SYNTHESIS OF 2-ALKYLTHIOQUINAZOL-4-ONES

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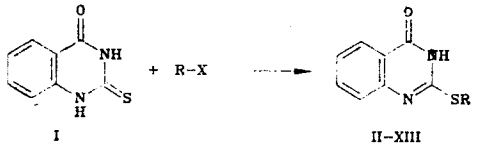
Alkylation of 2-thioxoquinazol-4-one by different alkylating agents was studied, and it was found that the reaction proceeds at the exocyclic sulfur atom with the formation of 2-alkylthioquinazol-4-ones.

2-Thioxoquinazol-4-one is an ambivalent compound and may exhibit dual reactivity in the reaction with electrophilic alkylating agents [1]. The alkylation reactions proceed with the participation of salts of heterocyclic thiamides, which during dissociation form a system with delocalized charge $O\cdots C_4\cdots N_3\cdots C_2\cdots S$. Addition of an alkyl radical may proceed either at the $N_{(3)}$ center of the ambivalent system [2] or at the exocyclic sulfur atom. The change in the direction of the reaction occurs with increase in the polarity of the solvent and rigidity of the alkylating agent. The direction of the alkylation can also be influenced by temperature, nature of the cation, and several other factors [3].

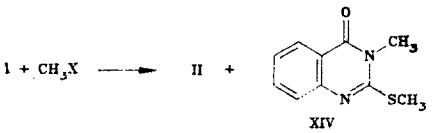
We found that the alkylation of 2-thioxoquinazol-4-one (I) in an alcoholic solution proceeds mainly at the exocyclic sulfur atom with the formation of 2-alkylthioquinazol-4-ones (II-XIII) (see Table 1). The concentration of the alkylation products at the $N_{(3)}$ atom does not exceed 3%, and the isomeric products are separated by recrystallization.



I II–XIII

X=Cl, Br, I, $CH_3C_6H_4SO_2O$; II R=CH_3; III R=C_2H_5; IV R=C_3H_7-p; V R=C_4H_9p; VI R=C_5H_{11}-p; VII R=C_6H_{13}-p; VIII R=C_7H_{15}-p; IX R=$CH_2C_6H_5$; X R=CH_2COOH; XI R=CH_2COOCH_3; XII R=$CH_2COOC_2H_5$; XIII R=CH_2CONH_2

The reaction of compound I with alkylating agents was carried out in an organic solvent, and the course of the reaction was controlled by TLC. According to the TLC data, 2-3 h after mixing the reagents, the formation of only one reaction product, the S-alkyl compound (II-XIII is observed in the reaction mixture. With increase in the time of alkylation of I, the appearance of the methylation product at the $N_{(3)}$ atom (XIV) is also observed. The reaction with methyl bromide, methyl iodide, and p-toluenesulfonyl chloride proceeds in the same way.



XIV

Increase in the polarity of the solvent (methanol, ethanol, propanol, DMFA, DMSO) leads to shortening of the reaction time, while the concentration of the N-alkyl product simultaneously increases. Extension of the range of the solvents is impossible because of the low solubility of compound I. Increase in the concentration of the alkylating agent leads to the appearance of dialkylated product XIV in the solution. For example, in the alkylation of compound I in DMFA by methyl tosylate, the formation of alkylation products of the medium and the dialkyl derivative XIV was observed [1].

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TABLE 1. 2-Alkylthioquinazol-4-ones II-XIV

Compounds	Alkylating agent	mp, deg C	R_f	Found, %				Empirical formula	Calculated, %				Yield, %
				C	H	N	S		C	H	N	S	
II	CH_3I	210—211	0,34	56,5	4,3	14,6	16,5	$C_9H_8N_2OS$	56,2	4,2	14,6	16,7	55
III	C_2H_5I	152—154	0,36	58,0	4,9	13,5	15,8	$C_{10}H_{10}N_2OS$	58,2	4,8	13,6	15,5	78
IV	C_3H_7Br	130—132	0,38	60,3	5,3	12,6	14,7	$C_{11}H_{12}N_2OS$	60,0	5,4	12,7	14,5	78
V	C_4H_9Cl	122—124	0,40	61,4	6,0	12,0	14,5	$C_{12}H_{14}N_2OS$	61,5	5,9	11,9	13,7	55
VI	$C_5H_{11}Br$	88—90	0,35	63,3	6,5	11,1	12,1	$C_{13}H_{16}N_2OS$	62,8	6,4	11,3	12,9	63
VII	$C_6H_{13}I$	80—81	0,37	63,7	6,9	10,5	12,9	$C_{14}H_{18}N_2OS$	64,1	6,8	10,7	12,2	60
VIII	$C_7H_{15}I$	70—72	0,38	65,1	7,1	10,1	13,7	$C_{15}H_{20}N_2OS$	65,2	7,2	10,1	13,3	75
IX	$C_6H_5CH_2Cl$	212—213	0,36	66,9	4,4	10,5	11,2	$C_{15}H_{12}N_2OS$	67,2	4,5	10,4	11,9	93
X	$ClCH_2COOH$	336—338	0,34	51,2	3,4	11,8	13,4	$C_{10}H_8N_2O_3S$	50,8	3,4	11,9	13,6	69
XI	$ClCH_2COOCH_3$	168—175	0,35	52,7	3,8	11,2	12,6	$C_{11}H_{10}N_2O_3S$	52,8	4,0	11,2	12,8	48
XII	$ClCH_2COOC_2H_5$	184—185	0,41	54,0	4,6	10,4	11,8	$C_{12}H_{12}N_2O_3S$	54,5	4,5	10,6	12,1	72
XIII	$ClCH_2CONH_2$	217—218	0,34	51,2	4,0	17,7	13,0	$C_{10}H_9N_3O_2S$	51,0	3,8	17,9	13,6	86
XIV	$CH_3C_6H_4SO_3CH_3$	79—80	0,6	58,6	4,9	13,7	15,3	$C_{10}H_9N_2OS$	58,2	4,8	13,6	15,5	77

The comopunds obtained are colorless, high-melting crystals, which are hydrolyzed by dilute hydrochloric acid with the formation of quinazoline-2,4-dione.

The structure of the alkylation products was confirmed by the results of UV spectra, in which bands at 221, 291 nm are observed, which practically completely coincide with the position of bands in the spectrum of 2-methylthioxoquinazolon-4-one (II) [2]. In the IR spectra of compounds II-XIV there are intense absorption bands in the 1700-1680 and 1680-1620 cm^{-1} regions, which wre assigned to the stretching vibrations of the conjugated carbonyl ($\nu_{C=O}$) and ring C=N ($\nu_{C=N}$) groups, respectively. The direction of mono- and dialkylation of methyl iodide was also confirmed by PMR data on proton shifts. In the spectra of compounds II and XIV, there are singlet signals at 2.58, 2.57, and 3.35 ppm, respectively. The alkylation of the exocyclic sulfur atom is selective because ethanol, a solvent of intermediate polarity, is used, in which the influence of the nature of the halogen atom in alkyl halide is moderated. This is explained by the specific solvation of the $N_{(1)}$ and $N_{(3)}$ atoms, whose basicity is apparently higher than that of the exocyclic sulfur atom, as confirmed by the known values of pK_a for 2-thiozoquinazol-4-one (pK_1 = 8.3, pK_2 = 13.4) [4]. The values are lower than those of 2-thiobarbituric acid (pK_1 = 3.7, pK_2 = 7.8), whose akylation proceeds less selectively [5].

The formation of O-alkyl derivatives in the case of 2-thiozoquinazol-4-one was not observed. This can be explained by the thermodynamic control of the process at the oxygen atom, which is characteristic for the well investigated series of thiazolidones [6].

EXPERIMENTAL

The IR spectra were run on a UR-20 spectrophotometer in KBr tablets, and the UV spectra, on an Hitachi EPS-3T spectrophotometer in ethanol (c × 10^{-4} mole/liter); the mass spectra were run on an MX-1303 spectrometer; and the PMR spectra were run on a JNM-4H-100 spectrometer in CF_3COOH, using HMDS as internal standard, in the δ scale. The TLC was carried out on Silufol UV-254 plates, using a 15:1 mixture of chloroform with methanol as eluent.

2-Ethylthioquinazol-4-one (III). A 100-ml portion of alcohol and 1.12 g (0.02 mole) of KOH are added to 3.56 g (0.02 mole) of I. The mixture is stirred, and 3.12 g (0.02 mmole) of ethyl iodide is added dropwise. The mixture is then heated for 3 h at 100°C. When cool, 100 ml of water is added, the material is extracted by chloroform (3 × 50 ml), and the extract is dried over magnesium sulfate. The precipitate is filtered and chloroform is distilled. The precipitate is recrystallized from alcohol. Yield, 3.2 g (75%), mp 152-154°C. IR spectrum: 1590 (C=N), 1685 (C=O), 3170 cm^{-1} (NH). PMR spectrum (CF_3COOH): 1.16 (3H, t, CH_3); 3.19 (2H, m, SCH_2), 7.2-8.1 ppm (4H, m, C_6H_4).

The methylation of I by methyl bromide and methyl tosylate is carried out in a similar way. The alkylation by methyl chloride is carried out with cooling to −30°C in alcohol. Compounds II, IV-XIII are obtained in a similar way.

1,3-Dimethylthioquinazol-4-one (XIV). A 100-ml portion of DMFA and 1.12 g (0.02 mole) of KOH are added to 3.56 g (0.02 mole) of compound II. The mixture is stirred, 3.56 g (0.02 mole) of methyl tosylate is added, and the mixture is heated for 3 h at 100°C. When cool, 100 ml of water is added, the material is extracted by chloroform (3 × 50 ml), and the

extract is dried over magnesium sulfate. The precipitate is filtered, and chloroform is distilled. Yield 77%, mp 79-80°C, IR spectrum: 1685 (C=O), 1620 cm^{-1} (C=N). PMR spectrum (CF_3COOH): 2.57 (3H, s, SCH_3); 3.57 ppm (3H, s, N_3CH_3).

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ELECTRONIC SPECTRA OF asym-TRIAZINYL GROUPS

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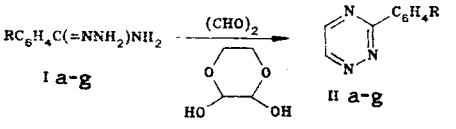
The induction, resonance, and Hammett constants of 3-, 5-, and 6-asym-triazinyl groups were calculated from the data of ^1H, ^{13}C, ^{19}F NMR spectra of isomeric aminophenyl-, hydroxyphenyl-, phenyl-, and fluorophenyl-asym-triazines.

Successive replacement of one, two, and more methine fragments in the benzene ring by a nitrogen atom leads to increase in the π-deficiency of the aromatic system in the series benzene, pyridine, diazines, triazines [1] and, as a result, to an increase in the electron-acceptor properties of the corresponding azinyl groups. The description of the electronic effects of different azinyl groups as substituents in the form of a given set of σ-constants may serve as a basis for establishing quantitative regularities with respect to the influence of aza-substitution on the induction and resonance characteristics of the above groups. In this regard it is of interest to examine the electronic effects of asym-triazinyl groups, in which three types of interactions of the heteroatoms in the six-membered ring are manifested simultaneously: 1, 2- as in pyridazine, 1,3- as in pyrimidine, and 1,4- as in pyrazine. However, no data are available in the literature, quantitatively characterizing the electronic effects of these groups.

The present work deals with the determination of σ-constants of 3-, 5-, and 6-asym-triazinyl groups (as-Tr) using the NMR method. For this purpose, we synthesized aryl-asym-triazines with phenyl- m-, and p-aminophenyl groups in the 3, 5, or 6-positions of the triazine ring, and also with m- and p-hydroxyphenyl and -fluorophenyl groups at the 3-position of the triazone ring (scheme), and recorded the ^1H, ^{13}C, ^{19}F NMR spectra in DMSO, selected as a standard solvent.



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