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OXIDATIVE CYCLOCONDENSATION OF THIO(SELENO)-AMIDES AND UREAS

1. 2-THIOXO-4-QUINAZOLONE

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It has been found for the first time that 2-thioxo-4-quinazolone in the presence of acid catalysts in dimethyl sulfoxide is converted to 8H,15H-*1,2,4-thiadiazolo[3,2-b:5,4-b']diquinazoline-8,15-dione. The reaction proceeds via oxidative cyclocondensation. The formation of this structure in preference to five other proposed isomers is substantiated using quantum-chemical methods.*

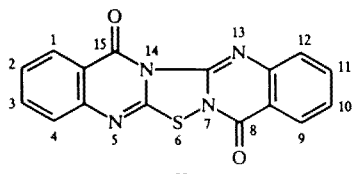
In containing our systematic studies on a series of 2-substituted 2-substituted 4-pyrimidinones condensed with benzene, thiophene, and other rings [1-4], we have found that 2-thioxo-4-quinazolone (I) in dimethyl sulfoxide in an acidic medium is converted to a compound with a molecular weight of 320. According to the results of elemental analysis and mass spectrometry, the product has the empirical formula $C_{16}H_8N_4O_2S$, which shows that it is formed from two molecules of 2-thioxo-4-quinazolone with the elimination of a molecule of hydrogen sulfide and the loss of two hydrogen atoms. In the mass spectrum there is a peak due to the molecular ion M^+ with *m/z* 292 (M^+-28, 5%), 262 (M^+-58, 15%), 234 (M^+-86, 20%), and 160 ($M^+/2$, 12%).

In the IR spectrum there are no NH absorption bands in the region 3200-3400 cm^{-1}. The carbonyl group appears as a broad band at 1680-1685 cm^{-1}. The stretching and bending absorption bands due to the C–H and C=O bonds are broadened and shifted to higher frequency, which suggests that strain occurs in the heterocycle as a whole. The new compound synthesized is insoluble in water, ethanol, ether, acetone, and other solvents, while it is slightly soluble in dimethyl sulfoxide.

The compound does not undergo alkylation or acylation in the presence or absence of sodium hydride, sodium hydroxide, and triethylamine. Judging by its spectroscopic data and chemical behavior, this compound can be classed as a condensed thiadiazole derivative [5].

Six structures (II-VII) that are dependent on the configuration of molecules of I during cyclocondensation can in theory be proposed for the compound obtained.

The formation of these compounds can be accounted for if the dimethyl sulfoxide used as solvent acts as an oxidizing agent. Thus, oxidation of compound I on the nitrogen atom at the 3-position or on the sulfur atom yields 3-hydroxy-2-thioxo-4-quinazolone or 2,2'-di(oxoquinazolyl) disulfide respectively. The former reacts with unreacted 2-thioxo-4-quinazolone, with the elimination of a water molecule, 3,3'- and 1,3'-bis(thioxo-4-quinolone) being formed. They subsequently undergo cyclization as a result of the elimination of a molecule of hydrogen sulfide to give compounds VI and VII. Other reaction routes, which involve the 2,2'-di(4-oxoquinazolyl) disulfide just mentioned, can lead to the formation of compounds II-V.



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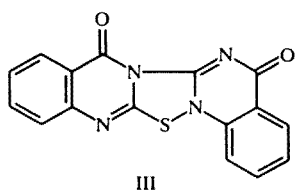

III

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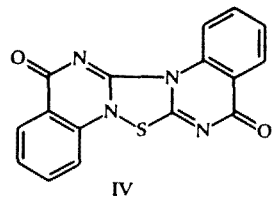

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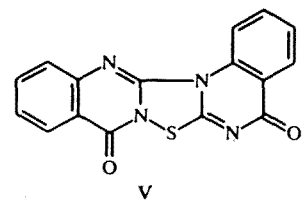

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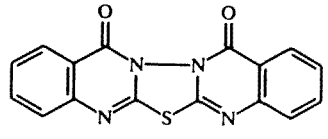

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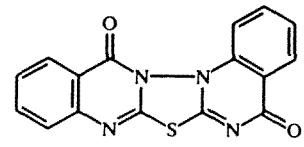
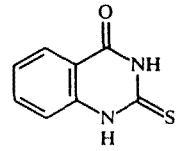
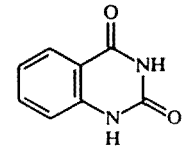


VII

The results of IR, mass spectrometry, and elemental analysis do not unequivocally provide confirmation for any one of these structures. Therefore, it was necessary to study certain chemical reactions of the compound obtained. Thus, hydrolysis in alkaline and acid media both at room temperature and on heating (80-85°C) yields a mixture of 2-oxo- and 2-thioxo-4-quinazolones (VIII) and (I).



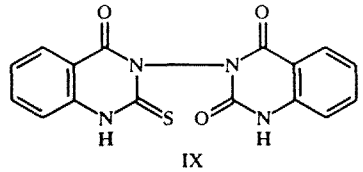
I



VIII

While the thiadiazole is fifty-percent hydrolyzed at room temperature (for 8 h), on heating to 80-85°C (for 4 h) it is completely hydrolyzed.

If it assumed that the N-N bond in the 1,3,4-thiadiazoles (VI, VII) is sufficiently stable towards alkalis and acids, hydrolysis of the compound obtained should give 2-thioxo-3-(2,4-dioxoquinazol-3-yl)-4-quinazolone (IX) or 2,2′,4,4′-tetraoxo-3,3-biquinazoline (X) instead of VIII and I.



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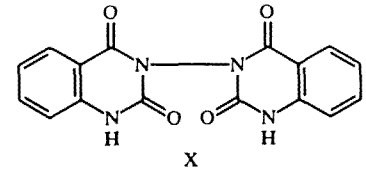
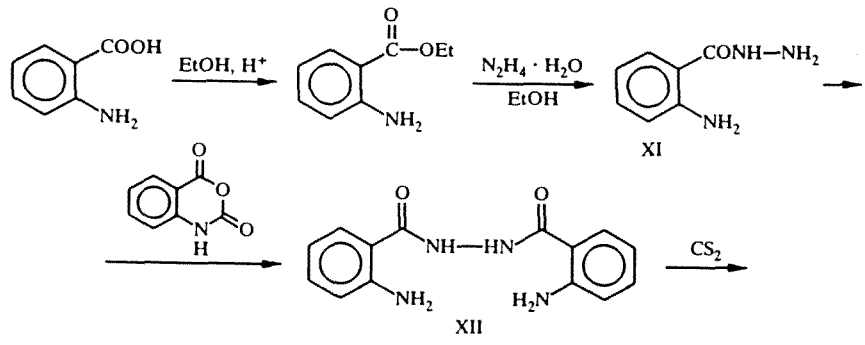


X

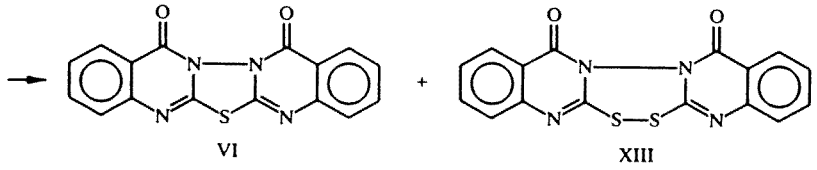
In order to establish unequivocally the structure of the product that we obtained, we carried out the counter-synthesis of compound VI from ethyl anthranilate via anthranilic acid hydrazide (XI), which reacts with isatoic anhydride to give *N,N′*-bisanthranylhydrazine (XII). Condensation of the latter with carbon disulfide in an alkaline medium leads to a mixture of 1,2,4,5-dithiadiazinodiquinazolinedione (XIII) and 12*H*,15*H*-1,3,4-thiadiazolo[2,3-*b*:5,4-*b*′]diquinazoline-12,15-dione (VI).



XII

TABLE 1. Quantum-Chemical Calculations of the Enthalpies of Formation of Isomers II-VII

Isomer	II	III	IV	V	VI	VII
ΔH_f, kcal/mole	31,7	37,8	41,6	36,3	64,2	74,6



VI XIII

On comparing the spectroscopic properties (mass spectra and IR spectra) of the compound obtained and that of the product derived from dimerization of 2-thioxo-4-quinazolone, the data are found to be almost the same for both compounds, apart from the broadened signal from the absorption band of the carbonyl groups in the region of 1675-1680 cm^{-1} in the case of compound VI. However, they have different melting points, and a mixed sample gives a depressed value for melting. They also have different solubilities in organic solvents. The results of alkaline and acid hydrolysis and those from the counter-synthesis demonstrate that the product from dimerization of 2-thioxo-4-quinazolone is not 1,3,4-thiadiazole derivative VI. Structure VII can also be rejected on the basis of these findings.

The most likely structure of the compound we obtained is that of 8*H*,15*H*-1,2,4-thiadiazolo[3,2-*b*:5,4-*b'*]diquinazoline-8,15-dione (II). The results of acid and alkaline hydrolysis fully support structure II. Thus, under acid catalysis conditions, one of the nitrogen atoms at the 1-position of the quinazoline ring, preferably N-13, undergoes attack by a proton. This protonation assists attack on the C-2 carbon atom of the quinazoline ring by a hydroxyl ion. Subsequently the C – N bond of the thiadiazole ring undergoes cleavage to form an unstable intermediate, which decomposes to give 2-oxo- and 2-thioxo-4-quinazolones. Attack on the N-13 nitrogen atom occurs more readily because its electron density is greater than on N-5, owing to the lesser withdrawal of the electrons than from N-5 by the neighboring sulfur atom.

With alkaline hydrolysis there is direct attack on the C-2 carbon atom of the quinazoline ring by hydroxide ion and the molecule subsequently undergoes cleavage.

Quantum-chemical calculations of the enthalpies of formation of isomers II-VII (Table 1) showed that compounds II-V are more stable than their counterparts VI and VII. Isomer II is the most favorable energetically. It may be noted that the molecules in which the heteroatoms alternate with carbon atoms are more stable. It is proposed to carry out a detailed quantum-chemical study of the electronic structure of compounds II-VII and the dimerization mechanism in the future.

Structure II — 8*H*,15*H*-1,2,4-thiadiazolo[3,2-*b*:5,4-*b'*] diquinazoline-8,15-dione — can be proposed for the product of dimerization of 2-thioxo-4-quinazolone on the basis of its spectroscopic properties, chemical reactions, and the results of quantum-chemical calculations. It is formed from 2-thioxo-4-quinazolone by oxidation and elimination of hydrogen sulfide and water, with dimerization occurring at the same time.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer using KBr pellets and on an IK-29 instrument in ethanol solution. The mass spectra were recorded on MKh-1303 and MS25RS spectrometers. The R_f values were determined on Silufol UV-254. Iodine vapor was used as developer, with UV light, $KMnO_4 + H_2SO_4 + H_2O$ (0.5 g + 2 ml + 48 ml).

2-Thioxo-4-quinazolone was synthesized by the literature method [6].

Anthranilic Acid Hydrazide. Hydrazine hydrate (21 ml, 400 mmole) was placed in a three-necked flask fitted with a dropping funnel, mechanical stirrer, and thermometer. Then ethyl anthranilate (60 ml, 400 mmole) was added dropwise with agitation. The reaction mixture was heated to 160°C and agitated at this temperature for 4 h. The mixture was cooled, and the precipitate filtered off, washed with water, and dried. The product was recrystallized from methanol. Yield 47.1 g (78%), mp 121-122°C.

***N,N'*-Bisanthranylhydrazine (XII).** To a solution of 1.63 g (10 mmole) of isotoic anhydride [7] in 40 ml of ethanol was added 1.51 g (10 mmole) of anthranilic acid hydrazide. The reaction mixture was refluxed on a water bath for 6 h. Yield 1.81 g (67%), mp 192°C, R_f 0.55 (acetone-benzene, 3:4). Mass spectrum, m^+/z (%): 270 (M^+, 24), 258 (M^+-18, 6), 239 (M^+-31, 18), 120 (M^+-150, 100). IR spectrum: 1660 cm^{-1} (ν_{CO}), 3220 cm^{-1} (ν_{CO}), 3300 cm^{-1} (ν_{CO}).

12*H*,15*H*-1,3,4-Thiadiazolo[2,3-*b*:5,4-*b'*]diquinazoline-12,15-dione (VI) and 1,2,4,5-Dithiadiazino[3,4-*b*:5,6-*b'*]diquinazoline-12,15-dione (XIII). To a solution of 0.4 g (1.4 mmole) of *N,N'*-bisanthranylhydrazine and 0.12 g (2.1 mmole) of potassium hydroxide in 35 ml of ethanol was added dropwise 0.5 ml (8.2 mmole) of carbon disulfide with agitation. The reaction mixture was refluxed on a water bath for 4 h. The mixture was left overnight, and the precipitate, which was a mixture of products VI and XIII, was filtered off, washed with water, dried, and was fractionally crystallized from an acetone-chloroform mixture to separate compounds VI and XIII. Compound VI, yield 0.061 g (26%), mp 303-305°C, R_f 0.45 (acetone-benzene, 3:4), IR spectrum: 1675 cm^{-1} (ν_{CO}). Mass spectrum, m^+/z (%): 320 (M^+, 100), 292 (M^+-28, 18), 262 (M^+-58, 30), 234 (M^+-86, 33), 176 (M^+-144, 76), 160 (M^+/2, 40), 144 (M^+-176, 89). Found, %: C 60.10; H 2.55; N 17.27. $C_{16}H_8N_4O_2S$. Calculated, %: C 60.00; H 2.50; N 17.50. Compound XIII, yield 0.08 g (30%), mp 350-352°C, R_f 0.67 (acetone-benzene, 3:4). Mass spectrum, m^+/z (%): 352 (M^+, 23), 318 (M^+-34, 100), 260 (M^+-92, 12), 234 (M^+-118, 15), 213 (M^+-139, 12), 177 (M^+-175, 66), 161 (M^+-191, 65), 145 (M^+-207, 54), 133 (M^+-219, 40), 119 (M^+-233, 53). Found, %: C 54.40; H 2.15; N 15.86.$C_{16}H_8N_4O_2S_2$. Calculated, %: C 54.54; H 2.27; N 15.90.

8*H*,15*H*-1,2,4-Thiadiazolo[3,2-*b*:5,4-*b'*]diquinazoline-8,15-dione (II). A. To a solution of 0.18 g (1 mmole) of 2-thioxo-4-quinazolone in 10 ml of DMSO was added 2 g (1.4 mmole) phosphorus pentoxide. The mixture was agitated at room temperature for 4 h, diluted with water, and the precipitate that formed was filtered off, washed with water and then dimethylformamide, and dried. Yield 0.16 g (60%), mp 322-324°C (DMF), R_f 0.34 (acetone-benzene, 2:5). IR spectrum: 1680-1685 cm^{-1} (ν_{CO}). Mass spectrum, m^+/z (%): 320 (M^+, 100), 292 (M^+-28, 5), 262 (M^+-58, 15), 234 (M^+-86, 20). Found, %: C 60.18, H 2.61; N 17.58. $C_{16}H_8N_4O_2S$. Calculated, %: C 60.00; H 2.50; N 17.50. *B.* To a solution of 0.3 g (1.6 mmole) of 2-thioxo-4-quinazolone in 15 ml of DMSO was added 3 ml of conc. H_2SO_4 with agitation, the latter being continued for 4 h. The precipitate was filtered off, washed with water, and dried. Yield 0.19 g (70%). The spectroscopic data matched that of the sample obtained by method A.

The quantum-chemical calculations were carried out by the MNDO-PM3 method [8] using an AMPAC computer program package.

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