

67. *Chemical Investigations of the Insecticide " DDT " and its Analogues.
Part II. Symmetrical Analogues.*

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A number of 4:4'-disubstituted derivatives of 1:1:1-trichloro-2:2-diphenylethane (" DT ") have been prepared, by standard methods, for insecticidal tests, including in particular a series of dialkyloxy derivatives.

Physiological evidence indicates that both steric and polar factors must be considered in any attempts to correlate insecticidal activity with chemical structure, whilst simple physico-chemical analogies between paraffinic character and lipoid penetrability do not seem to be cogent.

WHEN the outstanding insecticidal properties of DDT were first realised it was felt that, though the use as insecticides of compounds of the general type $RR'CH \cdot CX_3$ (where R, R' = substituted aryl, or similar group

and X = a halogen) had been patented by Messrs. J. R. Geigy of Basle (B.P. 547,871 and 547,874), the one technical product DDT ($R = R' = p\text{-ClC}_6\text{H}_4$; $X = \text{Cl}$) might not necessarily be the most effective agent for all purposes, and perhaps not the compound of this series which has the highest intrinsic insecticidal activity. Though it is easily made on the large scale, DDT has the drawback that its solubility in the hydrocarbon oils normally used in insecticidal sprays is only about 5%. This may be indicative of a low lipid solubility (a cogent factor in any contact poison) but, more significantly, it is a technical disadvantage, since it is often impracticable to compound spray mixtures from solid DDT and available oils in insect-infested areas, with the consequence that bulk transport of liquid sprays, or concentrates, has to be undertaken. Bearing in mind the technological advantages of a more soluble substitute for DDT, a series of analogues was synthesised for testing in this country against various insect pests. Though the valuable review by Lauger, Martin, and Muller (*Helv. Chim. Acta*, 1944, 27, 892), which became available when this work was nearly completed, has now made clear the general conceptions of the Swiss patentees, together with much valuable experimental evidence, it is considered that the systematic study of these substances will help to disclose further possible connections between insecticidal potency and chemical structure. Through the courtesy of Dr. J. R. Busvine, we have been able to indicate some points of interest which have already emerged from this work.

A few analogues of DDT were prepared by Zeidler and his colleagues in 1874, and between this date and 1940 certain other compounds of the "DT series" were described by other workers (see References 1—14 later) For systematic physiological testing, however, it has been necessary to prepare some known compounds, together with many new ones. Tables I and II summarise data, apart from preparative details and records of

TABLE I.

Alkyl, Halogen, etc., Derivatives of 1 : 1 : 1-Trichloro-2 : 2-diphenylethane ("DT").

Compound.	M. p. of $R_2\text{CH}\cdot\text{CCl}_3$.	M. p. of $R_2\text{C}\cdot\text{CCl}_2$.	Median lethal concn. (%) of $R_2\text{CH}\cdot\text{CCl}_3$ (white oil spray).	
			Lice.	Bugs.
DT	65°	80°	7.5	20
4 : 4'-Dimethyl-DT	92	87	1.7	3.6
4 : 4'-Diethyl-DT	ca. —20	—	5	5
2 : 4' : 2' : 4'-Tetramethyl-DT	109	—	W (as 5% in oil)	
4 : 4'-Difluoro-DT	31	—	Moderate (in oil)	
4 : 4'-Dichloro-DT	109	89	0.3	0.53
4 : 4'-Dibromo-DT	141	121	—	—
4 : 4'-Di-(ω -bromomethyl)-DT	144	—	—	—
(?) 4 : 4'-Dichloro-2 : 2'-dimethyl-DT	107	—	Inert	
(?) 2 : 2'-Dichloro-5 : 5'-dimethyl-DT	142	—	W	
Trichlorodi- α -naphthylethane	158	—	Inert	
Trichlorodi-(4-chloronaphthyl)ethane	223	190	W	
Trichlorodi-(4-bromonaphthyl)ethane	219	224	Inert	

(W = Weakly insecticidal (ca. 10% kill) when tested as undiluted dust. Inert = Not insecticidal as undiluted dust.)

TABLE II.

Alkylloxy, etc., Derivatives of 1 : 1 : 1-Trichloro-2 : 2-diphenylethane ("DT").

DT compound.	M. p. of $R_2\text{CH}\cdot\text{CCl}_3$.	M. p. of $R_2\text{C}\cdot\text{CCl}_2$.	Median lethal concn. (%) of $R_2\text{CH}\cdot\text{CCl}_3$ (white oil spray).	
			Lice.	Bugs.
4 : 4'-Dihydroxy-DT	206°	—	Inert	
4 : 4'-Dimethoxy-DT	92	109°	0.9	0.55
4 : 4'-Diethoxy-DT	109	109	1.8	0.8
4 : 4'-Dipropoxy-DT	62	80	4	2
4 : 4'-Diisopropoxy-DT	gum	—	—	—
4 : 4'-Dibutoxy-DT	52	76	4	4
4 : 4'-Diisobutoxy-DT	58	—	—	—
4 : 4'-Di- <i>n</i> -amyloxy-DT	66	60	4	4
4 : 4'-Diallyloxy-DT	82	66	Moderate (as dust)	
4 : 4'-Dicetyloxy-DT	79	—	Inert	
3 : 3' : 4 : 4'-Tetramethoxy-DT	116	126	W	
2 : 2' : 5 : 5'-Tetramethoxy-DT	120	146	W	
3 : 3'-Dibromo-4 : 4'-dimethoxy-DT	143	—	W	
4 : 4'-Dihydroxy-3 : 3'-dicarbomethoxy-DT ...	200	—	W	
4 : 4'-Dibenzoyloxy-DT	140	—	Inert	
4 : 4'-Di-(<i>p</i> -nitrobenzoyloxy)-DT	167	—	—	
4 : 4'-Di-(2 : 4-dinitrophenoxy)-DT	195	—	Inert	
4 : 4'-Di-(ω -carbomethoxymethyl)-DT	142	—	—	

some untested compounds of low solubility which are noted only in the Experimental section. For convenience it has been decided to call the parent substance, 1 : 1 : 1-trichloro-2 : 2-diphenylethane, "DT" (from "Diphenyltrichloroethane"), and to denote specifically by name and orientation only the substituents in the aryl nuclei; DDT itself thus being termed 4 : 4'-Dichloro-DT, and *iso*-DDT, 2 : 4'-Dichloro-DT.

Since all synthetic compounds of Tables I and II result from the condensation of chloral hydrate with an *ortho*-

para substituting aromatic compound, it has been assumed throughout this work that the pure main products isolated by crystallisation were always the 4 : 4'-disubstituted compounds. There is ample evidence that more soluble analogues of *iso*-DDT are also formed, but in view of the fact that *iso*-DDT itself is not a potent insecticide the troublesome isolation of its analogues was not undertaken. For the important compound 4 : 4'-dimethoxy-DT, the orientation of the methoxy groups has been rigorously confirmed by degradation to 4 : 4'-dimethoxybenzophenone.

The condensation of chloral hydrate with aromatic compounds in concentrated sulphuric acid proceeds readily with mono-halogeno benzene and naphthalene derivatives on warming, and with alkyl benzene derivatives in the cold. With di- or tri-halogeno, or nitro, benzene derivatives oleum has to be used as condensing agent (cf. U.S.P. 2,329,074). Benzyl chloride, acetophenone, and acetanilide did not react, whilst chlorophenols did not give products of normal DT type.

At the outset of this work it was known that 4 : 4'-dimethoxy-DT had some insecticidal properties, and hence the dialkyloxy compounds of the DT series were investigated in some detail, as well as a few diacyl derivatives. Two routes are available for the preparation of these substances : (a) alkylation of the easily-made condensation product of phenol with chloral, (b) condensation of chloral with phenyl alkyl ethers, usually in a mixture of acetic and concentrated sulphuric acids.

In practice it was found that only route (b) regularly gave clean products in good yield for the lower members of the series, though method (a) is useful for the preparation of higher members. The main drawback to method (a) is that hydrogen chloride may be eliminated from the $\text{CH}\cdot\text{CCl}_3$ group during the condensation, with consequent contamination of the products by ethylenic compounds, many of which have also been prepared. Though the number of compounds in this group could be extended indefinitely, it is considered that Table II includes all the potentially useful insecticides of dialkyloxy-DT type : other members are likely to be too insoluble for use in solution, or too costly for use in place of DDT itself in dusting powders. Tests with a few representative acyloxy derivatives of DT indicate that compounds of this type are most unlikely to have any insecticidal value.

Connections between Chemical Structure and Insecticidal Power.—The fact that *iso*-DDT is less effective than either DDT or even 4-chloro-DT (Busvine, *Nature*, 1945, 156, 169) indicates that the *position* of the substituent in the aromatic nucleus is quite as important as its mere presence. The fact that the Swiss investigators (Läuger *et al.*, *loc. cit.*) have found that two *para* substituents, R, must be present in all effective insecticides of the general type R-aryl-G-aryl-R where -G- is a group such as -S-, -SO₂-, >CH·CCl₃ etc., suggests that it is not just the " electronegative character " of the substituent R but the whole shape of the molecule which is significant. A mere mechanical view of tissue penetration by any contact poison leads to this view, and it is substantiated by the fact that toxicity vanishes in the DT series when the aryl groups become very large. The fact that *p*-alkyl and *p*-alkyloxy groups become less effective the longer the alkyl chain indicates that enhanced paraffinic character is not beneficial, even when it leads to a lowering of the m. p. and enhanced oil-solubility of the product. Thus simple analogies between lipid penetrability and fatty acid type of structure cannot be cogent (compare Busvine, *loc. cit.*).

The fact that the relative toxicities of DDT and 4 : 4'-dimethoxy-DT are different for bugs and lice (Table III) suggests that a specific toxic action of the substituent, in the *para* position, is at least as important as the steric factor, and indicates that the scope for investigation of *para*-substituted derivatives of DT may not yet be exhausted.

TABLE III.*

Insects.	Relative median lethal concentrations.		
	4 : 4'-Dichloro-DT.	4 : 4'-Dimethoxy-DT.	DT.
Lice	0.6	1.8	14
Bugs	1.0	1.0	40

* Results communicated by Dr. J. R. Busvine (compare *Nature*, 1945, 156, 169).

EXPERIMENTAL.

Analogues of DDT have been prepared by the following workers, and the references cited will subsequently be referred to by number :

- ¹ Zeidler, *et al.*, *Ber.*, 1874, 7, 1181.
- ² Goldschmidt, *Ber.*, 1873, 6, 985, 1504.
- ³ Elbs and Forster, *J. pr. Chem.*, 1889, 39, 300.
- ⁴ Elbs, *J. pr. Chem.*, 1893, 47, 66.
- ⁵ Grabowski, *Ber.*, 1878, 11, 298.
- ⁶ Calvet and Mejuto, *J.*, 1936, 554.
- ⁷ Dinesmann, *Compt. rend.*, 1905, 141, 201.
- ⁸ Rusanoff, *J. Russ. Phys. Chem. Soc.*, 1891, 23, 217.
- ⁹ Auwers, *Ber.*, 1903, 36, 1892.
- ¹⁰ Fritsch and Feldmann, *Annalen*, 1899, 306, 77.
- ¹¹ Frankforter and Kritchevsky, *J. Amer. Chem. Soc.*, 1915, 37, 386.
- ¹² Frankforter and Kritchevsky, *J. Amer. Chem. Soc.*, 1914, 36, 1511.
- ¹³ Frankforter and Harris, *J. Amer. Chem. Soc.*, 1926, 48, 3144.
- ¹⁴ Chattaway and Muir, *J.*, 1934, 701.

Notes on Preparations of Previously Known Substances.—The condensation of toluene and chloral hydrate gives

tarry products at 40° or above, and 4 : 4'-dimethyl-DT^(1, 13) was best prepared by adding toluene dropwise to stirred chloral hydrate in concentrated sulphuric acid at 0°.

2 : 4 : 2' : 4'-Tetramethyl-DT^(4, 13) was obtained similarly from technical xylene as a viscous solid from which, by distillation and subsequent crystallisation, a pure solid, m. p. 109—110°, was obtained (Found : C, 63.1; H, 5.26; Cl, 30.9. Calc. for C₁₈H₁₃Cl₃ : C, 63.2; H, 5.54; Cl, 31.0%).

4 : 4'-Dibromo-DT⁽¹⁾ required condensation at 90° for 1 hour. It yielded an ethylene, m. p. 121°, and a tetranitro-derivative, m. p. 224° (v. Part I).

4 : 4'-Dihydroxy-DT^(1, 8, 12) resulted from condensation at 20° in a 1 : 1 mixture of concentrated sulphuric and glacial acetic acids. It was easily soluble in aqueous alcohol, but sparingly soluble in benzene.

4 : 4'-Dimethoxy-DT^(10, 13) was obtained from anisole by the use of sulphuric/acetic acid mixture at 20°, and crystallised well from methyl alcohol in white prisms, m. p. 92°. Its ethylene, m. p. 109°, was oxidised by chromium trioxide in acetic acid to 4 : 4'-dimethoxybenzophenone, m. p. 144°. Methylation of 4 : 4'-dihydroxy-DT in methyl alcohol with methyl iodide and 1 equiv. of sodium methoxide yielded a gum, from which the dimethoxy-DT, m. p. and mixed m. p. 94°, was obtained in 75% yield. Ethyl, propyl, butyl, and amyl iodides all gave gummy alkylation products which could not be crystallised without great loss of yield.

Trichlorodi-(4-chloronaphthyl)ethane^(4, 8, 8, 11) was obtained by condensation with concentrated sulphuric acid at 30° for 2 hours, and crystallised from benzene-alcohol (1 : 2), m. p. 223° (Found : C, 58.3; H, 2.92; Cl, 39.2. Calc. for C₂₂H₁₃Cl₅ : C, 58.2; H, 2.88; Cl, 39.0%).

1 : 1-Dichloro-2-di-(4-chloro-*a*-naphthyl)ethylene was prepared from the above by refluxing for 3 hours with potassium hydroxide in pyridine, and crystallised from acetic acid in white needles, m. p. 190° (Found : C, 63.6; H, 3.27. C₂₂H₁₂Cl₄ requires C, 63.2; H, 2.89%).

Preparations of New Compounds.—1 : 1 : 1-Trichloro-2 : 2-di-(4-bromo-*a*-naphthyl)ethane was prepared by adding *α*-bromonaphthalene (60 g.) to a stirred mixture of chloral hydrate (40 g.) and concentrated sulphuric acid (300 ml.) at 30°, and crystallised from benzene-alcohol in plates (46 g.), m. p. 219° (Found : C, 48.8; H, 2.46; Cl, 19.7; Br, 29.5. C₂₂H₁₃Cl₃Br₂ requires C, 48.6; H, 2.39; Cl, 19.6; Br, 29.4%). The dichloroethylene had m. p. 224° (Found : C, 52.3; H, 2.4. C₂₂H₁₂Cl₂Br₂ requires C, 52.1; H, 2.4%).

4 : 4'-Diethyl-DT. Ethylbenzene (71 g.) was added dropwise during 2 hours to stirred chloral hydrate (57 g.) in concentrated sulphuric acid (200 ml.) at 0°. The product, after washing with cold sodium carbonate solution, distilled at 183—186°/0.5 mm. and solidified on freezing to -20°, but was a viscous gum at room temperature. On heating for 1 hour at 100° with nitric/sulphuric acid it gave a tetranitro-derivative which crystallised from acetic acid in pale yellow prisms, m. p. 194° (Found : C, 41.7; H, 3.0; N, 10.6. C₁₈H₁₅O₈N₄Cl₃ requires C, 41.4; H, 2.9; N, 10.4%). The dichloroethylene was also a gum.

4 : 4'-Di-(*ω*-bromomethyl)-DT. 5 g. of 4 : 4'-dimethyl-DT and 5 g. of bromine were warmed in carbon tetrachloride (20 ml.) in a strong light. Hydrogen bromide was evolved, and reaction was complete in 1 hour. The solution on evaporation gave a gum which solidified on addition of petrol, and on recrystallisation from absolute alcohol gave small white prisms, m. p. 144° (Found : C, 40.9; H, 3.0. C₁₈H₁₃Cl₃Br₂ requires C, 40.7; H, 2.8%). The compound was easily hydrolysed by sodium carbonate solution, but the resulting dialcohol was a viscous gum.

4 : 4'-Dichloro-2 : 2'-dimethyl-DT was obtained by condensing *m*-chlorotoluene with chloral hydrate in sulphuric acid at 60°. It crystallised from alcohol in colourless rhombs, m. p. 107° (Found : C, 50.2; H, 3.7; Cl, 46.4. C₁₆H₁₃Cl₂ requires C, 50.2; H, 3.4; Cl, 46.4%). By this procedure *o*-chlorotoluene gave an oil, b. p. 175—200°/1 mm. which could not be crystallised, and was presumably a mixture of isomers. *p*-Chlorotoluene yielded a solid, m. p. 156° which gave a dichloroethylene, m. p. 142° (Found : C, 55.3; H, 3.5; Cl, 41.1. C₁₆H₁₂Cl₂ requires C, 55.5; H, 3.5; Cl, 41.0%).

4 : 4'-Dihydroxy-3 : 3'-carbomethoxy-DT. The condensation product of chloral and salicylic acid⁽⁶⁾ by treatment with hydrogen chloride in methyl alcohol suspension have a dimethyl ester which crystallised from acetic acid in white plates, m. p. 200° (Found : C, 49.6; H, 3.8; Cl, 24.7. C₁₈H₁₅O₆Cl₃ requires C, 49.8; H, 3.5; Cl, 24.6%).

4 : 4'-Diethoxy-DT was prepared by adding phenetole (100 g.) dropwise during 4 hours to a stirred mixture of chloral hydrate (70 g.) in glacial acetic acid (400 ml.) and concentrated sulphuric acid (400 ml.) at 0°. The product was then poured on ice and the resulting viscous solid crystallised repeatedly from methyl alcohol, when it gave small needles (75 g.), m. p. 109° (Found : C, 57.5; H, 5.1; Cl, 28.5. C₁₈H₁₉O₂Cl₃ requires C, 57.6; H, 5.1; Cl, 28.5%). The same method was used in preparing the following homologues, from the corresponding, previously purified, phenyl ethers :

	M. p.	Found (%)			Required (%)		
		C.	H.	Cl.	C.	H.	Cl.
Dipropyl deriv.	62°	59.8	5.61	26.6	59.7	5.77	26.5
Diisopropyl deriv.	gum						
Dibutyl deriv.	52	61.1	5.98	24.4	61.4	6.33	24.8
Diisobutyl deriv.	58	61.3	5.93	—	61.4	6.33	24.8
Di- <i>n</i> -amyl deriv.	66	63.1	6.76	23.5	62.9	6.83	23.3

These products all gave dichloroethylenes when refluxed with alcoholic sodium hydroxide for 15 minutes.

	M. p.	Found (%)			Required (%)		
		C.	H.	Cl.	C.	H.	Cl.
Diethyl deriv.	109°	64.5	5.32	—	64.1	5.34	—
Dipropyl deriv.	80	65.9	5.91	19.3	65.7	6.07	19.4
Dibutyl deriv.	76	66.8	6.24	17.8	67.1	6.67	18.1
Di- <i>n</i> -amyl deriv.	60						

By condensation at 50°, tetramethoxy-DT products were obtained from veratrol, m. p. 116° (Found : C, 53.1; H, 4.7; Cl, 26.2. C₁₈H₁₉O₄Cl₃ requires C, 53.2; H, 4.7; Cl, 26.2%), and quinol dimethyl ether, m. p. 120° (Found : C, 53.3; H, 4.82; Cl, 26.4%), and these yielded ethylenes, m. p. 126° (Found : C, 58.6; H, 4.94; Cl, 19.2. C₁₈H₁₈O₄Cl₃ requires C, 58.5; H, 4.91; Cl, 19.2%) and 146° (Found : C, 58.3; H, 4.7; Cl, 19.2% respectively).

The following di-alkyloxy-DT compounds were prepared by refluxing the corresponding alkyl bromide, or chloride, with alcoholic 4 : 4'-dihydroxy-DT in the presence of 1.0 equivalents of sodium ethoxide.

R ₁ CH ₂ -CCl ₃ .	M. p.	Found (%)			Required (%)		
		C.	H.	Cl.	C.	H.	Cl.
Diallyl deriv.	82°	—	—	26.8	—	—	26.8
Dicyetyl deriv.	79	72.0	9.62	13.9	72.1	9.87	13.9
Dibenzyl deriv.	140	67.5	5.06	—	67.5	4.78	—
				N.			N.
Di- <i>p</i> -nitrobenzyl deriv.	167	57.2	3.88	4.85	57.2	3.60	4.77
Di-(2 : 4-dinitrophenyl) deriv.	195	48.4	2.73	8.63	48.0	2.83	8.62

Diallyl-DT gave a *dichloroethylene*, m. p. 66° (Found: C, 66.6; H, 5.2; Cl, 19.5. $C_{20}H_{18}O_2Cl_2$ requires C, 66.5; H, 5.0; Cl, 19.7%).

4 : 4'-*Di-(ω -carbomethoxymethyl)-DT* was obtained in low yield by adding a solution of sodium (0.2 mol.) in methanol to 4 : 4'-dihydroxy-DT (0.1 mol.) in methyl chloroacetate, and then refluxing for 6 hours. It crystallised in needles, m. p. 142° (Found: C, 52.4; H, 4.2; Cl, 22.7. $C_{20}H_{18}O_6Cl_2$ requires C, 52.0; H, 4.1; Cl, 23.1%).

The following diacyl derivatives of 4 : 4'-dihydroxy-DT were prepared by standard methods. With the exception of the dicinnamoyl ester, which gave a weakly insecticidal dust, they were all physiologically inert.

Diacyl Derivatives of 4 - 4'-Dihydroxy-DT.

	M. p.	Found (%)			Required (%)		
		C.	H.	Cl.	C.	H.	Cl.
Diacetyl deriv.	142°	—	—	—	—	—	—
Dinonoyl deriv.	59	63.7	6.92	18.3	64.2	7.25	17.8
Dibenzoyl deriv.	234	63.7	3.68	—	63.9	3.64	—
Di- <i>p</i> -nitrobenzoyl deriv.	248	54.5	3.0	—	54.6	2.78	—
Di- <i>o</i> -nitrobenzoyl deriv.	138	54.6	3.1	—	54.6	2.78	—
Dicinnamoyl deriv.	158	67.0	4.25	18.5	66.6	4.01	18.4
Di- <i>p</i> -toluenesulphonyl deriv.	220	54.0	4.04	17.1	53.7	3.71	17.0
		S, 10.5			S 10.5		

3 : 3'-*Dibromo-4 : 4'-dimethoxy-DT* was prepared by brominating dimethoxy-DT in boiling carbon tetrachloride. It crystallised from alcohol; m. p. 143° (Found: C, 38.1; H, 2.4. $C_{18}H_{13}O_2Cl_2Br_2$ requires C, 38.1; H, 2.7%).

All analyses were carried out microchemically by Mr. G. Ingram. The authors thank Dr. J. Forrest for assistance in preparing a few of the compounds listed in Table I, and Dr. J. R. Busvine (Ministry of Health Entomologist) for permission to quote results of his insecticidal tests. Acknowledgment is due to the Chief Scientific Officer of the Ministry of Supply for permission to publish this paper.

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[Received, November 1st, 1945.]