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THE MANNICH REACTION IN THE SYNTHESIS OF N,S-CONTAINING HETEROCYCLES. 7*. EFFECTIVE ONE-POT SYNTHESIS OF DERIVATIVES OF SPIRO[3,5,7,11-TETRAAZATRICYCLO-[7.3.1.$0^{2,7}$]TRIDEC-2-ENE-13,4′-PIPERIDINE]

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5,11-Disubstituted derivatives of 1'-isopropyl-8-thioxospiro[3,5,7,11-tetrazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-13,4'-piperidine]-1,9-dicarbonitrile was obtained by the interaction of 10-amino-9-aza-3-azonia-7,11-dicyano-3-isopropylspiro[5,5]undeca-7,10-diene-8-thiolate with 2 equiv. of a primary amine and excess of formaldehyde. An anomalous reaction product was obtained with o-*toluidine – 7,9-dicyano-1'-isopropyl-3-(2-methylphenyl)-1,2,3,4-tetrahydrospiro[pyrido[1,2-a][1,3,5]triazine-8,4'-piperidinium]-6-thiolate.*

Keywords: 10-amino-9-aza-3-azonia-7,11-dicyano-3-isopropylspiro[5,5]undeca-7,1-diene-8-thiolate, pyridine-2-thiolates, spiro[3,5,7,11]-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-13,4'-piperidine]-1,9-dicarbonitrile, aminomethylation, the Mannich reaction, cyclocondensation.

Functionally substituted derivatives of pyridine-2-(1H)-thione, and their tautomers 2-mercaptopyridines, and also their partially hydrogenated analogs have been enduring compounds in the arsenal of fine chemical synthesis for the last twenty years as promising reactive synthons [2-4], opening broad vistas for the preparation of a series of condensed heterocyclic systems [5-7]. Nevertheless there is only solary reports in the literature on the problem of aminomethylation of 2-mercaptopyridines [8]. It follows from multitudinous data in the literature that aminomethylation of 2-mercaptoazoles and -azines is a general method for the preparation of condensed derivatives of 1,3,5-thiadazines. In particular, derivatives of *sym*-triazolo[3,4-*b*][1,3,5]thiadiazine [9-16], thiazolo[3',4':1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazine [17], imidazo[2,1-*b*][1,3,5]thiadiazine [18, 19], 1,2,4-triazino[3,2-*b*][1,3,5]thiadiazine [19], and 1,3,5-thiadiazino[3,2-*a*]benzimidazole [20] have been obtained by "double" Mannich condensations. We have shown previously with a series of 2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates that, depending on the structure of the substrate, aminomethylation can lead to the formation of

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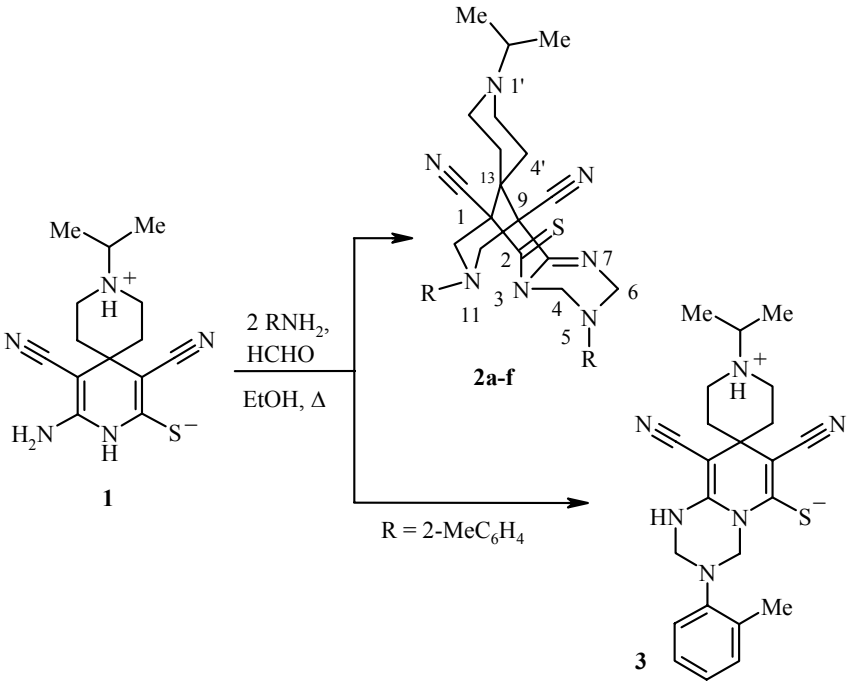
derivatives of pyrido[2,1-*b*][1,3,5]thiadiazine [21,22], 3,7-diazabicyclo[3.3.1]nonane [23], or tricyclic products [24]. In a continuation of investigation in this area, we paid attention to 10-amino-9-aza-3-azonia-7,11-dicyano-3-isopropyl-spiro[5,5]undeca-7,10-diene-8-thiolate, which has several active nucleophilic centers and consequently possesses a series of alternative possibilities for cyclocondensation under the conditions of aminomethylation.



1

2a-f

3

2 a R = Me, **b** R = CH_2Ph, **c** R = cyclohexyl,
d R = Ph, **e** R = 4-BrC_6H_4, **f** R = 3-MeC_6H_4

It has been established that the previously unknown spiro-coupled derivatives of 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene (**2**) are selectively produced in 37-86% yield by the reaction of thiolate **1** with 2 equiv. of a primary amine in the presence of an excess of formaldehyde. So the thiolate **1** did not react as the expected S,N-binucleophile in the Mannich reaction, but underwent aminomethylation at C-7 and C-11 and also at the nitrogen atom of the amino and imino groups. Both aliphatic and aromatic primary amines took part in this reaction. The yield of products did not depend to an important extent on the order of mixing of the reagents. For example compound **2a** was formed in 78.5% yield on successive treatment of the thiolate **1** with formalin and 40% methylamine solution, but in a yield of 80.5% on treatment of an aqueous alcoholic mixture of the betaine **1** and $MeNH_2$ with HCHO. An unexpected product, a derivative of pyrido[1,2-*a*][1,3,5]triazine **3**, was isolated in 25% yield from the reaction of thiolate **1** with 2 equiv of *o*-toluidine. In our opinion, the reason for this anomalous course of the reaction is, on the one hand, the sufficiently large volume of the N-isopropylpiperidine unit and the evident spatial hindrance of the electrophilic component, the product of hydroxymethylation of *o*-toluidine, on the other hand. Together these factors hinder electrophilic attack in positions C-3 and C-5 and thus make ring closing of the 3,7-azabicyclo[3.3.1]nonane system impossible, at the same time as N-aminomethylation proceeds in the normal way.

All the products have been characterized with the help of ^{1}H NMR and IR spectra and elemental analysis. Together with a number of characteristic signals observed in the ^{1}H NMR spectra of compounds **2**, the signals of the protons of the tetrahydro-1,3,5-triazine ring should be noted: a doublet of doublets (or a multiplet) of 2H-4 at δ 5.65-5.13 (^2J = 12.1-13.5) and a doublet of doublets of 2H-6 at δ 4.41-5.13 ppm (^2J = 16,7-17.0 Hz). The protons 2H-10 and 2H-12 resonate in the range δ 3.83-2.90 ppm and are observed as two doublets of doublets with

^2J = 11.6-13.0 Hz. Also characteristic is the presence of two sets of signals of the aromatic protons and a doublet at δ = 0.98-0.94 ppm (^2J = 6.2-6.6 Hz) assigned to the methyl groups of $NCH(CH_3)_2$. In the ^1H NMR spectrum of compound **3** a broad singlet of the NH group is present at δ 8.85, a group of signals of protons in the region δ 7.24-7.03 ppm, indicating the presence of one 2-methylphenyl substituent and also two doublets of doublets for the protons of the 1,3,5-triazine ring. It is characteristic that the signal of the methyl groups of the $NH(CH_3)_2$ is shifted by 0.25-0.30 ppm to weaker field relative to the analogous signals in the spectra of compounds **2**, evidently as a result of the positive charge on the nitrogen atom. In the IR spectra of compounds **2a-f** there are weak absorption bands at ν = 2243-2237 cm^{-1} (unconjugated CN groups) and intensive absorption bands in the 1660-1640 cm^{-1} range (C=N stretching vibrations). In the IR spectrum of compound **3** the absorption bands of the unconjugated nitrile groups are absent, but on the other hand there are absorptions in the 3430-3295 (N–H) and an intense broad band at ν = 2167 cm^{-1} (conjugated cyanide groups).

EXPERIMENTAL

^1H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on Varian Mercury VX-200 (200 MHz) instrument. IR spectra of nujol mulls were recorded with an IKS-29 spectrometer, elemental analyses were determined with a Perkin-Elmer C,H,N-analyzer. The course of reactions and the purity of compounds were monitored by TLC on Silufol UV-254 plates, with 1:1 acetone–heptane as eluent, and development with iodine vapor or UV light. Melting points were measured on a Kofler stage. The 10-amino-9-aza-3-azonia-7,11-dicyano-3-isopropylspiro[5,5]undeca-7,10-diene-8-thiolate (**1**) starting material was synthesized in 72% yield from a three component condensation of α-cyanothioacetamide, N-isopropylpiperidin-4-one, and malononitrile according to a known method [25].

Spiro[3,7,5,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-13,4′-piperidine]-1,9-dicarbonitriles 2a-f and Spiro[pyrido[1,2-*a*][1,3,5]triazine-8,4'-piperidinium]-6-thiolate (3) (General Method). A mixture of thiolate **1** (0.6 g, 2.07 mmol) was ground with an excess of 37% aqueous formaldehyde (3-4 ml), EtOH (10-15 ml) was added and the mixture was heated until homogenization was complete, and the corresponding primary amine (4.2 mmol) was added in one piece. The mixture was boiled for 3 min and stirred for 8 h at ~20°C. The precipitate was filtered off, washed with EtOH, and recrystallized from a suitable solvent.

1'-Isopropyl-5,11-dimethyl-8-thioxospiro[3,5,7,11-tetraazatricyclo[7.3.1.02,7]tridec-2-ene-13,4′-piperidine]-1,9-dicaronitrile (2a). Yield 0.65 g (78.5%), light-yellow crystals, mp 216-218°C (dec., Me_2CO). IR spectrum, ν, cm^{-1}: 2242 (2C≡N), 1655 (C=N). ^1H NMR spectrum, δ, ppm *(J*, Hz): 5.13 (2H, dd, ^2J = 12.1, H-4); 4.41 (2H, dd, ^2J = 16.8, H-6); 3.08 (2H, dd, ^2J = 12.8, H-10 or H-12); 2.95 (2H, br. d, ^2J = 11.8, H-12 or H-10); 2.92-2.69 (5H, m ($C\underline{H}_2)_2NC\underline{H}Me_2$); 2.38 (3H, s, NCH_3); 2.27 (3H, s, NCH_3); 2.22 and 1.83 (each 2H, both m, H-3' and H-5'); 0.95 (6H, d, ^3J = 6.4, $NCH(C\underline{H}_3)_2$). Found, %: C 59.50; H 7.37; N 24.42. $C_{20}H_{29}N_7S$ (*M* = 399.57). Calculated, %: C 60.12; H 7.32; N 24.54.

5,11-Dibenzyl-1′-isopropyl-8-thioxospiro[3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-13,4′-piperidine]-1,9-dicarbonitrile (2b). Yield 0.98 g (86%); yellow crystals, mp 101-103°C (1:1 EtOH-Me_2CO). IR spectrum, ν, cm^{-1}: 2237 (2C≡N), 1657 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.34-7.21 (10H, m, $2C_6H_5$); 5.16 (2H, dd, ^2J =13.0, H-4); 4.48 (2H, dd, ^2J = 16.7, H-6); 3.84-3.63 (4H, m, two overlapping dd, $C\underline{H}_2Ph$); 3.22 (2H, m, H-10 or H-12); 3.07 (2H, dd, ^2J = 11.6, H-12 or H-10); 2.83-2.72 (5H, m, ($C\underline{H}_2)_2NC\underline{H}Me_2$); 2.20 and 1.85 (each 2H, both m, H-3′ and H-5′); 0.95 (6H, d, ^3J = 6.4, $NCH(C\underline{H}_3)_2$). Found, %: C 70.61; H 6.87; N 17.49. $C_{32}H_{37}N_7S$ (*M* = 551.76). Calculated, %: C 69.66; H 6.76; N 17.77.

5,11-Dicyclohexyl-1′-isopropyl-8-thioxospiro[3.5.7.11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-13,4'-piperidine]-1,9-dicarbonitrile (2c). Yield 0.56 g (50%); light-yellow crystals, mp 144-146°C (1:1 EtOH–Me_2CO). IR spectrum, ν, cm^{-1}: 2243 (2C≡N), 1645 (C=N). ^1H NMR spectrum, δ, ppm *(J*, Hz): 5.28 (2H, dd, ^2J = 13.5, $C(4)H_2$); 4.56 (2H, m, H-6); 3.20 (2H, dd, ^2J =11.6, H-10 or H-12); 3.05 (2H, dd, ^2J = 11.8, H-12

or H-10); 2.81-2.69 (7H, m, ($C\underline{H}_2$)$_2$N and 3 N-C$\underline{H}$); 2.32-2.08 (4H, m, H-3′ and H-5′); 1.77-1.12 (2 H, m, H-2); 0.94 (6H, d, ^3J = 6.4, NCH($C\underline{H}_3$)$_2$). Found, %: C 67.67, H 8.50, N 18.19. $C_{30}H_{45}N_7S$ (M =535.80). Calculated, %: C 67.25, H 8.47, N 18.30.

1′-Isopropyl-5,11-diphenyl-8-thioxo-spiro[3,5,7,11-tetrazatricyclo[7.3.1.02,7]tridec-2-ene-13,4′-piperidine]-1,9-dicarbonitrile (2d). Yield 0.84 g (77%); light-yellow crystals, mp 202-204°C (1:3 EtOH–Me_2CO). IR spectrum, ν, cm^{-1}: 2240 (2C≡N), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.20-6.71 (10H, m, 2C_6H_5); 5.63 (2H, dd, ^2J = 13.5, H-4); 5.10 (2H, dd, ^2J =17.0, H-6); 3.82 (2H, m, H-10 or H-12); 3.73 (2H, dd, ^2J = 13.0, H-12 or H-10); 2.82-2.65 (5H, m, ($C\underline{H}_2$)$_2$NC$\underline{H}$Me$_2$); 2.32-2.20, 1.73 (each 2H, both m, H-3' and H-5′); 0.94 (6H, d, ^3J = 6.2, NCH($C\underline{H}_3$)$_2$). Found, %: C 69.01; H 6.36; N 18.62. $C_{30}H_{33}N_7S$ (M = 523.71). Calculated; %: C 68.80; H 6.35; N 18.72.

5,11-Di(4-bromophenyl)-1′-isopropyl-8-thioxospiro[3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-13,4′-piperidine]-1,9-dicarbonitrile (2e). Yield 0.52 g (37%); light-yellow crystals, mp 270°C (dec., 1:10 DMF–Me_2CO. IR spectrum, ν, cm^{-1}: 2139 (2C≡N), 1650 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.01 and 6.82 (each 4H, both dd, ^2J = 8.8, 2C_6H_4Br-4); 5.57 (2H, dd, ^2J = 13.5, H-4); 5.12 (2H, pseudo-t, ^2J = 17.0, H-6); 3.78 (2H, m, H-10 or H-12); 3.68 (2H, dd, ^2J = 12.4, H-12 or H-10); 2.88-2.74 (5H, m, ($C\underline{H}_2$)$_2$NC$\underline{H}$Me$_2$); 2.39-2.17, 1.83 (2H, both m, H-3' and H-5'); 0.98 (6H, d, ^3J = 6.6, NCH($C\underline{H}_3$)$_2$). Found, %: C 52.07, H 4.63, N 14.42. $C_{30}H_{31}Br_2N_7S$ (M = 681.50). Calculated, %: C 52.87, H 4.59, N 14.39.

1′-Isopropyl-5,11-di(3-methylphenyl)-8-thioxospiro[3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-13,4′-piperidine]-1,9-dicarbonitrile (2f). Yield 0.90 g (79%); pale-yellow crystals, mp 174-175°C (1:1 EtOH–Me_2CO). IR spectrum, ν, cm^{-1}: 2237 (2C≡N), 1660 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.05-6.46 (8H, m, 2Ar); 5.65 (2H, m, H-4); 5.11(2H, dd, ^2J = 17.0, H-6); 3.77 (2H, m, H-10 or H-12); 3.70 (2H, dd, ^2J = 12.4, H-12 or H-10); 2.83-2.64 (5H, m, ($C\underline{H}_2$)$_2$NC$\underline{H}$Me$_2$); 2.40-2.20, 1.74 (each 2H, both m, H-3' and H-5'); 2.15 and 1.97 (each 3H, both s, 2CH_3); 0.94 (6H, d, ^3J = 6.6, NCH($C\underline{H}_3$)$_2$). Found, %: C 70.18; H 6.73; N 17.92. $C_{32}H_{37}N_7S$ (M = 551.76). Calculated, %: C 69.66; H 6.76; N 17.77.

7,9-Dicyano-1′-isopropyl-3-(2-methylphenyl)-1,2,3,4-tetrahydrospiro[pyrido[1.2-*a*][1,3,5]triazine-8,4′-piperidinium)-6-thiolate (3). Yield 0.23 g (26,5%); beige powder, mp 235-240°C (dec.). IR spectrum, ν, cm^{-1}: 3430-3295 (NH); 2167 (C≡N), 1667 (2C=C). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.85 (1H, br. s, H-1); 7.24-7.03 (4H, m, Ar); 4.35 (2H, dd, ^2J = 15.2, 2H-2 or 2H-4); 3.68 (br. s, H^+, H_2O); 3.49 (2H, dd, ^2J = 11.2, 2H-4 or 2H-2); 3.77 (2H, m, 2H-10 or 2H-2); 3.30-2.71 (5H, m, ($C\underline{H}_2$)$_2$N$^+$C$\underline{H}$Me$_2$); 2.30 (3H, s, CH_3); 2.09-1.58 (4H, m, H-3' and H-5'); 1.23 (6H, d, ^3J = 6.4, NCH($C\underline{H}_3$)$_2$). Found, %: C 65.48, H 6.70, N 20.12. $C_{23}H_{28}N_6S$ (M = 420.58). Calculated, %: C 65.68, H 6.71, N 19.98.

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