STUDIES ON BENZODIAZINES

XIV*. OXIDATION OF TETRAZOLO[1,5-a]- AND s-TRIAZOLO[4,3-a]QUINOXALINES

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The oxidation of tetrazolo[1,5-a]quinoxaline and its 7,8-dimethyl derivative and of s-triazolo[4,3-a]quinoxaline has given the corresponding quinoxalin-4-ones. A calculation of the localization energies has shown the radical nature of the attack in position 4, and this has been confirmed by the results of the oxidation of 4-methyl- and 4-phenylquinoxalines.

It is known that quinoxaline N-oxide, like the N-oxides or many other heterocylic compounds, possesses physiological activity [2, 3]. In order to obtain N-oxides of polycyclic compounds including the quinoxaline nucleus, we have performed the oxidation of tetrazolo[1,5-a]quinoxaline (IVa) and its 7,8-dimethyl derivative (IVd) with hydrogen peroxide in glacial acetic acid, i.e., under the conditions customary for the preparation of quinoxaline N-oxides [4].

However, in place of the expected N-oxides, in both cases we isolated the corresponding tetrazolo-[1,5-a]quinoxalin-4-ones (V and VI, scheme).†

The oxidation of IVa with potassium permanganate in an alakaline medium also led to the quinoxalinones V and VI, although it is known that under these conditions simple quinoxaline derivatives form pyrazinedicarboxylic acids [7]. The oxidation of IVa with chromic anhydride in dilute sulfuric and glacial acetic acids also leads to the formation of the quinoxalinone V.

For comparison, we carried out the oxidation of s-triazolo[4,3-a]quinoxaline (VII) under similar conditions (hydrogen peroxide in glacial acetic acid and potassium permanganate in an alkaline medium), and again instead of the N-oxide we obtained a quinoxalinone derivative – s-triazolo[4,3-a]quinoxalin-4-one (VIIIa).

It appeared of interest to determine the mechanism of the oxidation reaction. Our MO LCAO calculations in Hückel's approximation of the localization energies with various types of attack on different carbon atoms show that the oxidation of compounds IV and VII at position 4 is possible only as the result of radical or nucleophilic attack on the carbon atom in position 4 (Table 1). If it is considered that under the oxidation conditions that we adopted nucleophilic substitution is unlikely, a radical mechanism for the formation of the quinoxalin-4-ones must be assumed. In the case of s-triazolo[4,3-a]quinoxaline, as can be seen from the results of the calculation, the localization energy for the attack of the C-1 carbon atom is lower than for the attack of the C-4 carbon atom. However, the greater value of the free valence

*For Communication XIII, see [1].

† The formation of quinoxalinones from quinoxaline compounds has been observed previously [5, 6].

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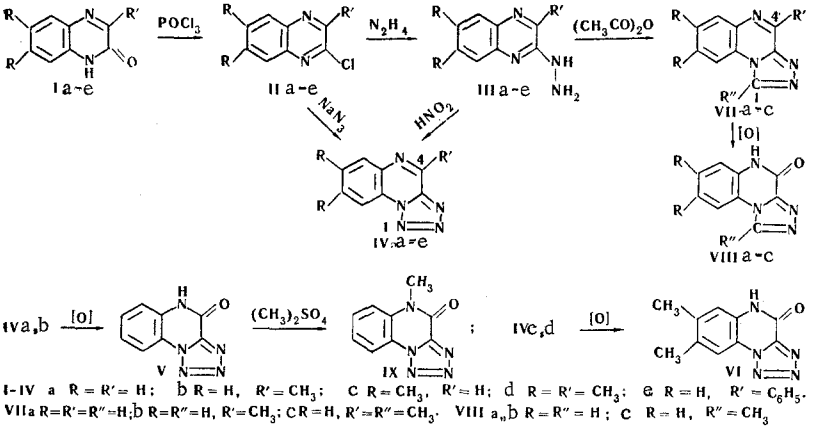
TABLE 1. Calculated Values of Localization Energies

Compound	Form of attack*	Localization energies in β units for the attack of the following atoms					
		C-1	C-4	C-6	C-7	C-8	C-9
IV	Nu	—	2,083	2,347	2,547	2,431	2,265
	R	—	2,299	2,375	2,493	2,461	2,312
	E	—	2,514	2,402	2,439	2,492	2,358
VII	Nu	2,160	2,084	2,362	2,561	2,442	2,472
	R	2,241	2,303	2,377	2,502	2,459	2,421
	E	2,322	2,521	2,392	2,443	2,475	2,369

*Nu = nucleophilic, R = radical, E = electrophilic.

index of the C-4 atom as compared with that for the C-1 atom that we calculated (0.451 and 0.437, respectively) permits the assumption that the s-triazolo[4,3-a]quinoxaline molecule reacts in a feebly polarized form. This can obviously explain the oxidation of compound VII at C-4, and not at C-1.



I-IV a R = R′ = H; b R = H, R′ = CH_3; c R = CH_3, R′ = H; d R = R′ = CH_3; e R = H, R′ = C_6H_5.
VIIa R = R′ = R″ = H; b R = R″ = H, R′ = CH_3; c R = H, R′ = R″ = CH_3. VIII a, b R = R″ = H; c R = H, R″ = CH_3

In order to determine the type of mechanism of the given reaction experimentally, we oxidized model compounds containing methyl and phenyl groups in position 4. The choice of groups is explained by the fact that the methyl group usually takes part in radical oxidation reactions readily, while such reactions are extremely rare for phenyl groups.

In actual fact, the oxidation of 4-methyltetrazolo[1,5-a]quinoxaline (IVb) gave us tetrazolo[1,5-a]-quinoxalin-4-one (V) as the oxidation product. This substance could be formed by the oxidation of the methyl group to a carboxy group, followed by decarboxylation and a radical attack on the C-4 carbon atom of the resulting tetrazolo[1,5-a]quinoxaline. Similarly, the oxidation of 4-methyl-s-triazolo[4,3-a]quinoxaline (VIIb) gave the oxidation product VIIIa. At the same time, 4-phenyltetrazolo[1,5-a]quinoxaline (IVe) does not oxidize under the reaction conditions given.

The high activity of a methyl group in position 4 must be noted. This follows from the fact that the oxidation of 4,7,8-trimethyltetrazolo[1,5-a]quinoxaline (IVd) gave 7,8-dimethyltetrazolo[1,5-a]quinoxalin-4-one (VI), i.e., only the 4-methyl group underwent oxidation, while the other methyl groups remained unchanged. The oxidation of 1,4-dimethyl-s-triazolo[4,3-a]quinoxaline (VIIc) gave a product with the 1-methyl group unaffected by oxidation, VIIIc.

The IR spectra of the initial quinoxalines and of the tetrazolo[1,5-a]quinoxalin-4-ones obtained have been studied. The IR spectrum of V has a very strong band of the stretching vibrations of a carbonyl group split into two $\nu_{C=O}$ bands at 1674 and 1723 cm^{-1}. Methylation with dimethyl sulfate in an alkaline medium gave a product the IR spectrum of which retained the carbonyl band (1682 cm^{-1}). This shows that the methylation reaction takes place at the N-5 position, and the product has the structure IX.

All the tetrazolo[1,5-a]quinoxalines exist in the stable tetrazole form and are not converted into the azide form even in trifluoroacetic acid, unlike the tetrazolo compounds of the quinazoline series [8].

The initial tetrazolo[1,5-a]quinoxalines (IV) were synthesized from the quinoxalin-2-ones I. These were converted by reaction with phosphorus oxychloride into the 2-chlorides II which, by reaction with hydrazine hydrate, gave the hydrazines III. Treatment of the hydrazines with sodium nitrite in acetic acid gave the tetrazolo[1,5-a]quinoxalines IV*. The s-triazolo[4,3-a]quinoxalines VII were obtained by the reaction of the hydrazinoquinoxalines III with acetic anhydride or orthoformic ester [10].

EXPERIMENTAL

Compounds I, IIa, b, e, IIIa, b, e, IVa, b, e, and VII were obtained by published methods [9-11], and their mp's corresponded to those given in the literature.

2-Chloro-3,6,7-trimethylquinoxaline (IId). A mixture of 4.5 g (0.024 mole) of 3,6,7-trimethylquinoxalin-2-one (Id), 40 ml of phosphorus oxychloride, and 30 ml ofdioxane was heated in the water bath for 3 h, cooled, and poured onto ice, and the precipitate was washed with water. The yield of II was 4 g (80%), mp 142-143°C; almost colorless needles from ethanol. Found, %: C 64.17; H 5.21; N 15.89; Cl 17.18. $C_{11}H_{11}ClN_2$. Calculated, %: C 63.93; H 5.36; N 15.5; Cl 17.15.

2-Chloro-6,7-dimethylquinoxaline (IIc). This was obtained from 6,7-dimethylquinoxalin-2-one (Ic) in a similar manner to IId with a yield of 75%. mp 91-92°C. Colorless prisms from ethanol. Found, %: C 62.34; H 4.90; N 14.52; Cl 18.67. $C_{10}H_9ClN_2$. Calculated, %: C 62.30; H 4.71; N 14.54; Cl 18.41.

2-Hydrazino-3,6,7-trimethylquinoxaline (IIId). A mixture of 0.35 g of IId, 0.3 ml of hydrazine hydrate, and 5 ml of ethanol was boiled in the water bath for 3 h and cooled, and the product was filtered off and washed with ethanol. The yield of IIId was 0.25 g (71.5%), mp 210-211°C, orange prisms from ethanol. Found, %: C 65.71; H 7.01; N 28.14. $C_{11}H_{14}N_4$. Calculated, %: C 65.32; H 6.98; N 27.70.

4,7,8-Trimethyltetrazolo[1,5-a]quinoxaline (IVd). a) An ice-cooled solution of 0.16 g (8 mmoles) of IIId in 5 ml of glacial acetic acid was treated at 10°C with a solution of an equimolar amount of sodium nitrite in 1 ml of water, and the mixture was kept at room temperature for 20 min, after which the product was filtered off and washed with water. The yield of IVd was 0.15 g (88%), mp 207-208°C, colorless needles from acetone. Found, %: C 62.41; H 5.21; N 33.29. $C_{11}H_{11}N_5$. Calculated, %: C 61.95; H 5.20; N 32.85.

b) To a heated solution of 0.5 g (0.025 mole) of IId in 10 ml of dimethylformamide was added 0.25 g of sodium azide and 1 ml of water to dissolve the azide. The mixture was boiled for 6 h and cooled, and the product was filtered off and crystallized from acetone. Yield 0.4 g (77%), colorless needles, mp 207-208°C. This product gave no depression of the melting point with the compound obtained by method (a).

7,8-Dimethyltetrazolo[1,5-a]quinoxaline (IVc). This was obtained from IIc and sodium azide in dimethylformamide in a similar manner to IVd with a yield of 70%, mp 209-210°C, colorless prisms from dimethylformamide. Found, %: C 60.49; H 4.55; N 35.18. $C_{10}H_9N_5$. Calculated, %: C 60.28; H 4.54; N 35.16.

Tetrazolo[1,5-a]quinoxalin-4-one (V). a) A solution of 5 mmoles of IVa or IVb in 20 ml of glacial acetic acid was treated with 4 ml of 30% hydrogen peroxide and the mixture was kept at 50°C for 16 h and cooled, and the product was filtered off and washed with water. Yield 44-50%, mp 284-285°C (according to the literature [11], 288°C), colorless elongated prisms from dimethylformamide. Found, %: C 51.35; H 2.77; N 37.95. $C_8H_5N_5O$. Calculated, %: C 51.34; H 2.67; N 37.73.

b) With stirring and heating in the boiling water bath, 9.5 g (0.06 mole) of $KMnO_4$ was added in small portions to a suspension of 0.01 mole of IVa or IVb in 20 ml of 2 N NaOH, and the mixture was kept at the same temperature for 1 h, by which time it has become completely decolorized, and was then filtered, and the manganese dioxide was treated with hot water; the combined filtrates were cooled and acidified with acetic acid to pH 5, and the precipitate that deposited was filtered off and washed with water. Yield 0.5 g (27%). From an analysis and a mixed melting point, the product was identical with the V obtained by method (a).

c) With heating, 0.92 g (5 mmoles) of IVb was dissolved in 10 ml of glacial acetic acid and 3.3 g (0.033 mole) of chromic anhydride was added in portions, after which the mixture was kept at 80°C for 1 h and poured into cold water, and the product was filtered off and washed with water. Yield 0.65 g (70%). It was identical with the compound obtained by methods (a) and (b).

* Compounds IV were also obtained by the reaction of the chlorides II with sodium azide.

7,8-Dimethyltetrazolo[1,5-a]quinoxalin-4-one (VI). This was obtained by the oxidation of IVc or IVd in a similar manner to V with hydrogen peroxide in glacial acetic acid with a yield of 57-60%, mp 289-290°C, colorless needles from dimethylformamide. Found, %: C 55.58; H 4.32; N 33.04. $C_{10}H_9N_5O$. Calculated, %: C 55.81; H 4.22; N 32.54.

s-Triazolo[4,3-a]quinoxalin-4-ones (VIIIa, b). These were obtained by the general method, VIIa,b being oxidized with potassium permanganate in 2 N NaOH with a yield of 30-35% or with hydrogen peroxide in glacial acetic acid with a yield of 64.3%; mp >350°C, colorless needles from dimethylformamide. Found, %: C 58.23; H 3.46; N 29.99. $C_9H_6N_4O$. Calculated, %: C 58.06; H 3.25; N 30.09.

1-Methyl-s-triazolo[4,3-a]quinoxalin-4-one (VIIIc). This was obtained by the oxidation of VIIc with potassium permanganate in 2 N NaOH with a yield of 44%, mp > 350°C, colorless plates from dimethylformamide. Found, %: C 59.45; H 4.04; N 28.10. $C_{10}H_8N_4O$. Calculated, %: C 59.99; H 4.03; N 27.99.

5-Methyltetrazolo[1,5-a]quinoxalin-4-one (IX). With heating, 0.47 g (2.5 mmoles) of V was dissolved in 10 ml of 2 N NaOH, the solution was cooled to 50°C, 1 ml of dimethyl sulfate was added, the mixture was shaken for 15 min, and the precipitate that had deposited was filtered off and washed with water. Yield 0.3 g (55%), mp 234-235°C, colorless elongated prisms from xylene. Found, %: C 53.95; H 3.76; N 34.67. $C_9H_7N_5O$. Calculated, %: C 53.73; H 3.51; N 34.81.

In the MO LCAO calculation we used Pullman's parameters [12, 13]. The solution of the secular determinants was performed on a BESM-4 computer.

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