N-OXIDES OF THE QUINOXALINE SERIES

XIII. Reaction of Quinoxaline N-Oxides with Benzenesulfonyl Chloride and Benzoyl Chloride*

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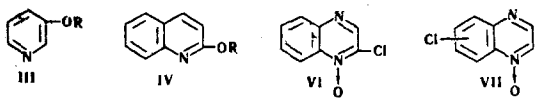
The reaction of quinoxaline N-oxides with benzenesulfonyl chloride and benzoyl chloride is investigated, and its mechanism discussed. The reaction products are investigated.

It is known that when the chlorides of inorganic acids ($POCl_3$, SO_2CL_2, etc.) are heated with pyridine and quinoline N-oxides, and some other heterocyclic compounds, they halogenate the ring primarily at the α- and γ-positions, with the accompaniment of deoxygenation of the N → O group [1–3]. Furthermore under similar conditions aromatic sulfonyl chlorides, e.g. tolyl chloride (I) or benzenesulfonyl chloride (II), chlorinate only the alkyl side chain. Thus the reaction of α-picoline N-oxide with I or II gives α-chloromethylpyridine [4, 5], but when I or II reacts with N-oxides of unsubstituted pyridine or quinoline, the main reaction products are arylsufonyloxy derivatives III [6] (with pyridine N-oxide) and IV (with quinoline N-oxide) [7].

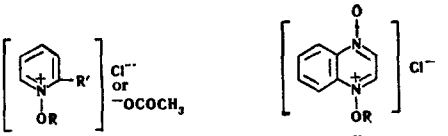


III IV VI VII

We previously showed that, unlike pyridine and quinoline N-oxides, quinoxaline 1, 4-di-N-oxide is readily chlorinated by II, giving 2-chloroquinoxaline 1-N-oxide benzenesulfonate, converted by neutralization to 2-chloroquinoxaline 1-N-oxide (VI) [8]. Closer investigation of this reaction showed that in addition to base VI (yield 66–69%) a mixture of side reaction products arises, from which an insignificant quantity of 2-hydroxyquinoxaline 4-N-oxide can be isolated, and the presence of 2, 3-dihydroxyquinoxaline also being shown by paper chromatography. In addition, chloroquinoxaline N-oxide (VII) is isolated in 2.0–2.5% yield (VII), isomeric with the main reaction product VI. Previously this compound was tentatively assigned the structure 2-chloroquinoxaline 4-N-oxide (VIII) [8], but it proved not to be identical with compound VIII synthesized by a known method, [9]. Therefore it could be a quinoxaline mono-N-oxide chlorinated in the benzene part of the molecule. This was confirmed by the PMR spectrum of VII. The latter's having two doublets at 8.61 and 8.80 ppm, corresponding to the H_2 and H_3 protons of quinoxaline 1-N-oxide, indicated that the hydrogens in the pyrazine part of the molecule were unsubstituted. In addition changes were observed in the multiplet due to benzene ring proton signals, showing that one of the hydrogens had been replaced.* The position of the halogen in the benzene part of the molecule remains to be specified.

A number of workers have studied the mechanism of the reaction of N-oxides of pyridine, quinoline, isoquinoline, and their α-methyl derivatives with chlorides of carboxylic and arylsulfonic acids. They have shown that the first stage is formation of type IX quaternary salts, whose further splitting and conversion to end products proceed primarily by an ionic mechanism involving heterolysis of the N—OR bond [4, 5, 10, 11]. There was no question of a free radical mechanism for the reaction, as adding inhibitors of radical reactions to the reactants was without effect on the yields of the main products [12].

A study has now been made of the effects of radial reaction inhibitors and promoters on the course of the reaction between quinoxaline di-N-oxide (V) and II, and it has been found that it does not proceed as do the reactions of II, and it has been found that it does not proceed as do the reactions of II with pyridine or quinoline N-oxides. The presence of small quantities of p-benzoquinone considerably lowered the yield of compound IV (see table), indicating that the main reaction involves free radicals. The yield of VI is practically unaltered by the presence of benzoyl peroxide, and this can obviously be explained by activation of side radical reactions. It can be postulated that the first stage in the reaction is also formation of quaternary salt Xa, but that the splitting of the latter and the ultimate conversion to end product VI involves a free radical mechanism, with homolytic breaking of the N—OR bond. Formation of a type X



IX X

R = $COCH_3$, $SO_2C_6H_4CH_3$, p-$SO_2C_6H_5$; R′ = H, CH_3

Xa R = $SO_2C_6H_5$; Xb R = COC_6H_5

*For Part XII see [17]

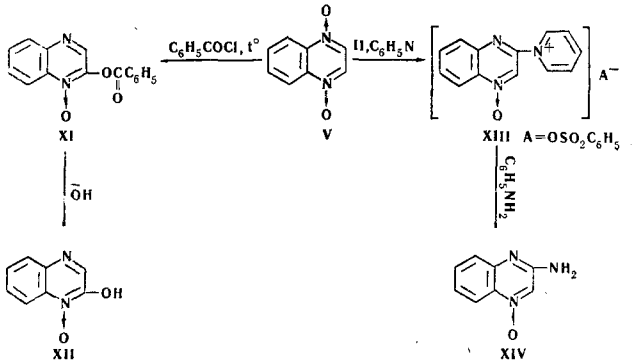
*The PMR spectrum of compound VII was determined with a JNM4H100 spectrometer, in $CDCl_3$ solution, with $SiMe_4$ as the internal standard.

Reaction Between Quinoxaline Di-N-oxide (V) and Benzenesulfonyl Chloride (II) in the Presence of Radical Reaction Inhibitors or Promoters.

Run no.	Amount of V		Amount of II		Amount of p-benzo-quinone, g	Amount of Bz_2O_2	Reaction temperature, °C	Reaction time, hr	Yield of Compound	
	g	g/mole	ml	g/mole					g	% Theoretical
1	4.0	0.0247	9.6	0.0753	—	—	20—25	48	3.0	67.4
2	4.0	0.0247	9.6	0.0753	—	—	20—25	48	2.90	65.0
3	4.0	0.0247	9.6	0.0753	—	—	20—25	64	3.10	69.6
4	4.0	0.0247	9.6	0.0753	0.15	—	20—25	48	1.38	31.0
5	4.0	0.0247	9.6	0.0753	0.15	—	20—25	48	1.62	36.4
6	4.0	0.0247	9.6	0.0753	0.15	—	20—25	68	1.80	40.4
7	4.0	0.0247	9.6	0.0753	—	0.15	20—25	48	2.92	65.6
8	4.0	0.0247	9.6	0.0753	—	0.15	20—25	68	2.80	62.9

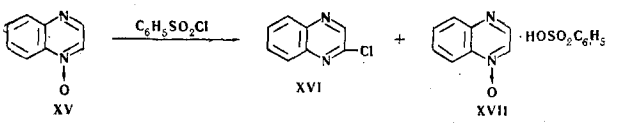
salt should be made harder by using chlorides of less reactive acids, e.g. benzoyl chloride (salt **Xb**). Actually, unlike **II**, benzoyl chloride did not react with **V** at room temperature [8]. Further study of this reaction showed that benzoyl chloride reacted with **V** at elevated temperature (90–95°), but that it led to formation of benzoxyl derivative **XI** instead of to ring chlorination, the structure of **XI** being proved by its conversion to the previously described 2-hydroxyquinoxaline 1-N-oxide (**XII**) [13]. Such a difference between the end products of reaction of **V** with **II** and with benzoyl chloride, could have been due to a difference between the structures of the reacting acid chlorides. Striking was the fact that chlorination with **II** took place at room temperature, while benzoxylation took place at elevated temperature, so it was interesting to investigate the effect of temperature on the courses of these reactions. The reaction of **V** with **II** was chosen for this purpose since, unlike the reaction with benzoyl chloride, it could be effected at various temperatures. At 60–65° **V** and **II** reacted mainly as at 29–25°, i.e. there was ring chlorination, but at 90–95° the reaction proceeded differently. At this temperature the product was resinous, and consisted of a mixture, which paper chromatography showed to contain only traces of chlorination product **VI**, but 2,3-dihydroxyquinoline could be isolated. The results of the runs showed that temperature considerably affects the course of the reaction of **V** with acid chlorides. It may be that the primary reaction product is 2-chloroquinoxaline 1-N-oxide (**VI**), which is converted to the corresponding hydroxy (aryloxy) derivatives by heating under the reaction conditions.

The fact that **V** reacted quite otherwise with **II** in the presence of pyridine is of interest. Then mixing the reactants at room temperature led to considerable heat evolution, and the reaction gave salt **XIII**. This was similar to the reaction of quinoline N-oxide with **I** [14].



Decomposition of salt **XIII** by the method usually used with compounds of that structure, i.e. heating with aniline [14], gives 3-aminoquinoxaline 1-N-oxide.

It was previously shown [13], that quinoxaline mono-N-oxide (XV), unlike its di-N-oxide (**I**), is unchanged when heated with acetic anhydride [13]. Further investigation showed that mono-N-oxide **XV** reacts with benzenesulfonyl chloride without heating, to give 2-chloro-quinoxaline (**XVI**) (~50% theoretical); the other 50% of the starting mono-N-oxide unites with the benzenesulfonic acid formed, to give salt **XVII**:



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EXPERIMENTAL

Reaction of quinoxaline di-N-oxide with benzenesulfonyl chloride (II) without heat. 100 ml (0.784 mole) **II** was added to 20 g (0.123 mole) **V**, and the whole stirred for 48 hr at 20–25°. The **V** gradually dissolved, and 2-chloroquinoxaline 1-N-oxide benzenesulfonate began crystallizing out after 24–26 hr. Finally the solid was filtered off and washed successively with benzenesulfonyl chloride and ether, yield 31.5 g, mp 159–160° (ex $CHCl_3$). The salt thus obtained was treated with aqueous $NaHCO_3$, and the 2-chloroquinoxaline 1-N-oxide (**VI**) filtered off (14.5–15.5 g, 66.5–69.5%), mp 115–116° (ex EtOH) [8]. The salt of compound **VI** was also decomposed to **VII**, by heating in water or EtOH. After removing the **VI**, the bicarbonate solution was extracted with $CHCl_3$, and the liquid distilled off, leaving a solid residue (3.8–4.0 g), which was heated at 40–45° for 15–20 min, with 10 ml 2.5 N NaOH. The insoluble material was filtered off, and the filtrate acidified to pH 2. The 2-hydroxyquinoxaline 1-N-oxide (**XIII**) that separated (1.30 g), was purified by reprecipitating from $NaHCO_3$ solution, mp 211–212° [13]. The solid undissolved by alkali (0.47 g) melted at 153–154° (ex MeOH). Depressed mixed mp with 2-chloroquinoxaline 4-N-oxide [9]. Found: Cl 19.68; N 15.48%, calculated for $C_8H_5ClN_2O$: Cl 19.63; N 15.50%. The bicarbonate solution was acidified to pH 3 and again extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave 0.3 g material, which was crystallized from EtOH, to give 0.2 g compound (mp 270–271°) identified by mixed mp and paper chromatography as 2-hydroxyquinoxaline 4-N-oxide [15]. Ether was added to the main products solution after removing the salt of compound **VI**, until cloudiness vanished. The resinous precipitate obtained was treated with $NaHCO_3$ solution, and the dark brown solid (2.2 g) filtered off. Paper chromatography of this, using markers, revealed 2,3-dihydroxyquinoxaline and two compounds of unknown structure.*

Reaction of quinoxaline di-N-oxide (V) with benzenesulfonyl chloride (II) at elevated temperature. 2 g (0.0123 mole) Di-N-oxide **V** was stirred for 4 hr at 60–62° with 10 ml (0.0784 mole) compound **II**, to give 2.8 g benzenesulfonate of compound **VI**.

b) 2 g Di-N-oxide **V** was stirred for 1 hr at 75° with 10 ml compound **II**, then for 4 hr at 90–96°. After cooling there was a viscous dark mass that did not crystallize, which was treated with ether to give a solid that was filtered off and mixed with aqueous $NaHCO_3$. The whole was again filtered, to give 1.57 g solid. Paper chromatography of this solid using markers showed a strong spot of 2,3-dihydryoxyquinoxaline (R_f 0.66, bright bluish-violet fluorescence in UV light) [16], a very weak spot of 2-chloroquinoxaline 1-N-oxide, and 2 spots of unknown substances. Reprecipitation from alkali and treatment with hot acetone gave 0.40 g 2,3-dihydroxyquinoxaline, which did not melt up to 360°, R_f 0.66 [16].

Reaction of quinoxaline di-N-oxide (V) with benzenesulfonyl chloride in the presence of pyridine. 4 ml **II** was added to 2 g **V** in 12 ml dry pyridine. After 3 min heating was observed, accompanied by rapid rise of the temperature to 90°, and separation of a precipitate. The mixture was cooled with ice water to 80°, after which, the temperature gradually fell to room temperature, without external cooling. It was then stirred for 1 hr more, cooled to 10–15°, and the 1-(4'-N-oxide quinoxalyl-2') pyridinium benzenesulfonate (**XIII**) filtered off, mass 4.3 g (89.9%), mp 223–224° (ex EtOH). Found: C 59.65; H 4.04; N 10.88; S 8.58%, calculated for $C_{19}H_{15}N_3O_4S$:

*The chromatographing was done in the system BuOH–5%AcOH (1:1).

C 59.80; H 3.97; N 11.00; S 8.4%. AcOEt was added to the main products solution after removing **XIII**, the resinous solid filtered off and recrystallized from a small amount of EtOH. The substance thus obtained (2.6 g), was identical with pyridine hydrochloride.

Decomposition of salt XIII. 7.5 ml Aniline was added to 3.6 g (0.0094 mole) **XIII** in 60 ml absolute EtOH, and the mixture refluxed for 45 min. The products were cooled and the solid filtered off, mass 1.24 g (81.5%) Compound **XIV** obtained melted at 278° (decomp). It was identified as 3-aminoquinoxaline 1-N-oxide by a mixed mp test and by paper chromatography. [16].

Reaction of quinoxaline di-N-oxide (V) with benzoyl chloride. 1 g (0.0062 mole) Di-N-oxide **V** was heated with 3 ml (0.9256 mole) benzoyl chloride at 90–95° for 45 min, until completely dissolved, and then for 3 hr more at 80–85°. The reaction products were cooled and the 2-benzoxyquinoxaline 1-N-oxide (**XI**) filtered off, yield 0.73 g (44.5%), mp 162–163° (ex MeOH). Found: C 68.00; H 4.00; N 10.73%, calculated for $C_{15}H_{10}N_2O_3$: C 67.67; H 3.78; N 10.52%.

3 ml 2.5 N NaOH was added to 0.6 **XI**, and the mixture heated on a steam bath until **XI** was completely dissolved, after which the solution was filtered and acidified to pH 1–2, the precipitate filtered off, dried, and treated a few times with ether. Evaporation of the ether gave 1.5 benzoic acid. The ether-insoluble material (0.30 g) had map 215–216°, and gave an undepressed mixed mp with known 2-hydroxyquinoxaline 1-N-oxide, prepared as described in [13].

Reaction of quinoxaline mono-N-oxide (XV) with benzenesulfonyl chloride. 2 g **XV** in 12 ml benzenesulfonyl chloride was left for 4 hr at room temperature, and the quinoxaline mono-N-oxide of benzenesulfonate (**XVII**) filtered off (2.1 g). Colorless crystals, mp 152–153° (ex absolute EtOH). Found: C 55.55; H 3.83; N 9.24; S 10.62%, calculated for $C_{14}H_{12}N_2O_4S$: C 55.25; H 3.97; N 9.24; S 10.54%. $NaHCO_3$ solution was added to the salt **XVII** (2 g) until evolution of CO_2 ceased. The products were extracted with $CHCl_3$, to give the N-oxide **XV** (1 g) mp 125–126° (ex ether–EtOH), picrate mp 184–185° [2]. After removing **XVII**, the main reaction products were treated with ether, the solution separated from the resin that precipitated, and the ether distilled off. The residue was treated (with cooling) with ammonia. The resultant crystalline mass was repeatedly extracted with petrol ether, and petrol ether–ether. The extracts were dried and the solvent distilled off, to give 0.88 g oily material, which crystallized on keeping, mp 46–47° (ex petrol ether). Undepressed mixed mp of the **XVI** prepared with 2-chloroquinoxaline.

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