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NEW DEVELOPMENTS IN THE SYSTEMIC COMBAT OF FUNGAL DISEASES OF PLANTS[1,2]

Met een samenvatting: Nieuwe ontwikkelingen in de bestrijding van schimmelziekten bij planten met systemisch werkzame middelen

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INTRODUCTION

While systemic insecticides and herbicides are used in practice for several years already, the development of systemic fungicides seems to lag behind. None has as yet reached the stage of practical application.

Yet several compounds are known which, under experimental conditions, display a certain amount of systemic activity against fungi. In the ideal case such compounds should permeate the entire plant and combat the penetrating moulds or those already present. An interesting feature is the fact that the compounds displaying such activity are not necessarily fungicides or derivatives which can give rise to fungicides, for it is known that also certain compounds, which *in vitro* are inactive on moulds, are able to confer considerable protection to plants against fungal diseases.

It is not intended to give here a survey of all compounds showing systemic activity, but rather to consider how the compounds might act.

THE TEST

For an evaluation of systemic antifungal activity a test is required in which the three components: the plant, the fungus and the compound each play a role.

A much adopted test is the development of *Botrytis fabae* on broad bean, the well-known chocolate spot disease (cf. FAWCETT, SPENCER & WAIN, 1955). In the United States *Fusarium oxysporum* on tomato has often been used (cf. DAVIS & DIMOND, 1953). In our Research Unit for Internal Therapy of Plant Diseases cucumber scab caused by *Cladosporium cucumerinum* was introduced as a standard test object by VAN RAALTE (cf. VAN RAALTE et al., 1955). The economically important diseases, as for instance potato late blight, apple scab and Dutch elm disease, do not lend themselves to continuous experimental study. This is certainly unfortunate because we have no guarantee whatsoever that a compound which is active in one test, will also work against another disease.

Usually the compounds are applied to the plants one or more days prior to inoculation with the parasite, and in order to obtain a proper idea of the translocatability of the test compound, its place of application must be different from the spot where the disease is evaluated. We know already from the systemic in-

[1] After a lecture held at the IXth International Botanical Congress at Montreal in 1959.

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secticides and herbicides that substances which are readily translocated upwards with the transpiration stream, do not necessarily also move downwards to any appreciable degree. The reverse is also found. Hence, root application as well as foliage application have to be studied in order to judge the effectiveness of a compound.

SYSTEMIC FUNGITOXIC COMPOUNDS

If we now turn to the first group of systemic compounds, namely the fungitoxic compounds, we may say that practice has taught us already that none of the present agricultural fungicides has appreciable systemic activity. Uptake and translocation by the plant of the known fungicides seem to be insufficient to give adequate systemic protection. Some compounds may be unable to penetrate, some may be adsorbed or metabolized by the plant, whereas other compounds are too toxic.

Yet various of the agricultural fungicides were shown to have some slight systemic activity against certain plant diseases as was shown by experiments of GROSSMANN (1957) with tetramethyl thiuramdisulfide against *Fusarium oxysporum* on tomato and of VOLGER (1959) with the same compound against diseases of seedlings of *Pinus silvestris*; NAPIER et al. (1957) showed systemic activity of "captan" against *Botrytis fabae* on broad bean and ROMBOUTS & KAARS SIJPESTEIJN (1958) obtained systemic effects with pyridine-2-thiol-N-oxide against this latter disease and *Cladosporium cucumerinum* on cucumber. Also with the sulfate of 8-hydroxyquinoline limited results have often been described.

Antifungal antibiotics often show more promising effects than the synthetic compounds as systemic fungicides. Griseofulvin and actidione have received ample attention (cf. BRIAN, WRIGHT, STUBBS & WAY, 1951; WALLEN & MILLAR, 1957). Rimocodin and pimaricin are able to combat the internal parasite *Ascochyta pisi* in pea seeds (DEKKER, 1957).

We have to conclude, however, that uptake and translocation of fungicides on the whole are insufficient to effect satisfactory systemic protection. Thus we are bound to look for other methods in order to provide the plants with this systemic protection.

"*Masked fungicides*"

Since the first requirement for a systemic compound surely must be its translocatability, it is not surprising that one has tried to attach certain groups to fungicides with the aim of preparing better translocatable compounds. If this group masks the activity of the molecule, it should be split off again by the fungus or the plant at the desired site of action. Though this idea may seem rather bold, we may not forget that it is according to this principle that the systemic insecticides "schradan" and "demeton", which are nowadays applied in vast amounts, are doing their work.

In the Research Unit for Internal Theraphy for Plant Diseases it was originally attempted to follow this principle (VAN RAALTE, KAARS SIJPESTEIJN, VAN DER KERK, OORT & PLUYGERS, 1955; VAN DER KERK, 1956). The investigation was based on the following observation of VAN RAALTE (1952). The petiole of a potato leaf was placed on a plate seeded with *Penicillium italicum*. The length of this petiole cutting was 5 mm; on its top was placed a piece of filter

paper dipped in a solution of TMTD (1), TMTM (2) or sodium dimethyldithiocarbamate (3).

(1) $(CH_3)_2NC(=S)-S-S-C(=S)-N(CH_3)_2$ TMTD

(2) $(CH_3)_2NC(=S)-S-C(=S)-N(CH_3)_2$ TMTM

(3) $(CH_3)_2NC(=S)-SNa$ NaDDC

(4) $(CH_3)_2NC(=S)-SCH_2COOH$ carboxymethyl-DDC

After incubation a distinct zone of inhibition was seen around the petiole when TMTM was used; TMTD and NaDDC, however, produced no inhibition zone. This result led to the hypothesis that TMTM might be regarded as a dithiocarbamic acid derivative which is translocatable owing to the presence of a special group. Thus many compounds with the general formula $(CH_3)_2NCSSR$ were prepared. Their systemic activity was evaluated against cucumber scab. The recent dissertation of PLUIJGERS (1959) gives a summary of the compounds and the results obtained. The best compound which issued from this project, was the carboxymethyl derivative (4).

When cucumber seedlings are placed for two days with their roots in a solution of 500 p.p.m. of this compound and the foliage is subsequently sprayed with conidia of *Cladosporium cucumerinum*, the cotyledons and hypocotyls of the treated plant become far less attacked than those of the untreated plants.

How does carboxymethyl-DDC act? The compound itself is only very slightly fungitoxic *in vitro*, but it was intended to be decomposed in the tissues and to give rise there to the fungitoxic dithiocarbamate. It may, however, be doubted, if in fact carboxymethyl-DDC acts according to this principle, because sap expressed from cucumber plants treated with this compound does not show fungicidal activity on *Cladosporium cucumerinum in vitro*. Neither was there activity on *Glomerella cingulata*, a mould which is much more sensitive to NaDDC than *Cladosporium cucumerinum*.

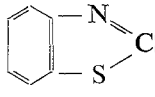
The following observation may offer another possible explanation for the systemic activity of carboxymethyl-DDC. When VAN RAALTE studied the merits of this compound against diseases of tomato plants, he was struck by a curious effect on these plants, for they showed the same picture as plants treated with 2,4-dichlorophenoxyacetic acid (2,4-D) namely a growth-regulator effect. Further studies revealed that carboxymethyl-DDC must indeed be regarded as a true plant growth regulator (VAN DER KERK, VAN RAALTE, KAARS SIJPESTEIJN & VAN DER VEEN, 1955).

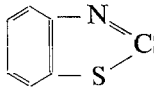
The fact that growth regulators may give systemic protection was at that time already a familiar phenomenon since DAVIS & DIMOND (1953) as well as other investigators had found that various plant growth regulators could induce sys-

temic protection to various diseases. Like carboxymethyl-DDC they are not fungitoxic *in vitro*.

Seen in this light it seems acceptable that the mode of action of carboxymethyl-DDC is the same as that, which is assumed for the other growth regulators, namely not a direct action on the parasite, but an interference with plant metabolism which leads to increased resistance of the plants to the parasite.

The case of carboxymethyl-DDC even shows a striking similarity with that of S-carboxymethyl-2-mercaptobenzothiazole (5) (cf. DAVIS & DIMOND, 1953). Both are derived from a fungicide (3 and 6 respectively) by attachment of a carboxymethyl group. Both are growth regulators and bring about systemic protection. This systemic protection must be ascribed rather to an increase of host resistance than to a decomposition to the fungitoxic principle.

(5)  S-carboxymethyl-2-mercaptobenzothiazole

(6)  2-mercaptobenzothiazole

In a similar way certain groups were added to the molecule of the antibiotic "actidione". HAMILTON, SZKOLNIK & SONDHEIMER (1956) found that the oxime, the semicarbazone and the acetate had appreciable systemic activity against cherry leaf spot (*Coccomyces hiemalis*), whereas "actidione" itself was inactive. It is supposed that the three active compounds are translocated as such to the new leaves where they are broken down again to the fungicidal "actidione". The same derivatives were found more active than "actidione" itself in the systemic control of wheat rust (WALLEN, 1958).

Up till now we have considered the improvement of translocatability by attachment of certain groups to the molecule; translocatability of fungicides can, however, also be influenced by formation of certain salts. Thus BAKKEREN (1958) reported that the cetylpyridinium salt of dimethyldithiocarbamic acid has a curative effect on apple scab. It can still be applied 3 days after infection, because it penetrates into the plant and kills the fungus there.

If we consider the results obtained up till now, we will have to admit that the improvement of translocatability of fungicides by attachment of labile groups to the molecule has not yielded a striking success in the field of systemic fungicides. This may be due to a large extent to our almost complete lack of knowledge of the relation between structure and uptake of organic compounds into the plants as well as their distribution and stability in the tissues.

Translocation studies

A first attempt to study the relation between structure and translocatability was made by CROWDY, ELIAS & RUDD JONES (1958) for a group of sulfonamides. In a typical experiment broad beans were placed for 13 days with their roots in a 0.01 % solution (= 100 p.p.m.) of these compounds. Subsequently the concentration of the compounds in the leaves was assessed. The following concentrations were found per fresh weight of the leaves: sulfanilamide 279 p.p.m., sulfa-

guanidine 75 p.p.m., sulfadiazine 218 p.p.m., sulfacetamide 228 p.p.m., sulfathiazole 44 p.p.m. and N^4-acetyl sulfanilamide 383 p.p.m. This result illustrates the differences in uptake and translocatability. It also shows that the concentration inside the plant may become higher than that of the solution in which the roots were placed. Of course, experiments of this kind do not give any information about the micro-distribution of the compounds within the leaves.

ROSS & LUDWIG (1957) made a quantitative study of the translocation of a series of ethylenethiourea derivatives in tomato plants. N-Octylethylenethiourea accumulated readily in the root system, whereas N-amyl- and N-ethylethylenethiourea are much more mobile and move upwards.

These two examples may stress the importance of further quantitative work on translocatability of organic compounds.

Stability in the plant

The systemic effect of a compound is not only determined by translocatability; the stability in the plant certainly is another factor of importance. As soon as a compound enters the plant cells, it becomes exposed to their full metabolic potential. Some compounds appear to be stable under these conditions, other compounds will be broken down. Special attention will be drawn here to the fact that foreign compounds may also become involved in synthetic reactions in the plant.

Better translocatable and less phyto- and fungitoxic substances can arise in this way. Thus sulfanilamide is transformed to a large extent into the less fungitoxic N^4-acetyl derivative; an equilibrium seems to exist since the latter compound in its turn gives rise to the former when taken up by the plant (CROWDY & RUDD JONES, 1958). Another example is the transformation of the herbicide aminotriazole into a glucoside (ROGERS, 1957) or into an alanine-aminotriazole derivative (MASSINI, 1959). Phenolic compounds are subject to β-glycosidation in the plant as was shown by several investigators (cf. HUTCHINSON, ROY & TOWERS, 1958 and WINTER & SCHÖNBECK, 1959). That similar reactions occur following the uptake of the fungicide sodium dimethyldithiocarbamate by various plants is suggested by the work of DEKHUIJZEN (in the press).

This kind of biochemical transformation of fungicides in the plant can be of advantage for the systemic combat of fungi if the new product is translocatable and if it is sufficiently fungitoxic itself or is broken down again by the moulds to give rise to the original fungicide.

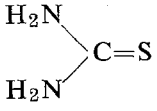
SYSTEMIC COMPOUNDS WHICH ARE NOT FUNGITOXIC IN VITRO

After having dealt with the systemic activity of fungicides and some of their derivatives we will now turn to that most interesting group of compounds which do show systemic protection, although they are not fungitoxic *in vitro*.

An almost classic example is the observation of DAVIS & DIMOND (1953) that plant growth regulators when applied to the roots protect tomatoes against *Fusarium oxysporum*. Their protective action is ascribed to interference with plant metabolism in such a way that resistance of the plant to the parasite results. There are many more examples of the action of growth regulators on plant diseases, but we will later come back to these compounds.

Thioureas. An interesting group of compounds seems to be thiourea with some derivatives. It was found by VAN ANDEL & PLUIJGERS (1957, unpublished results) that thiourea (7) as well as phenylthiourea (8) rendered cucumber plants resistant to attack by *Cladosporium cucumerinum* after application to roots or foliage. They are in fact much more active compounds than carboxymethyl-DDC, since protection is almost complete. At the same time KUC, WILLIAMS & SHAY (1957) published a short note in which they claimed that phenylthiourea showed systemic activity against apple scab.

FUCHS & BAUERMEISTER (1958) could suppress the development of wheat rust by treatment of the leaves with a derivative of thiourea namely thiosemicarbazide (9). Its mode of action may be the same as that of thiourea.



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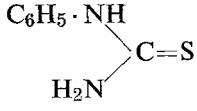

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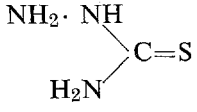

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How do these compounds act? As much as 500 p.p.m. is required for inhibition *in vitro*. It is not impossible that the concentration inside the plants reached this level. Yet the sap expressed from the leaves of cucumber plants treated with phenylthiourea shows no fungitoxic activity. Hence it seems rather that the compounds act by interfering with plant metabolism. Thioureas, after all, are known to react strongly with certain plant enzymes, as for instance the polyphenoloxidase.

Sulfonamides. As we have seen the work of CROWDY, ELIAS & RUDD JONES (1958) has shown that sulfonamides are easily translocated. They found that these compounds also bring about very effective systemic protection to rust of beans and wheat and to mildew of wheat and oats. It is left undecided whether this effect is due to direct action on the fungi or to interference with host metabolism.

Streptomycin. Another example is the control of *Phytophthora* in potato by streptomycin (MÜLLER, MACKAY & FRIEND, 1954). The action of streptomycin which is a bactericide but not a fungicide is ascribed by VÖRÖS, KIRALY & FARKAS (1957) to a stimulating action of streptomycin on the polyphenoloxidase activity of the plant.

Amino acids. Thioureas, sulfonamides and streptomycin are foreign compounds which alter the resistance of the plants by interference with plant metabolism. It may now be asked in how far resistance of the plant can be also altered by addition of plant metabolites. Indole acetic acid was already found active. KUC and coworkers (1957, 1959) studied the action of amino acids on apple scab and found phenylalanine and alanine to be very active. VAN ANDEL (1958) reported systemic activity of the amino acids serine and threonine against cucumber scab. It seems, however, most remarkable that KUC and coworkers as well as VAN ANDEL found that only the D-isomers are active, whereas the natural L-isomers are practically ineffective. Also the unnatural amino acid L-threo-β-phenylserine is very active against cucumber scab. The mechanism of their activity is still unknown, but it is supposed to be an interference with plant metabolism (OORT & VAN ANDEL, 1960).

Sugars. The addition of sugars also can seriously affect resistance. I will mention here only an example of YARWOOD (1934) who found that the addition of saccharose to clover leaflets reduced their susceptibility to *Stemphylium sarciniforme.* At the same time it increased their susceptibility to powdery mildew. The sugar level in fact appears to determine the degree of susceptibility of many plants towards various diseases. This concept was discussed by HORSFALL & DIMOND (1957) who distinguish "low sugar diseases" and "high sugar diseases". Any chemical that alters the sugar level in the plant, can thus be expected to alter susceptibility to these diseases in one way or another. As examples for low sugar diseases *Alternaria* on tomato and Dutch elm disease are mentioned; diseases caused by mildews and rusts and also *Botrytis fabae* on broad beans would belong to the high sugar diseases.

Growth regulators. On this basis HORSFALL & DIMOND (1957) have forwarded an elegant theory to explain the effect of growth regulators on the resistance to plant diseases. They point to the fact that these compounds after a slight initial increase, cause a fast decrease of the sugar level of foliage so that the level eventually falls below that of untreated plants. Thus growth regulators would induce plants to become more resistant to a high sugar disease and this is indeed so in many cases. Alternatively, treatment with growth regulators would induce plants to become more susceptible to low sugar diseases because the growth regulators lower the sugar level. This extremely attractive theory gives an explanation for many results obtained after treatment with growth regulators.

It is, moreover, intriguing that growth regulators as well as certain circumstances which affect the sugar level in the plant are also known to influence the development of certain virus diseases and bacterial diseases. Hence we may even ask in how far the sugar level can also determine susceptibility to these diseases.

In how far does the systemic activity of the growth regulator carboxymethyl-DDC fit into this picture? Does it act by lowering the sugar level in the cucumber plant and is cucumber scab a high sugar disease?

Evidence for the latter suggestion was readily obtained (KASLANDER & KAARS SIJPESTEIJN). When cucumber seedlings were placed in a glucose solution prior to spraying with the parasite the sugar level was high and disease became more severe than in the control plants. When alternatively plants were kept at low light intensity before and during incubation, the sugar level was low and disease became less severe. If, however, glucose was added simultaneously, it apparently counteracted the effect of darkness, the glucose level was high and disease was more severe again. These observations pointed definitely to a high sugar disease.

Our expectation was that treatment with the growth regulator carboxymethyl-DDC would lower the sugar level in cucumber seedlings. This frequently was found to be the case. If, moreover, carboxymethyl-DDC was given together with glucose, the suger level in the plant was high and disease severe. Thus we are inclined to believe that the protective effect of carboxymethyl-DDC is to a certain extent related to a decrease in sugar level in the plant. Yet other factors probably also play a role. It seems, moreover, an oversimplification to assume that the sugar level should influence susceptibility directly, because other factors, which are influenced by the sugar level, as for instance the osmotic value of the cell sap, might also be determinative for the degree of susceptibility.

Recently CORDEN & DIMOND (1959) offered a very different explanation for the systemic control of *Fusarium* in tomato by growth regulators. A correlation was found here between systemic control and inhibition of root elongation. The systemic control is thought to be due to the different state of the petic substances in the shorter roots (EDDINGTON & DIMOND, 1957).

The theory that growth regulators act by changing the sugar level might also offer an explanation for the fact that not only growth regulators themselves, but also closely related compounds without growth-regulating properties can have systemic effects against plant diseases.

Thus in England WAIN and coworkers prepared an impressive number of growth regulators, and related substances without growth-regulating effect. Many of these evoke some systemic protection against chocolate spot disease (cf. FAWCETT, SPENCER & WAIN, 1957). It would be of interest to know if the growth regulators which give systemic protection influence the sugar level in the same way as those analogues which are no growth regulators but which do give systemic protection.

It may be asked how far reaching the concept of HORSFALL & DIMOND will prove to be. Not only does it give an approach to the understanding of the effect of growth regulators on fungal diseases, it shows also quite generally how important the metabolic state of the host plant may be for susceptibility. This does not only apply to carbohydrate metabolism, also nitrogen metabolism of the host plays a role in determining the susceptibility of the plant. Carbohydrate metabolism and nitrogen metabolism are, moreover, closely interconnected.

The role which the metabolic state of the plant plays in susceptibility to disease is a field which, at its biochemical level, is only at the start of its exploration. Here we also touch the interesting field of natural resistance. For natural resistance only rarely depends on anatomical properties of the plant or on the presence of fungitoxic substances; it probably is more often determined by biochemical conditions. Knowledge of essential biochemical differences between resistant and susceptible races of the same plant species may therefore well have a stimulating effect on the development of systemic compounds which act by increasing the resistance of the plant.

In conclusion it may be stated that the development of systemic compounds which act by increasing the resistance of the host plant is as important as the development of systemic fungicides.

SUMMARY

A survey is given of some recent developments in the field of the systemic combat of fungus diseases of plants. The stage of practical application has not yet been reached.

Several examples are given of compounds which act by direct fungitoxic activity and of compounds which act by increasing host resistance.

SAMENVATTING

Er wordt een overzicht gegeven van enkele nieuwe ontwikkelingen op het gebied van de bestrijding van schimmelziekten bij planten met systemisch werkzame middelen. Het stadium van praktische toepassing van dergelijke middelen is nog niet bereikt.

Verschillende voorbeelden worden gegeven van stoffen die hun activiteit ontlenen aan directe fungitoxische werking en ook van stoffen die werkzaam zijn doordat zij de resistentie van de gastheer verhogen.

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