PARTIAL REDUCTION OF QUINOXALINE 1,4-DIOXIDE DERIVATIVES WITH L-ASCORBIC ACID

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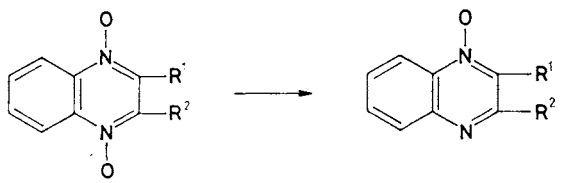
Partial reduction of quinoxaline 1,4-dioxide derivatives with L-ascorbic acid has been elaborated. Quinoxaline 1,4-dioxide, 2,3-dimethylquinoxaline 1,4-dioxide, 2-methylquinoxaline 1,4-dioxide and 2-(N-(2-hydroxyethyl)carbamoyl)-3-methylquinoxaline 1,4-dioxide afforded monoxides. In the monomethyl derivatives the more distant N—O bond is reduced. In addition to the monoxide, quinoxaline 1,4-dioxide afforded small amount of quinoxaline. Structures of all the compounds have been confirmed by ^{1}H and ^{13}C NMR spectroscopy.

Our previous paper[1] studied the reduction of quinoxaline 1,4-dioxide derivatives with amino acids in connection with detoxication of these compounds as possible residues of xenobiotics used in feeding farm animals. On boiling in an aqueous medium the derivatives studied were reduced at both the nitrogen atoms of the heterocyclic ring. An intermediate, quinoxaline monoxide, was isolated only in the case of quinoxaline 1,4-dioxide.

The present study concerns the reduction of quinoxaline 1,4-dioxide, 2-methyl- and 2,3-dimethylquinoxaline 1,4-dioxide, and particularly 2-(N-(2-hydroxyethyl)-carbamoyl)-3-methylquinoxaline 1,4-dioxide (*IV*) (used in Czechoslovakia as growth stimulator Olaquindox) with L-ascorbic acid (Table I).

On treatment with L-ascorbic acid in an aqueous medium, quinoxaline 1,4-dioxide derivatives (*A*) are partially reduced to give the corresponding monoxides (*B*) (Scheme 1). No reduction takes place at room temperature; only at elevated temperature the oxygen atom is selectively cleaved off.



A *B*

SCHEME 1

Quinoxaline 1,4-dioxide (*I*) affords the monoxide *V* as the principal product, along with small amounts of quinoxaline. 2,3-Dimethylquinoxaline 1,4-dioxide (*III*) is reduced to give 2,3-dimethylquinoxaline monoxide (*VII*). In 2-methylquinoxaline 1,4-dioxide (*II*) the reduction takes place at the position 4. The obtained monoxide *VI* was prepared already previously by direct oxidation of 2-methylquinoxaline[3]. 2-(N-(2-Hydroxyethyl)carbamoyl)-3-methylquinoxaline 1,4-dioxide (*IV*) reacts to afford 3-(N-(2-hydroxyethyl)carbamoyl)-2-methylquinoxaline 1-oxide (*VIII*), the reduction being analogous to that of the dioxide *II*. In compound *II* and *IV* the + *I* effect of the methyl group facilitates the removal of oxygen atom in position 4.

The structure of the starting dioxides as well as the obtained monoxides has been confirmed by ^{1}H and ^{13}C NMR spectroscopy (Table II). In addition, we measured the spectra of 2-methylquinoxaline (*IX*), 2,3-dimethylquinoxaline (*X*), and 2-(N-(2-hydroxyethyl)carbamoyl)-3-methylquinoxaline (*XI*) as the possible reduction products. The chemical shifts of quinoxaline mono- (*V*) and dioxide (*I*) were published in our previous paper[1]. From the chemical shift of the protons in position α and *peri* (ref.[4]) it can be deduced whether the reduction took place and which of the N-oxides was reduced. On reduction the positive mesomeric effect of the N—O group disappears and the signal of the α-proton is shifted downfield. Simultaneously, the chemical shift of the *peri*-proton is shifted upfield because the anisotropy of the N—O bond no longer exists. In the reduction of 2-methylquinox-

TABLE I

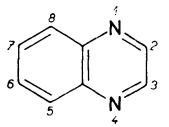
Reduction of quinoxaline 1,4-dioxide derivatives with L-ascorbic acid

Starting compound *A*			Reduced compound *B*		
No.	R^1	R^2	No.	Yield, g (%)	M.p., °C (solvent)
I	H	H	*V*	1·39 (48[b])	121—123[a] (cyclohexane)
II	CH_3	H	*VI*	1·85 (58)	93—94[c] (cyclohexane–ethanol)
III	CH_3	CH_3	*VII*	1·95 (56)	90—91[d] (cyclohexane–ethanol)
IV	CH_3	$CONH(CH_2)_2OH$	*VIII*	1·82 (37)	138—140·5[e] (cyclohexane–ethanol)

[a] 122—123°C (ref.[2]); [b] in addition, quinoxaline (9·4%) was isolated; [c] 93·5°C (ref.[3]); [d] 91°C (ref.[3]); [e] for $C_{12}H_{13}N_3O_3$ (247·2) calculated: 58·29% C, 5·30% H, 16·99% N; found: 58·13% C, 5·38% H, 17·21% N.

TABLE II

Chemical shifts δ(ppm) of the ^1H and ^{13}C NMR signals of the prepared compounds



No.	Substitution				^1H						^{13}C (—CH_3)	
	1	*2*	*3*	*4*	*2*	*3*	*5*	*6*	*7*	*8*	*2*	*3*
II	O	CH_3	H	O	2·62	8·29	8·59	7·86	7·82	8·62	15·66	—
III	O	CH_3	CH_3	O	2·74	2·74	8·61	7·8	7·8	8·61	14·61	14·61
IV	O	CH_3	R[a]	O	2·48	*b*	8·44	7·92	7·9	8·48	14·22	—
VI	O	CH_3	H	—	2·67	8·7	8·11	7·77	7·76	8·62	15·31	—
VII	O	CH_3	CH_3	—	2·69	2·75	7·98	7·66	7·7	8·52	13·62	23·64
VIII	O	CH_3	R[a]	—	3·10	*c*	8·07	7·80	7·8	8·6	13·84	—
IX	—	CH_3	H	—	2·72	8·68	7·98	7·69	7·65	8·03	22·39	—
X	—	CH_3	CH_3	—	2·73	2·73	7·98	7·65	7·65	7·98	23·11	23·11
XI	—	CH_3	R[a]	—	3·12	*c*	8·0	7·7	7·7	8·0	24·45	—

[a] R = $CONH(CH_2)_2OH$; [b] 8·9 t, 1 H (NH); 3·5 and 3·6 m, 2 × 2 H (CH_2); 4·7 t, 1 H (OH); [c] 8·4 br, 1 H (NH); 3·8 and 4·0 m, 2 × 2 H (CH_2); 2·7–3·0 t, 1 H (OH).

aline 1,4-dioxide (*II*) the chemical shift of the H-3 proton signal changed from 8·29 ppm to 8·70 ppm. Therefore, the reaction product is 2-methylquinoxaline 1-oxide (*VI*).

The reduction of heteroaromatic N-oxides causes marked changes also in the ^{13}C NMR spectra[5,6]. In the spectra of 2- or 3-methyl substituted quinoxaline N-oxide the ^{13}C methyl signals are shifted downfield when the methyl is in position α relative to the reduction site, and upfield when it is in position β. This change is due to disappearance of the positive mesomeric effect of the N—O group. The comparison of ^{13}C chemical shifts of the methyl group in 2-(N-(2-hydroxyethyl)-carbamoyl)-3-methylquinoxaline (*XI*) and its N-oxides *IV* and *VIII* shows that the methyl group of the latter is in position α relative to the N—O group.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Elemental analyses (C, H, N) were performed on a Hewlett–Packard 185 CHN Analyzer and differed by less than 0·3% from the theoretical values. The analytical samples were dried in vacuo over phosphorus pentoxide for 24 h. The starting compounds were prepared as described in ref.[1].

Reduction of Quinoxaline 1,4-Dioxide Derivatives with L-Ascorbic Acid

A mixture of the given quinoxaline 1,4-dioxide (0·02 mol), L-ascorbic acid (0·08 mol) and water (100 ml) was heated to 90—95°C for 5 h. After cooling, the reaction mixture was made alkaline (pH 12) with 5% sodium hydroxide solution, the product was taken up in ether and purified by crystallization. The yields and melting points are given in Table I.

Isolation of quinoxaline. The mother liquors from the crystallization of quinoxaline 1-oxide were extracted with 5% hydrochloric acid, the aqueous solution was made alkaline with 5% sodium hydroxide, quinoxaline was taken up in ether and distilled; m.p. 28—30°C.

NMR Spectroscopy

The NMR spectra were obtained on a Bruker WP 80 SY spectrometer (FT mode) at 80·13 MHz for ^{1}H and 20·15 MHz for ^{13}C in deuteriochloroform with tetramethylsilane (0·5%) as internal standard. Because of its poor solubility, compound *IV* was measured in a deuteriochloroform–hexadeuteriodimethyl sulfoxide mixture.

^{1}H NMR *spectra*: width 1 200 Hz, memory size 32 kB, digital resolution 0·07 Hz/point, pulse width 2·5 μs (flip angle 50°). To obtain accurate chemical shifts, the aromatic part of the spectrum (four-spin system) was simulated using a PANIC (Bruker) program.

^{13}C NMR *spectra*: ^{1}H noise-decoupling, width 4 900 Hz, memory size 16 kB, digital resolution 0·61 Hz/point, pulse width 5·0 μs (flip angle 41°), relaxation delay 4 s, exponential multiplication 3·0.

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