Quinoxaline Derivatives. XI.[1] The Reaction of Quinoxaline 1,4-Dioxide and Some of Its Derivatives with Acetyl Chloride

YUSUF AHMAD,* M. S. HABIB,[2] M. IKRAM QURESHI, AND M. A. FAROOQI

Chemical Research Division, P. C. S. I. R. Laboratories, Karachi-39, Pakistan

Received October 10, 1972

Quinoxaline 1,4-dioxide (Ia) with acetyl chloride gives 6-chloroquinoxaline 1-oxide (IIa). On heating, and progressively increasing the time of reaction, the yield of IIa increases, and 3-chloroquinoxaline 1-oxide (IIIa) and 6,7-dichloroquinoxaline appear as additional products. 7-Ethoxy- (Ib), 7-methoxy- (Ic), and 7-methylquinoxaline 1,4-dioxides (Id) show a similar behavior, giving corresponding 6-chloro (IIb–d) and 3-chloro derivatives (IIIb–d), as main products. Further increase in the reaction time results in the formation of 2,6-dichloro (Vb–d) and 2,3-dichloro (VIb–d) compounds as additional products. However none of the 2-chloro 4-oxide derivatives (IVb–d) were isolated. The mechanisms for these transformations have been proposed and discussed.

The chlorination of the heterocyclic ring in reactions of *N*-oxides with acyl chlorides has been reported.[3,4] Derivatives of pyridine *N*-oxide, quinoline *N*-oxide, and quinoxaline *N*-oxide with acetyl chloride give the corresponding 2- (or 4-) chloro compounds in good yields. This chlorination can be visualized to take place through the acylation of the *N*-oxide function, whereby the adjacent C-2 (or the vinylogous C-4) position becomes electron deficient and hence prone to nucleophilic attack by the chloride anion, with simultaneous loss of an acetic acid molecule. However, when the position adjacent to the *N*-oxide is occupied by a methyl group, chlorine substitution takes place in the methyl group. Thus 2,3-dimethylquinoxaline 1-oxide and 1,4-dioxide on reaction with acetyl chloride give[4] 2-chloromethyl-3-methylquinoxaline and 2,3-di-(chloromethyl)quinoxaline, respectively.

In contrast to these findings we have observed[5] that the chlorination is entirely directed to C-6 in quinoxaline 1-oxides which have a substituted C-2 position and also carry an oxygen function at C-3. Similar observations had been made earlier by Newbold and Spring,[6] Usherwood and Whitely,[7] and Clark-Lewis and Katekar.[8] However, the importance of the oxygen function at C-3 in directing the chlorine substitution to C-6 was not fully recognized. This novel pattern of a nucleophilic chlorine substitution in the *N*-oxides of the quinoxaline derivatives, and generality of this reaction, has been well established in these laboratories.

Elina has recently reported[9] that quinoxaline 1,4-dioxide with benzenesulfonyl chloride in the cold gives only 3% yield of the expected 3-chloroquinoxaline 1-oxide. The major product[10] is the benzenesulfonate of 2-chloroquinoxaline 1-oxide. These unusual findings prompted us to extend the study of the reaction of acetyl chloride to simpler quinoxaline *N*-oxides with unsubstituted heterocyclic rings.

Quinoxaline 1-oxide remained unchanged[11] (over 90% recovery) when heated under reflux with an excess of acetyl chloride for 24 hr. On the other hand, quinoxaline 1,4-dioxide (Ia) readily reacted with acetyl chloride. On stirring with an excess of acetyl chloride at room temperature for 1 hr, Ia gave 6-chloroquinoxaline 1-oxide (IIa) (about 20% yield). The latter compound was established by treating it with acetic anhydride and quantitatively isolating 6-chloro-2-hydroxyquinoxaline[12] (VIIa). When Ia was heated under reflux with acetyl chloride, the amount of IIa progressively increased until it reached a maximum yield of 60–65% after 8 hr. A second product (yield about 35%), isolated from the mother liquor of the reaction mixture after removal of IIa, proved to be 3-chloroquinoxaline 1-oxide (IIIa) by (1) hydrolysis with aqueous alkali to 3-hydroxyquinoxaline 1-oxide;[13] (2) reaction with $POCl_3$ to 2,3-dichloroquinoxaline[14] (VIa); and (3) reaction with acetic anhydride to 2-chloro-3-hydroxyquinoxaline, converted into VIa with $POCl_3$. When the heating time was increased to 16 hr the quantity of IIa in the reaction mixture decreased, the amount of IIIa remained unaltered, and a third product (yield 10–15%), identical with 6,7-dichloroquinoxaline,[14] was also isolated. The last named product was probably formed at the expense of IIa.

After an 8-hr reflux time, 6-methylquinoxaline 1,4-dioxide (Id) with acetyl chloride yielded two compounds. The insoluble product was identical with 6-chloro-7-methylquinoxaline 1-oxide[14] (IIId), a sample of which for comparison was kindly supplied by Dr. Landquist. This constitution of the product was initially indicated by the fact that it showed no absorption in the carbonyl region of its ir spectrum, and with acetic anhydride it underwent the familiar rearrangement of quinoxaline *N*-oxides to quinoxalinones, and the isomeric 6-chloro-2-hydroxy-7-methylquinoxaline (VIId) thus obtained with $POCl_3$ gave the same 2,6-dichloro-7-methylquinoxaline (Vd) as was obtained directly by the action of $POCl_3$ on the starting compound IId. The mother liquor of the reaction mixture afforded a second compound, an isomeric *N*-oxide of the structure IIId, since it showed no absorption in the carbonyl region of its ir spectrum and on reaction with $POCl_3$ yielded a

(1) Part X: Y. Ahmad, M. S. Habib, A. Mohammadi, B. Bakhtiari, and S. A. Shamsi, *J. Org. Chem.*, **38**, 201 (1968).

(2) M. S. H. presented this paper at the 3rd International Congress of Heterocyclic Chemistry, Sendai, Japan, Aug 1971.

(3) T. Itai, *J. Pharm. Soc. Jap.*, **65**, 70 (1945); *Chem. Abstr.*, **45**, 8525b (1951).

(4) Y. Ahmad, M. S. Habib, Ziauddin, and B. Bakhtiari, *J. Org. Chem.*, **31**, 2613 (1966).

(5) Y. Ahmad, M. S. Habib, Ziauddin, and N. Bashir, *Bull. Chem. Soc. Jap.*, **38**, 1654 (1965).

(6) (a) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 519 (1948); (b) W. Dawson, G. T. Newbold, and F. S. Spring, *ibid.*, 2579 (1949).

(7) E. A. Usherwood and M. A. Whitely, *ibid.*, **123**, 1069 (1923).

(8) J. W. Clark-Lewis and G. F. Katekar, *ibid.*, 2825 (1959).

(9) A. S. Elina, *Khim. Geterotsikl. Soedin.*, 545 (1968); *Chem. Abstr.*, **69**, 96660p (1968).

(10) Isolation of a very minor product having chlorine in the benzene portion of the molecule (on the evidence of nmr studies) has been reported by Elina.[9] The position of chlorine in the molecule, however, has remained undetermined.

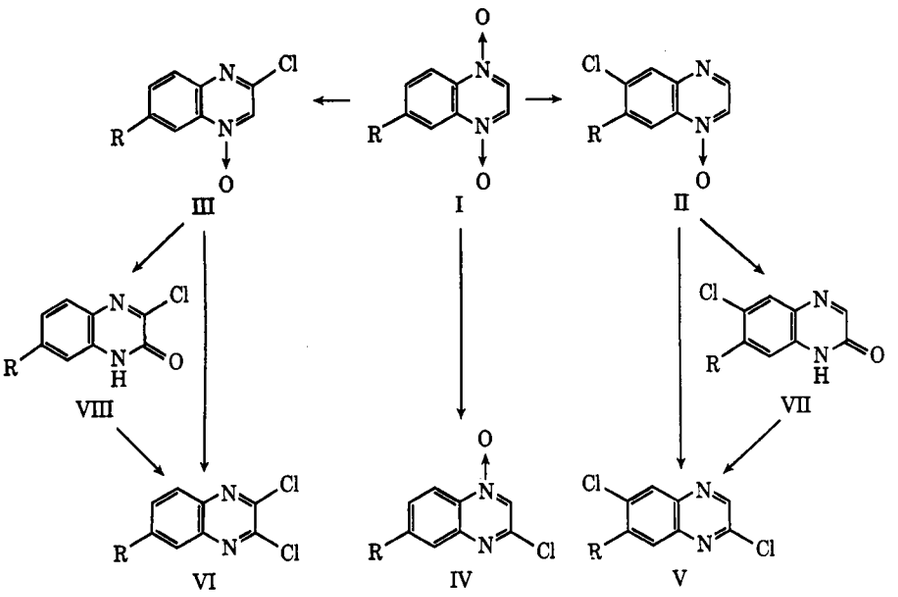
(11) Unpublished work.

(12) Y. Ahmad, M. S. Habib, M. Iqbal, M. I. Qureshi, and Ziauddiu, *Bull. Chem. Soc. Jap.*, **38**, 1659 (1965).

(13) G. Tennant, *J. Chem. Soc.*, 2428 (1963).

(14) J. K. Landquist, *ibid.*, 2816 (1953).

SCHEME I



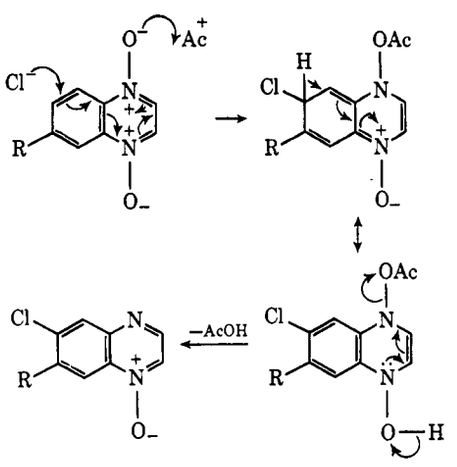
a, R = H b, R = EtO
c, R = MeO d, R = Me

product identical with 2,3-dichloro-7-methylquinoxaline[14] (VId).

When the time of heating was increased to 16 hr, in addition to IId and IIId, two more products were isolated by column chromatography over alumina. The latter compounds proved to be 2,3-dichloro- (VId) and 2,6-dichloro-7-methylquinoxaline (Vd) on comparison with authentic samples described above. These compounds were probably formed by the action of acetyl chloride on the primary products IId and IIId, initially produced in the reaction mixture.

6-Methoxyquinoxaline 1,4-dioxide (Ic) with acetyl chloride showed analogous behavior. Two corresponding primary products, the *N*-oxides IIc and IIIc, were isolated in 50–60 and 30–35% yields, after 8 hr of heating. When the heating time was increased to 16 hr, in addition to IIc and IIIc, the corresponding secondary products Vc and VIc were also isolated. Similarly, from 6-ethoxyquinoxaline 1,4-dioxide (Ib) two products (IIb and IIIb) were obtained after 8 hr of heating, whereas all four products (IIb, IIIb, Vb, and VIb) were isolated after heating for 16 hr. See Scheme I.

The mechanism illustrated below is proposed for the chlorine substitution in the benzene portion of the molecule during the reaction of quinoxaline 1,4-dioxides with acetyl chloride.



The mechanism of chlorine substitution into the heterocyclic ring is well known and has already been described in the opening paragraph of this paper.

These nucleophilic chlorinations seem to be influenced by certain factors as yet not understood, because none of the 2,3-dichloroquinoxaline from Ia and other 3-chloro 1-oxide derivatives (IVb–d) from Ib–d) could be isolated in these reactions, as expected from the above mechanisms.

Experimental Section[15]

Materials.—Quinoxaline 1,4-dioxide (Ia), 6-ethoxyquinoxaline 1,4-dioxide (Ib), 6-methoxyquinoxaline 1,4-dioxide (Ic), and 6-methylquinoxaline 1,4-dioxide (Id) were prepared by the reported[14] methods.

Reaction of Quinoxaline 1,4-Dioxide (Ia) with Acetyl Chloride. Reaction at Room Temperature.—A suspension of Ia (2.0 g) in acetyl chloride (30 ml) was vigorously stirred at room temperature for 1 hr. The filtrate, after removal of solid, on distillation left a negligible residue. The solid was exhaustively extracted with hot light petroleum. The insoluble part proved to be the starting material. The solution on evaporation left a residue (0.5 g, 20% yield) which on crystallization from ethanol gave colorless needles, mp 137–138°, which proved to be 6-chloroquinoxaline 1-oxide[16] (IIa).

Anal. Calcd for $C_8H_5ClN_2O$: C, 53.19; H, 2.77; Cl, 19.66; N, 15.52. Found: C, 53.06; H, 2.79; Cl, 19.62; N, 15.30.

(15) All melting points are uncorrected. The light petroleum used was of the boiling range 60–80°. Freshly distilled pure acetyl chloride was used and reasonable precautions against the ingress of moisture were observed throughout various operations in these reactions. Infrared spectra were measured in Nujol mulls with a Perkin-Elmer Model 137-B instrument. The compounds were considered identical when their mixture melting points remained undepressed and their ir spectra were superimposable. Brockmann alumina (activity I grade) was used for chromatography.

(16) The compound, mp 151–152°, obtained from Dr. Landquist for comparison, and reported[14] by him to be 6-chloroquinoxaline *N*-oxide, proved in fact to be the 7-chloroquinoxaline 1-oxide. The repetition of Landquist's oxidation of 6-chloroquinoxaline gave in our hands a mixture of two mono-*N*-oxides, mp 151–152 and 137–138°, which could be separated by chromatography on alumina and elution with light petroleum. Since the compound with mp 137–138° has now definitely been proved to be 6-chloroquinoxaline 1-oxide, the compound with mp 151–152° should therefore be 7-chloroquinoxaline 1-oxide.

On heating under reflux with acetic anhydride, and removal of solvent *in vacuo*, IIa gave in almost quantitative yield 6-chloro-2-hydroxyquinoxaline (VIIa), mp 320° dec, which was identical with its authentic sample[12] prepared, for comparison, by the decarboxylation of 6-chloro-2-hydroxyquinoxaline-3-carboxylic acid.

Reaction under Reflux for 8 Hr (Procedure A).—A mixture of the dioxide Ia (4.0 g) and acetyl chloride (60 ml) was heated under reflux for 8 hr. After the mixture was cooled to room temperature the solid was removed by filtration, washed with a little light petroleum, and crystallized from ethanol to give IIa in 65% yield. None of the unreacted Ia was recovered. The filtrate upon evaporation under reduced pressure left a sticky mass, which solidified after addition of a little water and storage overnight in the refrigerator. The solid was collected and crystallized from ethanol, and 3-chloroquinoxaline 1-oxide (IIIa) was isolated as yellow needles, mp 147–148° (yield 35%).

Anal. Calcd for $C_8H_5ClN_2O$: C, 53.19; H, 2.77; Cl, 19.66; N, 15.52. Found: C, 53.21; H, 2.71; Cl, 19.69; N, 15.54.

This material was identified by the following methods.

(1) On hydrolysis with 2.5 *N* potassium hydroxide on a water bath for 2 hr, it gave a clear solution, which on acidification precipitated a solid. Crystallization of the solid from glacial acetic acid gave greyish-white needles of 3-hydroxyquinoxaline 1-oxide (IIIa, OH for Cl), mp 271–273°, identical with an authentic sample.[13]

(2) After cautious addition of the above IIIa (0.3 g) to cooled $POCl_3$ (2 ml), the mixture was allowed to come to room temperature, and then refluxed for 15 min. Removal of excess $POCl_3$ under reduced pressure left a residue, which was triturated with ice-cold water, filtered, dried, and crystallized from light petroleum, whereby colorless needles of a solid identical with 2,3-dichloroquinoxaline[14] (VIa), mp 148–149°, were obtained.

(3) The compound (0.5 g) was refluxed with an excess of acetic anhydride (7 ml). After removal of the solvent *in vacuo* and work-up in the usual manner, the reaction product was recrystallized from ethanol and identified as 3-chloro-2-hydroxyquinoxaline (VIIIa), mp 322–324°.

Anal. Calcd for $C_8H_5ClN_2O$: C, 53.19; H, 2.77; Cl, 19.66; N, 15.52. Found: C, 53.48; H, 2.74; Cl, 19.61; N, 15.37.

The structure of the above compound (VIIIa) was further confirmed by its conversion to the known 2,3-dichloroquinoxaline by treatment with $POCl_3$.

Reaction under Reflux for 16 Hr (Procedure B).—Quinoxaline 1,4-dioxide (Ia) (4.0 g) and acetyl chloride (60 ml) were refluxed together for 16 hr. The dark grey, insoluble solid was removed by filtration. On working up as before and crystallization from ethanol, colorless needles of IIa were isolated, mp 137–138° (yield 40%). The filtrate on evaporation under reduced pressure left a dark brown, sticky residue which was triturated with cold water to decompose a trace of acetyl chloride. After being left overnight in a refrigerator it was collected and washed with water. The dried solid (2.1 g) was taken up in dry benzene and adsorbed onto alumina, dried again, and put on a column of alumina prepared in light petroleum. The chromatographic column was eluted with light petroleum. The first fraction (about 1 l.) afforded a colorless, crystalline product, mp 208–210° (10–15% yield), which proved to be 6,7-dichloroquinoxaline on comparison with an authentic sample[14] (reported mp 210°).

Anal. Calcd for $C_8H_4Cl_2N_2$: C, 48.23; H, 2.01; Cl, 35.68; N, 14.07. Found: C, 48.18; H, 2.16; Cl, 35.69; N, 14.10.

On further elution until exhaustion of the column with the same solvent (about 2 l. more), 3-chloroquinoxaline 1-oxide (IIIa) was obtained (30% yield) as the second crystalline product.

Reaction[17] of 6-Methylquinoxaline 1,4-Dioxide (Id) with Acetyl Chloride. Procedure A.—(1) The insoluble part of the reaction mixture afforded on crystallization from ethanol greyish-white needles of 6-chloro-7-methylquinoxaline 1-oxide (IId), mp 168–169° (lit.[14] mp 166–168°) (yield 55%).

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.52; H, 3.59; Cl, 18.25; N, 14.40. Found: C, 55.49; H, 3.43; Cl, 18.18; N, 14.38.

For further confirmation IId was treated with acetic anhydride and converted into 6-chloro-2-hydroxy-7-methylquinoxaline (VIId), mp 294–295° (greyish-white flakes from ethanol).

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.52; H, 3.59; N, 14.40. Found: C, 55.81; H, 3.70; N, 14.17.

Compound VIId was treated with $POCl_3$ and worked up in the usual manner to give 2,6-dichloro-7-methylquinoxaline (Vd), which crystallized from light petroleum as colorless needles, mp 136–137°.

Anal. Calcd for $C_9H_6Cl_2N_2$: C, 50.70; H, 2.81; Cl, 33.34; N, 13.14. Found: C, 50.78; H, 2.87; Cl, 33.31; N, 13.05.

(2) The filtrate from the reaction mixture after removal of acetyl chloride left a residue, which on processing as described earlier gave 3-chloro-7-methylquinoxaline 1-oxide (IIId) as pink needles (from ethanol), mp 142–143°, yield 34%.

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.52; H, 3.59; Cl, 18.25; N, 14.40. Found: C, 55.52; H, 3.53; Cl, 18.25; N, 14.39.

This isomeric product showed no absorption peak in the carbonyl region of its ir spectrum and on treatment with $POCl_3$ was converted to 2,3-dichloro-7-methylquinoxaline[14] (VId), which unambiguously established the structure of the compound as IIId.

Procedure B.—Upon heating for 16 hr no insoluble material was isolated but instead a clear red solution was obtained. The dark red residue left after removal of acetyl chloride was chromatographed on alumina in the usual manner. Three crystalline products eluted out with light petroleum in the following order.

The first 700 ml of eluent gave colorless needles of a compound (12% yield) identical with 2,6-dichloro-7-methylquinoxaline (Vd), mp 136–137°. The next 1 l. afforded pinkish-white crystals of a product (about 13% yield) identical with 2,3-dichloro-7-methylquinoxaline (VId), mp 114–115°. The third fraction (about 2 l.) gave pink needles of a compound (11% yield) identical with 3-chloro-7-methylquinoxaline 1-oxide (IIId), mp 142–143°. Further elution of the column failed to give any identifiable crystalline product.

Reaction[17] of 6-Methoxyquinoxaline 1,4-Dioxide (Ic) with Acetyl Chloride. Procedure A.—In this reaction Ic showed behavior comparable to that of Id described above, and corresponding products were obtained in this case.

(1) The insoluble part on crystallization from ethanol gave greyish-white needles of 6-chloro-7-methoxyquinoxaline 1-oxide (IIc), mp 190–192° (yield 57%).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.31; H, 3.32; Cl, 16.87; N, 13.30. Found: C, 50.76; H, 3.25; Cl, 16.79; N, 13.22.

With acetic anhydride IIc gave 6-chloro-2-hydroxy-7-methoxyquinoxaline (VIIc), mp 273–275° dec (cream-colored grains from ethanol).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.31; H, 3.32; N, 13.30. Found: C, 51.21; H, 3.18; N, 13.31.

On treatment with $POCl_3$ IIc and VIIc both yielded 2,6-dichloro-7-methoxyquinoxaline (Vc), which crystallized from light petroleum as colorless needles, mp 177–179°.

Anal. Calcd for $C_9H_6Cl_2N_2O$: C, 47.17; H, 2.62; Cl, 31.10; N, 12.23. Found: C, 47.41; H, 2.96; Cl, 30.68; N, 12.26.

(2) The residue, obtained from the filtrate after removal of acetyl chloride, afforded on crystallization from ethanol light brown flakes of 3-chloro-7-methoxyquinoxaline 1-oxide (IIIc), mp 150–152° (yield 33%).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.31; H, 3.32; Cl, 16.87; N, 13.30. Found: C, 51.16; H, 3.21; Cl, 16.81; N, 13.04.

With $POCl_3$ IIIc gave 2,3-dichloro-7-methoxyquinoxaline[18] (VIc), which crystallized from light petroleum as pinkish white needles, mp 160–161°.

Procedure B.—When Ic (4.0 g) in acetyl chloride (60 ml) was heated under reflux for 16 hr a brown-colored, clear solution resulted. The residue, obtained after removal of acetyl chloride, was chromatographed over alumina and eluted with light petroleum. The first fraction (about 1 l.) gave colorless needles of 2,6-dichloro-7-methoxyquinoxaline (Vc), mp 177–179° (yield 10–15%). The second fraction (about 1 l.) afforded pinkish-white flakes of 2,3-dichloro-7-methoxyquinoxaline (VIc), mp 160–161° (yield 14%). Further elution, even with change of solvents, failed to give any other identifiable product.

Reaction[17] of 6-Ethoxyquinoxaline 1,4-Dioxide (Ib) with Acetyl Chloride. Procedure A.—(1) The insoluble part on crystallization from ethanol gave greyish-white needles of 6-chloro-7-ethoxyquinoxaline 1-oxide (IIb), mp 188–189° (yield 58%).

(17) Unless otherwise stated, the same general procedures (A and B) and the same quantities (4.0 g and 60 ml) of the two reactants were used in the reaction study of the dioxides Ib, Ic, and Id with acetyl chloride.

(18) F. H. S. Curd, D. G. Davey, and G. J. Stacey, *J. Chem. Soc.*, 1271 (1949).

Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.00; Cl, 15.81; N, 12.47. Found: C, 53.36; H, 4.08; Cl, 15.95; N, 12.60.

With acetic anhydride the *N*-oxide (IIb) rearranged to 6-chloro-7-ethoxy-2-hydroxyquinoxaline (VIIb) as light brown needles from ethanol, mp 255° dec.

Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.00; N, 12.47. Found: C, 53.37; H, 4.04; N, 12.33.

Both IIb and VIIb with $POCl_3$ were converted to the same compound, 2,6-dichloro-7-ethoxyquinoxaline (Vb), as greyish-white needles from light petroleum, mp 133°.

Anal. Calcd for $C_{10}H_8Cl_2N_2O$: C, 49.39; H, 3.29; Cl, 29.22; N, 11.52. Found: C, 49.16; H, 3.33; Cl, 29.04; N, 11.55.

(2) The residue, obtained from the filtrate after removal of acetyl chloride, gave on crystallization from ethanol pink microneedles of 3-chloro-7-ethoxyquinoxaline 1-oxide (IIIb), mp 143–145°, yield 37%.

Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.00; Cl, 15.81; N, 12.47. Found: C, 53.30; H, 4.10; Cl, 15.71; N, 12.56.

With $POCl_3$ IIIb gave a compound, mp 137–138° (pinkish white flakes from light petroleum), identical with 2,3-dichloro-7-ethoxyquinoxaline (VIb) prepared by the reaction of 2,3-dihydroxy-7-ethoxyquinoxaline[19] with $POCl_3$.

Procedure B.—A dark brown, clear solution was obtained after 16 hr of heating. The dark red, sticky residue left after removal of acetyl chloride was chromatographed on alumina and eluted with light petroleum. The first fraction (about 800 ml) of the eluent yielded colorless needles of 2,6-dichloro-7-ethoxyquinoxaline (Vb), mp 135° (yield 12%). The subsequent fraction (1 l.) gave light pink needles of 2,3-dichloro-7-ethoxyquinoxaline (VIb), mp 137–138° (yield 15%). Further elution with various solvent failed to give any more identifiable products.

(19) W. Autenrieth and O. Hinsberg, *Ber.*, **25**, 492 (1892).

Registry No.—Ia, 2423-66-7; Ib, 39266-91-6; Ic, 39266-92-7; Id, 33368-89-7; IIa, 39266-93-8; IIb, 39266-94-9; IIc, 39266-95-0; IId, 39266-96-1; IIIa, 5227-59-8; IIIb, 39266-98-3; IIIc, 39266-99-4; IIId, 39267-00-0; Vb, 39267-01-1; Vc, 39267-02-2; Vd, 39267-03-3; VIc, 39267-04-4; VId, 39267-05-5; VIIa, 39267-06-6; VIIb, 39267-07-7; VIIc, 39267-08-8; VIId, 39267-09-9; VIIIa, 35676-70-1; acetyl, 75-36-5; 6,7-dichloroquinoxaline, 19853-64-6; 7-chloroquinoxaline 1-oxide, 39267-11-3.

Acknowledgment.—The authors wish to thank Dr. J. K. Lanquist for the supply of the reference samples mentioned in this paper. The elemental analyses are by Wellcome Research Laboratory, England (through the courtesy of Dr. H. T. Openshaw). This assistance is gratefully acknowledged.

The Reaction of Phenyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside with Alkali Azide

TOHRU SAKAKIBARA,* ROKURO SUDOH, AND TOSHIO NAKAGAWA[1]

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo, Japan

Received July 28, 1972

The title compound **3** reacts with sodium azide or lithium azide in various media to yield predominantly one of the following products by selecting appropriate conditions: nitro azide **5**, triazole **6**, and **7**. The key factor in determining product was found to be the basicity of the medium. Similar results were obtained when nitro olefin **4**, derived from the title compound, or nitro azide **5** was used as a starting material. Structures **6** and **7** were deduced from their nmr, mass, and ir spectra, and the mechanisms involved in the formation of **5**, **6**, and **7** are discussed.

In previous papers[2,3] we have dealt with the synthesis of a new type of nucleosides, in which the purine or pyrimidine moiety is linked to the C-2 position of a 3-nitroglucopyranoside. In this reaction α-nitro olefin **2**, formed from methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**) by the elimination of acetic acid, was assumed to be an intermediate.[4]

Recently the following similar substitution reaction was observed. The thermodynamically unstable *all-cis*- (1*r*,2*c*,3*c*) and *cis,trans*- (DL-1*r*,2*c*,3*t*) dianilino derivatives were isolated in 30 and 20% yields, respectively, on treatment of 1*r*,3*c*-diacetoxy-2*t*-nitrocyclohexane with aniline, but only a trace of thermodynamically more stable *all-trans* (1*r*,2*t*,3*c*) isomer was detectable by tlc.[5] The fact that the thermodynamically stable isomer was not formed in quantity in this reaction can be explained by assuming that subsequent epimerization of the two products is slow. If the reaction proceeds *via* a nitro olefin intermediate, the products may be formed by kinetic control; on the other hand, they may conceivably be formed by an SN2 reaction with starting material. We have therefore studied further the reaction of **3** with alkali azide, which is generally accepted as a typical SN2-type nucleophile, in a variety of media and we have found that this reaction affords the corresponding nitro azide **5** and/or the triazole derivatives (**6**, **7**) in excellent yield (Scheme I) and that one of the three products can be obtained exclusively by selecting appropriate reaction conditions. The details are described herewith.

Results and Discussions

Structural Assignment of the Products.—Phenyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**5**), phenyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-*erythro*-hexopyranosido[2,3-*d*]triazole (**6**), and phenyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-2-(phenyl 4′,6′-*O*-benzylidene-2′,3′-dideoxy-β-D-*erythro*-hexopyranosido[2′,3′-*d*]triazolyl)-β-D-glycopyranoside (**7**) were obtained as exclusive products by the reaction

(1) Department of Chemistry, Yokohama City University, Mutuura-cho, Kanazawa-ku, Yokohama 236, Japan.

(2) T. Nakagawa, T. Sakakibara, and S. Kumazawa, *Tetrahedron Lett.*, 1645 (1970).

(3) T. Sakakibara, S. Kumazawa, R. Sudoh, and T. Nakagawa, *Carbohyd. Res.*, in press.

(4) The chemistry of nitro sugars was reviewed by H. H. Baer: H. H. Baer, *Advan. Carbohyd. Chem.*, **24**, 69 (1969).

(5) T. Nakagawa, T. Sakakibara, and F. W. Lichtenthaler, *Bull. Chem. Soc. Jap.*, **43**, 3861 (1970).