635. *Insecticidal Activity and Chemical Constitution. Part V.* Synthesis of Some Di-*p*-chlorophenylalkanes.*

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A number of di-*p*-chlorophenylalkanes have been prepared in order to examine a suggestion that the toxicity of DDT is in some way associated with the presence of strongly electron-attracting groups in the aliphatic portion of the molecule.

An improved synthesis of 1 : 1-di-*p*-chlorophenylpropan-2-one is described.

Previous investigations of the relation of chemical structure with insecticidal potency in the DDT series have largely been concerned with altering nuclear substituents or varying the nature and number of the halogen atoms in the aliphatic portion of the molecule. In

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our earlier publications (*J.*, 1950, 2718; 1952, 2804, 2806) analogues (I; R = Cl or Me, R′ = Cl, Me, or OH) which were isosteric with DDT were synthesised but were found not to be contact insecticides against the grain weevil (*Calandra granaria* L.) which readily succumbs to DDT. This led to the suggestion that the high insecticidal activity of DDT might be in some way associated with the presence of strongly electropositive groups in the aliphatic portion of the molecule. Valuable support for this hypothesis lay in the high activity reported by Hass (*Agric. Chemicals*, 1949, **4**, No. 6, p. 67) for the nitro-compounds (II; R = H, R′ = Me, and R = H, R′ = Et) though the DDT analogue (III), containing the highly electron-attracting CF_3 group, had been shown by Kirkwood and Dacey (*Canad. J. Res.*, 1946, **24**, *B*, 69) to possess only 1% of the toxicity of DDT. This is probably because of an alteration in lipoid solubility since Kirkwood and Phillips (*J. Pharmacol.*, 1946, **87**, 375) have shown that this compound is not stored in the perirenal fat of rats.

$(p\text{-}C_6H_4R)_2\cdot CMe_2R'$ (I) $\quad$ $(p\text{-}C_6H_4Cl)_2CH\cdot CRR'\cdot NO_2$ (II) $\quad$ $(p\text{-}C_6H_4Cl)_2CH\cdot CF_3$ (III)

$(p\text{-}C_6H_4Cl)_2CH\cdot CHR\cdot NR'_2$ (IV) $\quad$ $(p\text{-}C_6H_4Cl)_2CH\cdot CHR\cdot NR'_3{}^+ X^-$ (V)

The present work was undertaken with a view to examine more fully this electronic interpretation of the high insecticidal potency of DDT.

Whilst the quaternary ammonium cation is highly electron-attracting, quaternary ammonium salts might be expected to be too polar to be readily lipoid-soluble. However, Cowan and Walter (*J. Physiol.*, 1937, **91**, 101) have shown that such an ion can produce repetitive impulses in sciatic-nerve preparations of frogs, in a manner similar to that produced in cray-fish motor neurons by DDT (Welsh and Gordon, *J. Cell. Comp. Physiol.*, 1947, **30**, 147). Moreover, Tattersfield and Gimingham (*Ann. Appl. Biol.*, 1927, **14**, 217) have shown that certain tetramethyl- and tetraethyl-ammonium salts possess some contact activity against *Aphis rumicis* L. The quaternary iodides (V; R = H or Me, R′ = Me, X = I) were therefore prepared, from the corresponding bases (IV; R = H or Me, R′ = H), and the chloride (V; R = R′ = Me, X = Cl) was obtained by the usual method. These salts and the corresponding bases are not contact insecticides against *Calandra granaria*. Attempts were also made to prepare the corresponding triethyl-ammonium iodides (V; R = H or Me, R′ = Et, X = I) in view of the reported superiority of tetraethyl- over tetramethyl-ammonium salts (Cowan and Walter, *loc. cit.*). Though the tertiary amines were isolated, no quaternary salt formation was observed, and an examination of atomic models indicates that such quaternary salts would be seriously sterically hindered.

Whilst the insecticidal potencies of the nitropropane and nitrobutane (II; R = H, R′ = Me and Et respectively) have been found to be 2·18 and 0·78, relative to DDT, the nitroethane (II; R = R′ = H) had no action on *Calandra granaria*. Successive substitution of chlorine atoms, forming the compounds (II; R = H, R′ = Cl, and R = R′ = Cl), also failed to produce insecticidal activity, which is significant in view of the close spatial and electrical similarity between the dichloro-compound and DDT.

To prepare the monochloro-compound (II; R = H, R′ = Cl) it was necessary to add a solution of the sodium salt of the *aci*-form of the nitroethane (II; R = R′ = H) to excess of chlorine in dioxan, since direct chlorination of the *aci*-salt would be expected to give a product contaminated with both the original material and with the dichloro-compound (cf. Meyer and Tscherniak, *Annalen*, 1876, **180**, 112, 123). The latter was readily prepared by chlorination in dioxan–methyl alcohol in the presence of excess of sodium hydroxide.

Chlorination of the nitropropane (II; R = H, R′ = Me) in dioxan in the presence of sodium methoxide formed 1 : 1-di-*p*-chlorophenyl-2-nitro-2-propyl chloride (II; R = Cl, R′ = Me) which possessed insecticidal activity of the same order as the parent compound. Whilst there is a slight increase in the toxicity of (II; R = Cl, R′ = Me)

over that of (II; R = H, R′ = Me), as would be expected if the presence of electrophilic groups increases insecticidal potency, the inactivity of the compounds (II; R = H, R′ = Cl, and R = R′ = Cl) throws some doubt on the validity of this suggestion. It is possible however that there is an optimum electronic density about the second carbon atom in the aliphatic portion of the molecule, above which there is an adverse effect on lipoid solubility and hence on cuticular penetration. The effect of the substitution of the methyl group in the non-toxic nitroethanes (II; R = R′ = H and R = Cl, R′ = H) to form the toxic molecules (II; R = H, R′ = Me, and R = Cl, R′ = Me) respectively may then be explained in terms of higher fat-solubility. The possibility that the methyl group plays some important steric rôle fails to explain the inactivity of the compound (II; R = Cl, R′ = H) which is isosteric with the highly toxic (II; R = Me, R′ = H).

Experimental

M. p.s are uncorrected. Microanalyses for carbon and hydrogen are by Drs. Weiler and Strauss, Oxford.

2 : 2-*Di*-p-*chlorophenylethylamine*.—A solution of 1 : 1-di-*p*-chlorophenyl-2-nitroethane (3·0 g.; prepared in 58% yield by Müller's method, U.S.P. 2,397,802) in ethyl alcohol (20 ml.) was shaken in hydrogen for 8 hours at room temperature and pressure in the presence of Raney nickel until there was no further uptake. After filtration, the solvent was removed, the residue taken up in ether, and the solution extracted three times with 8N-hydrochloric acid. The combined extracts were basified with 10N-sodium hydroxide, and the *amine* isolated with ether as a colourless viscous liquid (2·1 g., 78%), b. p. 158—162°/1·2 mm. (Found: Cl, 26·0. $C_{14}H_{13}NCl_2$ requires Cl, 26·7%).

The *hydrochloride* was prepared in ether and purified by repeated precipitation from ethyl alcohol by ether as needles, m. p. 227—228° [Found: Cl, 34·7 (total), 11·7 (ionisable). $C_{14}H_{14}NCl_3$ requires Cl, 35·2 (total), 11·7% (ionisable)]. The acetate was a viscous oil.

N-(2 : 2-*Di*-p-*chlorophenylethyl*)*trimethylammonium Iodide*.—The above amine (1 g.), methyl alcohol (5 ml.), methyl iodide (5 ml.) and excess of anhydrous potassium carbonate were refluxed for 16 hours. The hot solution was filtered and the quaternary *salt* purified by repeated precipitation with dry ether from ethyl alcohol. It formed prismatic plates, m. p. 218—219° (Found: I, 28·8. $C_{17}H_{20}NCl_2I$ requires I, 29·1%).

2-*Chloro*-1 : 1-*di*-p-*chlorophenyl*-2-*nitroethane*.—Sodium hydroxide (0·14 g.) in water (5 ml.) was added to a solution of 1 : 1-di-*p*-chlorophenyl-2-nitroethane (1 g.) in a mixture of dioxan (5 ml.) and methyl alcohol (5 ml.) at 0°, and the whole then added dropwise to dioxan (15 ml.) stirred at 0° during the passage of chlorine (cf. Meyer and Tscherniak, *Annalen*, 1876, **180**, 112, 126). Stirring and chlorination were continued for 5 minutes after the final addition and then the solution was evaporated *in vacuo*. The residue was extracted with ether, the extract washed with water and sodium hydrogen carbonate solution and dried, and the solvent removed. The residual *compound* crystallised from aqueous methyl alcohol in rhombic prisms (0·75 g., 67%), m. p. 86—87° (Found: C, 51·4; H, 3·1; Cl, 32·9. $C_{14}H_{10}O_2NCl_3$ requires C, 50·8; H, 3·1; Cl, 32·2%).

1 : 1-*Dichloro*-2 : 2-*di*-p-*chlorophenyl*-1-*nitroethane*.—A solution of the nitro-compound (II; R = R′ = H) (1 g.) in a mixture of dioxan (10 ml.) and methyl alcohol (7 ml.) was cooled to 0° and stirred during the addition of sodium hydroxide (0·4 g.) in water (3 ml.). A rapid stream of chlorine was passed through the solution for 0·5 hour and then the solvents were removed by distillation under reduced pressure. The *product*, isolated with ether, crystallised from methyl alcohol in well-formed octahedra (0·7 g., 57%), m. p. 76—78° (Found: C, 46·0; H, 2·5; Cl, 38·7. $C_{14}H_9O_2NCl_4$ requires C, 46·0; H, 2·5; Cl, 38·9%).

2-*Chloro*-1 : 1-*di*-p-*chlorophenyl*-2-*nitropropane*.—1 : 1-Di-*p*-chlorophenyl-2-nitropropane (12·4 g.) dissolved in anhydrous dioxan (120 ml.) was cooled to 0° and stirred for 1 hour in the presence of sodium methoxide (from 1·6 g. of sodium), during the passage of chlorine. The solvent was removed under reduced pressure, the residue extracted with ether, and the extract washed twice with water and saturated sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the ether gave a *product* which crystallised from methyl alcohol in monoclinic prisms, m. p. 96—97° (Found: C, 52·4; H, 3·6; Cl, 30·9. $C_{15}H_{12}O_2NCl_3$ requires C, 52·3; H, 3·5; Cl, 30·9%). Attempts to prepare this product by direct chlorination in carbon tetrachloride solution at 0° resulted in recovery of the original nitro-compound.

1 : 1-*Di*-p-*chlorophenyl*-2-*propylamine*.—(*a*) A solution of 1 : 1-di-*p*-chlorophenyl-2-oximino-

propane (3·5 g.; see below) in glacial acetic acid (130 ml.) was stirred for 12 hours and 3% sodium amalgam (350 g.) added in small portions (cf. Goldschmidt, *Ber.*, 1886, **19**, 3232; 1887, **20**, 728). Crushed ice (1 kg.) was added, the mixture made alkaline with 10N-sodium hydroxide, and the product extracted with ether. Removal of the solvent and distillation of the residue gave the *amine* as a viscous liquid (3·0 g., 90%), b. p. 180—182°/0·8 mm., which slowly solidified. Crystallisation from light petroleum (b. p. 40—60°) gave rectangular prisms, m. p. 90—91° (Found: C, 64·5; H, 5·4; N, 5·0; Cl, 25·1. $C_{15}H_{15}NCl_2$ requires C, 64·3; H, 5·4; N, 5·0; Cl, 25·3%).

(*b*) An ethyl-alcoholic solution (35 ml.) of the nitropropane (II; R = H, R′ = Me) (5·0 g.) was shaken for 12 hours in hydrogen at room temperature and 6 atmospheres in the presence of Raney nickel. The product, isolated as described in (*a*) above, was distilled (b. p. 175—180°/0·8 mm.) and crystallised from light petroleum (b. p. 40—60°) in rectangular prisms (3·6 g., 80%), m. p. 90—91°, undepressed by admixture with the product from (*a*). Hydrogenation at atmospheric pressure lowered the yield to 50%. The *acetate* crystallised from ethyl alcohol in minute prisms, m. p. 175—176° (Found: C, 63·5; H, 5·3. $C_{17}H_{17}ONCl_2$ requires C, 63·3; H, 5·3%). The *hydrochloride*, prepared in ether and purified as described for the hydrochloride of the ethylamine, formed needles, m. p. 261—262° [Found: Cl, 10·8. $C_{15}H_{16}NCl_3$ requires Cl (ionisable), 11·2%].

N-(1 : 1-*Di*-p-*chlorophenyl*-2-*propyl*)*trimethylammonium Iodide*.—The foregoing amine (1·0 g.), methyl iodide (5 ml.), methyl alcohol (5 ml.), and excess of anhydrous potassium carbonate were heated under reflux for 16 hours. The *iodide*, isolated as previously described, formed stout rectangular prisms which decomposed at 180—200° (Found: C, 49·7; H, 5·2; Cl, 15·2. $C_{18}H_{22}NCl_2I$ requires C, 48·0; H, 4·9; Cl, 15·8%). Attempts to prepare the corresponding triethylammonium iodide resulted in the formation of N-(1 : 1-*di*-p-*chlorophenyl*-2-*propyl*)*diethylamine*, b. p. 180—190°/0·5 mm. (Found: Cl, 21·0. $C_{19}H_{23}NCl_2$ requires Cl, 21·1%), which did not react further with ethyl iodide in ether.

1 : 1-*Di*-p-*chlorophenylpropane*-1 : 2-*diol*.—Ethyl lactate (11·8 g.) in anhydrous ether (35 ml.) was added dropwise with stirring to an ice-cooled solution of *p*-chlorophenylmagnesium bromide, prepared from magnesium turnings (7·3 g.) and *p*-bromochlorobenzene (57·5 g.) in anhydrous ether (150 ml.). The mixture was kept at 0° for 66 hours and then cautiously decomposed at this temperature with 2N-sulphuric acid. After being washed with 1% sodium hydrogen sulphite solution, water, and saturated sodium hydrogen carbonate solution, the ethereal layer was dried (Na_2SO_4). Removal of the solvent and distillation of the residue gave a fraction (19·2 g., 65%), b. p. 190—200°/1·0 mm., which solidified and crystallised from light petroleum (b. p. 60—80°) in rhombs, m. p. 96—97° (Found: C, 60·5; H, 4·7; Cl, 24·1. $C_{15}H_{14}O_2Cl_2$ requires C, 60·6; H, 4·7; Cl, 23·9%). This *diol* gave a *diacetate*, large rhombic prisms (from methyl alcohol), m. p. 131—132° (Found: C, 60·0; H, 4·6. $C_{19}H_{18}O_4Cl_2$ requires C, 59·8; H, 4·7%).

1 : 1-*Di*-p-*chlorophenylpropan*-2-*one*.—(*a*) This ketone, earlier reported as a crystalline solid, m. p. 52—53° (Skerrett and Woodcock, *loc. cit.*; cf. Erlenmeyer, Bitterli, and Sorkin, *Helv. Chim. Acta*, 1948, **31**, 466) has now been prepared by a much improved procedure based on Bowman's method (*J.*, 1950, 322). A mixture of ethyl malonate (48 g.), ethyl alcohol (14 ml.), and benzene (60 ml.) was slowly added to a vigorously stirred hot mixture of magnesium turnings (7·2 g.), benzene (22 ml.), ethyl alcohol (2 ml.), and carbon tetrachloride (0·1 ml.). When solution of the magnesium was complete the benzene–ethyl alcohol azeotrope was removed. Di-*p*-chlorophenylacetyl chloride (44·2 g.) was then added and the mixture heated under reflux for 3 hours and poured into water. The benzene layer was separated, washed with 2N-sulphuric acid and water, and evaporated to dryness on a water-bath under reduced pressure. The residual oil was heated under reflux for 6 hours with propionic acid (120 ml.) and concentrated sulphuric acid (1·2 ml.) and then for 1—2 days after the addition of 4N-sulphuric acid (12 ml.). Crystalline sodium acetate (22 g.) was then added and volatile acids were removed by distillation under reduced pressure. After the addition of ice to the residue, organic matter was extracted with ether, and the ethereal solution washed with 1% sodium hydroxide solution and water and dried. The solvent was removed and the residue distilled as a viscous liquid (35·5 g., 86%), b. p. 182—184°/1 mm., which slowly solidified. Crystallisation from methyl alcohol yielded monoclinic prisms, m. p. 52—53° (Found: C, 64·6; H, 4·3. Calc. for $C_{15}H_{12}OCl_2$: C, 64·5; H, 4·3%). When the method of Erlenmeyer *et al.* (*loc. cit.*) was used the distilled product solidified but was almost invariably contaminated with di-*p*-chlorophenylpropan-2-one, m. p. 146—147°, and ethyl di-*p*-chlorophenylacetate, m. p. 88—89°, both m. p.s being undepressed by admixture with the appropriate authentic specimens.

(*b*) 1 : 1-Di-*p*-chlorophenylpropane-1 : 2-diol (1·0 g.) was heated with potassium hydrogen sulphate (2·0 g.) for 70 minutes at 140°. The mixture was cooled and extracted with ether, the ethereal layer being washed with water and then saturated sodium hydrogen carbonate solution, and dried (Na_2SO_4). Removal of the solvent and distillation of the residue gave a viscous liquid (0·9 g., 99%), b. p. 180—190°/2 mm., which slowly solidified. It crystallised from methyl alcohol in prisms, m. p. 50—51° undepressed by admixture with the product obtained as in (*a*). An attempt to prepare this ketone by an adaptation of Stoermer's method (*Ber.*, 1906, **39**, 2288), *viz.*, by heating 1 : 1-di-*p*-chlorophenylpropane-1 : 2-diol with acetic anhydride under reflux for 3 hours, gave only the diacetyl derivative of the diol.

The oxime prepared in the usual way crystallised from ethyl alcohol in slender rectangular prisms, m. p. 173—174°. Erlenmeyer *et al.* (*loc. cit.*) reported m. p. 170—171°. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl alcohol–ethyl acetate in rhombs, m. p. 168—169° (Found : Cl, 15·8. $C_{21}H_{16}O_4N_4Cl_2$ requires Cl, 15·5%).

1 : 1-*Di*-p-*chlorophenylpropan*-2-*ol*.—The above ketone (8·2 g.) in anhydrous ether (25 ml.) was added to a solution of lithium aluminium hydride (0·8 g.) in anhydrous ether (50 ml.) at such a rate as to produce gentle ebullition. The mixture was set aside for 17 hours, cooled in ice-water, and cautiously decomposed by the addition of water (2 ml.) and then concentrated hydrochloric acid. The ethereal layer was separated, washed with 2N-hydrochloric acid and water and dried (Na_2SO_4). The solvent was removed and the residue on distillation yielded a viscous liquid (7·9 g., 95%), b. p. 190—195°/1·7 mm., which slowly solidified. The *alcohol* crystallised from light petroleum (b. p. 40—60°) in monoclinic prisms, m. p. 92—93° (Found : C, 64·1; H, 4·9; Cl, 25·0. $C_{15}H_{14}OCl_2$ requires C, 64·1; H, 5·0; Cl, 25·2%). The *acetate*, prepared in the usual manner, crystallised from methyl alcohol in rhombic prismatic plates, m. p. 94—95° (Found : C, 63·1; H, 5·0. $C_{17}H_{16}O_2Cl_2$ requires C, 63·1; H, 5·0%).

Attempts to prepare 1 : 1-di-*p*-chlorophenyl-2-propyl chloride by reaction of the above alcohol with thionyl chloride in pyridine gave only unchanged starting material.

2 : 2-*Di*-p-*chlorophenylethan*-1-*ol*.—A solution of di-*p*-chlorophenylacetic acid (5 g.) in anhydrous tetrahydrofuran (30 ml.) was added to a solution of lithium aluminium hydride (2 g.) in anhydrous ether (100 ml.), and the mixture refluxed for 7 hours (cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548). The reaction mixture was cooled in ice-water and decomposed by the addition of methyl alcohol (2 ml.) and concentrated hydrochloric acid, and the product isolated as for the preceding alcohol. It was a viscous liquid (4·3 g., 91%), b. p. 170—180°/2 mm., which solidified and crystallised from light petroleum (b. p. 60—80°) in massive rhombs, m. p. 97·5—98° (Found : C, 63·0; H, 4·5. Calc. for $C_{14}H_{12}OCl_2$: C, 62·9; H, 4·5%). Some 12 months after this compound had been prepared, Grummitt, Arters, and Stearns (*ibid.*, 1951, **73**, 2548) reported a 39% yield and m. p. 98·5—99·5°. The *acetate* crystallised from methyl alcohol in aggregates of prismatic plates, m. p. 67—68° (Found : C, 62·2; H, 4·4; Cl, 22·8. $C_{16}H_{14}O_2Cl_2$ requires C, 62·2; H, 4·5; Cl, 22·9%). Attempts to prepare a phenylurethane failed.

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