp = 182-184°C (from acetonitrile). IR spectrum: 1710 (CONH), 3200 (NH), 2210, 2260 cm^{-1} (C≡N). PMR spectrum: 1.76 (8H, m, $4CH_2$); 2.52 (3H, s, CH_3); 2.59 (2H, d, CH_2O); 5.24 (2H, m, CH_2=); 5.68 (1H, m, CH=); 11.19 ppm (1H, br. s, NH). Found, %: C 62.51; H 6.16; N 14.47; S 11.02. $C_{15}H_{17}N_3OS$. Calculated, %: C 62.69; H 5.96; N 14.62; S 11.16.

3-Amino-6-oxo-5-cyano-4,5-dihydro-4-(spirocyclopentane)pyrazolo[5,4-*b*]pyridin-6(7H)-one (XII). Here 1 ml (20 mmole) of hydrazine hydrate was added to a suspension of 2.5 g (10 mmole) of pyridone VIIIa in 15 ml of ethanol and the

mixture was boiled for 2 h and filtered. The filtrate was held at 20°C for 24 h. The sediment of product formed was separated and washed with ethanol and hexane. Yield of 1.5 g (63%). Mp = 273-275°C. IR spectrum: 1700 (CONH), 2262 ($C \equiv N$), 3300, 3385, 3480 cm^{-1} (NH_2). PMR spectrum: 1.73 (8H, m, $4CH_2$); 4.20 (1H, s, 5-H); 4.67 (2H, br. s, NH_2); 10.66 (1H, s, $N_{(2)}-H$); 10.79 ppm (1H, br. s, $N_{(7)}-H$). Found, %: C 56.95; H 5.72; N 30.11. $C_{11}H_{13}N_5OS$. Calculated, %: C 57.13; H 5.67; N 30.28.

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