MESOIONIC COMPOUNDS WITH A BRIDGED NITROGEN ATOM.

17.* THIAZOLO[3,2-c]QUINAZOLINIUM 3-OXIDES

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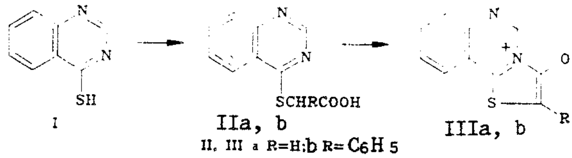
The cyclization of (4-quinazolinylthio)phenylacetic and acetic acids gives extremely reactive thiazolo[3,2-c]quinazolinium 3-oxides, which, depending on the structure of the mesoionic ring, react with either electrophilic or nucleophilic reagents.

Mesoionic heterocyclic compounds that display high and specific reactivities have recently attracted the constantly increasing attention of researchers [2]. Thus, for example, it has been shown that (2-pyrimidinylthio)acetic acids, depending on the conditions under which the cyclization is carried out, readily form diverse thiazolo[3,2-*a*] pyrimidinium 3-oxide derivatives that can be used to obtain new types of polymethine dyes [5].

In order to investigate the dependence of the colors and reactivities of mesoionic condensed heterocyclic compounds with a nodal nitrogen atom on their chemical structures it seemed of interest to synthesize new thiazoloazinium oxides and study their transformations.

In this connection we synthesized (4-quinazolinylthio)acetic acid (IIa) [7] and α-(4-quinazolinylthio)phenylacetic acid (IIb) from 4-mercaptoquinazoline (I) [6].



I IIa, b IIIa, b

II, III a R=H; b R=C_6H_5

It was found that, in contrast to unsubstituted derivative IIa [7], the action of acetic anhydride on phenyl-substituted acid IIb gives a rather stable substance, the structure of which is confirmed by the PMR spectral data. Thus the spectrum of IIIb does not contain the singlet of the aliphatic proton of the phenylacetic acid residue (5.63 ppm), while the signal of the proton of the methylidyne group in the 2 position of the quinazoline ring (8.73 ppm), because of the shielding effect of the electron pairs of the closely situated (as a result of cyclization) oxygen atom (the proton in the 5 position of the thiazoloquinazolinium ring), as in the spectra of other thiazoloazinium oxides [8], is shifted significantly (~1 ppm) to the weak-field region (9.70 ppm).

Like most mesoionic thiazoloazinium oxides, solutions of 2-phenylthiazolo[3,2-c]quinazolinium 3-oxide (IIIb) absorb in the visible part of the spectrum and display negative solvatochromism. For example, a decrease in the polarity of the solvent – transition from acetic acid to methanol, acetonitrile, benzene, and carbon tetrachloride – leads to deepening of the color: The maximum of the long-wave band undergoes a bathochromic shift (480, 500, 529, 562, and 572 nm, respectively).

The reaction of oxide IIIb with nucleophilic reagents proceeds unexpectedly – thiacarbocyanine V, which is identical to the compound described in [9] – is formed in its reaction with two equivalents of 2-methyl-3-ethylbenzothiazolium iodide (IV) in a medium consisting of acetic anhydride and triethylamine.

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*See [1] for Communication 16.

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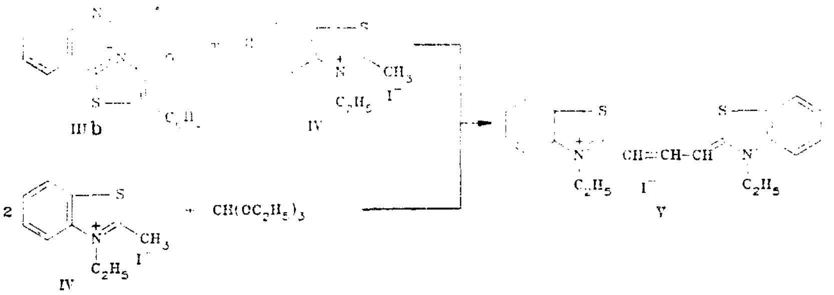
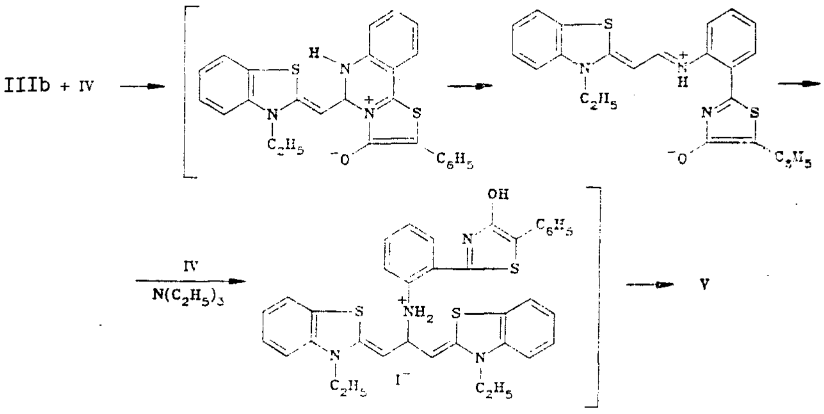
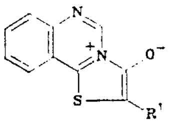


In analogy with the addition of heterocyclic C—H acids to the C═N bond of azomethines [10], one might assume that, in our case also, the reaction commences with the addition of salt IV to primarily the C═N bond of the quinazoline ring (the electrophilic center in the 5 position, see Fig. 1) with subsequent ring opening



The cyclization of acid IIa was accomplished previously; however, the structure of the substance isolated was not confirmed because of its extremely low stability [7]. On the basis of data from a study of the structures of the products of chemical transformations of thiazoloquinazolinium oxide IIIa we were able to establish its structure. It was found that the product of cyclization of (4-quinazolinylthio)acetic acid with acetic anhydride in pyridine, as in the case of 2-unsubstituted thiazolo[3,2-*a*]pyrimidinium 3-oxide [4], reacts readily with electrophilic reagents; for example, the corresponding derivatives VI-VIII are formed in the reaction with trifluoroacetic anhydride, 4-nitrobenzenediazonium tetrafluoroborate, and phenyl isothiocyanate.



VI-VIII

VI $R^1{=}COCF_3$; VII $R^1{=}N{=}NC_6H_4NO_2$-*p*; VIII $R^1{=}C({=}S)NHC_6H_5$

The structures of the synthesized compounds were proved by PMR spectral data and the results of elementary analysis. Thus the spectrum of a solution of 2-trifluoroacetyl-substituted oxide VI does not contain a signal of the protons of the methylene group of starting acid IIa (4.10 ppm), and only a multiplet of aromatic protons (7.4-8.2 ppm) and a singlet of a C—H proton in the 5 position at weaker field are observed; the chemical shifts of this signal (9.30 ppm) and 2-phenyl-substituted oxide IIIb are close.

Let us note that the introduction into the 2 position of oxide IIIa (absorption maximum 474 nm) of the electron-acceptor trifluoroacetyl group (VI) leads to a hypsochromic shift of the maximum of the long-wave absorption band (38 nm), while the advent of a phenyl (IIIb) and 4-nitrophenylazo group (VII) leads to bathochromic shifts of 55 and 84 nm. These groupings have a similar effect on the electronic spectra of compounds of the thiazolo[3,2-*a*]pyrimidinium 3-oxide series [4].

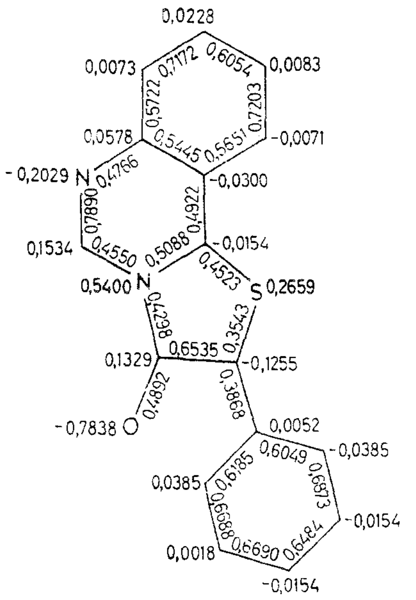


Fig. 1. π Electron-density distribution and bond orders in the ground state of the thiazolo[3,2-c]quinazolinium 3-oxide molecule calculated within the Pariser–Parr–Pople (PPP) approximation.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	λmax, nm (log ε) in CH_3CN	Yield, %
IIb	$C_{16}H_{12}N_2O_2S$	195...196		100
IIIb	$C_{16}H_{10}N_2OS$	271...273	529 (4,13)	72
VI	$C_{12}H_5F_3N_2O_2S$	253...254	436 (4,10)	66
VII	$C_{16}H_9N_5O_3S$	268...269	558 (4,50)	77
VIII	$C_{17}H_{11}N_3OS_2$	290...291	476 (4,24)	97
IX	$C_{23}H_{20}ClN_3O_5S$	271...273	580 (4,72)	29
X	$C_{21}H_{16}ClN_3O_6S$	200...201	540 (4,15)	85
XI	$C_{21}H_{16}ClN_3O_5S_2$	236...237	566 (4,78)	58
XII	$C_{19}H_{16}ClN_3O_5S$	283...284	611 (4,60)	92

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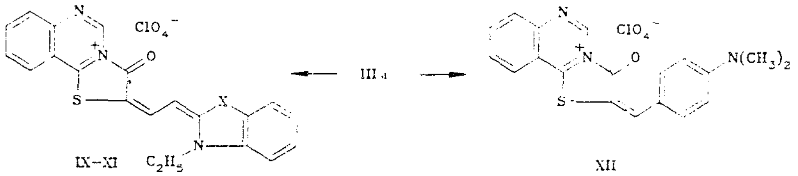
*The compounds were crystallized: IIb from ethanol, IIIb, VI, VII, and XII from acetic anhydride, VIII, IX, and XI from acetic acid, and X from acetonitrile–ether (1:1).

It was found that at the instant of its formation oxide IIIa reacts readily with 2-anilinovinyl- and 2-acetanilidovinyl-substituted derivatives of quaternary salts of nitrogen heterocycles. New dimethinecyanines IX-XI were synthesized by means of this method. Oxide IIIa reacts with 4-dimethylaminobenzaldehyde in an acidic medium to give benzylidene derivative XII.



IX X=$C(CH_3)_2$, X X=O, XI X=S; IX $R^2=CH_3$, X, XI $R^2=C_2H_5$

Solutions of the compounds obtained absorb in the visible part of the spectrum; however, the maxima of the bands are shifted hypsochromically as compared with the analogous characteristics of the dyes based on thiazolo[3,2-*a*]pyrimidinium 3-oxide [5].

EXPERIMENTAL

The PMR spectra of solutions in trifluoroacetic acid [with hexamethyldisiloxane (HMDS) as the internal standard] were obtained with a Tesla BS-467 spectrometer (60 MHz). The UV spectra of solutions in acetonitrile were obtained with an SF-8 spectrophotometer. The quantum-chemical calculations were made within the Pariser—Parr—Pople (PPP) approximation, as in [11].

The characteristics of the synthesized compounds are presented in Table 1. The results of elementary analysis for Hal, N, and S were in agreement with the calculated values.

α-(4-Quinazolinylthio)phenylacetic Acid (IIb). A solution of 2.15 g (1 mmole) of α-bromophenylacetic acid in 4 ml of 10% NaOH solution was added to a solution of 1.5 g (1 mmole) of 4-mercaptoquinazoline in 4 ml of 10% NaOH solution, the resulting solution was diluted with water to 50 ml, and the diluted solution was heated for 1 h at 120°C. The cold solution was neutralized cautiously with concentrated HCl, and the resulting precipitate was removed by filtration and crystallized. The yield was 3.0 g.

A solution of 1.48 g (0.5 mmole) of acid IIb in 5 ml of acetic anhydride was heated to the boiling point, and the precipitated crystals were removed by filtration, washed with ether, and crystallized. The yield was 0.96 g.

Cleavage of the Ring of Oxide IIIb. A 0.05-ml (0.5 mmole) sample of triethylamine was added dropwise to a hot solution of 0.14 g (0.5 mmole) of oxide IIIb and 0.31 g (1 mmole) of iodide IV in 5 ml of acetic anhydride, and the dye that precipitated after cooling was removed by filtration. The yield was 0.27 g (55%). The compound was identical to thiacarbocyanine V obtained by alternative synthesis [9].

2-(Trifluoroacetyl)thiazolo[3,2-c]quinazolinium 3-Oxide (VI). A 0.5-ml sample of trifluoroacetic anhydride was added to a solution of 0.22 g (1 mmole) of acid IIa in 2 ml of pyridine, and the mixture was allowed to stand at room temperature for 2 h. The resulting precipitate was removed by filtration and crystallized. The yield was 0.19 g.

2-(4-Nitrophenylaza)thiazolo[3,2-c]quinazolinium 3-Oxide (VII). A 0.24-g (1 mmole) sample of 4-nitrobenzenediazonium tetrafluoroborate and 0.1 g (1 mmole) of triethylamine were added to a solution of 0.20 g (1 mmole) of oxide IIIa in 20 ml of acetonitrile. The dye was removed by filtration and crystallized. The yield was 0.27 g.

Thiazolo[3,2-c]quinazolinium 3-Oxide (IIIa). A 1-ml sample of acetic anhydride was added to a solution of 0.44 g (2 mmole) of acid IIa in 2 ml of pyridine, and the mixture was allowed to stand for 30 min in a refrigerator. The resulting precipitate was removed by filtration and washed with ether. The yield was 0.4 g. This product was used subsequently without additional purification.

2-(N-Phenylthiocarbamoyl)thiazolo[3,2-c]quinazolinium 3-Oxide (VIII). A solution of 0.20 g (1 mmole) of oxide IIIa in 1 ml of phenyl isothiocyanate was refluxed for 2 min, and the resulting precipitate was removed by filtration and crystallized. The yield was 0.34 g.

2,3-Dihydro-3-oxo-2-[2-(2,3-dihydro-1,3,3-trimethyl-2-indolylidene)ethylidene]thiazolo[3,2-c]quinazolinium Perchlorate (IX). A 0.22-g (1 mmole) sample of acid IIa was added to a solution of 0.42 g (1 mmole) of 1,3,3-trimethyl-2-(2-acetanilidovinyl)-3H-indolium perchlorate in 3 ml of acetic anhydride, and the mixture was heated to the boiling point. It was then cooled, and the precipitate was removed by filtration and crystallized. The yield was 0.27 g.

2,3-Dihydro-3-oxo-2-[2-(3-ethyl-2(3H)-benzoxazolylidene)ethylidene]thiazolo[3,2-c]quinazolinium Perchlorate (X). This compound was obtained as in the preceding experiment from acid IIa and 3-ethyl-2-(2-acetanilidovinyl)benzoxazolium perchlorate.

2,3-Dihydro-3-oxo-2-[2-(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]thiazolo[3,2-c]quinazolinium Perchlorate (XI). A solution of 0.38 g (1 mmole) of 2-(2-anilinovinyl)-3-ethylbenzothiazolium perchlorate and 0.22 g (1 mmole) of oxide IIa was heated in 5 ml of acetic anhydride to the boiling point, after which it was cooled, and the dye was removed by filtration and crystallized. The yield was 0.22 g.

2,3-Dihydro-3-oxo-2-(4-dimethylamino)benzylidenethiazolo[3,2-c]quinazolinium Perchlorate (XX). A solution of 0.75 g (5 mmole) of 4-dimethylaminobenzaldehyde and 1.10 g (5 mmole) of acid IIa in 7 ml of acetic anhydride was heated for 10 min at 120°C, 0.55 ml (5 mmole) of 58% perchloric acid, and the mixture was then heated for another 40 min. It was then cooled, and the dye was removed by filtration and crystallized. The yield was 1.9 g.

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THIAZOLO(OXAZOLO)THIENO[b]PYRIMIDINES.

PREPARATION FROM 2-ALLYLTHIO(OXY)THIENO[2,3-d]PYRIMIDINES AND HYDROLYSIS

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Heterocyclization of 5,6-disubstituted 2-allylthio(oxy)-4-oxothieno[2,3-d]pyrimidines by treatment with halogens affords thieno[3,2-e]thiazolo[3,2-*a*]pyrimidine iminium salts. Treatment of these salts with aqueous sodium acetate results in cleavage of the thiazoline ring.

Pyrimidines condensed with the thiophene or thiazole nucleus are important members of the numerous heteroatomic bicyclic systems. The best known are the thienopyrimidines [1], which include many compounds showing a wide spectrum of biological activity [2]. Representatives of another type of binuclear heterocycles with two nitrogen atoms and one sulfur atom, the thiazolo[2,3-b]pyrimidines, also display various types of biological activity [3], and have therefore attracted the attention of many workers [4, 5].

Tricyclic systems in which the pyrimidine ring is condensed simultaneously with thiophene and thiazole nuclei are virtually unknown as a result of the lack of convenient methods for the preparation of thiazolothieno[b]pyrimidines. Retrosynthetic analysis, examination of the various routes to thiazoles and thiophenes, and assessment of the availability of the required starting materials suggested that the most logical route to these tricyclic systems should include annelation of the pyrimidine and thiazole rings. In such a case, convenient precursors would be 2-thio-4-oxothieno[2,3-d]pyrimidines, which have become

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