# Physicochemical-Activity Relationships in Asymmetrical Analogues of Methoxychlor

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Compounds of the general formula 2-aryl-2-(*p*-methoxyphenyl)-1,1,1-trichloroethane have been prepared and tested for toxicity toward houseflies, pretreated for 1 h with 2 μg of piperonyl butoxide. The majority of the compounds synthesized were chosen with the aid of computer programs designed to ensure well-spread sets of minimally correlated physicochemical parameter values. A nonlinear two-dimensional representation was used to map the active region of physicochemical parameter space and a regression equation was obtained relating the observed toxicity to a combination of these physicochemical parameters. The equation indicates that toxicity increases with the hydrophobicity of the molecules but is decreased markedly by the introduction of bulky substituents into the ortho positions of the benzene ring and less markedly by bulky substituents in the meta and para positions. Substituents which donate electrons to the benzene ring by the "resonance" effect favor high toxicity. The equation performs well in forecasting the toxicity of further members of the series.

2,2-Bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) has found large-scale use as an insecticide for over 40 years, and its accumulation in the biosphere has recently been a subject of considerable concern.[1] Also many insect strains have developed varying degrees of resistance to DDT.[2] These factors have led to the search for compounds related to the DDT analogue, 2,2-bis(*p*-methoxyphenyl)-1,1,1-trichloroethane (methoxychlor), which are both biodegradable and active against DDT-resistant species.[2-4] An initial study in this laboratory using the method of physicochemical-activity relationships[5] (the PAR method) and the data of Metcalf and Fukuto[2] led to the forecast of high insecticidal activity for a number of DDT analogues which had not then been reported. Some of these compounds have since been made[3] and in some cases the compounds were indeed potent insecticides as forecast.

Thus, the PAR method seemed to be a valid approach for this type of compound, and it was decided to initiate a more thorough study using data obtained in our own laboratories. The prime objective of the exercise was to assess the worth of the PAR method as a means of drug design. There are few cases in the literature where the forecasts of a PAR exercise have subsequently been verified (or disproven), and it was hoped that the present exercise would provide evidence along these lines.

**Methods. Physicochemical Parameters.** In attempting to correlate any biological activity with physicochemical parameters, the choice of which parameters to use is of fundamental importance. However, the possibilities of a statistically significant yet meaningless correlation occurring by chance increase with the number of parameters tested.[6] It is therefore desirable to decide beforehand on the set of parameters to be used and to avoid testing other parameters simply because they may provide a better fit to the data. A rational and self-consistent data bank of physicochemical parameters has recently been described,[7] and this data bank was used in the present study. The parameters involved were $\pi$, the log relative partition coefficient, for substituted benzoic acids,[8] the "field" and "resonance" components,[9,10] $F$ and $R$, of Hammett's $\sigma$ for substituted benzoic acids,[11] and MR, the molar refraction,[12] due to a substituent. These parameters provide estimates of the hydrophobic, electronic, and steric effects of substituents. In an attempt to differentiate between intra- and intermolecular steric effects, MR was subdivided into $MR_o$ at the ortho position and $MR_{m,p}$ summed over the meta and para positions.

**Choice of Compounds.** The reliability of a regression analysis depends on the number of biological observations (data points) available[6] and the range and spread of physicochemical parameter values for the compounds defining these data points. Thus, the selection of compounds for synthesis is a crucial factor in determining the success of a PAR analysis. Various methods to aid the selection of compounds have been proposed[13-15] which attempt to ensure a good range and spread of physicochemical parameter values. In a particular series of compounds, however, the requirement for well-conditioned sets of parameter values must be balanced against the ease of synthesis of the compounds chosen, as the aim of a commercial PAR exercise is to arrive at the most potent congeners in a series with the minimum of effort and cost.

In the present case, physicochemical parameter values were available for 35 different substituents.[7] With ten separate positions on two benzene rings at which to substitute, the number of theoretically possible compounds is astronomical. It was therefore apparent that certain restrictions on compound type were needed at the onset of the exercise.

The first restriction imposed was that substitution on one ring only would be allowed, with the *p*-methoxy substituent as the invariant substituent on the other ring. *p*-Methoxy was chosen in the hope that this would bias the compounds toward high (and thus measurable) toxicity.[3] This left five positions at which changes could be made, but molecular models indicated that the introduction of two ortho substituents would generally lead to considerable steric strain, and it was therefore decided to limit substitution to one ortho, two meta, and one para positions. Also, certain of the substituents of the data bank are bulky and again for steric reasons, limitations on the number of ortho neighbors for such substituents were imposed, particularly where steric interactions might lead to the twisting of groups from their preferred alignment with the phenyl ring, resulting in uncertainties in the prediction of physicochemical parameter values.[16] Thus, no ortho neighbors were allowed for Ph, $NMe_2$, $NO_2$, COMe, $CO_2Me$, $CO_2Et$, and $CONH_2$ and only one ortho neighbor was allowed for OR (R = alkyl, Ph, or Ac), NHCOMe, CHO, or SMe. Finally, it was considered unlikely that more than three substituents and two different types could be introduced easily into the phenyl ring, and a restriction to this effect was also imposed.

With these restrictions the number of theoretically possible compounds was reduced dramatically to only 6746. The problem then was to choose a set of compounds for

synthesis which would provide a good range and spread of uncorrelated sets of physicochemical parameter values within the parameter space defined by these 6746 theoretical compounds. Varying views concerning the number of compounds needed have been presented,[5,6,17] but in the present case it was thought that about 20 compounds would provide sufficient degrees of freedom for a reliable regression analysis involving up to ten physicochemical parameters if square terms were included.

Three methods were used to aid the selection of compounds, each involving the calculation of the distances between compounds in the five-dimensional physicochemical parameter space. To ensure that the parameters were given equal weightings in the calculation of intercompound distances, their values were scaled to lie in equivalent ranges. This was achieved using eq 1

$$x'_{ik} = (x_{ik} - \bar{x}_i)/r_i \quad (1)$$

where $x_{ik}$ represents the $k$th value of the parameter $x_i$, $\bar{x}_i$ is the mean of the highest and lowest possible values for $x_i$ (defined by the parameter values for the 6746 theoretical compounds), and $r_i$ is the range of $x_i$ values. Using this procedure the scaled values for each parameter, $x'_{ik}$, lie in the range $\pm 0.5$.

The first method used in the selection of compounds has not been reported previously. A five-dimensional regular polyhedron was constructed in the physicochemical parameter space and the space was searched for compounds lying close to the apices of this polyhedron. If a polyhedron could be constructed such that each apex was occupied by one of the theoretical compounds, the parameter values for the resulting set of compounds would be orthogonal. In practice, it was found that the theoretical compounds were scattered rather unevenly throughout the parameter space, and considerable manipulation of the size, orientation, and position of the center of the polyhedron was needed before synthetically feasible compounds could be found sufficiently close to the apices of the polyhedron to be well-spread in the parameter space. Due to the difficulties encountered in the practical application of this method, an alternative approach was sought for guiding the selection of further compounds.

The next compounds were chosen with the aid of a recently described method[15] in which a minimum distance between compounds in the physicochemical parameter space is maintained. In the present work a distance of 0.3 units in the scaled parameter space was selected, and the synthetically feasible compound closest in space to the center of gravity of the previously selected compounds, yet greater than 0.3 units from all previous compounds, was chosen each time. This method was also used to indicate an alternative compound whenever one of the selected compounds proved too difficult to synthesize.

When 12 compounds had been synthesized, correlations between the parameters $\pi$ and $MR_{m,p}$ of 0.81 and between $F$ and $R$ of $-0.62$ were noted. Also 5 of the 12 compounds showed little or no toxicity to houseflies when tested at the highest possible doses that their solubilities allowed. Because of these factors the method of guiding compound choice was again changed in an attempt to break the correlations and to produce measurably active compounds.

As in the previous method, the further selection of compounds was restricted to those compounds further than a defined distance in the parameter space from the compounds already selected. This distance was lowered to 0.25 units in view of the satisfactory interim spread of parameter values achieved. However, two extra criteria determining compound selection were introduced.

The first extra restriction involved the determinant of the interparameter correlation matrix for the parameter values of the selected compounds. This was recalculated after the inclusion of the parameter values for each remaining acceptable compound in turn, and the remaining compounds were listed out in increasing order of their determinant value, providing that the new value for the determinant was smaller than the old value (calculated for compounds already selected). Otherwise the compounds were rejected. In this way the selection of compounds from high on the lists had the effect of lowering generally the values for the interparameter correlation coefficients.

The second restriction involved an attempt to ensure that any further compounds synthesized would have measurable toxicity to houseflies because compounds could not be used in the calculation of regression equations if they had no measurable toxicity. Toxicity data were available for 7 of the 12 selected compounds and for 6 further compouds which were either synthesized as intermediates in the preparation of the selected compounds or were available from previous work on DDT analogues in these laboratories. A tentative regression equation relating the toxicities of these compounds to their predicted physicochemical properties was derived and used to forecast the toxicity of each of the remaining acceptable compounds. In listing out remaining compounds in order of determinant value, only those compounds with a forecast toxicity greater than a defined threshold value were listed. The threshold value was set somewhat lower than the average highest test dose possible in the hope that each new compound selected for synthesis would thus have a measurable toxicity. This restriction, of course, relied on the assumption that the regression equation calculated for a limited number of data points with insufficient degrees of freedom would already have some predictive worth.

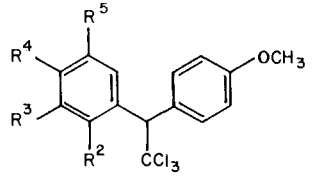
**Toxicity Measurements.** Batches of 30 female houseflies, *Musca domestica* L., were treated with 2 $\mu$g of piperonyl butoxide per insect applied topically in cellosolve solution to the ventral surface of the thorax. One hour after this treatment a range of concentrations of the test compounds in cellosolve solution was applied topically to the dorsal surface of the thorax and flies were given access to water and held for 24 h at 20 °C and 60% relative humidity before assessment of mortality. Each concentration was replicated on two to six occasions and the dose required to give 50% mortality ($LD_{50}$) of the flies in $\mu$g/fly was calculated, where possible, for each compound by probit analysis procedures described by Finney.[18] The 95% confidence intervals varied between 4 and 5% of the $LD_{50}$ for the most toxic compounds up to 15% of the $LD_{50}$ for some of the least toxic. For the regression analysis the toxicity data were transformed to a reciprocal log molar form, $A$, where $A = \log [MW/(1000 \times LD_{50})]$ and MW is the molecular weight of the compound.

## Results

Using a combination of three methods of aiding compound choice, 16 compounds were eventually synthesized and 11 of these had measurable toxicity values. Toxicity data for nine further compounds belonging to the present series were also available, and data for these 20 active compounds were therefore considered sufficient to allow a worthwhile regression analysis of the toxicities of the compounds against their predicted physicochemical properties to be attempted.

**Synthesis of Analogues.** Details of the synthesis and properties of the 25 methoxychlor analogues are given in Table I, and Table II lists the intermediates used in the

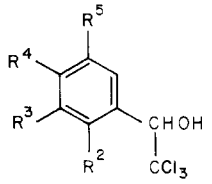
Table I. Synthesis and Properties of 2-Aryl-2-(4-methoxyphenyl)-1,1,1-trichloroethanes




| Compd | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Synthetic method[a] | | Crystn solvent | Yield, %[b] | Mp, °C | Formula | Analyses[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $(CH_3)_2CH$ | | | $(CH_3)_2CH$ | 38 | $H_2SO_4$ | $C_6H_{14}$ | 28 | 93.8-94.4 | $C_{21}H_{25}Cl_3O$ | C, H, Cl |
| 2 | | $C_2H_5O$ | $C_5H_{11}O$ | | 27 | $H_2SO_4$ | | | Oil | $C_{22}H_{27}Cl_3O_3$ | C, H, Cl |
| 3 | $CH_3$ | | $C_3H_7O$ | $CH_3$ | 26 | $H_2SO_4$ | $C_5H_{12}$ | 42 | 102.5-103.0 | $C_{20}H_{23}Cl_3O_2$ | C, H, Cl |
| 4 | F | | $CH_3O$ | | 26 | $H_2SO_4$ | $C_6H_{14}$ | 28[g] | 84.5-86.5 | $C_{16}H_{14}Cl_3FO_2$ | C, H, Cl |
| 5 | $(CH_3)_2CH$ | | $C_4H_9O$ | $(CH_3)_2CH$ | 26 | $H_2SO_4$ | | 32 | Oil | $C_{25}H_{33}Cl_3O_2$ | H, Cl; C[m] |
| 6 | | | $CH_3O$ | | | | | | 86.8-87.7[j] | $C_{16}H_{15}Cl_3O_2$ | |
| 7 | $C_2H_5O$ | | | | 28 | $H_2SO_4$ | Petr[f] | 47 | 94-96 | $C_{17}H_{17}Cl_3O_2$ | C, H |
| 8 | | | $CH_3SO_2$ | | d | | $CH_3OH$-$H_2O$ | 58[h] | 139.5-141 | $C_{16}H_{15}Cl_3O_3S$ | C, H, Cl, S |
| 9 | $C_4H_9O$ | | | | 29 | $H_2SO_4$ | Petr | 69 | 84-85 | $C_{19}H_{21}Cl_3O_2$ | C, H, Cl |
| 10 | | | $C_6H_5$ | | 39 | $H_2SO_4$ | $CH_3OH$ | 35 | 103.8-104.4 | $C_{21}H_{17}Cl_3O$ | C, H, Cl |
| 11 | $C_3H_7O$ | | | $NO_2$ | 30 | $CF_3SO_3H$ | $C_6H_6$-petr | 30 | 117-118 | $C_{18}H_{18}Cl_3NO_4$ | C, H, N |
| 12 | $CH_3O$ | | | $NO_2$ | 31 | $CF_3SO_3H$ | $C_6H_6$-petr | 38 | 162-163 | $C_{16}H_{14}Cl_3NO_4$ | C, H, N |
| 13 | | | $C_2H_5$ | | 40 | $H_2SO_4$ | $C_5H_{12}$ | 21[g] | 44.5-47.0 | $C_{17}H_{17}Cl_3O$ | C, H |
| 14 | | | Cl | | 32 | $BF_3$ | $C_5H_{12}$ | | 102.3-103.7[k] | $C_{15}H_{12}Cl_4O$ | C, H, Cl |
| 15 | | | Br | | 41 | $BF_3$ | $C_5H_{12}$ | | 103-107 | $C_{15}H_{12}BrCl_3O$ | C, H, Hal |
| 16 | | | $CH_3$ | | 33 | $H_2SO_4$ | $C_5H_{12}$ | | 80-81 | $C_{16}H_{15}Cl_3O$ | C, H, Cl |
| 17 | | | $CH_3S$ | | 26 | $H_2SO_4$ | $CH_3OH$ | 56 | 104.5-105.7 | $C_{16}H_{15}Cl_3OS$ | C, H, Cl, S |
| 18 | | $CH_3O$ | | | 34 | $BF_3$ | | 29 | Oil | $C_{16}H_{15}Cl_3O_2$ | C, H, Cl |
| 19 | Cl | | Cl | | 35 | $CF_3SO_3H$ | $C_2H_5OH$ | 24 | 93.4-95.1 | $C_{15}H_{11}Cl_5O$ | C, H, Cl |
| 20 | $CH_3O$ | | $CH_3O$ | | 26 | $H_2SO_4$ | $C_6H_6$-petr | 51 | 120-121 | $C_{17}H_{17}Cl_3O_3$ | C, H, Cl |
| 21 | $C_2H_5$ | | | | 42 | $H_2SO_4$ | | 20 | Oil | $C_{17}H_{17}Cl_3O$ | C, H; Cl[n] |
| 22 | Cl | | $C_2H_5O$ | Cl | 26 | $H_2SO_4$ | $C_6H_{14}$ | 40[g] | 88 | $C_{17}H_{15}Cl_5O_2$ | C, H, Cl |
| 23 | | | | | 36 | $CF_3SO_3H$ | $CH_3OH$ | 19 | 57.7-59.0 | $C_{15}H_{13}Cl_3O$ | C, H, Cl |
| 24 | | | $(CH_3)_2CHO$ | | 26 | $AlCl_3$[e] | | 52, 35[i] | Oil | $C_{18}H_{19}Cl_3O_2$ | H; C, Cl[o] |
| 25 | $CH_3O$ | | | | 37 | $H_2SO_4$ | $CH_3OH$ | 20 | 75.6-76.8[l] | $C_{16}H_{15}Cl_3O_2$ | C, H, Cl |

[a] Starting material and reactant are given in this column. [b] Yields were not optimized and are for purified product obtained from the last synthetic step, which is the alkylation of an aromatic substrate unless otherwise noted. Yields omitted from the table were not recorded. [c] Microanalyses for the elements indicated are within ±0.4% of the calculated values unless otherwise stated. [d] Compound obtained by oxidation of 17. [e] Aromatic reactant was phenol. [f] Petr refers to petroleum ether, bp 60-80 °C. [g] Yield of crude product. [h] Yield for oxidation of 17. [i] For condensation and isopropylation, respectively. [j] Reference 30 gives mp 92 °C. [k] Reference 3 gives mp 95 °C. [l] Reference 20 gives mp 79.5-80 °C. [m] C: calcd, 63.63; found, 64.15, 64.23. [n] Cl: calcd, 30.95; found, 30.49. [o] C: calcd, 58.75; found, 58.31, 58.28. Cl: calcd, 28.46; found, 28.00, 28.05.

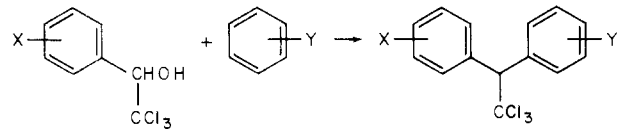
Table II. Synthesis and Properties of 1-Aryl-2,2,2-trichloroethanols



| Compd[a] | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield, % | Mp (recrystn solvent) or bp, °C (mm) | Characterized by[b] |
|---|---|---|---|---|---|---|---|
| 26 | | | $CH_3O$ | | 54 | 114-116 (0.2) | NMR, ir |
| 27 | | $C_2H_5O$ | $C_5H_{11}O$ | | 81 | 197-201 (0.35) | ir |
| 28 | $C_2H_5O$ | | | | 66 | 184-186 (20) | ir |
| 29 | $C_4H_9O$ | | | | 66 | 128-132 (0.08) | ir |
| 30 | $C_3H_7O$ | | | $NO_2$ | 70 | 105-106 ($C_6H_6$-petr)[d] | ir |
| 31 | $CH_3O$ | | | $NO_2$ | 49 | 106-107 ($C_6H_6$-petr)[d] | ir |
| 32 | | | Cl | | 65 | 118-125 (0.3) | NMR |
| 33 | | | $CH_3$ | | 76 | 93-97 (0.25) | NMR |
| 34 | | $CH_3O$ | | | 78 | 126-128 (0.1) | NMR |
| 35 | Cl | | Cl | | 62 | 114-116 (0.3) | NMR |
| 36 | | | | | 65 | 102-111 (0.5) | NMR |
| 37 | $CH_3O$ | | | | 83 | 112-114 (0.25) | NMR |
| 38 | $(CH_3)_2CH$ | | | $(CH_3)_2CH$ | 23 | 97-99 ($C_6H_{14}$) | NMR |
| 39 | | | $C_6H_5$ | | 68 | 120-121.5 ($CCl_4$) | NMR |
| 40 | | | $C_2H_5$ | | 56 | 100-104 (0.3) | NMR |
| 41 | | | Br | | c | 135-140 (8.0) | NMR |
| 42 | $C_2H_5$ | | | | 26 | 113-122 (0.4) | NMR |

[a] Compounds 26-37 were prepared from the araldehyde, chloroform, and potassium hydroxide in methyl digol,[22] compounds 38-42 from the aryl Grignard reagent and chloral.[23] [b] All compounds were estimated to be at least 93% pure. [c] Not recorded. [d] Petr refers to petroleum ether, bp 60-80 °C.

Scheme I



preparations. The crucial step in the synthesis of each analogue is the alkylation of a suitably substituted benzene with a 1-aryl-2,2,2-trichloroethanol (Scheme I). In this and previous work the reactions have usually been effected with concentrated sulfuric acid,[3,19,20] although aluminum chloride has also been used.[21] However, in common with Schneller and Smith,[21] we have found that the alkylation reactions are not successful when the electronic properties of the substituents X and Y shown in Scheme I differ greatly. For example, although sulfuric acid promotes the alkylation of chlorobenzene with 1-(4-bromophenyl)-2,-2,2-trichloroethanol (41),[22] and of benzene and toluene with 1-(4-chlorophenyl)-2,2,2-trichloroethanol (32),[19] we were unable to produce 2-(4-chlorophenyl)-2-(4-methoxyphenyl)-1,1,1-trichloroethane (14) from anisole, 32, and sulfuric acid. [Since this work was completed, Metcalf[3] reported the synthesis of compound 14 (mp 95°) by this method.] We therefore turned our attention to other potential alkylation catalysts.

Chlorosulfonic acid has been used to condense chloral with chlorobenzene to yield DDT, but when it was added to a mixture of 1-(4-chlorophenyl)-2,2,2-trichloroethanol (32) and anisole, the only product isolated was 1-(4-chlorophenyl)-2,2,2-trichloroethyl 4-methoxybenzenesulfonate. Treatment of the same organic mixture with boron trifluoride for 3 days yielded the demethylated methoxychlor analogue, 2-(4-chlorophenyl)-2-(4-hydroxyphenyl)-1,1,1-trichloroethane. Compounds 14 and 15 were therefore prepared by methylation (methyl iodide, potassium carbonate, dry acetone) of the phenolic methoxychlor analogues derived from the boron trifluoride induced condensation of phenol with carbinols 32 and 41, respectively. 1-(3-Methoxyphenyl)-2,2,2-trichloroethanol (34) also failed to alkylate anisole in the presence of sulfuric acid but condensed with anisole or phenol in the presence of boron trifluoride. Ether cleavage was avoided when carbon tetrachloride was used as a reaction solvent, and 18 was therefore prepared directly from 34 and anisole.

Trifluoromethanesulfonic acid was later found to promote alkylation of activated aromatic substrates with deactivated carbinols in hours rather than days, without causing the cleavage of methyl ethers often associated with the use of boron trifluoride. Being a much stronger acid than sulfuric acid, it is able to generate carbonium ions from even very deactivated carbinols without attacking any activated aromatic compounds present. It was used in the preparations of compounds 11, 12, 19, and 23.

1-Aryl-2,2,2-trichloroethanols were prepared from araldehydes, chloroform, and potassium hydroxide in methyl digol,[22] or from arylmagnesium bromides and anhydrous chloral.[23]

2-Bromo-1,4-diisopropylbenzene, the intermediate for compounds 1 and 5, was prepared by bromination of 1,-4-diisopropylbenzene using the procedure of Fuson and Corse.[24] For compound 5 the derived Grignard reagent was converted via the *tert*-butyl ether and phenol, using the method of Frisell and Lawesson,[25] to the *n*-butyl ether (*n*-butyl iodide, sodium ethoxide, and ethanol) in overall yield of 48%.

3-Ethoxy-4-pentyloxybenzaldehyde required for compound 2 was prepared by the method of Profft and Steinke.[26]

The thiomethyl ether 17 was oxidized with glacial acetic acid and hydrogen peroxide to provide the sulfoxide 8.

5-Nitro-2-propoxybenzaldehyde for compound 11 was prepared in 88% yield by heating the sodium salt of 5-nitrosalicylaldehyde[27] in dimethylformamide with 1-iodopropane, and 2-methoxy-5-nitrobenzaldehyde[28] for compound 12 was obtained by nitrating *o*-anisaldehyde. Compound 11 could not be prepared by nitration (cupric nitrate in acetic anhydride) of 2-(4-methoxyphenyl)-2-(2-propoxyphenyl)-1,1,1-trichloroethane which yielded instead 2-(4-methoxy-3-nitrophenyl)-2-(2-propoxy-

Table III. Predicted Physicochemical Properties and Measured Toxicities for the Compounds in Table I

| Compd | Predicted physicochemical properties[a] | | | | | $LD_{50}$[d] | Obsd toxicity[e] | Forecast toxicity[f] | Difference |
|---|---|---|---|---|---|---|---|---|---|
| | $\pi$ | $F$ | $R$ | $MR_o$[b] | $MR_{m,p}$[c] | | | | |
| 1 | 3.10 | −0.16 | −0.14 | 14.0 | 14.0 | 5% at 66 | <−2.218 | −1.625 | |
| 2 | 2.59 | 0.78 | −0.73 | 0 | 36.6 | 12.35 | −1.442 | −1.104 | −0.338 |
| 3 | 2.33 | 0.25 | −0.63 | 4.7 | 20.6 | 0.403 | −0.001 | −0.565 | 0.564 |
| 4 | −0.03 | 1.29 | −0.79 | −0.4 | 6.5 | 0.116 | 0.497 | 0.923 | −0.426 |
| 5 | 4.57 | 0.25 | −0.69 | 14.0 | 34.7 | 0% at 72 | <−2.184 | −1.829 | |
| 6 | −0.03 | 0.41 | −0.50 | 0 | 6.5 | 0.123 | 0.449 | −0.024 | 0.473 |
| 7 | 0.17 | 0.45 | −0.38 | 11.3 | 0 | 13.47 | −1.573 | −2.359 | 0.786 |
| 8 | −1.20 | 0.90 | 0.22 | 0 | 12.5 | 0% at 45 | <−2.058 | −4.838 | |
| 9 | 1.17 | 0.51 | −0.48 | 20.7 | 0 | 11.94 | −1.488 | −1.406 | −0.082 |
| 10 | 1.74 | 0.14 | −0.09 | 0 | 24.3 | 115.0 | −2.467 | −1.779 | −0.688 |
| 11 | 0.78 | 1.55 | −0.34 | 15.9 | 6.0 | 5% at 45 | <−2.032 | −3.315 | |
| 12 | −0.22 | 1.61 | −0.38 | 6.5 | 6.0 | 8% at 15 | <−1.584 | −2.913 | |
| 13 | 1.10 | −0.07 | −0.11 | 0 | 9.4 | 0.093 | 0.568 | 0.106 | 0.462 |
| 14 | 0.73 | 0.69 | −0.16 | 0 | 4.8 | 0.155 | 0.354 | 0.543 | −0.189 |
| 15 | 1.19 | 0.73 | −0.18 | 0 | 7.6 | 0.126 | 0.496 | 0.767 | −0.271 |
| 16 | 0.60 | −0.05 | −0.14 | 0 | 4.7 | 0.172 | 0.283 | 0.312 | −0.029 |
| 17 | 0.87 | 0.33 | −0.19 | 0 | 13.0 | 0.126 | 0.458 | −0.707 | 1.165 |
| 18 | 0.12 | 0.41 | −0.17 | 0 | 6.5 | 3.36 | −0.987 | −0.674 | −0.313 |
| 19 | 1.49 | 1.55 | −0.30 | 4.8 | 4.8 | 0.300 | 0.108 | 0.223 | −0.115 |
| 20 | −0.36 | 0.93 | −0.93 | 6.5 | 6.5 | 66.0 | −2.244 | −1.758 | −0.486 |
| 21 | 1.39 | −0.08 | −0.10 | 9.4 | 0 | 7.82 | −1.356 | −0.853 | −0.503 |
| 22 | 2.00 | 1.90 | −0.64 | 4.8 | 16.1 | 0.738 | −0.236 | −0.225 | −0.011 |
| 23 | 0 | 0 | 0 | 0 | 0 | 0.588 | −0.270 | −0.085 | −0.185 |
| 24 | 0.85 | 0.49 | −0.72 | 0 | 16.0 | 0.111 | 0.528 | 0.107 | 0.421 |
| 25 | −0.33 | 0.52 | −0.43 | 6.5 | 0 | 39.0 | −2.052 | −1.819 | −0.233 |

[a] Properties calculated from values given in ref 7. [b] Molar refraction due to the ortho substituent. [c] Molar refraction summed over the meta and para positions. [d] Dose in μg/fly to kill 50% of houseflies pretreated (1 h) with 2 μg of piperonyl butoxide or percentage kill at highest dose tested. [e] Log [mol wt/(1000 × $LD_{50}$)]. [f] Forecast from eq 2.

Table IV. Interparameter Correlations for the 20 Active Compounds

| | $\pi$ | $F$ | $R$ | $MR_o$ |
|---|---|---|---|---|
| $F$ | 0.129 | | | |
| $R$ | −0.017 | −0.553 | | |
| $MR_o$ | 0.026 | 0.061 | −0.172 | |
| $MR_{m,p}$ | 0.703 | 0.126 | −0.325 | −0.396 |

phenyl)-1,1,1-trichloroethane and 2-(4-methoxy-3-nitrophenyl)-2-(5-nitro-2-propoxyphenyl)-1,1,1-trichloroethane. Both compounds were characterized by NMR and microanalysis (C, H, N, Cl).

2-Ethylbenzaldehyde required for compound **21** was prepared from 2-ethylaniline via the diazonium salt using the method of Case.[29]

Compound **24** was prepared from 2-(4-methoxyphenyl)-2-(4-hydroxyphenyl)-1,1,1-trichloroethane[30] and 2-iodopropane in refluxing ethanol treated with sodium ethoxide added slowly so that excess base, which causes dehydrochlorination of the product, was avoided. Isopropylation of the phenolic analogue with 2-iodopropane and potassium carbonate in dry acetone was not successful, and all attempts to alkylate isopropoxybenzene with 1-(4-methoxyphenyl)-2,2,2-trichloroethanol (**26**) resulted in removal of the isopropyl group.

**Predicted Physicochemical Properties of the Compounds.** The predicted physicochemical properties and the observed toxicities of the 25 DDT analogues are given in Table III.

An interparameter correlation matrix for the 20 active compounds is shown in Table IV. The high correlations between $\pi$ and $MR_{m,p}$ and $F$ and $R$ apparent after 13 compounds had been made have been lowered but are still higher than would have been hoped for. This demonstrates that throughout the choice of compounds for synthesis it was necessary to comprise between ease of synthesis and the desirability of space-filling and minimizing interparameter correlations. It was often found that initial choices of compounds which were good for the latter proved impracticable when the syntheses were actually attempted. Other compounds were chosen instead which were not so desirable from the physicochemical parameter point of view but were easier to synthesize, and this is reflected in the bias toward certain substituent groupings such as alkoxy and alkyl. The prolific, but to some extent unavoidable, use of substituents belonging to such homologous series is largely responsible for the high interparameter correlation coefficients.

The range and spread of physicochemical parameter values for the 25 compounds synthesized compared with the total ranges of values for all 6746 theoretically possible compounds is depicted in Figure 1. In this diagram each vertical line represents a scaled parameter axis (±0.5 unit) and the points on the lines represent the positions of the compounds, numbered according to Table I, on each axis. The compounds selected for synthesis with the aid of the computer programs are shown to the left of each axis and the other remaining compounds to the right. The better range and spread for the former compounds are very marked in Figure 1. This may also be seen in Figure 2 which is a nonlinear two-dimensional representation of the distances between compounds in the five-dimensional parameter space. Figure 2 was produced using a computer program based on a method proposed by Sammon[31] involving mapping points in a multidimensional space to points in two dimensions such that the mutual distances between points are maintained as far as possible. In this representation the compounds selected for synthesis with the aid of the computer are seen to be well separated, whereas the other compounds form a closely spaced cluster.

Kowalski and Bender[32] have suggested that it should be possible to identify regions of similar biological activity in such nonlinear projections, provided the parameters chosen to define the dimensions are determinates of biological activity. In Figure 2 contours have been drawn around groups of compounds belonging to four arbitrary activity categories ($A > 0$, $0 > A > -1$, $-1 > A > -2$, $-2 > A$) thereby revealing that the position of each compound

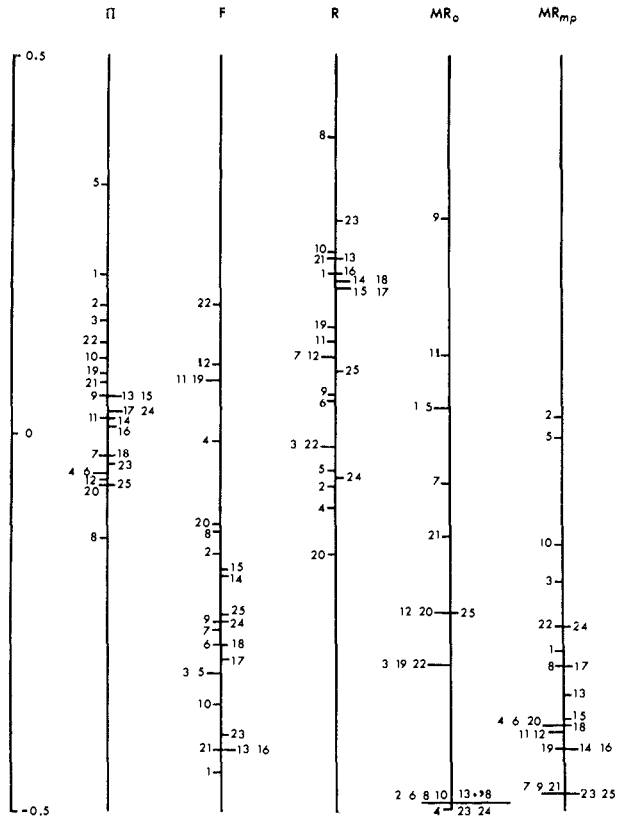



Figure 1. Distribution of predicted physicochemical parameter values for the 25 methoxychlor analogues. The range of each vertical parameter axis is equal to the total range possible for all theoretical compounds (see text). The values for the compounds are scaled within these ranges using eq 1. Compounds selected with the aid of computer programs are shown to the left of each axis and other compounds to the right. It may be seen that the computer-selected compounds are more widely spaced along each axis.

in the five-dimensional parameter space, as represented in this plot, does define its general order of activity reasonably well. This method of representing the data thus provides evidence of the dependence of toxicity on physicochemical parameters in this series of compounds. Though helpful in visualizing the data, the method is less useful than regression analysis, however, as it does not readily identify which parameters are the most relevant to toxicity.

**Regression Equation.** Regression equations were sought relating the biological activity $A$ to combinations of the predicted physicochemical parameters $\pi$, $F$, $R$, $MR_o$, $MR_{m,p}$ and the squares of $\pi$, $MR_o$, and $MR_{m,p}$. All possible combinations of parameters were considered except that squared terms were only allowed in equations containing the corresponding linear term.[5] This gave a total of 215 possible equations and the problem arose of choosing the best equation for forecasting the toxicity of further members of the series.

Only those parameters thought to be likely determinates of activity have been included in the analysis and it is therefore clear that, in order to avoid bias, the equation of choice should be the most statistically significant equation. Unfortunately, this criterion does not necessarily uniquely identify the best equation by the standard statistical tests applied in multiple regression analysis, since these tests do not strictly apply to the testing of multiple hypotheses, particularly when equations containing different numbers of parameters are involved. Also

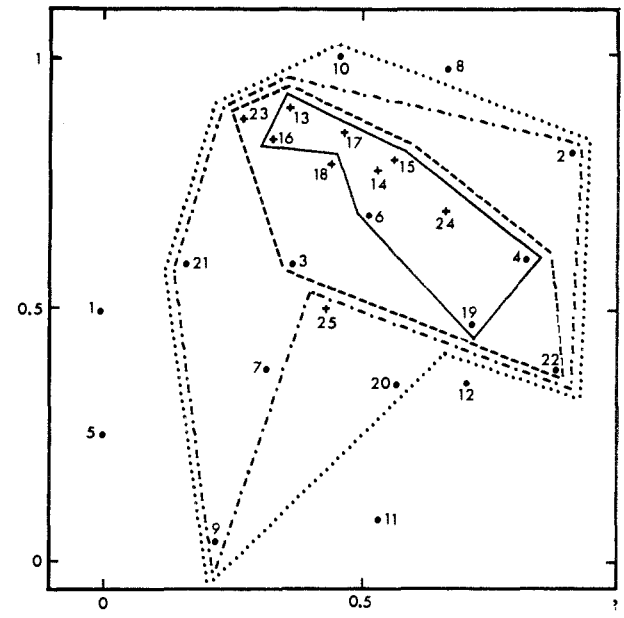



Figure 2. Two-dimensional representation of the distances between compounds in five-dimensional parameter space (see text): (·) compounds chosen with the aid of computer programs; (+) other compounds. The contour lines drawn enclose areas of similar measured toxicity: (——) $A > 0$; (- - -) $-1 < A < 0$; (- · - ·) $-2 < A - 1$; (· · ·) $A < -2$.

different authors seem to have different views on the relative importance of the various statistical criteria.[5,17,33] Bearing in mind these limitations, the best equation in the present study was chosen as eq 2.

$$A = 1.51\ (\pm 0.29)\ \pi - 2.66\ (\pm 0.67)\ R - 0.436\ (\pm 0.075)\ MR_o + 0.0109\ (\pm 0.0035)\ MR_o^2 - 0.188\ (\pm 0.033)\ MR_{m,p} - 0.0851 \quad (2)$$

$$n = 20,\ r = 0.889,\ F_{5,14} = 10.56$$

The standard errors for each regression coefficient are given in the brackets, $n$ is the number of compounds used to derive the regression, $r$ is the multiple correlation coefficient, and $F_{5,14}$ is the variance ratio with 5 and 14 degrees of freedom. The $F$ statistic for this equation is significant at better than the 0.1% level when tested conventionally, and the individual $t$ statistics for the coefficients of the equation are all significant at better than the 1% level. Thus, this equation appears to be significant and with a multiple correlation coefficient of 0.889 is the best five-term equation and explains 79% of the variation in the biological data. However, other statistically significant equations with different numbers of terms also exist and the choice of eq 2 as the best equation needs to be justified.

The best four-term equation is in $\pi$, $R$, $MR_o$, and $MR_{m,p}$ and the statistics for this equation are $n = 20$, $r = 0.805$, and $F_{4,15} = 6.91$. Clearly this equation is also significant, but the additional term in $MR_o^2$ in eq 2 has a $t$ statistic which is significant at the 1% level. The best six-term equation is in $\pi$, $R$, $MR_o$, $MR_o^2$, $MR_{m,p}$, and $MR_{m,p}^2$ with statistics $n = 20$, $r = 0.904$, and $F_{6,13} = 9.71$. Though this equation inevitably has a slightly better $r$ value than has eq 2, the $t$ statistic for the coefficient of $MR_{m,p}^2$ is only significant at the 20% level ($t = 1.391$). In fact, all possible six-term equations contain at least one coefficient with a similarly poor $t$ statistic. On balance, therefore, eq 2 is considered to be the most statistically significant equation and is the equation of choice for predicting the activity of

Table V. Data for Nine Compounds Prepared in Metcalf's Laboratory[a]

| Substituents | | | | Predicted physicochemical properties | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $R^2$ | $R^3$ | $R^4$ | $R^5$ | $\pi$ | $F$ | $R$ | $MR_o$ | $MR_{m,p}$ | $LD_{50}$[b] | Obsd toxicity[c] | Forecast toxicity[d] | Difference |
| | | F | | 0.15 | 0.71 | −0.34 | 0 | −0.4 | 11.5 | −0.236 | 1.121 | −1.357 |
| | | $(CH_3)_2CH$ | | 1.43 | −0.07 | −0.11 | 0 | 14.0 | 61.5 | −0.934 | −0.259 | −0.675 |
| | | $C_2H_5O$ | | 0.47 | 0.36 | −0.44 | 0 | 11.3 | 3.7 | 0.289 | −0.329 | 0.618 |
| | | $C_3H_7O$ | | 0.97 | 0.37 | −0.46 | 0 | 15.9 | 8.5 | −0.056 | −0.383 | 0.327 |
| | | $C_4H_9O$ | | 1.47 | 0.41 | −0.55 | 0 | 20.7 | 20.5 | −0.422 | −0.289 | −0.133 |
| | | $C_5H_{11}O$ | | 1.97 | 0.42 | −0.58 | 0 | 25.3 | 26 | −0.510 | −0.317 | −0.193 |
| | | $C_6H_{13}O$ | | 2.47[e] | 0.42 | −0.60 | 0 | 29.9 | 72.5 | −0.940 | −0.371 | −0.569 |
| | | $C_8H_{17}O$ | | 3.47[e] | 0.43 | −0.64 | 0 | 39.1 | >500 | <−1.750 | −0.480 | |
| Cl | | $CH_3O$ | | 0.73 | 1.27 | −0.64 | 4.8 | 6.5 | 0.160[f] | 0.376 | −0.344 | 0.720 |

[a] Toxicity data from ref 2, 3, and 34. [b] Dose in μg/g of flies to kill 50% of houseflies pretreated with piperonyl butoxide (50 μg/g). [c] Log [mol wt/(50 × $LD_{50}$)], i.e., assuming 20 flies/g. [d] Forecast from eq 2. [e] Properties estimated by extrapolation of values for lower OR substituents. [f] Data from ref 2 expressed as μg/fly.

further members of this series.

**Accuracy of Predictions.** The forecast activities for the methoxychlor analogues obtained using eq 2 are given in Table III. In individual cases the difference between observed and forecast activities is large, e.g., for compound **16** more than a tenfold difference in $LD_{50}$ values. However, the accuracy of the forecasts must be compared with the range of $LD_{50}$ values measured for all the compounds which is from 0.093 to 66 μg/fly, i.e., almost a 1000-fold variation. Expressed in relation to this total range, the accuracy of the forecasts is more acceptable. Also, eq 2 forecasts inactivity for three of the five compounds which are inactive and low activity for the other two.

The equation also forecasts that no great increase in potency for analogues of this series should be expected because to achieve this would necessitate increasing the $\pi$ value for the molecule without increasing substituent bulk and this is not easy.

**Testing the Equation.** Having established eq 2 as the equation of choice, the next stage of the PAR analysis should be to ascertain the forecasting ability of the equation by synthesizing and testing more compounds in the series. Unfortunately, this testing stage could not be fully carried out as work on the series was discontinued due to the commercial considerations involved. Three further compounds were still in the course of preparation when eq 2 was derived, but they were forecast to have only low activities. In fact, all three turned out to be inactive and so did not provide a worthwhile test of the forecasting power of the equation.

A number of methoxychlor analogues have been prepared by Metcalf and co-workers[2,3,34] and Table V gives details of nine of these which are members of the present series but were not, in fact, tested in the present work. Metcalf's results on these compounds are therefore available to test the forecasting ability of eq 2 and measured and forecast toxicity values are given in Table V. A statistical procedure has been devised to test the forecasting power of eq 2 for the eight compounds with a measured toxicity value.

Neither Metcalf's observations on the eight compounds nor our forecasts of their toxicities are perfectly accurate. Our own and Metcalf's observations may each be regarded as a set of observations from a larger and more general population. The question then arises whether the two populations are the same. If the populations are suitably described in terms of the parameters $\pi$, $R$, $MR_o$, $MR_o^2$, and $MR_{m,p}$ then they should be the same if eq 2 is to provide adequate forecasts, and this is the basis of the statistical test. It is assumed initially that Metcalf's observations and our own are distributed normally with the same variance and means which are the same linear function of the parameters. In other words, it is assumed that the two populations are identical, and this is the hypothesis to be tested. If the statistical calculation shows that this hypothesis should be rejected, one would also have to conclude that the forecasts provided by eq 2 were inadequate.

In order to carry out this calculation a weighted sums of squares and products of the differences between observations and forecasts for Metcalf's compounds have been constructed so that, given the above hypothesis, it is distributed like $\chi^2$ and is independent of the sums of squares of residuals for the regression eq 2. Thus, given the hypothesis, the ratio of this weighted sums of squares of differences to the sums of squares of residuals for the regression eq 2 should be distributed according to the $F$ distribution with 8 and 14 degrees of freedom. When the calculation was carried out, the value of this ratio was 1.292 which was not significant. Hence, there is no reason to reject the forecasts provided by eq 2 for Metcalf's eight compounds or, in nonstatistical language, eq 2 is as good as one would expect bearing in mind the experimental errors in the observations. It is interesting that, due to the positive dependence of activity on $\pi$ and the negative dependence on bulk in the meta and para positions, $MR_{m,p}$, all the *p*-alkoxy-substituted derivatives are forecast to have approximately the same activity. A weakness of the equation is thus apparent in this case, and this may be a reflection of the high correlation between $\pi$ and $MR_{m,p}$ for the data used in deriving it.

**Mechanistic Interpretation.** Holan[35] has described a mechanistic model for the biological activity of DDT-like insecticides. In this model the insecticide fits into a receptor on the insect nerve membrane which is a pore selective for the passage of sodium ions, and a leakage of sodium ions is thereby induced through the membrane. The pore is assumed to be wedge-shaped to accommodate the DDT-like molecule, with the aliphatic portion, the "apex", fitting down into the lipid region of the membrane and the benzenoid part, the "base", occupying the top of the wedge (the thick end) in the outer protein part of the membrane. The steric requirements of Holan's receptor are such that while the apex of the molecule must be of the correct molecular dimensions with very little variation in size permissible, para substituents on the base of the molecule may vary considerably in size without completely abolishing activity.

The whole of the receptor is thought to be hydrophobic in nature but a type of charge-transfer interaction with the $\pi$-electron systems of the benzene rings acting as donors is also envisaged. The charge-transfer interaction is supported by the high activity observed in DDT analogues having electron-donating substituents and by the inference from toxicity data that the amount of drug–receptor complex formed is inversely dependent on temperature.[36,37]

The mechanistic interpretation of eq 2 is fully compatible with the Holan model. The positive dependence of activity on $\pi$ provides further evidence for the hydrophobic nature of the receptor site, and the negative dependence on $R$ indicates that electron-donating substituents are desirable. However, no dependence of activity on $F$ was found, and this suggests that the enhancement of the $\pi$-electron density in the benzene ring is the important electronic effect. The high activity of DDT itself may now be reconciled with the strongly electron-withdrawing nature of this $p$-Cl substituent, for although the $F$ value for Cl is higher, the $R$ value is negative and thus Cl is electron donating by the resonance effect. The positive dependence of activity on $\pi$ is offset by the negative coefficients for the bulk parameters $MR_o$ and $MR_{m,p}$ as mentioned previously. However, the relative magnitude of the coefficients for $\pi$ and $MR_{m,p}$ allows for quite large substituents in the meta and para positions without destroying activity, in agreement with the Holan model. Para substitution is favored due to the generally higher resonance effects for para substituents compared to meta.

The dependence of activity on bulk in the ortho position, $MR_o$, assumes a parabolic form with a negative coefficient for the linear term and a positive coefficient for the square. This indicates that activity falls off markedly with the size of the ortho substituent but reaches a minimum value and would, in fact, begin to improve if sufficiently large substituents were used (other factors being equal). However, the worst value of $MR_o$ for activity may be calculated from eq 2 as 20.1 and since the range of $MR_o$ values used to derive the equation is from −0.4 to 20.7, only data on the falling half of the parabola are available. It therefore seems equally likely that the true dependence of activity on $MR_o$ is not parabolic but initially falls sharply and then asymptotes at high values and Hyde[38] has proposed the use of an alternative nonlinear function to represent this type of dependency.

One interpretation of this behavior would be to postulate that the presence of a bulky substituent in the ortho position prevents the molecule from assuming its optimum conformation for interaction with the receptor site. However, models show that only one conformation is sterically possible for this series of compounds and that this conformation can accommodate quite large substituents in one ortho position without steric strain. An alternative explanation for the observed behavior must therefore be sought. The Holan model postulates that the steric requirements at the apex of the molecule are rigid, and substituents in the ortho position are quite close to the apex of the molecule. It therefore seems possible that large ortho substituents prevent the fit of the apex of the molecule into the lipid interior of the membrane leading to a poorer association of this part of the molecule with the receptor. However, the less rigid steric requirements at the base of the molecule would still allow a fit of the molecule to this part of the receptor and the formation of the drug–receptor complex. Thus, the dependence of activity on $MR_o$ may also be interpreted on the basis of the Holan receptor model.

## Conclusion

The aim of the present work was to test the practical worth of the PAR method as a means of forecasting the biological activity of unknown compounds in a given series. Evidence obtained for one series of compounds cannot, of course, give an unequivocal answer, but in this case a statistically significant equation was obtained, and using this equation the activities of other members of the series were forecast sufficiently well in that the hypothesis that the same function applies to all members of the series could not be rejected. The successful application of the method here was largely due to the care taken in choosing compounds for synthesis to ensure well-spread sets of minimally correlated physiochemical parameter values. A similar PAR analysis of DDT analogues performed in Metcalf's laboratory[34] suffers from the poor spread of and correlations between physicochemical parameter values, and the equations generated have limited predictive worth. A valid criticism of the methods used here might be that the insistence on providing adequate sets of parameter values resulted in more difficult syntheses than are normally involved in the elaboration of a series of compounds. The compromise between ease of synthesis and the requirement for well-spread, uncorrelated sets of parameter values was probably biased too far toward the latter in this case, and, in the routine application of the PAR method, ease of synthesis would normally be given greater priority.

In performing this analysis no mechanistic model was required other than the basic hypothesis of the PAR method. A standard set of physicochemical parameters was used and the regression equation was chosen on purely statistical arguments. It was encouraging that the regression equation obtained agreed in detail with the Holan receptor-fit model,[35] but this was not a condition for acceptance of the validity of the equation and the reliability of its forecasts. In fact, the equation forecasts that no great increase in potency for DDT analogues of the defined series should be possible. This is in some respects a negative answer, but it has been pointed out that such a result can be very valuable, particularly with respect to commercial considerations, as it provides a convincing reason for stopping work on a particular series unless an alternative hypothesis can be found.[5] The results presented here, and obtained from other series of compounds in our laboratories,[39] suggest that the PAR method can be a valuable aid to the drug design scientist in the search for more potent drugs and in the understanding of some of the factors responsible for drug efficacy.

## Experimental Section

All methoxychlor analogues were purified by crystallization or chromatography or both, and their structures were supported by NMR. Each had a purity, estimated from NMR spectra and GLC or TLC, of >97%. Column chromatography was carried out using alumina, type O (Laporte Industries Ltd.), silica gel M.F.C. 100–200 mesh (Hopkins and Williams), or silica gel grade II (Woelm) eluted with hexane, hexane–benzene, hexane–ether, or benzene. Reactions yielding methoxychlor analogues were monitored by TLC on precoated 0.25 mm thick silica gel F254 plates (Merck) or by GLC on a Pye series 104 gas chromatograph fitted with a flame ionization detector and a 5 ft × $^1/_8$ in. column of 5% OV101 on Gas Chrom Q. Melting points are uncorrected. A Varian Associates HA-100 or T-60 instrument was used to record NMR spectra. Microanalyses are within ±0.4% of the calculated values unless otherwise noted.

**1-(4-Methoxyphenyl)-2,2,2-trichloroethanol (26).** A solution of 24.0 g (0.43 mol) of potassium hydroxide in 150 ml of methyl digol was added during 6 h to 49.0 g (0.36 mol) of 4-methoxybenzaldehyde in 200 ml of chloroform kept at 3–5 °C. The mixture was stirred at room temperature for 12 h, poured into 300 ml of ice-cold water, and separated. The chloroform layer was washed successively with water, 1 N HCl, water, 5% $NaHSO_3$, and water, dried over $MgSO_4$, and evaporated to leave a light brown clear oil. It was distilled at 114–116° (0.20 Torr) to yield 48.9 g (54%) of clear viscous oil which later solidified.

The 1-aryl-2,2,2-trichloroethanols **27–38** were prepared similarly and, after distillation or crystallization, they were characterized by ir or NMR. All were estimated to be better than 93% pure.

**1-(4-Biphenylyl)-2,2,2-trichloroethanol (39).** Dry chloral (14.9 g, 0.101 mol) in 20 ml of dry THF was added during 1 h

to a Grignard reagent solution prepared from 23.3 g (0.100 mol) of 4-bromobiphenyl in 110 ml of dry THF and 2.5 g (0.103 mol) of dry magnesium turnings at 50–60°. The mixture was kept at 40° during addition of the chloral (1 h), stored overnight in the refrigerator, and poured into 200 g of ice and 40 ml of concentrated HCl. The organic material was extracted with ether which was washed successively with water, 5% $NaHCO_3$, and brine. After drying ($MgSO_4$) and evaporating the solvent, the residue was crystallized from $CCl_4$ to give 16.9 g of white crystals, mp 120–121.5°. A second crop (3.5 g) brought the total yield to 68%. Compounds **40–42** were prepared similarly.

**2-(2,5-Diisopropylphenyl)-2-(4-methoxyphenyl)-1,1,1-trichloroethane** (1). A vigorously stirred suspension, prepared by cooling a solution of 6.2 g (0.020 mol) of 1-(2,5-diisopropylphenyl)-2,2,2-trichloroethanol (**38**) in 4.3 g (0.040 mol) of anisole, was treated with cooling (20–30°) with 10 ml of concentrated $H_2SO_4$ added during 10 min. After an additional 20 min the mixture was quenched in 100 g of ice and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residual oil was chromatographed on 300 g of grade II silica eluted with solvents graded from hexane to 3% benzene in hexane, the column being monitored by GLC at 210°. The first material eluted was crystallized from hexane to yield 1.3 g (16%) of white crystals, mp 63.5–65.0°, identified by NMR as the 2-methoxyphenyl analogue of 1. Anal. ($C_{21}H_{25}Cl_3O$) C, H, Cl.

Compound 1 was eluted later and crystallized from hexane as 2.2 g (28%) of white crystals, mp 93.8–94.4°. Anal. ($C_{21}H_{25}Cl_3O$) C, H, Cl.

All other alkylation reactions using sulfuric acid were conducted similarly, although no other 2-methoxyphenyl analogues of the desired compounds were isolated.

**2-(4-Methoxyphenyl)-2-(5-nitro-2-propoxyphenyl)-1,1,1-trichloroethane** (11). Trifluoromethanesulfonic acid (10 ml) was added dropwise during 10 min to a stirred mixture of 5.4 g (0.017 mol) of 1-(5-nitro-2-propoxyphenyl)-2,2,2-trichloroethanol (**30**) and 2.0 g (0.019 mol) of anisole cooled to 0°. The resulting thick red gel was kept overnight at 4°, added to 40 ml of ice-cold water, and extracted with ether. The ether was washed with water, dried ($MgSO_4$), and evaporated to leave 8.0 g of oil which was chromatographed on 200 g of grade I alumina eluted with benzene. The isolated product was recrystallized twice from benzene–petroleum ether to afford 2.05 g (30%) of the desired product as white crystals, mp 117–118°. Anal. ($C_{18}H_{18}Cl_3NO_4$) C, H, N.

Compounds **12**, **19**, and **23** were prepared similarly. The 2-methoxyphenyl analogue of **23** was also isolated as white crystals, mp 91–92°. Anal. ($C_{15}H_{13}Cl_3O$) C, H, Cl.

**2-(3-Methoxyphenyl)-2-(4-methoxyphenyl)-1,1,1-trichloroethane** (18). Anisole (2.32 g, 0.022 mol) and 5.12 g (0.020 mol) of 1-(3-methoxyphenyl)-2,2,2-trichloroethanol (**34**) in 25 ml of dry $CCl_4$ was cooled to 5°, saturated with $BF_3$, and stirred for 7 days with daily additions of $BF_3$. The solution was quenched in water and extracted with ether. The ether was washed successively with water, 2 N $Na_2CO_3$, water, and brine, dried ($MgSO_4$), and evaporated. Chromatography of the isolated oil on 200 g of grade II silica eluted with 1% ether in hexane yielded 2.0 g (29%) of viscous oil. Anal. ($C_{16}H_{15}Cl_3O_2$) C, H, Cl.

When this preparation was conducted without solvent, the products were mostly phenolic. They were methylated (MeI, $K_2CO_3$, acetone) to yield a mixture from which 18 was isolated by chromatography.

Compounds 14 and 15 were prepared by the $BF_3$ catalyzed reaction, in the absence of solvent, of phenol with **32** and **41**, respectively, followed by methylation of the products.

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