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SYNTHESIS OF QUATERNARY SALTS OF AMMONIA HAVING OXIME MOIETY AND THEIR PLANT GROWTH REGULATING ACTIVITY ON *ORYZA SATIVA*

NIRUPMA SOOD[1], SIMMI RANI[2] & M. L. SHARMA[3]

[1]Department of Chemistry, Khalsa College for Women, Ludhiana, Punjab, India

[2,3]Department of Chemistry, Punjab Agricultural University, Punjab, India

ABSTRACT

Twelve new quaternary salts of ammonia (1a-6a) and (1b-6b) from different aryl aldehydes(4-Cl, 3-NO_2, 2-Cl and 4-CH_3) and aryl ketones (acetophenone and benzophenone)were synthesized through the formation of their oximes . The oximes prepared were converted into epoxy compounds by reacting with epichlorohydrin. The epoxides thus procured were cleaved with secondary amines viz. diethyl amine and piperidine to get the desired hydroxy tertiary amines. The structure of these amines was established with the help of IR and PMR spectral studies. Biological activity of these compounds was tested using seed germination and seedling growth as bioassay of Oryza sativa. All the compounds showed plant growth retardant activity comparable to cycocel (CCC) at higher concentrations.

KEYWORDS: Aldehydes, Ketones, Cycocel, Germination, Seedling

INTRODUCTION

Plant growth regulators have been found to possess plant growth retardant activity as these have been used to manipulate the size, shape and overall quality of various crops. In the present work twelve new quaternary salts of ammonia (1a-6a) and (1b-6b) from different aryl aldehydes and ketones have been synthesized and tested as plant growth retardants

MATERIALS AND METHODS

Thin layer chromatography (TLC) was done to check the purity of analysed samples. PMR spectra were taken in $CDCl_3$ on BURKER AVANCE II 400 NMR spectrometer at SAIF, Panjab University, Chandigarh and IR spectra were recorded as neat liquid on Perkin Elmer- 800 spectrometer. Rice seedlings (Oryza sativa, PR- 116) for biological study of compounds were collected from seed technology section, Department of Plant Breeding and Genetics, PAU, Ludhiana. Drying of organic solvents was done over anhydrous Na_2SO_4. Ether was dried by passing sodium wires.

Preparation of 4-Chlorobenzaldoxime (7)

An aqueous solution of NaOH (8g, 0.2 mol) in 50 ml of water was added dropwise to a round bottom flask containing a suspension of hydroxylamine hydrochloride (13.9g, 0.2mol) and 4- chloro benzaldehyde (14.05g, 0.1 mol) in ethanol (100ml) with stirring. The mixture was stirred at room temperature for 10h. Most of the ethanol was removed from the reaction mixture by distillation. The residue was diluted with water (70 ml) and then extracted with ether (70ml x

3).The ether layer was dried over anhydrous Na_2SO_4, filtered and then distilled to get 4- chlorobenzaldoxime (7, 13g, 86%).

Preparation of 3- Nitrobenzaldoxime (10)

Prepared by same procedure as above by taking 3- nitrobenzaldehyde (15.1 g, 0.1 mol). Yield (10, 14 g, 87%)

Preparation of 2- Chlorobenzaldoxime (13)

Prepared by same procedure as above by taking 4-chlorobenzaldehyde (11.0 g, 0.1 mol). Yield (13, 13 g, 84%)

Preparation of 4-Methoxybenzaldoxime (16)

Prepared by same procedure as above by taking 4- methoxybenzaldehyde (12 g, 0.1 mol). Yield (16, 11 g, 81%)

Preparation of Benzophenoxime (19)

Prepared by same procedure as above by taking benzophenone (18, 22g, 0.1 mol). Yield (19, 16 g, 80 %)

Preparation of Acetophenoxime (22)

Preparedby same procedure as above by taking acetophenone (12 g, 0.1 mol) Yield (22, 12 g, 88 %)

Preparation of 4-Chlorobenzaldehyde *O*-Oxirane-2-Ylmethyl Oxime(8)

4-Chlorobenzaldoxime (7, 3.88 g, 0.025 mol), anhydrous K_2CO_3 (4.14 g. 0.030 mol) and epichlorohydrin (120 ml) were refluxed under stirring for 13h. The reaction mixture was filtered, filtrate was concentrated and residue was extracted with benzene. The organic phase was washed with 10 % NaOH (50 ml) water, saturated aqueous NaCl, dried and concentrated to get 4- chlorobenzaldehyde*O*-oxirane-2-ylmethyl oxime (8, 4g, 80%).

Preparation of 3-Nitrobenzaldehyde *O*-Oxirane-2-Ylmethyl Oxime (11)

Prepared by same procedure as above by taking 3- nitrobenzaldehyde (15.1 g, 0.1 mol). Yield (11, 4.5 g, 81 %)

Preparation of 2- Chlorobenzaldehyde *O*-Oxirane-2-Ylmethyl Oxime (14)

Prepared by same procedure as above by taking 2- chlorobenzaldoxime (13, 3.11 g, 0.020 mol). Yield (14, 3.9 g, 80%)

Preparation of 4-Methoxybenzaldehyde *O*-Oxiran-2-Ylmethyl Oxime (17)

Prepared by same procedure as above by taking 4-methoxybenzaldoxime (16, 5.03 g, 0.033 mol). Yield (17, 5.6 g, 76%)

Preparation of Benzophenone *O*- Oxiran-2-Ylmethyl Oxime (20)

Prepared by same procedure as above by taking benzophenoxime (19, 6.56 g, 0.033 mol).Yield (20, 7 g, 82%).

Preparation of Acetophenone *O* Oxirane-2-Ylmethyl Oxime (23)

Prepared by same procedure as above by taking acetophenoxime (22, 4.0 g, 0.029 mol). Yield (23, 4 g, 72%)

Preparation of 4-Chlorobenzaldehyde *O*-3-(Diethylamino)-2-Hydroxypropyl Oxime (9)

A mixture of epoxide (8, 3.5 g, 0.0165 mol), diethyl amine (6.04 g, 0.0827 mol) and absolute alcohol (35 ml) was refluxed over water bath for 2h, with constant stiring. The excess of ethanol was distilled off. The residue was diluted with water and extracted with ether. The ether extract was dried over anhydrous Na_2SO_4 and ether was removed by distillation, to get 4- chlorobenzaldehyde*O*-3-(diethylamino)-2-hydroxypropyl oxime (9, 4.3g, 90%).

$V_{max}(cm^{-1})$; 3389, 2970, 2818, 1648, 1596, 1463, 1386, 1342, 1275, 1203, 1172, 1090, 1055, 950, 851, 826, 762, 517.

δ 1.04[6H, t, -$N(CH_2CH_3)_2$] ; 2.48-2.51[4H, m, -$N(CH_2CH_3)_2$; 2.61[2H, d, CH_2-$N(C_2H_5)_2$]; 2.70-3.01[1H, m, CH(OH)] ; 3.7[1H, s, CH(OH)] ; 4.00[2H, d, CH_2ON] ; 7.52-7.96[4H. d, ArH] ; 8.1[1H,s, Ar-HC=N].

Preparation of 3- Nitrobenzaldehyde*o*-3-(Diethylamino)-2-Hydroxypropyl Oxime (12)

Prepared by same procedure as above by taking epoxide (11, 3.5 g, 0.016 mol), diethylamine (5.75 g, 0.08 mol). Yield (12, 4.0 g, 86%)

V_{max} (cm^{-1}) 3413, 2969, 2814, 1645, 1533, 1467, 1384, 1350, 1292, 1201, 1062, 977, 736, 679, 538

δ 1.05[6H, t, $N(CH_2CH_3)_2$] ; 2.46-2.51[4H, m, $N(CH_2CH_3)_2$] ; 2.61[2H, d, CH_2N] ; 2.97-3.02[1H, m, CH(OH)] ; 3.66-3.71[1H, m, CH(OH)] ; 4.24[2H, d, CH_2ON] ; 7.58[1H, t, Ar-H] ; 7.92-8.21[2H, d, Ar-H] ; 8.23[1H, s, Ar-HC=N].

Preparation of 2-Chlorobenzaldehyde *O*-3-(Diethylamino)-2-Hydroxypropyl Oxime (15)

Prepared by same procedure as above by taking epoxide (14, 3.0 g, 0.014 mol), diethylamine (5.2 g, 0.07 mol). Yield (15, 3.7 g, 92 %)

$V_{max}(cm^{-1})$ 3393, 2970, 2817, 2490, 2363, 2129, 1636, 1466, 1386, 1341, 1291, 1203, 1174, 1056, 953, 859, 758, 705, 559.

δ 1.05[6H, t, $N(CH_2CH_3)_2$] ; 2.50 -2.53[4H, m, $N(CH_2CH_3)_2$] ; 2.61[2H, d, CH_2-N] ; 2.97-3.03[1H, m, CH(OH)] ; 3.66-3.71[1H, m, CH(OH)] ; 4.22[2H, d, CH_2-ON] ; 7.34-7.38[2H, t, Ar-H] ; 7.85-7.88[2H, d, Ar-H] ; 8.55[1H, s, Ar-HC=N].

Preparation of 4-Methoxybenzaldehyde *O*-2-Hydroxy-3-(Piperidin-1-Yl)Propyl Oxime (18)

Prepared by same procedure as above by taking epoxide (17, 3.0 g, 0.014 mol) and piperidine (1.2 g, 0.014 mol) .Yield obtained was (18, 5.80 g, 91%).

$V_{max}(cm^{-1})$ 3395, 3057, 2935, 2854, 1511, 1455, 1386, 1303, 1256, 1168, 1106, 1031, 849, 771, 697, 611, 554.

δ 1.55-1.60[4H, m, piperidine] ; 1.73 1.78[2H, m, piperidine]; 2.39[4H, t, piperidine]; 2.51[2H, d, CH_2-piperidine] ; 3.58[1H, s, CH(OH)] ; 3.64-3.71[1H, m, CH(OH)] ; 3.84[3H, s, OCH_3] ; 4.33[2H, d, CH_2-ON] ; 7.83-7.98[4H, d, Ar-H] ; 8.59[1H, s, Ar-HC=N].

Preparation of Benzophenone O-2-Hydroxy-3-(Piperidin-1-Yl)Propyl Oxime (21)

Prepared by same procedure as above b taking epoxide (20, 3.5 g, 0.014 mol) and piperidine (1.2 g, 0.014 mol). Yield obtained was (21, 2.33 g, 89%)

V_{max} (cm^{-1}) 3395, 3057, 2935, 2854, 2804, 2362, 1658, 1598, 1490, 1446, 1317, 1277, 1210, 1155, 1117, 1031,

981, 941, 920, 864, 809, 768, 701, 657, 638, 553

δ 1.57-1.60[6H, m, piperidine] ; 2.39[4H, t, piperidine]; 2.85[2H, d, CH_2-piperidine] ; 3.67[1H, d, CH(OH)] ; 3.86-3.89[1H, m, CH(OH)] ; 4.18[2H, d, CH_2ON] ; 7.58-7.61[6H, t, Ar-H] ; 7.79-7.81[4H, d, Ar-H].

Preparation of Acetophenone *O*-2-Hydroxy-3-(Piperidin-1-Yl)Propyl Oxime (24)

Prepared by same procedure as above by taking epoxide (23, 3.5 g, 0.018 mol) and piperidine (1.4 g, 0.018 mol). The yield obtained was (24, 4.40 g, 88%).

$V_{max}(cm^{-1})$ 3390, 2939, 2110, 1679, 1599, 1446, 1362, 1315, 1267, 1172, 1143, 1090, 1040, 948, 928, 875, 836, 763, 694, 591.

δ 1.58-1.63[4H, m, piperidine] ; 1.77-1.79[2H, m, piperidine] ; 2.37[3H, s, $-CH_3$] ; 2.39[4H, t, piperidine] ; 2.42[1H, d, CH_2-N] ; 2.52[1H, d, CH_2-N] ; 3.54[1H, d, CH_2-ON] ; 3.71[1H, d, CH_2-ON] ; 3.77-3.81[1H, m, CH(OH)] ; 4.19[1H, d, CH(OH)] ; 7.55[3H, t, Ar-H] ; 7.63[2H, d, Ar-H]

Preparation of Bis-Quaternary Salt (1a)

The mixture of t- amine (9, 2g, 0.007 mol) and dibromoethane (0.66 g, 0.0035 mol) dissolved in dry acetone (20 ml) was refluxed for 4h on water bath. Excess of solvent was distilled off; the residue was scratched with anhydrous ether(to remove unreacted amine and alkyl halide, if any) and ether was decanted off to get quaternary salt of ammonia (1a).The compound formed was hygroscopic in nature so spectral studies were not done. It gave positive copper wire test. The yield was 1.3 g, 84.5%.

Preparation of Bis-Quaternary Salt (1b)

Prepared by same procedure as above by taking t-amine (9, 2 g, 0.007 mol) and dibromobutane (0.76g, 0.0035 mol). The yield was 1.23g, 85%.

Preparation of Bis-Quaternary Salt (2a)

Prepared by same procedure by taking t-amine (12, 2 g, 0.0067 mol) and dibromoethane (0.73 g, 0.0033 mol). The yield was 1.30 g, 86%.

Preparation of Bis-Quaternary Salt (2b)

Prepared by same procedure as above by taking t-amine (12, 2 g, 0.0067 mol) and dibromobutane (0.73 g, 0.0033 mol). The yield was 1.20 g, 80%.

Preparation of Bis-Quaternary Salt (3a)

Prepared by same procedure as above by taking t-amine (11, 2 g, 0.007 mol) and dibromoethane (0.66 g, 0.0035 mol). The yield was 1.20 g, 80%.

Preparation of Bis-Quaternary Salt (3b)

Prepared by same procedure as above by taking t-amine (11, 2 g, 0.007 mol) and dibromobutane (0.76 g, 0.0033 mol). The yield was 1.2 g, 81%.

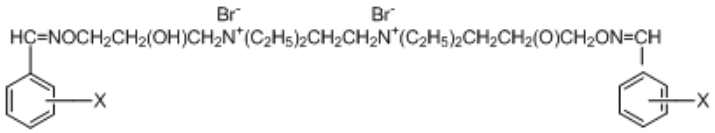
Preparation of Bis-Quaternary Salt (4a)

Prepared by same procedure as above by taking tertiary amine (15, 2 g, 0.0068 mol) and dibromoethane(0.55 g, 0.0034 mol). The yield was 1.30 g, 83%

$V_{max}(cm^{-1})$ 3403, 2985, 2934, 2628, 2576, 2536, 2362, 1655, 1598, 1450, 1317,1277, 1225, 1192, 1151, 1114, 1072, 1017, 965, 921, 856, 810, 767, 701, 668, 639, 599, 559, 487.

δ 1.57- 1.61[4H, m, piperidine] ; 1.69- 1.76[8H, m, piperidine] ; 3.05-3.08[8H, t, piperidine] ; 3.23[1H, d, CH_2-piperidine] ; 3.39-3.42[4H, t, CH_2CH_2] ; 3.65[1H, d, CH_2-piperidine] ; 3.74[2H, s, CH(OH)] ; 3.76[6H, s, OCH_3] ; 4.05-4.09[2H, m, CH(OH)] ; 4.16[2H, d, CH_2-ON] ; 7.23-7.72[4H, d, Ar-H] ; 8.32[2H, s, OCH_3].

CHART I



(1-3) a

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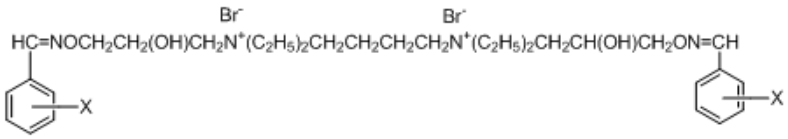
(2) X = m - NO_2
(3) X = o - Cl



((1-3) b

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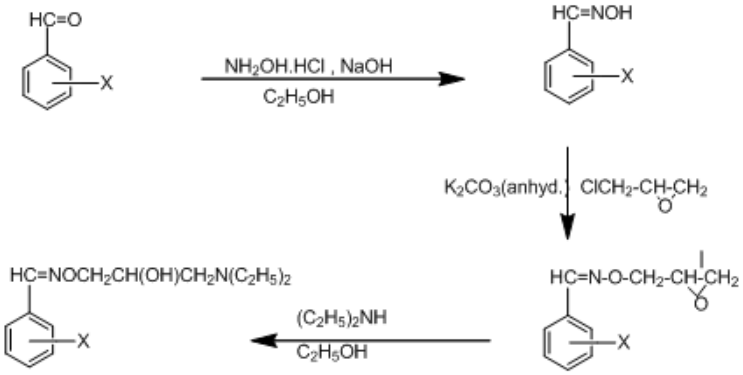
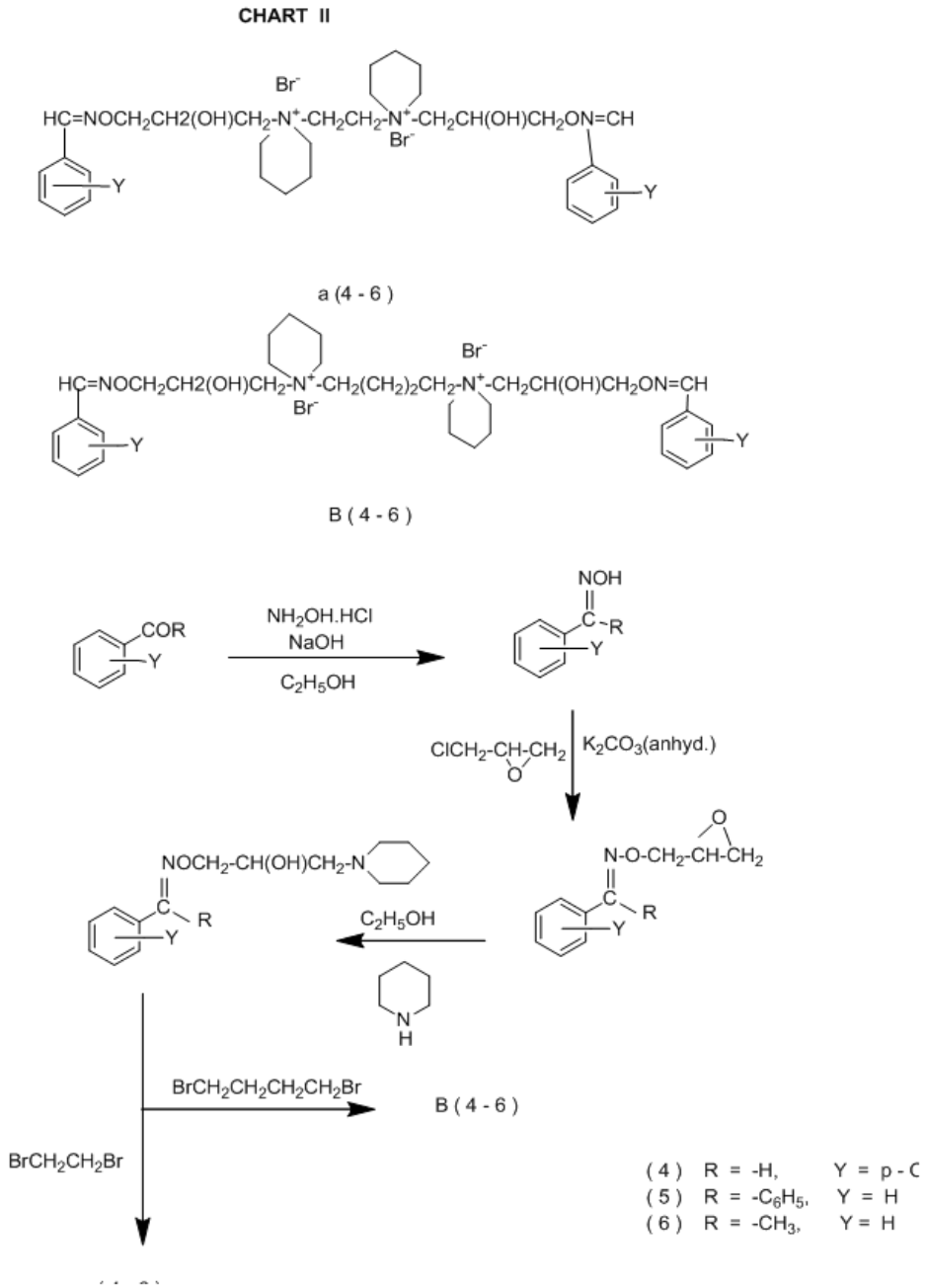
(2) X = m - NO_2
(3) X = o - Cl





Preparation of Bis- Quaternary Salt (4b)

Prepared by same procedure as above by taking t- amine(15, 2 g, 0.0068 mol) and dibromo butane(0.73 g, 0.0034 mol). The yield was 1.10 g, 85.7%.

Preparation of Bis-Quaternary Salt (5a)

Prepared by same procedure as above by taking t- amine (19, 2 g, 0.0059 mol) and dibromo ethane(0.55 g, 0.0029 mol) . The yield was 1.20 g, 79.8%.

Preparation of Bis-Quaternary Salt (5b)

Prepared by same procedure as above by taking t- amine (19, 2 g, 0.0059 mol) and dibromo butane(0.76

g, 0.0029 mol). The yield was 1.20 g, 80.3%.

Preparation of Bis-Quaternary Salt (6a)

Prepared by same procedures above by taking t-amine (23, 2 g, 0.007 mol) and dibromo ethane (0.66 g, 0.0035 mol). The yield was 1.27 g, 84.6%.

Preparation of Bis-Quaternary Salt (6b)

Prepared by same procedure as above by taking t- amine (23, 2 g,0.007 mol) and dibromo butane (0.76g, 0.0035 mol). The yield was 1.23 g, 85.2%.

RESULTS AND DISCUSSIONS

Twelve new bis quaternary ammonium salts having oxime moiety were synthesized from different carbonyl compounds and tested as bio-regulators. Various substituted benzaldehydes (p-Cl, m-NO_2,O-Cl and p-CH_3) and ketones viz. benzophenone and acetophenone were separately reacted with hydroxylamine hydrochloride in the presence of aqueous sodium hydroxide to get the corresponding oximes with *syn* geometry (Furniss et al 1989) in quantitative yields. Epoxypropylation of the oximino compounds (7, 10, 13, 16, 19 and 22) with epichlorohydrin in the presence of anhydrous potassium carbonate (Asthana et al 1987) yielded the corresponding 1-(2,3-epoxypropyloximino) derivatives (8, 11, 14, 17,20 and 23) .Reaction of epopropyloximino compounds with secondary amines (diethylamine and piperidine), (Leclerc et al 1977) in absolute alcohol afforded the corresponding (3-N,N – diethyl/piperidine-2-hydroxypropyloximino) aryl methanes (9, 12, 15, 18, 21, and 24). Characteristic peaks at about 3400 cm^{-1} (-OH) and 1645 cm^{-1} (C=N) in IR spectra and a triplet at δ 1.05 for six protons and a multiplet at δ 2.4-2.6 also for six protons, in the PMR spectra of N,N- diethyl tertiary amines confirm the structure of these amines. The structure of tertiary amines prepared with piperidine, showed characteristic peak at∼ 3400 cm^{-1} (-OH) and ∼ 1645 cm^{-1} (C=N) in their IR spectra and a multiplet at δ 1.5- 1.6 (OH), a triplet at ∼ δ 2.4 (4H) and a doublet at δ 2.5 (2H) (CH_2-piperidine) in their PMR spectra.

Tertiary amines (9, 12, 15, 18, 21 and 24)prepared thus were separately reacted with 1,2- dibromo ethane/1,4 – dibromo butane to get crystalline bis-quaternary ammonium salts (1a-6a) and (1b-6b) in quantitative yield. Most of these quaternary ammonium salts are hygroscopic as their crystals were turned into thick paste. All of them gave positive test with copper wire. NMR spectra of quaternary salt 4a which was not hygroscopic gave a characteristic peak at δ 3.23[1H, s, CH_2-piperidine], δ 3.39[4H, t, CH_2CH_2] and δ 3.74[2H, s, CH(OH).

Evaluation of the Quaternary Salts (1a-6a) and (1b-6b) As Plant Growth Regulators (Biological Testing)

The biological activity of bis quaternary salts of ammonia having oxime moiety (1a-6a) and (1b-6b) was tested by using seeds of *Oryza sativa* (PR-116). The effects of different concentrations of the salts on the percent germination, seedling growth in terms of root length, shoot length, changes in dry and fresh weights of root and shoot were studied. Cycocel, Betaine and ABA were used as standards for calibrating the potential tested compounds as retardant or inhibitor. Seeds germinated in water served as control. (Table 3 and 4) shows, increase in concentration from 50µg ml^{-1} to 500 µg ml^{-1} of different compounds significantly reduced the root lengths of seedlings of Oryza sativa, as compared to control .

Table 1: Effect of Bis-Quaternary Ammonium Salts Derived from Diethyl Amine on Seed Germination (%) of *Oryza sativa* (PR-116)

Seed Germination (%) of Oryza Sativa at Concentrations (µg Ml^{-1})							
Compounds		50	100	200	300	400	500
Control (H_2O)	100						
1a		95	90	85	80	75	75
1b		100	95	95	90	85	85
2a		95	90	90	85	85	70
2b		95	90	90	90	90	90
3a		95	95	95	90	90	80
3b		95	95	90	90	85	85
CCC		90	85	75	75	70	70
Betaine		95	90	90	90	85	75
ABA (5 µg ml^{-1})	85						

Table 2: Effect of Bis-Quaternary Ammonium Salts Derived from Piperidine on Seed Germination (%) of Oryza Sativa (PR-116)

Seed Germination (%) of Oryza Sativa at Concentrations (µg Ml^{-1})							
Compounds		50	100	200	300	400	500
Control (H_2O)	100						
4a		95	95	90	90	85	85
4b		95	95	90	90	85	80
5a		100	95	95	90	90	80
5b		100	90	90	85	80	75
6a		95	90	90	85	80	80
6b		95	90	90	85	80	80
CCC		90	85	75	75	70	70
Betaine		95	90	90	90	85	75
ABA (5µg ml^{-1})	85						

Table 3: Effect of Bis-Quaternary Ammonium Salts Derived from Diethyl Amine on Root Length (Cm) of *Oryza Sativa* (PR-116)

Root Length (Cm) of Oryza Sativa at Concentrations (µg Ml^{-1})								
Compounds		50	100	200	300	400	500	CD (5%)
Control (H_2O)	13.8							
1a		9.02	8.12	4.26	2.81	1.60	0.93	1.17
1b		4.80	6.00	2.71	2.33	1.75	0.85	3.37
2a		8.92	7.88	6.97	6.06	4.53	3.58	0.55
2b		5.38	3.58	2.58	2.07	1.63	1.37	0.44
3a		7.18	6.25	5.99	5.17	3.18	2.04	0.48
3b		6.90	6.28	5.74	4.90	3.72	1.66	0.63
CCC		7.06	6.40	5.92	5.52	4.46	2.35	0.52
Betaine		6.38	5.72	3.98	3.07	2.74	1.25	0.58
ABA (5µg ml^{-1})	2.60							

Table 4: Effect of Bis-Quaternary Ammonium Salts Derived from Piperidine on Root Length (Cm) of *Oryza sativa* (PR-116)

Root Length (Cm) of Oryza Sativa at Concentrations (µg Ml^{-1})								
Compounds		50	100	200	300	400	500	CD (5%)
Control (H_2O)	13.8							
4a		7.41	6.49	6.15	5.47	4.89	3.08	0.58
Table 4: Contd.,								
4b		6.81	5.99	5.00	3.28	2.00	1.22	0.68
5a		5.53	4.90	3.81	2.82	2.36	1.39	0.45
5b		5.99	5.52	3.61	2.66	2.46	1.71	0.64
6a		6.45	5.71	3.66	1.99	1.04	0.00	0.44
6b		7.18	6.25	5.99	5.17	3.18	2.04	0.48
CCC		7.06	6.40	5.92	5.52	4.46	2.35	0.52
Betaine		6.38	5.72	3.98	3.07	2.74	1.25	0.58
ABA (5µg ml^{-1})	2.60							

CONCLUSIONS

(Table 1 and 2) shows the effect of different concentrations of various compounds on percent germination of seeds of Oryza sativa after 48 h. In control germination was 100%. Different concentrations of newly synthesized compounds as well as Betaine, ABA and Cycocel (CCC), a compound with antigibberelline activity were applied to the seeds. Treatment of seeds with newly synthesized compounds resulted in reduction in seed germination, but the magnitude of inhibition was less than CCC and Betaine at all concentrations.(Table 3 and 4) shows that different compounds significantly reduced the root lengths of seedlings of *Oryza sativa* as compared to control. Quaternary salts prepared from ketones showed more retarding effect as compared to those prepared from aldehydes . Amongst the compounds having aldehydic moiety, the compound 2a showed better and 6a prepared from acetophenone showed the better inhibiting effect among ketone moiety. All these compounds show comparable or in some cases better inhibiting effect to that of CCC or betaine. More work on this type of compounds need to be carried out to draw some structure activity relationship or to made some recommendations regarding their use in agriculture.

REFERENCES

1. Sharma M.L, Talwar K.K. and Gupta A. (1997).Synthesis of quaternary salts of ammonia from aromatic compounds through the formation of glycydyl esters and their plant growth retardant activity. J. Indian Chem. Soc. 74: 343 -44.
2. Sharma M.L, Talwar K.K., Gupta A. and Kaur R (1995). Synthesis and plant growth retardant activity of trialkylammonium iodide from acyclic compounds. J. Indian Chem. Soc. 86: 245 -47.
3. Sinha A.K., Rastogi S.H.and Das S. R. (1991). Synthesis of 1,3-substituted –hydroxy propyloximino benzocycloalkanes as poetical antimoebic agent. Indian J.Chem 30 b:1041-45.
4. Zagsma J.and Nauta Th. W (1997) β-Adrenoceptors studies effect of alkyl substitution on β-adrenoceptors blocking. Antiarrhythmic and local anaesthetic activities of 1,1- (o-phenylene dioxy) bis (3-isopropylamino-2-propanol). J.Med. Chem. 20:527-31.