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SYNTHESIS OF SUBSTITUTED QUINOXALINE COMPOUNDS AND CHARACTERISATION OF STRUCTURAL FORMULA

Bablee Jyoti[1], Ram Vinay Thakur[2], Shabina Perween[1] and S.R. Kumar[1,*]
[1]Department of Chemistry, L.N.M.U., Dharbhanga, Bihar, India - 846004
[2]M.M. College, Azamnagar, Dharbhanga, Bihar, India - 846004

Abstract

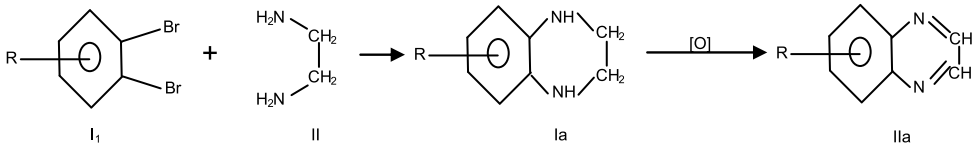
Quinoxaline and substituted quinoxaline derivatives constitute an interesting class of pharmacologically active compounds which have been extensively studied during the past two decades. In particular, large numbers of papers have been published because these compounds show remarkable antitumor and herbicidal properties. A solid phase and simple method of synthesis has been developed. In this strategy a one pot reaction from 2,3-diaminoanosol & glyoxal sodium bisulphite, which provided the compounds in good yields was demonstrated using this synthetic strategy. We prepared a representative set of such compounds, characterisation of structural formula were done by alternative method of synthesis elemental analysis as well as comparing the datas of IR, NMR, mass spectrum of the compounds in both series of compounds.

***Keywords*:** Quinoxaline, antitumor, herbicidal properties, 2,3-diaminoanisol.

Introduction

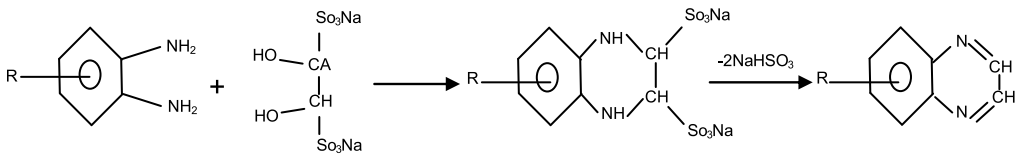
The structural diversity and biological importance of nitrogen containing heterocyclic compounds have made them attractive targets for synthesis over many years. Natural products show a broad spectrum of biological activities with a high potential for medicinal applications (Wiely, 1996; Wystach, 1967; Tisler and Stanovanik, 1968; Jacob, 1957; Manson and Aldous, 1973; Tjebbes, 1962). Quinoxaline and its derivatives are also structurally important components of such numerous biologically active natural products (Harada *et al*., 1985). Some of its N-linked and carbon linked derivatives are exhibiting anti-tumor and antifungal activities and have been widely used as particular and herbicides. Such significant and diversified pharmaceutical values have focused out interest on the study towards the synthesis of quinoxaline using simple methods of preparation with simple reagents (Chambers *et al*., 1975; Jyoti and Kumar, 2014). Quinoxaline are true heterocyclic compounds have two nitrogen atoms both are present in diazine ring. Diazines are six membered two nitrogen atoms containing heterocyclic ring. When both nitrogen atoms are present at 1 & 4 positions with respect to each other and fused such compounds is called quinoxaline.

There are various heterocyclic compounds which have been synthesised starting from substituted or unsubstituted carbonyl as well as aromatic diamino series of compounds. In the present work synthesis and characterisation of some quinoxaline have been with all the synthesis *i.e.* alternative method elemental analysis, melting point and mixed melting point. Finally comparing the spectral datas to elucidate (Kumar *et al*., 2017; Simpson, 1953; Brown, 1962). The structural formula may be obtained.



I1 II Ia IIa

Alternative method of preparation



I2 III IVa IIa

*Corresponding author Email: professorsrkumar@gmail.com

In $I_1 I_a, II_a IV_a$, R = p-Br

$I_2 I_b, II_b III_b$, R = o-Br

$I_3 I_c, II_c III_c$, R = m-Br

$I_4 I_d, II_d III_d$, R = p-OCH_3

$I_5 I_e, II_e III_e$, R = o-OCH_3

$I_6 I_f, II_f III_f$, R = p-NO_2

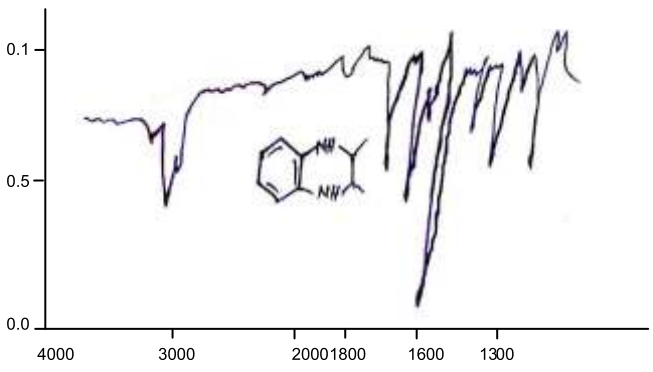
$I_7 I_g, II_g III_g$, R = o-NO_2

Material and Method

All melting points are uncorrected and were obtained in capillary using paraffin bath. FT-IR spectra were recorded using KBr disc on parkin Elmer FT-IR KBr spectrophotometer and ^{1}HNMR on Brucker advance II 400 NMR spectrometer using DMSO, CDCl3 as solvent. Purity of the compound is checked on silical gel G.glass plate using iodine vapours as a visualising agent. All aryl substances obtained in different steps were prepared by the extension of the known procedure.

Preparation of substiuted - 1,2,3,4-tetrahydroquinoxaline by the condensation of substituted o- dibromobenzene & 1,2-diamino ethane (Ia)

A solution of (0.5M) of substituted o-dibromobenzene in dry carbontetrachloride is a round bottomed flask fitted with reflux condenser is placed Ethylene diamine hydrochloride (0.5M) solution was added drop-wise with constant stirring (Kumar *et al*., 2017). The pot was kept in ice. The progress of reaction was made with the evolution of hydrogen bromide and further it was checked by TLC examination time to time. After completion of reaction, the reaction mixture was then poured into a mixture of ice and the ethereal extract washed with water and dried over anhydrous calcium chloride. Removal of ether and carbon disulphide by distillation left a gummy residue which crystallised on trituration with benzene and light petroleum ether. Recrystallisation from benzene gave the pure 1,2,3,4-tetrahydroquinoxaline (Simpson, 1953) as yellowish brown crystals, elemental analysis and melting point are placed in table. Primary amino compounds exhibit medium to strong N-H in plane bending vibrations near 1650-1580 cm^{-1} which is moved during reaction to give product in which it is slightly moved to higher frequency (Dickey and Gray, 1943). Aromatic secondary amineabsorb near 1490-1440 cm^{-1} and C-N stretching vibration at 1350-1310 cm^{-1}. There is much less interaction between these modes compared to the trans form. The N-H out of plane bending (wagging) vibration appears as a broad band near 800cm^{-1} and heat absorption at 3040 cm^{-1} assigned to aromatic C-H stretching vibration.



Preparation of quinoxaline by dehydrogenation of 1,2,3,4-tetrahydroquinoxaline prepared earlier[12] (IIa)

0.5 M of purified 1,2,3,4-tetrahydroquinoxaline in methanol is placed in round bottomed flask fitted with water condenser under reflux and then added 0.25g paladised charcoal in it and allowed heating to boil for about four hours in a slow current of carbon dioxide. After completion of heating the flask was kept in a ice chest overnight. The crude product obtained was filtered off and washed with 10% sulfuric acid and then with 10% sodium bicarbonate solution, followed by water, dried with anhydrous calcium sulphate and finally recrystalised from methanol. A brown crystal of substituted quinoxaline with 76% yield. Melting point and elemental analysis are placed in table

Alternative method of preparation of substituted quinoxalines

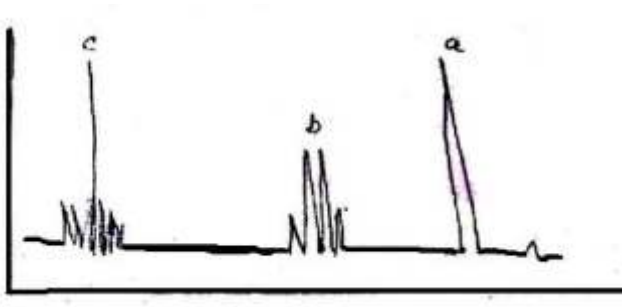
A mixture of substituted 1,2-diaminobenzene (0.5M) and glyoxal sodiumdibisulphite (0.5M) in aqueous solution of sodium acetate and acetic acid (10 ml) was taken and small amount of cone sulphuric acid (1 ml) was added to reaction mixture kept in a small round bottomed flask and heated under reflux on a water bath (Kumar and Sagar, 2013; Otter *et al*., 1971; Padwa *et al*., 1973; Gillman, 1943). The reaction was followed by TLC (Thin layer chromatography) which showed almost complete disappearance of the starting material after five hours of heating (Vogel, 2011; Wiley, 2011). Acetic acid was removed by distillation. The residue on cooling deposited a pale yellow mass. This was washed on cooling deposited a pale yellow mass. This was washed with benzene and ethanol. It was then recrystallised from ethanol to furnish the pure crystals of substituted quinoxaline crystals. Melting point and Mixed M. point determination of the proposed compound prepared here and earlier were found same and their elemental analysis spectral data were also found identical. On the same outline compound (Kumar, 1986) (IIa-IIg) were prepared and were compared physically (melting point spectral analysis & elemental analysis) and chemically (alternative method of synthesis) both.

Table: Elemental Analysis datas & mass spectra of compound (IIa - Iig)

	Yield	M.P	C°/%	H°/%	N°/%	O°/%	Br°/%	(m/e)⁺
6-p-Bromo-1,2,3,4-tetrahydroquinoxaline (Ia) $C_8H_{10}N_2Br$	78%	101°C	45.06 (45.00)	4.22 (4.20)	13.12 (13.14)	-	37.50 (37.55)	212,184
6-Bromoquinoxaline (IIa) $C_8H_6N_2Br$	72%	85°C	41. 10 (41.14)	2.12 (2.15)	13.40 (13.46)	-	32.50 (32.53)	208, 188
5-Bromoquinoxaline (IIIb) $C_8H_6N_2Br$	76%	178°	41.08 (41.14)	2.10	13.45 (13.46)	-	32.45	208, 188
7-Bromoquinoxaline (IIIc) $C_8H_6N_2Br$	68%	216°	41.13 (41.14)	2.14	13.42 (13.46)	-	32.42	208, 188
6-Methoxyquinoxaline (IIId) $C_9H_8N_2O$	75%	66°C	67.47 (67.50)	1.20 (1.25)	17.35 (17.50)	9.95 (10.00)	-	180, 154
5-Methoxyquinoxaline (IIIe) $C_9H_8N_2O$	70%	74°	67.45 (67.50)	1.22	17.40 (17.50)	9.98	-	108, 154
6-Nitroquinoxaline (IIIf) $C_8H_5N_3O_2$	74%	86°C	54.70 (54.85)	2.80 2.84	23.90 (24.00)	18.25 (18.28)	-	174, 126
6-Nitroquinoxaline (IIIg) $C_8H_5N_3O_2$	77%	163°C	54.72 (54.85)	2.75	23.98 (23.00)	18.20	-	174, 126

Results and Discussion

For the synthesis of compound (Ia-IIg) and (IIa - IIIg) the schemes shown above were followed. The substituted 1,2,3,4-tetrahydroquinoxaline were prepared by the standard method of preparation (Vogel, 2011; Wiley, 2011; Chlop, 2012). The compound (Ia-Ig) *i.e.* substituted 1,2,3,4-tetrahydroquinoxaline did not give the test of primary amine group. The pmr spectrum of the compound clearly indicated the signal showning protons for the presence of -NH-NH- moiety and other aromatic protons. In the typical synthesis of (Ia to IIg) *i.e.* tetrahydroquinoxaline. After completion of the reaction the crude product was recrystallised from 70% ethanol. In IR it has exhibited medium to strong in N-H- plane bending vibrations near 1450-1440 cm^{-1} and C-N stretching vibrations 1350-1310 cm^{-1}. The IR spectra do not show the band due to V_{NH}, $V_{C=C}$, V, but shows stretching frequency for substituted benzene. A singlet at $^{\delta}$0.6 ppm equivalent to 2H protons in due to identical two NH groups, A quartet at 2.61 ppm equivalent to 4H exhibits protons due to two identical methylene groups (b) and a resonance for three sets of aromatic protons of substituted benzene ring.



The mass spectrum of the compound showed presence of (M-1) peak at m/e - 212. Other important fragment peaks were located at 187,155 etc. The elemental analysis of the product indicated that molecular formula for Ia is $C_8H_9N_2Br$. On the basis of the above facts the compound Ia was assigned structure as 6 bromo-1,2,3,4- tetrahydroquinoxaline similarly the structured formulas for Ia to Ig were assigned.

The compound IIa as prepared by the dehydrogenation of Ia with paladised charcoal under heat. The IR spectrum indicated for the broad band and signals for -N=C at 1580 cm^{-1}, 1680 cm^{-1} for substituted benzene ring, 2130 cm^{-1} for -N=C-C=N- and 3050-3080 cm^{-1} for aromatic C-H stretching frequency. The PMR of the product IIa showed double singlet at $^{\delta}$4.8 and had a resonance of three sets of proton of aromatic protons $^{\delta}$8.4, $^{\delta}$7.8 and $^{\delta}$7.3. The elemental analysis also suggests in agreement with the theoretical value. All the above facts for the compound IIa was considered to assign the structure as 6-Bromoquinoxaline. Similarly all the other compounds IIIb to IIIg were prepared and their structures were assigned. On the same outline the structures of all compounds

(III b to III g) were synthesised and their structure were assigned.

Finally all the proposed compounds (III_a, III_b, III_c, III_d, III_e, III_f & III_g) were also synthesised and their structures were established by alternative method of synthesis compound obtained in each and every steps using standard method, were compared with the compounds obtained in previous method, it was found that elemental analysis, melting point &mixed melting points are same. More- over the comparison of data and signals obtained in their spectral analysis e.g. IR, NMR, Mass spectra are also identical. This confirmed the identity of same structure as proposed above for the substituted - 1,2,3,4-tetrahydro quinoxalines as well as substituted quinoxalines.

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