# PREPARATION AND ANTIMICROBIAL EVALUATION OF 1,1,1-TRICHLORO-2,2-BIS(CARBOXYMETHYLAMINOCARBONYLARYL)-ETHANES HAVING POTENT OF SOME NEW DDT ANALOGUES.

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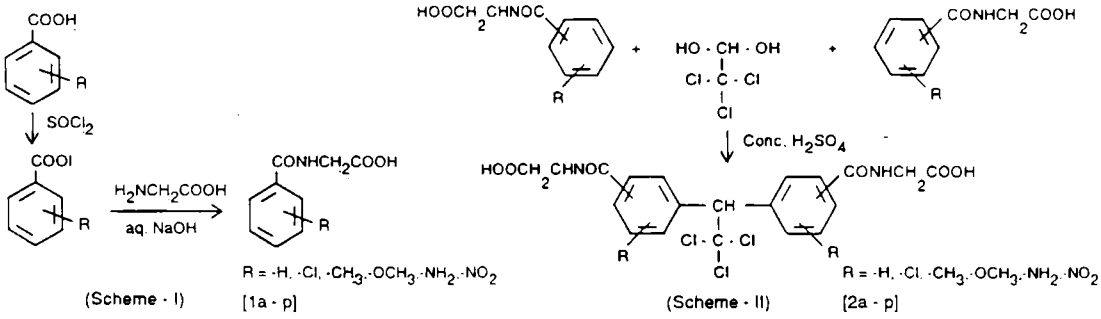
**ABSTRACT :**

Some new DDT analogues (2a-p) have been synthesised by the action of substituted benzoyl glycines with chloralhydrate in the presence of conc. sulphuric acid. The benzoylglycines were prepared by the action of aromatic acids with thionyl chloride and the latter were synthesised by the action of α-aminoaceticacid in basic medium. The biological activity of these compounds have been determined against various Gram +ve, Gram -ve baceteria and fungi. The constitution of the Products have been elucidation is based on elemental analysis and spectral (IR and PMR) data.

**INTRODUCTION :**

In view of achieving biodegrable analogoues of DDT molecules, as a part of our research study substituted benzoylglycine and chloral hydrate have been condensed in the presence of catalytic amount of conc. sulphuric acid to formed (2a-p) evaluted for their antimicrobial activity

1,1,1-trichloro-2,2-bis (p-chlorophenyl)-ethane (DDT) has a wide spectrum of biological activity against different families of insects and related organisms. The known pesticides "Triphan"[1], "Methoxychlor"[2,3] ,"Methiochlor"[4] chloral it self has a little insecticidal and herbicidal activity. "Meta-chloral"[5] is however a good herbicide . In many pharmacopoeas chloral hydrates derivatives have been approved for fungicidal wood protection[6]. It has also sedative and hypnotic effect were associated with reaction products from chloral with "Bromoisovalerylurea"[7] , "Cholin"[8] , "Bataine"[9] and "Carnitine"[10].




The titled compounds have been synthesised by the literature method[11-13] .The condensation of chloral hydrate and substituted benzoyl glycine in the presence of catalytic amount of conc. sulphuric acid to orienting influence of substituents 1,1,1-Trichloro-2,2-bis-(carboxymethylaminocarbonylaryl)-ethanes were fomed. The substituted benzoylglycine were prepared by the condensation of aromatic acids with thionyl chloride, the latter were aroyl chloride were condensed with glycine in aqueous sodium hydroxide solun.

The structures of these products were determined by elemental analyses IR, $^1$HNMR data. The antimicrobial activity of compounds (1a-p) are recorded in Table No. I and compounds (2a-p) are recorded in Table No.- II.

**Table - I : The physical data and antimicrobial activity of compounds [ 1a-p ]**

| Compd | R | Molecular formula | M.P. oC | Yield % | Nitrogen (%) | | Antibacterial activity Zone of inhibition in m.m | | | Antifungal activity Zone of inhibition in in m.m. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calcd | Found | B.mega | B.substilis | E.Coli | p.fluore-scens | A.awamori |
| 1a | -H | $C_9H_9O_3N$ | 189 | 56.08 | 7.82 | 7.76 | 18 | 14 | 16 | 15 | 14 |
| 1b | 4-$NH_2$ | $C_9H_{10}O_3N_2$ | 198 | 58.12 | 14.43 | 14.39 | 13 | 16 | 17 | 14 | 17 |
| 1c | 2-Cl | $C_9H_8O_3NCl$ | 129 | 55.97 | 6.55 | 6.42 | 19 | 18 | 19 | 17 | 20 |
| 1d | 3-Cl | $C_9H_8O_3NCl$ | 107 | 57.64 | 6.55 | 6.51 | 21 | 15 | 18 | 19 | 24 |
| 1e | 4-Cl | $C_9H_8O_3NCl$ | 148 | 60.51 | 6.55 | 6.45 | 24 | 19 | 24 | 23 | 21 |
| 1f | 2-OH | $C_9H_9O_4N$ | 166 | 58.30 | 7.17 | 7.08 | 23 | 14 | 15 | 20 | 17 |
| 1g | 2-$CH_3$ | $C_{10}H_{11}O_3N$ | 160 | 62.13 | 7.25 | 7.19 | 20 | 13 | 16 | 19 | 18 |
| 1h | 3-$CH_3$ | $C_{10}H_{11}O_3N$ | 139 | 67.92 | 7.25 | 7.23 | 19 | 17 | 18 | 17 | 16 |
| 1i | 4-$CH_3$ | $C_{10}H_{11}O_3N$ | 165 | 70.49 | 7.25 | 7.14 | 17 | 16 | 19 | 18 | 15 |
| 1j | 2-$OCH_3$ | $C_{10}H_{11}O_4N$ | 183 | 67.38 | 6.69 | 6.63 | 22 | 14 | 25 | 21 | 18 |
| 1k | 3-$OCH_3$ | $C_{10}H_{11}O_4N$ | 151 | 72.80 | 6.69 | 6.58 | 24 | 18 | 22 | 19 | 20 |
| 1l | 4-$OCH_3$ | $C_{10}H_{11}O_4N$ | 204 | 68.00 | 6.69 | 6.61 | 18 | 15 | 20 | 17 | 16 |
| 1m | 2-$NO_2$ | $C_9H_8O_5N_2$ | 156 | 75.15 | 12.50 | 12.48 | 17 | 16 | 19 | 15 | 17 |
| 1n | 3-$NO_2$ | $C_9H_8O_5N_2$ | 122 | 78.46 | 12.50 | 12.39 | 16 | 14 | 17 | 18 | 18 |
| 1o | 4-$NO_2$ | $C_9H_8O_5N_2$ | 132 | 73.11 | 12.50 | 12.45 | 19 | 13 | 18 | 16 | 19 |
| 1p | -H,4-CH=CH- | $C_{11}H_{11}O_3N$ | 106 | 58.43 | 7.21 | 7.16 | 15 | 16 | 17 | 19 | 15 |

**Table - II : The physical data and antimicrobial activity of compounds [ 2a-p ]**

| Compd | R | -CONHCH$_2$COOH = R' | Molecular formula | M.P. oC | Yield % | Chlorine (%) | | Antibacterial activity Zone of inhibition in m.m. | | | Antifungal activity Zone of inhibition in in m.m. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | R' | | | | Calcd | Found | B.mega | B.substilis | E.Coli | p.fluore-scens | A.awamori |
| 2a | -H | 3 - R' | $C_{20}H_{17}O_6N_2Cl_3$ | 263 | 69.86 | 21.84 | 21.78 | 15 | 12 | 18 | 14 | 16 |
| 2b | 4-$NH_2$ | 3 - R' | $C_{20}H_{19}O_6N_4Cl_3$ | 219 | 71.38 | 20.57 | 20.43 | 14 | 16 | 20 | 19 | 19 |
| 2c | 4-Cl | 3 - R' | $C_{20}H_{15}O_6N_2Cl_5$ | 178 | 76.87 | 31.89 | 31.70 | 18 | 15 | 25 | 21 | 20 |
| 2d | 3-Cl | 5 - R' | $C_{20}H_{15}O_6N_2Cl_5$ | 157 | 79.01 | 31.89 | 31.78 | 17 | 18 | 19 | 17 | 23 |
| 2e | 2-Cl | 5 - R' | $C_{20}H_{15}O_6N_2Cl_5$ | 188 | 81.09 | 31.89 | 31.83 | 20 | 22 | 21 | 18 | 18 |
| 2f | 4-OH | 3 - R' | $C_{20}H_{17}O_8N_2Cl_3$ | 203 | 65.87 | 20.50 | 20.43 | 19 | 14 | 17 | 24 | 19 |
| 2g | 4-$CH_3$ | 3 - R' | $C_{22}H_{21}O_6N_2Cl_3$ | 172 | 72.32 | 20.65 | 20.56 | 12 | 15 | 19 | 21 | 20 |
| 2h | 3-$CH_3$ | 5 - R' | $C_{22}H_{21}O_6N_2Cl_3$ | 165 | 78.57 | 20.65 | 20.58 | 14 | 17 | 16 | 17 | 21 |
| 2i | 2-$CH_3$ | 5 - R' | $C_{22}H_{21}O_6N_2Cl_3$ | 198 | 71.16 | 20.65 | 20.63 | 23 | 13 | 15 | 14 | 19 |
| 2j | 4-$OCH_3$ | 3 - R' | $C_{22}H_{21}O_8N_2Cl_3$ | 245 | 72.86 | 19.45 | 19.36 | 15 | 16 | 14 | 19 | 18 |
| 2k | 3-$OCH_3$ | 5 - R' | $C_{22}H_{21}O_8N_2Cl_3$ | 176 | 69.32 | 19.45 | 19.32 | 13 | 12 | 18 | 16 | 22 |
| 2l | 2-$OCH_3$ | 5 - R' | $C_{22}H_{21}O_8N_2Cl_3$ | 289 | 65.03 | 19.45 | 19.40 | 19 | 14 | 20 | 15 | 17 |
| 2m | 2-$NO_2$ | 3 - R' | $C_{20}H_{15}O_{10}N_4Cl_3$ | 236 | 68.22 | 18.44 | 18.40 | 17 | 13 | 12 | 13 | 24 |
| 2n | 3-$NO_2$ | 5 - R' | $C_{20}H_{15}O_{10}N_4Cl_3$ | 165 | 67.73 | 18.44 | 18.35 | 18 | 15 | 17 | 20 | 21 |
| 2o | 2-$NO_2$ | 5 - R' | $C_{20}H_{15}O_{10}N_4Cl_3$ | 188 | 69.08 | 18.44 | 18.37 | 20 | 17 | 19 | 18 | 25 |
| 2p | -H | 3-CH=CH-R' | $C_{24}H_{21}O_6N_2Cl_3$ | 169 | 72.52 | 19.74 | 19.60 | 16 | 14 | 21 | 17 | 18 |

**ANTIMICROBIAL ACTIVITY :**

All the compounds data were recorded in Table No.-I & II to tested in vitro for their antimicrobial activity under identical conditions. Antibacterial activity against **B.mega, B.subtilis, E.coli, P.fluorescens** and for antifungal activity against **A.awamori** using DMF as solvent at 50µg concentration by cup-plate method[14], after 24 hrs. of incubation at 37°C, the zone of inhibition were measured in m.m. The activity was compared with the known antibiotics viz.Ampicillin, Chloramphenicol, Norfloxacin and Griseofulvin at same concentration.

In the case of Antimicrobical activity and antifungal activity of compounds of types (1a-p,2a-p) showed moderate to good and comparable activity with known standard drugs Table -I & II.

In case of Antimicrobical activity of all the synthesised compounds (1a-p,2a-p) exhibited moderate to good activity against each strains of bacteria and fungi. However some of the compounds showed remarkable and comparable activity with known choosen standard drugs at same concentrations which is represented in Table -III.

**Table - III :**

**ANTIMICROBIAL ACTIVITY :**
Conclusion :
Maximum Antimicrobial activity :

| Compounds data | B.mega | B.substilis | E.coli | P.fluorescens | A. awamori |
|---|---|---|---|---|---|
| (1a-o) | 1e,1f,1k | 1c,1e,1k | 1e,1j | 1e | 1d |
| (2a-o) | 2i | 2e | 2c | 2f | 2d,2m,2o |
| Comparable activity with known standard drugs | | | | | |
| 1. Ampicillin (50 mg ) | 22 | 18 | 19 | 27 | - |
| 2. Chloramphanicol (50 mg) | 24 | 19 | 25 | 26 | - |
| 3. Norfloxacin (50 mg) | 24 | 19 | 25 | 26 | - |
| 4. Griseofulvin (50 mg) | - | - | - | - | 23 |

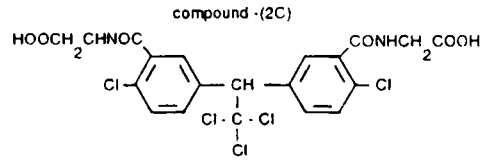
**IDENTIFICATION OF TOTAL NO. OF CHLORINE CONTENT IN THE COMPOUNDS (2a-p) :**

**Determine the total chloride content in the compound (2c) :**

Weight of compound -(2C) 0.2 g and transfer to 50 ml. volumetric flask dissolve sample in 5 ml of the benzene then dilute to volume with 99%. Isopropanol transfer 25 ml aliquot to 250-500 ml. conical flask.

Add 2.5 g of the Na and Shake flask to mix sample with the isopropanol, connect flask at reflux condenser and boiled gently at least 30 miniutes shaking flask occasionally. Eliminate excess Na by coutiously adding 10 ml 50% Isopropanol through condenser add 60 ml water, boil solution about 30 miniutes to expel isopropanol, cool flask and transfer contents to 250 ml

beaker. Add 2-3 drops phenolphthalein and neutralise with $HNO_3$ (1:1), then add 10 ml excess add slight excess 25 ml 0.1 N $AgNO_3$ and coagulate precipitated AgCl by digesting on steam bath 30 minutes stirring frequently. cool, filter through fast qualitative paper and wash thoughroughly with water add 5 ml standared Fe alum solution and determine excess $AgNO_3$ in filtrate by titraction with 0.1 N KCNS. Substract quantity $AgNO_3$ found in filtrate from that originally added. Difference is that required to combine with Cl in the newly synthesised DDT types derivatives.




m.w. 556.3 gm

$C_{20}H_{15}O_6N_2Cl_5$

1. Burette Reading = $\overline{19.3}$ ml
2. 25 ml of 0.1 N $AgNO_3$ unused for the taken sample = 19.3 ml
   .. $AgNO_3$ used up = 25.0 - 19.3 ml = 5.7 ml
3. 1.0 ml 0.1 N $AgNO_3$ = 0.05563 gm
   .. 5.7 ml 0.1 N $AgNO_3$ = 0.05563 gm x 5.7 ml = 0.317091
   % of chlorine **(practically)** = 0.317091 x 100
   = 31.70 % of chlorine in 2c compound.

**Theoritically** = 5 (No. of chlorine) x 35.5 (M. W. of chlorine) x 100 = 31.89 %
(Total m.w. of compound -2C) 556.3 gm.

Similary determine the total no. of chlorine content in the compounds (2a-p) by above estimation method, which is recorded in table no.-II.

**EXPERIMENTAL :**

Melting points were taken in open capillary and are uncorrected. IR absorption spectra ($\upsilon$in $cm^{-1}$) were recorded on a shimadzu IR-435 spectrophotometer using KBr pellet and 1HNMR spectra on BRUKER-spectrometer (300MHz) using DMSO and $CdCl_3$ as internal standard. The Purity of the compounds were routinely checked by TLC using silica gel G.

**4-methyl benzoylglycine - (1i) :**

(i) A mixture of P-Toluic (13.6 g ,0.1 mole) and thionyl chloride ( 0.2 mole) was condensed for 4 hrs on water bath. The excess of thionyl chloride was removed by distillation. So , residue are formed 4-methylbenzoylchloride.

(ii) A mixture of 4-Methylbenzoylchloride (14.0 ml ,0.1 mole) and glycine ( 7.5 g ,0.1 mole) in 250 ml of 10 percent sodium hydroxide solution containing in a conical flask. Stopper the vessel and shake vigrously after the content is poured into ice-cold water and acidify with 50 % hydrochloric acid. The islated product was crystallised from Dioxane. m.p. 165 $^oC$ , yield : 70.49 % . (Found : C, 62.09; H, 5.62 ; N, 7.14 ; $C_{10}H_{11}O_3N$ requires : C, 62.17; H, 5.69 ; N, 7.25 %) IR (KBr) : 2975 (C-H Str.), 1725 (C=O str.), $^1$HNMR (DMSO) : $\delta$ 1.41 (S,2H,$CH_2$), 2.41(S,3H,-$CH_3$), 6.76-8.43 (Ar-H), 8.44(-NH).

The compounds (1a-p) were prepared similarly and their physical data are recorded in table - I.

**1,1,1-Trichloro-2,2-bis-(2',methyl-5'-carboxymethylaminocarbonylphenyl)-ethane-(2i) :**

A mixture of 4-methylbenzoylglycine -(1i) (3.86 g ,0.02 mole),and chloralhydrate (1.57 g, 0.01 mole) heating in a water bath just liquidify, than after added catalytic amount of conc.sulphuric acid (25.0 ml) stirring vigorously 4 hrs. The resluting mixture was poured into crused ice-water and filtrate it. The isolated product was crystalled from Dioxane. m.p. 108 $^{o}$C , yield : 71.16 % . (Found : C, 51.16; H, 4.02 ; N, 20.63 ; $C_{22}H_{21}O_6N_2Cl_3$ requires : C, 51.21 ; H, 4.07 Cl; N, 20.65 %) IR (KBr) : 3440 (m,-NH Str.), 3030 (m,-$CH_2$ ), 2910 (m,s,-CH str.), 1670-1700 (S,-COOH str. vib.) 1455- (m,-$CH_2$,C-H bending) $^1$HNMR (DMSO) : 1.43 (s,2H,-$CH_2$ ), 2.40 (s,3H,-$CH_3$)6.65-8.43 (Ar-H) 8.43-8.46 (-NH).

The compounds (2a-p) were prepared similarly and their physical data are recorded in table - II.

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