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Note

Studies on synthesis and plant growth retardant activity of cyclic bis-quaternary salts of ammonia from phthalic acid using conventional and microwave methods

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Phthalic acid **1** has been converted to bis (oxiran-2-ylmethyl) phthalate **2** followed by ring opening to di-tertiary amines *viz*: bis (3-[diethylamino)-2-hydroxypropyl] phthalate **3** and bis [2-hydroxy-3-[piperidin-1-yl) propyl] phthalate **4**. Conversion is carried through conventional as well as non-conventional methods (microwave irradiation on solid support). Di-tertiary amines **3** and **4** have been quaternized to give cyclic bis-quaternary ammonium salts **3a-c** and **4a,b** which in turn are tested for their efficacy as plant growth regulators on rice (*Oryza sativa*). All the tested compounds are found to be good plant growth retardants. Compound **4c** is found to be the best plant growth retardant among the six newly synthesized compounds.

Keywords: Bis (oxiran-2-ylmethyl) phthalate, microwave, cyclic bis-quaternary salts, plant growth retardants, *Oryza sativa*

Quaternary ammonium salts are reported to influence the growth and development of plants[1]. They retard plant height physiologically without any formative effect. The use of plant growth retardants has been made for many years to manipulate the size; shape and overall quality of various crops. These are useful in the reduction of "lodging" in aerial crops, limiting size of fruit trees and in the treatment of decorative pot plants to produce more compact plants which are of great importance to horticulture. In continuation of our work on the synthesis and growth retardant activity of trialkyl ammonium salts[2,3], during the present investigation, cyclic bis-quaternary salts of ammonia from phthalic acid have been synthesized (*via* conventional and microwave methodology for the synthesis of tertiary amines from phthalic acid) and tested for their efficacy as plant growth retardants. Quats resemble a naturally occurring plant growth retardant *Betaine* [2-(trimethylammonio)acetate] and have the common effect of reducing stem growth by inhibiting cell division of sub-apical meristem[4-7] and have been found to be good plant growth retardants in case of *Oryza sativa* (PR-116).

Phthalic acid **1** was treated with epichlorohydrin[8] in the presence of 7% aqueous KOH to give a di-epoxy compound bis (oxiran-2-ylmethyl) phthalate **2** which was then refluxed with secondary amines *viz* diethylamine and piperidine in alcohol[9,10] separately to yield di-tertiary amines bis [3-(diethylamino)-2-hydroxypropyl] phthalate **3** and bis [2-hydroxy-3-(piperidin-1-yl) propyl] phthalate **4** in quantitative yield. This method is quite lengthy and cumbersome. To avoid this difficulty successful attempt has been made by carrying out the reaction under MORE (microwave assisted organic reaction rate enhancement). It has been identified as a current lead in organic synthesis and the initial doubts about MORE chemistry- a myth or reality[11] no longer hold good. During the last ten years, a number of publications and reviews[12,13] have advocated the use of microwave technology in organic synthesis. The use of domestic microwave ovens for carrying out organic synthesis has resulted in simplification of experimental techniques[14], since the reaction can be carried out in open borosil beakers/conical flasks using organic solvents such as ethanol, N,N-dimethylformamide (DMF), 1,2-dichroloethane (DCE), *o*-dichlorobenzene, *etc*.

In the microwave methodology, the tertiary amines **3** and **4** were prepared by subjecting the mixture of oxirane **2** and secondary amines; diethylamine and piperidine separately to microwave irradiation for about 2 min after adsorbing the reaction mixture over silica gel[15] (**Table I**).

Tertiary amine **3**, prepared by both the methods was characterized by signals at δ 1.02 as a triplet for 12 protons and a multiplet at δ 2.72-2.79 again for 12 protons in its ^{1}H NMR spectra (**Table II**).

Quaternisation of di-tertiary amines **3** and **4** was done by reacting these with chlorides of di-carboxylic acids (malonic acid, succinic acid and adipic acid separately, which in turn were prepared by reacting the respective acids with thionyl dichloride) to get cyclic bis quaternary salts **3a-c** and **4a-c** (**Chart 1, Tables III** and **IV)**).

Table I — Comparison of reaction time and product yield

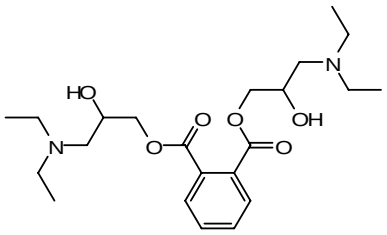
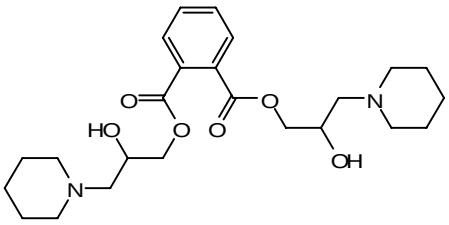
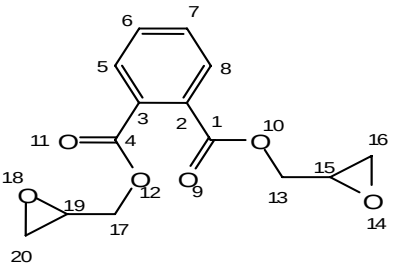
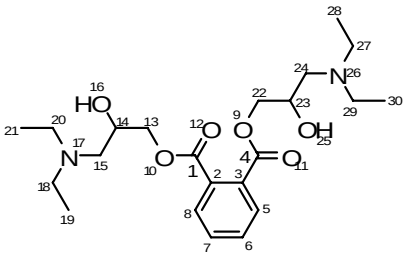
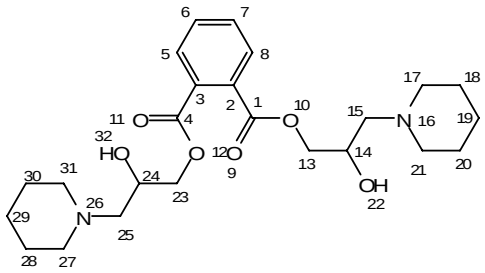
Compd	Synthesized tertiary amines	Conventional Heating (time and % yield)	Microwave irradiation (time and % yield)
3		4 hr 10 min 72%	2 min 82%
4		4 hr 76%	2 min 30 sec 78%

Table II — Spectroscopic data for oxirane and tertiary amines

Sr.No	Compd	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
2		2.3-2.7 [4 H, m,] 3.0-3.13[2H, m,], 4.25-4.50 [4H, m, -O-CH_2-], 7.7-8.2[4H, m, Ar-H].	C2,C3=132.4 C5,C8=128.0 C6,C7=132.9 C1,C4=167.8 C13,C17=66.4 C15,C19=49.2 C16,C20=44.1
3		1.02 [12 H, t, *J* = 7 Hz, 2-N(CH_2CH_3)$_2$], 2.72-2.79 [12H, m, 2-CH_2-N(CH_2CH_3)$_2$], 4.0-4.5 [6H, m, 2-O-CH_2-CH(OH)-], 7.5-8.1[4H, m, Ar-H].	C2,C3=132.4 C5,C8=128.0 C6,C7=132.9 C1,C4=167.8 C13,C22=68.5 C14,C23=66.1 C15,C24=57.9 C18,C20,C27,C29=47.7 C19,C21,C28,C30=13.3
4		1.49-1.59[12 H, m, 2-$(CH_2)_3$-], 2.30-2.63[12H, m, 2-CH_2-N(CH_2)$_2$-], 3.9-4.4[6H, m, 2-O-CH_2-CH(OH)-], 7.5-7.9[4H, m, Ar-H].	C2,C3=132.4 C5,C8=128.0 C6,C7=132.9 C1,C4=167.8 C13,C23=68.5 C14,C24=66.1 C15,C25=58.2 C17,C21,C27,C31=50.1 C18,C20,C28,C30=25.9 C19,C29=24.5

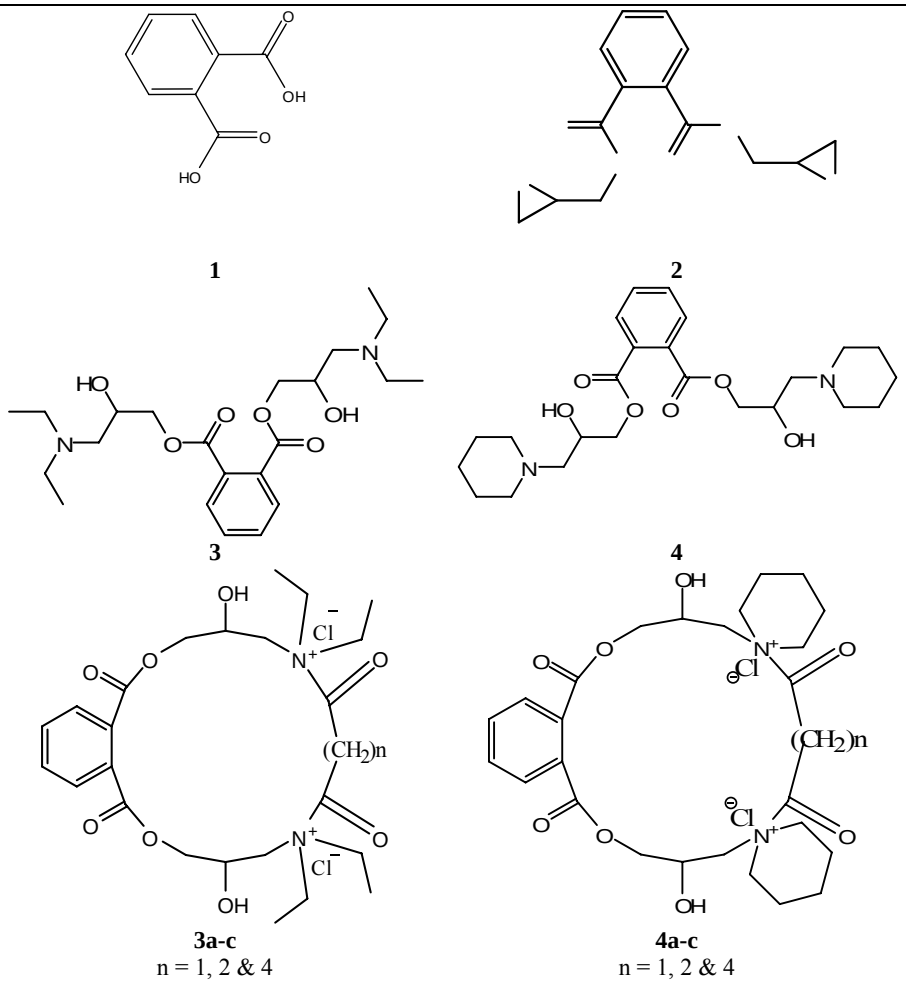


Chart 1

Biological activity

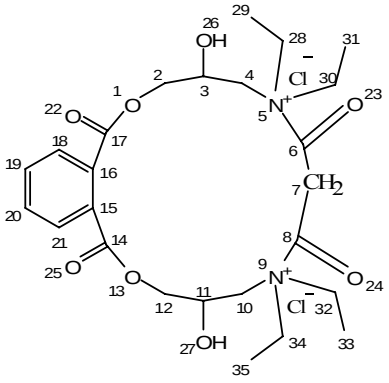
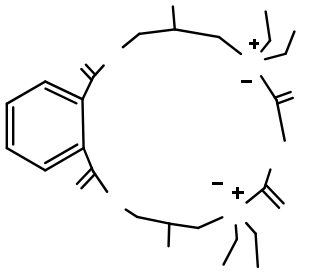
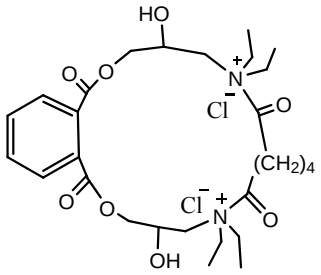
The newly synthesized cyclic bis-quaternary salts of ammonia **3a-c** and **4a-c** were tested for their efficacy as plant growth retardants on various parameters of growth on rice seeds (*Oryza sativa*). The effect of synthesized compounds on per cent seed germination, seedling growth (length of longest root, coleoptile and leaf), seedling dry mass and vigour index is shown in **Tables V-VII**.

All compounds were found to possess plant growth retardant activity at all the concentrations. Maximum inhibition in case of seed germination after 48 hr was found to be 35% in case of **4c** (**Table V**). Maximum inhibitory effect on length of longest root was found to be 85% in case of compound **4c** in response to 500 μgmL^{-1} (**Table V**). Growth of coleoptile and leaf was found to be the most inhibited by compound **4c** which was by about 69 and 45% respectively over control at 500 $\mu g\ mL^{-1}$ (**Table VI**). Similarly, **Table VII** shows that the decrease in dry mass was highest (55%) in response to treatment with compound **4c** at 500 μgmL^{-1}, and vigour index was also found to cause more inhibition in case of compound **4c** by about 66% as compared to control. The magnitude of inhibition increased with concentration of compounds. The inhibitory effect of newly synthesized compounds was greater than that of cycocel (CCC) at relative concentrations but less than ABA at 5 $\mu g\ mL^{-1}$.

Structure-activity relationship (SAR) studies

The compounds quaternised with piperidine **4a-c** were found to possess higher growth retarding effect as compared with that of diethylamine in most parameters of growth. This may be attributed to the higher basicity of piperidine as compared to diethylamine as it intensifies the positive charge on Nitrogen atom of quaternary ammonium salts. It was also seen that as the size of ring increases (in case of adipoyl moiety

Table III — Spectroscopic data for cyclic bis-quaternary ammonium salts containing diethylamine **3a-c**

Compd	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
 **3a**	3.51 [2 H, m, -[CH_2]- , 1.02 [12 H, t, *J* = 7 Hz, 2-N(CH_2CH_3)$_2$], 2.72-2.79 [12H, m, 2-CH_2-N(CH_2CH_3)$_2$], 4.0-4.5 [6H, m, 2-O-CH_2-CH(OH)-], 7.5-8.1[4H, m, Ar-H] .	C2,C12=70.9 C3,C11=64.7 C4,C10=58.1 C6,C8=200 C7=28.5 C14,C17=169.3 C15,C16=132.4 C18,C21=128.0 C19,C20=132.9 C28,C30,C32,C34=47.7 C29,C31,C33,C35=6.0
 **3b**	2.73 [4 H, m, -[(CH_2)$_2$]- , 1.02 [12 H, t, *J* = 7 Hz, 2-N(CH_2CH_3)$_2$], 2.72-2.79 [12H, m, 2-CH_2-N(CH_2CH_3)$_2$], 4.0-4.5 [6H, m, 2-O-CH_2-CH(OH)-], 7.5-8.1[4H, m, Ar-H].	C2,C13=68.9 C3,C12=64.7 C4,C11=58.4 C6,C9=201 C7,C8=26.1 C15,C18=167.0 C16,C17=132.4 C19,C22=128.0 C20,C21=132.9 C29,C31,C33,C35=13.3 C30,C32,C34,C36=6.0
 **3c**	2.40 [4 H, m, 2-[C(=O)- (CH_2)-]- , 1.62 [4 H, m, 2[-(CH_2)$_2$-]- , 1.02 [12 H, t, *J* = 7 Hz, 2-N(CH_2CH_3)$_2$], 2.72-2.79 [12H, m, 2-CH_2-N(CH_2CH_3)$_2$], 4.0-4.5 [6H, m, 2-O-CH_2-CH(OH)-], 7.5-8.1[4H, m, Ar-H].	C2,C15=72.1 C3,C14=64.7 C4,C13=58.4 C6,C11=201 C7,C10=29.1 C8,C9=24.6 C17,C20=167.0 C18,C19=132.4 C21,C24=128.0 C22,C23=132.9 C31,C33,C35,C37=48.0 C32,C34,C36,C38=6.0

containing quaternary ammonium salts); plant growth retarding effect also goes on increasing. This enhancement can be regarded to the bigger cavity size. Different configuration of compounds may also be one of the reasons for overall retarding effect. In order to see the effect of different substituents, ring size and configuration, more work in this field is in progress.

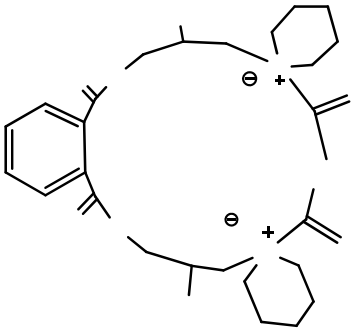
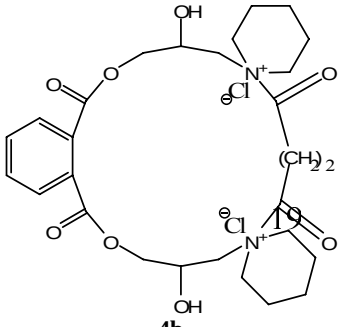
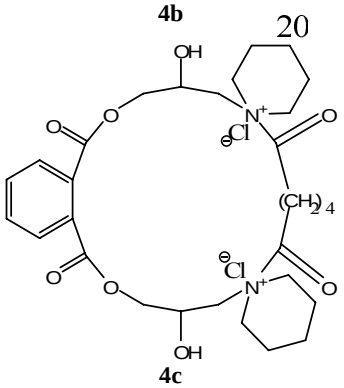
Experimental Section

All organic compounds were dried over anhyd. Na_2SO_4 and purity of analytical samples was checked by TLC. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Avance Π NMR spectrometer at SAIF Panjab University Chandigarh using TMS as internal standard (chemical shifts in δ, ppm). Domestic microwave LG Model MS-194W was used.

Bis (oxiran-2-ylmethyl) phthalate, 2

To the mixture of phthalic acid **1** (9.96 g, 0.06 mole) and KOH (7%, 100 mL), epichlorohydrin (40 mL) was added dropwise with constant stirring at RT and stirring was continued for 36 h. It was extracted

Table IV — Spectroscopic data for cyclic bis-quaternary ammonium salts containing piperidine **4a-c**

Compd	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
 **4a**	3.51 [2 H, m, -[CH_2]- , 1.49-1.59[12 H, m, 2-$(CH_2)_3$-], 2.30-2.63[12H, m, 2-CH_2-N$(CH_2)_2$-], 3.9-4.4[6H, m, 2-O-CH_2-CH(OH)-], 7.5-7.9[4H, m, Ar-H].	C2,C12=70.9 C3,C11=64.7 C4,C10=58.4 C6,C8 =200 C7=28.5 C14,C19=169.3 C15,C16=132.4 C18,C21=128.0 C19,C20=132.9 C1′,C5′,C1″,C5″=57.1 C2′,C4′,C2″,C4″=19.2 C3′,C3″=21.7
 **4b**	2.73-[4 H, m, -[$(CH_2)_2$]- , 1.49-1.59[12 H, m, 2-$(CH_2)_3$-], 2.30-2.63[12H, m, 2-CH_2-N$(CH_2)_2$-], 3.9-4.4[6H, m, 2-O-CH_2-CH(OH)-], 7.5-7.9[4H, m, Ar-H].	C2,C13=68.2 C3,C12=64.7 C4,C11=58.7 C6,C9=201 C7,C8=26.1 C15,C18=167.0 C16,C17=132.4 C19,C22=128.0 C20,C21=132.9 C1′,C5′,C1″,C5″=57.1 C2′,C4′,C2″,C4″=19.4 C3′,C3″=21.7
 **4c**	2.49 [4 H, m, 2-[C(=O)- (CH_2)-]- , 1.49-1.59[12 H, m, 2-$(CH_2)_3$-], 2.30-2.63[12H, m, 2-CH_2-N$(CH_2)_2$-], 3.9-4.4[6H, m, 2-O-CH_2-CH(OH)-], 7.5-7.9[4H, m, Ar-H].	C2,C15=78.1 C3,C14=64.7 C4,C13=58.7 C6,C11=201 C7,C10=29.1 C8,C9=24.6 C17,C20=167.0 C18,C19=132.4 C21,C24=128.0 C22,C23=132.9 C1′,C5′,C1″,C5″=57.1 C2′,C4′,C2″,C4″=19.2 C3′,C3″=21.7

with benzene and extract was washed with 10% aq. NaOH and water successively. Benzene from the dried extract (over anhyd. Na_2SO_4) was distilled and residue vacuum distilled to afford the epoxy compound **2**, as thick oily liquid. Yield (13.5 g, 80%), b.p. 120-24°C/10-12 mm. **Table II** shows the ^{1}H and ^{13}C NMR spectroscopic data.

Bis (3-(diethylamino)-2-hydroxypropyl) phthalate, 3

A solution of compound **2** (12 g, 0.043 mole) was prepared by dissolving in absolute alcohol (150 mL). To this diethylamine (23 mL, 0.22 mole) was added and the contents were refluxed for 4 hr and 10 min. Most of the alcohol was distilled off and the residue was diluted with water. It was extracted with ether followed by washing with water. Removal of the solvent from the dried extract (over anhyd. Na_2SO_4), followed by distillation under reduced pressure afforded the hydroxy tertiary amine **3** (13 g, 72%). ^{1}H and ^{13}C NMR spectroscopic studies were carried out to elucidate the structure (**Table II**).

Table V — Effect of cyclic bis-quaternary salts of ammonia from phthalic acid on seed germination (%) and (length of longest root in cm) of *Oryza sativa* (PR-116)

Compd	Concentration (μg mL^{-1})							
	0	25	50	100	200	400	500	CD (5%)
H_2O	100 (12.50)	-	-	-	-	-	-	-
3a	-	100.0 (9.33)	90.0 (9.00)	85.0 (8.66)	85.0 (8.50)	80.0 (7.00)	70.0 (4.50)	86.6 (1.129)
3b	-	90.0 (10.60)	90.0 (10.0)	85.0 (9.00)	80.0 (8.66)	80.0 (8.16)	75.0 (5.16)	86.6 (2.033)
3c	-	98.0 (11.33)	95.0 (9.00)	85.0 (9.33)	80.0 (8.50)	80.0 (7.66)	75.0 (7.50)	76.6 (1.583)
4a	-	100.0 (7.16)	95.0 (6.50)	95.0 (5.33)	90.0 (5.50)	90.0 (5.00)	90.0 (2.00)	93.3 (1.186)
4b	-	90.0 (10.35)	85.0 (9.65)	80.0 (8.66)	75.0 (6.00)	75.0 (4.65)	70.0 (2.50)	90.0 (1.716)
4c	-	90.0 (9.33)	80.0 (8.35)	70.0 (7.50)	70.0 (4.60)	65.0 (4.00)	65.0 (1.06)	93.3 (1.110)
CCC	-	100.0 (9.65)	90.0 (9.62)	85.0 (8.33)	80.0 (7.00)	75.0 (5.00)	75.0 (2.33)	93.3 1.677
ABA (5 μg mL^{-1})	20.0 (1.05)	-	-	-	-	-	-	

Table VI — Effect of cyclic bis-quaternary salts of ammonia from phthalic acid on coleoptile length (cm) and (leaf length in cm) of *Oryza sativa* (PR-116)

Compd	Concentration (μg mL^{-1})							
	0	25	50	100	200	400	500	CD (5%)
H_2O	6.58 (4.90)	-	-	-	-	-	-	-
3a	-	4.33 (4.53)	4.03 (4.36)	3.43 (4.16)	2.96 (3.50)	2.90 (3.16)	2.53 (2.80)	0.36 (0.17)
3b	-	4.20 (4.10)	4.06 (3.90)	3.63 (3.76)	3.33 (3.50)	2.53 (3.40)	2.66 (2.86)	0.38 (0.32)
3c	-	4.03 (4.23)	3.96 (4.23)	3.80 (3.86)	3.63 (3.80)	2.46 (3.66)	2.30 (3.26)	0.16 (0.18)
4a	-	4.26 (3.93)	3.80 (3.90)	4.13 (3.80)	3.83 (3.50)	2.73 (3.00)	2.63 (2.74)	0.32 (0.31)
4b	-	3.80 (4.10)	3.60 (3.86)	3.33 (3.73)	2.83 (2.90)	2.60 (2.96)	2.13 (2.80)	0.19 (0.28)
4c	-	4.43 (4.40)	3.40 (4.16)	2.90 (3.43)	2.90 (3.30)	2.53 (2.90)	2.06 (2.73)	0.32 (0.31)
CCC	-	5.60 (4.20)	5.20 (4.20)	4.80 (4.15)	4.80 (4.00)	4.40 (3.80)	3.50 (3.70)	0.37 (0.34)
ABA (5 μg mL^{-1})	0.2 (1.83)	-	-	-	-	-	-	-

Bis [2-hydroxy-3-(piperidin-1-yl) propyl] phthalate, 4

Similarly an ethanolic solution of bis (oxiran-2-ylmethyl) phthalate **2** (12 g, 0.043 mole) was treated with piperidine (16.8 mL, 0.17 mole) and the mixture was refluxed for 4 hr. The work-up afforded bis-hydroxy tertiary amine (2.2, 14.5 g, 76%). ^{1}H and ^{13}C NMR spectroscopic data are given in **Table II**.

Table VII — Effect of cyclic bis-quaternary salts of ammonia from phthalic acid on dry mass (g) and (seedling vigour index in g) of seedlings of *Oryza sativa* (PR-116)

Compd	Concentration (μg mL^{-1})						
	0	25	50	100	200	400	500
H_2O	0.110 (11.00)	-	-	-	-	-	-
3a	-	0.085 (8.50)	0.080 (7.20)	0.070 (5.95)	0.070 (5.95)	0.070 (5.20)	0.062 (4.34)
3b	-	0.100 (9.00)	0.095 (8.55)	0.092 (6.80)	0.080 (6.40)	0.080 (6.08)	0.076 (4.55)
3c	-	0.100 (9.80)	0.090 (8.55)	0.070 (5.95)	0.080 (6.40)	0.085 (6.80)	0.080 (6.00)
4a	-	0.100 (9.00)	0.090 (7.20)	0.090 (6.30)	0.080 (5.60)	0.080 (5.20)	0.075 (4.87)
4b	-	0.100 (11.00)	0.090 (9.50)	0.070 (8.10)	0.070 (8.10)	0.065 (7.20)	0.065 (7.20)
4c	-	0.110 (9.00)	0.100 (7.65)	0.090 (5.60)	0.090 (5.25)	0.080 (4.90)	0.050 (3.75)
CCC	-	0.100 (10.00)	0.090 (7.65)	0.090 (7.65)	0.080 (6.40)	0.080 (6.00)	0.070 (5.25)
ABA (5 μg mL^{-1})	0.050 (1.00)	-	-	-	-	-	-

Microwave assisted synthesis of bis (3-(diethylamino)-2-hydroxypropyl) phthalate, 3

To the mixture of oxirane **2** (2.5 g, 0.008 mole), and diethylamine (1.76 g, 0.024 mole) dissolved in minimum quantity of ethanol (5 mL), silica gel (50 g) was added. The whole mixture was stirred properly to adsorb the oxirane **2** and diethylamine get completely adsorbed over the solid support (silica gel). The mixture was then air dried to evaporate the whole solvent and the solvent free mixture was exposed to microwave irradiation at half level for 2 min. The mixture was cooled and eluted through a column with ethanol. Most of the alcohol was removed and the residue was extracted with ether, washed with water, saturated NaCl solution, dried (over anhyd. Na_2SO_4) and concentrated to give **3**. Yield (3.1 g, 82%). It gave all the characteristic data comparable with that of the compound prepared by conventional method.

Microwave assisted synthesis of bis [2-hydroxy-3-(piperidin-1-yl) propyl] phthalate, 4

Microwave assisted synthesis of bis[2-hydroxy-3-(piperidin-1-yl)propyl] phthalate **4** was carried out by the typical procedure mentioned earlier by dissolving compound **2** (2.5 g, 0.005 mole) and piperidine (3.4 mL, 0.034 mole) in minimum amount of ethanol (5 mL) adsorbed over silica gel (50 g) at half level for 2 min 30 sec. Yield was 3.1 g, 78%. Spectroscopic data was comparable with that of the compound **4** prepared by conventional method.

Preparation of quaternary salts of ammonia

General procedure for the preparation of quaternary salts 3a-c and 4a-c

Di-carboxylic acid chlorides (0.005 mole) (prepared by reacting di-carboxylic acids; malonic acid, succinic acid and adipic acid with thionyl dichloride), dissolved in chloroform (10 mL) were added separately to the solution of di-tertiary amines (**3** and **4**, 0.05 mole) in chloroform (10 mL) with continuous stirring at 0-5°C. Stirring was continued for another 3 hr at the same temperature and then at RT for 1 hr. Removal of chloroform followed by scratching of residual thick material with anhydrous ether afforded the cyclic bis-quaternary ammonium salts **3a-c** and **4a-c** on decantation of ether (yields 85-95%). Spectral data are given in **Tables III** and **IV**.

Biological activity

To test the germination and seedling growth study, uniform sized seeds of *Oryza sativa* (var PR-116) in three replications were surface sterilized using 0.1% mercuric chloride solution for 1 min. Sterilized seeds were placed on filter paper laid on the bottom of

petridishes of 9 cm diameter each to which 10 mL of test solutions of different concentrations (25, 50, 100, 200, 400 and 500 ppm) of the compounds were poured. Each dish was kept at 28±2°C for 7 days to record the various parameters of growth. Separate control treatment with ABA (5 μg mL^{-1}), cycocel and water was also performed simultaneously.

Following observations were recorded:

Seed germination

Expressed in per cent seed germination after 48 hr.

Seedling growth

After 7 days of germination, the data on length of longest root, coleoptile and leaf was measured using centimeter scale. Seedling dry mass was also recorded.

Vigour Index

VI = percent germination × total seedling dry mass

For controls, seeds were germinated in distilled water; CCC and ABA were used as standards for calibrating the potential of tested compounds as retardant or inhibitor.

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