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Stereoselective Synthesis of and Atropisomerism in 4-Pyridyl-3-(1-pyridinio)-3,4-trans-1,2,3,4-tetrahydropyridines and Their Transformation Products

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ABSTRACT

A series of 2-oxo-4-pyridyl-3-(1-pyridinio)-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridine-6-olates were prepared by condensation of pyridinium ylides with α,β-unsaturated carbonyl compounds or more conveniently by a three-component condensation of pyridinium ylides, pyridine aldehydes, and ethyl cyanoacetate ***3*** *and/or* ***6****. This analogues of the above tetrahydropyridines were prepared in a similar way starting from suitable substrates. Spectroscopic data revealed that the reaction leads to trans-isomers around the C^3–C^4 bond and is atroposelective. The conformation of and tautomerism in the tetrahydropyridines are discussed in the light of ^1H NMR data. The reaction of 5-cyano-3-(3-methyl-1-pyridinio)-2-oxo-4-(3-pyridyl)-1,2,3,4-tetrahydropyridine-6-thiolate* ***10c*** *with phenacyl bromide was found to give 3-hydroxy-5-oxo-7-(3-pyridyl)-6-(3-methyl-1-pyridinio)-3-phenyl-8-cyano-6,7-trans-2,3,6,7-tetrahydrothiazol[3,2a]pyridine bromide, the crystal and molecular structure of which has been determined by X-ray crystallographic analysis.*

INTRODUCTION

Pyridinium ylides are very useful reagents for the synthesis of di- and poly-pyridyls [1–4]. Practically all of the possible isomeric dipyridyls and tripyridyls have been synthesized by condensation of pyridinium ylides with pyridyl-substituted unsaturated carbonyl compounds or Mannich bases [1–4].

However, up to now, there are no examples of the use of pyridinium ylides for the synthesis of

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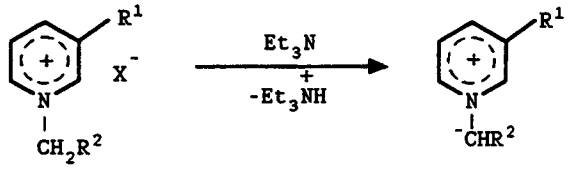
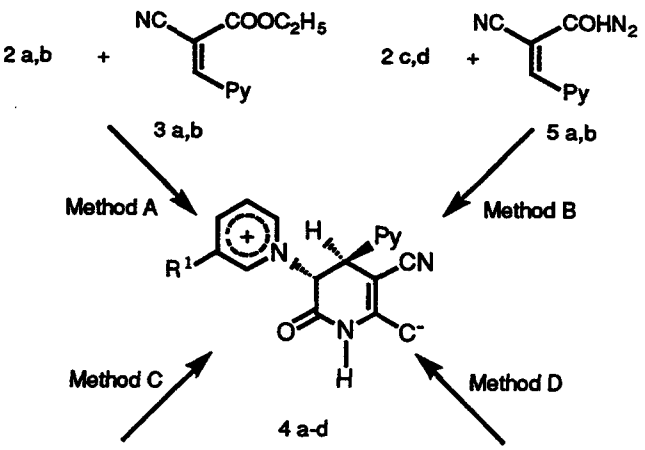


1a-e 2a-e

1a R^1=H, R^2=$CONH_2$, X=Cl 2a
1b R^1=CH_3, R^2=$CONH_2$, X=Cl 2b
1c R^1=H, R^2=$COOCH_3$, X=Br 2c
1d R^1=CH_3, R^2=$COOCH_3$, X=Br 2d
1e R^1=H, R^2=$CSSCH_3$, X=I 2e

SCHEME 1



3, 5, 6a, Py = 3-C_5H_4N
3, 5, 6b, Py = 4-C_5H_4N

4a, R^1 = H, Py = 3-C_5H_4N
4b, R^1 = H, Py = 4-C_5H_4N
4c, R^1 = CH_3, Py = 3-C_5H_4N
4d, R^1 = CH_3, Py = 4-C_5H_4N

SCHEME 2

hydropyridines containing pyridyl substituents. This class of compounds recently attracted the attention of many research groups because of their high biological activity. In several articles, the investigations of individual drugs [5,6] such as vasodilators and antihypertensive remedies—nifedipine and nitrendipine [7]—have been described. Moreover, dihydropyridines possess antioxidant [8], hepatoprotective [9], antimutagenic [10], antiatherosclerotic [11], and herbicidal [12] activity.

In this article, we wish to report methods for stereoselective synthesis of tetrahydropyridines involving reactions of pyridinium ylides with some pyridyl-containing unsaturated carbonyl and thiocarbonyl compounds as well as atropisomerism and tautomerism in and other physico-chemical properties of the products obtained.

RESULTS AND DISCUSSION

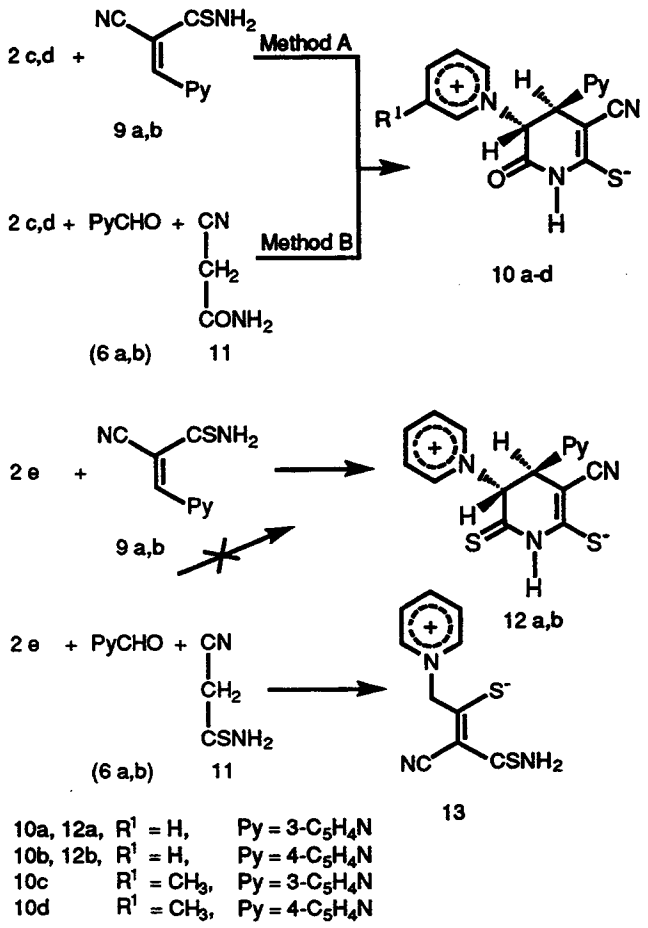
Synthesis of Tetrahydropyridines

Pyridinium ylides **2a–e** listed above were generated in situ from the corresponding pyridinium salts **1a–e** upon treatment with triethylamine.

It has been found that reactions of these ylides with α,β-unsaturated carbonyl compounds **3a,b** are regio- and stereoselective and result in the formation of the corresponding 2-oxo-4-pyridyl-3-(1-pyridinio)-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridine-6-olates **4a–d** (method A). Similarly, the regio- and stereoselectivity were observed in reactions between the ylides **2c,d** and unsaturated carbonyl partners **5a,b** which afford the tetrahydropyridines **4a–d** (method B). It is interesting to note that the simplest way for the synthesis of **4**, one that avoids the preparation of the unsaturated carbonyl compounds **3** or **5**, is a three-component condensation of the ylides **2a,b** with pyridine aldehydes **6a,b** and ethyl cyanoacetate **7** (method C) or with aldehydes **6a,b** and 2-cyanoacetamide **8** (method D), respectively.

By varying substituents in the reaction substrates, it is also possible to synthesize pyridinium-substituted tetrahydropyridines having oxygen or sulfur in positions 2 and 6, respectively. Thus, reactions of the ylides **2c,d** with α,β-unsaturated thiocarbonyl compounds **9a,b** produced 2-oxo-3-(1-pyridinio)-3,4-trans-1,2,3,4-tetrahydropyridin-6-thiolates **10a–d** (method A). These compounds were also obtained in good yields by a three-component condensation of the ylides **2c,d** with aldehydes **6a,b** and 2-cyanothioacetamide **11** (method B). As expected, treatment of the ylide **2d** with thiocarbonyl components **9a,b** gave the corresponding 2-thio-3-(1-pyridinio)-3,4-trans-1,2,3,4-tetrahydropyridin-6-thiolates **12a,b**. However, our attempt to prepare **12** by a three-component condensation of the ylide **2d**, pyridine aldehydes **6**, and 2-cyanothioacetamide **11** failed. Most probably, the condensation of the ylide **2d** with **11** is much faster than the reaction of **6** with **11**. Therefore, the betaine **13** is formed as the final condensation product and not the expected tetrahydropyridine **12**. In accord with this, the betaine **13** was obtained in 71% yield on reacting the ylide **2d** with 2-cyanothioacetamide **11**.

Some data on the synthesis and physical properties of the tetrahydropyridines **4**, **10**, and **12** are collected in Table 1.



SCHEME 3

Spectroscopic Studies of Structure and Conformation of Tetrahydropyridines

The results of spectroscopic studies revealed that the tetrahydropyridines **4**, **10**, **12**, and **13** obtained exist in the betaine form in which the positive and negative charges are delocalized in the pyridinium ring, Py^+, and the $N{=}C{-}C{=}C{-}X^-$ (X=O,S) fragment, respectively. Such a delocalization of the electron density results in the lowering of the vibration frequency of the cyano group in the IR spectra for the compounds **4**, **10**, **12**, and **13** up to 2168–2184 cm^{-1} and simultaneously in an increase of its intensity. Similar changes in IR spectra were observed for the salts of 3-cyano-1,4-dihydropyridin-2-thioles [13,14]. As a consequence of the above-mentioned electron conjugation, the $N{=}C{-}C{=}C{-}X^-$ fragment and the atoms attached to this skeleton are coplanar.

The IR spectra of the tetrahydropyridines under discussion also show a series of absorption bands for the N–H, C=O, and C=S groups at 1628–1664, 3022–3038, 1680–1704, and 1204–1212 cm^{-1}, respectively; this may be taken as evidence that these compounds (**4**, **10**, and **12**) exist in the 2-(1H)-pyridinone and 2-(1H)-pyridinethione tautomeric forms.

In the ^1H NMR spectra of the tetrahydropyridines **4**, **10**, and **12**, the signals for protons 3-H and 4-H of the tetrahydropyridine ring appear as two doublets at δ 5.86–6.50 and 4.40–4.74 with a coupling constant ^3J = 12.1–14.0 Hz. The latter value strongly suggests that the 3-H and 4-H protons adopt the diaxial arrangement like those in the previously examined 3,4-trans-1,2,3,4-tetrahydropyridin-6-thiolates [15,16]. Therefore, the substituents R^1Py^+ and Py should be pseudo equatorial. The signal for 3-H is shifted downfield in comparison with that of 4-H. This may be attributed to the polarization of the C^3–H bond caused by the electron deficient pyridinium cation as well as to the deshieding effect of the equatorial pyridine ring at C-4.

Taking into account the spectral data of the tetrahydropyridines **4**, **10**, and **12** investigated here, and comparison with the reported data for the salts of hydrogenated 3-cyanopyridine-2-thiolates **13–16**, one can assume that the tetrahydropyridines prepared by us exist either in a half-chair conformation **14** with a flat N^1–C^6 = C^5–C^4 fragment (the C^3 and C^2 atoms are below and above this plane) or else they adopt a distorted envelope conformation **15** in which the C^2–N^1–C^5–C^6 fragment is planar and the C^3 and C^4 atoms are on the opposite sides of this plane. However, in our opinion, the above-mentioned large value of the coupling constant $^3J_H3$-$_H4$ as well as the results of X-ray analysis of the compound **20** (see below) favor the latter conformation.

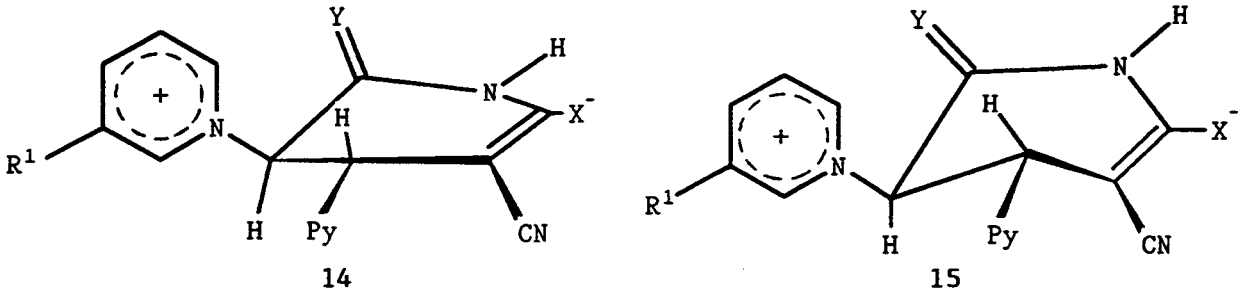
Atropisomerism in Tetrahydropyridines

In the case of the tetrahydropyridines **4c,d** and **10c,d** containing the 3′-methylpyridinium cation at C^3, the ^1H NMR spectra show one singlet for the methyl group at δ 2.38–2.42. Signals for other protons of the 3′-methylpyridinium cation are also not doubled. This observation strongly suggests that only one atropisomer is formed under the reaction conditions. It is interesting to note that a comparison of the chemical shifts for the protons 3-H and the pyridinium cation in the tetrahydropyridines **4a,b**, **10a,b** and **12a,b** with those of 3-H and 3′-methylpyridinium cation in **4a,d** and **10c,d** reveals that the latter signals are slightly shifted to higher field, $\Delta\delta$ = 0.09–0.22. This effect is most probably caused by the long-range steric screening of the methyl protons in the 3-methylpyridinium cation.

With regard to atropisomerism in the tetrahydropyridines **4c,d** and **10c,d** investigated, it should be noted that both substituents 3-R^1Py^+ and 4-Py do not undergo full rotation (180°) around the C^3–R^1–Py^+ and C^4–Py bonds. Their rotational changes are dependent on each other due to the vicinal effect [17].

TABLE 1 Substituted 4-Pyridyl-3-(1-pyridinio)-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridines **4**, **10**, **12**

Compound	Method	Yield (%)	Melting point (°C)	Formula	Analysis (%) Found/Calculated C	H	O	S
4a	A	92	173–175	$C_{16}H_{12}N_4O_2$	65,62/65,75	4,02/4,14	18,95/19,17	
	B	87						
	D	60						
4b	A	90	167–170	$C_{16}H_{12}N_4O_2$	65,34/65,75	3,92/4,14	18,82/19,17	
	B	84						
	C	59						
4c	A	98	142–143	$C_{17}H_{14}N_4O_2$	66,78/66,66	4,48/4,61	18,04/18,29	
	B	92						
4d	A	96	171–173	$C_{17}H_{14}N_4O_2$	66,37/66,66	4,46/4,61	17,93/18,29	
	B	88						
	C	49						
10a	A	92	193–195	$C_{16}H_{12}N_4OS$	62,47/62,32	3,70/3,92	18,04/18,17	10,06/10,40
10b	A	65	137–138	$C_{16}H_{12}N_4OS$	62,11/62,32	3,74/3,92	17,94/18,17	10,22/10,40
10c	A	80	169–172	$C_{17}H_{14}N_4OS$	63,11/63,34	4,20/4,38	17,16/17,38	9,64/9,95
10d	A	78	142–143	$C_{17}H_{14}N_4OS$	63,17/63,34	4,17/4,38	17,20/17,38	9,67/9,95
12a		54	224–226	$C_{16}H_{12}N_4S_2$	59,13/59,24	3,58/3,73	17,46/17,27	19,53/19,76
12b		54	135–138	$C_{16}H_{12}N_4S_2$	59,42/59,24	3,57/3,73	17,46/17,27	19,97/19,76



SCHEME 4

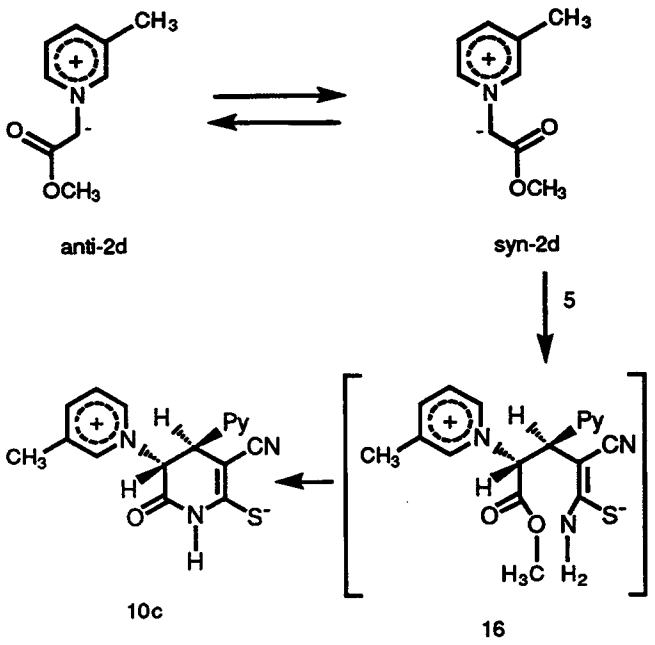
The ^{1}H NMR spectra of the tetrahydropyridines **4c,d**, **10**, and **12** recorded in a DMSO-d_6 solution in the temperature range 15–90°C show only negligible broadening of the signals due to 3-CH_3-Py^+ and 4-Py protons as a result of increasing rotational changes around the C^3–Py^+ and C^4–Py bonds. However, the temperature-dependent ^{1}H NMR spectra did not reveal the formation of other atropisomers arising from a full rotation around these bonds.

It is reasonable to assume that the formation of only one atropisomer in the compounds under discussion is taking place during the nucleophilic addition (Ad_N) of the 3-methylpyridinium ylide **2d** to the unsaturated reaction component **5**. Among two possible syn- and anti-isomers of the pyridinium ylide **2d**, only the syn-isomer is reactive. Its reaction with **5** leads to a single Michael adduct **16**. The next step, i.e., intramolecular 1,6-elimination of methanol, is stereoselective and gives rise to a single ap-atropisomer of **10c** having an anti-relationship between the 3-H atom and the methyl group in the pyridinium cation. On the basis that the energy barrier for syn ⇄ anti interconversion in pyridinium ylides is rather low (18–27 kJ/mol [18]), it may be anticipated that nonbonding steric interactions between two reacting compounds, **2d** and **5**, determine the atroposelectivity. Thus, for steric reasons, the nucleophilic addition of syn-**2d** to **5** is possible while anti-**2d** does not react.

The atroposelectivity discussed above for tetrahydropyridines containing the 3-methylpyridinium cation may also appear for 4-(3-pyridyl)-substituted analogues. This was found to be the case for the tetrahydropyridines **4a,c**, **10a,c**, and **12a** as revealed by their ^{1}H NMR spectra and the X-ray structure of the thiazolo[3,2-a]pyridinium salt **20**.

Tautomerism in Tetrahydropyridines

It has been found that the NH and 3-H hydrogen atoms in the tetrahydropyridines **4**, **10**, and **12** are exchanged by deuterium when D_2O is added to their solutions in DMSO-d_6. The hydrogen-deuterium



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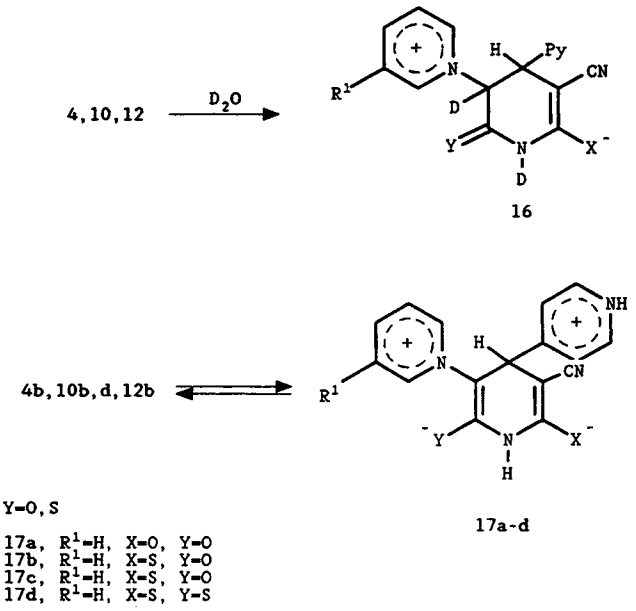


SCHEME 6

exchange under these conditions is nicely evidenced by the ^{1}H NMR spectra which show a broadening of the NH signal and the absence of a signal due to the 3-H proton. Consequently, instead of a doublet for the 4-H proton, one observes a singlet in this region. In this way, an increased C-H acidity of tetrahydropyridines is demonstrated. Undoubtedly, it is due to the C^3–H bond polarization induced by the electron-withdrawing 3-pyridinium and C^2=Y (Y = O,S) substituents and results in the formation in equilibrium of the dibetaines **17** from the tetrahydropyridines **4b**, **10b,d** and **12b** in DMSO-d_6 solution.

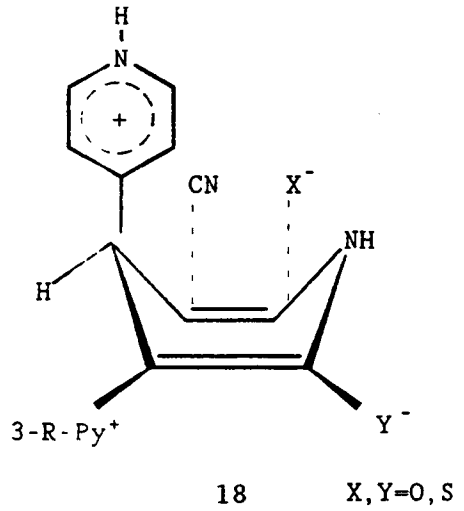
Tautomeric equilibrium between tetrahydropyridines and dibetaines **17** is shifted toward the former structure and lies in the range 2–8:1. It is of interest that the tetrahydropyridines containing oxygen and sulfur or two sulfur atoms in positions **2** and **6** exhibit better tendency to exist in the tautomeric dibetaine form **17** than those with two oxygen atoms.

In this context, one should note that the dibetaine formation was observed earlier for derivatives of 4-(4-pyridyl)-3-cyano-3,4-dihydropyridin-2(1H)-thiones [19] and 3-cyano-3,4-dihydronaphthyridin-2(1H)-thiones [20]. Taking into account our present observations, one can conclude that the dibetaine formation is a general rule for the hydrogenated pyridin-2(1H)-ones and the corresponding thiones containing electron-withdrawing substituents in the heterocyclic ring.

The formation of the dibetaines **17** discussed above is accompanied by a conformational change of the tetrahydropyridine ring, as indicated by the ^{1}H NMR spectra. Thus, a downfield shift for the 4-H and NH protons to δ = 5.40–5.75 and 10.26–11.20, respectively, is observed (Table 2). These chemical shift changes strongly suggest that the tetrahydropyridine ring in **17** adopts a flattened boat conformation **18** in which the N^1 and C^4 atoms are situated above the plane formed by the C^2, C^3, C^5, and C^6 atoms. Therefore, the 4-H and NH protons are deshielded. Moreover, in a boat conformation **18**, in contrast to **15**, both α and β protons of the 4-

TABLE 2 Bond Lengths in the Cation of **20** and with a Crystallosolvated Molecule of Ethanol

Bond		*Bond*	
S1–C2	1.84(1)	C8–C8a	1.33(1)
S1–C8a	1.72(1)	C8–C9	1.43(1)
O1–C3	1.39(2)	C11–C12	1.38(2)
O2–C5	1.24(1)	C11–C16	1.34(2)
N4–C3	1.49(1)	C14–C15	1.39(2)
N4–C5	1.35(1)	C15–C16	1.39(2)
N4–C8a	1.42(1)	C18–C19	1.37(1)
N10–C9	1.15(1)	C19–C20	1.42(2)
N13–C12	1.31(2)	C19–C29	1.46(2)
N13–C14	1.29(3)	C20–C21	1.35(2)
N17–C6	1.47(1)	C21–C22	1.37(2)
N17–C18	1.34(1)	C23–C24	1.36(2)
N17–C22	1.37(2)	C23–C28	1.42(1)
C2–C3	1.52(1)	C24–C25	1.40(2)
C3–C23	1.52(2)	C25–C26	1.42(1)
C5–C6	1.52(1)	C26–C27	1.33(2)
C6–C7	1.54(2)	C27–C28	1.39(2)
C7–C8	1.53(1)	O4–C30	1.35(7)
C7–C11	1.51(1)	C30–C31	1.61(8)



18 X,Y=O,S

SCHEME 7

pyridine substituents are deshielded and shifted downfield (Table 2). This change can also be caused by deshielding of the 4-Py protons as a result of the nitrogen protonation, similar to the case of the quaternary pyridines [21].

In a boat conformation **18**, the α-protons of the 3-pyridinium substituent are more shielded by a nonplanar tetrahydropyridine ring. Therefore, their NMR signals are diamagnetically shifted in comparison with the signals of the same proton in the compounds **4**, **10**, and **12** existing in a twist-chair conformation **15**. The signals of the remaining 3-Py^+ protons do not undergo changes. A comparison of the ^1H NMR data with a physico-chemical analysis [13] and X-ray structure determination [14] of the salts of 1,4-dihydropyridine-2-thiolates leads to the general conclusion that a flattened boat conformation is characteristic for substituted 1,4-dihydropyridines. Based on these data, one can assume that the 4-Py^+ substituent is occupying the sterically most favorable pseudo-equatorial position as in the salts of substituted 4-aryl-1,4-dihydropyridin-2-thiolates [13,14].

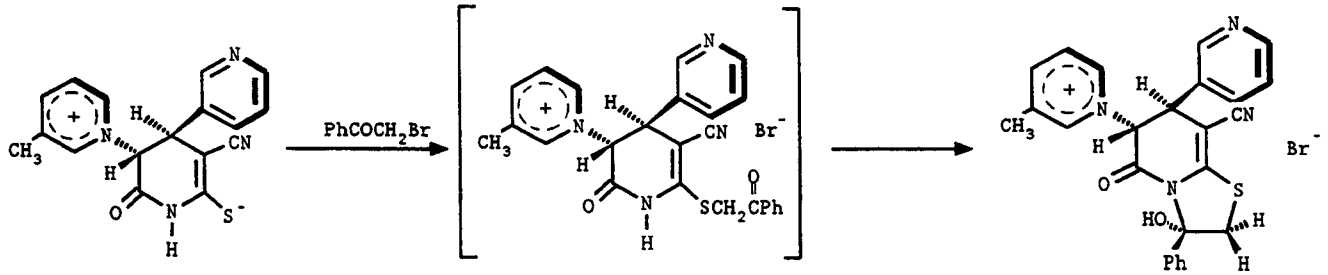
Although the negative charge in **10** may be concentrated on the exocyclic sulfur and oxygen atoms or on the endocyclic nitrogen, the reaction of **10c** with phenacyl bromide carried out in ethanol under reflux and affording the salt **20** revealed that, in this case, the sulfur atom is a reactive center. In the first step, phenacyl bromide reacts with **10c** at sulfur to give the substituted 6-phenacylthiodihydropyridine **19** which subsequently undergoes cyclization to **20** under the reaction conditions.

The latter reaction is fully stereoselective and takes place with the preservation of the cis-trans geometry at the C^3–C^4 bond as well as of atropisomerism in the starting compound **10c**. This was confirmed by spectral data and X-ray analysis of the bicyclic product **20**.

Crystal and Molecular Structure of 3-Hydroxy-5-oxo-7-(3-pyridyl)-6-(3-methyl-1-pyridinio)-3-phenyl-8-cyano-6,7-trans-2,3,6,7-tetrahydrothiazolo[3,2-a]pyridine bromide **20**

First of all, the structure of **20** was confirmed by X-ray analysis which showed that **20** crystallizes with one molecule of ethanol and water. The general view of the molecule of **20** with the atom numbering is presented in Figure 1. The bond lengths and valence angles in the cation of **20** and in the molecule of crystallosolvated ethanol are given in Tables 2 and 3.

An X-ray analysis revealed that the five-membered heterocyclic thiazolidine ring in the cation of **20** has a deformed twist conformation (modified [20] parameters of Cremer-Pople [23] are $\varphi_2 = 20.75°$ and $q_2 = 0.334$ Å), while this ring in the molecules investigated by us previously, 3-bromomethyl-2,3-dihydro-5,7-dimethyl-8-cyanothiazol[3,2-a]pyridine perchlorate, **21** [24], 4-iodo-6,8-dimethyl-9-cyano-1,2,3,4,4a,10a-hexahydrobenzothiazolo[3,2-a]pyridine triiodide **22** [25], and 4-bromo-6,8-dimethyl-9-cyano-1,2,3,4,4a,10a-hexahydrobenzothiazolo-[3,2-a]pyridine tetracyanopropenide **23** [26], adopts the almost ideal twist conformation in each case. The considerable conformational deformation of this



10c 19 20

SCHEME 8

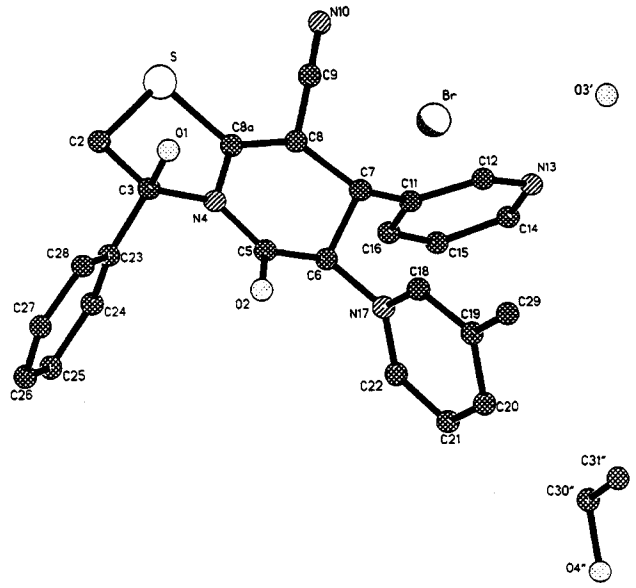


FIGURE 1 The general view of the molecule of **20** with atom numbering.

TABLE 3 Bond Angles in the Cation of **20** and with a Crystallosolvated Molecule of Ethanol

Angle		*Angle*	
C2S1C8a	92.5(5)	C6C7C8	105.7(7)
C3N4C5	123.0(7)	C6C7C11	111.1(9)
C3N4C8a	114.6(8)	C8C7C11	113.5(6)
C5N4C8a	120.3(7)	C7C8C8a	124.0(8)
C12N13C14	115(0)	C7C8C9	117.9(8)
C6N17C18	119.0(9)	C8aC8C9	116.9(9)
C6N17C22	118.5(8)	S1C8aN4	111.2(6)
C18N17C22	122.3(8)	S1C8aC8	127.1(8)
S1C2C3	106.3(7)	N4C8aC8	121.7(9)
O1C3N4	109.8(9)	N10C9C8	179.2(9)
O1C3C2	107(1)	C7C11C12	122(1)
N4C3C2	104.6(7)	C7C11C16	124(1)
O1C3C23	113.4(7)	C12C11C16	115(1)
N4C3C23	112(1)	N13C12C11	128(2)
C2C3C23	109.4(9)	N13C14C15	126(1)
O2C5N4	122.8(8)	C14C15C16	115(1)
O2C5C6	121.1(9)	C11C16C15	122(1)
N4C5C6	116.1(7)	N17C18C19	122(1)
N17C6C5	109.9(6)	C18C19C20	115(1)
N17C6C7	110.3(7)	C18C19C29	121(1)
C5C6C7	114.3(9)	C20C19C29	123(1)
C19C20C21	122(1)	C23C24C25	121.7(9)
C20C21C22	121(1)	C24C25C26	117(1)
N17C22C21	117(1)	C27C26C25	121(1)
C3C23C24	121.6(8)	C26C27C28	121.2(9)
C3C23C28	119(1)	C23C28C27	119(1)
C24C23C28	119(1)	O4C30C31	98(4)

TABLE 4 Short Nonbonding Contacts in the Cation of **20***

Distance		*Distance*	
S1. . .O1	3.21(1)	N4. . .C24	2.97(1)
S1. . .C9	3.02(1)	N17. . .C11	3.01(1)
O1. . .C5	3.11(1)	C2. . .C24	3.10(1)
O1. . .C8a	3.10(1)	C5. . .C18	2.94(1)
O1. . .C28	2.77(1)	C5. . .C24	3.30(1)
O2. . .N17	2.69(1)	C6. . .C16	3.06(1)
O2. . .C3	2.84(1)	C7. . .C18	3.04(1)
O2. . .C18	2.87(1)	C8. . .C16	3.17(1)
O2. . .C23	2.84(1)	C9. . .C11	2.96(1)

*The sum of Van der Wals radii between atoms: S and O, 3.32 Å, S and C, 3.50 Å, O and C, 3.22 Å, O and N, 3.07 Å, N and C, 3.25 Å; C and C, 3.40 Å (27).

ring in **20** is undoubtedly caused by the presence of short intermolecular nonbonding contacts (Table 4) which have an influence on the geometry of the cation as a whole.

The six-membered tetrahydropyridine ring has, in the crystal, a distorted-envelope conformation (modified [22] parameters being $\varphi_2 = 11.79°$ and $q_2 = 0.309$ Å). It should be noted that the best plane (0.004 Å) in this heterocyclic ring is formed by the C^5, N^4, C^{8a}, and C^8 atoms from which the C^6 and C^7 atoms are deflected by 0.47 and −0.118 Å, respectively. The pyridyl, 3-methylpyridinium, and phenyl substituents form with this plane the angles of 94.8, 94.3, and 101.0°, respectively. The torsional angle $H^7C^7C^6H^6 = 169.5°$ shows the trans arrangement of the hydrogens H^7 and H^6. Two heterocyclic substituents, i.e., pyridyl and 3-methylpyridinium, are cis-situated (torsional angle $C^{11}C^7C^6N^{17} = 66.5°$) and their planes form the dihedral angle of 67.5°.

Although the relatively low accuracy of the X-ray structural determination does not allow us to analyze in detail characteristic features of the geometry of the cation **20**, some bond lengths and angles differ distinctly from the standard values and deserve short comments. Thus, the C^{8a}–S^1 bond length of 1.72 Å is shorter than that of the standard C_{sp^2}-S distance that is equal to 1.751 Å [28]. It is, however, very close to the values of the corresponding C–S bond distances in the compounds **21**, **22**, and **23** mentioned above [1.737(6), 1.736(3), and 1.733(3) Å, respectively]. In the solid state, the cations **20** are connected with water molecules by hydrogen bonds [O^1–$H^1 \cdots O^3$ (X = 0.5, Y = 0.5, Z), $O^1 \cdots O^3$, 280(1), O^1–H^1, 0.85 and $H^1 \cdots O^3$, 2.00(5) Å, O^1–$H^1 \cdots O^3$ angle, 158(5)°]. Unfortunately, it was not possible to localize the hydrogen atoms of water and ethyl alcohol. Nevertheless, analysis of intermolecular distances indicates that there is an intermolecular contact between N^3 and O^3 of 3.07(1) Å, (X, 1 − Y, Z +0.5) which most probably corresponds to a hydrogen bond between the pyridine nitrogen atom and water.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Brucker WM-250 MHz instrument with DMSO-d_6 as a solvent and chemical shifts were referenced on the δ scale with respect to internal tetramethylsilane. A Specord M-80 instrument was used to record infrared spectra taken in KBr; absorptions are reported in cm^{-1}.

Substituted 3,4-Trans-1,2,3,4-tetrahydropyridines (**4a–d**)

Method A. A mixture of 5 mmoles of **1a,b** and 5 mmoles of **3a,b** dissolved in 10 mL of ethyl alcohol was boiled, and then 5 mmol of triethylamine was added with stirring. The reaction mixture was filtered and left to stand for 12 hours at 20°C. The precipitated solid was filtered off and the crystals washed with water, ethyl alcohol, and n-hexane. The product was recrystallized from ethyl alcohol.

Method B. To a mixture of 5 mmoles of compounds **1a,b** and 5 mmoles of **5a,b** dissolved in 10 mL of ethyl alcohol, 5 mmol of triethylamine was added under reflux. Then, the reaction mixture was worked up as above.

Method C. A mixture of 5 mmoles of **1a,b**, 5 mmoles of pyridinium aldehydes **6a,b**, and 5 mmoles of cyanoacetamide **7** dissolved in 10 mL of ethyl alcohol was boiled. Then, 5 mmoles of triethylamine was added. The reaction mixture was stirred for 2 hours at 20°C. The solid phase was filtered off and washed with water, ethyl alcohol, and n-hexane.

Method D. Tetrahydropyridines were prepared from equimolar amounts of the compounds **1c,d**, **6a,b**, and **8** according to method C.

5-Cyano-2-oxo-3-(1-pyridinio)-4-(3-pyridyl)-1,2,3,4,-tetrahydropyridine-6-olate (**4a**)

See Table 1. IR: 1662 (NH), 1680 (C=O), 2168 (C≡N), 3072, 3184 (NH); ^{1}H NMR: 4.55 (d, 1H, 4-H, ^3J = 12.1 Hz), 6.08 (d, 1H, 3-H, ^3J = 12.1 Hz), 7.28 (t, 3H, 5-$H_{pyridine}$, ^3J = 7.8 Hz, ^3J = 5.0 Hz), 7.65 (d, 1H, 4-$H_{pyridine}$, ^3J = 7.8 Hz), 8.06 (t, 2H, 3,5-$H_{pyridinio}$), 8.38 (d, 1H, 6-$H_{pyridine}$), 8.47 (t, 1H, 4-$H_{pyridinio}$, ^3J = 8.2 Hz), 8.90* (s, 1H, 2-$H_{pyridine}$), 8.90* (d, 2H, 2,6-$H_{pyridinio}$, ^3J = 6.2 Hz), 9.89 (s, 1H, NH).

5-Cyano-2-oxo-3-(1-pyridinio)-4-(4-pyridyl)-1,2,3,4-tetrahydropyridine-6-olate (**4b**)

See Table 1. IR: 1664 (NH), 1696 (C=O), 2168 (C≡N), 3064, 3112 (NH); ^{1}H NMR: 4.56 (d, 1H, 4-H, ^3J = 12.8 Hz), 6.19 (d, 1H, 3-H, ^3J = 12.8 Hz), 7.16 (d, 2H, 3,5-$H_{pyridine}$, ^3J = 5,9 Hz), 8.08 (t, 2H, 3.5-$H_{pyridinio}$) 8.19 (d, 2H, 2,6-$H_{pyridine}$), 8.56 (t, 1H, 4-$H_{pyridinio}$, ^3J = 8.1 Hz), 8.90 (d, 2H, 2,6-$H_{pyridinio}$, ^3J = 5.9 Hz), 9.97 (s, 1H, NH).

5-Cyano-3-(3-methyl-1-pyridinio)-2-oxo-4-(3-pyridyl)-1,2,3,4-tetrahydropyridine-6-olate (**4c**)

See Table 1. IR: 1648 (NH), 1698 (C=O), 2164 (C≡N), 3058, 3117 (NH); ^{1}H NMR: 2.40 (s, 3H, CH_3), 4.40 (d, 1H, 4-H, ^3J = 12.7 Hz), 5.96 (d, 1H, 3-H, ^3J = 12.7 Hz), 7.30 (t, 1H, 5-$H_{pyridine}$, ^3J = 7.9 Hz, ^3J = 5.2 Hz), 7.62 (d, 1H, 4-$H_{pyridine}$, ^3J = 7.9 Hz), 7.92 (t, 1H, 5-$H_{pyridinio}$), 8.30 (d, 1H, 2-$H_{pyridine}$), 8.40 (d, 1H, 4-$H_{pyridinio}$, ^3J = 8.6 Hz), 8.57* (d, 1H, 6-$H_{pyridinio}$, ^3J = 6.2 Hz), 8.57* (s, 1H, 2-$H_{pyridine}$), 8.78 (s, 1H, 2-$H_{pyridinio}$), 9.94 (s, 1H, NH).

5-Cyano-3-(3-methyl-1-pyridinio)-2-oxo-4-(4-pyridyl)-1,2,3,4-tetrahydropyridine-6-olate (**4d**)

See Table 1. IR: 1652 (NH), 1704 (C=O), 2168 (C≡N), 3064, 3128 (NH); ^{1}H NMR: 2.42 (s, 3H, CH_3), 4.56 (d, 1H, 4-H, ^3J = 13.0 Hz), 6.00 (d, 1H, 3-H, ^3J = 13.0 Hz), 7.17 (d, 2H, 3,5-$H_{pyridine}$, ^3J = 5.9 Hz), 7.94 (t, 1H, 5-$H_{pyridinio}$), 8.40* (d, 1H, 4-$H_{pyridinio}$, ^3J = 8.8 Hz), 8.40* (d, 2H, 2,6-$H_{pyridine}$), 8.56 (d, 1H, 6-$H_{pyridinio}$, ^3J = 6.3 Hz), 8.90 (s, 1H, 2-$H_{pyridinio}$), 9.97 (s, 1H, NH).

Substituted 3,4-trans-1,2,3,4-tetrahydropyridines (**10a-d**)

Method A. A mixture of 5 mmoles of **1c,d** and 5 mmoles of **9a,b** in 10 mL of ethyl alcohol was boiled, and 5 mmoles of triethylamine was added. Then, the reaction mixture was stirred for 2 hours at 20°C. After filtration, the residue was washed with water, ethyl alcohol, and n-hexane. The product was recrystallized from ethyl alcohol.

Method B. To a mixture of 5 mmoles of **1c,d**, 5 mmoles of compound **6a,b**, and 5 mmoles of cyanothioacetamide **11** in 10 mL of ethyl alcohol as a solvent, 5 mmoles of triethylamine was added with heating. Stirring was continued for 2 hours at 20°C. Then, the reaction mixture was worked up as in method A.

5-Cyano-2-oxo-3-(1-pyridinio)-4-(3-pyridyl)-1,2,3,4-tetrahydropyridine-6-thiolate (**10a**)

See Table 1. IR: 1652 (NH), 1690 (C=O), 2182 (C≡N), 3056, 3218 (NH); ^{1}H NMR: 4.70 (d, 1H, 4-H, ^3J = 13.4 Hz), 6.32 (d, 1H, 3-H, ^3J = 13.4 Hz), 7.30 (t, 1H, 5-$H_{pyridine}$, ^3J = 7.9 Hz, ^3J = 5.2 Hz), 7.60 (d, 1H, 4-$H_{pyridine}$, ^3J = 7.9 Hz), 8.10 (t, 2H, 3,5-$H_{pyridinio}$), 8.32 (d, 1H, 6-$H_{pyridine}$), 8.54 (t, 1H, 4-$H_{pyridinio}$, ^3J = 8.57 Hz), 8.90 (d, 2.6-$H_{pyridinio}$, ^3J = 6.1 Hz), 8.94 (s, 1H, 2-$H_{pyridine}$), 10.30 (s, 1H, NH).

5-Cyano-2-oxo-3-(1-pyridinio)-4-(4-pyridyl)-1,2,3,4-tetrahydropyridine-6-thiolate (**10b**)

See Table 1. IR: 1656 (NH), 1692 (C=O), 2184 (C≡N), 3048, 3224 (NH); ^{1}H NMR: 4.72 (d, 1H, 4-H, ^3J = 13.5 Hz), 6.34 (d, 1H, 3-H, ^3J = 13.5 Hz), 7.24 (d, 2H, 3,5-$H_{pyridine}$, ^3J = 5.9 Hz), 8.11 (t, 2H, 3,5-$H_{pyridinio}$), 8.46 (d, 2H, 2,6-$H_{pyridine}$), 8.58 (t, 1H, 4-$H_{pyridinio}$, ^3J = 8.7 Hz), 10.31 (s, 1H, NH).

5-Cyano-3-(3-methyl-1-pyridinio)-2-oxo-4-(3-pyridyl)-1,2,3,4-tetrahydropyridine-6-thiolate (**10c**)

See Table 1. IR: 1648 (NH), 1692 (C=O), 2184 (C≡N), 3032, 3200 (NH); ^{1}H NMR: 2.40 (s, 3H, CH_3), 4.70 (d, 1H, 4-H, ^3J = 14.0 Hz), 6.22 (d, 1H, 3-H, ^3J = 14.0 Hz), 7.31 (t, 1H, 5-$H_{pyridine}$, ^3J = 8.3 Hz, ^3J = 4.9 Hz), 7.70 (d, 1H, 4-$H_{pyridine}$, ^3J = 8.3 Hz), 7.96 (t, 1H, 5-$H_{pyridinio}$), 8.26 (d, 1H, 6-$H_{pyridine}$), 8.38 (d, 1H, 4-$H_{pyridinio}$, ^3J = 8.3 Hz), 8.42 (s, 1H, 2-$H_{pyridine}$), 8.68 (d, 1H, 6-$H_{pyridinio}$, ^3J = 6.2 Hz), 8.92 (s, 1H, 2-$H_{pyridinio}$), 10.28 (s, 1H, NH).

5-Cyano-3-(3-methyl-1-pyridinio)-2-oxo-4-(4-pyridyl)-1,2,3,4-tetrahydropyridine-6-thiolate (**10d**)

See Table 1. IR: 1652 (NH), 1700 (C=O), 2184 (C≡N), 3032, 3200 (NH); ^{1}H NMR: 2.38 (s, 3H, CH_3), 4.68 (d, 1H, 4-H, ^3J = 13.8 Hz), 6.25 (d, 1H, 3-H, ^3J = 13.8 Hz), 7.20 (d, 2H, 3,5-$H_{pyridine}$, ^3J = 5.8 Hz), 7.93 (t, 1H, 5-$H_{pyridinio}$), 8.38 (d, 1H, 4-$H_{pyridinio}$, ^3J = 8.5 Hz), 8.42 (d, 2H, 2,6-$H_{pyridine}$), 8.67 (d, 1H, 6-$H_{pyridinio}$, ^3J = 6.5 Hz), 8.90 (s, 1H, 2-$H_{pyridinio}$), 10.30 (s, 1H, NH).

Substituted 3,4-Trans 1,2,3,4-tetrahydropyridines (**12a,b**)

A mixture of 5 mmoles of **2d** and 5 mmoles of **9a,b** in 10 mL of ethyl alcohol was boiled, and 5 mmoles of triethylamine was added. After stirring for 3 hours at room temperature, the precipitate was filtered off and washed with water, ethyl alcohol, and n-hexane. The product was recrystallized from ethyl alcohol.

5-Cyano-3-(1-pyridinio)-4-(3-pyridyl)-2-thio-1,2,3,4-tetrahydropyridine-6-thiolate (**12a**)

See Table 1. IR: 1628 (NH), 1204 (C=S), 2180 (C≡N), 3047, 3308 (NH); ^{1}H NMR: 4.74 (d, 1H, 4-H, ^3J = 13.4 Hz), 6.49 (d, 1H, 3-H, ^3J = 13.4 Hz), 7.31 (t, 1H, 5-$H_{pyridine}$, ^3J = 7.9 Hz, ^3J = 4.9 Hz), 7.47 (d, 1H, 4-$H_{pyridine}$, ^3J = 7.9 Hz), 8.08 (t, 2H, 3,5-$H_{pyridinio}$), 8.38 (d, 1H, 2-$H_{pyridine}$), 8.52 (t, 1H, 4-$H_{pyridinio}$, ^3J = 8.3 Hz), 8.90 (s, 1H, 2-$H_{pyridine}$), 11.93 (s, 1H, NH).

5-Cyano-3-(1-pyridinio)-4-(4-pyridyl)-2-thio-1,2,3,4-tetrahydropyridine-6-thiolate (**12b**)

See Table 1. IR: 1628 (NH), 1212 (C=S), 2184 (C≡N), 3040 (NH); by ^{1}H NMR: 4.73 (d, 1H, 4-H, ^3J = 13.2 Hz), 6.50 (d, 1H, 3-H, ^3J = 13.2 Hz), 7.22 (d, 2H, 3,5-$H_{pyridine}$, ^3J = 5.9 Hz), 8.10 (t, 2H, 3,5-$H_{pyridinio}$), 8.43* (t, 1H, 4-$H_{pyridinio}$, ^3J = 8.2 Hz), 8.43* (d, 2H, 2,6-$H_{pyridine}$), 8.95 (d, 2H, 2,6-$H_{pyridinio}$, ^3J = 5.8 Hz), 11.94 (s, 1H, NH).

3-(1-Pyridino)-1-thioamides-1-cyanopzop-1-en-2-thiolate (**13**) $C_{10}H_9N_3S_2$

A mixture of the salt **2d** (10 mmoles), cyanothioacetamide **11** (10 mmoles), and 4-methylmorpholine (10 mmoles) in 20 mL of ethyl alcohol was allowed to boil, and the solid was quickly filtered off through the paper filter. The reaction mixture was kept for 5 hours at 25°C, and the residue was filtered off and washed with ethyl alcohol and n-hexane giving 1.67 g (71% yield) of the compound **13**. Mp =187–189°C. IR: 1634 ($CSNH_2$), 2134 (C≡N), 3170, 3242 (NH_2); ^{1}H NMR: 5.78 (s, 2H, CH_2); 8.11 (t, 2H, 3,5, H-pyridinio); 8.61 (t, 1H, 4-H pyridinio); 8.88 d (2H, 2,6-H pyridinio); 9.17 broad (s, 1H, NH); 10.05 broad (s, 1H, NH).

Substituted 6,7-Trans-thiazolo[3,2-a]pyridine (**20**)

A mixture of 5 mmoles of compound **10c** and 5 mmoles of phenacyl bromide in ethyl alcohol as a solvent was allowed to boil. After 8 hours, the precipitate was filtered off, washed with ethyl alcohol and n-hexane, and recrystallized from ethyl alcohol.

X-ray Structure Determination of **20**

The salt **20**, $[C_{25}H_{21}N_4O_2S]^+Br^-$ crystallized with water and ethanol molecules in a monoclinic system, space group C_c, a = 19.626(2), b = 11.093(3), c = 14.470(4) Å, β = 117.31(2)°, V = 2.7991(2.3) Å^3, d_{calc} = 1.396 g/cm^3, Z = 4. The crystal lattice parameters and intensities of 2536 independent reflections were collected at 20° on a Siemens P3/PC diffractometer (MoK_α radiation, λ = 0.71073 Å, graphite monochromator, $\Theta/2\Theta$ scan mode to Θ_{max} = 26°). The structure was solved by direct method and refined by full-matrix least squares. Nonhydrogen atoms were refined anisotropically using 2013 reflections with $I \geq 3\sigma$ according to the SHELXTL program. All hydrogen atoms were included in the final refinement with the fixed positional and thermal parameters. The final R factors were R = 0.055 and R_ω = 0.055.

All calculations were performed using the SHELXTL PLUS program (PC version). Table 5 lists the atom coordinates.

TABLE 5 Atom Coordinates ($\times 10^4$) of the sale of **20** with Crystallosolvated Molecules of Ethanol and Water

Atom	*X*	*Y*	*Z*
Br	4394	1090(1)	3170
S1	5197(2)	−2673(3)	5392(3)
O1	3550(4)	−2002(7)	3519(6)
O2	3092(4)	73(7)	4692(6)
N4	4118(4)	−1191(7)	5210(6)
N10	6810(5)	−594(9)	6500(8)
N13	6464(6)	3425(11)	7544(11)
N17	3907(4)	1957(6)	5836(6)
C2	4225(6)	−3281(10)	4939(11)
C3	3683(6)	−2215(9)	4534(8)
C5	3786(5)	−130(9)	5239(7)
C6	4306(5)	793(8)	6016(7)
C7	5088(5)	953(8)	6023(7)
C8	5381(5)	−319(8)	6016(7)
C8a	4928(5)	−1267(8)	5601(8)
C9	6177(5)	−464(9)	6288(8)
C11	5626(5)	1697(9)	6943(8)
C12	5984(7)	2709(11)	6819(11)
C14	6589(7)	3150(14)	8474(13)
C15	6293(7)	2159(15)	8756(10)
C16	5801(5)	1435(11)	7932(8)
C18	3662(5)	2494(8)	4907(7)
C19	3268(5)	3566(9)	4676(8)
C20	3106(5)	4031(11)	5468(10)
C21	3349(6)	3467(12)	6396(10)
C22	3752(6)	2412(11)	6600(8)
C23	2959(5)	−2483(9)	4627(8)
C24	2966(6)	−2579(10)	5570(8)
C25	2312(7)	−2900(11)	5660(10)
C26	1639(6)	−3164(12)	4730(10)
C27	1628(6)	−3094(11)	3802(10)
C28	2275(6)	−2746(11)	3710(8)
C29	2985(6)	4120(11)	3652(9)
O3*	7608(6)	4878(11)	2309(8)
O4**	4803(17)	6008(24)	9006(25)
C30**	5286(19)	5427(31)	8733(46)
C31**	4917(39)	5880(58)	7545(37)

*Atom of a water molecule.
**Atom of an ethanol molecule.

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