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QUINOXALINE N-OXIDES

XI. β-Acetoxyethylquinoxalines and Their N-oxides*

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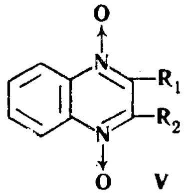
It is found that 2, 3-dimethylquinoxaline-1, 4-di-N-oxide reacts with formaldehyde only in the presence of alkaline reagents, and that independent of the amount of formaldehyde taken, 2-(β-hydroxyethyl)-3-methyl- and 2, 3-bis (β-hydroxyethyl) quinoxaline-di-N-oxides are formed. Oxidation of quinoxaline derivatives of general formula VI gives the corresponding mono- and di-N-oxides.

We previously showed that unlike 2-methyl- and 2, 3-dimethylquinoxalines, which are comparatively readily hydroxymethylated with formaldehyde in ethanol, under the same conditions their N-oxides do not undergo hydroxymethylation [1]. It was of interest to study the possibility of effecting this reaction in the presence of acids or alkalies. Attempts to effect hydroxymethylation of 2-methyl-(I) and 2, 3-dimethylquinoxaline-1, 4-di-N-oxides (II) by heating with formaldehyde in the presence of hydrochloric acid were unsuccessful, and the starting N-oxides were recovered unchanged.

Hydroxymethylation of II could be effected with 40% formaldehyde in ethanolic NaOH. Reaction occurred at 30°–35° C, and the yield was 45–55%. Using a 1:1 mole ratio of compound II: formaldehyde, one methyl group underwent hydroxymethylation, to give 2-(β-hydroxyethyl)-3-methylquinoxaline-1, 4-di-N-oxide (III). Doubling the quantity of formaldehyde resulted in both methyl groups of compound II being hydroxymethylated, and led to the isolation of 2, 3-bis (β-hydroxyethyl)-quinoxaline-1, 4-di-N-oxide (IV). When hydroxymethylation of I under the same conditions was attempted, considerable tar formation was observed, and no individual reaction productions could be isolated.

Acetylation of compounds III and IV with acetic anhydride in pyridine at room temperature gave 1, 4-di-N-oxides of the acetoxy derivatives, Va and Vb



V

Va $R_1=CH_2CH_2OCOCH_3$, $R_2=CH_3$;
Vb $R_1=R_2=CH_2CH_2OCOCH_3$;
Vc $R_1=CH_2CH_2OCOCH_3$, $R_2=H$;
Vd $R_1=CH(CH_2OCOCH_3)_2$, $R_2=H$.

Compound Vb was also prepared by oxidizing compound VIc (see table) with a peracetic acid solution. By the same method, compounds VIa and VIb gave compounds Vc and Vd, as well as compound VIe (apparently a 4-N-oxide); and 2-(α-acetoxymethyl-β-acetoxy) ethyl-3-(β-acetoxyethyl) quinoxaline. Hydrolysis of Vc with dilute hydrochloric acid gave 2-(β-hydroxyethyl) quinoxaline-1, 4-di-N-oxide (VIII).

Experimental

2-(β-Hydroxyethyl)-3-methylquinoxaline-1, 4-di-N-oxide (III). A mixture of 20.0 g (0.105 mole) compound II, 48 ml MeOH, 7.73 ml 39.2% formaldehyde (0.105 mole 100% CH_2O), and 15 ml 8% NaOH in MeOH (0.03 mole 100% NaOH) was held at 30°–35° C for 50–55 hr, cooled, and the precipitate filtered off. Yield 10.10 g (43.7%) compound III, mp 185°–186° C (ex AcOEt–MeOH). Found: C 60.21; H 5.52; N 12.90%. Calculated for $C_{11}H_{12}N_2O_3$: C 59.99; H 5.50; N 12.73%.

2, 3-Bis (β-hydroxyethyl) quinoxaline-1, 4-di-N-oxide (IV). This was prepared similarly to III, but using 15.4 ml 39.2% formaldehyde (0.21 mole 100% CH_2O). Yield 13.2 g (50.1%) compound IV, mp 187.5°–188.5° C (ex Me_2CO–MeOH). Found: C 57.80; H 5.60; N 11.40%. Calculated for $C_{12}H_{14}N_2O_4$: C 57.61; H 5.64; N 11.20%.

2-(β-Acetoxyethyl)-3-methylquinoxaline-1, 4-di-N-oxide (Va). A mixture of 3 g (0.0136 mole) III, 5 ml dry pyridine, and 2.7 ml Ac_2O was held at 20°–22° C for 15–18 hr. The reaction products were then poured on to ice, after 1 hr the pH adjusted to 2–3 with 2.5 N HCl, and the precipitate filtered off. Yield 2.74 g (76.8%) compound

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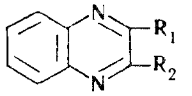
*For Part X see [3].

Va, mp 159°–160° C (ex MeOH). Found: C 59.29; H 5.47; N 10.68%. Calculated for $C_{13}H_{14}N_2O_4$: C 59.54; H 5.38; N 10.69%.

In the same way, IV gave 2,3-bis(β-acetoxyethyl)quinoxaline-1,4-di-N-oxide (Vb), in 90% yield, mp 130°–130.5° C (ex MeOH). Undepressed mixed mp with Vb prepared by oxidizing VIc.



VI

Compound	R_1	R_2	Mp °C (crystallizing solvent)	Formula	Found, %	Calculated, %	Yield, %
a*	$CH_2CH_2OCOCH_3$	H	Oily substance	Oxidized without purification			84.0
b*	$CH(CH_2OCOCH_3)_2$	H	Oily substance	Oxidized without purification			92.5
c	$CH_2CH_2OCOCH_3$	$CH_2CH_2OCOCH_3$	(MeOH)	$C_{16}H_{18}N_2O_4$	9.25	9.27	92.3
d	$CH(CH_2OCOCH_3)_2$	CH_3	62—63 (Aqueous MeOH)	$C_{16}H_{18}N_2O_4$	9.27	9.27	95.2
e	$CH_2CH_2OCOCH_3$	$CH(CH_2OCOCH_3)_2$	76—77.5 (MeOH)	$C_{19}H_{22}N_2O_6$	7.36	7.48	96.3

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* The reaction products were poured on to ice, 2.5 N HCl added, the whole extracted with $CHCl_3$, and the extract evaporated.

The methylol derivatives of 2-methyl- and 2,3-dimethylquinoxalines previously prepared [1], were acetylated similarly, and the acetyl derivatives are given in the table.

2-(β-Acetoxyethyl)quinoxaline-1,4-di-N-oxide (Vc). A mixture of 10.62 g (0.0492 mole) compound VIa, 164.6 ml 9.9% peracetic acid solution [2] (0.215 mole 100%), 2.42 g fused AcONa, and 0.004 g $Na_4P_2O_7$ was kept at 55°—60° C for 10 hr. Excess peroxide was destroyed by a solution of Na_2SO_3. The reaction products were evaporated almost to dryness under reduced pressure, treated with saturated $NaHCO_3$ solution (pH 5–6), then extracted with $CHCl_3$. The residue after distilling off the $CHCl_3$ was triturated with MeOH, cooled, and filtered, to give 5.23 g (42.8%) compound Vc, mp 129°–130° C (ex MeOH). Found: C 57.94; H 4.94; N 11.29%. Calculated for $C_{12}H_{12}N_2O_4$: C 58.05; H 4.87; N 11.29%.

The following N-oxide, 2,3-bis(β-acetoxyethyl)quinoxaline-1,4-di-N-oxide (Vb) was prepared similarly: mp 130°–130.5° C (ex MeOH). Found: C 57.70; H 5.31; N 8.25% . Calculated for $C_{16}H_{18}N_2O_6$: C 57.49; H 5.43; N 8.38%.

2-[(α-Acetoxymethyl-β-acetoxy)ethyl]quinoxaline (Vd). Yield 30%, mp 125.5°–127.0° C (ex benzene). Found: C 56.24; H 5.10; N 8.74%. Calculated for $C_{15}H_{16}N_2O_6$: C 56.28; H 5.03; N 8.75%.

2-(β-Acetoxyethyl)-3-[(α-acetoxymethyl-β-acetoxy)ethyl]-quinoxaline (VII). The reaction was carried out just as in preparing IVc. The $CHCl_3$ extract was dried, and run through an Al_2O_3 column. The first fractions, obtained by eluting with $CHCl_3$, gave on treatment with Me_2CO VII, yield 40.8%, mp 88.5°–90° C (ex MeOH). Found: C 58.44; H 5.73; N 7.22%. Calculated for $C_{19}H_{22}N_2O_7$: C 58.45; H 5.68; N 7.18%.

2-(β-Hydroxyethyl)quinoxaline-1,4-di-N-oxide (VIII). 1 g (0.004 mole) compound Vc and 20 ml 2.5 N HCl were heated together for 20 min at 100° C. The solution was cooled, neutralized with 2.5 N NaOH, and extracted with $CHCl_3$. The residue left after evaporating off the $CHCl_3$ was triturated with cold MeOH, and the crystalline material filtered off. Yield 0.2 g (24%) compound VIII, mp 126°–127° C (ex MeOH). Found: C 58.49; H 4.84; N 13.66%. Calculated for $C_{10}H_{10}N_2O_3$: C 58.21; H 4.88; N 13.58%.

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