PAUL H. MÜLLER

Dichloro-diphenyl-trichloroethane and newer insecticides

Nobel Lecture, December 11, 1948

Ladies and Gentlemen.

Since Perkin synthesized the first dyestuff in 1856, about 90 years have elapsed. During this period the synthesis of artificial dyestuffs has gone through enormous development.

The discovery of *fuchsines* by Emanuel Verguin in 1859, unlocked the triphenylmethane dyestuffs for the dyestuffs chemist.

The very important discovery of the *diazo* compounds by Peter Griess, in 1858, certainly brought about the most significant reaction in the chemistry of dyestuffs, a quite unique impetus to the development of this field of organic chemistry.

The most important milestones in this development are: the preparation of Bismarck brown by C. Martius in 1863, of Chrysoidine by O. N. Witt in 1876, and Congo Red, the first dyestuff capable of direct application to cotton, by P. Böttiger in 1884.

This large-scale development and the vast mass of experimental material available have called for a variety of attempted explanations. The relationships between composition and colour on the one hand, and fastness on the other, were the subjects of several attempts at theoretical explanation.

Particularly fruitful in this respect was the theory of O. N. Witt on chromophores and auxochromes, and the theory - valid only in special cases - of E. Schirm, *J. Prakt. Chem.,* 144 (1936) 69, concerning the connexion between composition and affinity to cellulose fibre.

Thanks to these results the dyestuffs chemist today, after about 90 years of untiring detailed study, is in the fortunate position to possess certain points of reference enabling him to set up his programme of work in bold outlines.

The field of synthetics is already very much more complicated in the case of the pharmaceutical chemist.

Today, certain basic substances and formulae are known, as for instance salicylic acid, the barbiturates and the sulfonamides which are able to release certain physiological activity.

Long years of patient detailed study have produced explanations of the constitution of important vitamins, hormones and bacteriostatic substances such as penicillin, streptomycin, etc., and later these were, in part, synthesized. Yet in spite of all these results we are still far removed from being able to predict with any degree of reliability, the physiological activity to be expected from any given constitution. In other words, the connexion between constitution and action are so far still quite unexplained. In addition we have the particularly difficult conditions caused by the uncertainty of tests on living material.

More difficult still are the relationships in the field of pesticides, and in particular of synthetic insecticides.

First of all then, we could consider synthesizing natural insecticides such as pyrethrum and rotenone of known composition and obtained from plants, but quite irrespective of the excessive price entailed in providing a synthesis of such a highly complicated chemical substance there are, as we shall soon see, other grave disadvantages.

We must be clear on this point, namely that we are in fact, moving into unknown territory where there are no points of reference to begin with so that we can only proceed by feeling our way. To this too we must add the grave difficulties of biological trials requiring multiple controls of the results.

When, in about 1935 and on behalf of my Company, J.R. Geigy A.G. in Basel, I began to study the field of insecticides, and in particular those insecticides of importance to agriculture, the situation looked desperate indeed. Already an immense amount of literature existed on the subject and a flood of patents had been taken out. Yet of the many patented pesticides there were practically none on the market and my own investigations showed that they were not comparable with known insecticides such as the arsenates, pyrethrum or rotenone.

This gave me the courage to press on. In other respects too, the chances were worse than poor; only a particularly cheap or remarkably effective insecticide had any prospects of being used in agriculture, since the demands put upon an agricultural insecticide must necessarily be strict. I relied upon my determination and powers of observation. I considered what my ideal insecticide should look like, and the properties it should possess.

I soon realized that a contact or "touch" insecticide would possess very much better prospects than an oral poison. The properties of this ideal insecticide should be as follows:

1. Great insect toxicity.

2. Rapid onset of toxic action.
3. Little or no mammalian or plant toxicity.
4. No irritant effect and no or only a faint odour (in any case not an unpleasant one).
5. The range of action should be as wide as possible, and cover as many Arthropoda as possible.
6. Long, persistent action, i.e. good chemical stability.
7. Low price (= economic application).

Known insecticides can be grouped as follows under these seven headings:

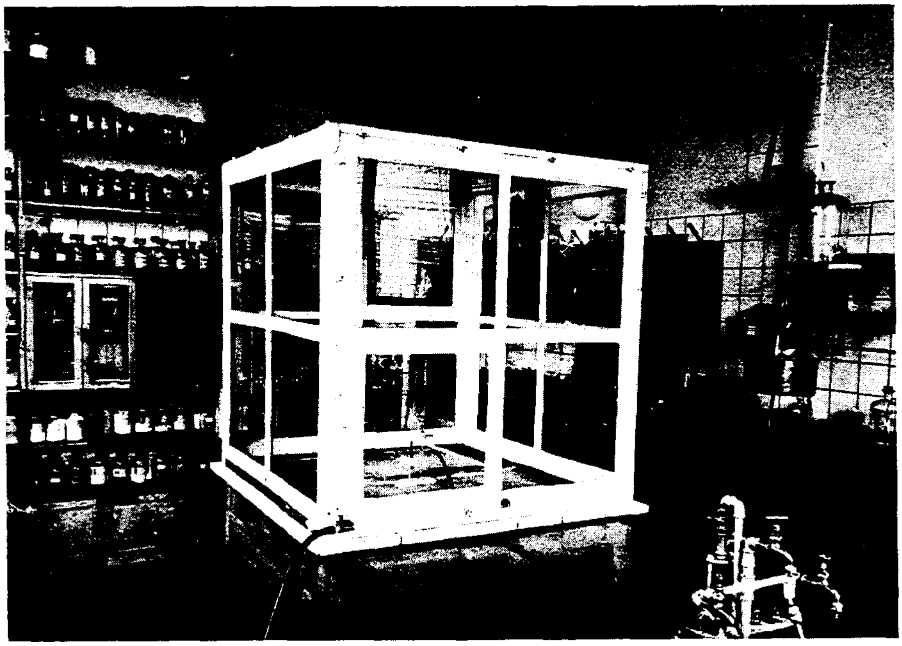
Insecticides	*Satisfies the following requirements:*	*Does not satisfy the following requirements:*
Nicotine	1, 2, 5, 7	3, 4, 6
Rotenone	1, 3, 4, 5	2, 6, 7
Pyrethrum	1, 2, 3, 4, 5	6, 7
Thiocyanate	1, 2, 5, 7	3, 4, 6
Phenothiazine	1, 3, 4, 7	2, 5, 6

First of all, a substance had to be found with greater contact insecticidal properties and this was obviously not so easy. My biological trials were conducted in a large glass chamber, of the Peet-Grady type, in which I put *Calliphora vomitoria* treated with a fine spray of the substance to be tested, in a non-toxic solvent. Suitable non-toxic or relatively non-toxic solvents are ethyl alcohol and acetone. I conducted my early experiments myself in those days and still do so today since, in my view, nothing is better than making one's own observations.

Such personally conducted biological investigations stimulate the chemist in his work, and at the same time he learns, by his observations, to understand the problems and uncertainties of biological tests and is thus better able to appreciate the difficulties facing his colleagues who work in biology. He will also test substances synthesized by himself with far more keenness and understanding than will a biologist working at a distance from him, who, unconsciously tends in time to lose interest because the tedious chemical formulae mean little to him.

Sometimes new and valuable discoveries may be made by small changes in methods of application, or again by the correct observation of apparently unimportant side-effects.

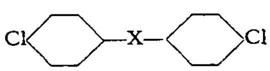
Our natural-science branches are today specialized in the extreme. This is



useful when some-small detail is to be examined; in my judgement, however, it becomes a fatal disadvantage when two branches - in our case chemical and biological - become intermingled.

After the fruitless testing of hundreds of various substances I must admit that it was not easy to discover a good contact insecticide. In the field of natural science only persistence and sustained hard work will produce results, and so I said to myself "Now, more than ever, must I continue with the search. " This capacity I owe probably - apart from my inborn determination - to strict upbringing by my teacher, Professor Fichter, who taught us that in chemistry results can only be achieved by using the utmost patience.

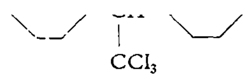
From earlier trials I knew that compounds with the group $-CH_2Cl$, for instance $-CO-CH_2Cl$, often showed a certain activity. From the work done at the same time in our firm by Dr. H. Martin and his colleagues on toxic substances for the control of moths, in which I personally took no part, I knew that compounds of the general formula:



$X = SO_2, SO, S, O$, etc.

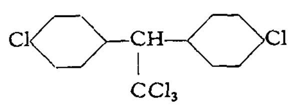
frequently showed considerable oral toxicity to moths.

In studying the literature, I came across an article by Chattaway and Muir in the *J. Chem. Soc.*, 1934, p. 701, which described the preparation of diphenyl-trichloroethane



I remembered my earlier experiments with substances comprising the -CH_2Cl group, for instance laurylchloroacetate, etc. and I was curious to know what effects the CCl_3 groups would have on the activity of contact insecticides.

The substance was prepared in September 1939 and tests showed a very considerable contact-insecticidal activity on flies. I began to prepare derivates from this basic material and, probably influenced by the results in the field of moth control, I synthesized the *p,p′*-dichloro combination



This compound, originally made as long ago as 1873 by an Austrian student in the course of his thesis, now showed a strong insecticidal contact action such as I had to date never observed in any substance.

My fly cage was so toxic after a short period that even after very thorough cleaning of the cage, untreated flies, on touching the walls, fell to the floor. I could carry on my trials only after dismantling the cage, having it thoroughly cleaned and after that leaving it for about one month in the open air.

Similar observations were made by American scientists during their first tests of dichlorodiphenyl-trichloroethane :

"The toxic action of DDT is so strong that some of the scientists who first used it, ruined important experiments because they failed to clean their insect cages before using them again, and the small amounts of DDT remaining were sufficient to kill the new insects introduced." (From *How Magic is DDT* , by General James Stevens Simmons, 1945, p. 4.)

Later the material was tested on other insects such as aphids, gnats *(Culex)* and finally cockchafers, Colorado beetles, etc. In all cases the new compound acted, although it often killed only in a matter of hours or days. This is also the reason why initially the biologists were not very interested in the substance; pyrethrum and rotenone had accustomed them to expect a rapid knock-down and they did not understand that long residual activity far outweighed the slow toxic process.

Finally these laboratory results were confirmed by field trials conducted by the research stations at both Wadenswil and Oerlikon (Switzerland) and by our own field trials, and it was found that the effects on the Colorado beetle lasted from four to six weeks.

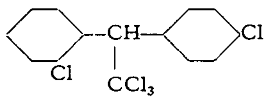
Insecticide	*Satisfies the following requirements:*	*Does not satisfy the following requirement:*
DDT	1, 3, 4, 5, 6, 7	2

DDT insecticides have now been introduced into all possible fields of insect control, for instance in hygiene, textile protection, storage and plant protection. It is noteworthy that in Sweden the application of DDT for timber protection is also being studied, and has already had considerable success.

After the recognition of the strong contact action of dichloro-diphenyl-trichloroethane all possible derivates and analogues were synthesized both by us and later also abroad, and tested.

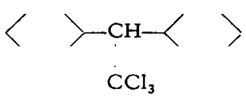
It is very surprising indeed how little has come of these trials, and it only indicates how strictly specific the action is. When the slighest, seemingly unimportant change is made in the dichloro-diphenyl-trichloroethane molecule, the whole wide range of activity possessed by the original substance is lost.

This is already shown by the isomers : e.g. the *o,p′*-compound

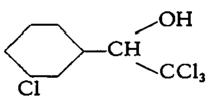


is present as an impurity to the extent of about 10% in the raw *p,p′*-dichloro-diphenyl-trichloroethane and its activity is, depending upon the insects treated, about 10-20 times less than that of the *p,p′*-combination.

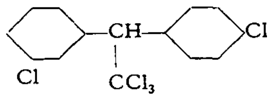
The *o,o′*-combination, estimated at 1% of the raw substance, behaves in the same way; it is only very slightly active.



The *m,p′-combination,* which may be prepared from



and chlorobenzol,



on the other hand, again shows a relatively strong insecticidal action which does not, however, approach that of the *p,p'*-isomer.

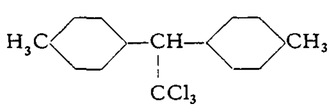
A survey of the properties of the isomers known to date has been made by my colleague Dr. Gatzi.

Isomer	*Melting point*	*Form of crystal (from alcohol)*	*Solubility in 96% alcohol (±0.5%)*		*Ability to split off 1 molecule HCl with 0.1 N alcoholic NaOH*	
			0°	*20°*	*45 min at 22°*	*10 min at 80°*
p,p'	108–109°	Needles	1.1%	1.7%	100%	100%
m,p'	oil	–	–	–	87%	98%
o,p'	73–74°	Thick prisms	1.8%	2.4%	12%	115%
o,o'	92.5–93°	Flat prisms	2.2%	2.5%	0%	73%

Of the many analogues and related substances of dichlorodiphenyl-trichloroethane which were prepared, only a few have any real application as insecticides.

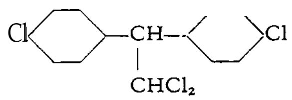
The most interesting perhaps is *p,p'* difluorodiphenyl-trichloroethane, which has shown a somewhat faster contact-insecticidal activity than *p,p'*-dichlorodiphenyl-trichloroethane but an insufficient residual activity, in addition to which the cost is too high for widespread use. Another interesting insecticide is *p,p'* dimethoxydiphenyl-trichloroethane, recommended particularly in America where, with some specific pests, it worked to some extent better than its older brother. It possesses the great advantage of having somewhat less mammalian toxicity than the DDT insecticide, but in the main its action is too specific.

A further specific insecticide is *p,p'*-ditolyl-trichloroethane



which is however too selective and has therefore found little application.

p,p'-Dichlorodiphenyl-dichloroethane, the so-called DDD



also has certain uses and is easily obtainable from dichloracetal and chloro-benzol. It is said to be equally toxic to mosquito larvae as dichloro-diphenyl-trichloroethane but at the same time less toxic to mammals. After great initial optimism, little is heard of it nowadays; clearly the product has failed to satisfy in some respect.

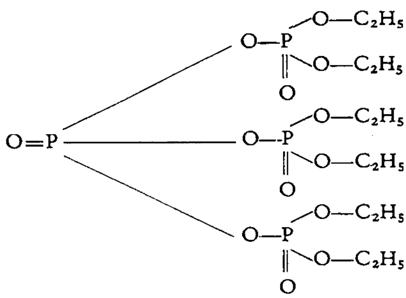
Naturally, the synthesis of these closely related substances of dichloro-diphenyl-trichloroethane does not represent the end of the road, and work continues uninterrupted.

The industrial chemist is, in this field, not in the happy position of his academic colleague of being able to freely publish his findings. In view of possible patents which might be taken out, he must bide his time until it has been confirmed as quite certain that no other application is possible.

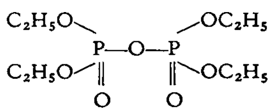
Since the discovery of dichloro-diphenyl-trichloroethane a number of other insecticides have been discovered.

γ-Hexachlorocyclohexane, again a substance long known to man (Michael Faraday first produced it in 1825 as the mixed isomers $\alpha, \beta, \gamma, \delta$) has found its uses as an insecticide for specific applications. Its very clinging, unpleasant smell militates against widespread use.

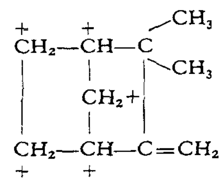
During the war, I. G. Farben developed an aphicide based on hexaethyl-tetraphosphate and having the complicated formula:



Today, the Americans (Victor Chemical Co.) have superseded this with their synthesized tetraethyl pyrophosphate having the formula :



A chlorinated camphene, the formula for which is not firmly established but is probably:

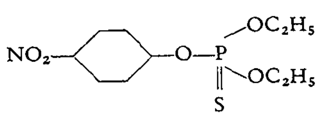


(The substitution by Cl probably occurs at +

was developed in America by the Hercules Powder Co. and was successfully used against certain cotton pests.

"Velsicol 1068" or "Chlordane", also called "Octachlor" is manufactured by the Velsicol Company and the Julius Hyman Corporation. The general formula for this compound is $C_{10}H_6Cl_8$. We seem here to be dealing with chlorinated dicyclopentadiene.

The most active insecticide in every respect, surpassing in most cases even dichlorodiphenyl-trichloroethane, is a phosphorus compound developed during the War by the German firm I.G. Farben. In Germany it is known as "E 605 ", while in America where large-scale trials have already been held it goes under the name of "Parathion"; it consists of *p*-nitrophenyldiethyl-thiophosphoric acid ester having the formula:



In the beginning all these insecticides were greeted with great optimism, and people prophesied only a short life for dichloro-diphenyl-trichloroethane.

Some of these insecticides have found a special application for certain purposes, and will probably continue to be used for these. E. 605 is possibly the most interesting, but it must be excluded in cases demanding the least possible toxicity to humans and maximum residual activity. E. 605 is a substance having a very high mammalian toxicity and decomposes rapidly on exposure to air and light, and because of this it is of little use in the fight against epidemic diseases.

On the whole there is now less talk of this new insecticide and DDT has, particularly in the field of hygiene, maintained and even improved its dominating position.

Ladies and gentlemen, we are today on the threshold of a new development in the field of pest control. Whilst before we had to depend on inorganic poisons such as the arsenates or the perishable active substances of plants such as pyrethrum or rotenone, we now have, besides dichloro-diphenyl-trichloroethane, a whole series of substances capable of being synthesized. This development appears to be paving a way similar to that in the field of dyestuffs, so that gradually insecticides and other pest-control agents will be available providing a whole range of specific properties.

In many respects this development can perhaps better be compared to that followed for several decades by the synthesis of medical products as outlined by S. Frankel in his *Die Arzneimittel-Synthese* (Synthesis of Medical Products), p. 9. In a somewhat more succinct and clear form, he says:

"The artist sees as his purpose not the slavish imitation of Nature degraded by art to simple reproduction. He rather employs his subjective conception of beauty in order to give birth to a new beauty which Nature does not offer in precisely that form. He creates this by using a natural form of representation which is none the less characteristic of the artist.

Similarly the synthetics chemist must create new types of substances, inspired by the action of substances found in Nature and guided by his chemical and pharmaco-dynamic knowledge of active groups.

In so doing, his imagination, too, must be given full rein, just as the artist creates from contemplation of what, subjectively, appears to him as being beautiful."

But at this stage it is of course presumptuous to wish to look into the future; the new fields are still hidden and decades of years ofpatient, painstaking study by biologists and chemists still lie ahead before one day we will perhaps finally be able to recognize the relationships between chemical constitution and mode of action.

Most certainly it was premature, when the insecticidal activity of dichloro-diphenyl-trichloroethane had only just been recognized and scant experimental material was made available, for theories regarding this relationship to be advanced from various quarters. Owing to the lack of appropriate bases these were found to be wrong, and further development has since confirmed this to be so.

Even the mode of action of DDT in poisoning an insect is far from fully explained. We may indeed assume with a fair degree of certainty that the poison enters the insect's body via the sense-organs and somehow travels along the nervous system. (In other words, dichloro-diphenyl-trichloroethane is a nerve poison, like pyrethrum.) However, the real cause of death is today still unknown in spite of the fact that all over the world, particularly in America and here in Europe, numerous laboratories are trying to find the answer to this question. The problem is not made easier by the fact that we now know that certain insects such as bees which develop a higher temperature in their hives and presumably also have a higher body-temperature than other insects, by virtue of this develop immunity to dichloro-diphenyl-trichloroethane.

The field of pest control is immense, and many problems impatiently await a solution. A new territory has opened up for the synthetics chemist, a territory which is still unexplored and difficult, but which holds out the hope that in time further progress will be made.

I am grateful and glad that I have been permitted to lay a first foundation stone in this puzzling and apparently endless domain,