REACTIONS OF CYCLAMMONIUM CATIONS

XXI.* DIRECT HETARYLATION OF THIAZOLIDONES WITH N-ACYL SALTS OF SIX-MEMBERED NITROGEN HETEROCYCLES

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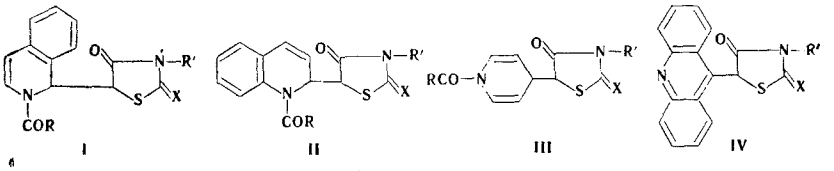
Heterocyclic derivatives of thiazolidones were obtained by the reaction of six-membered nitrogen heterocycles with thiazolidones in the presence of acyl halides. The compounds obtained were converted to heterocyclic thioglycolic acids by alkaline hydrolysis.

N-Acylcyclammonium salts in situ are convenient for electrophilic substitution of the hydrogen atom in nucleophilic organic compounds by a heterocyclic residue (the hetarylation reaction) [1, 2]. The hetarylation of thiazolidones is similarly accomplished with N-acyl pyridinium, quinolinium, isoquinolinium, and acridinium salts.

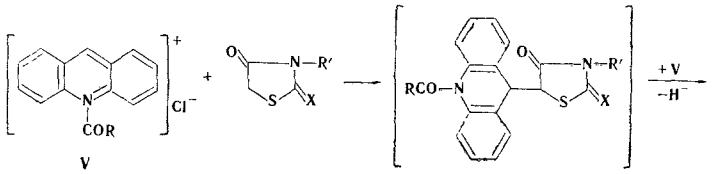
We obtained the best yields of the corresponding hetarylation products in the reactions of N-acyl acridinium and isoquinolinium salts, while quinolinium salts proved to be less reactive, and N-acylpyridinium salts were even less reactive. The reaction of N-acyl quinolinium, isoquinolinium, and pyridinium salts gave the corresponding α-substituted N-acyl derivatives of 1,2-dihydroisoquinolines (I), quinolines (II), and γ-substituted 1,4-dihydropyridines (III); in the reactions of acridinium salts, products of the dehydrogenation of the intermediately formed N-acyl dihydro derivatives (IV) are obtained immediately:



I II III IV

I-IV R=C_6H_5; N-$(C_6H_5)_2$, CH_3; OC_2H_5; furoyl; thienyl; R′=H; C_2H_5; C_6H_5; X=O; S; N-C_6H_5

In the case of the reaction of N-acylacridinium salts with dialkylanilines it has been shown [2] that the formation of aromatic derivatives of the IV type proceeds through a step involving formation of a 9-substituted N-acyl-9,10-dihydroacridine, which loses a hydride ion under the influence of excess N-acylacridinium cation to form N-acylacridan and the unstable 9-substituted N-acylacridinium cation, which is further decomposed by acridine to give the final reaction product. A similar scheme can apparently be assumed also in this case:



V

* See [1] for communication XX.

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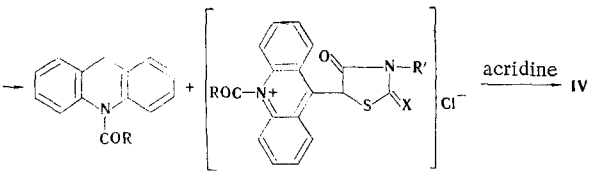
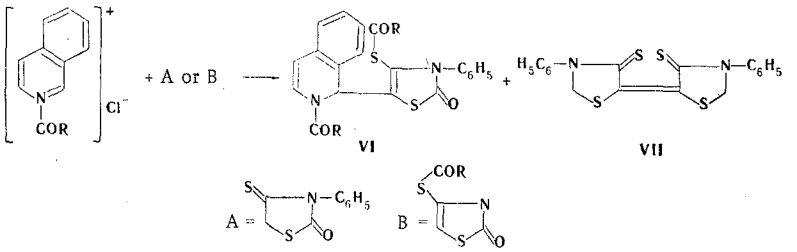


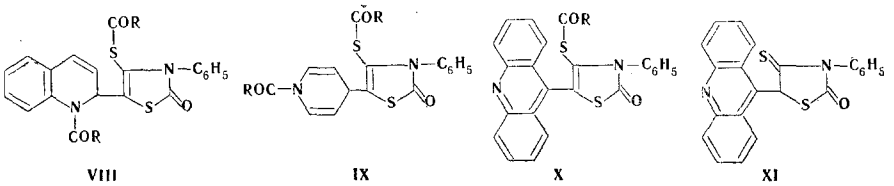
Acridinylthiazolidones were also obtained by the action of acridine hydrochloride on thiazolidones under the conditions of the acridinylation with acridine protic salts [2, 3].

It is known that the activity of the methylene group in 4-azolidones in reactions with electrophilic agents depends on the character of the substituent in the 2 position of the thiazolidone ring and decreases in the order rhodanine (X = S) > pseudothiohydantoin (X = NC_6H_5) > thiazolidine-2,4-dione (X = O) [4]. We also observed this same order in the hetarylation of thiazolidones with aromatic N-acylcyclammonium cations, which is evidence in favor of the electrophilic character of the substitution of the thiazolidone ring in this reaction. As is common in the electrophilic substitution of thiazolidones [5], replacement of an oxygen atom in the 4 position of the thiazolidine ring by sulfur facilitates the occurrence of the hetarylation reaction. However, other reactions also occur simultaneously in this case: acylation of the sulfhydryl group in the tautomeric equilibrium with the thione form and dimerization of 4-thionothiazolidone. For example, 4-acylthio-5-hetaryl derivatives of 3-phenylisorhodanine and a dimer – 5,5'-bis(3,3'-diphenyl-4,4'-dithionothiazolidine-2,2'-dione) [6] – are obtained in the hetarylation of N-phenylisorhodanine even at room temperature. The direction of the reaction is apparently determined by kinetic factors: the more electrophilic the N-acyl salt, the faster the hetarylation reaction and the higher the yield of hetarylation product. Thus both reaction products, with predominance of the hetarylated derivative, were isolated in the reaction of N-acylisoquinolinium salts with 3-phenylisorhodanine:



Compounds VI are formed in higher yields in the reaction of N-acylisoquinolinium salts with 3-phenyl-4-acylthioisorhodanine.

Only dimer VII is primarily formed in the reactions of less reactive N-acylquinolinium salts with 3-phenylisorhodanine; traces of the corresponding hetarylated derivative are detected only by chromatography. We were able to obtain similar compounds in the reaction of N-acyl salts with S-acylisorhodanine (VIII).



An exception to the above is the N,N-diphenylcarbamoylquinolinium salt, which reacts with 3-phenylisorhodanine to give both reaction products – 3-phenyl-4-N,N-diphenylcarbamoylthio-5-(1-N,N-diphenylcarbamoyl-1,2-dihydro-2-quinolinyl)isorhodanine [VIII, R = $(C_6H_5)_2N$] and the dimer. It should be noted that the isoquinolinium salt of N,N-diphenylcarbamoyl chloride also reacts with 3-phenylisorhodanine more smoothly (without resinification and side reactions) than does the isoquinolinium salt with other acyl halides.

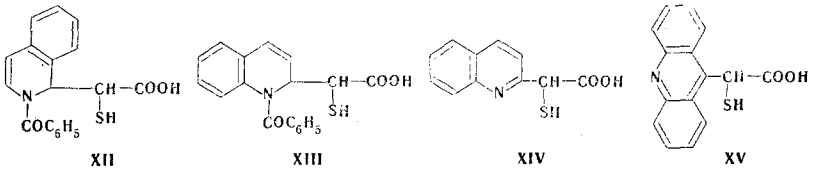
Only acylation occurs during the reaction of pyridine with 3-phenylisorhodanine in the presence of acyl halides at room temperature, while the product of pyridylation of S-acylisorhodanine (IX) is also formed at higher temperatures. Both compounds – dimer VII and acridinylisorhodanine X, which we have also obtained in the acridinylation of S-acylisorhodanine – are also obtained in the reactions of acridinium salts with 3-phenylisorhodanine.

The reaction described above could also be carried out with the acridine base, but, in contrast to the reaction with acridinium salts, it proceeds with N-phenylisorhodanine to give 3-phenyl-5-(9-acridinyl)isorhodanine (XI).

All of the heterocyclic derivatives of isorhodanine decompose to the starting heterocycle and 3-phenylisorhodanine under the influence of acids. The picrates of the starting heterocycles and the phenylhydrazone of 3-phenylisorhodanine were isolated in all cases, even when the picrates and hydrazones of the synthesized compounds were prepared by refluxing alcohol solutions of them with picric acid or phenylhydrazine. The ready cleavage of the C–C bond observed in this case is similar to the previously described elimination of a heterocyclic ring when a strong electron-acceptor substituent is bonded to the heterocycle [7].

The formation of isorhodanine dimers during the action of bases and air oxygen on isorhodanines was also observed in [6] and is apparently due to the same reasons as in the oxidation of indoxyl to indigo and the dimerization of pyrazolones and other compounds that contain a $-\overset{\overset{O}{\|}}{C}-CH_2-\ddot{X}-$ grouping, in which the methylene group is connected to the electron-acceptor C=O (or C=S) group and to some electron donor.

Heterocyclic thioglycolic acids are formed during alkaline hydrolysis of I, II, and IV, and this may serve as a convenient preparative method to obtain them:



XII XIII XIV XV

Attempts to accomplish the indicated reaction with 2,3-diphenyl-4-oxothiazolidone and its thio analog were unsuccessful. Instead of the expected 5-hetaryl derivatives, we isolated the starting thiazolidines; this is probably explained by the insufficient activity of the methylene group in these compounds [8]. The hetarylation reaction could not be carried out with 2,3-diphenyl-4-oxothiazolidine S,S-dioxide, the methylene group of which has higher activity; this is probably explained by steric factors.

The structures of the synthesized compounds flow out of the method used to prepare them and are confirmed by elementary analysis, chemical transformations, and IR spectra. The IR spectra of 5-hetarylthiazolidones of the I, II, and III type contain three characteristic absorption bands at 1600-1730 cm^{-1}, which are related to the stretching vibrations of the C=O groups of thiazolidones (1700-1730 cm^{-1}) and amides [1650-1680 cm^{-1} ($\nu_{C=O}$) and 1610-1620 cm^{-1} ($\nu_{C_3=C_4}$)]. In addition, there are characteristic bands of stretching vibrations of the C=S bond (1250 cm^{-1}). Bands of the stretching vibrations of C=O groups (1700 and 1750 cm^{-1}) and C=S groups (1250 cm^{-1}) are observed in the spectra of IV, but there are no bands at 1650-1680 cm^{-1}.

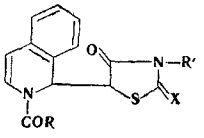
EXPERIMENTAL

The UV spectra of ethanol solutions were recorded with an SF-4A spectrometer. The IR spectra of chloroform solutions or KBr pellets were recorded with a UR-20 spectrophotometer. Chromatography in a thin layer of aluminum oxide (activity II) was accomplished by elution with benzene–hexane–chloroform (6 : 1 : 30) and development by iodine vapors in UV light.

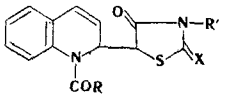
Hetarylation of Thiazolidones with N-Acyl Quinolinium (Isoquinolinium) Salts (Typical Method). A solution of 0.025 mole of isoquinoline, 0.005 mole of benzoyl chloride, and 0.005 mole of 3-phenylrhodanine in 10-15 ml of absolute benzene was heated at 80-90° until the starting thiazolidone in the reaction mixture had vanished, as monitored by thin-layer chromatography. The precipitate that formed after cooling was removed by filtration, washed with methanol, dried, and recrystallized from a suitable solvent. The yields, characteristics, and results of elementary analysis of the compounds obtained by this method are presented in Table 1.

3-Phenyl-4-N,N-diphenylcarbamoylthio-5-(2-N,N-diphenylcarbamoyl-1,2-dihydro-1-isoquinolinyl)-2-thiazolidone (VI). A solution of 6.5 g (0.05 mole) of isoquinoline, 1.4 g (0.005 mole) of N,N-diphenyl-

TABLE 1



Ia-j



IIa-c

Compound	R	R¹	X	mp, °C	R_f	Empirical formula	Found, %				Calc., %				Yield, %
							C	H	N	S	C	H	N	S	
Ia	C_6H_5	C_6H_5	O	189—190[a]	0,38	$C_{25}H_{18}N_2O_3S$	70,3	4,4	6,8	7,3	70,4	4,3	6,6	7,5	64
Ib	$N(C_6H_5)_2$	C_6H_5	O	233—234[b]	0,73	$C_{31}H_{23}N_3O_3S$	72,1	4,6	8,0	6,5	72,0	4,4	8,1	6,2	76
Ic	C_6H_5	H	O	202—203[a]	—	$C_{19}H_{14}N_2O_3S$	65,1	4,2	8,1	9,3	65,1	4,0	8,0	9,1	27
Id	C_6H_5	C_6H_5	N-C_6H_5	212—213[a]	0,25	$C_{31}H_{23}N_3O_2S$	74,3	4,8	8,4	6,3	74,2	4,6	8,4	6,4	87
Ie	C_6H_5	C_6H_5	S	211—212[a]	0,77	$C_{25}H_{18}N_2O_2S_2$	67,7	4,3	6,2	14,4	67,8	4,1	6,3	14,5	98
If	C_6H_5	C_2H_5	S	162—163[c]	0,45	$C_{21}H_{18}N_2O_2S_2$	63,8	4,9	7,3	16,3	63,9	4,6	7,1	16,2	51
Ig	CH_3	C_6H_5	S	172—173[a]	0,63	$C_{20}H_{16}N_2O_2S_2$	63,5	4,6	7,3	16,5	63,1	4,2	7,4	16,8	30,7
Ih	Furoyl	C_6H_5	S	175—176[a]	0,55	$C_{23}H_{16}N_2O_3S_2$	64,4	4,0	6,7	14,7	64,8	3,7	6,5	15,0	65
Ii	Thienyl	C_6H_5	S	174—175[a]	0,52	$C_{23}H_{16}N_2O_2S_3$	61,4	3,8	6,3	21,3	61,6	3,6	6,2	21,4	64
Ij	$N(C_6H_5)_2$	C_6H_5	S	223—224[d]	0,73	$C_{31}H_{23}N_3O_2S_2$	70,0	4,5	7,7	12,2	69,8	4,3	7,9	12,0	98
Ik	OC_2H_5	C_6H_5	S	195—196[a]	0,78	$C_{21}H_{18}N_2O_3S_2$	61,6	4,6	6,8	15,7	61,4	4,4	6,8	15,6	74,5
IIa	C_6H_5	C_2H_5	S	174—175[a]	0,50	$C_{21}H_{18}N_2O_2S_2$	64,1	4,9	7,1	16,4	63,9	4,6	7,1	16,2	35
IIb	C_6H_5	C_6H_5	S	212—213[f]	0,75	$C_{25}H_{18}N_2O_2S_2$	67,4	4,3	6,3	14,8	67,8	4,1	6,3	14,5	14
IIc	C_6H_5	C_6H_5	N-C_6H_5	274—275[a]	0,80	$C_{31}H_{23}N_3O_2S$	74,2	4,5	8,0	6,5	74,2	4,6	8,4	6,4	90

[a]From butanol.
[b]From hexanol.
[c]From methanol.
[d]From benzene.
[e]From acetone.
[f]From amyl alcohol.

carbamoyl chloride, and 1.1 g (0.005 mole) of 3-phenylisorhodanine in 25 ml of absolute benzene was held at room temperature for 24 h, after which the precipitate was removed by filtration and washed with methanol to give 2.5 g (49%) of a product with mp 269-270° (from hexanol) and R_f 0.26. Found: C 72.3; H 4.6; N 7.6; S 8.7%. $C_{44}H_{32}N_4O_3S_2$. Calculated: C 72.5; H 4.4; N 7.7; S 8.8%.

A total of 0.4 g of a dimer – 5,5'-bis(3,3'-diphenyl-4,4'-dithionothiazolidine-2,2'-dione) (VII) – was isolated from the reaction mass and was identified by comparison with a genuine sample [6].

3-Phenyl-4-benzoylthio-5-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)-2-thiazolidone (VI). This compound was similarly obtained in 11% yield and had mp 182-183° (from butanol) and R_f 0.31. Found: C 70.7; H 4.0; N 5.1; S 11.4%. $C_{32}H_{22}N_2O_3S_2$. Calculated: C 70.3; H 4.1; N 5.1; S 11.7%. This product was also obtained by the reaction of isoquinoline, benzoyl chloride, and 3-phenyl-4-benzoylthio-2-thiazolidone in absolute benzene at 100° for 7 h, and the yield was 65%. The substance was identical to that described above, as confirmed by the absence of a melting-point depression for a mixture with a genuine sample, chromatography in a thin layer of aluminum oxide, and identical IR spectra.

3-Phenyl-4-N,N-diphenylcarbamoylthio-5-(1-N,N-diphenylcarbamoyl-1,2-dihydro-2-quinolinyl)-2-thiazolidone (VIII). This compound was similarly obtained in 21% yield and had mp 95-96° (from butanol) and R_f 0.20. Found: C 72.1; H 4.6; N 7.4; S 8.6%. $C_{44}H_{32}N_4O_3S_2$. Calculated: C 72.5; H 4.4; N 7.7; S 8.8%.

3-Phenyl-4-benzoylthio-5-(1-benzoyl-1,2-dihydro-2-quinolinyl)-2-thiazolidone (VIII). This compound was obtained in 30% yield by the reaction of quinoline with 3-phenyl-4-benzoylthio-2-thiazolidone and benzoyl chloride by heating at 90-95° for 8 h. The product had mp 180-181° (from butanol) and R_f 0.77. Found: C 69.9; H 3.9; N 5.3; S 11.8%. $C_{32}H_{22}N_2O_3S_2$. Calculated: C 70.3; H 4.0; N 5.1; S 11.7%.

3-Phenyl-4-benzoylthio-5-(1-benzoyl-1,4-dihydro-4-pyridyl)-2-thiazolidone (IX). This compound was obtained in 76% yield as described above by reaction of pyridine with 3-phenylisorhodanine and benzoyl chloride at 70-75° for 6 h. The product had mp 221-222° (from butanol) and R_f 0.64. Found: C 67.5; H 3.9; N 5.9; S 12.7%. $C_{28}H_{20}N_2O_3S_2$. Calculated: C 67.7; H 4.0; N 5.6; S 12.9%.

3-Phenyl-4-benzoylthio-5-(9-acridinyl)-2-thiazolidone (X). This compound was obtained in 37% yield by reaction of acridine with 3-phenyl-4-benzoylthio-2-thiazolidone and benzoyl chloride by heating at 90-95° for 7-8 h. The product had mp 202-203° (from butanol) and R_f 0.32. Found: C 70.9; H 4.0; N 5.7; S 13.2%. $C_{29}H_{18}N_2O_2S_2$. Calculated: C 71.0; H 3.7; N 5.7; S 12.8%.

3-Phenyl-5-(9-acridinyl)isorhodanine (XI). This compound was obtained in 21% yield by reaction of acridine with 3-phenylisorhodanine. The product had mp 140-141° (from butanol) and R_f 0.65. Found: C 68.6; H 3.8; N 7.1; S 16.3%. $C_{22}H_{14}N_2OS_2$. Calculated: C 68.4; H 3.6; N 7.2; S 16.6%.

3-Phenyl-5-(9-acridinyl)rhodanine (IV). A solution of 2.1 g (0.01 mole) of 3-phenylrhodanine, 3.6 g (0.02 mole) of acridine, and 1.4 g (0.01 mole) of benzoyl chloride in 40 ml of absolute benzene was heated at 90-95° for 6 h. The reaction mixture was treated with water and petroleum ether, and the insoluble residue was crystallized from butanol to give 3.2 g (83%) of a product with mp 164-165° (from butanol) and R_f 0.65. Found: C 68.2; H 3.6; N 7.3; S 16.5%. $C_{22}H_{14}N_2OS_2$. Calculated: C 68.4; H 3.6; N 7.2; S 16.6%. The picrate had mp 261-262° (from acetic acid). Found: N 11.8%. $C_{22}H_{14}N_2OS_2 \cdot C_6H_3N_3O_7$. Calculated: N 11.4%.

The reaction of acridine hydrochloride with 3-phenylrhodanine in dimethylformamide at 90° for 8 h gave 3-phenyl-5-(9-acridinyl)rhodanine in 90% yield. The product did not depress the melting point of the sample described above.

3-Ethyl-5-(9-acridinyl)rhodanine (IV). This compound was obtained in 60% yield by the reaction of acridine hydrochloride with 3-ethylrhodanine and had mp 166-167° (from butanol) and R_f 0.75. Found: C 63.8; H 4.0; N 8.3; S 18.9%. $C_{18}H_{14}N_2OS_2$. Calculated: C 63.9; H 4.2; N 8.3; S 18.9%. The picrate had mp 244-245° (from acetic acid). Found: N 12.1%. $C_{18}H_{14}N_2OS_2 \cdot C_6H_3N_3O_7$. Calculated: N 12.3%.

3-Phenyl-5-(9-acridinyl)thiazolidine-2,4-dione (IV). This compound was obtained in 74% yield by the reaction of acridine hydrochloride with 3-phenylthiazolidine-2,4-dione and had mp 154-155° (from butanol) and R_f 0.60. Found: C 71.0; H 3.8; N 7.7; S 8.5%. $C_{22}H_{14}N_2O_2S$. Calculated: C 71.3; H 3.8; N 7.6; S 8.6%. The picrate had mp 250-251° (from acetic acid). Found: N 11.9%. $C_{22}H_{14}N_2O_2S \cdot C_6H_3N_3O_7$. Calculated: N 11.7%.

2-Benzoyl-1,2-dihydro-1-isoquinolinylthioglycolic Acid (XII). A 2.1-g sample of 3-phenyl-5-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)rhodanine was heated for 4-5 h in 40 ml of 5% sodium hydroxide so-

lution. The mixture was then cooled, filtered, and neutralized with hydrochloric acid (1:20). The light-yellow substance that formed was separated and reprecipitated from 5% sodium hydroxide solution by the addition of hydrochloric acid (1:20) to give 0.65 g (42%) of a product with mp 141-142°. Found: C 66.7; H 5.0; N 4.6; S 9.9%. $C_{18}H_{15}NO_3S$. Calculated: C 66.4; H 4.7; N 4.3; S 9.8%.

The alkaline hydrolysis of 3-phenyl-5-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)thiazolidine-2,4-dione gave the above-described 2-benzoyl-1,2-dihydro-1-isoquinolinylthioglycolic acid. The product did not depress the melting point of a genuine sample.

1-Benzoyl-1,2-dihydro-2-quinolinylthioglycolic Acid (XIII). The reaction of 0.7 g (0.005 mole) of 3-ethylrhodanine, 3.2 g (0.025 mole) of quinoline, and 0.7 g (0.005 mole) of benzoyl chloride in 10 ml of benzene gave 1 g of 3-ethyl-5-(2-benzoyl-1,2-dihydro-1-quinolinyl)rhodanine, the alkaline hydrolysis of which gave 0.23 g (35%) of 1-benzoyl-1,2-dihydro-2-quinolinylthioglycolic acid with mp 105-106°. Found: C 66.2; H 4.8; N 4.2; S 10.0%. $C_{18}H_{15}NO_3S$. Calculated: C 66.4; H 4.6; N 4.3; S 9.9%.

9-Acridinylthioglycolic Acid (XV). This compound was obtained in 31% yield by the alkaline hydrolysis of 3-phenyl-5-(9-acridinyl)rhodanine as described above and had mp 115-116°. Found: C 66.7; H 4.0; N 5.5; S 11.9%. $C_{15}H_{11}NO_2S$. Calculated: C 66.9; H 4.1; N 5.2; S 11.9%.

2-Quinolinylthioglycolic Acid (XIV). This compound was similarly obtained. The reaction of 2.1 g (0.01 mole) of 3-phenylrhodanine, 6.5 g (0.05 mole) of quinoline, and 1.4 g (0.01 mole) of benzoyl chloride gave 1.6 g of 3-phenyl-5-(1-benzoyl-1,2-dihydro-2-quinolinyl)rhodanine, the hydrolysis of which with alkali gave 0.4 g (50%) of XIV with mp 70-72°. Found: C 59.9; H 4.4; N 6.6; S 14.9%. $C_{11}H_9NO_2S$. Calculated: C 60.3; H 4.1; N 6.4; S 14.6%.

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