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Note

Synthesis of 1,1,1-trichloro-2,2-bis-(carboxymethoxyaryl)ethanes as potential antimicrobial and insecticidal agents

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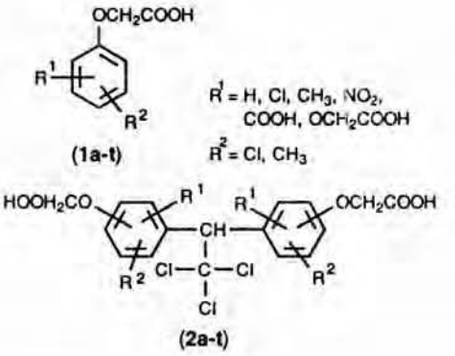
Some new 1,1,1-trichloro-2,2-bis-(carboxymethoxyaryl)-ethanes **2a-t** have been synthesised by the treating aryloxyacetic acid (two moles) with chloral hydrate (1 mole) in the presence of catalytic amount of conc. sulphuric acid. The aryloxyacetic acid are prepared by the reaction of substituted phenols with chloroacetic acid in the presence of aq. sodium hydroxide. The antimicrobial activity of these compounds have been assayed against various Gram+ve, Gram-ve bacteria and fungi. The constitution of the products have been elucidated by IR, ^{1}H NMR and mass spectral data and elemental analyses.

1,1,1-Trichloro-2,2-bis-(aryl)ethanes have a wide spectrum of biological activities against different families of insects and related organisms. The known pesticides triphen, methoxychlor, methiochlor, chloral, metachloral have remarkable insecticidal, herbicidal and fungicidal activities[1-6]. 1,1,1-Trichloro-2,2-bis-substituted ethane derivatives such as bromoisovalerylurea, cholin, betaine and carnitine are well documented as sedative and hypnotic agents in the literature[7-10].

With a view to achieving biodegrable analogous of 1,1,1- trichloro-2,2-bis (aryl)ethanes[11-13], the synthesis of aryloxyacetic acids **1a-t** and 1,1,1-trichloro-2,2-bis(carboxymethoxyaryl)ethanes **2a-t** has been undertaken as a part of our research work. Compounds **1a-t** were synthesised by the reaction of substituted phenols with chloroacetic acid in the presence of aq. sodium hydroxide[14]. The ethanes **2a-t** were synthesised by the reaction of **1a-t** (2 moles) with chloralhydrate (1 mole) in the presence of catalytic amount of conc. sulphuric acid.

The structures of the products **1a-t** and **2a-t** were established by their IR, ^{1}H NMR and mass spectral studies and elemental analyses (**Tables I** and **II**).



Antimicrobial activity

Compounds **1a-t** and **2a-t** were assayed for their antibacterial activity against Gram +ve bacteria *Bacillus megateriuim, Bacillus subtilis* and Gram -ve bacteria *Escheriacha coli* and *Pseudonomus fluorescens* and for antifungal activity against *Arobactor awamori* by cup-plate method[14] at concentration of 50 μg using DMF as solvent. After 24 hr. incubation at 37 °C, the zones of inhibition were measured in mm. The activity was compared with that of the known standard drugs ampicillin, chloramphenicol, norfloxacin and griseofulvin at the same concentration (50 μg).

The bactericidal data indicate that all the compounds are moderately to highly active against the test bacteria at 50 μg concentration. The activity of the compounds depends upon the nature and position of the substituent at the aryl moiety. The comparable activity of compounds **1f, 1g, 1i, 1s, 2e, 2b, 2f, 2i** and **2s** against *B. mega*, compounds **1e, 1f, 1g, 1h, 1i, 1p, 2d, 2m, 2q** and **2s** against *B. subtilis* and compounds **1e, 1g, 1h, 1i, 2c, 2d, 2e, 2f, 2h, 2i, 2l, 2m** and **2s** against *E. coli* and compounds **1f, 2i, 2r** against *P. fluorescens* was found.

The fungicidal data indicate that all the compounds are moderately to highly toxic to the test fungi at 50 μg concentration. The toxicity of the compounds depends upon the nature and position of the substituent at the aryl moiety. Compounds **1d, 1h, 1e, 1l, 1q, 2e, 2f, 2h, 2l, 2q, 2s, 2t** displayed promising antifungal activity against *A.awamori*.

Table I—Characterisation data of compounds **1a-t**

Compd	R^1	R^2	Mol. formula	m.p.	Found/(Calcd) %	
					C	H
1a	H	—	$C_8H_8O_3$	98	63.10	5.21
					(63.15	5.26)
1b	2-COOH	—	$C_9H_8O_5$	190	55.01	4.02
					(55.10	4.08)
1c	2-Cl	—	$C_8H_7O_3Cl$	146	51.39	3.70
					(51.47	3.75)
1d	3-Cl	—	$C_8H_7O_3Cl$	108	51.45	3.71
					(51.47	3.75)
1e	4-Cl	—	$C_8H_7O_3Cl$	156	51.41	3.69
					(51.47	3.75)
1f	2-Cl	3-Cl	$C_8H_6O_3Cl_2$	174	43.35	2.70
					(43.43	2.71)
1g	2-Cl	4-Cl	$C_8H_6O_3Cl_2$	139	43.40	2.69
					(43.43	2.71)
1h	3-Cl	5-Cl	$C_8H_6O_3Cl_2$	138	43.42	2.71
					(43.43	2.71)
1i	2,4-$(Cl)_2$	6-Cl	$C_8H_5O_3Cl_3$	182	37.51	1.90
					(37.57	1.95)
1j	2-CH_3	—	$C_9H_{10}O_3$	145	65.01	6.00
					(65.06	6.02)
1k	3-CH_3	—	$C_9H_{10}O_3$	101	65.05	6.01
					(65.06	6.02)
1l	4-CH_3	—	$C_9H_{10}O_3$	134	64.99	5.99
					(65.06	5.02)
1m	2-CH_3	4-CH_3	$C_{10}H_{12}O_3$	140	66.60	6.62
					(66.66	6.66)
1n	2-CH_3	5-CH_3	$C_{10}H_{12}O_3$	137	66.59	6.65
					(66.66	6.66)
1o	2-NO_2	—	$C_8H_7O_5N$	155	48.71	3.51
					(48.73	3.55)
1p	3-NO_2	—	$C_8H_7O_5N$	152	48.65	3.53
					(48.73	3.55)
1q	4-NO_2	—	$C_8H_7O_5N$	183	48.70	3.50
					(48.73	3.55)
1r	2-OCH_2COOH	—	$C_{10}H_{10}O_6$	220(d)	53.01	4.41
					(53.09	4.42)
1s	3-OCH_2COOH	—	$C_{10}H_{10}O_6$	193	53.01	4.39
					(53.09	4.42)
1t	4-OCH_2COOH	—	$C_{10}H_{10}O_6$	247	53.00	4.40
					(53.09	4.42)

% Yield varied from 70-87 %

Insecticidal activity

The rice leaf hopper *Nephotettic nigropictus* was used as the test insect and the activity was tested according to the method described in literature[15,16]. Blank experiments in 5 % ethanol were carried out and the mortality was found to be about 2 %.

The results of the insecticidal activity of the compounds **1a-t** and **2a-t** indicated that the mortality rate at concentrations 0.5, 1 and 2% was less than 60% while at concentrations 4 and 8%, it was moderate. None of the compounds showed insectieidal activity comparable to commercial insecticides like DDT, BHC, endosulphan which showed 100% mortality at 1% concentration.

Generally compounds such as **1e, 1g, 1h, 1g, 2d, 2m, 2s, 2r** and **2t** showed better insecticidal activity except 1,1,1-trichloro-2,2-bis(2,4,6-trichloro-5-carboxymethoxyphenyl-2′, 4′, 6′-trichloro-5′-carboxymethoxyphenyl)ethane **2i** which showed better insecticidal activity.

Table II—Characterization data of compounds **2a-t**

Compd	R^1	R^2	OCH_2COOH	Mol. formula	m.p. °C	Found/ (Calcd) % Cl
2a	H	—	4-OCH_2COOH	$C_{18}H_{15}O_6Cl_3$	207	24.52 (24.56)
2b	3-COOH	—	4-OCH_2COOH	$C_{20}H_{15}O_{10}Cl_3$	103	20.40 (20.42)
2c	3-Cl	—	4-OCH_2COOH	$C_{18}H_{13}O_6Cl_5$	119	35.27 (35.32)
2d	2-Cl	—	4-OCH_2COOH	$C_{18}H_{13}O_6Cl_5$	132	35.40 (35.32)
2e	2-Cl	—	4-OCH_2COOH	$C_{18}H_{13}O_6Cl_5$	146	35.25 (35.32)
2f	3-Cl	4-Cl	5-OCH_2COOH	$C_{18}H_{11}O_6Cl_7$	121	43.29 (43.48)
2g	2-Cl	4-Cl	5-OCH_2COOH	$C_{18}H_{11}O_6Cl_7$	143	43.43 (43.48)
2h	3-Cl	5-Cl	6-OCH_2COOH	$C_{18}H_{11}O_6Cl_7$	98	43.35 (43.48)
2i	2,4-$(Cl)_2$	6-Cl	5-OCH_2COOH	$C_{18}H_9O_6Cl_9$	215	49.82 (49.88)
2j	3-CH_3	—	4-OCH_2COOH	$C_{20}H_{19}O_6Cl_3$	205	23.02 (23.07)
2k	2-CH_3	—	4-OCH_2COOH	$C_{20}H_{19}O_6Cl_3$	182	23.01 (23.07)
2l	2-CH_3	—	5-OCH_2COOH	$C_{20}H_{19}O_6Cl_3$	194	22.99 (23.07)
2m	2-CH_3	4-CH_3	5-OCH_2COOH	$C_{22}H_{23}O_6Cl_3$	274	21.40 (21.75)
2n	2-CH_3	5-CH_3	3-OCH_2COOH	$C_{22}H_{23}O_6Cl_3$	192	21.62 (21.75)
2o	2-NO_2	—	3-OCH_2COOH	$C_{18}H_{13}O_{10}N_2Cl_3$	210	20.27 (20.34)
2p	5-NO_2	—	3-OCH_2COOH	$C_{18}H_{13}O_{10}N_2Cl_3$	238	20.30 (20.34)
2q	2-NO_2	—	5-OCH_2COOH	$C_{18}H_{13}O_{10}N_2Cl_3$	221	20.25 (20.34)
2r	3-OCH_2COOH-	—	4-OCH_2COOH	$C_{20}H_{19}O_{12}Cl_3$	242(d)	18.25 (18.31)
2s	2-OCH_2COOH-	—	4-OCH_2COOH	$C_{20}H_{19}O_{12}Cl_3$	195	18.28 (18.31)
2t	2-OCH_2COOH-	—	5-OCH_2COOH	$C_{20}H_{19}O_{12}Cl_3$	>300	18.10 (18.31)

% Yield varied from 75-85 %

Experimental Section

General. Melting points were taken in open capillaries and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a shimadzu-IR-435 spectrophotometer using KBr disc. ^1H NMR spectra in TFA solvent at 60 MHz on a HitachiR-1200 using TMS as internal reference, and mass spectra on a Jeol-JMSD 300 Mass spectrometer at 70 eV. Purity of the compounds were routinely checked by TLC using silica gel G

2,4-Dichlorophenoxyacetic acid[17] 1g. A mixture of 2,4-dichlorophenol (3.26g, 0.02 mole) and chloroacetic acid (1.90 g, 0.02 mole) in NaOH solution (2.2 g, 0.112 mole) was refluxed on a water-bath for 8 hr. The contents were poured on to crushed ice and filtered. The clear filtrate was neutralised with hydrochloric acid. The product so obtained was filtered, washed with water and recrystallised from benzene, yield 75.05 %, mp 139 °C. IR (KBr) : 2970(C-H str., asym.), 2876 (C-H str., sym.), 1340 (br) (C-H bend), 3074 (C-H str., aromatic), 1216(C-

H i.p. def), 810(C-H 0.0.p. def.), 1720 (C=Ostr.), 2615 (-OH str.), 1273 (C-O-C str., asym.), 1065 (C-O-C str., sym.), 800 625(br) (C-Cl str.); ^{1}H NMR (TFA) : δ 4.80 (s, 2H, $-OCH_2-$), 7.21-7.43 (m, 3H, Ar-H).

Similarly other aryloxyacetic acids **1a-t** were prepared and their characterization data are recorded in **Table I**.

1,1,1-Trichloro-2, 2-bis-(2′, 4′-dichloro-5′-carboxymethoxyphenyl)ethane 2g. A mixture of 2,4-dichloro-phenoxyacetic acid (4.429g, 0.02 mole) and chloralhydrate (1.55 g 0.01 mole) in 25 mL of conc. H_2SO_4 was stirred mechanically for 4 hr and then allowed to stand overnight. The reaction mixture was poured on to crushed ice and the isolated product crystallised from benzene, yield 79.92 %, mp 143 °C. Anal. Found: C, 37.53; H, 1.85; Cl, 43.43. Calcd for $C_{18}H_{11}O_6Cl_7$: C, 37.80; H, 1.92; Cl, 43.48 %; IR (KBr): 2970 (C-H str., asym), 2876 (C-H str., sym), 1460 (C-H def., asym), 1375 (C-H def., sym), 1340(C-H bend), 3074 (C-H str., aromatic), 1575 (C=C str.), 1216 (C-H

Table III—Spectral data of selected compounds **2a, 2b, 2c, 2i, 2k, 2m, 2o, 2r**

Compd	^{1}HNMR(TFA, δ ppm)	IR (ν_{max} in cm^{-1})	Mass(m/z)
2a	4.792 (s,4H,2 × OCH_2), 6.896-7.432 (m,9H,-CH + Ar-H).	3070(C-H Str)., 1705(C=O Str), 2603(-OH Str), 1260(C-O-C Str., asym.), 1065(C-O-C Str. Sym,) 805 (br) (C-Cl str).	433.5 (M^+)397,315, 309, 282.5, 202, 227(BP),199,171, 152,135,108,65,52.
2b	4.893 (s,4H,2 × OCH_2), 6.752 (m,9H,- CH + Ar-H).	3150(C-H Str)., 2650(-OH Str), 1700(C=O Str), 1245(C-O-C Str., asym.), 1055(C-O-C Str. Sym,) 817 (br) (C-Cl str).	521.5 (M^+)485,403 397,370.5,315(BP), 290,287, 259,240, 223,196,153,77,65,52.
2c	4. 989 (s,4H,2×OCH_2), 6.785-7.474 (m,7H,- CH + Ar-H).	3055(C-H Str)., 2600(-OH Str), 1710(C=O Str), 1255(C-O-C Str., asym.), 1060(C-O-C Str. Sym,) 710 (br) (C-Cl str).	502.5 (M^+)466,384 378,317,296(BP), 280.5,268.236.5, 222.5,185.5,168.5, 142.5,128.5,112.5,107.
2i	4. 798 (s,4H,2 × OCH_2), 6.592-7.796 (m,3H,- CH + Ar-H).	3080(C-H Str)., 2635(-OH Str), 1695(C=O Str), 1275(C-O-C Str., asym.), 1035(C-O-C Str. Sym,) 775 (br) (C-Cl str).	640.5 (M^+) 604,522 516,455 (B.P),434 418.5,406,374.5, 360.5,280.5,266.5, 245,118.5.
2k	2.484, (s,6H,2 × OCH_3) 4.987(s,4H,2×OCH_2) 7.236-8.098 (m,7H, -CH + Ar-H).	3115(C-H Str)., 2626(-OH Str), 1705(C=O Str), 1230(C-O-C Str., asym.), 1060(C-O-C Str. Sym,) 775 (br) (C-Cl str).	461.5 (M^+)425,339 337,309,296,(BP) 260,251,223,202, 166,149,121,107, 93,77,65.
2m	3.484, (s,12H,4 ×-CH_3) 4.975(s,4H,2 ×-OCH_2) 6.925-8.091 (m,5H, -CH + Ar-H).	3125(C-H Str)., 2600(-OH Str), 1695(C=O Str), 1265(C-O-C Str., asym.), 1085(C-O-C Str. Sym,) 685-705 (br) (C-Cl str).	485.5(M^+)449,363 361,333,310.5,275,274,247, 230,216, 180,163,135,121, 94,77,65,52(BP).
2o	4.843 (s,4H,2 ×-OCH_2) 6.739-7.698 (m,7H,- CH + Ar-H).	3235(C-H Str)., 2635(-OH Str), 1715(C=O Str), 1410(C-O-C Str., asym.), 1050(C-O-C Str. Sym,) 710 (br) (C-Cl str).	523.5(M^+)487,405 399,371,293,236 (BP) 207,171,112, 77,61,52.
2r	4.899 (s,8H,4 ×-OCH_2) 6.875-7.987 (m,7H,- CH + Ar-H).	3230(C-H Str)., 2650(br)(-OH Str), 1700(C=O Str), 1290(C-O-C Str., asym.), 1090(C-O-C Str. Sym,) 750,765 (br) (C-Cl str).	581.5(M^+)545,463 356.5,320,287,276 (BP)195,137,65, 52.

i.p. def.), 810 (C-H o.o.p. def), 1720 (C=O str., -COOH), 2615 (-OH str.), 1273 (C-O-C str., asym), 1065(C-O-C str., sym.), 800-625(br) (C-Cl str); ^{1}H NMR (TFA): δ 4.835(s, 4H, −2 × O-CH_2), 6.830-7.404 (m, 5H, CH+ Ar-H).

Similarly other 1,1,1-trichloro-2,2-bis(carboxymethoxyaryl)ethanes were prepared. The characterization data are recorded in **Tables I** and **II**. IR, ^{1}H NMR and mass fragmentation data of compounds **2a, 2b, 2c, 2l, 2k, 2m, 2o** and **2r** are recorded in **Table III.**

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