MESOIONIC COMPOUNDS WITH A BRIDGED NITROGEN ATOM.

18.* CYCLIZATION OF (2-QUINAZOLINYLTHIO)ACETIC ACIDS

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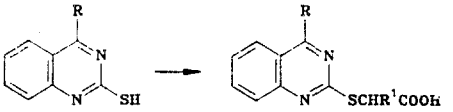
UDC 547.856'789.6.
07:543.422

It was established that mesoionic thiazoloquinazolinium oxides are formed in the action of acetic anhydride on (2-quinazolinylthio)acetic and -phenylacetic acids. The structures of the products were confirmed by their spectral characteristics and chemical transformtions.

We have previously shown [2, 3] tht mesoionic thiazolopyrimidinium oxides are formed in the action of acetic anhydride on (2-pyrimidinylthio)acetic and α-(2-pyrimidinylthio)phenylacetic acids; only one of the possible isomers is obtained in the case of substituted (in the pyrimidine ring) derivatives. The direction of the cyclization is determined not by the electronic nature of the substituent but by steric factors. In order to ascertain the principles of the formation of mesoionic thiazoloazinium oxides it seemed of interest to synthesize the benzo homologs of (2-pyrimidinylthio)acetic acids and investigate their reaction with acetic anhydride.

With this end in mind we synthesized (2-quinazolinylthio)acetic (IIa-c) and -phenylacetic (IIIa-c) acids on the basis of 2-mercaptoquinazolines Ia-c [4-6].



Ia-c IIa-c, IIIa-c

I—III a R=H, b R=CH_3, c R=C_6H_5; II R'=H; III R'=C_6H_5

It is known that unsubstituted quinazoline is methylated primarily at the nitrogen atom in the 3 position [7], whereas its 4-phenyl-substituted analog, on the other hand, is methylated in the 1 position [8], and that the mechanism of the formation of condensed thiazoloazinium oxides assumes electrophilic attack at the nitrogen atom [9]. One therefore could not foresee the direction of cyclization of carboxyalkylthio derivatives II and III. In addition, there is information that a condensed system is not formed at all in the action of acetic anhydride on (3,4-dihydro-4-oxo-2-quinazolinylthio)acetic acid, and only products of cleavage of the quinazoline ring are evidently formed [10].

We have found that (2-quinazolinylthio)phenylacetic acids IIIa-c are converted to new compounds under the influence of acetic anhydride. However, we were able to isolate and identify only products of transformation of 4-substituted acids, to which structures IVb,c can be assigned on the basis of the results of elementary analysis and the PMR spectral data.

In fact, when one compares the data from the PMR spectra of acids IIIb,c (more precisely, the cations formed when they are protonated) (Table 1) and the products of the reaction of the acids with acetic anhydride, viz. IVb,c (Table 2), it is apparent that the spectra of the latter do not contain a signal of an aliphatic proton of a phenylacetic acid residue and that a doublet (spin-spin coupling constant 8 Hz) of the proton in the 9 position is isolated from the multiplet of aromatic protons. The shift of the signal of this proton to weak field (~10.5 ppm) is due to the deshielding effect of the unshared pairs of the adjacent oxygen atom. The chemical shift of this proton is extremely close to the analogous characteristic of the corresponding proton in the 9 position of thiazolo[3,2-a]quinolinium 1-oxide (10.35 ppm [11]). Hence it should be concluded that mesoionic thiazolo[3,2-a]-quinazolinium 1-oxides IVb,c are actually formed by the action of acetic anhydride.

*See [1] for Communication 17.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 817-822, June, 1989. Original article submitted October 28, 1987; revision submitted april 21, 1988.

0009-3122/89/2506-0678$12.50

TABLE 1. Data from the PMR Spectra of Acids IIa-c and IIIa-c

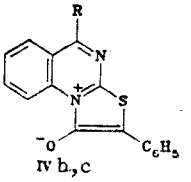
Compound	R	R¹	Solvent	Chemical shift, ppm		
				R	SCHR¹	Ar—H
IIa	H	H	DMSO-D_6	9,43	4,09	7,56 ... 8,15
			CF_3COOH	9,31	4,03	7,00 ... 8,20
IIb	CH_3	H	$CDCl_3$	2,78	3,90	7,40 ... 8,12
IIc	C_6H_5	H	$CDCl_3$	*	3,95	7,50 ... 8,20
			CF_3COOH	*	4,03	7,20 ... 8,20
IIIa	H	C_6H_5	$CDCl_3$	9,16	5,62	7,30 ... 7,90
IIIb	CH_3	C_6H_5	CF_3COOH	2,83	5,60	7,00 ... 8,00
IIIc	C_6H_5	C_6H_5	$CDCl_3$	*	5,64	7,30 ... 8,20

*The signal coincides with the multiplet of aromatic protons.

TABLE 2. Data from the PMR Spectra of Oxides IVb,c, VIc, and VIIc in $CDCl_3$

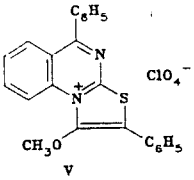
Compound	R	R²	Chemical shift, ppm			
			R	R²	Ar—H	9-H (d, J=8 Hz)
IVa	CH_3	C_6H_5	2,96	*	7,20 ... 8,20	10,49
IVb	C_6H_5	C_6H_5	*	*	7,20 ... 8,20	10,53
VIc	C_6H_5	H	*	5,90	7,00 ... 7,80	10,81
VIIc	C_6H_5	$COCF_3$	*	—	7,60 ... 8,40	10,12

*The signal coincides with the multiplet of aromatic protons.



IV b,c

According to the results of quantum-chemical calculations (Fig. 1), annelation of the benzene ring to the thiazolo[3,2-a]pyrimidinium 3-oxide molecule (i.e., transition to compounds of the IV type) leads to appreciable equalization of the bond orders in the thiazole fragment of the molecule and to pronounced alternation of the bonds in the quinazoline fragment; the $N_{(4)}$—$C_{(5)}$ bond approaches a double bond. The positive charges on the carbon atoms in the 1 and 5 positions increase significantly. The instability of unsubstituted oxide IVa is evidently explained by the possibility of the occurrence of side reactions involving the addition of various agents (most likely nucleophilic agents) to the highly polar double bond of the quinazoline fragment of the molecule. In conformity with the results of the calculations oxides IV react readily with electrophilic reagents. For example, 1-methoxy-substituted thiazoloquinazolinium perchlorate V was obtained by the reaction of derivative IVc with dimethyl sulfate.



V

Further investigations showed that cyclization to mesoionic thiaoloquinazolinium oxides VIb,c occurs in the action of acetic anhydride on (2-quinazolinylthio)acetic acids IIb,c. The structures of VIb,c were also confirmed by the PMR spectra and their chemical transformations. A light-colored product that we were unable to identify is liberated from acid IIa during the

TABLE 3. Characteristics of II-XIV

Compound	Empirical formula	mp, °C*	λ_{max}, nm (log ε)	$\Delta\lambda_{TQ}$	$\Delta\lambda_{TP}$**	Yield, %
IIa	$C_{10}H_8N_2O_2S$	213...214	—	—	—	73
IIb	$C_{11}H_{10}N_2O_2S$	154...157	—	—	—	64
IIc	$C_{16}H_{12}N_2O_2S$	131...132	—	—	—	82
IIIa	$C_{16}H_{12}N_2O_2S$	145...147	—	—	—	52
IIIb	$C_{17}H_{14}N_2O_2S$	130...132	—	—	—	83
IIIc	$C_{22}H_{16}N_2O_2S$	125...128	—	—	—	71
IVb	$C_{17}H_{12}N_2OS$	187...188	550 (4,11)	—	62	97
IVc	$C_{22}H_{16}N_2OS$	236...237	585 (4,23)	—	24	72
V	$C_{23}H_{17}ClN_2O_5S$	227 (dec.)	392 (4,15)	—	—	70
VIc	$C_{16}H_{10}N_2OS$	209...210	520 (3,96)	—	—	86
VIIc	$C_{18}H_9F_3N_2O_2S$	234...235	302 (4,12), 480 (4,15)	—	—	37
VIII	$C_{25}H_{19}ClN_3O_5S$	258...259	653 (4,54)	35	24	69
IX	$C_{29}H_{24}ClN_3O_5S$	243...245	614 (4,57)	22	12	89
X	$C_{27}H_{20}ClN_3O_6S$	271...272	603 (4,55)	37	18	64
XI	$C_{27}H_{20}ClN_3O_5S_2$	255...256	429 (4,43), 624 (4,69)	35	21	64
XII	$C_{29}H_{22}ClN_3O_5S$	252...253	430 (4,24), 628 (4,53)	—	16	57
XIII	$C_{39}H_{27}ClN_4O_5S$	>350	440 (4,44), 610 (4,51), 741 (4,95)	1	25	60
XIV	$C_{27}H_{19}ClN_4O_5S_3$	>350	418 (4,37), 548 (4,56)	—	19	36

*The compounds were crystallized; IIa-c from alcohol, IIIa-c From aqueous alcohol, IVb,c and VIIc from acetic anhydride, V from nitromethane—isopropyl alcohol (1:1), VIII-XII from nitromethane, XIII from nitromethane—acetic acid (1:1), and XIV from acetic acid.

**The shift of the absorption maximum (nm) on passing from the corresponding thiazoloquinoline ($\Delta\lambda_{TQ}$) and thiazolopyrimidine ($\Delta\lambda_{TP}$) derivatives to the investigated compounds.

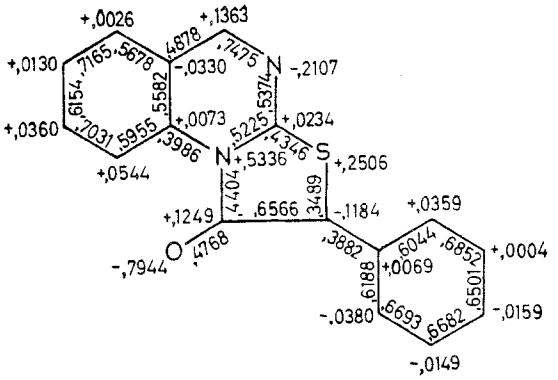
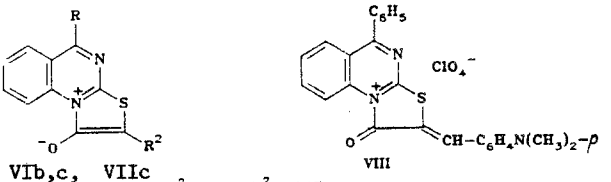
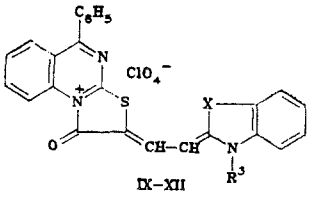


Fig. 1. Distribution of the π-electron density and bond orders in the 2-phenylthiazolo[3,2-a]quinazolinium 1-oxide molecule in the ground state.

reaction. At the instant of formation, oxides VI react readily with electrophilic reagents. Thus trifluoroacetyl derivative VIIc is obtained with trifluoroacetic anhydride.



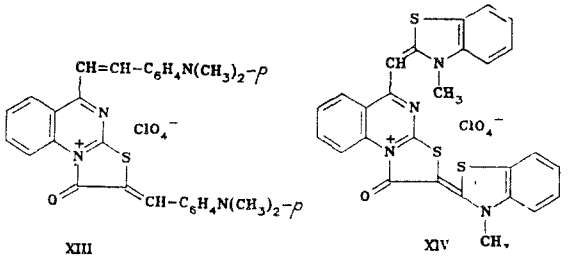
Oxide VIc reacts readily in the 2 position also with the electrophilic intermediates that are used for the synthesis of polymethine dyes. This pathway was used to obtain benzylidene derivative VIII and dimethinemerocyanines IX-XII.



IX–XII

IX $R^3=CH_3$, $X=C(CH_3)_2$; X–XII $R^3=C_2H_5$, X X=O, XI X=S, XII X=CH=CH

In the case of oxide VIb the reaction does not stop at this step, and condensation occurs also at the methyl group to give biscyanines. For example, styryl-substituted product XIII was obtained with p-dimethylaminobenzaldehyde, and thiamonomethinecyanine XIV was obtained with 3-methyl-2-methylthiobenzothiazolium perchlorate.



XIII XIV

Like the previously described thiazoloazinium oxides and dyes based on them, solutions of the synthesized compounds absorb in the visible part of the spectrum (Table 3). On the whole, the principles in their coloration are similar to those previously noted in the thiazolo[3,2-a]pyridinium 3-oxide [12] and thiazolo[3,2-a]pyrimidinium 3-oxide [13] series. Thus replacement of the methyl group in the 5 position (compound IVb) by a phenyl group (compound IVc), as in series of pyrimidine analogs, leads to a bathochromic shift of the absorption maximum; however, this effect is smaller by a factor of two (35 and 73 nm, respectively) in the case of benzo homologs IV. On the other hand, the introduction of an electron-acceptor trifluoroacetyl group (compound VIIc) into the 2 position in place of a phenyl substituent is accompanied by a significant hypsochromic shift (105 nm). The transition from the mesoionic compound (IVc) to the cation of the methoxy-substituted salt (V) leads to an even greater increase in the color (a 193-nm shift).

To ascertain the dependence of the color of thiazoloazinium oxides on the chemical structure of their molecules in Table 3 the long-wave absorption maxima of solutions of the synthesized thiazolo[3,2-a]quinazolinium 1-oxides are compared with the analogous characteristics of the corresponding derivatives of thiazolo[3,2-a]pyrimidinium 3-oxide [13, 14] and thiazolo[3,2-a]-quinolinium 1-oxide [15]. Bathochromic shifts ($\Delta\lambda_{TQ}$) are observed in all cases on passing from thiazoloquinolinium oxides to the investigated compounds. Similarly, benzoannelation of thiazolopyrimidinium oxide molecules leads to deepening of the color ($\Delta\lambda_{TP}$).

EXPERIMENTAL

The electronic spectra of solutions in acetonitrile were recorded with an SF-8 spectrophotometer. The PMR spectra were recorded with a WP-100SY spectrometer (100 MHz) with tetramethylsilane (TMS) as the internal standard. No fewer than 20 of the lowest-energy configurations were used in the quantum-chemical calculations. The parameters for the calculations and the geometries of the model systems were the same as in [12]. The characteristics of the synthesized compounds are presented in Table 3. The results of elementary analysis of II-XIV for N, Cl, and S were in agreement with the calculated values.

(4-R-2-Quinazolinylthio)acetic Acids (IIa-c). A 0.28-g (3 mmole) sample of monochloroacetic acid was added to a solution of 3 mmole of the coresponding 4-R-2-mercaptoquinazoline Ia-c in 15 ml of 10% NaOH solution, and the mixture was heated for 1 h at 110°C. The cooled solution was neutralized with hydrochloric acid, and the reaction product was removed by filtration and washed with water.

α-(4-R-2-Quinazolinylthio)phenylacetic Acids (IIIa-c) These compounds were obtained from 2 mmole of the corresponding thione Ia-c and 0.43 g (2 mmole) of α-bromophenylacetic acid, as in the case of acids IIa-c.

2-Phenyl-5-R-thiazolo[3,2-a]quinazolinium 1-Oxides (IVb,c.) A solution of 1.5 mmole of the corresponding phenylacetic acid IIIb,c in 5 ml of acetic anhydride was heated to the boiling point and cooled, and the reaction product was removed by filtration.

2,5-Diphenyl-1-methoxythiazolo[3,2-a]quinazolinium Perchlorate (V). A solution of 0.15 g (0.5 mmole) of oxide IVc in 2 ml of dimethyl sulfate was heated for 1 h at 100°C, after which it was cooled and diluted with ether. The precipitated salt ws separated and converted to the perchlorate by the action of sodium perchlorate in isopropyl alcohol. The yield was 0.15 g.

5-Phenylthiazolo[3,2-a]quinazolinium 1-Oxide (VIc). A 1-mmole sample of acid IIc was added to a mixture of 1.5 ml of triethylamine and 1.5 ml of acetic anhydride, and the mixture was allowed to stand for 30 min at 0°C. The precipitate was removed by filtration and dried in vacuo.

5-Phenyl-2-trifluoroacetylthiazolo[1,2-a]quinazolinium 1-Oxide (VII). A 1.5-ml sample of trifluoroacetic anhydride was added dropwise to a solution of 0.29 g (1 mmole) of acid IIc in 3 ml of pyridine, and the mixture was allowed to stand at room temperature for 2 h. The product was removed by filtration and crystallized. The yield was 0.1 g.

1,2-Dihydro-2-(4-dimethylaminobenzylidene)-1-oxo-5-Phenylthiazol[3,2-a]quinazolinium Perchlorate (VIII). A solution of 0.29 g (1 mmole) of (4-phenyl-2-quinazolinylthio)acetic acid (IIc) and 0.15 g (1 mmole) of 4-dimethylaminobenzaldehyde in 10 ml of acetic anhydride was heated to the boiling point and cooled, after which 0.1 ml (1 mmole) of 58% perchloric acid was added dropwise, and the mixture was again heated to the boiling point. The dye was removed by filtration and crystallized. The yield was 0.35 g.

1,2-Dihydro-1-oxo-5-phenyl-2-[2-(2,3-dihydro-1,3,3-trimethylindolylidene)ethylidene] thiazolo[3,2-a]quinazolinium Perchlorate (IX). A solution of 0.29 g (1 mmole) of acid IIc and 0.42 g (1 mmole) of 2-(2-acetanilidovinyl)-1,3,3-trimethyl-3H-indolium perchlorate in 3 ml of acetic anhydride was heated to the boiling point, after which it was cooled, and the dye was removed by filtration. The yield was 0.5 g.

1,2-Dihydro-2-oxo-5-phenyl-2-[2-(3-ethyl-2[3H]-benzoxazolylidene]ethylidene[thiazolo [3,2-a]quinazolinium Perchlorate (X). This compound was obtained from 0.29 g (1 mmole) of acid IIc and 0.41 g (1 mmole) of 2-(2-acetanilidovinyl)-3-ethylbenzoxazolium perchlorate as in the preparation of IX. The yield was 0.35 g.

1,2-Dihydro-2-oxo-5-phenyl-2-[2-(3-ethyl-2[3H]-benzothiazolylidene)ethylidene]thiazolo-[3,2-a]quinazolinium Perchlorate (XI). This compound was obtained from 0.29 g (1 mmole) of acid IIc and 0.42 g (1 mmole) of 2-(2-acetanilidovinyl)-3-ethylbenzothiazolium perchlorate as in the preparation of IX. The yield was 0.36 g.

1,2-Dihydro-2-oxo-5-phenyl-2-[2-(1-ethyl-2[1H]-quinolinylidene)ethylidene[thiazolo[3,2-a]quinazolinium Perchlorate (XII). This compound was obtained from 0.29 g (1 mmole) of acid IIc and 0.42 g (1 mmole) of 2-(2-acetanilidovinyl)-1-ethylquinolinium perchlorate as in the preparation of IX. The yield was 0.3 g.

1,2-Dihydro-2-(4-dimethylaminobenzylidene)-1-oxo-5-(4-dimethylaminostyryl)thiazolo-[3,2-a]quinazolinium Perchlorate (XIII). This compound was obtained from 0.23 g (1 mmole) of (4-methyl-2-quinazolinylthio)acetic acid (IIb) and 0.30 g (2 mmole) of 4-dimethylamino-benzaldehyde as in the preparation of VIII. The yield was 0.42 g.

1,2-Dihydro-2-[3-methyl-2[3H]-benzothiazolylidene]-5-[(3-methyl-2[3H]-benzothiazolyl-idene)methyl]-1-oxothiazolo[3,2-a]quinazolinium Perchlorate (XIV). A solution of 0.23 g (1 mmole) of acid IIb in 2 ml of pyridine was added to a solution of 0.62 g (2 mmole) of 2-methylthio-3-methylbenzothiazolium methylsulfate in 5 ml of acetic anhydride, and the mixture was heated to the boiling point. The precipitated dye was removed by filtration and converted to the perchlorate by the action of sodium perchlorate in acetic acid. The yield was 0.22 g.

LITERATURE CITED

1. K. V. Fedotov and N. N. Romanov, Khim. Geterotsikl. Soedin., No. 3, 404 (1989).
2. K. V. Fedotov, N. N. Romanov, and A. I. Tolmachev, Khim. Geterotsikl. Soedin., No. 5, 613 (1983).
3. K. V. Fedotov, N. N. Romanov, and A. I. Tolmachev, Khim. Geterotsikl. Soedin., No. 7, 969 (1984).
4. S. Gabriel, Berichte, 36, 800 (1903).
5. A. Brack, Annalen, 730, 166 (1969).
6. S. Solyom, J. Koczka, and G. Toth, Acta Chim., 68, 93 (1971).
7. R. Elderfield (editor), Heterocyclic Compounds [Russian translation], Vol. 6, Inostr. Lit., Moscow (1960), p. 305.
8. A. Katritzky and A. Boulton (editors), Advances in Heterocyclic Chemistry, Vol. 24, Academic Press, New York—San Francisco—London (1979), p. 461.
9. G. A. Stetsyuk, G. G. Dyadyusha, A. I. Tolmachev, K. V. Fedotov, and N. N. Romanov, Ukr. Khim. Zh., 49, 1092 (1983).
10. M. Dhatt and K. Narang, J. Ind. Chem. Soc., 31, 787 (1954).
11. M. Yu. Kornilov, A. V. Turov, K. V. Fedotov, and N. N. Romanov, Khim. Geterotsikl. Soedlin., No. 5, 619 (1983).
12. G. G. Dyadyusha, N. N. Romanov, A. D. Kachkovskii, and A. I. Tolmachev, Khim. Geterotsikl. Soedin., No. 12, 1618 (1980).
13. N. N. Romanov, K. V. Fedotov, A. A. Ishchenko, and A. I. Tolmachev, Ukr. Khim. Zh., 49, 857 (1983).
14. K. V. Fedotov and N. N. Romanov, Ukr. Khim. Zh., 52, 514 (1986).
15. L. T. Gorb, N. N. Romanov, K. V. Fedotov, and A. I. Tolmachev, Khim. Geterotsikl. Soedin., No. 4, 481 (1981).