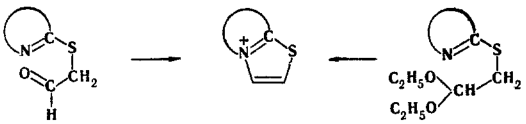
SYNTHESIS AND REACTIONS OF SOME DERIVATIVES OF 1,2-DIHYDROTHIAZOLO[3,2-*a*]PYRIDINIUM SALTS

E. D. Sych, V. N. Bubnovskaya,
L. T. Gorb, and M. Yu. Kornilov

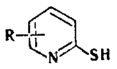
UDC 547.789.6'821.07:542.953

The condensation of 2-mercaptopyridine, 2-mercapto-4-methylpyridine, and 2-mercapto-6-methylpyridine with α-bromoacetaldehyde and its diethyl acetal has given cyclic products (3-hydroxy- and 3-ethoxy-2,3-thiazolo[3,2-*a*]pyridinium salts), from which cyanine dyes have been synthesized.

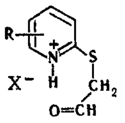
The reaction of 2-mercapto derivatives of pyridine and some other nitrogen heterocycles with α-bromoacetaldehyde and its acetals in the presence of bases has been described previously [1-4]. In the pyridine series, the intermediate products obtained in this reaction have not been investigated or converted further under the action of acids into unreduced thiazolo[3,2-*a*]pyridinium derivatives:



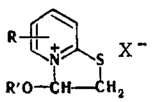
We have performed the reaction of 2-mercaptopyridine, 2-mercapto-4-methylpyridine, and 2-mercapto-6-methylpyridine (I, R = H or CH_3) with α-bromoacetaldehyde in the absence of bases and have isolated the addition product. This reaction could give an open-chain compound (II) or, in the case of subsequent ring closure, a dihydrothiazolo[3,2-*a*]pyridinium salt (III, R' = H), or an equilibrium mixture of the two forms. The IR spectra of the compounds that we obtained lacked the $\nu_{C=O}$ band, and their PMR spectra lacked the signals of aldehyde protons, which excluded structure (II). Also in favor of the structure of the quaternary salt (III, R' = H) was the increased capacity of the methyl groups in the pyridine ring for condensation reactions. The possibility of the formation of such a heterocyclic system has been discussed previously [2], but no proofs were given.



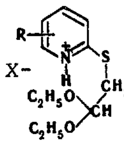
I



II



III



IV

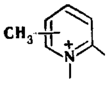
($X^- = Br^-, ClO_4^-$)

Similarly, in the reaction of (I) with α-bromoacetaldehyde diethyl acetal, the compound (IV) formed initially could, according to Bradsher and Lehr's hypothesis [1], give (II) with the splitting out of both ethoxy groups and then be converted into (III, R' = H). If only one ethoxy group were split out from (IV), subsequent ring closure could give the 3-ethoxydihydrothiazolo[3,2-*a*]pyridinium salt (III, R' = C_2H_5). A functional analysis and the PMR spectra of the condensation products showed the presence of one ethoxy group, i.e., the formation of structure (III, R' = C_2H_5). The shift of the signal of the 3-H methine proton into a relatively weak field (about 6 ppm) showed that this proton was adjacent to the positive center. In dihydrothiazolo[3,2-*a*]pyrimidinium derivatives of this structure the signals of the proton of the methine

---

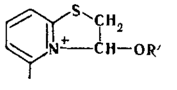
Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. T. G. Shevchenko Kiev State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1254-1257, September, 1973. Original article submitted July 17, 1972.

TABLE 1. Features of the UV and PMR Spectra of the 2,3-Dihydrothiazolo[3,2-*a*]pyridinium Salts (III, R' = C_2H_5)*

R	λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)	Chemical shifts, ppm (J, Hz)								
		CH_3—CH_2	CH_3—CH_2		2-CH_2	3-CH	5-H	6-H	7-H	8-H
5-CH_3	245 (0,71), 317 (0,77)	1,35 t (7,0)	3,92 m	2,95 s	5,26 d	6,02 q (3,0; 5,0)	—	7,56 d (8,0)	8,17 t	7,77 d (8,0)
7-CH_3	240 (0,78), 310 (0,80)	1,35 t (7,0)	3,91 m	2,73 s	5,25 d	5,98 q (1,0; 4,0)	8,39 d (1,5)	7,55 q	—	7,75 d (7,0)
H	245 (0,81), 314 (0,69)	1,36 t (7,0)	3,95 m	—	5,38 d	6,03 t (2,5)	8,75 d (7,0)	7,72 m	8,29 m	7,97 d (7,0)

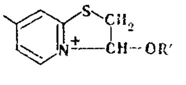
*The UV spectra were taken in ethanol on an SF-4 spectrophotometer. The PMR spectra were taken on a ZKR-60 spectrometer with a working frequency of 60 MHz in trifluoroacetic acid at 25°C using 0.2 M solutions with TMS as internal standard. Abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

TABLE 2. Properties of the Styryls and Monomethinecyanines. Symbols for the Radicals:



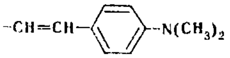
A

R' = C_2H_5

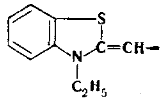


B

R' = H



C



D

Comp.	Abbrev. formula of dye	mp, °C	Empirical formula	Found, %				Calc., %				λ max, nm (ε · 10^{-4}) in methanol	Yield, %
				S	N	OC_2H_5	Cl	S	N	OC_2H_5	Cl		
VII	Aa—C	Above 300	$C_{19}H_{23}ClN_2O_5S$	7,6		10,3		7,5		10,6		480 (3,00)	33
VIII	Ab—C*	203	$C_{17}H_{19}BrN_2OS$		7,2				7,4			509 (1,88)	22
IX	Ba—C	159—160	$C_{19}H_{23}ClN_2O_5S$	7,5		10,2		7,5		10,6		490 (1,59)	26
X	Bb—C	162	$C_{17}H_{19}ClN_2O_5S$		6,9				7,0			510 (3,44)	20
XI	Aa—D*	218	$C_{19}H_{21}BrN_2OS_2$	14,8		10,7		14,7		10,3		458 (4,24)	30
XII	Ba—D	220—221	$C_{19}H_{21}ClN_2O_5S_2$	14,3			8,0	14,0			7,8	455 (6,88)	29

*These dyes were obtained in the form of bromides and the others in the form of perchlorates.

group attached to the quaternary nitrogen atom and to the ethoxy group are also found at 5.85-6.2 ppm [4]. A characteristic feature of all the salts (III, R' = C_2H_5) is the complex form of the signal of the methylene protons of the ethyl group. In the asymmetric cations of these salts the protons mentioned are diastereotopic, and their chemical shifts differ considerably (by approximately 0.18 ppm). Because of this, the observed spectrum of the CH_2 group corresponds to the AB part of an ABX_3 spin system. The methyl protons of the ethyl groups give triplets with J = 7.0 Hz. The protons of the methylene groups of the thiazoline ring are also diastereotopic, but their chemical shifts differ far less than in the preceding case; the corresponding PMR signals are weakly resolved doublets.

Both 3-hydroxy- and 3-ethoxy-2,3-dihydrothiazolo[3,2-a]pyridinium salts with methyl groups in the pyridine nucleus are readily converted into cyanine dyes, which is possible only if a quaternary nitrogen atom is present.

A mechanism for the cyclization of compounds of type (II) has been proposed [2] which consists in the addition of a proton to the carbonyl oxygen and subsequent attack from the direction of the nitrogen atom on the carbonyl carbon. This mechanism can also be extended to the reaction of (I) with α-bromoacetaldehyde diethyl acetal.

3-Hydroxy- and 3-ethoxy-2,3-dihydrothiazolo[3,2-a]pyridinium salts (III) differ widely in stability, in spite of the similarity of their structures. The 3-hydroxy derivatives are unstable on storage and in alcoholic solutions, especially in the presence of basic agents, and therefore the base-catalyzed preparation of dyes from them is rather difficult. The dyes obtained from the 3-hydroxy-2,3-dihydrothiazolo[3,2-a]-

pyridinium salts are also unstable. We connect this feature of the 3-hydroxy derivatives with the ease of opening of the thiazoline ring, which apparently takes place via a betaine structure.

Table 1 gives the features of the UV and PMR spectra of the 2,3-dihydrothiazolo[3,2-*a*]pyridinium salts studied, and Table 2 gives information on the styryls and monomethinecyanines obtained from them. It may be mentioned that the styryls with a 3-ethoxy group in the thiazoline nucleus are more highly colored than their analogs with a hydroxy group.

EXPERIMENTAL

2-Mercapto-6-methylpyridine (I, R = 6-CH_3). A mixture of 1.1 g (0.01 mole) of 2-hydroxy-6-methylpyridine and 1.1 g of phosphorus pentasulfide was fused at 160°C for 2 h. The melt was ground and treated with a solution of sodium carbonate until the reaction was neutral. The residue was filtered off and the solution was extracted with chloroform, and the solvent was distilled off. This gave 0.8 g (64%) of product with mp 149-150°C (from ethanol). Found, %: N 11.2; S 25.9. C_6H_7NS. Calculated, %: N 11.2; S 25.6.

3-Ethoxy-5-methyl-2,3-dihydrothiazolo[3,2-*a*]pyridinium Perchlorate (III, R = 5-CH_3, R' = C_2H_5, X^- = ClO_4^-). To a solution of 0.6 g (0.005 mole) of 2-mercapto-6-methylpyridine in 15 ml of dry acetone was added 0.9 g (0.005 mole) of α-bromoacetaldehyde diethyl acetal, after which the mixture was boiled for 9 h. The precipitate (0.55 g) was dissolved in the minimum amount of water and the solution was treated with 0.24 g of sodium perchlorate. After repeated crystallization from propanol, the yield of product was 0.3 g (21%), mp 134°C. Found, %: Cl 12.2; S 10.8. $C_{10}H_{14}ClNO_5S$. Calculated, %: Cl 12.0; S 10.8.

3-Ethoxy-7-methyl-2,3-dihydrothiazolo[3,2-*a*]pyridinium perchlorate (III, R = 7-CH_3, R' = C_2H_5, X^- = ClO_4^-) was obtained similarly from 2-mercapto-4-methylpyridine [6] with more prolonged heating. By precipitation with ether from the reaction mixture and then reprecipitation from solution in isopropanol, 1.5 g of 3-ethoxy-7-methyl-2,3-dihydrothiazolo[3,2-*a*]pyridinium bromide was obtained. It was dissolved in ethanol and the solution was treated with sodium perchlorate. The yield of desired product was 1.03 g (36%), mp 73-74°C. Found, %: Cl 12.0; S 11.0; OC_2H_5 15.3. $C_{10}H_{14}ClNO_5S$. Calculated, %: Cl 12.0; S 10.8; OC_2H_5 15.2.

3-Ethoxy-2,3-dihydrothiazolo[3,2-*a*]pyridinium perchlorate (III, R = H, R' = C_2H_5, X^- = ClO_4^-) was obtained in a similar manner to the preceding compound from 2-mercaptopyridine. Yield 30%, mp 124-125°C (from ethanol). Found, %: C 38.2; H 4.2; Cl 12.9; S 11.8; OC_2H_5 16.2. $C_9H_{12}ClNO_5S$. Calculated, %: C 38.4; H 4.3; Cl 12.6; S 11.4; OC_2H_5 16.0.

3-Hydroxy-5-methyl-2,3-thiazolo[3,2-*a*]pyridinium bromide (III, R = 5-CH_3, R' = H, X^- = Br^-) was obtained similarly from 2-mercapto-6-methylpyridine and freshly distilled α-bromoacetaldehyde. After the mixture had been boiled for 2 h, yield 60%; mp 180°C (from ethanol–isopropanol). Found, %: C 38.8; H 4.1; S 13.2. $C_8H_{10}BrNOS$. Calculated, %: C 38.7; H 4.1; S 12.9.

3-Hydroxy-7-methyl-2,3-dihydrothiazolo[3,2-*a*]pyridinium bromide (III, R = 7-CH_3, R' = H, X = Br) was obtained similarly from 2-mercapto-4-methylpyridine and α-bromoacetaldehyde. Yield 38%, mp 153-154°C (from isopropanol). Found, %: C 38.8; H 4.1; S 13.0. $C_8H_{10}BrNOS$. Calculated, %: C 38.7; H 4.1; S 12.9.

3-Hydroxy-2,3-dihydrothiazolo[3,2-*a*]pyridinium bromide (III, R = H, R' = H, X = Br) was obtained as in the preceding case from 2-mercaptopyridine and α-bromoacetaldehyde. Yield 42%, mp 124-126°C (from ethanol). Found, %: C 36.0; H 3.5; S 13.8. C_7H_8BrNOS. Calculated, %: C 35.9; H 3.4; S 13.7.

The styryls were obtained from the corresponding dihydrothiazolo[3,2-*a*]pyridinium salts by the method given below for 5-(p-dimethylaminostyryl)-3-ethoxy-2,3-dihydrothiazolo[3,2-*a*]pyridinium perchlorate (VIII). To a solution of 0.29 g (0.001 mole) of 3-ethoxy-5-methyl-2,3-dihydrothiazolo[3,2-*a*]pyridinium perchlorate in 1.5 ml of acetic anhydride was added 0.15 g (0.001 mole) of p-dimethylaminobenzaldehyde, and the mixture was heated to the boil for 1 h, giving 0.14 g of dye. It was purified by crystallization from ethanol. For some styryls, purification by chromatography of solutions on alumina was used. The yields and other information are given in Table 2.

Monomethinecyanines. 3-Ethoxy-5-(3-ethylbenzothiazolin-2-ylidenemethylene)-2,3-dihydrothiazolo-[3,2-*a*]pyridinium Bromide (XI) and 3-Ethoxy-7-(3-ethylbenzothiazolin-2-ylidenemethylene)-2,3-dihydrothiazolo[3,2-*a*]pyridinium Perchlorate (XII). To a solution of 0.001 mole of 3-ethoxy-5-methyl-2,3-dihydrothiazolo[3,2-*a*]pyridinium bromide or the corresponding 7-methyl derivative in 1 ml of absolute ethanol were added 0.001 mole of the ethyl tosylate derivative of 2-methylthiobenzothiazole and 0.001 mole of triethylamine, and the mixture was boiled for 45 min. If precipitation did not occur spontaneously, it was brought about by the addition of ether. The dye (XII) was isolated in the form of the perchlorate. The yields and other information are given in Table 2.

LITERATURE CITED

1. C. R. Bradsher and D. F. Lehr, J. Heterocyclic Chem., 27 (1966).
2. K. Undheim and K. R. Reistad, Acta Chem. Scand., 24, 2956 (1970).
3. P. M. Kochergin and M. N. Shchukina, Zh. Obshch. Khim., 26, 458 (1956).
4. G. Borman and F. Troxer, Helv. Chim. Acta, 54, 1687 (1971).
5. F. S. Babichev and V. N. Bubnovskaya, Ukr. Khim. Zh., 30, 848 (1964).
6. J. R. Thirtle, J. Amer. Chem. Soc., 68, 342 (1946).