# BEHAVIOUR OF *N*-BENZENESULPHONYLOXY- AND *N*-ACETOXY-2,3-QUINOXALINEDICARBOXIMIDES TOWARDS SOME NUCLEOPHILES[1].

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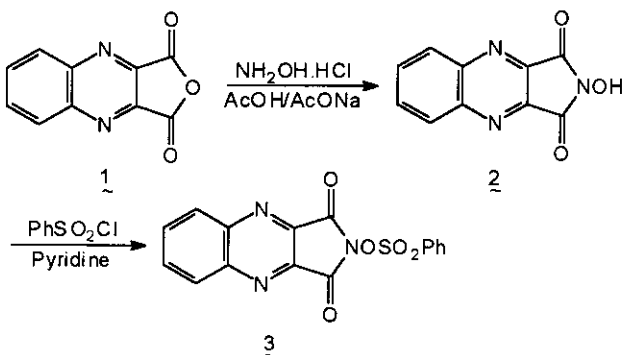
Abstract- The reactions of *N*-benzenesulphonyloxy- and *N*-acetoxy-2,3-quinoxalinedicarboximides with different nucleophilic reagents have been investigated.

In this investigation, which is a continuation of our previous works,[2,3] we have studied the Lossen rearrangement of *N*-benzenesulphonyloxy- and *N*-acetoxy-2,3-quinoxalinedicarboximides with different nucleophiles.

The starting *N*-benzenesulphonyloxy-2,3-quinoxalinedicarboximide (3) was prepared according to the method described by Bauer.[4] But, a one step procedure was developed to prepare the intermediate compound, *N*-hydroxy-2,3-quinoxalinedicarboximide (2), by treatment of quinoxaline-2,3-dicarboxylic anhydride (1) with hydroxylamine hydrochloride in acetic acid in the presence of sodium acetate in 80% yield instead of cyclization of 3-carboxy-2-quinoxalinecarbohydroxamic acid with phosphoryl chloride carried out by Bauer.[4]

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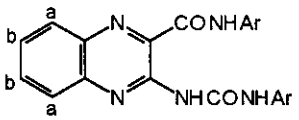
Reaction of *N*-benzenesulphonyloxy-2,3-quinolinedicarboximide (3) with excess aromatic amines namely, aniline, *p*-toluidine and/or *p*-anisidine in benzene at room temperature led to the formation of 3-arylureidoquinoxaline-2-arylcarboxamides (4a-c)



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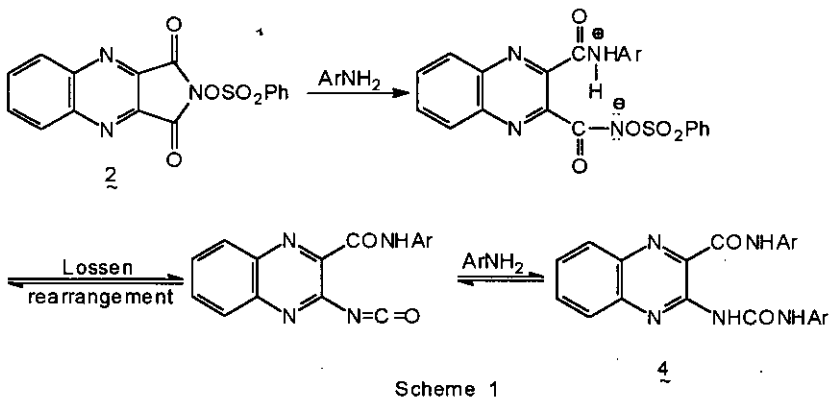
a, Ar = $C_6H_5$ ; b, Ar = $C_6H_4CH_3(p)$ ; c, Ar = $C_6H_4OCH_3(p)$

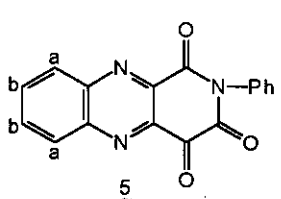
The structures of compounds (4a-c) were confirmed on the basis of elemental analyses as well as spectroscopic data. The $^1$H-NMR spectrum of 4a revealed a multiplet at δ 8.0-8.4 ppm assigned to the four protons indicated by letters a and b in structure 4, and a multiplet at δ 7.2-7.8 ppm integrated to the ten protons assigned to the phenyl rings protons. Furthermore, compound 4a showed also signals at δ 10.95 and 10.8 ppm integrated to the three protons assigned to (CONH) and (NHCONH) protons. On the other hand, the $^1$H-NMR spectra for 4b and 4c showed the 6H-methyl groups at δ 2.3 and 2.4 ppm (4b) and at δ 3.7 and 3.75 ppm assigned to the 6H-$OCH_3$ groups (4c). The other protons were detected in their expected location (cf. Experimental). Moreover, the IR spectra of 4a-c showed an NH absorption in the region 3340-2800 cm$^{-1}$ and an C=O absorption in the region 1770-1650 cm$^{-1}$.

The reaction of 3 with aromatic amines may be explained by ring opening followed by the Lossen rearrangement with the loss of sulphonate ion to give the intermediate isocyanate, which added another mole of aromatic amine to give 4 (Scheme 1).



Scheme 1

Fusion of *N*-sulphonyloxy derivative (3) with aniline on a water bath for 2 h afforded the cyclized product, 3-phenyl-1*H*-pyrimido[4,5-*b*]quinoxaline-2,4-dione (5).



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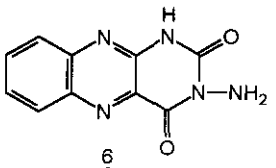
The structure of 5 was confirmed by elemental analysis and spectroscopic data. The $^1$H-NMR spectrum showed the protons indicated by letters a and b as a multiplet signals at δ 8.0-8.5 ppm and at δ 7.3-7.5 ppm integrated to five protons assigned to the phenyl ring protons. The imino group was detected as a singlet signal at δ 11.95 ppm.

Treatment of 3 with hydrazine hydrate in dry benzene at room temperature gave the cyclized product, 3-amino-1*H*-pyrimido[4,5-*b*]quinoxaline-2,4-dione (6).



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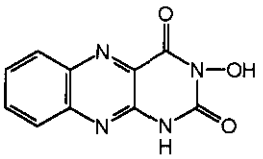
Strurctural reasoning for 6 was based on compatible analytical and spectral data. The $^1$H-NMR spectrum revealed a singlet signal at δ 5.55 ppm integrated to the protons assigned to the amino group, whereas the imino group was detected as a singlet signal at δ 12.3 ppm. The other protons were detected in their expected location (cf. Experimental).

When hydroxylamine hydrochloride was added to 3 in dry pyridine at room temperature it afforded 3-hydroxy-1*H*-pyrimido[4,5-*b*]quinoxaline-2,4-dione (7), which was identical with that prepared by the previous methods.[4,5]



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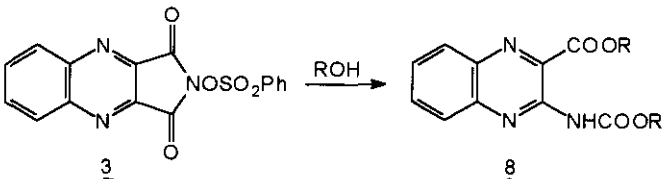
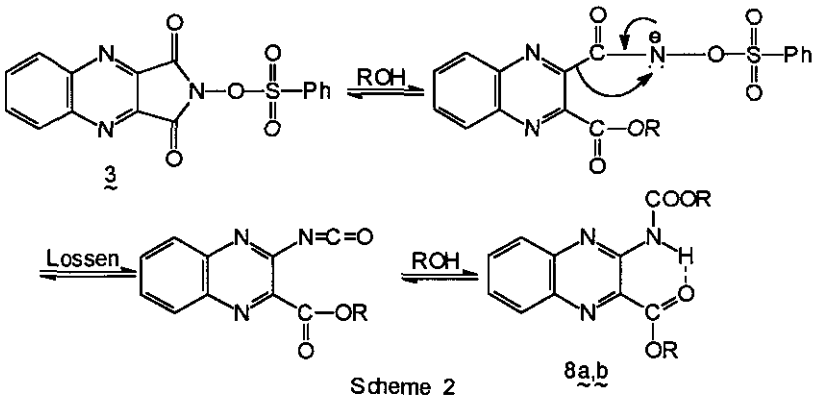
Alcoholysis of *N*-benzenesulphonyloxy-2,3-quinoxalinedicarboximide (3) with methanol or ethanol in the presence of pyridine as basic catalyst gave methyl 3-methoxycarbonylamino-2-quinoxalinecaboxylate or ethyl 3-ethoxycarbonylamino-2-quinoxalinecarboxylate (8a-b).



3 8

a, R = $CH_3$
b, R = $C_2H_5$

The reaction may proceed according to the following mechanism (Scheme 2).



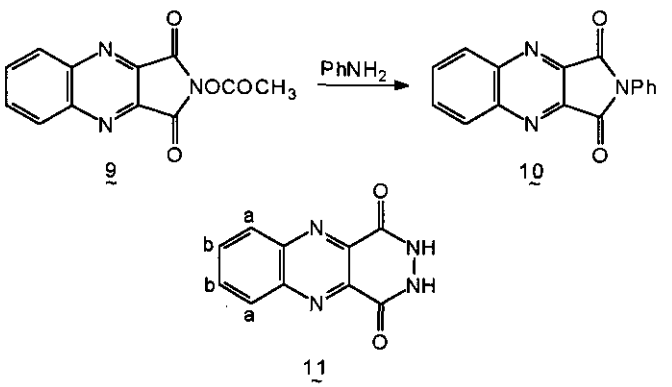
Scheme 2

Structural reasonings for 8a,b were based upon elemental and spectroscopic evidences. The $^1$H-NMR for 8a showed signals at δ 3.8, 4.0 and 10.2 ppm assigned to the methyl and (NH) protons, whereas compound 8b showed signals at δ 1.3 and 1.5 ppm assigned to the methyl protons and at δ 4.25 and 4.55 ppm assigned to the methylene protons. The other protons were detected in their expected location (cf. Experimental).

On the other hand, *N*-acetoxyquinoxaline-2,3-dicarboximide (9) failed to undergo the Lossen rearrangement when it treated with aromatic amines or hydrazine to alloxazine derivatives. Instead, it reacted with aniline in benzene and gave the corresponding mixture of *N*-phenylquinoxaline-2,3-dicarboximide (10) and acetanilide.

The structure of 10 was identical in all aspects with that reported in the literatures[6,7] by another methods.

The above reaction probably took place *via* the intermediate formation of *N*-hydroxyquinoxaline-2,3-dicarboximide (2). This was confirmed from the fact that the reaction of 2 with aniline gave 10. Hydrazinolysis of 9 with hydrazine hydrate at reflux in boiling benzene gave the cycloquinoxalhydrazide (11).

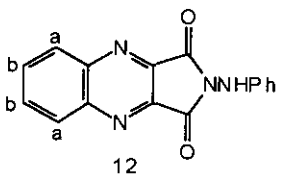


The structure of 11 was identical with that prepared from either quinoxaline-2,3-dicarboxylic acid anhydride (1) and hydrazine hydrate or treatment of 2 with hydrazine hydrate in acetic acid. The $^1$H-NMR

spectrum of 11 showed a signal at δ 11.65 ppm assigned to (NH) protons along with the signal assigned to the protons indicated by letters a and b. Moreover, the mass spectrum showed molecular ion at m/z 214 (base peak). This ion underwent the fragmentation given in experimental.

In a similar way, 9 reacted with phenylhydrazine in dry benzene to give *N*-anilino-2,3-quinoxalinedicarboximide (12).

The structure of 12 was established on the basis of its spectral data. The $^1$H-NMR spectrum revealed a multiplet at δ 8.0-8.4 ppm assigned to the four protons indicated by letters a and b, and a multiplet at δ 7.6-7.8 ppm integrated to the five protons assigned to the phenyl ring protons. The (NH) proton was detected as a singlet signal at δ 10.1 ppm.

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In conclusion, *N*-benzenesulphonyloxy-2,3-quinoxalinedicarboximide underwent the Lossen rearrangement with different nucleophiles and gave alloxazine derivatives, whereas, *N*-acetoxy derivative failed to undergo the same rearrangement.

## EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using the potassium bromide wafer technique. The $^1$H-NMR spectra were obtained on a Varian EM 390 spectrophotometer.

*N*-Hydroxy-2,3-quinoxalinedicarboximide (2).

A mixture of hydroxylamine hydrochloride (5 g, 0.023 mol) and anhydrous sodium acetate (5 g, 0.061 mol) in glacial acetic acid (50 mL) was refluxed for 5 min. The precipitated sodium chloride was filtered off and quinoxaline-2,3-dicarboxylic anhydride (5 g, 0.025 mol) was added to the filtrate. The mixture was refluxed for further 20 min. The solid obtained on cooling was collected by filtration and recrystallized from acetic acid as pale yellow needles, yield 4.3 g (80%), mp 283-285°C (decomp), lit.,[4] mp 285°C (decomp).

3-Arylureidoquinoxaline-2-arylcarboxamides (4a-d), General method.

A mixture of *N*-benzenesulphonyloxy-2,3-quinoxalinedicarboximide (3) (0.710 g, 0.002 mol) and primary aromatic amine (0.008 mol) in dry benzene (30 mL) was stirred at rt for 6 h. The solvent was removed under vacuo. The solid product was washed with ethanol and crystallized from acetic acid. The IR spectra showed the presence of NH in the region 3340 - 2800 cm$^{-1}$ and C=O in the region 1770-1650 cm$^{-1}$.

Compound (4a): yellow crystals, mp 235 - 237°C, yield 0.63 g (82%); $^1$H-NMR (DMSO-$d_6$): δ 8.0-8.4 (m, 4H, a and b), 7.2 - 7.8 (m, 10H, phenyl rings), 10.95 (s, 1H, CONH) and 10.8 (s, 2H, NHCONH). Anal. Calcd for $C_{22}H_{17}N_5O_2$ : C, 68.91; H, 4.47; N, 18.27. Found : C, 69.11; H, 4.50; N, 17.96.

Compound (4b): yellow powder, mp 181-183°C, yield 0.72 g (87%); $^1$H-NMR ($CF_3COOH$): δ 10.2 (s, 1H, CONH), 9.2 (s, 2H, NHCONH), 8.1 - 8.6 (m, 4H, a and b), 7.2 - 7.4 (m, 8H, phenyl rings) and 2.3 and 2.4 (2s, 6H, $2CH_3$): Anal. Calcd for $C_{24}H_{21}N_5O_2$ : C, 70.07; H, 5.11; N, 17.03. Found : C, 70.27; H, 5.18; N, 17.25.

Compound (4c): pale yellow powder, mp 170 - 171°C, yield 0.8 g (90%), $^1$H-NMR (DMSO-$d_6$): δ 7.8 - 8.3 (m, 4H, a and b), 7.2 - 7.5 (m, 8H, phenyl rings), 9.9 (s, 1H, CONH), 9.8 (s, 2H, NHCONH) and 3.7, 3.75 (s, 6H, $2OCH_3$). Anal. Calcd for $C_{24}H_{21}N_5O_4$ : C, 65.01; H, 4.74; N, 15.80. Found : C, 65.33; H, 4.81; N, 16.01.

3-Phenyl-1*H*-pyrimido[4,5-*b*]quinoxaline-2,4-dione (5).

*N*-Benzenesulphonyloxy-2,3-quinoxalinedicarboximide (3) (0.710 g, 0.002 mol) and aniline (0.73 mL, 0.008 mol) were heated on a water bath for 2 h. The solid formed was collected, washed with methanol and crystallized from acetic acid as greenish yellow crystals, yield 0.41 g (70%), mp 255-257°C; IR (KBr) revealed the presence of NH at 3380 - 3260 $cm^{-1}$ and two C=O's at 1710-1680, 1630 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 8.0 - 8.5 (m, 4H, a and b), 7.3 - 7.5 (m, 5H, phenyl ring) and 11.95 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{10}N_4O_2$ : C, 66.20; H, 3.47; N, 19.30. Found : C, 65.82; H, 3.79; N, 19.40.

3-Amino-1*H*-pyrimido[4,5-*b*]quinoxaline-2,4-dione (6).

99-100% Hydrazine hydrate (0.4 mL, 0.008 mol) was added to a suspension of 3 (0.710 g, 0.002 mol) in dry benzene (30 mL). The reaction mixture was stirred at rt for 5 h and the solvent was removed under vacuo. The solid formed was washed with methanol and crystallized from acetic acid, yellow crystals, mp 293°C, yield 0.22 g (48%); IR (KBr): 3360, 3300 - 2800 $cm^{-1}$ ($NH_2$, NH) and 1750, 1690 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$): δ 5.55 (s, 2H, $NH_2$), 7.6 - 8.3 (m, 4H, a and b) and 12.3 (s, 1H, NH). Anal. Calcd for $C_{10}H_7N_5O_2$ : C, 52.40; H, 3.08; N, 30.56. Found : C, 52.70; H, 3.30; N, 30.26.

3-Hydroxy-1*H*-pyrimido[4,5-*b*]quinoxaline-2,4-dione (7).

To a solution of 3 (0.710 g, 0.002 mol) in dry pyridine (10 mL), hydroxylamine hydrochloride (0.45 g, 0.008 mol) was added. The reaction mixture was stirred at rt for 2 h and diluted with water. The solid product obtained was identical in all aspects (elemental analysis, mp, IR and $^1$H-NMR) with that previously prepared.[4]

Action of alcohols on 3. Formation of 8a,b.

*N*-Benzenesulphonyloxy-2,3-quinoxalinedicarboximide (3) (0.710 g, 0.002 mol) was refluxed with methanol or ethanol (50 mL) in the presence of few drops of pyridine for 3 h. The solvent was removed

under vacuo and the solid formed washed with water and crystallized from chloroform-petroleum ether to give alkyl 3-alkoxycarbonylamino-2-quinoxalinecarboxylate 8a,b.

8a: Yellow coloured powder, mp 155°C, yield 0.3 g (58%); IR (KBr): 3320-3290 $cm^{-1}$ (NH) and 1770, 1700 $cm^{-1}$ (C=O); $^1$H-NMR ($CDCl_3$): δ 3.8 (s, 3H, $CH_3$), 4.0 (s, 3H, $CH_3$), 7.4 - 8.1 (m, 4H, a and b) and 10.2 (s, 1H, NH). Anal. Calcd for $C_{12}H_{11}N_3O_4$ : C, 55.17; H, 4.24; N, 16.09. Found : C, 54.90; H, 4.16; N, 16.40.

8b: Yellow coloured powder, mp 150°C, yield 0.41 g (70%); IR (KBr): 3320 $cm^{-1}$ (NH) and 1770, 1695 $cm^{-1}$ (C=O); $^1$H-NMR ($CDCl_3$): δ 1.3 and 1.5 (2t, J=7 Hz, 6H, $2CH_3$), 4.25 and 4.55 (2q, J=7 Hz, 4H, $2CH_2$), 7.5 - 8.1 (m, 4H, a and b) and 10.2 (s, 2H, NH). Anal. Calcd for $C_{14}H_{15}N_3O_4$ : C, 58.13; H, 5.23; N, 14.53. Found : C, 58.11; H, 5.25; N, 14.64.

Action of primary aromatic amines on 9. Formation of 10.

A mixture of *N*-acetoxy-2,3-quinoxalinedicarboximide (9) (1.3 g, 0.005 mol) and aniline (1.9 mL, 0.02 mol) was refluxed in dry benzene (30 mL) on a water bath for 3 h. The precipitated solid was collected, washed with benzene and dried. The product was recrystallized from acetic acid-$H_2O$ as pale yellow coloured powder, yield 1.15 g (83%), mp > 300°C, lit.,[6,7] > 300°C.

Evaporation of the mother liquor of this reaction gave a colourless product. It was shown to be acetanilide, by comparing its IR and mixed mp with authentic sample.

Action of hydrazine hydrate on 9. Formation of 11.

*N*-Acetoxy derivative (9) (0.7 g, 0.0025 mol) and 99-100% hydrazine hydrate (0.5 mL, 0.01 mol) were refluxed in dry benzene (10 mL) for 2 h whereby a yellow product was separated during reflux. The product was collected and recrystallized from acetic acid as yellow coloured powder, yield 0.41 g (70%), mp > 320°C; IR (KBr): 3230 $cm^{-1}$ (NH) and 1660 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$): δ 8.1 - 8.5 (m, 4H, a and b) and 11.65 (s, 2H, 2NH); MS (70 eV): m/z (rel intensity) = 214 (100), 186 (43), 170 (12), 158 (53), 143 (13), 129 (71), 116 (12), 102 (62), 90 (8), 76 (46), 64 (12), 58 (5), 51 (32), 39 (8). Anal. Calcd for $C_{10}H_6N_4O_2$ : C, 56.07. H, 2.80; N, 26.17. Found : C, 56.29; H, 3.03; N, 26.31.

Action of phenylhydrazine on 9. Formation of 12.

A mixture of *N*-acetoxy derivative (9) (0.7 g, 0.0025 mol) and phenylhydrazine (1.08 g, 0.01 mol) in 30 mL of dry benzene was refluxed on a water bath for 2 h. The solvent was removed under vacuo and the red coloured precipitate was collected and crystallized from dioxan-water as red crystals, mp 239°C, yield 0.63 g (80%); IR (KBr): 3320 $cm^{-1}$ (NH) and 1670 $cm^{-1}$ (C=O). $^1$H-NMR (DMSO-$d_6$): δ 8.0 - 8.4 (m, 4H, a and b), 7.6 - 7.8 (m, 5H, phenyl ring) and 10.1 (s, 1H, NH). Anal. Calcd for $C_{16}H_{10}N_4O_2$ : C, 66.20; H, 3.47; N, 19.30. Found : C, 65.90; H, 3.51; N, 19.16.

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