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Quinoxaline Derivatives. XII. The Reactions of Quinoxaline 1,4-Dioxides with Acetic Anhydride

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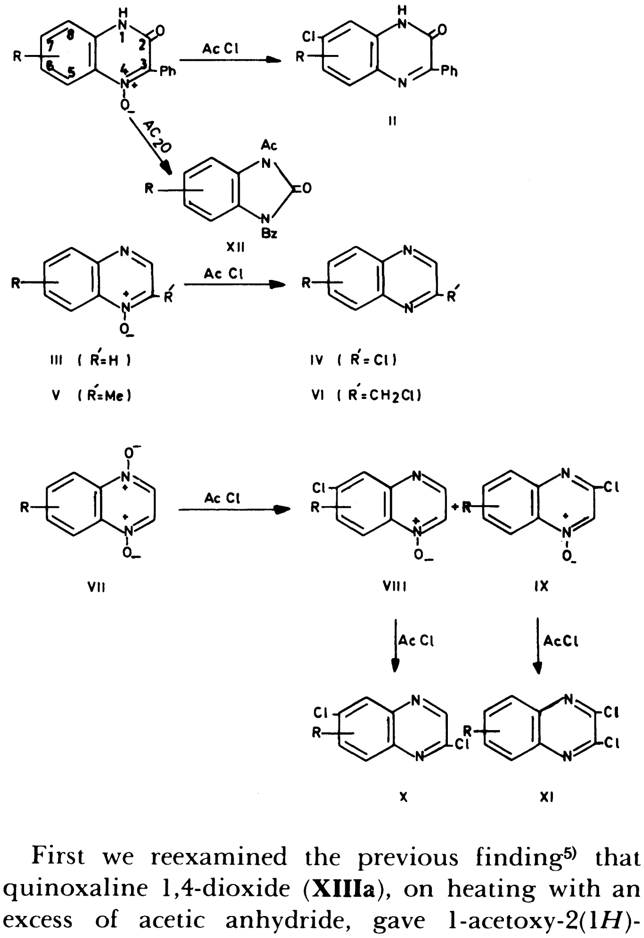
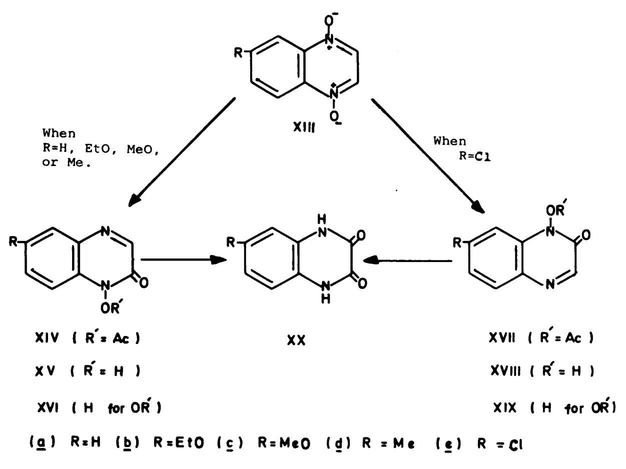
Quinoxaline 1,4-dioxide (**XIIIa**) with acetic anhydride gave 1-acetoxy-2(1*H*)-quinoxalinone (**XIVa**) which was prone to facile hydrolysis to yield 1-hydroxy-2(1*H*)-quinoxalinone (**XVa**). Both **XIVa** and **XVa** were isolated from the reaction mixture. On prolonged heating with acetic anhydride, **XIIIa**, **XIVa**, and **XVa** were converted slowly to the same end product, 2,3(1*H*,4*H*)-quinoxalinedione (**XXa**). 6-Ethoxy- (**XIIIb**), 6-methoxy- (**XIIIc**), and 6-methylquinoxaline 1,4-dioxide (**XIIId**) behaved similarly, except that the attack of the reagent took place exclusively on *N*-oxide para to the electron-donating substituents, and none of the other expected isomeric compounds **XVIIb—d** were isolated. Whereas 6-chloroquinoxaline 1,4-dioxide (**XIIIe**) bearing an electron-attracting chloro substituent on the benzene ring gave exclusively the other isomers **XVIIe**, **XVIIIe**, and **XXe**. A mechanism for this novel rearrangement is proposed and discussed.

We have reported[1)] earlier that 2(1*H*)-quinoxalinone 4-oxides substituted at position 3, on heating under reflux with acetyl chloride, undergo nucleophilic chlorine substitution at C-7 position with simultaneous loss of the oxide function (**I**→**II**). In the absence of carbonyl function at C-2, the chlorine substitution primarily goes to the position adjacent to the *N*-oxide when it is unsubstituted (**III**→**IV**),[2)] and in case there be a methyl group at C-3 it undergoes chlorine-substitution (**V**→**VI**);[2)] both of these take place at the expense of the oxide function. In the case of 1,4-dioxides of quinoxalines (**VII**) the primary products[3)] of the reactions with acetyl chloride were 6-chloroquinoxaline 1-oxides (**VIII**; 60—70%) and 3-chloroquinoxaline 1-oxide (**IX**; 30—40%). On prolonged heating these primary products gave 2,6- and 2,3-dichloroquinoxalines (**X** and **XI**), and all four products (**VIII** to **XI**) were isolated.[3)] The presence of electron donating or withdrawing substituent on the benzene ring of the molecule is shown to control the direction of chlorine substitution through the attack of the reagent on one *N*-oxide in preference to the other.

It would be expected that the reaction of acetic anhydride will take place in a similar manner to that of acetyl chloride, resulting in acetoxylation instead of the chlorine nucleophilic substitution (**I**→**II**: AcO for Cl in the above reactions). In a previous paper[4)] we have reported that 3-phenyl-2-(1*H*)-quinoxalinone 4-oxides (**I**) gave 1-acetyl-3-benzoyl-1*H*-benzimidazol-2(3*H*)-ones (**XII**) instead of the expected 7-acetoxy-3-phenyl-2(1*H*)-quinoxalinones (**III**; AcO for Cl).[4)] However 1-methylated compound **I** gave the normal 7-acetoxy-1-methyl-3-phenyl-2(1*H*)-quinoxalinone[4)] (**II**; Me for H and AcO for Cl). These observations prompted us to study the action of acetic anhydride on quinoxaline 1,4-dioxides.



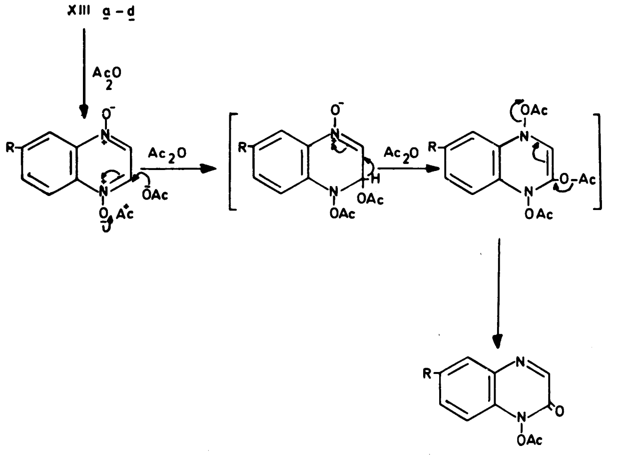
First we reexamined the previous finding[5)] that quinoxaline 1,4-dioxide (**XIIIa**), on heating with an excess of acetic anhydride, gave 1-acetoxy-2(1*H*)-quinoxalinone (**XIVa**) in a 30% yield. However the yield was much higher than that reported, and further we observed that **XIVa** was easily hydrolyzed to give 1-hydroxy-2(1*H*)-quinoxalinone (**XVa**) merely on leaving with water. On reduction both **XIVa** and **XVa** afforded 2(1*H*)-quinoxalinone (**XVIa**), which was identical with an authentic sample, establishing the structures of **XIVa** and **XVa**.



On prolonged heating of **XIIIa** with acetic anhydride, in addition of **XIVa** and **XVa**, a third product, 2,3(1*H*,4*H*)-quinoxalinedione (**XXa**), was also obtained. The amount of **XXa** progressively increased with prolonging the time of heating (9 h and then 16 h), while the amount of **XIVa** and **XVa** decreased, which obviously meant that **XIVa** and **XVa** were slowly converted to the same product **XXa**.

Similarly, 6-ethoxy (**XIIIb**), 6-methoxy (**XIIIc**), and 6-methylquinoxaline 1,4-dioxide (**XIIId**), on heating under reflux for 1 h with acetic anhydride, gave the corresponding 1-acetoxy (**XIVb—d**) and 1-hydroxy-6-substituted-2(1*H*)-quinoxalinone (**XVb—d**). The reduction of **XIVb—d** and **XVb—d** with sodium dithionite in aqueous ethanol gave 6-ethoxy-, 6-methoxy, and 6-methyl-2(1*H*)-quinoxalinones (**XVIb—d**), respectively, which were identical with authentic samples previously prepared and reported by us[6] or synthesized individually in this work (see Experimental). None of the other expected isomers (**XVIIb—d** and **XVIIIb—d**) were formed in these reactions.

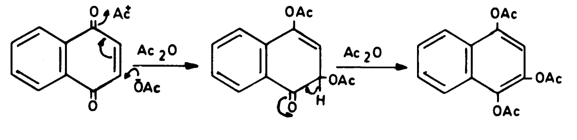
On the other hand, the reaction of 6-chloroquinoxaline 1,4-dioxide (**XIIIe**) with acetic anhydride gave 1-acetoxy- and 1-hydroxy-7-chloro-2(1*H*)-quinoxlinone, both of which on reduction with sodium dithionite in aqueous ethanol gave 7-chloro-2(1*H*)-quinoxalinone (**XIXe**); identical with an authentic sample.[7] The other isomers **XIVe** were not formed in this case too. The results are summarized in the table in the experimental section.



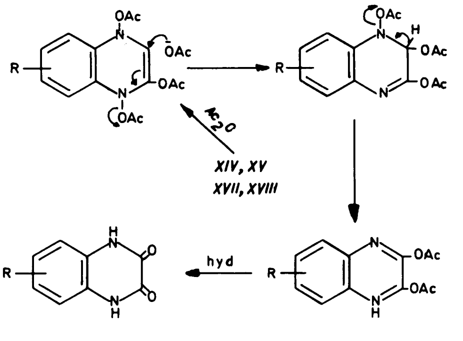
To explain the different behavior of quinoxaline 1,4-dioxides, we propose the following mechanism.

The electron-donating substituents (R) on the benzene ring increase the electron density at the oxygen atom of the *N*-oxide para to R, whereby the attack of Ac$^+$ takes place more favorably to this *N*-oxide than to the other *N*-oxide, resulting in the formation of 1-acetoxy-6-R-2(1*H*)-quinoxalinone as illustrated above. When R is an electron-withdrawing group (viz. chloro, as in **XIIIe**) the electron density is decreased at the oxygen atom of the *N*-oxide para to R, and the attack of Ac$^+$ therefore takes place to the other *N*-oxide, resulting in the formation of the other isomeric compound 1-acetoxy-7-chloro-2(1*H*)-quinoxalinone (**XVIIe**). The 1-hydroxy derivatives are formed by the facile hydrolysis of the acetoxy compounds.

The formation of the postulated triacetoxy intermediate (see above) has its analogy in the Thiel's reaction[8] of 1,4-naphthoquinone with acetic anhydride to give 1,2,4-triacetoxynaphthalene.



When the time of heating in the reaction of 1,4-dioxides (**XIIIa—e**) with acetic anhydride is prolonged from 1 to 9 h, a third product, the corresponding 2,3(1*H*,4*H*)-quinoxalinedione (**XXa—e**) is formed in addition to the acetoxy and hydroxy compounds, the quantities of which decrease accordingly. On further prolonging the time of heating, the quantities of 2,3(1*H*,4*H*)-quinoxalinediones gradually increase and those of the corresponding acetoxy and hydroxy derivatives decrease. It appears that the postulated triacetoxy intermediate further leads very slowly to the formation of the 2,3(1*H*,4*H*)-quinoxalinediones as shown below.



Experimental

Materials. Quinoxaline 1,4-dioxide (**XIIIa**), 6-ethoxyquinoxaline 1,4-dioxide (**XIIIb**), 6-methoxyquinoxaline 1,4-dioxide (**XIIIc**), 6-methylquinoxaline 1,4-dioxide (**XIIId**), and 6-chloroquinoxaline 1,4-dioxide (**XIIIe**) were prepared by the methods already reported.[9] Pet. ether means light petroleum; bp 60—80 °C. Identical structure means undepressed mixed melting point and superimposible IR spectra of the two compounds. All 1-hydroxy-2(1*H*)-quinoxalinones give blood red color on addition of aq iron(III) chloride to their ethanolic solutions (a characteristic of hydroxamic -N(OH)-CO- moiety in a molecule). The solutions were decolorized, whenever necessary, with activated charcoal.

Reaction of Quinoxaline 1,4-Dioxide (XIIIa) with Acetic Anhydride. Procedure A: A mixture of **XIIIa** (2 g) and acetic anhydride (20 ml) was heated under reflux for 1 h. The sticky brown residue, left after removal of acetic anhydride on a vacuum rotary evaporator, was exhaustively extracted with boiling pet. ether. The volume of pet. ether extract was reduced until the crystallization started, whereby small white needles of 1-acetoxy-2(1*H*)-quinoxalinone (**XIVa**); mp 110—111 °C (lit,[5] mp 110.5—111 °C) were obtained (yield 70%). To the residue which could not be extracted with pet. ether, a small amount of water was added and left overnight in a refrigerator. The solidified product, on recrystallization from ethanol gave reddish brown flakes of 1-hydroxy-2(1*H*)-quinoxalinone (**XVa**); mp 210—212 °C (lit,[5] mp 208—209 °C) in a 30% yield.

Both **XIVa** and **XVa**, on treatment with sodium dithionite in 50% aqueous ethanol, gave 2(1*H*)-quinoxalinone (**XVIa**); mp 272 °C (lit,[6] mp 270—272 °C), identical with an authentic sample.[6]

Procedure B: The time of heating was prolonged to 9 h **XIVa** and **XVa** were obtained in 60 and 25% yields, respectively. The extraction of pet. ether insoluble part with ethanol left a residue (13%). The crystallization of the residue from glacial acetic acid gave colorless needles of 2,3(1*H*,4*H*)-quinoxalinedione (**XXa**); mp >360 °C, identical with an authentic sample.[6] **XIVa** and **XVa** afforded three products **XIVa**, **XVa**, and **XXa** in each case when they were treated separately with acetic anhydride under the same conditions.

Table 1.

Starting material	Procedure	Products/%
XIIIb	A	**XIVb** (65) **XVb** (30)
	B	**XIVb** (60) **XVb** (25) **XXb** (10)
	C	**XIVb** (56) **XVb** (20) **XXb** (13)
XIIIc	A	**XIVc** (55) **XVc** (45)
	B	**XIVc** (50) **XVc** (35) **XXc** (10)
	C	**XIVc** (45) **XVc** (30) **XXc** (15)
XIIId	A	**XIVd** (50) **XVd** (40)
	B	**XIVd** (42) **XVd** (36) **XXd** (11)
	C	**XIVd** (36) **XVd** (29) **XXd** (15)
XIIIe	A	**XVIIe** (55) **XVIIIe** (40)
	B	**XVIIe** (50) **XVIIIe** (35) **XXe** (10)
	C	**XVIIe** (43) **XVIIIe** (30) **XXe** (15)

Procedure C: When the time of heating was further prolonged to 16 h, all three products **XIVa** (55%), **XVa** (20%), and **XXa** (15%) were obtained.

Similarly the results of the reactions of other quinoxaline 1,4-dioxides (**XIIIb—e**) with acetic anhydride are summarized in Table 1.

XIVb: Mp 132—133 °C (white needles from pet. ether). Found: C, 58.43; H, 5.02; N, 11.12%. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.83; N, 11.29%.

XVb: Mp 173—175 °C (needles from ethanol). Found: C, 58.48; H, 5.02; N, 13.58%. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.85; N, 13.59%.

The reactions of both **XIVb** and **XVb** with sodium dithionite in 50% aqueous ethanol gave 6-ethoxy-2(1*H*)-quinoxalinone (**XVIb**); mp 241—242 °C, identical with an authentic sample.[6]

XXb: Mp >360°, identical with an authentic sample.[6]

XIVc: Mp 115—117 °C (colorless needles from pet. ether). Found: C, 56.72; H, 4.34; N, 12.10%. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.27; N, 11.96%.

XVc: Mp 190—191 °C (needles from ethanol). Found: C, 56.45; H, 4.09; N, 14.62%. Calcd for $C_9H_8N_2O_2$: C, 56.25; H, 4.16; N, 14.58%.

The reactions of both **XIVc** and **XVc** with sodium dithionite in 50% aqueous ethanol gave the same compound, 6-methoxy-2(1*H*)-quinoxalinone (**XVIc**); mp 271—272 °C, identical with an authentic sample.[6]

XXc: Mp >350 °C, identical with an authentical sample.[6]

XIVd: Mp 104 °C (micro-needles from pet. ether). Found: C, 60.73; H, 4.53; N, 12.90%. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.59; N, 12.84%.

XVd: Mp 180—182° (ethanol). Found: C, 61.50; H, 4.51; N, 16.00%. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.54; N, 15.90%.

Both **XIVd** and **XVd**, on reduction with sodium dithionite in 50% aqueous ethanol, gave 6-methyl-2(1*H*)-quinoxalinone (**XVId**), mp 248 °C, identical with an authentic sample (the synthesis is described below).

XXd: Mp 345 °C, identical with sample, prepared by the condensation of 4-methyl-*o*-phenylenediamine and diethyl oxalate (yield 85%), and crystallized from ethanol as white needles, mp 345 °C. Found: C, 61.63; H, 4.61; N, 15.82%. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.54; N, 15.90%.

XVIIe: Mp 125—126 °C (white needles from pet. ether). Found: C, 50.42; H, 3.12; N, 11.93%. Calcd for $C_{10}H_7ClN_2O_3$: C, 50.31; H, 2.93; N, 11.74%.

XVIIIe: Mp 260 °C (ethanol). Found: C, 48.67; H, 2.50; Cl, 18.24; N, 14.01%. Calcd for $C_8H_5ClN_2O_2$: C, 48.85; H, 2.54; Cl, 18.07; N, 14.25%.

The reduction of both **XVIIe** and **XVIIIe** with sodium dithionite in 50% aqueous ethanol gave the same product, 7-chloro-2(1*H*)-quinoxalinone, (**XIXe**); mp 251—252 °C, identical with an authentic sample.[7]

XXe: Mp >360 °C, identical with an authentic sample.[6]

Preparation of Authentic 6-Methyl-2(1*H*)-quinoxalinone (XVId). α-Cyano-4-methyl-2-nitroacetanilide was prepared from 4-methyl-2-nitroaniline and ethyl cyanoacetate by the procedure described previously.[6] The anilide (yield 60%) crystallized from benzene as yellowish brown flakes; mp

146—147 °C.

Found: C, 55.20; H, 4.16; N, 19.32%. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.11; N, 19.17%.

A solution of the anilide (10 g) in pyridine (50 ml), was shaken with 1 mol dm^{-3} aq NaOH (50 ml) for 1 h. The color of the solution changed to dark red. Neutralization with dil HCl gave a precipitate, which was filtered, washed successively with dil HCl and water, and dried (yield 65%). Crystallization from ethanol gave yellowish brown needles of 3-cyano-6-methyl-2(1*H*)-quinoxalinone 4-oxide; mp 251—253 °C (decomp).

Found: C, 59.50; H, 3.56; N, 21.6%. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.48; N, 20.90%.

3-Cyano-6-methyl-2(1*H*)-quinoxalinone 4-oxide treated with sodium dithionite in 50% aqueous ethanol for elimination of the oxide, also lost the nitrile group as observed and reported by us,⁶⁾ giving an authentic sample of **XVId**; mp 248 °C.

Found: C, 67.81; H, 4.96; N, 17.63%. Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50%.

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