Tetrahedron, 1965, Vol. 21, pp. 861 to 865. Pergamon Press Ltd. Printed in Northern Ireland

QUINOXALINE DERIVATIVES—IV[1]

CYCLIZATION OF α-ARYL-*o*-NITROACETANILIDES TO QUINOXALINE-N-OXIDES

YUSUF AHMAD, M. S. HABIB*, ZIAUDDIN and NAZ BASHIR
Chemical Research Division, Central Laboratories, Pakistan
Council of Scientific and Industrial Research, Karachi, Pakistan

(*Received* 20 *May* 1964; *in revised form* 25 *November* 1964)

Abstract—Cyclization of a number of α-phenyl and α-(*p*-nitrophenyl)-*o*-nitroacetanilides (Ie-n) in the presence of a basic catalyst to the corresponding 2-phenyl and 2-(*p*-nitrophenyl)-3-hydroxyquinoxaline 1-oxides (IIe-n) is described. The influence of various substituents on the ease of cyclization has been discussed.

A NOVEL method for the preparation of quinoxaline derivatives has been described.[1] It involves a base catalysed cyclization of α-cyano-*o*-nitroacetanilides (Ia) to the corresponding 2-cyano-3-hydroxyquinoxaline 1-oxides (IIa). Whereas *o*-nitroacetanilide itself fails to ring-close under these conditions,[2] it hydrolyses easily in the presence of a base and cyclization to quinoxaline derivatives can be effected if the methylene group in the acetyl side chain is activated by the presence of a suitable electron-withdrawing group. α-Acyl-*o*-nitroacetanilides (Ib and c) conform to this condition, and Tennant[3] cyclized them to the corresponding 2-acyl-3-hydroxyquinoxaline 1-oxide (IIb and c). Similarly, 1-(*o*-nitro-phenylcarbamoylmethyl)pyridinium chloride (Id) cyclizes[3] to the quinoxaline 1-oxide derivative (IId), the pyridinium moiety of which under the conditions of the reaction splits, yielding 2-amino-3-hydroxyquinoxaline 1-oxide (IIe; NH_2 for Ph).

Other *o*-nitroacetanilides, which fulfil these requirements have been synthesized to extend the scope of this cyclization for the preparation of quinoxalines, and particularly their N-oxides, which in many cases are not available by the usual methods.

o-Nitroaniline reacts with phenylacetyl chloride to yield *o*-nitro-α-phenylacetanilide (Ie), m.p. 80°, the pyridine solution of which on being heated in aq. potassium hydroxide solution at 100° gives a good yield of a compound X, m.p. 307°; the elementary analysis of which agrees with $C_{14}H_{10}N_2O_2$. Its structure was proved to be 3-hydroxy-2-phenylquinoxaline 1-oxide (IIe), on the basis of the following evidence.

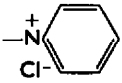
(i) The usual absorption peaks of the nitro group present in the starting nitroanilide are missing in the IR-spectrum of X.

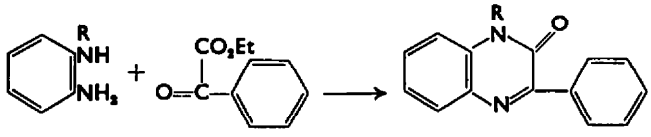
(ii) Sodium dithionite in aqueous ethanol deoxygenates X to a product, which is identical (IR-spectrum and mixed m.p.) with 3-hydroxy-2-phenylquinoxaline (IIIe), which was also synthesized by the condensation of ethyl phenylglyoxalate with *o*-phenylenediamine. The m.p. (258–260°) of 3-hydroxy-2-phenylquinoxaline obtained

* C/O Burroughs Wellcome & Co. (Pakistan) Ltd., D/43, S.I.T.E., Karachi.

[1] Part III, Y. Ahmad, M. S. Habib and Ziauddin, *Tetrahedron* **20**, 1107 (1964).
[2] O. C. M. Davis, *J. Chem. Soc.* **95**, 1397 (1909).
[3] G. Tennant, *J. Chem. Soc.* 2428 (1963).

I II III

	R	R′	R″		R	R′	R″
(a)	H	H	CN	(h)	EtO	H	Ph.
	(Cl, EtO or MeO)						
(b)	H	H	COMe	(i)	MeO	H	Ph.
(c)	H	H	COPh	(j)	H	H	$C_6H_4NO_2(p)$.
(d)	H	H		(k)	Cl	H	$C_6H_4NO_2(p)$.
(e)	H	H	Ph	(l)	Cl	Cl	$C_6H_4NO_2(p)$.
(f)	Cl	H	Ph	(m)	EtO	H	$C_6H_4NO_2(p)$.
(g)	Cl	Cl	Ph	(n)	MeO	H	$C_6H_4NO_2(p)$.



IV

by either of the above methods was higher than that reported by Burton and Shoppee,[4] who had obtained it by the reaction of phenylglyoxalic acid with *o*-phenylenediamine.

(iii) Deoxygenation of the product of methylation of compound X is identical (IR-spectrum and mixed m.p.) with 3,4-dihydro-4-methyl-3-oxo-2-phenylquinoxaline (IV, R = Me), which was obtained by methylation of 3-hydroxy-2-phenylquinoxaline (IIIe). Cheeseman[5] obtained the latter compound by the action of benzenediazonium chloride on 3,4-dihydro-4-methyl-3-oxoquinoxaline and reported the same m.p. for it.

4-Chloro-; 4,5-dichloro-; 4-ethoxy-; or 4-methoxy derivatives of *o*-nitroaniline on reaction with phenylacetyl chloride afford 4-chloro-; 4,5-dichloro-; 4-ethoxy-; or 4-methoxy-*o*-nitro-α-phenylacetanilides (Ie-i) respectively. All these compounds with substituents only in the anilide ring smoothly ring-close to the corresponding 3-hydroxy-2-phenylquinoxaline 1-oxides (IIe-i) under the conditions described for the cyclization of the parent 2-nitro-α-phenylacetanilide. Their structure follows by analogy and on the basis of their elementary analyses. On being heated with sodium dithionite in aqueous ethanol they yield the corresponding deoxygenated bases (IIIe-i). Hydrogen peroxide in acetic acid fails to reoxidize these deoxygenated compounds to their N-oxides and all are recovered unchanged even on prolonged heating with this reagent.

2-Nitro-α-(*p*-chlorophenyl)-acetanilide (Ie; R″ = *p*-chlorophenyl for Ph), the preparation and conversion of which to 2-(*p*-chlorophenyl)-3-hydroxyquinoxaline 1-oxide (IIe, R″ = *p*-chlorophenyl for Ph) is being reported in a subsequent paper, also requires stronger alkali and application of heat for cyclization.

2-Nitro-α-(*p*-nitrophenyl)-acetanilide (Ij), obtained by the action of *p*-nitrophenylacetyl chloride on *o*-nitroaniline, cyclizes with extreme ease, without application of

[4] H. Burton and C. W. Shoppee, *J. Chem. Soc.* 546 (1937).
[5] G. H. W. Cheeseman, *J. Chem. Soc.* 1246 (1961).

heat, when a pyridine solution of this anilide is treated with very mild alkali at room temperature.

Other substituted 2-nitro-α-(*p*-nitrophenyl)-acetanilides (Ik-n) obtained by the action of *p*-nitrophenylacetyl chloride on 4-chloro-; 4,5-dichloro-; 4-ethoxy-; or 4-methoxy derivatives of *o*-nitroaniline cyclize with the same ease. Substituted 3-hydroxy-2-(*p*-nitrophenyl)quinoxaline 1-oxides (IIk-n) are all very sparingly soluble in most organic solvents and can only be crystallized from dimethylformamide.

Substituents in the anilide ring have little effect on the cyclization but substituents in the phenyl ring of the α-phenyl-*o*-nitroacetanilides have a very profound influence on the ease (or otherwise) of cyclization to quinoxaline derivatives. This is in accordance with the mechanism proposed.[1] The anion derived from the active methylene in the acetyl side chain of *o*-nitroacetanilides, attacks the *ortho* nitro group with resultant ring closure and formation of the quinoxaline derivatives. Electron-withdrawing groups in the phenyl ring of these anilides should promote anion formation whereas the substituents in the anilide ring have very little effect.

EXPERIMENTAL

IR spectra were measured in Nujol Mull using a Perkin-Elmer model 137 B. Light petroleum used had b.p. 60–80°.

Materials. Commercial *o*-Nitroaniline was used. 4-Chloro-2-nitroaniline,[6] 4,5-dichloro-2-nitroaniline,[7] 4-ethoxy-2-nitroaniline,[8] 4-methoxy-2-nitroaniline,[9] phenylacetyl chloride,[10] *p*-nitrophenylacetyl chloride,[11] and ethyl phenylglyoxalate[12] were prepared according to the published methods.

2-Nitro-α-phenylacetanilide (Ie). *o*-Nitroaniline (1·0 mole) and phenylacetyl chloride (1·2 moles) were intimately mixed for ½ hr. The reaction mixture after being taken up in benzene was washed with 5% NaOH aq and then with water. The benzene layer was dried (Na_2SO_4) and evaporated to dryness. The residue crystallized from benzene–light petroleum as yellow needles of the anilide (Ie) in 85% yield, m.p. 80°. (Found: C, 65·7; H, 4·4; N, 11·3 $C_{14}H_{12}N_2O_3$ requires: C, 65·6; H, 4·7; N, 10·9%.) This general procedure was employed for the preparation of other substituted anilides described below.

4-Chloro-2-nitro-α-phenylacetanilide (If). 4-Chloro-2-nitroaniline gave in 80% yield, yellow needles (from benzene–light petroleum) of the *4-Chloroanilide* (If), m.p. 109–110°. (Found: Cl, 11·7; N, 9·7 $C_{14}H_{11}ClN_2O_3$ requires: Cl, 12·2; N, 9·6%.)

4,5-Dichloro-2-nitro-α-phenylacetanilide (Ig). 4,5-Dichloro-2-nitroaniline gave in 78% yield, yellow needles (from benzene–light petroleum) of the *4,5-dichloroanilide* (Ig), m.p. 118°. (Found: Cl, 21·0; N, 7·8 $C_{14}H_{10}Cl_2N_2O_3$ requires: Cl, 21·8; N, 7·7%.)

4-Ethoxy-2-nitro-α-phenylacetanilide (Ih). 4-Ethoxy-2-nitroaniline gave in 83% yield, yellow plates (from benzene–light petroleum) of the *4-ethoxyanilide* (Ih), m.p. 95°. (Found: C, 64·1; H, 5·4; N, 8·95 $C_{16}H_{16}N_2O_4$ requires: C, 64·0, H, 5·4; N, 9·3%.)

4-Methoxy-2-nitro-α-phenylacetanilide (Ii). 4-Methoxy-2-nitroaniline gave in 85% yield, yellow needles (from benzene) of the *4-methoxyanilide* (Ii), m.p. 84°. (Found: N, 9·75 $C_{15}H_{14}N_2O_4$ requires: N, 9·8%.)

2-Nitro-α-(p-nitrophenyl)acetanilide (Ij). *o*-Nitroaniline (1·0 mole) and *p*-nitrophenylacetyl chloride (1·1 moles) were heated on a water bath for 10–15 min. The reaction mixture was taken up in benzene and washed with 5% $NaHCO_3$ aq and then with water. The solvent was removed from the dried (Na_2SO_4) benzene solution and the residue crystallized from benzene as yellow needles of the *p-nitrophenylanilide* (Ij) in 86% yield, m.p. 178–180°. (Found: C, 55·2; H, 3·8; N, 14·05 $C_{14}H_{11}N_3O_5$

[6] M. K. Bose, *J. Indian Chem. Soc.* **22**, 169 (1945).
[7] Von F. Beilstein and A. Kurbatow, *Liebigs Ann.* **196**, 214 (1879).
[8] H. van Erp, *J. Prakt. Chem.* **129**, 327 (1931).
[9] P. E. Fanta and D. S. Tarbell, *Org. Syntheses* **25**, 78 (1945).
[10] F. M. Hamer, *J. Chem. Soc.* 1480 (1956).
[11] E. Fourneau and V. Nicolitch, *Bull. Soc. Chim. Fr.* **43**, 1232 (1928); *Chem. Abstr.* **23**, 4463 (1929).
[12] J. Vène, *Bull. Soc. Chim. Fr.* **12**, 506 (1945); *Chem. Abstr.* **40**, 4661 (1946).

requires: C, 55·8; H, 3·7; N, 13·95%.) Similarly the following anilides were prepared by the reaction of *p*-nitrophenylacetyl chloride with the corresponding anilines.

4-Chloro-2-nitro-α-(p-nitrophenyl)acetanilide (Ik). 4-Chloro-2-nitroaniline gave in 82% yield yellow needles (from benzene) of the *4-Chloro*-p-*nitrophenylanilide* (Ik), m.p. 169–170°. (Found: Cl, 10·7; N, 12·2 $C_{14}H_{10}ClN_3O_5$ requires: Cl, 10·6; N, 12·5%.)

4,5-Dichloro-2-nitro-α-(p-nitrophenyl)acetanilide (Il). 4,5-Dichloro-2-nitroaniline gave in 78% yield yellow needles (from benzene) of the *4,5-dichloro*-p-*nitrophenylanilide* (Il), m.p. 205°. (Found: Cl, 19·05; N, 11·15 $C_{14}H_9Cl_2N_3O_5$ requires: Cl, 19·2; N, 11·35%.)

4-Ethoxy-2-nitro-α-(p-nitrophenyl)acetanilide (Im). 4-Ethoxy-2-nitroaniline gave in 86% yield yellow needles (from benzene) of the *4-ethoxy*-p-*nitrophenylanilide* (Im), m.p. 156°. (Found: C, 55·4; H, 4·1; N, 12·0 $C_{16}H_{15}N_3O_6$ requires: C, 55·6; H, 4·4; N, 12·2%.)

4-Methoxy-2-nitro-α-(p-nitrophenyl)acetanilide (In). 4-Methoxy-2-nitroaniline gave in 84% yield pale yellow microneedles (from benzene) of the *4-methoxy*-p-*nitrophenylanilide* (In), m.p. 208°. (Found: N, 12·2 $C_{15}H_{13}N_3O_6$ requires: N, 12·7%.)

3-Hydroxy-2-phenylquinoxaline 1-oxide (IIe). A solution of Ie (5·0 g) in pyridine (25 ml) and 20% KOH aq (50 ml) was heated on a water bath for 1 hr. The reaction mixture was diluted with water and neutralized with dil. HCl. The precipitate thus obtained was washed with dil. HCl, and then with water and crystallized from EtOH as yellow needles of the *1-oxide* (IIe), in 78% yield, m.p. 307°. (Found: C, 70·9; H, 4·1; N, 11·4 $C_{14}H_{10}N_2O_2$ requires: C, 70·6; H, 4·2; N, 11·8%.) Methylation with methyl sulphate in 1 N NaOH gave a good yield (yellow needles; from EtOH) of the *3,4-Dihydro-4-methyl-3-oxo-2-phenylquinoxaline 1-oxide* (IIe; Me for H′), m.p. 192–193°. (Found: N, 10·9; $C_{15}H_{12}N_2O_2$ requires: N, 11·1%.) This on reduction with sodium dithionite in EtOH aq gave in 83% yield IIIe, (Me for H′), m.p. 137–138°, which crystallized from EtOH. Cheeseman[6] reported m.p. 138–139°.

3-Hydroxy-2-phenylquinoxaline (IIIe). (a) A mixture of IIe (1·0 g) in 50% EtOH aq (150 ml) and sodium dithionite (4·0 g) was heated under reflux for 2 hr and the volume reduced to 50 ml under red. press. The product (IIIe; 80%) crystallized from EtOH, as pale yellow microneedles, m.p. 258–260°. (Found: N, 12·3 Calc. for $C_{14}H_{10}N_2O$ N, 12·6%.)

(b) To *o*-phenylenediamine (0·2 g) in EtOH (5 ml) ethyl phenylglyoxalate (0·4 g) was added. The product (IIIe; 0·4 g) separated on slight warming and crystallized from EtOH in pale yellow needles, m.p. 258–260°. It was identical (IR-spectrum; mixed m.p.) with a sample prepared under (a). Burton and Shoppee[4] reported the m.p. as 247°. Methylation of IIIe with methyl sulphate (0·5 ml) in acetone (50 ml) and anhydrous Na_2CO_3 gave in good yield IIIe (Me for H′), m.p. 136–138° as pale yellow microneedles (from EtOH). This was identical (IR-spectrum and mixed m.p.) with a sample obtained by the reduction of IIe (Me for H′).

Attempts to reoxidize this base to the N-oxide with H_2O_2–ACOH were unsuccessful.

7-Chloro-3-hydroxy-2-phenylquinoxaline 1-oxide (IIf). Similarly, If gave in 72% yield yellow needles (from EtOH) of the *7-Chloro 1-oxide* (IIf), m.p. 312–313° (dec). (Found: C, 61·6; H, 3·1; Cl, 13·2; N, 10·4 $C_{14}H_9ClN_2O_2$ requires: C, 61·65; H, 3·3; Cl, 13·0; N, 10·3%.) This on reduction with sodium dithionite in EtOH aq gave in 77% yield the *7-Chloro-3-hydroxy-2-phenylquinoxaline* (IIIf) m.p. 262–263°, which crystallized from EtOH as pale yellow needles. (Found: Cl, 14·0; N, 11·1 $C_{14}H_9ClN_2O$ requires: Cl, 13·84; N, 10·9%.)

6,7-Dichloro-3-hydroxy-2-phenylquinoxaline 1-oxide (IIg). Similarly Ig afforded in 70% yield the *6,7-dichloro 1-oxide* (IIg) m.p. 305–306° as yellow microneedles from dimethylformamide–water. (Found: C, 54·7; H, 2·7; Cl, 22·9; N, 8·95 $C_{14}H_8Cl_2N_2O_2$ requires: C, 54·7; H, 2·6; Cl, 23·1; N, 9·1%.) The N-oxide (IIg) on reduction with sodium dithionite in EtOH aq gave *6,7-dichloro-3-hydroxy-2-phenylquinoxaline* (IIIg), which was crystallized from EtOH as yellow needles m.p. 291–292°. (Found: N, 9·4 $C_{14}H_8Cl_2N_2O$ requires: N, 9·6%.)

7-Ethoxy-3-hydroxy-2-phenylquinoxaline 1-oxide (IIh). Similarly Ih gave in 74% yield the *7-ethoxy 1-oxide* (IIh), which crystallized from EtOH as yellow needles m.p. 290–292°. (Found: C, 68·1; H, 4·9; N, 9·7 $C_{16}H_{14}N_2O_3$ requires: C, 68·1; H, 5·0; N, 9·9%.) This N-oxide on reduction with sodium dithionite gave in 82% yield pale yellow needles (from EtOH) of the *7-ethoxy-3-hydroxy-2-phenylquinoxaline* (IIIh) m.p. 263–264°. (Found: C, 69·0; H, 5·3; N, 10·0 $C_{16}H_{14}N_2O_2 \cdot \frac{1}{2}H_2O$ requires: C, 69·8; H, 5·1; N, 10·0%.)

7-Methoxy-3-hydroxy-2-phenylquinoxaline 1-oxide (IIi). Similarly Ii gave in 72% yield the *7-methoxy 1-oxide* (IIi), m.p. 297–300°, (orange needles from EtOH). (Found: C, 67·0; H, 4·2; N,

10·3 $C_{15}H_{12}N_2O_3$ requires: C, 67·1; H, 4·5; N, 10·4%.) The N-oxide (IIi) on reduction with sodium dithionite in glacial acetic acid, gave yellow needles (from EtOH) of *3-hydroxy-7-methoxy-2-phenylquinoxaline* (IIIi), m.p. 234–235° (65% yield). (Found: C, 67·8; H, 4·5; N, 9·7 $C_{15}H_{12}N_2O_2.H_2O$ requires: C, 66·7; H, 5·2; N, 10·0%.)

3-Hydroxy-2-(p-nitrophenyl)quinoxaline 1-oxide (IIj). A mixture of Ij (3·0 g) in pyridine (15 ml) and 1 N NaOH (15 ml) was shaken at room temp for 10–15 min. The reaction mixture on acidification gave a solid which crystallized from dimethylformamide as yellow needles of the *2-(p-nitrophenyl)-1-oxide* (IIj) in 88% yield, m.p. >325°. (Found: C, 59·0; H, 3·3; N, 15·0 $C_{14}H_9N_3O_4$ requires: C, 59·4; H, 3·2; N, 14·8%.)

7-Chloro-3-hydroxy-2-(p-nitrophenyl)quinoxaline 1-oxide (IIk). Similarly, Ik gave in 84% yield yellow needles (from dimethylformamide–water) of the *7-Chloro-2-(p-nitrophenyl)-1-oxide* (IIk), m.p. >325°. (Found: Cl, 11·15; N, 12·65 $C_{14}H_8ClN_3O_4$ requires: Cl, 11·2; N, 13·2%.)

6,7-Dichloro-3-hydroxy-2-(p-nitrophenyl)quinoxaline 1-oxide (III). Similarly, Il afforded light brown microneedles from dimethylformamide–water, of the *6,7-dichloro-2-(p-nitrophenyl)-1-oxide* (III), in 73% yield, m.p. >310°. (Found: N, 11·5 $C_{14}H_7Cl_2N_3O_4$ requires: N, 11·9%.)

7-Ethoxy-3-hydroxy-2-(p-nitrophenyl)quinoxaline 1-oxide (IIm). Similarly, Im gave in 78% yield yellow needles (from dimethylformamide–water) of the *7-ethoxy-2-(p-nitrophenyl)-1-oxide* (IIm), m.p. >310°. (Found: N, 13·0 $C_{16}H_{13}N_3O_5$ requires: N, 12·8%.)

3-Hydroxy-7-methoxy-2-(p-nitrophenyl)quinoxaline 1-oxide (IIn). Similarly, In afforded in 81% yield yellow needles (from dimethylformamide–water) of the *7-methoxy-2-(p-nitrophenyl)-1-oxide* (IIn), m.p. 278° (dec). (Found: N, 13·1 $C_{15}H_{11}N_3O_5$ requires: N, 13·4%.)

Acknowledgement—We wish to thank Dr. S. Siddiqui, F.R.S., Chairman P.C.S.I.R. for his interest and encouragement. Analyses were carried out by M/S. Pascher & Pascher, Germany and Microanalytical Section, Central Laboratories, P.C.S.I.R., Karachi.