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STUDIES IN THE QUINOXALINE SERIES.

17.* PREPARATION AND PROPERTIES OF SOME DERIVATIVES OF 2-SULFONYLMETHYLQUINOXALINE

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UDC 547.863.1:543.422:541.623

Ketimines of 2-methylthiomethyl- and 2-methylsulfonylmethyl-3-oxodihydroquinoxaline have been prepared with the object of studying their tautomeric forms. The enaminoester of 1,3-bis(ethoxycarbonyl)-4,9-dihydrothienol[3,4-b]-quinoxaline-2,2-dioxide is very stable: it does not eliminate sulfur dioxide on boiling in diphenyl ether, under UV irradiation, or under electron bombardment. Reductive decomposition does not lead to the expected dienaminoester.

In preceding communications [1-3], the preparation and properties of several derivatives of 2-carbonylmethylene- and 2-cyanomethylene-3-oxo-1,2,3,4-tetrahydroquinoxaline (I) have been described. The present paper is concerned with methods for the preparation of analogs containing sulfonyl groups and a study of their properties. Among derivatives of this type only 2-phenylsulfonylmethyl-3,4-dihydro-3-oxoquinoxaline (II) is described in the literature [4] as having a ketimine structure. It was prepared by condensation of phenylmethylsulfone with diethyloxalate under the influence of sodium hydride, and subsequent reaction of the product with o-phenylenediamine.

In view of the fact that a similar reaction does not occur with dimethylsulfone, we used a more effective basic catalyst for ester condensations — sodium dimsylate in tetrahydrofuran [5]. The ethyl 2-methylsulfonyl-pyruvate which we prepared was reacted with o-phenylenediamine to give 2-methylsulfonylmethyl-3,4-dihydro-3-oxoquinoxaline (III) which possesses the ketimine structure B similar to the phenylene analog II. The lactim structure C does not seem to occur in compounds of this type [6].

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*For Communication 16, see [1].

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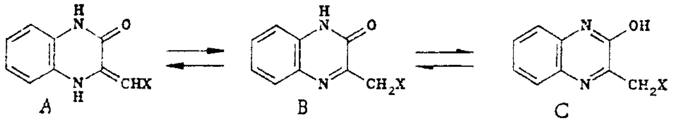
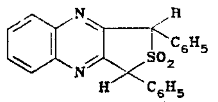


I X=COR, COOR, CN; II $X=SO_2C_6H_5$; III $X=SO_2CH_3$; IV $X=SCH_3$

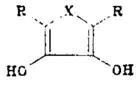
Confirmation of this is provided by the C=O band at 1675 and the NH band at 3180 cm^{-1} in the infrared spectrum of compound III and the spectroscopic data for related compounds [2-4].

We attempted to prepare the sulfoxide analog of derivative III. Reaction of 2-bromomethyl-3,4-dihydro-3-oxoquinoxaline with CH_3SNa in methanol gave 2-methylthiomethyl-3,4-dihydro-3-oxoquinoxaline (IV). The same substance was prepared by reaction of ethyl 3-methylthio-pyruvate [7] with o-phenylenediamine. Attempts to oxidize the sulfide IV to the sulfoxide or sulfone by the action of potassium permanganate, hydrogen peroxide, hypochlorite, periodate, and 3-chloroperoxybenzoic acid were unsuccessful and led to breakdown of the quinoxaline skeleton. Attempts to oxidize ethyl 3-methylthio-pyruvate or to condense dimethylsulfoxide with diethyloxalate were equally unproductive.

Moriconi and co-workers [8] have described the separation of sulfur dioxide from a mixture of cis- and trans-isomers of 1,3-diphenyl-1,3-dihydrothieno[3,4-b]quinoxaline-2,2-dioxide (V) with the formation of 2,3-dibenzylquinoxaline. The dioxide V was obtained by condensation of 2,5-diphenyl-3,4-dihydroxythiophene-1,1-dioxide (VI) with o-phenylenediamine [9]. Using a similar method we attempted to prepare 2,3-bis(ethoxy-carbonylmethyl)-1,2,3,4-tetrahydroquinoxaline and to study the properties of the sulfone formed as an intermediate and also the corresponding sulfide.



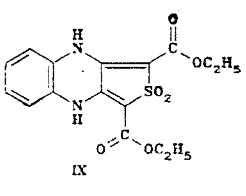
V



VI–VIII

VI $X=SO_2$, $R=C_6H_5$; VII X=S, $R=COOC_2H_5$; VIII $X=SO_2$, $R=COOC_2H_5$

A known method [10] was used to prepare the diethyl-3,4-dihydroxy-thiophene-2,5-dicarboxylate (VII). Its infrared spectrum showed bands at 1685, and, for OH, at 3260 cm^{-1} which are close to the wave numbers for the bands in the spectrum of ethyl salicylate. While the thiophene VII does not react with o-phenylenediamine, the diethyl-3,4-dihydroxythiophene-2,5-dicarboxylate-1,1-dioxide (VIII) [11] gives a product identified from analytical data as 1,3-bis(ethoxycarbonyl)-4,9-dihydrothieno[3,4-b]quinoxaline-2,2-dioxide (IX). Bands at 1670 and 1635 cm^{-1} in its infrared spectrum were assigned to stretching vibrations of the ester carbonyl groups and conjugated vibrations of C=C and NH [12]. The band assigned to stretching vibrations of the NH group associated with intramolecular hydrogen bonding with the oxygen atoms of the carbonyl group appears at 3230 cm^{-1}. In the spectrum of the 4,9-D_2-deuteroanalog the ND band is observed at 2395 cm^{-1} (degree of deuteration = 1.35), and the displacement of the 1635 cm^{-1} band into the 1585 cm^{-1} region supports the vibrational conjugation referred to above. The increase in the wave number of the C=O absorption to 1678 cm^{-1} is evidence that the carbonyl group of the ester enters into reaction with a —C=C—NH fragment [12]. In comparison with a model compound — ethyl-3-phenylaminocrotonate [13] — the wave number of the ester carbonyl group is some 10 cm^{-1} higher, probably as a result of the electron-acceptor properties of the sulfonyl group. The bands characteristic of the other functional groups and of the benzene nucleus appear at their usual positions. The absence of doublet bands is evidence of the symmetry of the molecule of the enamino-ester IX which is in accord with the observed symmetry of the multiplets of the aromatic protons in the NMR spectrum. The presence of the enaminoester groups gives rise to a shift of the absorption bands in the electron spectrum in comparison with the spectrum of the sulfone V [8].



IX

The molecular ion of compound IX (peak intensity 4% of maximum) is similar to the enaminoester I (X = $COOC_2H_5$ [14, 15]) in that they decompose with subsequent separation of two ethoxy groups or a molecule of ethanol. The elimination of SO_2 is not a very significant process, the peak intensity of the $[M-SO_2]^+$ ion being only 0.2% of the maximum. In the mass spectrum of the sulfone V the molecular ion peak is not observed at all and the maximum signals with m/z = 308 and 306 (91 and 100%, respectively) result from the (possibly thermal) separation of sulfur dioxide and a molecule of hydrogen [8, 16].

The difference in behavior under the conditions of mass spectroscopy reflects the structural differences of the two sulfones and also provides evidence of the retention of the tautomeric structure of the molecule in the gaseous state. The great stability of the sulfone IX accounts for our unsuccessful attempts to split off sulfur dioxide by boiling for 1 h in diphenyl ether and three days irradiation with UV light. Attempts to effect reductive decomposition [8] by means of Raney nickel, sodium borohydride, and aluminum amalgam also failed to give the expected dienamino ester. Such behavior of the sulfone IX is evidently connected with its stability which results from conjugation and internal hydrogen bonding.

EXPERIMENTAL

Infrared spectra were run on Spektromom-200 or Perkin Elmer 684 instruments as either nujol mulls or KBr disks; the wave number scale was calibrated with polystyrene film. NMR spectra were obtained on a JNM-FX 100 instrument (100 MHz) in the pulsed regime in DMSO-D_6 and mass spectra on a Varian MAT-44-S at 230°C. A Specord M-40 instrument was used for the electronic spectra.

2-Methylsulfonylmethyl-3,4-dihydro-3-oxoquinoxaline (III). Sodium hydride (5.6 g, 0.2 mole) was dissolved in a mixture of dimethyl sulfone and tetrahydrofuran and heated 30 min at 60°C. Diethyl oxalate (13 g, 0.089 mole) in 20 ml tetrahydrofuran was added at 20°C with stirring. At the end of the weakly exothermic reaction the mixture was heated to 60°C for 1 h. The cooled mixture was then poured onto ice and extracted twice with 30 ml chloroform. The basic aqueous layer was acidified with 10 ml HCl and extracted 15 times with 50 ml chloroform. The extract was evaporated and distilled in vacuum through a spiral microcolumn. After distillation of the residual diethyl oxalate and the solidified dimethyl sulfone, a substance was distilled with bp 160-170°C (1 kPa). The crude distillate was mixed with an excess (2.5 g) o-phenylenediamine in ethanol. After brief heating and cooling, the crystals which separated were filtered off and recrystallized from 100 ml acetic acid to yield 2.9 g (66%) of a compound with mp 248-254°C with decomposition (sublimation commenced at 190°C). Samples for analysis were purified on a column of silica gel with 1:1 pyridine:ethyl acetate mobile phase; the dark parts of the column, resulting from contaminants, were not eluted. After separation, the product was recrystallized from methanol, mp 262.5-264°C, sublimation commenced at 230°C. Proton NMR spectrum (ppm): 3.10 (s, CH_3); 1.61 (s, CH). Found, %: C 50.7, H 4.4, N 11.6, S 13.4; M 238. $C_{10}H_{10}N_2S$. Calculated, %: C 50.4, H 4.2, N 11.8, S 13.5.

2-Methylthiomethyl-3,4-dihydro-3-oxoquinoxaline (IV). A. To a solution of 6.8 g (0.295 mole) sodium in 300 ml anhydrous ethanol 15 g (excess) cold methanthiol was added at 0°C. The reaction mixture was cooled to 0°C and 28.2 g (0.118 mole) 2-bromomethyl-3-oxo-3,4-dihydroquinoxaline [17] was added with stirring over 5 min. Stirring was continued for 2 h at 20°C and the solid filtered off and dissolved in 400 ml water. Acidification with HCl resulted in the separation of 12.35 g (51%) crude product, mp 180-183°C (sublimation commenced at 160°C). Recrystallization twice from 50% ethanol yielded colorless needles, mp 184-186°C.

B. Mixing 16.2 g (0.1 mole) ethyl-3-methylsulfonyl-pyruvate [5] and 18.8 g (0.1 mole) o-phenylenediamine in 70 ml ethyl acetate with a drop of acetic acid and leaving the mixture to stand for 2 h gave crystals which were filtered off and washed with cold ethanol to yield 12.4 g (60%) of a compound of mp 181-182°C. When a sample of this was mixed with a sample of the preparation from A there was no depression of melting point. IR spectrum (in KBr disc) (cm^{-1}): 1670 (C=O), 2500-3200 (N-H). Proton NMR spectrum (ppm): 2.14 (s, CH_3); 3.75 (s, CH_2); 7.10-7.90 (m, arom. protons); 12.46 (s, NH). Found, %: C 58.5, H 5.2, N 13.6; M 206. $C_{10}H_{10}N_2OS$. Calculated, %: C 58.2, H 4.9, N 13.8.

1,3-Bis(ethoxycarbonyl)-4,9-dihydrothieno[3,4-b]quinoxaline-2,2-dioxide (IX). To a boiling solution of 16.8 g (0.05 mole) of the sodium salt of the dienolate VIII in 60 ml dilute (3:2) acetic acid was added 5.4 g (0.05 mole) of a saturated solution of o-phenylenediamine. The reaction product which separated after cooling was filtered off and twice recrystallized from ethanol (220 ml for 1 g product) to yield 3 g (15%) yellow crystals mp 235-236°C. Proton NMR spectrum (ppm): 1.33 (t, CH_3); 4.34 (q, CH_2); 11.40 (s, NH); centers of aromatic proton multiplets at 7.25 and 7.85 ppm (peri). UV spectrum in methanol, λ_{max}, nm (log ε): 252 (4.51); 371 (4.16); 392 (4.28), 418 (4.13). Found, %: C 52.4, H 4.5, N 7.8, S 8.8; M 364. $C_{16}H_{16}N_2O_6S$. Calculated, %: C 52.8, H 4.4, N 7.7, S 8.8.

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SYNTHESIS AND PROPERTIES OF DERIVATIVES OF sym-TRIAZINE.

5.* SYNTHESIS AND MASS SPECTROMETRIC STUDY OF CARBAMIDE DERIVATIVES OF sym-TRIAZINE

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Dibi Ammar, and A. F. Lunin

UDC 547.491.8107:543.51

The reaction of 2-amino- and 2,4-diamino-sym-triazines with nitrourea and phenyl isocyanate was studied; it gives N-mono- and N,N'-disubstituted ureas that contain sym-triazine segments. General features were established for the decomposition of carbamide derivatives of sym-triazine under electron impact.

Among the carbamide derivatives of sym-triazine are substances having bactericidal and antitumor properties, fungicides, and prospective herbicides [2-4]. But until now such sym-triazine derivatives have been difficult to obtain in spite of a number of partial or multistep methods of synthesis [5-8].

The present work is a study of the reaction of a number of 2-amino-4,6-disubstituted sym-triazines (I-VII) and 2,4-diamino-6-alkyl(aryl)-sym-triazines (VIII-XIII) with nitrourea and phenyl isocyanate.

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*For Communication 4, see [1].

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