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REACTION OF N-METHYLMORPHOLINIUM 5-CYANO-2-OXO-4-(2-THIENYL)-1,2,3,4-TETRA-HYDROPYRIDINE-6-THIOLATE WITH α-BROMO KETONES

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Treatment of N-methylmorpholinium 5-cyano-2-oxo-4-(2-thienyl)-1,2,3,4-tetrahydropyridine-6-thiolate with α-bromo ketones in ethanol gives a 1:1 mixture of the corresponding 6-alkylthiopyridines and thiazolo[3,2-a]pyridines which are used in the synthesis of substituted 1-acyl-6-alkylthiopyridines and thieno[2,3-b]pyridines.

Keywords: 6-alkylthiopyridines, α-bromo ketones, 2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate, thiazolo[3,2-*a*]pyridines and thieno[2,3-*b*]pyridines, X-ray analysis.

As a result of a cascade heterocyclization of 2-thieno aldehyde, cyanothioacetamide, and Meldrum's acid in the presence of N-methylmorpholine we were previously able to prepare a substituted N-methylmorpholinium 2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate (**1**) [1]. Continuing our investigation of the properties of partially hydrogenated sulfur-containing pyridines we have now studied the reaction of thiolate **1** with the α-bromo ketones **2a,b**.

Using ^{1}H NMR spectroscopy we have found that a short heating of compound **1** and **2** in ethanol leads to the formation of a 1:1 mixture of 6-alkylthiopyridines **3** and thiazolo[3,2-b]pyridines **4**. At the same time, according to X-ray analytical data, the crystallization of the product of reaction of thiolate **1** with phenacylbromide **2a** gives exclusively compound **4a**, subsequent solution of which again leads to an equimolar mixture of compounds **3a** and **4a**. Evidently, both compounds are found in equilibrium in solution. In this connection it should be noted that with the alkylated isostructural analogs of compound **1** (the N-methylmorpholinium 4-aryl-3-carbethoxy-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates) the α-bromo ketones also form not a mixture of the *cis* and *trans* isomers of 6-alkylthiotetrahydropyridines as noted previously [2] but a mixture of compounds **3** and **4**.

A general view of the molecules **4a** is shown in Figure 1 and the basic geometric parameters are given in Table 1. The central bicyclic system is only approximately planar with a deviation of the atoms from the root mean square plane as great as 0.28 Å and a dihedral angle between the rings $N_{(1)}C_{(1\text{-}5)}$ and $S_{(1)}C_{(1)}N_{(1)}C_{(11)}C_{(12)}$ equal to 8.3°. In addition, if the five-membered heterocycle $S_{(1)}C_{(1)}N_{(1)}C_{(11)}C_{(12)}$ is planar within the limits 0.10 Å, then the six-membered heterocycle $N_{(1)}C_{(1\text{-}5)}$ is markedly distorted towards a half boat conformation. The modified Kremer-Pople parameters [3] for this ring are $S = 0.57$, $\theta = 46.07°$, and $\psi = 23.39°$.

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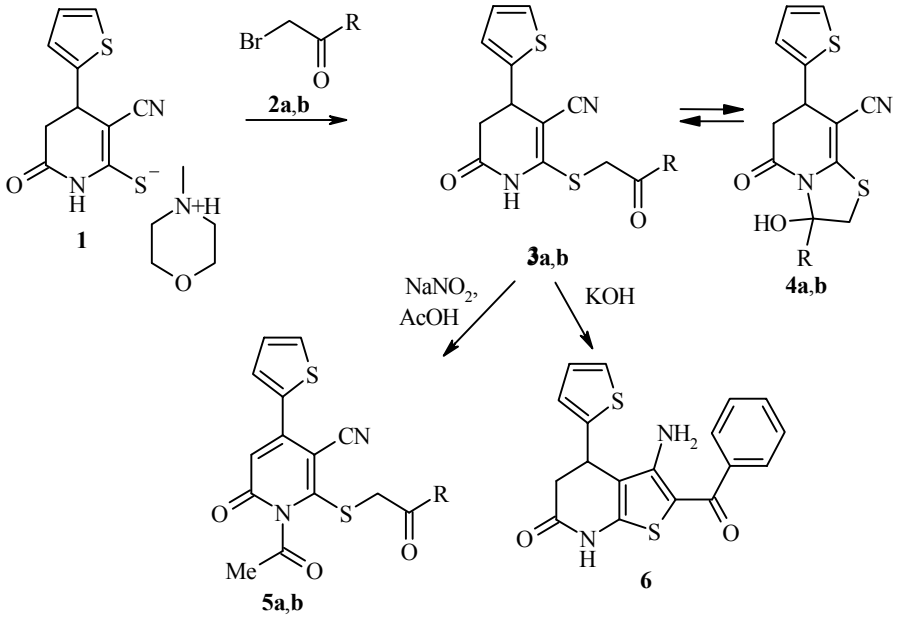

a R = Ph, **b** R = 4-BrC_6H_4

The thiophene $S_{(2)}C_{(7\text{-}10)}$ and benzene $C_{(13\text{-}18)}$ rings are virtually orthogonal to the central bicyclic system due to steric factors, the corresponding dihedral angles being 82.3 and 83.4°. The $N_{(1)}$ atom has a planar trigonal configuration of bonds (the sum of the valence angles at this atom being 360.0 (1.2)°). The participation of the lone electron pair of this atom in conjugation with the π-system of the double bonds $O_{(1)}=C_{(5)}$ and $C_{(1)}=C_{(2)}$ leads

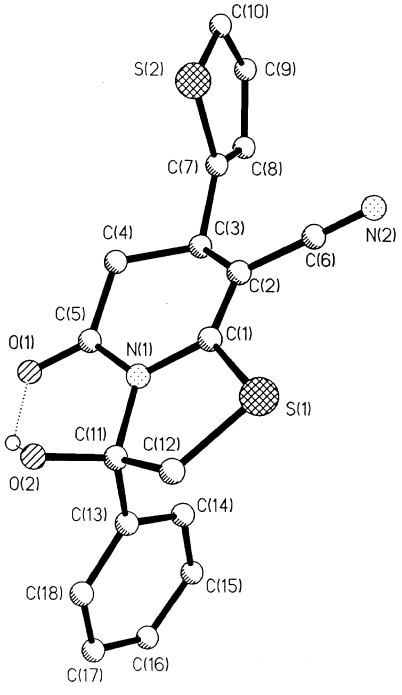

Fig. 1. General view of the molecule of compound **4a** with atomic numbering
(for simplification, only the hydrogen atom taking part in the intramolecular bond is shown).

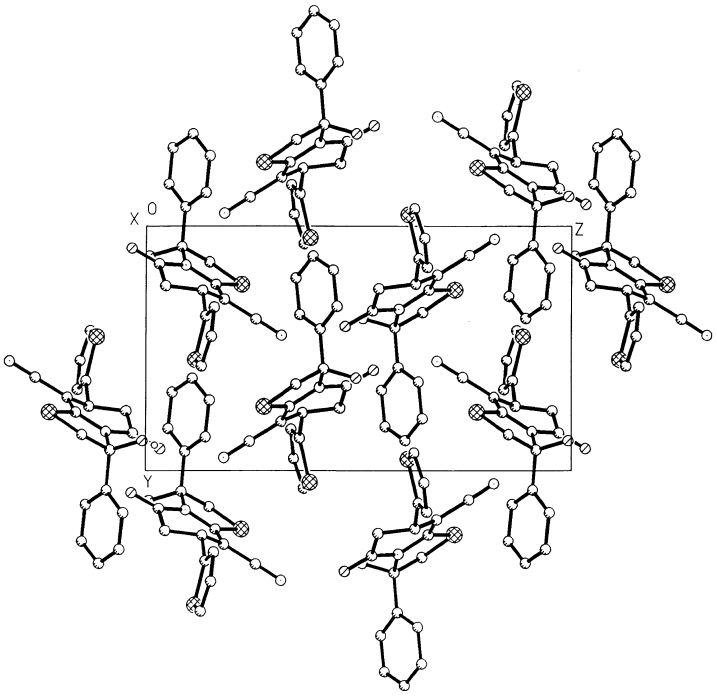

Fig. 2. Crystal structure of compound **4a** (*bc* projection).

to a marked shortening of the $N_{(1)}$–$C_{(5)}$ 1.386(5) and $N_{(1)}$–$C_{(1)}$ 1.386(5) Å bonds when compared with the range of 1.43-1.45 Å typical of a purely N(sp^2)–C(sp^2) single bond [4, 5]. Apparently, the shortening of the $S_{(1)}$–$C_{(1)}$ bond to 1.734(4) Å when compared with the $S_{(1)}$–$C_{(12)}$ bond (1.785(6) Å) depends to a significant degree on an $n(S_{(1)})$-π*($C_{(1)}$=$C_{(2)}$) conjugation effect. From the other features of the structure of compound **4a** we noted an extremely strong [6] intramolecular $O_{(2)}$–$H_{(02)}$···$O_{(1)}$ hydrogen bond which forms the 6-membered $O_{(1)}H_{(01)}O_{(2)}C_{(11)}N_{(1)}C_{(5)}$ ring. The basic geometric parameters for this H-bond are: $O_{(1)}$···$O_{(2)}$ 2.713(5), $O_{(2)}$–$H_{(02)}$ 0.76(9), $O_{(1)}$···$H_{(02)}$ 2.09(9) Å, and $O_{(1)}H_{(02)}O_{(2)}$ angle 140(6)°. In the crystals the molecules of compound **4a** are associated by van der Waal forces without shortened intermolecular contacts. The crystal packing of compound **4a** is shown in Fig. 2.

TABLE 1. Basic Bond Lengths (*d*) and Valence Angles (ω) in the Molecule of Compound **4a**

Bond	*d*, Å	Angle	ω, deg.	Angle	ω, deg.
$S_{(1)}$–$C_{(1)}$	1.734(4)	$C_{(1)}$–$S_{(1)}$–$C_{(12)}$	93.5(2)	$C_{(7)}$–$C_{(3)}$–$C_{(2)}$	115.8(4)
$S_{(1)}$–$C_{(12)}$	1.785(6)	$C_{(5)}$–$N_{(1)}$–$C_{(1)}$	122.9(4)	$O_{(1)}$–$C_{(5)}$–$N_{(1)}$	120.7(4)
$N_{(1)}$–$C_{(1)}$	1.386(5)	$C_{(5)}$–$N_{(1)}$–$C_{(11)}$	120.1(4)	$O_{(1)}$–$C_{(5)}$–$C_{(4)}$	124.6(4)
$N_{(1)}$–$C_{(5)}$	1.386(5)	$C_{(1)}$–$N_{(1)}$–$C_{(11)}$	117.0(4)	$N_{(1)}$–$C_{(5)}$–$C_{(4)}$	114.5(4)
$C_{(1)}$–$C_{(2)}$	1.339(6)	$C_{(2)}$–$C_{(1)}$–$N_{(1)}$	122.6(4)	$O_{(2)}$–$C_{(11)}$–$N_{(1)}$	110.2(4)
$C_{(2)}$–$C_{(3)}$	1.528(6)	$C_{(2)}$–$C_{(1)}$–$S_{(1)}$	125.9(3)	$O_{(2)}$–$C_{(11)}$–$C_{(13)}$	111.9(4)
$C_{(3)}$–$C_{(4)}$	1.497(6)	$N_{(1)}$–$C_{(1)}$–$S_{(1)}$	111.4(3)	$N_{(1)}$–$C_{(11)}$–$C_{(13)}$	110.7(4)
$C_{(4)}$–$C_{(5)}$	1.500(6)	$C_{(1)}$–$C_{(2)}$–$C_{(6)}$	118.6(4)	$O_{(2)}$–$C_{(11)}$–$C_{(12)}$	105.3(4)
$O_{(1)}$–$C_{(5)}$	1.205(5)	$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	119.3(4)	$N_{(1)}$–$C_{(11)}$–$C_{(12)}$	105.7(4)
$O_{(2)}$–$C_{(11)}$	1.409(6)	$C_{(6)}$–$C_{(2)}$–$C_{(3)}$	121.7(4)	$C_{(13)}$–$C_{(11)}$–$C_{(12)}$	112.7(4)
$N_{(1)}$–$C_{(11)}$	1.491(6)	$C_{(4)}$–$C_{(3)}$–$C_{(7)}$	111.8(4)	$C_{(11)}$–$C_{(12)}$–$S_{(1)}$	109.8(3)
$C_{(11)}$–$C_{(12)}$	1.526(6)	$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	108.0(4)		

TABLE 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic (Isotropic for the $H_{(02)}$ atom) Thermal Parameters U_{eq} ($\times 10^3$) in the Structure **4a**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
$S_{(1)}$	3105(1)	2388(2)	2244(1)	59(1)
$S_{(2)}$	7122(2)	5472(2)	1147(1)	72(1)
$O_{(1)}$	3787(3)	895(4)	-326(2)	56(1)
$O_{(2)}$	1549(3)	1223(4)	75(3)	60(1)
$N_{(1)}$	3674(3)	1599(4)	924(2)	42(1)
$N_{(2)}$	6029(5)	4473(5)	3167(3)	68(1)
$C_{(1)}$	4160(4)	2387(5)	1640(3)	35(1)
$C_{(2)}$	5329(4)	2992(5)	1837(3)	40(1)
$C_{(3)}$	6247(5)	2630(6)	1325(3)	52(1)
$C_{(4)}$	5468(4)	2441(6)	452(3)	50(1)
$C_{(5)}$	4272(4)	1542(5)	301(3)	41(1)
$C_{(6)}$	5733(5)	3809(6)	2575(3)	47(1)
$C_{(7)}$	7336(5)	3672 (5)	1398(3)	46(1)
$C_{(8)}$	8580(5)	3313 (5)	1600(3)	46(1)
$C_{(9)}$	9358(5)	4511(7)	1534(3)	60(2)
$C_{(10)}$	8718(5)	5720(6)	1295(3)	57(2)
$C_{(11)}$	2426(4)	839(5)	828(3)	43(1)
$C_{(12)}$	1872(5)	1473(7)	1488(4)	71(2)
$C_{(13)}$	2623(4)	-787(5)	908(3)	37(1)
$C_{(14)}$	3748(5)	-1377(6)	1398(3)	46(1)
$C_{(15)}$	3885(5)	-2873(6)	1487(3)	55(2)
$C_{(16)}$	2913(7)	-3772(6)	1080(3)	63(2)
$C_{(17)}$	1801(6)	-3203(6)	603(3)	59(2)
$C_{(18)}$	1646(4)	-1720(6)	517(3)	47(1)
$H_{(O2)}$	1915(89)	967(109)	-220(58)	180(49)

Refluxing a mixture of the pyridines **3, 4** in acetic acid in the presence of excess $NaNO_2$ gave the corresponding sulfides **5** which form compound **3** *via* dehydrogenation and acylation under these conditions. The addition to the same mixture of isomers **3** and **4** in ethanol of an equimolar amount of an aqueous solution of KOH causes a concurrent Thorpe cyclization involving the activated methylene group of the 6-alkylthio substituent and the cyano group of the pyridine **3a** leading to the hydrogenated thieno[2,3-*b*]pyridine **6**.

EXPERIMENTAL

^{1}H NMR spectra were measured on a Bruker AM-300 (300 MHz) instrument using DMSO-d_6 solvent and TMS internal standard. IR spectra were recorded on an IRS-29 spectrophotometer using vaseline oil and mass spectra on a Kratos MS-30 spectrometer with direct introduction of the sample into the source. Elemental analysis for C, H, and N was carried out on a Perkin-Elmer C-, H-, N- analyzer instrument. Monitoring of the reaction course and the purity of the synthesized compound was carried out using TLC on Silufol UV-254 plates in the system acetone–hexane (3:5) and revealed using iodine vapor. Melting points were determined on a Koffler stage.

X-ray Analytical Investigation of the monocrystal of compound **4a** was carried out at room temperature on an automatic, four-circle Enraf-Nonius CAD-4 diffractometer (λMoKα irradiation, graphite monochromator, scanning rate ratio $\omega/2\theta = 1{,}2$, $\theta = 23°$, spherical segment $0 \le h \le 11$, $0 \le k \le 10$, $-18 \le l \le 17$). In order to determine the unit cell parameters and the orientation matrix, a crystal of compound **4a** with linear size $0.17 \times 0.25 \times 0.31$ mm, 22 reflections with $12 < \theta < 13°$ were used. In all, 2390 reflections were used, of

which 2254 are independent (mean R factor 0.032). Crystals of compound **4a** are monoclinic with a = 10.842(2), b = 9.203(2), c = 16.955(3) Å; β = 106.11(3)°; V = 1625.3(5) Å^3; Z = 4; d_{calc} = 1.45 g/cm^3; μ = 0.341 mm^{-1}; F(000) = 736; space group $P2_1/n$ (No. 14). The structure was solved by the heavy atom method with full matrix least squares refinement in the anisotropic approximation using the SHELXS and SHELXL93 programs [7, 8]. In the refinement 1450 reflections with $I > 2\sigma(I)$ (221 refined parameters, number of reflections per parameter 6.56) and using the weighting scheme

$$\omega = 1/[\sigma^2(Fo^2) + (0.0525\ P)^2 + 0.7276\ P],$$

where $P = (Fo^2 + 2Fc^2)/3$ is the ratio of maximum to mean error shift in the latter ring 0.045/0.003). A correction for anomalous dispersion was included but one for absorption was not introduced. All of the hydrogen atoms were revealed directly from electron density difference synthesis and included in the refinement with fixed thermal and positional parameters (with the exclusion of the $H_{(02)}$ hydrogen atom which was refined isotropically). The final difference factor values were $R1$ (F) 0.0556 and R_w (F^2) 0.1164, GOF 1.044. The residual electron density from the Fourier series difference 0.50 and -0.22 e/Å^3. The atomic coordinates are given in Table 2.

6-Benzoylmethylthio-5-cyano-2-oxo-4-(2-thienyl)-1,2,3,4-tetrahydropyridine (3a) and 8-Cyano-3-hydroxy-5-oxo-3-phenyl-7-(2-thienyl)-2,3,4,5,6,7-hexahydrothiazolo[3,2-*c*]pyridine (4a). A mixture of salt **1** (3.38 g, 10 mmol) and bromide **2a** (1.99 g, 10 mmol) in ethanol (25 ml) was heated until the starting reagents dissolved and the hot solution was filtered through filter paper. After 6 h the precipitate formed in the filtrate was separated and washed with ethanol and hexane. The yield of compound **4a** 3.16 g (89%); mp 135-137°C. IR spectrum, ν, cm^{-1}: 3215-3249 (OH), 2195 (CN), 1680 (CO). Mass spectrum (EI, 70 eV), *m/z*, (peak with I_{max}, I_{rel}, %): 39 (21), 51 (29), 77 (68), 105 (100), 249 (17), 354 (12). ^{1}H NMR spectrum, δ, ppm, J (Hz), (1:1 mixture of compounds **3a-4a**): 2.59-2.79, 2.92-3.18 (both m, CH_2); 3.43 , 3.54 (both d, SCH_2, ^2J = 10.2); 4.23 (dd, CH, ^3J = 5.6 and 7.2); 4.36 (dd, CH, ^3J = 6.7 and 8.3); 4.78 (s, CH_2); 6.96, 7.32-8.01 (both m, Ar, Het, OH); 10.53 (s, NH). Found, %: C 59.84; H 4.08; N 7.73. $C_{18}H_{14}N_2O_2S_2$. Calculated, %: C 61.00; H 3.98; N 7.90.

6-(4-Bromobenzoyl)methylthio-5-cyano-2-oxo-4-(2-thienyl)-1,2,3,4-tetrahydropyridine (3b) and 3-(4-Bromophenyl)-8-cyano-3-hydroxy-5-oxo-7-(2-thienyl)-2,3,4,5,6,7-hexahydrothiazolo[3,2-*a*]pyridine (4b) were prepared similarly to compounds **3a**, **4a** using the bromide **2b** (2.78 g) in place of compound **2a**. The yield of compound **4b** 3.21 g (74%); mp 163-165°C. IR spectrum, δ, cm^{-1}: 3226-3258 (OH), 2198 (CN), 1683 (CO). ^{1}H NMR spectrum, δ, ppm, J (Hz), (1:1 mixture of compounds **3b-4b**): 2.56-2.75, 2.91-3.21 (both m, CH_2); 3.47, 3.58 (both d, SCH_2, ^2J = 10.8); 4.28 (dd, CH, ^3J = 5.9 and 7.7); 4.41 (dd, CH, ^3J = 6.9 and 8.5); 4.77 (s, SCH_2); 7.34-7.91 (m, Ar, Het and OH); 10.59 (s, NH). Found, %: C 49.71; H 3.18; N 6.25. $C_{18}H_{13}BrN_2O_2S_2$. Calculated, %: C 49.89; H 3.02; N 6.46.

1-Acetyl-6-benzoylmethylthio-5-cyano-2-oxo-4-(2-thienyl)-1,2-dihydropyridine (5a). $NaNO_2$ (1.38 g, 20 mmol) was added portionwise to the mixture of **3a** and **4a** (1.77 g, 5 mmol) in refluxing acetic acid (20 ml) and the reaction was left for 12 h at room temperature. The precipitate formed of the pyridone **5a** was filtered off and washed with ethanol and hexane. Yield 1.60 g (81%); mp 105-107°C. IR spectrum, ν, cm^{-1}: 2220 (CN), 1650, 1666 (3 CO). ^{1}H NMR spectrum, δ, ppm, J (Hz): 2.49 (3H, s, Me); 4.74 (2H, s, SCH_2); 7.36-7.89 (9H, m, Ar, Het, CH). Found, %: C 59.77; H 3.41; N 6.82. $C_{20}H_{14}N_2O_3S_2$. Calculated, %: C 60.90; H 3.58; N 7.10.

1-Acetyl-6-(4-bromobenzoyl)methylthio-5-cyano-2-oxo-4-(2-thienyl)-1,2-dihydropyridine (5b) was prepared similarly to pyridine **5a** using the mixture of **3b**, **4b** (2.17 g) in 1.97 g (83%) yield; mp 121-123°C. IR spectrum, ν, cm^{-1}: 2220 (CN), 1653, 1660 (3 CO). ^{1}H NMR spectrum, δ, ppm, J (Hz): 2.23 (3H, s, Me); 4.82 (2H, s, SCH_2); 7.32, 7.80-8.03 (8H, both m, Ar, Het, CH). Found, %: C 50.55; H 2.56; N 5.91. $C_{20}H_{13}BrN_2O_3S_2$. Calculated, %: C 50.75; H 2.77; N 5.92.

3-Amino-2-benzoyl-4-(2-thienyl)-4,5-dihydrothieno[2,3-*b*]pyridin-6(7H)-one (6). Aqueous KOH solution (10%, 2.8 ml, 5 mmol) was added to a mixture of compounds **3a**, **4a** (1.77 g, 5 mmol) after which the reaction mixture was heated to reflux and filtered through filter paper. After 12 h the precipitate formed in the filtrate was separated and washed with ethanol and hexane. Yield of the thienopyridone **6** (1.12 g, 63%); mp 204-207°C. IR spectrum, ν, cm^{-1}: 3391, 3244 (NH, NH_2), 1655, 1682 (2 CO). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.61 (1H, dd, 5-H, ^2J = 14.2, ^3J = 6.3); 3.19 (1H, dd, 5-H, ^2J = 14.2, ^3J = 7.3); 4.59 (1H, dd, 4-H, ^3J = 6.3 and 7.3); 6.88-7.87 (10H, m, Ar, Het, NH_2); 11.05 (1H, s, NH). Found, %: C 59.68; H 3.79; N 7.85. $C_{18}H_{14}N_2O_2S_2$. Calculated, %: C 61.00; H 3.98; N 7.90.

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