QUINOXALINE N-OXIDES

XIV. Nucleophilic Substitution in Halogen Derivatives of Quinoxaline N-Oxides

A. S. Elina

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 5, 940–943, 1967

UDC 547.863.13:542.944.9

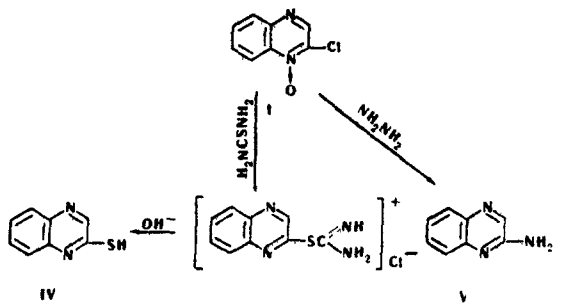
It is found that 2-chloroquinoxaline 1-N-oxide readily undergoes nucleophilic substitution with ammonia, alkalies, and 4-acetylaminobenzenesulfonamide, giving the 1-N-oxides of 2-amino, 2-hydroxy, and 2-(4'-acetylaminobenzenesulfonamido) derivatives of quinoxaline. Treatment of 2-chloroquinoxaline 1-N-oxide with thiourea or hydrazine leads not only to nucleophilic substitution, but also to oxidation-reduction processes, with formation of respectively 2-thio- and 2-aminoquinoxaline. With 2-bromomethylquinoxaline 1,2-di-N-oxide, replacement of the bromine by a thiuronium group is not accompanied by deoxidation of the nitrogen atoms.

In the present paper a study is made of nucleophilic replacement of halogen in N-oxides of halogen derivatives of quinoxaline.

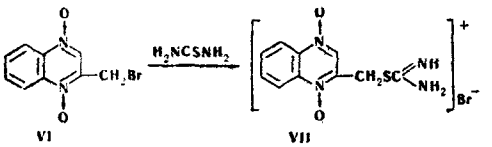
It is found that in 2-chloroquinoxaline 1-N-oxide I, the chlorine undergoes nucleophilic replacement considerably more easily than that in 2-chloroquinoxaline. Thus while 2-aminoquinoxaline is usually obtained by heating 2-chloroquinoxaline with ethanolic ammonia at 150°–155° [1], 2-aminoquinoxaline 1-N-oxide II is readily formed by heating compound I with aqueous or ethanolic ammonia at 60°–80°, and even at room temperature the chlorine group of compound I is found to undergo replacement by the amino group. Brief heating of I with dilute NaOH gives 2-hydroxyquinoxaline 1-N-oxide. Heating I with 4-acetylaminobenzenesulfonamide in the presence of K_2CO_3 gives 2-(4'-acetylaminobenzenesulfonamido)quinoxaline 1-N-oxide (III).

The results of investigating the reactions of compound I with thiourea of hydrazine hydrate are of interest. When I is treated with thiourea, not only is there nucleophilic replacement of halogen, but oxidation reduction processes, leading to deoxidation of the ring nitrogen, also take place. A crystalline compound with a high sulfur content (about 75%) is isolated from the reaction products, obviously a product of the oxidation of thiourea, while 2-mercaptoquinoxaline (IV) is isolated by treating the evaporated solution of reaction products with aqueous alkali.

Treatment of I with hydrazine hydrate leads to profounder oxidation reduction processes, and instead of 2-hydrazinoquinoxaline the main product is 2-aminoquinoxaline (V).



IV V



VI VII

The way in which the above reaction proceeds indicates that the N → O bond in the quinoxaline N-oxides is weaker than in pyridine and quinoline N-oxides, since it is known that 2- and 4-halogeno-substituted pyridine and quinoline N-oxides do not, when treated with Na_2S or thiourea, suffer N-deoxidation, but give N-oxides of the corresponding thiol derivatives [2, 3].

Compound I reacts with thiourea at room temperature, and with hydrazine hydrate even at 0°. The ease with which these reactions are effected obviously in the first place points to occurrence of nucleophilic replacement of the chlorine, with oxidation-reduction processes occurring only subsequently. If the sequence of the processes were reversed, i.e., if the cyclic nitrogen atom was first deoxidized and this were followed by nucleophilic replacement of the chlorine, more drastic temperature would in all probability be needed to effect this latter reaction. In addition it was shown that when the halogen and the substituent introduced $\left(-SC\begin{matrix}NH\\NH_2\end{matrix}\right)$ are separated from the ring by a methylene group, only nucleophilic replacement of the halogen occurs, and that the N → 0 group is not reduced. Thus 2-bromomethylquinoxaline 1,4-di-N-oxide (VI) reacts with thiourea to give the corresponding isonitrone salt (compound VII). Compound VI is obtained by oxidizing 2-bromomethylquinoxaline with perhydrol in acetic acid. Oxidation of 2-(dibromomethyl)quinoxaline under the same conditions gives only the mono-N-oxide, which is very probably 2-(dibromomethyl) quinoxaline 4-N-oxide, since N-1, adjacent to the dibromomethyl group, should oxidize with greater difficulty than N-4.

I thank O. Yu. Magidson for his interest in the present work.

EXPERIMENTAL

Reaction of 2-chloroquinoxaline 1-N-oxide (I) with ammonia. a) 1 g (5.53 mmole) I was heated at 60° with 7 ml conc. ammonia for 10 hr. The products were evaporated to dryness, yield 0.67 g (75%) 2-aminoquinoxaline 1-N-oxide (II), mp 187°–188°. Undepressed mp with

and authentic specimen of II of proven structure [4], and identity with the latter also proved by paper chromatrography.*

b) 1.3 g (7.2 mmole) I in 10 ml 18% NH_3 in EtOH was heated for 5 hr in an autoclave at 70° (bath), then for 1 hr at 80°. After cooling the reaction products were filtered and the EtOH distilled off to dryness. Yield 0.85 g (73.3%) II.

c) 1 g (5.53 mmole) I was dissolved in 45–50 ml 18–19% ethanolic NH_3 and the mixture left at room temperature. After standing overnight the solid dissolved. A sample of the reaction products gave with $FeCl_3$ the dark blueish-green color characteristic of compound II. From the solution of reaction products 0.5 g I, and 0.35 g of a mixture of substances, consisting of I and II were isolated (shown by paper chromatography using visualizers.)

Reaction of 2-chloroquinoxaline 1-N-oxide (I) with NaOH. 1 g I was heated with 4 ml 2.5N NaOH at 80° until solution was complete (20–30 min). The resultant solution was decolorized with active charcoal, filtered, and acidified with 2.5 N HCl, to pH 1–2. Yield 0.72 g (80.2%) crystalline compound mp 209°–210°, which was identified as the previously described 2-hydroxyquinoxaline 1-N-oxide [5], by the characteristic cherry red color which it gave with $FeCl_3$, and by its undepressed mixed mp.

2-(4'-Acetylaminobenzenesulfamido)quinoxaline 1-N-oxide. (III). A mixture of 3 g I, 3.4 g 4-acetylaminobenzenesulfonamide, and 4.6 g anhydrous K_2CO_3 was refluxed and stirred for 9 hr, then the products cooled, the solid filtered off, and treated with 2N HCl. Yield 5.1 g (86.5%) III, mp 236°–237° (ex EtOH); II gave a deep violet color with $FeCl_3$. Found: N 15.80; S 9.10%, calculated for $C_{16}H_{14}N_4O_4S$: N 15.83; S 8.94%. Heating II (0.2 g) with 2.5 ml HCl (d 1.19) at 96°–97° until solution is complete, leads to hydrolysis of the 3-aminobenzenesulfonamide group. On cooling the reaction products a crystalline compound separates, identical in mp (241.5°) and color reaction with $FeCl_3$ with the hydrochloride of compound II [4].

2-(4'-aminobenzenesulfonamido)quinoxaline 1-N-oxide (VIII). mixture of 1.5 g VII, 85 ml water, and 15 ml 2N NaOH was heated on a steam bath for 8 hr, the products filtered, and the filtrate acidified to pH 3–4. The solid was filtered off and crystallized from dilute AcOH, yield 0.75 g (56.9%) VIII, mp 218°–219°. Found: N 17.34; S 9.98%, calculated for $C_{14}H_{12}N_4O_3S$: N 17.7; S 10.13%.

Reaction of 2-chloroquinoxaline 1-N-oxide with hydrazine hydrate.

a) A mixture of 0.5 g I and 1 ml hydrazine hydrate in 15 ml absolute EtOH was kept at 0°–2° for 10–12 hr. The products were filtered, and the filtrate vacuum evaporated to dryness of 30°. The residue was crystallized from water, yield 0.25 g (62.5%) compound mp 151°–152°. Found: C 65.90; H 4.70; N 28.99%, calculated for $C_8H_7N_3$: C 66.26; H 4.86; N 28.98%. Undepressed mixed mp with the compound prepared from 2-aminoquinoxaline [1].

b) Reaction of I with a smaller amount of hydrazine hydrate (for 1 g I, 0.5 ml $NH_2NH_2 \cdot H_2O$) at room temperature gave 0.1 g dark red substance mp 283°–284°, and evaporation of the solution of reaction products, gave 0.8 g of a mixture consisting of V and I.

Reaction of 2-chloroquinoxaline 1-N-oxide (I) with thiourea. A mixture of 1 g I and 0.85 g thiourea in 7 ml MeOH was left for 35 hr. First of all there was complete solution, then a solid separated (0.6 g), and this was filtered off and recrystalized a few times from $CHCl_3$–ether, mp 184°–185°. Found: N 7.33; S 75.26%. After removing the crystalline substance, the solution of reaction products was vacuum evaporated at 30°, the residue treated with 2.5N NaOH, then left at room temperature for 30 minutes. The solution was filtered and acidified, when a yellow crystalline substance separated, yield 0.4 g (40.5%), mp 200°–201° (ex EtOH). Undepressed mixed mp with 2-mercaptoquinoxaline [6]. Found: N 17.56; S 19.72%, calculated for $C_8H_6N_2S$: N 17.26; S 19.76%.

2-Bromomethylquinoxaline di-N-oxide (VI). A mixture of 85 ml glacial AcOH, 36 ml Ac_2O, and 38 ml 30% perhydrol was held for 5 hr/40°, then 0.5 g 2-bromomethylquinoxaline added, and the mixture held at 50°/30 hr. The reaction products were evaporated to small volume, ether added to the residue, and the crystalline solid separated off. Yield 5.5 g VI, mp 160°–161° (ex MeOH). Found: Br 31.17; N 10.72%, calculated for $C_9H_7BrN_2O_2$, Br 31.32; N 10.98%.

3-(Dibromomethyl)quinoxaline 4-N-oxide. A mixture of 240 ml AcOH, 100 ml Ac_2O, and 140 ml 30% perhydrol was kept for 5 hr/40°, then 18 g 2-(dibromomethyl)quinoxaline added, and the whole heated for 30 hr/50°. After cooling the 2-(dibromomethyl)quinoxaline 4-N-oxide which separated was filtered off, (11.4 g), mp 191°–192° (decomp., ex dichloroethane-petrol ether). Found: Br 50.30; N 8.93%, calculated for $C_9H_6Br_2N_2O$: Br 50.26; N 8.81%.

2-Isothiuronium bromide 1,4-di-N-oxide (VII). A mixture of 2-bromomethylquinoxaline di-N-oxide and 0.75 g thiourea in 22.5 ml MeOH was heated at 50°–55°/15 min, the products cooled, and 1.69 g VII filtered off; pale yellow crystals, mp 190°–191°. Found: Br 24.27; N 16.57%, calculated for $C_{10}H_{11}BrN_4O_2S$: Br 24.13; N 16.92%.

Quinoxaline-2-isothiuronium bromide. A mixture of 3 g 2-bromomethylquinoxaline, 2.01 g thiourea, and 21 ml MeOH was heated at 53°–55°/15 min, the products cooled, and ether added until crystallization began, then 4.2 g quinoxaline-2-isothiuronium bromide filtered off, mp 153°–154° (decomp., ex MeOH-ether). Found: Br 26.71; N 18.87; S 10.33%, calculated for $C_{10}H_{11}BrN_4S$: Br 26.7; N 18.72; S 10.72%.

REFERENCES

1. A. H. Gowenlock, G. T. Newbold, and F. S. Spring, J. Chem. Soc., 622, 1945.

2. E. Shaw, J. Bernstein, K. Losee, and W. A. Lot, J. Am. Chem. Soc., 72, 4362, 1950.

3. United States Patent 2749350, 1956; C. A., 51, 494, 1957.

4. A. S. Elina and L. G. Tsyrul'nikova, ZhOKh, 33, 1544, 1963.

5. A. S. Elina, ZhOKh, 32, 2967, 1962.

6. F. J. Wolf, R. M. Wilson, Jr, and M. Tishler, J. Am. Chem., 76, 2266, 1954.

3 January 1966

Ordzhonikidze All-Union Chemical and Pharmaceutical Research Institute, Moscow

*Here and below the system BuOH–5% AcOH was used for chromatographing.