The Mannich reaction in the synthesis of N,S-containing heterocycles
4.* Aminomethylation of 6-amino-3,5-dicyano-1,4-dihydropyridine-2-thiolates: a convenient regioselective route to 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene derivatives

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Treatment of *N*-methylmorpholinium 4-R-6-amino-3,5-dicyano-1,4-dihydropyridine-2-thiolates (R = 2-ClC_6H_4 and 2-$MeOC_6H_4$) with primary amines in the presence of an excess of formaldehyde gave 13-R-8-thioxo-3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-1,9-dicarbonitrile derivatives in high yields (66—95%). In a similar way, aminomethylation of 3-R-10-amino-7,11-dicyano-9-aza-3-azoniaspiro[5.5]undeca-7,10-diene-8-thiolates (R = Me and Et) afforded 1´-alkyl-8-thioxospiro[3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-13,4´-piperidine]-1,9-dicarbonitriles in 43—91% yields. Alternatively, these compounds were obtained by multicomponent cyclocondensation of *N*-alkylpiperidin-4-ones, cyanothioacetamide, primary amines, and aqueous formaldehyde. The starting 3-R-10-amino-7,11-dicyano-9-aza-3-azoniaspiro[5.5]undeca-7,10-diene-8-thiolates were prepared by a new method from *N*-alkylpiperidin-4-ones and cyanothioacetamide. The structure of 5,11-bis(4-ethoxyphenyl)-13-(2-methoxyphenyl)-8-thioxo-3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-1,9-dicarbonitrile was examined by X-ray diffraction analysis.

Key words: *N*-methylmorpholinium 6-amino-4-aryl-3,5-dicyano-1,4-dihydropyridine-2-thiolates, the Mannich reaction, cyclocondensation, X-ray diffraction analysis, 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-1,9-dicarbonitriles, 3-R-10-amino-7,11-dicyano-9-aza-3-azoniaspiro[5.5]undeca-7,10-diene-8-thiolates, 1´-alkyl-8-thioxospiro[3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-13,4´-piperidine]-1,9-dicarbonitriles, cyanothioacetamide, *N*-alkylpiperidin-4-ones.

The Mannich reaction is one of the most efficient and preferred methods of designing azaheterocyclic systems.[1] Aminomethylation of binucleophilic substrates, specifically *N*,*S*-binucleophiles, is of particular interest for the synthesis of nitrogen-containing heterocycles. For instance, reactions of dithiocarbamates, as well as a number of other substrates containing a thioamide fragment, with formaldehyde and primary amines are known to be a general method for the synthesis of 1,3,5-thiadiazine derivatives[2] many of which exhibit a broad range of biological activity.[3] Cyclic thioamides behave in a similar way: in recent years, the "double" Mannich cyclocondensation has been successfully used to obtain derivatives of *symm*-triazolo[3,4-*b*][1,3,5]thiadiazine,[4—11] thiazolo[3´,4´:1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazine,[12] imidazo[2,1-*b*][1,3,5]thiadiazine, 1,2,4-triazino[3,2-*b*]-[1,3,5]thiadiazine,[13] and 1,3,5-thiadiazino[3,2-*a*]benzimidazole.[14] This approach has also been employed in the synthesis of pyrido[2,1-*b*][1,3,5]thiadiazine[15] and imidazo[2,1-*b*][1,3,5]thiadiazine derivatives.[16] Functionalized, partially hydrogenated 3-cyanopyridine-2-thiolates[17] can behave abnormally under the Mannich reaction conditions. For instance, 3,7-diazabicyclo[3.3.1]nonane deriva-

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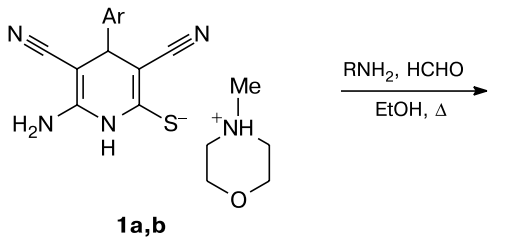
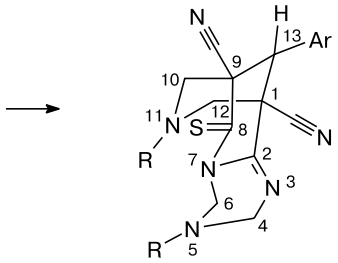
tives[18] have been obtained in some cases together with the expected *N*,*S*-diaminomethylation products, namely, pyrido[2,1-*b*][1,3,5]thiadiazines.[15] Proceeding further in these investigations, we studied the aminomethylation of a number of earlier prepared *N*-methylmorpholinium 6-amino-4-aryl-3,5-dicyano-1,4-dihydropyridine-2-thiolates (**1**), which are promising *N*,*S*-binucleophilic substrates.

In the aminomethylation of thiolates **1a,b** (thiolate : primary amine = 1 : 1, excess of HCHO), we isolated only products **2a—f** in low yields (13—43%) rather than the expected pyrido[2,1-*b*][1,3,5]thiadiazines. Compounds **2a—f** are representatives of a novel heterocyclic system, *viz.*, 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene. To optimize the reaction conditions, we doubled the amount of the starting amine; as the result, the yields of tricyclic compounds **2** were increased to 66—95% (Scheme 1).

Scheme 1



1a,b



2a—f

1: Ar = 2-MeOC$_6$H$_4$ (**a**); 2-ClC$_6$H$_4$ (**b**)

2: Ar = 2-MeOC$_6$H$_4$, R = 4-EtOC$_6$H$_4$ (**a**); Ar = 2-MeOC$_6$H$_4$, R = 2-MeC$_6$H$_4$ (**b**); Ar = 2-MeOC$_6$H$_4$, R = 2-EtC$_6$H$_4$ (**c**); Ar = 2-ClC$_6$H$_4$, R = 4-EtOC$_6$H$_4$ (**d**); Ar = 2-ClC$_6$H$_4$, R = CH$_2$Ph (**e**); Ar = 2-ClC$_6$H$_4$, R = 3,4-Me$_2$C$_6$H$_3$ (**f**)

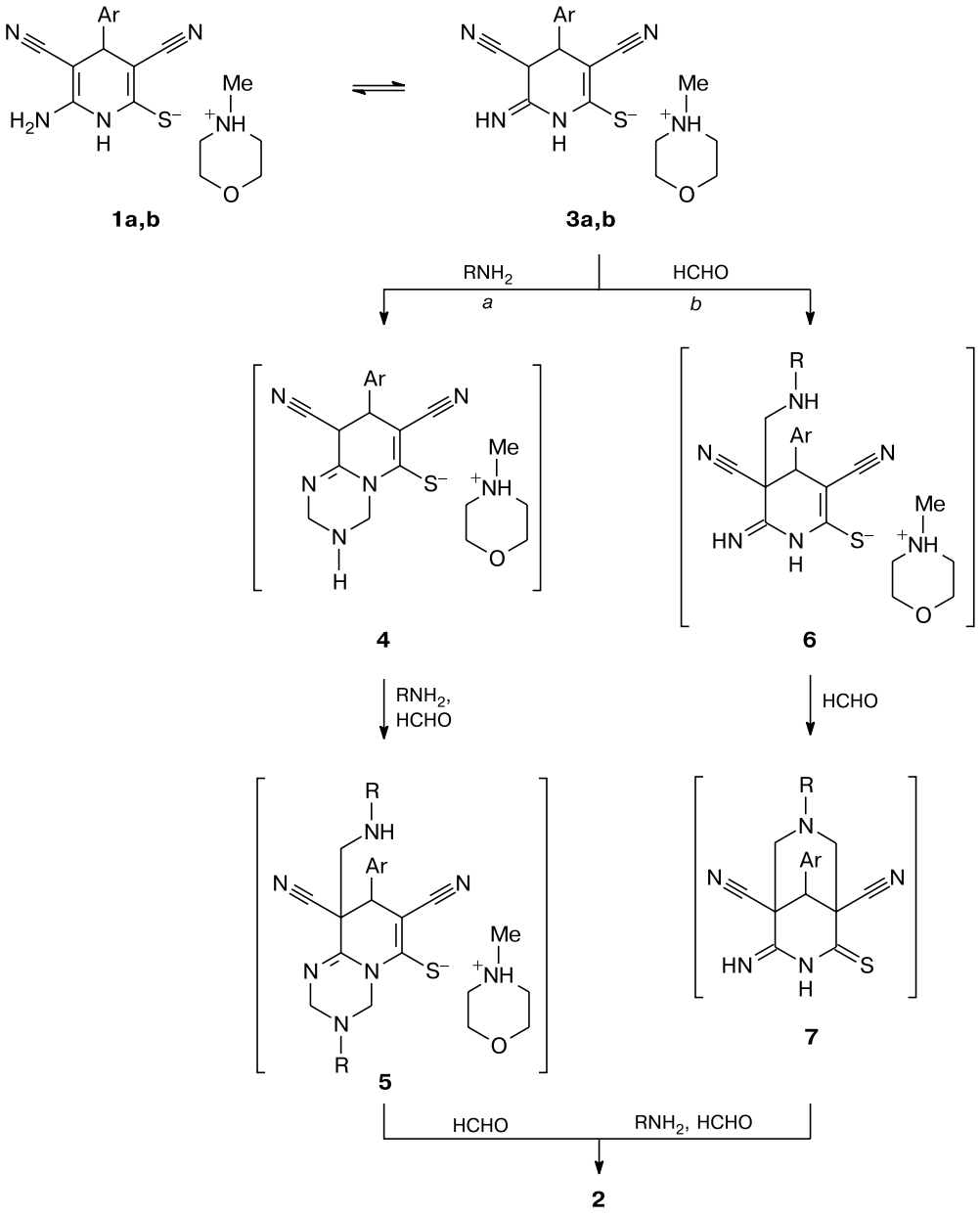
Thus, model thiolates **1** under the Mannich reaction conditions do not act as *N*,*S*-binucleophiles, undergoing regioselective aminomethylation at the C(3) and C(5) atoms and the N atoms of the exocyclic amino and endocyclic imino groups. It follows from numerous literature data[19] that the aminomethylation of piperidin-4-ones and other 3,5-dinucleophilic substrates of the pyridine series occurs at the C(3) and C(5) atoms to give 3,7-diazabicyclo[3.3.1]nonane (DABCN, bispidine) derivatives.[20] It should be noted that DABCN derivatives are of both theoretical (because of their peculiar conformational structures)[21] and practical interest due to the specific ability to form strong complexes with transition metal cations[22] and a broad spectrum of biological activity inherent in bispidines.[19,20,22,23] In the reactions with thiolates **1**, the formation of a bispidine-like structure was unexpectedly accompanied by parallel cyclocondensation resulting in closure of a tetrahydro-1,3,5-triazine ring. At the same time, it is known that close structural analogs of dihydropyridine-2-thiolates **1**, *viz.*, 3,5-bis(alkoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridines (Hantzsch dihydropyridines), do not form 3,7-diazabicyclo[3.3.1]nonane derivatives in the Mannich reaction, undergoing aminomethylation at the methyl group, the N(1) atom, and either the C(3) or C(5) atom to yield derivatives of 1,6-naphthyridine and pyrimido[5,6,1-*ij*][1,6]naphthyridine.[24] The one-step transformation of thiolates **1** into 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-enes **2** we describe here has no direct documented analogs.

The synthesis of tricyclic structures of the type **2** under the above conditions is not very variable since sterically unhindered primary amines should be employed only. For instance, we failed to carry out the reaction with 2,6-dimethylaniline, *tert*-butylamine, or 2-ethyl-6-methylaniline. However, the corresponding tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-enes **2** were easily obtained from *o*-toluidine and 2-ethylaniline. The order of mixing of the reagents substantially did not affect the yields of the final products. The plausible reaction mechanism is shown in Scheme 2. It is highly probable that thiolates **1** react in the form of imino tautomers **3**, which have been reliably detected.[25]

Subsequent aminomethylation can follow alternative pathways (see Scheme 2, pathways *a* and *b*). According to the first, the initially formed pyridotriazine **4** is further transformed into intermediate **5** and final product **2**. Pathway *b* involves the initial formation of *C*-aminomethylation product **6** and *N,N′*-diaminomethylation of bispidine intermediate **7**, giving tricyclotridecene **2**. However, it is not improbable that both pathways are in fact followed in parallel. Apparently, the formation of the diazabicyclo[3.3.1]nonane framework begins with aminomethylation at the C(5) atom of the dihydropyridine ring. This is indirectly supported by the fact that 4-aryl-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-2-thiolates, which have only one carbon nucleophilic center (C(3) atom), behave in the Mannich reaction like typical *N*,*S*-binucleophiles and do not form *C*-aminomethylation products.[15]

To study the range of application of the aforementioned reaction, we used structural analogs of thiolates **1**: 3-alkyl-10-amino-7,11-dicyano-9-aza-3-azoniaspiro[5.5]undeca-7,10-diene-8-thiolates **8**. These promising

Scheme 2

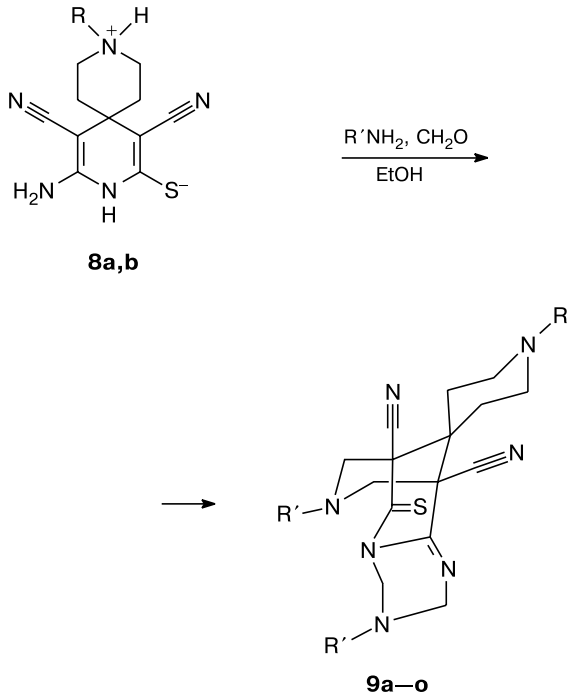


polyfunctional reagents can be easily prepared by three-component cyclocondensation of *N*-alkylpiperidin-4-ones, malononitrile, and cyanothioacetamide.[26]

We found that aminomethylation of 4,4´-spirobipyridinethiolates **8a,b** with an excess of formaldehyde and two equivalents of a primary amine gives spiro[3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-13,4´-piperidine]-1,9-dicarbonitriles **9a—o** in 43—91% yields, which are analogous to compounds **2** (Scheme 3). Thus, as with structurally close thiolates **1**, the aminomethylation occurs at all accessible nucleophilic centers in compound **8**, except for the S atom. Therefore, one can state that aminomethylation of compounds containing the 6-amino-3,5-dicyano-1,4-dihydropyridine-2-thiolate structural fragment is a general and so far sole route to derivatives of a novel heterocyclic system, namely, 3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene.

An alternative approach to the synthesis of compounds **9**, which is however of no preparative value, involves reactions of *N*-alkylpiperidin-4-ones **10** with cyanothioacetamide **11** followed by aminomethylation of the *in situ* formed condensation product (Scheme 4). Earlier,[27] we have demonstrated that treatment of R,R-methylenecyanothioacetamides **12** with

Scheme 3



8a,b

9a—o

8: R = Me (**a**); Et (**b**)

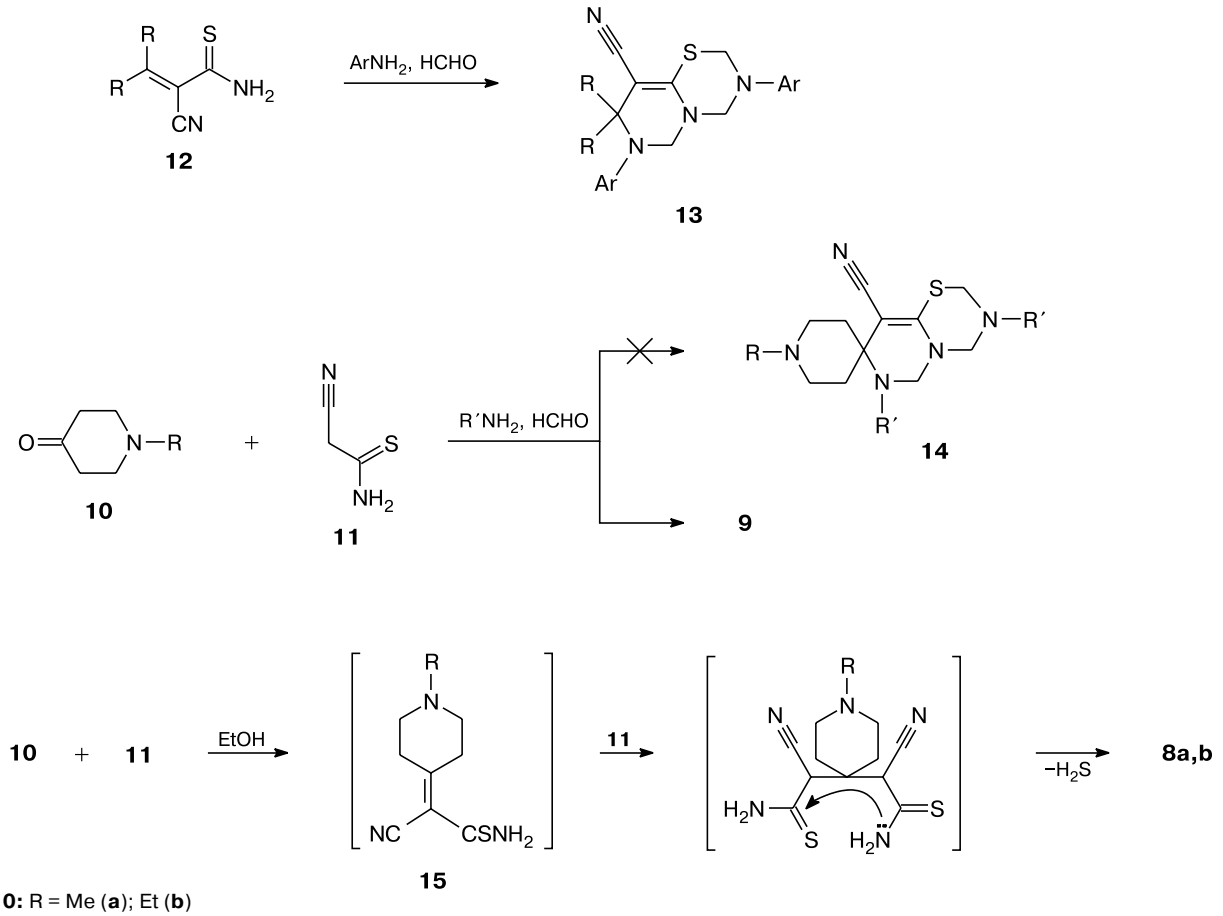
9: R = R′ = Me (**a**); R = Me, R′ = CH_2Ph (**b**);
R = Me, R′ = $(CH_2)_2Ph$ (**c**); R = Me, R′ = Ph (**d**);
R = Me, R′ = 4-MeC_6H_4 (**e**); R = Me, R′ = 4-FC_6H_4 (**f**);
R = Me, R′ = 4-ClC_6H_4 (**g**); R = Et, R′ = Me (**h**);
R = Et, R′ = cyclopentyl (**i**); R = Et, R′ = CH_2Ph (**j**);
R = Et, R′ = furfuryl (**k**); R = Et, R′ = Ph (**l**);
R = Et, R′ = 4-MeC_6H_4 (**m**); R = Et, R′ = 3-MeC_6H_4 (**n**);
R = Et, R′ = 4-ClC_6H_4 (**o**)

primary amines and formaldehyde gives pyrimido[6,1-*b*][1,3,5]thiadiazine derivatives **13** as the result of a cascade reaction. When developing a multicomponent approach to the synthesis of pyrimidothiadiazines of the type **13**, we assumed that "one-pot" reactions of piperidones **10a,b** with thioamide **11** (molar ratio 1 : 1, EtOH, 20 °C, 1 h) followed by treatment with two equivalents of a primary amine and an excess of 37% formalin (reflux, 3—5 min) should yield spiro-fused pyrimidothiadiazine derivatives **14**. Nevertheless, we isolated only compounds **9** in low (15—23% with respect to cyanothioacetamide) yields, which were identical with those obtained in the aminomethylation of thiolates **8**. This reaction outcome can be explained by the Knoevenagel condensation of piperidones **10a,b** with cyanothioacetamide **11** followed by the easy Michael addition of a second molecule of thioamide **11** to condensation product **15**, thus giving thiolates **8**. Obviously, the reaction is autocatalytic because of the pronounced basic properties of piperidones **10**. This assumption was confirmed by easy reactions of piperidones **10** with cyanothioacetamide **11** in the molar ratio 1 : 1 under mild conditions, which afford thiolates **8** in 40—45% yields. In a similar way, when piperidones **10a,b** and thioamide **11** were used in the molar ratio 1 : 2 and a small amount of *N*-methylmorpholine (0.1 equiv.) was added, thiolates **8a,b** were obtained in 82—84% yields.

The structures of tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-enes **2** and **9** were confirmed by spectroscopic methods and elemental analysis (Tables 1 and 2). For instance, the IR spectra of the compounds obtained show no absorption bands due to the N—H stretching vibrations and those of the conjugated C≡N group. At the same time, a weak broadened band at 2253—2233 cm^{-1} indicates the presence of nonconjugated C≡N groups and a band at 1660—1645 cm^{-1} corresponds to the C=N stretching vibrations. The ^1H NMR spectra of compounds **2** and **9** show four sets of signals for four methylene groups. The C(10)H_2 and C(12)H_2 protons resonate at δ 3.04—4.09. The resulting signals are either two pairs of doublets with ^2J = 10.7—12.8 Hz or a complex multiplet due to partial overlapping of the signals. The protons of the tetrahydro-1,3,5-triazine ring are also resolved as either doublets of doublets or multiplets at δ = 4.41—5.12 (C(6)H_2, ^2J = 16.4—17.4 Hz) and 5.11—5.80 (C(4)H_2, ^2J = 12.5—13.6 Hz). The signal for the C(13)H proton in the spectra of compounds **2** appears at δ 4.52—4.76 as a narrow singlet. In addition, the ^1H NMR spectra of compounds **2** contain three sets of signals for the aromatic substituents: one for the *C*-aryl substituents and two for the primary amine. The presence of the absorption band due to the stretching vibrations of the N—H bond and the conjugated C≡N group in the IR spectra of thiolates **8a,b** confirms the proposed structure and agrees with the literature data.[26]

The spatial structure of compound **2a** was examined by X-ray diffraction analysis. The general view of structure **2a** with selected bond lengths and angles are shown in Fig. 1. The geometrical parameters of the central tricyclic system N(1)—N(4)C(1)—C(9) are close to the corresponding parameters in a structural analog of compounds **2** we have studied earlier.[28] The conformation of the six-membered heterocycles N(1)—N(3)C(1)—C(3) and N(3)C(2)C(4)—C(7) is intermediate between the half-chair and the half-boat: the fragment N(2)C(2)N(3)C(3) is planar to within 0.026 Å, making with the corner N(1)—C(1)—C(3) a dihedral angle of 50.0°; analogously, the fragment N(3)C(2)C(7)C(5)C(6) is planar to within 0.087 Å, making with the corner C(5)—C(6)—C(7) a dihedral angle of 49.9°. The conformation of the ring N(4)C(5)—C(9) is a typical chair. The N(1) and N(4) atoms have a nearly trigonal planar bond configuration (the sums of the bond angles at these atoms are 341.1° and 345.0°, respectively). The bond configuration of the N(3) atom is trigonal planar (the sum of the bond angles is 359.7°). Because of an efficient

Scheme 4



8—10: R = Me (**a**); Et (**b**)

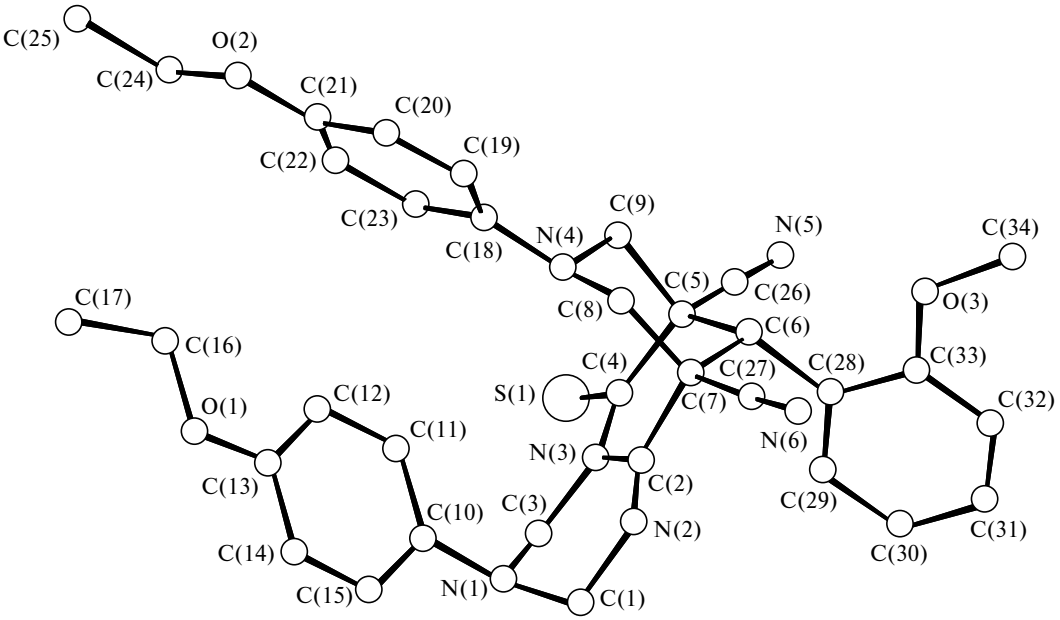


Fig. 1. General view of structure **2a**. Selected bond lengths: S(1)—C(4) 1.642(2) Å, N(1)—C(1) 1.459(2) Å, N(1)—C(3) 1.432(2) Å, N(2)—C(1) 1.453(2) Å, N(2)—C(2) 1.270(2) Å, N(3)—C(2) 1.417(3) Å, N(3)—C(3) 1.506(2) Å, N(3)—C(4) 1.355(2) Å, N(4)—C(8) 1.468(1) Å, N(4)—C(9) 1.455(2) Å.

Table 1. Yields and physicochemical characteristics of compounds **2** and **9**

Compound	Yield (%)	M.p. /°C (solvent)	Found / Calculated (%)			Molecular formula
			C	H	N	
2a	77	207—208	66.70	5.69	13.94	$C_{34}H_{34}N_6O_3S$
		(Me_2CO—MeOH (1 : 1))	67.31	5.65	13.85	
2b	72	240—245	71.09	5.48	15.55	$C_{32}H_{30}N_6OS$
		(decomp., Me_2CO)	70.30	5.53	15.37	
2c	66	212—214	71.88	6.01	14.65	$C_{34}H_{34}N_6OS$
		(Me_2CO—MeOH (1 : 1))	71.05	5.96	14.96	
2d	84	215—217	65.88	5.15	13.88	$C_{33}H_{31}ClN_6O_2S$
		(decomp., Me_2CO)	64.85	5.11	13.75	
2e	95	122—124	68.28	5.02	15.09	$C_{31}H_{27}ClN_6S$
		(EtOH—Me_2CO (1 : 1))	67.56	4.94	15.25	
2f	72	209—211	67.88	5.43	14.55	$C_{33}H_{31}ClN_6S$
		(Me_2CO)	68.44	5.40	14.51	
9a	72	236—237	57.78	6.81	26.48	$C_{18}H_{25}N_7S$
		(decomp., Me_2CO)	58.19	6.78	26.39	
9b	75	194—196	69.28	6.31	18.74	$C_{30}H_{33}N_7S$
		(Me_2CO—EtOH (1 : 1))	68.80	6.35	18.72	
9c	69	155—156	69.84	6.80	17.73	$C_{32}H_{37}N_7S$
		(Me_2CO)	69.66	6.76	17.77	
9d	59	179—181	67.24	5.91	19.75	$C_{28}H_{29}N_7S$
		(Me_2CO—EtOH (1 : 1))	67.85	5.90	19.78	
9e	66	231—233	69.14	6.36	18.68	$C_{30}H_{33}N_7S$
		(decomp., Me_2CO—EtOH (1 : 1))	68.80	6.35	18.72	
9f	43	244—245	63.74	5.11	18.39	$C_{28}H_{27}F_2N_7S$
		(decomp., Me_2CO—EtOH (1 : 1))	63.26	5.12	18.44	
9g	44	260—262	60.04	4.83	17.35	$C_{28}H_{27}Cl_2N_7S$
		(decomp., Me_2CO—EtOH (1 : 1))	59.57	4.82	17.37	
9h	87	229—231	59.38	7.06	25.40	$C_{19}H_{27}N_7S$
		(decomp., DMF—EtOH (1 : 2))	59.19	7.06	25.43	
9i	91	210—211	65.64	7.96	19.83	$C_{27}H_{39}N_7S$
		(decomp., EtOH)	65.68	7.96	19.86	
9j	58	162—163	69.53	6.58	18.13	$C_{31}H_{35}N_7S$
		(Me_2CO—EtOH (1 : 1))	69.24	6.56	18.23	
9k	51	164—166	62.84	6.06	18.89	$C_{27}H_{31}N_7O_2S$
		(Me_2CO—EtOH (1 : 1))	62.65	6.04	18.94	
9l	69	218—220	68.45	6.13	19.20	$C_{29}H_{31}N_7S$
		(Me_2CO—EtOH (1 : 1))	68.34	6.13	19.24	
9m	79	219—220	69.50	6.57	18.18	$C_{31}H_{35}N_7S$
		(decomp., Me_2CO—EtOH (1 : 1))	69.24	6.56	18.23	
9n	78	235—236	69.59	6.58	18.18	$C_{31}H_{35}N_7S$
		(decomp., Me_2CO—EtOH (1 : 1))	69.24	6.56	18.23	
9o	45	270	60.56	5.07	17.00	$C_{29}H_{29}Cl_2N_7S$
		(decomp., DMF—EtOH (1 : 1))	60.20	5.05	16.95	

conjugation of the lone electron pair of the N(3) atom with the π-system of the S(1)=C(4) double bond, the N(3)—C(4) bond (1.355(2) Å) is substantially shorter than the ordinary N(sp^2)—C(sp^2) bond (1.43—1.45 Å).[29,30]

In summary, 6-amino-3,5-dicyano-1,4-dihydropyridine-2-thiolates in the Mannich reaction form abnormal aminomethylation products that belong to a novel heterocyclic system: 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene.

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument (200 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on an IKS-29 spectrophotometer (Nujol). Elemental analysis was carried out on a Perkin—Elmer C,H,N-Analyzer instrument. The purity of the compounds obtained was checked by TLC on Silufol UV 254 plates (acetone—heptane (1 : 1), iodine vapor, UV detector).

Table 2. Spectroscopic characteristics of compounds **2** and **9**

Compound	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ, J/Hz
2a	2250 (C≡N); 1660 (C=N)	1.38 (q, 6 H, signal overlapping, 2 C$\underline{H}_3$CH$_2$O, ^3J = 7.0); 3.70—4.00 (m, 8 H, 2 CH$_3$C$\underline{H}_2$O, C(10)H$_2$, C(12)H$_2$); 3.91 (s, 3 H, MeO); 4.60 (s, 1 H, C(13)H); 5.03 (q, 2 H, C(6)H$_2$, ^2J = 16.8); 5.76 (q, 2 H, C(4)H$_2$, ^2J = 13.2); 6.44—7.41 (m, 12 H, 3 Ar)
2b	2245 (C≡N); 1655 (C=N)	1.84, 2.40 (both s, 3 H each, 2 $\underline{H}_3$CAr); 3.55—3.99 (m, 4 H, signal overlapping C(10)H$_2$ and C(12)H$_2$); 3.94 (s, 3 H, MeO); 4.72 (s, 1 H, C(13)H); 4.95 (dd, 2 H, C(6)H$_2$, ^2J = 17.0); 5.68 (dd, 2 H, C(4)H$_2$, ^2J = 13.2); 6.70—7.40 (m, 12 H, 3 Ar)
2c	2248 (C≡N); 1650 (C=N)	1.07, 1.31 (both t, 3 H each, 2 C$\underline{H}_3$CH$_2$, ^3J = 7.5); 2.32, 2.74 (both q, 2 H each, 2 C$\underline{H}_3$CH$_2$, ^3J = 7.5); 3.49 (pseudotriplet, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 11.0); 3.91 (s, 3 H, MeO); 3.94 (dd, 2 H, C(12)H$_2$ or C(10)H$_2$, ^2J = 10.7); 4.76 (s, 1 H, C(13)H); 4.88 (dd, 2 H, C(6)H$_2$, ^2J = 17.2); 5.60 (dd, 2 H, C(4)H$_2$, ^2J = 13.1); 6.63—7.40 (m, 12 H, 3 Ar)
2d	2253 (C≡N); 1653 (C=N)	1.29—1.39 (m, 6 H, signal overlapping 2 OCH$_2$C$\underline{H}_3$); 3.77—3.96 (m, 8 H, signal overlapping 2 OC$\underline{H}_2$CH$_3$, C(10)H$_2$ and C(12)H$_2$); 4.70 (s, 1 H, C(13)H); 5.06 (dd, 2 H, C(6)H$_2$, ^2J = 16.9); 5.80 (m, 2 H, C(4)H$_2$); 6.44—7.60 (m, 12 H, 3 Ar)
2e	2240 (C≡N); 1649 (C=N)	3.17—3.62 (m, 4 H, signal overlapping C(10)H$_2$, C(12)H$_2$); 3.83 (m, 4 H, signal overlapping 2 C$\underline{H}_2$Ph); 4.49 (dd, 2 H, C(6)H$_2$, ^2J = 16.8); 4.52 (s, 1 H, C(13)H); 5.34 (q, 2 H, C(4)H$_2$, ^2J = 12.9); 7.09—7.61 (m, 14 H, 3 Ar)
2f	2250 (C≡N); 1655 (C=N)	1.98, 2.08, 2.15, 2.17 (all s, 3 H each, 4 Me); 3.82, 3.99 (both d, 1 H each, C(10)H$_2$ or C(12)H$_2$, ^2J = 11.9); 3.89, 4.09 (both d, 1 H each, C(12)H$_2$ or C(10)H$_2$, ^2J = 12.2); 4.71 (s, 1 H, C(13)H); 5.12 (q, 2 H, C(6)H$_2$, ^2J = 17.1); 5.70 (q, 2 H, C(4)H$_2$, ^2J = 13.3); 6.40—7.59 (m, 10 H, 3 Ar)
9a	2237 (C≡N); 1650 (C=N)	1.84, 2.20, 2.59, 2.71 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.19, 2.25, 2.37 (all s, 3 H each, 3 NCH$_3$); 3.04 (dd, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 11.2); 3.16 (m, 2 H, C(12)H$_2$ or C(10)H$_2$); 4.41 (dd, 2 H, C(6)H$_2$, ^2J = 16.7); 5.13 (dd, 2 H, C(4)H$_2$, ^2J = 12.8)
9b	2240 (C≡N): 1650 (C=N)	1.86, 2.20, 2.61, 2.68 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.19 (s, 3 H, NCH$_3$); 2.99—3.22 (m, 4 H, C(10)H$_2$ and C(12)H$_2$, signal overlapping); 3.72 (q, 2 H, C$\underline{H}_2$Ph, ^2J = 13.2); 3.74 (q, 2 H, C$\underline{H}_2$Ph, ^2J = 13.4); 4.47 (dd, 2 H, C(6)H$_2$, ^2J = 17.0); 5.18 (dd, 2 H, C(4)H$_2$, ^2J = 12.9); 7.20—7.34 (m, 10 H, 2 Ph)
9c	2242 (C≡N); 1650 (C=N)	1.84, 2.23, 2.58, 2.73 (all m, 12 H, 2 NC$\underline{H}_2$CH$_2$, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.07 (m, 4 H, 2 C$\underline{H}_2$Ph); 2.19 (s, 3 H, NCH$_3$); 3.04—3.26 (m, 4 H, C(10)H$_2$, C(12)H$_2$, signal overlapping); 4.47 (dd, 2 H, C(6)H$_2$, ^2J = 17.1); 5.13 (dd, 2 H, C(4)H$_2$, ^2J = 12.7); 6.93—7.22 (m, 10 H, 2 Ph)
9d	2238 (C≡N); 1658 (C=N)	1.76, 2.23, 2.35, 2.53, 2.71 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.18 (s, 3 H, NCH$_3$); 3.72 (dd, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 12.4); 3.82 (m, 2 H, C(12)H$_2$ or C(10)H$_2$); 5.10 (dd, 2 H, C(6)H$_2$, ^2J = 16.8); 5.13 (dd, 2 H, C(4)H$_2$, ^2J = 13.4); 6.70—7.20 (m, 10 H, 2 Ph)
9e	2245 (C≡N); 1657 (C=N)	1.79, 2.33, 2.54, 2.71 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.19 (m, 9 H, 2 ArC$\underline{H}_3$, NCH$_3$); 3.63 (dd, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 12.8); 3.74 (m, 2 H, C(12)H$_2$ or C(10)H$_2$); 5.06 (dd, 2 H, C(6)H$_2$, ^2J = 16.9); 5.65 (dd, 2 H, C(4)H$_2$, ^2J = 13.3); 6.63 (dd, 4 H, 4-MeC$_6$H$_4$, ^3J = 8.4); 6.80 (dd, 4 H, 4-MeC$_6$H$_4$, ^3J = 8.5)
9f	2233 (C≡N); 1657 (C=N)	1.84, 2.33, 2.59, 2.72 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.20 (s, 3 H, NCH$_3$); 3.61 (dd, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 12.1); 3.73 (dd, 2 H, C(12)H$_2$ or C(10)H$_2$, ^2J = 12.5); 5.09 (m, 2 H, C(6)H$_2$); 5.73 (dd, 2 H, C(4)H$_2$, ^2J = 13.3); 6.59—6.98 (m, 8 H, 2 4-FC$_6$H$_4$)
9g	2240 (C≡N); 1656 (C=N)	1.86, 2.32, 2.60, 2.72 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.21 (s, 3 H, NCH$_3$); 3.66 (dd, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 12.0); 3.76 (m, 2 H, C(12)H$_2$ or C(10)H$_2$); 5.11 (dd, 2 H, C(6)H$_2$, ^2J = 17.4); 5.74 (dd, 2 H, C(4)H$_2$, ^2J = 13.6); 6.73 (dd, 4 H, 4-MeC$_6$H$_4$, ^3J = 9.0); 6.94 (dd, 4 H, 4-MeC$_6$H$_4$, ^3J = 8.9)
9h	2245 (C≡N); 1650 (C=N)	0.97 (t, 3 H, NCH$_2$C$\underline{H}_3$, ^3J = 7.0); 1.85, 2.20, 2.65, 2.76 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.26 (s, 3 H, NCH$_3$); 2.37 (m, 5 H, signal overlapping NCH$_3$, NC$\underline{H}_2$CH$_3$); 3.05 (dd, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 11.0); 3.20 (m, 2 H, C(12)H$_2$ or C(10)H$_2$); 4.41 (dd, 2 H, C(6)H$_2$, ^2J = 16.7); 5.11 (dd, 2 H, C(4)H$_2$, ^2J = 12.6)
9i	2238 (C≡N); 1653 (C=N)	0.97 (t, 3 H, NCH$_2$C$\underline{H}_3$, ^3J = 7.0); 1.37—1.83, 2.21, 2.63—2.76 (all m, 26 H, 2 C$_5$H$_9$, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.37 (q, 2 H, NC$\underline{H}_2$CH$_3$, ^3J = 7.0); 2.94—3.19 (m, 4 H, C(10)H$_2$ and C(12)H$_2$, signal overlapping); 4.55 (dd, 2 H, C(6)H$_2$, ^2J = 17.0); 5.35 (dd, 2 H, C(4)H$_2$, ^2J = 12.6)
9j	2242 (C≡N); 1645 (C=N)	0.98 (t, 3 H, NCH$_2$C$\underline{H}_3$, ^3J = 7.0); 1.86, 2.22, 2.67, 2.76 (all m, 8 H, (CH$_2$)$_2$N(CH$_2$)$_2$); 2.38 (q, 2 H, NC$\underline{H}_2$CH$_3$, ^3J = 7.0); 3.08 (dd, 2 H, C(10)H$_2$ or C(12)H$_2$, ^2J = 11.6); 3.17 (dd, 2 H, C(12)H$_2$ or C(10)H$_2$, ^2J = 11.4); 3.72 (q, 2 H, C$\underline{H}_2$Ph, ^2J = 13.4); 3.75 (q, 2 H, C$\underline{H}_2$Ph, ^2J = 13.3); 4.48 (dd, 2 H, C(6)H$_2$, ^2J = 17.1); 5.17 (dd, 2 H, C(4)H$_2$, ^2J = 12.7); 7.20—7.35 (m, 10 H, 2 Ph)

(*to be continued*)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}	^1H NMR (DMSO-d_6), δ, *J*/Hz
9k	2241 (C≡N); 1651 (C=N)	0.97 (t, 3 H, $NCH_2C\underline{H}_3$, ^3J = 6.8); 1.83, 2.18, 2.64, 2.75 (all m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.36 (q, 2 H, $NC\underline{H}_2CH_3$, ^3J = 6.8); 3.07 (dd, 2 H, C(10)H_2 or C(12)H_2, ^2J = 11.0); 3.16 (dd, 2 H, C(12)H_2 or C(10)H_2, ^2J = 11.2); 3.69 and 3.74 (both m, 2 H each, 2 CH_2, furfuryl); 4.49 (dd, 2 H, C(6)H_2, ^2J = 16.8); 5.14 (dd, 2 H, C(4)H_2, ^2J = 12.5); 6.21 and 6.30 (both m, 1 H each, 2 C(3)H, furan); 6.35 and 6.40 (both m, 1 H each, 2 C(4)H, furan); 7.48 and 7.61 (both m, 1 H each, 2 C(5)H, furan)
9l	2245 (C≡N); 1658 (C=N)	0.97 (t, 3 H, $NCH_2C\underline{H}_3$, ^3J = 6.9); 1.75, 2.22, 2.58, 2.77 (all m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.37 (q, 2 H, $NC\underline{H}_2CH_3$, ^3J = 6.9); 3.72 (dd, 2 H, C(10)H_2 or C(12)H_2, ^2J = 12.6); 3.83 (m, 2 H, C(12)H_2 or C(10)H_2); 5.10 (dd, 2 H, C(6)H_2, ^2J = 16.4); 5.64 (dd, 2 H, C(4)H_2, ^2J = 13.5); 6.71—7.20 (m, 10 H, 2 Ph)
9m	2240 (C≡N); 1650 (C=N)	0.97 (t, 3 H, $NCH_2C\underline{H}_3$, ^3J = 7.0); 1.78, 2.20, 2.60, 2.76 (all m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.03 and 2.19 (both s, 3 H each, 2 $ArC\underline{H}_3$); 2.38 (q, 2 H, $NC\underline{H}_2CH_3$, ^3J = 7.0); 3.63 (dd, 2 H, C(10)H_2 or C(12)H_2, ^2J = 12.4); 3.73 (m, 2 H, C(12)H_2 or C(10)H_2); 5.06 (dd, 2 H, C(6)H_2, ^2J = 17.2); 5.64 (dd, 2 H, C(4)H_2, ^2J = 13.2); 6.63 (dd, 4 H, 4-MeC_6H_4, ^3J = 8.2); 6.80 (dd, 4 H, 4-MeC_6H_4, ^3J = 8.4)
9n	2245 (C≡N); 1656 (C=N)	0.97 (t, 3 H, $NCH_2C\underline{H}_3$, ^3J = 7.1); 1.77, 2.22, 2.60, 2.77 (all m, 8 H, $(CH_2)_2N(CH_2)_2$); 1.97 and 2.15 (both s, 3 H each, 2 $ArC\underline{H}_3$); 2.38 (q, 2 H, $NC\underline{H}_2CH_3$, ^3J = 7.1); 3.69 (dd, 2 H, C(10)H_2 or C(12)H_2, ^2J = 12.6); 3.77 (m, 2 H, C(12)H_2 or C(10)H_2); 5.11 (dd, 2 H, C(6)H_2, ^2J = 17.2); 5.65 (br.pseudotriplet, 2 H, C(4)H_2, ^2J = 13.6); 6.45—7.05 (m, 8 H, 2 Ar)
9o	2242 (C≡N); 1654 (C=N)	0.98 (t, 3 H, $NCH_2C\underline{H}_3$, ^3J = 6.8); 1.84, 2.23, 2.65, 2.77 (all m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.39 (q, 2 H, $NC\underline{H}_2CH_3$, ^3J = 6.8); 3.65 (dd, 2 H, C(10)H_2 or C(12)H_2, ^2J = 12.8); 3.76 (m, 2 H, C(12)H_2 or C(10)H_2); 5.11 (m, 2 H, C(6)H_2); 5.64 (dd, 2 H, C(4)H_2, ^2J = 13.2); 6.73 (dd, 4 H, 4-ClC_6H_4, ^3J = 8.6); 6.94 (dd, 4 H, 4-MeC_6H_4, ^3J = 8.3)

Melting points were measured on a Kofler hot stage and are given uncorrected. The starting thiolates **1a,b** were prepared according to a known procedure.[25] *N*-Alkylpiperidin-4-ones **10** were commercial chemicals (Acros). Cyanothioacetamide **11** was synthesized from malononitrile and hydrogen sulfide.[31] Thiolates **8** were prepared according to a known method[26] and as described below.

9-Aza-3-azoniaspiro[5.5]undeca-7,10-diene-8-thiolates (8). An appropriate piperidone **10a,b** (25 mmol) and *N*-methylmorpholine (0.55 mL, 5 mmol) were added to a suspension of cyanothioacetamide **11** (5 g, 50 mmol) in EtOH (40 mL). The mixture was heated with vigorous stirring to complete homogenization. (*Caution! Hydrogen sulfide evolves!*) The reaction mixture was stirred at ~25 °C for 6 h and left for ~14 h. Then a double volume of acetone was added and the mixture was stirred for 2 h. The yellowish orange precipitate of thiolate **8a,b** was filtered off, washed with acetone and ether, and used in subsequent transformations without additional purification.

10-Amino-7,11-dicyano-3-methyl-9-aza-3-azoniaspiro[5.5]undeca-7,10-diene-8-thiolate (8a). The yield was 82%, m.p. 225—230 °C (decomp.). Found (%): C, 55.92; H, 5.81; N, 26.73. $C_{12}H_{15}N_5S$. Calculated (%): C, 55.15; H, 5.79; N, 26.80. IR, ν/cm^{-1}: 3410, 3310, 3200 (NH, NH_2); 2158 (2 C≡N). ^1H NMR (DMSO-d_6), δ: 1.81 (m, 4 H, C(3′)H_2, C(5′)H_2); 2.71 (s, 3 H, NMe); 3.29 (m, 4 H, C(2′)H_2, C(6′)H_2); 5.63 (br.s, 2 H, NH_2); 8.29 (s, 1 H, NH).

10-Amino-7,11-dicyano-3-ethyl-9-aza-3-azoniaspiro[5.5]undeca-7,10-diene-8-thiolate (8b). The yield was 84%, m.p. 240—245 °C (decomp.). Found (%): C, 57.24; H, 6.26; N, 25.30. $C_{13}H_{17}N_5S$. Calculated (%): C, 56.70; H, 6.22; N, 25.43. IR, ν/cm^{-1}: 3420, 3320, 3195 (NH, NH_2); 2163 (2 C≡N). ^1H NMR (DMSO-d_6), δ: 1.17 (t, 3 H, $NCH_2C\underline{H}_3$, ^3J = 6.8 Hz); 1.83 (m, 4 H, C(3′)H_2, C(5′)H_2); 3.03 (q, 2 H, $NC\underline{H}_2CH_3$, ^3J = 6.8 Hz); 3.29 (m, 4 H, C(2′)H_2, C(6′)H_2); 5.62 (br.s, 2 H, NH_2); 8.29 (s, 1 H, NH).

3,5,7,12-Tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitriles 2 (general procedure). An excess (4—5 mL) of 37% HCHO was added to a suspension of an appropriate thiolate **1a,b** (2.5 mmol) in EtOH (20 mL) and the mixture was heated with stirring to complete dissolution. An appropriate primary amine (5.0 mmol) was added in one portion to the resulting solution. The mixture was refluxed with vigorous stirring for 3 min and then stirred at ~20 °C for 5 h. The precipitate of compound **2** was filtered off and washed three times with EtOH and heptane. The physicochemical characteristics of compounds **2** are specified in Tables 1 and 2.

5,11-Disubstituted 1′-alkyl-8-thioxospiro[3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-13,4′-piperidine]-1,9-dicarbonitriles 9 (general procedure). Thiolate **8** (2 mmol) was thoroughly pulverized in a mortar, mixed with an excess of 37% formalin (3.5—4 mL), and heated with stirring for 2 min. Then EtOH (5—7 mL) and an appropriate primary amine (4.1 mmol) were added. The mixture was refluxed with stirring for 3—5 min to complete dissolution of thiolate **8**, filtered through a paper filter, and left at ~20 °C for 48 h. The crystals of compounds **9a—o** were filtered off and washed with EtOH and heptane. The physicochemical characteristics of compounds **9** are specified in Tables 1 and 2.

Single-crystal X-ray diffraction analysis of compound 2a was carried out on an Enraf—Nonius CAD-4 automatic four-circle diffractometer (Cu-Kα radiation, λ = 1.54178 Å, scan rate ratio $2\theta/\omega = 1.2$, $\theta_{max} = 65°$, sphere segment $0 \le h \le 10$, $0 \le k \le 12$,

$-36 \leq l \leq 36$) at ~20 °C for a single crystal with the linear dimensions 0.19×0.32×0.56 mm. The total number of reflections was 6027, out of which 5356 reflections were independent; $R_{int} = 0.023$). The crystals of compound **2a** are monoclinic: a = 9.212(2) Å, b = 11.295(3) Å, c = 30.984(8) Å, β = 95.56(2)°, V = 3208.6(1.4) Å^3, M = 606.7, Z = 4, d_{calc} = 1.26 g cm^{-3}, μ = 12.47 cm^{-1}, $F(000)$ = 1280, space group $P2_1/n$ (No. 14). The structure was solved by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation with the CRYSTALS program package.[32] In refinement, 3906 reflections with $I > 3\sigma(I)$ were used (397 parameters refined, the number of reflections per parameter was 9.8); 80% of the H atoms were located from the electron density difference map; the positions of the other H atoms were calculated geometrically. All the H atoms were refined with fixed coordinates and thermal parameters. The Chebyshev weighting scheme[33] with five parameters (1.11, −0.45, 0.33, −0.56, and −0.20) was used in refinement. Final residuals were R = 0.048 and R_w = 0.052, GOOF = 1.113. The residual electron densities from the difference Fourier synthesis were 0.32 and −0.31 e Å^{-3}. Absorption correction was applied by azimuthal scanning.[34] The comprehensive X-ray diffraction data for compound **2a** have been deposited with the Cambridge Crystallographic Data Center (CCDC 611690; CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk).

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